IMMUNE-RELATED ADVERSE EVENTS FOR PATIENTS WITH LUNG CANCER, 2nd Edition

EDITED BY: Xuelei Ma, Hubing Shi, Benjamin Frey and Udo S. Gaipl
PUBLISHED IN: Frontiers in Oncology and Frontiers in Immunology

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88976-354-2
DOI 10.3389/978-2-88976-354-2

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

IMMUNE-RELATED ADVERSE EVENTS FOR PATIENTS WITH LUNG CANCER,
2nd Edition

Topic Editors:
Xuelei Ma, Sichuan University, China
Hubing Shi, Sichuan University, China
Benjamin Frey, University Hospital Erlangen, Germany
Udo S. Gaipl, University Hospital Erlangen, Germany

Publisher's note: In this 2nd edition, the following article has been added: Yang R, Wang H, Yin X, Frey B, Gaipl US, Shi H and Ma X (2022) Editorial: Immune-Related Adverse Events for Patients With Lung Cancer. *Front. Oncol*. 12:898576. doi: 10.3389/fonc.2022.898576

Citation: Ma, X., Shi, H., Frey, B., Gaipl, U. S., eds. (2022). Immune-Related Adverse Events For Patients With Lung Cancer, 2nd Edition. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88976-354-2

Table of Contents

frontiers | Frontiers in Oncology

EDITORIAL
published: 04 May 2022
doi: 10.3389/fonc.2022.898576

Editorial: Immune-Related Adverse Events for Patients With Lung Cancer

Ruoning Yang[1,2†], Haiyang Wang[3†], Xiaomeng Yin[1], Benjamin Frey[4], Udo S. Gaipl[4*], Hubing Shi[1*] and Xuelei Ma[1*]*

[1] Department of Biotherapy, State Key Laboratory of Biotherapy, Cancer Center, West China Hospital, Sichuan University, Chengdu, China, [2] Department of Breast Surgery, Clinical Research Center for Breast, West China Hospital, Sichuan University, Chengdu, China, [3] Department of Otolaryngology Head and Neck Surgery, West China Hospital, Sichuan University, Chengdu, China, [4] Translational Radiobiology, Universitätsklinikum Erlangen, Erlangen, Germany

Keywords: editorial, lung cancer, immunotherapy, immune-related adverse events (IRAEs), management, pathogenesis

Editorial on the Research Topic

Immune-Related Adverse Events for Patients with Lung Cancer

OPEN ACCESS

Edited and reviewed by:
Catherine Sautes-Fridman, INSERM U1138 Centre de Recherche des Cordeliers (CRC), France

***Correspondence:**
Benjamin Frey
benjamin.frey@uk-erlangen.de
Udo S. Gaipl
udo.gaipl@uk-erlangen.de
Hubing Shi
shihb@scu.edu.cn
Xuelei Ma
drmaxuelei@gmail.com

†These authors contributed equally to this work

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Oncology

Received: *17 March 2022*
Accepted: *28 March 2022*
Published: *04 May 2022*

Citation:
Yang R, Wang H, Yin X, Frey B, Gaipl US, Shi H and Ma X (2022) Editorial: Immune-Related Adverse Events for Patients With Lung Cancer. Front. Oncol. 12:898576. doi: 10.3389/fonc.2022.898576

Currently, immune checkpoint inhibitors (ICIs) including programmed cell death-1 (PD-1) inhibitors, programmed cell death ligand 1 (PD-L1) inhibitors, and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors, show overall improvement of clinical outcomes and better tolerance for patients with lung cancer. However, many immune-related adverse events (irAEs) induced by immunotherapy are reported, which are considered to be a major challenge for immunotherapy. The most common management strategy for irAEs is early prevention, early detection and early treatment. This Research Topic recruited studies that discuss new discoveries in the field of pathogenesis and management of irAEs for patients with lung cancer.

We are very pleased to note that so many excellent work was submitted to these important topics. Finally, 15 papers were published, including two case reports. The research was carried out in different countries, including China, USA and Italy. The papers discuss the occurrence of irAEs, common irAEs, and the management of irAEs. Some studies comprehensively summarized the mechanism, diagnosis, and management of irAEs in patients with lung cancer, including immunotherapy and multimodal therapies (Fu et al., Hou et al., Wang et al., Li et al., Zheng and Wei, and Zhao et al.). Specific irAEs were partly discussed in detail. For example, Zhou and Wei reviewed immune checkpoint inhibitor (ICI) associated ocular side effects in lung cancer, and Zhang et al. and Zhu et al. both discussed another important irAE, namely checkpoint inhibitor-induced pneumonitis (CIP). And Tian et al. conducted a systematic review and meta-analysis to reveal the relationship between PD-1/PD-L1 inhibitors and neurological toxicities among cancer patients. As it is known to us, irAEs can happen to any organ, such as lung, liver, skin, kidney, digestive system, or endocrine system. Simultaneous involvement of multiple organs is rare but still reported. Deng et al. reported about a 71-year-old man with NSCLC showing severe multiple-organs injuries after tislelizumab treatment, which provides a reference for the management of multiple-organs irAEs. Proper management is important to mitigate the negative effects of irAEs. Most of irAEs are mild and can be managed through transient immunosuppression with corticosteroids. Thus, immunotherapy can continue under close monitoring after mild irAEs. The incidence of moderate to severe irAEs is very low, but it can lead to serious organ dysfunction and even death. Sometimes, discontinuing current therapy is necessary. Studies about the clinical outcomes of patients with lung cancer following immunotherapy interruption because of irAEs are still scarce,

and there is no consensus on whether treatment interruption will affect disease progression. Damato et al. reported about a woman with NSCLC that discontinued pembrolizumab because of severe colitis, keeping a partial response of the oncological disease in the following 24 months, but not completely recovering from colitis. This case showed that the treatment interruption didn't compromise the control of the oncological disease. The management of lung cancer patients with a history of prior autoimmune disease (AID) is another controversial topic. It has recently been reported that irAEs are more common among patients with autoimmune diseases and previous viral infections, which are patients with preexisting antibodies (Zheng and Wei). Tang et al. discussed the efficacy and safety of ICIs in patients with cancers and AID. They proposed that although irAEs occur more frequently, AID isn't an absolute contraindication for ICI treatment. Patients with AID need more close administration to reduce the injury of irAEs.

Compared with other irAEs, CIP is more worthy of our concern and vigilance. For patients with lung cancer, immune-mediated lung injury occurs in about 3% to 5% of patients receiving immunotherapy, which is higher than that in patients with other cancers (1). And the symptoms of CIP will overlap with the original respiratory signs, which makes diagnosis very difficult. CIP is usually an exclusionary diagnosis, and particularly, CIP may appear several months after the end of treatment. Accurate diagnosis is of primary importance, especially the level assessment. Corticosteroid regimen for CIP is still being explored (Zhang et al.). As for the risk factors for lung cancer, there is no consensus. For clinicians, they should focus on patients with a history of smoking, previous radiation therapy and previous lung disease (Zhu et al.).

In recent years, the prospect of adequate biomarkers in immunotherapy has gradually emerged. By having biomarkers for prognosis and prediction, we aim to achieve tailored treatment for each patient, resulting in maximizing the probability of response while minimizing the occurrence of irAEs, and thus reducing the harm of treatment. Unfortunately, till now, there have been no useful predictive biomarkers to assess the development of immune-related adverse events in the clinic (Burke and Rashdan). Currently, no validated biomarkers to predict irAEs induced by ICIs, not only for lung cancer but for all solid tumors, are available. Although CD8+ T cells and Interleukin 17 were reported to have connections with irAEs, the threshold is still unclear (2). In addition, Zhao et al. proposed that the occurrence of irAEs is strongly associated with better survival and response in NSCLC patients treated with PD-1 inhibitors, suggesting that irAE may be a potential predictive biomarker in this scenario (Zhang et al.).

In conclusion, there are many studies on irAEs in patients with lung cancer, but the diagnosis and management of irAEs still require more exploration. Firstly, timely and accurate diagnosis is essential. Secondly, risk stratification of irAEs is one basis of treatment. Thirdly, until today there is no optimal strategy for the pharmacotherapy of irAEs, which requires more time and larger clinical sample size to be evaluated. More and more excellent research will contribute to this field in the future.

This Research Topic accepted many excellent studies, mainly involving the diagnosis, grading and management of adverse events. We hope to improve the quality of life of patients with lung cancer through a better understanding of irAEs. We appreciate all the reviewers and authors for their contributions to this Research Topic. We hope this Research Topic can even arise more attention in the related fields.

AUTHOR CONTRIBUTIONS

Literature review, and data collection and were performed by RJ, XY and HW. The first draft of the manuscript was written by RY and XM. The final version of the editorial was written by USG, BF and HS. All authors read and approved the final manuscript.

REFERENCES

1. Wang P-F, Chen Y, Song S-Y, Wang T-J, Ji W-J, Li S-W, et al. Immune-Related Adverse Events Associated With Anti-Pd-1/Pd-L1 Treatment for Malignancies: A Meta-Analysis. *Front Pharmacol* (2017) 8:730. doi: 10.3389/fphar.2017.00730
2. Seidel JA, Otsuka A, Kabashima K. Anti-Pd-1 and Anti-Ctla-4 Therapies in Cancer: Mechanisms of Action, Efficacy, and Limitations. *Front Oncol* (2018) 8:86. doi: 10.3389/fonc.2018.00086

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

REVIEW
published: 11 September 2020
doi: 10.3389/fonc.2020.01785

Pneumonitis Induced by Immune Checkpoint Inhibitors: From Clinical Data to Translational Investigation

Shicong Zhu[1†], Yang Fu[2†], Bo Zhu[3], Bicheng Zhang[1] and Jun Wang[4*]*

[1] Cancer Center, Renmin Hospital of Wuhan University, Wuhan, China, [2] Department of Oncology, Xiangyang Hospital, Hubei University of Chinese Medicine, Xiangyang, China, [3] Department of Oncology, Xinqiao Hospital, Army Medical University, Chongqing, China, [4] Department of Oncology, The First Affiliated Hospital of Shandong First Medical University, Jinan, China

Immune checkpoint inhibitors (ICIs) have been applied to clinical practice and achieved significant therapeutic benefit in a variety of human malignancies. These drugs not only enhance the body's antitumor immune response but also produce side effects called immune-related adverse events (irAEs). Although checkpoint inhibitor pneumonitis (CIP) has a low clinical incidence, it is likely to cause the delay or termination of immunotherapy and treatment-related death in some severe cases. An increasing number of CIP cases have been reported since 2015, which are attributed to the augmentation of approvals and uses of ICIs, but a comprehensive understanding of CIP is still lacking. This review focuses on the epidemiology, clinical characteristics, treatment strategies, and underlying mechanisms of CIP to strengthen the recognition of pulmonary toxicity among clinicians and researchers.

Keywords: immune-related adverse events, programmed cell death 1, programmed cell death ligand 1, immune checkpoint inhibitor, pneumonitis

OPEN ACCESS

Edited by:
Benjamin Frey, University Hospital Erlangen, Germany

Reviewed by:
Claudia Schweizer, University Hospital Erlangen, Germany
Shetal Arvind Patel, University of North Carolina at Chapel Hill, United States

***Correspondence:**
Bicheng Zhang
bichengzhang@hotmail.com
Jun Wang
ggjun2005@126.com

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Oncology

Received: *11 May 2020*
Accepted: *11 August 2020*
Published: *11 September 2020*

Citation:
Zhu S, Fu Y, Zhu B, Zhang B and Wang J (2020) Pneumonitis Induced by Immune Checkpoint Inhibitors: From Clinical Data to Translational Investigation. Front. Oncol. 10:1785. doi: 10.3389/fonc.2020.01785

INTRODUCTION

Immune checkpoint inhibitors (ICIs) can restore the body's antitumor immune response and promote T cell-mediated clearance of tumor cells by blocking the inhibitory signaling pathways of T cells (1). As immune checkpoints work, the inhibitory signals are mediated by programmed cell death 1 (PD-1) binding to its two specific ligands, programmed cell death ligand 1 (PD-L1), and programmed cell death ligand 2 (PD-L2) expressed on tumor cells, as well as cytotoxic T lymphocyte-associated protein 4 (CTLA-4), binding to B7-1 (CD80), and B7-2 (CD86) molecules on antigen-presenting cells (APCs).

In recent years, immunotherapy with ICIs, consisting of PD-1 inhibitors, PD-L1 inhibitors and CTLA-4 inhibitors, has become an important therapeutic strategy for advanced malignant tumors. Two PD-1 inhibitors (nivolumab and pembrolizumab), three PD-L1 inhibitors (atezolizumab, durvalumab, and avelumab), and one CTLA-4 inhibitor (ipilimumab) have been approved by the US Food and Drug Administration (FDA) for multiple types of malignancies, mainly containing advanced melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). Over 50 immunotherapy agents are under drug research and development in the United States, and more than 800 clinical studies for tumor immunotherapy are ongoing (2).

With the wide application of these drugs, immune-related adverse events (irAEs) have also increased, mainly including fatigue, skin toxicity, colitis, hepatitis, thyroiditis, and pneumonitis (3).

The degrees of irAEs are mostly from mild to moderate, but there are also serious adverse reactions that endanger patients' lives, such as immune-related pneumonitis, nephritis, and myocarditis. Pneumonitis induced by ICIs is now referred to as checkpoint inhibitor pneumonitis (CIP) (4). Although CIP is rare, it has a poor prognosis, accounting for 28% of fatal events (5). More and more cases of CIP have been reported in recent years, but knowledge about it remains limited. In this review, the clinical features of CIP and related translational investigations will be discussed.

INCIDENCE AND RISK FACTORS

A meta-analysis containing 26 studies showed that the overall incidence of CIP was 2.7% for all grades and 0.8% for grade 3 or above (6). About 0.2% of patients died from pneumonitis, and 0.2% to 4.0% of patients discontinued the PD-1 inhibitors due to pneumonitis (6). It is worth noting that a recent research in patients with NSCLC suggested that the incidence of CIP seemed higher in the real world, with an all-grade incidence rate of 19% and a high-grade (grade 3 or 4) incidence rate of 11% (7). The data in meta-analysis and multicenter clinical trials are shown in **Table 1** (6, 8–12).

However, it is different in terms of the incidence within different drugs. Due to the different toxicity profiles of ICIs, PD-1 inhibitors were more likely to induce the CIP than CTLA-4 inhibitors (OR 6.4, 95% CI 3.2–12.7) (13). In addition, the toxicity profiles of the PD-1 and PD-L1 inhibitors may also be different. A meta-analysis showed that the incidence of all-grade pneumonitis relative to PD-1 inhibitors was higher than PD-L1 inhibitors (3.6% vs. 1.3%), also for grades 3 and 4 (1.1% vs. 0.4%) (14). Likewise, the incidence of CIP caused by different PD-1 inhibitors did not seem to be precisely the same. The patients treated with pembrolizumab were more likely to experience pneumonitis for all grades than the patients treated with nivolumab (OR 2.08, 95% CI 1.52–2.85), but there was no significant difference for high grades between these two drugs. In addition, the study showed that atezolizumab and nivolumab or atezolizumab and pembrolizumab had no significant difference regarding the incidence of pneumonitis at all grades and higher (15).

Moreover, the incidence of CIP varied in different tumor types. According to a systematic review, pneumonitis appeared more likely to occur in NSCLC or RCC patients (6). Studies showed that the incidence of pneumonitis in NSCLC patients was significantly higher than that in melanoma patients for both all grades (4.1% vs. 1.6%) and higher grades (1.8% vs. 0.2%). However, the odds of all-grade pneumonitis were higher in RCC than melanoma (4.1% vs. 1.6%) but have no difference in grade 3 or higher (0.8% vs. 0.2%) (6, 15), although in the same type of tumor, different pathological types seemed to have an impact on the incidence of CIP. Data from a retrospective study indicated that adenocarcinoma tumor histology was associated with a lower risk of CIP compared with non-adenocarcinoma histology (including squamous NSCLC; OR 0.38, 95% CI 0.17–0.82) (5).

Furthermore, the incidence of pneumonitis in combination therapy and monotherapy was also different. In the checkmate227 study, the incidence of all-grade (3.8% vs. 2.3%), or grade 3–4 pneumonitis (2.3% vs. 1.5%) in nivolumab plus ipilimumab group was higher than that in the nivolumab monotherapy group (16). A meta-analysis compared the incidence of CIP among different therapeutic regimens in melanoma, and the result showed that combination therapy had a higher incidence of CIP than PD-1 inhibitor monotherapy for all grades (6.6% vs. 1.6%) and grade 3 or higher (1.5% vs. 0.2%) (6). The combination described above included a combination of dual ICIs and ICIs plus peptide vaccines. Subsequently, another meta-analysis including melanoma, NSCLC, small cell lung cancer, and other tumor types indicated that the risk of all-grade CIP (3.47 times) and severe CIP (3.48 times) was higher in combination therapy (ipilimumab plus nivolumab) than nivolumab or ipilimumab alone (17). However, there are no data on the incidence of CIP in ICIs plus chemotherapy vs. ICI monotherapy.

Besides, researchers are also concerned about many other related risk factors for CIP. One study showed that patients with a history of asthma/chronic obstructive pulmonary disease (COPD; 5.4% vs. 3.1%) or who had previously received chest radiotherapy (6.0% vs. 2.6%) were more susceptible to CIP than those without COPD or chest radiotherapy, respectively (18). Some studies also manifested that high-risk populations for CIP included those with NSCLC possessing sensitizing epidermal growth factor receptor (EGFR) mutation when treated with EGFR–tyrosine kinase inhibitor (TKI) in combination with ICIs, and those with an active lung infection (7, 19, 20). Kato et al. pointed out that male gender, smoking history, and early multiline treatment were the potential risk factors for pneumonitis caused by nivolumab (21), although some studies did not consider gender as a risk factor (6). Naidoo et al. found that smoking and baseline lung disease were not only the potential risk factors of CIP but also related to poor response to steroid therapy for CIP (12). Interestingly, research indicated that extrathoracic metastasis was associated with a significantly lower incidence of CIP (22). However, the occurrence of CIP caused by PD-1 inhibitors seemed to have no significant relationship with the dose of ICIs and the age of the patients (23).

The relationship between the occurrence of CIP and immunotherapy efficacy is also one of the concerns of researchers. Several studies reported that the occurrence of irAEs was related to a better efficacy or even survival outcome in patients treated with ICIs (24, 25). However, as one of many irAEs, whether CIP can also be taken for an excellent prognostic indicator remains a question. A multi-institutional analysis suggested that the development of pneumonitis was significantly associated with increased progression-free survival (PFS) and overall survival (OS) in patients with advanced NSCLC treated with nivolumab (26). Nevertheless, some other studies found that treatment efficacy and survival were significantly decreased in patients with CIP compared with those without ICI therapy in NSCLC (5, 27, 28), while another retrospective study showed that no significant survival differences were seen with the

TABLE 1 | Incidence of CIP.

Study author	Numbers of		Tumor type	ICIs	Incidence of		
	Trials	Patients			All grade	Grade 3/4	Pneumonitis-related death
Nishino et al. (6)	20	4,496	Melanoma, NSCLC, RCC, etc.	Nivolumab, pembrolizumab, and ipilimumab	2.7%	0.8%	0.2–2.3%
Abdel-Rahmen et al. (8)	11	6,671	Melanoma, NSCLC, RCC, prostate cancer	Nivolumab, pembrolizumab, and ipilimumab	1.3–11%	0.3–2.0%	–
Costa et al. (9)	9	5,353	Melanoma, NSCLC, RCC, etc.	Nivolumab, pembrolizumab, and ipilimumab	2.65%	–	–
Nishijima et al. (10)	7	3,450	Melanoma, NSCLC	Nivolumab, pembrolizumab, and atezolizumab	3.4%	1.3%	–
Delaunay et al. (11)	–	1,826	Melanoma, NSCLC	CTLA-4, PD-1, and PD-L1 inhibitors	3.5%	1.26%	0.33%
Naidoo et al. (12)	–	915	Melanoma, NSCLC, RCC, etc.	CTLA-4, PD-1, and PD-L1 inhibitors	4.7%	1.2%	0.1%

CIP, checkpoint inhibitor pneumonitis; ICIs, immune checkpoint inhibitors; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; CTLA-4, cytotoxic T lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; and PD-L1, programmed cell death-ligand 1.

occurrence of pneumonitis in metastatic melanoma treated with nivolumab (29).

CLINICAL PRESENTATION

The time from the administration of ICIs to the occurrence of CIP varied from 2 to 24 months, with a median time of 2.8 months (12). Moreover, studies reported that high-grade CIP occurred earlier than low-grade CIP (7).

There was no difference in onset time between different ICIs, but patients with combination therapy seemed to have an earlier onset of CIP (median, 2.7 vs. 4.6 months). A retrospective study indicated that patients with NSCLC developed pneumonitis earlier than patients with malignant melanoma (median, 2.1 vs. 5.2 months) (11).

The main clinical symptoms of CIP include dyspnea (53%), cough (35%), fever (12%), and chest pain (7%) (30). Most patients with CIP had mild symptoms, with grade 1–2 CIP accounting for about 73% (30). It is worth noting that recurrent pneumonitis was usually more severe than the first event (31). However, there was no difference in the distribution of severity between monotherapy and combination therapy (12). In addition, approximately 25% of patients have other immune-related symptoms at the same time or have no symptoms.

The radiographic features of CIP are diverse and non-specific. Most can be shown as traction bronchiectasis, consolidation, reticular opacities, ground-glass opacity (GGO), centrilobular nodularity, and honeycombing (32). Naidoo et al. summarized radiologic features as five subtypes: cryptogenic organizing pneumonia (COP) like (19%), mainly manifested as discrete patchy or confluent shadows with or without air bronchography; GGO (37%), mainly manifested as frosted glass-like nodules in the periphery or under the pleura; non-specific interstitial pneumonia (NSIP; 7%), chest CT showed thickened lobular septa, infiltrated around the bronchial blood vessels, and severe cases showed a subpleural mesh or honeycomb structure; hypersensitivity pneumonitis (HP; 22%), mainly manifested as nodules in the center of the leaflets or bronchiole-like appearance of tree-like micro-nodules; and others (15%) (12). Moreover, acute interstitial pneumonia (AIP), and acute respiratory distress syndrome (ARDS) have also been reported (33). In addition to the typical manifestations of pneumonia, some case reports suggested the presence of small subpleural nodules, hilar lymphadenopathy, and granulomatous changes (12). According to previous research reports, the radiologic subtypes are consistent throughout the patients' clinical course, with a few exceptions, including the evolution from COP-like subtype to severe GGO type and the additional interstitial appearance of GGO type (12).

In clinical practice, the differential diagnosis of CIP is of considerable significance, but it often cannot be definitively diagnosed by imaging alone. Firstly, CIP often needs to be distinguished from infectious pneumonia, including bacteria, viruses, tuberculosis, and fungi. Infected patients usually have symptoms of fever, sputum, and elevated white blood cells. Compared with infectious pneumonia, CIP is less prone to fever and more prone to respiratory failure (34). The imaging manifestation of infectious pneumonia is ground-glass shadow in the early stage, bacterial pneumonia lesions are limited to lung lobes or lung segments, and viral pneumonia can be multiple ground-glass shadows. Lung consolidation may occur after the disease progresses. A combination of bronchoscopy and various etiological examinations (such as nasal swab, blood culture, sputum culture, and urine culture) may help exclude infection (35). Furthermore, tumor progression that leads to new lesions also needs to be identified with CIP. The clinical manifestations of tumor progression are cough, hemoptysis, chest pain, weight loss, dyspnea, and cough. Besides, serum tumor markers are often higher than before. Imaging manifestations of the progression of the primary lesion of lung cancer are often an increase in the primary lesion of lung cancer and new nodular shadows, patchy shadows, ground-glass shadows. Imaging of lung cancer lymphangitis due to progress is characterized by the thickening

of multiple leaflet septa and multiple small nodules. Radiation pneumonia most often occurs between 2 and 6 months after lung radiotherapy. Most of the lesions are confined to the radiation field, with or without respiratory symptoms, and symptoms may include cough, dyspnea, and low fever. Bronchoalveolar lavage (BAL) can be used in the differential diagnosis, often manifested by an increase in the proportion of lymphocytes. In addition, a prospective observational study suggested that lung function tests during treatment might be helpful for risk stratification to screen for CIP (36). Usually, a bronchoscopic biopsy is not considered, but it can be used when it is difficult to make a differential diagnosis (37).

CLINICAL MANAGEMENT

Clinically, the treatment of CIP is carried out according to the principle of classification (38). Clinical classification of CIP refers to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 and European Society for Medical Oncology (ESMO) Guidelines for Immunotherapeutic Toxicity Management (37, 39). However, the use of CTCAE still has some limitations on toxicity grading, sometimes underestimating or overestimating the probability and severity of toxicities (40).

According to the range of clinical symptoms and lesions involved, the guidelines classify toxicity into five grades: G1, mild toxicity; G2, moderate toxicity; G3, severe toxicity; G4, life-threatening toxicity; and G5, death-related toxicity (41). The classification description of CIP is shown in **Table 2**. For the management of G1 toxicities, closely observe the patient's condition, repeat CT, and monitor the lung capacity in 3 to 4 weeks. Baseline examinations for CIP patients include chest CT, blood oxygen saturation, blood routine, liver and kidney function, electrolytes, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and lung function. If improvement is observed, continue to follow up; if no improvement is observed, stop using ICIs and treat as G2. For the management of G2 toxicities, continue to stop using ICIs until there is improvement to G1 or less. Administer prednisone 1 to 2 mg/kg/day by intravenous drip. If improvement is observed, taper by 5 to 10 mg/week over 4 to 6 weeks; if no improvement is observed, treat as G3∼G4. For the management of G3∼G4 toxicities, permanently stop using ICIs. Administer methylprednisolone 2 mg/kg/day by intravenous injection. After steroid treatment for 48 h, if improvement is observed, the treatment continues until there is improvement to G1 or less, and taper corticosteroids over 4 to 6 weeks; if no improvement is observed, consider administering infliximab 5 mg/kg by intravenous drip, or mycophenolate mofetil (MMF) 1 *g* twice a day or immunoglobulin by intravenous injection. The management of CIP is described in **Table 3**.

Steroid therapy is the most basic treatment for CIP. Regularly, adequate steroids can control 70–80% of CIP (35). Other treatments include infliximab, cyclophosphamide, MMF, tocilizumab, and immunoglobulin. The major guidelines are relatively uniform for the dosage of steroids in G2 (1–2 mg/kg/day), but when dealing with G3∼G4, the recommended dose in ESMO is higher than that of other guidelines (2–4 vs. 1–2 mg/kg/day). Regarding the overall course of steroid use, similarly, the opinions of the guidelines are relatively uniform in G2, and it is recommended that the overall course of treatment should be controlled within 4 weeks. However, as

TABLE 2 | Gradation of CIP.

Grades	Description
G1	No symptom
	Limited to a single lobe or <25% lung parenchyma
G2	New symptoms or worsening symptoms, including shortness of breath, cough, chest pain, fever, and anoxia
	Involves multiple lung lobes and reaches 25–50% of lung parenchyma, affecting daily life, requiring drug intervention
G3	Serious new complications
	Involves all lung lobes or >50% of lung parenchyma, limited personal self-care ability, requiring oxygen inhalation and hospitalization
G4	Life-threatening dyspnea, acute respiratory distress syndrome (ARDS) requiring urgent intervention such as intubation

CIP, checkpoint inhibitor pneumonitis.

TABLE 3 | Management of CIP.

Grades	Guideline for the management
G1	• Consider holding ICIs Monitor symptoms every 2–3 days
	• May offer one repeat CT in 3–4 weeks
	• In patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3–4 weeks
	○ If improvement is observed, continue to follow up
	○ If condition worsens, treat as G2 or 3–4
G2	• Hold ICIs until resolution to G1 or less
	• Consider infectious workup: nasal swab for potential viral pathogens sputum culture, blood culture, and urine culture
	• Consider chest CT with contrast Repeat chest CT in 3–4 weeks
	• Consider empirical antibiotics if infection has not yet been fully excluded
	• Prednisone IV 1–2 mg/kg/day
	○ If improvement is observed, start slow steroid taper by 5 to 10 mg/week over 4 to 6 weeks
	○ If condition worsens, treat as G3–4
G3/ G4	• Permanently discontinue ICIs
	• Pulmonary consultation for bronchoscopy with BAL
	Consider biopsies for atypical lesions Methylprednisolone IV 2–4 mg/kg/day
	○ If improvement is observed, taper corticosteroids over 4–6 weeks
	○ If not improving or worsening after 48 h: add infliximab IV 5 mg/kg
	or MMF IV 1 g BID
	or IVIG for 5 days
	or cyclophosphamide

ICIs, immune checkpoint inhibitors; CT, computed tomography; DLCO, carbon monoxide diffusing capacity; IV, intravenous; BAL, bronchoalveolar lavage; MMF, mycophenolate mofetil; BID, two times daily; and IVIG, intravenous immunoglobulin.

for G3∼G4, ESMO and Society for Immunotherapy of Cancer (SITC) emphasize that the process of steroid reduction should be slower. The recommended total course of treatment is 8 weeks in ESMO and SITC but 4–6 weeks in American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN).

It is worth noting that steroids and antibiotics are often used in CIP patients, but there seems to be a specific relationship between these two types of drugs and the efficacy of immunotherapy. The effect of using steroids on the survival of patients receiving ICI treatment is not entirely certain. A retrospective study showed that the patients who received prednisone >10 mg at the start of immunotherapy had a shorter median OS than those who received 0–10 mg of prednisone (4.9 vs. 11.2 months) (42). However, a recent meta-analysis pointed out that the use of steroids to mitigate adverse events did not negatively affect OS (43). Moreover, some studies showed that the use of antibiotics often leads to worse treatment response and OS in patients treated with ICIs (44, 45). Therefore, it is still necessary to be cautious when using steroids and antibiotics in CIP patients.

Patients with no clinical improvement after 48 to 72 h of corticosteroid therapy are considered to be steroid resistant. The evaluation of clinical signs and symptoms can include assessment of general condition, change in dyspnea or cough, and need for supplemental oxygen. Comprehensive judgment can be combined with objective indicators such as oxygen saturation and blood gas analysis. If necessary, review chest CT or chest radiograph to make a judgment. For these steroid-refractory CIP patients, it is recommended to consider administrating infliximab, MMF, or immunoglobulin as described above, but there is no consensus on the optimal choice and usage. Guacimara et al. reported that a case of mycophenolate-resistant CIP was successfully treated with infliximab, and they thought that infliximab might be preferable than other classical immunosuppressants (46). Another case report pointed out that repeated administration of infliximab for a certain period may be beneficial in the treatment of steroid-refractory CIP (47). However, after these treatments, there are still some cases that are reported to be deteriorating. Vickie et al. reported that a patient developed a diffuse alveolar hemorrhage and died of respiratory failure after high-dose corticosteroids, empiric antibacterial therapy, and infliximab (48). Recently, the success of triple combination therapy (high-dose corticosteroids, tacrolimus, and cyclophosphamide) for steroid-refractory CIP was reported (49). In addition to these traditional immunosuppressants, Filipe et al. proposed new perspectives to manage steroid-refractory CIP (50). They indicated that other anti-TNFα drugs (including etanercept, adalimumab, certolizumab, and golimumab) could be alternatives to infliximab and that anti-IL-1 therapy (anakinra or canakinumab) might be helpful for patients with severe anti-TNFα-refractory pneumonitis (50). Moreover, an anti-IL-6 (tocilizumab) strategy was also considered as an effective treatment option for steroid-refractory CIP (51). Nevertheless, further investigations are needed to seek a better management approach for steroid-refractory CIP.

For patients who suspend ICI treatment after CIP treatment, some of them can consider the rechallenge of ICIs. A pooled analysis collected 170 patients from 10 studies, 20 of whom developed CIP. Seven patients (35%) resumed treatment after suspending ICIs, and two patients developed CIP again and recovered after using steroids again (32). Patients receiving rechallenge should regularly evaluate the efficacy and closely monitor the adverse events, including CIP and other irAEs. If CIP relapses again, then no longer consider rechallenge after treatment.

In addition, empirical anti-infective treatment should be performed simultaneously if the cause of infection cannot be completely ruled out for G2∼G4 patients. For patients with more than 20 mg of prednisone (or equivalent doses) for >4 weeks, antibiotics should be considered for the prevention of pneumocystis pneumonia. When using glucocorticoids, clinicians are supposed to consider using proton pump inhibitors (PPIs) to prevent gastrointestinal reactions, and if using steroids for a long time, patients need to be supplemented with calcium and vitamin D.

MECHANISM OF CHECKPOINT INHIBITOR PNEUMONITIS AND TRANSLATIONAL INVESTIGATIONS

Currently, the mechanisms for CIP are poorly understood. 20 years ago, studies reported that PD-L1 or CTLA-4 gene-deficient mice developed multisystem autoimmune diseases including pneumonitis (52). Michael et al. pointed out several possible mechanisms of irAEs, including increased T cell activity, increased autoantibody levels, increased levels of inflammatory cytokines, and enhanced complement-mediated inflammation (3). The above expositions could explain the possible mechanisms of myocarditis, colitis, thyroiditis, and pituitary inflammation caused by immunotherapy with ICIs, but whether these mechanisms are responsible for CIP remains unknown.

Which and How Do Immune Cells Play an Important Role in Checkpoint Inhibitor Pneumonitis?

Due to the lack of preclinical models, several studies focused on the patient's BAL fluid (BALF) and lesion tissue to explore the underlying mechanisms of CIP.

Several studies have reported that an increased number of lymphocytes and a small number of eosinophils and neutrophils can be found in BALF of the patients with CIP (53–55). In an autopsy case, Koelzer et al. found that interstitial lymphocytic infiltration and fibrotic rings occurred between lung lobules, around the bronchioles and under the pleura, rich in CD8 + T cells, with high expression of PD-1 and cytotoxic granule-associated RNA binding protein (TIA-1) (56). Another research performed PD-L1 staining on lung biopsy tissue and found a large number of macrophages with high PD-L1 expression in the alveolar space (57). These findings indicate that T lymphocytes and macrophages may play a role in the occurrence and development of CIP.

A study analyzed the landscape of the immune cells in alveolar and found that proinflammatory subsets (central memory T cells, IL-1β^{hi} populations) increased and the anti-inflammatory process was inhibited (decreased expression of CTLA-4 and PD-1 in T regulatory cells and decreased expression of counter-regulatory interleukin-1 receptor antagonist) in both T cells and myeloid cells in BALF, providing the possible underlying mechanisms of immune dysregulation in patients with CIP (58). Another study compared the T cell clonality between the resected pneumonitis lesion and the primary tumor of a patient with CIP, finding that there is a clear overlap between them. Through the above research, the author suggests that one possible mechanism of CIP is that tumor-specific T cells via the blood circulation to the lung sharing antigens with the tumor result in the immune response in the patient (59). But whether these are tumor-infiltrating lymphocytes (TILs) requires further investigation.

Is There a Key Cytokine, Chemokine, or Molecule?

Several animal studies indicated that PD-L2 played an essential role in the mechanisms of CIP. The expression of PD-L2 mainly concentrates on immune cells, such as dendritic cells (DCs), and Th2 cells, which belong to the subset of CD4 + T cells and can secrete Th2 cytokines (such as IL-4, IL-5, IL-10, and IL-13). As for non-immune cells, PD-L2 expresses in epithelial cells, especially lung epithelial cells. An animal experiment indicated that the PD-L2 could combine with the repulsive guidance molecule b (RGMb) secreted by lung interstitial macrophages and alveolar cells and could promote the increase of initial T cells that leads to respiratory immune tolerance (60). Anti-PD-1 agents could promote the combination of PD-L2 and RGMb by reducing the combination of PD-L2 and PD-1, thus leading to vigorous clonal expansion of lung resident T cells. At the same time, the PD-1 blockade would hinder the respiratory immune tolerance of this expanded clone and eventually led to immune-mediated toxicity in the lungs (61). In addition to RGMb, some scholars pointed out that the Th2 inflammation caused by the blockade of PD-1/PD-L2 interaction was also a possible mechanism of CIP (62). Moreover, IL-6 seems to play an important role in CIP, and it is considered to be a biomarker for irAEs, including indirect signs of high inflammation associated with IL-6, such as increased CRP (63). IL-6 was reported to function as a main cytokine in the generation of a cytokine release syndrome (CRS) and viral respiratory distress syndrome (ARDS) by stimulating T cell proliferation and affecting the ability of pulmonary DCs to prime naive T cells (64). And a study proved that anti-IL-6 could also be effective for CIP in addition to treating CRS (51). Nevertheless, it requires more basic researches to support and to explore the specific mechanism of IL-6 in the occurrence of CIP.

Is There a Direct Result of Immune Checkpoint Inhibitor Drugs or a Combination of Factors?

Because the mechanisms of pneumonia are still poorly understood, it is unknown whether there are multiple factors involved in the occurrence of CIP. A previously combined underlying disease may be one of several factors, including asthma, COPD, and chronic/low-grade infection. Besides, other previous or ongoing cancer treatment may be another factor involved, including chemotherapies, targeted therapies, radiation therapy, or other immune therapies. Some other factors, such as active or passive exposure to cigarette smoke, different cancer types, and different ages, may also have an impact on CIP (6, 35, 65). In addition, in the checkmate078 study with the East Asian population as the main subject, the rate of overall lung toxicity induced by nivolumab was 7%, and in a phase II study in Japanese patients, the incidence was 8% (66, 67). In comparison, the rates in the checkmate017 and checkmate057 studies with the white population as the main subjects were 3% and 5%, respectively (67). The incidence of CIP in the eastern population seems to be a little bit higher than in the western population, but whether different races will affect the development of CIP still needs more data.

DISCUSSION

At present, the risk factors for CIP are not completely clear. Based on our current understanding of it, clinicians should focus on the patients who have a smoking history, previous radiotherapy, and baseline lung disease, prior TKI, etc. All patients treated with ICIs should be alert to the possibility of CIP when they have new respiratory symptoms or increased initial respiratory symptoms.

Due to the lack of specificity of the clinical manifestations and imaging features of CIP, the diagnosis of CIP is a diagnosis of exclusion, and there is no unified diagnostic standard. Clinicians need to make a comprehensive judgment based on the history of ICI medication, clinical manifestations, imaging features, and laboratory examinations. In patients with suspected CIP, the possibility of lung infection, tumor progression, interstitial pulmonary diseases caused by other causes, pulmonary vasculitis, and pulmonary edema, etc., needs to be ruled out.

Moreover, due to the lag and persistence of the immune response, CIP can occur at any time during the treatment process, even after the end of treatment. Therefore, the patient's condition is supposed to be monitored and followed up throughout the survival time.

In addition, there exists a controversy about the relationship between the occurrence of CIP and the efficacy of immunotherapy. One possible reason is that these studies are retrospective, and the incidence of CIP is low, resulting in a small number of patients in the CIP group (the minimum is 3 and the maximum is 38). Besides, one of these studies pointed out that non-specific manifestations of lower grade CIP, such as fatigue, might lead to misclassification (5). In the future, prospective, multicenter, large-scale researches are still warranted to explore related issues. At the same time, it is necessary to strengthen the understanding of CIP and improve the accuracy of diagnosis.

For now, many confusing issues need to be clarified. At present, the pathogenesis of CIP remains at the stage of research on individual cases. To better understand the biological mechanism of CIP, the treatment of CIP patients and the results of various examinations (including chest CT, pulmonary function

testing, blood routine, and liver and kidney function) should be accurately and completely recorded, and the preservation of specimens (including BAL, lung biopsy tissue, and blood) should be ensured. The above data and specimens can be used as the bases for translation studies. Besides, there is no CIP-related animal model, so the establishment and application of the experimental model are also one of the difficulties that need to be overcome. In the future, a large number of samples need to be systematically studied and summarized to provide a more comprehensive understanding of CIP. Additionally, more translational and basic research is urgently needed to understand the underlying mechanisms better.

AUTHOR CONTRIBUTIONS

SZ, YF, BoZ, BiZ, and JW analyzed the literatures and researches and drafted the manuscript. SZ and YF contributed equally to this work. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov.* (2018) 8:1069–86. doi: 10.1158/2159-8290.CD-18-0367
2. The LO. Calling time on the immunotherapy gold rush. *Lancet Oncol.* (2017) 18:981. doi: 10.1016/S1470-2045(17)30521-1
3. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *New Engl J Med.* (2018) 378:158–68. doi: 10.1056/NEJMra1703481
4. Sears CR, Peikert T, Possick JD, Naidoo J, Nishino M, Patel SP, et al. Knowledge gaps and research priorities in immune checkpoint inhibitor–related pneumonitis. An official American thoracic society research statement. *Am J Resp Crit Care.* (2019) 200:e31–43. doi: 10.1164/rccm.201906-1202ST
5. Suresh K, Psoter KJ, Voong KR, Shankar B, Forde PM, Ettinger DS, et al. Impact of checkpoint inhibitor pneumonitis on survival in NSCLC patients receiving immune checkpoint immunotherapy. *J Thorac Oncol.* (2019) 14:494–502. doi: 10.1016/j.jtho.2018.11.016
6. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of programmed cell death 1 inhibitor–related pneumonitis in patients with advanced cancer. *Jama Oncol.* (2016) 2:1607. doi: 10.1001/jamaoncol.2016.2453
7. Suresh K, Voong KR, Shankar B, Forde PM, Ettinger DS, Marrone KA, et al. Pneumonitis in non–small cell lung cancer patients receiving immune checkpoint immunotherapy: incidence and risk factors. *J Thorac Oncol.* (2018) 13:1930–9. doi: 10.1016/j.jtho.2018.08.2035
8. Abdel-Rahman O, Fouad M. Risk of pneumonitis in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. *Ther Adv Respir Dis.* (2016) 10:183–93. doi: 10.1177/1753465816636557
9. Costa R, Carneiro BA, Agulnik M, Rademaker AW, Pai SG, Villaflor VM, et al. Toxicity profile of approved anti-PD-1 monoclonal antibodies in solid tumors: a systematic review and meta-analysis of randomized clinical trials. *Oncotarget.* (2017) 8:8910. doi: 10.18632/oncotarget.13315
10. Nishijima TF, Shachar SS, Nyrop KA, Muss HB. Safety and tolerability of PD-1/PD-L1 inhibitors compared with chemotherapy in patients with advanced cancer: a meta-analysis. *Oncologist.* (2017) 22:470–9. doi: 10.1634/theoncologist.2016-0419
11. Delaunay M, Cadranel J, Lusque A, Meyer N, Gounaut V, Moro-Sibilot D, et al. Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. *Eur Respir J.* (2017) 50:1700050. doi: 10.1183/13993003.00050-2017
12. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in patients treated with anti–programmed death-1/programmed death ligand 1 therapy. *J Clin Oncol.* (2017) 35:709–17. doi: 10.1200/JCO.2016.68.2005
13. Khoja L, Day D, Wei-Wu CT, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. *Ann Oncol.* (2017) 28:2377–85. doi: 10.1093/annonc/mdx286
14. Khunger M, Rakshit S, Pasupuleti V, Hernandez AV, Mazzone P, Stevenson J, et al. Incidence of pneumonitis with use of programmed death 1 and programmed death-ligand 1 inhibitors in non-small cell lung cancer: a systematic review and meta-analysis of trials. *Chest.* (2017) 152:271–81. doi: 10.1016/j.chest.2017.04.177
15. Ma K, Lu Y, Jiang S, Tang J, Li X, Zhang Y. The relative risk and incidence of immune checkpoint inhibitors related pneumonitis in patients with advanced cancer: a meta-analysis. *Front Pharmacol.* (2018) 9:1430. doi: 10.3389/fphar.2018.01430
16. Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med.* (2018) 378:2093–104. doi: 10.1056/NEJMoa1801946
17. Su Q, Zhu EC, Wu JB, Li T, Hou YL, Wang DY, et al. Risk of pneumonitis and pneumonia associated with immune checkpoint inhibitors for solid tumors: a systematic review and meta-analysis. *Front Immunol.* (2019) 10:108. doi: 10.3389/fimmu.2019.00108
18. Sul J, Blumenthal GM, Jiang X, He K, Keegan P, Pazdur RFDA. Approval summary: pembrolizumab for the treatment of patients with metastatic non-small cell lung cancer whose tumors express programmed death-ligand 1. *Oncologist.* (2016) 21:643–50. doi: 10.1634/theoncologist.2015-0498
19. Ahn MJ, Yang J, Yu H, Saka H, Ramalingam S, Goto K, et al. 136O: osimertinib combined with durvalumab in EGFR-mutant non-small cell lung cancer: results from the TATTON phase Ib trial. *J Thorac Oncol.* (2016) 11:S115. doi: 10.1016/S1556-0864(16)30246-5
20. Oshima Y, Tanimoto T, Yuji K, Tojo A. EGFR-TKI-associated interstitial pneumonitis in nivolumab-treated patients with non-small cell lung cancer. *Jama Oncol.* (2018) 4:1112–5. doi: 10.1001/jamaoncol.2017.4526
21. Kato T, Masuda N, Nakanishi Y, Takahashi M, Hida T, Sakai H, et al. Nivolumab-induced interstitial lung disease analysis of two phase II studies patients with recurrent or advanced non-small-cell lung cancer. *Lung Cancer.* (2017) 104:111–8. doi: 10.1016/j.lungcan.2016.12.016
22. Cho JY, Kim J, Lee JS, Kim YJ, Kim SH, Lee YJ, et al. Characteristics, incidence, and risk factors of immune checkpoint inhibitor-related pneumonitis in patients with non-small cell lung cancer. *Lung Cancer.* (2018) 125:150–6. doi: 10.1016/j.lungcan.2018.09.015
23. Abdel-Rahman O. Evaluation of efficacy and safety of different pembrolizumab dose/schedules in treatment of non-small-cell lung cancer and melanoma: a systematic review. *Immunotherapy.* (2016) 8:1383–91. doi: 10.2217/imt-2016-0075
24. Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. *JAMA Oncol.* (2018) 4:374–8. doi: 10.1001/jamaoncol.2017.2925
25. Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. *J Clin Oncol.* (2017) 35:785–92. doi: 10.1200/JCO.2015.66.1389
26. Ricciuti B, Genova C, De Giglio A, Bassanelli M, Dal Bello MG, Metro G, et al. Impact of immune-related adverse events on survival in patients with advanced non-small cell lung cancer treated with nivolumab: long-term outcomes from a multi-institutional analysis. *J Cancer Res Clin Oncol.* (2019) 145:479–85. doi: 10.1007/s00432-018-2805-3
27. Tone M, Izumo T, Awano N, Kuse N, Inomata M, Jo T, et al. High mortality and poor treatment efficacy of immune checkpoint inhibitors in patients with

severe grade checkpoint inhibitor pneumonitis in non-small cell lung cancer. *Thorac Cancer.* (2019) 10:2006–12. doi: 10.1111/1759-7714.13187
28. Fukihara J, Sakamoto K, Koyama J, Ito T, Iwano S, Morise M, et al. Prognostic impact and risk factors of immune-related pneumonitis in patients with non-small-cell lung cancer who received programmed death 1 inhibitors. *Clin Lung Cancer.* (2019) 20:442–50. doi: 10.1016/j.cllc.2019.07.006
29. Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. *Clin Cancer Res.* (2016) 22:886–94. doi: 10.1158/1078-0432.CCR-15-1136
30. Hassel JC, Heinzerling L, Aberle J, Bähr O, Eigentler TK, Grimm M, et al. Combined immune checkpoint blockade (anti-PD-1/anti-CTLA-4): evaluation and management of adverse drug reactions. *Cancer Treat Rev.* (2017) 57:36–49. doi: 10.1016/j.ctrv.2017.05.003
31. Asher N, Marom EM, Ben Betzalel G, Baruch EN, Steinberg Silman Y, Schachter J, et al. Recurrent pneumonitis in patients with melanoma treated with immune checkpoint inhibitors. *Oncologist.* (2019) 24:640–7. doi: 10.1634/theoncologist.2018-0352
32. Nishino M, Ramaiya NH, Awad MM, Sholl LM, Maattala JA, Taibi M, et al. PD-1 inhibitor-related pneumonitis in advanced cancer patients: radiographic patterns and clinical course. *Clin Cancer Res.* (2016) 22:6051–60. doi: 10.1158/1078-0432.CCR-16-1320
33. Nishino M, Chambers ES, Chong CR, Ramaiya NH, Gray SW, Marcoux JP, et al. Anti-PD-1 inhibitor-related pneumonitis in non-small cell lung cancer. *Cancer Immunol Res.* (2016) 4:289–93. doi: 10.1158/2326-6066.CIR-15-0267
34. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors. *Jama Oncol.* (2016) 2:1346. doi: 10.1001/jamaoncol.2016.1051
35. Suresh K, Naidoo J, Lin CT, Danoff S. Immune checkpoint immunotherapy for non-small cell lung cancer. *Chest.* (2018) 154:1416–23. doi: 10.1016/j.chest.2018.08.1048
36. Franzen D, Schad K, Kowalski B, Clarenbach CF, Stupp R, Dummer R, et al. Ipilimumab and early signs of pulmonary toxicity in patients with metastastic melanoma: a prospective observational study. *Cancer Immunol Immunother.* (2018) 67:127–34. doi: 10.1007/s00262-017-2071-2
37. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up†. *Ann Oncol.* (2017) 28(Suppl. 4):v119–42. doi: 10.1093/annonc/mdx225
38. Puzanov I, Diab A, Abdallah K, Bingham CR, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the society for immunotherapy of cancer (SITC) toxicity management working Group. *J Immunother Cancer.* (2017) 5:95. doi: 10.1186/s40425-017-0300-z
39. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. Management of immunotherapy-related toxicities, Version 1.2019. *J Natl Compr Canc Netw.* (2019) 17:255–89. doi: 10.6004/jnccn.2019.0013
40. Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev.* (2016) 44:51–60. doi: 10.1016/j.ctrv.2016.02.001
41. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: american society of clinical oncology clinical practice guideline. *J Clin Oncol.* (2018) 36:1714–68. doi: 10.1200/JCO.2017.77.6385
42. Ricciuti B, Dahlberg SE, Adeni A, Sholl LM, Nishino M, Awad MM. Immune checkpoint inhibitor outcomes for patients with non-small-cell lung cancer receiving baseline corticosteroids for palliative versus nonpalliative indications. *J Clin Oncol.* (2019) 37:1927–34. doi: 10.1200/JCO.19.00189
43. Petrelli F, Signorelli D, Ghidini M, Ghidini A, Pizzutilo EG, Ruggieri L, et al. Association of steroids use with survival in patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Cancers (Basel).* (2020) 12:546. doi: 10.3390/cancers12030546
44. Elkrief A, El RL, Richard C, Messaoudene M, Belkaid W, Malo J, et al. Antibiotics are associated with decreased progression-free survival of advanced melanoma patients treated with immune checkpoint inhibitors. *Oncoimmunology.* (2019) 8:e1568812. doi: 10.1080/2162402X.2019.1568812
45. Pinato DJ, Howlett S, Ottaviani D, Urus H, Patel A, Mineo T, et al. Association of prior antibiotic treatment with survival and response to immune checkpoint inhibitor therapy in patients with cancer. *Jama Oncol.* (2019) 5:1774–8. doi: 10.1001/jamaoncol.2019.2785
46. Ortega Sanchez G, Jahn K, Savic S, Zippelius A, Läubli H. Treatment of mycophenolate-resistant immune-related organizing pneumonia with infliximab. *J Immunother Cancer.* (2018) 6:85. doi: 10.1186/s40425-018-0400-4
47. Sawai Y, Katsuya Y, Shinozaki-Ushiku A, Iwasaki A, Fukayama M, Watanabe K, et al. Rapid temporal improvement of pembrolizumab-induced pneumonitis using the anti-TNF-α antibody infliximab. *Drug Discov Ther.* (2019) 13:164–7. doi: 10.5582/ddt.2019.01032
48. Shannon VR, Subudhi SK, Huo L, Faiz SA. Diffuse alveolar hemorrhage with nivolumab monotherapy. *Respir Med Case Rep.* (2020) 30:101131. doi: 10.1016/j.rmcr.2020.101131
49. Utsumi H, Araya J, Okuda K, Watanabe J, Takekoshi D, Fujita Y, et al. Successful treatment of steroid-refractory immune checkpoint inhibitor-related pneumonitis with triple combination therapy: a case report. *Cancer Immunol. Immunother.* (2020). doi: 10.1007/s00262-020-02600-0 [Epub ahead of print].
50. Martins F, Sykiotis GP, Maillard M, Fraga M, Ribi C, Kuntzer T, et al. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. *Lancet Oncol.* (2019) 20:e54–64. doi: 10.1016/S1470-2045(18)30828-3
51. Stroud CR, Hegde A, Cherry C, Naqash AR, Sharma N, Addepalli S, et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. *J Oncol Pharm Pract.* (2019) 25:551–7. doi: 10.1177/1078155217745144
52. Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity.* (1999) 11:141–51. doi: 10.1016/S1074-7613(00)80089-8
53. Sano T, Uhara H, Mikoshiba Y, Kobayashi A, Uchiyama R, Tateishi K, et al. Nivolumab-induced organizing pneumonia in a melanoma patient. *Jpn J Clin Oncol.* (2016) 46:270–2. doi: 10.1093/jjco/hyv199
54. Watanabe S, Kimura H, Takato H, Waseda Y, Hara J, Sone T, et al. Severe pneumonitis after nivolumab treatment in a patient with melanoma. *Allergol Int.* (2016) 65:487–9. doi: 10.1016/j.alit.2016.04.009
55. Ishiwata T, Ebata T, Iwasawa S, Matsushima J, Ota S, Nakatani Y, et al. Nivolumab-induced acute fibrinous and organizing pneumonia (AFOP). *Internal Med.* (2017) 56:2311–5. doi: 10.2169/internalmedicine.8271-16
56. Koelzer VH, Rothschild SI, Zihler D, Wicki A, Willi B, Willi N, et al. Systemic inflammation in a melanoma patient treated with immune checkpoint inhibitors—an autopsy study. *J Immunother Cancer.* (2016) 4:13. doi: 10.1186/s40425-016-0117-1
57. Li H, Ma W, Yoneda KY, Moore EH, Zhang Y, Pu LLQ, et al. Severe nivolumab-induced pneumonitis preceding durable clinical remission in a patient with refractory, metastatic lung squamous cell cancer: a case report. *J Hematol Oncol.* (2017) 10:64. doi: 10.1186/s13045-017-0433-z
58. Suresh K, Naidoo J, Zhong Q, Xiong Y, Mammen J, de Flores MV, et al. The alveolar immune cell landscape is dysregulated in checkpoint inhibitor pneumonitis. *J Clin Invest.* (2019) 130:4305–15. doi: 10.1172/JCI128654
59. Läubli H, Koelzer VH, Matter MS, Herzig P, Dolder Schlienger B, Wiese MN, et al. The T cell repertoire in tumors overlaps with pulmonary inflammatory lesions in patients treated with checkpoint inhibitors. *Oncoimmunology.* (2018) 7:e1386362. doi: 10.1080/2162402X.2017.1386362
60. Xiao Y, Yu S, Zhu B, Bedoret D, Bu X, Francisco LM, et al. RGMb is a novel binding partner for PD-L2 and its engagement with PD-L2 promotes respiratory tolerance. *J Exp Med.* (2014) 211:943–59. doi: 10.1084/jem.20130790
61. Tabchi S, Messier C, Blais N. Immune-mediated respiratory adverse events of checkpoint inhibitors. *Curr Opin Oncol.* (2016) 28:269–77. doi: 10.1097/CCO.0000000000000291
62. Jodai T, Yoshida C, Sato R, Kakiuchi Y, Sato N, Iyama S, et al. A potential mechanism of the onset of acute eosinophilic pneumonia triggered by an anti−PD−1 immune checkpoint antibody in a lung cancer patient. *Immun Inflamm Dis.* (2018) 7:3–6. doi: 10.1002/iid3.238

63. Ke W, Zhang L, Dai Y. The role of IL-6 in immunotherapy of non-small cell lung cancer (NSCLC) with immune-related adverse events (irAEs). *Thorac Cancer*. (2020) 11:835–9. doi: 10.1111/1759-7714.13341
64. Addeo A, Obeid M, Friedlaender A. COVID-19 and lung cancer: risks, mechanisms and treatment interactions. *J Immunother Cancer*. (2020) 8:e000892. doi: 10.1136/jitc-2020-000892
65. Kenmotsu H, Sakai F, Kato T, Kusumoto M, Baba T, Kuwano K, et al. Nivolumab-induced interstitial lung disease (ILD) in Japanese patients with non-small cell lung cancer: a study on risk factors using interim results of post-marketing all-case surveillance. *J Clin Oncol*. (2017) 35(15 Suppl):9078. doi: 10.1200/JCO.2017.35.15_suppl.9078
66. Vansteenkiste J. Nivolumab for NSCLC in Japanese patients: similar benefits, but beware of pneumonitis. *ESMO Open*. (2017) 2(Suppl. 1):e119. doi: 10.1136/esmoopen-2016-000119
67. Wu Y, Lu S, Cheng Y, Zhou C, Wang J, Mok T, et al. Nivolumab versus docetaxel in a predominantly chinese patient population with previously treated advanced NSCLC: CheckMate 078 randomized phase III clinical trial. *J Thorac Oncol*. (2019) 14:867–75. doi: 10.1016/j.jtho.2019.01.006

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Immunology

SYSTEMATIC REVIEW
published: 18 December 2020
doi: 10.3389/fimmu.2020.595655

Immune-Related Neurological Toxicities of PD-1/PD-L1 Inhibitors in Cancer Patients: A Systematic Review and Meta-Analysis

Yuan Tian[1,2,3], *Aiqin Gao*[1], *Qing Wen*[4], *Shuyun Wang*[1], *Shuisheng Zhang*[5], *Xiaowei Yang*[6], *Guohai Su*[7*] and *Yuping Sun*[1,8*]

[1] Department of Oncology, Jinan Central Hospital Affiliated to Shandong University, Jinan, China, [2] Department of Radiotherapy Oncology, Shandong Provincial Qianfoshan Hospital, Shandong University, Jinan, China, [3] Department of Radiotherapy Oncology, Shandong Provincial Qianfoshan Hospital, The First Hospital Affiliated With Shandong First Medical University, Jinan, China, [4] Jinan Clinical Research Center of Shandong First Medical University, Jinan, China, [5] Department of General Surgery, Peking University Third Hospital, Beijing, China, [6] Department of Hepatobiliary Intervention, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China, [7] Department of Cardiovascular Diseases, Jinan Central Hospital Affiliated to Shandong University, Jinan, China, [8] Department of Oncology, Jinan Central Hospital affiliated to Shandong First Medical University, Jinan, China

OPEN ACCESS

Edited by:
Xuelei Ma,
Sichuan University, China

Reviewed by:
Patrick Dillon,
University of Virginia, United States
Guido Cavaletti,
University of Milano-Bicocca, Italy

***Correspondence:**
Guohai Su
guohaisu0531@126.com
Yuping Sun
sunyuping@live.cn

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Immunology

Received: *17 August 2020*
Accepted: *16 November 2020*
Published: *18 December 2020*

Citation:
Tian Y, Gao A, Wen Q, Wang S, Zhang S, Yang X, Su G and Sun Y (2020) Immune-Related Neurological Toxicities of PD-1/PD-L1 Inhibitors in Cancer Patients: A Systematic Review and Meta-Analysis. Front. Immunol. 11:595655. doi: 10.3389/fimmu.2020.595655

Background: Systematic assessment of PD-1/PD-L1 inhibitor-related neurological toxicities is important for guiding anti-PD-1 and anti-PD-L1 immunotherapy. Therefore, we conducted this meta-analysis to reveal the relationship between PD-1/PD-L1 inhibitors and neurological toxicities among cancer patients.

Methods: Clinical trials investigating PD-1/PD-L1 inhibitors in cancer patients were identified by a systematic search of PubMed. The random-effect model was used to synthesize individual studies. Neurological toxicities, including all-grades and grades 3–5, were taken into account for the final comprehensive meta-analysis. The Newcastle Ottawa Scale (NOS) was used to assess the quality of included trials.

Results: Thirty-one clinical trials containing data of neurological toxicities were included. Compared with chemotherapy, the risk of all-grade neurological toxicities caused by PD-1/PD-L1 inhibitors was much lower in terms of peripheral neuropathy [OR = 0.07, 95%CI:(0.04, 0.13)], peripheral sensory neuropathy [OR = 0.07, 95%CI(0.04, 0.12)], dysgeusia [OR = 0.26, 95%CI:(0.19, 0.35)], paraesthesia [OR = 0.23, 95%CI:(0.14, 0.36)], and polyneuropathy [OR = 0.12, 95%CI:(0.01, 0.94)]. However, for grades 3–5, the statistically significant results were only seen in peripheral neuropathy [OR = 0.15, 95%CI:(0.07, 0.34)] and peripheral sensory neuropathy [OR = 0.13, 95%CI:(0.04, 0.40)]. No statistically significant difference regarding the risk of headache, dizziness, and Guillain–Barré syndrome was found between PD-1/PD-L1 inhibitors and chemotherapy. For PD-1/PD-L1 inhibitors plus chemotherapy, the risk trends of the above-mentioned neurological toxicities, especially grades 3–5 peripheral neuropathy [OR = 1.76, 95%CI:(1.10, 2.82)] was increased compared to chemotherapy alone.

Conclusion: Our comprehensive analysis showed that PD-1/PD-L1 inhibitors alone exhibited lower neurological toxicities than chemotherapy. However, the risk of headache, dizziness, and Guillain–Barré syndrome was similar between PD-1/PD-L1 and chemotherapy. For PD-1/PD-L1 inhibitors plus chemotherapy, the incidence trend of neurological toxicities would be increased, especially for peripheral neuropathy of grades 3–5.

Keywords: neurological toxicities, cancer, meta-analysis, PD-1, PD-L1

INTRODUCTION

Cancer immunotherapies, developed to overcome the immune escape mechanisms of cancer progression and metastatic dissemination, are becoming familiar to oncologists (1), especially for programmed cell death protein 1 (PD-1) and its ligand (PD-L1) inhibitors. PD-1/PD-L1 inhibitors belong to immune checkpoint blocking drugs (1); they can block the binding of tumor cells to PD-1 of T cells by means of PD-L1, restore the ability to recognize tumor cells, and further restore the cell recognition and killing ability of T cells (1). Immunotherapies, including cytotoxic T lymphocyte antigen-4 (CTLA-4) and PD-1/PD-L1 had changed the treatment landscape for plenty of solid tumors but conferred unique toxicity profiles owing to their unique mechanism of actions (1–3).

Most of those toxic reactions had aroused sufficient attention from clinicians and researchers, and guidelines for related treatment had been developed for reference (2, 4). Neurological toxicities, including peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, dysgeusia, paraesthesia, headache, dizziness, Guillain–Barré syndrome, neurotoxicity, myasthenia gravis, noninfectious encephalitis/myelitis, and polyneuropathy, were mostly reported in the form of case reports or reviews and were considered to be rare immune-related adverse events (1, 5–14). The appearance of neurological toxicities might be diverse, involving any aspect of the central or peripheral nervous system accompanied by different diagnostic signs and symptoms (1).

As more and more clinical trials investigating the clinical efficacy and safety of PD-1/PD-L1 in cancer patients are being conducted, various treatment induced adverse events had been gradually reported (1, 2). However, regarding the neurological toxicities of PD-1/PD-L1, no systematic reviews and meta-analysis have been conducted in this regard (1–14). Therefore, in order to clarify the relationship between PD-1/PD-L1 inhibitors and the risk of neurological toxicities, this systematic review and meta-analysis was conducted.

Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PICOS, Participants, Interventions, Comparisons, Outcomes, and Study design; PD-1, Programmed Cell Death-1; PD-L1, Programmed Cell Death Ligand 1; HR, Hazard Ratios; OR. Odds Ratio; RD, Risk Difference; CI, Confidence Interval; RE, Random Effect; NSCLC, Non-Small Cell Lung Cancer; SCLC, Small Cell Lung Cancer; OSCC, Esophageal Squamous Cell Carcinoma; HNSCC, Head and Neck Squamous Cell Carcinoma; UC, Urothelial Cancer; BC, Breast Cancer; RCC, Renal Cell Carcinoma; NOS, Newcastle-Ottawa scale.

METHOD

This research was conducted and reported according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (15).

Types of Enrolled Studies

Randomized, open-label, controlled clinical trials investigating the efficacy and safety of PD-1/PD-L1 inhibitors in cancer patients were included. Phase III clinical trials, limited to solid tumors, were given a priority. Then, clinical trials of other phases would be checked for eligibility and placed in an alternative location. Clinical trials investigating hematological malignancies were beyond our consideration. In order to collect as many articles as possible, the control group was not restricted to a certain therapeutic agent or intervention. For inclusion, the study must report the data of at least one type of neurological toxicities related to immunotherapy. Articles must be published in English.

Search Strategy

Keywords, including neoplasm, cancer, precancer, malignant, premalignant, tumor, PD-1, PD-L1, and clinical trial, were used for the PubMed search with reference to participants, interventions, comparisons, outcomes, and study design (PICOS) (15). The published date was limited to the last 10 years (July 9, 2010 to July 9, 2020). Of note, some data regarding peripheral neuropathy was also collected from a former systematic review and meta-analysis (16). Four authors were designated to check the eligibility of all retrieved reports. They were also responsible for the extraction of relevant data from finally included trials. In the case of duplicated clinical trials, only one was included in the final analysis step. The corresponding authors (YS and GS) were responsible for resolving all disagreements.

Evaluation of Study Quality and Publication Bias

Funnel plots, Egger's test, and the Newcastle-Ottawa scale (NOS) were used to check publication bias and risk of bias of individual trials, respectively (15, 17–20). The quality assessment included the appraisal of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting (shown in a single figure). Harbord's test was used to check the risk of publication bias of enrolled clinical trials

(21). A *P-value* of <0.05 was used as the cut-off value for statistical significance.

Outcome and Exposure of Interest

Any data of neurological toxicities, including peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, dysgeusia, paraesthesia, headache, dizziness, Guillain-Barré syndrome, neurotoxicity, and polyneuropathy, were collected and further analyzed. Baseline characteristics of included articles are summarized in (**Table 1**). The risk of neurological toxicities relating to all grades was our primary outcome of interest in the final meta-analysis. Grading of neurological toxicities ranged from one (mild symptoms that do not interfere with activities of daily living) to five (fatal neurological toxicities).

Assessment of Heterogeneity and Statistical Analysis

Heterogeneity of all enrolled clinical trials was identified by Cochrane's Q statistic test (21). The grade of heterogeneity was estimated by the DerSimonian–Laird method and I^2 values together, which was suggested by Higgins and colleagues (15, 21). Heterogeneity was deemed to be low, moderate, or high according to I^2 values < 25, 25–50, and > 50%, respectively (16). All data analyses were completed by the software Review Manager 5.3. Owing to the existence of inherent heterogeneity among included trials, the random effect (RE) was used for the evaluation of odds ratio (OR) and their corresponding 95% confidence interval (CI) (58). Sometimes, the fixed effects (FE) model was used as a supplement. All reported *P* values are two-sided, and $P<0.05$ was deemed to be statistically significant. Subgroup analysis was made according to tumor types, treatment regimens, and PD-1/PD-L1 inhibitors.

RESULTS

Literature Search Results

A total of 471 PD-1/PD-L1 inhibitor-related clinical trials were identified through PubMed, while 31 related studies were collected from the former published meta-analysis (16). Fifty-two articles met our preliminary screening criteria, of which 36 articles (reporting the data of neurological toxicities of 31 clinical trials involving 9960 patients) were included in the final analysis phase (22–57). Results of different periods of the same clinical trial 'CheckMate 067' (NCT01844505) were reported by four articles (51–54), while the results of the clinical trial 'PACIFIC' (NCT02125461) was reported by three articles (55–57). The baseline characteristics of the 36 enrolled articles are displayed in (**Table 1**) (22–57). The PRISMA flow diagram of the screening process of our review was provided in (**Figure 1**), while the quality of included studies is shown in (**Figure 2**) (22–57). After reviewing the full-texts of all included trials, 10 types of neurological toxicities were reported, including peripheral neuropathy (24–32, 34, 35, 38–41, 43, 44, 46, 50), peripheral sensory neuropathy (24–26, 29–34, 41, 42, 46, 50), dysgeusia (22, 23, 25, 26, 32–37, 41–43, 45, 47, 50), paraesthesia (25, 28, 32, 41–44, 49), headache (22, 23, 25, 26, 34, 41, 43, 47, 48, 51–57), dizziness (22, 25, 34, 36, 38, 41–44, 47, 51, 52), peripheral motor neuropathy (51), Guillain–Barré syndrome (25, 27, 33, 42, 51), neurotoxicity (25), and polyneuropathy (10, 25, 51).

Characteristics of Identified Trials

Twenty-five studies were phase III clinical trials (22–35, 37, 38, 47–49, 49–57), three were phase II trials (36, 40, 48), one was phase I/II trial (39), and one was phase II/III trial (41). Twelve clinical trials (reported in 14 articles) investigated PD-L1 (22, 23, 26–28, 30, 32, 33, 35, 40, 49, 55–57), while the remaining 18 clinical trials (reported in 22 articles) investigated PD-1 (24, 25, 29, 31, 34, 36–39, 41–48, 50–53). Among included clinical trials, nine types of tumors were reported, including non-small cell lung cancer (NSCLC) (N = 14) (24, 28–30, 33, 35–37, 40, 41, 43, 44, 47, 55–57), small cell lung cancer (SCLC) (N = 3) (27, 39, 49), renal cell carcinoma (RCC) (N = 3) (22, 23, 45), esophageal squamous cell carcinoma (OSCC) (N = 1) (46), head and neck squamous cell carcinoma (HNSCC) (N = 2) (25, 38), urothelial cancer (UC) (N = 2) (32, 34), breast cancer (BC) (N = 2) (26, 50), melanoma (N = 3) (42, 48, 51–53, 56), and gastric or junction cancer (N = 1) (31). Previous therapies were reported in 16 clinical trials (25, 30–35, 38–41, 43–46, 55–56), while PD-1/PD-L1 inhibitors were administered as a first-line therapy in the remaining 15 clinical trials (22–24, 26–29, 36, 37, 42, 47–54).

Risk of Bias

The results of the publication bias assessment, in the form of funnel plots, are provided in the supplement (**Supplementary Figures 1–3**, **5**, **7**, **9**) (15, 17–20, 22–57). Low risk of bias was identified in all clinical trials regarding selection bias, performance bias, detection bias, attrition bias, and reporting bias (**Figure 2**) (22–57). An unclear risk relating to other biases was identified in four clinical trials (36, 39, 40, 48). None of the included trials had a high risk of bias.

Risk of Peripheral Neuropathy

Peripheral neuropathy was reported in 20 clinical trials (24–32, 34, 35, 38–41, 43, 44, 46, 50), 19 of which were included in the final meta-analysis (24–32, 34, 35, 38, 40, 41, 43, 44, 46, 50). When PD-1/PD-L1 inhibitors were compared with chemotherapy, the risk of peripheral neuropathy of all grades was noticeably lower [OR = 0.07, 95%CI:(0.04, 0.13), I^2 = 62%, Z = 8.48 (P < 0.00001); **Figure 3A1**], even for every subgroup relating to different tumor types (24–26, 30–32, 34, 38, 40, 41, 43, 44, 46). High heterogeneity was found (I^2 = 62%), which was caused mainly by the NSCLC subgroup involving PD-L1 inhibitors (I^2 = 75%, **Figure 3A1**) (26, 30, 40). The corresponding funnel plot is provided in the supplement (**S Figure 1A1**). Similarly, reduced risk of peripheral neuropathy of grades 3¯5 was also noted [OR = 0.15, 95%CI:(0.07, 0.340, I^2 = 0%, Z = 8.48 (P <0.00001); **Figure 3A2**]. The corresponding funnel plot is provided in the supplement (**S Figure 1A2**) (24, 26, 30–32, 34, 41, 43, 44, 46).

TABLE 1 | Baseline characteristics of included studies (N = 37 articles of 31 clinical trials).

NO	Reference	NCT Number	Trial Name	Drug Name	PD-1/ PD-L1	Treatment Regimen	Previous Therapy	Phase	Tumor Type	Involving Patients
1	Motzer et al. (22)	NCT02684006	JAVELIN Renal 101	Avelumab	PD-L1	Avelumab + Axitinib vs. Sunitinib	NO	III	RCC	873
2	Rini et al. (23)	NCT02420821	IMmotion151	Atezolizumab	PD-L1	Atezolizumab + Bevacizumab vs. Sunitinib	NO	III	RCC	897
3	Mok et al. (24)	NCT02220894	KEYNOTE-042	Pembrolizumab	PD-1	Pembrolizumab vs. Platinum-based Chemotherapy	NO	III	NSCLC	1241
4	Cohen et al. (25)	NCT02252042	KEYNOTE-040	Pembrolizumab	PD-1	Pembrolizumab vs. (Methotrexate, Docetaxel, Cetuximab)	YES	III	HNSCC	480
5	Schmid et al. (26)	NCT02425891	IMpassion130	Atezolizumab	PD-L1	Atezolizumab + Nab-paclitaxel vs. Nab-paclitaxel	NO	III	BC	890
6	Horn et al. (27)	NCT02763579	IMpower133	Atezolizumab	PD-L1	Atezolizumab + CE vs. CE	NO	III	SCLC	394
7	Socinski et al. (28)	NCT02366143	IMpower150	Atezolizumab	PD-L1	Atezolizumab + BCP vs. BCP	NO	III	NSCLC	787
8	Paz-Ares et al. (29)	NCT02775435	KEYNOTE-407	Pembrolizumab	PD-1	Pembrolizumab + CP vs. CP	NO	III	NSCLC	558
9	Barlesi et al. (30)	NCT02395172	JAVELIN Lung 200	Avelumab	PD-L1	Avelumab vs. Docetaxel	YES	III	NSCLC	792
10	Shitara et al. (31)	NCT02370498	KEYNOTE-061	Pembrolizumab	PD-1	Pembrolizumab vs. Paclitaxel	YES	III	Gastric or junction Cancer	570
11	Powles et al. (32)	NCT02302807	IMvigor211	Atezolizumab	PD-L1	Atezolizumab vs. Vinflunine, Paclitaxel, or Docetaxel	YES	III	UC	902
12	Hida et al. (33)	NCT02008227	OAK	Atezolizumab	PD-L1	Atezolizumab vs. Docetaxel	YES	III	NSCLC	101
13	Bellmunt et al. (34)	NCT02256436	KEYNOTE-045	Pembrolizumab	PD-1	Pembrolizumab vs. Paclitaxel, Docetaxel, or Vinflunine	YES	III	UC	521
14	Rittmeyer et al. (35)	NCT02008227	OAK	Atezolizumab	PD-L1	Atezolizumab vs. Docetaxel	YES	III	NSCLC	1187
15	Langer et al. (36)	NCT02039674	KEYNOTE-021	Pembrolizumab	PD-1	Pembrolizumab + PC vs. PC	NO	II	NSCLC	121
16	Reck et al. (37)	NCT02142738	KEYNOTE-024	Pembrolizumab	PD-1	Pembrolizumab vs. Platinum-based chemotherapy	NO	III	NSCLC	304
17	Ferris et al. (38)	NCT02105636	CheckMate 141	Nivolumab	PD-1	Nivolumab vs. (Methotrexate, Docetaxel, or Cetuximab)	YES	III	HNSCC	347
18	Antonia et al. (39)	NCT01928394	CheckMate 032	Nivolumab	PD-1	Nivolumab vs. Nivolumab + Ipilimumab	YES	I/II	SCLC	213
19	Fehrenbacher et al. (40)	NCT01903993	POPLAR	Atezolizumab	PD-L1	Atezolizumab vs. Docetaxel	YES	II	NSCLC	277
20	Herbst et al. (41)	NCT01905657	KEYNOTE-010	Pembrolizumab	PD-1	Pembrolizumab vs. Docetaxel	YES	II/III	NSCLC	991
21	Hodi et al. (42)	NCT01927419	CheckMate 069	Nivolumab	PD-1	Nivolumab + Ipilimumab vs. Ipilimumab	NO	III	Melanoma	140
22	Borghaei et al. (43)	NCT01673867	CheckMate 057	Nivolumab	PD-1	Nivolumab vs. Docetaxel	YES	III	NSCLC	555
23	Brahmer et al. (44)	NCT01642004	CheckMate 017	Nivolumab	PD-1	Nivolumab vs. Docetaxel	YES	III	NSCLC	260
24	Motzer et al. (45)	NCT01668784	CheckMate 025	Nivolumab	PD-1	Nivolumab vs. Everolimus	YES	III	RCC	821
25	Kato et al. (46)	NCT02569242	ATTRACTION-3	Nivolumab	PD-1	Nivolumab vs. Paclitaxel or Docetaxel	YES	III	OSCC	417
26	Gandhi et al. (47)	NCT02578680	KEYNOTE-189	Pembrolizumab	PD-1	Pembrolizumab + PC vs. PC	NO	III	NSCLC	439
27	Ascierto et al. (48)	NCT02130466	N/A	Pembrolizumab	PD-1	Pembrolizumab + DT vs. DT	NO	II	Melanoma	120
28	Paz-Ares et al. (49)	NCT03043872	CASPIAN	Durvalumab	PD-L1	Durvalumab + EP vs. EP	NO	III	SCLC	431
29	Schmid et al. (50)	NCT03036488	KEYNOTE-522	Pembrolizumab	PD-1	Pembrolizumab + CP vs. CP	NO	III	TNBC	1170
30	Hodi et al. (51)	NCT01844505	CheckMate 067	Nivolumab	PD-1	Nivolumab +lipilimumab or Nivolumab alone vs. Ipilimumab	NO	III	Melanoma	937

(Continued)

TABLE 1 | Continued

NO	Reference	NCT Number	Trial Name	Drug Name	PD-1/ PD-L1	Treatment Regimen	Previous Therapy	Phase	Tumor Type	Involving Patients
31	Wolchok et al. (52)									
32	Larkin et al. (53)									
33	Larkin et al. (54)									
34	Antonia et al. (55)	NCT02125461	PACIFIC	Durvalumab	PD-L1	Durvalumab vs. placebo	YES	III	NSCLC	709
35	Antonia et al. (56)									
36	Hui et al. (57)									

vs., Versus; N/A, Not Available; RCC, Renal Cell Carcinoma; NSCLC, Non Small Cell Lung Cancer; HNSCC, Head-and-Neck Squamous Cell Carcinoma; SCLC, Small Cell Lung Cancer; EC, Etoposide + Carboplatin; BCP, Bevacizumab plus Carboplatin plus Paclitaxel; CP, Carboplatin + Paclitaxel; UC, Urothelial Carcinoma; OSCC, Oesophageal Squamous Cell Carcinoma; DT, Dabrafenib + Trametinib; TNBC, Triple-Negative Breast Cancer; BC, Breast Cancer; UC, Urothelial Carcinoma.

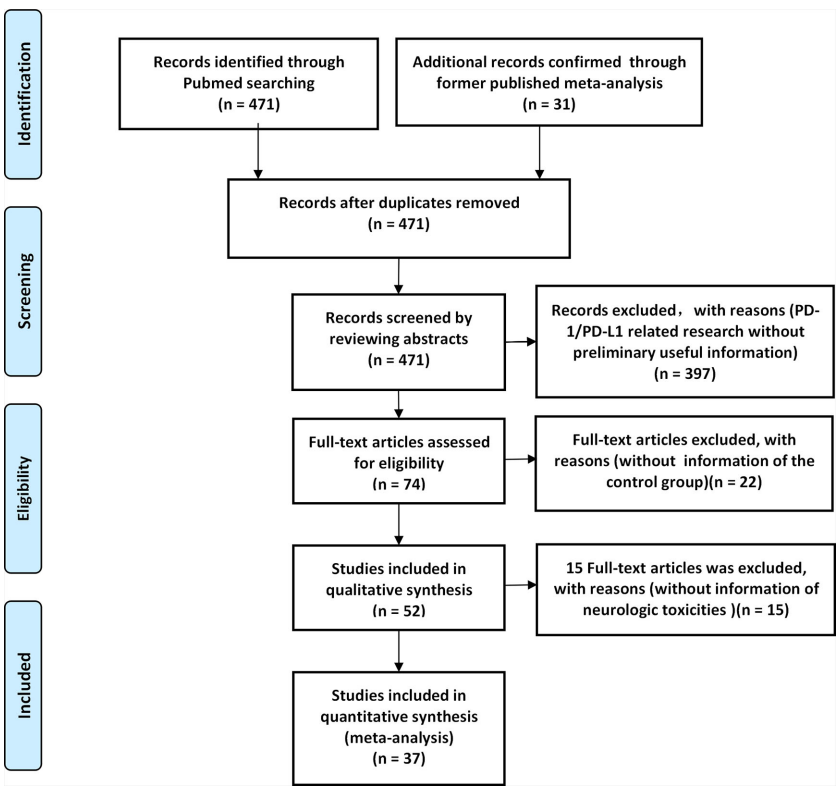

FIGURE 1 | A PRISMA flow diagram of the screening process of our review.

When PD-1/PD-L1 inhibitors plus chemotherapy were compared with chemotherapy (**Figures 3B1, B2**) (26–29, 50), a significant increase in the risk of peripheral neuropathy could only be seen in grades 3–5 [OR = 1.76, 95%CI:(1.10, 2.82), I^2 = 0%, Z = 2.37 (P = 0.02); **Figure 3B2**] (26–29, 50). The corresponding funnel plots are provided in the supplement (**S Figure 1B1, B2**) (26–29, 50).

Risk of Peripheral Sensory Neuropathy

Peripheral sensory neuropathy was reported in 13 clinical trials (24–26, 29–34, 41, 42, 46, 50), 12 of which were included in the final meta-analysis (24–26, 29–34, 41, 46, 50). When PD-1/PD-L1 inhibitors were compared with chemotherapy, the risk of peripheral sensory neuropathy of all grades was obviously lower [OR = 0.07, 95%CI:(0.04, 0.12), I^2 = 13%, Z = 9.50(P < 0.00001);

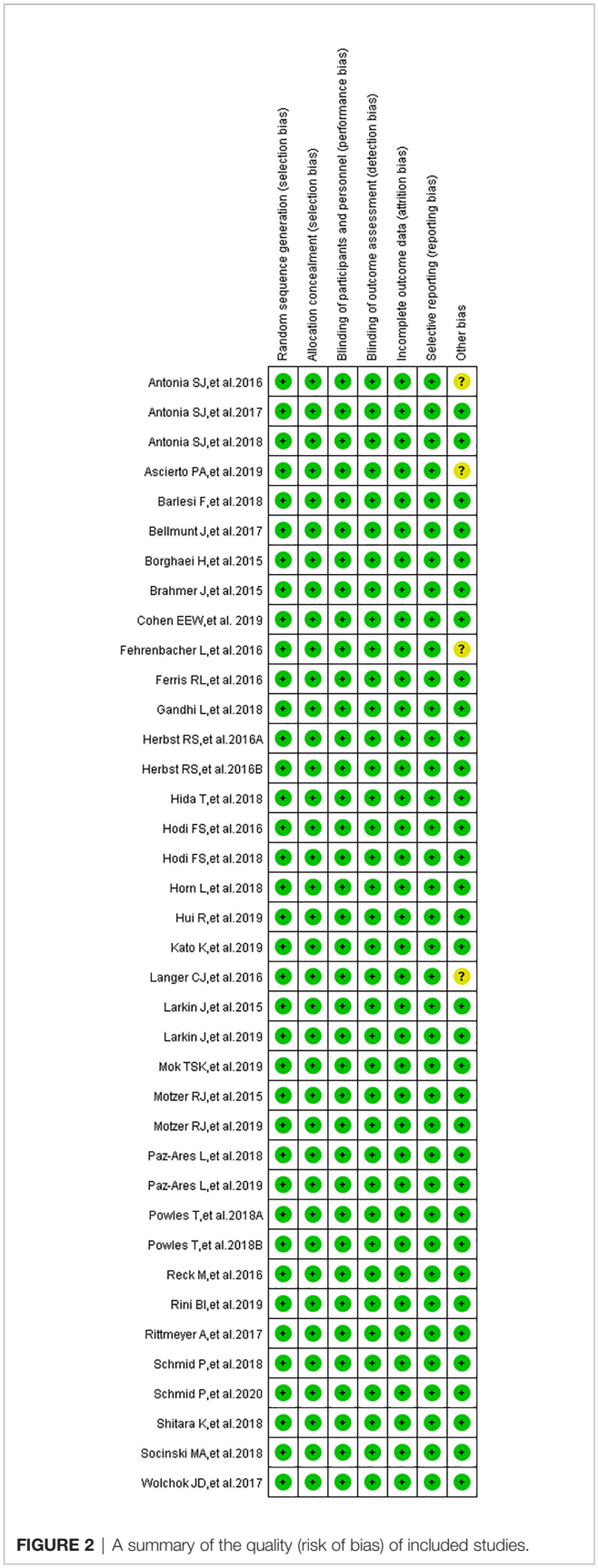

FIGURE 2 | A summary of the quality (risk of bias) of included studies.

Figure 4A1] (24, 25, 30–34, 41, 46), while similar risk trends of grades 3–5 were seen between both arms [OR = 0.13, 95%CI: (0.04, 0.40), I^2 = 0%, Z=3.57 (P = 0.0004); **Figure 4A2**] (24, 30–32, 34, 46). The corresponding funnel plots are provided in the supplement (**S Figure 2A1, A2**) (24–26, 29–34, 41, 46, 50).

When PD-1/PD-L1 inhibitors plus chemotherapy were compared with chemotherapy (**Figures 4B1, B2**) (26–29, 50), no statistically significant difference was found (26, 29, 50). The corresponding funnel plots are provided in the supplement **(S Figure 2B1, B2**) (26, 29, 50).

Risk of Dysgeusia

Dysgeusia was reported in 16 clinical trials (22, 23, 25, 26, 32–37, 41–43, 45, 47, 50), 14 of which were included in the final meta-analysis (22, 23, 25, 26, 32–37, 41, 43, 47, 50). When PD-1/PD-L1 inhibitors were compared with chemotherapy, the risk of dysgeusia of all grades was obviously lower [OR=0.26, 95%CI: (0.19, 0.35), I^2 = 0%, Z = 8.44 (P < 0.00001); **Figure 5A**] (25, 32–35, 37, 41, 43), especially for subgroups relating to NSCLC and UC (32–35, 37, 41, 43). The corresponding funnel plot is provided in the supplement (**S Figure 3A1**) (25, 32–35, 37, 41, 43).

When PD-1/PD-L1 inhibitors plus chemotherapy were compared with chemotherapy (**Figure 5B**), no statistically significant difference was noted [OR = 1.24, 95%CI:(0.98, 1.58), I^2 = 0%, Z = 1.77 (P = 0.08); **Figure 5B**] (26, 36, 47, 50). The corresponding funnel plot is provided in the supplement (**S Figure 3A2**) (26, 36, 47, 50).

When PD-1/PD-L1 inhibitors plus targeted therapy were compared with targeted therapy (**Figure 5C**), the risk of dysgeusia of all grades was obviously lower [OR = 0.16, 95%CI: (0.11, 0.23), I^2 = 0%, Z = 9.61 (P < 0.00001); **Figure 5C**] (22, 23). The corresponding funnel plot is provided in the supplement (**S Figure 3A3**) (22, 23).

The risk of dysgeusia grades 3–5 could not be analyzed in the meta-analysis due to the limited data available in the included trials (23, 47).

Risk of Paraesthesia

Paraesthesia was reported in eight clinical trials (25, 28, 32, 41–44, 49), seven of which were included in the final meta-analysis (25, 28, 32, 41, 43, 44, 49). When PD-1/PD-L1 inhibitors were compared with chemotherapy, the risk of paraesthesia of all grades was obviously lower [OR = 0.23, 95%CI:(0.14, 0.36), I^2 = 0%, Z = 6.40 (P < 0.00001); **Figure 6A**] (25, 28, 32, 41, 43, 44, 49), especially for subgroups relating to NSCLC and UC (32, 41, 43, 44). No heterogeneity was found (**Figure 6A**, I^2 = 0%) (25, 28, 32, 41, 43, 44, 49). The corresponding funnel plot is provided in the supplement (**S Figure 3B1**) (25, 28, 32, 41, 43, 44, 49).

When PD-1/PD-L1 inhibitors plus chemotherapy were compared with chemotherapy, no statistically significant difference was found for paraesthesia of all grades [OR = 1.19, 95%CI:(0.79, 1.78), I^2 = 0%, Z = 0.83 (P = 0.40); **Figure 6B)** (28, 49). The corresponding funnel plot is provided in the supplement (**S Figure 3B2)** (28, 49).

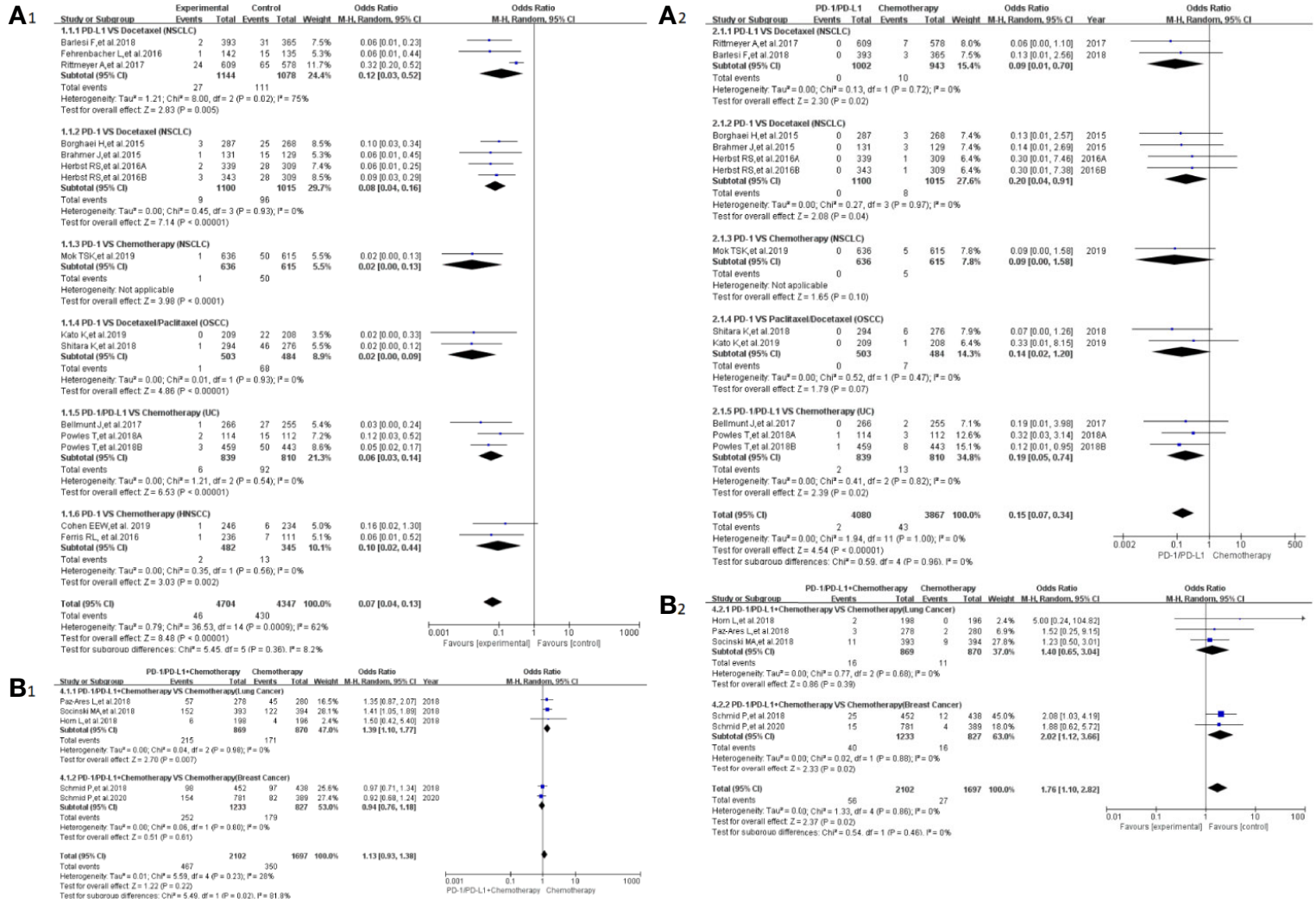

FIGURE 3 | Forest plots of the risk of peripheral neuropathy. **(A1)** The risk of all-grade peripheral neuropathy calculated by the random effect (RE) model (PD-1/PD-L1 *vs* chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(A2)** The risk of peripheral neuropathy of grades 3–5 calculated by the random effect (RE) model (PD-1/PD-L1 *vs* chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(B1)** The risk of all grade peripheral neuropathy calculated by the random effect (RE) model (PD-1/PD-L1 + chemotherapy *vs* chemotherapy): subgroup analysis was put into practice based on tumor types in both groups. **(B2)** The risk of peripheral neuropathy of grades 3–5 calculated by the random effect (RE) model (PD-1/PD-L1 + chemotherapy *vs* chemotherapy): subgroup analysis was put into practice based on tumor types in both groups.

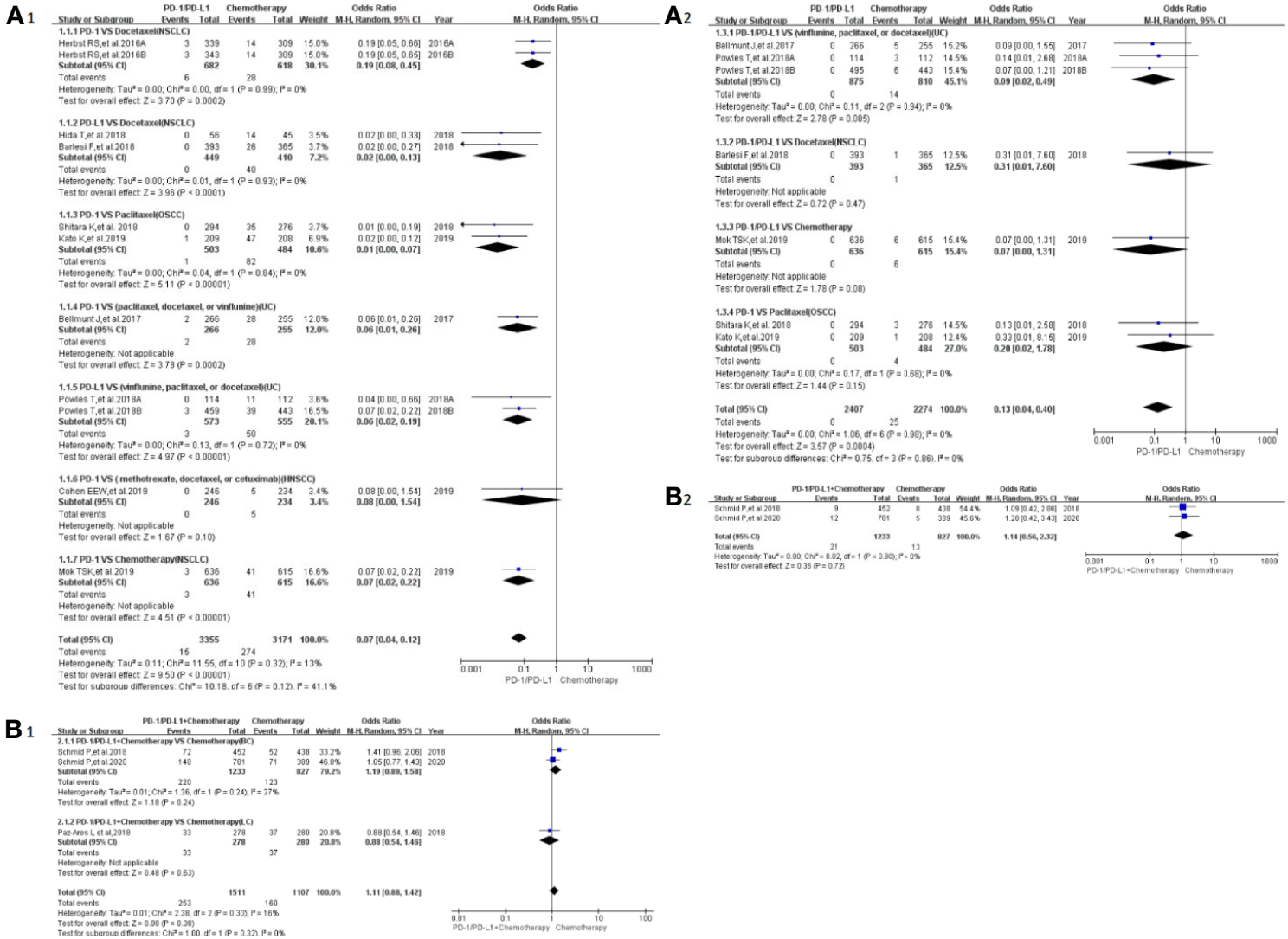

FIGURE 4 | Forest plots of the risk of peripheral sensory neuropathy **(A1)** The risk of all-grade peripheral sensory neuropathy calculated by the random effect (RE) model (PD-1/PD-L1 *vs* chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(A2)** The risk of peripheral sensory neuropathy of grades 3–5 calculated by the random effect (RE) model (PD-1/PD-L1 *vs* chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(B1)** The risk of all-grade peripheral sensory neuropathy calculated by the random effect (RE) model (PD-1/PD-L1 + chemotherapy *vs* chemotherapy): subgroup analysis was put into practice based on tumor types in both groups. **(B2)** The risk of peripheral sensory neuropathy of grades 3–5 calculated by the random effect (RE) model (PD-1/PD-L1+ chemotherapy *vs.* chemotherapy): subgroup analysis was put into practice based on tumor types in both groups.

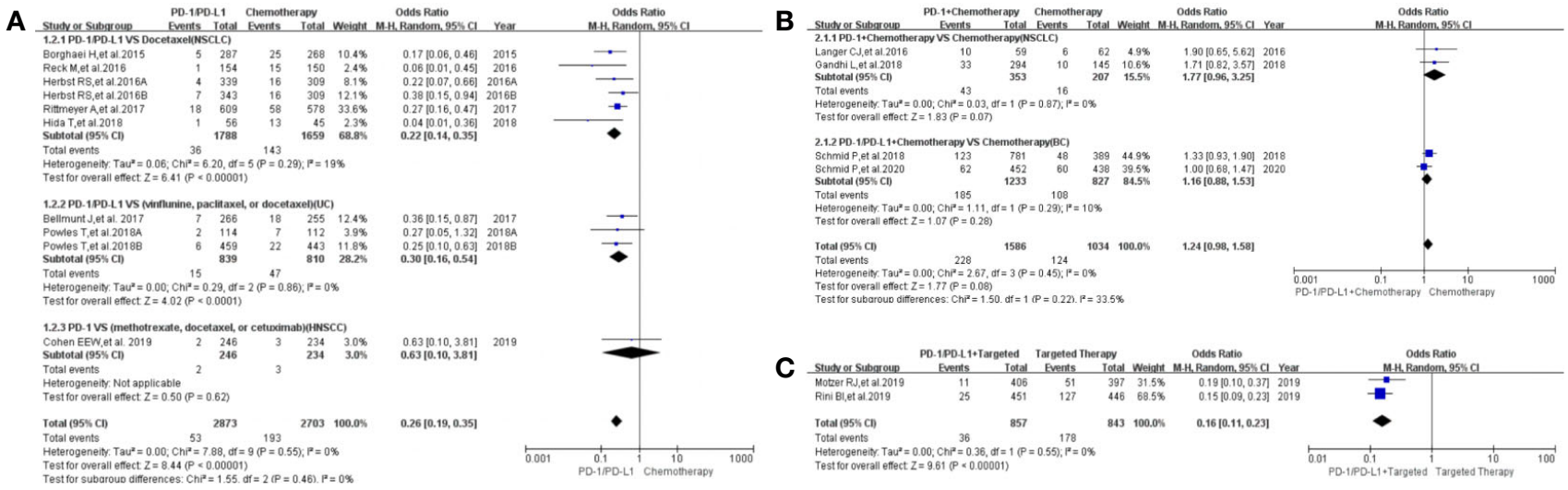

FIGURE 5 | Forest plots of the risk of dysgeusia. **(A)** The risk of all-grade dysgeusia calculated by the random effect (RE) model (PD-1/PD-L1 *vs* chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(B)** The risk of all-grade dysgeusia calculated by the random effect (RE) model (PD-1/PD-L1+ chemotherapy *vs.* chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(C)** The risk of all-grade dysgeusia calculated by the random effect (RE) model (PD-1/PD-L1+ targeted *vs.* targeted therapy): subgroup analysis was put into practice based on tumor types in both groups.

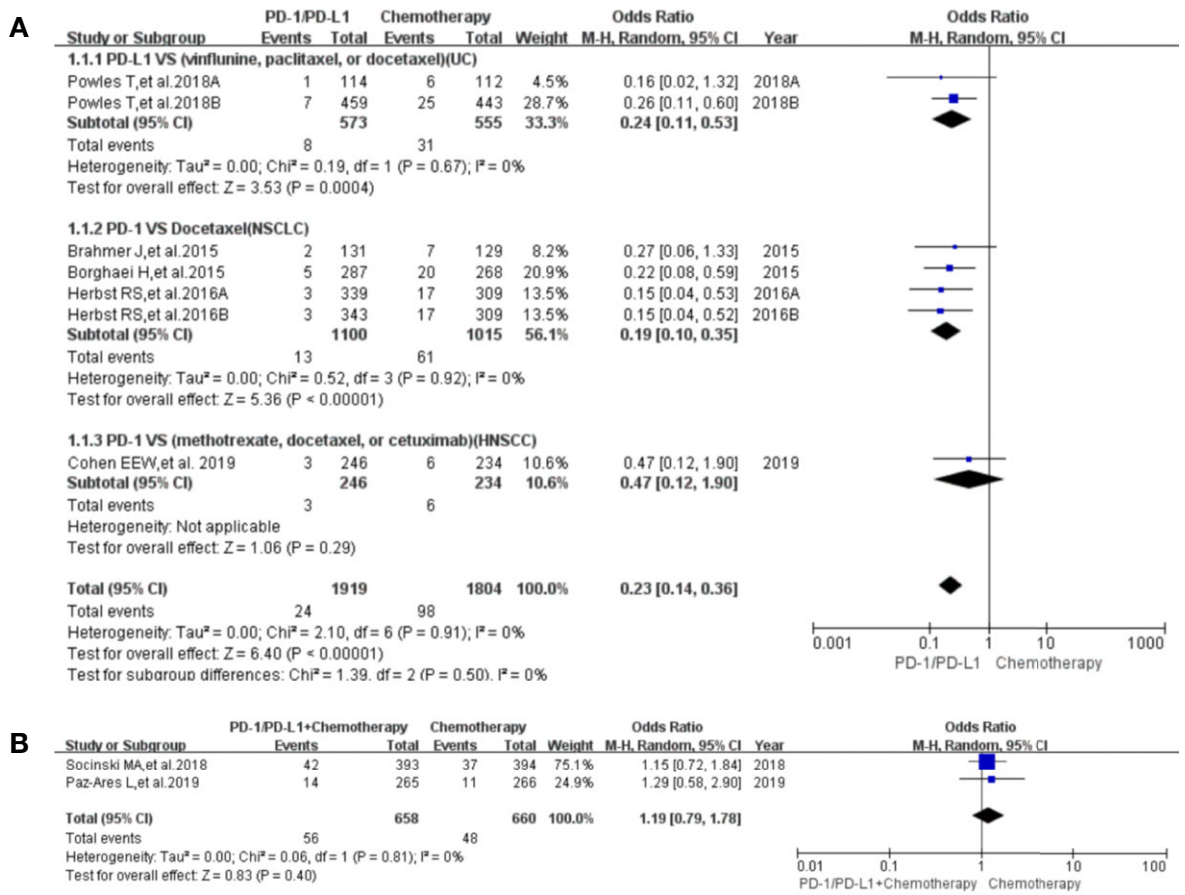

FIGURE 6 | Forest plots of the risk of paraesthesia. **(A)** The risk of all-grade paraesthesia calculated by the random effect (RE) model (PD-1/PD-L1 *vs.* chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(B)** The risk of all-grade dysgeusia calculated by the random effect (RE) model (PD-1/PD-L1 + chemotherapy *vs.* chemotherapy).

Risk of Headache

Headache was reported in 17 articles, involving 12 clinical trials (22, 23, 25, 26, 34, 41, 43, 47, 48, 51–57). When PD-1/PD-L1 inhibitors were compared with chemotherapy, no statistically significant differences were found in terms of all grade and grades 3–5 headache (**S Figure 4A1, A2**) (25, 34, 41, 43). A similar risk trend was also noted when PD-1/PD-L1 inhibitors plus others were compared with the control groups (**S Figure 4B, C2, D1, D2**) (22, 26, 47, 48, 51, 54).

When PD-1/PD-L1 inhibitors plus targeted therapy were compared with targeted therapy, the risk of headache of all grades was obviously higher [OR = 1.43, 95%CI:(1.09, 1.86), I^2 = 0%, Z=2.62 (P = 0.0009); **Supplementary Figure 4C1**) (22, 23, 48). The corresponding funnel plots are provided in the supplement (**S Figure 5**) (22, 23, 25, 26, 34, 41, 43, 47, 48, 51, 54).

Risk of Dizziness

Dizziness was reported in 12 articles, involving 11 clinical trials (22, 25, 34, 36, 38, 41–44, 47, 51, 52). According to different treatment regimens, we divided all included clinical trials into four groups to investigate the risk of dizziness of all grades and grades 3–5. However, no statistically significant differences were noted (**Supplementary Figure 6**) (25, 34, 36, 38, 41–44, 47, 51). The corresponding funnel plots are provided in the supplement (**S Figure 7**) (25, 34, 36, 38, 41–44, 47, 51).

Risk of Rarely Reported Neurologic Toxicities

Other types of neurological toxicities were reported in a limited number of studies, including peripheral motor neuropathy (51), Guillain–Barré syndrome (**Supplementary Figure 8A,B**) (25, 27, 33, 42, 51), polyneuropathy (**Supplementary Figure 8C**) (10, 25, 51), neurotoxicity (25). For Guillain–Barré syndrome and polyneuropathy, compared with chemotherapy, a statistically significant reduction in their associated risk was only observed in polyneuropathy [OR = 0.12, 95%CI:(0.01, 0.940, I^2 = 0%, Z = 2.02 (P = 0.04); **Supplementary Figure 8C**) (10, 25, 51). The corresponding funnel plots are provided in the supplement (**Supplementary Figure 9**) (10, 25, 27, 33, 42, 51). Due to the unavailability of relevant data regarding the other two neurological toxicities (neurotoxicity and peripheral motor

neuropathy), they could not be included in the meta-analysis (25, 51).

DISCUSSION

Most of the neurological toxicities caused by PD-1/PD-L1 inhibitors might be presented as low-grade appearances, with the potential to involve any aspect of the central or peripheral nervous system (7, 8). As more and more clinical trials reporting the efficacy and safety of PD-1/PD-L1 in cancer patients are being conducted, the reporting of drug-induced neurological toxicities has gradually increased (1, 2, 22–57). In order to clarify the relationship between PD-1/PD-L1 inhibitors and the risk of neurological toxicities in cancer patients, this meta-analysis was designed. It was the first time that neurological toxicities were comprehensively investigated through a meta-analytic approach instead of case reports and reviews (1, 5–14). It would be helpful in guiding anti-PD-1 and anti-PD-L1 immunotherapy.

Thirty-six articles, including 31 clinical trials with available data regarding neurological toxicities, were included in our study (22–57). Among the included clinical trials, lung cancer-related clinical trials accounted for the largest proportion (N = 17) (24, 27–30, 33, 35–37, 39–41, 43, 44, 47, 49, 55–57). Of note, the majority of the included clinical trials were of high quality (low risk of bias) (22–57). Therefore, the conclusion drawn from those data would be of higher credibility.

In our meta-analysis, we noted that the risk of all-grade neurological toxicities in the PD-1/PD-L1 inhibitors group was lower compared to the chemotherapy arm. These neurological toxicities included peripheral neuropathy, peripheral sensory neuropathy, dysgeusia, paraesthesia, and polyneuropathy (**Figure 3A1**, **4A1**, **5A1**, **6A1**, **S Figure 4A1**, **8C**). A similar observation was noted regarding peripheral neuropathy and peripheral sensory neuropathy of grades 3–5 (**Figure 3A2**, **4A2**) (10, 22–47, 49–51). These findings highlight the need to pay more attention to the risk of neurological toxicities associated with chemotherapy in clinical practice, especially for docetaxel (26, 30–32, 34, 40, 41, 43, 44, 46). The subgroup analyses suggested that the encountered high heterogeneity in our analyses (I^2=62%) might be related to the NSCLC subgroup (I^2 = 75%, **Figure 3A1**) (26, 30, 40). In addition, the treatment plans involved in the three NSCLC clinical trials included in the comprehensive analysis belonged to different treatment lines (first, second, or third line); this probably might be a potential contributor to the heterogeneity of the result (I^2 = 75%, **Figure 3A1**) (26, 30, 40). That being said, no obvious risk of publication bias was found from the corresponding funnel plots (**Supplementary Figure 1A1**, **2A1**, **3A1, B1**, **5A1**, **9C**). Interestingly, for headache, dizziness, and Guillain-Barré syndrome, the risk was found to be of no significance (**Supplementary Figure 4A**, **6A**, **8A**) (22, 23, 25–27, 33, 34, 36, 38, 41–44, 47, 48, 51–57), which meant that the risk trend of the aforementioned three neurological toxicities caused by PD-1/PD-L1 inhibitors was similar to that of the chemotherapy group. This finding is novel and has not been reported nor investigated by other studies in the literature.

Furthermore, Guillain–Barré syndrome was reported in five PD-1/PD-L1 groups (all cases were reported in the PD-1/PD-L1 group), while the incidence rate of the control groups was 0 (25, 27, 33, 42, 51). No statistically significant difference was noted and this could be attributed to the small number of included trials and the sensitivity of the analysis method (25, 27, 33, 42, 51). That being said, we cannot rule out the possibility that Guillain–Barré syndrome is a unique neurological toxicity of PD-1/PD-L1 inhibitors. Despite the fact that our analyses revealed some statistically insignificant results; however, the reported risks should not be ignored in clinical practice, and more attention should be paid to those fatal and rare reported neurological toxicities (25, 27, 33, 42, 51). These results might be of significant value in clinical practice. Once Guillain-Barré syndrome happened, we should first consider its associations with PD-1/PD-L1 inhibitors (25, 27, 33, 42, 51).

When PD-1/PD-L1 inhibitors plus chemotherapy were compared with chemotherapy, the trends in the risk of all-grade neurological toxicities increased without statistically significant differences (**Figure 3B1**, **4B1**, **5B**, **6B**, **Supplementary Figure 4B**, **6B**) (26–29, 36, 47, 49, 50). Statistically significant results were only found in terms of peripheral neuropathy of grades 3–5, especially for the breast cancer subgroup [OR = 1.76, 95%CI:(1.10, 2.82), I^2 = 0%, Z = 2.37 (P = 0.02); **Figure 3B2**] (26–29, 50). In order to draw a definite conclusion, more relevant clinical trials are still warranted to be conducted, and sufficient subgroup analyses still need to be carried out.

When PD-1/PD-L1 inhibitors plus targeted therapy were compared with targeted therapy (**Figure 5C**), the risk of all-grade dysgeusia was notably lower than that of the control group [OR = 0.16, 95%CI:(0.11, 0.23), I^2 = 0%, Z = 9.61 ($P < 0.00001$); **Figure 5C**) (22, 23). On the contrary, the risk of all-grade headache was increased compared to the targeted therapy group [OR = 1.43, 95%CI:(1.09, 1.86), I^2 = 0%, Z = 2.62 (P = 0.0009); **Supplementary Figure 4C1**] (22, 23, 48). However, the number of analyzed studies was low, and thus, a definite conclusion could not be reached (22, 23, 48). This was also observed when PD-1/PD-L1 inhibitors plus CTLA-4 were compared with CTLA-4 analog **Supplementary Figure 4D1, D2**, **6C**, **8B**). Eventually, based on the low number of analyzed studies and the minimal data reported in these studies, our findings should be interpreted with caution, and no clinical recommendations should be implemented from these data.

STRENGTHS AND LIMITATIONS

Strengths

This article was designed according to the PRISMA guidelines. The literature searching process was carried out in accordance with the PICOS principle. We strictly limited the selection criteria to clinical trials and checked the accuracy of the extracted data carefully. The quality of the majority of the

included trials was high. Subgroup analyses were put into practice as much as possible. Therefore, our meta-analysis provided a much more reliable evaluation of the relationship between PD-1/PD-L1 inhibitors and the associated risk of neurological toxicities in cancer patients compared to available evidence in the literature.

Limitations

First, compared with the control group, all the analysis results just showed the relative risk of neurological toxicities in cancer patients. Even when the associated risk of neurological toxicity was lower than that of the control group, it did not mean that PD-1/PD-L1 would not cause neurological toxicity in the experimental group. Second, the low number of studies that reported the data of certain neurological toxicities, along with the unavailability of relevant data, made it difficult to conduct a meta-analysis in this regard. Therefore, a definite conclusion could not be reached.

CONCLUSION

Our comprehensive review showed that PD-1/PD-L1 inhibitors alone exhibited lower neurological toxicities than chemotherapy. However, in terms of headache, dizziness, and Guillain–Barré syndrome, the risk trends were similar between both interventions. Regarding PD-1/PD-L1 inhibitors plus chemotherapy, the risk of neurological toxicities would be increased, especially for peripheral neuropathy of grades 3–5.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

The corresponding authors (YS and GS) had the right to deal with all the data and were responsible for the decision to submit this manuscript for publication. YT, AG, SW, SZ, and XY had the full data of the manuscript. YT, AG, SW, and SZ were responsible for checking and evaluating the quality of the data and included studies. YT was assigned to write the text of this manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by the Academic Promotion Program of Shandong First Medical University (2019QL025; YS), Natural Science Foundation of Shandong Province (ZR2019MH042; YS), Jinan Science and Technology Program (201805064; YS), and the National Science and Technology Major Project of the Ministry of Science and Technology of China (2020ZX09201025; GS).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2020.595655/full#supplementary-material

SUPPLEMENTARY FIGURE 1 | Funnel plots of the risk of peripheral neuropathy. **(A1)** The risk of all-grade peripheral neuropathy calculated by the fixed effect (FE) model (PD-1/PD-L1 *vs.* chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(A2)** The risk of peripheral neuropathy of grades 3–5 calculated by the fixed effect (FE) model (PD-1/PD-L1 *vs*. chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(B1)** The risk of all-grade peripheral neuropathy calculated by the fixed effect (FE) model (PD-1/PD-L1 + chemotherapy *vs.* chemotherapy): subgroup analysis was put into practice based on tumor types in both groups. **(B2)** The risk of peripheral neuropathy of grades 3–5 calculated by the fixed effect (FE) model (PD-1/PD-L1 + chemotherapy *vs.* chemotherapy): subgroup analysis was put into practice based on tumor types in both groups.

SUPPLEMENTARY FIGURE 2 | Funnel plots of the risk of peripheral sensory neuropathy. **(A1)** The risk of all-grade peripheral sensory neuropathy calculated by the fixed effect (FE) model (PD-1/PD-L1 *vs.* chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(A2)** The risk of peripheral sensory neuropathy of grades 3–5 calculated by the fixed effect (FE) model (PD-1/PD-L1 *vs*. chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(B1)** The risk of all-grade peripheral sensory neuropathy calculated by the fixed effect (FE) model (PD-1/PD-L1 + chemotherapy *vs.* chemotherapy): subgroup analysis was put into practice based on tumor types in both groups. **(B2)** The risk of peripheral sensory neuropathy of grades 3–5 calculated by the fixed effect (FE) model (PD-1/PD-L1 + chemotherapy *vs.* chemotherapy): subgroup analysis was put into practice based on tumor types in both groups.

SUPPLEMENTARY FIGURE 3 | (A) Funnel plots of the risk of dysgeusia. **(A1)** The risk of all-grade dysgeusia calculated by the fixed effect (FE) model (PD-1/PD-L1 *vs.* chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(A2)** The risk of all-grade dysgeusia calculated by the fixed effect (FE) model. (PD-1/PD-L1 + chemotherapy *vs.* chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(A3)** The risk of all-grade dysgeusia calculated by the fixed effect (FE) model. (PD-1/PD-L1 + targeted *vs*. targeted therapy): subgroup analysis was put into practice based on tumor types in both groups. **(B)** Funnel plots of the risk of paraesthesia. **(B1)** The risk of all-grade paraesthesia calculated by the fixed effect (FE) model (PD-1/PD-L1 *vs.* chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(B2)** The risk of all-grade paraesthesia calculated by the fixed effect (FE) model (PD-1/PD-L1 + chemotherapy *vs.* chemotherapy).

SUPPLEMENTARY FIGURE 4 | Forest plots of the risk of headache. **(A1)** The risk of all-grade headache calculated by the random effect (RE) model (PD-1/PD-L1 *vs.* chemotherapy): subgroup analysis was put into practice based on tumor types in both groups. **(A2)** The risk of headache of grades 3–5 calculated by the random effect (RE) model (PD-1/PD-L1 *vs.* chemotherapy). **(B)** The risk of all-grade headache calculated by the random effect (RE) model (PD-1/PD-L1 + targeted *vs.* targeted chemotherapy): subgroup analysis was put into practice based on PD-1 or PD-L1. **(C1)** The risk of all-grade headache calculated by the random effect (RE) model (PD-1/PD-L1 + targeted *vs.* targeted therapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(C2)** The risk of headache of grades 3–5 calculated by the random effect (RE) model (PD-1/PD-L1 + targeted *vs.* targeted therapy). **(D1)** The risk of all-grade headache calculated

by the random effect (RE) model (PD-1/PD-L1 + CTLA-4 *vs.* CTLA-4). **(D2)** The risk of headache of grades 3–5 calculated by the random effect (RE) model (PD-1/PD-L1 + CTLA-4 *vs*. CTLA-4).

SUPPLEMENTARY FIGURE 5 | Funnel plots of the risk of headache. **(A1)** The risk of all-grade headache calculated by the fixed effect **(FE)** model (PD-1/PD-L1 *vs*. chemotherapy): subgroup analysis was put into practice based on tumor types in both groups. **(A2)** The incidence risk of headache of grades 3–5 calculated by the fixed effect **(FE)** model (PD-1/PD-L1 *vs.* chemotherapy). **(B)** The risk of all-grade headache calculated by the fixed effect **(FE)** model (PD-1/PD-L1 + targeted *vs.* targeted therapy): subgroup analysis was put into practice based on PD-1 or PD-L1. **(C1)** The risk of all-grade headache calculated by the fixed effect **(FE)** model (PD-1/PD-L1 + targeted *vs.* targeted therapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(C2)** The risk of headache of grades 3–5 calculated by the fixed effect **(FE)** model (PD-1/PD-L1 + targeted *vs.* targeted therapy). (**D1**) The risk of all-grade headache calculated by the fixed effect **(FE)** model (PD-1/PD-L1 + CTLA-4 *vs.* CTLA-4). (**D2**) The risk of headache of grades 3–5 calculated by the fixed effect **(FE)** model (PD-1/PD-L1 + CTLA-4 *vs.* CTLA-4).

SUPPLEMENTARY FIGURE 6 | Forest plots of the risk of dizziness. **(A1)** The risk of all-grade dizziness calculated by the random effect (RE) model (PD-1/PD-L1 *vs.* chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(A2)** The risk of dizziness of grades 3–5 calculated by random effect (RE) model (PD-1/PD-L1 *vs.* chemotherapy). **(B)** The risk of all-grade dizziness calculated by the random effect (RE) model (PD-1/PD-L1 +c hemotherapy *vs*. chemotherapy). **(C)** The risk of all-grade dizziness calculated by the random effect (RE) model (PD-1/PD-L1 + CTLA-4 *vs*. CTLA-4).

SUPPLEMENTARY FIGURE 7 | Funnel plots of the risk of dizziness. **(A1)** The risk of all-grade dizziness calculated by the fixed effect **(FE)** model (PD-1/PD-L1 *vs*. chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. (A2) The risk of dizziness of grades 3–5 calculated by the fixed effect **(FE)** model (PD-1/PD-L1 *vs.* chemotherapy). **(B)** The risk of all-grade dizziness calculated by the fixed effect **(FE)** model (PD-1/PD-L1 + chemotherapy *vs.* chemotherapy). **(C)** The risk of all-grade dizziness calculated by the fixed effect **(FE)** model (PD-1/PD-L1 + CTLA-4 *vs*. CTLA-4).

SUPPLEMENTARY FIGURE 8 | Forest plots of the risk of rarely reported neurological toxicities. **(A1)** The risk of all-grade Guillain–Barré Syndrome calculated by the random effect (RE) model (PD-1/PD-L1 *vs*. chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(A2)** The risk of Guillain–Barré Syndrome of grades 3–5 calculated by the random effect (RE) model (PD-1/PD-L1 *vs.* chemotherapy). **(B)** The risk of all-grade Guillain–Barré Syndrome calculated by the random effect (RE) model (PD-1/PD-L1 + CTLA-4 *vs*. CTLA-4). **(C)** The risk of all-grade polyneuropathy calculated by the random effect (RE) model (PD-1/PD-L1 + CTLA-4 *vs.* CTLA-4).

SUPPLEMENTARY FIGURE 9 | Funnel plots of the risk of rarely reported neurological toxicities. **(A1)** The risk of all-grade Guillain–Barré Syndrome calculated by the fixed effect **(FE)** model (PD-1/PD-L1 *vs*. chemotherapy): subgroup analysis was put into practice based on PD-1/PD-L1 and tumor types in both groups. **(A2)** The risk of Guillain–Barré Syndrome of grades 3–5 calculated by the fixed effect **(FE)** model (PD-1/PD-L1 *vs.* chemotherapy). **(B)** The risk of all-grade Guillain–Barré Syndrome calculated by the fixed effect **(FE)** model (PD-1/PD-L1 + CTLA-4 *vs.* CTLA-4). **(C)** The risk of all-grade polyneuropathy calculated by the fixed effect **(FE)** model (PD-1/PD-L1 + CTLA-4 *vs*. CTLA-4).

REFERENCES

1. Kennedy LB. Salama AKS. A review of cancer immunotherapy toxicity. *CA Cancer J Clin* (2020) 70(2):86–104. doi: 10.3322/caac.21596
2. Thompson JA. New NCCN guidelines: recognition and management of immunotherapy-related toxicity. *J Natl Compr Canc Netw* (2018) 16(suppl 5):594–6. doi: 10.6004/jnccn.2018.0047
3. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* (2018) 378:158–68. doi: 10.1056/NEJMra1703481
4. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* (2018) 36:1714–68. doi: 10.1200/JCO.2017.77.6385
5. Larkin J, Chmielowski B, Lao CD, Hodi FS, Sharfman W, Weber J, et al. Neurologic serious adverse events associated with nivolumab plus ipilimumab or nivolumab alone in advanced melanoma, including a case series of encephalitis. *Oncologist* (2017) 22(6):709–18. doi: 10.1634/theoncologist.2016-0487
6. Johnson DB, Manouchehri A, Haugh AM, et al. Neurologic toxicity associated with immune checkpoint inhibitors: a pharmacovigilance study. *J Immunother Cancer* (2019) 7:134. doi: 10.1186/s40425-019-0617-x
7. Cuzzubbo S, Javeri F, Tissier M, Roumi A, Barlog C, Doridam J, et al. Neurological adverse events associated with immune checkpoint inhibitors: review of the literature. *Eur J Cancer* (2017) 73:1–8. doi: 10.1016/j.ejca.2016.12.001
8. Touat M, Talmasov D, Ricard D, Psimaras D. Neurological toxicities associated with immune-checkpoint inhibitors. *Curr Opin Neurol* (2017) 30:659–68. doi: 10.1097/WCO.0000000000000503
9. Liao B, Shroff S, Kamiya-Matsuoka C, Tummala S. Atypical neurological complications of ipilimumab therapy in patients with metastatic melanoma. *Neuro Oncol* (2014) 16:589–93. doi: 10.1093/neuonc/nou001
10. Vallet H, Gaillet A, Weiss N, Vanhaecke C, Saheb S, Touitou V, et al. Pembrolizumab-induced necrotic myositis in a patient with metastatic melanoma. *Ann Oncol* (2016) 27(7):1352–3. doi: 10.1093/annonc/mdw126
11. Kim A, Keam B, Cheun H, Lee ST, Gook HS, Han MK. Immune-checkpoint-inhibitor-induced severe autoimmune encephalitis treated by steroid and intravenous immunoglobulin. *J Clin Neurol* (2019) 15:259–61. doi: 10.3988/jcn.2019.15.2.259
12. Hottinger AF, de Micheli R, Guido V, Karampera A, Hagmann P, Du Pasquier R. Natalizumab may control immune checkpoint inhibitor-induced limbic encephalitis. *Neurol Neuroimmunol Neuroinflamm* (2018) 5:e439. doi: 10.1212/NXI.0000000000000439
13. Puzanov I, Diab A, Abdallah K, Bingham CO 3rd, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* (2017) 5(1):95. doi: 10.1186/s40425-017-0300-z
14. Mirabile A, Brioschi E, Ducceschi M, Piva S, Lazzari C, Bulotta A, et al. PD-1 Inhibitors-Related Neurological Toxicities in Patients with Non-Small-Cell Lung Cancer: A Literature Review. *Cancers (Basel)* (2019) 11(3):296. doi: 10.3390/cancers11030296
15. Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* (2009) 151:264–69. W64. doi: 10.7326/0003-4819-151-4-200908180-00135
16. Si Z, Zhang S, Yang X, Ding N, Xiang M, Zhu Q, et al. The Association Between the Incidence Risk of Peripheral Neuropathy and PD-1/PD-L1 Inhibitors in the Treatment for Solid Tumor Patients: A Systematic Review and Meta-Analysis. *Front Oncol* (2019) 9:866. doi: 10.3389/fonc.2019.00866
17. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. Cochrane Bias Methods Group and Cochrane Statistical Methods Group.. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* (2011) 343:d5928. doi: 10.1136/bmj.d5928
18. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* (1994) 50(4):1088–101. doi: 10.2307/2533446
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* (1997) 315(7109):629–34. doi: 10.1136/bmj.315.7109.629
20. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses(2009). Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (Accessed July 6, 2012).
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557

22. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med* (2019) 380(12):1103–15. doi: 10.1056/NEJMoa1816047
23. Rini BI, Powles T, Atkins MB, et al. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet* (2019) 393(10189):2404–15. doi: 10.1016/S0140-6736(19)30723-8
24. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* (2019) 393(10183):1819–30. doi: 10.1016/S0140-6736(18)32409-7
25. Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet* (2019) 393(10167):156–67. doi: 10.1016/S0140-6736(18)31999-8
26. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med* (2018) 379(22):2108–21. doi: 10.1056/NEJMoa1809615
27. Horn L, Mansfield AS, Szczęsna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. *N Engl J Med* (2018) 379(23):2220–9. doi: 10.1056/NEJMoa1809064
28. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med* (2018) 378(24):2288–301. doi: 10.1056/NEJMoa1716948
29. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *N Engl J Med* (2018) 379(21):2040–51. doi: 10.1056/NEJMoa1810865
30. Barlesi F, Vansteenkiste J, Spigel D, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study [published correction appears in Lancet Oncol. 2018 Nov;19(11):e581]. *Lancet Oncol* (2018) 19(11):1468–79. doi: 10.1016/S1470-2045(18)30673-9
31. Shitara K, Özgüroğlu M, Bang YJ, Di Bartolomeo M, Mandalà M, Ryu MH, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet* (2018) 392(10142):123–33. doi: 10.1016/S0140-6736(18)31257-1
32. Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial [published correction appears in Lancet. 2018 Oct 20;392(10156):1402]. *Lancet* (2018) 391(10122):748–57. doi: 10.1016/S0140-6736(17)33297-X
33. Hida T, Kaji R, Satouchi M, et al. Atezolizumab in Japanese Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer: A Subgroup Analysis of the Phase 3 OAK Study. *Clin Lung Cancer* (2018) 19(4):e405–15. doi: 10.1016/j.cllc.2018.01.004
34. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. *N Engl J Med* (2017) 376(11):1015–26. doi: 10.1056/NEJMoa1613683
35. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial [published correction appears in Lancet. 2017 Apr 8;389(10077):e5]. *Lancet* (2017) 389(10066):255–65. doi: 10.1016/S0140-6736(16)32517-X
36. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol* (2016) 17(11):1497–508. doi: 10.1016/S1470-2045(16)30498-3
37. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* (2016) 375(19):1823–33. doi: 10.1056/NEJMoa1606774
38. Ferris RL, Blumenschein GJr, Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med* (2016) 375(19):1856–67. doi: 10.1056/NEJMoa1602252
39. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial [published correction appears in Lancet Oncol. 2016 Jul;17 (7):e270] [published correction appears in Lancet Oncol. 2019 Feb;20(2):e70]. *Lancet Oncol* (2016) 17(7):883–95. doi: 10.1016/S1470-2045(19)30018-X
40. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* (2016) 387(10030):1837–46. doi: 10.1016/S0140-6736(16)00587-0
41. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* (2016) 387(10027):1540–50. doi: 10.1016/S0140-6736(15)01281-7
42. Hodi FS, Chesney J, Pavlick AC, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. *Lancet Oncol* (2016) 17(11):1558–68. doi: 10.1016/S1470-2045(16)30366-7
43. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med* (2015) 373(17):1627–39. doi: 10.1056/NEJMoa1507643
44. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med* (2015) 373(2):123–35. doi: 10.1056/NEJMoa1504627
45. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med* (2015) 373(19):1803–13. doi: 10.1056/NEJMoa1510665
46. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial [published correction appears in Lancet Oncol. 2019 Nov;20(11):e613]. *Lancet Oncol* (2019) 20(11):1506–17. doi: 10.1016/S1470-2045(19)30626-6
47. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med* (2018) 378(22):2078–92. doi: 10.1056/NEJMoa1801005
48. Ascierto PA, Ferrucci PF, Fisher R, et al. Dabrafenib, trametinib and pembrolizumab or placebo in BRAF-mutant melanoma. *Nat Med* (2019) 25(6):941–6. doi: 10.1038/s41591-019-0448-9
49. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet* (2019) 394(10212):1929–39. doi: 10.1016/S0140-6736(19)32222-6
50. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. *N Engl J Med* (2020) 382(9):810–21. doi: 10.1056/NEJMoa1910549
51. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol* (2018) 19(11):1480–92. doi: 10.1016/S1470-2045(18)30700-9
52. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med* (2017) 377(14):1345–56. doi: 10.1056/NEJMoa1709684
53. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med* (2015) 373(1):23–34. doi: 10.1056/NEJMoa1504030
54. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med* (2019) 381(16):1535–46. doi: 10.1056/NEJMoa1910836
55. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med* (2017) 377(20):1919–29. doi: 10.1056/NEJMoa1709937

56. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med* (2018) 379(24):2342–50. doi: 10.1056/NEJMoa1809697
57. Hui R, Özgüroğlu M, Villegas A, et al. Patient-reported outcomes with durvalumab after chemoradiotherapy in stage III, unresectable non-small-cell lung cancer (PACIFIC): a randomised, controlled, phase 3 study. *Lancet Oncol* (2019) 20(12):1670–80. doi: 10.1016/S1470-2045(19)30519-4
58. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* (1986) 7:177–88. doi: 10.1016/0197-2456(86)90046-2

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

REVIEW
published: 22 February 2021
doi: 10.3389/fonc.2021.625872

The Efficacy and Safety of Immune Checkpoint Inhibitors in Patients With Cancer and Preexisting Autoimmune Disease

Hui Tang, Jianfeng Zhou and Chunmei Bai*

Department of Medical Oncology,Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Immune checkpoint inhibitor (ICI) is a revolutionary breakthrough in the field of cancer treatment. Because of dysregulated activation of the immune system, patients with autoimmune disease (AID) are usually excluded from ICI clinical trials. Due to a large number of cancer patients with preexisting AID, the safety and efficacy of ICIs in these patients deserve more attention. This review summarizes and analyzes the data regarding ICI therapy in cancer patients with preexisting AID from 17 published studies. Available data suggests that the efficacy of ICIs in AID patients is comparable to that in the general population, and the incidence of immune-related adverse events (irAEs) is higher but still manageable. It is recommended to administer ICIs with close monitoring of irAEs in patients with a possibly high benefit-risk ratio after a multidisciplinary discussion based on the patient's AID category and severity, the patient's tumor type and prognosis, alternative treatment options, and the patient's intention. Besides, the prevention and management of irAEs in AID patients have been discussed.

Keywords: autoimmune disorder, solid tumors, immunotherapy, immune-related adverse events, PD-1, CTLA-4

OPEN ACCESS

Edited by:
Xuelei Ma,
Sichuan University, China

Reviewed by:
Asaf Maoz,
Dana-Farber Cancer Institute, United States
Martina Spiljar,
University of Geneva, Switzerland

****Correspondence:***
Jianfeng Zhou
ZhouJF@pumch.cn

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Oncology

Received: *04 November 2020*
Accepted: *05 January 2021*
Published: *22 February 2021*

Citation:
Tang H, Zhou J and Bai C (2021) The Efficacy and Safety of Immune Checkpoint Inhibitors in Patients With Cancer and Preexisting Autoimmune Disease. Front. Oncol. 11:625872. doi: 10.3389/fonc.2021.625872

INTRODUCTION

The approved immune checkpoint inhibitors (ICIs) mainly involve several immune checkpoint–directed antibodies targeting cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1). CTLA-4 inhibits an immune response in several ways, including hindering autoreactive T-cell activation at a proximal step in the immune response, typically in lymph nodes (1, 2). In contrast, the PD-1 pathway regulates T cells at a later stage of the immune response, typically in peripheral tissues (3). Differing from traditional chemotherapy and targeted therapy, ICI can break the state of immune tolerance in the tumor microenvironment (TME) and activate the body's anti-tumor immunity. Clinical trials of ICI therapy are in full swing, showing remarkable efficacy as well as fewer and milder adverse events compared to chemotherapy, and the indications for ICIs continue to expand across malignancies (4).

Autoimmune diseases (AIDs) represent a family of at least 80 diseases that share a common pathogenesis: an improper activation of the immune system attacking the body's own organs (5).

By increasing the activity of the immune system, ICI may result in immune-related adverse events (irAEs). Although the precise underlying mechanism is unknown, irAEs show many common clinical manifestations and pathophysiology features similar to AID (6). The role of PD-1 and CTLA-4 in autoantigen tolerance has been widely recognized (7), so ICI may exacerbate the damage done by one's own immune system to AID patients and bring forth autoimmune inflammatory manifestations similar to or unrelated to the baseline AID. AID patients were usually excluded from clinical trials of ICI therapy due to the potential for increased toxicity (8).

AIDs may cause chronic inflammation and increase the risk of carcinogenesis (9–12). Cancer can also increase the risk of AIDs (13). The incidence of AIDs in lung cancer patients was reported to be as high as 14% to 25% (8), and some cancers show clinical features similar to AIDs (9, 14). Due to a large number of cancer patients with preexisting AID, the safety and efficacy of ICIs in these patients deserve more attention. Furthermore, there is a tendency toward immune activation in AID patients, so some clinicians proposed that AID patients may be likely to benefit more from ICI (15). At present, there is no reported prospective randomized controlled study on this issue. Whether the efficacy and safety of ICIs in patients with cancer and preexisting AID differ from that in the general population is unclear.

RELATIONSHIP BETWEEN IMMUNE CHECKPOINTS AND AID

CTLA-4 signaling has been shown to be involved in the pathogenesis of many AIDs including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), and type-1 diabetes (T1D) (16). Polymorphisms in CTLA-4 gene were also associated with disease susceptibility to many AIDs like SLE, RA, MS, T1D, and so on (1). Human patients with heterozygous loss of function mutations in CTLA-4 developed widespread autoimmunity including autoimmune hepatitis, T1D, and arthritis (17). CTLA-4 gene deletion could lead mice to develop lymphoproliferative disease and die by 3–4 weeks of age (18). By contrast, mice with ablation of CTLA-4 expression during adulthood developed severe, but not fatal, autoimmunity (19). Preclinical models showed CTLA-4 blockade worsened autoimmune thyroiditis, with a more aggressive mononuclear cells infiltration in thyroid (20).

PD-1 signaling were also involved in the pathogenesis of many AIDs like autoimmune hepatitis, inflammatory bowel disease (IBD), SLE, myocarditis, and RA (21). Polymorphisms in PDCD1 gene were associated with disease susceptibility to many AIDs including SLE, RA, Graves' disease, and so on (1). The engagement of Tregs with autoreactive B cells *via* the PD-1/L1 inhibitory axis can trigger B cells apoptosis and inhibit the production of autoantibody (22). In patients with RA, lymphocytes infiltrating the synovium commonly express PD-1, the synovial lining cells express PD-L1, and the number of PD-1-positive lymphocytes was significantly larger in RA than in osteoarthritis (23). In addition, the PD-L1 expression on synovial lining cells was positively related to the number of infiltrating T cells and Krenn's synovitis score (23), indicating an important role of PD-1 pathway in RA. Notably, in non-obese diabetic mice, both anti–CTLA-4 and anti–PD-1 treatment can prevent anergy induction in islet antigen–specific T cells, but only PD-1/L1 blockade can reverse experimentally induced anergy, indicating a unique function for PD-1 signaling in maintaining T cells anergy (24).

Furthermore, the administration of ICI may conflict with the management of AIDs. For example, abatacept is a fusion protein comprising the extracellular domain of CTLA-4, that competitively blocks the T cells CD28-CD80 pathway signaling and improves the prognosis of RA (25). Therefore, in contrast, the use of ipilimumab which blockades CTLA-4 signaling may conflict with the management of RA.

LITERATURE EXPERIENCE WITH ICIs IN AID PATIENTS

To evaluate the efficacy and safety of ICIs in patients with cancer and preexisting AID, we summarized the retrospective studies published before October 2020 (**Table 1**). Inclusion criteria was articles available in full text, published in English, and reporting safety or efficacy data on patients with preexisting AID and cancer treated with ICI. Further, case reports and review articles were excluded. After screening, 17 published studies were included, from which the following data were extracted: author, publication year, sample size, characteristics of AID, cancer and ICI type; the number and proportion of AID flares, newly developed irAEs, treatment discontinuation and response; survival time. The irAEs reported in these studies can be divided into two categories. The first type is the flare of preexisting AIDs, and the second type is the newly developed irAEs that does not have a clear causal link with preexisting AIDs. We refer to the two types collectively as total irAEs (TirAEs). Most studies included patients regardless of the treatment line, so caution should be exercised when comparing studies' efficacy data with previous clinical trials.

Efficacy and Safety of ICIs in Patients With Melanoma and AID

Rich experience has been accumulated in ICI therapy for malignant melanoma. There were three retrospective studies of anti-CTLA-4 therapy for melanoma patients with AID (26–28) (**Table 1**). Two studies reported that the objective response rate (ORR) was no more than 20% (26, 27), and another study, with just eight patients, reported an ORR as high as 50% (28). As to the safety, Johnson et al. (27) reported that the incidence of TirAEs in AID patients was 50%, including an incidence rate of AID flare of 27%. Kähler et al. (26) reported that the incidence of TirAEs in AID patients was 44%. The incidence of both AID flare and newly developed irAEs were 29%, and 17% of patients discontinued ICIs because of AID flare. Both studies (26, 27) supported that the incidence of TirAEs in AID patients did not exceed that observed in the general population included in

TABLE 1 | Data summary of cancer patients with preexisting autoimmune disease treated with immune checkpoint inhibitors.

Cancer	Target	Study	Main AID	N	Efficacy			Safety			
					ORR	mPFS (months)	mOS (months)	TirAEs (grade ≥3)	Preexisting AID flare (grade ≥3)	Newly developed irAEs (grade ≥3)	Treatment discontinuation
Melanoma	CTLA-4	Kähler (26)	Thyroiditis (37%), Ps (17%), RA (15%)	41	12%	NA	NA	44% (NA)	29% (NA)	29% (NA)	17% due to AID flare
Melanoma	CTLA-4	Johnson (27)	RA (20%), IBD (20%), Ps (17%)	30	20%	3.0	12.5	50% (NA)	27% (NA)	33% (33%)	NA
Melanoma	CTLA-4	Lee (28)	RA (100%)	8	50%	NA	NA	100% (63%)	75% (25%)	50% (50%)	63% due to TirAEs
Melanoma	PD-1	Menzies (15)	RA (25%), Ps (12%), Colitis (10%)	52	33%	6.2	NR	NA	38% (6%)	29% (10%)	4% and 8% permanent discontinuation due to AID flare and newly developed irAEs, respectively
Melanoma	PD-1	Gutzmer (29)	Thyroiditis (26%), RA (21%), Ps (16%)	19	32%	NA	NA	58% (16%)	42% (11%)	16% (5%)	None
NSCLC	PD-1	Yoneshima (30)	ANA positivity (100%)	18	28%	2.9	11.6	33% (11%)	NA	NA	11% due to TirAEs
NSCLC	PD-1	Leonardi (31)	Ps (25%), RA (20%), Thyroiditis (16%)	56	22%	NA	NA	55% (NA)	23% (4%)	38% (11%)	0% and 14% permanent discontinuation due to AID flare and newly developed irAEs, respectively
Urological cancers	PD-1	Loriot (32)	Ps (43%), Thyroiditis (17%), RA (11%)	35	11%	8.2	4.4	46% (14%)	11% (6%)	NA	14% due to TirAEs
Urological cancers	PD-1 or CTLA-4	Martinez Chanza (33)	Ps (23%), Thyroiditis (13%), RA (11%)	106	35%	NA	NA	58% (NA)	36% (6%)	38% (12%)	6% and 8% permanent discontinuation due to AID flare and newly developed irAEs, respectively
Various	PD-1	Danlos (34)	Vitiligo (38%), Ps (27%), Thyroiditis (16%)	45	38%	NA	NA	44% (11%)	24% (NA)	22% (NA)	11% due to TirAEs
Various	PD-1	Cortellini (35)	Ps (40%), RA (27%), IBD (13%)	15[a]	50%	6.8	9.8	73% (13%)	47% (13%)	NA	13% due to TirAEs
			Thyroiditis (76%), Ps (10%), Vitiligo (3%)	70[b]	38%	14.4	15.7	64% (9%)	47% (9%)	NA	6% due to TirAEs
Various	PD-1 or CTLA-4	Tison (36)	Ps (28%), RA (18%), IBD (13%)	112	49%[c]	NA	NA	71% (NA)	47% (13%)	42% (16%)	21% permanent discontinuation due to TirAEs
Various	PD-1 or CTLA-4	Richter (37)	RA (31%), Polymyalgia rheumatica (31%), Sjogren's syndrome (13%)	16	NA	NA	NA	38% (25%)	6% (0%)	31% (25%)	38% due to TirAEs
Various	PD-1 or CTLA-4	Kaur (38)	Hypothyroidism (61%), RA (9%), Ps (9%)	46	NA	NA	NA	NA	20% (NA)	NA	2% due to AID flare
Various	PD-1 or CTLA-4	Abu-Sbeih (39)	IBD (100%)	102	NA	NA	NA	NA	36% (17%)	NA	32% due to TirAEs
Various	PD-1 or CTLA-4	Braga Neto (40)	IBD (100%)	13	NA	NA	NA	NA	31% (NA)	NA	None
Various	PD-1 or CTLA-4	Efuni (41)	RA (100%)	22	NA	NA	NA	73%	55%	32% (9%)	9% and 5% permanent discontinuation due to AID flare and newly developed irAEs, respectively

AID, autoimmune disease; ANA, antinuclear antibody; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; IBD, inflammatory bowel disease; irAEs, immune-related adverse events; mOS, median overall survival; mPFS, median progression free survival; NA, not available; NR, not reached; NSCLC, non–small cell lung cancer; ORR, objective response rate; PD-1, programmed cell death protein 1; Ps, psoriasis; RA, rheumatoid arthritis; TirAEs, total irAEs (i.e. AID flare and/or newly developed irAEs).

[a]*Clinically active AID.*

[b]*Clinically inactive AID.*

[c]*In patients without prior ICI therapy.*

previous large clinical trials (42, 43). Furthermore, AID flares and newly developed irAEs were usually manageable according to established algorithms (44–46), mostly with corticosteroids or other immunosuppressants, and did not preclude clinical benefit.

There were also two retrospective studies (15, 29) on anti-PD-1 therapy for melanoma patients with AID (**Table 1**). Both Menzies et al. (15) and Gutzmer et al. (29) reported that the ORR of anti-PD-1 antibodies in melanoma patients with preexisting AID exceeded 30%. Intriguingly, large clinical trials demonstrated that ORR of anti-PD-1 therapy in melanoma was 33% to 45% in the first-line treatment (42, 43, 47) and 21% to 32% after ipilimumab (48, 49). Considering the high prevalence of adverse prognostic features (such as 31% of patients had brain metastases, 48% of patients had elevated serum LDH, and 56% of patients' ECOG grade were ≥1) and 54% of patients had previous anti-CTLA-4 therapy in the included patients, Menzies et al. (15) speculated that patients with a tendency toward autoimmunity might be more likely to benefit from anti-PD-1 therapy. Taken together, the above two studies (15, 29) suggested that the efficacy of anti-PD-1 therapy in patients with melanoma and AID was not inferior to that in the general population. As to the safety, Gutzmer et al. (29) reported that the incidence of any grade and grade 3/4 TirAEs were as high as 58% and 16%, respectively. The discontinuation rates of anti-PD-1 therapy in the study of Menzies et al. (15) were comparable to those in general melanoma patients (42, 43, 47), and the immune damage of AID flare was generally mild and manageable.

Efficacy and Safety of ICIs in Patients With Other Cancers and AID

There are relatively few studies on ICI therapy in patients with non–small cell lung cancer (NSCLC) and preexisting AID. Yoneshima et al. (30) found that antinuclear antibody (ANA) positivity had no significant effect on ORR and the incidence of irAEs in NSCLC patients treated with anti-PD-1, but both the median progression-free survival (mPFS) and median overall survival (mOS) were significantly shorter in ANA-positive patients than in ANA-negative patients (2.9 *versus* 3.8 months, 11.6 *versus* 15.8 months, $p = 0.03$ for each instance). Moreover, the authors also identified three patients with increased ANA titer during the anti-PD-1 treatment, all of whom subsequently developed irAEs. The study of Leonardi et al. (31) demonstrated that the ORR was 22% in NSCLC patients with AID, the incidence of TirAEs was 55%, and the safety was comparable to that in the general population.

There were 141 patients with urological cancers and AID in the studies reported by Martinez Chanza et al. (33) and Loriot et al. (32). The most common preexisting AIDs were psoriasis (Ps, n = 39), thyroiditis (n = 30), and RA (n = 16). In the studies reported by Martinez Chanza et al. (33), the rates of AID flare and newly developed irAEs were as high as 36% and 38%, respectively. However, TirAEs in the above two studies (58% and 46%, respectively) were generally mild and reversible, especially in patients with asymptomatic or mildly symptomatic AID, and the efficacy was similar in AID and non-AID patients. As to AIDs of clinical concern, such as Guillain-Barre syndrome (GBS), MS, and IBD, flares did not appear more frequent but might be more aggressive as most of them resulted in ICI discontinuation.

In the studies on the use of ICIs in cancer patients with unlimited tumor types and preexisting AID, the majority of malignant tumor types were still melanoma and/or NSCLC (**Table 1**) (34–40) Danlos et al. (34) analyzed data from a large prospective study of anti-PD-1 treatment and found that the 45 patients with AID had no significant difference in ORR or mOS compared with those without AID, but the median irAE-free survival time was significantly shorter (5.4 *versus* 13.0 months, $p = 0.0002$) and the incidence of TirAEs was higher in patients with AID (44% *versus* 29%). Tison et al. (36) reported a large multicenter retrospective study including 112 AID patients treated for various cancers with ICIs. Forty-nine percent of 105 patients without prior ICI therapy were considered to be responders. After a median follow-up period of 8 months, the mPFS of melanoma and NSCLC patients was 12.9 months and 11.8 months, respectively, and the mOS was not reached and 22.4 months. However, the incidences of TirAEs and permanent treatment discontinuation (71% and 21%, respectively) were higher than that of the general population, which needs to be noticed. In the study of Cortellini et al. (35), the ORR of anti-PD-1 treatment in 85 cancer patients with AID was 40%. Unfortunately, the incidence of TirAEs in both inactive and active AID patients were significantly higher than that of the general population (64% *versus* 40%, $p = 0.0005$, and 73% *versus* 40%, $p = 0.0162$, respectively). The incidence of TirAEs is alarming and implies that clinicians should be vigilant when using ICIs in AID patients, especially in those with active AID. Nevertheless, the AID comorbidity in this study was not significantly related to the incidence of grade 3/4 irAEs, treatment discontinuation rate, ORR, PFS, or OS.

Summarily, the above studies tend to support the conclusion that the efficacy of ICIs in patients with AID is comparable to that in the general population, while the incidence of TirAEs is higher, most TirAEs are mild and manageable.

The Effect of AID Status and Immunosuppressive Therapy on Efficacy and Safety of ICIs

It is controversial whether the use of glucocorticoids at a daily dose of 10 mg, or more of prednisone or other immunosuppressants, at the beginning of ICI therapy or within 1 month would affect the efficacy of ICI (50, 51). In the study of Kähler et al. (26), 11 of the 41 patients were undergoing at least one systemic immunosuppression at the time of ipilimumab initiation, including eight patients receiving a low-dose prednisone. The result suggested that patients receiving immunosuppressive therapy had a similar ORR of 9% compared to patients without immunosuppressive therapy. The studies of Gutzmer et al. (29) and Leonardi et al. (31) also supported that the use of immunosuppressants at the beginning of treatment does not affect the efficacy of ICI. However, in the study

reported by Menzies et al. (15), 20 of the 52 patients with AID were on systemic immunosuppression at the start of anti-PD-1 therapy, including 14 patients receiving corticosteroids. The result showed that the ORR in the patients undergoing immunosuppressive therapy was significantly lower than in those not undergoing immunosuppressive therapy (15% *versus* 44%, $p = 0.033$). The meta-analysis of Xie et al. (52) also demonstrated that there was a trend toward lower ORR in patients with immunosuppressants at ICI start ($p > 0.05$). However, due to the heterogeneity of included patients, the data on the pooled ORR may not be so meaningful. As for survival data, Tison et al. (36) reported that the 51 patients receiving immunosuppressive therapy had a shorter mPFS than those without immunosuppressive agents (3.8 *versus* 12 months, $p = 0.006$), but the mOS difference was not significant. Furthermore, Cortellini et al. (35) reported that the patients with active AID tended to have a higher ORR but shorter mPFS and mOS when compared with patients with inactive AID.

On the aspect of safety, Menzies et al. (15) reported that flares occurred more often in patients with active AID than in those with inactive AID (60% *versus* 30%, $p = 0.039$), and there was a trend for more flares in patients on immunosuppression treatment than in those not on immunosuppression (50% *versus* 31%, $p > 0.05$). The study of Martinez Chanza et al. (33) also reached a conclusion consistent with that of Menzies et al. Similarly, the study of Leonardi et al. (31) suggested that AID was more likely to flare in patients with active symptoms, and Kähler et al. (26) also reported that flares occurred more often in patients on immunosuppression at the start of treatment. However, Abu-Sbeih et al. (39) reported that there was no significant correlation between active IBD within 3 months before ICIs initiation and all grades of gastrointestinal (GI) adverse events, but patients with active IBD had more severe GI adverse events. The meta-analysis of Xie et al. (52) reported that the pooled incidence of AID flare and newly developed irAEs were 35% and 33%, respectively, and there was no statistical difference between patients with and without immunosuppressive therapy regarding AID flare. Besides, almost all AID flares occurred at the beginning of ICI therapy—2 weeks to 1 year after initiation, but mostly around 1–2 months (15, 27, 29, 31, 33, 41). Most AID flares had similar manifestations and affected the same anatomic sites as prior AID symptoms (27, 31, 36).

Summarily, available studies mainly supported that immunosuppressive therapy controlling AID might have little influence on the efficacy of ICIs, but the incidence of TirAEs or AID flare would be higher in patients with active AID or undergoing immunosuppressive therapy. Furthermore, it is important to note that there are few patients with severe active AID included in the retrospective studies. It may be necessary to properly treat and control severe active AID before ICI initiation for safety's sake.

The Effect of AID and ICI Category on the Safety of ICIs

Almost all common AIDs have been included in the retrospective studies. However, some AIDs (such as neurological AIDs) will result in devastating consequences if they flare, so clinicians would rarely use ICIs in patients with those AIDs. Therefore, patients with those AIDs may be underrepresented in the retrospective studies. Many studies yielded similar conclusions (15, 26–29, 31, 33–36, 38). That is, preexisting rheumatologic AIDs (such as RA, polymyalgia rheumatica) and Ps were most likely to effect AID flare after ICI therapy (the incidences of AID flare were 50% to 68% and 20% to 67% in patients with rheumatologic AIDs and Ps, respectively). This is in line with the review of Ramos-Casals et al. (53) and the meta-analysis of Xie et al. (52). Most of the studies suggested that autoimmune thyroiditis, GI AIDs (such as IBD/colitis), neurological AIDs, and respiratory AIDs (such as asthma) were less likely to effect AID flare (15, 26, 29, 31, 33, 34). Part of the possible reason for this is that the pathogenesis of various AIDs is heterogeneous. The PD-1/L1 pathway plays an important role in rheumatism, while many other AIDs do not involve or rely heavily on the PD-1-signaling pathway (15). For example, GBS is a typical B-cell-mediated disease, while chronic inflammation of RA is characterized by PD-1-positive T-cell infiltration (54, 55). However, due to a higher mortality rate in neurologic irAEs, NCCN guidelines had recommended more aggressive measures to neurological irAEs (46). Therefore, ICIs should be used more cautiously in patients with preexisting neurological AID.

As to ICI category, Tison et al. (36) reported that newly developed irAEs appeared to be more frequent (11/14 [79%] *versus* 34/95 [36%]) and severe in the ipilimumab group than in the anti-PD-1 therapy group. This is consistent with the conclusion that the incidence and severity of irAEs induced by anti-CTLA-4 treatment were higher or severer than that of anti-PD-1 treatment in the general population (56). This is also in line with severe autoimmunity and lymphoproliferative disorder observed in CTLA-4 gene deletion mice (18, 19) compared to moderate autoimmunity, including aplastic anemia, glomerulonephritis, and arthritis, seen in PD-1-deficient mice (57, 58). Colitis and hypophysitis were two common ipilimumab-induced irAEs in AID patients (26–28, 37). It is still not entirely clear why ICIs at different targets could produce organ-specific irAEs, and CTLA-4 expression on normal pituitary cells might explain hypophysitis induced by anti-CTLA-4 therapy (59, 60).

Colitis is a particularly frequent and potentially fatal ipilimumab-induced irAE, so the use of ipilimumab in IBD patients was of particular clinical interest. The study reported by Abu-Sbeih et al. (39) enrolled 102 IBD patients treated with ICIs, 17 of those patients receiving ipilimumab. The results showed that anti–CTLA-4 therapy and IBD involving the colon before ICIs initiation were possible risk factors for GI toxicities. However, no GI adverse event–related death was reported, and the response to ICIs in patients with underlying IBD was comparable to that in non-IBD patients, indicating the potential clinical benefit. The study reported by Johnson et al. (27) included six asymptomatic or minimally symptomatic IBD patients receiving ipilimumab. Three patients had prior colectomies, and the other three patients were receiving

aminosalicylate derivatives or topical hydrocortisone at the time of ipilimumab initiation. After ipilimumab treatment, one patient with ulcerative colitis developed an AID flare and another patient with Crohn disease had newly developed ipilimumab-induced colitis; these were resolved by infliximab and corticosteroids, respectively. There were three IBD patients receiving ipilimumab in the study of Kähler et al. (26), and two of them were receiving mesalazine at the time of ipilimumab initiation. Only one patient with ulcerative colitis developed an AID flare, and this was resolved after treatment discontinuation and prednisone pulse therapy. Therefore, we suggest that ipilimumab might be considered for cancer patients with IBD, if necessary, provided that IBD status is stable and closely monitored.

A systematic review conducted by Abdel-Wahab et al. (61) in 2018 included 123 patients with preexisting AID receiving ICIs. The results demonstrated that no differences in irAEs were observed in patients with active *versus* inactive AID, and patients receiving immunosuppressive therapy at the time of ICIs initiation appeared to have fewer irAEs. In this systematic review, the incidence of AID flare induced by anti-PD-1 was higher than that by ipilimumab, and more newly developed irAEs were reported with ipilimumab. Some conclusions reached by this systematic review were contradictory to other reviews (6, 56), including ours. This may be partly due to the small number of cases and the variety of AID included in the study of Abdel-Wahab et al., so prospective studies are needed to determine the safety and efficacy of ICIs in patients with AID (6).

STRATEGIES TO PREVENT AND MANAGE irAEs IN AID PATIENTS

Immunotherapy-induced inflammation and tumor lysis generate numerous antigens that can be presented by antigen-presenting cells and trigger a secondary immune response to autoantigen. This process is defined as epitope spreading, which plays a crucial role in the initial stage of irAE development (62). Multiple studies demonstrated that the incidence of irAEs is significantly associated with the efficacy of ICIs (63), which can be partly explained by epitope spreading. Epitope spreading can also explain why different tumors treated with ICIs are associated with specific irAEs. For instance, in terms of antigenic epitopes, skin is the organ that shares T cell antigens with NSCLC only second to the lung and had the second highest incidence of irAEs (64). Berner et al. (64) identified nine shared T cell antigens in the lung tumor and skin in 25 patients with ICIs-induced skin toxicity. Besides, melanoma patients were more likely to develop mucosal and dermatological toxicities (65). Therefore, the use of ICIs should be prudent in melanoma or NSCLC patients with dermatological AIDs. Moreover, as mentioned above, some AIDs were inclined to worsen or result in devastating consequences during ICI therapy. Hence, in these specific situations, such as RA or GBS with active disease status, ICI applications should be avoided as much as possible. Furthermore, there have been many studies on biomarkers predicting irAEs (66), and increased autoantibody titers can also detect irAEs early (30, 67, 68). Therefore, we do not think it is safe enough to use ICIs in patients with biomarkers that indicate a predisposition to specific irAEs in the same organs involved by their AID. For example, in a study of 26 melanoma patients treated with anti-CTLA-4, Firmicutes were associated with ICIs-induced colitis (69). Therefore, we should be more careful if we use ICIs in IBD patients with increased Firmicutes in the gut microbiome. However, those biomarkers predicting irAEs need to be validated prospectively.

To lower the risk of compromising ICIs efficacy, corticosteroids should be avoided as much as possible at the time of ICIs initiation. However, it is necessary to properly treat and control the preexisting AID before ICIs initiation. Therefore, Haanen et al. (70) proposed a two-step strategy for managing irAEs in AID patients. First, non-selective immunosuppressants (such as corticosteroids and mycophenolate mofetil) could be replaced by specific selective immunosuppressants (such as tocilizumab [anti-IL-6 receptor antibody], infliximab [anti-TNF-α antibody], and vedolizumab [anti-α4β7 integrin antibody]) to control AIDs for a short period. Subsequently, combining ICIs with selective immunosuppressants could prevent the flare of preexisting AID. In a study of 87 patients who developed irAEs after treatment with nivolumab, clinical improvement was observed in 79% of 34 patients who received anti-IL-6 receptor antibody tocilizumab (71). On the aspect of efficacy, inhibition of IL-6 has been reported to have synergistic anti-tumor activity when combined with ICIs in mouse models (65). Small series and several cases also have reported the safe and effective administration of ICIs in active AIDs under selective immunosuppressants (70). Theoretically, the two-step strategy recommended by Haanen et al. (70) seems to be valid when administrating ICIs in AID patients. Nevertheless, it is also important to note that the strategy is based on small-scale retrospective studies. Further studies are needed to confirm the effectiveness and safety of this strategy.

Intriguingly, irAEs can be prevented to some extent by modifying ICIs so that they are only active within the TME, or restricting their delivery to the TME. For example, ICIs can be loaded onto nanoparticles which possess intrinsic properties, like magnetism, and then be actively directed to accumulate in TME with the help of external devices (72). However, biomaterial-based cancer immunotherapies are mainly explored in animal studies, and deserve further validation in clinical trials.

CONCLUSION

There is no available prospective study on whether the efficacy and safety of ICIs in patients with cancer and preexisting AID differ from that in the general population. The results of the existing retrospective studies seemed to support that the efficacy of ICIs in patients with preexisting AID was comparable to that in the general population, and while the incidence of irAEs was higher, most irAEs were mild and manageable. However, there is a selection bias that most of the AID patients included in the

existing retrospective studies were in stable disease status, patients' performance status was fair, and certain AIDs inclined to result in devastating consequences during ICI therapy may be under-represented. Given the existing data, preexisting AID may not be an absolute contraindication to ICI therapy. It is recommended to weigh the benefits and risks of immunotherapy in a multidisciplinary approach including rheumatologists based on a patient's AID category and severity, the patient's cancer type and prognosis, alternative treatment options, and the patient's intention. After that, ICIs could be administered with close monitoring of irAEs in patients with good performance status and mild AID status who could benefit from immunotherapy. Moreover, there are several strategies for preventing and meagering irAEs that can be taken when administrating ICIs in AID patients. Two phase I clinical trials of nivolumab in patients with AID and lung cancer (NCT03656627) or across tumor types (NCT03816345) are ongoing. The results of the above two trials and more real-world retrospective studies would reach more instructive conclusions about the existing controversies.

AUTHOR CONTRIBUTIONS

Conception and design: HT and JZ. Literature review and analysis: HT and JZ. Drafting of the manuscript: HT and JZ. Supervision: JZ and CB. All authors contributed to the article and approved the submitted version.

FUNDING

This work is supported by a grant from CAMS Innovation Fund for Medical Sciences (no. 2016-I2M-1-001).

REFERENCES

1. Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. *Immunol Rev* (2008) 224:166–82. doi: 10.1111/j.1600-065X.2008.00662.x
2. Krummel MF, Allison JP. CTLA-4 engagement inhibits IL-2 accumulation and cell cycle progression upon activation of resting T cells. *J Exp Med* (1996) 183:2533–40. doi: 10.1084/jem.183.6.2533
3. Boussiotis VA. Molecular and Biochemical Aspects of the PD-1 Checkpoint Pathway. *N Engl J Med* (2016) 375:1767–78. doi: 10.1056/NEJMra1514296
4. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. *Nat Rev Clin Oncol* (2019) 16:563–80. doi: 10.1038/s41571-019-0218-0
5. Rose NR. Prediction and Prevention of Autoimmune Disease in the 21st Century: A Review and Preview. *Am J Epidemiol* (2016) 183:403–6. doi: 10.1093/aje/kwv292
6. Kennedy LC, Bhatia S, Thompson JA, Grivas P. Preexisting Autoimmune Disease: Implications for Immune Checkpoint Inhibitor Therapy in Solid Tumors. *J Natl Compr Canc Netw* (2019) 17:750–7. doi: 10.6004/jnccn.2019.7310
7. Wieder T, Eigentler T, Brenner E, Röcken M. Immune checkpoint blockade therapy. *J Allergy Clin Immunol* (2018) 142:1403–14. doi: 10.1016/j.jaci.2018.02.042
8. Khan SA, Pruitt SL, Xuan L, Gerber DE. Prevalence of Autoimmune Disease Among Patients With Lung Cancer: Implications for Immunotherapy Treatment Options. *JAMA Oncol* (2016) 2:1507–8. doi: 10.1001/jamaoncol.2016.2238
9. Labrador-Horrillo M, Selva-O'Callaghan A. Cancer-associated Dermatomyositis: Does the PD-1 Checkpoint Pathway Play a Role? *J Rheumatol* (2018) 45:731–2. doi: 10.3899/jrheum.180007
10. Franks AL, Slansky JE. Multiple associations between a broad spectrum of autoimmune diseases, chronic inflammatory diseases and cancer. *Anticancer Res* (2012) 32:1119–36. doi: ar.iiarjournals.org/content/32/4/1119.long
11. Liang Y, Yang Z, Qin B, Zhong R. Primary Sjogren's syndrome and malignancy risk: a systematic review and meta-analysis. *Ann Rheum Dis* (2014) 73:1151–6. doi: 10.1136/annrheumdis-2013-203305
12. Mao S, Shen H, Zhang J. Systemic lupus erythematosus and malignancies risk. *J Cancer Res Clin Oncol* (2016) 142:253–62. doi: 10.1007/s00432-015-2032-0
13. Kazarian M, Laird-Offringa IA. Small-cell lung cancer-associated autoantibodies: potential applications to cancer diagnosis, early detection, and therapy. *Mol Canc* (2011) 10:33. doi: 10.1186/1476-4598-10-33
14. Dalmau J, Rosenfeld MR. Autoimmune encephalitis update. *Neuro Oncol* (2014) 16:771–8. doi: 10.1093/neuonc/nou030
15. Menzies AM, Johnson DB, Ramanujam S, Atkinson VG, Wong ANM, Park JJ, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann Oncol* (2017) 28:368–76. doi: 10.1093/annonc/mdw443
16. Zhang Q, Vignali DA. Co-stimulatory and Co-inhibitory Pathways in Autoimmunity. *Immunity* (2016) 44:1034–51. doi: 10.1016/j.immuni.2016.04.017
17. Verma N, Burns SO, Walker LSK, Sansom DM. Immune deficiency and autoimmunity in patients with CTLA-4 (CD152) mutations. *Clin Exp Immunol* (2017) 190:1–7. doi: 10.1111/cei.12997
18. Tivol EA, Borriello F, Schweitzer AN, Lynch WP, Bluestone JA, Sharpe AH. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. *Immunity* (1995) 3:541–7. doi: 10.1016/1074-7613(95)90125-6
19. Klocke K, Sakaguchi S, Holmdahl R, Wing K. Induction of autoimmune disease by deletion of CTLA-4 in mice in adulthood. *Proc Natl Acad Sci USA* (2016) 113:E2383–2392. doi: 10.1073/pnas.1603892113
20. Sharma R, Di Dalmazi G, Caturegli P. Exacerbation of Autoimmune Thyroiditis by CTLA-4 Blockade: A Role for IFNγ-Induced Indoleamine 2, 3-Dioxygenase. *Thyroid* (2016) 26:1117–24. doi: 10.1089/thy.2016.0092
21. Zamani MR, Aslani S, Salmaninejad A, Javan MR, Rezaei N. PD-1/PD-L and autoimmunity: A growing relationship. *Cell Immunol* (2016) 310:27–41. doi: 10.1016/j.cellimm.2016.09.009
22. Gotot J, Gottschalk C, Leopold S, Knolle PA, Yagita H, Kurts C, et al. Regulatory T cells use programmed death 1 ligands to directly suppress autoreactive B cells in vivo. *Proc Natl Acad Sci USA* (2012) 109:10468–73. doi: 10.1073/pnas.1201131109
23. Matsuda K, Miyoshi H, Hiraoka K, Hamada T, Yoshida S, Ishibashi Y, et al. Clinicopathological value of programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) expression in synovium of patients with rheumatoid arthritis. *Clin Exp Med* (2018) 18:487–94. doi: 10.1007/s10238-018-0515-4
24. Fife BT, Guleria I, Gubbels Bupp M, Eagar TN, Tang Q, Bour-Jordan H, et al. Insulin-induced remission in new-onset NOD mice is maintained by the PD-1-PD-L1 pathway. *J Exp Med* (2006) 203:2737–47. doi: 10.1084/jem.20061577
25. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* (2005) 353:1114–23. doi: 10.1056/NEJMoa050524
26. Kähler KC, Eigentler TK, Gesierich A, Heinzerling L, Loquai C, Meier F, et al. Ipilimumab in metastatic melanoma patients with pre-existing autoimmune disorders. *Cancer Immunol Immunother* (2018) 67:825–34. doi: 10.1007/s00262-018-2134-z
27. Johnson DB, Sullivan RJ, Ott PA, Carlino MS, Khushalani NI, Ye F, et al. Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting

Autoimmune Disorders. *JAMA Oncol* (2016) 2:234–40. doi: 10.1001/jamaoncol.2015.4368
28. Lee B, Wong A, Kee D, Neeson P, Shackleton M, McArthur G, et al. The use of ipilimumab in patients with rheumatoid arthritis and metastatic melanoma. *Ann Oncol* (2016) 27:1174–7. doi: 10.1093/annonc/mdw056
29. Gutzmer R, Koop A, Meier F, Hassel JC, Terheyden P, Zimmer L, et al. Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity. *Eur J Cancer* (2017) 75:24–32. doi: 10.1016/j.ejca.2016.12.038
30. Yoneshima Y, Tanaka K, Shiraishi Y, Hata K, Watanabe H, Harada T, et al. Safety and efficacy of PD-1 inhibitors in non-small cell lung cancer patients positive for antinuclear antibodies. *Lung Cancer* (2019) 130:5–9. doi: 10.1016/j.lungcan.2019.01.014
31. Leonardi GC, Gainor JF, Altan M, Kravets S, Dahlberg SE, Gedmintas L, et al. Safety of Programmed Death-1 Pathway Inhibitors Among Patients With Non-Small-Cell Lung Cancer and Preexisting Autoimmune Disorders. *J Clin Oncol* (2018) 36:1905–12. doi: 10.1200/JCO.2017.77.0305
32. Loriot Y, Sternberg CN, Castellano D, Oosting SF, Dumez H, Huddart R, et al. Safety and efficacy of atezolizumab in patients with autoimmune disease: Subgroup analysis of the SAUL study in locally advanced/metastatic urinary tract carcinoma. *Eur J Cancer* (2020) 138:202–11. doi: 10.1016/j.ejca.2020.07.023
33. Martinez Chanza N, Xie W, Issa M, Dzimitrowicz H, Tripathi A, Beuselinck B, et al. Safety and efficacy of immune checkpoint inhibitors in advanced urological cancers with pre-existing autoimmune disorders: a retrospective international multicenter study. *J Immunother Cancer* (2020) 8:e000538. doi: 10.1136/jitc-2020-000538
34. Danlos FX, Voisin AL, Dyevre V, Michot JM, Routier E, Taillade L, et al. Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease. *Eur J Cancer* (2018) 91:21–9. doi: 10.1016/j.ejca.2017.12.008
35. Cortellini A, Buti S, Santini D, Perrone F, Giusti R, Tiseo M, et al. Clinical Outcomes of Patients with Advanced Cancer and Pre-Existing Autoimmune Diseases Treated with Anti-Programmed Death-1 Immunotherapy: A Real-World Transverse Study. *Oncologist* (2019) 24:e327–37. doi: 10.1634/theoncologist.2018-0618
36. Tison A, Quéré G, Misery L, Funck-Brentano E, Danlos FX, Routier E, et al. Safety and Efficacy of Immune Checkpoint Inhibitors in Patients With Cancer and Preexisting Autoimmune Disease: A Nationwide, Multicenter Cohort Study. *Arthritis Rheumatol* (2019) 71:2100–11. doi: 10.1002/art.41068
37. Richter MD, Pinkston O, Kottschade LA, Finnes HD, Markovic SN, Thanarajasingam U. Brief Report: Cancer Immunotherapy in Patients With Preexisting Rheumatic Disease: The Mayo Clinic Experience. *Arthritis Rheumatol* (2018) 70:356–60. doi: 10.1002/art.40397
38. Kaur A, Doberstein T, Amberker RR, Garje R, Field EH, Singh N. Immune-related adverse events in cancer patients treated with immune checkpoint inhibitors: A single-center experience. *Med (Baltimore)* (2019) 98:e17348. doi: 10.1097/MD.0000000000017348
39. Abu-Sbeih H, Faleck DM, Ricciuti B, Mendelsohn RB, Naqash AR, Cohen JV, et al. Immune Checkpoint Inhibitor Therapy in Patients With Preexisting Inflammatory Bowel Disease. *J Clin Oncol* (2020) 38:576–83. doi: 10.1200/JCO.19.01674
40. Braga Neto MB, Ramos GP, Loftus EVJr., Faubion WA, Raffals LE. Use of Immune Checkpoint Inhibitors in Patients With Pre-established Inflammatory Bowel Diseases: Retrospective Case Series. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc* (2020). doi: 10.1016/j.cgh.2020.06.031
41. Efuni E, Cytryn S, Boland P, Niewold TB, Pavlick A, Weber J, et al. Risk of Toxicity After Initiating Immune Checkpoint Inhibitor Treatment in Patients With Rheumatoid Arthritis. *J Clin Rheumatol Pract Rep Rheumatic Musculoskeletal Dis* (2020). doi: 10.1097/RHU.0000000000001314
42. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol* (2018) 19:1480–92. doi: 10.1016/S1470-2045(18)30700-9
43. Schachter J, Ribas A, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). *Lancet* (2017) 390:1853–62. doi: 10.1016/S0140-6736(17)31601-X
44. Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2018) 29:iv264–6. doi: 10.1093/annonc/mdy162
45. Puzanov I, Diab A, Abdallah K, Bingham CO,3, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* (2017) 5:95. doi: 10.1186/s40425-017-0300-z
46. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. NCCN Guidelines Insights: Management of Immunotherapy-Related Toxicities, Version 1.2020. *J Natl Compr Canc Netw* (2020) 18:230–41. doi: 10.6004/jnccn.2020.0012
47. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* (2015) 372:320–30. doi: 10.1056/NEJMoa1412082
48. Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* (2015) 16:375–84. doi: 10.1016/S1470-2045(15)70076-8
49. Ribas A, Puzanov I, Dummer R, Schadendorf D, Hamid O, Robert C, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol* (2015) 16:908–18. doi: 10.1016/S1470-2045(15)00083-2
50. Ricciuti B, Dahlberg SE, Adeni A, Sholl LM, Nishino M, Awad MM. Immune Checkpoint Inhibitor Outcomes for Patients With Non-Small-Cell Lung Cancer Receiving Baseline Corticosteroids for Palliative Versus Nonpalliative Indications. *J Clin Oncol* (2019) 37:1927–34. doi: 10.1200/JCO.19.00189
51. Arbour KC, Mezquita L, Long N, Rizvi H, Auclin E, Ni A, et al. Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non-Small-Cell Lung Cancer. *J Clin Oncol* (2018) 36:2872–8. doi: 10.1200/JCO.2018.79.0006
52. Xie W, Huang H, Xiao S, Fan Y, Deng X, Zhang Z. Immune checkpoint inhibitors therapies in patients with cancer and preexisting autoimmune diseases: A meta-analysis of observational studies. *Autoimmun Rev* (2020) 19:102687. doi: 10.1016/j.autrev.2020.102687
53. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, et al. Immune-related adverse events of checkpoint inhibitors. *Nat Rev Dis Primers* (2020) 6:38. doi: 10.1038/s41572-020-0160-6
54. van den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, van Doorn PA. Guillain-Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. *Nat Rev Neurol* (2014) 10:469–82. doi: 10.1038/nrneurol.2014.121
55. Gu-Trantien C, Willard-Gallo K. PD-1(hi)CXCR5(-)CD4(+) T(FH) Cells Play Defense in Cancer and Offense in Arthritis. *Trends Immunol* (2017) 38:875–8. doi: 10.1016/j.it.2017.10.003
56. El Osta B, Hu F, Sadek R, Chintalapally R, Tang SC. Not all immune-checkpoint inhibitors are created equal: Meta-analysis and systematic review of immune-related adverse events in cancer trials. *Crit Rev Oncol Hematol* (2017) 119:1–12. doi: 10.1016/j.critrevonc.2017.09.002
57. Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity* (1999) 11:141–51. doi: 10.1016/S1074-7613(00)80089-8
58. Hollinger MK, Giudice V, Cummings NA, Rivell G, Zhang H, Kajigaya S, et al. PD-1 deficiency augments bone marrow failure in a minor-histocompatibility antigen mismatch lymphocyte infusion model. *Exp Hematol* (2018) 62:17–23. doi: 10.1016/j.exphem.2018.03.001
59. Caturegli P, Di Dalmazi G, Lombardi M, Grosso F, Larman HB, Larman T, et al. Hypophysitis Secondary to Cytotoxic T-Lymphocyte-Associated Protein 4 Blockade: Insights into Pathogenesis from an Autopsy Series. *Am J Pathol* (2016) 186:3225–35. doi: 10.1016/j.ajpath.2016.08.020
60. Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P. Pituitary expression of CTLA-4 mediates hypophysitis secondary to

administration of CTLA-4 blocking antibody. *Sci Transl Med* (2014) 6:230ra245. doi: 10.1126/scitranslmed.3008002
61. Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. Use of Immune Checkpoint Inhibitors in the Treatment of Patients With Cancer and Preexisting Autoimmune Disease: A Systematic Review. *Ann Intern Med* (2018) 168:121–30. doi: 10.7326/M17-2073
62. Yang H, Yao Z, Zhou X, Zhang W, Zhang X, Zhang F. Immune-related adverse events of checkpoint inhibitors: Insights into immunological dysregulation. *Clin Immunol* (2020) 213:108377. doi: 10.1016/j.clim.2020.108377
63. Petrelli F, Grizzi G, Ghidini M, Ghidini A, Ratti M, Panni S, et al. Immune-related Adverse Events and Survival in Solid Tumors Treated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. *J Immunother (Hagerstown Md 1997)* (2020) 43:1–7. doi: 10.1097/CJI.0000000000000300
64. Berner F, Bomze D, Diem S, Ali OH, Fässler M, Ring S, et al. Association of Checkpoint Inhibitor-Induced Toxic Effects With Shared Cancer and Tissue Antigens in Non-Small Cell Lung Cancer. *JAMA Oncol* (2019) 5:1043–7. doi: 10.1001/jamaoncol.2019.0402
65. Esfahani K, Elkrief A, Calabrese C, Lapointe R, Hudson M, Routy B, et al. Moving towards personalized treatments of immune-related adverse events. *Nat Rev Clin Oncol* (2020) 17:504–15. doi: 10.1038/s41571-020-0352-8
66. von Itzstein MS, Khan S, Gerber DE. Investigational Biomarkers for Checkpoint Inhibitor Immune-Related Adverse Event Prediction and Diagnosis. *Clin Chem* (2020) 66:779–93. doi: 10.1093/clinchem/hvaa081
67. Tahir SA, Gao J, Miura Y, Blando J, Tidwell RSS, Zhao H, et al. Autoimmune antibodies correlate with immune checkpoint therapy-induced toxicities. *Proc Natl Acad Sci U States A* (2019) 116:22246–51. doi: 10.1073/pnas.1908079116
68. Gowen MF, Giles KM, Simpson D, Tchack J, Zhou H, Moran U, et al. Baseline antibody profiles predict toxicity in melanoma patients treated with immune checkpoint inhibitors. *J Trans Med* (2018) 16:82. doi: 10.1186/s12967-018-1452-4
69. Chaput N, Lepage P, Coutzac C, Soularue E, Le Roux K, Monot C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. *Ann Oncol* (2017) 28:1368–79. doi: 10.1093/annonc/mdx108
70. Haanen J, Ernstoff MS, Wang Y, Menzies AM, Puzanov I, Grivas P, et al. Autoimmune diseases and immune-checkpoint inhibitors for cancer therapy: review of the literature and personalized risk-based prevention strategy. *Ann Oncol* (2020) 31:724–44. doi: 10.1016/j.annonc.2020.03.285
71. Stroud CR, Hegde A, Cherry C, Naqash AR, Sharma N, Addepalli S, et al. Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. *J Oncol Pharm Pract Off Publ Int Soc Oncol Pharm Practitioners* (2019) 25:551–7. doi: 10.1177/1078155217745144
72. Hu D, Zhang W, Tang J, Zhou Z, Liu X, Shen Y. Improving safety of cancer immunotherapy via delivery technology. *Biomaterials* (2020) 265:120407. doi: 10.1016/j.biomaterials.2020.120407

Conflict of Interest: The authors declare that the review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

ORIGINAL RESEARCH
published: 18 March 2021
doi: 10.3389/fonc.2021.611012

Comparative Efficacy and Safety of Immunotherapy Alone and in Combination With Chemotherapy for Advanced Non-small Cell Lung Cancer

Xue Wang†, *Xiaomin Niu*†, *Na An*, *Yile Sun* and *Zhiwei Chen**

Department of Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China

There is a lack of direct cross-comparison studies in clinical trials between immunotherapy alone and combination treatment, especially in Non-Small Cell Lung Cancer (NSCLC) patients with high PD-L1 expression. To determine if anti-PD-(L)1 antibody combined with chemotherapy is more efficient than immune checkpoint inhibitor (ICI) monotherapy for advanced NSCLC patients in the real-world data. We retrospectively collected 325 patients with advanced NSCLC treated with ICI alone with or without chemotherapy from 11th July 2016 to 26th May 2020 to investigate which treatment scenario is the most efficient, and how clinical factors impact response. Patients with advanced NSCLC were treated with ICI monotherapy (178/325, 54.8%) or in combination with chemotherapy (147/325, 45.2%). The objective response rate and disease control rate were higher in the combination group than the monotherapy group. Patients (including those with distant metastasis) treated with chemo-immunotherapy were associated with a significantly longer median PFS and OS compared with the monotherapy group, irrespective of the PD-L1 expression level and previous treatment lines. No significant increase in the risk of immune-related adverse events (irAEs) was found after combination with chemotherapy (50.6 vs. 57.8%). IrAEs predicted better PFS of immunotherapy in the monotherapy group, especially for patients with late irAEs (after ≥4 cycles). Collectively, we demonstrated that ICI monotherapy plus chemotherapy might have better anti-tumor activity and an acceptable side-effect profile regardless of PD-L1 level or previous treatment lines. Both regimens were well-tolerated and cost-effective, the more efficient is usually recommended.

Keywords: immunotherapy, chemotherapy, immune-related adverse event, NSCLC, PD-L1

OPEN ACCESS

Edited by:
Udo S. Gaipl,
University Hospital Erlangen, Germany

Reviewed by:
Shaodong Hong,
Sun Yat-sen University Cancer Center (SYSUCC), China
Kohei Fujita,
National Hospital Organization Kyoto Medical Center, Japan

***Correspondence:**
Zhiwei Chen
czw75@shchest.org

†*These authors have contributed equally to this work*

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Oncology

Received: *28 September 2020*
Accepted: *23 February 2021*
Published: *18 March 2021*

Citation:
Wang X, Niu X, An N, Sun Y and Chen Z (2021) Comparative Efficacy and Safety of Immunotherapy Alone and in Combination With Chemotherapy for Advanced Non-small Cell Lung Cancer. Front. Oncol. 11:611012. doi: 10.3389/fonc.2021.611012

INTRODUCTION

The advent of immune checkpoint inhibitors (ICIs) has radically changed the therapy paradigm in advanced NSCLC over the past 5 years. A remarkable improvement in the management of metastatic NSCLC occurred in 2015, when nivolumab was approved for the treatment of patients with progressive disease during or after a platinum-doublet treatment (1). Both anti-programmed death 1 (PD-1) and anti- programmed death ligand-1 (PD-L1) antibodies have demonstrated their benefits in comparison with standard chemotherapy (2–5).

Due to the encouraging results from clinical trials, the U.S. Food and Drug Administration (FDA) granted approval for ICIs as monotherapy in advanced NSCLC. What's more, pembrolizumab is recommended as the first-line treatment in oncogene-negative tumors with high (Tumor Proportion Score, TPS $\geq$50%; category 1) or low PD-L1 expression (1% $\leq$ TPS $<$50%; category 2B); and atezolizumab or pembrolizumab combined with carboplatin-based doublet as the front-line treatment is also approved (category 1) (6). Chemotherapy or immunotherapy alone (no previous ICI treatment) is preferred as the second-line treatment for PS 0–2. Nevertheless, deciding between therapeutics remains a challenge today.

The objective of this retrospective study is to investigate the efficacy and safety of ICI monotherapy or in combination with chemotherapy for advanced NSCLC patients in the real-world.

MATERIALS AND METHODS

Participants

325 patients had stage IIIB-IV NSCLC were retrospectively included from Shanghai Chest Hospital from 11th July 2016 to 26th May 2020; measurable disease on the basis of the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1); a baseline Eastern Cooperative Oncology Group performance status (ECOG PS) of 1; and all stage IIIB patients were not suitable for radiotherapy ($n = 36$). Baseline distant metastases were ascertained by CT scans or MRI with contrast imaging.

32/37 (86.4%) patient were epidermal growth factor receptor (EGFR) sensitizing mutations (exon 19 deletion, exon 21 L858R, L861Q or L861R, exon 20 S786I or T790M mutations), and 28/32 (87.5%) patients had progressive disease or intolerance to treatment with approved first-, second-, and/or third-generation EGFR-TKIs. 2/32 (6.25%) patients with exon 21L858R mutation were treatment-naïve; and another 2/32 (6.25%) received chemotherapy. Nobody had anaplastic lymphoma kinase (ALK) translocations. PD-L1 expression was analyzed by immunohistochemistry assay in archival or freshly collected tumor tissue with different antibodies [5/325 (1.54%) were 22C3, 20/325 (6.15%) were SP263, 86/325 (26.46%) were E1L3N, and 6/325 (1.85%) were 28-8]. Histologic slides with a minimum of 100 tumor cells were required for PD-L1 assessment.

Treatments

Patients were treated with anti-PD-(L)1 alone ($n = 178$) or combined with chemotherapy ($n = 147$), and it was their first exposure to ICIs. The dosage of drugs administered are shown in **Supplementary Table 1**. 281/325 (86.46%) patients received anti-PD-1 antibody treatment [71/281 (25.27%) combined with pemetrexed and carboplatin, 19/281 (6.76%) with paclitaxel and carboplatin, 15/281 (5.34%) with nab-paclitaxel and carboplatin, 23/281 (8.19%) with other chemotherapeutics]; 44/325 (13.54%) received anti-PD-L1 antibody treatment [19/44 (43.18%) combined with pemetrexed and carboplatin].

Treatment was given until disease progression, severe toxicity, or death. Assessments of progression occurred every two cycles until disease progression as per RECIST v1.1 (tumor assessments of nivolumab occurred every three cycles).

Outcomes

All patients were followed up for survival until death, or loss-to follow-up (4/325, 1.2%) from 11th July 2016 to 26th May 2020. Progression-free survival (PFS) and Overall survival (OS) were measured as the time between start of treatment and documented disease progression or death owing to any cause (PFS) or to the latter (OS). Time to treatment failure (TTF) was assessed from immunotherapy to cessation of ICI treatment for any reason. Disease control rate (DCR) refers to the proportion of patients with complete response (CR), partial response (PR) or stable disease (SD) for at least 6 months. Objective response rate (ORR) was defined as the proportion of patients with CR or PR for at least 6 months. Duration of response (DOR), defined as initial CR or PR to progressive disease (PD) or death.

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4, and were classified according to their characteristics: treatment-related AEs (trAEs) and immunotherapy-related AEs (irAEs) (7–10). Assessments were done by at least three independent medical professionals.

In addition, progression in no-target lesions was quantified based on four progression items: pre-existing lesions, new intrathoracic metastasis, new extrathoracic metastasis, or new malignant effusion (11, 12). Score 1 point for each progression item and add up the total. The final score will show the level of tumor burden.

Statistical Analyses

Associations between variables and PFS or OS were analyzed using Kaplan-Meier survival curves, the log-rank test, and univariate or multivariate Cox regression models. Multivariate hazard ratios (HRs) were estimated with a stratified Cox regression model, and 95% confidence Intervals (CIs) were calculated with the Brookmeyer-Crowley method. Subgroup analyses were done with unstratified HRs estimated from a cox proportional hazards model. Analyses were carried out using IBM SPSS Statistics 21.0 software. Categorical variables were compared in the same platform by the Fisher's exact or chi-square test. A two-tailed $p < 0.05$ was considered significant.

RESULTS

Clinicopathologic Features and Outcomes

178/325 (54.8%) patients were administered a single ICI, whereas the remainder of patients were combined with chemotherapy (147/325, 45.2%). The baseline characteristics are demonstrated in **Table 1**. Immunotherapy group had a significantly lower ORR in comparison with combination group (27 of 178, 15.2% vs. 64 of 147, 43.5%, respectively), similar results were obtained in DCR (72 of 178, 40.4% vs. 100 of 147, 68.0%, respectively). The median DOR was 18.9 months (95% CI: NR) with combination group and 21.5 months (95% CI: 12.2–30.7) with immunotherapy group; 50 (69.4%) of 72 patients in the combination group and 15 (48.4%) of 31 patients in the immunotherapy group had an ongoing response at the time of data cutoff (**Table 2**). PFS was significantly reduced in monotherapy arm [(combination vs. immunotherapy) HR:

TABLE 1A | Population characteristics.

Characteristic	Immunotherapy (*N* = 178)	Combination (*N* = 147)	*P*-value
Age (mean ± SD, y)	63.3 ± 8.5	60.9 ± 8.9	0.013
ECOG PS, *n* (%)			
1	178 (100.0)	147 (100.0)	
Gender, n (%)			
Male	147 (82.6)	113 (76.9)	0.200
Female	31 (17.4)	34 (23.1)	
BMI, *n* (%)			
<18.5, underweight	17 (9.6)	4 (2.7)	0.674
18.5–22.9, normal	64 (36.0)	65 (44.1)	
23.0–24.9, overweight	44 (24.7)	37 (25.2)	
≥25, obesity	53 (29.8)	41 (27.9)	
Smoking status, *n* (%)			
Never-smoker	54 (30.3)	52 (35.4)	0.335
Former/active smoker	124 (69.4)	95 (64.6)	
Pack-year of smoking, *n* (%)[a]			
<20	14 (7.9)	15 (10.2)	
20–<40	40 (22.5)	35 (23.8)	0.117
≥40	70 (39.3)	45 (30.6)	
Tumor histology, *n* (%)			
Adenocarcinoma	98 (55.1)	101 (68.7)	0.015
Squamous carcinoma	60 (33.7)	35 (23.8)	
NSCLC	9 (5.1)	1 (0.7)	
Others[b]	11 (6.2)	10 (6.8)	
Metastatic sites, *n* (%)			
Bone	55 (30.9)	48 (32.7)	0.742
Lung/pleura	98 (55.1)	84 (57.1)	
Brain	24 (13.5)	25 (17.0)	
Distant lymph nodes	25 (14.0)	24 (16.3)	
Adrenal glands	19 (10.7)	11 (7.5)	
Liver	13 (7.3)	10 (6.8)	
Others[c]	18 (10.1)	9 (6.1)	
EGFR, *n* (%)			
Mutation[d]	23 (12.9)	14 (9.5)	0.004
Wild-type	132 (74.2)	128 (87.1)	
Unknown	23 (12.4)	5 (3.4)	
PD-L1, *n* (%)			
Negative or <25%	34 (19.1)	37 (25.2)	0.416
≥25%	33 (8.5)	26 (17.7)	
Unknown	111 (62.4)	84 (57.1)	

[a] *Packs per day × years smoked in ever smokers;*

[b] *Immunotherapy: 2 neuroendocrine tumors, 1 severe dysplasia, 1 sarcomatoid carcinoma, 1 adenosquamous carcinoma, 6 malignant tumors; Combination: 2 lymphoepithelioma-like carcinomas, 3 adenosquamous tumors, 4 malignant tumors, 1 neuroendocrine carcinoma.*

[c] *Immunotherapy: 8 soft tissues, 5 peritoneum, 3 pancreases, 2 kidneys; Combination: 6 soft tissues, 2 peritoneum, 1 kidney.*

[d] *Immunotherapy: 19 del (5 cases), 21 L858R (10 cases), 21 L858R and 20 S786I (1 case), EGFR 20 T790M and S786I (1 case), 20 S786I (1 case), 21 L861Q (1 case), 21 L861R (1 case), 21 L858R and 20 T790M (1 case), and non-sensitive EGFR mutations (2 cases); Combination: 19 del (4 cases), 21 L858R (3 cases), 21 L858R and 20 S786I (1 case), 21 L858R and 20 T790M (1 case), 19 del and 20 T790M (2 cases), and non-sensitive EGFR mutations (3 cases).*

PS, Performance Status; SD, standard deviation; BMI, body mass index; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; IO, immunotherapy alone; Chemo, chemotherapy.

TABLE 1B | Characteristics of treatment regimens.

Characteristic, *N* (%)	Immunotherapy (*N* = 178)	Combination (*N* = 147)	*P*-value
Previous treatment lines			
None	33 (18.5)	114 (77.6)	<1*10^(−6)
1L	109 (61.2)	19 (12.9)	
≥2L	36 (20.2)	14 (9.5)	
ICI			
Nivolumab	98 (55.1)	9 (6.1)	<1*10^(−6)
Pembrolizumab	25 (14.0)	50 (34.0)	
Tislelizumab	11 (6.2)	46 (31.3)	
Sintilimab	15 (8.4)	18 (12.2)	
Toripalimab	4 (2.2)	4 (2.7)	
Camerelizumab	0 (0)	1 (0.7)	
Atezolizumab	5 (2.8)	19 (12.9)	
Durvalumab	20 (11.2)	0 (0)	
Target of ICI			
PD-1	153 (86.0)	128 (87.1)	0.769
PD-L1	25 (14.0)	19 (12.9)	
Chemotherapeutic			
Pemetrexed		90 (60.5)	
Paclitaxel		19 (12.9)	
Nab-Paclitaxel		15 (10.2)	
Docetaxel		14 (9.5)	
Gemcitabine		5 (3.4)	
Others[a]		4 (2.7)	
Maintenance treatment			
IO+Chemo		60 (40.8)	
IO		32 (21.8)	
Chemo		7 (4.8)	

[a] *Three patients received vinorelbine therapies; 1 patient received etoposide therapy.*

0.430, 95% CI: 0.319–0.579, log-rank $p < 1*10^{(-6)}$] (**Figure 1A**). The median OS for combination treatment has not been reached [(combination vs. immunotherapy) HR: 0.296, 95% CI: 0.171–0.511, log-rank $P = 4*10^{(-6)}$] (**Figure 1B**). Reasons for drug withdrawal are mainly progression disease (**Figure 1C**). However, there was no significant difference in the scores of tumor burden between them ($P = 0.284$; **Figure 1D**; **Table 2**). The predominant sites for disease progression after ICIs were shown in **Figure 1F**, there was no significant difference between those two groups except soft tissue ($P = 0.016$) (baseline metastases were demonstrated in **Figure 1E**, no significant difference was found).

Subgroup analyses revealed that almost all subgroups were significantly associated with improved PFS in combination group, except for EGFR mutation, previous treatment line = 1 and baseline liver, adrenal gland, or lymph node metastasis (**Supplementary Figure 1A**). Similar results were demonstrated in OS, whereas patients with brain, liver, distant lymph node or adrenal gland metastases, 1 or ≥2 previous treatment lines, PD-L1 TPS expression <25%, EGFR mutation and overweight were not associated with better OS in the combination group

TABLE 2 | Treatment efficacy results.

Characteristic	Immunotherapy (*N* = 178)	Combination (*N* = 147)	*P*-value
Best response, *n* (%)			
Partial response	31 (17.4)	72 (49.0)	<1*10^(−6)
Stable disease	75 (42.1)	62 (42.2)	
Progressive disease	72 (40.4)	13 (8.8)	
ORR[a], *n* (%) [95% CI]	27 (15.2) [9.8–20.5]	64 (43.5) [35.4–51.6]	<1*10^(−6)
DCR[b], *n* (%) [95% CI]	72 (40.4) [33.2–47.7]	100 (68.0) [60.4–75.7]	1*10^(−6)
DOR, months, median (95% CI)	21.5 (12.2–30.7)	18.9 (NR-NR)	0.803
TTF, months, median (95% CI)	3.6 (1.5–5.8)	9.8 (7.5–12.1)	1.2*10^(−5)
PFS, months, median (95% CI)	4.6 (2.1–7.1)	15.5 (9.8–21.3)	<1*10^(−6)
OS, months, median (95% CI)	24.8 (16.3–33.3)	NR (NR-NR)	4*10^(−6)
Scores of tumor burden, mean ± SD	1.45 ± 0.67	1.56 ± 0.70	0.284

[a] *The proportion of patients with CR or PR for at least 6 months;*
[b] *The proportion of patients with CR or PR or SD for at least 6 months;*
ORR, objective response rate; DCR, disease control rate; DOR, duration of response; TTF, time to failure; PFS, progression-free survival; OS, overall survival.

(**Supplementary Figure 1B**). Furthermore, multivariate analysis demonstrated that the PD-L1 ≥25% or unknown, 0, 1, or ≥2 previous treatment lines and obesity were related with better PFS or OS of patients with advanced-stage NSCLC (**Supplementary Tables 2, 3**; **Supplementary Figure 2**).

Conclusively, the efficacy observed in the combination group was better and not due to higher PD-L1 expression or less previous treatment.

Distinct Baseline Metastases Have Differential Outcomes

Given that metastasis is the dominant lethal event in NSCLC patients, most immunotherapy trials set stringent requirements for the eligible participants. Our study showed that, in patients with baseline bone metastases, the combination group provided an survival benefit when compared with monotherapy [median OS (95% CI): NR (NR–NR) vs. 18.3 (9.2–27.3), HR (95% CI): 0.271 (0.118–0.625); median PFS (95% CI): 8.4 (6.0–10.8) vs. 2.4 (0.2–4.6), HR (95% CI): 0.460 (0.287–0.736); **Figures 2A,B**]. Similar trend of PFS benefit was demonstrated in patients with liver, adrenal gland or distant lymph node metastases when received combination treatment though no statistically significant differences were found (Log Rank test); and no univariate benefit in OS was observed in those three subgroups. Considering the small number of patients with liver, adrenal gland or lymph node metastasis (23/325, 7.1%; 30/325, 9.2%; 49/325, 15.1%, respectively, **Figures 2C–J**), further research is warranted.

The incidence of brain metastasis is apparently high in advanced NSCLC. The current standard regimen is becoming, early local therapies before or in conjunction with ICIs (13, 14). In order to evaluate the efficacy of immunotherapy, patients with target brain metastases (15) [without receiving whole-brain radiotherapy (WBRT) or stereotactic radiosurgery (SBS)] before immunotherapy were analyzed. The basic characteristics are shown in **Table 3** and **Figure 3A**. Of patients with ICI alone, 2/11 (18.2%) had brain metastasis responses (CR; **Figure 3B**). The confirmed central nervous system (CNS) responses were durable (at data cutoff, responses had lasted 35.27, 4.23 months, respectively), but one patient discontinued ICI due to progression of pulmonary lesions. 2/11 (18.2%) patients had SD and 6/11 (54.5%) patients had PD in the CNS. 1/11 (9.1%) patient was unconfirmed in the CNS due to sudden death caused by rapid systemic progression. In contrast, all patients received combination treatment had brain lesion responses. The best response was CR in 1/3 (33.3%) patient. 2/3 (67.7%) patients had PR in the brain, although one patient had PD within half a year. Another patient with PR remained on treatment at data cutoff. In conclusion, combination ICI with chemotherapy has demonstrated a survival benefit for metastatic NSCLC patients.

Adverse Events and Outcomes

Notable trAEs that were in a higher incidence rate in the combination vs. immunotherapy group (≥1.5 times) were elevated transaminase or bilirubin, myelosuppression, electrolyte disturbance, ECG abnormalities, myalgia, dysfunction of intestine, constipation, nausea, and vomiting, hyperglycemia, pyrexia, alopecia, elevated creatinine and peripheral neuropathy (**Table 4**, **Supplementary Table 5**). Whereas, the incidence of hypothyroidism (≥1.5 times) was higher in immunotherapy arm. With these exceptions, the occurrence rates of dash, fatigue, hyperthyroidism, pneumonitis, decreased appetite, xerostomia, diarrhea, and hypertension were similar. Serious AEs (SAEs; stages 3–4) were reported in 10 (5.6%) patients from the immunotherapy group and 56 (38.1%) patients from the combination group (**Supplementary Table 4**). The SAEs were primarily related to myelosuppression in the Combination arm, of which the incidence rate was 32.7% (48/147). Of the SAEs that resulted in treatment delay ($n = 17$, 9.6%; $n = 31$, 21.1%, respectively), 12 (6.7%) and 20 (13.6%) patients were considered related to ICIs, respectively. Moreover, 12 (6.7%) patients in immunotherapy arm (7 interstitial lung disease cases, three

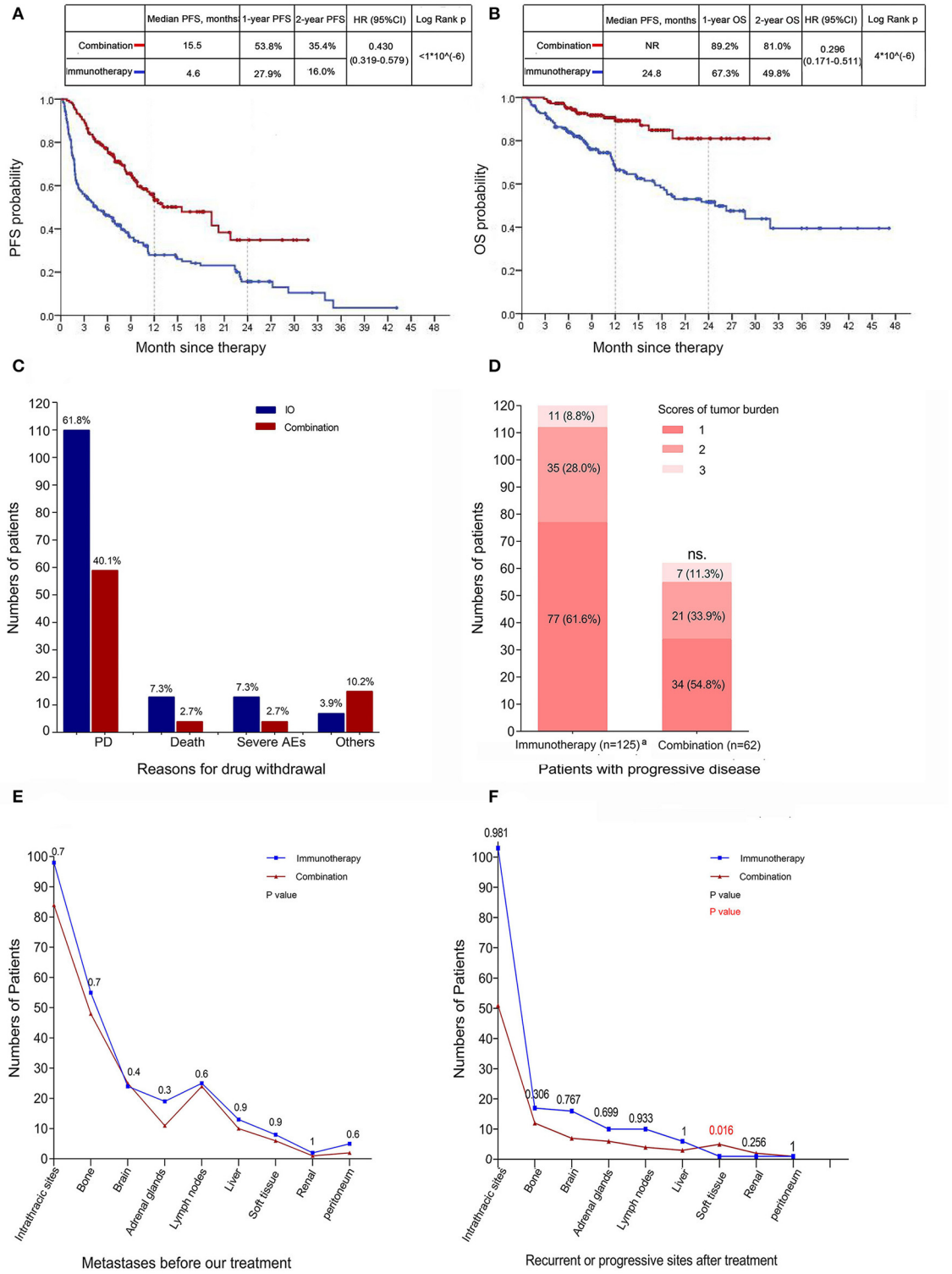

FIGURE 1 | Outcomes of advanced lung cancer patients treated with ICI alone or in combination with chemotherapy. **(A,B)** PFS and OS in tumors treated with immunotherapy alone ($n = 178$) or in combination with chemotherapeutics ($n = 147$) [HR 0.430, 95% CI 0.319–0.579, log-rank $p < 1*10^{(-6)}$]. **(C)** Reasons for drug withdrawal in tumors from patients received immunotherapy or combination therapy. **(D)** Tumor burden scores of patients with progressive disease in different group ($P = 0.284$). **(E,F)** Metastases before our treatment **(E)** and recurrent or progressive sites after immunotherapy **(F)** were shown. Statistical analysis for Kaplan-Meier plots used the log-rank test and statistical analysis for progressive sites used Chi-square test; tumor burden score was tested by Independent samples *t*-test. PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval. [a]Information on disease progression in two patients was not available.

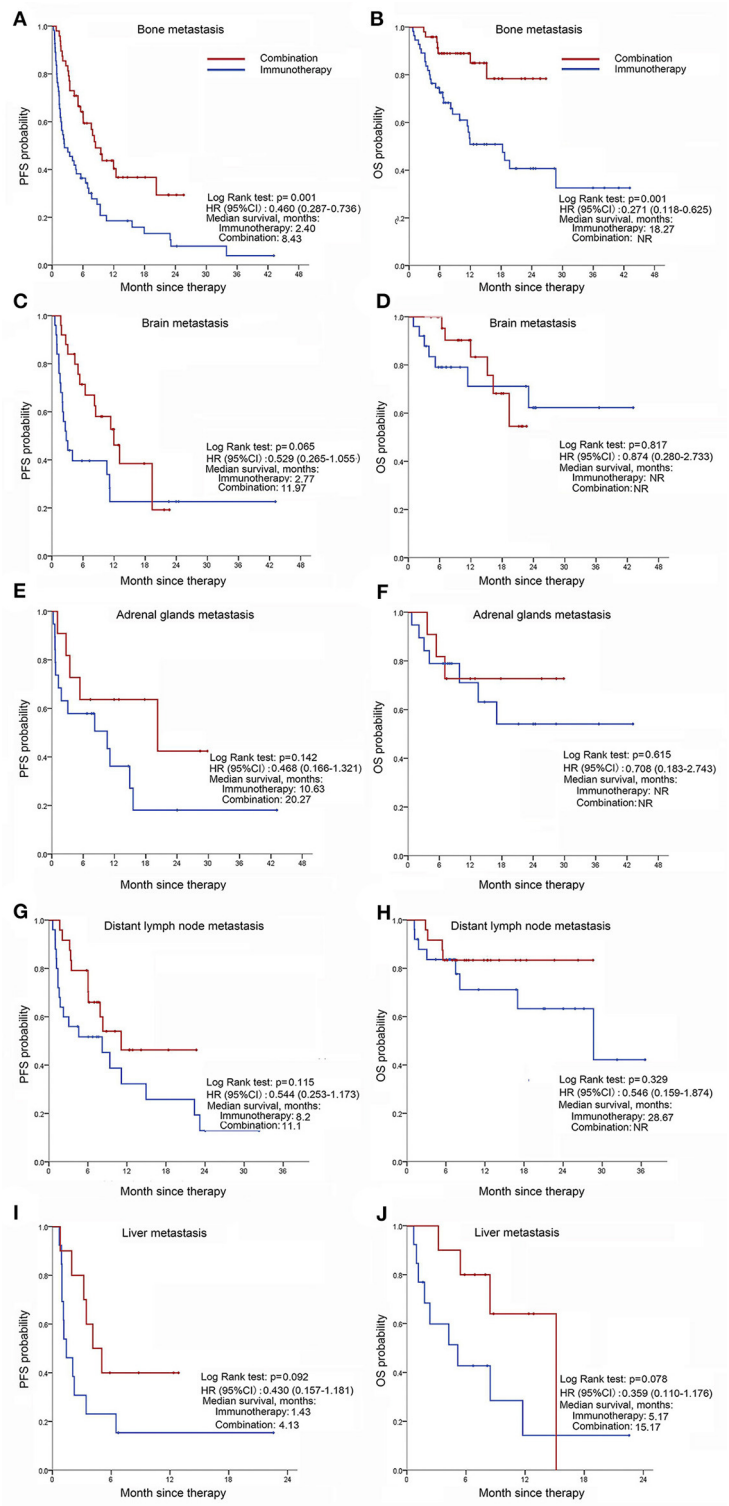

FIGURE 2 | Distant metastases before immunotherapy associated with progression-free survival, and overall survival of tumors treated differently. **(A,B)** PFS **(A)** and OS **(B)** in patients with bone metastasis that had ICI monotherapy or in combination with chemotherapy; **(C,D)** PFS **(C)** and OS **(D)** in patients with brain metastasis that received immunotherapy alone or in combination with chemotherapy; **(E,F)** PFS **(E)** and OS **(F)** in patients with adrenal gland metastasis that had anti-PD-(L)1 antibody therapy or in combination with chemotherapeutics; **(G,H)** PFS **(G)** and OS **(H)** in patients with distant lymph node metastasis treated with ICI monotherapy or in combination with chemotherapy; **(I,J)** PFS **(I)** and OS **(J)** in patients with liver metastasis treated differently.

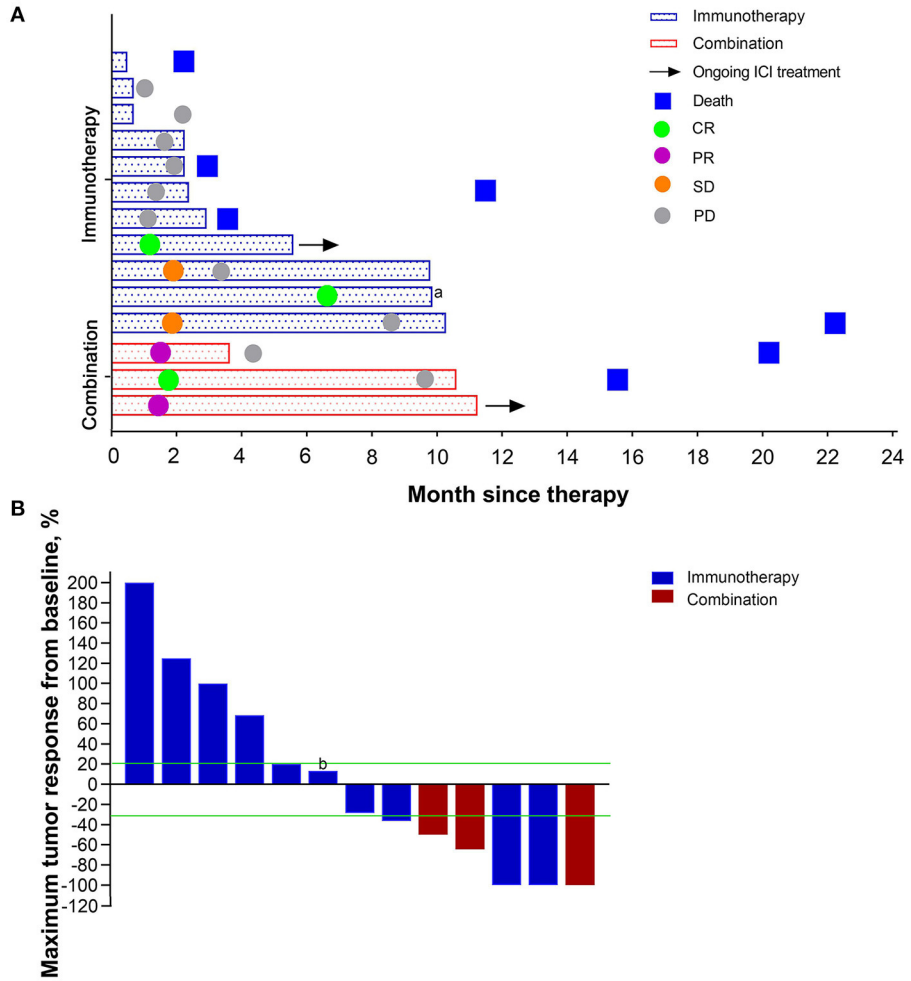

FIGURE 3 | The responses and outcomes of patients with targeted brain metastases received immunotherapy alone or chemo-immunotherapy. **(A)** Time to brain metastasis response and duration of treatment. Bars represent individual patients who received immunotherapy. **(B)** Best brain metastasis response in assessable patients. The lower dashed line represents the −30% cut-off that defines an objective response. And the upper dashed line represents 20% cut-off that defines progression disease. CR, complete response; PR partial response; SD, stable disease; PD, progressive disease. [a]One patient had developed progression of lung tumors and withdrew from immunotherapy despite 100% shrinkage of brain metastasis. [b]One patient had progressive disease despite <20% enlargement due to the development of new brain metastasis.

hypothyroidism cases, one ICI-related encephalitis and one fatigue case) and 5 (3.4%) patients in combination arm (two interstitial lung disease cases, two dash cases, and one ICI-related myocarditis case) withdrew from treatment due to SAEs. Up to now, no treatment-related death was reported. Similar results were obtained in irAEs (**Supplementary Table 6**). All AEs were assessed by at least three independent medical professionals. Overall, no significant increase in the risk of irAEs was found after combination treatment.

In our study, outcomes of patients with and without early irAEs (16) were shown in **Supplementary Figure 3**. The analysis showed that the development of early irAEs was significantly associated with increased PFS in immunotherapy arm [log-rank $P = 0.053$; multivariate HR (95% CI), 0.621 (0.411–0.941), $P = 0.024$], which were consistent with previous studies (16, 17). However, similar trend was not found in combination group (**Supplementary Figures 3, 4**).

Patients with irAEs after 1 or 2–3 cycles of ICI-alone therapy had moderate prognosis; non-irAE predicted poorest outcome; while patients with late irAEs (≥4 cycles) had best outcomes [(irAEs after four or more cycles vs. non-irAEs) PFS: multivariate HR (95% CI), 0.220 (0.128–0.378), $p < 1*10^{(-6)}$; OS: multivariate HR (95% CI), 0.403 (0.192–0.844), $P = 0.016$] in the immunotherapy group (**Figure 4**). Conclusively, irAEs predicted better outcomes of immunotherapy, especially for patients with late irAEs.

DISCUSSION

In this real-world study, we assembled a cohort of 325 patients with advanced NSCLC treated with ICI to retrospectively investigate which treatment scenario is the most efficient: ICI monotherapy or in combination with chemotherapy, and how

TABLE 3 | Baseline characteristics of patients with target brain metastases.

Characteristic	Immunotherapy (*N* = 11)	Combination (*N* = 3)
Age (mean ± SD, y)	63.27 ± 9.21	66.00 ± 8.19
Gender, *n* (%)		
Male	7 (63.6%)	3 (100%)
ECOG performance status, *n* (%)		
0–1	11 (100%)	3 (100%)
Tumor histology, *n* (%)		
Adenocarcinoma	9 (81.8%)	3 (100%)
Squamous cell carcinoma	1 (9.1%)	0 (0%)
NSCLC	0 (0%)	0 (0%)
Other	1 (9.1%)	0 (0%)
PD-L1 status, *n* (%)		
Known	6 (54.5%)	1 (33.3%)
Positive	5 (45.5%)	1 (33.3%)
≥25%	3 (27.3%)	1 (33.3%)
Numbers of target brain lesions per patient, mean ± SD	1.36 ± 0.924	1.33 ± 0.577
Total number of targeted lesions		
Previously untreated	15	4
Progressing after previous treatment	0	0
Size of all target lesions (mm)	158.35	30.23
Lines of ICIs, *n* (%)		
1	3 (27.3%)	3 (100%)
2	8 (72.7%)	0 (0%)
≥3	0 (0%)	0 (0%)

clinical factors impact response and survival of those patients. The combination group demonstrated promising anti-tumor activity and an acceptable side-effect profile regardless of PD-L1 level or previous treatment lines. Both regimens were well-tolerated, the more efficient is usually recommended.

Currently, there are many controversial issues regarding immunotherapy in the real-world practice. Firstly, the lack of direct cross-comparison studies in clinical trials between ICI monotherapy and chemo-immunotherapy. Secondly, the low detection rate and positive predictive value (19, 20) of PD-L1 or tumor mutation burden (TMB) in clinical practice of immunotherapy. Thirdly, ICI alone have demonstrated minimal benefit in liver metastases [a common metastasis and a negative prognostic indicator for lung cancer (21, 22)]. Some combination regimens were investigated in various randomized phase III studies (23, 24), but the final conclusion is still pending. Lastly, severe irAEs require high-dose intravenous steroids and even temporary or permanent discontinuation of ICIs (25). But the occurrence of irAEs was related to better outcomes in NSCLC subjects treated with ICIs (16, 17). How to balance between safety and efficacy of ICIs in the clinical practice? Our study has partially answered those issues.

Preclinical data have emerged suggesting that chemotherapy can significantly enhance the efficacy of certain forms of cancer immunotherapy (26). But the exact mechanism is still unclear. For one thing, studies have indicated that local chemotherapy combined with anti-PD-1 antibody facilitates an antitumor immune response and improves survival ($p < 0.001$) in glioblastoma, but addition of systemic chemotherapy to anti-PD-1 treatment resulted in systemic and intratumoral lymphodepletion, with decreased immune memory in long-term survivors (27); and the toxicity of some chemotherapeutic agents to immune cells limits the extent of immune stimulation and can lead to immunosuppression (28). For another, other researchers have demonstrated that certain conventional chemotherapies may have positive effects on tumor immunity: chemotherapy-induced immunogenic cell death activates innate immune responses and elicits a tumor-specific adaptive immune response (29, 30); it can directly block immunosuppressive pathways in the tumor microenvironment (TME) (31, 32).

Emerging data from clinical trials demonstrated that chemo-immunotherapy combination had better efficacy than ICI alone in certain clinical scenarios. We summarized these results in **Supplementary Table 7**. The survival benefits of combination treatment were significantly higher than ICI monotherapy. In the high PD-L1 cohort, the combinations of chemotherapy with ICIs were overall the better treatments regarding PFS; in the low PD-L1 arm (including negative), all combinations with chemotherapy examined (pembrolizumab, atezolizumab, nivolumab) showed superior outcomes to immunotherapy-alone regarding PFS and OS. Similar results were shown in our study, especially for patients with unknown PD-L1 status (195/325, 60%), which had longer PFS and OS in the combination group compared with the ICI monotherapy. When talking for the patients with PD-L1 ≥50%, it requires more prospective or external cohort data to further confirm whether combination treatment would be better as first-line treatment or not (**Supplementary Table 2**).

For most subgroups, the magnitude of treatment efficacy was greater in the combination arm than ICI-alone arm. Interestingly, we found that immunotherapy/chemotherapy seems to benefit more men than women [(median PFS, moths) monotherapy arm 6.27, 2.23, respectively, combination arm 15.53, 9.47, respectively]. However, different studies have different conclusions (33, 34). In addition, patients who smoke responded better to ICI combination therapies than non-smokers, which is consistent with previous studies (35, 36). And fundamental research had revealed that higher level of aryl hydrocarbon receptor (AhR) may play a role (37). BMI ≥25 was correlated with better outcomes of patients treated with ICI monotherapy according to previous studies (38), and our results also found that patients in the Combination arm had a similar trend (**Supplementary Figure 2**). Overweight could be considered a tumorigenic immune-dysfunction that could be effectively reversed by ICIs (39, 40). ICI combination treatment can improve outcomes in metastatic NSCLC patients according to our subgroup analyses, but a larger cohort of patients is necessary.

Safety is another primary concern. Our results revealed that patients with irAEs had longer PFS in ICI alone group, while no evidence showed that the occurrence of toxicity in

TABLE 4 | Incidence of treatment-related adverse events (trAEs)[a].

Events, *N* (%)	Immunotherapy (*N* = 178)					Combination (*N* = 147)				
	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4
Any adverse event	91 (51.1)					126 (85.7)				
Dash	34 (19.1)	27 (15.2)	6 (3.4)	1 (0.6)	0 (0)	33 (22.4)	24 (16.3)	3 (2.0)	4 (2.7)	2 (1.4)
Fatigue	30 (16.9)	27 (15.2)	0 (0)	2 (1.1)	0 (0)	33 (22.4)	28 (12.0)	5 (3.4)	0 (0)	0 (0)
Hyperthyroidism	20 (11.2)	19 (10.7)	1 (0.6)	0 (0)	0 (0)	13 (8.8)	13 (8.8)	0 (0)	0 (0)	0 (0)
Hypothyroidism	20 (11.2)	10 (5.6)	10 (5.6)	0 (0)	0 (0)	10 (6.8)	10 (6.8)	0 (0)	0 (0)	0 (0)
Elevated transaminase or bilirubin	16 (9.0)	15 (8.4)	0 (0)	1 (0.6)	0 (0)	39 (26.5)	34 (23.1)	2 (1.4)	2 (1.4)	1 (0.7)
Pneumonitis	15 (8.4)	2 (1.1)	10 (5.6)	1 (0.6)	2 (1.1)	15 (10.2)	5 (3.4)	7 (4.8)	3 (2.0)	0 (0)
Decreased appetite	11 (6.2)	11 (6.2)	0 (0)	0 (0)	0 (0)	9 (6.1)	8 (5.4)	1 (0.7)	0 (0)	0 (0)
Myelosuppression	10 (5.6)	5 (2.8)	3 (1.7)	2 (1.1)	0 (0)	106 (72.1)	22 (15.0)	36 (24.5)	33 (22.4)	15 (10.2)
Electrolyte disturbance	8 (4.5)	8 (4.5)	0 (0)	0 (0)	0 (0)	10 (6.8)	8 (5.4)	1 (0.7)	1 (0.7)	0 (0)
ECG abnormalities[b]	7 (3.9)	6 (3.4)	1 (0.6)	0 (0)	0 (0)	10 (6.8)	8 (5.4)	0 (0)	1 (0.7)	1 (0.7)
Myalgia	4 (2.2)	3 (1.7)	1 (0.6)	0 (0)	0 (0)	11 (7.5)	8 (5.4)	2 (1.4)	1 (0.7)	0 (0)
Constipation	3 (1.7)	3 (1.7)	0 (0)	0 (0)	0 (0)	6 (4.1)	5 (3.4)	1 (0.7)	0 (0)	0 (0)
Diarrhea	2 (1.1)	2 (1.1)	0 (0)	0 (0)	0 (0)	2 (1.4)	1 (0.7)	0 (0)	1 (0.7)	0 (0)
Nausea, vomiting	2 (1.1)	1 (0.6)	1 (0.6)	0 (0)	0 (0)	15 (10.2)	12 (8.2)	2 (1.4)	1 (0.7)	0 (0)
Hyperglycemia	2 (1.1)	2 (1.1)	0 (0)	0 (0)	0 (0)	13 (8.8)	13 (8.8)	0 (0)	0 (0)	0 (0)
Diarrhea	2 (1.1)	2 (1.1)	0 (0)	0 (0)	0 (0)	2 (1.4)	1 (0.7)	0 (0)	1 (0.7)	0 (0)
Hypertension	2 (1.1)	0 (0)	0 (0)	2 (1.1)	0 (0)	2 (1.1)	0 (0)	2 (1.1)	0 (0)	0 (0)
Myocarditis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.7)	0 (0)

[a] *The cutoff date was May 26, 2019; trAEs with an incidence of more than 5% are listed, and all grades 3–4 trAEs are listed.*
[b] *Arrhythmias, prolonged QT interval, inverted T wave, etc.*
ECG, electrocardiogram.

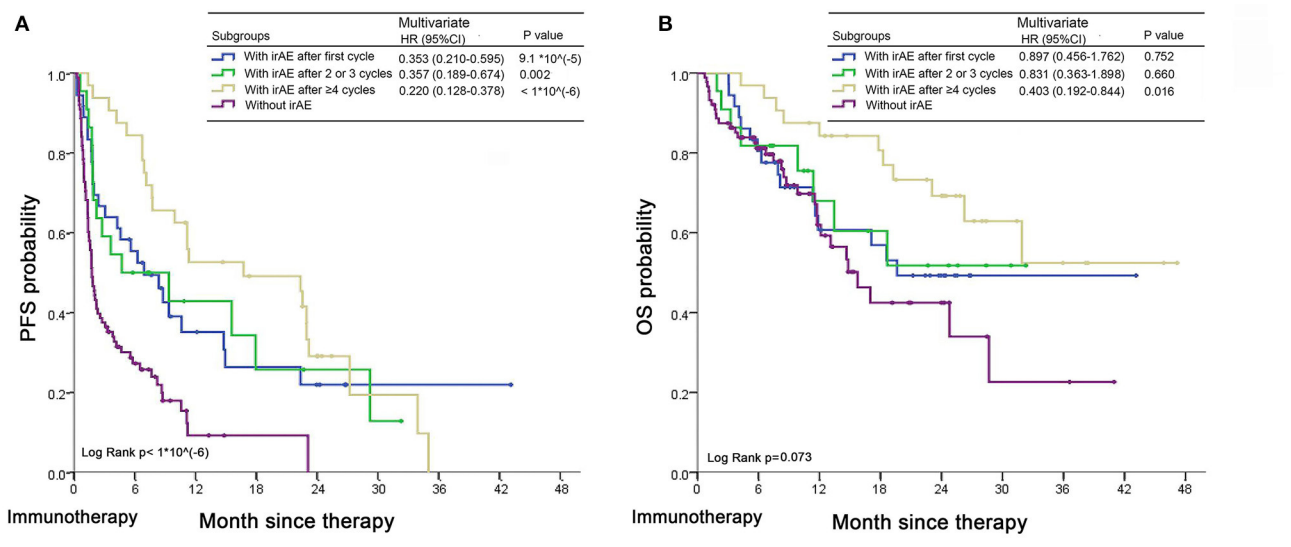

FIGURE 4 | Time to onset irAEs and association with outcomes in advanced NSCLC patients treated with ICI monotherapy. **(A,B)** Kaplan-Meier curves of PFS **(A)** and OS **(B)** in patients with early (after 1–3 cycles), late (after four or more cycles) or without irAEs after commencement of ICI therapy. The multivariate HRs, 95% CIs and *P*-values were analyzed using a stratified Cox proportional hazards model taking into account gender (male, female), age (<65, ≥65), BMI (18) (<18.5, 18.5–22.9, 23–24.9, ≥25), smoking status (non-smoker, smoker), histology (adenocarcinoma, squamous carcinoma, NSCLC, neuroendocrine neoplasm, others), EGFR mutation (wild-type, mutation, unknown), PD-L1 expression level (<25%, ≥25%, unknown) and previous treatment lines (0, 1, ≥2). Log Rank *p*-values were calculated by log-rank test.

the combination arm for patients is related to the efficacy. Previous studies have demonstrated that patients treated with immunotherapy with early irAEs had better outcomes (16, 17), nevertheless, other researches showed that the response of immunotherapy had no relationship with the side effects (41). Therefore, more research is needed on the relationship between efficacy and toxicity.

However, rational combination of chemotherapy and immunotherapy faces many challenges (42): the requirement for an accurate predictive biomarker of efficacy; optimization efficacy, safety and tolerability through appropriate drug ratios, dosing and scheduling; and possible combination approaches for patients who had low response rates after immunotherapy (such as EGFR mutations, liver metastasis and so on). The proportion of NSCLC patients with PD-L1 $\geq$50% was around 30% (43). In the real world, accurate expression level of PD-L1 is largely unknown (60%, our result). And the dynamics of PD-L1 expression may limit its use as a tissue-based predictive biomarker (44, 45). TMB also has many limitations (46, 47). To address the first challenge, we should make further efforts to deepen the mechanism study and careful design of biomarker exploratory studies. Recently, the number of ICIs and clinical trials of ICI combination treatment have growth rapidly. Different doses (36), sequencing possibilities (48, 49), combination therapy regimens (23, 50), and inclusion criteria (PD-L1 level, driver genes, PS ECOG and so on) (5, 9, 51) have different outcomes. Under the premise of ensuring safety, it is not an easy task to decide which regimen is best. Undoubtedly, it is unwise to simply increase the number of drugs in combination therapy. Comprehensive analysis of our study and clinical trials, the approach of ICI plus chemotherapy might have better anti-tumor activity than ICI monotherapy regardless of PD-L1 level in advanced NSCLC patients.

Our study has several limitations. Firstly, this research was a single-center retrospective study with a limited sample, inevitably, the AEs could be underreported due to the retrospective nature. The prospective or external cohort validations were needed to verify in the future. Secondly, there is 60% patients in this study without PD-L1 expression data. It is well-known that PD-L1 plays a crucial role in the progression of tumor by altering status of immune surveillance. KEYNOTE-024 study showed that pembrolizumab was associated with significantly longer PFS and OS, and is preferred as 1L treatment in advanced NSCLC with PD-L1 $\geq$50%. However, the ability of PD-L1 level to predict efficacy of immunotherapy in NSCLC is controversial (52, 53). TMB, neutrophil-to-lymphocyte ratio, MSI and some other biomarkers have also been reported to be predictive. Therefore, PD-L1 combined with other clinical biomarkers could benefit to predict the outcomes of immunotherapy. Thirdly, patients in the immunotherapy alone group at later line were relatively more, and patients in the immunotherapy combination group at first-line were relatively more, while this is the characteristic and real record of the real-world research. To balance the discrepancy and the multiple confounding factors, we did the cox proportional analysis in overall patients taking account into the number of treatment lines as a confounding factor. The results show that chemo-immunotherapy group had better PFS and OS in the multivariate analysis. Further univariate analysis among the first-line, second-line or later line, respectively repeated that combination treatment had better survival in each group (**Supplementary Table 2**). More prospective and external cohort validations are required to further confirm our results.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Shanghai Chest Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

XN and ZC: administrative support. XW, XN, and ZC: provision of study materials or patients. XW and XN: collection and assembly of data. XW, NA, and YS: data analysis and interpretation. All authors: conception, design, drafting manuscript, and final approval of manuscript.

FUNDING

This work was supported by Project of China Center for Evidence Based Traditional Chinese Medicine [ZXZL-6], the National Natural Science Foundation of China [No. 81972187], Projects of the Committee of Shanghai Science and Technology [No. 19ZR1449800 and 20Y11913700], Clinical Research Project of Shanghai Municipal Public Health Bureau [No. 201840122], Advanced Appropriate Technology Promotion Project of Shanghai Municipal Public Health Bureau [No. 2019SY048], Doctoral Innovation Fund of Shanghai Jiao Tong University School of Medicine [No. BXJ201952], and Interdisciplinary Program of Shanghai Jiao Tong University [No. YG2017MS80], and Project of Shanghai Talent Development Fund (No. 2019074).

ACKNOWLEDGMENTS

The authors acknowledge all the health care workers at Shanghai Chest Hospital.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.611012/full#supplementary-material

REFERENCES

1. Kazandjian D, Suzman DL, Blumenthal G, Mushti S, He K, Libeg M, et al. FDA approval summary: nivolumab for the treatment of metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy. *Oncologist*. (2016) 21:634–42. doi: 10.1634/theoncologist.2015-0507
2. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. (2019) 393:1819—30. doi: 10.1016/S0140-6736(18)32409-7
3. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. (2018) 379:2040–51. doi: 10.1056/NEJMoa1810865
4. Jotte R, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Rodríguez-Abreu D, Hussein M, et al. Atezolizumab in combination with carboplatin and nab-paclitaxel in advanced squamous NSCLC (IMpower131): results from a randomized phase III trial. *J Thorac Oncol*. (2020) 15:1351–60. doi: 10.1016/j.jtho.2020.03.028
5. Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, Domine M, et al. Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. (2020) 21:387–97. doi: 10.1016/S1470-2045(19)30801-0
6. Ettinger DS, Wood DE, Aggarwal C, Aisner DL, Akerley W, Bauman JR, et al. NCCN guidelines insights: non-small cell lung cancer, version 1.2020. *J Natl Compr Canc Netw*. (2019) 17:1464—72. doi: 10.6004/jnccn.2019.0059
7. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. (2015) 373:123–35. doi: 10.1056/NEJMoa1504627
8. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. (2018) 378:2288–301. doi: 10.1056/NEJMoa1716948
9. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fülöp A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. (2016) 375:1823–33. doi: 10.1056/NEJMoa1606774
10. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. (2016) 387:1540–50. doi: 10.1016/S0140-6736(15)01281-7
11. Yang JJ, Chen HJ, Yan HH, Zhang XC, Zhou Q, Su J, et al. Clinical modes of EGFR tyrosine kinase inhibitor failure and subsequent management in advanced non-small cell lung cancer. *Lung Cancer*. (2013) 79:33–9. doi: 10.1016/j.lungcan.2012.09.016
12. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. *Chest*. (2009) 136:260–71. doi: 10.1378/chest.08-0978
13. Page S, Milner-Watts C, Perna M, Janzic U, Vidal N, Kaudeer N, et al. Systemic treatment of brain metastases in non-small cell lung cancer. *Eur J Cancer*. (2020) 132:187–98. doi: 10.1016/j.ejca.2020.03.006
14. Achrol AS, Rennert RC, Anders C, Soffietti R, Ahluwalia MS, Nayak L, et al. Brain metastases. *Nat Rev Dis Primers*. (2019) 5:5. doi: 10.1038/s41572-018-0055-y
15. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. (2016) 17:976–83. doi: 10.1016/S1470-2045(16)30053-5
16. Teraoka S, Fujimoto D, Morimoto T, Kawachi H, Ito M, Sato Y, et al. Early immune-related adverse events and association with outcome in advanced non-small cell lung cancer patients treated with nivolumab: a prospective cohort study. *J Thorac Oncol*. (2017) 12:1798–805. doi: 10.1016/j.jtho.2017.08.022
17. Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. *JAMA Oncol*. (2018) 4:374–8. doi: 10.1001/jamaoncol.2017.2925
18. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. (2004) 363:157–63. doi: 10.1016/S0140-6736(03)15268-3
19. Sacher AG, Gandhi L. Biomarkers for the clinical use of PD-1/PD-L1 inhibitors in non-small-cell lung cancer: a review. *JAMA Oncol*. (2016) 2:1217–22. doi: 10.1001/jamaoncol.2016.0639
20. Ng TL, Liu Y, Dimou A, Patil T, Aisner DL, Dong Z, et al. Predictive value of oncogenic driver subtype, programmed death-1 ligand (PD-L1) score, and smoking status on the efficacy of PD-1/PD-L1 inhibitors in patients with oncogene-driven non-small cell lung cancer. *Cancer*. (2019) 125:1038–49. doi: 10.1002/cncr.31871
21. Vokes EE, Ready N, Felip E, Horn L, Burgio MA, Antonia SJ, et al. Nivolumab versus docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases. *Ann Oncol*. (2018) 29:959–65. doi: 10.1093/annonc/mdy041
22. Sridhar S, Paz-Ares L, Liu H, Shen K, Morehouse C, Rizvi N, et al. Prognostic significance of liver metastasis in durvalumab-treated lung cancer patients. *Clin Lung Cancer*. (2019) 20:e601–8. doi: 10.1016/j.cllc.2019.06.020
23. Reck M, Mok TSK, Nishio M, Jotte RM, Cappuzzo F, Orlandi F, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. *Lancet Respir Med*. (2019) 7:387–401. doi: 10.1016/S2213-2600(19)30084-0
24. West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. (2019) 20:924–37. doi: 10.1016/S1470-2045(19)30167-6
25. Simonaggio A, Michot JM, Voisin AL, Le Pavec J, Collins M, Lallart A, et al. Evaluation of readministration of immune checkpoint inhibitors after immune-related adverse events in patients with cancer. *JAMA Oncol*. (2019) 5:1310–7. doi: 10.1001/jamaoncol.2019.1022
26. Vanmeerbeek I, Sprooten J, De Ruysscher D, Tejpar S, Vandenberghe P, Fucikova J, et al. Trial watch: chemotherapy-induced immunogenic cell death in immuno-oncology. *Oncoimmunology*. (2020) 9:1703449. doi: 10.1080/2162402X.2019.1703449
27. Mathios D, Kim JE, Mangraviti A, Phallen J, Park CK, Jackson CM, et al. Anti-PD-1 antitumor immunity is enhanced by local and abrogated by systemic chemotherapy in GBM. *Sci Transl Med*. (2016) 8:370ra180. doi: 10.1126/scitranslmed.aag2942
28. Shurin MR, Naiditch H, Gutkin DW, Umansky V, Shurin GV. ChemoImmunoModulation: immune regulation by the antineoplastic chemotherapeutic agents. *Curr Med Chem*. (2012) 19:1792–803. doi: 10.2174/092986712800099785
29. Wu J, Waxman DJ. Immunogenic chemotherapy: dose and schedule dependence and combination with immunotherapy. *Cancer Lett*. (2018) 419:210–21. doi: 10.1016/j.canlet.2018.01.050
30. Yu WD, Sun G, Li J, Xu J, Wang X. Mechanisms and therapeutic potentials of cancer immunotherapy in combination with radiotherapy and/or chemotherapy. *Cancer Lett*. (2019) 452:66–70. doi: 10.1016/j.canlet.2019.02.048
31. Obeid M, Tesniere A, Panaretakis T, Tufi R, Joza N, van Endert P, et al. Ecto-calreticulin in immunogenic chemotherapy. *Immunol Rev*. (2007) 220:22–34. doi: 10.1111/j.1600-065X.2007.00567.x
32. Heinhuis KM, Ros W, Kok M, Steeghs N, Beijnen JH, Schellens JHM. Enhancing antitumor response by combining immune checkpoint inhibitors with chemotherapy in solid tumors. *Ann Oncol*. (2019) 30:219–35. doi: 10.1093/annonc/mdy551
33. Conforti F, Pala L, Bagnardi V, De Pas T, Martinetti M, Viale G, et al. Reply to Jeffrey Graham, Omar Abdel-Rahman, Toni K. Choueiri, and Daniel Y.C. Heng's Letter to the Editor re: Fabio Conforti, Laura Pala, Vincenzo Bagnardi, et al. cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. Lancet Oncol 2018;19:737–46: outcomes of metastatic renal cell carcinoma by gender: contrasting results

from the international mRCC database consortium. *Eur Urol*. (2019) 75:e34–5. doi: 10.1016/j.eururo.2018.08.034
34. Wallis CJD, Butaney M, Satkunasivam R, Freedland SJ, Patel SP, Hamid O, et al. Association of patient sex with efficacy of immune checkpoint inhibitors and overall survival in advanced cancers: a systematic review and meta-analysis. *JAMA Oncol*. (2019) 5:529–36. doi: 10.1001/jamaoncol.2018.5904
35. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. (2015) 373:1627–39. doi: 10.1056/NEJMoa1507643
36. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. (2015) 372:2018–28. doi: 10.1056/NEJMoa1501824
37. Wang GZ, Zhang L, Zhao XC, Gao SH, Qu LW, Yu H, et al. The Aryl hydrocarbon receptor mediates tobacco-induced PD-L1 expression and is associated with response to immunotherapy. *Nat Commun*. (2019) 10:1125. doi: 10.1038/s41467-019-08887-7
38. Kichenadasse G, Miners JO, Mangoni AA, Rowland A, Hopkins AM, Sorich MJ. Association between body mass index and overall survival with immune checkpoint inhibitor therapy for advanced non-small cell lung cancer. *JAMA Oncol*. (2020) 6:512–8. doi: 10.1001/jamaoncol.2019.5241
39. Wang Z, Aguilar EG, Luna JI, Dunai C, Khuat LT, Le CT, et al. Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. *Nat Med*. (2019) 25:141–51. doi: 10.1038/s41591-018-0221-5
40. McQuade JL, Daniel CR, Hess KR, Mak C, Wang DY, Rai RR, et al. Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis. *Lancet Oncol*. (2018) 19:310−22. doi: 10.1016/S1470-2045(18)30078-0
41. Horvat TZ, Adel NG, Dang TO, Momtaz P, Postow MA, Callahan MK, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at memorial Sloan Kettering Cancer Center. *J Clin Oncol*. (2015) 33:3193–8. doi: 10.1200/JCO.2015.60.8448
42. Gotwals P, Cameron S, Cipolletta D, Cremasco V, Crystal A, Hewes B, et al. Prospects for combining targeted and conventional cancer therapy with immunotherapy. *Nat Rev Cancer*. (2017) 17:286–301. doi: 10.1038/nrc.2017.17
43. Adam J, Le Stang N, Rouquette I, Cazes A, Badoual C, Pinot-Roussel H, et al. Multicenter harmonization study for PD-L1 IHC testing in non-small-cell lung cancer. *Ann Oncol*. (2018) 29:953–8. doi: 10.1093/annonc/mdy014
44. Mansfield AS, Aubry MC, Moser JC, Harrington SM, Dronca RS, Park SS, et al. Temporal and spatial discordance of programmed cell death-ligand 1 expression and lymphocyte tumor infiltration between paired primary lesions and brain metastases in lung cancer. *Ann Oncol*. (2016) 27:1953–8. doi: 10.1093/annonc/mdw289
45. McLaughlin J, Han G, Schalper KA, Carvajal-Hausdorf D, Pelekanou V, Rehman J, et al. Quantitative assessment of the heterogeneity of PD-L1 expression in non-small-cell lung cancer. *JAMA Oncol*. (2016) 2:46–54. doi: 10.1001/jamaoncol.2015.3638
46. Chan TA, Yarchoan M, Jaffee E, Swanton C, Quezada SA, Stenzinger A, et al. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. *Ann Oncol*. (2019) 30:44–56. doi: 10.1093/annonc/mdy495
47. Heeke, Hofman S. Tumor mutational burden assessment as a predictive biomarker for immunotherapy in lung cancer patients: getting ready for prime-time or not? *Transl Lung Cancer Res*. (2018) 7:631–8. doi: 10.21037/tlcr.2018.08.04
48. Park SE, Lee SH, Ahn JS, Ahn MJ, Park K, Sun JM. Increased response rates to salvage chemotherapy administered after PD-1/PD-L1 inhibitors in patients with non-small cell lung cancer. *J Thorac Oncol*. (2018) 13:106–11. doi: 10.1016/j.jtho.2017.10.011
49. Blumenthal GM, Zhang L, Zhang H, Kazandjian D, Khozin S, Tang S, et al. Milestone analyses of immune checkpoint inhibitors, targeted therapy, and conventional therapy in metastatic non-small cell lung cancer trials: a meta-analysis. *JAMA Oncol*. (2017) 3:e171029. doi: 10.1001/jamaoncol.2017.1029
50. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. (2019) 381:2020–31. doi: 10.1056/NEJMoa1910231
51. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol*. (2016) 17:1497–508. doi: 10.1016/S1470-2045(16)30498-3
52. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med*. (2017) 376:2415–26. doi: 10.1056/NEJMoa1613493
53. Park W, Kwon D, Saravia D, Desai A, Vargas F, El Dinali M, et al. Developing a predictive model for clinical outcomes of advanced non-small cell lung cancer patients treated with nivolumab. *Clin Lung Cancer*. (2018) 19:280–8.e4. doi: 10.1016/j.cllc.2017.12.007

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

REVIEW
published: 18 March 2021
doi: 10.3389/fonc.2021.604227

Immune Check Point Inhibitors and Immune-Related Adverse Events in Small Cell Lung Cancer

*Wanting Hou†, Xiaohan Zhou†, Cheng Yi and Hong Zhu**

Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Small cell lung cancer (SCLC) is a malignant solid tumor. In recent years, although immune check point inhibitors (ICIs) have achieved important advances in the treatment of SCLC, immune-related adverse events (irAEs) have occurred at the same time during the therapeutic period. Some irAEs lead to dose reduction or treatment rejection. The immune microenvironment of SCLC is complicated, therefore, understanding irAEs associated with ICIs is of great importance and necessity for the clinical management of SCLC. However, the lack of comprehensive understanding of irAEs in patients with SCLC remains remarkable. This review aims to provide an up-to-date overview of ICIs and their associated irAEs in patients with SCLC based on present clinical data.

Keywords: small cell lung cancer, immune check point inhibitors (ICIs), immune-related adverse events (irAEs), programmed cell death protein 1 (PD-1), programmed cell death ligand protein 1 (PD-L1), cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)

OPEN ACCESS

Edited by:
Udo S. Gaipl,
University Hospital Erlangen, Germany

Reviewed by:
Yong Lu,
Wake Forest School of Medicine, United States
Carlo Genova,
San Martino Hospital (IRCCS), Italy

***Correspondence:**
Hong Zhu
zhuhonghuaxi@163.com

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Oncology

Received: *09 September 2020*
Accepted: *15 February 2021*
Published: *18 March 2021*

Citation:
Hou W, Zhou X, Yi C and Zhu H (2021) Immune Check Point Inhibitors and Immune-Related Adverse Events in Small Cell Lung Cancer. Front. Oncol. 11:604227. doi: 10.3389/fonc.2021.604227

INTRODUCTION

Lung cancer has jeopardized the health of millions of people worldwide (1). Histologically, lung cancer is usually classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Although NSCLC is diagnosed more often, SCLC is much more likely to be associated with a worse prognosis. SCLC is characterized by rapid growth, early metastasis, and frequent relapse (2) and its diagnoses are further sub-divided into limited-stage SCLC (LS-SCLC) or extensive-stage SCLC (ES-SCLC). LS-SCLC is diagnosed when the diseased region is confined to one hemithorax within a tolerable radiation field, while ES-SCLC is diagnosed when the disease has spread beyond one hemithorax. The prognosis of patients with LS-SCLC is better than those with ES-SCLC, the survival time of patients with LS-SCLC ranges from 15 to 20 months and their 5-year survival rate is ∼20–25%. In comparison, the survival time of patients with ES-SCLC ranges from 8 to 13 months, with a 5-year survival rate of only about 2% (3, 4). Unfortunately, ∼70% of SCLC patients are diagnosed with ES-SCLC (5).

Compared with NSCLC, SCLC's effective therapy regimens are limited. In the past, platinum-based chemotherapy has been the cornerstone of the SCLC therapeutic landscape. The overall response rate (ORR) of ES-SCLC patients receiving first-line chemotherapy is ∼67%, with most patients showing resistance to chemotherapy within a short time and overall survival (OS) of <1 year. Less than 30% of patients are diagnosed with LS-SCLC and they respond well to chemotherapy (ORR: 82–87%). However, preventing relapse and progression is still challenging (6). At present, second-line treatment options for patients with relapsed SCLC are limited. In 2007, the FDA approved topotecan as a second-line treatment option for SCLC. The response rate to topotecan of patients who have relapsed is 20–25%, with a 1-year survival rate of 10–30% (7, 8). Over the years, there are a few new explorations in the therapeutic landscape of SCLC. The success

of immunotherapy for NSCLC is great inspiration for SCLC therapy. Several clinical trials on monoclonal antibodies targeting programmed cell death ligand protein 1 (PD-L1), programmed cell death protein 1 (PD-1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) have been or are currently being conducted for SCLC. The response rate to immunotherapy is lower for SCLC than for other tumors such as NSCLC and melanoma, as a possible result of the lack of biomarkers for choosing beneficial populations. Nevertheless, immunotherapy still brings breakthroughs for SCLC therapy. Based on the encouraging results of CheckMate032, KEYNOTE028, and KEYNOTE158, FDA approved nivolumab and pembrolizumab monotherapy as third or later line for the treatment of patients with relapsed SCLC. Compared with chemotherapy alone, the PD-L1 inhibitors atezolizumab and durvalumab plus the chemotherapy agent's platinum and etoposide have demonstrated prolonged OS among ES-SCLC patients. In addition, these two PD-L1 inhibitors plus chemotherapy have been approved by FDA as first-line therapy for ES-SCLC (**Table 1**). Recently, several meta-analyses analyzed different first-line treatments for ES-SCLC patients and demonstrated that PD-L1 inhibitors durvalumab and atezolizumab plus etoposide-based chemotherapy may be the best choice as first-line therapy for ES-SCLC patients (9–11).

Meanwhile, there is increasing concern regarding immune-related adverse events (irAEs) of ICIs (12–14). The appearance of some irAEs have beenshown to be related to the efficacy of ICI agents in patients with NSCLC and melanoma (15, 16), but this relationship has not been established in patients with SCLC. SCLC is characterized by complex immunophenotypes, and autoimmune-related paraneoplastic syndromes are commonly reported among SCLC patients (17). Understanding irAEs of ICIs is crucial for the clinical management of SCLC and for further improvement of the immunotherapeutic approach to SCLC, but few studies have focused on irAEs in SCLC recently. Therefore, in this article, we present an up-to-date review of ICIs and irAEs in SCLC based on data from present clinical trials.

Mechanism of ICIs and irAEs

Under normal conditions, immune inhibitor molecules such as CTLA-4 and PD-1/PD-L1 function as negative regulators and maintain the balance of the immune system. CTLA-4 and CD28 are commonly expressed on the surface of T cells, where they compete with the same binding sites as CD80/CD86 on the surface of antigen-presenting cells (APCs). CD28 combines with CD80/CD86 to provide an activation signal for T cells. The combination of CTLA-4 and CD80/CD86 impedes T-cell activation and downregulates T-cell responses (18, 19). Unlike CTLA-4, PD-1 is expressed on the surface T cells or other immune cells, and its ligand, PD-L1, is expressed on the surface of APCs and other immune cells. Tumor cells can also express PD-L1, and PD-1 and PD-L1 combine on the surface of tumor cells, leading to downregulation of the T-cell response, and helping tumor cells to escape from the host immune response (20, 21). Tumor cells upregulate these immune inhibitor molecules to evade the immune system, resulting in tumor initiation, progression, and metastasis. The ICI blockade of PD1/PD-L1 or CTLA-4 activates the body's antitumor immunity (**Figure 1**).

IrAEs also occur in this context. IrAEs are generally considered to be related to the damage of normal tissues, which results from immunotherapy, and immune tolerance is affected by ICIs, resulting in activated T cells targeting non-tumor antigens or self-peptides. IrAEs affect almost all organs. The most common irAEs include rash, pruritus, colitis, hypothyroidism, hyperthyroidism, and pneumonitis. The precise pathophysiology of irAEs is still undefined. Existing studies suggest that autoantibodies play an important role in irAEs. Some autoantibodies may have cross-reactivity with antibodies during immunotherapy (22). One example is vitiligo, which is caused by an autoantibody attack on melanocytes, and it is also frequently observed among melanoma patients who have received ICI therapy (23). In addition, some cytokines may be involved in irAEs (22). For instance, the levels of the interleukin-17 were obviously higher in patients with ipilimumab-related colitis (24). Host factors, intestinal microbiota, genetic risk factors, and specific antigen exposures may all be involved in irAEs (25). Viruses or co-administered drugs can also provoke irAEs (26). CTLA-4 and PD1/PD-L1 inhibitors usually display different irAEs. Reportedly, the occurrence rate of diarrhea and colitis in patients administered CTLA-4 is higher than that in those administered PD-1/PD-L1 antibodies. Thyroiditis and pneumonitis are more commonly observed in patients who received PD-1/PD-L1 inhibitors. Compared with ICI monotherapy, combinations of ICIs increase the risk of irAEs. Tumors also influence irAEs, with colitis and skin irAEs being more common in patients treated with ICIs for melanoma and pneumonitis occurring more frequently in lung cancer patients treated with ICIs (25). Accurately recognizing irAEs and closely following up patients who have used ICIs are essential parts of immunotherapy.

The Immune Characteristics and Response to ICIs of SCLC

The efficacy of immunotherapy is largely determined by the internal immune microenvironment of the tumor (27). However, it is widely regarded that SCLC has a unique and complex immune microenvironment.

Consistently, previous studies regard SCLC as a kind of immunogenic cancer) One of the hallmarks of SCLC is high tumor mutational burdens (TMBs) (28, 29), which are usually used as a predictor of ICI efficacy for many cancer types, including NSCLC (30) and melanoma (31). Reportedly, High TMBs could influence further neo-antigens to activate the immune system (32). Moreover, paraneoplastic syndromes are commonly observed in SCLC patients and are mediated by autoantibodies. Evidence shows that SCLC patients with neurologic paraneoplastic syndromes present with better prognosis (33, 34). While immunosuppression does exist in SCLC, lower expression of class I major histocompatibility antigens, tumor-infiltrating lymphocytes, and PD-L1 have also been reported in some SCLC patients (3).

TABLE 1 | FDA approved ICIs in SCLC.

Agent	Target	Therapy line	Patients	Approve time	Based clinical trail
Nivolumab	PD-1	Third line or later line	Relapsed-SCLC	2018.08	CheckMate032
Atezolizumab+ platinum-etoposide	PD-L1	First line	ES-SCLC	2019.03	IMpower133
Pembrolizumab	PD-1	Third line or later line	Relapsed-SCLC	2019.06	KEYNOTE028 and KEYNOTE158
Durvalumab+ platinum-etoposide	PD-L1	First line	ES-SCLC	2020.03	CASPIAN

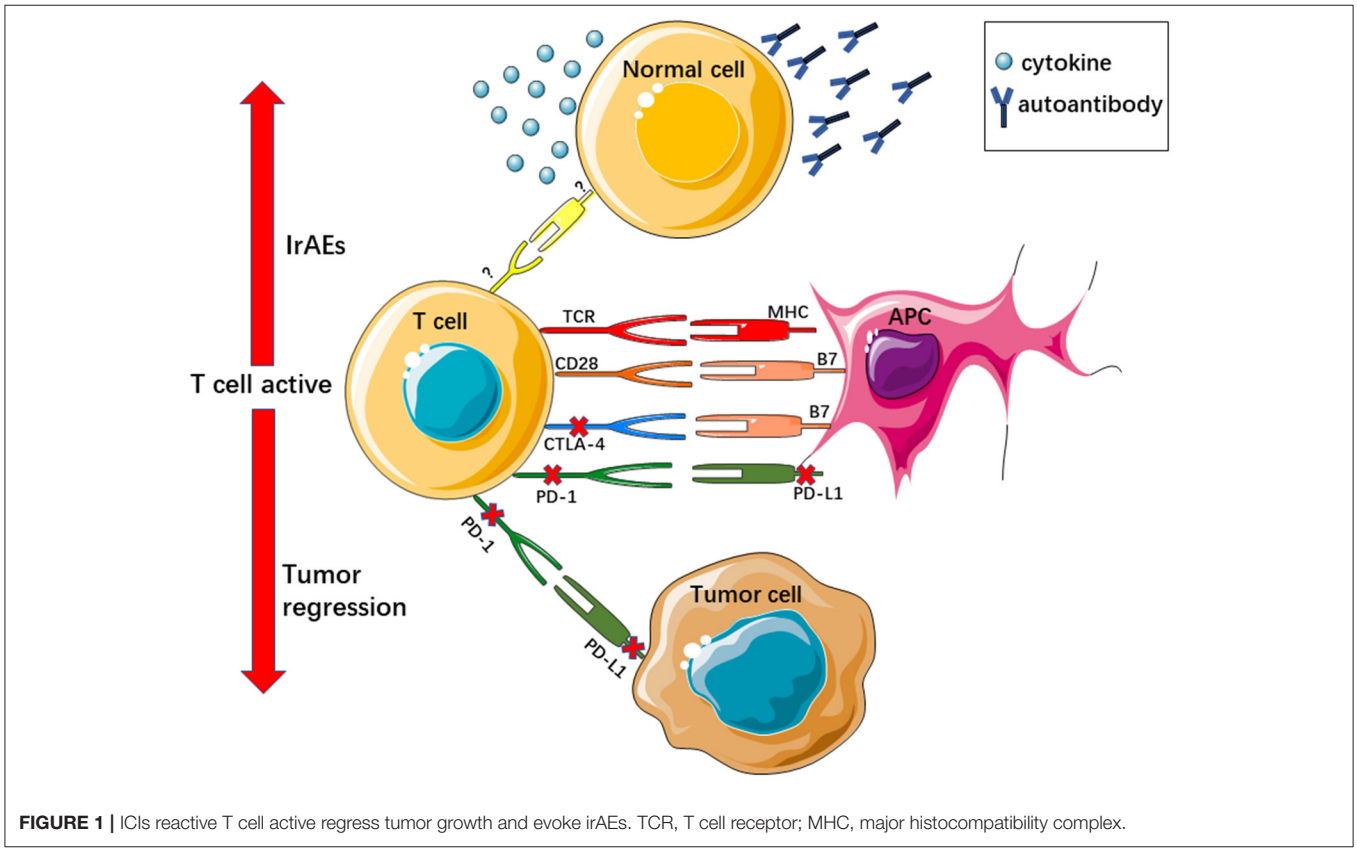

FIGURE 1 | ICIs reactive T cell active regress tumor growth and evoke irAEs. TCR, T cell receptor; MHC, major histocompatibility complex.

The response rate to ICIs, particularly ICI monotherapy, was lower in most patients with SCLC than in those with other tumors. PD-1 antibody nivolumab monotherapy did not present any advantage in the improvement of OS or progression-free survival (PFS) as second-line treatment setting for relapsed SCLC according to the Checkmate 331 study (35). Moreover, the PD-L1 inhibitor durvalumab monotherapy for relapsed SCLC patients presented a confirmed ORR of only 9.5% (36).

Furthermore, the overall low response to ICIs of SCLC patients may be due to the lack of biomarkers. In the past years, relatively few tumor specimens for SCLC have been available. In addition, immune heterogeneities have been found among SCLC patients; in particular, tumor cell PD-L1 expression was different among various studies (37). No reliable biomarkers have yet been confirmed in terms of the population of SCLC patients who will benefit from ICI immunotherapy, which could influence the ORR. Recently, comprehensive research related to SCLC's biomarkers in the tumor stromal cell or in the blood are largely being conducted (38, 39). However, the findings still need to be assessed in large samples. Nevertheless, compared with single chemotherapy, PD-L1 inhibitor with chemotherapy for SCLC patients presented beneficial OS (A et al., 2019) (40), and there is increasing evidence that shows that combination therapy, such as combined with chemotherapy, radiotherapy, and other targeted therapy, may overcome the low response to ICI among SCLC patients (38, 41, 42).

PD-1 Inhibitors and irAEs in SCLC

Three PD-1 inhibitors, namely nivolumab, pembrolizumab, and tislelizumab, have been investigated in SCLC clinical trials as monotherapy or in combination chemotherapy.

In the nivolumab monotherapy arm of the Checkmate 032 study, the SCLC cohort comprised 109 chemotherapy-refractory SCLC patients who received nivolumab (3 mg/kg) as third-line or later-line therapy. After a median follow-up time of 28.3 months, the reported ORR was 11.9%. The median duration of response (DOR) was 17.9 months (range: 3.0–42.1). The median PFS and median OS were 1.4 months (95% CI: 1.3–1.6) and 5.6 months

(95% CI: 3.1–6.8), respectively. Approximately 55% of patients in the nivolumab monotherapy group experienced treatment-related adverse events (TRAEs), and grade 3 to 4 TRAEs were reported in 11.9% of patients. Most irAEs reported in the study, including reactions of the skin (21.1%), endocrine system (9.2%), gastrointestinal tract (6.4%), hepatic system (4.6%), pulmonary system (1.8%), renal system (0.9%), and hypersensitivity/infusion reactions (3.7%), were mild (grade 1 to 2). Grade 3 to 4 irAEs included pneumonitis (1.8%), rash (0.9%), and aspartate aminotransferase (0.9%). One patient experienced grade 3–4 treatment-related encephalitis, and one death was reported due to treatment-related pneumonitis (43). Based on these promising results, the FDA approved nivolumab as third-line or later-line therapy for relapsed SCLC.

Nivolumab as second-line treatment for relapsed SCLC was evaluated in Checkmate 331 (NCT02481830). The preliminary results showed no significant differences in OS, PFS, ORR, and DOR during nivolumab monotherapy. The TRAEs were reported to be lower in the nivolumab group (grade 3 = 55%, grade 4 = 14%) than in the chemotherapy group (grade 3 = 90%, grade 4 = 73%) (35). Further details of TRAEs/irAEs associated with Checkmate 331 are still pending.

Pembrolizumab was another immunoglobulin G4 (IgG4) monoclonal antibody of PD-1 (44). Pembrolizumab first showed efficacy among the PD-L1-positive SCLC patients of the Keynote 028 study, with promising primary end point ORR (33.3%, 95% CI: 15.6–55.3%) and secondary end points (median DOR, median PFS, and median OS). The median DOR observed was 19.4 months, and the observed median PFS and median OS were 1.9 months and 9.7 months, respectively. TRAEs occurred in 66.7% of patients, and the most common events include arthralgia (16.6%), asthenia (16.6%), rash (16.7%), diarrhea (12.5%), and fatigue (12.5%). Two patients (8.3%) experienced treatment-related grade 3 to 5 AEs (one grade 3 bilirubin elevation and one grade 5 colitis/intestinal ischemia) (45).

Then, the Keynote 158 study enrolled 107 patients with SCLC (14% were PD-L1 positive) who received 200 mg of pembrolizumab treatment. Reportedly, the overall ORR was 18.7%. Significantly, difference was found in the ORR, median PFS, and median OS of the PD-L1-positive and PD-L1-negative cohorts. The ORR, median PFS, and median OS in the PD-L1-positive cohort presented superiority to that of the PD-L1-negative cohort. TRAEs were reported in 60% of all enrolled patients, with 12% of patients experiencing grade 3 to 4 TRAEs. Additionally, a total of 33% of patients experienced irAEs, with 5% of patients experiencing (suffering) grade 3-4 irAEs. The most common irAEs were hypothyroidism and hyperthyroidism, which occurred in 12% and 7% of the patients, respectively. Severe skin reactions were reported in 3% patients. Adrenal insufficiency, nephritis, pneumonitis and pancreatitis were all reported in 2% of the patients (46). In the according to subsequent pooled analysis of Keynote 028 and Keynote 158, the ORR was 19.3% (95% CI: 11.4–29.4) and the median time to response was 2.1 months (range: 1.7–4.1). The median PFS and median OS was 2.0 months (95% CI: 1.9–3.4) and 7.7 months (95% CI: 5.2–10.1), respectively. TRAEs occurred in 61.4% of the patients, with 7.2% of patients experiencing grade 3 TRAEs. IrAEs were considered to have occurred in 24.1% of patients, with the most common events being hypothyroidism, hyperthyroidism, and infusion reactions. Grade 3 irAEs occurred in 6.0% patients, including colitis, adrenal insufficiency, pancreatitis, and pneumonitis. Most of the irAEs could be alleviate by systemic corticosteroid treatment (47). Based on these promising results, pembrolizumab was also approved as third-line or later-line therapy for relapsed SCLC.

Regarding maintenance therapy, pembrolizumab monotherapy did not show any improvement in median PFS for patients with ES-SCLC (48). The median PFS of 45 enrolled patients was 1.4 months (95% CI: 1.3–2.8), and the median OS was 9.6 months (95% CI: 7.0–12). Higher median PFS and higher median OS were observed in patients with tumor stromal expressing PD-L1. Most reported TRAEs were mild (grade 2 or lower). Three adverse events, including rash (18%), hypothyroidism (9%), and type I diabetes mellitus with diabetic ketoacidosis (11%), were considered asirAEs.

Pembrolizumab was well tolerated during consolidation thoracic radiotherapy in a combination setting. In a single-institution phase I trial, after induction chemotherapy, 33 ES-SCLC patientwere treated with 45 Gy thoracic radiotherapy plus pembrolizumab. No dose-limiting toxicities were observed in the first 35 days, and the median PFS and OS were 6.1 months and 8.4 months, respectively. No grade 4 or 5 treatment-related toxicities were reported. TRAEs occurred in 6% of patients, but the investigator considered these were unlikely to be related to treatment (49). Furthermore, pembrolizumab combined with concurrent chemoradiation therapy were assessed in LS-SCLC patients, with the median follow-up time of 23.1 months, and the reported median PFS and median OS were 19.7 months and 39.5 months, respectively. Most TRAEs were mild; only one grade 4 respiratory failure and two grade 4 neutropenia were reported. Fatigue, dysphagia, dyspnea, and anemia were the most common grade 1-2 TRAEs. Conversely, neutropenia and anemia were the most common grade 3 TRAEs. Treatment-related pneumonitis was reported in 15% of patients (49).

In the NCT02551432 study, it was reported that the pembrolizumab plus paclitaxel as second-line therapy in relapsed or refractory SCLC patients were not inferior to the traditional second-line chemotherapy. The reported ORR was 23.1% (95% CI: 6.9–39.3%). The median PFS and median OS were 5.0 months (95% CI: 2.7–6.7) and 9.1 months (95% CI: 6.5–15.0), respectively. All enrolled patients experienced adverse events., with ∼46% grade 3 or 4 adverse events were reported, including febrile neutropenia, neutropenia, asthenia, hyponatremia, and type I diabetes (50).

Recently, combination of pembrolizumab plus etoposide/platinum (EP) as the first-line therapeutic regimens for ES-SCLC patients were also evaluated in the Keynote 604 study. The results indicate that pembrolizumab plus EP significantly improved PFS, but the significance threshold for OS was not reached. A total of 24.7% irAEs were reported in the pembrolizumab plus chemotherapy group, and 10.3% of irAEs were reported in the chemotherapy group. The most common irAEs were hypothyroidism, hyperthyroidism, and pneumonitis. Grade 3 irAEs reported in the pembrolizumab

plus chemotherapy group were 7.2% vs. the 0.9% in the chemotherapy group. The most common grade 3 irAEs were severe skin reactions (1.8%), pneumonitis (1.3%), and hepatitis (1.3%) (51).

Tislelizumab is, a PD-1 antibody with high affinity and specificity, was explored in the first-line SCLC treatment setting in a phase II study (NCT03432598). 17 Chinese ES-SCLC patients were treated with tislelizumab (200 mg) plus etoposide and platinum. The ORR was 77% (95% CI: 50.1–93.2). The median PFS and median OS in the SCLC cohort was 6.9 months and 15.6 months.IrAEs in the SCLC cohort included thyroid disorders (29.4%), pneumonitis (5.9%), and type 1 diabetes mellitus (5.9%) (52).

PD-L1 Inhibitors and irAEs in SCLC

PD-L1 inhibitor atezolizumab and durvalumab as combination agents with platinum–etoposide indicated a promising profile as first-line therapy for ES-SCLC patients.

NCT01375842, a first phase Ia study, assess atezolizumab's single agent clinical activity in patients with ES-SCLC. The study enrolled 17 patients, and after 6.7 months of follow-up, the confirmed ORR was 6%. The reported median PFS and median OS were 1.5 months and 5.9 months, respectively. Most patients (65%) experienced various grades of TRAEs, with the most common being fatigue (24%). One grade 3 pneumonitis and one grade 5 hepatic failure were reported (53).

The IMpower133 trial further evaluated atezolizumab plus chemotherapy as first-line treatment option for ES-SCLC patients. The median OS and median PFS in the combined therapy group were both longer than in monotherapy group. The secondary end points ORR and DOR were similar between the two groups. IrAEs occurred in 39.9% of patients in the atezolizumab group and in 24.5% of patients in the placebo group. The most common irAEs included rash (18.7 vs. 10.2%), hypothyroidism (12.6 vs. 0.5%), hepatitis (7.1 vs. 4.6%), infusion-related reactions (5.6 vs. 5.1%), hyperthyroidism (5.6 vs. 2.6%), pneumonitis (2.0 vs. 2.6%), and colitis (1.5 vs. 0%). The grade 3-4 irAEs reported in the atezolizumab group included rash (2.0%), hepatitis (1.5%), infusion-related reaction (2.0%), pneumonitis (0.5%), colitis (1.0%), pancreatitis (0.5%), rhabdomyolysis (0.5%), nephritis (0.5%), and Guillain–Barre syndrome (0.5%) (54). A following study further presented the safety and tolo data of the induction and maintenance phases of the IMpower133 trial. The results were similar to those that had previously been reported. IrAEs were more frequently reported in the atezolizumab arm during both induction therapy and maintenance therapy, with rash and hypothyroidism being the most common irAEs (40).

In contrast, atezolizumab monotherapy failed to demonstrate clinic efficacy for relapsed SCLC patients in second line management setting in the non-comparative phase II IFCT-1603 study. The ORR of the atezolizumab group was only 2.3%, and the median PFS of the chemotherapy group was longer than that of the atezolizumab group. Difference in median OS was observed between the two groups. IrAEs in the atezolizumab group included hepatitis (4.2%), colitis (4.2%), arthralgia (6.3%), dysthyroidism (4.2%), musculoskeletal and connective tissue disorders (12.5%), and gastrointestinal disorders (18.8%). Most of the irAEs were mild (grade 1 or 2) (55).

In March 2020, another anti-PD-L1 antibody, durvalumab, in combination with platinum–etoposide was approved by the FDA as first-line therapy of ES-SCLC patients based on the findings of the CASPIAN trial (NCT03043872). The CASPIAN study was designed as an open-label, phase 3 trial to assess durvalumab with or without tremelimumab in combination with platinum–etoposide as first-line treatment for ES-SCLC patients. Firstly, the result of durvalumab plus platinum–etoposide group and the platinum–etoposide group have been published in the planned interim analysis. The reported median OS in the durvalumab plus platinum–etoposide group was slightly longer than the platinum–etoposide group (13.0 months vs. 10.3 months, respectively). The median PFS and 6-month PFS was similar between the two groups. The 12-month PFS rates and 18-month OS rates were higher in the durvalumab plus platinum–etoposide arm. The confirmed ORR in the two groups was 68% and 58%, respectively. Reported TRAEs were similar between the two groups (89 and 90%, respectively). The grade 3–4 TRAEs were similar between the chemotherapy group and in the durvalumab plus chemotherapy group (both are 62%). IrAEs were experienced by 20% of patients in the durvalumab plus chemotherapy group, with only 5% of patients experiencing grade 3 or 4 irAEs. Only 3% of patients in the chemotherapy group experienced irAEs and the occurrence rate of grade 3 or 4 irAEs was <1%. The most common irAEs were hypothyroid events (9 vs. 1%), hyperthyroid events (5 vs. 0%), pneumonitis (3 vs. 1%), hepatic events (3 vs. 0%), dermatitis/rash (2 vs. 1%), and diarrhea/colitis (2 vs. <1%). Thyroiditis and type 1 diabetes mellitus only occurred in the durvalumab plus chemotherapy group. Other rare irAEs included one patient in the durvalumab plus chemotherapy group who experienced adrenal insufficiency, and one patient in the durvalumab plus chemotherapy group who experienced grade 3 or 4 pancreatic events. Grade 3 or 4 irAEs in the durvalumab plus chemotherapy group included pneumonitis (1%), hepatic events (2%), diarrhea/colitis (<1%), type 1 diabetes mellitus (2%), and pancreatic events (<1%). Deaths due to irAEs occurred in <1% of patients in each group. One therapy-related hepatotoxicity caused death in the durvalumab plus chemotherapy group and one therapy-related pneumonitis caused death in the platinum–etoposide group (56).

Similarly, the durvalumab monotherapy failed for relapsed SCLC patients. The confirmed ORR was only 9.5% (95% CI: 1.2–30.4). The median PFS and OS were 1.5 months (95% CI: 0.9–1.8) and 4.8 months (95% CI: 1.3–10.4). The 12-month OS rate was 27.6% (95% CI: 10.2–48.4). A total of 33.3% of patients had TRAEs, all grade 1 or 2. Nausea, fatigue, and maculo-papular rash were the most commonly reported TRAEs. No TRAEs led to discontinuation or death (36).

CTLA-4 Inhibitors and irAEs in SCLC

CA184-041 (NCT00527735) was the first phase II study exploring the clinical efficiency and tolerability of the CTLA-4 inhibitor ipilimumab in ES-SCLC patients. Chemotherapy-naïve ES-SCLC patients were randomized to receive paclitaxel/carboplatin with either placebo, concurrent ipilimumab (ipilimumab plus

paclitaxel/carboplatin followed by maintenance treatment with ipilimumab), or phased ipilimumab (paclitaxel/carboplatin administered before ipilimumab, followed by maintenance treatment with ipilimumab). Prolonged immune-related PFS (irPFS) was only reported in the phased ipilimumab group. Nonsignificant improvement in PFS and OS was observed in both the ipilimumab groups. The grade 3/4 TRAEs were more common in the ipilimumab-containing arms. The most common irAEs were related to skin events (rash and pruritus), gastrointestinal events (diarrhea), and liver function (increases in alanine aminotransferase and aspartate aminotransferase), both of which occurred more frequently in both the concurrent ipilimumab and the phased ipilimumab groups. Most grade 3/4 irAEs could be managed well after follow-up or systemic corticosteroid treatment. Thus, phased ipilimumab demonstrated both efficacy and safety in previously untreated ES-SCLC patients in this clinical study (57).

In another phase II open-label study (NCT01331525), 42 chemotherapy-naïve ES-SCLC patients were treated with six cycles of carboplatin and etoposide plus ipilimumab. The study did not meet the primary endpoint (1-year PFS). The median PFS and median OS were 6.9 months and 17.0 months, respectively. In total, 69.2% of patients experienced serious irAEs ($\geq$ grade 3), with the most frequent irAEs being diarrhea and skin rash. Serious ipilimumab-related neurological adverse events (grade 3 or higher) were reported in 7.6% of patients. Moreover, five deaths related to ipilimumab occurred; two of which were reported shortly after treatment (cardiac arrest, neutropenic sepsis) and three occurred 4–5 months after the last treatment (pneumonia, autoimmune encephalitis, and sepsis). This study additionally presented an association between improved outcomes and baseline autoimmunity of the therapy (58).

The phase III study CA184-156 (NCT01450761) investigated the efficacy and safety of ipilimumab plus etoposide and platinum for newly diagnosed ES-SCLC patients. The results showed that the addition of ipilimumab to chemotherapy did not present a survival benefit in ES-SCLC patients. The median OS and median PFS was found to be similar between the chemotherapy plus ipilimumab group and the chemotherapy plus placebo group. Patients receiving ipilimumab had more TRAEs, which required discontinuation of therapy (18 vs. 2%). Gastrointestinal and skin-related AEs were the most common irAEs (34 vs. 29%). The other irAEs that presented in more than 5% of patients were diarrhea (25 vs. 10%), rash (19 vs. 3%), pruritus (12 vs. 2%), colitis (6 vs. 1%), alopecia (5 vs. 7%), endocrine irAEs (10 vs. 2%), and peripheral sensory neuropathy (2 vs. 1%). Moreover, 76% of grade 2-4 irAEs were completely resolved. Neurologic events required more time (28.9 weeks) to resolve compared with other irAEs (59).

Double Check Point Inhibitors and irAEs in SCLC

Different from PD-1/PD-L1, CTLA-4 activates T cells in the early stage. In theory, the combination of these two inhibitors would be more effective than either of them alone. Previously, the combination of double checkpoint inhibitors has shown survival benefits in some solid tumors, such as advanced melanoma and relapsed malignant pleural mesothelioma (60, 61).

Some clinical trials of ICI combinations in SCLC patients have also been reported (62). In the Checkmate 451 study, ES-SCLC patients were randomly receiving nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg), nivolumab (240 mg) as a single agent, or placebo. Neither nivolumab alone or in combination with ipilimumab significantly improved OS compared with placebo, and 86% of patients receiving nivolumab plus ipilimumab experienced adverse events. Toxicity-induced discontinuation of therapy was reportedly higher in the combination group than in the nivolumab monotherapy and placebo groups (32% vs. 9% vs. 1%, respectively). Moreover, the deaths of seven patients that were related to the treatment were reported in the nivolumab plus ipilimumab group (63).

In the Checkmate 032 study, eligible SCLC patients (both limited- and extensive-stage) were treated with nivolumab monotherapy (3 mg/kg) or nivolumab combined ipilimumab (nivolumab 1 mg/kg plus ipilimumab 1 mg/kg, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg). The results showed that nivolumab plus ipilimumab significantly improved ORR in SCLC patients. In addition, the median OS was improved in the combination group, but the median PFS of the nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) group was similar to that of the nivolumab monotherapy group. Adverse events, including all grades of adverse events, were also higher in the combination group. Increased lipase and diarrhea were the most commonly reported grade 3–4 TRAEs. The incidence of discontinued treatment due to TRAEs was higher in the nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) cohort, whereas that of discontinued treatment due to TRAEs was similar in the nivolumab monotherapy (3 mg/kg) cohort and the nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) cohort. Two treatment-related deaths were reported in the nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) cohort (including myasthenia gravis and worsening of renal failure), and one treatment-related pneumonitis caused death in the nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) cohort. The 1-year survival rate of patients with high TMBs was significantly higher (59b).

In a phase I dose-exploration and expansion study (NCT02261220), another double check point inhibitor group, durvalumab in combination with tremelimumab, demonstrated a promising clinical activity for ES-SCLC patients who received prior systematic therapy. The confirmed ORR was 13.3%, and the median DOR was 18.9 months (95% CI: 16.3–18.9). The disease control rate at 16 weeks was 20.0% (95% CI: 7.7–38.6). The median PFS and median OS were 1.8 months and 7.9 months, respectively. The 12-month OS was 41.7% (95% CI: 23.3–59.2). However, 67% of patients experienced TRAEs, with 23% experiencing grade 3/4 TRAEs. Fatigue (23%) and pruritus (23%) were the most common TRAEs (64).

In arm A of the BALTIC (NCT02937818) phase II study, the efficacy of durvalumab plus tremelimumab in platinum-refractory/resistant ES-SCLC patients was further tested. In this study, 25 patients were treated with durvalumab

TABLE 2 | Clinical trials' efficacy data of ICIs in patients with SCLC.

Agent	Trial	Phase	Line of therapy	Population	Treatment arms	Primary end point	Secondary end points	Median follow-up time	Publish year
Nivolumab	CheckMate032 (NCT01928394)	Phase I/II	Third or later line	SCLC	NIvolumab 3 mg/kg	ORR: 11.9% (95% CI: 6.5–19.5)	mDOR: 17.9 m (95% CI:3.0–42.1); mOS: 5.6 m (95% CI: 3.1–6.8); mPFS: 1.4 m (95% CI: 1.3–1.6)	28.3 m	2018
	CheckMate331 (NCT02481830)	Phaseiii	Second line	Relapsed SCLC	Nivolumab 240 mg	mOS: 7.46 m (95% CI: 5.65–9.20)	mPFS: 1.45 m (95% CI:1.41- 1.51); ORR: 13.7% (95% CI:10.0–18.3); DOR:72%	15.8 m	2018
Pembrolizumab	KEYNOTE028 (NCT02054806)	Phase Ib	Third line	ES-SCLC	Pembrolizumab 10 mg/kg	ORR: 33% (95 CI: 16–55%)	mDOR: 19.4 m (95% CI:3.6–20.0); mPFS:1.9 m (95% CI:1.7–5.9); mOS: 9.7 m (95% CI: 4.1- not reached).	9.8 m	2017
	KEYNOTE158 (NCT02628067)	Phase II	Third line	ES-SCLC	Pembrolizumab 200 mg	ORR: 18.7% (95% CI: 11.8% −27.4%)	mPFS: 2.0 m (95%CI: 1.9–2.1); mOS: 8.7 m (95% CI: 5.6–12)	10.1 m	2018
	pool analysis of KEYNOTE028 and KEYNOTE158	Phase Ib/phase II	Third line	ES-SCLC	Pembrolizumab 10 mg/kg or 200 mg	ORR: 19.3% (95% CI: 11.4–29.4%)	mPFS: 2.0 m (95% CI: 1.9–3.4); mOS:7.7 m (95% CI: 5.2–10.1)	25.9 m	2020
	Gadgeel et al. (48)	Phase II	Maintenance therapy	ES-SCLC	Pembrolizumab 200 mg	mPFS: 1.4 m (95% CI: 1.3–2.8)	mOS: 9.6 m (95% CI: 7.0–12)	5 w	2018
	NCT02402920	Phase I	Second line	ES-SCLC	45 Gy thoracic radiotherapy +pembrolizumab 50–200 mg	Safety	mPFS: 6.1 m (95% CI 4.1–8); mOS: 8.4 m (95%; CI: 6.7–10.1)	7.3 m	2020
	Welsh et al. (49)	phase I/II	-	LS-SCLC	Concurrent chemoradiotherapy +pembrolizumab 100–200 mg	Safety	mPFS:19.7 m (95% CI 8.8–30.5); mOS:39.5 months (95% CI:8.0–71.0)	23.1 m	2020
	NCT02551432	Phase II	Second line	ES-SCLC	Paclitaxel +pembrolizumab 200 mg	ORR: 23.1% (95% CI: 6.9–39.3)	mPFS: 5.0 m (95% CI: 2.7–6.7); mOS:9.1m (95% CI: 6.5–15.0)	11.1 m	2019
	KEYNOTE604 (NCT03066778)	Phase III	First line	ES-SCLC	Pembrolizumab 200 mg + etoposide+platinum	mPFS: 4.5 m (95% CI: 4.3–5.4); mOS: 10.8 m (95% CI: 9.2–12.9)	ORR: 70.6% (95% CI: 64.2–76.4); mDOR: 4.2 m (95% CI:1.01–26.01)	22 m	2020
					Placebo + etoposide +platinum	mPFS: 4.3 m (95% CI: 4.2–4.4); mOS: 9.7 m (95% CI: 8.6–10.7)	ORR: 61.8% (95% CI: 55.1–68.2); mDOR: 3.7 m (95% CI:1.41–25.81)		
Tislelizumab	NCT03432598	Phase II	First line	ES-SCLC	Tislelizumab 200 mg + etoposide+platinum	ORR: 77% (95% CI: 50.1–93.2)	mPFS: 6.9 m (95% CI: 4.9–10.09)	15.3 m	2020

(Continued)

TABLE 2 | Continued

Agent	Trial	Phase	Line of therapy	Population	Treatment arms	Primary end point	Secondary end points	Median follow-up time	Publish year
Atezolizumab	NCT01375842	Phase Ia	First line	ES-SCLC	Atezolizumab 15 mg/kg or 1200 mg	Safety	ORR: 6%; mPFS: 1.5 m (95% CI: 1.2–2.7); mOS: 5.9 m (95% CI: 4.3–20.1)	6.7 m	2016
	IMpower133 (NCT02763579)	Phase I/III	First line	ES-SCLC	Atezolizumab 1,200 mg+carboplatin + etoposide	mOS: 12.3 m (95% CI:10.8–15.9); mPFS:5.2 m (95% CI: 4.4–5.6)	ORR: 60.2% (95% CI:53.1–67.0); DOR: 4.2 m (95%CI: 1.4+ −19.5)	13.9 m	2018
					Placebo+ carboplatin+ etoposide	mOS:10.3 m (95% CI: 9.3–11.3); mPFS: 4.3 m (95% CI: 4.2–4.5)	ORR: 64.4% (95% CI: 57.3–71.0); DOR: 3.9 m (95% CI:2.0–16.1+)		
	IFCT-1603 (NCT03059667)	Phase II	Second line	relapsed ES-SCLC	Atezolizumab 1,200 mg	ORR: 2.3% (95% CI: 0.0–6.8)	mPFS:1.4 m (95%CI: 1.2–1.5); mOS: 9.5 m (95% CI: 3.2–14.4)	13.7 m	2019
					Chemotherapy	ORR: 10% (95% CI: 0.0–23.1)	mPFS:4.3 m (95%CI: 1.5–5.9); mOS:8.7m (95% CI:4.1–12.7)		
Durvalumab	CASPIAN (NCT03043872)	Phase III	First line	ES-SCLC	Durvalumab 1,500 mg + etoposide+ platinum	mOS: 13.0 m (95% CI: 11.5–14.8)	mPFS: 5.1 m(95% CI 4.7–6.2); ORR: 68%	14.2 m	2019
					Etoposide+platinum	mOS: 10.3 m (95%CI: 9.3–11.2)	mPFS: 5.4 m (95% CI:4.8–6.2); ORR: 58%		
	Goldman et al. (36)	Phase I/II	Second line	Relapsed SCLC	Durvalumab 10 mg/kg	Safety	ORR: 9.5% (95% CI: 1.2–30.4); mPFS: 1.5 m (95% CI: 0.9–1.8); mOS: 4.8 m (95% CI: 1.3–10.4)	NA	2018
Ipilimumab	CA184-041 (NCT00527735)	Phase II	First line	ES-SCLC	Placebo/ paclitaxel /carboplatin	irPFS: 5.3 m	mOS: 9.9 m; irBORR: 53% (95% CI: 38–68%); irDCR: 96% (95% CI: 85–100%)	11.1 m	2013
					Ipilimumab 10 mg/kg/placebo+ paclitaxel/ carboplatin(concurrent)	irPFS: 5.7 m	mOS: 9.1 m; irBORR: 49% (95% CI: 33–65%); irDCR: 81% (95% CI: 67–92%)		
					Ipilimumab 10 mg/kg/placebo+ paclitaxel/ carboplatin(phased)	irPFS: 6.4 m	mOS: 12.9 m; irBORR: 71% (95% CI: 55%- 84%); irDCR: 93% (95% CI: 81–99%)		
	NCT01331525	Phase II	First line	ES-SCLC	Ipilimumab 10 mg/kg+ carboplatin+ etoposide	not meet	mPFS: 6.9 m (95%CI: 5.5–7.9); mOS: 17.0 m (95% CI: 7.9–24.3); median irPFS:7.3 m (95% CI: 5.5–8.8)	8.5 m	2016

(Continued)

TABLE 2 | Continued

Agent	Trial	Phase	Line of therapy	Population	Treatment arms	Primary end point	Secondary end points	Median follow-up time	Publish year
	NCT01450761	Phase III	First line	ES-SCLC	Ipilimumab 10 mg/kg+etoposide +platinum (cisplatin+ carboplatin)	mOS: 11.0 m	mPFS: 4.6 m; mDOR: 4.01 (95% CI: 3.32–4.17)	10.5 m	2016
					Placebo+ etoposide+ platinum (cisplatin+ carboplatin)	mOS: 10.9 m	mPFS: 4.4 m; mDOR: 3.45 m (95% CI: 3.25–4.07)	10.2 m	
Nivolumab +ipilimumab	CheckMate451 (NCT02538666)	Phase III	Maintenance therapy	Relapsed ES-SCLC	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg	mOS: 9.17 m (95% CI:8.15–10.25)	mPFS: 1.74 (95% CI: 1.48–2.63)	9 m	2019
					Nivolumab 1 mg/kg	mOS: 10.41 m (95% CI:9.46–12.12)	mPFS: 1.87 (95% CI: 1.61–2.63)		
					Placebo	mOS: 9.56 m (95% CI:8.18–11.01)	mPFS: 1.45 (95% CI: 1.41–1.48)		
	CheckMate032 (NCT01928394)	Phase I/II	Second or later line	SCLC	Nivolumab 3mg/kg	ORR:10%	mOS: 4.4 m (95% CI: 3.0–9.3); mPFS: 1.4 m (95% CI: 1.4–1.9)	198.5 d	2016
					Nivolumab 1 mg/kg + ipilimumab 3 mg/kg	ORR:23%	mOS: 7.7 m (95% CI: 3.6–18.0); mPFS: 2.6 m (95% CI: 1.4–4.1)	361.0 d	
					Nivolumab 3 mg/kg + ipilimumab 1 mg/kg	ORR:19%	mOS: 6.0 m (95% CI: 3.6–11.0); mPFS: 1.4 m (95% CI: 1.3–2.2)	260.5 d	
Durvalumab+ tremelimumab	NCT02261220	Phase I	Third line	ES-SCLC	Durvalumab 20 mg/kg+tremelimumab 1 mg/kg	safety	ORR: 13.3%; DOR: 18.9 m (95% CI: 16.3–18.9); mPFS: 1.8 m (95% CI: 1.0–1.9); mOS: 7.9 m (95% CI: 3.2–15.8)	NR	2018
	BALTIC (NCT02937818)	Phase II	First line	ES-SCLC	Durvalumab 1,500 mg + tremelimumab 75 mg	ORR: 9.5% (95% CI: 1.17–30.38)	12 weeks DCR: 38.1%	14 w	2018

(Continued)

TABLE 2 | Continued

Agent	Trial	Phase	Line of therapy	Population	Treatment arms	Primary end point	Secondary end points	Median follow-up time	Publish year
Durvalumab+ tremelimumab	CASPIAN (NCT03043872)	Phase III	First line	ES-SCLC	durvalumab 1,500 mg + tremelimumab 75 mg+platinum +etoposide	mOS: 10.4 m (95% CI 9.6–12.0)	mPFS: 4.9 m (95% CI 4.7–5.9); unconfirmed objective response: 74%	25.1 m	2021
					Durvalumab 1,500 mg+platinum +etoposide	mOS: 12.9 m (95% CI: 11.3–14.7)	mPFS: 5.1 m (95% CI 4.7–6.2); unconfirmed objective response: 79%		
					Platinum+ etoposide	mOS: 10.5 m (95%CI: 9.3–11.2)	mPFS: 5.4 m (95% CI 4.8–6.2); unconfirmed objective response: 71%		

mDOR, median disease control rate; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; irPFS, immune-related progression-free survival; irBORR, immune related best overall response rate; irDCR, immune related disease control rate; +, denotes a censored observation; NA, not available.

(1,500 mg) plus tremelimumab (75 mg) for up to 4 months, followed by durvalumab (1,500 mg) until progressive disease or discontinuation. The reported ORR was 9.5% (95% CI: 1.17–30.38); 23.8% of patients had stable disease and 4.8% of patients had an unconfirmed partial response. Grade 3 or higher TRAEs were experienced by 19% of patients; however, the updated information has not yet been published (65).

On December 2020, the updated results of CASPIAN trial published the data of durvalumab plus chemotherapy group and durvalumab plus tremelimumab plus chemotherapy group. Safety profiles of the durvalumab plus chemotherapy group and the chemotherapy group were consistent with previously reported. Immune-mediated adverse events were reported in patients in the durvalumab plus tremelimumab plus chemotherapy group, durvalumab plus chemotherapy group and chemotherapy group were 36, 20, and 3%, respectively. Usually reported irAEs were hypothyroid events, hyperthyroid events, diarrhea or colitis and dermatitis or rash. Grade 3 or 4 immune mediated adverse events occurred in 14% patients in the durvalumab plus tremelimumab plus chemotherapy group, 5% patients in the durvalumab plus chemotherapy group, and <1% patients in chemotherapy group. Deaths caused by irAEs occurred in 1% patients receiving durvalumab plus tremelimumab plus chemotherapy (enterocolitis, pneumonitis, pneumonitis and hepatitis), 1% patients receiving durvalumab plus platinum–etoposide (hepatotoxicity and interstitial lung disease) and <1% receiving platinum–etoposide (pneumonitis) (66).

DISCUSSION

For many years, few breakthroughs in SCLCs have been reported. Chemotherapy and radiotherapy were the only effective therapeutic methods for ES-SCLC patients. However, in recent years, immunotherapy has brought new hope for patients with SCLC. Some ICIs have improved chemotherapy's efficacy in ES-SCLC patients, but a comprehensive understanding of the mechanisms and preclinical rationale of immunotherapy in SCLC patients is still required. In this review, we summarized the available clinical trial data on ICIs for the treatment of SCLC. We are particularly concerned about IRAES, which are often overlooked by existing reviews.

A systematic collection of the efficacy and safety data of ICIs in the treatment of SCLC is performed in this review. Two reviewers independently searched current literature from the Cochrane Library, Clinical Trials, PubMed, and MEDLINE databases, using the following key words: "Small cell lung cancer," "immune checkpoint inhibitor," "nivolumab," "pembrolizumab," "atezolizumab," "avelumab," "durvalumab," and "ipilimumab." Clinical trials reporting both efficacy and safety data were included. A total of 23 studies covering 5 PD-1/PD-L1 inhibitors and 1 CTLA-4 antibody were included.

To intuitively compare the efficacy of ICIs and the occurrence of irAEs in SCLC, we summarized the results in **Tables 2**, **3**. Overall, the efficacy of different mechanisms in ICIs also varied (**Table 2**). The anti-PD1 inhibitors nivolumab and

TABLE 3 | Clinical trials' safety data of ICIs in patients with SCLC.

Target	NCT number	Treatment	Enrolled number	TRAEs	TRAEs (grade≥3)	IRAEs	IRAEs (grade≥3)	Most common TRAEs/IRAEs	TRAEs/IRAEs (grade≥3)	Death related to TRAEs/IRAEs
PD-1	CheckMate032 (NCT01928394)	Nivolumab 3 mg/kg	109	55%	11.9%	48%	4%	• **IRAEs:** • Skin reactions (21.1%), • Endocrine (9.2%), • Gastrointestinal (6.4%), • Hepatic (4.6%), • Infusion reaction (3.7%), • Pulmonary (1.8%), renal (0.9%)	• **IRAEs:** • Pneumonitis (1.8%), • Rash (0.9%), • AST increased (0.9%)	Pneumonitis (0.9%)
	CheckMate331 (NCT02481830)	Nivolumab 240 mg	282	55%	14%	NA	NA	NA	NA	NA
		Chemotherapy (either topotecan or amrubicin)	265	90%	73%	NA	NA	NA	NA	NA
	KEYNOTE028 (NCT02054806)	Pembrolizumab 10 mg/kg	24	66.7%	8.3%	NA	NA	• **TRAEs:** • Arthralgia (16.6%), • Asthenia (16.6%), • Rash (16.7%), • Diarrhea (12.5%), fatigue (12.5%)	• **TRAEs:** • Grade 3 bilirubin elevation (4.2%), • Grade 5 colitis/intestinal ischemia (4.2%)	Colitis and intestinal ischemia (4.2%)
	KEYNOTE158 (NCT02628067)	Pembrolizumab 200 mg	107	60%	12%	33%	5%	• **IRAEs:** • Hypothyroidism (12%), • Hyperthyroidism (7%), • Severe skin reactions (3%), • Adrenal insufficiency (2%), nephritis (2%), • Pneumonitis (2%), pancreatitis (2%)	• **IRAEs:** • Severe skin reactions (1%), • Adrenal insufficiency (1%), • Pancreatitis (2%), • Pneumonitis (1%), colitis (1%)	• Pneumonitis (0.9%), • Encephalopathy (0.9%)
	Pool analysis of KEYNOTE-028 and KEYNOTE-158	Pembrolizumab 10 mg/kg or 200 mg	83	61.4%	7.2%	24.1%	6%	• **IRAEs:** • Hypothyroidism (10.8%), • Hyperthyroidism (6.0%), • Infusion reactions (3.6%), • Colitis (2.4%), • Severe skin reactions (1.2%), • Adrenal insufficiency (1.2%), • Pneumonitis (1.2%), • Nephritis (1.2%), • Thyroiditis (2.4%), • Pancreatitis (1.2%), hepatitis (1.2%)	• **IRAEs:** • Colitis (2.4%), • Adrenal insufficiency (1.2%), • Pancreatitis (1.2%), • Pneumonitis (1.2%)	• Pneumonia (1.2%), • Intestinal ischemia (1.2%), • Encephalopathy (1.2%)
	Gadgeel et al. (48)	Pembrolizumab 200 mg	45	NA	NA	NA	NA	• **IRAEs:** • Rash (18%), • Hypothyroidism (9%), • Type I diabetes mellitus with diabetic Ketoacidosis (11%)	None	None

(Continued)

TABLE 3 | Continued

Target	NCT number	Treatment	Enrolled number	TRAEs	TRAEs (grade≥3)	IRAEs	IRAEs (grade≥3)	Most common TRAEs/IRAEs	TRAEs/IRAEs (grade≥3)	Death related to TRAEs/IRAEs
	NCT02402920	45 Gy thoracic radiotherapy + pembrolizumab 50–200 mg	33	NA	NA	NA	NA	NA	NA	NA
	Welsh et al. (49)	Concurrent chemoradiotherapy + pembrolizumab 100–200 mg	40	100%	88%	NA	NA	• **TRAEs:** • Fatigue (60%), • Dysphagia (58%), • Dyspnea (50%), • Esophagitis (43%), • Nausea (35%)	• **TRAEs:** • Anemia (13%), • Neutropenia (13%), • Lung infection (8%), • Pneumonitis (8%)	None
	NCT02551432	Paclitaxel + pembrolizumab 200 mg	26	100%	46%	NA	NA	• **TRAEs:** • Peripheral sensory neuropathy (57.7%), • Myalgia (34.6%), • Anemia (23.1%), • Diarrhea (23.1%), • Anorexia (19.2%), • Pneumonia (19.2%)	• **TRAEs:** • Neutropenia (7.7%), • Febrile neutropenia (7.7%), • Asthenia (7.7%), • Hyponatremia (7.7%), • Type I diabetes mellitus (3.9%), • Anemia (3.9%), • Myalgia (3.9%)	None
	KEYNOTE-604 (NCT03066778)	Pembrolizumab 200 mg + etoposide + platinum	223	97.8%	63.7%	24.7%	8.1%	• **IRAEs:** • Hypothyroidism (10.3%), • Hyperthyroidism (6.7%), • Pneumonitis (4.0%), • Severe skin reactions (2.2%), • Hepatitis (1.8%), • Colitis (1.3%), • Adrenal insufficiency (0.9%), • Hypophysitis (0.9%), • Nephritis (0.9%), • Encephalitis (0.9%), • Myositis (0.4%), • Pancreatitis (0.4%), • Type 1 diabetes mellitus (0.4%), • Uveitis (0.4%)	• **IRAEs:** • Severe skin reactions (1.8%), pneumonitis (1.3%), • Hepatitis (1.3%), • Adrenal insufficiency (0.9%), • Hyperthyroidism (0.4%), • Colitis (0.4%), • Nephritis (0.4%), • Myositis (0.4%), • Pancreatitis (0.4%), • Type 1 diabetes mellitus (0.4%), uveitis (0.4%)	• Neutropenic sepsis (1.3%), • Cardiopulmonary failure (0.4%), • Respiratory failure (0.4%), • Sepsis (0.4%)
		Placebo + etoposide platinum	223	95.5%	61%	10.3%	0.9%	• **IRAEs:** • Hypothyroidism (2.2%), • Hyperthyroidism (2.7%), • Pneumonitis (2.2%), • Severe skin reactions (0.9%), • Colitis (0.9%), • Adrenal insufficiency (0.4%), • Myasthenic syndrome (0.4%), • Myocarditis (0.4%)	• **IRAEs:** • Colitis (0.9%)	Neutropenic sepsis (0.4%)

(Continued)

TABLE 3 | Continued

Target	NCT number	Treatment	Enrolled number	TRAEs	TRAEs (grade≥3)	IRAEs	IRAEs (grade≥3)	Most common TRAEs/IRAEs	TRAEs/IRAEs (grade≥3)	Death related to TRAEs/IRAEs
	NCT03432598	Tislelizumab 200 mg + etoposide + platinum	17	100%	76.5%	35.3%	None	• **IRAEs:** • Thyroid disorders (29.4%), • Pneumonitis (5.9%), • Type 1 diabetes mellitus (5.9%)	None	None
PD-L1	NCT01375842	Atezolizumab 15 mg/kg or 1,200 mg	17	65%	17.6%	NA	NA	• **TRAEs:** • Fatigue (24%)	• **TRAEs:** • Pneumonitis (5.9%), • Hepatic failure (5.9%)	None
	IMpower133 (NCT02763579)	Atezolizumab 1,200 mg + carboplatin + etoposide	198	94.9%	58.1%	39.9%	10.5%	• **IRAEs:** • Rash (18.7%), • Hypothyroidism (12.6%), • Hepatitis (7.1%), • Infusion-related reaction (5.6%), • Hyperthyroidism (5.6%), • Pneumonitis (2.0%), • Colitis (1.5%), • Pancreatitis (0.5%), • Severe cutaneous reaction (1.0%), • Rhabdomyolysis (1.0%), • Nephritis (0.5%), • Hypophysitis (0.5%), • Diabetes mellitus (0.5%), • Guillain–Barre Syndrome (0.5%)	• **IRAEs:** • Rash (2.0%), • Hepatitis (1.5%), • Infusion-related reaction (2.0%), • Pneumonitis (0.5%), • Colitis (1.0%), • Pancreatitis (0.5%), • Rhabdomyolysis (0.5%), • Nephritis (0.5%), • Guillain–Barre Syndrome (0.5%)	• Neutropenia (0.5%), • Pneumonia (0.5%), • Unspecified cause (0.5%)
		Placebo + carboplatin + etoposide	196	92.3%	57.6%	24.5%	2.5%	• **IRAEs:** • Rash (10.2%), • Hypothyroidism (0.5%), • Hepatitis (4.6%), • Infusion-related reaction (5.1%), • Hyperthyroidism (2.6%), • Pneumonitis (2.6%), • Pancreatitis (1.0%), • Adrenal insufficiency (1.0%), • Nephritis (0.5%), • Vasculitis (0.5%)	• **IRAEs:** • Infusion-related reaction (0.5%), • Pneumonitis (1.0%), pancreatitis(1.0%)	• Pneumonia (0.5%), • Septic shock (0.5%), • Cardiopulmonary failure (0.5%)
	IFCT-1603 (NCT03059667)	Atezolizumab 1,200 mg	48	NA	NA	22.9%	NA	• **IRAEs:** • Hepatitis (4.2%), • Colitis (4.2%), • Arthralgia (6.3%), • Dysthyroidism (4.2%)	NA	None
		Chemotherapy	24	NA	NA	NA	NA	NA	NA	None

(Continued)

TABLE 3 | Continued

Target	NCT number	Treatment	Enrolled number	TRAEs	TRAEs (grade≥3)	IRAEs	IRAEs (grade≥3)	Most common TRAEs/IRAEs	TRAEs/IRAEs (grade≥3)	Death related to TRAEs/IRAEs
	CASPIAN (NCT03043872)	Durvalumab 1,500 mg + etoposide + platinum	265	89%	46%	20%	5%	**IRAEs:** • Hypothyroid (9%), • Hyperthyroid (5%), • Pneumonitis (3%), • Hepatic events (3%), • Dermatitis/rash (2%), • Diarrhoea/colitis (2%)	• **IRAEs:** • Pneumonitis (1%), • Hepatic events (2%), • Diarrhoea/colitis (<1%), • Type 1 diabetes mellitus (2%), • Pancreatic (<1%)	• **IRAEs:** • Cardiac arrest (<1%), • Dehydration (<1%), • Hepatotoxicity (<1%), • Pancytopenia (<1%), sepsis (<1%)
		Etoposide + platinum	266	90%	52%	3%	<1%	• IRAEs: • Hypothyroid (1%), • Pneumonitis (1%), • Dermatitis/rash (1%), • Diarrhoea/colitis (<1%)	• **IRAEs:** • Pneumonitis (<1%)	• Pancytopenia (<1%), • Thrombocytopenia/ haemorrhage (<1%)
	Goldman et al. (36)	Durvalumab 10 mg/kg	21	33%	0%	NA	NA	• **TRAEs:** • Nausea (9.5%), • Fatigue (9.5%), • Rash maculo-papular (9.5%)	None	None
CTLA-4	CA184-041 (NCT00527735)	Placebo/paclitaxel/ carboplatin	44	91%	30%	NA	9%	• **TRAEs:** • Rash (4.5%), • Pruritus (11.4%), • Diarrhea (25%)	• **TRAEs:** • Diarrhea (11.3%)	None
		Ipilimumab 10 mg/kg/placebo + paclitaxel/carboplatin (concurrent)	42	84%	43%	NA	21%	• **TRAEs:** • rash (73.8%), • pruritus (57.1%), • diarrhean (50%)	• **TRAEs:** • Diarrhea (9.5%), • ALT increases (16.7%), • AST increase (11.9%), • Hepatitis (2%)	Hepatotoxicity (2.4%)
		Ipilimumab 10 mg/kg/placebo + paclitaxel/carboplatin (phased)	42	95%	50%	NA	17%	• **TRAEs:** • Rash (57.1%), • Pruritus (40.4%), • Diarrhea (57.1%)	• **TRAEs:** • Diarrhean(23.8%), • Colitis (2.38%), • Arthralgia (9.52%), • ALT increases (4.76%), • AST increases (7.14%), • Hepatitis (2%)	None
	NCT01331525	Ipilimumab 10 mg/kg + carboplatin + etoposide	39	100%	89.7%	NA	NA	• **IRAEs:** • Diarrhea (72%), • Skin rash (51%)	• **IRAEs:** • Ipilimumab related neurological adverse events (7.6%)	• Cardiac arrest (2.56%), • Neutropenic sepsis (2.56%), • Pneumonia (2.56%), • Autoimmune encephalitis (2.56%), • Sepsis (2.56%)

(Continued)

TABLE 3 | Continued

Target	NCT number	Treatment	Enrolled number	TRAEs	TRAEs (grade≥3)	IRAEs	IRAEs (grade≥3)	Most common TRAEs/IRAEs	TRAEs/IRAEs (grade≥3)	Death related to TRAEs/IRAEs
	NCT01450761	Ipilimumab 10 mg/kg + etoposide + platinum (cisplatin + carboplatin)	478	82%	48%	57%	20%	• **IRAEs:** • Diarrhea (25%), • Rash (19%), • Pruritus (12%), • Colitis (6%), alopecia (5%)	• **IRAEs:** • Rash (2%), • Pruritus (1%), • Diarrhea (7%), • Colitis (4%), • ALT increased (1%), • AST increased (1%)	• Colitis (0.42%), • Liver toxicity (0.21%)
		Placebo + etoposide + platinum (cisplatin + carboplatin)	476	76%	44%	28%	2%	• **IRAEs:** • Diarrhea (10%), • Rash (3%), • Pruritus (2%), • Colitis (1%), • Alopecia (7%)	• **IRAEs:** • Diarrhea (1%)	• Sepsis (0.21%), • Bone marrow suppression (0.21%)
Double ICIs	CheckMate 451 (NCT02538666)	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg	278	86%	52%	NA	NA	NA	NA	NA
		Nivolumab 1 mg/kg	279	61%	12%	NA	NA	NA	NA	NA
		Placebo	273	50%	8%	NA	NA	NA	NA	NA
	CheckMate032	(NCT01928394)	Nivolumab 3 mg/kg	98	53%	13%	NA	NA	• **TRAEs:** • Fatigue (11%), • Pruritus (11%), • Diarrhoea (7%), • Nausea (7%), • Decreased appetite (6%), • Pneumonitis (3%), • Vomiting (3%), • Hypothyroidism (3%), • Hyperthyroidism (2%), • Rash (2%) All <1%	None

(Continued)

TABLE 3 | Continued

Target	NCT number	Treatment	Enrolled number	TRAEs	TRAEs (grade≥3)	IRAEs	IRAEs (grade≥3)	Most common TRAEs/IRAEs	TRAEs/IRAEs (grade≥3)	Death related to TRAEs/IRAEs
		Nivolumab 1 mg/kg + ipilimumab 3 mg/kg	61	79%	30%	NA	NA	• **TRAEs:** • Fatigue (26%), • Pruritus (20%), • Diarrhoea (21%), • Nausea (12%), • Decreased appetite (7%), • Pneumonitis (3%), • Vomiting (5%), • Hypothyroidism (17%), • Hyperthyroidism (11%), • Rash (19%)	• **TRAEs:** • Increased lipase (9%), • Diarrhoea (5%)	• Myasthenia gravis (2%), • Worsening of renal failure (2%)
		Nivolumab 3 mg/kg + ipilimumab 1 mg/kg	54	75%	19%	NA	NA	• **TRAEs:** • Fatigue (22%), • Pruritus (9%), • Diarrhoea (17%), • Nausea (7%), • Decreased appetite (11%), • Pneumonitis (6%), • Vomiting (9%), • Hypothyroidism (7%), • Hyperthyroidism (6%), • Rash (7%)	• **TRAEs:** • Dyspnoea (4%)	Pneumonitis (1%)
	NCT02261220	Durvalumab 20 mg/kg + tremelimumab 1 mg/kg	30	67%	23%	NA	NA	• **TRAEs:** Fatigue (23%), Pruritus (23%)	NA	NA
	BALTIC (NCT02937818)	Durvalumab 1,500 mg + tremelimumab 75 mg	25	NA	19%	NA	NA	NA	NA	NA
	CASPIAN (NCT03043872)	Durvalumab 1,500 mg + tremelimumab 75 mg + platinum + etoposide	266	90%	55%	36%	14%	• **IRAEs:** • Hypothyroid events (9%), • Hyperthyroid events (8%), • Diarrhoea/colitis (8%), • Dermatitis/rash (7%), • Hepatic events (4%), • Pneumonitis (3%)	• **IRAEs:** • Diarrhoea/colitis (3%), • Dermatitis/rash (2%), • Hepatic events (3%),	• Enterocolitis (0.5%), • Pneumonitis (0.5%), • Pneumonitis and hepatitis in the same patient (0.5%)
		Durvalumab 1,500 mg + platinum + etoposide	265	89%	46%	20%	5%	• **IRAEs:** • Hypothyroid events (9%), • Hyperthyroid events (5%), • Hepatic events (3%), • Pneumonitis (3%)	• **IRAEs:** • Diarrhoea/colitis (1%), • Type 1 diabetes mellitus (2%),	• Hepatotoxicity (0.5%), • Interstitial lung disease (0.5%)
		Platinum + etoposide	266	90%	52%	3%	<1%	• **IRAEs:** • Hypothyroid events (1%), • Diarrhoea/colitis (1%), • Pneumonitis (1%)	• **IRAEs:** • Pneumonitis (<1%)	Pneumonitis (<1%)

AST, aspartate aminotransferase; ALT, alanine transaminase; NA, not available.

pembrolizumab as third-line therapy presented the tolerable response for relapsed SCLC. Pembrolizumab combined with thoracic radiotherapy or concurrent chemoradiation therapy presented a good degree of tolerance in preliminary findings. Pembrolizumab combined with platinum–etoposide as the first-line therapy for ES-SCLC patients improved PFS, but the significance threshold for OS was not reached. In contrast, nivolumab monotherapy and pembrolizumab combined with chemotherapy were all not superior to chemotherapy as second-line therapy in recurrent SCLC. Another anti-PD1, tislelizumab plus platinum–etoposide, presented a higher ORR for Chinese ES-SCLC patients, but the result needs to be validated in further studies with large sample sizes. Anti-PD-L1 inhibitors atezolizumab and durvalumab both improved the survival benefits of chemotherapy for SCLC patients, but atezolizumab monotherapy or durvalumab monotherapy failed in second-line therapy for refractory SCLC patients. The results of CTLA-4 inhibitors were also dismal. Ipilimumab monotherapy or combined with chemotherapy did not exhibit significant efficacy for newly diagnosed ES-SCLC patients and refractory ES-SCLC patients. Moreover, existing studies could not affirm the efficacy of the combined checkpoint inhibitors in SCLC, as the results of the durvalumab and tremelimumab arm of the CASPIAN study are still pending. However, the double checkpoint inhibitors increased the risk of irAEs. The overall irAEs' occurrence rate in patients with SCLC ranged from 20% (CASPIAN) to 57% (NCT01450761) (**Table 3**). The most commonly reported irAEs were rash, diarrhea, hypothyroidism/hyperthyroidism, colitis, and pneumonia. In addition, nephritis, hepatitis, pancreatitis, and some nervous system-related irAEs were observed. The rate of high grade (grade $\geq$3) irAEs was less than 10% in most trials, and most irAEs were manageable through systematic therapy in most studies. Pneumonitis was the most frequently reported death-related irAE. Hypothyroidism and hyperthyroidism are reported relatively less frequently in CTLA-4 inhibitors compared with PD-1/PD-L1 inhibitors, which was consistent with the findings of a previous study (67). No special safety data were reported. To determine different rates and types of irAEs in SCLC, we compared irAEs reported in other cancer type cohorts from the Checkmate 032, Keynote 028, Keynote 158, NCT01375842 and NCT03432598 (**Supplementary Table 1**) studies; however, no specific irAEs of SCLC were found. Furthermore, it is difficult to further quantify and compare these indicators because of the variations between studies in terms of the length of median follow-up. Moreover, irAEs in most trials were evaluated by the investigators, which might not be objective and could be lacking a uniform standard. Some studies only reported TRAEs instead of irAEs, and the details of irAEs in most trials are unavailable.

In the 23 trials included (**Table 2**) in this review, the most commonly reported irAEs/TRAEs were mild. Pneumonitis was the most frequently reported death-related irAE. Other death-related irAEs include colitis/intestinal ischemia, encephalopathy, neutropenic sepsis, cardiopulmonary failure, hepatotoxicity, myasthenia gravis, worsening of renal failure, sepsis, and septic shock. Nevertheless, these only account a tiny proportion of irAEs, usually less than 5%. Serious irAEs were the indicator for ICI reduction or discontinuation in most studies, but the treatment details of irAEs were not described.

Some guidelines have been published for the diagnosis and management of irAEs (68, 69). IrAEs are graded according to the Common Terminology Criteria for Adverse Events. Mild irAEs graded 1 or 2 could gradually disappear after the discontinuation of ICIs. Moreover, the early identification is of great importance for the management of irAEs. Serious irAEs (grade $\geq$3) threaten the patients' life, corticosteroid therapy was usually needed, and the associated complications, such as infection, were also a source of concern. During the period of clinical therapy, the irAEs had greater complexity, hence individualized treatment and management strategies could be a future research direction.

Furthermore, the study areas of irAEs in SCLC patients that should be addressed are as follows: [1] peculiar irAEs, such as Fanconi syndrome, which was reported in an ES-SCLC patient after he received nivolumab plus ipilimumab as second-line therapy (70); [2] the occurrence rate of irAEs, as this was higher in a real-world report (71); [3] the difference in irAEs between SCLC and NSCLC, as a previous meta-analysis has reported that the occurrence of ICI-related TRAEs in SCLC patients was higher than that in NSCLC patients (72); [4] irAEs of other ICI agents and combination therapies, as new target ICI agents and combination strategies are emerging in SCLC (73); and [5] irAEs of specific populations, as patients with autoimmune diseases are usually excluded from clinical trials, but many patients with SCLC experience paraneoplastic syndromes, and therefore the advantages or disadvantages of ICIs for these populations should be explored in future studies.

CONCLUSION AND PROSPECTS

The current review summarizes the efficacy and safety data of ICIs in all existing clinical trials in the SCLC treatment field. ICI agents generally demonstrate a promising clinical activity in SCLC therapy, with manageable irAEs, although more detailed data are required. Future study directions include finding reliable biomarkers for the selection of patients that will most benefit from therapy, and verifying the rationale of various combination therapeutic regimens. Moreover, further details regarding irAEs are encouraged to be record and reported in future investigations, which could be of great significance for clinical practice and would benefit the increasing number of patients with SCLC.

AUTHOR CONTRIBUTIONS

WH, XZ, CY, and HZ: conception and design and collection and assembly of data. CY: administrative support. CY and HZ: provision of study materials or patients. WH and XZ: manuscript writing. All authors final approval of manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.604227/full#supplementary-material

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA.* (2018) 68:394–424. doi: 10.3322/caac.21492
2. Semenova E, Nagel R, Berns A. Origins, genetic landscape, and emerging therapies of small cell lung cancer. *Genes Dev.* (2015) 29:1447–62. doi: 10.1101/gad.263145.115
3. Calles A, Aguado G, Sandoval C, Álvarez R. The role of immunotherapy in small cell lung cancer. *Clin Translat Oncol.* (2019) 21:961–76. doi: 10.1007/s12094-018-02011-9
4. Zimmerman S, Das A, Wang S, Julian R, Gandhi L, Wolf J. 2017–2018 scientific advances in thoracic oncology: small cell lung cancer. *J Thoracic Oncol.* (2019) 14:768–83. doi: 10.1016/j.jtho.2019.01.022
5. Van Meerbeeck JP, Fennell DA, De Ruysscher DKM. Small-cell lung cancer. *Lancet.* (2011) 378:1741–55. doi: 10.1016/S0140-6736(11)60165-7
6. Simeone E, Grimaldi A, Festino L, Trojaniello C, Vitale M, Vanella V, et al. Nivolumab for the treatment of small cell lung cancer. *Exp Rev Respirat Med.* (2020) 14:5–13. doi: 10.1080/17476348.2020.1681977
7. Eckardt JR, Joachim VP, Jean-Louis P, Zsolt P, Elisabeth Q, Andrea A, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol Official.* (2007) 25:2086–92. doi: 10.1200/JCO.2006.08.3998
8. Owonikoko TK, Behera M, Chen Z, Bhimani C, Ramalingam SS. Meta-analysis of second line chemotherapy efficacy in sensitive and refractory small cell lung cancer (SCLC) patients. *J Thoracic Oncol.* (2010) 5:S551–2. doi: 10.1097/JTO.0b013e31824c7f4b
9. Facchinetti F, Di Maio M, Tiseo M. Adding PD-1/PD-L1 inhibitors to chemotherapy for the first-line treatment of extensive stage small cell lung cancer (SCLC): a meta-analysis of randomized trials. *Cancers.* (2020) 12:2645. doi: 10.3390/cancers12092645
10. Wang B, Xiao B, Li P, Kuang B, Chen W, Li P, et al. Efficacy and safety of first-line immunotherapy in combination with chemotherapy for patients with extensive-stage small cell lung cancer: a systematic review and network meta-analysis. *J Oncol.* (2020) 2020:2368164. doi: 10.1155/2020/2368164
11. Zhou T, Zhang Z, Luo F, Zhao Y, Hou X, Liu T, et al. Comparison of first-line treatments for patients with extensive-stage small cell lung cancer: a systematic review and network meta-analysis. *JAMA Netw Open.* (2020) 3:e2015748. doi: 10.1001/jamanetworkopen.2020.15748
12. Sławiński G, Wrona A, Dabrowska-Kugacka A, Raczak G, Lewicka E. Immune checkpoint inhibitors and cardiac toxicity in patients treated for non-small lung cancer: a review. *Int J Mol Sci.* (2020) 21:7195. doi: 10.3390/ijms21197195
13. Liu YH, Zang XY, Wang JC, Huang SS, Xu J, Zhang P. Diagnosis and management of immune related adverse events (irAEs) in cancer immunotherapy. *Biomed Pharmacother.* (2019) 120:109437. doi: 10.1016/j.biopha.2019.109437
14. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. *JAMA Oncol.* (2016) 2:1346–53. doi: 10.1001/jamaoncol.2016.1051
15. Park R, Lopes L, Saeed A. Anti-PD-1/L1-associated immune-related adverse events as harbinger of favorable clinical outcome: systematic review and meta-analysis. *Clin Transl Oncol.* (2020) 23:100–9. doi: 10.1007/s12094-020-02397-5
16. Shimozaki K, Sukawa Y, Beppu N, Kurihara I, Suzuki S, Mizuno R, et al. Multiple immune-related adverse events and anti-tumor efficacy: real-world data on various solid tumors. *Cancer Manage Res.* (2020) 12:4585–93. doi: 10.2147/CMAR.S247554
17. Iams WT, Porter J, Horn L. Immunotherapeutic approaches for small-cell lung cancer. *Nat Rev Clin Oncol.* (2020) 17:300–12. doi: 10.1038/s41571-019-0316-z
18. Quandt D, Hoff H, Rudolph M, Fillatreau S, Brunner-Weinzierl MC. A new role of CTLA-4 on B cells in thymus-dependent immune responses *in vivo*. *J Immunol.* (2007) 179:7316–24. doi: 10.4049/jimmunol.179.11.7316
19. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science.* (2011) 331:1565–70. doi: 10.1126/science.1203486
20. Sznol M, Chen L. Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer–response. *Clin Cancer Res.* (2013) 19:5542. doi: 10.1158/1078-0432.CCR-13-2234
21. Zhou X, Hou W, Gao L, Shui L, Yi C, Zhu H. Synergies of antiangiogenic therapy and immune checkpoint blockade in renal cell carcinoma: from theoretical background to clinical reality. *Front Oncol.* (2020) 10:1321. doi: 10.3389/fonc.2020.01321
22. Longo DL, Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med.* (2018) 378:158–68. doi: 10.1056/NEJMra1703481
23. Byrne EH, Fisher DE. Immune and molecular correlates in melanoma treated with immune checkpoint blockade. *Cancer.* (2017) 123:2143. doi: 10.1002/cncr.30444
24. Callahan MK, Yang A, Tandon S. Evaluation of serum IL-17 levels during ipilimumab therapy: correlation with colitis. *J Clin Oncol.* (2011) 29:319–21. doi: 10.1200/jco.2011.29.15_suppl.2505
25. Fan Y, Geng Y, Shen L, Zhang Z. Advances on immune-related adverse events associated with immune checkpoint inhibitors. *Front Med.* (2020) 15:33–42. doi: 10.1007/s11684-019-0735-3
26. Mangan B, McAlister R, Balko J, Johnson D, Moslehi J, Gibson A, et al. Evolving insights into the mechanisms of toxicity associated with immune checkpoint inhibitor therapy. *Br J Clin Pharmacol.* (2020) 86:1778–89. doi: 10.1111/bcp.14433
27. Alissafi T, Hatzioannou A, Legaki A, Varveri A, Verginis P. Balancing cancer immunotherapy and immune-related adverse events: the emerging role of regulatory T cells. *J Autoimmunity.* (2019) 104:102310. doi: 10.1016/j.jaut.2019.102310
28. Chalmers Z, Connelly C, Fabrizio D, Gay L, Ali S, Ennis R, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med.* (2017) 9:34. doi: 10.1186/s13073-017-0424-2
29. McGranahan N, Furness A, Rosenthal R, Ramskov S, Lyngaa R, Saini S, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science.* (2016) 351:1463–9. doi: 10.1126/science.aaf1490
30. Reck M, Schenker M, Lee K, Provencio M, Nishio M, Lesniewski-Kmak K, et al. Nivolumab plus ipilimumab versus chemotherapy as first-line treatment in advanced non-small-cell lung cancer with high tumour mutational burden: patient-reported outcomes results from the randomised, open-label, phase III CheckMate 227 trial. *Eur J Cancer.* (2019) 116:137–47. doi: 10.1016/j.ejca.2019.05.008
31. Rizvi N, Hellmann M, Snyder A, Kvistborg P, Makarov V, Havel J, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science.* (2015) 348:124–8. doi: 10.1126/science.aaa1348
32. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. *Science.* (2015) 348:69–74. doi: 10.1126/science.aaa4971
33. Iams WT, Shiuan E, Meador CB, Roth M, Bordeaux J, Vaupel C, et al. Improved prognosis and increased tumor-infiltrating lymphocytes in patients who have SCLC with neurologic. *J Thorac Oncol.* (2019) 14:1970–81. doi: 10.1016/j.jtho.2019.05.042
34. Maddison P, Newsom-Davis J, Mills K, Souhami R. Favourable prognosis in Lambert-Eaton myasthenic syndrome and small-cell lung carcinoma. *Lancet.* (1999) 353:117–8. doi: 10.1016/S0140-6736(05)76153-5
35. Reck M, Vicente D, Ciuleanu T, Gettinger S, Peters S, Horn L, et al. LBA5 – Efficacy and safety of nivolumab (nivo) monotherapy versus chemotherapy (chemo) in recurrent small cell lung cancer (SCLC): results from CheckMate 331. *Annals Oncol.* (2018) 29:43. doi: 10.1093/annonc/mdy511.004
36. Goldman JW, Dowlati A, Antonia SJ, Nemunaitis JJ, Gadgeel SM. Safety and antitumor activity of durvalumab monotherapy in patients with pretreated extensive disease small-cell lung cancer (ED-SCLC). *J Clin Oncol.* (2018) 36:8518. doi: 10.1200/JCO.2018.36.15_suppl.8518
37. Cai H, Zhang H, Jiang Y. Prognostic and clinicopathological value of programmed cell death ligand1 expression in patients with small cell lung cancer: a meta-analysis. *Front Oncol.* (2020) 10:1079. doi: 10.3389/fonc.2020.01079
38. Melosky B, Cheema P, Brade A, McLeod D, Liu G, Price P, et al. Prolonging survival: the role of immune checkpoint inhibitors in the treatment of extensive-stage small cell lung cancer. *Oncologist.* (2020) 25:981–92. doi: 10.1634/theoncologist.2020-0193

39. Reddy H, Qin A, Kalemkerian G. Emerging drugs for small cell lung cancer: a focused review on immune checkpoint inhibitors. *Exp Opin Emerg Drugs.* (2020) 25:353–66. doi: 10.1080/14728214.2020.1798929
40. Mansfield A, Kazarnowicz A, Karaseva N, Sanchez A, De Boer R, Andric Z, et al. Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small-cell lung cancer (IMpower133): a randomized phase I/III trial. *Annals Oncol.* (2020) 31:310–7. doi: 10.1016/j.annonc.2019.10.021
41. Huang W, Chen J, Xing R, Zeng Y. Combination therapy: Future directions of immunotherapy in small cell lung cancer. *Translat Oncol.* (2020) 14:100889. doi: 10.1016/j.tranon.2020.100889
42. Xue Y, Gao S, Gou J, Yin T, He H, Wang Y, et al. Platinum-based chemotherapy in combination with PD-1/PD-L1 inhibitors: preclinical and clinical studies and mechanism of action. *Exp Opin Drug Delivery* 2020:1–17. doi: 10.1080/17425247.2021.1825376
43. Ready N, Farago A, de Braud F, Atmaca A, Hellmann M, Schneider J, et al. Third-Line Nivolumab Monotherapy in Recurrent SCLC: checkMate 032. *J Thoracic Oncol.* (2019) 14:237–44. doi: 10.1016/j.jtho.2018.10.003
44. Fessas P, Lee H, Ikemizu S, Janowitz T. A molecular and preclinical comparison of the PD-1-targeted T-cell checkpoint inhibitors nivolumab and pembrolizumab. *Semin Oncol.* (2017) 44:136–40. doi: 10.1053/j.seminoncol.2017.06.002
45. Ott PA, Elez E, Hiret S, Kim DW, Morosky A, Saraf S, et al. Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the phase Ib KEYNOTE-028 study. *J Clin Oncol.* (2017) 35:3823–9. doi: 10.1200/JCO.2017.72.5069
46. Chung HC, Lopez-Martin JA, Kao CH, Miller WH, Piha-Paul SA. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158. *J Clin Oncol.* (2018) 36:8506. doi: 10.1200/JCO.2018.36.15_suppl.8506
47. Chung H, Piha-Paul S, Lopez-Martin J, Schellens J, Kao S, Miller W, et al. Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: results from the KEYNOTE-028 and KEYNOTE-158 studies. *J Thoracic Oncol.* (2020) 15:618–27. doi: 10.1016/j.jtho.2019.12.109
48. Gadgeel S, Pennell N, Fidler M, Halmos B, Bonomi P, Stevenson J, et al. Phase II study of maintenance pembrolizumab in patients with extensive-stage small cell lung cancer (SCLC). *J Thoracic Oncol.* (2018) 13:1393–9. doi: 10.1016/j.jtho.2018.05.002
49. Welsh J, Heymach J, Chen D, Verma V, Cushman T, Hess K, et al. Phase I trial of pembrolizumab and radiation therapy after induction chemotherapy for extensive-stage small cell lung cancer. *J Thoracic Oncol.* (2020) 15:266–73. doi: 10.1016/j.jtho.2019.10.001
50. Kim YJ, Keam B, Ock CY, Song S, Heo DS. A phase II study of pembrolizumab and paclitaxel in patients with relapsed or refractory small-cell lung cancer. *Lung Cancer.* (2019) 136:122–8. doi: 10.1016/j.lungcan.2019.08.031
51. Rudin C, Awad M, Navarro A, Gottfried M, Peters S, Csoszi T, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. *J Clin Oncol.* (2020) 38:2369–79. doi: 10.1200/JCO.20.00793
52. Wang Z, Zhao J, Ma Z, Cui J, Shu Y, Liu Z, et al. A Phase 2 Study of tislelizumab in combination with platinum-based chemotherapy as first-line treatment for advanced lung cancer in chinese patients. *Lung Cancer.* (2020) 147:259–68. doi: 10.1016/j.lungcan.2020.06.007
53. Sequist LV, Chiang A, Gilbert J, Gordon M, Gettinger S. Clinical activity, safety and predictive biomarkers results from a phase Ia atezolizumab (atezo) trial in extensive-stage small cell lung cancer (ES-SCLC). *Annals Oncol.* (2016) 27(suppl_6):vi493. doi: 10.1093/annonc/mdw389.03
54. Horn L, Mansfield A, Szczęsna A, Havel L, Krzakowski M, Hochmair M, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med.* (2018) 379:2220–9. doi: 10.1056/NEJMoa1809064
55. Pujol J, Greillier L, Audigier-Valette C, Moro-Sibilot D, Uwer L, Hureaux J, et al. A randomized non-comparative phase II study of anti-programmed cell death-ligand 1 atezolizumab or chemotherapy as second-line therapy in patients with small cell lung cancer: results from the IFCT-1603 trial. *J Thoracic Oncol.* (2019) 14:903–13. doi: 10.1016/j.jtho.2019.01.008
56. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet.* (2019) 394:1929–39. doi: 10.1016/S0140-6736(19)32222-6
57. Reck M, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. *Annals Oncol.* (2013) 24:75–83. doi: 10.1093/annonc/mds213
58. Arriola E, Wheater M, Galea I, Cross N, Maishman T, Hamid D, et al. Outcome and biomarker analysis from a multicenter phase 2 study of ipilimumab in combination with carboplatin and etoposide as first-line therapy for extensive-stage SCLC. *J Thoracic Oncol.* (2016) 11:1511–21. doi: 10.1016/j.jtho.2016.05.028
59. Reck M, Luft A, Szczesna A, Havel L, Kim S, Akerley W, et al. Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. *J Clin Oncol.* (2016) 34:3740–8. doi: 10.1200/JCO.2016.67.6601
60. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob J-J, Rutkowski P, Cowey CL, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol.* (2018) 19:1480–92. doi: 10.1016/S1470-2045(18)30700-9
61. Scherpereel A, Mazieres J, Greillier L, Lantuejoul S, Dô P, Bylicki O, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. *Lancet Oncol.* (2019) 20:239–53. doi: 10.1016/S1470-2045(18)30765-4
62. Antonia S, López-Martin J, Bendell J, Ott P, Taylor M, Eder J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol.* (2016) 17:883–95. doi: 10.1016/S1470-2045(16)30098-5
63. Ready N, Owonikoko TK, Postmus PE, Zhu H. CheckMate 451: a randomized, double-blind, phase III trial of nivolumab (nivo), nivo plus ipilimumab (ipi), or placebo as maintenance therapy in patients (pts) with extensive-stage disease small cell lung cancer (ED-SCLC) after first-line platinum-based doublet chemotherapy (PT-DC). *J Clin Oncol.* (2016) 34(15_Suppl). doi: 10.1200/JCO.2016.34.15_suppl.TPS8579
64. Cho DC, Mahipal A, Dowlati A, Chow WA, Segal NH, Chung KY, et al. Safety and clinical activity of durvalumab in combination with tremelimumab in extensive disease small-cell lung cancer (ED-SCLC). *J Clin Oncol.* (2018) 36:8517. doi: 10.1200/JCO.2018.36.15_suppl.8517
65. Bondarenko I, Juan-Vidal O, Pajkos G, Kryzhanivska A, Pápai Székely Z, Vicente D, et al. 1665PDPreliminary efficacy of durvalumab plus tremelimumab in platinum-refractory resistant ED-SCLC from arm A of the phase II BALTIC study. *Annal Oncol.* (2018) 29(suppl_8). doi: 10.1093/annonc/mdy298.001
66. Goldman J, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol.* (2021) 22:51–65. doi: 10.1016/S1470-2045(20)30539-8
67. Del Rivero J, Cordes L, Klubo-Gwiezdzinska J, Madan R, Nieman L, Gulley J. Endocrine-related adverse events related to immune checkpoint inhibitors: proposed algorithms for management. *Oncologist.* (2020) 25:290–300. doi: 10.1634/theoncologist.2018-0470
68. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Thompson JA. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy american society of clinical oncology clinical practice guideline. *J Oncol Pract.* (2018) 36:JOP1800005. doi: 10.1200/JOP.18.00005
69. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Scavone JL. Management of immunotherapy-related toxicities, version 1.2019, NCCN clinical practice guidelines in oncology. *J Natl Comprehens Cancer Netw.* (2019) 17:255–89. doi: 10.6004/jnccn.2019.0013
70. Farid S, Latif H, Nilubol C, Kim C. Immune checkpoint inhibitor-induced fanconi syndrome. *Cureus.* (2020) 12:e7686. doi: 10.7759/cureus.7686

71. Schmid S, Mauti LA, Friedlaender A, Blum V, Früh M. Outcomes with immune checkpoint inhibitors for relapsed small-cell lung cancer in a Swiss cohort. *Cancer Immunol Immunother.* (2020) 69:1605–13. doi: 10.1007/s00262-020-02565-0
72. Shao J, Wang C, Ren P, Jiang Y, Tian P, Li W. Treatment- and immune-related adverse events of immune checkpoint inhibitors in advanced lung cancer. *Biosci Rep.* (2020) 40:BSR20192347. doi: 10.1042/BSR20192347
73. Saltos A, Shafique M, Chiappori A. Update on the biology, management, and treatment of small cell lung cancer (SCLC). *Front Oncol.* (2020) 10:1074. doi: 10.3389/fonc.2020.01074

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Immunology

SYSTEMATIC REVIEW
published: 30 March 2021
doi: 10.3389/fimmu.2021.627197

Toxicity Profile of Combining PD-1/PD-L1 Inhibitors and Thoracic Radiotherapy in Non-Small Cell Lung Cancer: A Systematic Review

*Butuo Li[1], Chao Jiang[2], Linlin Pang[1], Bing Zou[1], Mingjun Ding[1,3], Xindong Sun[1], Jinming Yu[1] and Linlin Wang[1]**

[1] Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Science, Jinan, China, [2] Department of Otorhinolaryngology & Head and Neck Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China, [3] Department of Radiation Oncology, Shandong First Medical University and Shandong Academy of Medical Sciences, Tai'an, China

OPEN ACCESS

Edited by:
Xuelei Ma,
Sichuan University, China

Reviewed by:
Michael Orth,
University Hospital LMU Munich, Germany
Michael Hader,
University Hospital Erlangen, Germany

***Correspondence:**
Linlin Wang
wanglinlinatjn@163.com

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Immunology

Received: *08 November 2020*
Accepted: *02 March 2021*
Published: *30 March 2021*

Citation:
Li B, Jiang C, Pang L, Zou B, Ding M, Sun X, Yu J and Wang L (2021) Toxicity Profile of Combining PD-1/PD-L1 Inhibitors and Thoracic Radiotherapy in Non-Small Cell Lung Cancer: A Systematic Review. Front. Immunol. 12:627197. doi: 10.3389/fimmu.2021.627197

Background: The combination of immune checkpoint inhibitors (ICIs) and thoracic radiotherapy (TRT) has shown significant clinical activity in patients with non-small cell lung cancer (NSCLC). However, the currently available data on adverse events (AEs) were derived from a small subset of patients included in prospective clinical trials or retrospective studies. Thus, we conducted this systematic review to determine the AEs associated with this combination treatment.

Methods: An electronic literature search was performed in databases and conference proceedings of prospective clinical trials assessing the combination of ICIs and TRT for patients with NSCLC. The systematic analysis was conducted to determine the profile and incidence of AEs of combination treatment. We further performed the comparison of AEs between programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors, and sequential and concurrent administration of ICIs and TRT to help identify high risk patients. The systematic analyses were conducted with the Review Manager (version 5.3; The Cochrane Collaboration, Oxford, United Kingdom) and Stata version 12.0 (StataCorp, College Station, TX, USA) software.

Results: Eleven clinical trials involving 1,113 patients with NSCLC were eligible for analysis. The incidence of all-grade AEs was 95.5%; that of high-grade AEs (grade ≥3) was 30.2%. The most frequent all-grade AE was fatigue (49.7%), while pneumonitis was the most common high-grade AE (3.8%) and grade 5 AE (0.6%). Notably, the toxicity profiles of PD-1 and PD-L1 inhibitors were similar. Concurrent treatment was associated with a higher incidence of higher-grade AEs (41.6% vs 24.8%, P=0.17) and pneumonitis (7.1% vs 3.9%, P=0.14) compared to sequential treatment, but no significant difference was observed.

Conclusion: Most AEs of this combination treatment are tolerable; as the most common high-grade AE, pneumonitis deserves the utmost attention of physicians. The toxicity

profiles of patients receiving PD-1 or PD-L1 were similar, and no significant difference was observed between concurrent and sequential treatment.

Keywords: toxicity profile, safety, immunotherapy, immune checkpoint inhibitors, thoracic radiotherapy, systemic analysis

INTRODUCTION

Cancer immunotherapy targets immunosuppressive molecules, such as programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) and cytotoxic T-lymphocyte associated antigen 4 (CTLA-4). These immune checkpoint inhibitors (ICIs) were successfully used for the treatment of patients with non-small cell lung cancer (NSCLC) of all stages and shown significant clinical activity and marked efficacy (1–3). This type of therapy has been approved by the US Food and Drug Administration for both first-and second-line treatment of metastatic NSCLC, based on significant improvements in overall response rate, progression-free survival (PFS), and overall survival (OS) (1–6). In addition, radiotherapy (RT) is also an important treatment modality for lung cancer, exerting its effects by damaging the DNA of tumor cells (7). Importantly, RT has also been recognized as an immune modulator (8). It can not only function as an "*in-situ* vaccine" by increasing the presentation of tumor-specific antigens (9), but also modulates the local tumor environment, resulting in an enhanced immune response (10).

Multiple preclinical studies have suggested a synergistic activity between ICIs and RT, by inducing the activation and recruitment of more antitumor effector T cells (11, 12), as well as the modulation of the tumor immune microenvironment (from "cold" tumor to "hot" tumor) (13–15). In addition, it has been indicated that the synergistic activity of ICIs and RT translates into prolonged survival and abscopal effect in preclinical animal models (16, 17). Furthermore, recent clinical trials also suggested the amplified antitumor effect of combination of ICIs and thoracic radiotherapy (TRT) in patients with NSCLC. The secondary analysis of 98 metastatic NSCLC patients treated with pembrolizumab in Keynote-001 trial compared patients who received previous RT with those who did not. The results revealed significantly prolonged PFS (4.4 vs. 2.1 months, respectively, P=0.019) and OS (10.7 vs. 5.3 months, respectively, P=0.026) in the former group (18). The PACIFIC trial performed the comparison of durvalumab against placebo after definitive chemoradiation for stage III NSCLC. Treatment with durvalumab was associated with significant improvements of PFS (17.2 vs 5.6 months, respectively, P<0.001) and OS (28.3 vs. 16.2 months, respectively, P<0.001) (6).

Of note, the synergistic effect of combining TRT and ICIs through modulation of the immune response may also affect the spectrum, incidence, and severity of treatment-related AEs. By targeting T cell negative feedback loops, the ICIs can impair the immune tolerance of the tumor and induce the infiltration of immune cells in normal tissues, resulting in autoimmune disease or syndromes and distinctive toxicity profiles, such as pneumonitis and thyroid dysfunction (19, 20). RT may cause a wide range of AEs through the ionizing radiation-induced DNA damage and subsequent inflammation on normal tissues, including pneumonitis, mucositis, esophagitis, fibrosis (particularly in lung tissue), and others (21).

Owing to a certain degree of overlap of the toxicity mechanism and spectrum, the combination of ICIs and TRT may exacerbate the toxicity in patients with NSCLC, particularly pneumonitis. Both the Keynote-001 and PACIFIC studies indicated a higher incidence of all-grade pneumonitis in patients who received the combination therapy. Nevertheless, the risk of developing high-grade pneumonitis did not increase significantly (6, 18). Importantly, the available evidence regarding the AEs of the combination of ICIs with TRT is limited and derived from a small subset of patients included in prospective clinical trials or retrospective studies (22).

An enhanced understanding of the spectrum and severity of toxicity would enable better prevention and management of the AEs of this combination therapy, thereby informing the clinical application and design of prospective trials. This systematic review focused on prospective clinical trials assessing the AEs of combination of ICIs with TRT in patients with NSCLC, in order to provide a complete toxicity profile and investigate the incidence of AEs of combination treatment. Notably, the treatment sequence, type of ICIs and RT was thought to have impact on the occurrence of toxicity of combination therapy. We further evaluated the role of different ICIs or treatment sequence on the incidence of AEs, so as to help identify high risk patients and guide the clinical administration of combination of ICIs and TRT.

MATERIALS AND METHODS

Study Search and Inclusion Criteria

A comprehensive and methodical literature search was conducted to identify all prospective clinical trials investigating the combination of ICIs and TRT for patients with NSCLC. Data searches were conducted in databases, including PubMed, Embase, and the Cochrane database, from January 2000 to November 2020. Keywords included NSCLC, RT, immune checkpoint, PD-1, PD-LI, and specific ICIs drug names. Clinical trials that met the following inclusion criteria were taken into account: (1) patients with histologically confirmed NSCLC; (2) NSCLC patients receiving combination of ICIs and TRT treatment; (3) studies reporting AEs; (4) studies published in English. Retrospective studies were excluded in order to minimize the risk of bias. Abstracts and presentations were also reviewed to identify relevant clinical trials from major conference proceedings, including the American Society of Clinical Oncology, European Society of Medical Oncology, and

American Society for Radiation Oncology Annual Meeting, between 2010 and 2020. The detailed information of the search strategy for the eligible studies is presented in the flow diagram according to PRISMA. All studies identified by the search strategy that met the eligibility criteria were evaluated by two independent reviewers.

Data Extraction and Statistical Analysis

The following information was extracted from each study: National Clinical Trial number, first author, year of publication, phase of the trial, number of patients available for the analysis, age, gender, smokers, histology, line of therapy, type and dose of ICIs drugs, control groups, patterns of combination of ICIs and TRT, dose and segmentation of radiation, and number and incidence of AEs of interest (including fatigue, respiratory system, gastrointestinal tract, skin, and endocrine system toxicities). Newcastle-Ottawa-Scale (NOS) evaluation was performed to assess the quality of included studies. All data were independently reviewed and extracted by two investigators.

Some degree of heterogeneity was expected; thus, the data on AEs extracted from the studies were analyzed using DerSimonian and Laird random effect models. The inverse variance method was used to calculate the pooled incidence of AEs and their 95% confidence interval (CI). Statistical heterogeneity was evaluated with the Cochrane chi-squared test and I^2 statistics. The publication bias was assessed by Egger's linear regression test and funnel plots recommended by the Cochrane Collaboration. $P < 0.05$ was defined as significant publication bias, then non-parametric "trim-and-fill" method was performed to minimize the influence of publication bias on the results. The Z test was used to compare the AEs linked to PD-1 and PD-L1 inhibitors, as well as the sequential and concurrent administration of ICIs and TRT. All analyses were performed using the Review Manager (version 5.3; The Cochrane Collaboration, Oxford, United Kingdom) and Stata version 12.0 (StataCorp, College Station, TX, USA) software. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Characteristics of Eligible Studies

A total of 623 studies were retrieved and reviewed from the database searches. Of those, 56 duplicate studies were excluded. After careful screening and assessment, 11 clinical trials involving 1,113 patients with NSCLC were finally included in the analysis (6, 23–33). **Figure 1** illustrates the flow diagram of study selection.

The main characteristics of the included studies are summarized in **Table 1**. The NOS of included studies ranged from 6-8. There was 10 phase II trials and one phase III trial. Notably, PD-1 inhibitors were utilized in eight trials and PD-L1 inhibitors were utilized in three trials. Sequential administration of ICIs and RT was performed in eight trials, while concurrent therapy was performed in five trials. Patients from 9 trials received only conventional fractionated RT, while patients in one trial received only stereotactic body RT.

Incidence of All-Grade AEs of Interest

The incidence of all-grade AEs in patients treated with ICIs and TRT was 95.5% (95% CI: 91.2–99.8%). The Egger's test indicated that no significant publication bias existed except for all-grade fatigue (P=0.03). Then "trim-and-fill" analysis was conducted to addressed the bias, and fatigue was found to be the most frequent AE with the incidence of 49.7% (95% CI: 32–67.4%). AEs of the respiratory system were the second common, and the incidence of cough, dyspnea, and pneumonitis was 43.3%, 34.1%, and 23%,

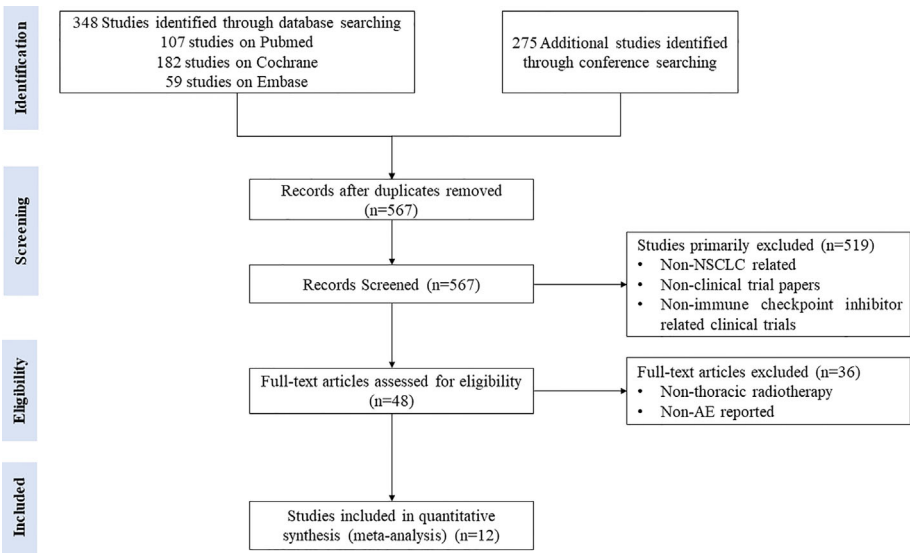

FIGURE 1 | Flow diagram of study inclusion.

TABLE 1 | Characteristic of clinical trials included in the analysis.

NCT number	First author	Phase	Stage of NSCLC	Median age (Range)	Gender distribution (male/female)	Smokers/ non-smokers	Histology	Drugs	Line of therapy	Comparator group	Number of patients	Sequence	Radiotherapy	Newcastle-Ottawa-Scale (NOS) evaluation
NCT02125461	Antonia et al. (6)	Phase III	Unresectable III	64 (31-84)	70.2%/29.8%	91%/9%	Non-squamous 51.9%/ Squamous 47.1%	Durvalumab 10mg/ kg	Consolidation	Placebo	473	Sequential	Conventional 54-66Gy	8
NCT02343952	Durm et al. (23)	Phase II	Unresectable IIIA/B	66 (45-84)	64%/36%	94.6%/5.4%	Non-squamous 55%/ Squamous 41%	Pembrolizumab 200mg q3w	Consolidation	None	93	Sequential	Conventional 59.4-66.6 Gy	7
NCT02434081	Peters et al. (24)	Phase II	IIIA/B	62 (41-78)	67.1%/32.9%	96.2%/3.8%	Non-squamous 59.5%/ Squamous 35.4%/Missing 5.1%	Nivolumab 360mg q3w-480mg/q4w	1st line	None	77	Concurrent	Conventional 66Gy/33f	8
NCT01820754	Boyer et al. (25)	Phase II	IB-IIIA	(49-75)	56%/44%	94%/6%	Adenocarcinoma 56%/ Squamous 44%	Ipilimumab 10mg/ kg q3w	Neo-adjuvant	None	16	Sequential	Conventional 36-60Gy	7
NCT03053856	Ahn et al. (26)	Phase II	IIIA-N2	64 (39-74)	62.2%/37.8%	N/A	Adenocarcinoma 73%/Others 27%	Pembrolizumab 200mg q3w	Neo-adjuvant	None	37	Sequential	Conventional 44Gy/22f	6
NCT03285321	Yan et al. (27)	Phase II	Unresectable IIIA/B	Arm A/B 64/62	N/A	N/A	Non-squamous 54%/ Squamous 46%	Nivolumab 480mg q4w	Consolidation	Nivolumab 3mg/kg +ipilizumab 1mg/kg	50	Sequential	Conventional 59.4-66.6Gy	7
NCT02621398	Jabbour et al. (28)	Phase I/II	III	69 (53-85)	48%/52%	95%/5%	Adenocarcinoma 52%/ Squamous and Others 48%	Pembrolizumab 100-200mg q3w	Consolidation	None	21	Concurrent	Conventional 60Gy/30f	6
NCT02525757	Lin et al. (29)	Phase II	IIb-IIIc	67 (50-83)	68%/32%	78%/22%	Adenocarcinoma 55%/ Squamous 35%/Others 10%	Atezolizumab 1200mg q3w	Consolidation	None	40	Concurrent/ sequential	Conventional 60-66 Gy/30-33f	8
NCT02447741	Welsh et al. (30)	Phase I/II	IV	N/A	65%/35%	75%/25%	Adenocarcinoma 80%/ Squamous 15%/NOS 5%	Pembrolizumab 200mg q3w	Unlimited	Pembrolizumab alone	40	Concurrent	Conventional 45Gy/15f or SBRT50Gy/4f	8
NCT03631784	Jabbour et al. (31)	Phase II	Unresectable III	N/A	N/A	N/A	N/A	Pembrolizumab 200mg q3w	1st line	None	185	Concurrent	Conventional 60Gy/30f	6
NCT03102242	Ross et al. (32)	Phase II	Unresectable III	63.9 (38.1-36.5)	48.4%/51.6%	61.3%/38.7%	N/A	Atezolizumab 1200mg q3w	Neo-adjuvant+ Consolidation	None	62	Sequential	Conventional 60Gy/30f	6
NCT02492568	Theelen et al. (33)	Phase II	IV	62 (35-78)	56%/44%	N/A	Nonsquamous 86%/ Squamous 14%	Pembrolizumab 200mg q3w	At least 2nd line	Pembrolizumab 200mg q3w alone	35	Sequential	SBRT 24Gy/3f	8

respectively. The funnel plots of all-grade fatigue and pneumonitis were shown in **Supplementary Figure 1**. Among those who received ICIs and TRT, nausea and diarrhea (AEs related to the gastrointestinal tract) occurred in 29.1% and 15.8% of patients, respectively. Of note, the incidence of pruritus, dermatitis, rash, and thyroiditis was 12.4%, 11.2%, 13.4%, and 9.4%, respectively (**Table 2**).

Incidence of High-Grade AEs of Interest

Table 3 represents the incidence of high-grade (grade ≥3) AEs in patients treated with ICIs and TRT. The funnel plots of high-grade AEs and pneumonitis were shown in **Supplementary Figure 1**. The Egger's test indicated the publication bias of high-grade fatigue, dyspnea, pneumonitis, nausea, colitis, and rash, and "trim-and-fill" analysis was conducted to address the bias and calculate the pooled incidence. The incidence of high-grade AEs among all patients was 30.2% (95% CI: 18.2–42.1%). Pneumonitis was the most common high-grade AE (3.8%, 95% CI: 2.0–6.9%), followed by dyspnea (2.1%) and colitis (0.5%). Besides, the incidence of high-grade fatigue, cough, nausea and colitis was 0.3%, 0.3%, 0.1% and 0.5%, respectively. Notably, the incidence of grade 5 AEs was 1.5% (95% CI: 0–3.1%), and pneumonitis also exhibited the highest incidence (0.6%, 95% CI: 0.1–1.1%).

TABLE 2 | Incidence of all-grade AEs of interest.

	Incidence	95%CI	Heterogeneity	χ^2	Egger test P
All-grade AEs	95.5%	91.2%-99.8%	64.1%	5.56	0.48
Fatigue	49.7%	32%-67.4%	95.2%	126.3	0.03
Cough	43.3%	25.2%-61.5%	96.5%	170.1	0.46
Dyspnea	34.1%	21.8%-46.4%	91.6%	71.49	0.17
Pneumonitis	23%	14.2%-31.7%	85.6%	48.4	0.27
Nausea	29.1%	15.8%-42.5%	94.8%	115.8	0.13
Diarrhea	15.8%	9.8%-21.7%	72.1%	17.9	0.89
Rash	13.4%	9.4%-17.5%	37.6%	8.02	0.40
Dermatitis	11.2%	0%-22.6%	85.3%	13.6	0.11
Pruritus	12.4%	9.4%-15.3%	14.7%	4.69	0.63
Thyroiditis	9.4%	3.3%-15.4%	90.3%	61.7	0.1

TABLE 3 | Incidence of high-grade AEs of interest.

	Incidence	95%CI	Heterogeneity	χ^2	Egger test P
High-grade AEs	30.2%	18.2%-42.1%	93.5%	122.2	0.97
Fatigue	0.3%	0-1.8%	52.9%	25.9	0.02
Cough	0.3%	0-0.8%	0.0	0.85	0.67
Dyspnea	2.1%	0%-4.2%	36.3%	16.4	0.008
Pneumonitis	3.8%	1.1%-6.6%	80.1%	52.2	0.009
Nausea	0.1%	0%-0.3%	0.0	0.43	0.005
Colitis	0.5%	0-1.3%	0.0	2.34	0.016
Rash	0.3%	0-0.8%	0.0	6.19	0.038
Grade 5 AEs	1.5%	0%-3.1%	70.8%	20.5	0.20
Pneumonitis	0.6%	0.1%-1.1%	0.0	5.21	0.16

Difference in the Incidence of AEs Between PD-1 and PD-L1 Inhibitors Combined With TRT

The comparison of AEs between PD-1 and PD-L1 inhibitors combined with TRT is shown in **Table 4**. In terms of all-grade AEs, fatigue was the most common in the PD-1 inhibitor group and showed a similar incidence to that observed in the PD-L1 inhibitor group (50.2% vs. 49%, respectively, P=0.97). All-grade cough was most frequent in patients with PD-L1 inhibitors and TRT; however, there was no significant difference observed compared with PD-1 inhibitors (60% vs. 36.6%, respectively, P=0.39). Notably, the incidence of pneumonitis was comparable between PD-1 and PD-L1 inhibitors combined with TRT (20.7% vs. 30%, respectively, P=0.21). Furthermore, we did not find significant differences in the incidence of other AEs.

Moreover, the incidence of high-grade AEs was similar between the PD-1 and PD-L1 inhibitor groups (25.6% vs. 36.6%, respectively, P=0.25). Pneumonitis was the most common high-grade AE in the PD-1 inhibitor group, and there was no significant difference observed compared with the PD-L1 inhibitor group (6% vs. 3.3%, respectively, P=0.18). Besides, there was also no significant difference in the incidence of high-grade fatigue, cough, dyspnea, and rash. In summary, no significant difference of the incidence of AEs was observed in the PD-1 or PD-L1 inhibitors when combined with TRT.

Difference in the Incidence of AEs Between Concurrent and Sequential Administration of ICIs and TRT

Table 5 describes the comparison of the toxicity profile between the concurrent and sequential administration of ICIs and TRT. In terms of all-grade AEs, fatigue was the most common in both groups, and there was no significant difference observed between sequential and concurrent treatment (45.5% vs. 57.3%, respectively, P=0.49). Compared with patients receiving sequential ICIs and TRT, those who received concurrent treatment had a slightly higher incidence of all-grade pneumonitis; however, this difference was not statistically significant (25.8% vs. 21.3%%, respectively, P=0.66). Although no significant difference was observed, the incidence of other respiratory AEs, including cough and dyspnea, was also higher in concurrent treatment group. Moreover, there were also no significant differences in the incidence of all-grade nausea, thyroiditis, and pruritus between concurrent and sequential ICIs and RT.

Concurrent treatment with ICIs and TRT was related to a slightly higher incidence of high-grade AEs compared with sequential treatment (41.6% vs. 24.8%, respectively, P=0.09). Although no significant difference was observed, concurrent ICIs and TRT was associated with higher rate of high-grade pneumonitis compared to sequential treatment (7.1% vs 3.9%, P=0.14). Besides, the risk of high-grade fatigue, cough, dyspnea, nausea, and colitis was also similar between the concurrent and sequential treatment groups. In summary, the incidence of AEs of patients receiving concurrent ICIs and TRT was comparable to sequential treatment.

TABLE 4 | Difference in incidence of AEs with PD-1 vs PD-L1 inhibitors combined with thoracic radiotherapy.

	PD-1	PD-L1	P
All-grade AEs			
Fatigue	50.2% (32.2%-68.2%)	49% (0%-99.1%)	0.97
Cough	36.6% (14.5%-58.8%)	60% (11.5%-99%)	0.39
Dyspnea	30.6% (15.3%-46%)	44.4% (0.2%-88.6%)	0.56
Pneumonitis	20.7% (11%-30.5%)	30% (19.1%-40.8%)	0.21
Nausea	28.2% (8.2%-48.2%)	33.8% (0%-74%)	0.81
Diarrhea	13.3% (5.5%-21.1%)	18.8% (13.2%-20.8%)	0.20
Thyroiditis	7.3% (1.1%-13.6%)	11.8% (9%-14.6%)	0.20
Rash	12.4% (7.5%-17.3%)	18.3% (3.7%-32.9%)	0.45
Pruritus	12.6% (7.3%-17.8%)	12.5% (9.5%-15.5%)	0.97
High-grade AEs			
Grade≥3 AEs	25.6% (5.8%-45.4%)	36.6% (19.3%-53.8%)	0.25
Fatigue	1.5% (0%-3.2%)	5.2% (0-17.1%)	0.542
Cough	0.5% (0-1.3%)	0.4% (0-0.9%)	0.85
Dyspnea	3.7% (0.7-6.6%)	3.1% (0%-8.3%)	0.84
Pneumonitis	6% (2.4%-9.6%)	3.3% (1.7%-4.8%)	0.18
Rash	1.6% (0-3.4%)	0.3% (0-0.7%)	0.32

TABLE 5 | Difference in incidence of AEs with concurrent vs sequential ICIs and thoracic radiotherapy.

	Sequential	Concurrent	P
All-grade AEs			
Fatigue	45.5% (26.2%-54.8%)	57.3% (35.1%-68.7%)	0.49
Cough	44.5% (26.8%-62.2%)	51.9% (13.7%-90.1%)	0.73
Dyspnea	24.5% (17.5%-31.6%)	45% (16.5%-73.4%)	0.17
Pneumonitis	21.3% (10.1%-32.5%)	25.8% (9.3%-42.2%)	0.66
Nausea	16.4% (9.1%-23.8%)	41.9% (10.2%-73.6%)	0.13
Diarrhea	18.2% (14.2%-22.2%)	14.1% (5%-23.3%)	0.42
Thyroiditis	10.2% (7.3%-13.2%)	9% (0%-21.4.4%)	0.84
Pruritus	13.5% (8.9%-18%)	10.5% (9.5%-15.3%)	0.42
High-grade AEs			
Grade≥3 AEs	24.8% (13.1%-36.5%)	41.6% (22.1%-61%)	0.17
Fatigue	1.9% (0-4.7%)	1.6% (0-4.2%)	0.89
Cough	0.5% (0-1%)	0.4% (0-1.4%)	0.93
Dyspnea	4.3% (0.2%-8.5%)	2.1% (0-4.2%)	0.35
Pneumonitis	3.9% (0.7%-7.1%)	7.1% (4.4%-9.7%)	0.14
Nausea	1.3% (0-3.1%)	0.7% (0-2%)	0.62
Colitis	0.8% (0-2.0%)	0.5% (0-1.9%)	0.80

DISCUSSION

The potential synergistic effect of the combination of ICIs and TRT has been reported in several preclinical studies (11–15). According to prospective clinical trials, this effect translates into survival benefit for patients with NSCLC (1, 4–6). However, the currently available safety information is primarily based on a limited set of studies. Thus, the present study is the first to systematically characterize the toxicity profiles and demonstrate the safety and tolerability of the combination of ICIs and TRT in patients with NSCLC.

The efficacy of combining TRT and immunotherapy is believed that 1 + 1 equal more than 2 (15), whether the synthetic effect of combination treatment would double the

toxicities remains to be clarified. The potential mechanisms involved in the toxicity associated with this combination treatment are unknown. While both ICIs and TRT have the capacity to evoke toxicities in normal tissues when administered alone, and the synthetic effect may also induce the overlap of the profile and mechanism of toxicity (34, 35).

The underlying etiology and mechanisms of AEs associated with ICIs is suggested to be related to the disruption of immunologic homeostasis (36). This results in an immune-boosting effect through a series of processes involving autoreactive lymphocytes, autoantibodies, and cytokines (37, 38). The AEs associated with ICIs are the consequences of excessive immunity against normal tissue, involving autoimmune and pro-inflammatory manifestations in the skin, endocrine, gastrointestinal, respiratory, and cardiovascular systems, etc. (36). In addition, TRT may also cause a wide range of AEs, including pneumonitis, mucositis, esophagitis, fibrosis (particularly in lung tissue), and others (39, 40), which is suggested to be induced by the induction of DNA breaks, production of reactive oxygen species (41), and the release of damage-associated molecular patterns (DAMPs) (42, 43). These effects lead to subsequent acute inflammation-like pneumonitis, mucositis, and esophagitis in the short term (44, 45). And succeeding repair and regeneration processes could manifest as chronic events to drive excessive tissue remodeling, resulting in late-onset toxicity such as fibrosis (45–47). The immunological response and altered microenvironment play a central role in the development of either short- or long- term toxicity related to TRT.

The administration of ICIs could also magnify the inflammatory response in irradiated normal tissue and result in infiltration of redundant immunocytes infiltrating and release of inflammatory factors. Furthermore, there may be a certain degree of overlap between the toxicities of RT and immunotherapy. In theory, the combination of TRT and ICIs should be associated with increased toxicity in patients with NSCLC; yet, the degree of increase remains unclear.

We performed this systematic analysis of 1,113 patients with NSCLC who received treatment with the combination of ICIs and TRT in 11 prospective clinical trials; the incidence of all-grade AEs was 95.5%, while that of high-grade AEs was 30.2%. These rates are higher than those of AEs caused by ICIs monotherapy in a previous meta-analysis (65.8% and 16.5%, respectively) (48). As expected, the combination of ICIs and TRT was associated with higher toxicity; however, the observed increase remained within acceptable levels. Even so, stricter screening prior to initiating treatment and closer monitoring during treatment should be performed for NSCLC patients receiving combination of TRT and ICIs, which would help to decrease the incidence of AE and avoid fatal AE.

Similar to treatment with ICIs, the combination of ICIs and TRT also results in a wide variety of AEs, including fatigue, skin toxicity, and events related to the respiratory system, gastrointestinal tract, and endocrine system. Fatigue was the most frequent among all-grade AEs in patients with NSCLC treated with the combination of ICIs and TRT, which was consistent with the toxicity profile of ICIs (49, 50). Besides, colitis, thyroiditis and hepatitis are the common autoimmune disease of ICIs, mediated by cytotoxic T cells against corresponding organs. Our systemic review found that the incidence of high-grade colitis in NSCLC patients receiving ICIs and TRT was 0.5%, which was similar to the high-grade colitis caused by ICIs monotherapy (0.6%) (51). And thyroiditis was also well-tolerated with the incidence of 9.4%. Whereas only 2 studies reported the incidence of hepatitis among 11 studies. Ahn et al. reported one cases of grade 3 autoimmune hepatitis among 37 patients (8.1%) (26), and Theelen et al. reported that none of 35 patients developed hepatitis (33). The combination of ICIs and TRT didn't significantly expand the incidence of hepatitis compared to ICIs monotherapy (5-10%) (52). In summary, the outer-pulmonary toxicity of ICIs and TRT was well-tolerated, and was not significantly elevated compared to ICIs monotherapy. Just as ICIs monotherapy, regular measurement of thyroid and liver function is also required during combination treatment. Besides, the occurrence of diarrhea should be alert to colitis, whose symptom may not correlate with colitis severity as seen by endoscopy and histology (53).

The potential mechanisms of outer-pulmonary AEs induced by ICIs may include the similar antigenic epitope and cross-reactivity of T cells against tumor and normal tissue, and elevated cytokines (36). With the joint of RT, the "*in-situ* vaccination and immunomodulation effect" leads to the increased release of antigen and elevated infiltration of lymphocytes. Then the similar antigenic epitope in normal tissue induced the elevated recruitment of immune cells, and release of cytokines and antibodies, followed by excessive immunity against normal tissue, involving autoimmune and pro-inflammatory manifestations. Due to the limited amount of specific antigen in outer-pulmonary tissues, there was no significant increase of infiltrated immune cells and excessive immunity on normal tissues. Thus, only a slightly increase of related outer-pulmonary AEs was observed in this systemic review, with an incidence of high-grade AEs less than 3%.

However, the cumulative toxicity of radiation and ICIs could give rise to the higher incidence of inter-pulmonary AEs. The incidence of all-grade cough, dyspnea and pneumonitis was 43.3%, 34.1% and 23%. Thus, the pulmonary function test and routine CT scans prior to initial treatment are recommended to guide the patterns of combination treatment, such as the dose and fraction of TRT. Pneumonitis was the most common among high-grade AEs (3.8%) and grade 5 AEs (0.6%), which is higher than that of ICIs monotherapy (52), and associated with increased treatment discontinuation and mortality in NSCLC patients treated with combination therapy (6, 26). CT scans should also be performed in the process of treatment to evaluate pneumonitis, and early detection and timely intervention (such as dose adjustment) could decrease the rate of discontinuation of treatment and treatment-related death to a great extent.

The TRT-induced DNA damage contributes to the injury of lung tissue, and is followed by the release of antigen and inflammatory factors (e.g., tumor necrosis factor [TNF] and

transforming growth factor beta [TGF-β]). And the administration of ICIs unleashes T cells to kill the tumor and repair normal tissue. Moreover, the recruitment of redundant immunocytes in lung tissue may magnify inflammation and exacerbate the pulmonary toxicity (54). Previous pre-clinical studies also showed that changes in inflammatory and a 2.1-fold increase of CD8+ T-cells were observed in irradiated lung tissues of mice receiving RT and ICIs compared with RT alone; however, there was no significant elevation in mortality (55). And elevated TNF, which mediates the synergistic effect of the combination treatment, was also associated with pulmonary toxicity (13, 56).

In addition, exposure to smoking and poor condition of the lung due to other diseases (e.g., obstructive pulmonary disease) are related to increased toxicity in patients with NSCLC (57). Also, the presence of tumor burden in the lung may limit the tolerance to injury. Thus, it is recommended that clinicians carefully evaluate the risk of pneumonitis based on the smoking history, pulmonary function test, and others, and allocate more of their attention to prevent, monitor, recognize, and manage pneumonitis at the early stage of treatment with ICIs and TRT. Thorough understanding of the mechanism of toxicity caused by the combination treatment is urgently needed to determine useful biomarkers for the identification of high-risk patients.

The exploration of related factors of toxicity could help to identify high risk patients and enable better prevention and management of the AEs of combination of TRT and ICIs. And the parameters of ICIs drugs or radiotherapy, and sequence of treatment were thought to play important roles on the AEs of combination treatment. At present, there is no head-to-head study to compare the difference in AEs between PD-1 and PD-L1 inhibitors combined with TRT. A previous study stated that the toxicity profiles of PD-1 and PD-L1 inhibitors in NSCLC patients are similar (58). And PD-1 inhibitors have been associated with a significantly higher incidence of high-grade immune-related pneumonitis (1.1% vs 0.4%, P=0.01) (59). The potential mechanism involved in the higher incidence of pneumonitis may be the blockage of PD-1-PD-L2 induced by PD-1 inhibitors. This blockage assists in the release of cytokines and proliferation of self-reactive T cells, leading to the enhancement of the antitumor effect and AEs (60).

When combined with TRT, no significant difference was recorded between PD-1 and PD-L1 inhibitor in our systemic review. Notably, the combination of TRT and PD-1 or PD-L1 inhibitors were related to higher incidence of pneumonitis compared to PD-1 or PD-L1 monotherapy. Both ICIs and TRT participated in the development and progression of pneumonitis, and TRT predominated on account of the DNA damage, subsequent inflammatory response, and collagen deposition on normal lung tissue. The leading role of TRT rather than ICIs might be the reason for the similar incidence of PD-1 and PD-L1 inhibitors when combined with TRT. Thus, the selection of candidate ICIs is recommended, primarily depending on their efficacy rather than the toxicity.

Moreover, the role of treatment sequence of TRT and ICIs on the incidence of toxicity was of close concern. Due to the time-dependent effect induced by TRT in normal tissue, the toxicity ranges from acute inflammatory effects towards chronic fibrotic side effects (45, 61, 62). Thus, concurrent or sequential treatment with ICIs and TRT may induce different side effects, particularly in lung tissue. Concurrent treatment is theoretically associated with higher toxicity due to the acute phase inflammation and overlapping toxicity. However, the collective available evidence on the safety of concurrent or sequential treatment with ICIs and TRT is varied. The secondary analysis of the PACIFIC study revealed that patients with NSCLC who received durvalumab within 14 days from the last session of TRT had superior survival and a higher rate of pneumonitis (63). Nevertheless, another retrospective study of 79 patients did not find differences in AEs between the concurrent and sequential administration of ICIs and RT (22).

As expected, this systematic analysis revealed that concurrent administration of ICIs and TRT led to an improved toxicity profile, particularly with regard to pneumonitis; while no statistical significance was found. In addition, the increase of outer-pulmonary AEs by concurrent treatment was not obvious. Thus, pulmonary function test and routine CT scans are essential for NSCLC patients receiving concurrent ICIs and TRT. The potential mechanisms for the statistically undifferentiated incidence of AEs between the concurrent and sequential treatments are unknown, and a hypothesis is provided below. Firstly, previous evidence has demonstrated the "long tail effect" of ICIs on the survival of patients with NSCLC (64–66). While the "long tail effect" and immunological memory of ICIs could also give rise to long-lasting AEs, which may contribute to the increased incidence of AEs when combined with subsequent RT. Moreover, immunotherapy followed by RT was also found to induce radiation recall pneumonitis, which was triggered by a "remembered" and "overreacted" process of the immunomodulatory effect (67). Thus, sequential treatment could not completely avoid the overlapping toxicity and significantly decrease the occurrence of AEs, as initially envisioned. Further studies are warranted to identify the acute and long-term toxicity, as well as the respective mechanisms of different sequences of RT and ICIs combination therapy.

Except for the sequence of treatment, the dose and fraction of TRT were also associated with the toxicity of TRT and ICIs. Welsh et al. performed an exploratory analysis and revealed that the median PFS was better in SBRT group compared to traditional RT (20.8 vs 6.8 months, P=0.03) in metastatic NSCLC patients, and 3 and 5 patients experienced high-grade AEs in SBRT and traditional RT group respectively. Based on available data, there was no significant difference on toxicity between two groups (30). However, further studies are needed to assess the difference on efficacy between SBRT and conventional radiotherapy combined with ICIs, especially for metastatic NSCLC patients. In addition, the radiotherapy dose and site for metastatic NSCLC should also be taken into consideration in future studies to evaluate the safety and efficacy of combining ICIs and TRT.

A limitation of this study is the relatively small number of eligible studies included in our analyses. However, all published clinical trials of the combination of ICIs and TRT in patients with NSCLC were included to capture the safety data. In addition, the assessment of AEs was somewhat subjective and varied between studies. Thus, our analysis depended on the quality of AE reporting by investigators. Moreover, there was heterogeneity among the studies included in this systematic analysis. Further larger scale, multicenter, randomized controlled trials and real-word studies are warranted to evaluate the safety of the combination of ICIs and TRT in patients with NSCLC.

CONCLUSION

This systematic review, for the first time, draws attention to the toxicity profile of the combination of ICIs and TRT for patients with NSCLC, and focused comprehensive effort at the comparison of AEs based on different ICIs and different treatment settings. Most AEs of the combination treatment are tolerable. Nonetheless, pneumonitis was the most common high-grade AE and deserves the utmost attention of physicians due to its leading role in AE-related death. Careful selection of patients at high risk and close monitoring for pneumonitis in patients with NSCLC receiving the combination of ICIs and TRT are recommended. This systematic analysis also demonstrated similar safety profiles between PD-1 and PD-L1 inhibitors combined with TRT, and a relatively higher incidence of AEs induced by concurrent treatment. Above all, optimal treatment selection is recommended, primarily depending on the efficacy rather than the safety of the candidate drugs. Furthermore, the identification of patients at high risk of toxicity is necessary prior to the administration of concurrent ICIs and RT. The findings of this comprehensive analysis could lay a foundation to accelerate the development of ICIs and TRT combination treatment, and achieve the goal of maximizing benefit and minimizing toxicity.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

Methodology, BL, CJ, LP, and BZ. Software, BL and MD. Validation, XS, JY, and LW. Formal analysis, BL, CJ, BZ, and LW. Data curation, BL, LP, BZ, MD, and XS. Writing–original draft preparation, BL, CJ, LP, and LW. Writing–review and editing, BL, CJ, XS, and LW. Visualization, MD, BZ, JY, and XS. Project administration, XS, JY, and LW. Funding acquisition, JY and LW. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the following grant: Natural Science Foundation of Shandong Province (Grant No. ZR2019LZL012), the Innovation Project of Shandong Academy of Medical Sciences (2019-04), and the Academic Promotion Program of Shandong First Medical University (2019ZL002).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.627197/full#supplementary-material

Supplementary Figure 1 | Funnel plots for **(A)**. All-grade fatigue, **(B)**. All-grade pneumonitis, **(C)**. High-grade AEs, **(D)**. High-grade pneumonitis. Due to the publication bias of all-grade fatigue and high-grade pneumonitis, the figure presents the funnel plot with the missing studies imputed by the trim-and-fill method.

REFERENCES

1. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet (London England)* (2017) 389(10066):255–65. doi: 10.1016/s0140-6736(16)32517-x
2. Horn L, Spigel DR, Vokes EE, Holgado E, Ready N, Steins M, et al. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). *J Clin Oncol* (2017) 35 (35):3924–33. doi: 10.1200/jco.2017.74.3062
3. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim S-W, Carcereny Costa E, et al. Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer. *N Engl J Med* (2019) 381(21):2020–31. doi: 10.1056/NEJMoa1910231
4. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. *N Engl J Med* (2015) 373(17):1627–39. doi: 10.1056/NEJMoa1507643
5. Hui R, Garon EB, Goldman JW, Leighl NB, Hellmann MD, Patnaik A, et al. Pembrolizumab as first-line therapy for patients with PD-L1-positive advanced non-small cell lung cancer: a phase 1 trial. *Ann Oncol* (2017) 28 (4):874–81. doi: 10.1093/annonc/mdx008
6. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med* (2018) 379(24):2342–50. doi: 10.1056/NEJMoa1809697
7. Santivasi WL, Xia F. Ionizing radiation-induced DNA damage, response, and repair. *Antioxid Redox Signal* (2014) 21(2):251–9. doi: 10.1089/ars.2013.5668
8. Burnette B, Weichselbaum RR. Radiation as an immune modulator. *Semin Radiat Oncol* (2013) 23(4):273–80. doi: 10.1016/j.semradonc.2013.05.009
9. Rodriguez-Ruiz ME, Vanpouille-Box C, Melero I, Formenti SC, Demaria S. Immunological Mechanisms Responsible for Radiation-Induced Abscopal Effect. *Trends Immunol* (2018) 39(8):644–55. doi: 10.1016/j.it.2018.06.001
10. Barker HE, Paget JT, Khan AA, Harrington KJ. The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. *Nat Rev Cancer* (2015) 15(7):409–25. doi: 10.1038/nrc3958
11. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest* (2014) 124(2):687–95. doi: 10.1172/JCI67313

12. Sharabi AB, Nirschl CJ, Kochel CM, Nirschl TR, Francica BJ, Velarde E, et al. Stereotactic Radiation Therapy Augments Antigen-Specific PD-1-Mediated Antitumor Immune Responses via Cross-Presentation of Tumor Antigen. *Cancer Immunol Res* (2015) 3(4):345–55. doi: 10.1158/2326-6066.cir-14-0196
13. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti–PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest* (2014) 124(2):687–95. doi: 10.1172/JCI67313
14. Wirsdorfer F, Cappuccini F, Niazman M, de Leve S, Westendorf AM, Ludemann L, et al. Thorax irradiation triggers a local and systemic accumulation of immunosuppressive CD4+ FoxP3+ regulatory T cells. *Radiat Oncol (London England)* (2014) 9:98. doi: 10.1186/1748-717x-9-98
15. Demaria S, Coleman CN, Formenti SC. Radiotherapy: Changing the Game in Immunotherapy. *Trends Cancer* (2016) 2(6):286–94. doi: 10.1016/j.trecan.2016.05.002
16. Demaria S, Kawashima N, Yang AM, Devitt ML, Babb JS, Allison JP, et al. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. *Clin Cancer Res* (2005) 11(2 Pt 1):728–34.
17. Herter-Sprie GS, Koyama S, Korideck H, Hai J, Deng J, Li YY, et al. Synergy of radiotherapy and PD-1 blockade in Kras-mutant lung cancer. *JCI Insight* (2016) 1(9):e87415. doi: 10.1172/jci.insight.87415
18. Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol* (2017) 18(7):895–903. doi: 10.1016/S1470-2045(17)30380-7
19. Fujii T, Colen RR, Bilen MA, Hess KR, Hajjar J, Suarez-Almazor ME, et al. Incidence of immune-related adverse events and its association with treatment outcomes: the MD Anderson Cancer Center experience. *Invest New Drugs* (2018) 36(4):638–46. doi: 10.1007/s10637-017-0534-0
20. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of Immunotherapy for the Practitioner. *J Clin Oncol* (2015) 33(18):2092–9. doi: 10.1200/jco.2014.60.0379
21. Hanania AN, Mainwaring W, Ghebre YT, Hanania NA, Ludwig M. Radiation-Induced Lung Injury: Assessment and Management. *Chest* (2019) 156(1):150–62. doi: 10.1016/j.chest.2019.03.033
22. von Reibnitz D, Chaft JE, Wu AJ, Samstein R, Hellmann MD, Plodkowski AJ, et al. Safety of combining thoracic radiation therapy with concurrent versus sequential immune checkpoint inhibition. *Adv Radiat Oncol* (2018) 3(3):391–8. doi: 10.1016/j.adro.2018.05.001
23. Durm GA, Jabbour SK, Althouse SK, Liu Z, Sadiq AA, Zon RT, et al. A phase 2 trial of consolidation pembrolizumab following concurrent chemoradiation for patients with unresectable stage III non-small cell lung cancer: Hoosier cancer research network LUN 14-179. *Cancer* (2020) 126(19):4353–61. doi: 10.1002/cncr.33083
24. Peters S, Felip E, Dafni U, Belka C, Guckenberger M, Irigoyen A, et al. Safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-radiotherapy regimen in stage III non-small cell lung cancer-The ETOP NICOLAS trial. *Lung Cancer (Amsterdam Netherlands)* (2019) 133:83–7. doi: 10.1016/j.lungcan.2019.05.001
25. Boyer MJ, Gu L, Wang X, Kelsey CR, Yoo DS, Onaitis MW, et al. Toxicity of definitive and post-operative radiation following ipilimumab in non-small cell lung cancer. *Lung Cancer (Amsterdam Netherlands)* (2016) 98:76–8. doi: 10.1016/j.lungcan.2016.05.014
26. Ahn M-J, Park S, Jung HA, Cho JH, Sun J-M, Lee S-H, et al. Phase II, prospective single-arm study of adjuvant pembrolizumab in N2 positive non-small cell lung cancer (NSCLC) treated with neoadjuvant concurrent chemoradiotherapy followed by curative resection: Preliminary results. *J Clin Oncol* (2019) 37(15_suppl):8520–. doi: 10.1200/JCO.2019.37.15_suppl.8520
27. Yan M, Durm GA, Mamdani H, Ernani V, Jabbour SK, Naidoo J, et al. Consolidation nivolumab/ipilimumab versus nivolumab following concurrent chemoradiation in patients with unresectable stage III NSCLC: A planned interim safety analysis from the BTCRC LUN 16-081 trial. *J Clin Oncol* (2020) 38(15_suppl):9010–. doi: 10.1200/JCO.2020.38.15_suppl.9010
28. Jabbour SK, Berman AT, Decker RH, Lin Y, Feigenberg SJ, Gettinger SN, et al. Phase 1 Trial of Pembrolizumab Administered Concurrently With Chemoradiotherapy for Locally Advanced Non-Small Cell Lung Cancer: A Nonrandomized Controlled Trial. *JAMA Oncol* (2020) 6(6):848–55. doi: 10.1001/jamaoncol.2019.6731
29. Lin SH, Lin Y, Yao L, Kalhor N, Carter BW, Altan M, et al. Phase II Trial of Concurrent Atezolizumab With Chemoradiation for Unresectable NSCLC. *J Thorac Oncol* (2020) 15(2):248–57. doi: 10.1016/j.jtho.2019.10.024
30. Welsh J, Menon H, Chen D, Verma V, Tang C, Altan M, et al. Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: a randomized phase I/II trial. *J Immunother Cancer* (2020) 8(2):e001001. doi: 10.1136/jitc-2020-001001
31. Jabbour SK, Lee KH, Frost N, Kowalski D, Breder VV, Pollock T, et al. Phase II study of pembrolizumab (pembro) plus platinum doublet chemotherapy and radiotherapy as first-line therapy for unresectable, locally advanced stage III NSCLC: KEYNOTE-799. *J Clin Oncol* (2020) 38(15_suppl):9008–. doi: 10.1200/JCO.2020.38.15_suppl.9008
32. Ross HJ, Kozono DE, Urbanic JJ, Williams TM, Dufrane C, Bara I, et al. AFT-16: Phase II trial of atezolizumab before and after definitive chemoradiation (CRT) for unresectable stage III non-small cell lung cancer (NSCLC). *J Clin Oncol* (2020) 38(15_suppl):9045–. doi: 10.1200/JCO.2020.38.15_suppl.9045
33. Theelen W, Peulen HMU, Lalezari F, van der Noort V, de Vries JF, Aerts J, et al. Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial. *JAMA Oncol* (2019) 5(9):1276–82. doi: 10.1001/jamaoncol.2019.1478
34. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients With Advanced Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol* (2016) 2(12):1607–16. doi: 10.1001/jamaoncol.2016.2453
35. Formenti SC, Demaria S. Systemic effects of local radiotherapy. *Lancet Oncol* (2009) 10(7):718–26. doi: 10.1016/s1470-2045(09)70082-8
36. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. *N Engl J Med* (2018) 378(2):158–68. doi: 10.1056/NEJMra1703481
37. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Antibody-mediated thyroid dysfunction during T-cell checkpoint blockade in patients with non-small-cell lung cancer. *Ann Oncol* (2017) 28(3):583–9. doi: 10.1093/annonc/mdw640
38. Esfahani K, Miller WHJr. Reversal of Autoimmune Toxicity and Loss of Tumor Response by Interleukin-17 Blockade. *N Engl J Med* (2017) 376(20):1989–91. doi: 10.1056/NEJMc1703047
39. Ratikan JA, Micewicz ED, Xie MW, Schaue D. Radiation takes its Toll. *Cancer Lett* (2015) 368(2):238–45. doi: 10.1016/j.canlet.2015.03.031
40. Mavragani IV, Laskaratou DA, Frey B, Candéias SM, Gaipl US, Lumniczky K, et al. Key mechanisms involved in ionizing radiation-induced systemic effects. A current review. *Toxicol Res (Camb)* (2015) 5(1):12–33. doi: 10.1039/c5tx00222b
41. Amaravadi RK, Thompson CB. The roles of therapy-induced autophagy and necrosis in cancer treatment. *Clin Cancer Res* (2007) 13(24):7271–9. doi: 10.1158/1078-0432.CCR-07-1595
42. Ludgate CM. Optimizing cancer treatments to induce an acute immune response: radiation Abscopal effects, PAMPs, and DAMPs. *Clin Cancer Res* (2012) 18(17):4522–5. doi: 10.1158/1078-0432.CCR-12-1175
43. Hernandez C, Huebener P, Schwabe RF. Damage-associated molecular patterns in cancer: a double-edged sword. *Oncogene* (2016) 35(46):5931–41. doi: 10.1038/onc.2016.104
44. Schaue D, Micewicz ED, Ratikan JA, Xie MW, Cheng G, McBride WH. Radiation and inflammation. *Semin Radiat Oncol* (2015) 25(1):4–10. doi: 10.1016/j.semradonc.2014.07.007
45. Simone CB2nd. Thoracic Radiation Normal Tissue Injury. *Semin Radiat Oncol* (2017) 27(4):370–7. doi: 10.1016/j.semradonc.2017.04.009
46. Yarnold J, Brotons MC. Pathogenetic mechanisms in radiation fibrosis. *Radiother Oncol* (2010) 97(1):149–61. doi: 10.1016/j.radonc.2010.09.002
47. Tsoutsou PG, Koukourakis MI. Radiation pneumonitis and fibrosis: mechanisms underlying its pathogenesis and implications for future research. *Int J Radiat Oncol Biol Phys* (2006) 66(5):1281–93. doi: 10.1016/j.ijrobp.2006.08.058
48. Magee DE, Hird AE, Klaassen Z, Sridhar SS, Nam RK, Wallis CJD, et al. Adverse event profile for immunotherapy agents compared with chemotherapy in solid

organ tumors: a systematic review and meta-analysis of randomized clinical trials. *Ann Oncol* (2020) 31(1):50–60. doi: 10.1016/j.annonc.2019.10.008
49. De Velasco G, Je Y, Bosse D, Awad MM, Ott PA, Moreira RB, et al. Comprehensive Meta-analysis of Key Immune-Related Adverse Events from CTLA-4 and PD-1/PD-L1 Inhibitors in Cancer Patients. *Cancer Immunol Res* (2017) 5(4):312–8. doi: 10.1158/2326-6066.cir-16-0237
50. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. *Ann Oncol* (2017) 28(10):2377–85. doi: 10.1093/annonc/mdx286
51. Nishijima TF, Shachar SS, Nyrop KA, Muss HB. Safety and Tolerability of PD-1/PD-L1 Inhibitors Compared with Chemotherapy in Patients with Advanced Cancer: A Meta-Analysis. *Oncologist* (2017) 22(4):470–9. doi: 10.1634/theoncologist.2016-0419
52. Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* (2017) 28 (suppl_4):iv119–iv42. doi: 10.1093/annonc/mdx225
53. Geukes Foppen MH, Rozeman EA, van Wilpe S, Postma C, Snaebjornsson P, van Thienen JV, et al. Immune checkpoint inhibition-related colitis: symptoms, endoscopic features, histology and response to management. *ESMO Open* (2018) 3(1):e000278. doi: 10.1136/esmoopen-2017-000278
54. Hwang WL, Pike LRG, Royce TJ, Mahal BA, Loeffler JS. Safety of combining radiotherapy with immune-checkpoint inhibition. *Nat Rev Clin Oncol* (2018) 15(8):477–94. doi: 10.1038/s41571-018-0046-7
55. Xue J, Du S, Lu Y, Dicker A, Lu B. Abstract 3671: Anti-PD-1 treatment may potentiate the radiation-induced lung injury. *Cancer Res* (2017) 77(13 Supplement):3671–71. doi: 10.1158/1538-7445.am2017-3671
56. Xue J, Li X, Lu Y, Gan L, Zhou L, Wang Y, et al. Gene-modified Mesenchymal Stem Cells Protect Against Radiation-induced Lung Injury. *Mol Ther* (2013) 21(2):456–65. doi: 10.1038/mt.2012.183
57. Bouros D, Hatzakis K, Labrakis H, Zeibecoglou K. Association of malignancy with diseases causing interstitial pulmonary changes. *Chest* (2002) 121 (4):1278–89. doi: 10.1378/chest.121.4.1278
58. Pillai RN, Behera M, Owonikoko TK, Kamphorst AO, Pakkala S, Belani CP, et al. Comparison of the toxicity profile of PD-1 versus PD-L1 inhibitors in non-small cell lung cancer: A systematic analysis of the literature. *Cancer* (2018) 124(2):271–7. doi: 10.1002/cncr.31043
59. Khunger M, Rakshit S, Pasupuleti V, Hernandez AV, Mazzone P, Stevenson J, et al. Incidence of Pneumonitis With Use of Programmed Death 1 and Programmed Death-Ligand 1 Inhibitors in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis of Trials. *Chest* (2017) 152(2):271–81. doi: 10.1016/j.chest.2017.04.177
60. Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nat Immunol* (2001) 2(3):261–8. doi: 10.1038/85330
61. Kim JH, Jenrow KA, Brown SL. Mechanisms of radiation-induced normal tissue toxicity and implications for future clinical trials. *Radiat Oncol J* (2014) 32(3):103–15. doi: 10.3857/roj.2014.32.3.103
62. Rube CE, Uthe D, Schmid KW, Richter KD, Wessel J, Schuck A, et al. Dose-dependent induction of transforming growth factor beta (TGF-beta) in the lung tissue of fibrosis-prone mice after thoracic irradiation. *Int J Radiat Oncol Biol Phys* (2000) 47(4):1033–42. doi: 10.1016/s0360-3016(00)00482-x
63. Raben D, Faivre-Finn C, Spigel D, Daniel D, Villegas A, Vincente D, et al. PACIFIC: Overall Survival with Durvalumab versus Placebo after Chemoradiotherapy in Stage III NSCLC. *Int J Radiat Oncol Biol Phys* (2018) 102(5):1607–8. doi: 10.1016/j.ijrobp.2018.08.057
64. Borcoman E, Kanjanapan Y, Champiat S, Kato S, Servois V, Kurzrock R, et al. Novel patterns of response under immunotherapy. *Ann Oncol* (2019) 30 (3):385–96. doi: 10.1093/annonc/mdz003
65. Rekers NH, Olivo Pimentel V, Yaromina A, Lieuwes NG, Biemans R, Zegers CML, et al. The immunocytokine L19-IL2: An interplay between radiotherapy and long-lasting systemic anti-tumour immune responses. *Oncoimmunology* (2018) 7(4):e1414119. doi: 10.1080/2162402x.2017.1414119
66. Chiang AC, Herbst RS. Frontline immunotherapy for NSCLC — the tale of the tail. *Nat Rev Clin Oncol* (2020) 17(2):73–4. doi: 10.1038/s41571-019-0317-y
67. Chen Y, Huang Z, Xing L, Meng X, Yu J. Radiation Recall Pneumonitis Induced by Anti-PD-1 Blockade: A Case Report and Review of the Literature. *Front Oncol* (2020) 10:561–61. doi: 10.3389/fonc.2020.00561

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Immunology

CASE REPORT
published: 10 May 2021
doi: 10.3389/fimmu.2021.619147

Case Report: THSD7A-Positive Membranous Nephropathy Caused by Tislelizumab in a Lung Cancer Patient

Minjiang Chen[1†], *Lei Zhang*[2†], *Wei Zhong*[1*], *Ke Zheng*[2], *Wei Ye*[2] *and Mengzhao Wang*[1*]

[1] Department of Respiratory and Critical Care Medicine, Peking Union Medical College Hospital, Beijing, China, [2] Department of Nephrology, Peking Union Medical College Hospital, Beijing, China

Immune checkpoint inhibitors (ICIs) became the standard treatment for many different kinds of cancers and can result in a variety of immune-related adverse events (irAEs). IrAEs of kidney are uncommon and consists of different pathology types. Among the different types, membranous nephropathy (MN) is rare and have not been well-described. Since MN can also be associated with malignancies, differential diagnosis in patients receiving ICIs who develop MN can be very difficult. We present the case of a 74-year-old man with metastatic non-small cell lung cancer who developed MN after ICIs therapy. The patient tested positive for thrombospondin type-1 domain-containing 7A antibodies (THSD7A) when diagnosed with MN. Supplementary examinations revealed the predisposing antigen in the primary tumor and present of the antibody after immunotherapy, which corresponded to the patient's clinical course of nephropathy. Treatment consisting of systemic glucocorticoids and rituximab resulted in a good clinical response, and the THSD7A antibodies were no longer detected. In this case, we first discuss the potential mechanism of immunotherapy related MN, in which the activation of humoral immunity may play an important role.

Keywords: immune checkpoint inhibitors, immune related adverse event, membranous nephropathy, non-small cell lung cancer, THSD7A (thrombospondin type 1 domain-containing protein 7A)

OPEN ACCESS

Edited by:
Udo S. Gapil,
University Hospital Erlangen, Germany

Reviewed by:
Naoka Murakami,
Brigham and Women's Hospital and Harvard Medical School, United States
Rolf A. K. Stahl,
University of Hamburg, Germany

***Correspondence:**
Wei Zhong
weizhong_pumch@163.com
Mengzhao Wang
mengzhaowang@sina.com

[†]*These authors have contributed equally to this work*

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Immunology

Received: *19 October 2020*
Accepted: *21 April 2021*
Published: *10 May 2021*

Citation:
Chen M, Zhang L, Zhong W, Zheng K, Ye W and Wang M (2021) Case Report: THSD7A-Positive Membranous Nephropathy Caused by Tislelizumab in a Lung Cancer Patient. Front. Immunol. 12:619147. doi: 10.3389/fimmu.2021.619147

INTRODUCTION

The use of immune checkpoint inhibitors (ICIs) caused a variety of immune-mediated adverse events (irAEs). The underlying mechanism includes an increasing T cell activity and autoimmune antibodies (1). Kidney irAEs, albeit uncommon, is being increasingly recognized with the expanded ICIs use (2, 3). Membranous nephropathy (MN) has rarely been reported and the underlying mechanism remains unclear.

Herein, we describe an interesting MN case with non-small cell lung cancer after tislelizumab (a PD-1 inhibitor) (4) treatment. In particular, this patient tested positive for THSD7A antibodies, which was rare and had been proven to play an important role in the development of MN (5, 6). In this case report, we described the changes in autoimmune antibodies in during the development and

remission of nephropathy and highlight the possibility of humoral immunity activation as a pathogenic mechanism in ICI-related MN.

CASE REPORT

A 74-year-old man with metastatic lung adenocarcinoma and no history of chronic renal disease enrolled in the BGB-A317-304 open labeled trial (NCT03663205) on June 25, 2019. His baseline urine protein and serum albumin and creatinine levels were within the normal range (**Table 1**). He was randomly categorized into the immunotherapy group and was initially treated with a tislelizumab and chemotherapy combination that included pemetrexed and carboplatin for 4 cycles, followed by maintenance therapy with tislelizumab and pemetrexed for 11 cycles until April 23, 2020. Partial response was achieved and persisted after 2 cycles (**Figure 1**). However, the patient experienced fatigue and chronic onset of mild edema of both lower extremities from late April. On May 7, laboratory findings revealed a decrease in serum albumin level to 19 g/L, and a substantial increase in 24-hour urine protein level to 20.16 g. Serological markers of MN, THSD7A and antigen phospholipase A2 receptor 1 (PLA2R1) antibodies were also tested using a cell based indirect immunofluorescence assay (7). The results were negative for PLA2R1 antibodies and positive for THSD7A with a titer of 1:100. Nephrotic syndrome was diagnosed, and the patient was referred to the nephrology department.

Renal biopsy was performed. Light microscopy showed stiffness in the glomeruli with scattered subepithelially localized immune deposits (Masson stain) containing slightly focal tubular atrophy and interstitial fibrosis, consistent with early MN (**Figures 2A, B**). Immunofluorescence staining showed granular immunoglobulin G (IgG) deposits (**Figure 2C**), including IgG1, IgG2 and IgG4, uniformly and subepithelially distributed in the glomeruli (**Figures 2D–F**). The immunofluorescence staining of IgG3 was negative. Electron microscopy showed discrete electron-dense deposits at the subepithelial surface of the glomerular capillary wall, accompanied by effacement of overlying epithelial cell foot processes (**Figure 2G**). Immunohistochemical analyses revealed positive staining for THSD7A along the glomerular basement membrane (**Figure 2H**).

The differential diagnosis during renal biopsy was nephrotic syndrome either due to tislelizumab treatment or as a paraneoplastic sign. Determinate when the THSD7A antibodies appeared helped in distinguishing between the two different pathogenies.

The THSD7A tumor antigen and antibodies against it were tested using archived tumor and consecutive serum specimens. The baseline tumor tissue tested positive for the THSD7A antigen tested positive (**Figure 2I**). The patient tested negative for THSD7A antibodies at baseline but tested positive after 4 cycles of maintenance tislelizumab therapy (**Figure 3**). Therefore, MN was thought to be related with the ICI treatment.

Tislelizumab was discontinued following the diagnosis of nephropathy. To treat biopsy-proven MN, intravenous methylprednisolone (60 mg) was administered for 14 consecutive days, followed by oral prednisone (60 mg) once daily. Rituximab (1 g) was also administered once at the beginning of treatment. Two months after initiating glucocorticoid therapy, the 24-hour urine protein level decreased to 2.53 g and the serum albumin level improved to 36 g/L (**Table 1**). The serum also tested negative for THSD7A antibodies. Consequently, treatment with prednisone was slowly tapered. After a total course of about six months the systemic glucocorticoids were stopped at the end of November 2020. The patient was followed-up till the March 2021. His laboratory test

TABLE 1 | Laboratory values and treatment timeline.

Date	WBC (10^9/L)	HGB (G/L)	PLT (10^9/L)	ALB (G/L)	Cr (μmol/L)	Urea (mmol/L)	K (mmol/L)	Na (mmol/L)	Ca (mmol/L)	Urine protein (g/L)	24h Urine protein (g)	THSD7A antibodies (titer)	Treatment and events timeline
June 19, 2019	6.00	153	169	41	67	5.38	4.3	140	2.24	Negative	NE	Negative	Baseline before treatment
September 20, 2019	5.02	129	199	49	69	5.07	4.3	139	2.44	Negative	NE	Negative	Four cycles of induced treatment
December 12, 2019	5.41	128	213	43	64	3.94	4.3	141	2.21	Negative	NE	1:100	Four cycles of maintenance therapy
May 7, 2020	5.97	137	176	19	82	4.72	3.9	139	1.99	≥3.0	20.16	1:100[#]	Eleven cycles of maintenance therapy; Nephrotic syndrome
May 14, 2020	5.97	124	170	20	78	6.65	3.4	141	1.98	≥3.0	11.63	NE*	Renal Biopsy; Glucocorticoids administered
May 27, 2020	13.95	142	176	26	84	7.17	4.3	139	2.11	1.0	9.85	NE	Rituximab administered
July 13, 2020	9.25	136	161	36	62	5.22	3.8	141	2.22	0.3	2.53	Negative	Two months after therapy; Prednisone tapered
Nov 30,2020	7.48	144	145	44	63	4.91	4.0	141	2.43	Negative	0.59	NE	Prednisone stopped
Feb 22, 2021	5.58	149	127	38	57	6.62	4.4	140	2.24	Negative	0.17	Negative	Follow-up visit

**NE: not evaluated; [#]the THSD7A antibodies were tested on May 12, 2020.*

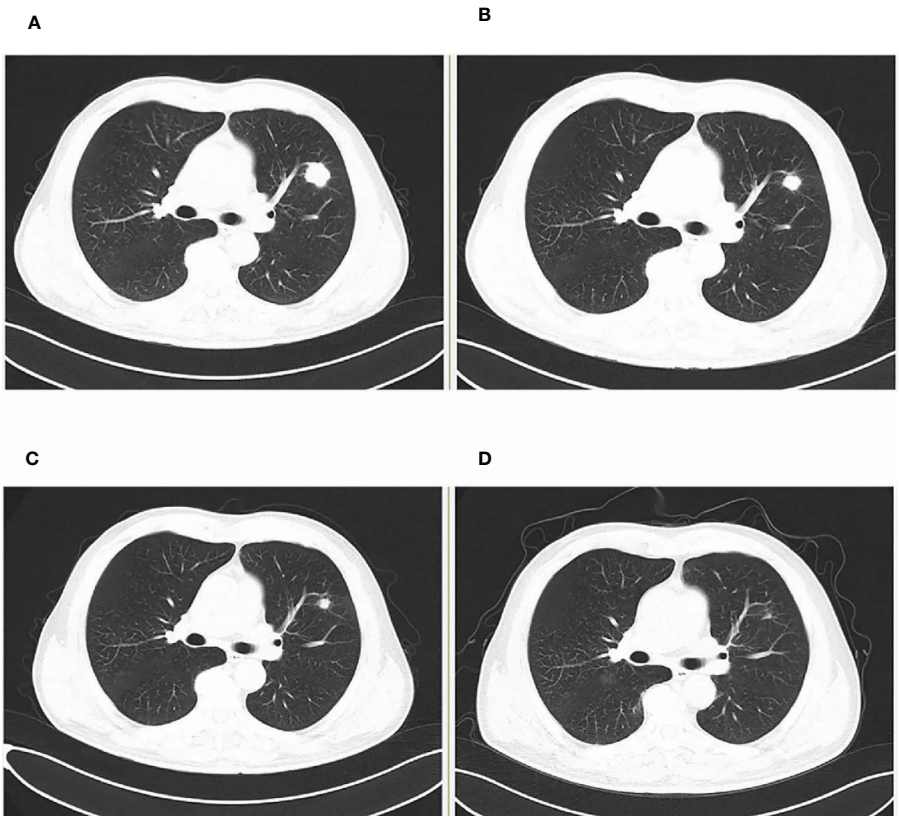

FIGURE 1 | Tumor assessment during tislelizumab treatment. **(A)** Baseline before treatment. **(B)** After two cycles of induction treatment. **(C)** After four cycles of induction treatment. **(D)** At membranous nephropathy diagnosis.

including serum albumin, creatinine levels, and urinalyses were all in the normal range (**Table 1**). He did not receive any antitumor therapy after MN. CT scans including chest and abdomen were regularly performed, which showed persistent partial response of lung cancer.

DISCUSSION

Renal immune-mediated adverse events (irAEs), which had different clinical and histological manifestations, have not been commonly reported in previous studies (2). Among the different types of renal irAEs, acute interstitial nephritis characterized by diffuse interstitial inflammation with a predominant T-lymphocytic infiltrate (3) was the most common. Glomerular was less affected by immunotherapy, and pauci-immune glomerulonephritis, podocytopathies, and complement 3 glomerulonephritis are the most frequently reported histology subtypes (8). MN is an antibody-mediated autoimmune glomerular disease (9) that typically present with marked elevation in urine protein levels and decline in serum albumin levels and is rarely reported to be associated with ICIs therapy (10). In patients with underlying cancers, MN was also considered to be a paraneoplastic sign, especially if THSD7A antibodies were present (6, 11). To our knowledge, this is the first report of THSD7A-positive MN related with ICIs therapy.

THSD7A, which is also expressed in various tumors, is the target podocyte antigen identified in MN (12). A potential mechanism for the association between cancer and MN with respect to the THSD7A antibodies has been described (5). However, with the commonly present antigens in tumors, the THSD7A antibodies are rare in patients with cancer prior to treatment (11), as shown in this case. Moreover, paraneoplastic glomerular diseases often appeared when cancer is activated or recurrent (13, 14) and should be achieved with treatment of the underlying cancer.

In our patient, despite the redisposing THSD7A antigen in the primary tumor, the THSD7A antibody tested positive after immunotherapy, and symptomatic nephropathy subsequently developed while the tumor was still in remission. After systemic glucocorticoids and rituximab treatment, the patient tested negative for the antibodies together with the remission of nephropathy. Because of the timeline of ICIs therapy, MN, and mismatched kidney disease with tumor response, we speculated that tislelizumab-associated humoral immunity activation, which leads to an increase of THSD7A antibody titer or an

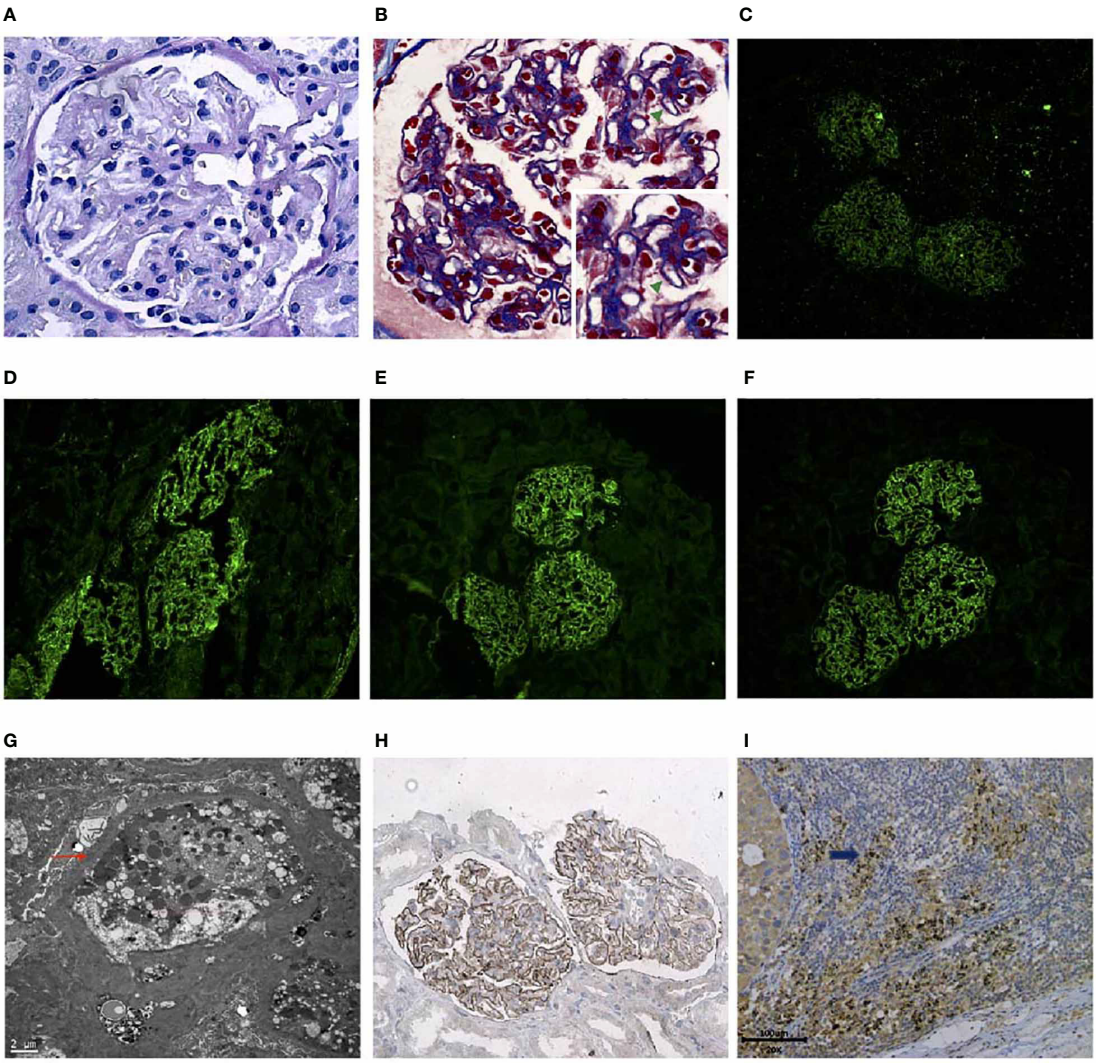

FIGURE 2 | Renal biopsy findings showing a THSD7A-associated MN Renal histology specimens and baseline tumor tissue. **(A)** Periodic acid-Schiff (PAS) stain showing stiff glomeruli (Original magnification, 400×). **(B)** Masson trichrome stain showing subepithelially localized immune deposits (green arrow) (Original magnification, 400×). **(C)** Immunofluorescence of IgG deposition in the subepithelial area. (Original magnification, 200×). **(D)** Immunofluorescence of subepithelial IgG1 deposition. (Original magnification, 200×). **(E)** Immunofluorescence of subepithelial IgG2 deposition. (Original magnification, 200×). **(F)** Immunofluorescence of subepithelial IgG4 deposition. (Original magnification, 200×). **(G)** Electron microscopy showing discrete electron-dense subepithelial deposits (red arrow). (Original magnification, 6000×). **(H)** Positive staining for thrombospondin type-1 domain-containing 7A (THSD7A) along the glomerular basement membrane. (Original magnification × 200). **(I)** The tumor cells of baseline metastases lymph node were positive for thrombospondin type-1 domain-containing 7A (THSD7A) by immunohistochemistry (blue arrows).

de novo production of THSD7A antibodies, may have contributed to the development of renal irAEs, as observed in our case.

While a T cell-mediated mechanism is considered the predominant mechanism for irAEs, it is increasingly recognized that humoral immunity may also play an important role in irAEs (15). Similar autoantibodies have also been reported for different irAEs such as bullous pemphigoid and myasthenia gravis with their autoimmune disease counterparts (16, 17). Reactivation of some previously unrecognized antibodies were also found in some irAEs (18). Moreover, well-controlled pre-existing autoimmune or antibody-mediated diseases, such as PLA2R antibody-positive primary MN, could also be reactivated during ICI therapy (19, 20).

Based on the above information, we hypothesized that anti-CD20 antibodies may be effective in the treatment of irAEs. In this case, the patients' MN was thought to be mediated by humoral immunity and had been well-controlled by prednisone and rituximab (a monoclonal anti-CD20 antibody). This suggested us that the treatment for irAEs could be selected according to the different underlying mechanisms.

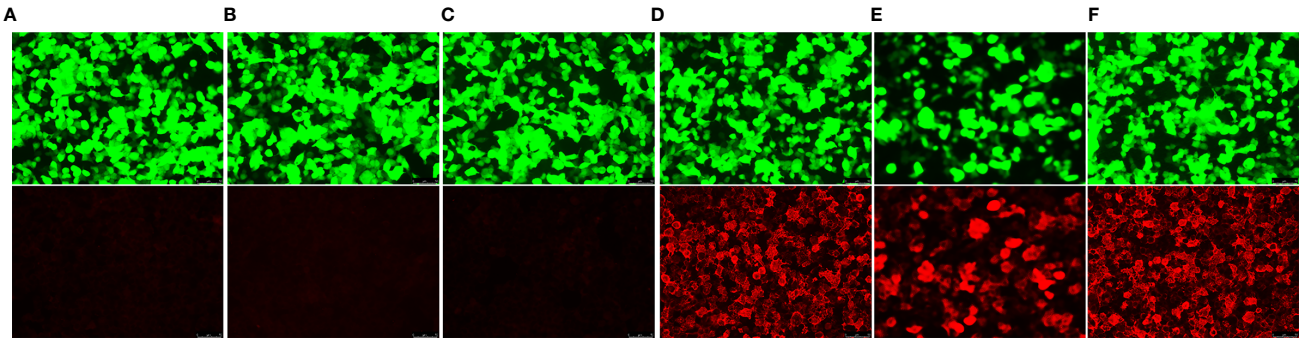

FIGURE 3 | Series anti-thrombospondin type-1 domain-containing 7A (THSD7A) antibody tests. THSD7A IgG detected in the serum using cell-based indirect immunofluorescence test. Images on the top show transfection cells express green fluorescent protein. The images on the bottom show transfected cells with the red fluorescent-labeled secondary antibody on detection of anti-THSD7A IgG. **(A)** Negative control. **(B)** Baseline before treatment (June 19, 2019). **(C)** After four cycles of induced treatment (September 20, 2019). **(D)** After four cycles of maintenance therapy (December 12, 2019). **(E)** At nephrotic syndrome diagnosis (May 12, 2020). **(F)** Positive control.

CONCLUSION

MN is a rare renal manifestation associated with ICIs. The underlying mechanism likely involves the production of podocyte antibodies including THSD7A antibodies. This case demonstrated that similar autoantibodies may be present in cases of immune-related glomerular diseases and may also have a similar mechanism with idiopathic MN, in which the humoral immunity may play an important role. A better understanding of the underlying mechanism might be useful in monitoring and individualized treatments of irAEs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The studies involving human participants were reviewed and approved by Center for Ethics in Peking Union Medical College Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MC analyzed the patient data, designed the case report, and drafted the manuscript. WZ provided significant contributions to the collection of patient data and sample preparation. WY and LZ performed the renal biopsy and provided the renal pathology images. KZ and MW provided significant contributions to the analysis of the patient data and designed the case report. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the National Natural Science Foundation (Grant No. 81702292).

ACKNOWLEDGMENTS

We thank the patient for providing his information for this study.

REFERENCES

1. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated With Immune Checkpoint Blockade. *N Engl J Med* (2018) 378 (2):158–68. doi: 10.1056/NEJMra1703481
2. Shingarev R, Glezerman IG. Kidney Complications of Immune Checkpoint Inhibitors: A Review. *Am J Kidney Dis* (2019) 74:529–37. doi: 10.1053/j.ajkd.2019.03.433
3. Wanchoo R, Karam S, Uppal NN, Barta VS, Deray G, Devoe C, et al. Adverse Renal Effects of Immune Checkpoint Inhibitors: A Narrative Review. *Am J Nephrol* (2017) 45(2):160–9. doi: 10.1159/000455014
4. Lee A, Keam SJ. Tislelizumab: First Approval. *Drugs* (2020) 80(6):617–24. doi: 10.1007/s40265-020-01286-z
5. Tomas NM, Beck LH Jr, Meyer-Schwesinger C, Seitz-Polski B, Ma H, Zahner G, et al. Thrombospondin Type-1 Domain-Containing 7A in

Idiopathic Membranous Nephropathy. *N Engl J Med* (2014) 371(24):2277–87. doi: 10.1056/NEJMoa1409354
6. Bobart SA, Tehranian S, Sethi S, Alexander MP, Nasr SH, Moura Marta C, et al. A Target Antigen-Based Approach to the Classification of Membranous Nephropathy. *Mayo Clin Proc* (2021) 96(3):577–91. doi: 10.1016/j.mayocp.2020.11.028
7. Hoxha E, Beck LH Jr, Wiech T, Wiech T, Tomas NM, Probst C, et al. An Indirect Immunofluorescence Method Facilitates Detection of Thrombospondin Type 1 Domain-Containing 7a-Specific Antibodies in Membranous Nephropathy. *J Am Soc Nephrol* (2017) 28(2):520–31. doi: 10.1681/ASN.2016010050
8. Kitchlu A, Jhaveri KD, Wadhwani S, Deshpande P, Harel Z, Kishibe T, et al. A Systematic Review of Immune Checkpoint Inhibitor-Associated Glomerular Disease. *Kidney Int Rep* (2020) 6(1):66–77. doi: 10.1016/j.ekir.2020.10.002
9. Tesar V, Hruskova Z. Autoantibodies in the Diagnosis, Monitoring, and Treatment of Membranous Nephropathy. *Front Immunol* (2021) 12:593288. doi: 10.3389/fimmu.2021.593288
10. Mamlouk O, Selamet U, Machado S, Abdelrahim M, Glass WF, Tchakarov A, et al. Nephrotoxicity of Immune Checkpoint Inhibitors Beyond Tubulointerstitial Nephritis: Single-Center Experience. *J Immunother Cancer* (2019) 7:2. doi: 10.1186/s40425-018-0478-8
11. Hoxha E, Wiech T, Stahl PR, Zahner G, Tomas NM, Meyer-Schwesinger C, et al. A Mechanism for Cancer-Associated Membranous Nephropathy. *N Engl J Med* (2016) 374:1995–6. doi: 10.1056/NEJMc1511702
12. Stahl PR, Hoxha E, Wiech T, Schröder C, Simon R, Stahl RAK. THSD7A Expression in Human Cancer. *Genes Chromosom Cancer* (2017) 56:314–27. doi: 10.1002/gcc.22440
13. Wang T, Zhang Y, Liu M, Kang X, Kang L, Zhang H. THSD7A as a Marker for Paraneoplastic Membranous Nephropathy. *Int Urol Nephrol* (2019) 51(2):371–3. doi: 10.1007/s11255-018-02068-z
14. Taguchi S, Koshikawa Y, Ohyama S, Miyachi H, Ozawa H, Asada H. Thrombospondin Type-1 Domain-Containing 7A-Associated Membranous Nephropathy After Resection of Rectal Cancer: A Case Report. *BMC Nephrol* (2019) 20(1):43. doi: 10.1186/s12882-019-1236-y
15. Das R, Bar N, Ferreira M, Newman AM, Zhang L, Bailur JK, et al. Early B Cell Changes Predict Autoimmunity Following Combination Immune Checkpoint Blockade. *J Clin Invest* (2018) 128(2):715–20. doi: 10.1172/JCI96798
16. Naidoo J, Schindler K, Querfeld C, Busam K, Cunningham J, Page DB, et al. Autoimmune Bullous Skin Disorders With Immune Checkpoint Inhibitors Targeting PD-1 and PD-L1. *Cancer Immunol Res* (2016) 4(5):383–9. doi: 10.1158/2326-6066.CIR-15-0123
17. Dadu R, Rodgers TE, Trinh VA, Kemp EH, Cubb TD, Patel S, et al. Calcium-Sensing Receptor Autoantibody-Mediated Hypoparathyroidism Associated With Immune Checkpoint Inhibitor Therapy: Diagnosis and Long-Term Follow-Up. *J Immunother Cancer* (2020) 8(1):e000687. doi: 10.1136/jitc-2020-000687
18. Wilson R, Menassa DA, Davies AJ, Michael S, Hester J, Kuker W, et al. Seronegative Antibody-Mediated Neurology After Immune Checkpoint Inhibitors. *Ann Clin Transl Neurol* (2018) 5(5):640–5. doi: 10.1002/acn3.547
19. Tison A, Quéré G, Misery L, Funck-Brentano E, Danlos FX, Routier E, et al. Safety and Efficacy of Immune Checkpoint Inhibitors in Patients With Cancer and Preexisting Autoimmune Disease: A Nationwide, Multicenter Cohort Study. *Arthritis Rheumatol* (2019) 71(12):2100–11. doi: 10.1002/art.41068
20. Lin JS, Wang DY, Mamlouk O, Glass WF, Abdelrahim M, Yee C, et al. Immune Checkpoint Inhibitor Associated Reactivation of Primary Membranous Nephropathy Responsive to Rituximab. *J Immunother Cancer* (2020) 8(2):e001287. doi: 10.1136/jitc-2020-001287

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

REVIEW
published: 21 May 2021
doi: 10.3389/fonc.2021.628243

Organ-Specific Immune-Related Adverse Events for PD-1 Antibodies in Lung Cancer Treatment

Xiaohu Zheng[1,2] *and Haiming Wei*[1,2,3]*

[1] Division of Molecular Medicine, Hefei National Laboratory for Physical Sciences at Microscale, The CAS Key Laboratory of Innate Immunity and Chronic Disease, School of Life Sciences, University of Science and Technology of China, Hefei, China, [2] Institute of Immunology, University of Science and Technology of China, Hefei, China, [3] Research Unit Of NK Cells, Chinese Academy Of Medical Sciences, Hefei, China

Anti-PD-1 therapy has revolutionized the clinical treatment of lung cancer. With the increasing number of lung cancer patients being treated, there is also an increase in the number of immune-related adverse events (irAEs) being reported. These irAEs involve multiple organs and systems, mainly manifest as inflammatory side effects, and are different from the adverse events observed with traditional lung cancer treatment. These effects are often mild and treatable and reversible; however, in a few cases the side effects can be severe and lead to termination of immunotherapy. Management involves glucocorticoid-based related immunomodulators, which should be carefully prescribed to balance the efficacy and side effects of the PD-1 antibody treatment. This review will describe the characteristics and mechanisms of irAEs in specific organs, and will serve as a guide to help optimize treatment plans and improve patient outcomes.

Keywords: lung cancer, immune-related adverse events (irAE), PD-1 antibody therapy, inflammatory, side effect

OPEN ACCESS

Edited by:
Hubing Shi,
Sichuan University, China

Reviewed by:
Julie Shabto,
Emory University, United States
Enrique J. Arenas,
Vall d'Hebron Institute of Oncology (VHIO), Spain

***Correspondence:**
Haiming Wei
ustcwhm@ustc.edu.cn

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Oncology

Received: *11 November 2020*
Accepted: *04 May 2021*
Published: *21 May 2021*

Citation:
Zheng X and Wei H (2021) Organ-Specific Immune-Related Adverse Events for PD-1 Antibodies in Lung Cancer Treatment. Front. Oncol. 11:628243. doi: 10.3389/fonc.2021.628243

INTRODUCTION

Immunocheckpoint inhibitors (ICIs), especially PD-1 antibodies, have been a revolutionary success in the clinical treatment of tumors by blocking immune checkpoints to enhance anti-tumor immune responses. Normally, immune checkpoints include PD-1, which downregulates the T-cell response and serves to protect the body from potentially damaging immune responses. Tumors can hijack the system and evade the immune system by activating immune checkpoints and suppressing the T-cell response. Thus, interference with these immune checkpoint pathways can induce an anti-tumor immune response and deliver therapeutic benefits in cancer patients.

Several PD-1 antibodies have been approved by the United States Food and Drug Administration. Specifically, pembrolizumab and nivolumab were approved for the treatment of metastatic non-small-cell lung cancer (NSCLC). These antibody drugs have indeed shown significant efficacy in clinical trials. Programmed cell death 1 (PD-1) is a key molecule mediating immune tolerance in the body (1, 2). Blocking antibodies can definitely enhance the activity of the immune system, although this often results inflammatory side effects, which are referred to as immune-related adverse events (irAEs). The presence of irAEs has been reported in retrospective clinical trials evaluating PD-1 antibodies, which mainly included pembrolizumab and nivolumab, for the treatment of NSCLC (1–4).

Clinical trial data suggest that the irAEs produced by PD-1 antibody in lung cancer treatment involve the thyroid, lung, skin, intestinal tract, and liver. Less common are the pancreas, kidney, pituitary gland, and musculoskeletal system (**Figure 1**). The majority of cases are mild irAEs and Anti-PD-1 therapy can usually be continued under close monitoring. Despite the very low incidence of moderate to severe irAEs, these may be associated with a serious decline in unique organ function and quality of life (5–9). Therefore, these toxicities require early detection and appropriate management. In this review, we focus on the pathological features, potential pathogenic mechanisms, and associated outcomes of irAEs in each unique organ, which is conducive to a more rational clinical management of lung cancer patients receiving PD-1 antibody treatment.

THYROID DYSFUNCTION

Clinical Characteristics

Thyroid dysfunction is a common and clinically mild irAE and is an early event among lung cancer patients treated with PD-1 antibodies (10). Most patients with anti-PD-1 drug-induced thyroid dysfunction are asymptomatic or present with hypothyroidism, hyperthyroidism, or thyroiditis (4, 5, 7–9, 11–14). The overall incidence rates of hypothyroidism and hyperthyroidism are 9.1% and 7.8%, respectively, while thyroiditis has the lowest reported incidence (2.6%) among PD-L1-positive NSCLC patients treated with pembrolizumab monotherapy (15). Hyperthyroidism occurs shortly after the initiation of pembrolizumab treatment and presents at median after 32 days (10). The onset of hypothyroidism occur later, at median time of 98 days. Many patients who eventually develop hypothyroidism experience a brief period of asymptomatic hyperthyroidism before the onset of the disease. Hypothyroidism may be asymptomatic or mild, and continued immunotherapy should not be precluded (7, 8, 10).

Therapeutic Management

Clinically, patients with thyroid dysfunction are routinely given long-term thyroid hormone replacement therapy (10). Patients reporting this irAE did not experience a significant recovery of thyroid function, although none of the patients required corticosteroids, β-blocker, or methimazole therapy. Patients with abnormal thyroid function test (TFT) do not need to

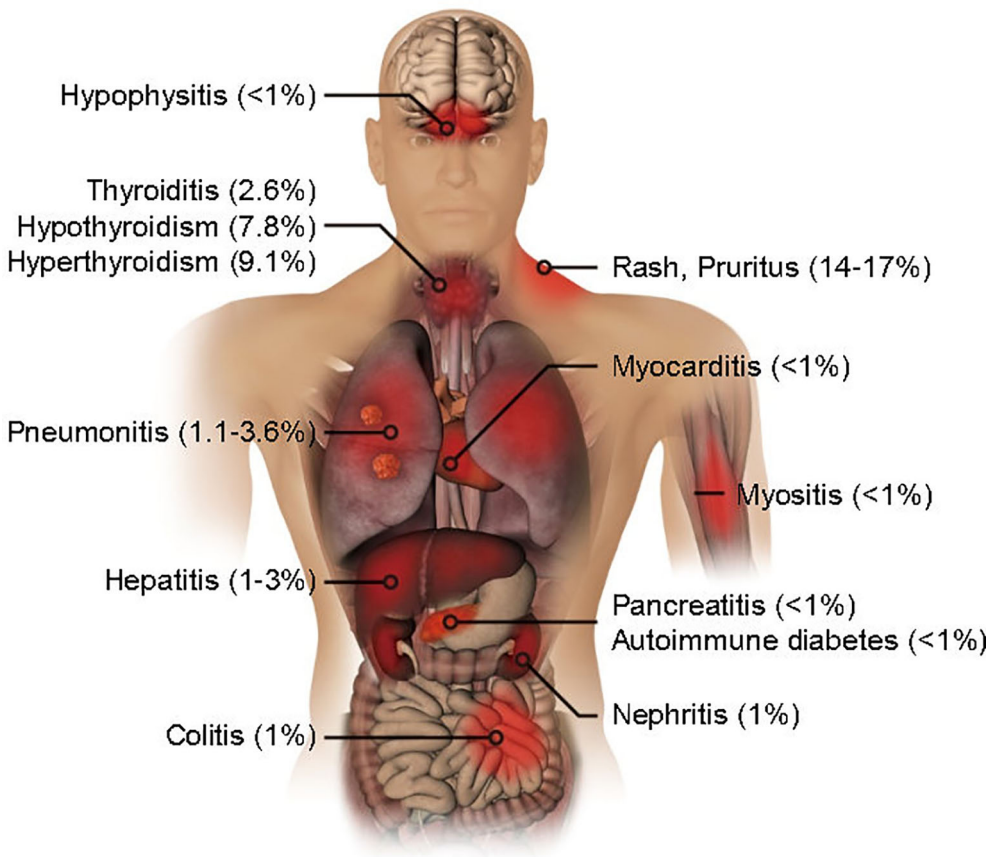

FIGURE 1 | Organ-specific immune-related adverse events by PD-1 blockade in lung cancer treatment. The incidence rates are shown.

delay or stop using pembrolizumab due to the clinical impact of the thyroid dysfunction (8, 10, 12, 13, 15).

Association With Clinical Outcomes

There was no significant difference in baseline clinical characteristics between patients with thyroid dysfunction and those without thyroid dysfunction. Interestingly, pembrolizumab-treated NSCLC patients with thyroid dysfunction had significantly higher median OS rates than patients without thyroid dysfunction (10). Whether there is a specific mechanistic association between antithyroid immunity and antitumor immunity is unclear, and larger clinical trials involving higher patient volumes are needed to verify the association.

Possible Mechanisms/Pathophysiology

During anti-PD-1 therapy, patients with anti-thyroid antibodies may develop thyroid dysfunction, whether or not these antibodies are present at baseline or are detected after treatment begins. In addition, many patients who eventually develop hypothyroidism experience a brief period of asymptomatic hyperthyroidism before the onset of the disease (10). In addition, to T-cell-mediated cellular immunity, anti-PD-1 therapy may also regulate humoral immunity or enhance the activity of pre-existing anti-thyroid antibodies. PD-1 plays an important role in maintaining tolerance, and Anti-PD-1 therapy may disrupt the immune system's ability to attack what it is meant to protect (16). Although it is suspected that the destruction of self-tolerance leads to thyroid autoimmunity, the mechanism through which PD-1 blocking leads to such autoimmunity is not clear.

CUTANEOUS REACTIONS

Clinical Characteristics

Dermatologic toxicity is one of the most common irAEs reported in lung cancer patients treated with PD-1 antibodies. Dermatologic toxicity manifests in a variety of forms, and commonly includes rash, pruritus, dry skin, pruritus, and dermatitis acneiform (1, 2, 14, 17). Clinically, a rash is relatively common. Specific symptoms include plaques, papules, and erythematous macules, mainly distributed to the trunk and extremities, and rashes can also be associated with pruritus (18). Dermatologic toxicity often develops in the early days following a 2–5-week treatment with anti-PD-1 blockage therapy. Dermatologic irAEs have been reported to occur in 14% to 17% of patients treated with nivolumab and pembrolizumab (7–9, 12–14, 19). Clinically, diagnosis is usually achieved by physical examination to assess the skin appearance, while skin biopsies are performed based on the dermatologist's clinical diagnosis to define the cause (20).

Therapeutic Management

Severe skin irAEs (grade 3–5 severity, according to the CTCAE) occur in only 1–10% of lung patients receiving PD-1 antibody therapy. Although this may vary according to clinical severity, for most patients topical corticosteroids are sufficient for treatment of rashes caused by immunotherapy (2).

Association With Clinical Outcomes

The association observed between pembrolizumab treatment and irAEs has clinical relevance because the systemic side effects of pembrolizumab can act as a proxy for therapeutic response, similar to rashes treated with EGFR tyrosine kinase inhibitors (21). A previous meta-analysis of patients with advanced melanoma who had received PD-1 antibody immunotherapy found that the risk of death in patients with vitiligo was significantly lower than in patients without vitiligo (22, 23). As in the case of interleukin (IL)-2, dermatologic AEs resulting from targeted therapy are often associated with higher response rates, efficacy, and survival (24–26). Clinical data have suggested that dermatologic AEs are associated with a favorable outcomes in patients treated with pembrolizumab (27). There is still insufficient clinical data to determine whether PD-1-antibody-induced irAEs are associated with a favorable outcome in lung cancer.

Possible Mechanisms/Pathophysiology

On histological evaluation, patients treated with pembrolizumab often present with an interface dermatitis or lichenoid tissue reaction. This may be due to non-specific activation of T cells after PD-1 blockade, resulting in attacks on susceptible keratinocytes. Ipilimumab inhibits tumor cells from evasive immune responses by suppressing the immune checkpoint cytotoxic T lymphocyte antigen-4 (CTLA-4), which also triggers autoimmune damage in previously protected normal cells. A similar mechanism may result for nivolumab and pembrolizumab as these antibodies target another immune checkpoint, the PD-1 receptor (18, 28–30).

HEPATITIS

Clinical Characteristics

Hepatitis has a prevalence of 1–3% among anti- PD-1 trials in lung cancer patients. The most common manifestation of hepatitis is an asymptomatic increase in transaminase levels, which only occurs in patients with very severe or chronic disease (1, 17). Monitoring of transaminase and bilirubin levels before initiation of treatment with immune checkpoint inhibitors (ICI) and after each dose is necessary for hepatitis screening. Individuals with abnormal liver enzymes should undergo additional tests to rule out viral causes or chronic disease-related liver dysfunction (1, 2, 12, 15). Abdominal computed tomography (CT) scans show that the severity of liver side effects varies. In mild cases, the liver appears normal. However, severe cases are characterized by hepatomegaly, weakened hepatic parenchyma, and periportal edema similar to acute hepatitis (31, 32).

Viral infections of the liver are a risk factor for inducing hepatitis in lung cancer patients treated with PD-1 antibodies. Patients with past exposure to a high viral load of hepatitis B virus (HBV) can develop hepatitis during or after PD-1 antibody therapy. Patients with HBV infection can trigger more severe transaminase elevations (grade 3 or higher) (33).

Therapeutic Management and Association With Clinical Outcomes

With the possibility of clinical therapeutic benefit and no remarkably increased risk, patients with hepatitis can choose continuous PD-1 antibody therapy. All events were of grade 3-4 and were subsequently treated with glucocorticoid or checkpoint inhibitor treatment was interrupted.

Data from case reports and phase II trials suggest that ICIs achieve a durable response and manageable safety in patients with controlled HBV or hepatitis C virus (HCV) infection (34). When treating patients presenting a history of hepatitis infection with ICI, regular monitoring of the status of the hepatitis virus is needed. Prospective studies are still needed to determine the true safety of ICI for the treatment of patients with viral hepatitis.

Possible Mechanisms/Pathophysiology

The liver is an immune-tolerant organ. PD-1 is a key molecule mediating immune tolerance of T cells. Any immunotherapy that blocks the PD-1 receptor is bound to break the immune tolerance microenvironment of the liver and induce hepatitis (1, 32). In patients with viral infection of the liver, the resting state of the virus may be disrupted, triggering viral activity and the onset of hepatitis (32, 33).

DIARRHEA OR COLITIS

Clinical Characteristics

For the treatment of lung cancer with PD-1 inhibitors, diarrhea is one of the most common irAEs (8–12.5%). In contrast, colitis has been reported in 1% of patients (1, 4, 5, 7–9, 12–14). The typical diagnosis of colitis includes an assessment to exclude the cause of infection and CT images to identify the severity and extent of colitis and to exclude the possibility of intestinal perforation. When a diagnosis is obscure, endoscopy is helpful. It can be used to assess patients with severe, refractory, or recurrent colitis and can help exclude cytomegalovirus-associated colitis and other high-risk characteristics (1, 35–37).

Therapeutic Management and Association With Clinical Outcomes

Clinicians should first exclude infectious colitis in the differential diagnosis by obtaining the patient's medical history, by examining physical appearance, or examining stool. For grade 1 symptoms, it is recommended to continue immunotherapy symptomatic treatment and close monitoring. For grade 2 symptoms, antidiarrheal use and symptomatic treatment are recommended. For persistent grade 2 symptoms, systemic corticosteroids should be attempted. If grade 3 or 4 symptoms occur, immunotherapy is discontinued with corticosteroid treatment. A monoclonal antibody against tumor necrosis factor (infliximab) is recommended for exacerbated severe symptoms and has been shown to significantly improve symptoms (31, 38–40).

Possible Mechanisms/Pathophysiology

The histopathological characteristics of PD-1 antibody-associated colitis are very similar. The most common type of injury was active colitis with crypt atrophy and increased apoptosis. On biopsy, the mucosal lesions were mainly manifested as a neutrophilic crypt microabscess and inflammation, crypt atrophy, and edema. Another pattern of injury observed involved lymphocytic colitis, where biopsies showed increased intraepithelial lymphocytes (IELs), superficial epithelial injury, and increased laminar mononuclear inflammatory cells (33, 41–43).

PNEUMONITIS

Clinical Characteristics

The incidence of pneumonia at all levels in lung cancer was significantly higher than in other tumor types. One study reported that lung cancer patients treated with PD-1 inhibitors had significantly higher rates of full-grade interstitial lung disease (3.6% vs. 1.3%) and advanced interstitial lung disease (1.1% vs. 0.4%) than those treated with programmed death-ligand 1 (PD-L1) inhibitors (44). Pneumonia is first determined by checking oxygen saturation whilst ambulatory, and is then confirmed by CT images, determination of the infectious agent, and the degree of inflammation. CT images exhibit variable features, including interlobular septal thickening, cryptogenic tissue, ground-glass opacity, pneumonia-like or bronchiolitis-like appearance (44). The median time from the start of treatment to the onset of pneumonia was reported to be 2.6 months. The symptoms of most pneumonia patients include cough and dyspnea (45, 46).

Therapeutic Management

As a clinical practice, PD-1 antibody therapy should not be terminated due to pneumonia. The vast majority of patients only need to receive corticosteroid treatment, and very few need to receive infliximab treatment. The prolonged time from the beginning of treatment to the onset of pneumonia (0.5 to 11.5 months) indicates that follow-up of signs and careful observation are important throughout therapy (11, 14, 46).

Association With Clinical Outcomes

PD-1 inhibitor-associated pneumonia exhibits a range of imaging patterns that are associated with the level of toxicity. The safety evaluation of nivolumab in two phase I clinical trials reported pneumonitis-related death occurred in 3 cases (2.3%) (47) and in 1 case (1.1%) (48), respectively. The safety evaluation of pembrolizumab in two clinical trials reported pneumonitis-related death occurred in 3 cases (0.5%) (7) and in 1 case (0.2%) (3), respectively. A multidisciplinary approach exploring pulmonology, radiology, oncology, and pathology is required to optimize patient care.

Possible Mechanisms/Pathophysiology

Lung cancer patients experience a higher incidence of pneumonia. The possible reasons are as follows: (1) the load of the primary lung tumor limits the stress and recovery capacity of the lung; and (2) these patients exhibit pulmonary fibrosis and chronic obstructive pulmonary disease.

NEPHRITIS

Clinical Characteristics

In a systematic review of multiple randomized controlled trials of panitumumab and nivolumab for lung cancer, the incidence of nephritis was reported to be low (about 1%). Elevated serum creatinine levels was the most common characteristic of renal toxicity induced by ICIs (5, 9, 11, 12). A case of interstitial nephritis was reported in the nivolumab group receiving treatment for lung cancer (9). Pauci-immune glomerulonephritis also commonly presents as a renal injury. Generally, renal injuries occur during the later stages of PD-1 antibody therapy, that is, after 6–12 months of treatment (49).

Therapeutic Management and Association With Clinical Outcomes

Most patients achieve complete relief with intravenous or oral steroid after 1–3 months. Very few patients require additional clinical hemodialysis (49).

Possible Mechanisms/Pathophysiology

Histopathologic analysis of renal biopsies from cancer patients treated with nivolumab revealed mild, diffuse, active interstitial inflammation, mild edema, and tubular epithelial injury, consisting of abundant $CD3^+$ and $CD4^+$ T lymphocytes, and a small number of plasma cells, eosinophils and macrophages (49). In renal tissue, renal cells block the activity of PD-1 positive T cells by upregulating PD-L1 expression. Therefore, when PD-1 is blocked by antibodies, the PD-1/PD-L1 signaling pathway will also be blocked, and T cells will further proliferate and become activated, leading to cytotoxicity and kidney injury (49, 50). Thus, PD-1 antibody treatment may result in nephritis as a form of altered autoimmunity, similar to how autoimmune diabetes, may be based on the loss of peripheral tolerance of reactive T cells. Any situation that leads to an increase in T cell migration and function, may cause clinically significant kidney damage (49, 51, 52).

MYOSITIS

Clinical Characteristics

Muscle injury mainly includes myalgia and myositis, and its typical symptoms include varying degrees of muscle weakness and pain. Less than 1% of lung cancer patients treated with PD-1 antibodies experience myositis, which is usually classified as mild (CTCAE grades 1 and 2). In general, the average onset time of myositis caused by immunotherapy is 25 days. Interestingly, ICI-associated myositis may manifest as classic muscle inflammatory symptoms, as well as ocular symptoms, similar to the autoimmune diseases observed at the neuromuscular junction (53).

Therapeutic Management and Association With Clinical Outcomes

Of particular concern is that a high percentage of myositis occurs in association with myocarditis or myasthenia gravis, both of which cause a high percentage of deaths. Therefore, clinicians need to maintain a high index of suspicion and a low threshold for skeletal muscle biopsy results. Further, more systematic heart screening is required when myocarditis occurs simultaneously (53, 54).

Possible Mechanisms/Pathophysiology

At present, most reports on myositis have not provided detailed clinical, immunological, and histopathological profiles, although a clinical trial study has shown that inflammation is the dominant feature and that most patients develop myositis-related autoantibodies, such as anti-muscarinic acetylcholine receptors (mAChR) antibodies (54–56).

HYPOPHYSITIS

Clinical Characteristics

Hypophysitis is an irAE that commonly presents following CTLA-4 antibody blockage but not with PD-1 inhibitor treatment (1). Symptoms of pituitary dysfunction are extensive, and include headache, weakness, visual changes, and enlargement of the pituitary gland (57). Pituitary inflammation induces secondary adrenal insufficiency, secondary adrenocorticotropic hormone (ACTH) deficiency, secondary hypothyroidism, and hypogonadotropin hypogonadism (1).

Therapeutic Management

Several retrospective cohort studies have suggested that high doses of systemic corticosteroid therapy are not effective in reducing pituitary inflammation (58). Therefore, endocrine-related irAEs still require clinical exploration of more effective control methods, as long as immunotherapy is not terminated or the efficacy of antibodies is not affected.

Association With Clinical Outcomes

A clinical study of CTLA-4 antibody in melanoma patients with hypophysitis suggested better antitumor efficacy was achieved (59).

Possible Mechanisms/Pathophysiology

Some data suggest that pituitary inflammation may be associated with B-cell immunotoxicity and autoantibody production, including upregulation of anti-GNAL antibodies, or anti-ITM2B antibodies in patients with pituitary inflammation (1).

PANCREATITIS

Clinical Characteristics

The pancreas is an organ rarely affected by PD-1 antibody treatment in lung cancer therapy. The clinical features of irAE-associated pancreatitis are varied and difficult to identify. Asymptomatic elevation of serum lipase and/or amylase levels during ICI treatment hampers the diagnostic process. During ICI therapy, serum lipase and/or amylase may be elevated, but the patient remains asymptomatic (60).

Therapeutic Management and Association With Clinical Outcomes

The treatment of pancreatitis remains a difficult clinical problem, and immunotherapy may have to be suspended in due course. At present, the treatment of pancreatitis involves large doses of systemic glucocorticoids, and requires long-term administration, which gradually reduces patient symptoms and allows normalization of serum lipase levels. Delayed secondary pancreatic insufficiency may occur even after successful treatment, and patients must be regularly monitored (60).

Possible Mechanisms/Pathophysiology

Pancreatitis is a rare immune-associated adverse event with PD-1 antibody treatment. Its imaging features are similar to those of autoimmune pancreatitis. Clinical evidence suggests that the pathologic characteristics of nivolumab in treating pancreatitis are similar to those of autoimmune pancreatitis (60, 61).

TREATMENT OF IRAES IN LUNG CANCER TREATMENT

Steroids and/or immunosuppressants are common clinical treatments for irAEs, and may this be associated with reduced efficacy of cancer immunotherapy. Given their immunosuppressive activity, the potential effects of glucocorticoids on the anticancer activity on inhibition of immune checkpoints must be considered. The results of multiple retrospective studies investigating melanoma are exciting (62). Steroid use was not associated with reduced efficacy of CTLA-4 inhibitors and PD-1 or PD-L1 inhibitors. Interestingly, patients exhibiting irAEs experienced a longer progression-free survival than patients without irAEs, and the benefits did not change with steroid use. Nonetheless, the use of prednisone during early treatment is associated with a poorer prognosis in lung cancer patients (63). Thus, prospective studies are still needed to determine the effects of steroid use on lung cancer outcomes in patients receiving PD-1 antibody therapy. These data suggest caution in the use of steroids or immunosuppressants.

In addition, low doses of corticosteroids can significantly impair the antitumor activity of T cells. Different organs also present different adverse effects (64). Therefore, additional clinical trials are needed to verify whether safer targeted drugs or antibody drugs are more feasible based on the organ-specific mechanisms associated with immune-related adverse events following treatment with ICIs. For now, treatments for moderate or severe irAEs in a timely manner is needed.

DISCUSSION

Inhibition of immune checkpoints, especially PD-1 blockade, represents an increasingly important strategy in cancer treatment. Overall, treatment with PD-1 antibodies is relatively safe for lung cancer, and most induced irAEs are clinically manageable (1, 15). Most toxic effects are reversible, except effects on the endocrine system may be long-lasting. Deaths from irAEs are rare, but myocarditis, pneumonia and colitis may likely trigger them. Therefore, attentive clinical monitoring and management is very important.

Here, we mainly review the irAEs in lung cancer treated with PD-1 antibody. Is there any difference with other types of cancer? Cutaneous malignancies (including melanoma, squamous cell carcinoma of the skin, and basal cell carcinoma) with treatment with PD-1 antibody have a high incidence of dermatitis as to 43%, and the incidence of head and neck cancer was also increased to 20%, both significantly higher than that of lung cancer patients. Patients with cutaneous malignancies were significantly more likely to develop dermatitis than patients with noncutaneous malignancy, including lung cancer (65). Pneumonitis is a relatively rare irAE in PD-1 therapy. The incidence of pneumonia was ~1% in melanoma and renal cell carcinoma patients receiving PD-1 inhibitor monotherapy, and rose to 3.1% in non-small cell lung cancer patients (66, 67). These data suggest that tumorigenetic organs may exhibit a higher frequency of irAEs. In general, there is no significant difference in the occurrence of irAEs among different types of tumors (1).

Currently, several PD-1 inhibitor drugs have been marketed, among which the most widely used are pembrolizumab and nivolumab (1). There is no a depth view of the difference in percentage of irAEs regarding different anti PD-1 therapies such as pembrolizumab and nivolumab. Shrujal et al. reported that organ specific irAEs were evaluated with 2993 patients in the investigational arm (pembrolizumab 1459, nivolumab 1534) (2). Among the 1459 patients exposed to pembrolizumab 1.1% had colitis, 0.2% had hepatitis, 3.1% had pneumonitis, 7.6% had hypothyroidism and 0.4% had hypophysitis. Among the 1534 patients exposed to nivolumab 0.3% had colitis, 0.0% had hepatitis, 2.2% had pneumonitis, 5.9% had hypothyroidism and 0.3% had hypophysitis (2). These data suggest organ specific irAEs are uncommon with the anti-PD-1 drugs. General irAEs are largely similar. The rates of pembrolizumab induced irAEs was slightly higher than that of nivolumab. The reason for this slight difference remains an open question.

Consistent with the different functions of immune checkpoints, the types of irAEs associated with monotherapy targeting the CTLA-4 or PD-1 pathways also differ (68). Typically, PD-1 inhibitors are better tolerated than CTLA-4 inhibitors. Grade 3 and 4 irAEs are more common in CTLA-4 inhibitors than in PD-1 inhibitors (69). Of note, colitis, rash and hypophysitis were more common with CTLA-4 inhibitors, whereas arthralgia, pneumonitis, vitiligo, and hypothyroidism were more common with PD-1 inhibitors (70). The exact biological explanation for the differences in organ selectivity and severity in irAEs with different ICIs is not fully understood. Theoretically, CTLA-4 blockade might induce larger T cell proliferation and also down-regulate regulatory T (Treg) cells, while PD-1 blockade only activates T cell clones in a small number of lesions (71).

There have been few studies on biomarkers for the risk of developing irAEs of immune checkpoint inhibitor therapy. Specific

CD8+ T cells, Interleukin 17, eosinophil counts have been related to irAEs but not Set the threshold (72, 73). There are some preliminary clinical data suggesting that a family history of autoimmune diseases, previous viral infections, and known autoimmunotoxic drugs are also potential related risk factors (74, 75). It has recently been reported that irAEs were more frequent among patients with he preexisting antibodies (76). For example, skin reactions are more common in patients who already have rheumatoid factor than in patients who don't (76). Thyroid dysfunction is more common in patients with pre-existing anti-thyroid antibodies. Suzuki et al. reported that 12 of 9869 cancer patients treated with nivolumab developed myasthenia gravis, 10 of whom had pre-existing acetylcholine receptor antibodies (77). Therefore, it is worth further investigation that pre-existing factor is associated with the development of irAEs.

AUTHOR CONTRIBUTIONS

HW and XZ conceived and conducted the project. HW supervised the project. XZ and HW wrote the paper. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Natural Science Foundation of China (Reference Numbers: 81872318), CAMS Innovation Fund for Medical Sciences (CIFMS, 2019-I2M-5-073) and the Strategic Priority Research Program of the Chinese Academy of Sciences (XDPB1002).

REFERENCES

1. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, et al. Immune-Related Adverse Events of Checkpoint Inhibitors. *Nat Rev Dis Primers* (2020) 6:38. doi: 10.1038/s41572-020-0160-6
2. Baxi S, Yang A, Gennarelli RL, Khan N, Wang Z, Boyce L, et al. Immune-Related Adverse Events for anti-PD-1 and anti-PD-L1 Drugs: Systematic Review and Meta-Analysis. *Bmj* (2018) 360:k793. doi: 10.1136/bmj.k793
3. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the Treatment of non-Small-Cell Lung Cancer. *New Engl J Med* (2015) 372:2018–28. doi: 10.1056/NEJMoa1501824
4. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab Versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. *New Engl J Med* (2015) 373:1627–39. doi: 10.1056/NEJMoa1507643
5. Gettinger S, Rizvi NA, Chow LQ, Borghaei H, Brahmer J, Ready N, et al. Nivolumab Monotherapy for First-Line Treatment of Advanced non–Small-Cell Lung Cancer. *J Clin Oncol* (2016) 34:2980–7. doi: 10.1200/JCO.2016.66.9929
6. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, Activity, and Immune Correlates of anti-PD-1 Antibody in Cancer. *New Engl J Med* (2012) 366:2443–54. doi: 10.1056/NEJMoa1200690
7. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, et al. Pembrolizumab Versus Docetaxel for Previously Treated, PD-L1-positive, Advanced non-Small-Cell Lung Cancer (KEYNOTE-010): A Randomised Controlled Trial. *Lancet* (2016) 387:1540–50. doi: 10.1016/S0140-6736(15)01281-7
8. Leighl NB, Hellmann MD, Hui R, Carcereny E, Felip E, Ahn M-J, et al. Pembrolizumab in Patients With Advanced non-Small-Cell Lung Cancer (KEYNOTE-001): 3-Year Results From an Open-Label, Phase 1 Study. *Lancet Respir Med* (2019) 7:347–57. doi: 10.1016/S2213-2600(18)30500-9
9. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, et al. Nivolumab Versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *New Engl J Med* (2015) 373:123–35. doi: 10.1056/NEJMoa1504627
10. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Antibody-Mediated Thyroid Dysfunction During T-cell Checkpoint Blockade in Patients With non-Small-Cell Lung Cancer. *Ann Oncol* (2017) 28:583–9. doi: 10.1093/annonc/mdw640
11. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer. *New Engl J Med* (2015) 372:2018–28. doi: 10.1056/NEJMoa1501824
12. Hui R, Garon EB, Goldman JW, Leighl NB, Hellmann MD, Patnaik A, et al. Pembrolizumab as First-Line Therapy for Patients With PD-L1-positive Advanced non-Small Cell Lung Cancer: A Phase 1 Trial. *Ann Oncol* (2017) 28:874–81. doi: 10.1093/annonc/mdx008
13. Mok TSK, Wu Y-L, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab Versus Chemotherapy for Previously Untreated, PD-L1-expressing, Locally Advanced or Metastatic non-Small-Cell Lung Cancer (KEYNOTE-042): A Randomised, Open-Label, Controlled, Phase 3 Trial. *Lancet* (2019) 393:1819–30. doi: 10.1016/S0140-6736(18)32409-7
14. Rizvi NA, Mazières J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, et al. Activity and Safety of Nivolumab, an anti-PD-1 Immune Checkpoint Inhibitor, for Patients With Advanced, Refractory Squamous non-Small-Cell Lung Cancer (CheckMate 063): A Phase 2, Single-Arm Trial. *Lancet Oncol* (2015) 16:257–65. doi: 10.1016/S1470-2045(15)70054-9
15. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab Versus Chemotherapy for PD-L1–Positive non–Small-Cell Lung Cancer. *New Engl J Med* (2016) 375:1823–33. doi: 10.1056/NEJMoa1606774
16. McLachlan SM, Rapoport B. Breaking Tolerance to Thyroid Antigens: Changing Concepts in Thyroid Autoimmunity. *Endocr Rev* (2014) 35:59–105. doi: 10.1210/er.2013-1055
17. Postow MA, Longo DL, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated With Immune Checkpoint Blockade. *New Engl J Med* (2018) 378:158–68. doi: 10.1056/NEJMra1703481
18. Min Lee CK, Li S, Tran DC, Zhu GA, Kim J, Kwong BY, et al. Characterization of Dermatitis After PD-1/PD-L1 Inhibitor Therapy and Association With Multiple Oncologic Outcomes: A Retrospective Case-Control Study. *J Am Acad Dermatol* (2018) 79:1047–52. doi: 10.1016/j.jaad.2018.05.035
19. Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, et al. Overall Survival and Long-Term Safety of Nivolumab (Anti–Programmed Death 1 Antibody, Bms-936558, ONO-4538) in Patients With Previously Treated Advanced non–Small-Cell Lung Cancer. *J Clin Oncol* (2015) 33:2004–12. doi: 10.1200/JCO.2014.58.3708
20. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* (2018) 36:1714–68. doi: 10.1200/JCO.2017.77.6385
21. Lee Y, Shim HS, Park MS, Kim JH, Ha SJ, Kim SH, et al. High EGFR Gene Copy Number and Skin Rash as Predictive Markers for EGFR Tyrosine Kinase Inhibitors in Patients With Advanced Squamous Cell Lung Carcinoma. *Clin Cancer Res* (2012) 18:1760–8. doi: 10.1158/1078-0432.CCR-11-2582
22. Teulings HE, Limpens J, Jansen SN, Zwinderman AH, Reitsma JB, Spuls PI, et al. Vitiligo-Like Depigmentation in Patients With Stage III-IV Melanoma Receiving Immunotherapy and its Association With Survival: A Systematic Review and Meta-Analysis. *J Clin Oncol* (2015) 33:773–81. doi: 10.1200/JCO.2014.57.4756
23. Mohamed MK, Ramalingam S, Lin Y, Gooding W, Belani CP. Skin Rash and Good Performance Status Predict Improved Survival With Gefitinib in Patients With Advanced non-Small Cell Lung Cancer. *Ann Oncol* (2005) 16:780–5. doi: 10.1093/annonc/mdi157
24. Pérez-Soler R, Chachoua A, Hammond LA, Rowinsky EK, Huberman M, Karp D, et al. Determinants of Tumor Response and Survival With Erlotinib in Patients With non–Small-Cell Lung Cancer. *J Clin Oncol* (2004) 22:3238–47. doi: 10.1200/JCO.2004.11.057

25. Poprach A, Pavlik T, Melichar B, Puzanov I, Dusek L, Bortlicek Z, et al. Skin Toxicity and Efficacy of Sunitinib and Sorafenib in Metastatic Renal Cell Carcinoma: A National Registry-Based Study. *Ann Oncol* (2012) 23:3137–43. doi: 10.1093/annonc/mds145
26. Phan GQ, Attia P, Steinberg SM, White DE, Rosenberg SA. Factors Associated With Response to High-Dose Interleukin-2 in Patients With Metastatic Melanoma. *J Clin Oncol* (2001) 19:3477–82. doi: 10.1200/JCO.2001.19.15.3477
27. Sanlorenzo M, Vujic I, Daud A, Algazi A, Gubens M, Luna SA, et al. Pembrolizumab Cutaneous Adverse Events and Their Association With Disease Progression. *JAMA Dermatol* (2015) 151:1206–12. doi: 10.1001/jamadermatol.2015.1916
28. Delyon J, Mateus C, Lefeuvre D, Lanoy E, Zitvogel L, Chaput N, et al. Experience in Daily Practice With Ipilimumab for the Treatment of Patients With Metastatic Melanoma: An Early Increase in Lymphocyte and Eosinophil Counts is Associated With Improved Survival. *Ann Oncol* (2013) 24:1697–703. doi: 10.1093/annonc/mdt027
29. Joseph RW, Cappel M, Goedjen B, Gordon M, Kirsch B, Gilstrap C, et al. Lichenoid Dermatitis in Three Patients With Metastatic Melanoma Treated With anti-PD-1 Therapy. *Cancer Immunol Res* (2015) 3:18–22. doi: 10.1158/2326-6066.CIR-14-0134
30. Okiyama N, Fujimoto M. Clinical Perspectives and Murine Models of Lichenoid Tissue Reaction/Interface Dermatitis. *J Dermatol Sci* (2015) 78:167–72. doi: 10.1016/j.jdermsci.2015.03.001
31. Cramer P, Bresalier RS. Gastrointestinal and Hepatic Complications of Immune Checkpoint Inhibitors. *Curr Gastroenterol Rep* (2017) 19:3. doi: 10.1007/s11894-017-0540-6
32. Hofmann L, Forschner A, Loquai C, Goldinger SM, Zimmer L, Ugurel S, et al. Cutaneous, Gastrointestinal, Hepatic, Endocrine, and Renal Side-Effects of anti-PD-1 Therapy. *Eur J Cancer (Oxford England: 1990)* (2016) 60:190–209. doi: 10.1016/j.ejca.2016.02.025
33. Karamchandani DM, Chetty R. Immune Checkpoint Inhibitor-Induced Gastrointestinal and Hepatic Injury: Pathologists' Perspective. *J Clin Pathol* (2018) 71:665–71. doi: 10.1136/jclinpath-2018-205143
34. Davar D, Wilson M, Pruckner C, Kirkwood JM. Pd-1 Blockade in Advanced Melanoma in Patients With Hepatitis C and/or HIV. *Case Rep Oncol Med* (2015) 2015:737389. doi: 10.1155/2015/737389
35. Geukes Foppen MH, Rozeman EA, van Wilpe S, Postma C, Snaebjornsson P, van Thienen JV, et al. Immune Checkpoint Inhibition-Related Colitis: Symptoms, Endoscopic Features, Histology and Response to Management. *ESMO Open* (2018) 3:e000278. doi: 10.1136/esmoopen-2017-000278
36. Hughes MS, Zheng H, Zubiri L, Molina GE, Chen ST, Mooradian MJ, et al. Colitis After Checkpoint Blockade: A Retrospective Cohort Study of Melanoma Patients Requiring Admission for Symptom Control. *Cancer Med* (2019) 8:4986–99. doi: 10.1002/cam4.2397
37. Abu-Sbeih H, Ali FS, Luo W, Qiao W, Raju GS, Wang Y. Importance of Endoscopic and Histological Evaluation in the Management of Immune Checkpoint Inhibitor-Induced Colitis. *J Immunother Cancer* (2018) 6:95. doi: 10.1186/s40425-018-0411-1
38. Weber JS, Postow M, Lao CD, Schadendorf D. Management of Adverse Events Following Treatment With Anti-Programmed Death-1 Agents. *Oncol* (2016) 21:1230–40. doi: 10.1634/theoncologist.2016-0055
39. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of Immunotherapy for the Practitioner. *J Clin Oncol* (2015) 33:2092–9. doi: 10.1200/JCO.2014.60.0379
40. Fecher LA, Agarwala SS, Hodi FS, Weber JS. Ipilimumab and its Toxicities: A Multidisciplinary Approach. *Oncol* (2013) 18:733–43. doi: 10.1634/theoncologist.2012-0483
41. Assarzadegan N, Montgomery E, Anders RA. Immune Checkpoint Inhibitor Colitis: The Flip Side of the Wonder Drugs. *Virchows Archiv* (2018) 472:125–33. doi: 10.1007/s00428-017-2267-z
42. Chen JH, Pezhouh MK, Lauwers GY, Masia R. Histopathologic Features of Colitis Due to Immunotherapy With Anti-PD-1 Antibodies. *Am J Surg Pathol* (2017) 41:643–54. doi: 10.1097/PAS.0000000000000829
43. Gonzalez RS, Salaria SN, Bohannon CD, Huber AR, Feely MM, Shi C. PD-1 Inhibitor Gastroenterocolitis: Case Series and Appraisal of 'Immunomodulatory Gastroenterocolitis'. *Histopathology* (2017) 70:558–67. doi: 10.1111/his.13118
44. Nishino M, Ramaiya NH, Awad MM, Sholl LM, Maattala JA, Taibi M, et al. Pd-1 Inhibitor-Related Pneumonitis in Advanced Cancer Patients: Radiographic Patterns and Clinical Course. *Clin Cancer Res* (2016) 22:6051–60. doi: 10.1158/1078-0432.CCR-16-1320
45. Nishino M, Sholl LM, Hodi FS, Hatabu H, Ramaiya NH. Anti-Pd-1-Related Pneumonitis During Cancer Immunotherapy. *New Engl J Med* (2015) 373:288–90. doi: 10.1056/NEJMc1505197
46. Nishino M, Chambers ES, Chong CR, Ramaiya NH, Gray SW, Marcoux JP, et al. Anti-Pd-1 Inhibitor-Related Pneumonitis in Non-Small Cell Lung Cancer. *Cancer Immunol Res* (2016) 4:289–93. doi: 10.1158/2326-6066.CIR-15-0267
47. Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, et al. Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, Bms-936558, ONO-4538) in Patients With Previously Treated Advanced non-Small-Cell Lung Cancer. *J Clin Oncol* (2015) 33:2004–12. doi: 10.1200/JCO.2014.58.3708
48. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and Ipilimumab Versus Ipilimumab in Untreated Melanoma. *New Engl J Med* (2015) 372:2006–17. doi: 10.1056/NEJMoa1414428
49. Wanchoo R, Karam S, Uppal NN, Barta VS, Deray G, Devoe C, et al. Adverse Renal Effects of Immune Checkpoint Inhibitors: A Narrative Review. *Am J Nephrol* (2017) 45(2):160–9. doi: 10.1159/000455014
50. Vandiver JW, Singer Z, Harshberger C. Severe Hyponatremia and Immune Nephritis Following an Initial Infusion of Nivolumab. *Target Oncol* (2016) 11:553–6. doi: 10.1007/s11523-016-0426-9
51. Ramos-Casals M, Lambotte O, Kostine M, Calabrese L, Suarez-Almazor M, Bingham C, et al. Thu0649 Phenotypic Clusters of Rheumatic/Systemic Immune-Related Adverse Events Induced by Cancer Immunotherapies (Immunocancer International Registry). *Poster Present* (2019) pp:620–1. doi: 10.1136/annrheumdis-2019-eular.2870
52. Perazella MA, Shirali AC. Immune Checkpoint Inhibitor Nephrotoxicity: What do We Know and What Should We do? *Kidney Int* (2020) 97:62–74. doi: 10.1016/j.kint.2019.07.022
53. Gonzalez NL, Puwanant A, Lu A, Marks SM, Živković SA. Myasthenia Triggered by Immune Checkpoint Inhibitors: New Case and Literature Review. *Neuromusc Disord: NMD* (2017) 27:266–8. doi: 10.1016/j.nmd.2017.01.002
54. Anquetil C, Salem JE, Lebrun-Vignes B, Johnson DB, Mammen AL, Stenzel W, et al. Immune Checkpoint Inhibitor-Associated Myositis: Expanding the Spectrum of Cardiac Complications of the Immunotherapy Revolution. *Circulation* (2018) 138:743–5. doi: 10.1161/CIRCULATIONAHA.118.035898
55. Touat M, Maisonobe T, Knauss S, Ben Hadj Salem O, Hervier B, Auré K, et al. Immune Checkpoint Inhibitor-Related Myositis and Myocarditis in Patients With Cancer. *Neurology* (2018) 91:e985–94. doi: 10.1212/WNL.0000000000006124
56. Arbuckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, et al. Development of Autoantibodies Before the Clinical Onset of Systemic Lupus Erythematosus. *New Engl J Med* (2003) 349:1526–33. doi: 10.1056/NEJMoa021933
57. Dillard T, Yedinak CG, Alumkal J, Fleseriu M. Anti-CTLA-4 Antibody Therapy Associated Autoimmune Hypophysitis: Serious Immune Related Adverse Events Across a Spectrum of Cancer Subtypes. *Pituitary* (2010) 13:29–38. doi: 10.1007/s11102-009-0193-z
58. Min L, Hodi FS, Giobbie-Hurder A, Ott PA, Luke JJ, Donahue H, et al. Systemic High-Dose Corticosteroid Treatment Does Not Improve the Outcome of Ipilimumab-Related Hypophysitis: A Retrospective Cohort Study. *Clin Cancer Res* (2014) 21:749–55. doi: 10.1158/1078-0432.CCR-14-2353
59. Faje AT, Sullivan R, Lawrence D, Tritos NA, Fadden R, Klibanski A, et al. Ipilimumab-Induced Hypophysitis: A Detailed Longitudinal Analysis in a Large Cohort of Patients With Metastatic Melanoma. *J Clin Endocrinol Metab* (2014) 99:4078–85. doi: 10.1210/jc.2014-2306
60. Kohlmann J, Wagenknecht D, Simon JC, Ziemer M. Immune-Related Pancreatitis Associated With Checkpoint Blockade in Melanoma. *Melanoma Res* (2019) 29:549–52. doi: 10.1097/CMR.0000000000000611
61. Saito H, Ono K. Nivolumab-Induced Pancreatitis: An Immune-related Adverse Event. *Radiology* (2019) 293:521. doi: 10.1148/radiol.2019191603
62. Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, et al. Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma. *J Clin Oncol* (2017) 35:785–92. doi: 10.1200/JCO.2015.66.1389

63. Arbour KC, Mezquita L, Long N, Rizvi H, Auclin E, Ni A, et al. Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non-Small-Cell Lung Cancer. *J Clin Oncol* (2018) 36:2872–8. doi: 10.1200/JCO.2018.79.0006
64. Maher VE, Fernandes LL, Weinstock C, Tang S, Agarwal S, Brave M, et al. Analysis of the Association Between Adverse Events and Outcome in Patients Receiving a Programmed Death Protein 1 or Programmed Death Ligand 1 Antibody. *J Clin Oncol* (2019) 37:2730–7. doi: 10.1200/JCO.19.00318
65. Hassel JC, Heinzerling L, Aberle J, Bähr O, Eigentler TK, Grimm MO, et al. Combined Immune Checkpoint Blockade (Anti-PD-1/Anti-CTLA-4): Evaluation and Management of Adverse Drug Reactions. *Cancer Treat Rev* (2017) 57:36–49. doi: 10.1016/j.ctrv.2017.05.003
66. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients With Advanced Cancer: A Systematic Review and Meta-Analysis. *JAMA Oncol* (2016) 2:1607–16. doi: 10.1001/jamaoncol.2016.2453
67. Ma K, Lu Y, Jiang S, Tang J, Li X, Zhang Y. The Relative Risk and Incidence of Immune Checkpoint Inhibitors Related Pneumonitis in Patients With Advanced Cancer: A Meta-Analysis. *Front Pharmacol* (2018) 9:1430. doi: 10.3389/fphar.2018.01430
68. Pauken KE, Dougan M, Rose NR, Lichtman AH, Sharpe AH. Adverse Events Following Cancer Immunotherapy: Obstacles and Opportunities. *Trends Immunol* (2019) 40:511–23. doi: 10.1016/j.it.2019.04.002
69. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *New Engl J Med* (2015) 373:23–34. doi: 10.1056/NEJMoa1504030
70. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and Class-Specific Patterns of Immune-Related Adverse Events of Immune Checkpoint Inhibitors: A Systematic Review. *Ann Oncol* (2017) 28:2377–85. doi: 10.1093/annonc/mdx286
71. Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and Anti-CTLA-4 Therapies in Cancer: Mechanisms of Action, Efficacy, and Limitations. *Front Oncol* (2018) 8:86. doi: 10.3389/fonc.2018.00086
72. Shahabi V, Berman D, Chasalow SD, Wang L, Tsuchihashi Z, Hu B, et al. Gene Expression Profiling of Whole Blood in Ipilimumab-Treated Patients for Identification of Potential Biomarkers of Immune-Related Gastrointestinal Adverse Events. *J Trans Med* (2013) 11:75. doi: 10.1186/1479-5876-11-75
73. Subudhi SK, Aparicio A, Gao J, Zurita AJ, Araujo JC, Logothetis CJ, et al. Clonal Expansion of CD8 T Cells in the Systemic Circulation Precedes Development of Ipilimumab-Induced Toxicities. *Proc Natl Acad Sci USA* (2016) 113:11919–24. doi: 10.1073/pnas.1611421113
74. Champiat S, Lambotte O, Barreau E, Belkhir R, Berdelou A, Carbonnel F, et al. Management of Immune Checkpoint Blockade Dysimmune Toxicities: A Collaborative Position Paper. *Ann Oncol* (2016) 27:559–74. doi: 10.1093/annonc/mdv623
75. Manson G, Norwood J, Marabelle A, Kohrt H, Houot R. Biomarkers Associated With Checkpoint Inhibitors. *Ann Oncol* (2016) 27:1199–206. doi: 10.1093/annonc/mdw181
76. Toi Y, Sugawara S, Sugisaka J, Ono H, Kawashima Y, Aiba T, et al. Profiling Preexisting Antibodies in Patients Treated With Anti-Pd-1 Therapy for Advanced non-Small Cell Lung Cancer. *JAMA Oncol* (2019) 5:376–83. doi: 10.1001/jamaoncol.2018.5860
77. Suzuki S, Ishikawa N, Konoeda F, Seki N, Fukushima S, Takahashi K, et al. Nivolumab-Related Myasthenia Gravis With Myositis and Myocarditis in Japan. *Neurology* (2017) 89:1127–34. doi: 10.1212/WNL.0000000000004359

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Immunology

REVIEW
published: 28 May 2021
doi: 10.3389/fimmu.2021.663986

Immune Checkpoint Inhibitor-Associated Pneumonitis in Non-Small Cell Lung Cancer: Current Understanding in Characteristics, Diagnosis, and Management

Qin Zhang[1,2†], *Liansha Tang*[3†], *Yuwen Zhou*[3†], *Wenbo He*[4] *and Weimin Li*[1*]

[1] Department of Respiratory and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, China, [2] Department of Postgraduate Student, West China Hospital, Sichuan University, Chengdu, China, [3] Department of Biotherapy, Cancer Center, West China Hospital, Sichuan University, Chengdu, China, [4] Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, China

OPEN ACCESS

Edited by:
Benjamin Frey,
University Hospital Erlangen, Germany

Reviewed by:
Josef Singer,
Karl Landsteiner University of Health Sciences, Austria
Santiago Viteri,
Instituto Oncológico Dr Rosell, Spain

***Correspondence:**
Weimin Li
weimi003@scu.edu.cn

†These authors contributed equally to this work

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Immunology

Received: 04 February 2021
Accepted: 04 May 2021
Published: 28 May 2021

Citation:
Zhang Q, Tang L, Zhou Y, He W and Li W (2021) Immune Checkpoint Inhibitor-Associated Pneumonitis in Non-Small Cell Lung Cancer: Current Understanding in Characteristics, Diagnosis, and Management. Front. Immunol. 12:663986. doi: 10.3389/fimmu.2021.663986

Immunotherapy that includes programmed cell death-1 (PD-1), programmed cell death-ligand 1 (PD-L1) and cytotoxic T lymphocyte antigen 4 (CTLA-4) inhibitors has revolutionized the therapeutic strategy in multiple malignancies. Although it has achieved significant breakthrough in advanced non-small cell lung cancer patients, immune-related adverse events (irAEs) including checkpoint inhibitor pneumonitis (CIP), are widely reported. As the particularly worrisome and potentially lethal form of irAEs, CIP should be attached more importance. Especially in non-small cell lung cancer (NSCLC) patients, the features of CIP may be more complicated on account of the overlapping respiratory signs compromised by primary tumor following immunotherapy. Herein, we included the previous relevant reports and comprehensively summarized the characteristics, diagnosis, and management of CIP. We also discussed the future direction of optimal steroid therapeutic schedule for patients with CIP in NSCLC based on the current evidence.

Keywords: immune checkpoint inhibitor, pneumonitis, non-small-cell lung cancer, diagnosis, management

HIGHLIGHTS

- Immune checkpoint inhibitor-associated pneumonitis in non-small cell lung cancer presents complicated clinical and radiological manifestations.
- The management of corticosteroids combined with immunosuppressive drugs is deemed to be effective for immune checkpoint inhibitor-associated pneumonitis.
- Patients with immune checkpoint inhibitor-associated pneumonitis tend to suffer from a poor prognosis.

INTRODUCTION

Lung cancer has the greatest death rate, at 25%, of all types of cancer, with an estimated 135,720 deaths in the United States in 2020 (1). Non–small cell lung cancer (NSCLC) is the most common lung cancer subtype, and it comprises two major histological types: squamous cell carcinoma (SCC) and adenocarcinoma (AC) (2). Nearly 70% of patients with NSCLC are initially diagnosed at a locally advanced stage and suffer from a poor prognosis (2). The 5-year survival rate is less than 3% for patients with advanced NSCLC (3). Historically, the standard management recommended for patients with NSCLC who present with advanced-stage disease was chemotherapy regimens combined with radiotherapy (RT). However, the treatment provided generally modest responses, with an overall survival (OS) of approximately 12 to 18 months and a median progression-free survival (PFS) of just 4 to 8 months (4, 5).

Recently, immunotherapy that includes programmed cell death-1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors, which enhance anti-tumor activity, has revolutionized the therapeutic strategy for multiple malignancies (6). PD-1, a type I transmembrane protein, exists inherently on activated T cells, B cells, natural killer cells, macrophages, dendritic cells, and monocytes. PD-L1 is highly expressed on both cancer cells and antigen-presenting cells (7). The interaction of these two molecules could promote self-tolerance and attenuate autoimmunity through T-cell exhaustion and reduced cytokine production (8). CTLA-4, a critical surface protein receptor and co-inhibitor, is typically located in stimulated CD4+/CD8+ T cells to dampen T-cell activity by binding CD80/CD86/CD28. Using the inhibitory mechanism checkpoint pathways or molecules, immune checkpoint inhibitors (ICIs) can tilt the immune equilibrium toward the beneficial promotion of tumor killing and the boosting of an immune attack (6, 9).

In advanced NSCLC, an increasing body of clinical studies suggests that the application of ICIs could achieve significant breakthroughs in PFS and OS (10–13). Therefore, the US Food and Drug Administration has rapidly incorporated ICIs into first-line therapies for advanced NSCLC (14). In the PACIFIC regimen, durvalumab (a PD-L1 inhibitor) has become the new standard of care after platinum-based chemoradiotherapy for unresectable stage III NSCLC in the United States, Europe, and Japan (15).

However, along with the killed tumor cells, virtually every organ system could be affected by ICIs (5). Immune-related adverse events (irAEs), such as cutaneous lesions, myocarditis, hepatitis, colitis, endocrinopathies, inflammatory arthritis, and pneumonitis, are widely reported (15, 16). The incidence of irAEs might be higher with combination ICI use, specific cancer types, and non-trial conditions (17, 18). Among all reported irAEs, checkpoint inhibitor pneumonitis (CIP) is particularly worrisome and potentially lethal (18–21). CIP may occur more often and have a faster onset in NSCLC than in other types of cancer (22). Since before ICI therapies, pulmonary function has been compromised by tumor location and size in patients with NSCLC. In addition, pre-existing lung comorbidities, such as chronic inflammatory respiratory diseases, interstitial fibrosis lung diseases, and radiation-induced pneumonitis (RIP), may cloud diagnostic accuracy because of the overlapping respiratory symptoms and signs (5, 6, 9, 14, 23). As a result, recognizing the unique clinical and imaging patterns of CIP is essential to facilitate expeditious diagnosis and optimized management principles.

Although previous studies have elucidated the incidence, potential mechanisms, diagnosis, risk factors, and management of CIP, they focused on variable focuses that were not comprehensive and deep enough (5, 6, 9, 14, 23, 24). This review offers a summary of cases or case series concerning CIP in NSCLC, and it aims to identify the characteristics of typical patients who develop CIP. We also comprehensively summarize the current knowledge and relevant studies of ICI-associated pneumonitis, and we discuss the future direction of evidence-based therapeutic schedules for patients with CIP in NSCLC.

INCIDENCE AND ONSET OF CIP

The definition of CIP is the occurrence of respiratory symptoms/signs related to a new emerging infiltration viewed on a chest X-ray but excluding new infections tested by sputum and/or bronchoalveolar lavage (BAL) (5). In different tumor types, the overall incidence of CIP varied from 3% to 5% for all grades and ranged from 0.8% to 1.0% for grade ≥ 3 CIP (5, 14, 25, 26). The overall fatality rate of CIP was 10% to 17%. In NSCLC, the incidence of CIP mainly originated from clinical trial and real-world data. In clinical trial data (10, 27–44), the incidence of CIP for all grades was approximately 2% to 38%, and incidence for grade ≥ 3 CIP was approximately 0.6% to 2.7%. In real-world data, the incidence of CIP in patients with NSCLC was 4.8% to 39.3% (18, 24, 27, 28, 45–52). The discrepancy between data from these two sources might be partly attributed to the increasing awareness of CIP in the medical community, which contributed to more frequent clinical detection and less stringent inclusion criteria for real-world studies compared with randomized trials.

The median time to the onset of CIP was typically approximately 2.8 months, and the overall range spanned from 9 days to 19.2 months (18, 20, 53, 54). We included 44 occurrences of CIP in patients with NSCLC (**Figure 1**; **Table 1**) by searching Pubmed and Web of Science from 2016 up to April 15th, 2020. We used the search terms "immune checkpoint inhibitors *" OR "immunotherapy *" AND "non-small cell lung cancer*" AND "pneumonitis*" with related terms including MeSH terms as well as keywords. All case reports were included. And we found that the mean time to CIP onset from the start of ICI therapy was approximately 10 weeks (2.5 months; **Table 2**). No difference was found in the median time from treatment to CIP onset between patients with improved/resolved CIP and deteriorated/maintained CIP (P=0.547) (**Table 2**). The onset of CIP reportedly occurred as early as hours to days—or as late as several months—after the first ICI dose; however, more severe CIP grades usually had onset within the first 100 to 200 days of ICI therapy (87). The median time to CIP onset was not related to disease severity (88), and onset seemed to occur earlier for patients treated with combination ICIs (18). Of note, CIP might develop months after therapy termination, which

FIGURE 1 | Summary of checkpoint inhibitor pneumonitis patients with NSCLC, including deteriorated or recurrence (n = 20) and improved or resolved (n = 24) patients with more details in **Table 1**.

suggests that continuous vigilance after drug discontinuation is necessary (54).

POTENTIAL MECHANISM OF CIP

In animal models with deficiencies of PD-1 and CTLA-4, animals exhibited lung infiltration (89, 90), which could clarify questions about how CIP develops (91). The potential mechanisms driving ICI-related pneumonitis are outlined in the following sections.

Increased T-cell Activity Against Cross-Antigens

Enhanced and/or targeted T-cell activity against cross-antigens shared between tumor and normal tissues may result in irAEs (14, 91). Furthermore, cytotoxic antigen-directed T-cell responses may drive CIP pathogenesis. Significant lymphocytosis enriched with CD8+ T cells has been examined in the pulmonary tissues and BAL from patients with clinical typical CIP (92, 93). In NSCLC, Suresh et al. (94) noted that CD4+ T cells predominated in the BAL of patients with CIP. Notably, decreased expression of PD-1 and CTLA-4 and increased numbers of central memory T cells were observed within the regulatory T-cell population, which suggested that dysregulation of T cells may result from activation of pro-inflammatory immune subsets (alveolar T cells) and weakening of the anti-inflammatory regulatory T-cell phenotype.

In addition, Laubli et al. (95) conducted T-cell receptor sequencing on tumor-infiltrating lymphocytes and T cells infiltrating the inflammatory CIP lesions and found a notable overlap of T-cell repertoire in these sites but not in the secondary lymphoid organs or peripheral blood. Despite the indeterminant nature of antigen specificity, these data highlighted the cytotoxic effects of T cells on the instigation of CIP. Moreover, the predictive value of tumor-infiltrating lymphocytes has been illustrated in meta-analyses (96, 97). An elevated level of

TABLE 1 | Published case reports and case series of immune checkpoint inhibitor-associated pneumonitis.

Author	Year	Patient	Country	Cancer Type	Histologic type	Genomic alterations (PD-1/PD-L1) (%)	Drug		Previous therapy	Time of onset	Grade of CIP	withdrew the drug	Time to withdrew the drug	Treatment	Outcome		
							PD-1 inhibitors	PD-L1 inhibitors							CIP	CIP course (weeks)	Other iAEs
Yin et al. (55)	2021	62/M	China	NSCLC	AC	55	pembrolizumab		chemotherapy	After 27 weeks	2	Yes	After 27 weeks	prednisolone	Improved	3	/
Shannon (9)	2020	62/F	USA	NSCLC	AC	/	pembrolizumab		radiotherapy	After 11 days	3	Yes	After 11 days	solumedrol	Improved	/	/
Shannon (9)	2020	82/M	USA	NSCLC	unknown	/	nivolumab		/	After 6 weeks	3	Yes	After 6 weeks	/	Deteriorated	/	/
Shannon (9)	2020	66/F	USA	NSCLC	unknown	/	pembrolizumab		/	After 6 weeks	2	Yes	After 6 weeks	steroid	Resolved	/	/
Shannon (9)	2020	69/M	USA	NSCLC	unknown	/	nivolumab		/	After 6 weeks	2	Yes	After 6 weeks	steroid	Improved	/	/
Davies et al. (56)	2020	68/M	USA	NSCLC	AC	1	pembrolizumab		chemotherapy	After 12 weeks	2	Yes	After 12 weeks	prednisone; PPI; TMP/SMX	Recurrent(8w)-Resolved	16	/
Utsumi et al. (57)	2020	59/M	Japan	NSCLC	unknown	1	pembrolizumab		radiochemotherapy	After 3 weeks	4	Yes	After 3 weeks	methylprednisolone; prednisolone; tacrolimus; cyclophosphamide	Deteriorated(1w)-Improved	8.4	/
Julie et al. (58)	2020	61/M	USA	NSCLC	unknown	1	pembrolizumab		radiochemotherapy	After 12 weeks	4	Yes	After 12 weeks	antibiotics; high dose steroids	Deteriorated	/	NSTEMI and CHF exacerbation
Wang et al. (59)	2020	55/M	China	NSCLC	AC	60	pembrolizumab		chemotherapy	After 24 weeks	3	Yes	After 24 weeks	methylprednisolone	Not completely resolved	3	/
Hirohide et al. (60)	2020	/	Japan	NSCLC	AC	55	pembrolizumab		radiochemotherapy	After 7 weeks	3	Yes	After 7 weeks	methylprednisolone	Improved	33	grade 1 typical radiation pneumonitis
Li et al. (61)	2019	57/M	China	NSCLC	unknown	60		atezolizumab	concurrent radio-chemotherapy; bevacizumab	After 5 days	3	Yes	After 5 days	antibiotics; methylprednisolone	Improved	/	thrombocytopenia, and cardiac dysfunction
Michael et al. (62)	2019	79/M	Austria	NSCLC	both	20	nivolumab		radiochemotherapy	After 8 weeks	3	Yes	After 8 weeks	antibiotics; corticosteroids; TMP/SMX	Deteriorated	/	/
Michael et al. (62)	2019	53/M	Austria	NSCLC	AC	70	nivolumab		surgery; radiochemotherapy	After 6 weeks	4	Yes	After 6 weeks	antibiotic; corticosteroid mycophenolate mofetil; TMP/SMX; ganciclovir	Deteriorated (8W)	/	/
Petri et al. (63)	2019	76/F	USA	NSCLC	AC	/	pembrolizumab		chemotherapy	After 12 weeks	4	Yes	After 12 weeks	antibiotics; methylprednisolone; prednisone; immunoglobulin	Improved	16	/
Eeden et al. (64)	2019	56/F	USA	NSCLC	unknown	/	nivolumab		radiochemotherapy	About 6 months	3	Yes	About 6 months	antibiotics; corticosteroids; antituberculosis treatment	Deteriorated	/	grade 2 diarrhea
Tonk et al. (65)	2019	72/M	The Netherlands	NSCLC	unknown	/		durvalumab	radiochemotherapy	During infusion of the first cycle	3	Yes	During infusion of the first cycle	clemastin; dexamethasone and acetaminophen; prednisolone; mycophenolic acid	Recurrent after 12w,51w, finally maintained	73.4	/
Blanchard and Bouchard (66)	2019	69/F	Canada	NSCLC	SC	40	pembrolizumab		chemotherapy	After 21 weeks	4	Yes	After 21 weeks	methylprednisolone; bronchodilators; azithromycin	Not completely improved	40.4	/
Dickey et al. (67)	2019	60/F	Austria	NSCLC	SC	75	pembrolizumab		radiotherapy	After 15 weeks	2	Yes	After 15 weeks	antibiotics; methylprednisolone; prednisone	Recurrent(3W)-not completely improved	3.4	thrombotic thrombocytopenic purpura
Sato et al. (68)	2019	62/M	Japan	NSCLC	AC	80	pembrolizumab		/	After 9 weeks	2	Yes	After 9 weeks	dexamethasone	Improved	/	bowel perforation with acute diffuse peritonitis
Maria et al. (69)	2019	72/M	Greece	NSCLC	SC	/	nivolumab		radiochemotherapy	After 15 weeks	2	/	After 15 weeks	prednisolone	Resolved	22	grade 2 colitis; hypercalcemia
Fan et al. (70)	2019	80/M	China	NSCLC	SC	50	nivolumab		chemotherapy	After 10 weeks	2	Yes	After 12 weeks	prednisolone	Resolved	12	Febrile neutropenia

(Continued)

TABLE 1 | Continued

Author	Year	Patient	Country	Cancer Type	Histologic type	Genomic alterations (PD-1/PD-L1) (%)	Drug		Previous therapy	Time of onset	Grade of CIP	withdrew the drug	Time to withdrew the drug	Treatment	Outcome		
							PD-1 inhibitors	PD-L1 inhibitors							CIP	CIP course (weeks)	Other iAEs
Neal et al. (25),	2018	66/M	USA	NSCLC	unknown	70	nivolumab		radiochemotherapy	After 18 weeks	3	Yes	After 18 weeks	methylprednisolone; prednisone; infliximab	Recurrent (2w, 4w) for 2 times finally resolved	6.8	/
Neal et al. (25)	2018	63/F	USA	NSCLC	unknown	60	pembrolizumab		radiotherapy	After 48 days	4	Yes	After 48 days	antibiotics; methylprednisolone; infliximab, cyclophosphamide	Deteriorated (2w)	2	/
Corine et al. (71)	2018	58/F	USA	NSCLC	unknown	1	nivolumab		radiochemotherapy; bevacizumab	After 14 weeks	3	Yes	After 14 weeks	antibiotics; prednisone	Recurrent for several times (6.4; 12.9; 17.1) and finally resolved	38.6	/
Koyoma et al. (72)	2018	46/M	Japan	NSCLC	unknown	/	nivolumab		chemotherapy; bevacizumab	After 2 weeks	3	/	After 2 weeks	methylprednisolone; prednisolone	Improved	1	/
Koyoma et al. (72)	2018	59/M	Japan	NSCLC	unknown	/	nivolumab		chemotherapy; erlotinib; bevacizumab	After 2 weeks	3	/	After 2 weeks	prednisolone	Deteriorated-Improved	/	/
Foukas et al. (73)	2018	58/M	USA	NSCLC	SC	/	nivolumab		radiochemotherapy	After 4 weeks	3	Yes	After 4 weeks	antibiotics; prednisolone; TMP/SMX	Recurrent after 4w and improved	12	/
Li et al. (74)	2018	52/M	China	NSCLC	unknown	50	pembrolizumab		radiochemotherapy	After 9 weeks	2	Yes	After 9 weeks	prednisolone	Not completely improved	16	/
Eduard et al. (75)	2018	77/M	Spain	NSCLC	AC	85	nivolumab		chemotherapy	After 36 weeks	2	Yes	After 28 weeks	antibiotics; methylprednisolone; TMP/SMX	Resolved	3	nephritis, hepatitis
Akella et al. (76)	2018	80/F	USA	NSCLC	unknown	/	nivolumab		chemotherapy	After 10 months	2	Yes	After 10 months	methylprednisolone	Resolved	16.4	/
Jodai et al. (77)	2018	62/M	Japan	NSCLC	AC	/	nivolumab		chemotherapy	After 6 weeks	2	Yes	After 6 weeks	antibiotics; prednisolone	Improved	/	/
Li et al. (78)	2017	67/M	USA	NSCLC	SC	50	nivolumab		radiochemotherapy	After 4 weeks	3	Yes	After 6 weeks	antibiotics; corticosteroid	Deteriorated(5w)-Improved	13	/
Kanai et al. (79)	2017	71/M	Japan	NSCLC	AC	/	nivolumab		chemotherapy	After 16 weeks	3	Yes	After 16 weeks	prednisolone; cyclosporine A; methylprednisolone; infliximab	Deteriorated (8W)	10.4	/
Takeru et al. (80)	2017	82/M	Japan	NSCLC	unknown	/	nivolumab		radiochemotherapy	After 3 weeks	2	/	/	methylprednisolone	Improved	14.4	radiation pneumonitis 2months after radiation; steroid
Kato et al. (81)	2017	39/M	Japan	NSCLC	unknown	/	nivolumab		radiochemotherapy	After 4 days	2	Yes	After 4 days	prednisone	Recurrent(12w)-improved	28	/
Kenji et al. (82)	2017	74/F	Japan	NSCLC	unknown	/	nivolumab		chemotherapy; bevacizumab	After 3 days	3	Yes	After 3 days	methylprednisolone; prednisolone	Deteriorated	1.5	/
Kenji et al. (82)	2017	67/F	Japan	NSCLC	unknown	/	nivolumab		radiochemotherapy; erlotinib; bevacizumab	After 1 week	3	Yes	After 1 week	betamethasone; methylprednisolone	Improved	3.9	/
Kenji et al. (82)	2017	75/F	Japan	NSCLC	unknown	/	nivolumab		radiochemotherapy	After 5 days	3	Yes	After 5 days	methylprednisolone; cyclophosphamide	Not completely improved	2.7	/
Balaji et al. (83)	2017	73/M	USA	NSCLC	unknown	/	nivolumab		chemotherapy	After 4 weeks	2–4	Yes	After 10 weeks	prednisone; bronchodilators; TMP/SMX	Recurrent (3weeks; 5weeks; 9 weeks) - maintained	11.3	/
Balaji et al. (83)	2017	70/F	USA	NSCLC	unknown	/	nivolumab		surgery; chemotherapy; ipilimumab (3 mg/kg)	After 3 days	3	Yes	After 3 days	prednisone	Recurrent(9W)-Improved	13.3	/
Naqash et al. (84)	2017	53/F	USA	NSCLC	AC	0		atezolizumab	concurrent radiochemotherapy	After 7 weeks	2	Yes	After 7 weeks	prednisone; tocilizumab	Resolved	5.6	arthritis
Shibaki et al. (85)	2017	68/M	Japan	NSCLC	SC	/	nivolumab		radiotherapy	After 8 weeks	2	Yes	After 8 weeks	prednisolone	Improved	4	
Shibaki et al. (85)	2017	55/M	Japan	NSCLC	unknown	/	nivolumab		radiotherapy	After 24 weeks	2	Yes	After 24 weeks	prednisolone	Improved	4	
Gounant et al. (86)	2016	70/M	USA	NSCLC	SC	80	nivolumab		chemotherapy; necitumumab (anti-EFGR monoclonal antibody)	After 12 weeks	2	Yes	After 12 weeks	prednisone	Recurrent 20w later-finally resolved	23.4	grade 2 hyperthyroidism

NSCLC, non-small cell lung cancer; TMP/SM, trimethoprim/sulfamethoxazole; PPI, proton pump inhibitors; NSTEMI, non–ST-segment elevation myocardial infarction; CHF, Congestive heart failure.

TABLE 2 | Baseline characteristics of the NSCLC cases with CIP according to the CIP outcome.

CIP outcome Mean ± SD/N (%)	Total	Improved/Resolved	Deteriorated/Maintained	P-value
N	44	34	10	
Age	65.23 ± 9.84	64.27 ± 9.83	68.40 ± 9.69	0.232
Sex				0.798
Female	14 (32.56%)	11 (33.33%)	3 (30.00%)	
Male	29 (67.44%)	22 (66.67%)	7 (70.00%)	
Genomic alterations (%)	45.90 ± 29.62	47.82 ± 29.60	37.75 ± 32.66	0.554
Country				0.195
USA	18 (40.91%)	13 (38.24%)	5 (50.00%)	
Japan	14 (31.82%)	12 (35.29%)	2 (20.00%)	
China	5 (11.36%)	5 (14.71%)	0 (0.00%)	
Austria	3 (6.82%)	1 (2.94%)	2 (20.00%)	
Canada	1 (2.27%)	1 (2.94%)	0 (0.00%)	
Greece	1 (2.27%)	1 (2.94%)	0 (0.00%)	
The Netherlands	1 (2.27%)	0 (0.00%)	1 (10.00%)	
Spain	1 (2.27%)	1 (2.94%)	0 (0.00%)	
Grade of CIP				**0.002**
Grade 2	18 (40.91%	18 (52.94%)	0 (0.00%)	
Grade 3	19 (43.18%)	13 (38.24%)	6 (60.00%)	
Grade 4	7 (15.91%)	3 (8.82%)	4 (40.00%)	
Histologic type				0.079
AC	12 (27.27%)	10 (29.41%)	2 (20.00%)	
SC	8 (18.18%)	8 (23.53%)	0 (0.00%)	
Both	1 (2.27%)	0 (0.00%)	1 (10.00%)	
Unknown	23 (52.27%)	16 (47.06%)	7 (70.00%)	
ICIs				0.548
PD-1 inhibitors	41 (93.18%)	32 (94.12%)	9 (90.00%)	
PD-L1 inhibitors	3 (6.82%)	2 (5.88%)	1 (10.00%)	
Recurrence times				0.325
0	34 (77.27%)	26 (76.47%)	8 (80.00%)	
1	6 (13.64%)	6 (17.65%)	0 (0.00%)	
2	2 (4.55%)	1 (2.94%)	1 (10.00%)	
3	2 (4.55%)	1 (2.94%)	1 (10.00%)	
Dose of onset	4.18 ± 3.80	4.26 ± 3.93	3.90 ± 3.51	0.793
Time of onset	10.14 ± 9.48	10.62 ± 10.12	8.53 ± 7.09	0.547
Steroid initial dose(mg/d)	425.29 ± 451.82	474.43 ± 475.24	196.00 ± 263.30	0.301
Steroid initial dose groups(mg/d)				0.222
Low-dose <60	5 (29.41%)	3 (21.43%)	2 (66.67%)	
Intermediate-dose 60-500	6 (35.29%)	5 (35.71%)	1 (33.33%)	
High-dose 501-1000	6 (35.29%)	6 (42.86%)	0 (0.00%)	
Steroid initial dose(mg/kg/d)	1.24 ± 0.58	1.15 ± 0.57	1.80 ± 0.28	0.149
Steroid initial dose groups(mg/kg/d)				0.177
Low-dose <1	8 (53.33%	8 (61.54%)	0 (0.00%)	
Intermediate-dose1-2	6 (40.00%)	4 (30.77%)	2 (100.00%)	
High-dose >2	1 (6.67%)	1 (7.69%)	0 (0.00%)	
Steroid taper time	10.46 ± 9.94	10.20 ± 10.13	12.00 ± 10.58	0.649
Steroid course	14.43 ± 15.14	13.46 ± 11.20	19.72 ± 30.35	0.404
Antibiotics				0.077
No	28 (63.64%)	24 (70.59%)	4 (40.00%)	
Yes	16 (36.36%)	10 (29.41%)	6 (60.00%)	
Immunosuppressive drugs				0.081
No	35 (79.55%)	29 (85.29%)	6 (60.00%)	
Yes	9 (20.45%)	5 (14.71%)	4 (40.00%)	
OS				**0.001**
Alive	20 (57.14%)	19 (73.08%)	1 (11.11%)	
Dead	15 (42.86%)	7 (26.92%)	8 (88.89%)	
Survival weeks	55.35 ± 46.26	61.44 ± 49.71	34.49 ± 23.88	0.168
CIP Course (weeks)	12.64 ± 14.20	11.66 ± 10.81	16.45 ± 23.93	0.402
Clinical response				**0.027**
Complete response	2 (5.71%)	2 (7.69%)	0 (0.00%)	
Partial response	6 (17.14%)	6 (23.08%)	0 (0.00%)	
Tumor progressed	5 (14.29%)	5 (19.23%)	0 (0.00%)	
Stable	7 (20.00%)	6 (23.08%)	1 (11.11%)	
Unknown	15 (42.86%)	7 (26.92%)	8 (88.89%)	

NSCLC, non-small cell lung cancer; CIP, checkpoint inhibitor pneumonitis; SC, squamous cell carcinoma; AC, adenocarcinoma; ICIs, immune checkpoint inhibitors; OS, overall survival. Bold values: two-sided P-values less than 0.05 were considered to identify statistical significance.

CD4+/CD8+ T-cell infiltration in the malignant cells showed superior outcomes in survival. However, an increasing number of FOXP3+ regulatory T cells, a subtype of CD4+ T cells with immunosuppressive actions, was associated with poor survival. These results have been reported from patients with ICI-related pneumonitis, and more evidence is needed from future studies to explore CIP mechanisms.

Increased Level of Autoantibodies and Inflammatory Cytokines

Pre-existing autoantibodies potentially linked to the development of irAEs in NSCLC, such as anti–thyroid peroxidase antibodies, anti-thyroglobulin antibodies, antinuclear antibodies, anti–rheumatoid factor antibodies, have been explored in recent studies (98). Tahir et al. (99) performed a mass screening of autoantibodies in patients who underwent ICI therapy by using high-throughput serological analysis of recombinant cDNA expression (i.e. SEREX). They identified an elevated plasma level of anti-CD74 from two patients with CIP in a discovery cohort and subsequently verified a 1.34-fold increase from 10 patients with CIP in a confirmation cohort. Intriguingly, samples of viral-mediated interstitial pneumonitis have also displayed an overexpression of CD74 (100), presenting a pathogenic nidus for CIP development. However, the specific antibodies associated with CIP should be prioritized for exploration. In terms of inflammatory cytokines, case reports of severe CIP have identified some cytokines linked to the appearance of CIP. Interleukin-6 (IL-6), IL-17A, IL-35, C-reactive protein (CRP), procalcitonin (PCT), surfactant protein-D (SP-D), and Krebs von den Lungen-6 (KL-6) were reportedly more common in patients with NSCLC who developed CIP than in those without CIP (25, 52, 57, 82, 84). In particular, SP-D and KL-6 reflected alveolar epithelial cell injury. All these cytokines also broadly serve as biomarkers for adverse events caused by ICIs.

Enhanced Complement-Mediated Inflammation

The function of complement-mediated inflammation may be enhanced by the direct combination of anti–CTLA-4 with CTLA-4 located on benign tissues, including the pituitary gland (14, 91). This mechanism may explain why pituitary inflammation could be a specific irAE of anti–CTLA-4 antibodies (101). Although CIP is more frequently observed with PD-1/PD-L1 blockades than with CTLA-4 blockades (102), CIP has not yet become a symbolic irAE of anti–PD-1/PD-L1 antibodies. After a review of the relevant literature, we speculate that the major causes of CIP may be the first two mechanisms described before. Additional exploration is required to deepen our understanding of CIP in NSCLC.

RISK FACTORS OF CIP

Current evidence from retrospective studies and case reports has identified many potential risk factors for ICI-related pneumonitis (6, 24, 53, 72, 103–105). These include baseline patient characteristics, disease features, and therapy management. Specific factors include age, sex, smoking status, previous lung disease, tumor histological type, PD-1 blockade, combination therapy, and prior RT.

Baseline Patient Characteristics

The influence of age on the response to immunotherapy has not been studied comprehensively or systematically. Cho et al. (28) found that patients who had CIP were often older than 70 years (54.5% of total population studied, P=0.025). However, other literature has suggested that older age would not adversely relate to rates of toxicities or therapeutic response to ICI therapies (106, 107). A retrospective study recruited 205 patients with NSCLC and reported a higher incidence of CIP in women than in men, though the difference was not significant (24). Similarly, in another study, former or current smokers developed CIP more often than nonsmokers (P=0.03) (108). The evidence must be verified, but it does offer a new direction for continued research (87).

Disease Features

Pre-existing pulmonary diseases, including interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD), asthma, pneumothorax, pleural effusion, and pulmonary fibrosis, have been closely associated with the development of CIP in patients with NSCLC (19, 27, 29, 49, 50). The incidence of ICI-related pneumonitis in patients with pre-existing ILD was approximately three times higher than in those without ILD (29% vs 10%, P=0.027) (49). Patients with asthma and COPD were more likely to develop CIP (2.3% higher incidence vs those without COPD) (27). Notably, Nicholas et al. (29) found increasing numbers of lymphocytes dominated by CD4+/CD8+ T cells and high PD-L1 expression in the lungs of patients with NSCLC who had COPD, which might suggest longer PFS in patients receiving ICIs without COPD. A case-control study that included patients with pneumothorax, pleural effusion, and pulmonary fibrosis found a high risk of CIP in these patients but noted a low mortality rate and a high remission rate in the same group after treatment with corticosteroids (104). With regard to the tumor type, subgroup analyses of previous research showed that patients with the SCC subtype of NSCLC experienced a greater occurrence of CIP, but a lower mortality rate, compared with those diagnosed with the AC subtype (5, 10, 11, 21, 24, 37, 38, 41).

Therapy Management

RT reportedly has a synergistic effect with immunotherapy (14, 23). Intriguingly, RT itself could induce radiation pneumonitis in more than 30% of patients (109). Even when the radiation pneumonitis resolves, patients may present with severe radiation recall pneumonitis after treatment with ICIs (60). The Keynote-001 trial (110) explored the clinical efficacy of PD-1 inhibitors in patients with NSCLC and found a higher incidence of any-grade CIP in patients who received RT before ICI therapy (pembrolizumab, 13%) compared with those who did not receive RT (1%, P<0.05). The timing of RT and ICI use must be studied and discussed in more detail, whether a shorter interval between the two treatments could increase mutual toxicity or not remains unclear. The PACIFIC trial (111)

compared CIP rates according to the initial time to start durvalumab after chemoradiotherapy (within 14 days or between 14 and 56 days) and found that the earlier start time did not increase the risk of CIP. RT parameters that may influence the development of CIP have also been studied, dosimetric parameters of prior chest RT, courses, timing, and technique were not considered significant risk factors for CIP development (48).

Monotherapy and combination therapy with ICIs appear to have distinct incidences of CIP in NSCLC. With ICI monotherapy, use of PD-1/PD-L1 inhibitors instead of CTLA-4 inhibitors increased the risk of CIP development (64). A meta-analysis (87) that included 19 trials found that PD-1 blockade treatment was associated with a statistically significantly higher incidence of CIP than PD-L1 blockade (3.6% vs 1.3%, P=0.001). In addition, the analysis reported no significant difference in the incidence of CIP in patients who received pembrolizumab or nivolumab. However, Fukihara et al. (47) found that more patients treated with pembrolizumab than with nivolumab developed CIP (63% vs 37%, P=0.004). Moreover, the incidence of CIP in patients treated with combination therapy increased twofold to threefold compared with patients treated with monotherapy (30, 87). The need for antibiotics and immunosuppressive drugs (112) were also predominant risk factors for pulmonary infection after ICIs.

MANIFESTATIONS OF CIP

Clinical Manifestations

The main clinical symptoms of CIP are relatively nonspecific and usually are similar to certain forms of ILD (23). CIP is characterized by fever, cough, chest pain, shortness of breath, dyspnea, fatigue, or respiratory failure (104). Bloody sputum or hemoptysis, hypotension, tachycardia or palpitation, diarrhea, and joint pain are less common (**Supplemental Table 1**). In our analysis, dyspnea accounted for the most significant symptom of CIP (63.64%), followed by cough (36.36%) and fever (25.00%). Rashes were also commonly reported. Crackles on thorax auscultation manifested only in more advanced-grade CIP (23, 86).

Imaging Manifestations

As awareness and experience with CIP increase among researchers, large-scale studies have categorized the various radiologic patterns. Acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS)/diffuse alveolar damage (DAD), cryptogenic organizing pneumonia (OP), ground-glass opacities (GGOs), nonspecific interstitial pneumonia, hypersensitivity pneumonitis (HP), bronchiolitis, radiation recall pneumonia, and an unclassified type have been recognized as subtypes of CIP according to imaging features in several studies concerning NSCLC (5, 6, 18, 20, 23, 88, 113). These different radiographic patterns of CIP could also be described as a spectrum of the pulmonary injury evolution process, from the acute stage (AIP/ARDS/DAD) to the organizing stage (OP) and fibrotic stage (nonspecific interstitial pneumonia) (5, 6). The GGOs and consolidation (**Figure 2**) non-segmentally distributed in the dominant lung or bilaterally opposite the tumor, which have been considered typical computed tomography (CT) features in CIP of NSCLC (104, 113), represented 54.55% (24/44) and 31.82% (14/44), respectively, of the CT presentations in our analysis.

The OP pattern was the most common pattern for CIP in NSCLC (6, 113). The common manifestation of the OP pattern was bilateral peribronchovascular and subpleural GGOs, predominately in the middle to lower lung (113). Reversed atoll or halo sign, a circumferential consolidation surrounding an interior area of mosaic (ground-glass) attenuation, has been considered a relatively specific characteristic for OP in CIP (114). In addition, peribronchovascular pulmonary nodules smaller than 10 mm have been depicted in the OP pattern (113). However, the nodules could be mass-like with spiculated margins (115) or could be a peritumoral shadow (80, 104), reflecting obscure presentations of the tumor. This phenomenon has been regarded as pseudoprogression of malignancy (80, 104, 115). Two cases (80, 81) that we included presented with GGOs associated with an increase in tumor size (pseudoprogression). Pseudoprogression could be distinguished from CIP by evaluation of serum markers (carcinoembryonic antigen, cytokeratin fragment) (116) and by bronchoscopic narrow-band imaging and biopsy (117).

The nonspecific interstitial pneumonia pattern was the second most frequently reported pattern of CIP (113). It commonly manifests with GGOs and reticulation in the lower lobe of the lung (118). The specific finding was described as a subpleural sparing of the dependent and posterior lower lobe of the lung (115). Conversely, the HP pattern was a relatively uncommon radiologic abnormality of CIP. Centrilobular or diffuse GGOs with the predominance of mid-to upper-lobe location were the radiologic features of the HP pattern (113). This pattern can be distinguished from an HP pattern related to allergen exposure by obtaining definite patient histories about occupational and other exposures. The AIP/ARDS/DAD pattern exhibited the most severe extent of pulmonary involvement on imaging, presenting with diffuse or patchy GGOs or consolidation with involvement in the majority or all of the lung. This presentation often exhibits a "crazy-paving" pattern and interlobular septal thickening (115). Bronchiolitis has been found only in one retrospective cohort study and a few case reports (66, 86, 88, 118). Typically, it appears as a tree-in-bud pattern in the region of centrilobular nodularity. However, even bronchiolitis may be investigated as a distinct CIP pattern without infectious symptoms.

Radiation recall pneumonia is an inflammatory reaction that occurs in previously irradiated regions after exposure to some inciting agents; it manifests as consolidation and GGOs limited to the previously radiated area. Possible mechanisms of this type of pneumonia include stem cell function changes in the irradiated field triggered by hypersensitivity reactions to an idiosyncratic drug (119). Some case reports have presented radiation recall pneumonia in patients with NSCLC after treatment with ICIs (60, 85). Patients who receive RT and develop new pulmonary changes demarcated from the adjacent

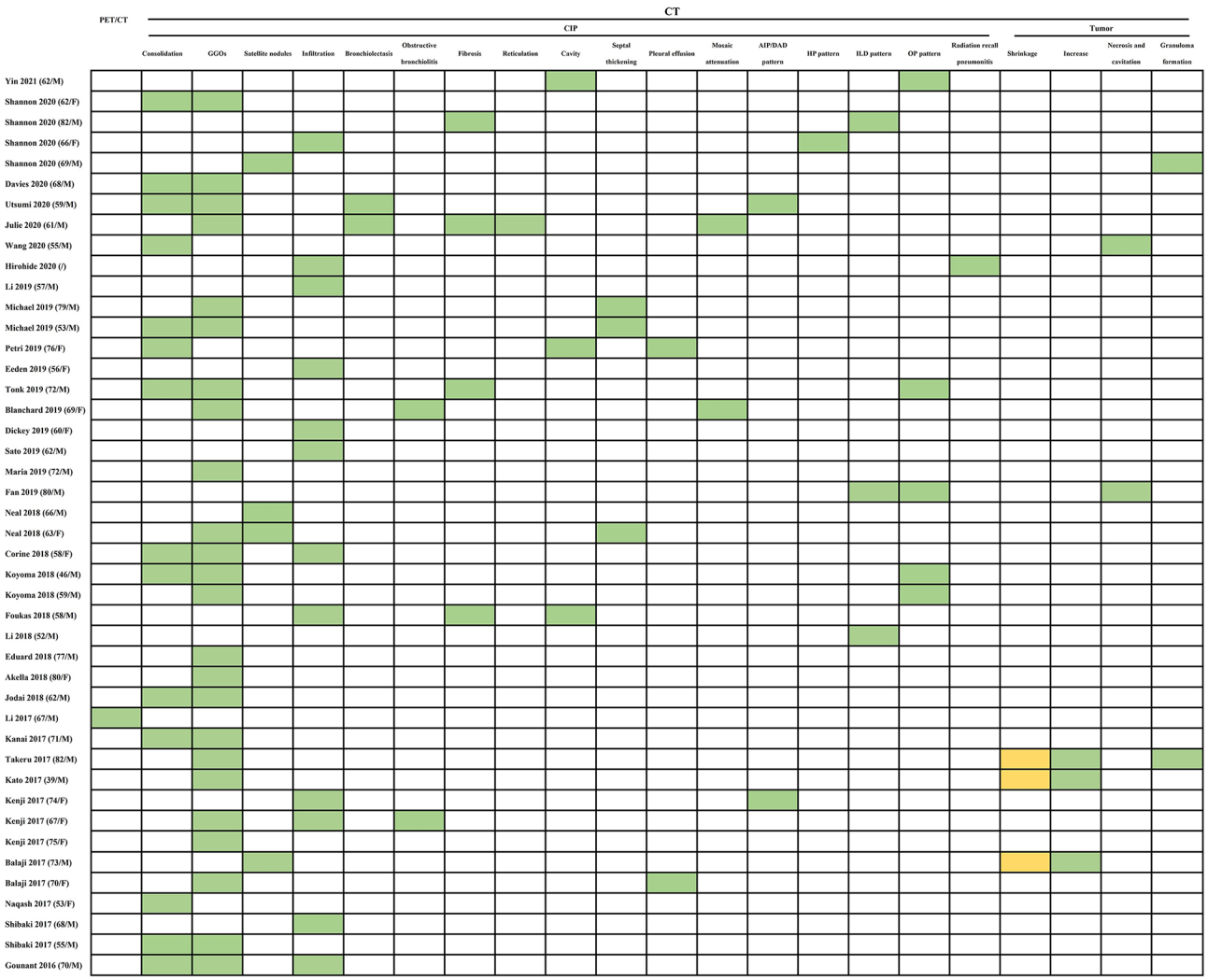

FIGURE 2 | Summarized results of radiological tests for diagnosis in published cases reports/case series. The radiological tests include PET/CT and CT findings. PET/CT, positron emission tomography/computed tomography; CT, computed tomography; GGOs, ground-glass opacities; AIP/DAD, Acute interstitial pneumonia (AIP)/diffuse alveolar damage (DAD); HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; OP, organizing pneumonia. Abnormal: green grid; normal: orange grid; undone: white grid.

lung in the initial radiation field should be preferentially suspected of having radiation recall pneumonia.

Pathological Manifestations

Not all patients with CIP will receive lung biopsy, especially in patients with ICI-related ILD. In our analysis, only 5 of 44 patients were considered for this examination (**Figure 3**). Lung biopsies may increase the risk of acute deterioration in ILD and may not obtain definite histologic types if the harvested specimen is small. However, transbronchial lung biopsy could rule out alternative etiologies during the differential diagnosis. Literature reports have provided a limited pathological pattern of CIP, with a range of different presentations that includes OP, DAD, eosinophilic pneumonia, cellular interstitial pneumonitis, and nonspecific or granulomatous inflammation (6, 18, 88). The interstitial inflammatory infiltration might include elevated levels of eosinophil, poorly formed granulomas, and lymphocytes (18). The cases that we included specifically mentioned the pathological manifestation of alveolar parenchyma with fibroblast foci (four cases) (73, 78, 79, 85), mild collagen expansion of the alveolar septa (one case) (78), nonspecific chronic inflammation (four cases) (73, 78, 85), and atypical cells (one case) (79).

DIAGNOSIS OF CIP

Because specific clinical or radiologic markers are absent, diagnosis of CIP is quite difficult. CIP is typically a diagnosis of exclusion, one that should rule out infection, tumor

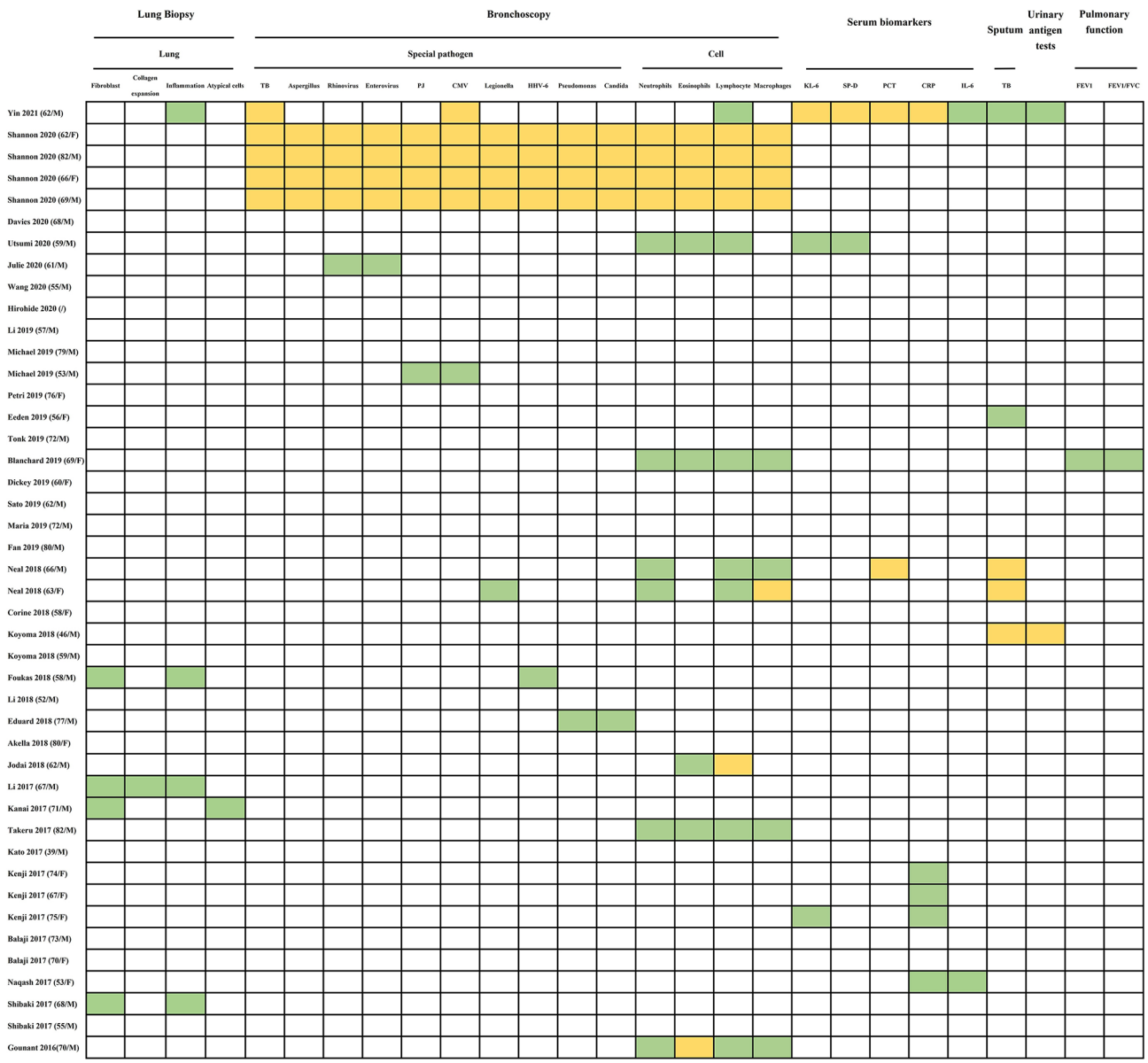

FIGURE 3 | Summarized results of histological, laboratory and pulmonary function tests for diagnosis in published cases reports/case series. The histological test includes lung biopsy. The laboratory tests include BAL (special pathogen and cells) in bronchoscopy, serum, sputum, urinary antigen test. The pulmonary function tests include FEV1 and FEV1/FVC. TB, tuberculosis; PJ, pneumocystis jirovecii; CMV, cytomegalo-virus; HHV-6, human herpes virus 6; KL-6, krebs von den Lungen-6; SP-D, surfactant protein-D; PCT, procalcitonin; CRP, C-reactive protein; IL-6, interleukin-6; FEV1, forced expiratory volume in one second; FEV1/FVC, fractional volume change. Abnormal: green grid; normal: orange grid; undone: white grid.

progression, and radiation-related pneumonitis (25). New emerging or the deterioration of respiratory symptoms—especially dry cough, dyspnea, and decreasing oxygen saturation—after ICI therapy for NSCLC require consideration of CIP (23). The diagnostic workup (**Figure 3**) to identify an etiology should include tests for a source of infection (including nasal swab, sputum/urine culture, and blood culture); tests for special pathogens (fungus, tuberculosis spot test); chest radiography (high-resolution CT); and bronchoscopy with BAL (17, 18, 20). Lung biopsy is not mandatory, and both drugs and infectious history can occasionally help to interpret results. Utilization of diagnostic tests is related to the suspected pneumonitis grade (6).

Common differential diagnoses for CIP include pulmonary infections, pulmonary embolism, DAD, lung cancer with underlying progression, cancerous lymphangitis, pulmonary interstitial edema caused by heart failure, fulminant myocarditis (120), and RIP (5, 23). Opportunistic pulmonary infections, including tuberculosis (TB) pneumonia, *aspergillosis*, *cytomegalovirus* pneumonia (CMVP), and *Pneumocystis jirovecii*

pneumonia (PJP), have been the foremost differential diagnoses for CIP in the NSCLC population (26, 121–125). Inthasot et al. (26) reported two cases of severe lung infections complicating the treatment of nivolumab for NSCLC and emphasized the importance of eliminating the possibility of opportunistic infections. Notably, ICIs could cause special pathogen infections in some patients through induction of CIP. We included several cases of patients who developed CIP during ICI therapy and consequently developed rhinovirus/enterovirus (58), CMVP (62), PJP (62), *legionella* (25), human herpesvirus 6 (HHV-6) (73), *pseudomonas*, or *candida* (75) infections (**Figure 3**). Because ICIs activate tumor immunity by inhibiting PD-1/PD-L1/CTLA-4, they might also simultaneously inhibit immunity to infection. Although the infections we described here as differential diagnoses are not usually categorized as drug-induced pneumonias, we included this series of reports to exemplify challenges in differentiating intensified infection from drug-induced pneumonia. Since from a drug safety perspective, the infection did lead to a few deaths.

The CT manifestations of CIP in patients with pulmonary AC sometimes resembled those of interstitial pneumonitis (126), especially of the OP pattern. Ichikawa et al. (127) reported that 2% of patients (13/564) with resected pulmonary AC presented with an OP pattern. Kanai et al. (79) reported a case of coexisting CIP and tumor invasion, which complicated the diagnosis and management of the lung disease. Aggressive lung biopsy was recommended in that study to correctly diagnose CIP in patients with NSCLC that mimicked the OP pattern or existed the tumor invasion.

RIP, an early lung injury induced by radiation, is also a difficult differential diagnosis in CIP. The approximate onset (1 to 3 months), similar imaging features (GGOs and diffuse haziness), and shared pathological feature (lymphocytic alveolitis) increased the level of challenge in distinguishing CIP from RIP (128–130). However, a distinct lesion location may assist in finding the difference between the two. RIP mainly exists in the radioactive region, and CIP mostly occurs outside the RT fall-off dose or in the low-dose field (48). Interestingly, both CIP and RIP have the same first-line therapy (corticosteroids) (121, 128). Meanwhile, radionics has emerged as a new approach to predict CIP by automatically extracting radiologic features for synthesis analysis (131).

In summary, CIP requires a precise diagnosis, including grade assessment, and monitoring of CIP requires a multidisciplinary method. Such monitoring often involves infectious disease specialists, pathologists, radiologists, pulmonologists, and cardiologists (121).

MANAGEMENT OF CIP

CIP is deemed a self-limiting disease. No prospective trials, to our knowledge, have evaluated the optimal therapeutic modality for CIP (5, 24). Current guidelines for CIP, therefore, recommended corticosteroids as the primary therapy approach (121, 132, 133). These decisions are based on the strength of case reports and clinical experience (5, 24). Different definitions of CIP grades are shown in **Supplemental Table 2** (121, 133). Clinical improvement is usually observed after 48 to 72 hours of corticosteroid use, and patients without regression of CIP-related symptoms have been considered steroid refractory and treated with immunosuppressive agents (121, 133).

For patients with grade 1 CIP, clinical symptoms, imaging changes, and pulmonary function (diffusing capacity and spirometry) should be closely monitored for 3 to 4 weeks (122, 123, 134, 135). Tentatively stopping ICI treatment can be considered reasonable for mild cases of CIP (23). When the condition worsens, though, interruption of the ICI should be combined with initiation of low-dose steroids (0.5 to 1 mg/kg/d) (9, 136).

For patients with grade 2 CIP, withholding the ICIs and beginning intermediate-dose steroids (1 to 2 mg/kg/d) followed by a taper by 5 to 10 mg/week for 4 to 6 weeks have been proposed (133). In our analysis, we summarized the management characteristics stratifed by CIP grade (**Table 3**) and listed every drug that every case used (**Figure 4**). We converted the different steroid doses to methylprednisolone (MP) equivalents and divided these into three groups (low-dose, intermediate-dose, and high-dose groups) according to the initial equivalent administered at the beginning of the therapy. We also noticed that some cases did not describe the weight of patients, which led to two different specifications of steroid dose (mg/d and mg/kg/d). In patients with grade 2 CIP (**Table 3**), 60% of patients were administered intermediate-dose steroids (60 to 500 mg/d). In other cases, 80% of patients with grade 2 CIP started with low-dose steroids (< 1 mg/kg/d). In addition, bronchoscopy and/or BAL plus initiation of empirical antibiotics when infection is suspected are recommended (14, 137). If clinical improvement does not happen after 2 to 7 days of monitoring, increasing the corticosteroid dose and adding immunosuppressive drugs should be considered (121, 138). Restarting ICI therapy may be considered when CIP is stable, has improved to grade ≤ 1, or has improved with 10 mg/d of prednisone (23). After re-initiation, physicians should evaluate clinical indicators every 3 days and perform chest imaging once a week to monitor for the flare and recurrence of CIP (9).

For patients with grade 3 to 4 CIP, ICI therapy should be discontinued immediately and permanently. The initial doses of steroids (1 to 2 mg/kg/d and 2 to 4 mg/kg/d) were approved and included in guidelines by the American Society of Clinical Oncology guidelines and the European Society for Medical Oncology (15, 121), respectively. However, no clinical trials have identified optimal corticosteroid doses or durations; therefore, therapy duration has always been adjusted largely on the basis of response to steroid treatment. Our analysis showed that patients with grade 3 or 4 CIP most often received glucocorticoid pulse therapy (44% of patients with grade 3 and 33% of patients with grade 4; **Table 3**). Initial steroid dosages of 1 to 2 mg/kg/d were mostly used in patients with severe CIP (**Table 3**), and this dosage was consistent with the recommendations of the American Society of Clinical Oncology. Institutionally, we continue at the initial dosage until patients improve or remain

stable (usually 1 week), at which time corticosteroids can be very slowly tapered during at least 5 to 8 weeks (9). Our data showed that the mean duration of a steroid taper was nearly 10 weeks, and the longest duration was in patients with grade 3 CIP (mean ± standard deviation of 16.37 ± 14.60 weeks) (**Table 3**). Additional immunosuppressants, including infliximab (IFX), mycophenolate mofetil, intravenous immunoglobulin, tacrolimus, ciclosporin (57, 79), and cyclophosphamide, should be considered when the symptoms do not regress after 48 to 72 hours of treatment with corticosteroids (6, 14, 23, 137). Empirical antibiotics may be used to prevent opportunistic infection (122, 139–141). Our data also showed that the rates of immunosuppressive drug use (grade 2: 5.56%, grade 3: 21.05%, grade 4: 57.14%, P=0.016) and antibiotic use (grade 2: 22.22%, grade 3: 31.58%, grade 4: 85.71%, P=0.011) gradually increased with increasing severity of CIP (**Table 3**).

Moreover, it has been reported that nearly one-fourth to one-third of patients experience CIP flares or recurrence after rapid corticosteroid tapers and appear recalcitrant to corticosteroid treatment (5). CIP recurrence may occur early in patients with more severe grade (grade 3 or 4) initially and have occurred most often in patients whose therapeutic course was shorter than 5 weeks (71, 142). The lengths of steroid courses from our data varied from 1 week to 73.4 weeks, and the mean duration for grade ≥ 2 CIP was more than 10 weeks (**Tables 2** and **3**). However, in patients whose steroid course was shorter than 5 weeks (25, 49, 55, 59, 67, 72, 75, 82), two patients (25, 67) experienced CIP recurrence. The highest CIP recurrence rate, 22.22%, occurred in patients with grade 2 CIP (**Table 3**). In addition, the steroid courses were centrally distributed in the first 5 weeks (**Figure 4**), which suggests that the changes to steroid dosages (in grade 2 CIP) and drugs (in grade 3 or 4 CIP) usually occurred in this window.

Current experience with immunosuppressive drugs to treat CIP is based mostly on extrapolation from data about their use to treat other irAEs, which lacked pathophysiological evidence (5). IFX and cyclophosphamide have been approved to treat ICI-related digestive toxicities, especially colitis (133, 143, 144).

TABLE 3 | The characteristics related to management of CIP stratified by grade of CIP.

Grade of CIP Mean ± SD/N (%)	Total	Grade 2	Grade 3	Grade 4	P-value
N	44	18	19	7	
Steroid initial dose (mg/d)	425.29 ± 451.82	280.40 ± 411.75	527.56 ± 469.29	360.00 ± 554.26	0.426
Steroid initial dose groups (mg/d)					0.379
Low-dose <60	5 (29.41%)	1 (20.00%)	2 (22.22%)	2 (66.67%)	
Intermediate-dose 60-500	6 (35.29%)	3 (60.00%)	3 (33.33%)	0 (0.00%)	
High-dose 501-1000	6 (35.29%)	1 (20.00%)	4 (44.44%)	1 (33.33%)	
Steroid initial dose (mg/kg/d)	1.24 ± 0.58	0.86 ± 0.10	2.00 ± 0.40	2.00 ± 0.00	**<0.001**
Steroid initial dose groups (mg/kg/d)					**0.007**
Low-dose <1	8 (53.33%)	8 (80.00%)	0 (0.00%)	0 (0.00%)	
Intermediate-dose 1-2	6 (40.00%)	2 (20.00%)	2 (66.67%)	2 (100.00%)	
High-dose >2	1 (6.67%)	0 (0.00%)	1 (33.33%)	0 (0.00%)	
Steroid taper time	10.46 ± 9.94	7.20 ± 5.35	16.37 ± 14.60	8.25 ± 4.79	0.154
Steroid course	14.43 ± 15.14	12.23 ± 8.54	16.35 ± 20.75	15.62 ± 14.75	0.776
Immunosuppressive drugs					**0.016**
No	35 (79.55%)	17 (94.44%)	15 (78.95%)	3 (42.86%)	
Yes	9 (20.45%)	1 (5.56%)	4 (21.05%)	4 (57.14%)	
Antibiotics					**0.011**
No	28 (63.64%)	14 (77.78%)	13 (68.42%)	1 (14.29%)	
Yes	16 (36.36%)	4 (22.22%)	6 (31.58%)	6 (85.71%)	
Recurrent times					0.312
0	34 (77.27%	14 (77.78%)	14 (73.68%)	6 (85.71%)	
1	6 (13.64%)	4 (22.22%)	2 (10.53%)	0 (0.00%)	
2	2 (4.55%)	0 (0.00%)	2 (10.53%)	0 (0.00%)	
3	2 (4.55%)	0 (0.00%)	1 (5.26%)	1 (14.29%)	
CIP outcome					**0.003**
Improved/Resolved	34 (77.27%)	18 (100.00%)	13 (68.42%)	3 (42.86%)	
Deteriorated/Maintained	10 (22.73%)	0 (0.00%)	6 (31.58%)	4 (57.14%)	
CIP course (weeks)	12.64 ± 14.20	10.30 ± 7.90	14.85 ± 19.20	12.96 ± 13.09	0.673
OS					**0.019**
Alive	20 (57.14%)	12 (85.71%)	5 (35.71%)	3 (42.86%)	
Dead	15 (42.86%)	2 (14.29%)	9 (64.29%)	4 (57.14%)	
Survival time (weeks)	55.35 ± 46.26	72.92 ± 58.13	41.00 ± 29.64	46.00 ± 37.33	0.198
Clinical response					**0.018**
Complete response	2 (5.71%)	0 (0.00%)	2 (14.29%)	0 (0.00%)	
Partial response	6 (17.14%)	6 (42.86%)	0 (0.00%)	0 (0.00%)	
Tumor progressed	5 (14.29%)	2 (14.29%)	2 (14.29%)	1 (14.29%)	
Stable	7 (20.00%)	4 (28.57%)	1 (7.14%)	2 (28.57%)	
Unknown	15 (42.86%)	2 (14.29%)	9 (64.29%)	4 (57.14%)	

CIP, checkpoint inhibitor pneumonitis; OS, overall survival.

Bold values: two-sided P-values less than 0.05 were considered to identify statistical significance.

However, IFX could itself cause ILD and liver injury (145–147). In addition, it could weaken the ongoing anticancer immune activity initially launched by ICI treatment (25); this hypothesis is consistent with a prior study (18), which reported that half of patients with grade 3 CIP died despite receiving additional immunosuppressive drugs. As a second-line drug, mycophenolate mofetil remains controversial because of its suppressive effects on the T-cell response (148). IL-17 blockade reportedly relieved ICI-related gastrointestinal and skin irAEs (149). Current guidelines also recommend cyclophosphamide, mycophenolate mofetil intravenously (1 g twice daily), or IFX (5 mg/kg) as supportive care (121, 133, 135) for steroid-resistant patients with irAEs. Intravenous immunoglobulin was effective in ICI-mediated myasthenia gravis and did not blunt infection responses (150). Thus, intravenous immunoglobulin could become a logical choice for treating CIP in patients with suspected comorbid infections (24). Tocilizumab, an IL-6 inhibitor, has been used to treat rheumatologic irAEs (84). A case report showed that a patient with NSCLC and CIP experienced significant symptom relief after additional therapy with tocilizumab (151). However, whether tocilizumab should be included as an option in the second-line drugs to treat steroid-refractory patients with irAEs remains undetermined, because that approach lacks a comparison with other second-line drugs.

PROGNOSIS OF CIP

Most studies have found that patients with CIP, especially with lower-grade disease, could see symptoms improve or resolve if they received corticosteroid therapies (18, 152). Similarly, our data (**Table 3**) demonstrated that patients with grade 2 CIP all experienced improvements in or resolution of CIP and had the highest OS (85.71%) versus patients with grade 3 or 4 CIP (OS of 35.71% or 42.86%, respectively, P=0.019). In addition, nearly half of patients with grade 2 CIP experienced a partial tumor response, whereas most patients with grade 3 or 4 CIP experienced tumor progression or maintenance. However, a single-center study (20) recently reported poor prognoses in patients with NSCLC who developed CIP. Suresh et al. (45) demonstrated that the ICIs did not significantly influence the short-term survival (disease control rate, overall response rate, or PFS) but did affect OS which decreased by 10 months in patients with CIP. Fukihara et al. (47) came to a similar conclusion regarding the decrease in OS. Patients with CIP (8.7 months) had a shorter OS after PD-1 blockade compared with those without CIP (23.0 months, P=0.015). We also evaluated the association between CIP and OS (**Figure 5**), and we found that patients who experienced deteriorated or maintained CIP were significantly more likely to have a poor prognosis compared with patients who experienced improved or resolved CIP (P=0.006). One potential reason might be that patients with CIP were more likely to be forced to quit ICI therapy to avoid lethal respiratory failure. Moreover, as a result of deteriorating physical status, abrasive pulmonary symptoms, and prolonged steroid management for CIP, patients with CIP tended to reject—and their physicians were more likely to hesitate or delay commencement or continuation of—aggressive anti-tumor treatment.

Recurrent phenomena related to the management of CIP have been explored in patients with NSCLC who received ICI therapy. These phenomena included recurrent pneumonia after completion of a steroid taper with or without restarting immunotherapy. Reports of reusing ICI therapy mainly occurred in patients with grade 1 or 2 CIP initially, since patients identified with grade 3 or 4 CIP generally withdrew treatment permanently (47). The reported recurrence ratio after reusing immunotherapy varied from 17% to 30% (18, 55, 122). Our analysis (**Table 2**) showed that the overall recurrence ratios with and without re-challenge ICI therapy were 6.82% (3/44) and 22.73% (10/44), respectively. Among three patients (65, 73, 81) who re-challenged ICI therapy after clinical regression of CIP, two experienced recurrence after restarting ICIs (65, 81), and one patient successfully improved by discontinuing immunotherapy and beginning treatment with antibiotics and steroids (73). Recurrent pneumonitis severity, location of involvement, and pattern might vary compared with the initial manifestation of CIP.

Predictive factors for CIP are still under investigation. Currently, the exploration of serum markers, cytokines/chemokines, and cellular biomarkers have interested clinicians (137). Increased carcinoembryonic antigen (CEA) serum levels reportedly relate to both tumor progression and the simultaneous regression of recurrent CIP (153), which represents an early association with both durable toxicity and durable response. In addition, a low level of serum albumin was an independent predictor of CIP in patients with NSCLC (odds ratio=0.381, 95% CI=0.179–0.808, P=0.012) (71). In solid tumors, other research found that elevated baseline lymphocyte levels were linked to irAEs (47). In patients with melanoma who experienced severe irAEs, peripheral blood samples were evaluated early during treatment, and 11 elevated cytokines were recruited in the validation group for the predictive model (154).

We also evaluated the relationship between the initial steroid dose and OS (**Supplement Figures 1**, **2**). Unfortunately, no significant difference in OS was found among low-dose, intermediate-dose, and high-dose steroid groups. Some reasons might be that the sample size was small and the precise data about steroid doses were limited, so the optimal steroid dose for OS was not determined. Therefore, extensive multicenter studies, which have detailed management of steroid therapy, should be conducted in the future.

POST-CIP EVOLUTION AND TYPICAL SEQUELA

The evolution of post-CIP patients is largely dependent on their CIP status. Patients with moderate or well-controlled CIP would have various subsequent treatment options including only supportive care, cytotoxic chemotherapy alone and ICIs rechallenge, based on the primary tumor response, irAEs evaluation, and patients' willingness (155). Yamagata et al. (156) conducted a retrospective analysis concerning the NSCLC patients with CIP and reported the cancer therapy after CIP. They found that 34.6% of CIP patients decided to treat with cytotoxic chemotherapy, and 30.8% of CIP patients chose the best

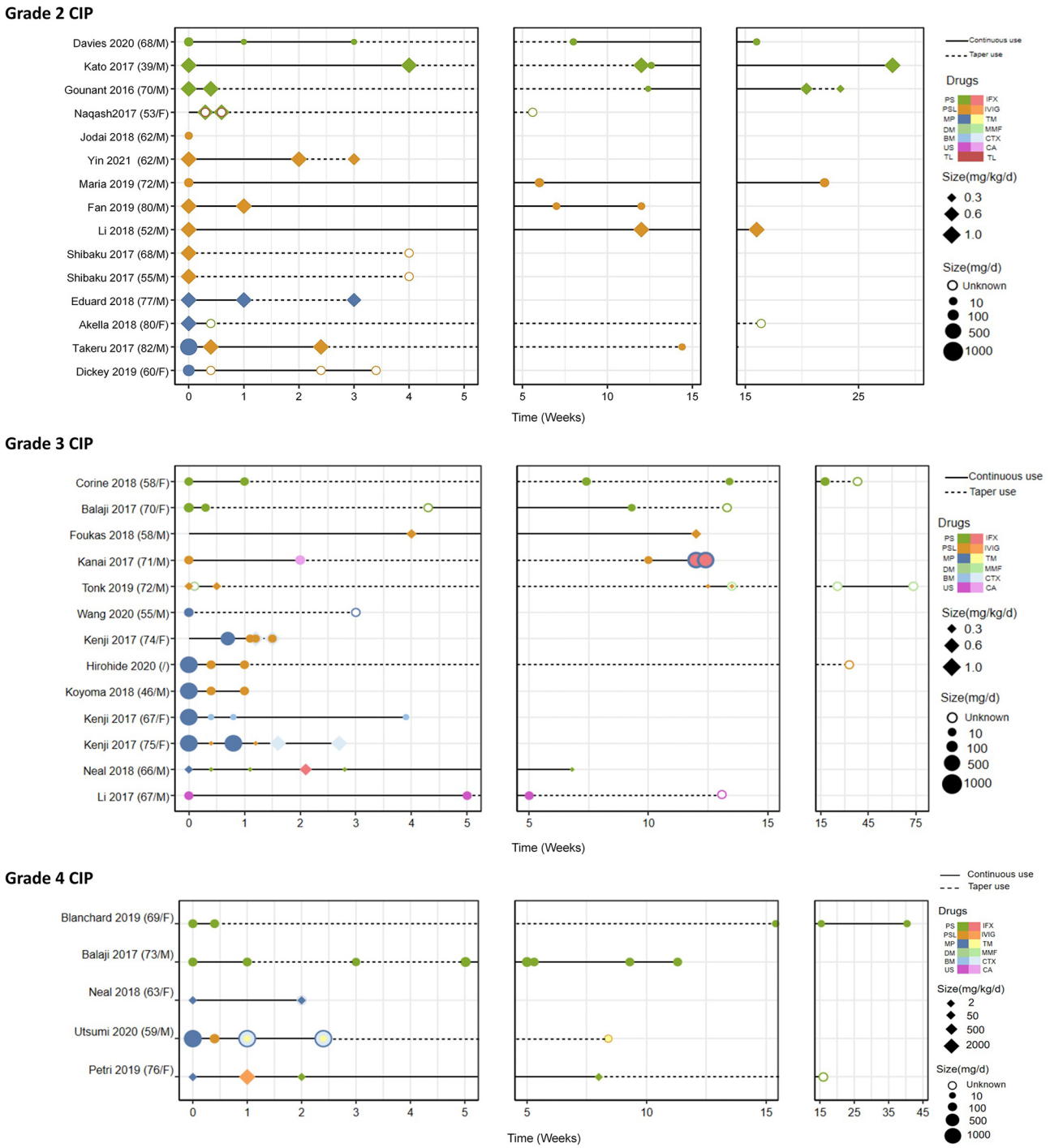

FIGURE 4 | The steroid therapy including every drug that every case utilized and the definite continuous and taper time. PS, prednisone; PSL, prednisolone; MP, methylprednisolone; DM, dexamethasone; BM, betamethasone; US, unspecific; TL, tocilizumab; IFX, infliximab; IVIG, immunoglobulin; TM, tacrolimus; MMF, mycophenolate mofetil or mycophenolic acid; CTX, cyclophosphamide; CA, cyclosporine A.

supportive care after CIP. The rechallenge of ICIs only applied on 3% of CIP patients. Actually, if the patients get complete or partial remission (CR or PR), the therapeutic strategies without ICIs could be considered for continued use (157). However, the options of rechallenge should be deliberated in the context of personalized consideration and multidisciplinary evaluation.

Patients with neurologic, cardiac, or any grade 4 irAEs are not recommended to continue or rechallenge ICIs (158). The

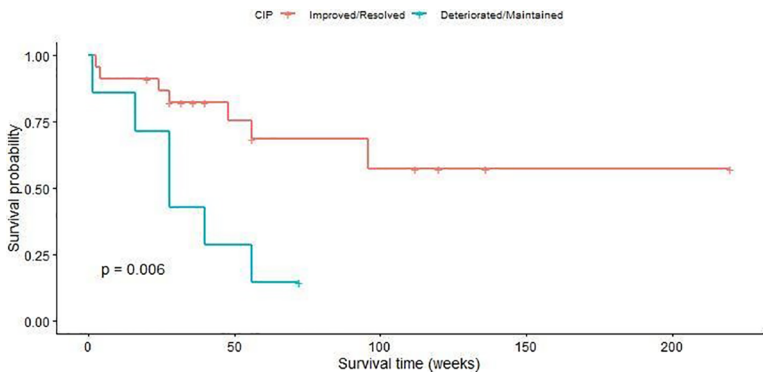

FIGURE 5 | Overall survival curves of patients with checkpoint inhibitor pneumonitis.

evaluation of ICIs rechallenge mainly depends on risk-reward ratio (158). At present, there is no acknowledged guidance for re-challenging ICIs. Whether patients should resume ICI monotherapy after receiving doublet ICI therapy is still being investigated. A recent study recruited 80 patients with irAEs on doublet ICI therapy who subsequently reinstated ICIs as monotherapy, and the results indicated that the incidence of CIP (33%) was significantly higher than ophthalmic or gastrointestinal immune-related toxicity (159). However, in most instances, the ICI utilized for re-initiation in NSCLC could be the same ICIs used before, another PD-1/PD-L1 inhibitors, or the switching from PD-1 to PD-L1 inhibitors or the converse (160–164). Kitagawa et al. (157) included prior reports about ICIs rechallenge in NSCLC and analyzed its efficacy and safety. The results showed the generally lower overall response rate (ORR), disease control rate (DCR), and the median PFS presented in patients received the second ICI than in those received the first ICI among these studies. The greatest DCR (58.8%) and longest median PFS (4.0 months) during the second ICI treatment were showed in the 17 patients Kitagawa et al. (157) included. All these 17 patients switched the ICIs type when ICI rechallenge, of which 58.8% obtained PR or stable disease (SD) after switching ICIs administration. However, the efficacy of ICIs rechallenge is still controversial (165–167). Between two ICIs administration, shorter interval may exert better effects on outcome. Besides, the potential predictive factors of ICIs rechallenge outcome include early irAEs development, irAE therapy intensity, CIP phenotype, PD-1 inhibitors, and age more than 65 (155). As for the safety, the second attempt of ICIs could cause same irAEs or moderate new irAEs. Naidoo et al. (168) reported that 3 of 12 patients who reinstated ICI therapy developed CIP recurrence (initial CIP grade of 1 or 2), and 38 of 68 patients developed irAEs after re-treatment. Once patients experience recurrent CIP, the discontinued ICIs in time and the monotherapy of same steroid administrated before is universally acknowledged (19), while with a slower dose tapering and longer course (142).

Notably, there might exist durable anti-tumor activity after discontinuing ICIs therapy (44, 169, 170). This continuous treatment tendency could hold on until intolerable irAEs appearance, tumor progression or no more than 2 years. The correlation of tumor response and toxicity enhances the complexity of ICIs therapy and requires to be demonstrated further. Gauci et al. (170) found that the favorable predictive factors for prolonged response after stopping ICIs therapy included CR patients before discontinuation, with 13% increase of keeping disease stability compared to PR patients.

There are few reports about the sequela of CIP. The typical sequela might be the sustaining pulmonary interstitial fibrosis and poor pulmonary function caused by severe CIP (171, 172). Nintedanib, as an angiokinase blocker, has been reported to play significant role in progressive fibrosing interstitial lung disease, contributing to slow down the decline rate of forced vital capacity (FVC) (173) and further potentially strengthen the prevention of CIP (174).

FUTURE DIRECTIONS FOR CIP

Although quite a few researchers have intensively studied the characteristics of CIP in NSCLC, the studies with regard to the diagnosis, treatment and risk stratification require more exploration (175). First, timely and accurate diagnosis of CIP is necessary. The current biomarkers are based on the mechanism of irAEs. Among the various biomarkers, Isono et al. (176) recently found idiopathic interstitial pneumonias became the only risk factor of CIP in the multivariate Cox regression model. Therefore, the ability of these biomarkers to predict CIP should be investigated deeply.

Second, the management of CIP remains inconclusive. The optimal drug regimen of corticosteroid (taper and continuous time) for CIP and ICIs (onset) for post-CIP need more clinical studies with large sample size to evaluate. Currently, the corresponding two clinical protocols, NCT04036721 and NCT04169503, are ongoing and expected to present profound results.

Third, risk stratification for CIP contributes to precise treatment. CIP presents with different incidence and death rates in different histological types of NSCLC, which may be

ascribed to the intrinsic features of tumor histological subtypes (19, 24). Thus, we need more research about the clinical, radiological, histological, and biological characteristics of CIP to determine whether specific subsets of patients should be treated prophylactically.

STATISTICS ANALYSIS

We conducted the descriptive analyses to delineate the baseline characteristics and the intergroup differences in different CIP outcomes and CIP grade groups. Kruskal-Wallis test and chi-square or Fisher's exact test were utilized to analyze continuous and categorical variables, respectively. The former variables were presented by means and standard deviations, and the latter variables were expressed as counts and proportions. The overall and CIP survival rate were estimated by Kaplan-Meier method with a log-rank test. The statistical software packages R and EmpowerStats (X&Y Solutions Inc., Boston, MA, USA) were utilized to conduct all the statistical analyses. Two-sided P-values less than 0.05 were considered to identify statistical significance.

AUTHOR CONTRIBUTIONS

QZ and LT searched the literature and wrote the manuscript. YZ helped to collect literature and participated in discussions. LT and WH performed the statistics analysis. WL examined and verified the study. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.663986/full#supplementary-material

Supplementary Figure 1 | Relationship between initial corticosteroids dose and checkpoint inhibitor pneumonitis outcome. Kaplan-Meier curves by initial corticosteroids dose (mg/d) **(A)**, by initial corticosteroids dose (mg/kg/d) **(B)**.

Supplementary Figure 2 | Relationship between initial corticosteroids dose and overall survival. Kaplan-Meier curves by initial corticosteroids dose (mg/d) **(A)**, by initial corticosteroids dose (mg/kg/d) **(B)**.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2020. *CA Cancer J Clin* (2020) 70(1):7–30. doi: 10.3322/caac.21590
2. Bodor JN, Boumber Y, Borghaei H. Biomarkers for Immune Checkpoint Inhibition in non-Small Cell Lung Cancer (NSCLC). *Cancer* (2020) 126 (2):260–70. doi: 10.1002/cncr.32468
3. Ozkaya S, Findik S, Dirican A, Atici AG. Long-Term Survival Rates of Patients With Stage IIIB and IV non-Small Cell Lung Cancer Treated With Cisplatin Plus Vinorelbine or Gemcitabine. *Exp Ther Med* (2012) 4(6):1035–8. doi: 10.3892/etm.2012.714
4. Bradley JD, Hu C, Komaki RR, Masters GA, Blumenschein GR, Schild SE, et al. Long-Term Results of NRG Oncology RTOG 0617: Standard- Versus High-Dose Chemoradiotherapy With or Without Cetuximab for Unresectable Stage III non-Small-Cell Lung Cancer. *J Clin Oncol* (2020) 38(7):706–+. doi: 10.1200/JCO.19.01162
5. Suresh K, Naidoo J, Lin CT, Danoff S. Immune Checkpoint Immunotherapy for Non-Small Cell Lung Cancer: Benefits and Pulmonary Toxicities. *Chest* (2018) 154(6):1416–23. doi: 10.1016/j.chest.2018.08.1048
6. Naidoo J, Nishino M, Patel SP, Shankar B, Rekhtman N, Illei P, et al. Immune-Related Pneumonitis After Chemoradiotherapy and Subsequent Immune Checkpoint Blockade in Unresectable Stage III Non-Small-Cell Lung Cancer. *Clin Lung Cancer* (2020) 21(5):E435–44. doi: 10.1016/j.cllc.2020.02.025
7. Lin X, Lu X, Luo GS, Xiang H. Progress in PD-1/PD-L1 Pathway Inhibitors: From Biomacromolecules to Small Molecules. *Eur J Medicinal Chem* (2020) 186:111876. doi: 10.1016/j.ejmech.2019.111876
8. Hayashi H, Nakagawa K. Combination Therapy With PD-1 or PD-L1 Inhibitors for Cancer. *Int J Clin Oncol* (2020) 25(5):818–30. doi: 10.1007/s10147-019-01548-1
9. Shannon VR. Pneumonitis Associated With Immune Checkpoint Inhibitors Among Patients With non-Small Cell Lung Cancer. *Curr Opin Pulm Med* (2020) 26(4):326–40. doi: 10.1097/MCP.0000000000000689
10. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab Versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *New Engl J Med* (2015) 373(2):123–35. doi: 10.1056/NEJMoa1504627
11. Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, Ahn MJ, et al. Five-Year Overall Survival for Patients With Advanced non-Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. *J Clin Oncol* (2019) 37(28):2518–+. doi: 10.1200/JCO.19.00934
12. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival With Durvalumab After Chemoradiotherapy in Stage III NSCLC. *New Engl J Med* (2018) 379(24):2342–50. doi: 10.1056/NEJMoa1809697
13. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *New Engl J Med* (2017) 377(20):1919–29. doi: 10.1056/NEJMoa1709937
14. Zhai X, Zhang J, Tian Y, Li J, Jing W, Guo H, et al. The Mechanism and Risk Factors for Immune Checkpoint Inhibitor Pneumonitis in non-Small Cell Lung Cancer Patients. *Cancer Biol Med* (2020) 17(3):599–611. doi: 10.20892/j.issn.2095-3941.2020.0102
15. Brahmer JR, Govindan R, Anders RA, Antonia SJ, Sagorsky S, Davies MJ, et al. The Society for Immunotherapy of Cancer Consensus Statement on Immunotherapy for the Treatment of non-Small Cell Lung Cancer (NSCLC). *J Immunother Cancer* (2018) 6(1):75. doi: 10.1186/s40425-018-0382-2
16. Hahn AW, Gill DM, Agarwal N, Maughan BL. PD-1 Checkpoint Inhibition: Toxicities and Management. *Urol Oncol Seminars Original Invest* (2017) 35 (12):701–7. doi: 10.1016/j.urolonc.2017.08.005
17. Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, et al. Toxicities of the anti-PD-1 and anti-PD-L1 Immune Checkpoint Antibodies. *Ann Oncol* (2015) 26(12):2375–91. doi: 10.1093/annonc/mdv383
18. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. *J Clin Oncol* (2017) 35(7):709–+. doi: 10.1200/JCO.2016.68.2005
19. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi S. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients With Advanced Cancer A Systematic Review and Meta-Analysis. *JAMA Oncol* (2016) 2(12):1607–16. doi: 10.1001/jamaoncol.2016.2453
20. Nishino M, Ramaiya NH, Awad MM, Sholl LM, Maattala JA, Taibi M, et al. PD-1 Inhibitor-Related Pneumonitis in Advanced Cancer Patients: Radiographic Patterns and Clinical Course. *Clin Cancer Res* (2016) 22 (24):6051–60. doi: 10.1158/1078-0432.CCR-16-1320
21. Nishino M, Chambers ES, Chong CR, Ramaiya NH, Gray SW, Marcoux JP, et al. Anti-PD-1 Inhibitor-Related Pneumonitis in Non-Small Cell Lung Cancer. *Cancer Immunol Res* (2016) 4(4):289–93. doi: 10.1158/2326-6066.CIR-15-0267
22. Wang PF, Chen Y, Song SY, Wang TJ, Ji WJ, Li SW, et al. Immune-Related Adverse Events Associated With Anti-PD-1/PD-L1 Treatment for

Malignancies: A Meta-Analysis. *Front Pharmacol* (2017) 8:730. doi: 10.3389/fphar.2017.00730
23. Sun Y, Shao C, Li S, Xu Y, Xu K, Zhang Y, et al. Programmed Cell Death 1 (PD-1)/PD-ligand 1(PD-L1) Inhibitors-Related Pneumonitis in Patients With Advanced Non-Small Cell Lung Cancer. *Asia Pacif J Clin Oncol* (2020). doi: 10.1111/ajco.13380
24. Suresh K, Khinh Ranh V, Shankar B, Forde PM, Ettinger DS, Marrone KA, et al. Pneumonitis in Non-Small Cell Lung Cancer Patients Receiving Immune Checkpoint Immunotherapy: Incidence and Risk Factors. *J Thoracic Oncol* (2018) 13(12):1930–9. doi: 10.1016/j.jtho.2018.08.2035
25. Andruska N, Mahapatra L, Hebbard C, Patel P, Paul V. Severe Pneumonitis Refractory to Steroids Following anti-PD-1 Immunotherapy. *BMJ Case Rep* (2018) 2018:225937. doi: 10.1136/bcr-2018-225937
26. Inthasot V, Bruyneel M, Muylle I, Ninane V. Severe Pulmonary Infections Complicating Nivolumab Treatment for Lung Cancer: A Report of Two Cases. *Acta Clin Belg* (2020) 75(4):308–10. doi: 10.1080/17843286.2019.1629078
27. Galant-Swafford J, Troesch A, Tran L, Weaver A, Doherty TA, Patel SP. Landscape of Immune-Related Pneumonitis in Cancer Patients With Asthma Being Treated With Immune Checkpoint Blockade. *Oncology* (2020) 98(2):123–30. doi: 10.1159/000503566
28. Cho JY, Kim J, Lee JS, Kim YJ, Kim SH, Lee YJ, et al. Characteristics, Incidence, and Risk Factors of Immune Checkpoint Inhibitor-Related Pneumonitis in Patients With Non-Small Cell Lung Cancer. *Lung Cancer* (2018) 125:150–6. doi: 10.1016/j.lungcan.2018.09.015
29. Mark NM, Kargl J, Busch SE, Yang GHY, Metz HE, Zhang H, et al. Chronic Obstructive Pulmonary Disease Alters Immune Cell Composition and Immune Checkpoint Inhibitor Efficacy in Non-Small Cell Lung Cancer. *Am J Respir Crit Care Med* (2018) 197(3):325–36. doi: 10.1164/rccm.201704-0795OC
30. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab Plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *N Engl J Med* (2018) 379(21):2040–51. doi: 10.1056/NEJMoa1810865
31. Ahn MJ, Yang J, Yu H, Saka H, Ramalingam S, Goto K, et al. Osimertinib Combined With Durvalumab in EGFR-mutant Non-Small Cell Lung Cancer: Results From the TATTON Phase Ib Trial. *J Thoracic Oncol* (2016) 11(4):S115–5. doi: 10.1016/S1556-0864(16)30246-5
32. Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab Plus Ipilimumab in Lung Cancer With a High Tumor Mutational Burden. *N Engl J Med* (2018) 378(22):2093–104. doi: 10.1056/NEJMoa1801946
33. Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, et al. Nivolumab Plus Ipilimumab as First-Line Treatment for Advanced Non-Small-Cell Lung Cancer (CheckMate 012): Results of an Open-Label, Phase 1, Multicohort Study. *Lancet Oncol* (2017) 18(1):31–41. doi: 10.1016/S1470-2045(16)30624-6
34. Ready N, Hellmann MD, Awad MM, Otterson GA, Gutierrez M, Gainor JF, et al. First-Line Nivolumab Plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer (CheckMate 568): Outcomes by Programmed Death Ligand 1 and Tumor Mutational Burden as Biomarkers. *J Clin Oncol* (2019) 37(12):992–1000. doi: 10.1200/JCO.18.01042
35. Yang JC, Gadgeel SM, Sequist LV, Wu CL, Papadimitrakopoulou VA, Su WC, et al. Pembrolizumab in Combination With Erlotinib or Gefitinib as First-Line Therapy for Advanced Nsclc With Sensitizing EGFR Mutation. *J Thorac Oncol* (2019) 14(3):553–9. doi: 10.1016/j.jtho.2018.11.028
36. Yang JC, Shepherd FA, Kim DW, Lee GW, Lee JS, Chang GC, et al. Osimertinib Plus Durvalumab Versus Osimertinib Monotherapy in EGFR T790M-Positive NSCLC Following Previous EGFR TKI Therapy: CAURAL Brief Report. *J Thorac Oncol* (2019) 14(5):933–9. doi: 10.1016/j.jtho.2019.02.001
37. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab Plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med* (2018) 378(22):2078–92. doi: 10.1056/NEJMoa1801005
38. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med* (2018) 378(24):2288–301. doi: 10.1056/NEJMoa1716948
39. Borghaei H, Langer CJ, Gadgeel S, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. 24-Month Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin With or Without Pembrolizumab as First-Line Therapy For Advanced Nonsquamous non-Small Cell Lung Cancer. *J Thorac Oncol* (2019) 14(1):124–9. doi: 10.1016/j.jtho.2018.08.004
40. Reck M, Socinski MA, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Primary PFS and Safety Analyses of a Randomized Phase III Study of Carboplatin Plus Paclitaxel Plus /- Bevacizumab, With or Without Atezolizumab in 1L non-Squamous Metastatic NSCLC (Impower150). *J Thoracic Oncol* (2018) 13(4):S77–8. doi: 10.1016/S1556-0864(18)30409-X
41. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab Versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med* (2015) 373(17):1627–39. doi: 10.1056/NEJMoa1507643
42. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab Versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* (2016) 375(19):1823–33. doi: 10.1056/NEJMoa1606774
43. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab Versus Docetaxel in Patients With Previously Treated Non-Small-Cell Lung Cancer (OAK): A Phase 3, Open-Label, Multicentre Randomised Controlled Trial. *Lancet* (2017) 389(10066):255–65. doi: 10.1016/S0140-6736(16)32517-X
44. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab Versus Docetaxel for Previously Treated, PD-L1-positive, Advanced non-Small-Cell Lung Cancer (KEYNOTE-010): A Randomised Controlled Trial. *Lancet* (2016) 387(10027):1540–50. doi: 10.1016/S0140-6736(15)01281-7
45. Suresh K, Psoter KJ, Voong KR, Shankar B, Forde PM, Ettinger DS, et al. Impact of Checkpoint Inhibitor Pneumonitis on Survival in NSCLC Patients Receiving Immune Checkpoint Immunotherapy. *J Thorac Oncol* (2019) 14(3):494–502. doi: 10.1016/j.jtho.2018.11.016
46. Cui P, Huang D, Wu Z, Tao H, Zhana S, Ma J, et al. Association of Immune-Related Pneumonitis With the Efficacy of PD-1/PD-L1 Inhibitors in non-Small Cell Lung Cancer. *Ther Adv Med Oncol* (2020) 12:175883592092203. doi: 10.1177/1758835920922033
47. Fukihara J, Sakamoto K, Koyama J, Ito T, Iwano S, Morise M, et al. Prognostic Impact and Risk Factors of Immune-Related Pneumonitis in Patients With Non-Small-Cell Lung Cancer Who Received Programmed Death 1 Inhibitors. *Clin Lung Cancer* (2019) 20(6):442–50.e444. doi: 10.1016/j.cllc.2019.07.006
48. Voong KR, Hazell SZ, Fu W, Hu C, Lin CT, Ding K, et al. Relationship Between Prior Radiotherapy and Checkpoint-Inhibitor Pneumonitis in Patients With Advanced Non-Small-Cell Lung Cancer. *Clin Lung Cancer* (2019) 20(4):e470–9. doi: 10.1016/j.cllc.2019.02.018
49. Shibaki R, Murakami S, Matsumoto Y, Yoshida T, Goto Y, Kanda S, et al. Association of Immune-Related Pneumonitis With the Presence of Preexisting Interstitial Lung Disease in Patients With non-Small Lung Cancer Receiving Anti-Programmed Cell Death 1 Antibody. *Cancer Immunol Immunother* (2020) 69(1):15–22. doi: 10.1007/s00262-019-02431-8
50. Oshima Y, Tanimoto T, Yuji K, Tojo A. EGFR-TKI-Associated Interstitial Pneumonitis in Nivolumab-Treated Patients With non-Small Cell Lung Cancer. *JAMA Oncol* (2018) 4(8):1112–5. doi: 10.1001/jamaoncol.2017.4526
51. Yamaguchi T, Shimizu J, Hasegawa T, Horio Y, Inaba Y, Yatabe Y, et al. Pre-Existing Pulmonary Fibrosis is a Risk Factor for anti-PD-1-related Pneumonitis in Patients With non-Small Cell Lung Cancer: A Retrospective Analysis. *Lung Cancer* (2018) 125:212–7. doi: 10.1016/j.lungcan.2018.10.001
52. Wang YN, Lou DF, Li DY, Jiang W, Dong JY, Gao W, et al. Elevated Levels of IL-17A and IL-35 in Plasma and Bronchoalveolar Lavage Fluid are Associated With Checkpoint Inhibitor Pneumonitis in Patients With Non-Small Cell Lung Cancer. *Oncol Lett* (2020) 20(1):611–22. doi: 10.3892/ol.2020.11618
53. Cui P, Liu Z, Wang G, Ma J, Qian Y, Zhang F, et al. Risk Factors for Pneumonitis in Patients Treated With Anti-Programmed Death-1 Therapy: A Case-Control Study. *Cancer Med* (2018) 7(8):4115–20. doi: 10.1002/cam4.1579
54. Mandalà M, Merelli B, Indriolo A, Tondini C. Late-Occurring Toxicity Induced by an Immune Checkpoint Blockade in Adjuvant Treatment of a

Stage III Melanoma Patient. *Eur J Cancer* (2018) 95:130–2. doi: 10.1016/j.ejca.2018.02.019
55. Yin B, Xiao J, Li J, Liu X, Wang J. Immune-Related Organizing Pneumonitis in non-Small Cell Lung Cancer Receiving PD-1 Inhibitor Treatment: A Case Report and Literature Review. *J Cancer Res Ther* (2020) 16(7):1555–9. doi: 10.4103/jcrt.JCRT_971_20
56. Davies MJ, Chiang AC. Management of Pneumonitis and Neuropathy in Patients Receiving PD-1-Based Therapy for Non-Small-Cell Lung Cancer. *JCO Oncol Pract* (2020) 16(2_suppl):4s–9s. doi: 10.1200/JOP.19.00676
57. Utsumi H, Araya J, Okuda K, Watanabe J, Takekoshi D, Fujita Y, et al. Successful Treatment of Steroid-Refractory Immune Checkpoint Inhibitor-Related Pneumonitis With Triple Combination Therapy: A Case Report. *Cancer Immunol Immunother* (2020) 69(10):2033–9. doi: 10.1007/s00262-020-02600-0
58. LG JA, Sher A. Anti-PD-1-Related Exacerbation of Interstitial Lung Disease in a Patient With Non-Small Cell Lung Cancer: A Case Presentation and Review of the Literature. *Cancer Invest* (2020) 38(6):365–71. doi: 10.1080/07357907.2020.1783677
59. Wang R, Li K, Pi J, Meng L, Zhu M. Cavitation and Fatal Hemoptysis After Immunotherapy for Advanced Lung Adenocarcinoma: A Case Report. *Thorac Cancer* (2020) 11(9):2727–30. doi: 10.1111/1759-7714.13578
60. Itamura H, Ohguri T, Yahara K, Nakahara S, Kakinouchi S, Morisaki T, et al. Pembrolizumab-Induced Radiation Recall Pneumonitis After the Resolution of Typical Asymptomatic Radiation Pneumonitis. *J UOEH* (2020) 42(3):261–6. doi: 10.7888/juoeh.42.261
61. Li J, Deng X, Wang B, Li W. Fatal Outcome of Atezolizumab in a Patient With Immune-Mediated Pneumonitis, Thrombocytopenia, and Cardiac Dysfunction: A case Report. *Int J Clin Pharmacol Ther* (2019) 57(12):607–11. doi: 10.5414/CP203448
62. Schwarz M, Kocher F, Niedersuess-Beke D, Rudzki J, Hochmair M, Widmann G, et al. Immunosuppression for Immune Checkpoint-Related Toxicity can Cause Pneumocystis Jirovecii Pneumonia (PJP) in Non-small-cell Lung Cancer (NSCLC): A Report of 2 Cases. *Clin Lung Cancer* (2019) 20(3):e247–50. doi: 10.1016/j.cllc.2018.12.006
63. Petri CR, Patell R, Batalini F, Rangachari D, Hallowell RW. Severe Pulmonary Toxicity From Immune Checkpoint Inhibitor Treated Successfully With Intravenous Immunoglobulin: Case Report and Review of the Literature. *Respir Med Case Rep* (2019) 27:100834. doi: 10.1016/j.rmcr.2019.100834
64. van Eeden R, Rapoport BL, Smit T, Anderson R. Tuberculosis Infection in a Patient Treated With Nivolumab for Non-small Cell Lung Cancer: Case Report and Literature Review. *Front Oncol* (2019) 9:659. doi: 10.3389/fonc.2019.00659
65. Tonk EHJ, van Lindert ASR, Verhoeff JJC, Suijkerbuijk KPM. Acute-Onset Pneumonitis While Administering the First Dose of Durvalumab. *Case Rep Oncol* (2019) 12(2):621–4. doi: 10.1159/000502202
66. Blanchard A, Bouchard N. Pembrolizumab-Induced Obstructive Bronchiolitis in a Patient With Stage IV non-Small-Cell Lung Cancer. *Curr Oncol* (2019) 26(4):e571–3. doi: 10.3747/co.26.4859
67. Dickey MS, Raina AJ, Gilbar PJ, Wisniowski BL, Collins JT, Karki B, et al. Pembrolizumab-Induced Thrombotic Thrombocytopenic Purpura. *J Oncol Pharm Pract* (2020) 26(5):1237–40. doi: 10.1177/1078155219887212
68. Sato S, Senmaru N, Ishido K, Saito T, Poudel S, Muto J, et al. Perforation of Small Intestinal Metastasis of Lung Adenocarcinoma Treated With Pembrolizumab: A Case Report. *Surg Case Rep* (2019) 5(1):166. doi: 10.1186/s40792-019-0730-6
69. Deligiorgi MV, Panayiotidis MI, Trafalis DT. Parathyroid Hormone Related Protein (PthrP)-mediated Hypercalcemia in Malignancy Associated With anti-PD-1 Immune Checkpoint Inhibitor Treatment and Related Inflammatory Reactions. *Int Immunopharmacol* (2019) 77:105942. doi: 10.1016/j.intimp.2019.105942
70. Fan FS, Yang CF, Chang CL. Nivolumab Plus Carboplatin and Paclitaxel as the First-line Therapy for Advanced Squamous Cell Carcinoma of the Lung With Strong Programmed Death-ligand 1 Expression: A Case Report. *Cureus* (2019) 11(10):e5881. doi: 10.7759/cureus.5881
71. de Jong C, Peters BJM, Schramel F. Recurrent Episodes of Nivolumab-Induced Pneumonitis After Nivolumab Discontinuation and the Time Course of Carcinoembryonic Antigen Levels: A Case of a 58-Year-Old Woman With Non-Small Cell Lung Cancer. *Chemotherapy* (2018) 63(5):272–7. doi: 10.1159/000494841
72. Koyama N, Iwase O, Nakashima E, Kishida K, Kondo T, Watanabe Y, et al. High Incidence and Early Onset of Nivolumab-Induced Pneumonitis: Four Case Reports and Literature Review. *BMC Pulm Med* (2018) 18(1):23. doi: 10.1186/s12890-018-0592-x
73. Foukas PG, Tsiodras S, Economopoulou P, Spathis A, Mademli M, Leventakos K, et al. Concomitant Human Herpes Virus 6 and Nivolumab-Related Pneumonitis: Potential Pathogenetic Insights. *IDCases* (2018) 11:101–3. doi: 10.1016/j.idcr.2018.01.013
74. Li D, He C, Xia Y, Du Y, Zhang J. Pembrolizumab Combined With Stereotactic Body Radiotherapy in a Patient With Human Immunodeficiency Virus and Advanced Non-Small Cell Lung Cancer: A Case Report. *J Med Case Rep* (2018) 12(1):104. doi: 10.1186/s13256-018-1667-2
75. Teixidor E, Sais E, Vásquez CA, Carbajal W, Hernández A, Sánchez G, et al. Immune-Related Adverse Events and Atypical Radiological Response With Checkpoint Inhibitor Immunotherapy in an Elderly Patient With High PD-L1 Expressing Lung Adenocarcinoma. *Oncotarget* (2018) 9(68):33043–9. doi: 10.18632/oncotarget.25984
76. Akella P, Loganathan S, Jindal V, Akhtar J, Lal A. Anti PD-1 Immunotherapy Related Interstitial Lung Disease Presenting as Respiratory Failure - A Review With Case Series. *Respir Med Case Rep* (2019) 26:17–22. doi: 10.1016/j.rmcr.2018.11.005
77. Jodai T, Yoshida C, Sato R, Kakiuchi Y, Sato N, Iyama S, et al. A Potential Mechanism of the Onset of Acute Eosinophilic Pneumonia Triggered by an anti-PD-1 Immune Checkpoint Antibody in a Lung Cancer Patient. *Immun Inflamm Dis* (2019) 7(1):3–6. doi: 10.1002/iid3.238
78. Li H, Ma W, Yoneda KY, Moore EH, Zhang Y, Pu LL, et al. Severe Nivolumab-Induced Pneumonitis Preceding Durable Clinical Remission in a Patient With Refractory, Metastatic Lung Squamous Cell Cancer: A Case Report. *J Hematol Oncol* (2017) 10(1):64. doi: 10.1186/s13045-017-0433-z
79. Kanai O, Nakatani K, Fujita K, Okamura M, Mio T. Concurrence of Nivolumab-Induced Interstitial Lung Disease and Cancer Invasion. *Respirol Case Rep* (2017) 5(6):e00257. doi: 10.1002/rcr2.257
80. Kashiwada T, Saito Y, Minegishi Y, Kokuho N, Takahashi A, Takahashi S, et al. Granuloma-Forming Interstitial Pneumonia Induced by Nivolumab: A Possible Immune-Related Adverse Event of the Lung. *Int Cancer Conf J* (2017) 6(3):131–4. doi: 10.1007/s13691-017-0291-0
81. Kato R, Hayashi H, Tanizaki J, Tanaka K, Takeda M, Nakagawa K. Peritumoural Ground-Glass Opacity Associated With Tumour Pseudoprogression in a Patient With non-Small Cell Lung Cancer Treated With Nivolumab. *ESMO Open* (2017) 2(1):e000145. doi: 10.1136/esmoopen-2016-000145
82. Nakahama K, Tamiya A, Taniguchi Y, Sasaki Y, Akira M, Atagi S. Severe Acute Interstitial Lung Disease After Nivolumab in Three Non-Small Cell Lung Cancer Patients With Imaging Findings of Airway Obstruction Adjacent to Lung Tumors. *J Infect Chemother* (2017) 23(12):826–9. doi: 10.1016/j.jiac.2017.07.006
83. Balaji A, Verde F, Suresh K, Naidoo J. Pneumonitis From Anti-PD-1/ PD-L1 Therapy. *Oncol (Williston Park)* (2017) 31(10):739–46, 754.
84. Naqash AR, Yang LV, Sanderlin EJ, Atwell DC, Walker PR. Interleukin-6 as One of the Potential Mediators of Immune-Related Adverse Events in Non-Small Cell Lung Cancer Patients Treated With Immune Checkpoint Blockade: Evidence From a Case Report. *Acta Oncol* (2018) 57(5):705–8. doi: 10.1080/0284186X.2017.1406668
85. Shibaki R, Akamatsu H, Fujimoto M, Koh Y, Yamamoto N. Nivolumab Induced Radiation Recall Pneumonitis After Two Years of Radiotherapy. *Ann Oncol* (2017) 28(6):1404–5. doi: 10.1093/annonc/mdx115
86. Gounant V, Brosseau S, Naltet C, Opsomer MA, Antoine M, Danel C, et al. Nivolumab-Induced Organizing Pneumonitis in a Patient With Lung Sarcomatoid Carcinoma. *Lung Cancer* (2016) 99:162–5. doi: 10.1016/j.lungcan.2016.07.010
87. Khunger M, Rakshit S, Pasupuleti V, Hernandez AV, Mazzone P, Stevenson J, et al. Incidence of Pneumonitis With Use of Programmed Death 1 and Programmed Death-Ligand 1 Inhibitors in Non-Small Cell Lung Cancer. *Chest* (2017) 152(2):271–81. doi: 10.1016/j.chest.2017.04.177
88. Delaunay M, Cadranel J, Lusque A, Meyer N, Gounant V, Moro-Sibilot D, et al. Immune-Checkpoint Inhibitors Associated With Interstitial Lung

Disease in Cancer Patients. *Eur Respir J* (2017) 50(2):1700050. doi: 10.1183/13993003.00050-2017
89. Waterhouse P, Penninger JM, Timms E, Wakeham A, Shahinian A, Lee KP, et al. Lymphoproliferative Disorders With Early Lethality in Mice Deficient in Ctla-4. *Science* (1995) 270(5238):985–8. doi: 10.1126/science.270.5238.985
90. Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of Lupus-Like Autoimmune Diseases by Disruption of the PD-1 Gene Encoding an ITIM Motif-Carrying Immunoreceptor. *Immunity* (1999) 11(2):141–51. doi: 10.1016/S1074-7613(00)80089-8
91. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated With Immune Checkpoint Blockade. *N Engl J Med* (2018) 378 (2):158–68. doi: 10.1056/NEJMra1703481
92. Shea M, Rangachari D, Hallowell RW, Hollie NI, Costa DB, VanderLaan PA. Radiologic and Autopsy Findings in a Case of Fatal Immune Checkpoint Inhibitor-Associated Pneumonitis. *Cancer Treat Res Commun* (2018) 15:17–20. doi: 10.1016/j.ctarc.2018.02.004
93. Wang GX, Kurra V, Gainor JF, Sullivan RJ, Flaherty KT, Lee SI, et al. Immune Checkpoint Inhibitor Cancer Therapy: Spectrum of Imaging Findings. *Radiographics* (2017) 37(7):2132–44. doi: 10.1148/rg.2017170085
94. Suresh K, Naidoo J, Zhong Q, Xiong Y, Mammen J, de Flores MV, et al. The Alveolar Immune Cell Landscape is Dysregulated in Checkpoint Inhibitor Pneumonitis. *J Clin Invest* (2019) 129(10):4305–15. doi: 10.1172/JCI128654
95. Läubli H, Koelzer VH, Matter MS, Herzig P, Dolder Schlienger B, Wiese MN, et al. The T Cell Repertoire in Tumors Overlaps With Pulmonary Inflammatory Lesions in Patients Treated With Checkpoint Inhibitors. *Oncoimmunology* (2018) 7(2):e1386362. doi: 10.1080/2162402X.2017.1386362
96. Geng Y, Shao Y, He W, Hu W, Xu Y, Chen J, et al. Prognostic Role of Tumor-Infiltrating Lymphocytes in Lung Cancer: A Meta-Analysis. *Cell Physiol Biochem* (2015) 37(4):1560–71. doi: 10.1159/000438523
97. Zeng DQ, Yu YF, Ou QY, Li XY, Zhong RZ, Xie CM, et al. Prognostic and Predictive Value of Tumor-Infiltrating Lymphocytes for Clinical Therapeutic Research in Patients With Non-Small Cell Lung Cancer. *Oncotarget* (2016) 7(12):13765–81. doi: 10.18632/oncotarget.7282
98. Toi Y, Sugawara S, Sugisaka J, Ono H, Kawashima Y, Aiba T, et al. Profiling Preexisting Antibodies in Patients Treated With Anti-PD-1 Therapy for Advanced non-Small Cell Lung Cancer. *JAMA Oncol* (2019) 5(3):376–83. doi: 10.1001/jamaoncol.2018.5860
99. Tahir SA, Gao J, Miura Y, Blando J, Tidwell RSS, Zhao H, et al. Autoimmune Antibodies Correlate With Immune Checkpoint Therapy-Induced Toxicities. *Proc Natl Acad Sci U S A* (2019) 116(44):22246–51. doi: 10.1073/pnas.1908079116
100. de Souza Costa VHJr., Baurakiades E, Viola Azevedo ML, Traiano G, Kowal Rosales J, Kunze Larsen KS, et al. Immunohistochemistry Analysis of Pulmonary Infiltrates in Necropsy Samples of Children With non-Pandemic Lethal Respiratory Infections (RSV; ADV; PIV1; PIV2; PIV3; FLU A; FLU B). *J Clin Virol* (2014) 61(2):211–5. doi: 10.1016/j.jcv.2014.06.026
101. Caturegli P, Di Dalmazi G, Lombardi M, Grosso F, Larman HB, Larman T, et al. Hypophysitis Secondary to Cytotoxic T-Lymphocyte-Associated Protein 4 Blockade: Insights Into Pathogenesis From an Autopsy Series. *Am J Pathol* (2016) 186(12):3225–35. doi: 10.1016/j.ajpath.2016.08.020
102. Postow MA. Managing Immune Checkpoint-Blocking Antibody Side Effects. *Am Soc Clin Oncol Educ Book* (2015) 2015:76–83. doi: 10.14694/EdBook_AM.2015.35.76
103. Sul J, Blumenthal GM, Jiang X, He K, Keegan P, Pazdur R. Fda Approval Summary: Pembrolizumab for the Treatment of Patients With Metastatic non-Small Cell Lung Cancer Whose Tumors Express Programmed Death-Ligand 1. *Oncologist* (2016) 21(5):643–50. doi: 10.1634/theoncologist.2015-0498
104. Kato T, Masuda N, Nakanishi Y, Takahashi M, Hida T, Sakai H, et al. Nivolumab-Induced Interstitial Lung Disease Analysis of Two Phase II Studies Patients With Recurrent or Advanced non-Small-Cell Lung Cancer. *Lung Cancer* (2017) 104:111–8. doi: 10.1016/j.lungcan.2016.12.016
105. Kanai O, Kim YH, Demura Y, Kanai M, Ito T, Fujita K, et al. Efficacy and Safety of Nivolumab in non-Small Cell Lung Cancer With Preexisting Interstitial Lung Disease. *Thorac Cancer* (2018) 9(7):847–55. doi: 10.1111/1759-7714.12759
106. Lichtenstein MRL, Nipp RD, Muzikansky A, Goodwin K, Anderson D, Newcomb RA, et al. Impact of Age on Outcomes With Immunotherapy in Patients With Non-Small Cell Lung Cancer. *J Thorac Oncol* (2019) 14 (3):547–52. doi: 10.1016/j.jtho.2018.11.011
107. Ninomiya K, Oze I, Kato Y, Kubo T, Ichihara E, Rai K, et al. Influence of Age on the Efficacy of Immune Checkpoint Inhibitors in Advanced Cancers: A Systematic Review and Meta-Analysis. *Acta Oncol* (2020) 59(3):249–56. doi: 10.1080/0284186X.2019.1695062
108. Voong KR, Hazell S, Hu C, Hayman J, Hales R, Marrone K, et al. Receipt of Chest Radiation and Immune-Related Pneumonitis in Patients With NSCLC Treated With Anti-PD-1/PD-L1. *J Thoracic Oncol* (2017) 12(11):S1837–7. doi: 10.1016/j.jtho.2017.09.529
109. Chun SG, Hu C, Choy H, Komaki RU, Timmerman RD, Schild SE, et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. *J Clin Oncol* (2017) 35 (1):56–+. doi: 10.1200/JCO.2016.69.1378
110. Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC, et al. Previous Radiotherapy and the Clinical Activity and Toxicity of Pembrolizumab in the Treatment of non-Small-Cell Lung Cancer: A Secondary Analysis of the KEYNOTE-001 Phase 1 Trial. *Lancet Oncol* (2017) 18(7):895–903. doi: 10.1016/S1470-2045(17)30380-7
111. Vansteenkiste J, Naidoo J, Faivre-Finn C, Ozguroglu M, Villegas A, Daniel D, et al. Pacific Subgroup Analysis: Pneumonitis in Stage Iii, Unresectable Nsclc Patients Treated With Durvalumab vs. Placebo After CRT. *J Thoracic Oncol* (2018) 13(10):S370–1. doi: 10.1016/j.jtho.2018.08.350
112. Del Castillo M, Romero FA, Argüello E, Kyi C, Postow MA, Redelman-Sidi G. The Spectrum of Serious Infections Among Patients Receiving Immune Checkpoint Blockade for the Treatment of Melanoma. *Clin Infect Dis* (2016) 63(11):1490–3. doi: 10.1093/cid/ciw539
113. Baba T, Sakai F, Kato T, Kusumoto M, Kenmotsu H, Sugiura H, et al. Radiologic Features of Pneumonitis Associated With Nivolumab in non-Small-Cell Lung Cancer and Malignant Melanoma. *Future Oncol* (2019) 15 (16):1911–20. doi: 10.2217/fon-2019-0102
114. Fragkou P, Souli M, Theochari M, Kontopoulou C, Loukides S, Koumarianou A. A Case of Organizing Pneumonia (OP) Associated With Pembrolizumab. *Drug Target Insights* (2016) 10:9–12. doi: 10.4137/DTI.S31565
115. Ferguson EC, Berkowitz EA. Lung CT: Part 2, The Interstitial Pneumonias–Clinical, Histologic, and CT Manifestations. *AJR Am J Roentgenol* (2012) 199 (4):W464–76. doi: 10.2214/AJR.10.7309
116. Dall'Olio FG, Brocchi S, Massucci M, Sperandi F, Melotti B, Ardizzoni A. Distinguishing Between Immune-Related Pneumonitis and Disease Progression in Advanced Non Small Cell Lung Cancer Treated With PD-1 Inhibitors: Can Serum Tumour Markers Have a Role? *Eur J Cancer* (2018) 95:127–9. doi: 10.1016/j.ejca.2018.02.020
117. Morikawa K, Kida H, Handa H, Inoue T, Miyazawa T, Mineshita M. Drastic Healing Process After Pembrolizumab Monotherapy in a Case of Advanced Squamous Cell Carcinoma With Severe Bronchial Stenosis Observed Over a Two-Year Period Using Continuous Bronchoscopy: A Case Report. *Thorac Cancer* (2020) 11(5):1339–43. doi: 10.1111/1759-7714.13390
118. Nishino M, Hatabu H, Hodi FS, Ramaiya NH. Drug-Related Pneumonitis in the Era of Precision Cancer Therapy. *JCO Precis Oncol* (2017) 1:1–12. doi: 10.1200/PO.17.00026
119. Burris HA3rd, Hurtig J. Radiation Recall With Anticancer Agents. *Oncologist* (2010) 15(11):1227–37. doi: 10.1634/theoncologist.2009-0090
120. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant Myocarditis With Combination Immune Checkpoint Blockade. *N Engl J Med* (2016) 375(18):1749–55. doi: 10.1056/NEJMoa1609214
121. Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of Toxicities From Immunotherapy: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. *Ann Oncol* (2017) 28 (suppl_4):iv119–42. doi: 10.1093/annonc/mdx225
122. Rashdan S, Minna JD, Gerber DE. Diagnosis and Management of Pulmonary Toxicity Associated With Cancer Immunotherapy. *Lancet Respir Med* (2018) 6(6):472–8. doi: 10.1016/S2213-2600(18)30172-3
123. Picchi H, Mateus C, Chouaid C, Besse B, Marabelle A, Michot JM, et al. Infectious Complications Associated With the Use of Immune Checkpoint Inhibitors in Oncology: Reactivation of Tuberculosis After Anti PD-1 Treatment. *Clin Microbiol Infect* (2018) 24(3):216–8. doi: 10.1016/j.cmi.2017.12.003
124. Fujita K, Terashima T, Mio T. Anti-PD1 Antibody Treatment and the Development of Acute Pulmonary Tuberculosis. *J Thorac Oncol* (2016) 11 (12):2238–40. doi: 10.1016/j.jtho.2016.07.006

125. Reungwetwattana T, Adjei AA. Anti-PD-1 Antibody Treatment and the Development of Acute Pulmonary Tuberculosis. *J Thorac Oncol* (2016) 11 (12):2048–50. doi: 10.1016/j.jtho.2016.10.008
126. Fujita K, Shim J, Nakatani K, Mio T. Patient With Lung Adenocarcinoma Manifesting as an Unusual Migratory Pulmonary Infiltration. *BMJ Case Rep* (2015) 2015:211771. doi: 10.1136/bcr-2015-211771
127. Ichikawa T, Hattori A, Suzuki K, Matsunaga T, Takamochi K, Oh S, et al. Clinicopathological Characteristics of Lung Cancer Mimicking Organizing Pneumonia on Computed Tomography-a Novel Radiological Entity of Pulmonary Malignancy. *Jpn J Clin Oncol* (2016) 46(7):681–6. doi: 10.1093/jjco/hyw053
128. Sekine I, Sumi M, Ito Y, Nokihara H, Yamamoto N, Kunitoh H, et al. Retrospective Analysis of Steroid Therapy for Radiation-Induced Lung Injury in Lung Cancer Patients. *Radiother Oncol* (2006) 80(1):93–7. doi: 10.1016/j.radonc.2006.06.007
129. Chen Y, Williams J, Ding I, Hernady E, Liu W, Smudzin T, et al. Radiation Pneumonitis and Early Circulatory Cytokine Markers. *Semin Radiat Oncol* (2002) 12(1 Suppl 1):26–33. doi: 10.1053/srao.2002.31360
130. Chuzi S, Tavora F, Cruz M, Costa R, Chae YK, Carneiro BA, et al. Clinical Features, Diagnostic Challenges, and Management Strategies in Checkpoint Inhibitor-Related Pneumonitis. *Cancer Manag Res* (2017) 9:207–13. doi: 10.2147/CMAR.S136818
131. Colen RR, Fujii T, Bilen MA, Kotrotsou A, Abrol S, Hess KR, et al. Radiomics to Predict Immunotherapy-Induced Pneumonitis: Proof of Concept. *Invest New Drugs* (2018) 36(4):601–7. doi: 10.1007/s10637-017-0524-2
132. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. Nccn Guidelines Insights: Management of Immunotherapy-Related Toxicities, Version 1.2020. *J Natl Compr Canc Netw* (2020) 18(3):230–41. doi: 10.6004/jnccn.2020.0012
133. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* (2018) 36(17):1714–68. doi: 10.1200/JCO.2017.77.6385
134. Weber JS, Postow M, Lao CD, Schadendorf D. Management of Adverse Events Following Treatment With Anti-Programmed Death-1 Agents. *Oncologist* (2016) 21(10):1230–40. doi: 10.1634/theoncologist.2016-0055
135. Puzanov I, Diab A, Abdallah K, Bingham CO3rd, Brogdon C, Dadu R, et al. Managing Toxicities Associated With Immune Checkpoint Inhibitors: Consensus Recommendations From the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* (2017) 5(1):95. doi: 10.1186/s40425-017-0300-z
136. Delaunay M, Prévot G, Collot S, Guilleminault L, Didier A, Mazières J. Management of Pulmonary Toxicity Associated With Immune Checkpoint Inhibitors. *Eur Respir Rev* (2019) 28(154):190012. doi: 10.1183/16000617.0012-2019
137. Kalisz KR, Ramaiya NH, Laukamp KR, Gupta A. Immune Checkpoint Inhibitor Therapy-Related Pneumonitis: Patterns and Management. *Radiographics* (2019) 39(7):1923–37. doi: 10.1148/rg.2019190036
138. Gubens MA, Davies M. Nccn Guidelines Updates: New Immunotherapy Strategies for Improving Outcomes in Non-Small Cell Lung Cancer. *J Natl Compr Canc Netw* (2019) 17(5.5):574–8. doi: 10.6004/jnccn.2019.5005
139. Matsumoto T, Fujita M, Hirano R, Sasaki T, Watanabe K. Risk Factors for Pneumocystis Pneumonia Onset in HIV-negative Patients Treated With High-Dose Systemic Corticosteroids. *Infect Dis (Lond)* (2019) 51(4):305–7. doi: 10.1080/23744235.2018.1558368
140. Park JW, Curtis JR, Kim MJ, Lee H, Song YW, Lee EB. Pneumocystis Pneumonia in Patients With Rheumatic Diseases Receiving Prolonged, Non-High-Dose Steroids-Clinical Implication of Primary Prophylaxis Using Trimethoprim-Sulfamethoxazole. *Arthritis Res Ther* (2019) 21(1):207. doi: 10.1186/s13075-019-1996-6
141. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis Associated With Infliximab, a Tumor Necrosis Factor Alpha-Neutralizing Agent. *N Engl J Med* (2001) 345(15):1098–104. doi: 10.1056/NEJMoa011110
142. Asher N, Marom EM, Ben-Betzalel G, Baruch EN, Steinberg-Silman Y, Schachter J, et al. Recurrent Pneumonitis in Patients With Melanoma Treated With Immune Checkpoint Inhibitors. *Oncologist* (2019) 24 (5):640–7. doi: 10.1634/theoncologist.2018-0352
143. Beck KE, Blansfield JA, Tran KQ, Feldman AL, Hughes MS, Royal RE, et al. Enterocolitis in Patients With Cancer After Antibody Blockade of Cytotoxic T-lymphocyte-associated Antigen 4. *J Clin Oncol* (2006) 24(15):2283–9. doi: 10.1200/JCO.2005.04.5716
144. Dougan M. Checkpoint Blockade Toxicity and Immune Homeostasis in the Gastrointestinal Tract. *Front Immunol* (2017) 8:1547. doi: 10.3389/fimmu.2017.01547
145. Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, Presentation, and Outcomes in Patients With Drug-Induced Liver Injury in the General Population of Iceland. *Gastroenterology* (2013) 144(7):1419–25, 1425.e1411-1413; quiz e1419-1420. doi: 10.1053/j.gastro.2013.02.006
146. Ostör AJ, Chilvers ER, Somerville MF, Lim AY, Lane SE, Crisp AJ, et al. Pulmonary Complications of Infliximab Therapy in Patients With Rheumatoid Arthritis. *J Rheumatol* (2006) 33(3):622–8.
147. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, et al. Interstitial Lung Disease Induced or Exacerbated by TNF-Targeted Therapies: Analysis of 122 Cases. *Semin Arthritis Rheumatol* (2011) 41 (2):256–64. doi: 10.1016/j.semarthrit.2010.11.002
148. Martins F, Sykiotis GP, Maillard M, Fraga M, Ribi C, Kuntzer T, et al. New Therapeutic Perspectives to Manage Refractory Immune Checkpoint-Related Toxicities. *Lancet Oncol* (2019) 20(1):e54–64. doi: 10.1016/S1470-2045(18)30828-3
149. Esfahani K, Miller WHJr. Reversal of Autoimmune Toxicity and Loss of Tumor Response by Interleukin-17 Blockade. *N Engl J Med* (2017) 376 (20):1989–91. doi: 10.1056/NEJMc1703047
150. Makarious D, Horwood K, Coward JIG. Myasthenia Gravis: An Emerging Toxicity of Immune Checkpoint Inhibitors. *Eur J Cancer* (2017) 82:128–36. doi: 10.1016/j.ejca.2017.05.041
151. Cappelli LC, Gutierrez AK, Baer AN, Albayda J, Manno RL, Haque U, et al. Inflammatory Arthritis and Sicca Syndrome Induced by Nivolumab and Ipilimumab. *Ann Rheum Dis* (2017) 76(1):43–50. doi: 10.1136/annrheumdis-2016-209595
152. Pollack MH, Betof A, Dearden H, Rapazzo K, Valentine I, Brohl AS, et al. Safety of Resuming anti-PD-1 in Patients With Immune-Related Adverse Events (irAEs) During Combined anti-CTLA-4 and anti-PD1 in Metastatic Melanoma. *Ann Oncol* (2018) 29(1):250–5. doi: 10.1093/annonc/mdx642
153. von Itzstein MS, Khan S, Gerber DE. Investigational Biomarkers for Checkpoint Inhibitor Immune-Related Adverse Event Prediction and Diagnosis. *Clin Chem* (2020) 66(6):779–93. doi: 10.1093/clinchem/hvaa081
154. Diehl A, Yarchoan M, Hopkins A, Jaffee E, Grossman SA. Relationships Between Lymphocyte Counts and Treatment-Related Toxicities and Clinical Responses in Patients With Solid Tumors Treated With PD-1 Checkpoint Inhibitors. *Oncotarget* (2017) 8(69):114268–80. doi: 10.18632/oncotarget.23217
155. Kartolo A, Holstead R, Khalid S, Emack J, Hopman W, Baetz T. Safety of Immunotherapy Rechallenge After Immune-Related Adverse Events in Patients With Advanced Cancer. *J Immunother* (2021) 44(1):41–8. doi: 10.1097/CJI.0000000000000337
156. Yamagata A, Yokoyama T, Fukuda Y, Ishida T. Impact of Interstitial Lung Disease Associated With Immune Checkpoint Inhibitors on Prognosis in Patients With Non-Small-Cell Lung Cancer. *Cancer Chemother Pharmacol* (2021) 87(2):251–8. doi: 10.1007/s00280-020-04205-x
157. Kitagawa S, Hakozaki T, Kitadai R, Hosomi Y. Switching Administration of anti-PD-1 and anti-PD-L1 Antibodies as Immune Checkpoint Inhibitor Rechallenge in Individuals With Advanced non-Small Cell Lung Cancer: Case Series and Literature Review. *Thorac Cancer* (2020) 11(7):1927–33. doi: 10.1111/1759-7714.13483
158. Simonaggio A, Michot JM, Voisin AL, Le Pavec J, Collins M, Lallart A, et al. Evaluation of Readministration of Immune Checkpoint Inhibitors After Immune-Related Adverse Events in Patients With Cancer. *JAMA Oncol* (2019) 5(9):1310–7. doi: 10.1001/jamaoncol.2019.1022
159. Santini FC, Rizvi H, Plodkowski AJ, Ni A, Lacouture ME, Gambarin-Gelwan M, et al. Safety and Efficacy of Re-treating With Immunotherapy After Immune-Related Adverse Events in Patients With NSCLC. *Cancer Immunol Res* (2018) 6(9):1093–9. doi: 10.1158/2326-6066.CIR-17-0755
160. Fujita K, Uchida N, Kanai O, Okamura M, Nakatani K, Mio T. Retreatment With Pembrolizumab in Advanced non-Small Cell Lung Cancer Patients Previously Treated With Nivolumab: Emerging Reports of 12 Cases. *Cancer Chemother Pharmacol* (2018) 81(6):1105–9. doi: 10.1007/s00280-018-3585-9

161. Niki M, Nakaya A, Kurata T, Yoshioka H, Kaneda T, Kibata K, et al. Immune Checkpoint Inhibitor Re-Challenge in Patients With Advanced non-Small Cell Lung Cancer. *Oncotarget* (2018) 9(64):32298–304. doi: 10.18632/oncotarget.25949
162. Watanabe H, Kubo T, Ninomiya K, Kudo K, Minami D, Murakami E, et al. The Effect and Safety of Immune Checkpoint Inhibitor Rechallenge in Non-Small Cell Lung Cancer. *Jpn J Clin Oncol* (2019) 49(8):762–5. doi: 10.1093/jjco/hyz066
163. Fujita K, Uchida N, Yamamoto Y, Kanai O, Okamura M, Nakatani K, et al. Retreatment With Anti-Pd-L1 Antibody in Advanced non-Small Cell Lung Cancer Previously Treated With Anti-PD-1 Antibodies. *Anticancer Res* (2019) 39(7):3917–21. doi: 10.21873/anticanres.13543
164. Katayama Y, Shimamoto T, Yamada T, Takeda T, Yamada T, Shiotsu S, et al. Retrospective Efficacy Analysis of Immune Checkpoint Inhibitor Rechallenge in Patients With Non-Small Cell Lung Cancer. *J Clin Med* (2019) 9(1):102. doi: 10.3390/jcm9010102
165. Pardoll DM. The Blockade of Immune Checkpoints in Cancer Immunotherapy. *Nat Rev Cancer* (2012) 12(4):252–64. doi: 10.1038/nrc3239
166. Toi Y, Sugawara S, Kawashima Y, Aiba T, Kawana S, Saito R, et al. Association of Immune-Related Adverse Events With Clinical Benefit in Patients With Advanced Non-Small-Cell Lung Cancer Treated With Nivolumab. *Oncologist* (2018) 23(11):1358–65. doi: 10.1634/theoncologist.2017-0384
167. Dupont R, Bérard E, Puisset F, Comont T, Delord JP, Guimbaud R, et al. The Prognostic Impact of Immune-Related Adverse Events During anti-PD1 Treatment in Melanoma and non-Small-Cell Lung Cancer: A Real-Life Retrospective Study. *Oncoimmunology* (2020) 9(1):1682383. doi: 10.1080/2162402X.2019.1682383
168. Naidoo J, Schindler K, Querfeld C, Busam K, Cunningham J, Page DB, et al. Autoimmune Bullous Skin Disorders With Immune Checkpoint Inhibitors Targeting PD-1 and PD-L1. *Cancer Immunol Res* (2016) 4(5):383–9. doi: 10.1158/2326-6066.CIR-15-0123
169. Robert C, Ribas A, Hamid O, Daud A, Wolchok JD, Joshua AM, et al. Durable Complete Response After Discontinuation of Pembrolizumab in Patients With Metastatic Melanoma. *J Clin Oncol* (2018) 36(17):1668–74. doi: 10.1200/JCO.2017.75.6270
170. Gauci ML, Lanoy E, Champiat S, Caramella C, Ammari S, Aspeslagh S, et al. Long-Term Survival in Patients Responding to Anti-PD-1/PD-L1 Therapy and Disease Outcome Upon Treatment Discontinuation. *Clin Cancer Res* (2019) 25(3):946–56. doi: 10.1158/1078-0432.CCR-18-0793
171. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. *Am J Respir Crit Care Med* (2016) 194(3):265–75. doi: 10.1164/rccm.201604-0801CI
172. Nguyen M, Islam MR, Lim SW, Sahu A, Tamjid B. Pembrolizumab Induced Ocular Hypotony With Near Complete Vision Loss, Interstitial Pulmonary Fibrosis and Arthritis. *Front Oncol* (2019) 9:944. doi: 10.3389/fonc.2019.00944
173. Fabre A, Nicholson AG. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *N Engl J Med* (2020) 382(8):780. doi: 10.1056/NEJMc1917224
174. Reguera-Nuñez E, Xu P, Chow A, Man S, Hilberg F, Kerbel RS. Therapeutic Impact of Nintedanib With Paclitaxel and/or a PD-L1 Antibody in Preclinical Models of Orthotopic Primary or Metastatic Triple Negative Breast Cancer. *J Exp Clin Cancer Res* (2019) 38(1):16. doi: 10.1186/s13046-018-0999-5
175. Atchley WT, Alvarez C, Saxena-Beem S, Schwartz TA, Ishizawar RC, Patel KP, et al. Immune Checkpoint Inhibitor-Related Pneumonitis in Lung Cancer: Real-World Incidence, Risk Factors, and Management Practices Across Six Health-Care Centers in North Carolina. *Chest* (2021) S0012-3692(21):00340–8. doi: 10.1016/j.chest.2021.02.032
176. Isono T, Kagiyama N, Takano K, Hosoda C, Nishida T, Kawate E, et al. Outcome and Risk Factor of Immune-Related Adverse Events and Pneumonitis in Patients With Advanced or Postoperative Recurrent non-Small Cell Lung Cancer Treated With Immune Checkpoint Inhibitors. *Thorac Cancer* (2021) 12(2):153–64. doi: 10.1111/1759-7714.13736

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

REVIEW
published: 31 May 2021
doi: 10.3389/fonc.2021.603658

Toxicities of Immunotherapy for Small Cell Lung Cancer

Yang Fu[†], *Yue Zheng*[†], *Pei-Pei Wang and Zhen-Yu Ding*[*]

Department of Biotherapy, Cancer Center, West China Hospital, West China Medical School, Sichuan University, Chengdu, China

Small cell lung cancer (SCLC), composing 15–20% of lung cancer, is a fatal disease with extremely poor prognosis. In the past two decades, etoposide platinum doublet chemotherapy remained the only choice of therapy, with disappointing overall survival ≤1 year for the metastatic disease. Novel treatments including immunotherapy are urgently needed and extensively explored. Recently, in two phase III trials, atezolizumab and durvalumab were shown to bring survival benefit to patients. While immunotherapy brings better outcome, it is accompanied by adverse events different from traditional treatments. Although these immune-related adverse events (irAEs) are generally mild and can be managed, some irAEs (myocarditis, pneumonitis) may be severe and even life-threatening. Accompanying with the increasing application of immunotherapy in clinical practice, the irAEs should not be overlooked. In this review, the irAEs profile in clinical trials of immunotherapy for SCLC will be summarized, also its unique features compared with irAEs in other malignancies will be explored. This review may be helpful for the appropriate clinical use of immunotherapy for SCLC.

Keywords: small cell lung cancer, immune-related adverse events, neuromuscular toxicity, immune checkpoint inhibitors, death

OPEN ACCESS

Edited by:
Udo S. Gaipl,
University Hospital Erlangen, Germany

Reviewed by:
Takaaki Tokito,
Kurume University, Japan
Jie Li,
Washington University in St. Louis, United States
Yu Zhang,
Guizhou Provincial People's Hospital, China

***Correspondence:**
Zhen-Yu Ding
dingzhenyu@scu.edu.cn

[†]*These authors have contributed equally to this work*

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Oncology

Received: *07 September 2020*
Accepted: *11 May 2021*
Published: *31 May 2021*

Citation:
Fu Y, Zheng Y, Wang P-P and Ding Z-Y (2021) Toxicities of Immunotherapy for Small Cell Lung Cancer. Front. Oncol. 11:603658. doi: 10.3389/fonc.2021.603658

INTRODUCTION

Small cell lung cancer (SCLC) is a fatal disease, with a 5-year survival less than 7% (1, 2). Platinum doublet chemotherapy, usually combined with etopside, remains the standard-of-care for decades (3–5). Patients have a high initial response rates of 60%, while most relapse within 6 months and decease within 10 months (5–7).

Immune checkpoint helps to maintain the immune stability, while during carcinogenesis it is hijacked by tumors to evade immune surveillance. Immune checkpoint inhibitors (ICIs) including antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA-4) or programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) act to reverse the immunosuppression imparted by tumor cells, either by blocking CTLA-4 pathway or interrupting the interaction between PD-1 and PD-L1 (8, 9). ICI has been widely used in a variety of malignancies, including non-small cell lung cancer, melanoma, triple-negative breast cancer, and non-Hodgkin lymphoma etc. (8, 10–12). Especially in SCLC which has a notorious reputation of poor prognosis, PD-L1 inhibitors including atezolizumab and durvalumab show promising efficacy (9, 13).

While immunotherapy brings better outcome, it is accompanied by adverse events different from traditional treatments. Mounted immune response is directed to not only tumor, but also normal tissues and causes immune-related adverse events (irAEs) (14). Although these irAEs are generally mild and can be managed, some irAEs (myocarditis, pneumonitis) may be severe and even life-threatening (15, 16).

Recently, in two phase III trials (IMPower 133 and CASPIAN), atezolizumab and durvalumab were shown to bring survival benefit to patients (9, 13). Accompanying with the increasing application of immunotherapy in clinical practice, the irAEs should not be overlooked. In SCLC, due to the poor life expectance, also the high incidence of neurological complications, it is intriguing to ask whether the irAEs would be different from other tumors. This review provided a brief summary of irAEs from published clinical trials in the field of SCLC treatment.

OVERVIEW OF SCLC

SCLC is a distinct form of lung cancer, with dominant component of neuroendocrine tumor cells, and early and frequent distant metastases (17). Mutations in p53 gene (TP53) and retinoblastoma1 gene (RB1) are universal genetic events in SCLC (18). Studies also showed although SCLC harbors a high tumor mutational burden, tumor infiltrating lymphocytes are scarce in the microenvironment (19). Neither SCLC tends to express PD- L1, as it is found ≤20% tumor cells express PD-L1 (>1%) (20, 21).

Etoposide plus platinum combination chemotherapy is recommended for metastatic SCLC patients (extensive stage, ES). For those in the limited stage (LS, non-metastatic), chest radiation at a dose of 45 Gy administered in 1.5 Gy fractions twice-daily for 30 days with chemotherapy, followed by prophylactic cranial irradiation is recommended (22). For relapsed or platinum-refractory SCLC, topotecan was the only approved drug by FDA in second-line treatment (23). Meanwhile, clinical trials on inhibitors of PARP, EZH2, WEE1, DLL3, and Aurora kinase etc. are all actively ongoing at this time, which is beyond the scope of this review (24). Here, we restrict our focus on the clinical data of the immunotherapy for SCLC.

DATA ACQUISITION

All relevant articles are identified by using the keywords "small cell lung cancer," "SCLC," "immunotherapy," "CTLA-4," "PD-1," "PD-L1," "clinical trial" on Pubmed, clinicaltrials.gov, Embase and Web of science. Abstracts and presentation were also reviewed from major conference including ASCO (https://www.asco.org/) and ELCC (https://www.esmo.org/) from 2015 to 2020.The literature or abstract was viewed, and those with only protocol design or lack of AEs results were excluded. Finally, fifteen studies involving ICIs for SCLC therapy with full description of the AEs were selected.

LANDSCAPE OF IMMUNOTHERAPY FOR SCLC

First Line

The first one being tested was ipilimumab, a fully human monoclonal antibody for CTLA-4. Following a successful phase II study (NCT00527735), a phase III trial (CA184-156) investigated the efficacy and safety of ipilimumab combined with chemotherapy (25, 26). However, the addition of ipilimumab failed to demonstrate any improvement in neither OS, ORR, nor duration of response. IMPower133 was a phase III trial to investigate the efficiency of atezolizumab (a humanized monoclonal PD-L1 antibody) combined with chemotherapy. The combination regimen showed benefit in both PFS (5.2 m *vs* 4.7 m) and OS (12.3 m vs 10.3 m) (9). A similar good outcome was also achieved by durvalumab, another high-affinity human IgG1 monoclonal antibody for PD-L1. In the phase III CASPIAN study, the combination of durvalumab and chemotherapy achieved an OS of 13.3 m (13). The results of PD-1 antibodies seemed less favorably. KEYNOTE-604 was a phase III trial to investigate the efficacy of pembrolizumab (a humanized monoclonal IgG4 antibody) in ES-SCLC patients (27). The results showed that pembrolizumab significantly improves PFS, while OS narrowly had significant difference. Nivolumab is another monoclonal antibody for PD-1. A phase II randomized study (EA5161) evaluated the combination of nivolumab with EP for the ES-SCLC patients. Preliminary results were reported in ASCO 2020, nivolumab significantly improved PFS (5.5 and 4.7 m, p = 0.047) in treated population while OS was no statistical difference (11.3 and 8.5 m, p = 0.14) (28).

Maintenance

A phase III study (CHECKMATE-451) tested either nivolumab monotherapy, or nivolumab plus ipilimumab, or placebo as maintenance therapy after platinum-based first-line chemotherapy. However, nivolumab has a shorter OS compared with placebo (29). Another phase II, single-arm trial (NCT02359019) studied pembrolizumab as maintenance therapy. The 1-year PFS and OS rates were only 13 and 37% respectively (30).

Second Line

Salvage therapy for the relapsed SCLC is more difficult. At least two randomized controlled trial tested the efficacy of immunotherapy. In IFCT-1603 study, atezolizumab monotherapy was compared with topotecan or re-induction of initial chemotherapy (31). A phase III trial CHECKMATE-331 investigated the efficacy and safety of nivolumab monotherapy in the second line of therapy (32). Both trials demonstrated no superiority of immunotherapy over traditional chemotherapy.

Monotherapy seems inappropriate, and following studies tested combination therapy. In a multi-center, single arm, phase II study (NCT02551432), pembrolizumab was combined with chemotherapy drug paclitaxel (33). In another phase II study (NCT02484404), Durvalumab was tested in combination

with olaparib (PARP inhibitors) (34). The preliminary reports of these small sample sized showed promising results.

Third Line or Later

Some early, small-scale studies were performed in these very late-staged patients. Nivolumab was the first ICIs approved by FDA for third-line therapy of SCLC, based on the results of CHECKMATE-032 in 2016 (35). KEYNOTE-028 (NCT02054806) and KEYNOTE-158 studies both tested pembrolizumab in the third line therapy. Based on the results, pembrolizumab monotherapy was approved to SCLC in third-line or later (36, 37).

TOXICITIES

Ipilimumab

In the phase II study (NCT00527735), ipilimumab plus chemotherapy led to higher frequency of AE, either any grade (49 and 43%) or ≥grade 3 (G3, 46 and 30%) AE than chemotherapy alone. Common severe irAEs included G4 diarrhea (n = 1), G3 colitis (n = 1), G4 hepatitis (n = 2), and death (n = 1) attributed to hepatotoxicity (25). In the following phase III study (CA184-156), the combination also had higher incidence of irAEs of all grade (57% in ipilimumab group, and 28% in control) or ≥G3 (20 and 2%). Gastrointestinal and skin toxicity (34 and 29%) were the most common irAEs in ipilimumab group. Endocrine irAEs occurred in 10% of patients in the ipilimumab group including hypothyroidism (3%), hyperthyroidism (2%), hypophysitis (1%), and adrenal insufficiency (1%). Two deaths due to colitis (n = 1) and ulcerative colitis (n = 1) were reported. The incidence of nervous system irAEs was 4% which involved 2% of peripheral sensory neuropathy (26).

Atezolizumab

In IMPower133 study, the incidence of AEs was 39.9% in the atezolizumab group and 24.5% in the control group. The most common irAEs was rash (18.7%), hypothyroidism (12.6%), hepatitis (7.1%), and hyperthyroidism (5.6%). The less frequent (≤5%) of irAEs were pneumonitis (2.0%), colitis (1.5%), rhabdomyolysis (1.0%), severe cutaneous reaction (1.0%), pancreatitis (0.5%), nephritis (0.5%), hypophysitis (0.5%), and diabetes mellitus (0.5%). Severe irAEs (≥G3) were rash (2%), hepatitis (1.5%), infusion-related reaction (2%), and colitis (1%) (9). In IFCT-1603 study, the incidence of AE, including 12.5% musculoskeletal or connective tissue disorders, 18.8% gastrointestinal disorders, 4.2% hepatitis, 4.2% colitis, 6.3% arthralgia, 2.1% hyperthyroidism and 2.1% hypothyroidism. No≥G3 irAE was reported (31).

Durvalumab

In CASPIAN study, three groups were enrolled, including durvalumab and chemotherapy, combo immunotherapy durvalumab and tremelimumab with chemotherapy, and chemotherapy. The incidences of ≥G3 AEs were 62.3, 70.3, and 62.8% in each of these groups. G5 AEs were 4.9, 10.2 and 5.6%, respectively. For G3–4 irAEs, the incidence was 5% in durvalumab group and ≤1% in control group, and it was 20 and 3% for any grade. Endocrine-related adverse events were the most common irAEs including hypothyroidism (9%), hyperthyroidism (5%), thyroiditis (4%), type 1 diabetes mellitus (T1DM, 2%), rash (2%), adrenal insufficiency (<1%). The incidence of immune-related pneumonitis was 3% of all grades and 1% of G3–4. There were also reports of immune-related colitis, pancreatic events, and hepatic events. Two immune-related deaths due to hepatotoxicity (n = 1) and pneumonitis (n = 1) were reported (13).

The phase II study (NCT02484404) was an exploratory study. In this study, nine patients (45%) had G3–4 TRAEs including anemia, lymphopenia, thrombocytopenia, and hypophosphatemia. In five patients' hypothyroidism was observed attributed to immunotherapy (34).

Pembrolizumab

In the 1st line setting (KEYNOTE-604), when pembrolizumab used with chemotherapy, the incidence of irAEs (any grade) was 53%, compared with 84% in the control group. Hypothyroidism (10.3%), hyperthyroidism (6.7%), and pneumonitis (4%) were the most common. G3 irAEs occurred in only 7.2% of patients, and no G4–5 irAEs occurred (27). The only maintenance therapy study (NCT02359019) reported three categories of irAEs, rash (n = 8), hypothyroidism (n = 4), T1DM with diabetic ketoacidosis (n = 1) (30). In late lines of pembrolizumab monotherapy (KEYNOTE-028), the most frequent AEs were arthralgia, asthenia, and rash (n = 4 each) as well as diarrhea and fatigue (n = 3 each). Only two patients experienced G3 AE. One had G3 bilirubin elevation, and the other was a lethal case of colitis concurrent with G3 bilirubin elevation. Another similar study (KEYNOTE-158) reported AE of any grade and G3–5 were 33.7 and 5.1%, respectively. Most common irAEs included hypothyroidism (12.1%), hyperthyroidism (6.5%), severe skin reactions (2.8%), adrenal insufficiency, nephritis, pancreatitis, and pneumonitis (1.9% each). G3 AE occurred in six patients, mostly manageable, and no fatal irAE was reported (36, 37). In an early-phase exploratory study (NCT02551432), AEs occurred in all patients. Pneumonia (19.2%), T1DM (7.7%), rush (7.7%), and hypothyroidism (3.9%) were among the most common irAEs. Four patients discontinued treatment (33).

Nivolumab

In the study CheckMate-331, TRAEs of all grade (≥G3) occurred in 55% (14%) of nivolumab group, and 90% (73%) of chemotherapy group. There were five treatment-related death, two with nivolumab and three with chemotherapy. The incidences of irAEs (all grade) of endocrine, skin, gastrointestinal, liver, lung and kidney were 12, 11, 7, 5, 1 and <1% respectively (32). In study CheckMate-032, skin toxicity (any grade, 21.1%) was the most common. Other irAEs including endocrine, gastrointestinal, hepatic, pulmonary and renal toxicity were 9.2, 6.4, 4.6, 1.8 and 0.9% respectively. The incidence of G3–4 pneumonitis, rash, aspartate aminotransferase increase was 1.8, 0.9, and 0.9%, respectively.

One immune-related encephalitis (grades 3–4) was reported. One death due to checkpoint inhibitor pneumonitis was noted (35). While in study CheckMate-451, the most frequently occurred serious AEs was pneumonitis (3.8%). Other serious included colitis (3.6%), endocrine (2.5%), hepatitis (0.7%), and nervous system (3.7%). Myocarditis was reported in two cases (0.7%) in group. AEs in nervous system were encephalitis (n = 2), myasthenia gravis (n = 1), and Guillain–Barré syndrome (n = 1). There were eight treatment-related deaths in the nivolumab group versus one in the control group (29). In study EA5161, the incidence of grade 3/4 TRAEs was 77% *vs* 62%. Treatment-related fatal adverse events were similar in the two groups (n = 9 and 7) (28).

DISCUSSION

This review summarized 15 trials in SCLC immunotherapy, including phase III (n = 5) and phase I/II trials (n = 10, **Figure 1**). Among them, IMpower133, CASPIAN, CA184-156, KEYNOTE-604 and EA5161 evaluated the efficacy of atezolizumab, durvalumab, ipilimumab, pembrolizumab, or nivolumab, when combined with chemotherapy. CheckMate-331 and IFCT-1603 tested the efficacy of nivolumab and atezolizumab monotherapy in 2nd-line. Six trials investigated efficacy and safety of ICIs in later-line or maintenance treatment. Most trials were performed in ICIs combined with chemotherapy. More studies are ongoing (**Table 1**).

When all the 15 trials combined for analysis, PD-1/PD- L1 inhibitors had a better tolerance than CTLA-4 inhibitors (**Figure 2A**). Dermal events (23.8%), colitis (5.6%), hepatitis (4.3%), hypophysitis (0.4%), myasthenic (0.3%), and myocarditis (0.3%) were more common with CTLA-4 inhibitors, whereas pneumonitis (3.7%), thyroid events (14.3%), pancreatic events (1.0%), and rheumatic events (0.2%) were more common with PD-1/PD- L1 inhibitors. It was also interesting to observe the difference of toxicities between PD-1 and PD-L1 inhibitors. Generally, the rate of irAE by PD-L1 inhibitors was lower than that of PD-1 inhibitors, including pneumonitis (4.3% *vs* 2.1%), dermal events (12.4% *vs* 8.1%), colitis (2.3% *vs* 1.7%), adrenal insufficiency (0.7% *vs* 0.2%), nephritis (0.6% *vs* 0.2%), myositis (0.4% *vs* 0), rheumatic disease (0.4% *vs* 0), hypophysitis (0.2% *vs* 0), and myocarditis (0.1% *vs* 0, **Figure 2B**).

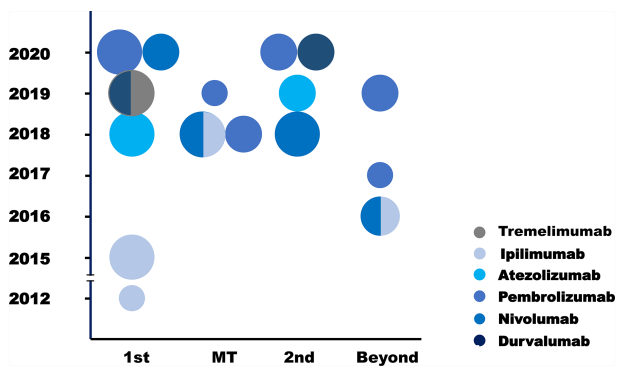

FIGURE 1 | Clinical trials of ICIs in SCLC. Each circle standed for one trial. The different circle areas represented phase I, phase II and phase III trials respectively, and different color meant different drugs. Y axis stood for the year of the publication of each trial, and X trials was the clinical situation where each trial was performed. 1st, first line; MT, maintenance therapy; 2nd, second line; Beyond, later line.

In CheckMate-451 trial, the frequency of irAEs of the nivolumab plus ipilimumab group was higher than that of nivolumab group. Not only occurrence, but the severity (frequency of ≥G3 irAEs) was also worse in the combo therapy. Similarly, immunotherapy plus chemotherapy showed better efficacy in IMpower133 and CASPIAN study, but at the price of more irAE events. Furthermore, adding ipilimumab to this combination brought no additional benefit, but significantly higher toxicities.

The exact pathophysiology of irAEs is unclear, but the toxicity between CTLA-4 and PD-L1/PD-1 inhibitors is quite different. Pituitary cells translocate to express CTLA-4. The CTLA-4 antibody binds to the pituitary and induces lymphocyte infiltration, and tissue destruction is triggered (38, 39). PD-L1 was highly expressed on the surface of myocardial cells in two patients with immune myocarditis, leading to the recognition of myocardial and tumor surface antigens by the same T cell clone, which ultimately cause destruction of organ (16). In Keynote001 trial, 10 patients were newly diagnosed with hypothyroidism after receiving pembrolizumab, and eight of them were diagnosed with anti–thyroid antibody (40). It was suggested that irAE may be associated with autoantibodies. CTLA-4 Inhibitors reduce the number and activity of Treg cells, resulting in increased activity of TH17 cells and increased IL-17 release, contributing to the onset of immune-related colitis (41–43).

Because SCLC is a kind of neuroendocrine tumor, also autoimmune encephalitis was frequently reported for this disease, we proposed there might be an increased occurrence of neuromuscular toxicity during the immunotherapy. To test this hypothesis, we performed a pooled analysis of the reported neuromuscular toxicity from the above trials. We found less occurrence in the control group, compared with that in immunotherapy group (**Figure 3A**). To confirm this observation, we performed a similar analysis in NSCLC trials. Conversely, immunotherapy and control groups had comparable toxicity (**Figure 3B**). This further supported the notion the neuromuscular toxicity of immunotherapy was specifically restricted in SCLC.

We paid special attention to the fatal toxicities. Immunotherapy and chemotherapy had a similar incidence of treatment-related death for SCLC patients. Totally 36 and 27 death events occurred from seven head-to-head trials respectively (**Figure 4**). From all the trials, the most common reason of reported death were sepsis (n = 7) and pneumonitis (n = 7), followed by multiorgan failure (n = 3), hematologic

TABLE 1 | Ongoing trial with PD-1/PD-L1 inhibitors in the treatment of small cell lung cancer.

Trial		Treatment	Phase	Intervention	Population	Patients	Therapy	Status
NCT02580994	REACTION	First line	II	RCT	ES-SCLC	125	Pembrolizumab + EC/EP *vs* EC/EP	Recruiting
NCT02402920		First line	I	Parallel	SCLC	80	Pembrolizumab + Concurrent Chemo/Radiotherapy	Recruiting
NCT02963090		Second line	II	RCT	Relapsed	98	Pembrolizumab *vs* Topotecan	Active
NCT03371979		Second line	I/II	Single arm	Relapsed	84	Pembrolizumab + Pegzilarginase(AEB1102)	Active
NCT04358237	LUPER	Second line	I/II	Single arm	Relapsed	42	Pembrolizumab + Lurbinectedin (PM01183)	Not yet recruiting
NCT03253068		Second line	II	Single arm	Relapsed	25	Pembrolizumab + Amurubicin	Recruiting
NCT04173325		Second line	I	Single arm	Relapsed	10	Nivolumab + Irinotecan	Recruiting
NCT03406715		Second line	II	Multicohort	SCLC	40	Nivolumab+ Ipilimumab+ Dendritic Cell p53 Vac	Recruiting
NCT03083691	BIOLUMA	Second line	II	Multicohort	Relapsed	106	Nivolumab + Ipilimumab	Recruiting
NCT03670056		Second line	II	Single arm	Relapsed	40	Nivolumab + Ipilimumab	Recruiting
NCT03728361		Second line	II	Multicohort	Relapsed	53	Nivolumab + Temozolomide	Recruiting
NCT03575793		Second line	I/II	Parallel	Relapsed	55	Nivolumab + Ipilimumab + Plinabulin	Recruiting
NCT03662074		Second line	II	Single arm	Relapsed	14	Nivolumab + Gemcitabine	Active
NCT02247349		Second line	I/II	Parallel	Relapsed	172	BMS-986012 + Nivolumab *vs* BMS-986012	Active
NCT03325816		Maintenance	I/II	Single arm	ES-SCLC	9	Nivolumab + Lutathera	Active
NCT03958045		Maintenance	II	Single arm	SCLC	36	Nivolumab + Rucaparib	Recruiting
NCT02046733	STIMULI	Maintenance	II	Parallel	LS-SCLC	264	Nivolumab + Ipilimumab After Chemo-radiotherapy	Active
NCT04189094		First line	II	RCT	LS-SCLC	140	Sintilimab + EC/EP + RT *vs* EC/EP + RT	Not yet recruiting
NCT04192682		Second line	II/III	Single arm	Relapsed	40	Sintilimab + Anlotinib after Chemo-radiotherapy	Not yet recruiting
NCT04055792		Beyond	II	RCT	ES-SCLC	52	Sintilimab + Anlotinib *vs* Anlotinib	Recruiting
NCT03983759		Maintenance	II	Single arm	ES-SCLC	40	Sintilimab After Chemotherapy + R-CIK	Recruiting
NCT04449861	ORIENTAL	First line	IIIb	Single arm	ES-SCLC	300	Durvalumab + EC/EP	Not yet recruiting
NCT03509012	CLOVER	First line	I	Multicohort	SCLC	360	Durvalumab ± Tremelimumab + EC/EP + Radiotherapy	Active
NCT04361825		Second line	II	Single arm	Relapsed	45	Durvalumab + AZD6738	Recruiting
NCT02701400		Second line	II	Parallel	Relapsed	18	Durvalumab + Tremelimumab ± RT	Active
NCT02937818		Second line	II	Parallel	Refractory*	72	Durvalumab + Tremelimumab *vs* AZD1775 + carboplatin *vs* AZD6738 + Olaparib	Active
NCT04314297		Maintenance	II	Single arm	ES-SCLC	33	Durvalumab + Anlotinib after Chemo-radiotherapy	Not yet recruiting
NCT04472949		Maintenance	II	Single arm	ES-SCLC	46	RT+ Durvalumab after Durvalumab + EC	Not yet recruiting
NCT03585998		Maintenance	II	Single arm	LS-SCLC	51	Durvalumab after Chemo-radiotherapy + Durvalumab	Active
NCT03703297	ADRIATIC	Maintenance	III	RCT	LS-SCLC	600	4Durvalumab + 4Placebo;Durvalumab 4Durvalumab + 4Tremelimumab;Durvalumab 4 Placebo; Placebo	Recruiting
NCT03923270		Maintenance	I	Parallel	ES-SCLC	54	RT followed by Durvalumab or Durvalumab + Tremelimumab or Olaparib	Recruiting
NCT04256421	SKYSCRAPER-02	First line	III	RCT	ES-SCLC	400	Atezolizumab + EC+ Tiragolumab *vs* Atezolizumab + EC	Recruiting
NCT03041311		First line	II	RCT	ES-SCLC	105	Atezolizumab + EC + Trilaciclib(G1T28) *vs* Atezolizumab + EC	Active
NCT03540420		First line	II	RCT	LS-SCLC	212	Atezolizumab *vs* standard care after Chemo-radiotherapy	Recruiting
NCT04028050	MAURIS	First line	IIIb	RCT	ES-SCLC	150	Atezolizumab + EC	Recruiting
NCT04422210		First line	Ib	Single arm	ES-SCLC	62	Venetoclax + Atezolizumab + EC	Recruiting
NCT03262454		Second line	II	Single arm	Relapsed	35	Radiotherapy Followed by Atezolizumab	Recruiting
NCT03059667		Second line	II	RCT	SCLC	70	Atezolizumab *vs* Topotecan/Etoposide/Carboplatin	Active
NCT04402788	RAPTOR	Second line	II/III	RCT	ES-SCLC	324	Atezolizumab + RT *vs* Atezolizumab	Not yet recruiting
NCT04308785		Maintenance	II	RCT	LS-SCLC	242	Atezolizumab + EC/EP+ radiotherapy *vs* EC/EP + radiotherapy	Not yet recruiting
NCT04462276	TREASURE	Maintenance	II	RCT	ES-SCLC	104	Atezolizumab + RT *vs* Atezolizumab after Atezolizumab + EC	Not yet recruiting
NCT04373369		Maintenance	II	Single arm	ES-SCLC	33	Atezolizumab + Vorolanib	Not yet recruiting
NCT03811002		First line	II/III	RCT	LS-SCLC	506	Atezolizumab + EC/EP + RT *vs* EC/EP + RT	Recruiting
NCT04418648		consolidation	II	RCT	LS-SCLC	170	Toripalimab *vs* Observation	Not yet recruiting
NCT04363255		Maintenance	II	Single arm	ES-SCLC	20	EC/EP followed by Toripalimab + Anlotinib	Not yet recruiting
NCT04012606		First line	III	RCT	ES-SCLC	420	Toripalimab(JS001) + EC/EP *vs* EC/EP	Recruiting

**Platinum Refractory ES-SCLC.*

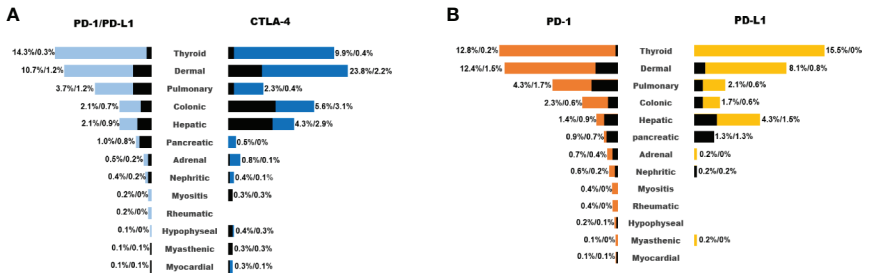

FIGURE 2 | List of common irAEs for different ICIs (**A**: PD-1/PD-L1 inhibitors vs CTLA-4 inhibitors; **B**: PD-1 inhibitors vs PD-L1 inhibitors). Colored and black bar indicated the occurrence of irAEs of any grade and ≥grade 3.

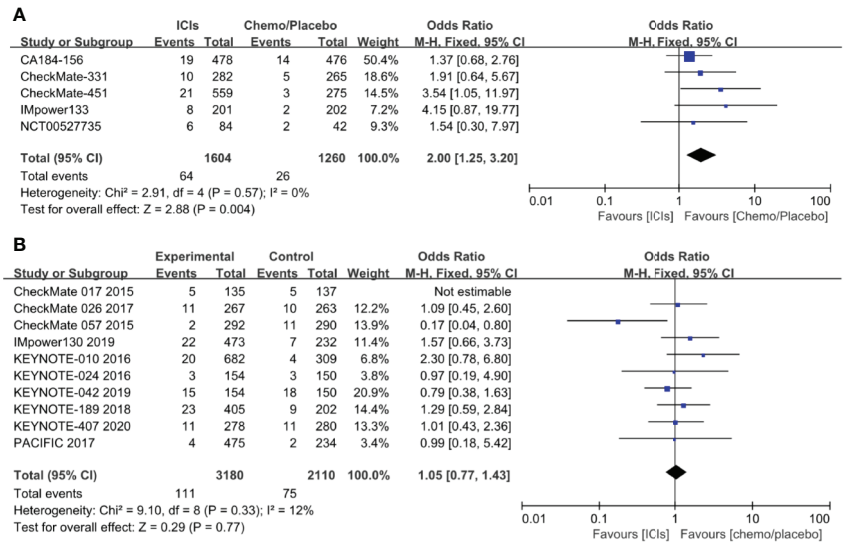

FIGURE 3 | Pooled analysis of neuromuscular toxicity in SCLC **(A)** and NSCLC **(B)**.

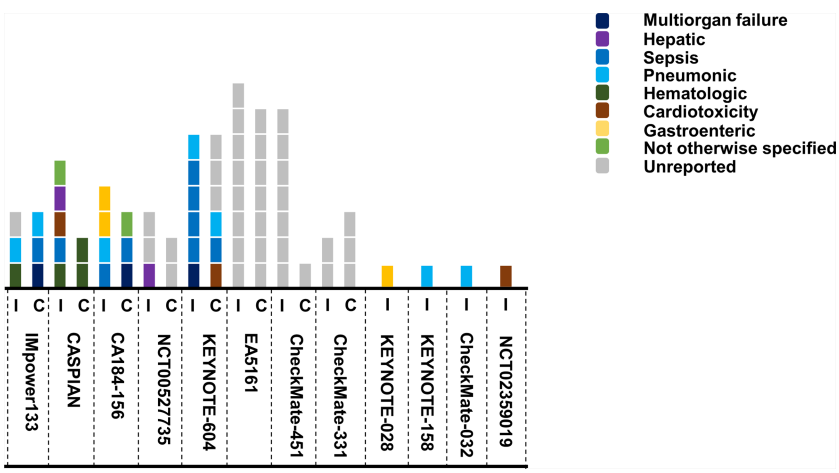

FIGURE 4 | Summary of death events in SCLC trials. Each square represented one event, and different color stood for the causes of death. I, ICIs group; C, chemo/placebo group.

disease (n = 2), cardiotoxicity (n = 3), hepatitis (n = 3), and other unspecified cause (n = 2).

CONCLUSION

This paper reviewed the current status of immunotherapy in SCLC. Immunotherapy brings new hope to this formidable disease, and also unprecedented toxicity profile. Immunotherapy combined with either chemotherapy or other immunotherapies, led to higher occurrence of AE than immunotherapy alone. The toxicity of immunotherapy in SCLC seemed to be different with those in NSCLC, esp. for neuromuscular toxicity. This review may be helpful for the appropriate clinical use of immunotherapy for SCLC.

AUTHOR CONTRIBUTIONS

Z-YD and YZ contributed conception. YF drafted the manuscript, Z-YD reviewed the manuscript, and P-PW edited the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Byers LA, Rudin CM. Small Cell Lung Cancer: Where Do We Go From Here? *Cancer* (2015) 121(5):664–72. doi: 10.1002/cncr.29098
2. Gaspar LE, McNamara EJ, Gay EG, Putnam JB, Crawford J, Herbst RS, et al. Small-Cell Lung Cancer: Prognostic Factors and Changing Treatment Over 15 Years. *Clin Lung Cancer* (2012) 13(2):115–22. doi: 10.1016/j.cllc.2011.05.008
3. Socinski MA, Smit EF, Lorigan P, Konduri K, Reck M, Szczesna A, et al. Phase III Study of Pemetrexed Plus Carboplatin Compared With Etoposide Plus Carboplatin in Chemotherapy-Naive Patients With Extensive-Stage Small-Cell Lung Cancer. *J Clin Oncol* (2009) 27(28):4787–92. doi: 10.1200/JCO.2009.23.1548
4. Früh M, De Ruysscher D, Popat S, Crinò L, Peters S, Felip E, Esmo Guidelines Working Group. Small-Cell Lung Cancer (SCLC): ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. *Ann Oncol* (2013) 24 Suppl 6:vi99–105. doi: 10.1093/annonc/mdt178
5. Farago Anna F, Keane Florence K. Current Standards for Clinical Management of Small Cell Lung Cancer. *Transl Lung Cancer Res* (2018) 7:69–79. doi: 10.21037/tlcr.2018.01.16
6. Jones GS, Elimian K, Baldwin DR, Hubbard RB, McKeever TM. A Systematic Review of Survival Following Anti-Cancer Treatment for Small Cell Lung Cancer. *Lung Cancer* (2020) 141:44–55. doi: 10.1016/j.lungcan.2019.12.015
7. Demedts IK, Vermaelen KY, van Meerbeeck JP. Treatment of Extensive-Stage Small Cell Lung Carcinoma: Current Status and Future Prospects. *Eur Respir J* (2010) 35:202–15. doi: 10.1183/09031936.00105009
8. Mok TSK, Wu Y-L, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab Versus Chemotherapy for Previously Untreated, PD-L1-expressing, Locally Advanced or Metastatic Non-Small-Cell Lung Cancer (KEYNOTE-042): A Randomised, Open-Label, Controlled, Phase 3 Trial. *Lancet* (2019) 393:1819–30. doi: 10.1016/S0140-6736(18)32409-7
9. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-Line Atezolizumab Plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. *N Engl J Med* (2018) 379:2220–9. doi: 10.1056/NEJMoa1809064
10. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab Plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med* (2018) 378:2078–92. doi: 10.1056/NEJMoa1801005
11. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med* (2018) 379:2108–21. doi: 10.1056/NEJMoa1809615
12. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 Blockade With Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma. *N Engl J Med* (2015) 372:311–9. doi: 10.1056/NEJMoa1411087
13. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab Plus Platinum-Etoposide Versus Platinum-Etoposide in First-Line Treatment of Extensive-Stage Small-Cell Lung Cancer (CASPIAN): A Randomised, Controlled, Open-Label, Phase 3 Trial. *Lancet* (2019) 394:1929–39. doi: 10.1016/S0140-6736(19)32222-6
14. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated With Immune Checkpoint Blockade. *N Engl J Med* (2018) 378:158–68. doi: 10.1056/NEJMra1703481
15. Hu Y-B, Zhang Q, Li H-J, Michot JM, Liu H-B, Zhan P, et al. Evaluation of Rare But Severe Immune Related Adverse Effects in PD-1 and PD-L1 Inhibitors in Non-Small Cell Lung Cancer: A Meta-Analysis. *Transl Lung Cancer Res* (2017) 6:S8–20. doi: 10.21037/tlcr.2017.12.10
16. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant Myocarditis With Combination Immune Checkpoint Blockade. *N Engl J Med* (2016) 375:1749–55. doi: 10.1056/NEJMoa1609214
17. Gazdar AF, Bunn PA, Minna JD. Small-Cell Lung Cancer: What We Know, What We Need to Know and the Path Forward. *Nat Rev Cancer* (2017) 17 (12):725–37. doi: 10.1038/nrc.2017.87
18. George J, Lim JS, Jang SJ, Cun Y, Ozretić L, Kong G, et al. Comprehensive Genomic Profiles of Small Cell Lung Cancer. *Nature* (2015) 524:47–53. doi: 10.1038/nature14664
19. Iams WT, Shiuan E, Meador CB, Roth M, Bordeaux J, Vaupel C, et al. Improved Prognosis and Increased Tumor-Infiltrating Lymphocytes in Patients Who Have Sclc With Neurologic Paraneoplastic Syndromes. *J Thorac Oncol* (2019) 14:1970–81. doi: 10.1016/j.jtho.2019.05.042
20. Yu H, Batenchuk C, Badzio A, Boyle TA, Czapiewski P, Chan DC, et al. Pd-L1 Expression by Two Complementary Diagnostic Assays and Mrna In Situ Hybridization in Small Cell Lung Cancer. *J Thorac Oncol* (2017) 12:110–20. doi: 10.1016/j.jtho.2016.09.002
21. Zhao X, Kallakury B, Chahine JJ, Hartmann D, Zhang Y, Chen Y, et al. Surgical Resection of SCLC: Prognostic Factors and the Tumor Microenvironment. *J Thorac Oncol* (2019) 14:914–23. doi: 10.1016/j.jtho.2019.01.019
22. Turrisi AT, Kim K, Blum R, Sause WT, Livingston RB, Komaki R, et al. Twice-Daily Compared With Once-Daily Thoracic Radiotherapy in Limited Small-Cell Lung Cancer Treated Concurrently With Cisplatin and Etoposide. *N Engl J Med* (1999) 340:265–71. doi: 10.1056/NEJM199901283400403
23. Ardizzoni A, Hansen H, Dombernowsky P, Gamucci T, Kaplan S, Postmus P, et al. Topotecan, a New Active Drug in the Second-Line Treatment of Small-Cell Lung Cancer: A Phase II Study in Patients With Refractory and Sensitive Disease. The European Organization for Research and Treatment of Cancer Early Clinical Studies Group and New Drug Development Office, and the Lung Cancer Cooperative Group. *J Clin Oncol* (1997) 15:2090–6. doi: 10.1200/JCO.1997.15.5.2090
24. Sabari Joshua K, Lok Benjamin H, Laird James H, Poirier John T, Rudin Charles M. Unravelling the Biology of SCLC: Implications for Therapy. *Nat Rev Clin Oncol* (2017) 14:549–61. doi: 10.1038/nrclinonc.2017.71
25. Reck M, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in Combination With Paclitaxel and Carboplatin as First-Line Therapy in Extensive-Disease-Small-Cell Lung Cancer: Results From a Randomized, Double-Blind, Multicenter Phase 2 Trial. *Ann Oncol* (2013) 24:75–83. doi: 10.1093/annonc/mds213
26. Reck M, Luft A, Szczesna A, Havel L, Kim S-W, Akerley W, et al. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. *J Clin Oncol* (2016) 34:3740–8. doi: 10.1200/JCO.2016.67.6601
27. Rudin CM, Awad MM, Navarro A, Gottfried M, Peters S, Csőszi T, et al. Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase Iii KEYNOTE-604 Study. *J Clin Oncol* (2020) 38:2369–79. doi: 10.1200/JCO.20.00793

28. Leal TA, Wang Y, Dowlati A, Lewis DA, Chen Y, Mohindra AR, et al. Randomized Phase II Clinical Trial of Cisplatin/Carboplatin and Etoposide (CE) Alone or in Combination With Nivolumab as Frontline Therapy for Extensive-Stage Small Cell Lung Cancer (ES-SCLC): ECOG-ACRIN EA5161. *J Clin Oncol* (2020) 38(no. 15_suppl):9000. doi: 10.1200/JCO.2020.38.15_suppl.9000
29. Owonikoko TK, Kim HR, Govindan R, Ready N, Reck M, Peters S, et al. Nivolumab Plus Ipilimumab, Nivolumab, or Placebo as Maintenance Therapy in Patients With Extensive Disease Small Cell Lung Cancer After First-Line Platinum-Based Chemotherapy: Results From the Double-Blind, Randomized Phase 3 CheckMate 451 Study. *Ann Oncol* (2019) 30(suppl_2):ii77–80. doi: 10.1093/annonc/mdz094
30. Gadgeel SM, Pennell NA, Fidler MJ, Halmos B, Bonomi P, Stevenson J, et al. Phase II Study of Maintenance Pembrolizumab in Patients With Extensive-Stage Small Cell Lung Cancer (SCLC). *J Thorac Oncol* (2018) 13:1393–9. doi: 10.1016/j.jtho.2018.05.002
31. Pujol J-L, Greillier L, Audigier-Valette C, Moro-Sibilot D, Uwer L, Hureaux J, et al. A Randomized non-Comparative Phase Ii Study of Anti-Programmed Cell Death-Ligand 1 Atezolizumab or Chemotherapy as Second-Line Therapy in Patients With Small Cell Lung Cancer: Results From the IFCT-1603 Trial. *J Thorac Oncol* (2019) 14:903–13. doi: 10.1016/j.jtho.2019.01.008
32. Spigel DR, Vicente D, Ciuleanu TE, Gettinger S, Peters S, Horn L, et al. Second-Line Nivolumab in Relapsed Small-Cell Lung Cancer: CheckMate 331. *Ann Oncol* (2021) 32(5):631–41. doi: 10.1016/j.annonc.2021.01.071
33. Kim Y-J, Keam B, Ock C-Y, Song S, Kim M, Kim SH, et al. A Phase II Study of Pembrolizumab and Paclitaxel in Patients With Relapsed or Refractory Small-Cell Lung Cancer. *Lung Cancer* (2019) 136:122–8. doi: 10.1016/j.lungcan.2019.08.031
34. Thomas A, Vilimas R, Trindade C, Erwin-Cohen R, Roper N, Xi L, et al. Durvalumab in Combination With Olaparib in Patients With Relapsed SCLC: Results From a Phase II Study. *J Thorac Oncol* (2019) 14:1447–57. doi: 10.1016/j.jtho.2019.04.026
35. Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab Alone and Nivolumab Plus Ipilimumab in Recurrent Small-Cell Lung Cancer (CheckMate 032): A Multicentre, Open-Label, Phase 1/2 Trial. *Lancet Oncol* (2016) 17:883–95. doi: 10.1016/S1470-2045(16)30098-5
36. Ott PA, Elez E, Sandrine H, Kim D-W, Morosky A, Saraf S, et al. Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study. *J Clin Oncol* (2017) 35:3823–9. doi: 10.1200/JCO.2017.72.5069
37. Chung HC, Piha-Paul SA, Lopez-Martin J, Schellens JHM, Kao S, Miller WH, et al. Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic Sclc: Results From the KEYNOTE-028 and KEYNOTE-158 Studies. *J Thorac Oncol* (2020) 15(4):618–27. doi: 10.1016/j.jtho.2019.12.109
38. Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P, et al. Pituitary Expression of CTLA-4 Mediates Hypophysitis Secondary to Administration of CTLA-4 Blocking Antibody. *Sci Transl Med* (2014) 6:230ra45. doi: 10.1126/scitranslmed.3008002
39. Caturegli P, Di Dalmazi G, Lombardi M, Grosso F, Larman HB, Larman T, et al. Hypophysitis Secondary to Cytotoxic T-Lymphocyte-Associated Protein 4 Blockade: Insights Into Pathogenesis From an Autopsy Series. *Am J Pathol* (2016) 186:3225–35. doi: 10.1016/j.ajpath.2016.08.020
40. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Antibody-Mediated Thyroid Dysfunction During T-cell Checkpoint Blockade in Patients With Non-Small-Cell Lung Cancer. *Ann Oncol* (2017) 28:583–9. doi: 10.1093/annonc/mdw640
41. von Euw E, Chodon T, Attar N, Jalil J, Koya RC, Comin-Anduix B, et al. CTLA4 Blockade Increases Th17 Cells in Patients With Metastatic Melanoma. *J Transl Med* (2009) 7:35. doi: 10.1186/1479-5876-7-35
42. Anderson R, Theron AJ, Rapoport BL. Immunopathogenesis of Immune Checkpoint Inhibitor-Related Adverse Events: Roles of the Intestinal Microbiome and Th17 Cells. *Front Immunol* (2019) 10:2254. doi: 10.3389/fimmu.2019.02254
43. Esfahani K, Miller WH. Reversal of Autoimmune Toxicity and Loss of Tumor Response by Interleukin-17 Blockade. *N Engl J Med* (2017) 376:1989–91. doi: 10.1056/NEJMc1703047

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

CASE REPORT
published: 17 June 2021
doi: 10.3389/fonc.2021.670415

Persistent Response and Prolonged Survival Following Pembrolizumab Discontinuation Due to Long-Lasting Autoimmune Colitis in Advanced NSCLC: A Case Report

Angela Damato[1,2*], *Loredana De Marco*[3], *Silvia Serra*[3], *Mario Larocca*[1], *Alicia Garcia Arias*[1], *Ermanno Rondini*[1] and *Carmine Pinto*[1]

[1] Medical Oncology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy, [2] Department of Medical Biotechnologies, University of Siena, Siena, Italy, [3] Pathology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

Pembrolizumab is a programmed death receptor-1 (PD-1) inhibitor that has been approved for treatment of a wide variety of malignancies including non-small-cell lung cancer (NSCLC). Immune-mediated colitis is a known adverse effect of pembrolizumab which can lead to the treatment interruption, although not compromising the control of the oncological disease. Herein, we report the case of a 59-year-old woman on pembrolizumab for advanced NSCLC which developed a severe and persistent colitis treated with infliximab for several months following anti-PD-1 antibody discontinuation. This strategy resulted in an improvement but not complete recovery of the gastrointestinal toxicity despite revealed sustained response and control of the oncological disease with prolonged survival over 24 months.

Keywords: immune checkpoint inhibitors, pembrolizimab, non-small-cell lung cancer, colitis, survival

OPEN ACCESS

Edited by:
Xuelei Ma,
Sichuan University, China

Reviewed by:
Eric Vick,
University of Cincinnati, United States
Carlo Astarita,
Sbarro Health Research Organization (SHRO), United States
Jordi Remon,
Hospital HM Delfos, Spain

****Correspondence:***
Angela Damato
Angela.damato@ausl.re.it

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Oncology

Received: *21 February 2021*
Accepted: *28 May 2021*
Published: *17 June 2021*

Citation:
Damato A, De Marco L, Serra S, Larocca M, Arias AG, Rondini E and Pinto C (2021) Persistent Response and Prolonged Survival Following Pembrolizumab Discontinuation Due to Long-Lasting Autoimmune Colitis in Advanced NSCLC: A Case Report. Front. Oncol. 11:670415. doi: 10.3389/fonc.2021.670415

INTRODUCTION

In NSCLC with programmed death-ligand 1 (PD-L1) expression on ≥50% of tumor cells, first-line treatment with the PD-1 inhibitor pembrolizumab improves survival compared with platinum-doublet chemotherapy (1–3). However, the most gastrointestinal immune-related adverse event (irAE) related to pembrolizumab is colitis and in NSCLC recurred in 1.3% of cases (2, 3). The first choice of treatment for moderate or severe colitis is systemic corticosteroids with symptom improvement, but in some cases it is necessary to consider up-front monoclonal antibody and a discontinuation of immune-checkpoint inhibitor. Despite this, clinical cases of patients with irAEs and sustained response of disease over time after immunotherapy discontinuation are described.

In this clinical case we describe a woman affected by advanced NSCLC treated in first line therapy with pembrolizumab which developed severe colitis requiring symptomatic treatments and

simultaneous permanent pembrolizumab discontinuation, keeping a partial response of the oncological disease in the following 24 months, improving the overall survival.

CASE PRESENTATION

This is the case of 59-year-old Caucasian woman from Italy, non-smoker, with no alcohol or drug intake for chronic pathologies. In 2001 she underwent the removal of cystic lymphangioma in the left neck, and in post-surgery she manifested an anaphylactic shock to dexamethasone. In 2008 she was diagnosed with left breast cancer and subjected to bilateral mastectomy, adjuvant chemotherapy, and subsequently, until 2013 she took hormone therapy with tamoxifen.

The oncological history began in December 2017, in which a computed tomography (CT) scan detected a pulmonary lesion in the apical right lobe suspected for neoplasm, bilateral pulmonary micronodules, mediastinal and right para-aortic lymph nodes, and lytic bone lesion in the left sacroiliac synchondrosis. The patient underwent CT-guided needle biopsy of the right lower lobe lesion and histological findings highlighted an adenocarcinoma of pulmonary origin, non-oncogene addicted (EGFR, KRAS and BRAF wild type, ALK and ROS1 not rearranged); PD-L1 tumor proportion score (TPS) expression was positive and equal to 70%. Taking into account the dissemination of the disease and molecular findings (PD-L1 TPS 70%), in January 2018, she started the first line treatment with an anti-PD-1 antibody, pembrolizumab 200 mg at flat dose every three weeks. Therefore, she was exposed to pain-relieving radiotherapy in five fractions (total dose of 20 Gray) on bone lesion.

In January 2019, after 1 year of treatment with pembrolizumab, CT scan confirmed the response of disease, with disappearance of the mediastinal lymph nodes and stability of the other disease sites. Despite the excellent response to treatment, after the last administration in January 2019, the patient developed severe grade 4 diarrhea according to Common Terminology Criteria for Adverse Event (CTCAE) version 4.0. For this reason, she was hospitalized and administered intravenous parenteral nutrition and electrolyte supplementation in association with loperamide hydrochloride oral medication. After ruling out a bacterial infection linked to diarrhea such as clostridium difficile, salmonellosis or shigellosis, taken into account the previous heavy steroid allergy resulting in anaphylactic distress, it was not possible to recourse the use of prednisone as treatment of choice for immune-related toxicity. Therefore, in February 2019 an anti-TNF alpha antibody, infliximab 5 mg/kg, was administered with prompt improvement of diarrhea up to grade 2. After 4 weeks, there was a new clinical worsening with abdominal pain, grade 4 diarrhea, weight loss, and cachexia, for which the patient was referred to the emergency department of the hospital and then admitted in our division to start symptomatic cure (intravenous parenteral nutrition, electrolyte supplementation) with further two infliximab administrations, the last in April 2019. The laboratory tests found a remarkable increase of fecal calprotectin in recurrent determinations and variable decrease after infliximab injections (**Figure 1**). To assess the presence of steady, and extensive colonic inflammation, endoscopic assessment with colonoscopy was performed in November 2019 finding marked changes as edematous, thinned, and friability mucosa with diffuse inflammation as an autoimmune colitis. Histopathological features of colon biopsy revealed the mucosa with a pattern of collagenous colitis characterized by the deposition of a subepithelial collagen band and accompanied by inflammatory infiltrate. The lamina propria lymph-plasmacytosis, patchy subepithelial collagen deposition of variable thickness, injury to and detachment of the surface epithelium, and glandular atrophy were seen (**Figure 2**). From June 2019 to December 2019, further six infliximab administrations were given up to decrease the intensity of diarrhea to grade 1. Despite repeated administration of infliximab, no clinical signs of infection were found. At follow-

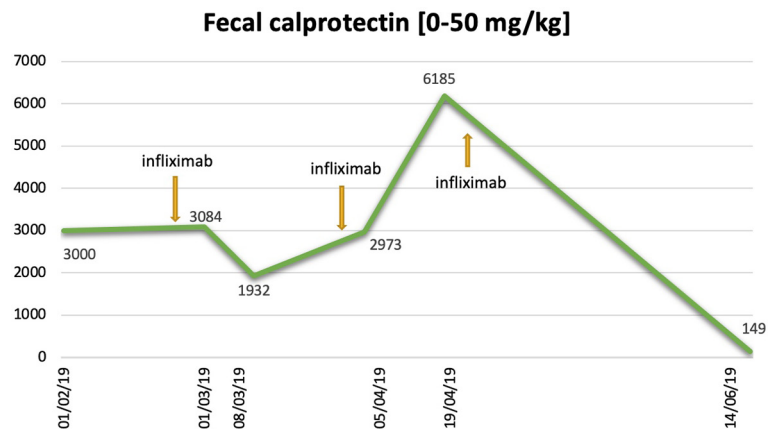

FIGURE 1 | Fecal calprotectin dosage trend and infliximab administrations.

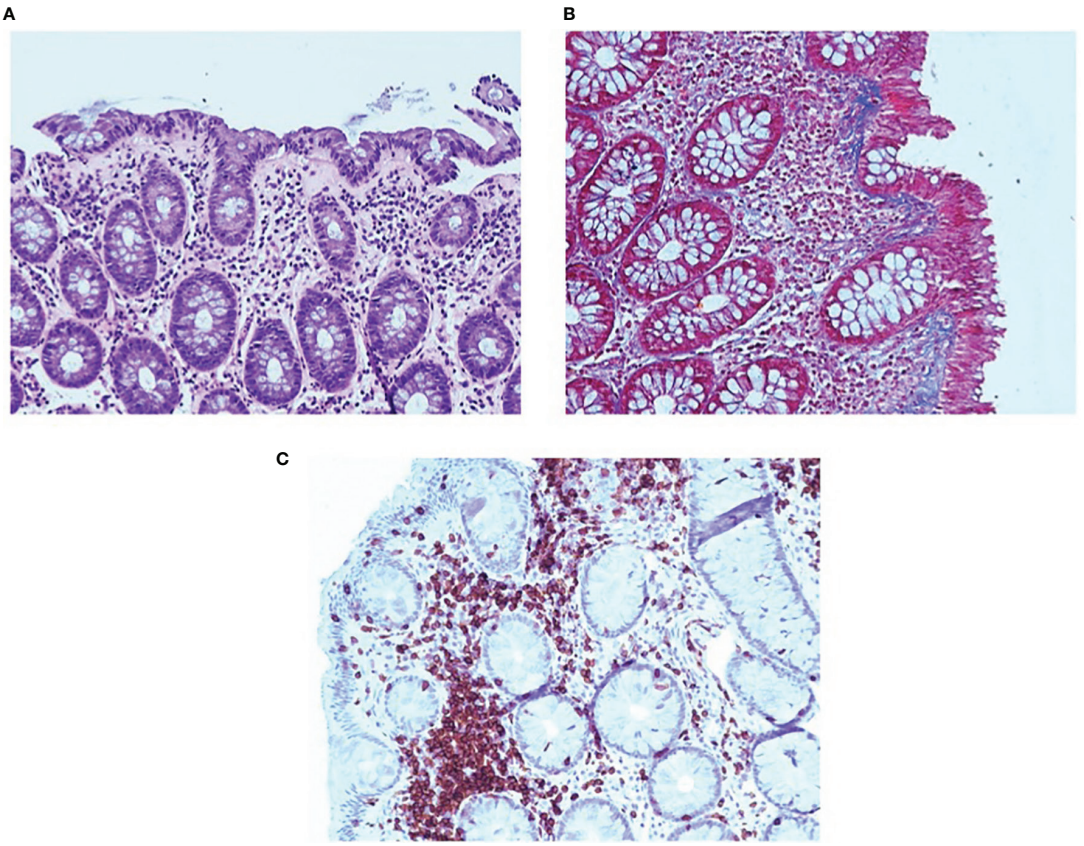

FIGURE 2 | Collagenous colitis pattern. The pink band is seen beneath the surface epithelium and the lamina propria contains increased chronic inflammation **(A)**. Masson trichrome stain highlights the irregularly expanded subepithelial collagen thickening. Note the entrapped inflammatory cells and small vessels **(B)**. CD3 immunostain. The CD3 immunostain confirms that the lymphocytes CD3+ T-cells are predominantly in the lamina propria and are increased **(C)**.

up of 10 months after the last infliximab administration, the medical conditions of patient revealed weight recovery, occasional abdominal pain, and grade 1 diarrhea.

The instrumental follow-up with CT scan achieved in January 2021, 24 months after the latest administration of pembolizumab (carried out on January 2019), showed a persistent and remarkable stability of oncological disease in lung, lymph-nodes, and bone, despite the widespread inflammation of the colon *in toto* described as bowel wall thickening and colonic distension (**Figure 3**). The trend over time of the radiological response to immunotherapy and gastrointestinal toxicity evolution is shown in **Figure 4**.

DISCUSSION

The immunotherapy era has meaningfully improved cancer management and survival outcomes, mostly in patients with NSCLC (1–3). In first-line setting, pembrolizumab as monotherapy alone or in combination with chemotherapy improved long-term outcomes. In the phase I KEYNOTE-001 study, pembrolizumab improved clinical outcomes in patients with advanced NSCLC PD-L1 TPS ≥50% treated compared with tumors with lower PD-L1 levels (1). As a result, a PD-L1 expression level of ≥50% was selected for the KEYNOTE-024 study, a randomized phase III trial which demonstrated prolonged overall survival (OS) in first-line with pembrolizumab compared with platinum doublet chemotherapy for advanced NSCLC (2). At the median follow-up of 5 years, the median OS (mOS) was 26.3 months *versus* 13.4 months with chemotherapy [CI 95%, HR 0.62 (0.48–0.81)] and overall response rate (ORR) of 32% (3). Furthermore, in the phase III KEYNOTE-042 study, pembrolizumab alone compared to chemotherapy in first line setting, according to the PD-L1 TPS level 1–19, 20–49, and ≥50% revealed a median OS improvement of 16.7, 17.7, and 20.0 months, respectively in each subgroup (4).

Because of the synergy between chemotherapy and immunotherapy, the first-line combined treatment based on pembrolizumab is another option in non-squamous NSCLC as suggested by KEYNOTE-189 phase III study (5). However, an unresolved question is whether to use pembrolizumab monotherapy or pembrolizumab plus chemotherapy in patients with PD-L1 level ≥50%. It is necessary to identify biomarkers to select patients who respond to pembrolizumab in monotherapy and spare patients the added toxicities of chemotherapy.

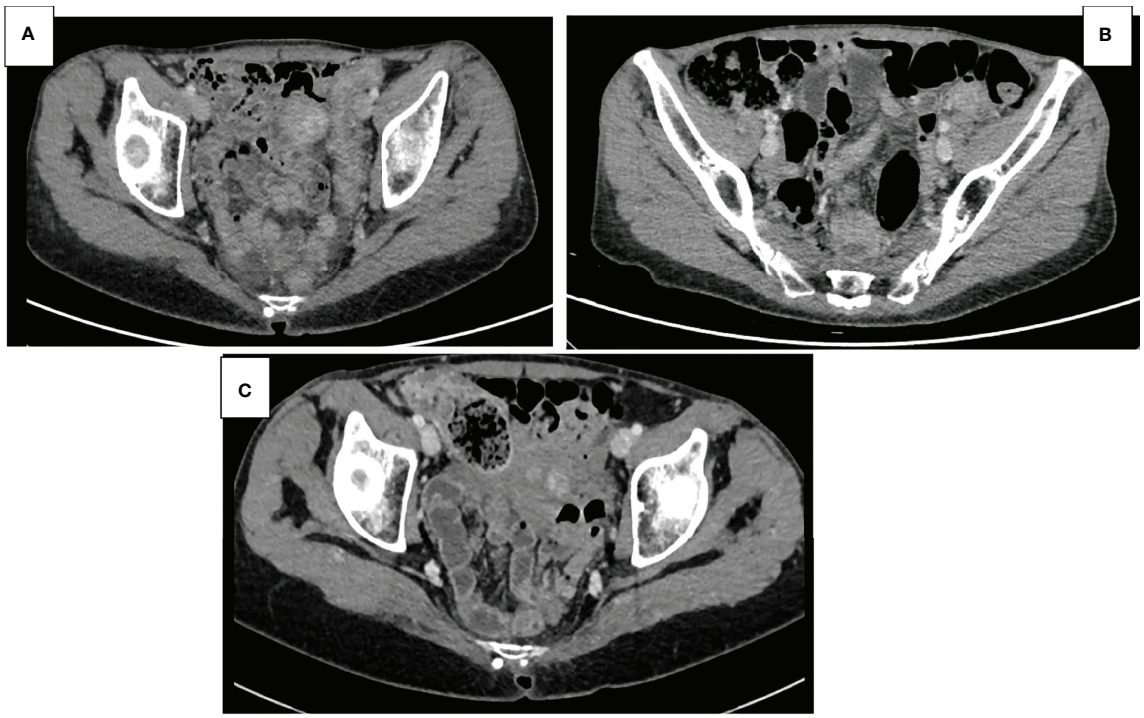

FIGURE 3 | Basal abdominal CT scans at the onset symptoms of pan-colitis with diffuse thickening of the colon walls **(A)**. Improvement of pan-colitis after 8 months of infliximab treatment and 9 months of Pembrolizumab discontinuation **(B)**. Persistent mild colitis after 24 months of Pembrolizumab discontinuation **(C)**.

The immune check point inhibitors (ICIs) are involved in the downregulation of cytotoxic T cells, stimulating cytotoxic T-cell survival, strengthening of tumor surveillance and antitumor action. Despite these activities, ICIs also trigger global T-cell responses that prompt several immune-related adverse events (irAEs), of which the most serious and clinically relevant is colitis (6, 7). One of the suggestive symptoms is diarrhea defined as loose, watery stools a day that occurs in 12.1–13.7% and colitis associated to presence of abdominal pain, rectal bleeding, and mucous in the stools of patients treated with anti-PD-1 antibody (8–10). Colitis is defined by endoscopically mucosal ulcerations or fecal calprotectin dosage. Moreover, stools should be checked for bacterial, parasitic, and viral infections including *Clostridium difficile* (11–13). A widespread and detailed history, physical examination, and early endoscopic assessment are encouraged to diagnosis and make a prognosis of immune-mediated colitis when

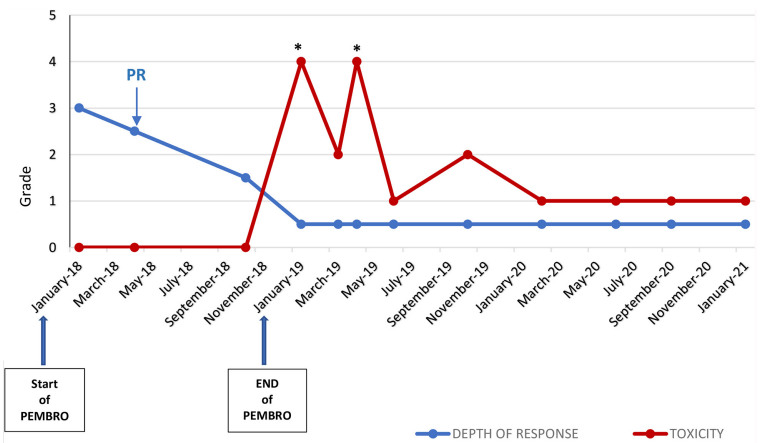

FIGURE 4 | Trend over time of the radiological response to pembrolizumab by RECIST Criteria version 1.0 and grade of gastrointestinal irAE (diarrhea) by CTCAE version 4.0 *Hospitalization; PD, Partial Response (according to RECIST v1.0); PEMBRO, pembrolizumab.

immunotherapy is considered (14). Mucosal ulcerations are present in 30–40% of cases, whereas in 35–40% of cases edema, exudate, unusual vascularity, and erosions were found (15). These features demand systemic therapy and hospitalizations to control symptoms and electrolyte imbalance. Systemic corticosteroids such as prednisone 1–2 mg/kg are the first-line approach for irAEs and described to be effective in 87.5% of patients (16). Once clinical improvement to grade 1 or less is achieved, steroids should be progressively reduced, and anti-PD-1/L1 inhibitors can usually be resumed when symptoms have resolved or prednisone is tapered to daily doses of 10 mg or less. The risk of recurrent gastrointestinal irAEs is reported as high as 19–36% (17). Cases of persistent inflammation up to 6–18 months from initial diagnosis (18) are described, as in our clinical case. Although we performed the intestinal biopsy about 10 months after the drug discontinuation, it is likely that what was seen corresponds to the outcome of a collagenous colitis linked to the intake of the anti PD-1 antibody. An escalation of biologic agents is recommended for steroid-refractory immune-colitis or those who cannot use the steroids as a therapy. Infliximab, a tumor necrosis factor (TNF)-alpha antagonist, is effective with faster symptom resolution in a median of 3 days (18). This inhibition enhances tumor immunity by facilitating the proliferation and function of T-regs and myeloid-derived suppressor cells, overcoming resistance to anti–PD-1 antibodies (19). Furthermore, after infliximab exposure, the risk of immunogenicity due to sporadic dosing should be considered for patients with recurrent disease, with potential infusion reactions or weakening effectiveness. Apart from this, infliximab therapy influences the gut microbiota dysbiosis by modifying microbiota composition and function, especially in Chron's disease, highlighting a reduction in pathogenic bacteria such as *Fusobacterium*, *Enterobacter*, and *Escherichia–Shigella*, and an increase in short-chain fatty acid-producing bacteria such as the family Lachnospiraceae (20). Although in the cancer setting there is little evidence, this gut microbioma could be a biomarker for monitoring response to treatment.

Few and discordant data exist regarding the clinical outcomes in advanced NSCLC following immunotherapy interruption due to irAEs. In a retrospective analysis of nivolumab-treated patients with advanced NSCLC who developed colitis had a lower median OS compared to those who did not (4.4 *vs.* 10.6 months, P= .010) (21). Conversely, in a series of retrospective studies including patients with metastatic renal-cell carcinoma who discontinued PD-1 or PD-L1 antibodies after an initial response due to irAEs revealed a prolonged time to progression (22). A recent large real-world analysis of patients with NSCLC with PD-L1 expression ≥50%, treated with single-agent pembrolizumab including frail patients showed a significant association between irAE occurrence and improved PFS, except for gastrointestinal irAEs not associated with an improved ORR and OS. The authors concluded that irAE occurrence may be a surrogate of clinical activity and improved outcomes in this setting (23). Naquash et al. conducted a pooled exploratory analysis of 531 patients with advanced NSCLC treated with nivolumab derived from five retrospective cohorts showing an improved PFS and OS in patients that had irAEs during the treatment (24). At last, a record of 1,959 patients treated with nivolumab in an Italian NSCLC expanded access program, confirmed a significantly higher response rate, disease control rate, mPFS, and mOS in patients developing irAE of any grade (25).

These considerations might differ depending on tumor types, treatment protocols, and may be, by the physicians' experience in reporting irAEs and its management. Supporting the data of the retrospective studies, our clinical case revealed, 24 months from immunotherapy discontinuation due to the onset of colitis, a sustained response and control of the oncological disease with prolonged survival in line with the retrospective cases reported above.

CONCLUSIONS

Pembrolizumab-induced immune-mediated colitis can occur in patients with NSCLC. Accurate diagnosing of immunotherapy-related colitis is mandatory, by acting with systemic and appropriate care. The first choice of treatment to counteract the symptoms are steroidal anti-inflammatory drugs (SAIDs) however, in some peculiar cases, patients may require biological therapy as anti-TNF-alpha antibody. It is worth noticing that pharmacological therapy may not be sufficient to control the gastrointestinal irAEs and a prolonged and conclusive immunotherapy discontinuation is necessary. Interestingly, the clinical outcome in such patients has been under investigation and in our clinical case, we report a remarkable and prolonged response of the oncological disease, which is maintained over time impacting positively on patient's survival. Further analysis should investigate the interplay between immune-mediated colitis and survival, and also biological studies of correlation with toxicities.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by AUSL—IRCCS Reggio Emilia. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

AD, ER, ML, and AA interacted with the patient. AD wrote the manuscript. LM and SS prepared and analyzed pathology. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab Versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* (2016) 19:1823–33. doi: 10.1056/NEJMoa1606774
2. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. *J Clin Oncol* (2019) 37:537–46. doi: 10.1200/JCO.18.00149
3. Brahmer JR, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. KEYNOTE-024 5-Year OS Update: First-line (1L) Pembrolizumab (Pembro) *vs* Platinum-Based Chemotherapy (Chemo) in Patients (Pts) With Metastatic NSCLC and PD-L1 Tumour Proportion Score (TPS) ≥50%. *Ann Oncol* (2020) 31(suppl_4):S1142–215. doi: 10.1016/annonc/annonc325
4. Mok TSK, Wu Y-L, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab Versus Chemotherapy for Previously Untreated, PD-L1–Expressing, Locally Advanced or Metastatic Non–Small Cell Lung Cancer (KEYNOTE-042): A Randomized, Open-Label, Controlled, Phase 3 Trial. *Lancet* (2019) 393:1819–30. doi: 10.1016/S0140-6736(18)32409-7
5. Gadgeel S, Rodriguez-Abreu D, Speranza G, Esteban E, Felip E, Domine M, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. *J Clin Oncol* (2020) 38:1505–17. doi: 10.1200/JCO.19.03136
6. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen ER. Tumour- and Class-Specific Patterns of Immune-Related Adverse Events of Immune Checkpoint Inhibitors: A Systematic Review. *Ann Oncol* (2017) 28(10):2377–85. doi: 10.1093/annonc/mdx286
7. Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of Toxicities From Immunotherapy: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. *Ann Oncol* (2017) 28 (Suppl 4):iv119–42. doi: 10.1093/annonc/mdx225
8. Wang DY, Ye F, Zhao S, et al. Incidence of Immune Check Point Inhibitor Related Colitis in Solid Tumor Patients: A Systematic Review and Meta-Analysis. *Oncoimmunology* (2017) 6(10):e1344805. doi: 10.1080/2162402X.2017.1344805
9. Abdel-Rahman O, ElHalawani H, Fouad M. Risk of Gastrointestinal Complications in Cancer Patients Treated With Immune Checkpoint Inhibitors: A Meta-Analysis. *Immunotherapy* (2015) 7(11):1213–27. doi: 10.2217/imt.15.87
10. Shah R, Witt D, Asif T, Mir FF. Ipilimumab as a Cause of Severe Pan-Colitis and Colonic Perforation. *Cureus* (2017) 9(4):e1182. doi: 10.7759/cureus.1182
11. Du-Thanh A, Pallure V, Girard C, Dereure O, Guillot B. Clostridium Difficile Infection may Loom Behind Ipilimumab-Induced Auto-Immune Colitis. *Eur J Dermatol* (2015) 25(4):344. doi: 10.1684/ejd.2015.2561
12. Lankes K, Hundorfean G, Harrer T, Pommer AJ, Agaimy A, Angelovska I, et al. Anti-TNF-Refractory Colitis After Checkpoint Inhibitor Therapy: Possible Role of CMV-Mediated Immunopathogenesis. *Oncoimmunology* (2016) 5(6):e1128611. doi: 10.1080/2162402X.2015.1128611
13. McCutcheon JL, McClain CM, Puzanov I, et al. Infectious Colitis Associated With Ipilimumab Therapy. *Gastroenterol Res* (2014) 7(1):28–31. doi: 10.14740/gr594e
14. Wang Y, Abu-Sbeih H, Mao E, Smith TA. Endoscopic and Histologic Features of Immune Checkpoint Inhibitor-Related Colitis. *Inflammat Bowel Dis* (2018) 24(8):1695–705. doi: 10.1093/ibd/izy104
15. Abu-Sbeih H, Ali FS, Luo W, Qiao W, Raju GS, Wang Y. Importance of Endoscopic and Histological Evaluation in the Management of Immune Checkpoint Inhibitor-Induced Colitis. *J Immunother Cancer* (2018) 6(1):95. doi: 10.1186/s40425-018-0411-1
16. Collins M, Michot JM, Danlos FX, Mussini C, Soularue E, Mateus C, et al. Inflammatory Gastrointestinal Diseases Associated With PD-1 Blockade Antibodies. *Ann Oncol* (2017) 28(11):2860–5. doi: 10.1093/annonc/mdx403
17. Zhuang X, Tian Z, Feng R, Li M, Li T, Zhou G, et al. Fecal Microbiota Alterations Associated With Clinical and Endoscopic Response to Infliximab Therapy in Crohn's Disease. *Inflamm Bowel Dis* (2020) 26(11):1636–47. doi: 10.1093/ibd/izaa253
18. Johnson DH, Zobniw CM, Trinh VA, Ma J, Bassett RL Jr, Abdel-Wahab N, et al. Infliximab Associated With Faster Symptom Resolution Compared With Corticosteroids Alone for the Management of Immune-Related Enterocolitis. *J Immunother Cancer* (2018) 6(1):103. doi: 10.1186/s40425-018-0412-0
19. Ksienski D, Wai ES, Croteau N, Fiorino L, Brooks E, Poonja Z, et al. Efficacy of Nivolumab and Pembrolizumab in Patients With Advanced Non Small-Cell Lung Cancer Needing Treatment Interruption Because of Adverse Events: A Retrospective Multicenter Analysis. *Clin Lung Cancer* (2019) 20(1):e97–e106. doi: 10.1016/j.cllc.2018.09.005
20. Bertrand F, Montfort A, Marcheteau E, Imbert C, Gilhodes J, Filleron T, et al. TNFalpha Blockade Overcomes Resistance to Anti-PD-1 in Experimental Melanoma. *Nat Commun* (2017) 8(1):2256. doi: 10.1038/s41467-017-02358-7
21. Martini DJ, Hamish L, McKay R, Harshman LC, Brandao R, Norton CK, et al. Durable Clinical Benefit in Metastatic Renal Cell Carcinoma Patients Who Discontinued PD-1/PD-L1 Therapy for Immune- Related Adverse Events. *Cancer Immunol Res* (2018) 6:402408. doi: 10.1158/2326-6066.CIR-17-0220
22. Cortellini A, Friedlaender A, Banna GL, Porzio G, Bersanelli M, Capuzzo F, et al. Immune-Related Adverse Events of Pembrolizumab in a Large Real-World Cohort of Patients With NSCLC With a PD-L1 Expression ≥ 50% and Their Relationship With Clinical Outcomes. *Clin Lung Cancer* (2020) 21 (6):498–508. doi: 10.1016/j.cllc.2020.06.010
23. Naqash AR, Ricciuti B, Owen DH, Florou V, Toy Y, Cherry C, et al. Outcomes Associated With Immune-Related Adverse Events in Metastatic Non-Small Cell Lung Cancer Treated With Nivolumab: A Pooled Exploratory Analysis From a Global Cohort. *Cancer Immunol Immunother* (2020) 69:1177–87. doi: 10.1007/s00262-020-02536-5
24. Baldini E, Lunghi A, Cortesi E, Turci D, Signorelli D, Stati V, et al. Immune-Related Adverse Events Correlate With Clinical Outcomes in NSCLC Patients Treated With Nivolumab: The Italian NSCLC Expanded Access Program. *Lung Cancer* (2020) 140:59–64. doi: 10.1016/j.lungcan.2019.12.014
25. Abu-Sbeih H, Ali FS, Naqash AR, et al. Resumption of Immune Checkpoint Inhibitor Therapy After Immune-Mediated Colitis. *J Clin Oncol* (2019) 37:2738–45. doi: 10.1200/JCO.19.00320

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Immunology

REVIEW
published: 24 August 2021
doi: 10.3389/fimmu.2021.701951

Ocular Immune-Related Adverse Events Associated With Immune Checkpoint Inhibitors in Lung Cancer

*Lin Zhou and Xin Wei**

Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu, China

Immune checkpoint inhibitors (ICIs) are novel immunotherapy-based drugs that have become increasingly popular in the treatment of lung cancer. Researchers have recognized ocular immune-related adverse events (irAEs) secondary to ICIs because of their vision-threatening characteristics. However, they are incompletely characterized and no studies have reported the ICI-related ocular irAEs in lung cancer. Therefore, we aimed to comprehensively illustrate the clinical characteristics, contributory factors, diagnosis, and management of ICI-related ocular irAEs in lung cancer, based on previously reported 79 patients. Ophthalmoplegia (40.51%), uveitis (20.25%), and dry eye (17.72%) were the most common ICI-related ocular irAEs in lung cancer. Ptosis was the most common (36.71%) and the highest mortality (23.33%) of ophthalmoplegia. Patients in Asia and patients who underwent combination therapy with programmed cell death-1 and cytotoxic T-lymphocyte-associated antigen 4 inhibitors demonstrated significantly higher frequency of ophthalmoplegia than other ocular irAEs. Most ICI-related ophthalmoplegia and uveitis in lung cancer were observed in the first 10 weeks following the initiation of ICIs. Furthermore, the onset time of dry eye and other ocular irAEs was much longer. In addition, 92.31% of the patients with ocular irAEs other than ophthalmoplegia could be remised. In conclusion, ocular irAEs secondary to ICIs in lung cancer are non-negligible, particularly ophthalmoplegia. Ethnicity and the type of ICIs play important roles in the distribution of ocular irAEs. ICI-related ophthalmoplegia in lung cancer presented with early onset and worse prognosis features, thus necessitating further attention.

Keywords: ocular immune-related adverse events, immune checkpoint inhibitors, lung cancer, ophthalmoplegia, uveitis, dry eye

OPEN ACCESS

Edited by:
Benjamin Frey,
University Hospital Erlangen, Germany

Reviewed by:
Ji Dan,
Central South University, China
Xin Huang,
Renmin Hospital of Wuhan University, China

***Correspondence:**
Xin Wei
weixin_1982@163.com

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Immunology

Received: *28 April 2021*
Accepted: *05 August 2021*
Published: *24 August 2021*

Citation:
Zhou L and Wei X (2021) Ocular Immune-Related Adverse Events Associated With Immune Checkpoint Inhibitors in Lung Cancer. Front. Immunol. 12:701951. doi: 10.3389/fimmu.2021.701951

INTRODUCTION

Lung cancer is diagnosed in approximately two million people (11.6% of the total cancer cases), and is a leading cause of cancer death worldwide (1–3). Based on the histologic subtypes, lung cancer has been classified as large cell carcinoma, squamous carcinoma, and adenocarcinoma (NSCLC, non-small cell carcinoma), and small cell lung cancer. With the identification of molecular mechanisms by which cancerous cells evade T cell-mediated cytotoxic damage, immunotherapy has been considered as an effective treatment for patients with lung cancer (4–6).

Immune system plays an important role in monitoring and destructing cancer cells. However, this natural defense can be evaded by tumor cells and the upregulation of key immune checkpoints could increase the tolerance. Antitumor immunity may be blocked by suppression through the activation of immune checkpoints, including the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death-1 protein (PD-1) pathways. Blocking the inhibitory molecular axis using monoclonal antibodies targeting PD-1 (nivolumab, pembrolizumab), PD-L1 (atezolizumab, avelumab, and durvalumab), or CTLA-4 (ipilimumab) can reactivate the effector and cytotoxic T cells to destroy the tumor cells (7, 8). Immune checkpoint inhibitors (ICIs) provide a long-lasting response to treatment in both at the early and late stage of lung cancer (9–11). It has been considered as the first choice of second-line therapy for advanced NSCLC and as first-line therapy (4, 12, 13).

Compared to the traditional therapy, ICIs can over-activate the non-specific the immune system, which could cause autoimmune toxicities known as immune-related adverse events (irAEs) (14–18). This in turn can affect any organ system, including the skin, heart, lungs, liver, kidneys, central nervous, gastrointestinal, endocrine, musculoskeletal, haematological, and ocular systems. The most common systemic irAEs include fatigue (26%–53%), skin pruritus (25%–35%), skin rash (1%–50%), lymphocytopenia (10%–49%), and abnormal liver function (1%–46%) (19). Following ICIs, the aforementioned irAEs may manifest as a wide variety of forms ranging from mild to severe (20), and vary based on the organ system and severity (21, 22). The prevalence of ICI-related pneumonitis is higher in NSCLC than in other tumor type, based on data from the Immuno-Cancer International Registry (23, 24). In addition, lung cancer is reportedly one of the most common tumor with ICI-related ocular irAEs (25).

Ocular irAEs following ICIs can cause a deterioration of the quality of life and exert an influence on the compliance of patients. Approximately 2.8-4.3% of the patients suffered ocular irAEs, based on the Food and Drug Administration (FDA) Adverse Event Reporting System pharmacovigilance database (26–28). However, no studies have comprehensively analyzed ocular irAEs in lung cancer following ICIs. We aim to evaluate uncommon and serious ICI-related ocular irAEs associated with lung cancer. Based on relevant literature on ocular irAEs in lung cancer, we intent to illustrate the epidemiology, clinical characteristics, contributory factors, diagnosis, and management of ICI-associated ocular side effects in lung cancer.

EPIDEMIOLOGY OF OCULAR irAEs IN LUNG CANCER

Despite being infrequent, ocular irAEs can cause a deterioration of the quality of life and affect patient compliance. Initially, the incidence of ICI-related ocular irAEs was estimated to be approximately 0.4%-1% in patients with moderate-to-severe ocular irAEs (19, 29). Recently, three studies with large sample sizes have reported an incidence of 2.8-4.3% (26, 30, 31). In addition, the actual frequency of ocular irAEs following ICIs could be underestimated because of insufficient attention. The incidence of ICI-associated ocular complications may be higher in real-world practice.

Ocular side effects secondary to ICIs are immune-related, and can affect any part of the eye and orbit. The distribution and frequency vary in different ocular irAEs on ICIs. In 2018, uveitis and dry eye had been reported as the most frequent ICI-related ocular side effects. Ocular irAEs were reported in 2.80% patients in a cohort of 996 patients with ICIs reported in Mayo clinic (31). Dry eye was observed in 57.14% of the patients with ocular irAEs, followed by uveitis in 14.28% of the patients (31). In relation to ICI-associated ocular surface toxicity, dry eye, conjunctivitis, and keratitis were reportedly the most common irAEs in a previous review involving 29 studies (32). However, a systematic review on ipilimumab considered uveitis (4.3%) as the most common ocular irAE (27, 28). Anterior uveitis is the most common phenotype among all types of uveitis (30). Despite some reports on ophthalmoplegia, it is not considered as a common side effect (19).

In this review, we summarized the reported ocular irAEs following ICIs in lung cancer by searching the PubMed database until April 2021 (25, 29, 33–86). The key words were a combination of 'adverse events', 'lung', and names of ICIs. We included studies describing ocular irAEs secondary to ICIs in lung cancer, and restricted the language of the selected literature to English. A total of 79 cases were detected, and the most frequently reported ocular irAEs following ICIs were ophthalmoplegia (40.51%), uveitis (20.25%), and dry eye (17.72%). In addition, we also identified retinopathy (5.06%), conjunctivitis (5.06%), optic neuritis (3.80%), and other frequent ocular irAEs, such as orbital inflammation (2.53%), amaurosis fugax (1.27%), giant cell arteritis (1.27%), corneal graft rejection (1.27%) and corneal perforation (1.27%) (**Figure 1**, **Tables 1**, **2**).

CLINICAL CHARACTERISTIC OF OCULAR irAEs IN LUNG CANCER WITH ICIs

The Onset Time of Ocular irAEs in Lung Cancer

The mean time to the onset of ocular irAEs in lung cancer was approximately 35 days, and the overall time ranged from 28.0–111.5 days (19, 87). Moreover, 73% of the patients developed ocular irAEs within 60 days following ICIs initiation. While intraocular inflammation was detected after a median 9 weeks, 83.6%-91.67% of the patients were diagnosed with uveitis within 6 months (median 63 days) (28, 88). Ophthalmoplegia was diagnosed at a median onset of 35 days. According to recent reviews on ocular adverse events, the average onset time of ophthalmoplegia was approximately 6 weeks after ICIs initiation (range 2–12 weeks) (19, 89–91). The median interval between the onset of ICIs use and the diagnosis of dry eye was 6.5 months in 26 patients secondary to ICIs (24). In this review, the

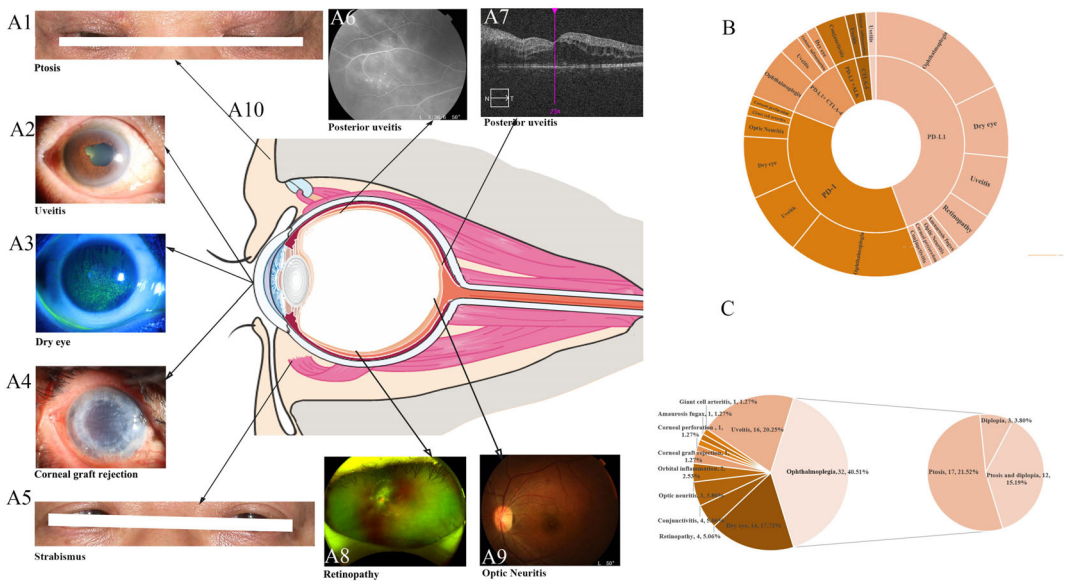

FIGURE 1 | Clinical characteristics **(A)** and the distribution **(B, C)** of immune checkpoint inhibitor-mediated ocular side events. **(A)** The clinical characteristics of common ocular irAEs in lung cancer. **(B)** The distribution of ocular irAEs in different therapies. **(C)** A summary of all reported ocular irAEs in lung cancer following treatment with ICIs.

average onset time of ocular irAEs in lung cancer was 57.28 days following ICIs (**Tables 1**, **2**, **Figures 2**, **3**). The average time was significantly shorter in patients with uveitis and ophthalmoplegia (32.22 days and 38.26 days, respectively) than those with other ocular irAEs (96.5 days) in lung cancer. More importantly, all ICI-related ophthalmoplegia and the majority of uveitis occurred in the first 10 weeks. However, the onset time of dry eye and other ocular irAEs was much longer (**Figures 2**, **3**). Furthermore, we did not detect a significant difference in the onset time of ocular irAEs in lung cancer among different ICIs, age, sex, and ethnicity (**Figure S1**).

The Clinical Manifestation of Ocular irAEs in Lung Cancer

All of the ocular irAEs following ICIs were noninfectious and caused by the over-activate the immune system. **Table 3** summarizes the clinical characteristics and necessary examinations for different ocular irAEs. Ophthalmoplegia, uveitis and dry eye were the most common ocular irAEs secondary to ICIs in lung cancer have been described separately in detail as follows. Other ocular surface complications (conjunctivitis, corneal perforation, corneal graft rejection, retinopathy, optic neuritis, amaurosis fugax, giant cell arteritis and orbital inflammation) are also briefly discussed.

Ophthalmoplegia in Lung Cancer Secondary to ICIs

Ophthalmoplegia is the dysfunction (weakness or paralysis) of one or more muscles that control eye movement. Ptosis is the earliest and most common manifestation of ophthalmoplegia, followed by diplopia and strabismus. In this review, 53.12% of patients with ophthalmoplegia suffered ptosis, 37.50% suffered ptosis with diplopia/strabismus. Only three patients (9.38%) complained of diplopia. Ptosis occurs when the upper eyelid droops over the eye, which in turn makes the affected eye appear smaller than normal eyes. The eyelid may droop just a little or completely covering the pupil (92). Moreover, it can be unilateral or bilateral. According to previous studies, ophthalmoplegia in lung cancer secondary to ICIs were accompanied by myasthenia gravis (MG) in all patients (25, 34–39, 46, 47, 49–51, 55–57, 60, 64, 69–76, 79, 81). Ptosis is the key manifestation of immune-related MG, and accounts for 75%–78.7% of ICI-induced MG (irMG) (93–96). Only 15% of ptosis continue to be isolated ocular complaints throughout the course of MG. MG is an autoimmune neuromuscular disease caused by antibodies directed against the postsynaptic muscle membrane. Moreover, it is reported as a life-threatening irAE with rapid deterioration shortly following ICI use (93, 97, 98). The most common reported manifestations of ICI-related MG are ptosis (75%), dyspnea (62%), limb weakness (55%), dysphagia (48%), and diplopia (42%) following ICI use (93). Severe muscle dysfunction with respiratory affectation, myocarditis, and/or myositis can also be detected in approximately two-thirds of individuals suffering from MG, and are the most fatal manifestations requiring mechanical support (89, 93). Approximately 20% of the individuals could die of MG upon an increase in respiratory dysfunction (99). In addition, the appearance of ophthalmoplegia caused by irMG can rapidly progress (96). Despite such patients with ptosis in ICI-related MG receiving discontinued ICIs and appropriate treatment with immunosuppression, their mortality rates are reportedly above 40% (100).

The high incidence of ophthalmoplegia in MG and the high mortality of life-threatening inhibitor-induced MG in lung

TABLE 1 | Summary of reported ocular irAEs in lung cancer treated with immune checkpoint inhibitors.

Patient ID	Basic information									Treatment			Outcome		Ref
	Ocular irAEs	Age (years)	Genders	Country	Cancers Diagnosis	Onset (d)	ICIs	Target	Grade	ICIs	Treatment	Follow-up (d)	Ocular	Systemic	
1	Ophthalmoplegia	72	F	Japan	LC	NA	Pembrolizumab	PD-1	NA	NA	PSL (0.5 mg/kg), IVMP	NA	CCR	Alive	46
2	Ophthalmoplegia	77	F	Japan	NSCLC	48	Pembrolizumab	PD-1	NA	NA	NA	203	CCR	Alive	85
3	Uveitis	69	F	USA	SCLC	14	Ipilimumab and nivolumab	PD-L1+ CTLA-4	3	Stop	TS	60	CCR	Alive	73
4	Ophthalmoplegia	79	F	Belgium	LUAD	NA	Pembrolizumab	PD-1	NA	Stop	CHO-I, PSL	97	CCR	Alive	52
5	Uveitis	NA	NA	USA	NSCLC	NA	Pembrolizumab	PD-1	NA	NA	NA	NA	NA	NA	54
6	Uveitis	NA	NA	Japan	NSCLC	NA	pembrolizumab	PD-1	NA	NA	NA	NA	NA	NA	24
7	Dry eye	51	M	Spain	LC	90	Durvalumab	PD-L1	NA	NO	TS	NA	NA	NA	67
8	Uveitis	NA	NA	USA	NSCLC	NA	Avelumab	PD-L1	NA	NA	NA	NA	NA	NA	48
9	Conjunctivitis	NA	NA	Spain	NSCLC	NA	Nivolumab and Ceritinib	PD-L1 +ALK	NA	NA	NA	NA	NA	NA	48
10	Conjunctivitis	NA	NA	Spain	NSCLC	NA	Nivolumab and Ceritinib	PD-L1 +ALK	NA	NA	NA	NA	NA	NA	24
11	Dry eye	72	M	Spain	LC	60	Pembrolizumab	PD-1	NA	NO	NA	NA	NA	NA	24
12	Dry eye	58	M	Spain	LC	180	Pembrolizumab	PD-1	NA	NO	TS	NA	NA	NA	53
13	Uveitis	NA	NA	USA	NSCLC	NA	Pembrolizumab and CPB	PD-1+ chemotherapy	NA	NA	NA	NA	NA	NA	24
14	Dry eye	61	F	Spain	LC	300	Nivolumab	PD-L1	NA	NO	TS,	NA	NA	NA	24
15	Dry eye	64	M	Spain	LC	30	Durvalumab	PD-L1	NA	Stop	TS, PSL, IVMP, PE	NA	NA	NA	24
16	Dry eye	70	M	Spain	LC	540	Nivolumab	PD-L1	NA	Stop	TS	NA	NA	NA	24
17	Dry eye	71	M	Spain	LC	60	Nivolumab	PD-L1	NA	NO	TS	NA	NA	NA	68
18	Orbital inflammation	70	M	Italy	LUAD	30	Durvalumab and tremelimumab	PD-L1+ CTLA-4	NA	Stop	PSL (25 mg)	NA	NA	NA	65
19	Giant cell arteritis	88	F	USA	NSCLC	14	Pembrolizumab	PD-1	NA	NO	PSL	NA	NA	NA	38
20	Dry eye	50	F	Spain	LC	150	Pembrolizumab	PD-1	NA	NO	TS, PSL	NA	NA	NA	38
21	Dry eye	79	F	Spain	LC	30	Pembrolizumab	PD-1	NA	NO	TS, PSL, IVMP	NA	NA	NA	48
22	Conjunctivitis	NA	NA	Spain	NSCLC	NA	Nivolumab and Ceritinib	PD-L1 +ALK	NA	NA	NA	NA	NA	NA	24
23	Dry eye	68	F	Spain	LC	180	Nivolumab	PD-L1	NA	Stop	TS	NA	NA	NA	24
24	Dry eye	72	F	Spain	LC	210	Ipilimumab and nivolumab	PD-L1+ CTLA-4	NA	NO	TS, PSL	NA	NA	NA	67
25	Dry eye	NA	NA	USA	NSCLC	NA	Avelumab	PD-L1	NA	NA	NA	NA	NA	NA	24
26	Dry eye	71	M	Spain	LC	210	Pembrolizumab	PD-1	NA	Stop	TS	NA	NA	NA	69
27	Ophthalmoplegia	NA	NA	USA	SCLC	NA	Ipilimumab and nivolumab	PD-L1+ CTLA-4	NA	NA	NA	NA	NA	NA	56
28	Ophthalmoplegia	NA	NA	China	NSCLC	NA	Pembrolizumab	PD-1	NA	NA	NA	NA	NA	NA	41
29	Corneal graft rejection	58	F	France	NSCLC	126	Nivolumab	PD-L1	NA	Stop	TS, PSL, IVMP	30	Aggravation	Death	37
30	Ophthalmoplegia	57	M	China	LUSC	14	Ipilimumab and nivolumab	PD-L1+ CTLA-4	NA	NA	CHO-I, PSL (1mg/kg/d), IVMP	14	Remission	Alive (PD)	44
31	Orbital inflammation	68	F	USA	NSCLC	14	Ipilimumab	CT+2:73LA-4	NA	Stop	TS, PSL	7	Remission	Alive (PD)	44
32	Uveitis	54	F	USA	NSCLC	28	Ipilimumab	CTLA-4	3	NA	TS	42	Remission	Death	51
33	Ophthalmoplegia	65	M	Italy	LUSC	27	Nivolumab	PD-L1	NA	NA	CHO-I, PSL, IVMP	49	Aggravation	Death	36
34	Ophthalmoplegia	70	M	USA	SCLC	16	Ipilimumab and nivolumab	PD-L1+ CTLA-4	NA	Stop	PSL (90 mg), IVMP, PE	29	Aggravation	Death	76

(Continued)

TABLE 1 | Continued

Patient ID	Basic information									Treatment			Outcome		Ref
	Ocular irAEs	Age (years)	Genders	Country	Cancers Diagnosis	Onset (d)	ICIs	Target	Grade	ICIs	Treatment	Follow-up (d)	Ocular	Systemic	
35	Ophthalmoplegia	74	M	USA	LC	NA	Pembrolizumab	PD-1	NA	NA	CHO-I, PSL (10 mg), IVMP	28	Aggravation	Alive (PD)	25
36	Ophthalmoplegia	64	M	USA	NSCLC	NA	Durvalumab	PD-L1	NA	NA	PSL	NA	Aggravation	Death	37
37	Ophthalmoplegia	65	M	China	LUSC	53	Nivolumab	PD-L1	NA	NO	CHO-I, PSL (1mg/kg),	27	Aggravation	Alive (PD)	34
38	Ophthalmoplegia	76	F	Japan	LUAD	26	Nivolumab	PD-L1	NA	Stop	PSL (10mg), IVMP, PE	65	Remission	Death	74
39	Ophthalmoplegia	68	F	USA	NSCLC	70	Nivolumab	PD-L1	NA	Stop	CHO-I, PSL (60 mg)	18	Aggravation	Death	79
40	Ophthalmoplegia	61	M	France	NSCLC	NA	Nivolumab	PD-L1	NA	Stop	IVMP	77	Remission	Death	78
41	Uveitis	60	F	USA	LC	NA	Ipilimumab and nivolumab	PD-L1+ CTLA-4	NA	NO	PSL, immunosuppressive	84	Remission	Alive (PD)	50
42	Ophthalmoplegia	73	F	Japan	LUSC	140	Nivolumab	PD-L1	NA	NO	CHO-I, PSL (20 mg)	120	Aggravation	Alive (PD)	84
43	Dry eye	36	F	France	LC	39	Pembrolizumab	PD-1	NA	NA	TS, PSL (10 mg)	60	Remission	Alive	57
44	Ophthalmoplegia	73	M	Japan	LUAD	23	Pembrolizumab	PD-1	NA	NA	PSL (20 mg), IVMP	120	Remission	Alive	62
45	Corneal perforation	68	M	Belgium	LUAD	126	Pembrolizumab	PD-1	NA	Stop	TS, Surgery, PSL (32 mg)	30	Remission	Alive	47
46	Uveitis	71	M	Japan	LUSC	14	Pembrolizumab	PD-1	3	Stop	TS, PSL (70 mg)	21	Remission	Alive	81
47	Ophthalmoplegia	69	F	Japan	NSCLC	NA	Nivolumab	PD-L1	NA	NA	PSL, IVMP	36	Remission	Alive	66
48	Retinopathy	40	M	USA	NSCLC	13	Atezolizumab	PD-L1	NA	Stop	NA	21	Remission	Alive	86
49	Retinopathy	64	M	Spain	NSCLC	600	Durvalumab	PD-L1	NA	NO	PSL (30 mg), IVMP	60	Remission	Alive	87
50	Uveitis	53	M	USA	NSCLC	19	Nivolumab	PD-L1	3	Stop	Surgery, PSL (1mg/kg)	9	Remission	Alive	80
51	Uveitis	68	M	USA	LUAD	NA	Atezolizumab	PD-L1	4	Stop	NA	90	Remission	Alive	35
52	Ophthalmoplegia	65	M	USA	NSCLC	14	Nivolumab	PD-L1	NA	Stop	CHO-I,	42	Remission	Alive	45
53	Uveitis	54	F	Japan	LC	NA	Nivolumab	PD-L1	3	NO	TS, PSL (30mg)	135	Remission	Alive	33
54	Optic Neuritis	76	M	Spain	NSCLC	72	pembrolizumab	PD-1	NA	NA	PSL(0.5mg/Kg/day), IVMP	21	Remission	Alive	66
55	Retinopathy	50	M	USA	NSCLC	13	Atezolizumab	PD-L1	NA	Stop	NA	21	Remission	Alive	30
56	Amaurosis fugax	84	M	USA	NSCLC	NA	Nivolumab	PD-L1	NA	NA	NA	NA	Remission	Alive	43
57	Uveitis	61	F	USA	NSCLC	60	Durvalumab	PD-L1	4	NO	TS	30	Remission	Alive	29
58	Uveitis	63	F	France	NSCLC	36	Nivolumab	PD-L1	3	NA	TS	42	Remission	Alive	63
59	Uveitis	61	M	Japan	NSCLC	63	Pembrolizumab	PD-1	NA	Stop	PSL	NA	Remission	Alive	42
60	Retinopathy	64	F	USA	LUAD	7	Nivolumab	PD-L1	NA	Stop	PSL (60mg)	21	Remission	Alive	46
61	Ophthalmoplegia	53	M	Japan	NSCLC	27	Nivolumab	PD-L1	NA	NA	PSL (30mg), IVMP	49	Remission	Alive	60
62	Ophthalmoplegia	83	M	Japan	LUSC	38	Pembrolizumab	PD-1	NA	NA	CHO-I,PSL (20 mg)	51	Remission	Alive	38
63	Ophthalmoplegia	65	M	Espada	LUAD	–	Nivolumab	PD-L1	NA	Stop	CHO-I	NA	Remission	Alive	46
64	Ophthalmoplegia	46	F	Japan	NSCLC	30	Nivolumab	PD-L1	NA	NA	NA	14	Remission	Alive	55
65	Ophthalmoplegia	77	F	Japan	LUAD	49	Pembrolizumab	PD-1	NA	NA	PSL, IVMP	209	Remission	Alive	25
66	Optic Neuritis	74	M	USA	NSCLC	NA	Pembrolizumab	PD-1	NA	Stop	NA	NA	Remission	Alive	46
67	Ophthalmoplegia	78	M	Japan	NSCLC	38	Pembrolizumab	PD-1	NA	NA	PSL (80mg), IVMP	91	Remission	Alive	46
68	Ophthalmoplegia	83	M	Japan	NSCLC	28	Pembrolizumab	PD-1	NA	NA	PSL (20mg)	42	Remission	Alive	71
69	Ophthalmoplegia	66	M	China	LUAD	21	Sintilimab	PD-1	NA	NA	CHO-I, PSL (60 mg), IVMP, IVIg, PE	90	Remission	Alive	61
70	Uveitis	55	F	USA	LC	42	Pembrolizumab	PD-1	2	NA	TS	42	Remission	Alive	83
71	Conjunctivitis	67	M	Switzerland	LUAD	182	Nivolumab	PD-L1	NA	NO	TS	NA	Remission	Alive	82
72	Optic Neuritis	64	M	Japan	NSCLC	365	Pemetrexed	PD-L1	NA	NA	PSL (30 mg), IVMP	3	Remission	Alive	70

(Continued)

TABLE 1 | Continued

Patient ID	Basic information								Treatment			Outcome		Ref
	Ocular irAEs	Age (years)	Genders	Country	Cancers Diagnosis	Onset (d)	ICIs	Target	Grade	ICIs	Treatment	Follow-up (d)	Ocular	Systemic	
73	Ophthalmoplegia	66	M	Australia	LUAD	49	Durvalumab	PD-L1	NA	Stop	CHO-I, PSL (60 mg), IVIg	14	Remission	Alive	75
74	Ophthalmoplegia	66	M	Spain	LC	28	Ipilimumab and nivolumab	PD-L1+ CTLA-4	NA	Stop	CHO-I, IVMP	28	Remission	Alive	46
75	Ophthalmoplegia	73	M	Japan	NSCLC	33	Pembrolizumab	PD-1	NA	NA	PSL (20mg), IVMP	98	Remission	Alive	39
76	Ophthalmoplegia	68	M	USA	NSCLC	30	Durvalumab and tremelimumab	PD-L1+ CTLA-4	NA	NO	PSL (60mg)	30	Remission	Alive	58
77	Uveitis	71	M	Japan	NSCLC	NA	Pembrolizumab	PD-1	3	NA	PSL (30 mg), IVMP	84	Remission	Alive	47
78	Ophthalmoplegia	76	M	South Korea	NSCLC	NA	Nivolumab	PD-L1	NA	NO	CHO-I, PSL, IVMP	30	Remission	Alive	64
79	Ophthalmoplegia	63	F	USA	LUAD	28	Pembrolizumab	PD-1	NA	NA	CHO-I, PSL, IVg	NA	Remission	Alive	75

NSCLC, n-small cell lung cancer; SCLC, small cell lung cancer; LUAD, Lung adenocarcinoma; LUSC, Lung Squamous Cell Cancer; NA, t available; IVMP, Intravenous methylprednisolone; IVig, Intravenous methylprednisolone. CHO-I, cholinesterase inhibitor; TS, Topical steroid; RTD, artificial tear drops; PE, Plasma exchange; CCR, Complete clinical recovery; Ref, reference; PD, Progressive disease; NO, continue.

cancer necessitate an increase in ophthalmoplegia vigilance. This will ensure the timely identification of irMG signs and early treatment, particularly in the early stages of irAEs. In this review, all recruited patients with ophthalmoplegia were diagnosed with MG in lung cancer following the use of ICIs. It could be unilateral (57.89%) or bilateral (42.11%), and the average onset time of ophthalmoplegia was 37.73 days following ICI initiation (**Table 2**). There were 66.67% men, and 66.67% patients were older than 65 years. Ptosis accounted for 90.63% of the patients with ICI-related ophthalmoplegia in lung cancer, followed by diplopia and strabismus.

It is difficult to make a definitive diagnosis of ophthalmoplegia in MG based on the clinical characteristics (101). However, electrophysiology and detectable antibodies could facilitate the diagnosis (102). The edrophonium test, ice pack test, antibody assays (acetylcholine receptor auto-antibodies; anti-muscle-specific tyrosine kinase auto-antibodies; low-density lipoprotein receptor-related protein 4), and neurophysiological tests (repetitive nerve stimulation and single-fibre electromyography) are the necessary examinations for the diagnosis of ptosis in MG (**Table 3**). Ophthalmoplegia in MG in lung cancer secondary to ICIs should be differentiated from other causes, which might also result in ptosis, including central disorders of ocular motility, congenital ptosis, inherited ptosis-associated syndrome, aponeurotic ptosis, and ptosis caused by local eye problems or muscles (103, 104).

Uveitis in Lung Cancer Secondary to ICIs

Uveitis describes a group of inflammatory diseases that produce swelling and destroy the uveal tract. The uveal tract consists of a pigmented, highly vascular, and loose fibrous tissue, prone to immune disorders. It can be divided into three anatomical regions as follows: anterior (involves the iris), intermediate (involves the vitreous humor), posterior (involves the choroid), and panuveitis (widespread involvement across anatomical regions) by the Standardisation of Uveitis Nomenclature Working Group. The aforementioned types of uveitis have varied clinical characteristics, diagnostic tests, and treatment (**Table 3**). Symptoms of pain, redness, photophobia, blurred vision, or floaters can be detected in patients with uveitis. Anterior uveitis is characterized by anterior chamber cells and flare, keratic precipitates, posterior synechiae, iris nodules, and cataracts. The clinical features of intermediate uveitis include grey-white fibrovascular plaques (snowbanks), the presence of cells suspended in the vitreous, vitreous haze, and inflammatory aggregates within the vitreous. In contrast, the characteristics of posterior uveitis include lesions within the retina or choroid, commonly known as white spots. All clinical features of the above-mentioned three types of uveitis were revealed in panuveitis (**Table 3**). Moreover, Vogt-Koyanagi-Harada disease is a common ocular irAE associated with ICIs (45, 58, 105). It is a type of bilateral granulomatous uveitis, associated with exudative retinal detachment and extraocular manifestations, such as pleocytosis in the cerebrospinal fluid and, in some cases, vitiligo, poliosis, alopecia, and dysacusis.

The majority of previously described uveitis on ICI therapy exhibited relatively mild to moderate severity, with ≤2+ anterior

TABLE 2 | Comparison of the ophthalmoplegia, uveitis and other ocular irAEs secondary to ICIs in lung cancer.

	Total (%)	A Ophthalmoplegia (%)	B Uveitis (%)	C Dry eye (%)	D Others (%)	P value Ophthalmoplegia *VS* other irAEs (Uveitis, Dry eye and Others)
NO.	79(100.00)	32(40.51)	16 (20.25)	14 (17.72)	17 (21.52)	
Age	66.22 ± 9.95	69.03 ± 8.22	61.67 ± 6.52	63.31 ± 11.40	66.79 ± 11.94	
Gender						(Male *VS* Female)
Male	42 (53.16)	20 (62.5)	5 (31.25)	7 (50)	10 (58.82)	8.00E-02
Female	27 (34.18)	10 (31.25)	7 (43.75)	6 (42.86)	4 (23.53)	
NA	10 (12.66)	2 (6.25)	4 (25)	1 (7.14)	3 (17.65)	
Age						(≤65 *VS* >65)
≤65	30 (37.97)	10 (31.25)	8 (50)	6 (42.86)	6 (35.29)	2.46E-02
>65	39 (49.37)	20 (62.5)	4 (25)	7 (50)	8 (47.06)	
NA	10 (12.66)	2 (6.25)	4 (25)	1 (7.14)	3 (17.65)	
Onset(d)	86.31 ± 119.81	37.73 ± 26.10	34.50 ± 18.18	159.92 ± 136.79	130.17 ± 136.79	
Ethnicity						(Caucasian *VS* Asian)
Caucasian	59 (74.68)	18 (56.25)	11 (68.75)	14 (100)	16 (94.12)	1.21E-06
Asian	20 (25.32)	14 (43.75)	5 (31.25)	0 (0)	1 (5.88)	
Unilateral or Bilateral						(Unilateral *VS* Bilateral)
Unilateral	28 (35.44)	11 (34.38)	10 (62.5)	0 (0)	7 (41.18)	1.46E-01
Bilateral	16 (20.25)	8 (25.00)	2 (12.5)	0 (0)	6 (35.29)	
NA	35 (44.3)	13 (40.63)	4 (25.00)	14 (100)	4 (23.53)	
ICIs						(PD-1 *VS* PDL-1 *VS* PD-L1+CTLA4)
PD-1	29 (36.71)	13 (40.63)	6 (37.5)	6 (42.86)	4 (23.53)	2.07E-01
PD-L1	35 (44.3)	14 (43.75)	6 (37.5)	7 (50)	8 (47.06)	
PD-L1+CTLA4	9 (11.39)	5 (15.63)	2 (12.5)	1 (7.14)	1 (5.88)	
Others	6 (7.59)	0 (0)	2 (12.5)	0 (0)	4 (23.53)	
Outcome(Ocular)						(Aggravation *VS* Remission)
Aggravation	9 (11.39)	7 (21.88)	0 (0)	1 (7.14)	1 (5.88)	3.98E-04
Remission	47 (59.49)	23 (71.88)	12 (75)	1 (7.14)	11 (64.71)	
NA	23 (29.11)	2 (6.25)	4 (25)	12 (85.71)	5 (29.41)	
Survival state						(Death *VS* Alive)
Death	8 (10.13)	7 (21.88)	1 (6.25)	0 (0)	0 (0)	1.82E-09
Alive	48 (60.76)	23 (71.88)	11 (68.75)	2 (14.29)	12 (70.59)	
NA	23 (29.11)	2 (6.25)	4 (25)	12 (85.71)	5 (29.41)	

NO., number; d, days; NA, not available; d, days; NS, no significant difference; CCR, Complete clinical recovery.

chamber cells and vitreous cells (28, 30, 77). In our review, 16 patients with uveitis and six patients did not manifest the detailed clinical features. Among the remaining patients with lung cancer, 70.00% were classified as grade 3 with anterior uveitis, comprising ≥3+ cells or intermediate posterior or panuveitis, based on the Common Terminology Criteria for Adverse Events (Version 5.0). While a total of 20.00% were classified as grade 4, only 10.00% were classified as grade 1 (**Table 2**). The average onset days of uveitis was 34.50 days on ICIs (**Tables 2**, **3**). There were 41.67% male patients, and 33.33% patients were older than 65 years. Moreover, 83.33% cases were unilateral.

Ocular examination including slit-lamp examination, ultrasound biomicroscopy, optical coherence tomography (OCT), ophthalmoscopy, fluorescein angiography or indocyanine green angiography are adapted for the diagnosis of uveitis. Diagnosis could be made based on clinical evidence including the clinical features and positive signs for auxiliary examination. Uveitis in lung cancer secondary to ICIs need to be differentiated from other disorder which might to presents as uveitis, including: infectious uveitis due to tuberculosis, syphilis or toxoplasma or other bacteria, autoimmune related uveitis, masquerade uveitis (105) (**Table 3**).

Dry Eye in Lung Cancer Secondary to ICIs

Dry eye disease is a multifactorial disorder of the tears and ocular surface, that caused by tear deficiency or excessive tear evaporation (106). It has been classified as dry eye with reduced tear production (occupying approximately 10%) and dry eye with increased evaporation of the tear film (hyperevaporative disorders) (107). Dysfunction of the meibomian glands is the primary cause of the hyperevaporative disorders and occupied more than 80% of the patients with dry eye (108). Dryness, redness, fatigue, photophobia, a sensation of burning, stinging or foreign body or pruritus could be detected. Pronounced conjunctival redness and punctate epithelial erosions of the cornea are typical clinical manifestations of dry eye (107). Inflammation of the lid margin or meibomian glands could be detected in dry eye caused by hyperevaporative disorders. In addition, dry eye could be one of the manifestations of systemic syndrome, such as Sjögren's syndrome. Sjögren's syndrome is an intractable autoimmune disease, characterized by dry eye, dry mouth, and extra glandular syndrome (109). In this review, patients with sjögren's syndrome consisted of 92.86% of dry eye following ICI in lung cancer.

A comprehensive history (symptoms, systemic diseases and medication history), tear film break-up time with fluorescein, schirmer test, examination of the eyelid margins and meibomian

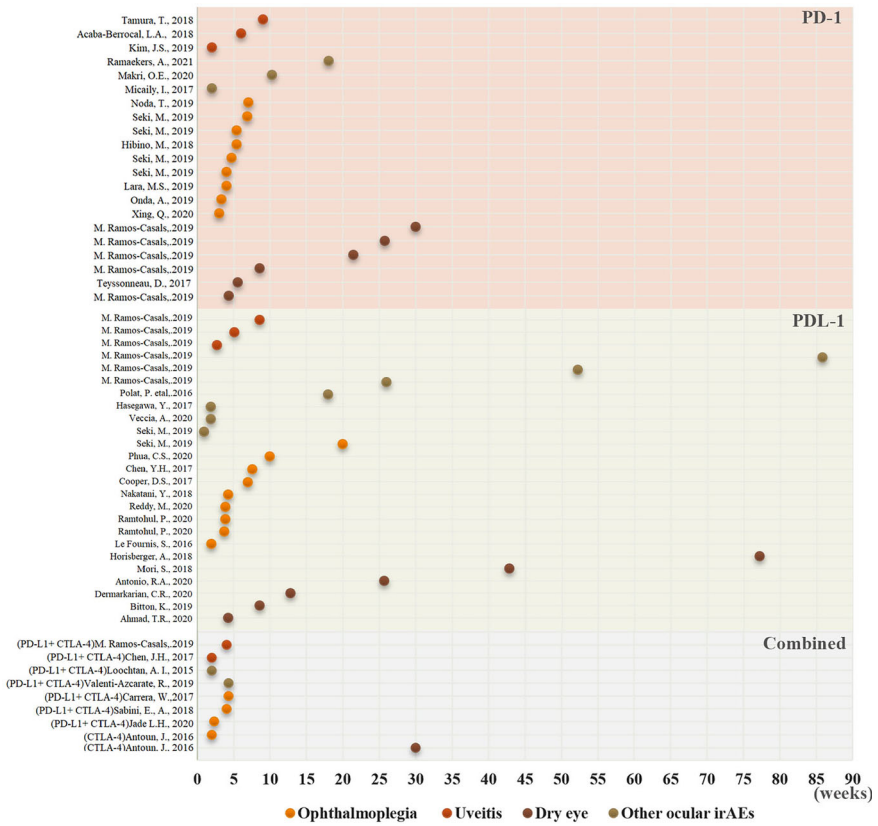

FIGURE 2 | The onset time of the distribution of different ocular irAEs in lung cancer following ICI use. The onset time of ocular irAE detection has been recorded as a dot. Yellow, ophthalmoplegia; dark yellow, uveitis; brown, dry eye; and darkgray, other ocular irAEs.

gland orifices with expression of meibomian secretion could be conducted based on the diagnostic guidelines were published in 2007 by the Dry Eye Workshop (107, 110). In addition, screening for autoimmune diseases should be done as well, especially for Sjögren syndrome (111). The Gum test, the unstimulated whole saliva, saxon test, the labial salivary glands biopsy, and parotid glands biopsy are helpful for the diagnosis of Sjögren syndrome (109).

Conjunctivitis

Conjunctivitis caused by ICIs are the inflammation of conjunctiva which covers the inner surface of the eyelids and the white part of the eyeball. The blood vessels are enlarged and become more prominent in conjunctivitis. Red eye is the most common signs of conjunctivitis. Itchy, watery, burning or stinging eye and foreign-body sensation could be detected in patients with conjunctivitis. Ophthalmologist could give a diagnosis of conjunctivitis based on the Slit-lamp examination. Sodium hyaluronate, antihistamine eye drops or topical corticosteroids can help with symptoms of conjunctivitis after use of ICIs.

Corneal Perforation

Corneal perforation is the thinning and perforation of the cornea. Red eyes, severe pain, foreign-body sensation, tears, thick discharge, blurry vision, pain when looking at bright lights, swollen eyelids, and a white round spot on the cornea that is visible to the naked eye. The classic signs are shallowing or flattening of the anterior chamber, aqueous leakage, brown pigment from the iris in the wound could be detected. For the treatment of the corneal perforation, the first step is to discontinue the ICIs (112). Medical treatment is the second therapeutic step, including artificial tear drops, corticosteroids and cyclosporine. Timely diagnosis and prompt medical treatment could improve the rate of the surgical success (62, 112). Several surgical strategies could be used and it depends on the size, position, and depth of the ulceration (112, 113). The surgical management of corneal perforation includes corneal gluing, Collagen cross-linking with photo-activated riboflavin, Amniotic membrane transplantation, Conjunctival flap transplantation, Corneal transplantation.

Corneal Graft Rejection

Corneal graft rejection is a complex immune-mediated response, which leads to corneal graft decompensation (114). The rejection can occur in all of the layers of the cornea (epithelium, stroma and endothelium). Pain, redness, and decreased vision could be present in patients suffering corneal graft rejection. Conjunctival

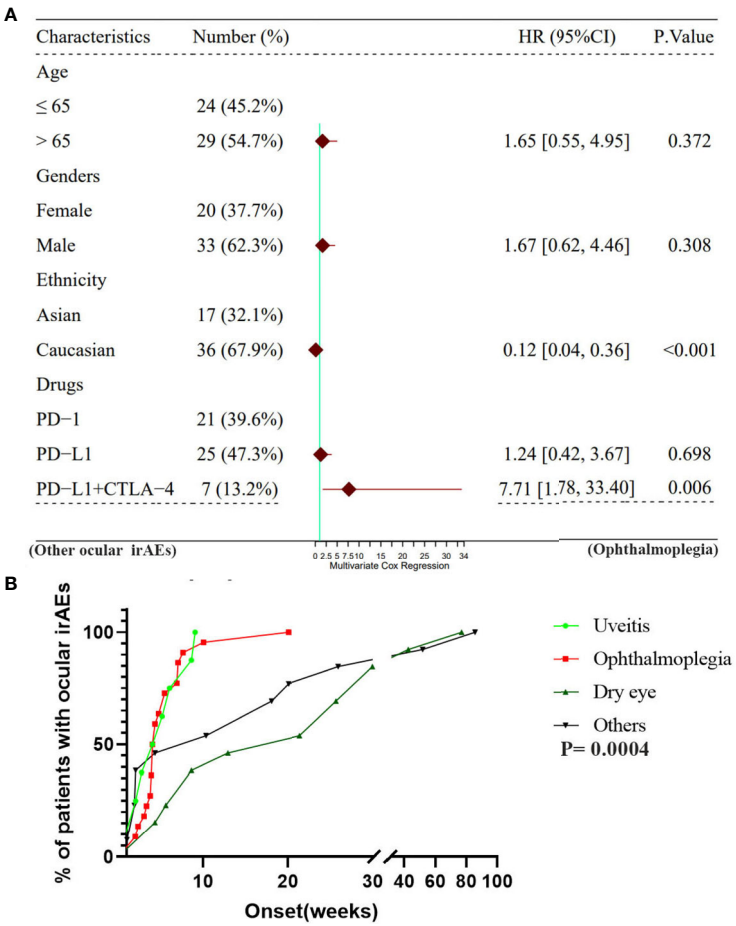

FIGURE 3 | **(A)** A multivariate cox regression analysis for the ocular irAEs among age, gender, ethnicity, ICIs drugs. **(B)** A comparison of the onset time of ocular irAEs among ophthalmoplegia, uveitis, dry eye, and other ocular irAEs.

hyperemia, keratic precipitates, opacity and edema of corneal graft could be detected. It is not difficult to give diagnosis of corneal graft rejection based on the slit-lamp microscope. Prevention, early detection, and rapid management are crucial for the management of graft rejection (114, 115). Stop the ICIs is the essential which have been recommended in the previous study (41). Corticosteroids (Topical and systemic corticosteroids, intravenous pulsed corticosteroid therapy), cytotoxic agents (azathioprine), cyclosporin A have been used for management of corneal graft rejection (114).

Retinopathy

Retinopathy after use of ICIs might be caused by abnormal cross-reactivity of autoantibodies directed to retinal antigens. Vision loss, scotomas, photopsia, nyctalopia could be found in patients with retinopathy (116). Optical coherence tomography, fundus autofluorescence, visual field and electrophysiology could help us to detect to lesion on the retina. Medical history and physical exam findings are important for us to determine the risk factors of immune related retinopathy. High suspicion and early diagnosis and treatment are essential to reduce the risk of irreversible immune damage to retinal cells. Systemic and/or topical corticosteroids, immunomodulators (cyclosporine, infliximab, et al), biologics (rituximab, alemtuzumab, et al), intravenous immunoglobulin (IVIG) and plasmapheresis have been advocated for the treatment of immune related retinopathy (116–118).

Optic Neuritis

Typically, optic neuritis is unilateral. Eye pain, vison loss, the loss of the visual field, flashing lights could be detected in patients with optic neuritis. Ocular examination including slit-lamp examination, pupillary light reaction test, optical coherence tomography, visual field test, visual evoked response is adapted for the diagnosis of optic neuritis (119, 120). High-dose corticosteroids is effective for the treatment of optic neuritis. For the steroid-resistant optic neuritis, plasma exchange is needed (119).

Amaurosis Fugax

Amaurosis fugax refers to transient visual loss caused by the temporary ceasing of the retinal blood flow (121, 122). The time

TABLE 3 | The clinical characteristics, diagnosis, and treatment for ocular irAEs on ICIs therapy in lung cancer.

Ocular irAEs		Clinical characteristics	Diagnosis test	Treatment
Ophthalmoplegia		Ocular: ptosis, diplopia, blurred vision	1. Edrophonium test 2. The ice pack test 3.Antibody assays (ACht Ab; Anti-MuSK Ab; LRP4	1. Cholinesterase inhibitor 2. Systemic Corticosteroids 3. IVMP, IVig, PE, Stop ICIs when necessary
		Systemic: Difficulty in breathing, swallowing, chewing, walking, using arms or hands, or holding up head.	4.Neurophysiological tests (RNS and SfEMG)	
Uveitis	Anterior uveitis	Pain, redness, photophobia, blurred vision; Anterior chamber cells and flare; keratic precipitates, posterior synechiae, iris nodules and cataract.	Slit-lamp examination	1. Topical Corticosteroids 2. Topical mydriatics
	Intermediate uveitis	Floaters and blurred vision; Vitreous cells, vitreous haze, 'snowbanks' (grey-white fibrovascular plaques).	Slit-lamp examination; Anterior segment OCT	1. Topical Corticosteroids 2. Systemic Corticosteroids
	Posterior uveitis	'Floaters', blurred vision and blind spots; Unifocal, or multifocal, generally white lesions.	Ophthalmoscopy; OCT; FFA	1. Topical corticosteroids 2. Systemic corticosteroids 3. Subconjunctival/Periocular corticosteroids 4. IVMP, IVig, PE, Stop ICIs when necessary
	Panuveitis	All clinical characteristics of the anterior, intermediate and posterior uveitis	All diagnosis test of the anterior, intermediate and posterior uveitis	All diagnosis treatment of the anterior, intermediate and posterior uveitis
Dry eye		Eye dryness, eye redness, eye fatigue, photophobia, a sensation of burning, stinging or foreign body	Ocular: Tear film break-up time with fluorescein, Schirmer test, examination of the eyelid margins and meibomian gland orifices with expression of meibomian secretion (For dry eye in Sjögren syndrome) Systemic: The Gum test, the unstimulated whole saliva, Saxon test, the labial salivary glands biopsy, and parotid glands biopsy	Artificial tears, Autologous serum eyedrops, Topical corticosteroid, Topical Cyclosporine A
Conjunctivitis		Red, itchy, watery, burning or stinging eye and foreign-body sensation	Slit-lamp microscope	1. Topical sodium hyaluronate, antihistamine eye drops 2. Topical corticosteroids
Corneal perforation		Red eyes, severe pain, foreign-body sensation, tears, blurry vision, swollen eyelids	Slit-lamp microscope	1. Discontinue the ICIs 2. Topical artificial tear drops, corticosteroids and cyclosporine; 3. IVMP, IVig, PE when necessary
		White spot on cornea, edema of cornea		
Corneal graft rejection		Pain, redness, and decreased vision, conjunctival hyperemia, keratic precipitates, opacity and edema of corneal graft	Slit-lamp microscope	1. Discontinue the ICIs 2. Topical artificial tear drops, corticosteroids and cyclosporine; 3. IVMP, IVig, PE,cytotoxic agents, cyclosporin A when necessary
Retinopathy		Vision loss, scotomas, photopsia, nyctalopia	OCT, FFA, VF and electrophysiology	1. Topical Corticosteroids 2. Systemic Corticosteroids 3. IVMP, IVig, PE when necessary
Optic neuritis		Eye pain, vison loss, the loss of the visual field, flashing lights	Slit-lamp microscope, pupillary light reaction test, OCT, visual field test, visual evoked response	1. Systemic corticosteroids 2. Subconjunctival/Periocular corticosteroids 3. IVMP, IVig, PE when necessary
Amaurosis fugax		Transient visual loss	Comprehensive ocular examination and assessment of cardiovascular system (electrocardiogram, magnetic resonance angiography, blood test)	Control and treat potential vascular risk factors

(Continued)

TABLE 3 | Continued

Ocular irAEs	Clinical characteristics	Diagnosis test	Treatment
Giant cell arteritis	Blurred vision, diplopia, amaurosis fugax and blindness Headaches, scalp tenderness, jaw claudication, absent pulses and limb claudication	Ophthalmoscopy, FFA and ICGA are needed. Additionally, biopsy of the temporal artery, high-resolution color doppler ultrasound of the cranial and axillary arteries, MRI, CT scan	1. Systemic corticosteroids 2. Subconjunctival/Periocular corticosteroids 3. IVMP, IVig, PE, Stop ICIs when necessary
Orbital inflammation	Eye pain, proptosis, decreased visual acuity, and diplopia	Laboratory evaluation, Orbital ultrasound, Computed Tomography, and Magnetic Resonance Imaging	1. Systemic corticosteroids 2. Nonspecific steroid-sparing agents(methotrexate, cyclosporin-A et al), biologic agents (infliximab, adalimumab and so on) and radiation therapy

OCT, Optical Coherence Tomography; VEP, Visual Evoked Potential; FFA, Fundus Fluorescein Angiography; UBM, Ultrasound Biomicroscopy; CT, Computed Tomographic Scans; TBUT, tear film break-up time with fluorescein; IVMP, Intravenous methylprednisolone; IVig, Intravenous methylprednisolone; PE, Plasma exchange.

of amaurosis fugax could be last 2-30 minutes. Hypoperfusion, vasospasm, thromboembolism from a carotid plaque, elevated plasma viscosity and cerebrovascular disease could be pathogenic causes of amaurosis fugax (121). Comprehensive ocular examination and assessment of cardiovascular system is essential. An electrocardiogram, Magnetic resonance angiography, blood test and so on should be performed. The primary goal of treatment is to control and treat potential vascular risk factors (121).

Giant Cell Arteritis

Giant cell arteritis is primary vasculitis which mostly invades large vessels. The clinical characteristics is with strong heterogeneity, the common systemic manifestations are headaches, scalp tenderness, jaw claudication, vision loss, absent pulses and limb claudication (123, 124). About two-thirds patients could be detected ocular symptoms. Blurred vision is the most common manifestations (125). Diplopia, amaurosis fugax and blindness could be also present. Comprehensive ocular examination including ophthalmoscopy, FFA and ICGA are needed. Additionally, biopsy of the temporal artery, high-resolution color doppler ultrasound of the cranial and axillary arteries, MRI, CT scan need to be recommended for the diagnosis of Giant cell arteritis. Glucocorticoids has been considered as the primary treatment for Giant cell arteritis. Tocilizumab is also been approved by the FDA (124).

Orbital Inflammation

Orbital inflammation is characterized by infiltration of inflammatory cells, which is confined to the orbit, but may extend to the extraorbital area. Categories of orbital inflammation include dacryoadenitis, myositis, perineuritis of the optic nerve, periscleritis, diffuse sclerosing inflammation, and orbital apex inflammation. Eye pain, proptosis, decreased visual acuity, and eye movement restriction that may result in diplopia were the most common symptoms. Obvious orbital masses can be found by radiologic examination (126). Laboratory evaluation, Orbital ultrasound, Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) may aid in the diagnosis when combined with clinical findings (127). Current therapeutic methods available for orbital inflammation include corticosteroids, nonspecific steroid-sparing agents(methotrexate, cyclosporin-A et al), biologic agents (infliximab, adalimumab and so on) and radiation therapy (128).

CONTRIBUTORY FACTORS OF OCULAR irAEs IN LUNG CANCER SECONDARY TO ICIS

Ethnicity

Asian and Caucasian patients with lung cancer have different epidemiology, molecular profiles, and genetic susceptibilities (129, 130). Different incidences of irAEs secondary to ICIs could be detected between Asian populations and Western populations. The irAEs of grades 3–5 also present different prevalence rates between Asian and Western populations

(131). Moreover, researchers could also detect differences in ocular irAEs associated with ICIs. A review of the IRIS Registry reported on a higher frequency of ocular irAEs in the Black population (9.7%, six of 62 patients) than that in the White population (3.5%, 91 of 2623 patients) (30). In addition, the Black population demonstrated a higher rate of ICI-related uveitis than their White counterparts.

In this review, among all patients with lung cancer and ocular side effects, 68.12% and 31.88% were Caucasians and Asians, respectively. The majority of patients with ICI-related ocular irAEs were reported in America (42.03%) and Japan (26.09%). The incidence of ophthalmoplegia was 43.75% (14/32) in Asians, compared to 12.77% (6/47) in Caucasians (**Table 2**, **Figure 3**, and **Figure S1**). Based on the multivariate Cox regression analysis, ethnicity was presented as an important factor that influenced ocular irAEs (**Figure 3**). Ophthalmoplegia was more frequently detected in Asians than in Caucasians (**Table 2** and **Figure 3**). However, no significant difference has been detected in the onset time of ocular irAEs in lung cancer (**Figure S1**). Thus, ethnicity could be an important factor in the type of ocular irAEs following ICI use.

Types of ICIs

CTLA-4 inhibitors are reportedly associated with a higher frequency of irAEs and distinct profiles, compared to PD-1 inhibitors (132, 133). Moreover, the proportion of grade 3-4 irAEs is higher with CTLA-4 inhibitors (31%), compared to PD-1 inhibitors (10%) (132, 134). Data from a recent clinical trial reported on lower overall incidence of AEs in monotherapy with ICIs than that of combination therapy in NSCLC (89, 135). Furthermore, PD-L1 inhibitors combined with chemotherapy have a higher incidence of irAEs than monotherapy with PD-L1 inhibitors (98.2% *vs*. 70.9%, respectively) in NSCLC (92, 116, 117). Researchers have also identified differences in the distribution and incidence of ocular irAEs. Ocular surface adverse effects occur more frequently with PD-L1 (31). Uveitis is more likely to occur in patients following ICI therapy with CTLA-4 inhibition than in those with PD1 inhibition (14, 30, 136). In addition, ocular myasthenia reveals the highest association with nivolumab, followed by pembrolizumab (136).

Based on the reported ICI-related ocular irAEs, 44.30% of the patients with lung cancer were treated with PD-L1 inhibitors. In contrast, 36.71% and 11.39% were treated with PD-1 inhibitors and PD-L1 plus CTLA4 inhibitors, respectively. There was no significant difference in the distribution of ocular irAEs between PD-L1 inhibitors and PD-1 inhibitors. Nonetheless, significant differences were detected between monotherapy (PD-L1/PD-1 inhibitors) and combined therapy (PD-L1 plus CTLA4 inhibitors) (**Table 2** and **Figure 3**). Based on the multivariate Cox regression analysis, combined therapy was significantly more prone to ophthalmoplegia than monotherapy (**Figure 3**). The average onset time of ICI-related ocular irAEs with combined therapy with PD-L1 plus CTLA4 inhibitors (6.98 weeks) was shorter than that in patients treated with PD-1 (8.88 weeks) and PD-L1 inhibitors (17.47 weeks). However, the difference was insignificant (**Figure S1**).

Pre-Existing Disorders

Pre-existing disorders are the most important risk factors for ICI-induced irAEs (137, 138). Moreover, 27% of the patients with a history of autoimmune diseases could suffer from exacerbations of the autoimmune condition, which requires systemic treatment following the use of ICIs (30). With a history of non-ophthalmic autoimmune diseases, ocular irAEs could be detected in 27-40% patients undergoing ICI treatment (30, 139). The incidence of ICI-related uveitis could be as high as 51.10% in patients with prior uveitis diagnosis, and up to 36.40% of patients experience various neuro-ophthalmic complications (139). In addition, approximately 20.00% of the patients with Sicca/Sjögren's syndrome following the use of PD-1/PD-L1 checkpoint inhibitors reportedly have a history of previous autoimmune diseases (personal or familial), thereby indicating a predisposing immunogenetic background, according to the data from the International Immuno Cancer Registry (ICIR) (24). In this review, one patient with lung cancer reported a history of inactive uveitis. Following ICI use for 2 months, uveitis with 2+ anterior chamber cells and fine keratic precipitates were detected in both eyes (43). Therefore, pre-existing autoimmune diseases could play a non-negligible role in the occurrence of ICI-related ocular irAEs, thus warranting more attention to medical history.

Other Factors

Age

According to a retrospective study, patients older than 70 years demonstrated comparable efficacy and safety outcomes for ICIs than younger patients (140). Better long-term outcomes were detected in older patients (140, 141). Furthermore, irAEs followed by ICIs had similar efficacy outcomes. Grade 3–4 irAEs rates did not reveal statistical differences between older (11%, ≥70 years) and younger patients (12%, <70 years) (142, 143). In this review, the mean age at the time of ocular irAE diagnosis in patients with lung cancer was 66.84 ± 10.36 years. Based on the multivariate Cox regression analysis, the age was not an influencing factor for ocular irAEs (p= 0.37). However, patients in pivotal clinical trials were commonly selected, particularly older patients with ICIs as are frailer (144, 145). In addition, there are limited reports on ocular irAEs in lung cancer, therefore necessitating further evaluation of the efficacy and safety of ICIs for older patients in a real-life setting (**Figure 3** and **Figure S1**). Moreover, the onset time of ocular irAEs is not related to the age of patients with lung cancer.

Gender

Throughout the course of life, the incidence of malignancy is higher in men than women (146). However, cancer treatments in men have also demonstrated significantly better outcomes than those in women. Gender is a reportedly relevant element that modulates the expression of the PD-1 pathway (147). In addition, male patients demonstrate a better efficacy of single agent ICIs treatment than their female counterparts (147, 148). No studies have illustrated the difference in ICI-related irAEs between men and women (146, 149). Considering the

vulnerability of women to autoimmune responses, the frequency of irAEs following ICIs might be more likely to occur in women than in men. In this review, females accounted for 39.13% of the patients with ocular irAEs in lung cancer. Moreover, we detected no significant gender difference among patients with ophthalmoplegia and other ocular irAEs, based on the multivariate Cox regression (**Table 2**, **Figure 3**, and **Figure S1**).

Types of Tumor

Different tumor types may cause different irAEs following ICIs. In a previous review involving 6938 patients with different tumor types, melanoma showed a higher incidence of gastrointestinal and skin irAE and lower incidence of pneumonitis after use of ICIs (132). In general, NSCLC represents 85% of all lung tumors, and the other 15% is SCLC (150, 151). In a review involving 14256 patients with lung cancer, it concluded that the incidence of ICI-related irAEs in individuals with NSCLC is less than with SCLC (21). While in this review, only three patients with SCLC suffered ocular irAEs. No studies with a large sample size of individuals focus on the ocular irAEs are reported and we cannot conclude the difference of the incidence of ocular irAEs between SCLC and NSCLC (21).

MANAGEMENT STRATEGIES AND OUTCOMES FOR OCULAR irAEs

For the treatment of the ocular irAEs following ICIs, almost all cases of ocular irAEs were managed with conservative treatment, including topical or periocular corticosteroids. Symptomatic treatment is essential for controlling ocular irAEs, such as topical sodium hyaluronate for dry eye and cyclosporine for corneal perforation (152–154). Systemic treatment and suspension of ICIs were used in uncontrolled and serious cases, such as corneal graft rejection, corneal perforation. Based on the recommended guidelines of the ocular irAEs. The management and outcome of ophthalmoplegia, uveitis and dry eye had been described in detail as follows. Other ocular irAEs have been simply described clinical manifestation of ocular irAEs in part 3.

Management Strategies and Outcomes for Ophthalmoplegia

Cholinesterase inhibitors (pyridostigmine) are the mainstay of therapy for ophthalmoplegia in MG. They are quick, safe, and free of long-term side effects (155). However, corticosteroids are required if cholinesterase inhibitors produce no response. A randomized controlled trial compared prednisone and placebo in patients with ocular MG who had previously failed to achieve minimal manifestation status, following 4 to 6 weeks of pyridostigmine use. Eighty-three percent of the patients under prednisone treatment acquired faster and better remission than those receiving placebo (156). Corticosteroids are widely available and cheap, and are the next step of treatment. They reportedly reduce the rate of generalization in patients with ptosis in MG (157). Low-dose corticosteroids might be more effective for ptosis in MG, and may decrease side effects with high-dose corticosteroids. Therapy with immunosuppressive and intravenous immunoglobulin or plasmapheresis have been found effective in a cohort of patients with MG (93, 94). It could also be used in patients treated with corticosteroids who were still symptomatic or had contraindications to corticosteroids, and experienced severe side effects with advanced systemic affections (89, 158). Suspending ICIs therapy is not necessary for the treatment of ophthalmoplegia in severe autoimmune MG (159). In this review, 84% of ocular irAEs in lung cancer followed by ICIs could acquire complete clinical recovery (**Table 2** and **Figure 4**). The rate of ophthalmoplegia aggravation (23.33%) was significantly higher than that of other ocular irAEs (7.69%). In addition, the mortality of patients with ICI-related ophthalmoplegia was higher in lung cancer as well.

Management Strategies and Outcomes for Uveitis

Therapies for ICI-induced uveitis focus on controlling inflammation and decreasing the frequency of recurrence. Mydriasis prevents the formation of iris adhesions. Moreover, it can relieve photophobia from iris sphincter spasm and the pain of ciliary muscle action associated with iridocyclitis. Topical corticosteroids and systemic corticosteroids are the mainstays of treatment. The probability of uveitis relapse necessitates the maintenance of corticosteroids for patients who continue ICI therapy (160). Topical corticosteroids are usually effective in controlling inflammation in anterior uveitis. However, systemic corticosteroids are required for severe anterior uveitis, posterior uveitis, or panuveitis in lung cancer following ICI use (161). In addition, subconjunctival corticosteroids, intravitreal dexamethasone implant, and triamcinolone periocular space injection could also be effective. Uveitis detection might not be a sign to suspend ICI therapy, as the majority of ocular irAEs could acquire an excellent and rapid response to conventional treatment, with generally favorable clinical outcomes (28). In our review, all patients with uveitis in lung cancer following ICI use could be remised or acquired complete clinical recovery. Moreover, the average time of remission was 62.82 ± 38.48 days (**Table 2** and **Figure 4**), consistent to previous studies (28, 32, 88).

Management Strategies and Outcomes for Dry Eye

Preservative-free artificial tears are the mainstay of therapy for all severity grades of dry eye, which could increase tear film stability, improve contrast sensitivity and the optical quality of the surface. Autologous serum eyedrops could be useful and apply in in severe cases of dry eye. In addition, anti-inflammatory treatment should be conducted in moderate to severe cases with dry eye. Topical corticosteroid eyedrops for 2 to 4 weeks had been reported symptomatic improvement in a randomized and double-masked study (162). Cyclosporine A could increase the production of tear fluid, and had been reported to reduce symptoms, improve the Schirmer test values in previous studies (109, 111, 163). It had been

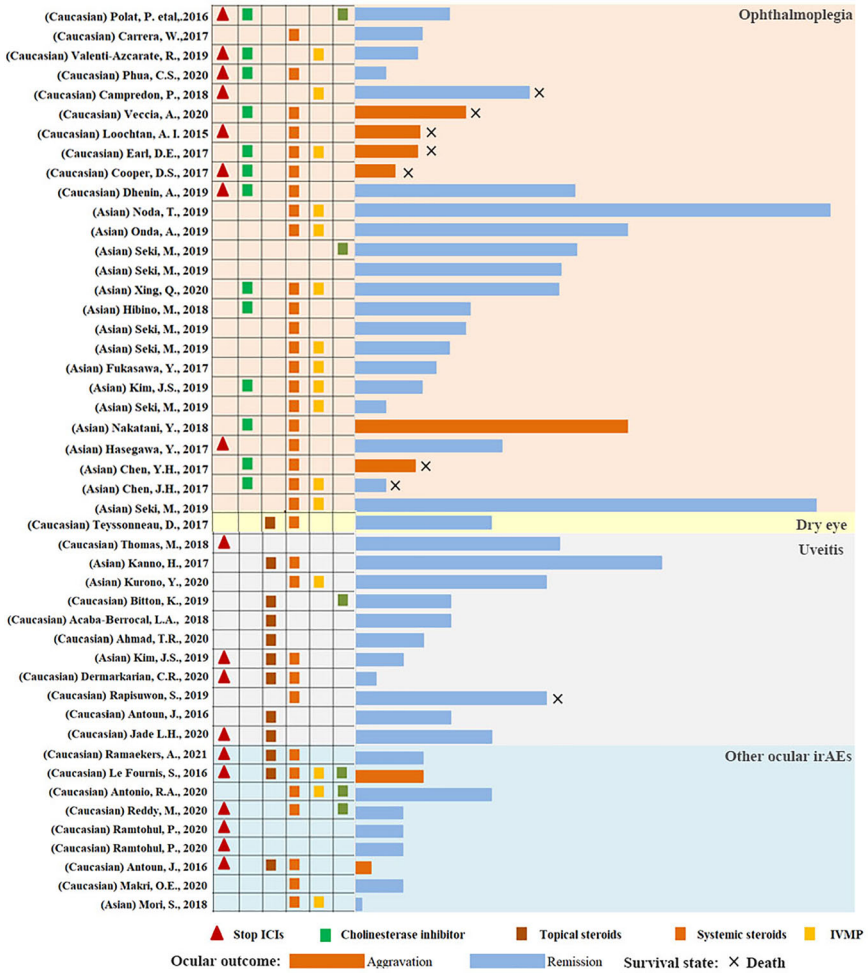

FIGURE 4 | The course of the ocular irAEs following ICI use in lung cancer. The column indicates the length of the complication in each patient with ocular irAEs. Light pink, light gray, light yellow, and light blue represent ophthalmoplegia, uveitis, dry eye, and other ocular irAEs. The blue column represents remission or complete recovery. The dark yellow column represents an aggravation of disease or death.

approved by FDA for treatment of dry eye. However, systemic corticosteroid, immunosuppression or suspension of ICIs are not recommended for dry eye (109).

LIMITATIONS

There are several limitations in this review. At first, the sample size is limited. Only 79 patients with ocular irAEs in lung cancer had been searched. Most of the recruited cases are from case report or case series, we cannot deduce the accurate incidence of the ocular irAEs in lung cancer following ICIs. Moreover, some ocular irAEs with a lower frequency might not be reported. Secondly, most of studies were focused on the systemic irAEs not the ocular irAEs and the detailed clinical characteristics of the ocular irAEs are not available. The treatment of the ocular irAEs in different studies were not identical as well, including the initiation time and dose of the drugs, the types of drugs, following time and so on. We do not summarize the detailed features and treatment of each ocular irAEs based on the recruited studies.

CONCLUSIONS

ICIs have greatly changed the prognosis of lung cancer, which was previously considered as a fatal tumor. With the widespread use of ICIs, more and more related toxicities have been reported. Although ocular irAEs are infrequent based on the previous study, they can cause a deterioration of the quality of life and exert an influence on the compliance of patients. Lots of studies have reported the ocular adverse events secondary to ICIs (19, 25, 26, 30, 31, 153, 164–168) and the grade of the adverse events had been published recently based on Common Terminology Criteria for Adverse Events. While no study had reported the ocular irAEs in lung cancer. Previously, dry eye and uveitis were

the most common ocular irAEs. However, ophthalmoplegia especially ptosis, has been considered as the most common reported irAEs in lung cancer in this study.

All of the patients with ophthalmoplegia secondary to ICIs are the complication of myasthenia gravis in this study. While the most fatal manifestations including respiratory depression and myocarditis can be detected in approximately two-thirds of individuals with myasthenia gravis. The high incidence of ophthalmoplegia with myasthenia gravis in ocular irAEs and the high mortality of life-threatening myasthenia gravis in lung cancer necessitate an increase in ophthalmoplegia vigilance. This reminds us of timely identification of the ophthalmoplegia with myasthenia gravis, particularly in the early stages of irAEs. Based on this study, we found that the prevalence of ophthalmoplegia in Asian, the combination therapy of PD-L1+CTLA4 inhibitors were significantly higher than uveitis or other ocular irAEs. Pre-exiting autoimmune diseases could cause a higher incidence of the ocular irAEs in lung cancer. The onset time of the ophthalmoplegia is earlier than other ocular irAEs (within 10 weeks after initiation of ICIs). This could help us to easily diagnose and identify the ocular irAEs, especially for ophthalmoplegia.

Due to the sample size of ocular irAEs in lung cancer is limited and most of the recruited patients were come from case reports, further additionally studies on ocular irAEs were urgently needed to illustrate the ICI-related ocular irAEs. The understanding of ocular irAEs is necessary to guide the proper prevention and treatment plan and improve the quality of life of patients. Open communication between internist, oncologist and ophthalmologists is necessary to identify and manage the ocular irAEs.

AUTHOR CONTRIBUTIONS

LZ searched the literature and wrote the manuscript and conducted the statistics analysis. XW revised the manuscript, and verified the study. All authors contributed to the article and approved the submitted version.

FUNDING

Supported by grants from the Natural Science Foundation of China (No. 82070954); The Applied Basic Research Programs of Science and Technology Commission Foundation of Sichuan Province (No. 19YYJC0790); The Innovative Spark Grant of Sichuan University (No. 2018SCUH0062).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.701951/full#supplementary-material

REFERENCES

1. Cai Z, Xu D, Zhang Q, Zhang J, Ngai SM, Shao J. Classification of Lung Cancer Using Ensemble-Based Feature Selection and Machine Learning Methods. *Mol Biosyst* (2015) 11:791–800. doi: 10.1039/c4mb00659c
2. Bade BC, Dela Cruz CS. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. *Clin Chest Med* (2020) 41:1–24. doi: 10.1016/j.ccm.2019.10.001
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* (2018) 68:394–424. doi: 10.3322/caac.21492
4. Suresh K, Naidoo J, Lin CT, Danoff S. Immune Checkpoint Immunotherapy for Non-Small Cell Lung Cancer: Benefits and Pulmonary Toxicities. *Chest* (2018) 154:1416–23. doi: 10.1016/j.chest.2018.08.1048
5. Bodor JN, Boumber Y, Borghaei H. Biomarkers for Immune Checkpoint Inhibition in Non-Small Cell Lung Cancer (NSCLC). *Cancer* (2020) 126:260–70. doi: 10.1002/cncr.32468
6. Khan M, Lin J, Liao G, Tian Y, Liang Y, Li R, et al. Comparative Analysis of Immune Checkpoint Inhibitors and Chemotherapy in the Treatment of Advanced Non-Small Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials. *Med (Baltimore)* (2018) 97:e11936. doi: 10.1097/MD.0000000000011936
7. Apetoh L, Ladoire S, Coukos G, Ghiringhelli F. Combining Immunotherapy and Anticancer Agents: The Right Path to Achieve Cancer Cure? *Ann Oncol* (2015) 26:1813–23. doi: 10.1093/anNonc/mdv209
8. Bodor JN, Kasireddy V, Borghaei H. First-Line Therapies for Metastatic Lung Adenocarcinoma Without a Driver Mutation. *J Oncol Pract* (2018) 14:529–35. doi: 10.1200/JOP.18.00250
9. Motzer RJ, Escudier B, George S, Hammers HJ, Srinivas S, Tykodi SS, et al. Nivolumab *Versus* Everolimus in Patients With Advanced Renal Cell Carcinoma: Updated Results With Long-Term Follow-Up of the Randomized, Open-Label, Phase 3 CheckMate 025 Trial. *Cancer* (2020) 126:4156–67. doi: 10.1002/cncr.33033
10. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab *Versus* Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med* (2015) 373:1803–13. doi: 10.1056/NEJMoa1510665
11. Lai LT, Zhan ZY, Feng M, Li F, Lai LF, Zhong LX. Immune Checkpoint Inhibitors for the Management of Advanced Non-Small-Cell Lung Carcinoma: A Meta-Analysis. *Anticancer Drugs* (2020) 31:637–45. doi: 10.1097/CAD.0000000000000921
12. Yoneda K, Imanishi N, Ichiki Y, Tanaka F. Immune Checkpoint Inhibitors (ICIs) in Non-Small Cell Lung Cancer (NSCLC). *J UOEH* (2018) 40:173–89. doi: 10.7888/juoeh.40.173
13. Morgensztern D, Herbst RS. Nivolumab and Pembrolizumab for Non-Small Cell Lung Cancer. *Clin Cancer Res* (2016) 22:3713–7. doi: 10.1158/1078-0432.CCR-15-2998
14. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated With Immune Checkpoint Blockade. *N Engl J Med* (2018) 378:158–68. doi: 10.1056/NEJMra1703481
15. La-Beck NM, Jean GW, Huynh C, Alzghari SK, Lowe DB. Immune Checkpoint Inhibitors: New Insights and Current Place in Cancer Therapy. *Pharmacotherapy* (2015) 35:963–76. doi: 10.1002/phar.1643
16. Mazarico Gallego JM, Herrera Juarez M, Paz-Ares L. The Safety and Efficacy of Pembrolizumab for the Treatment of Non-Small Cell Lung Cancer. *Expert Opin Drug Saf* (2020) 19:233–42. doi: 10.1080/14740338.2020.1736554
17. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chavez A, Keegan N, Khamashta MA, et al. Immune-Related Adverse Events of Checkpoint Inhibitors. *Nat Rev Dis Primers* (2020) 6:38. doi: 10.1038/s41572-020-0160-6
18. Davies M, Duffield EA. Safety of Checkpoint Inhibitors for Cancer Treatment: Strategies for Patient Monitoring and Management of Immune-Mediated Adverse Events. *Immunotargets Ther* (2017) 6:51–71. doi: 10.2147/ITT.S141577

19. Dalvin LA, Shields CL, Orloff M, Sato T, Shields JA. CHECKPOINT INHIBITOR IMMUNE THERAPY: Systemic Indications and Ophthalmic Side Effects. *Retina* (2018) 38:1063–78. doi: 10.1097/IAE.0000000000002181
20. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of Immunotherapy for the Practitioner. *J Clin Oncol* (2015) 33:2092–9. doi: 10.1200/JCO.2014.60.0379
21. Shao J, Wang C, Ren P, Jiang Y, Tian P, Li W. Treatment- and Immune-Related Adverse Events of Immune Checkpoint Inhibitors in Advanced Lung Cancer. *Biosci Rep* (2020) 40:BSR20192347. doi: 10.1042/BSR20192347
22. Ferrari SM, Fallahi P, Elia G, Ragusa F, Ruffilli I, Patrizio A, et al. Autoimmune Endocrine Dysfunctions Associated With Cancer Immunotherapies. *Int J Mol Sci* (2019) 20:2560. doi: 10.3390/ijms20102560
23. Ma K, Lu Y, Jiang S, Tang J, Li X, Zhang Y. The Relative Risk and Incidence of Immune Checkpoint Inhibitors Related Pneumonitis in Patients With Advanced Cancer: A Meta-Analysis. *Front Pharmacol* (2018) 9:1430. doi: 10.3389/fphar.2018.01430
24. Ramos-Casals M, Maria A, Suarez-Almazor ME, Lambotte O, Fisher BA, Hernandez-Molina G, et al. Sicca/Sjogren's Syndrome Triggered by PD-1/PD-L1 Checkpoint Inhibitors. Data From the International ImmunoCancer Registry (ICIR). *Clin Exp Rheumatol* (2019) 37:114–22.
25. Sun MM, Seleme N, Chen JJ, Zekeridou A, Sechi E, Walsh RD, et al. Neuro-Ophthalmic Complications in Patients Treated With CTLA-4 and PD-1/PD-L1 Checkpoint Blockade. *J Neuroophthalmol* (2020). doi: 10.1097/WNO.0000000000001148
26. Bomze D, Meirson T, Hasan Ali O, Goldman A, Flatz L, Habot-Wilner Z. Ocular Adverse Events Induced by Immune Checkpoint Inhibitors: A Comprehensive Pharmacovigilance Analysis. *Ocul Immunol Inflammation* (2020) 1–7. doi: 10.1080/09273948.2020.1773867
27. Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse Events Associated With Immune Checkpoint Blockade in Patients With Cancer: A Systematic Review of Case Reports. *PloS One* (2016) 11:e0160221. doi: 10.1371/journal.pone.0160221
28. Sun Mm M.D PD, Levinson RMD, Filipowicz ADO, Anesi SMD, Kaplan HMD, P.D. Wang WMD, et al. Uveitis in Patients Treated With CTLA-4 and PD-1 Checkpoint Blockade Inhibition. *Ocul Immunol Inflamm* (2020) 28:217–27. doi: 10.1080/09273948.2019.1577978
29. Bitton K, Michot JM, Barreau E, Lambotte O, Haigh O, Marabelle A, et al. Prevalence and Clinical Patterns of Ocular Complications Associated With Anti-PD-1/PD-L1 Anticancer Immunotherapy. *Am J Ophthalmol* (2019) 202:109–17. doi: 10.1016/j.ajo.2019.02.012
30. Sun MM, Kelly SP, Mylavarapu Bs AL, Holland GN, Coleman AL, Yu F, et al. Ophthalmic Immune-Related Adverse Events After Anti-CTLA-4 or PD-1 Therapy Recorded in the American Academy of Ophthalmology Intelligent Research in Sight Registry. *Ophthalmology* (2020) 128:910–9. doi: 10.1016/j.ophtha.2020.11.001
31. Fortes BH, Liou H, Dalvin LA. Ophthalmic Adverse Effects of Immune Checkpoint Inhibitors: The Mayo Clinic Experience. *Br J Ophthalmol* (2020) 0:1–9. doi: 10.1136/bjophthalmol-2020-316970
32. Park RB, Jain S, Han H, Park J. Ocular Surface Disease Associated With Immune Checkpoint Inhibitor Therapy. *Ocul Surf* (2021) 20:115–29. doi: 10.1016/j.jtos.2021.02.004
33. Makri OE, Dimitrakopoulos FI, Tsapardoni F, Tsekouras I, Argyriou AA, Kalofonos H, et al. Isolated Optic Neuritis After Pembrolizumab Administration for Non-Small-Cell Lung Carcinoma. *Int J Neurosci* (2020) 1–6. doi: 10.1080/00207454.2020.1831489
34. Hasegawa Y, Kawai S, Ota T, Tsukuda H, Fukuoka M. Myasthenia Gravis Induced by Nivolumab in Patients With Non-Small-Cell Lung Cancer: A Case Report and Literature Review. *Immunotherapy* (2017) 9:701–7. doi: 10.2217/imt-2017-0043
35. Polat P, Donofrio PD. Myasthenia Gravis Induced by Nivolumab Therapy in a Patient With Non-Small-Cell Lung Cancer. *Muscle Nerve* (2016) 54:507. doi: 10.1002/mus.25163
36. Loochtan AI, Nickolich MS, Hobson-Webb LD. Myasthenia Gravis Associated With Ipilimumab and Nivolumab in the Treatment of Small Cell Lung Cancer. *Muscle Nerve* (2015) 52:307–8. doi: 10.1002/mus.24648
37. Chen JH, Lee KY, Hu CJ, Chung CC. Coexisting Myasthenia Gravis, Myositis, and Polyneuropathy Induced by Ipilimumab and Nivolumab in a Patient With Non-Small-Cell Lung Cancer: A Case Report and Literature Review. *Med (Baltimore)* (2017) 96:e9262. doi: 10.1097/MD.0000000000009262
38. Reyes-Bueno JA, Rodriguez-Santos L, Serrano-Castro PJ. Myasthenia Gravis Induced by Inmuno Checkpoints Inhibitors: First Case Report Secondary to Avelumab Therapy and Review of Published Cases. *Rev Neurol* (2019) 68:333–8. doi: 10.33588/rn.6808.2018497
39. Carrera W, Baartman BJ, Kosmorsky G. A Case Report of Drug-Induced Myopathy Involving Extraocular Muscles After Combination Therapy With Tremelimumab and Durvalumab for Non-Small Cell Lung Cancer. *Neuroophthalmology* (2017) 41:140–3. doi: 10.1080/01658107.2017.1291686
40. Brahmer JR, Lacchetti C, Thompson JA. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline Summary. *J Oncol Pract* (2018) 14:247–9. doi: 10.1200/JOP.18.00005
41. Le Fournis S, Gohier P, Urban T, Jeanfaivre T, Hureaux J. Corneal Graft Rejection in a Patient Treated With Nivolumab for Primary Lung Cancer. *Lung Cancer* (2016) 102:28–9. doi: 10.1016/j.lungcan.2016.10.008
42. Reddy M, Chen JJ, Kalevar A, Terribilini R, Agarwal A. Immune Retinopathy Associated With Nivolumab Administration for Metastatic Non-Small Cell Lung Cancer. *Retin cases Brief Rep* (2020) 14:120–6. doi: 10.1097/ICB.0000000000000675
43. Ahmad TR, Doan T, Gonzales JA, Acharya NR, Tsui E. Clinical Course of Preexisting Uveitis During Treatment of Lung Cancer With Durvalumab. *Ocul Immunol Inflamm* (2020) 28:566–70. doi: 10.1080/09273948.2019.1678652
44. Antoun J, Titah C, Cochereau I. Ocular and Orbital Side-Effects of Checkpoint Inhibitors: A Review Article. *Curr Opin Oncol* (2016) 28:288–94. doi: 10.1097/CCO.0000000000000296
45. Kanno H, Ishida K, Yamada W, Nishida T, Takahashi N, Mochizuki K, et al. Uveitis Induced by Programmed Cell Death Protein 1 Inhibitor Therapy With Nivolumab in Metastatic Melanoma Patient. *J Infect Chemother* (2017) 23:774–7. doi: 10.1016/j.jiac.2017.04.007
46. Seki M, Uruha A, Ohnuki Y, Kamada S, Noda T, Onda A, et al. Inflammatory Myopathy Associated With PD-1 Inhibitors. *J Autoimmun* (2019) 100:105–13. doi: 10.1016/j.jaut.2019.03.005
47. Kim JS, Nam TS, Kim J, Kho BG, Park CK, Oh IJ, et al. Myasthenia Gravis and Myopathy After Nivolumab Treatment for Non-Small Cell Lung Carcinoma: A Case Report. *Thorac Cancer* (2019) 10:2045–9. doi: 10.1111/1759-7714.13177
48. Felip E, de Braud FG, Maur M, Loong HH, Shaw AT, Vansteenkiste JF, et al. Ceritinib Plus Nivolumab in Patients With Advanced ALK-Rearranged Non-Small Cell Lung Cancer: Results of an Open-Label, Multicenter, Phase 1b Study. *J Thorac Oncol* (2020) 15:392–403. doi: 10.1016/j.jtho.2019.10.006
49. Chen YH, Liu FC, Hsu CH, Chian CF. Nivolumab-Induced Myasthenia Gravis in a Patient With Squamous Cell Lung Carcinoma: Case Report. *Med (Baltimore)* (2017) 96:e7350. doi: 10.1097/MD.0000000000007350
50. Nakatani Y, Tanaka N, Enami T, Minami S, Okazaki T, Komuta K. Lambert-Eaton Myasthenic Syndrome Caused by Nivolumab in a Patient With Squamous Cell Lung Cancer. *Case Rep Neurol* (2018) 10:346–52. doi: 10.1159/000494078
51. Veccia A, Kinspergher S, Grego E, Peterlana D, Berti A, Tranquillini E, et al. Myositis and Myasthenia During Nivolumab Administration for Advanced Lung Cancer: A Case Report and Review of the Literature. *Anticancer Drugs* (2020) 31:540–4. doi: 10.1097/CAD.0000000000000903
52. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab *Versus* Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. *J Clin Oncol* (2019) 37:537–46. doi: 10.1200/JCO.18.00149
53. Gadgeel SM, Stevenson JP, Langer CJ, Gandhi L, Borghaei H, Patnaik A, et al. Pembrolizumab and Platinum-Based Chemotherapy as First-Line Therapy for Advanced Non-Small-Cell Lung Cancer: Phase 1 Cohorts From the KEYNOTE-021 Study. *Lung Cancer* (2018) 125:273–81. doi: 10.1016/j.lungcan.2018.08.019
54. Satouchi M, Nosaki K, Takahashi T, Nakagawa K, Aoe K, Kurata T, et al. First-Line Pembrolizumab *vs* Chemotherapy in Metastatic Non-Small-Cell Lung Cancer: KEYNOTE-024 Japan Subset. *Cancer Sci* (2020) 111:4480–9. doi: 10.1111/cas.14647

55. Noda T, Kageyama H, Miura M, Tamura T, Ito H. A Case of Myasthenia Gravis and Myositis Induced by Pembrolizumab. *Rinsho Shinkeigaku* (2019) 59:502–8. doi: 10.5692/clinicalneurol.cn-001251
56. Ma Y, Fang W, Zhang Y, Yang Y, Hong S, Zhao Y, et al. KEYNOTE-032: A Randomized Phase I Study of Pembrolizumab in Chinese Patients With Advanced Non-Small Cell Lung Cancer. *Oncologist* (2020) 25:650–e1145. doi: 10.1634/theoncologist.2020-0067
57. Onda A, Miyagawa S, Takahashi N, Gochi M, Takagi M, Nishino I, et al. Pembrolizumab-Induced Ocular Myasthenia Gravis With Anti-Titin Antibody and Necrotizing Myopathy. *Intern Med* (2019) 58:1635–8. doi: 10.2169/internalmedicine.1956-18
58. Kurono Y, Takeda T, Kunimatsu Y, Tani N, Hashimoto I, Hirose K. Vogt-Koyanagi-Harada Disease During Chemoimmunotherapy for Non-Small Cell Lung Cancer. *Respirol Case Rep* (2020) 8:e00545. doi: 10.1002/rcr2.545
59. Razak AR, Cleary JM, Moreno V, Boyer M, Calvo Aller E, Edenfield W, et al. Safety and Efficacy of AMG 820, an Anti-Colony-Stimulating Factor 1 Receptor Antibody, in Combination With Pembrolizumab in Adults With Advanced Solid Tumors. *J Immunother Cancer* (2020) 8:e001006. doi: 10.1136/jitc-2020-001006
60. Hibino M, Maeda K, Horiuchi S, Fukuda M, Kondo T. Pembrolizumab-Induced Myasthenia Gravis With Myositis in a Patient With Lung Cancer. *Respirol Case Rep* (2018) 6:e00355. doi: 10.1002/rcr2.355
61. Acaba-Berrocal LA, Lucio-Alvarez JA, Mashayekhi A, Ho AC, Dunn JP, Shields CL. Birdshot-Like Chorioretinopathy Associated With Pembrolizumab Treatment. *JAMA Ophthalmol* (2018) 136:1205–7. doi: 10.1001/jamaophthalmol.2018.1851
62. Ramaekers A, Aspeslagh S, De Brucker N, Van Mierlo C, Ten Tusscher M, Schauwvlieghe PP, et al. Bilateral Corneal Perforation in a Patient Under Anti-PD1 Therapy. *Cornea* (2021) 40:245–7. doi: 10.1097/ICO.0000000000002490
63. Tamura T, Akimoto E, Matsumoto C, Mori S, Nishi T, Kudo K, et al. Vogt-Koyanagi-Harada Syndrome Induced by Pembrolizumab in a Patient With Non-Small Cell Lung Cancer. *J Thorac Oncol* (2018) 13:1606–7. doi: 10.1016/j.jtho.2018.04.026
64. Lara MS, Afify A, Ellis MP, Phan CT, Richman DP, Riess JW. Immune Checkpoint Inhibitor-Induced Myasthenia Gravis in a Patient With Advanced NSCLC and Remote History of Thymoma. *Clin Lung Cancer* (2019) 20:e489–91. doi: 10.1016/j.cllc.2019.04.007
65. Micaily I, Chernoff M. An Unknown Reaction to Pembrolizumab: Giant Cell Arteritis. *Ann Oncol* (2017) 28:2621–2. doi: 10.1093/anNonc/mdx306
66. Ramtohul P, Freund KB. Clinical and Morphological Characteristics of Anti-Programmed Death Ligand 1-Associated Retinopathy: Expanding the Spectrum of Acute Macular Neuroretinopathy. *Ophthalmol Retina* (2020) 4:446–50. doi: 10.1016/j.oret.2019.11.006
67. Gulley JL, Rajan A, Spigel DR, Iannotti N, Chandler J, Wong DJL, et al. Avelumab for Patients With Previously Treated Metastatic or Recurrent Non-Small-Cell Lung Cancer (JAVELIN Solid Tumor): Dose-Expansion Cohort of a Multicentre, Open-Label, Phase 1b Trial. *Lancet Oncol* (2017) 18:599–610. doi: 10.1016/S1470-2045(17)30240-1
68. Sabini E, Sframeli A, Marino M. A Case of Drug-Induced Graves' Orbitopathy After Combination Therapy With Tremelimumab and Durvalumab. *J Endocrinol Invest* (2018) 41:877–8. doi: 10.1007/s40618-018-0906-0
69. Antonia SJ, Lopez-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab Alone and Nivolumab Plus Ipilimumab in Recurrent Small-Cell Lung Cancer (CheckMate 032): A Multicentre, Open-Label, Phase 1/2 Trial. *Lancet Oncol* (2016) 17:883–95. doi: 10.1016/S1470-2045(16)30098-5
70. Phua CS, Murad A, Fraser C, Bray V, Cappelen-Smith C. Myasthenia Gravis and Concurrent Myositis Following PD-L1 Checkpoint Inhibitor for Non-Small Cell Lung Cancer. *BMJ Neurol Open* (2020) 2:e000028. doi: 10.1136/bmjno-2019-000028
71. Xing Q, Zhang ZW, Lin QH, Shen LH, Wang PM, Zhang S, et al. Myositis-Myasthenia Gravis Overlap Syndrome Complicated With Myasthenia Crisis and Myocarditis Associated With Anti-Programmed Cell Death-1 (Sintilimab) Therapy for Lung Adenocarcinoma. *Ann Transl Med* (2020) 8:250. doi: 10.21037/atm.2020.01.79
72. Kamo H, Hatano T, Kanai K, Aoki N, Kamiyama D, Yokoyama K, et al. Pembrolizumab-Related Systemic Myositis Involving Ocular and Hindneck Muscles Resembling Myasthenic Gravis: A Case Report. *BMC Neurol* (2019) 19:184. doi: 10.1186/s12883-019-1416-1
73. Dhenin A, Samartzi V, Lejeune S, Seront E. Cascade of Immunologic Adverse Events Related to Pembrolizumab Treatment. *BMJ Case Rep* (2019) 12:e229149. doi: 10.1136/bcr-2018-229149
74. Cooper DS, Meriggioli MN, Bonomi PD, Malik R. Severe Exacerbation of Myasthenia Gravis Associated With Checkpoint Inhibitor Immunotherapy. *J Neuromuscul Dis* (2017) 4:169–73. doi: 10.3233/JND-170219
75. Valenti-Azcarate R, Esparragosa Vazquez I, Toledano Illan C, Idoate Gastearena MA, Gallego Perez-Larraya J. Nivolumab and Ipilimumab-Induced Myositis and Myocarditis Mimicking a Myasthenia Gravis Presentation. *Neuromuscul Disord* (2020) 30:67–9. doi: 10.1016/j.nmd.2019.10.006
76. Earl DE, Loochtan AI, Bedlack RS. Refractory Myasthenia Gravis Exacerbation Triggered By Pembrolizumab. *Muscle Nerve* (2018) 57:E120–1. doi: 10.1002/mus.26021
77. Deitch-Harel IM, Raskin EM, Habot-Wilner ZM, Friling RM, Amer RM, Kramer MM. Uveitis Induced by Biological Agents Used in Cancer Therapy. *Ocul Immunol Inflammation* (2020) 1–5. doi: 10.1080/09273948.2020.1760310
78. Rapisuwon S, Izar B, Batenchuk C, Avila A, Mei S, Sorger P, et al. Exceptional Response and Multisystem Autoimmune-Like Toxicities Associated With the Same T Cell Clone in a Patient With Uveal Melanoma Treated With Immune Checkpoint Inhibitors. *J Immunother Cancer* (2019) 7:61. doi: 10.1186/s40425-019-0533-0
79. Campredon P, Imbert P, Mouly C, Grunenwald S, Mazieres J, Caron P. Severe Inflammatory Ophthalmopathy in a Euthyroid Patient During Nivolumab Treatment. *Eur Thyroid J* (2018) 7:84–7. doi: 10.1159/000485742
80. Thomas M, Armenti ST, Ayres MB, Demirci H. Uveal Effusion After Immune Checkpoint Inhibitor Therapy. *JAMA Ophthalmol* (2018) 136:553–6. doi: 10.1001/jamaophthalmol.2018.0920
81. Fukasawa Y, Sasaki K, Natsume M, Nakashima M, Ota S, Watanabe K, et al. Nivolumab-Induced Myocarditis Concomitant With Myasthenia Gravis. *Case Rep Oncol* (2017) 10:809–12. doi: 10.1159/000479958
82. Mori S, Kurimoto T, Ueda K, Enomoto H, Sakamoto M, Keshi Y, et al. Optic Neuritis Possibly Induced by Anti-PD-L1 Antibody Treatment in a Patient With Non-Small Cell Lung Carcinoma. *Case Rep Ophthalmol* (2018) 9:348–56. doi: 10.1159/000491075
83. Horisberger A, La Rosa S, Zurcher JP, Zimmermann S, Spertini F, Coukos G, et al. A Severe Case of Refractory Esophageal Stenosis Induced by Nivolumab and Responding to Tocilizumab Therapy. *J Immunother Cancer* (2018) 6:156. doi: 10.1186/s40425-018-0481-0
84. Teyssonneau D, Cousin S, Italiano A. Gougerot-Sjogren-Like Syndrome Under PD-1 Inhibitor Treatment. *Ann Oncol* (2017) 28:3108. doi: 10.1093/anNonc/mdx531
85. J LH, L MB, El Rahi C, A CS, Bernicker EH. Panuveitis in Patient on Ipilimumab/Nivolumab Combination for Small-Cell Lung Cancer Treated With an Intravitreal Dexamethasone Implant. *J Oncol Pharm Pract* (2020) 27:1078155220969792. doi: 10.1177/1078155220969792
86. A RA, Moll-Udina A, Martin R, Cilveti E, Subira O, Disfetano L, et al. Retinal Vasculitis Secondary to Durvalumab. *Case Rep Ophthalmol* (2020) 11:161–6. doi: 10.1159/000507609
87. Dermarkarian CR, Patel NA, Villegas VM, Harbour JW. Bilateral Uveitis Associated With Nivolumab Therapy for Metastatic Non-Small Cell Lung Cancer. *Am J Ophthalmol* (2020) 18:100691. doi: 10.1016/j.ajoc.2020.100691
88. Dow ER, Yung M, Tsui E. Immune Checkpoint Inhibitor-Associated Uveitis: Review of Treatments and Outcomes. *Ocul Immunol Inflamm* (2021) 29:203–11. doi: 10.1080/09273948.2020.1781902
89. Su C, Wang H, Liu Y, Guo Q, Zhang L, Li J, et al. Adverse Effects of Anti-PD-1/PD-L1 Therapy in Non-Small Cell Lung Cancer. *Front Oncol* (2020) 10:554313. doi: 10.3389/fonc.2020.554313
90. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. *JAMA Oncol* (2018) 4:1721–8. doi: 10.1001/jamaoncol.2018.3923
91. Mancone S, Lycan T, Ahmed T, Topaloglu U, Dothard A, Petty WJ, et al. Severe Neurologic Complications of Immune Checkpoint Inhibitors: A Single-Center Review. *J Neurol* (2018) 265:1636–42. doi: 10.1007/s00415-018-8890-z
92. Diaz-Manera J, Luna S, Roig C. Ocular Ptosis: Differential Diagnosis and Treatment. *Curr Opin Neurol* (2018) 31:618–27. doi: 10.1097/WCO.0000000000000600

93. Safa H, Johnson DH, Trinh VA, Rodgers TE, Lin H, Suarez-Almazor ME, et al. Immune Checkpoint Inhibitor Related Myasthenia Gravis: Single Center Experience and Systematic Review of the Literature. *J Immunother Cancer* (2019) 7:319. doi: 10.1186/s40425-019-0774-y
94. Europa TA, Nel M, Heckmann JM. Myasthenic Ophthalmoparesis: Time To Resolution After Initiating Immune Therapies. *Muscle Nerve* (2018) 58:542–9. doi: 10.1002/mus.26172
95. Narayanaswami P, Sanders DB, Wolfe G, Benatar M, Cea G, Evoli A, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology* (2021) 96:114–22. doi: 10.1212/WNL.0000000000011124
96. Melson AT, McClelland CM, Lee MS. Ocular Myasthenia Gravis: Updates on an Elusive Target. *Curr Opin Neurol* (2020) 33:55–61. doi: 10.1097/WCO.0000000000000775
97. Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B, Johnson DB. Increased Reporting of Fatal Immune Checkpoint Inhibitor-Associated Myocarditis. *Lancet* (2018) 391:933. doi: 10.1016/S0140-6736(18)30533-6
98. Mier A, Laroche C, Green M. Unsuspected Myasthenia Gravis Presenting as Respiratory Failure. *Thorax* (1990) 45:422–3. doi: 10.1136/thx.45.5.422
99. Choi J, Lee SY. Clinical Characteristics and Treatment of Immune-Related Adverse Events of Immune Checkpoint Inhibitors. *Immune Netw* (2020) 20: e9. doi: 10.4110/in.2020.20.e9
100. Becquart O, Lacotte J, Malissart P, Nadal J, Lesage C, Guillot B, et al. Myasthenia Gravis Induced by Immune Checkpoint Inhibitors. *J Immunother* (2019) 42:309–12. doi: 10.1097/CJI.0000000000000278
101. Smith SV, Lee AG. Update on Ocular Myasthenia Gravis. *Neurol Clin* (2017) 35:115–23. doi: 10.1016/j.ncl.2016.08.008
102. Fortin E, Cestari DM, Weinberg DH. Ocular Myasthenia Gravis: An Update on Diagnosis and Treatment. *Curr Opin Ophthalmol* (2018) 29:477–84. doi: 10.1097/ICU.0000000000000526
103. Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren J. Myasthenia Gravis. *Nat Rev Dis Primers* (2019) 5:30. doi: 10.1038/s41572-019-0079-y
104. Pasnoor M, Dimachkie MM, Farmakidis C, Barohn RJ. Diagnosis of Myasthenia Gravis. *Neurol Clin* (2018) 36:261–74. doi: 10.1016/j.ncl.2018.01.010
105. Krishna U, Ajanaku D, Denniston AK, Gkika T. Uveitis: A Sight-Threatening Disease Which can Impact All Systems. *Postgrad Med J* (2017) 93:766–73. doi: 10.1136/postgradmedj-2017-134891
106. Rouen PA, White ML. Dry Eye Disease: Prevalence, Assessment, and Management. *Home Healthc Now* (2018) 36:74–83. doi: 10.1097/NHH.0000000000000652
107. Messmer EM. The Pathophysiology, Diagnosis, and Treatment of Dry Eye Disease. *Dtsch Arztebl Int* (2015) 112:71–81. doi: 10.3238/arztebl.2015.0071
108. Lemp MA, Crews LA, Bron AJ, Foulks GN, Sullivan BD. Distribution of Aqueous-Deficient and Evaporative Dry Eye in a Clinic-Based Patient Cohort: A Retrospective Study. *Cornea* (2012) 31:472–8. doi: 10.1097/ICO.0b013e318225415a
109. Sumida T, Azuma N, Moriyama M, Takahashi H, Asashima H, Honda F, et al. Clinical Practice Guideline for Sjogren's Syndrome 2017. *Mod Rheumatol* (2018) 28:383–408. doi: 10.1080/14397595.2018.1438093
110. Lemp MA, Baudouin C, Baum J, Dogru M, Foulks GN, Kinoshita S, et al The Definition and Classification of Dry Eye Disease: Report of the Definition and Classification Subcommittee of the International Dry Eye WorkSho). *Ocul Surf* (2007) 5:75–92. doi: 10.1016/s1542-0124(12)70081-2
111. Nelson JD, Craig JP, Akpek EK, Azar DT, Belmonte C, Bron AJ, et al. TFOS DEWS II Introduction. *Ocul Surf* (2017) 15:269–75. doi: 10.1016/j.jtos.2017.05.005
112. Stamate AC, Tataru CP, Zemba M. Update on Surgical Management of Corneal Ulceration and Perforation. *Rom J Ophthalmol* (2019) 63:166–73. doi: 10.22336/rjo.2019.25
113. Deshmukh R, Stevenson LJ, Vajpayee R. Management of Corneal Perforations: An Update. *Indian J Ophthalmol* (2020) 68:7–14. doi: 10.4103/ijoIJO_1151_19
114. Panda A, Vanathi M, Kumar A, Dash Y, Priya S. Corneal Graft Rejection. *Surv Ophthalmol* (2007) 52:375–96. doi: 10.1016/j.survophthal.2007.04.008
115. Yin J. Advances in Corneal Graft Rejection. *Curr Opin Ophthalmol* (2021) 32:331–7. doi: 10.1097/ICU.0000000000000767
116. Dutta Majumder P, Marchese A, Pichi F, Garg I, Agarwal A. An Update on Autoimmune Retinopathy. *Indian J Ophthalmol* (2020) 68:1829–37. doi: 10.4103/ijo.IJO_786_20
117. Mizener JB, Kimura AE, Adamus G, Thirkill CE, Goeken JA, Kardon RH. Autoimmune Retinopathy in the Absence of Cancer. *Am J Ophthalmol* (1997) 123:607–18. doi: 10.1016/s0002-9394(14)71073-6
118. Detrick B, Hooks JJ. Immune Regulation in the Retina. *Immunol Res* (2010) 47:153–61. doi: 10.1007/s12026-009-8146-1
119. Wilhelm H, Schabet M. The Diagnosis and Treatment of Optic Neuritis. *Dtsch Arztebl Int* (2015) 112:616–25. doi: 10.3238/arztebl.2015.0616
120. Toosy AT, Mason DF, Miller DH. Optic Neuritis. *Lancet Neurol* (2014) 13:83–99. doi: 10.1016/S1474-4422(13)70259-X
121. Tadi P, Najem K, Margolin E. *Amaurosis Fugax*. Treasure Island (FL: StatPearls (2021).
122. Nicolaescu MM. Amaurosis Fugax. *Oftalmologia* (2009) 53:46–54.
123. Donaldson L, Margolin E. Vision Loss in Giant Cell Arteritis. *Pract Neurol* (2021). doi: 10.1136/practneurol-2021-002972
124. Maz M, Chung SA, Abril A, Langford CA, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. *Arthritis Care Res (Hoboken)* (2021) 73:1071–87. doi: 10.1002/acr.24632
125. Baalbaki H, Jalaledin D, Lachance C, Febrer G, Rheaume M, Makhzoum JP. Characterization of Visual Manifestations and Identification of Risk Factors for Permanent Vision Loss in Patients With Giant Cell Arteritis. *Clin Rheumatol* (2021) 40:3207–17. doi: 10.1007/s10067-021-05643-5
126. Zborowska B, Ghabrial R, Selva D, McCluskey P. Idiopathic Orbital Inflammation With Extraorbital Extension: Case Series and Review. *Eye (Lond)* (2006) 20:107–13. doi: 10.1038/sj.eye.6701780
127. Dagi Glass LR, Freitag SK. Orbital Inflammation: Corticosteroids First. *Surv Ophthalmol* (2016) 61:670–3. doi: 10.1016/j.survophthal.2016.01.005
128. Yesiltas YS, Gunduz AK. Idiopathic Orbital Inflammation: Review of Literature and New Advances. *Middle East Afr J Ophthalmol* (2018) 25:71–80. doi: 10.4103/meajo.MEAJO_44_18
129. Peng L, Wu YL. Immunotherapy in the Asiatic Population: Any Differences From Caucasian Population? *J Thorac Dis* (2018) 10:S1482–93. doi: 10.21037/jtd.2018.05.106
130. Lee J, Sun JM, Lee SH, Ahn JS, Park K, Ahn MJ. Are There Any Ethnic Differences in the Efficacy and Safety of Immune Checkpoint Inhibitors for Treatment of Lung Cancer? *J Thorac Dis* (2020) 12:3796–803. doi: 10.21037/jtd.2019.08.29
131. Yang J, He X, Lv Q, Jing J, Shi H. Management of Adverse Events in Cancer Patients Treated With PD-1/PD-L1 Blockade: Focus on Asian Populations. *Front Pharmacol* (2019) 10:726. doi: 10.3389/fphar.2019.00726
132. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and Class-Specific Patterns of Immune-Related Adverse Events of Immune Checkpoint Inhibitors: A Systematic Review. *Ann Oncol* (2017) 28:2377–85. doi: 10.1093/anNonc/mdx286
133. Wills B, Brahmer JR, Naidoo J. Treatment of Complications From Immune Checkpoint Inhibition in Patients With Lung Cancer. *Curr Treat Options Oncol* (2018) 19:46. doi: 10.1007/s11864-018-0562-9
134. Jacquin-Porretaz C, Nardin C, Puzenat E, Roche-Kubler B, Aubin F. And a.-C. Comite De Suivi Des Effets Secondaires Des Immunotherapies). [Adverse Effects of Immune Checkpoint Inhibitors Used to Treat Melanoma and Other Cancer]. *Presse Med* (2017) 46:808–17. doi: 10.1016/j.lpm.2017.05.032
135. Wang XJ, Lin JZ, Yu SH, Wu SX, Luo HS, Du ZS, et al. First-Line Checkpoint Inhibitors for Wild-Type Advanced Non-Small-Cell Cancer: A Pair-Wise and Network Meta-Analysis. *Immunotherapy* (2019) 11:311–20. doi: 10.2217/imt-2018-0107
136. Fang T, Maberley DA, Etminan M. Ocular Adverse Events With Immune Checkpoint Inhibitors. *J Curr Ophthalmol* (2019) 31:319–22. doi: 10.1016/j.joco.2019.05.002
137. Nakanishi Y, Masuda T, Yamaguchi K, Sakamoto S, Horimasu Y, Nakashima T, et al. Pre-Existing Interstitial Lung Abnormalities Are Risk Factors for Immune Checkpoint Inhibitor-Induced Interstitial Lung Disease in Non-Small Cell Lung Cancer. *Respir Investig* (2019) 57:451–9. doi: 10.1016/j.resinv.2019.05.002
138. El-Refai SM, Brown JD, Black EP, Talbert JC. Immune Checkpoint Inhibition and the Prevalence of Autoimmune Disorders Among Patients With Lung and Renal Cancer. *Cancer Inform* (2017) 16:1176935117712520. doi: 10.1177/1176935117712520
139. Johnson DB, Sullivan RJ, Ott PA, Carlino MS, Khushalani NI, Ye F, et al. Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting

Autoimmune Disorders. *JAMA Oncol* (2016) 2:234–40. doi: 10.1001/jamaoncol.2015.4368
140. Corbaux P, Maillet D, Boespflug A, Locatelli-Sanchez M, Perier-Muzet M, Duruisseaux M, et al. Older and Younger Patients Treated With Immune Checkpoint Inhibitors Have Similar Outcomes in Real-Life Setting. *Eur J Cancer* (2019) 121:192–201. doi: 10.1016/j.ejca.2019.08.027
141. Hurez V, Padron A, Svatek RS, Curiel TJ. Considerations for Successful Cancer Immunotherapy in Aged Hosts. *Exp Gerontol* (2018) 107:27–36. doi: 10.1016/j.exger.2017.10.002
142. Elias R, Giobbie-Hurder A, McCleary NJ, Ott P, Hodi FS, Rahma O. Efficacy of PD-1 & PD-L1 Inhibitors in Older Adults: A Meta-Analysis. *J Immunother Cancer* (2018) 6:26. doi: 10.1186/s40425-018-0336-8
143. Chiarion Sileni V, Pigozzo J, Ascierto PA, Grimaldi AM, Maio M, Di Guardo L, et al. Efficacy and Safety of Ipilimumab in Elderly Patients With Pretreated Advanced Melanoma Treated at Italian Centres Through the Expanded Access Programme. *J Exp Clin Cancer Res* (2014) 33:30. doi: 10.1186/1756-9966-33-30
144. Prieske K, Trillsch F, Oskay-Ozcelik G, Chekerov R, Bleich C, Oliveira-Ferrer L, et al. Participation of Elderly Gynecological Cancer Patients in Clinical Trials. *Arch Gynecol Obstet* (2018) 298:797–804. doi: 10.1007/s00404-018-4886-2
145. Denson AC, Mahipal A. Participation of the Elderly Population in Clinical Trials: Barriers and Solutions. *Cancer Control* (2014) 21:209–14. doi: 10.1177/107327481402100305
146. Klein SL, Morgan R. The Impact of Sex and Gender on Immunotherapy Outcomes. *Biol Sex Differ* (2020) 11:24. doi: 10.1186/s13293-020-00301-y
147. Conforti F, Pala L, Bagnardi V, De Pas T, Martinetti M, Viale G, et al. Cancer Immunotherapy Efficacy and Patients' Sex: A Systematic Review and Meta-Analysis. *Lancet Oncol* (2018) 19:737–46. doi: 10.1016/S1470-2045(18)30261-4
148. Brueckl WM, Ficker JH, Zeitler G. Clinically Relevant Prognostic and Predictive Markers for Immune-Checkpoint-Inhibitor (ICI) Therapy in Non-Small Cell Lung Cancer (NSCLC). *BMC Cancer* (2020) 20:1185. doi: 10.1186/s12885-020-07690-8
149. Ozdemir BC, Csajka C, Dotto GP, Wagner AD. Sex Differences in Efficacy and Toxicity of Systemic Treatments: An Undervalued Issue in the Era of Precision Oncology. *J Clin Oncol* (2018) 36:2680–3. doi: 10.1200/JCO.2018.78.3290
150. Reck M, Rabe KF. Precision Diagnosis and Treatment for Advanced Non-Small-Cell Lung Cancer. *N Engl J Med* (2017) 377:849–61. doi: 10.1056/NEJMra1703413
151. Slawinski G, Wrona A, Dabrowska-Kugacka A, Raczak G, Lewicka E. Immune Checkpoint Inhibitors and Cardiac Toxicity in Patients Treated for Non-Small Lung Cancer: A Review. *Int J Mol Sci* (2020) 21:7195. doi: 10.3390/ijms21197195
152. Park RB, Jain S, Han H, Park J. Ocular Surface Disease Associated With Immune Checkpoint Inhibitor Therapy. *Ocul Surf* (2021) 20:115–29. doi: 10.1016/j.jtos.2021.02.004
153. Hori J, Kunishige T, Nakano Y. Immune Checkpoints Contribute Corneal Immune Privilege: Implications for Dry Eye Associated With Checkpoint Inhibitors. *Int J Mol Sci* (2020) 21:3962. doi: 10.3390/ijms21113962
154. Nguyen AT, Elia M, Materin MA, Sznol M, Chow J. Cyclosporine for Dry Eye Associated With Nivolumab: A Case Progressing to Corneal Perforation. *Cornea* (2016) 35:399–401. doi: 10.1097/ICO.0000000000000724
155. Kerty E, Elsais A, Argov Z, Evoli A, Gilhus NE. EFNS/ENS Guidelines for the Treatment of Ocular Myasthenia. *Eur J Neurol* (2014) 21:687–93. doi: 10.1111/ene.12359
156. Benatar M, McDermott MP, Sanders DB, Wolfe GI, Barohn RJ, Nowak RJ, et al. Efficacy of Prednisone for the Treatment of Ocular Myasthenia (EPITOME): A Randomized, Controlled Trial. *Muscle Nerve* (2016) 53:363–9. doi: 10.1002/mus.24769
157. Agius MA. Treatment of Ocular Myasthenia With Corticosteroids. Yes. *Arch Neurol* (2000) 57:750–1. doi: 10.1001/archneur.57.5.750
158. Farmakidis C, Pasnoor M, Dimachkie MM, Barohn RJ. Treatment of Myasthenia Gravis. *Neurol Clin* (2018) 36:311–37. doi: 10.1016/j.ncl.2018.01.011
159. Makarious D, Horwood K, Coward JIG. Myasthenia Gravis: An Emerging Toxicity of Immune Checkpoint Inhibitors. *Eur J Cancer* (2017) 82:128–36. doi: 10.1016/j.ejca.2017.05.041
160. Moorthy RS, Moorthy MS, Cunningham ETJr. Drug-Induced Uveitis. *Curr Opin Ophthalmol* (2018) 29:588–603. doi: 10.1097/ICU.0000000000000530
161. Fierz FC, Meier F, Chaloupka K, Boni C. Intraocular Inflammation Associated With New Therapies for Cutaneous Melanoma - Case Series and Review. *Klin Monbl Augenheilkd* (2016) 233:540–4. doi: 10.1055/s-0042-102668
162. Pflugfelder SC, Maskin SL, Anderson B, Chodosh J, Holland EJ, De Paiva CS, et al. A Randomized, Double-Masked, Placebo-Controlled, Multicenter Comparison of Loteprednol Etabonate Ophthalmic Suspension, 0.5%, and Placebo for Treatment of Keratoconjunctivitis Sicca in Patients With Delayed Tear Clearance. *Am J Ophthalmol* (2004) 138:444–57. doi: 10.1016/j.ajo.2004.04.052
163. Yoshida A, Fujihara T, Nakata K. Cyclosporin A Increases Tear Fluid Secretion *via* Release of Sensory Neurotransmitters and Muscarinic Pathway in Mice. *Exp Eye Res* (1999) 68:541–6. doi: 10.1006/exer.1998.0619
164. Davis ME, Francis JH. Cancer Therapy With Checkpoint Inhibitors: Establishing a Role for Ophthalmology. *Semin Oncol Nurs* (2017) 33:415–24. doi: 10.1016/j.soncn.2017.08.003
165. Wladis EJ, Kambam ML. Ophthalmic Complications of Immune Checkpoint Inhibitors. *Orbit* (2021) 1–6. doi: 10.1080/01676830.2020.1867192
166. Liu X, Wang Z, Zhao C, Wang H, Guo X, Zhou J, et al. Clinical Diagnosis and Treatment Recommendations for Ocular Toxicities of Targeted Therapy and Immune Checkpoint Inhibitor Therapy. *Thorac Cancer* (2020) 11:810–8. doi: 10.1111/1759-7714.13327
167. Chelala E, Hoyek S, Arej N, Kattan J, Kourie HR, Baakliny J, et al. Ocular and Orbital Side Effects of ALK Inhibitors: A Review Article. *Future Oncol* (2019) 15:1939–45. doi: 10.2217/fon-2018-0608
168. Alba-Linero C, Alba E. Ocular Side Effects of Checkpoint Inhibitors. *Surv Ophthalmol* (2021). doi: 10.1016/j.survophthal.2021.01.001

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Oncology

CASE REPORT
published: 02 September 2021
doi: 10.3389/fonc.2021.664809

Immune-Related Multiple-Organs Injuries Following ICI Treatment With Tislelizumab in an Advanced Non-Small Cell Lung Cancer Patient: A Case Report

*Chao Deng[1], Meng Yang[2], Hong Jiang[3], Renbin Wang[4], Zhaojun Yang[5], Hongliang Sun[6] and Huijuan Cui[1]**

[1] Department of Medical Oncology, Integrated Traditional Chinese and Western Medicine, China-Japan Friendship Hospital, Beijing, China, [2] Department of Respiratory and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China, [3] Department of Cardiology, Integrated Traditional Chinese and Western Medicine, China-Japan Friendship Hospital, Beijing, China, [4] Department of Neurology, China-Japan Friendship Hospital, Beijing, China, [5] Department of Endocrinology, China-Japan Friendship Hospital, Beijing, China, [6] Department of Radiology, China-Japan Friendship Hospital, Beijing, China

OPEN ACCESS

Edited by:
Xuelei Ma,
Sichuan University, China

Reviewed by:
Damini Chand,
Canada's Michael Smith Genome Sciences Centre, Canada
Chunxia Su,
Shanghai Pulmonary Hospital, China

***Correspondence:**
Huijuan Cui
cuihj1963@sina.com

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Oncology

Received: *06 February 2021*
Accepted: *12 August 2021*
Published: *02 September 2021*

Citation:
Deng C, Yang M, Jiang H, Wang R, Yang Z, Sun H and Cui H (2021) Immune-Related Multiple-Organs Injuries Following ICI Treatment With Tislelizumab in an Advanced Non-Small Cell Lung Cancer Patient: A Case Report. Front. Oncol. 11:664809. doi: 10.3389/fonc.2021.664809

Immune-related adverse events (irAEs) following treatment with immune checkpoint inhibitors (ICIs) can affect almost any organ systems. Multiple-organs irAEs are a rare occurrence which makes its management and treatment very challenging. This is a case report of a 71-year-old man with advanced non-small cell lung cancer (NSCLC) who developed multiple-organs irAEs (lung, muscle, myocardium, liver, and pituitary) after a single cycle (21 days) of the BGB-A317 (Tislelizumab). After more than two months of immunosuppression treatment with glucocorticoids, the tumor and inflammatory lesions in the lung were reduced. The levels of serum creatase, cardiac troponin T (TNT), and hepatic transaminase were also reduced. Four months after the termination of ICI therapy, the lung tumor reappeared in the previous site. This rare case report supplies several experiences in the management of multiple-organs irAEs, including full-scale monitoring of immunological indicators, early differential diagnosis, and prompt glucocorticoid therapy. This patient was not a candidate for the ICI re-challenge therapy due to the number and seriousness of irAEs. Multiple-organs irAEs add complexity to the management, and additional research is needed to develop optimal therapeutic guidelines.

Keywords: immune checkpoint inhibitors (ICIs), tislelizumab, immune-related adverse events (irAEs), non-small cell lung cancer (NSCLC), programmed cell death-1(PD-1)

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have emerged as revolutionary and promising immune-based therapies for cancer, demonstrating durable antitumor responses in multiple cancer types (1, 2). However, T cells can be activated by ICIs, resulting in immune-related adverse events (irAEs), which can affect multiple body systems, primarily the pulmonary, endocrine, skin, and gastrointestinal systems (3, 4).

The occurrence of irAEs has been associated with improved tumor responses and survival outcomes in most cancer patients undergoing ICI therapy (5, 6). The number of irAEs is related to the antitumor effects of ICIs used as well as to the degree of autoimmune activation by the ICIs (7, 8).

A single target organ is most often affected in mild irAEs, which can occur in 60%–70% of patients accepting a monotherapy of programmed cell death-1 (PD-1)/programmed cell death-Ligand 1 (PD-L1) inhibitor (9). However, both single and multiple-organs irAEs can be life-threatening. The myositis occurred in approximately 0.6% of ICI-treated patients, however, among the myositis cases, 95.3% are serious to require at least a hospitalization, with a fatality rate of 22.3% (10). The fatal outcome may be variably impacted due to the other concomitant irAEs, such as myasthenia gravis, rhabdomyolysis, and myocarditis (11, 12). The incidence of ICI-associated myocarditis has been reported to range from 0.06% to 1%. It is difficult to diagnose for lack of specificity in the clinical presentation compared to other cardiovascular diseases (13). Hypophysitis is also rare, with an incidence of only 0.4% for PD-1 inhibitors (14). Pneumonitis and hepatitis are observed much more frequently, which occurs in 3%–10% and 1%–10% of patients accepting ICI, respectively (15, 16).

Tislelizumab is an anti-PD-1 monoclonal antibody, that is similar to Nivolumab and Pembrolizumab in anti-tumor efficacy, safety, and tolerability for advanced NSCLC patients.

We report a case of a 71-year-old man with advanced non-small cell lung cancer (NSCLC) who developed successive multiple-organ irAEs including myositis, myocarditis, pneumonia, hepatitis, and hypophysitis, after the first cycle treatment with Tislelizumab. The tumor in the lung nearly disappeared. IrAEs were reduced after the discontinuation of PD-1 inhibitor and the initiation of treatment with corticosteroids. Unfortunately, the lung tumor reoccurred in the same site after termination of ICI therapy but was reduced with subsequent chemotherapy.

CASE PRESENTATION

This case report involved a 71-year-old male with advanced NSCLC (cT2N2M0 IIIa), without tumor driver genes mutations. The patient was diagnosed by percutaneous needle lung biopsy (PNLB) in October 2019. The main past history including the anticoagulant therapy for thrombus in the lower extremity veins from December 2019, a smoking history of 50 years, and the death of his sister from ovarian cancer. The Tumor Mutational Burden (TMB) of the patient was 9.68 mut/Mb. The expression rate of PD-L1 was 80% to 90% in tumor cells, and approximately 1% in immune cells. The patient was treated with first-line chemotherapy alone (pemetrexed plus carboplatin), rather than a combination therapy with ICIs or bevacizumab, due to medical expense and anticoagulant therapy (for thrombus in the lower extremity veins). When the tumor did not respond to this treatment, the patient agreed to a treatment of a single cycle of the ICI Tislelizumab (200 mg d1, 21 days a cycle; BeiGene, China) on March 12, 2020. Fever, weakness, and cough appeared in the afternoon and evening of the first day of treatment.

A computerized tomography (CT) of chest scan showed the presence of the tumor before ICI treatment (**Figure 1A**), and two weeks after the treatment, interstitial pneumonia appeared around the tumor (**Figure 1B**). An increase in serum interleukin-6 (IL-6) and tumor necrosis factor (TNF) was detected (**Figure 2E**). Myalgia occurred 10 days after the termination of ICI treatment. Anti-inflammatory treatment (Prednisone, 20 mg, qd; meloxicam,7.5 mg, qd) was administrated. Five days later, the patient felt weakness in the lower extremities (muscle force, grade 3) and could not stand or walk. The patient would gasp for breath after activity. It is not uncommon that ICI treatment of patients can result in the late-onset of immunological complications, including those involving the musculature, nervous, pulmonary, and endocrine systems.

The ability of the patient to perform daily physical activities was limited, especially in the lower limbs. Serum levels of creatine kinase (CK), lactic dehydrogenase (LDH), and α-hydroxybutyric dehydrogenase (α-HBDH) had increased (**Figure 2A**). Electromyography showed neural normal conduction, myotonic discharges in the bilateral anterior tibial, right quadriceps, iliopsoas, and biceps brachii were detected. Magnetic resonance imaging (MRI) found a diffuse exudation in the muscles of the backside and lower limbs (**Figure 3A**). Although the antinuclear antibody spectrum, myositis auto-antibody spectrum, immunoglobulin, and alexin were all negative, severe myositis was still considered a possible irAE based on the clinical manifestation above.

Myocarditis was believed to be another irAE concurrent with myositis. The level of cardiac troponin T (TNT) was remarkably high (**Figure 2B**). An electrocardiogram (ECG) indicated complete right bundle branch block (CRBBB), and potential inferior myocardial infarction, rather than the normal manifestation prior to ICI therapy (**Supplementary Image 1**). Cardiac ultrasonography (UCG) and cardiac magnetic resonance (CMR) did not indicate abnormalities in the structure and function of the heart. The possibility of acute myocardial infarction (AMI) and pulmonary embolism (PE) were excluded by coronary and pulmonary angiography. Myocardial damage was considered to be an irAE induced by ICI therapy based on the clinical manifestations above.

Both serum glutamic-pyruvic transaminase (ALT) and glutamic-oxaloacetic transaminase (AST) also increased (**Figure 2B**). The patient denied a history of hepatic diseases. Hepatic damage was considered an irAE based on a comparison of AST and ALT pre- and post-ICI treatment.

The level of cortisol (COR) and adrenocorticotrophic hormone (ACTH) was lower than normal values from April 17, which fluctuated following glucocorticoid therapy (**Figure 2C**). The levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone (TESTO) were normal, yet transitorily lower than the base value on April 17, while thyroid-stimulating hormone (TSH) and free thyroxine (FT4) were normal. (**Figure 2D**). Secondary adrenal insufficiency

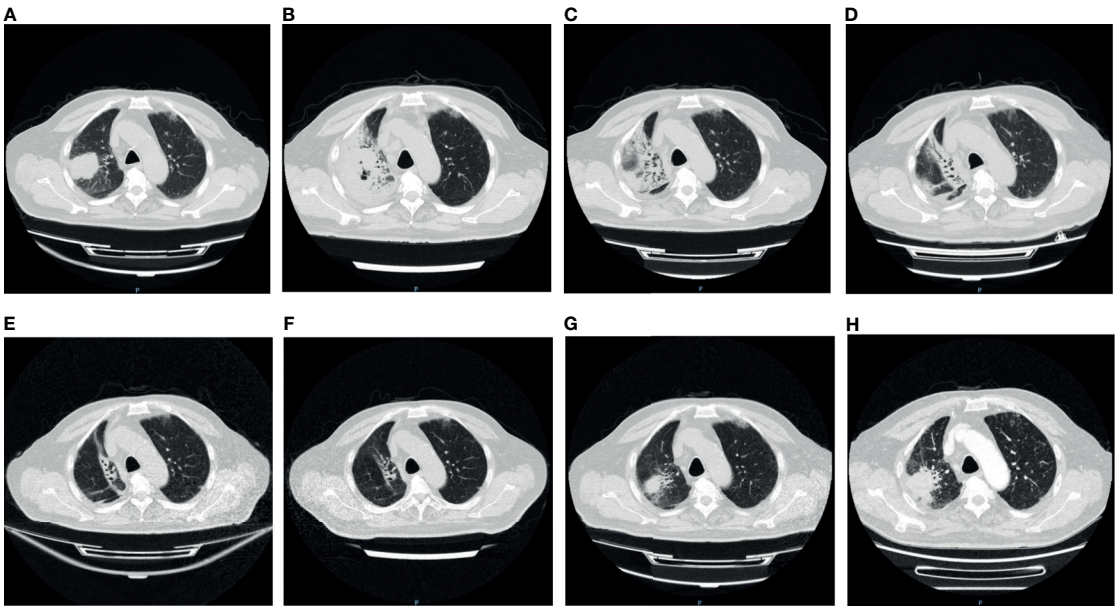

FIGURE 1 | The variation of the tumor and inflammation in Chest CT. **(A)** Pre-immunotherapy: the tumor was seen in the right lung; **(B)** 2 weeks after immunotherapy: patchy shadows appeared around the tumor and air holes occurred in the tumor; **(C)** 4 weeks after immunotherapy: more air holes developed in the tumor and patchy shadows; **(D)** 5 weeks after immunotherapy: the tumor and patchy shadows were dissipating; **(E, F)** 8/12 weeks after immunotherapy: the tumor disappeared, with several linear shadows leaving; **(G)** 16 weeks after immunotherapy: the tumor reappeared in original site; **(H)** 18 weeks after immunotherapy: the tumor enlarged.

was clinically diagnosed as an irAE (hypophysitis) with isolated ACTH deficiency (IAD) despite the lack of a pituitary MRI.

This patient initially accepted 80 mg of methylprednisolone intravenously to suppress the autoimmune reaction with the dose reduced gradually, until adjusted to oral prednisone with reduction sequentially. In addition, meloxicam (7.5 mg, qd) and total glucosides of paeonia (TGP) (0.6 g, tid) were administered to suppress inflammation and to regulate immune function. Coenzyme Q (Co-Q), fructose1, 6-diphosphate (FDP), and vitamin C were administered to protect the myocardium. Metroprolol succinate was administered to alleviate the workload of heart. To reverse the ICI-induced hepatic damage, reduced glutathione was administered. After the comprehensive treatment, the abnormal indications induced by ICI gradually recovered to normal. And the diffuse exudation reduced in the muscles of the right lower limbs (**Figure 3B**). The therapeutic process of irAEs is shown in **Figure 4**.

Although the multiple-organs irAEs appeared, the efficacy of ICI therapy was encouraging. Following the treatment, the tumor lesion and inflammation around the tumor both diminished gradually until the final disappearance (**Figures 1C–F**). Meanwhile, the serum tumor markers (CA125, CYFRA211, and CEA) showed a downward trend (**Figure 2F**). Despite this initial success, cancer reoccurred in the right lung 4 months after the termination of ICI treatment (**Figures 1G, H**).

Positron emission tomography-computed tomography (PET-CT) examination confirmed the relapse of the tumor (**Supplementary Image 2A**). As a result of the seriousness of the irAEs of the patient, an ICI re-challenge therapy was not administered, and chemotherapy (vinorelbine plus carboplatin) plus bevacizumab was initiated as the subsequent treatment. After two cycles of the treatment, the area of the right lung lesion was reduced (**Supplementary Image 2B**).

After six cycles of the chemotherapy (vinorelbine plus carboplatin) plus bevacizumab, the right lung lesion increased again and directly invaded the pleura, then the patient chose the argon-helium knife cryotherapy as local therapy, and the chemotherapy (Abraxane plus carboplatin) plus bevacizumab as systemic therapy. However, after two cycles of the chemotherapy, serious myelosuppression appeared, and, meanwhile, the physical condition was poor, the patient began to accept the optimal supportive care until August 8, 2021.

The overall survival of this patient is 22 months up to now. Although multiple-organs irAEs occurred after only one cycle of immunotherapy, the patient may still obtain a benefit from the remarkable efficacy of immunotherapy to prolong survival.

DISCUSSION

As far as we know, this is a rare case report that describes the development of multiple-organs irAEs after a single cycle of ICI monotherapy (Tislelizumab) in a 71-year-old man treated for NSCLC. After ICI therapy, pneumonitis appeared before an

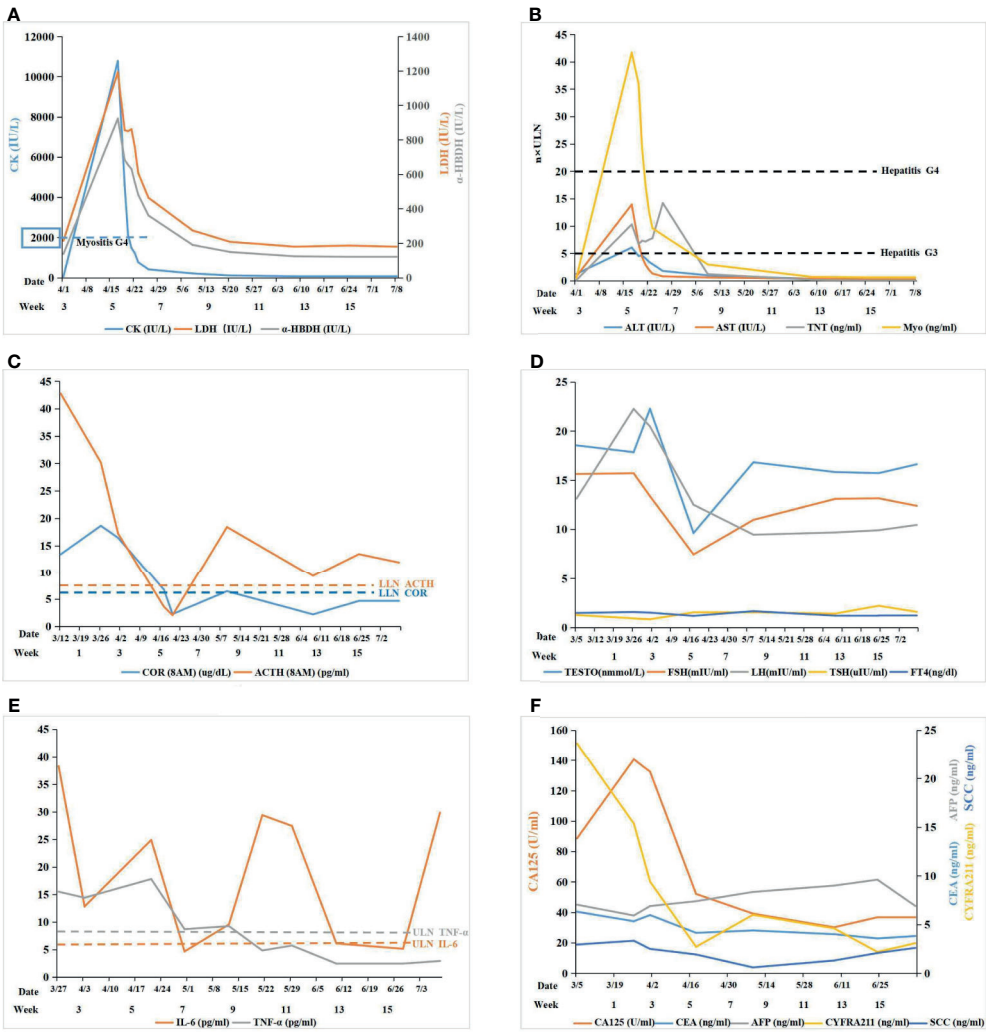

FIGURE 2 | **(A)** Myositis: the level of serum creatase was used to monitor immune related myositis after immunotherapy; **(B)** Myocarditis+ Hepatitis: cardiac markers and hepatic transaminase were used to monitor myocarditis and hepatitis, respectively, after immunotherapy; **(C)** Pituitary-Adrenal Axis: the level of COR and ACTH were used to monitor the function of the pituitary-adrenal axis: COR and ACTH both declined remarkably after ICI therapy; ACTH was maintained at a low level while COR was still lower than the normal value by glucocorticoid replacement therapy; **(D)** Pituitary-Gonad Axis: the level of FSH, LH, and TESTO were used to monitor the function of the pituitary-gonad axis: all of them fluctuated in the range of normal values; TSH and FT4 were both normal in the pituitary-thyroid axis; **(E)** Autoimmune Reponse: IL-6 and TNF-α was used to monitor the autoimmune response induce by ICI: IL-6 fluctuated beyond the upper limit of normal (ULN) while TNF-α fell to normal gradually after glucocorticoid replacement therapy; **(F)** Tumor Marker: tumor markers was used to monitor efficacy of ICI.

acute onset of myositis, with the subsequent and concomitant irAEs of myocarditis, hepatitis, and hypophysitis.

Myositis is an ICI-induced neuromuscular irAE, with an all-grade incidence of less than 1% (17). Our reported case of ICI-related myositis is consistent with previous cases, in which muscle weakness of the limbs (32%), myalgia (42%), and CK elevation (43%) are manifested. As our observations, myositis-associated auto-antibodies are not detected in most cases (17). Electromyography, muscle MRI, and muscle biopsy are needed for the diagnosis of myositis. A muscle biopsy of this case was not performed because of the risk of bleeding and poor healing resulting from anticoagulant therapy used for thrombus in the lower extremity veins.

Myocarditis is the most fatal complication of ICI therapy with a mortality of 50% (18), which can occur concomitantly with other irAEs, such as myositis (17.3%), hepatitis (6.8%), and pneumonitis (4.5%) (19). The clinical manifestation of myocarditis can range from mild, nonspecific symptoms to sudden cardiac death, and may present with the decline of left ventricular ejection fraction (EF) and arrhythmia in fulminant progression (20, 21). The patient did not display specific cardiac symptoms but had high levels of TNT along with abnormal electrical conduction of cardiac rhythms. However, the normal findings on both echocardiogram and CMR do not rule out myocarditis (22). As a gold standard for diagnosis, endomyocardial biopsy is limited due to its invasive nature. Thus, it is recommended that broad differential

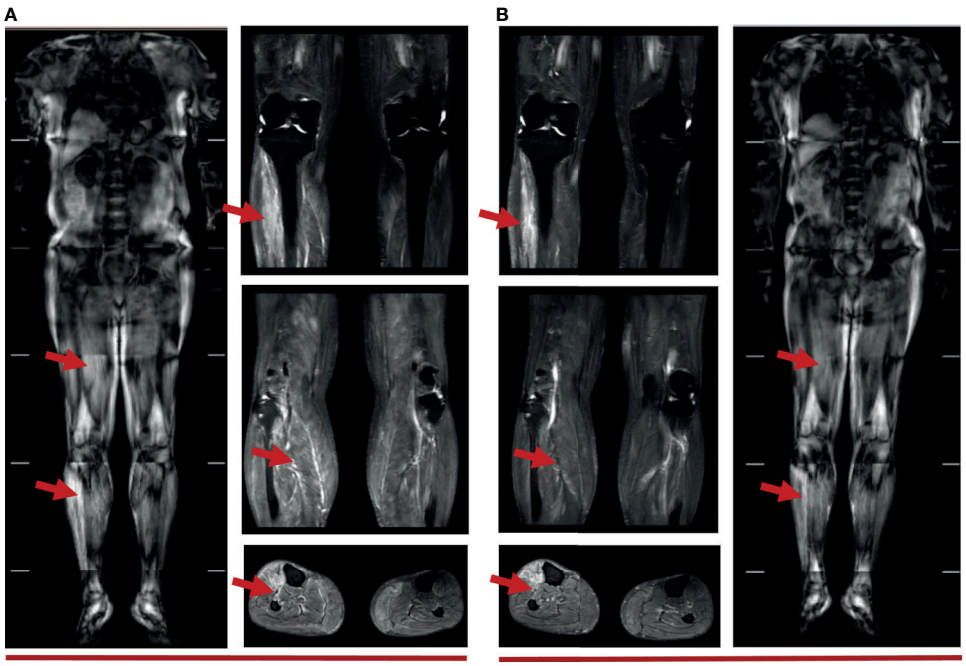

FIGURE 3 | **(A)** Muscle MRI of 5 weeks after immunotherapy: diffuse strip-shaped high-signal shadows were seen in the back and lower limbs, as indicated by the red arrows; **(B)** Muscle MRI of 10 weeks after immunotherapy: high-signal shadows receded after 40 days of glucocorticoid treatment, especially in the right lower limbs, as indicated by the red arrows.

Date	Mar 12-	Apr 8-	Apr 13-	Apr 17-	Apr 21-	Apr 26	Apr 27-	Jun 16-	Jul 13
Symptom	Fever Weakness Cough	No fever	Weakness Myalgia	Severe weakness Mild myalgia	Mild weakness Palpitation Chest oppression			Normal	
Examination	Chest CT	--	Chest CT	Chest CT UCG/ECG Electromyography	Muscle MRI CMR Coronary angiography Pulmonary angiography		UCG/ECG	Muscle MRI Chest CT UCG/ECG	Chest CT UCG/ECG
Immune-related diagnosis	Pneumonia G2			Myositis G4 Myocarditis G3 Hepatitis G3 Pneumonia G2 Hypophysitis G1	Myositis G3 Myocarditis G3 Hepatitis G2 Pneumonia G1 Hypophysitis G1		Myositis G2 Myocarditis G2 Hepatitis G1 Hypophysitis G1	Hypophysitis G1	
Glucocorticoid therapy	--		P 20mg qd	MP 80mg qd	MP 40mg qd	MP 30mg qd	P 35mg qd gradual reduction of 5mg weekly		--
Other medications	Ibuprofen Celecoxib	--	Meloxicam Pantoprazole	Sodium bicarbonate		--			
				GS/NS+VitC/Pantoprazole/GSH			Pantoprazole		--
				--	Meloxicam/TGP			--	
				--	Metroprolol succinate/Co-Q/FDP				
Status	**Outpatient**			**Hospitalization**			**Outpatient**		

FIGURE 4 | The process of diagnosis and treatment of irAEs after ICI therapy. P, prednisone; MP, methylprednisolone; GS, glucose solution; NS, normal saline; TGP, total glucosides of paeonia; Co-Q, coenzyme Q; FDP, fructose1, 6-diphosphate. Note: The grade of irAEs refer to the management of immunotherapy-related toxicities from the NCCN clinical practice guidelines and the consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group.

diagnoses by a cardiologist be considered for patients with suspected myocarditis.

Pneumonitis, if not treated, is a life-threatening irAE, accounting for 28% of ICI-induced deaths (23). The risk of pulmonary toxicity occurs earlier and is more extensive in NSCLC than in other tumor types (24). The chest CT of this patient showed a large shadow around the tumor lesion prior to the appearance of subsequent irAEs. In addition to the lung, liver and endocrine are also the common organ sites in multiple-organs irAEs reported in a review (25). Concerning liver and pituitary function, we detected no symptoms in the patient beyond the elevation of ALT/AST levels and the decline of COR/ACTH levels. Secondary adrenal insufficiency due to hypophysitis was diagnosed based on the detection of low cortisol levels. Normal secretion of pituitary hormones other than ACTH is termed isolated ACTH deficiency (IAD), a rare pituitary disorder in which structural pituitary defects are absent typically (26), which is similar to the mild pituitary enlargement in most ICI-related hypophysitis (27).

The mechanism by which multiple-organs irAEs manifest is still poorly understood. It is possible that common antigens or antibody receptors coexist in the affected organs, and that certain antigens are either released from tumor cells killed by T lymphocytes or shared between tumor and normal tissues, resulting in uncontrolled autoimmune reactions across multiple organ systems (20, 28).

Guidelines have been established for the management and treatment of individual organ irAEs (29), but there is little experience in treating multiple-organs irAEs. It is important to seek consultation from multiple specialists for the differential diagnoses of non-immune diseases versus ICI-induced irAEs. Meanwhile, the appropriate monitoring is needed in the balance between the efficacy and safety of the ICI therapy. The correlation between increased IL-6 and grade 3 or greater irAEs was identified in a retrospective analysis (30), IL-6 has been reported to be a biomarker in autoimmune responses in a preliminary study (31), TNF-α was another potential biomarker of irAEs in a plasma biomarkers screening (32). In our case, the level of IL-6 was markedly elevated when irAEs occurred, and after glucocorticoid therapy, IL-6 appeared to temporary decline, but it still fluctuated beyond the upper limit of normal in the whole treatment, probably because of the degree of autoimmune responses and the gradual reduction of glucocorticoid. Thus, the potential value of IL-6 as a biomarker still requires further investigation. While, TNF-α fell to normal gradually after glucocorticoid replacement therapy, which was almost consistent with the previous studies.

A key treatment in this report was the early application of low-dose steroids with dose adjustment by the evolution and severity of multiple-organs irAEs. In our patient, low-dose prednisone was administrated with the initial occurrence of myalgia, which may be beneficial to the suppression of the fulminant progress of multiple-organs irAEs, especially for the fatal complication, such as myocarditis and myositis. This point still requires more evidences to support.

ICI re-challenge therapy after the development of irAEs is still in dispute. In a cross-sectional cohort study, the recurrence rate of the same irAE was 28.8% with re-challenge using the same ICI after discontinuation of ICI therapy (33). Patients with grade 3 or 4 irAEs tended to develop severe irAEs on re-challenge with an ICI (34). Because of the seriousness of irAEs and the short-lived response to tumor occurring in this patient, ICI re-challenge therapy was not considered as the next treatment.

As a sort of ICI used in our case, Tislelizumab is an anti-PD-1 monoclonal antibody, with a different binding orientation to PD-1 in comparison with other PD-1 inhibitors such as pembrolizumab and nivolumab (35). The clinical evidence for Tislelizumab is limited at present, though it has demonstrated encouraging results across several clinical trials for the treatment of advanced NSCLC (36). As shown in **Supplementary Table 1** (37–41), Tislelizumab monotherapy is similar to Nivolumab and Pembrolizumab in anti-tumor efficacy, safety, and tolerability, but more clinical data are still needed to feature Tislelizumab.

CONCLUSION

Our case report supplies several experiences in the management of multiple-organs irAEs, including full-scale monitoring of immunological indicators, early differential diagnosis, and prompt glucocorticoid therapy, which are crucial for the outcome of patients with multiple-irAEs, especially for the deadly complication like myocarditis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CD is the drafter of the manuscript. HC proposed the concept of this case report. HC and CD administered the whole course of diagnosis and treatment in this patient. HC, MY, HJ, RW, and ZY contributed to the multi-disciplinary consultation in immune-related pneumonia, myocarditis, myositis, hepatitis, and hypophysitis, respectively. HS was responsible for radiological imaging diagnosis in CT and MRI. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors are grateful to the patient and his family for their active cooperation during the treatment, and allowing us to share all of his case data.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.664809/full#supplementary-material

Supplementary Image 1 | The baseline and abnormal ECG after immunotherapy. **(A)** Pre-immunotherapy: normal; **(B)** 5 weeks after immunotherapy: sinus tachycardia, CRBBB, and potential inferior myocardial infarction.

Supplementary Image 2 | The image change of the lung before and after the subsequent anti-cancer treatment following irAEs. **(A)** PET-CT before treatment: tumor with hypermetabolism was seen in the right lung; **(B)** Chest CT after two cycles of treatment: the tumor was reduced with air holes formed.

Supplementary Table 1 | Different PD-1 inhibitors monotherapy trials in patients with advanced NSCLC.

REFERENCES

1. Choi YY, Kim H, Shin SJ, Kim HY, Lee J, Yang HK, et al. Microsatellite Instability and Programmed Cell Death-Ligand 1 Expression in Stage II/III Gastric Cancer: Post Hoc Analysis of the CLASSIC Randomized Controlled Study. *Ann Surg* (2019) 270:309–16. doi: 10.1097/SLA.0000000000002803
2. Yarchoan M, Hopkins A, Jaffee EM. Tumor Mutational Burden and Response Rate to PD-1 Inhibition. *N Engl J Med* (2017) 377:2500–1. doi: 10.1056/NEJMc1713444
3. Johnson DB, Chandra S, Sosman JA. Immune Checkpoint Inhibitor Toxicity in 2018. *JAMA* (2018) 320:1702–3. doi: 10.1001/jama.2018.13995
4. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chavez A, Keegan N, Khamashta MA, et al. Immune-Related Adverse Events of Checkpoint Inhibitors. *Nat Rev Dis Primers* (2020) 6:38. doi: 10.1038/s41572-020-0160-6
5. Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non-Small-Cell Lung Cancer. *JAMA Oncol* (2018) 4:374–8. doi: 10.1001/jamaoncol.2017.2925
6. Matsuoka H, Hayashi T, Takigami K, Imaizumi K, Shiroki R, Ohmiya N, et al. Correlation Between Immune-Related Adverse Events and Prognosis in Patients With Various Cancers Treated With Anti PD-1 Antibody. *BMC Cancer* (2020) 20:656. doi: 10.1186/s12885-020-07142-3
7. Shimozaki K, Sukawa Y, Beppu N, Kurihara I, Suzuki S, Mizuno R, et al. Multiple Immune-Related Adverse Events and Anti-Tumor Efficacy: Real-World Data on Various Solid Tumors. *Cancer Manag Res* (2020) 12:4585–93. doi: 10.2147/CMAR.S247554
8. Bouhlel L, Doyen J, Chamorey E, Poudenx M, Ilie M, Gal J, et al. Occurrence and Number of Immune-Related Adverse Events are Independently Associated With Survival in Advanced Non-Small-Cell Lung Cancer Treated by Nivolumab. *Bull Cancer* (2020) 107:946–58. doi: 10.1016/j.bulcan.2020.04.019
9. Johnson DB, Jakubovic BD, Sibaud V, Sise ME. Balancing Cancer Immunotherapy Efficacy and Toxicity. *J Allergy Clin Immunol Pract* (2020) 8:2898–906. doi: 10.1016/j.jaip.2020.06.028
10. Nguyen T, Maria A, Ladhari C, Palassin P, Quantin X, Lesage C, et al. Rheumatic Disorders Associated With Immune Checkpoint Inhibitors: What About Myositis? An Analysis of the WHO's Adverse Drug Reactions Database. *Ann Rheum Dis* (2020). doi: 10.1136/annrheumdis-2020-217018
11. Solimando AG, Crudele L, Leone P, Argentiero A, Guarascio M, Silvestris N, et al. Immune Checkpoint Inhibitor-Related Myositis: From Biology to Bedside. *Int J Mol Sci* (2020) 21:3054. doi: 10.3390/ijms21093054
12. Heinzerling L, Goldinger SM. A Review of Serious Adverse Effects Under Treatment With Checkpoint Inhibitors. *Curr Opin Oncol* (2017) 29:136–44. doi: 10.1097/CCO.0000000000000358
13. Ganatra S, Neilan TG. Immune Checkpoint Inhibitor-Associated Myocarditis. *Oncologist* (2018) 23:879–86. doi: 10.1634/theoncologist.2018-0130
14. Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, et al. Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-Analysis. *JAMA Oncol* (2018) 4:173–82. doi: 10.1001/jamaoncol.2017.3064
15. Suzman DL, Pelosof L, Rosenberg A, Avigan MI. Hepatotoxicity of Immune Checkpoint Inhibitors: An Evolving Picture of Risk Associated With a Vital Class of Immunotherapy Agents. *Liver Int* (2018) 38:976–87. doi: 10.1111/liv.13746
16. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients With Advanced Cancer: A Systematic Review and Meta-Analysis. *JAMA Oncol* (2016) 2:1607–16. doi: 10.1001/jamaoncol.2016.2453
17. Moreira A, Loquai C, Pfohler C, Kahler KC, Knauss S, Heppt MV, et al. Myositis and Neuromuscular Side-Effects Induced by Immune Checkpoint Inhibitors. *Eur J Cancer* (2019) 106:12–23. doi: 10.1016/j.ejca.2018.09.033
18. Al-Kindi SG, Oliveira GH. Reporting of Immune Checkpoint Inhibitor-Associated Myocarditis. *Lancet* (2018) 392:382–3. doi: 10.1016/S0140-6736(18)31542-3
19. Guha A, Al-Kindi S, Jain P, Tashtish N, ElAmm C, Oliveira GH. Association Between Myocarditis and Other Immune-Related Adverse Events Secondary to Immune Checkpoint Inhibitor Use. *Int J Cancer* (2020) 147:1753–4. doi: 10.1002/ijc.32960
20. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant Myocarditis With Combination Immune Checkpoint Blockade. *N Engl J Med* (2016) 375:1749–55. doi: 10.1056/NEJMoa1609214
21. Norwood TG, Westbrook BC, Johnson DB, Litovsky SH, Terry NL, McKee SB, et al. Smoldering Myocarditis Following Immune Checkpoint Blockade. *J Immunother Cancer* (2017) 5:91. doi: 10.1186/s40425-017-0296-4
22. Abdel-Aty H, Boye P, Zagrosek A, Wassmuth R, Kumar A, Messroghli D, et al. Diagnostic Performance of Cardiovascular Magnetic Resonance in Patients With Suspected Acute Myocarditis: Comparison of Different Approaches. *J Am Coll Cardiol* (2005) 45:1815–22. doi: 10.1016/j.jacc.2004.11.069
23. De Velasco G, Je Y, Bosse D, Awad MM, Ott PA, Moreira RB, et al. Comprehensive Meta-Analysis of Key Immune-Related Adverse Events From CTLA-4 and PD-1/PD-L1 Inhibitors in Cancer Patients. *Cancer Immunol Res* (2017) 5:312–8. doi: 10.1158/2326-6066.CIR-16-0237
24. Ma K, Lu Y, Jiang S, Tang J, Li X, Zhang Y. The Relative Risk and Incidence of Immune Checkpoint Inhibitors Related Pneumonitis in Patients With Advanced Cancer: A Meta-Analysis. *Front Pharmacol* (2018) 9:1430. doi: 10.3389/fphar.2018.01430
25. Remolina-Bonilla YA, Jimenez-Franco B, Lam ET, Bourlon MT. Immune-Related Adverse Events Involving Multiple Organ Sites in a Patient Treated With Nivolumab Plus Ipilimumab. *Oncol (Williston Park)* (2020) 34:171–4.
26. Andrioli M, Pecori GF, Cavagnini F. Isolated Corticotrophin Deficiency. *Pituitary* (2006) 9:289–95. doi: 10.1007/s11102-006-0408-5
27. Faje A. Immunotherapy and Hypophysitis: Clinical Presentation, Treatment, and Biologic Insights. *Pituitary* (2016) 19:82–92. doi: 10.1007/s11102-015-0671-4
28. June CH, Warshauer JT, Bluestone JA. Is Autoimmunity the Achilles' Heel of Cancer Immunotherapy? *Nat Med* (2017) 23:540–7. doi: 10.1038/nm.4321
29. Puzanov I, Diab A, Abdallah K, Bingham CR, Brogdon C, Dadu R, et al. Managing Toxicities Associated With Immune Checkpoint Inhibitors: Consensus Recommendations From the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* (2017) 5:95. doi: 10.1186/s40425-017-0300-z
30. Phillips GS, Wu J, Hellmann MD, Postow MA, Rizvi NA, Freites-Martinez A, et al. Treatment Outcomes of Immune-Related Cutaneous Adverse Events. *J Clin Oncol* (2019) 37:2746–58. doi: 10.1200/JCO.18.02141

31. Akberova D, Kiassov AP, Abdulganieva D. Serum Cytokine Levels and Their Relation to Clinical Features in Patients With Autoimmune Liver Diseases. *J Immunol Res* (2017) 2017:9829436. doi: 10.1155/2017/9829436
32. Costantini A, Takam KP, Julie C, Corjon A, Dumenil C, Dumoulin J, et al. Plasma Biomarkers Screening by Multiplex ELISA Assay in Patients With Advanced Non-Small Cell Lung Cancer Treated With Immune Checkpoint Inhibitors. *Cancers (Basel)* (2020) 13:97. doi: 10.3390/cancers13010097
33. Dolladille C, Ederhy S, Sassier M, Cautela J, Thuny F, Cohen AA, et al. Immune Checkpoint Inhibitor Rechallenge After Immune-Related Adverse Events in Patients With Cancer. *JAMA Oncol* (2020) 6:865–71. doi: 10.1001/jamaoncol.2020.0726
34. Haanen J, Ernstoff M, Wang Y, Menzies A, Puzanov I, Grivas P, et al. Rechallenge Patients With Immune Checkpoint Inhibitors Following Severe Immune-Related Adverse Events: Review of the Literature and Suggested Prophylactic Strategy. *J Immunother Cancer* (2020) 8:e000604. doi: 10.1136/jitc-2020-000604
35. Zhang T, Song X, Xu L, Ma J, Zhang Y, Gong W, et al. The Binding of an Anti-PD-1 Antibody to Fcgammariota has a Profound Impact on its Biological Functions. *Cancer Immunol Immunother* (2018) 67:1079–90. doi: 10.1007/s00262-018-2160-x
36. Liu SY, Wu YL. Tislelizumab: An Investigational Anti-PD-1 Antibody for the Treatment of Advanced Non-Small Cell Lung Cancer (NSCLC). *Expert Opin Investig Drugs* (2020) 29:1355–64. doi: 10.1080/13543784.2020.1833857
37. Shen L, Guo J, Zhang Q, Pan H, Yuan Y, Bai Y, et al. Tislelizumab in Chinese Patients With Advanced Solid Tumors: An Open-Label, Non-Comparative, Phase 1/2 Study. *J Immunother Cancer* (2020) 8:e000437. doi: 10.1136/jitc-2019-000437
38. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. *N Engl J Med* (2017) 376:2415–26. doi: 10.1056/NEJMoa1613493
39. Wu YL, Lu S, Cheng Y, Zhou C, Wang J, Mok T, et al. Nivolumab Versus Docetaxel in a Predominantly Chinese Patient Population With Previously Treated Advanced NSCLC: Checkmate 078 Randomized Phase III Clinical Trial. *J Thorac Oncol* (2019) 14:867–75. doi: 10.1016/j.jtho.2019.01.006
40. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. *J Clin Oncol* (2019) 37:537–46. doi: 10.1200/JCO.18.00149
41. Mok T, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab Versus Chemotherapy for Previously Untreated, PD-L1-Expressing, Locally Advanced or Metastatic Non-Small-Cell Lung Cancer (KEYNOTE-042): A Randomised, Open-Label, Controlled, Phase 3 Trial. *Lancet* (2019) 393:1819–30. doi: 10.1016/S0140-6736(18)32409-7

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Oncology

SYSTEMATIC REVIEW
published: 15 September 2021
doi: 10.3389/fonc.2021.708195

Immune-Related Adverse Events Associated With Outcomes in Patients With NSCLC Treated With Anti-PD-1 Inhibitors: A Systematic Review and Meta-Analysis

Zhe Zhao[1,2], Xinfeng Wang[3], Jinghan Qu[1], Wei Zuo[1], Yan Tang[1], Huijuan Zhu[4]* and Xiaoguang Chen[2]**

[1] Department of Pharmacy, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China, [2] State Key Laboratory of Bioactive Substrate and Function of Natural Medicine, Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China, [3] Department of Thoracic Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, [4] Department of Endocrinology, Key Laboratory of Endocrinology of National Health Commission, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

OPEN ACCESS

Edited by:
Xuelei Ma,
Sichuan University, China

Reviewed by:
Samer Srour,
University of Texas MD Anderson Cancer Center, United States
Khaled Murshed,
Hamad Medical Corporation, Qatar

***Correspondence:**
Yan Tang
1371766691@qq.com
Huijuan Zhu
shengxin2004@163.com
Xiaoguang Chen
chxg@imm.ac.cn

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Oncology

Received: 11 May 2021
Accepted: 31 August 2021
Published: 15 September 2021

Citation:
Zhao Z, Wang X, Qu J, Zuo W, Tang Y, Zhu H and Chen X (2021) Immune-Related Adverse Events Associated With Outcomes in Patients With NSCLC Treated With Anti-PD-1 Inhibitors: A Systematic Review and Meta-Analysis. Front. Oncol. 11:708195. doi: 10.3389/fonc.2021.708195

Background and Objective: Although anti-programmed cell death protein 1 (PD-1) antibodies have exerted remarkable anticancer activity in non-small cell lung cancer (NSCLC), it remains a challenge to identify patients who can benefit from these treatments. Immune-related adverse events (irAEs) may be associated with improved clinical outcomes after immune checkpoint inhibition. However, no conclusive evidence of this correlation has been summarized in patients with NSCLC receiving PD-1 inhibitors. We performed a systematic review and meta-analysis to evaluate the association between irAEs induced by anti-PD-1 antibodies and clinical outcomes in patients with NSCLC.

Methods: Various databases were searched from their inception to January 9, 2021, followed by screening of eligible studies. Hazard ratios were used for the pooled analysis of overall survival (OS) and progression-free survival (PFS), while odds ratios (ORs) were utilized to pool objective response rates (ORRs) and disease control rates (DCRs). A random-effects model was applied to all analyses.

Results: A total of 26 cohorts, including 8,452 patients with NSCLC receiving anti-PD-1 antibodies, were enrolled in the study. Significantly improved OS (HR: 0.51; 95% CI: 0.44-0.60; $P < 0.01$) and PFS (HR: 0.50; 95% CI: 0.43-0.58; $P < 0.01$) were found to be correlated with irAEs. In addition, patients with NSCLC who developed irAEs after PD-1 inhibition demonstrated better responses to therapies, confirmed by pooled ORs of ORRs (OR: 3.41; 95% CI: 2.66-4.35; $P < 0.01$) and DCRs (OR: 4.08; 95% CI: 2.30-7.24; $P < 0.01$). Furthermore, subgroup analysis suggested that both skin and endocrine irAEs are closely correlated with a reduced risk of death, whereas pulmonary irAEs showed no association with longer OS.

Conclusions: In patients with NSCLC treated with anti-PD-1 therapies, the presence of irAEs was strongly correlated with better survival and response, suggesting its potential role as a predictive biomarker for outcomes after PD-1 inhibition.

Keywords: immune-related adverse event, non-small cell lung cancer, PD-1 inhibitor, outcome, prognosis

INTRODUCTION

In recent decades, immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) have revolutionized the treatment landscape for patients with advanced cancer (1). Anti-PD-1 antibodies (nivolumab and pembrolizumab), which have significant anticancer activity, have garnered approvals from the U.S. Food and Drug Administration for various malignancies, including advanced non-small cell lung cancer (NSCLC), melanoma, head and neck squamous cell carcinoma, renal cell carcinoma, and urothelial carcinoma (2).

Nevertheless, the efficacy of anti-PD-1 drugs varies among individuals, only a fraction of whom benefit from immune checkpoint inhibition. Among all cancer types, previously treated NSCLC exhibited a relatively low response rate to PD-1 inhibitors (<20%) (3–6). Therefore, there is an urgent need to establish predictive biomarkers to identify patients with NSCLC who may benefit from PD-1 inhibition. Several predictive approaches have recently been developed for NSCLC treatment, including biomarkers of PD-L1 expression (6, 7), tumor-infiltrating lymphocytes (8), and tumor mutation burden (9). While these biomarkers were developed primarily to focus on the histological or molecular features of the tumor, evidence for predictive capacity of other clinical characteristics is unclear.

Recent studies have demonstrated some correlations between immune-related adverse events (irAEs) and outcomes after ICI treatments. IrAEs are inflammatory side effects related to the activation of the immune system that are triggered by an immune checkpoint blockade, with most involving the skin, endocrine glands, gastrointestinal tract, liver, and lungs (10). In a recent pooled analysis of 30 studies and 4,324 patients, irAEs were shown to predict favorable responses and survival in patients with solid tumors receiving various ICI treatments (11). In addition, another review of 48 clinical trials of nivolumab, used to treat multiple solid tumors, revealed that the objective response rates (ORRs) of nivolumab were positively associated with incidence rates of gastrointestinal, skin, and endocrine irAEs (12). In a retrospective analysis of 1,010 patients with NSCLC treated with pembrolizumab, irAEs were shown to be significantly related to higher ORRs and better progression-free survival (PFS) and overall survival (OS) (13). However, no existing articles have comprehensively summarized a conclusive association between irAEs and the outcomes of anti-PD-1 regimens in patients with NSCLC. Hence, our current study involved a systematic review and pooled analyses of the literature to reveal possible correlations between the irAEs induced by PD-1 blockade and favorable clinical outcomes in patients with NSCLC.

MATERIALS AND METHODS

Search Strategy

We performed a literature search of the PubMed, EMBASE, and the Cochrane Library databases from their inception to January 9, 2021 for published studies assessing prognostic effects of irAEs in patients with NSCLC receiving anti-PD-1 regimens. The search strategy was developed by combining different descriptions of irAEs, various prognostic outcomes, keywords specific to NSCLC, and currently available anti-PD-1 antibodies. Detailed keywords used for the search are listed in **Supplementary Table S1**. Additionally, we screened studies included in two recent systematic reviews (11, 14) and identified 13 related published articles.

Study Selection

All the research was independently screened by two investigators to select eligible studies for further analysis. We only included studies that met the following criteria: (1) full text original research including patients diagnosed with NSCLC receiving anti-PD-1 treatment; (2) published articles in the English language; and (3) reported correlations between irAEs and clinical outcomes (OS, PFS, or ORR). We excluded case reports, reviews, meta-analyses, systematic reviews, conference abstracts, and correspondence letters. In addition, studies that included patients with another type of cancer or who were treated with other ICIs were also excluded.

Data Extraction

The following data were extracted from each study: name of the first author, year of publication, patient number, study type, median time of follow-up, country or area of study, irAE type and grade, irAE evaluation criteria, drugs administered, and any correlations between irAEs and ICI treatment outcomes (survival data or ORRs). The Newcastle-Ottawa Scale (NOS), ranging from 0 to 9, was applied as a quality assessment of all included studies.

Statistical Analysis

To evaluate the association between irAEs and clinical outcomes, hazard ratios (HRs) with 95% confidence intervals (CIs) were used for survival data (OS or PFS), while odds ratios (ORs) were calculated for ORRs and disease control rates (DCRs). The heterogeneity among the different studies was assessed by the Cochrane's χ^2 and Higgins and Thompson's I^2 statistic (15). For heterogeneity analysis, P value < 0.05 studies were considered as significant heterogeneity. I^2 values < 50%, 50-75%, and > 75% were respectively defined as low, moderate, and high heterogeneity.

For pooled analysis, a random-effects model was utilized. Funnel plots were used to assess any publication bias. In this study, *P* values less than 0.05 were considered statistically significant. All analyses were performed using the "meta" package of the R software (V3.6.2).

RESULTS

Characteristics of Eligible Studies

A total of 3,866 studies were identified in our initial search. After the removal of duplicate records, 3,195 were left for screening. Thereafter, 3,153 articles were excluded due to irrelevant titles or abstracts. The full text of the remaining 42 studies was further assessed for eligibility, and 17 additional publications were excluded. Eventually, 25 articles, including 8,452 patients with confirmed NSCLC receiving anti-PD-1 treatment, were enrolled in our meta-analysis (13, 16–39). The process of study selection is illustrated in **Figure 1**.

The characteristics of these selected articles are listed in **Table 1** and **Supplementary Table S2**. As one article included two independent cohorts, we are presenting them as two separate studies (26). The 26 included studies consisted of 21 retrospective cohorts and 5 prospective cohorts. In 18 studies, clinical outcomes for patients with and without any irAEs were compared. The other eight cohorts included specific adverse events (AEs), including skin reactions (two studies), pneumonitis (three studies), and thyroid dysfunction (three studies). The average incidence of irAEs triggered by PD-1 blockade was 34.9%, which varied from 10% to 67%. In 12 cohorts, patients were treated with nivolumab, while pembrolizumab was administered in six studies. Additionally, eight studies included patients receiving either nivolumab or pembrolizumab monotherapy. Some other detailed clinical features of the enrolled NSCLC patients in each study were illustrated in **Supplementary Table S2**, including clinical stage, histological type, PD-L1 expression status and driver gene mutation information.

Correlation Between irAEs and Survival Results

The occurrence of irAEs in patients with NSCLC treated with anti-PD-1 antibodies was associated with better survival. The pooled OS data from the 18 studies enrolled in our analysis revealed a significantly lower risk of death in patients with irAEs (HR: 0.51; 95% CI: 0.44–0.60; $P < 0.01$; **Figure 2A**). Meanwhile, moderate but significant heterogeneity was observed in the pooled OS data (I^2 =

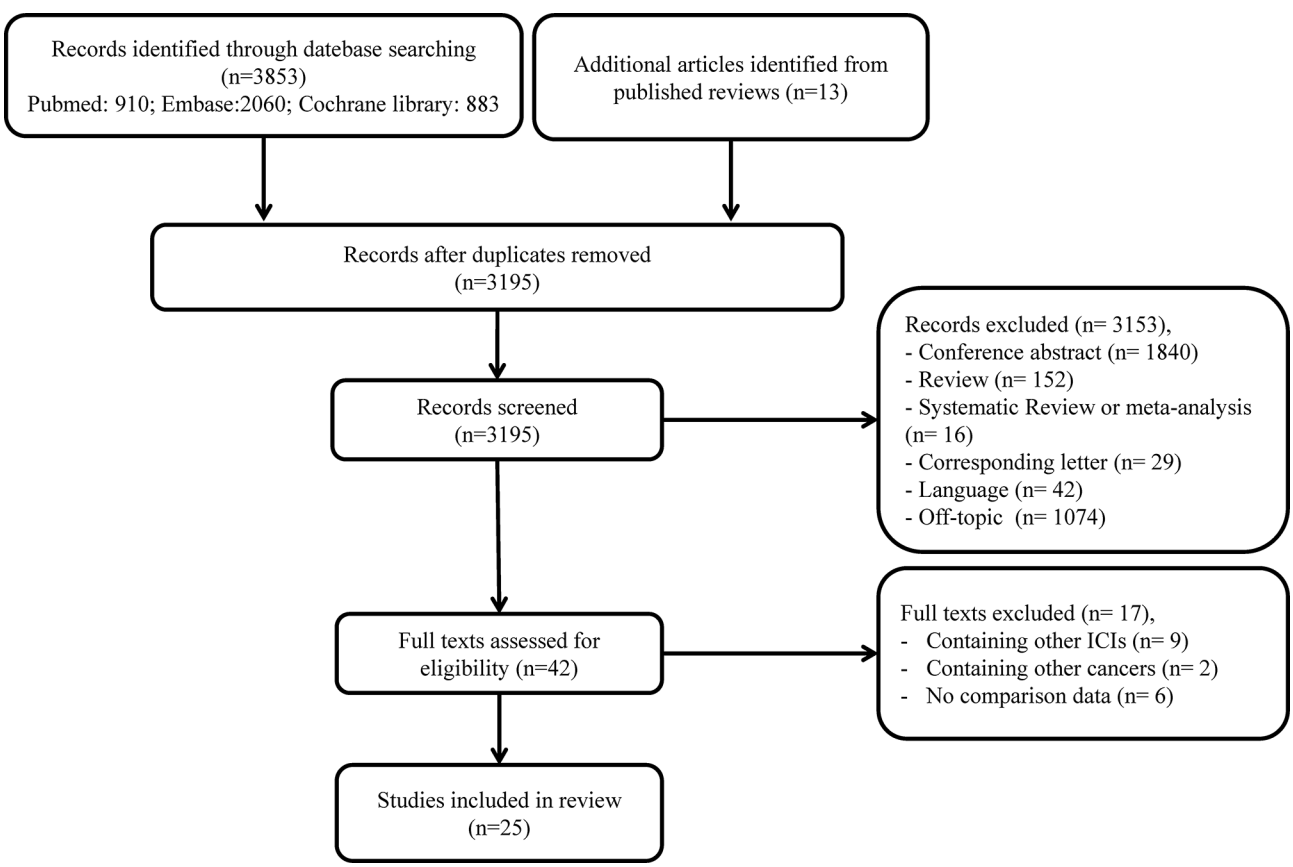

FIGURE 1 | Study selection flow chart.

TABLE 1 | Characteristics of included studies.

Author/ year	N	Country	Study type	Follow up (months)	Type of toxicity/criteria	% irAEs	Drug	OS (HR, 95%CI)	PFS (HR, 95%CI)	ORR	Analysis	NOS
Ahn/2019	155	Korea	retrospective	NR	any G1-4/CTCAE v4.0	61.9	P N	0.38 (0.23-0.64)	0.37 (0.23-0.58)	41.2 *vs.* 26.7	UVA	6
Aso/2020	155	Japan	retrospective	NR	skin reaction all grades/ CTCAE v4.0	58.1	P N	0.34 (0.20–0.60)	0.38 (0.25-0.58)	57 *vs.* 19	UVA	6
Baldini/ 2020	1959	Italy	retrospective	NR	any G1-4/CTCAE v4.0	17.8	N	0.60 (0.51-0.71)	0.69 (0.60-0.79)	27.2 *vs.* 16.5	UVA	7
Barlesi/ 2020	1420	France	prospective cohort	18	any G1-4/-	34.9	N	0.55 (0.48–0.64)	–	–	UVA	8
Barron/ 2020	101	Mexico	retrospective	9.22	pneumonitis G≥2/CTCAE v4.0	21.8	P N	2.48 (1.18–5.23)	–	–	UVA	8
Cortellini/ 2019	559	Italy	retrospective	11.2	any G1-4/CTCAE v4.0	41.3	P N	0.47 (0.36-0.60)	0.53 (0.42-0.66)	46.5 *vs.* 25.7	UVA	7
Cortellini/ 2020	1010	Italy	retrospective	14.8	any G1-4/CTCAE v4.0	32.9	P	0.39 (0.30-0.51)	0.48 (0.39-0.59)	61.5 *vs.* 41.3	UVA	9
Fujimoto/ 2018	613	Japan	retrospective	NR	pneumonitis G3-5/CTCAE v4.0	10	N	–	0.71 (0.52–0.97)	37 *vs.* 18	MVA	4
Fukihara/ 2019	170	Japan	retrospective	9.9	pneumonitis G1-5/CTCAE v4.0	16	P N	–	–	30 *vs.* 24		8
Haratani/ 2018	134	Japan	retrospective	NR	any all grades/-	51	N	0.54 (0.29-0.97)	0.28 (0.10-0.67)	–	MVA	6
Hasan/ 2016	41	Switzerland	retrospective	NR	skin reaction Grade 1-2/ CTCAE v4.0	17	N	–	–	71.4 *vs.* 21.9		4
Hosoya/ 2020	148	Japan	retrospective	NR	any G1-4/CTCAE v4.0	27	P	–	0.55 (0.31-0.98)	77 *vs.* 44	UVA	6
Hosoya/ 2020	76	Japan	prospective cohort	NR	any G1-4/CTCAE v4.0	49	N	0.92 (0.47-1.79)	0.60 (0.36-0.99)	39 *vs.* 13	UVA	6
Kim/2018	58	Korea	prospective cohort	3	thyroid disfunction all grades/-	32.7	P N	0.11 (0.01-0.92)	0.38 (0.17-0.85)	31.6 *vs.* 10.3	MVA	7
Ksienski/ 2019	190	Canada	retrospective	6.1	any G1-2/-	34.7	P	0.66 (0.29-1.48)	–	–	MVA	6
Lim/2020	299	Korea	retrospective	30.1	any G1-4/CTCAE v4.0	32	N	0.44 (0.29-0.67)	0.46 (0.35-0.62)	32 *vs.* 11	UVA	7
Lisberg/ 2018	97	US	retrospective	NR	any G1-4/CTCAE v4.0	40	P	0.72 (0.49-1.05)	0.62 (0.4-0.96)	38.5 *vs.* 8.9	MVA	6
Naqash/ 2020	531	US	retrospective	NR	any G1-4/CTCAE v4.0	33	N	0.66 (0.52–0.82)	0.68 (0.55–0.85)	40.1 *vs.* 14.1	UVA	5
Noguchi/ 2020	94	Japan	retrospective	9.4	any G1-4/CTCAE v4.0	67	P	–	0.24 (0.13-0.42)	–	UVA	6
Osorio/ 2017	51	US	retrospective	NR	thyroid disfunction all grades/ CTCAE v4.0	21	P	0.29 (0.09-0.94)	0.58 (0.27-1.21)	–	UVA	5
Ricciuti/ 2019	195	Italy	retrospective	26	any G1-4/CTCAE v4.0	43.6	N	0.33 (0.23-0.47)	0.41 (0.30-0.57)	43.5 *vs.* 10	UVA	8
Sato/ 2018	38	Japan	prospective cohort	5.6	any G1-4/CTCAE v4.0	36.8	N	–	0.10 (0.02-0.37)	63.6 *vs.* 7.4	UVA	6
Suh/2018	54	Korea	retrospective	26.2	any all grades/CTCAE v4.0	22.2	P N	0.48 (0.20-1.14)	0.5 (0.22-1.13)	66.6 *vs.* 23.8	UVA	8
Teraoka/ 2017	43	Japan	prospective cohort	NR	any G1-4/CTCAE v4.0	44.2	N	–	–	37 *vs.* 17	UVA	5
Toi/2018	70	Japan	retrospective	NR	any G1-4/CTCAE v4.0	40	N	–	0.43 (0.21-0.83)	57 *vs.* 12	UVA	5
Zhou/ 2021	191	China	retrospective	NR	thyroid disfunction all grades/ CTCAE v5.0	20.9	P N	0.33 (0.20–0.57)	–	–	MVA	6

CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; HR, hazard ratio; irAEs, immune-related adverse events; MVA, multivariate analysis; N, nivolumab; NR, not reported; NOS, Newcastle-Ottawa Scale; ORR, objective response rate; OS, overall survival; P, pembrolizumab; PFS, progression-free survival; UVA, univariate analysis.

67%, $P < 0.01$; **Figure 2A**). Correspondingly, significantly improved PFS correlated with the existence of irAEs (HR: 0.50; 95% CI: 0.43–0.58; $P < 0.01$; **Figure 2B**). For the PFS analysis, pooled HRs also showed moderate heterogeneity ($I^2 = 60\%$, $P < 0.01$; **Figure 2B**).

Correlation Between irAEs and Responses to PD-1 Blockade

Further pooled analyses of ORRs and DCRs revealed remarkably higher responses to anti-PD-1 inhibition in patients who exhibited irAEs. Among all the included studies, 19 studies compared ORRs

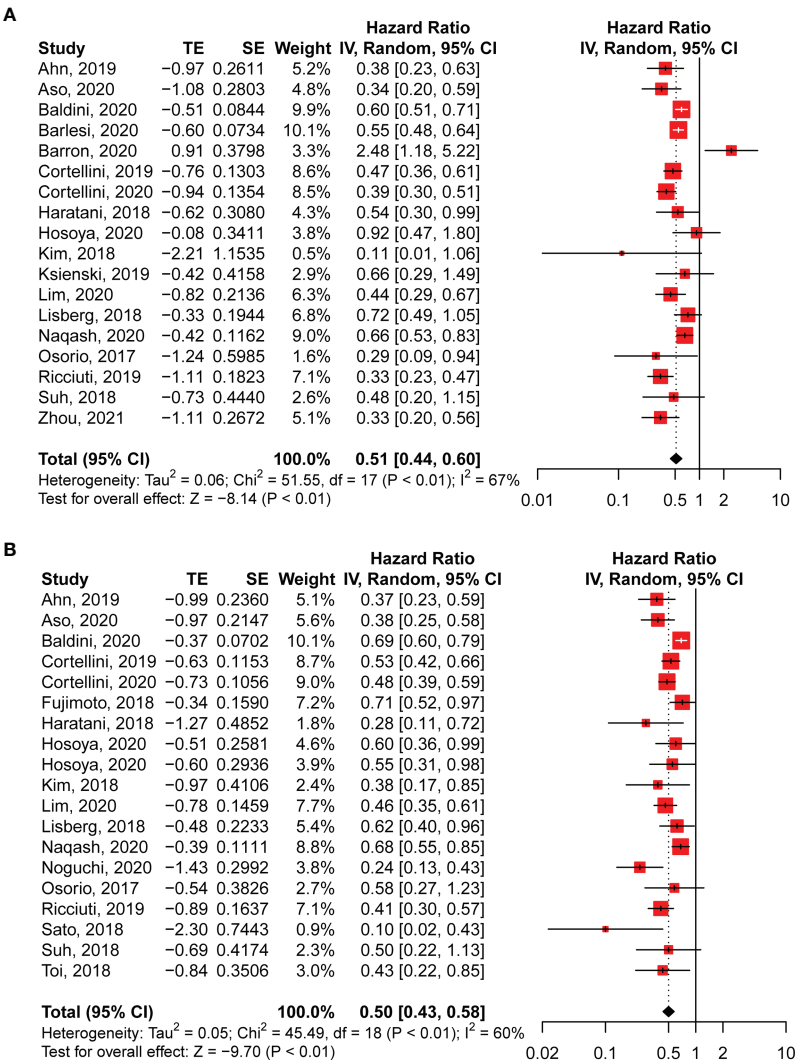

FIGURE 2 | Pooled hazard ratios of overall survival **(A)** and progression-free survival **(B)** in patients with NSCLC with and without irAEs treated with anti-PD-1 antibodies. CI, confidence interval.

between patients with and without irAEs, whereas only nine cohorts investigated DCRs. For ORR analyses, we found that irAEs were significantly related to higher rates of objective responses to PD-1 blockade (OR: 3.41; 95% CI: 2.66–4.35; $P < 0.01$; **Figure 3A**) with moderate heterogeneity ($I^2 = 56\%$, $P < 0.01$; **Figure 3A**). Likewise, pooled ORs of DCRs demonstrated that patients exhibiting irAEs had better responses to anti-PD-1 regimens than patients without irAEs (OR: 4.08; 95% CI: 2.30–7.24; $P < 0.01$; **Figure 3B**). The analyses of DCRs showed high heterogeneity ($I^2 = 79\%$, $P < 0.01$; **Figure 3B**).

Publication Bias and Study Quality Assessment

Begg's funnel plots along with Egger's tests ($P = 0.5479$) illustrated that the pooled analysis of OS in this study did not have any obvious publication bias (**Supplementary Figure S1**). However, possible publication bias existed in the analyses of PFS ($P = 0.0041$; **Supplementary Figure S2**) and ORR results ($P = 0.0010$; **Supplementary Figure S3**). The number of studies with DCR results did not meet the level of publication bias. In the enrolled 26 studies, the median NOS score was 6 (range: 4–9). Over one-half of the studies (14/26) did not report the follow-up time for the cohorts, lowering their NOS scores. In addition, we performed sensitivity analysis by omitting one study at a time for the pooled analyses to evaluate the potential influence of each study on our conclusions. The results showed that not a single study affected the association between better outcome and irAEs (**Supplementary Figure S4**).

Subgroup Analysis

To further investigate the influence of different AEs, we performed subgroup analyses for pulmonary, skin, and

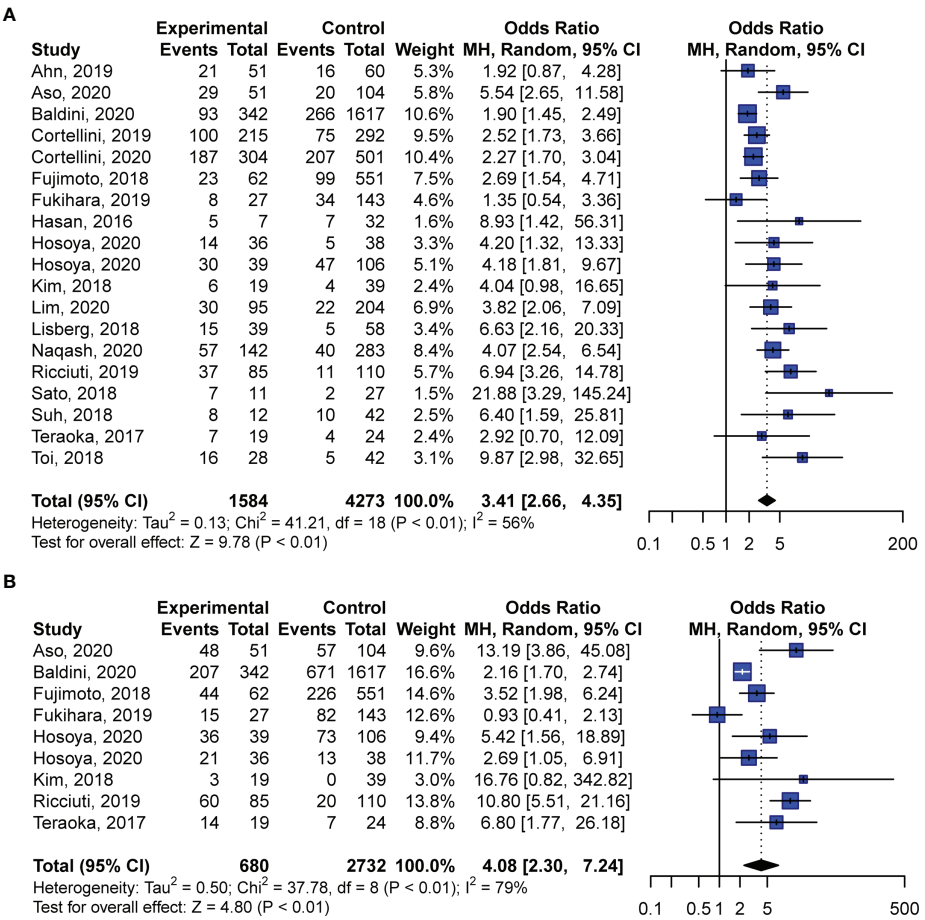

FIGURE 3 | Pooled odds ratios of objective response rates **(A)** and disease control rates **(B)** in patients with NSCLC with and without irAEs treated with anti-PD-1 antibodies. CI, confidence interval.

endocrine irAEs. In addition to the aforementioned eight studies of specific irAEs (17, 20, 22, 23, 25, 27, 33, 39), we also extracted survival data from the other five articles that reported HRs for these three AEs (13, 16, 21, 24, 34). The analysis revealed that skin (HR: 0.41; 95% CI: 0.32–0.52; $P < 0.01$) and endocrine (HR: 0.41; 95% CI: 0.33–0.51; $P < 0.01$) irAEs were significantly associated with longer OS, whereas pulmonary irAEs showed no correlation (HR: 0.98; 95% CI: 0.53–1.83; $P = 0.96$) (**Figure 4A**). In addition, the subgroup analysis of PFS found that all three irAEs had significant associations with better disease control (**Figure 4B**).

More subgroup analyses based on the features of the included studies were also performed. The pooled analyses for prospective studies suggested that irAEs were associated with better PFS (HR: 0.36; 95% CI: 0.16–0.81; $P = 0.01$) but not OS (HR: 0.60; 95% CI: 0.35–1.03; $P = 0.07$) (**Supplementary Figure S5**). For retrospective studies, the occurrence of irAEs was found to have correlations with better OS (HR: 0.50; 95% CI: 0.42–0.61; $P < 0.01$) and PFS (HR: 0.51; 95% CI: 0.44–0.59; $P < 0.01$) (**Supplementary Figure S5**). Also, the subgroup analyses for Asian and non-Asian studies both showed that the presence of irAEs was correlated with longer OS and PFS (**Supplementary Figure S6**). Additionally, the subgroup analyses separated by the anti-PD-1 drugs used in the studies revealed that the association between irAEs and better outcomes existed no matter nivolumab or pembrolizumab was used for treatment (**Supplementary Figure S7**).

DISCUSSION

This is the first and most comprehensive review of studies investigating the association between irAEs and clinical outcomes of patients with NSCLC receiving anti-PD-1 antibodies. In our pooled analysis of the 26 cohorts, we report a strong correlation between the presence of irAEs and improved patient response and prognosis, suggesting the significance of irAEs as a predictor of anti-PD-1 therapeutic efficacy in patients with NSCLC.

In addition to the recognition of antigens combined with major histocompatibility complexes by T-cell receptors, the stimulation of B7-CD28, known as the costimulatory signal, is

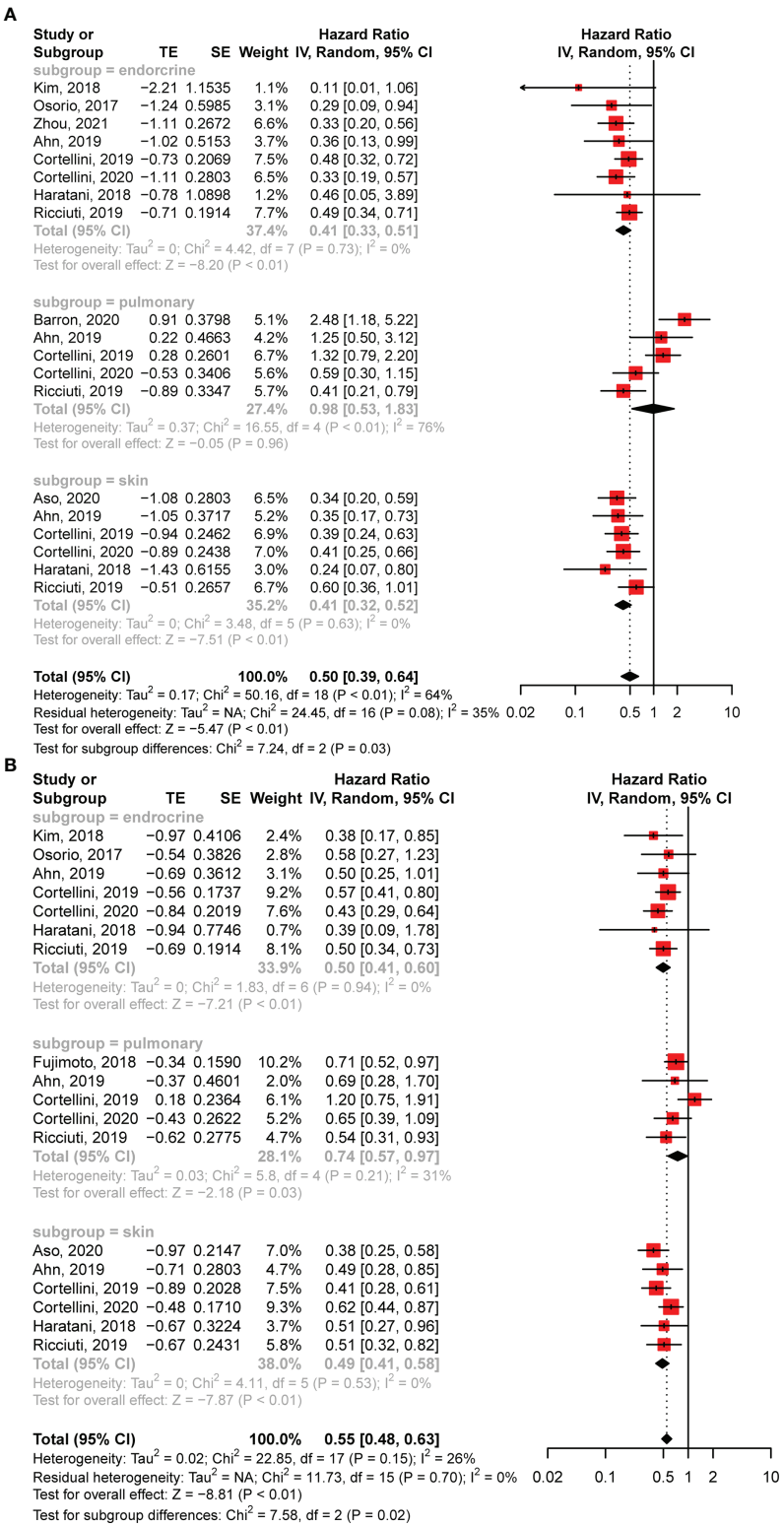

FIGURE 4 | Forest plots of subgroup analysis. **(A)** The association between overall survival and different toxicity types in patients with NSCLC treated with anti-PD-1 antibodies. **(B)** The association between progression-free survival and various irAEs in patients with NSCLC receiving anti-PD-1 antibodies. CI, confidence interval.

indispensable for T-cell activation (40). To avoid the overactivation of T-cells and restrict their autoimmune responses, CTLA-4 (on T-cells) (41, 42) and PD-1 (on T-cells, B-cells, monocytes, natural killer cells, and dendritic cells) exert inhibitory effects by binding to their ligands (PD-L1 or PD-L2) (43). However, in tumor tissues, these immune checkpoint pathways help cancer cells escape the immune system (44). Therefore, ICIs are used to block the overactivation of these pathways to enhance the antitumor immune responses mediated by T-cells (**Figure 5**). Two anti-PD-1 inhibitors (nivolumab and pembrolizumab), which exhibit outstanding efficacy to prolong cancer patient survival, have been approved for the treatment of NSCLC.

Apart from their anticancer efficacy, ICIs also trigger autoimmunity, which results in irAEs (45). Although the precise pathophysiology of irAE onset is still unclear, the possible mechanisms may involve the overactivation of T-cells, stimulation of autoantibodies, and elevation of cytokine levels (**Figure 5**) (10). Therefore, the occurrence of irAEs demonstrates that a patient's immune responses have been activated and that irAE development might be an effective biomarker of ICI efficacy. However, whether this clinical event can help predict responses to ICIs requires additional evidence. Certain irAEs specific to some cancer types have been found to be more strongly associated with improved clinical outcomes. For example, vitiligo, an irAE that mainly occurs in melanoma patients treated with ICIs but rarely in patients with other cancers, has been shown to be closely correlated with favorable outcomes (46, 47). Except for this well-established correlation, other real-world studies have failed to provide definitive associations (37, 48–50). Recent systematic reviews and meta-analyses have suggested the presence of significant associations between irAEs and beneficial clinical outcomes in a pan-cancer setting (11, 51). However, these studies involve patients with different cancers receiving various ICIs, which contradicts the principles of personalized medicine. Further comprehensive research of patients with specific cancer types receiving specific ICIs is thus urgently needed for clinical application.

To avoid such heterogeneity and improve study comparability, we focused our analysis on patients with NSCLC treated with anti-PD-1 antibodies. Consistent with the subgroup analysis results of NSCLC from other systematic reviews (11, 51, 52), our research revealed that the occurrences of irAEs in patients with NSCLC treated with anti-PD-1 antibodies were closely associated with improved clinical outcomes, including OS, PFS, ORRs, and DCRs. Our results demonstrated that patients with NSCLC who developed any irAE after anti-PD-1 treatment showed a 50% reduction in the risks of death and disease progression compared to those without any AEs related to ICIs. Additionally, patients with irAEs

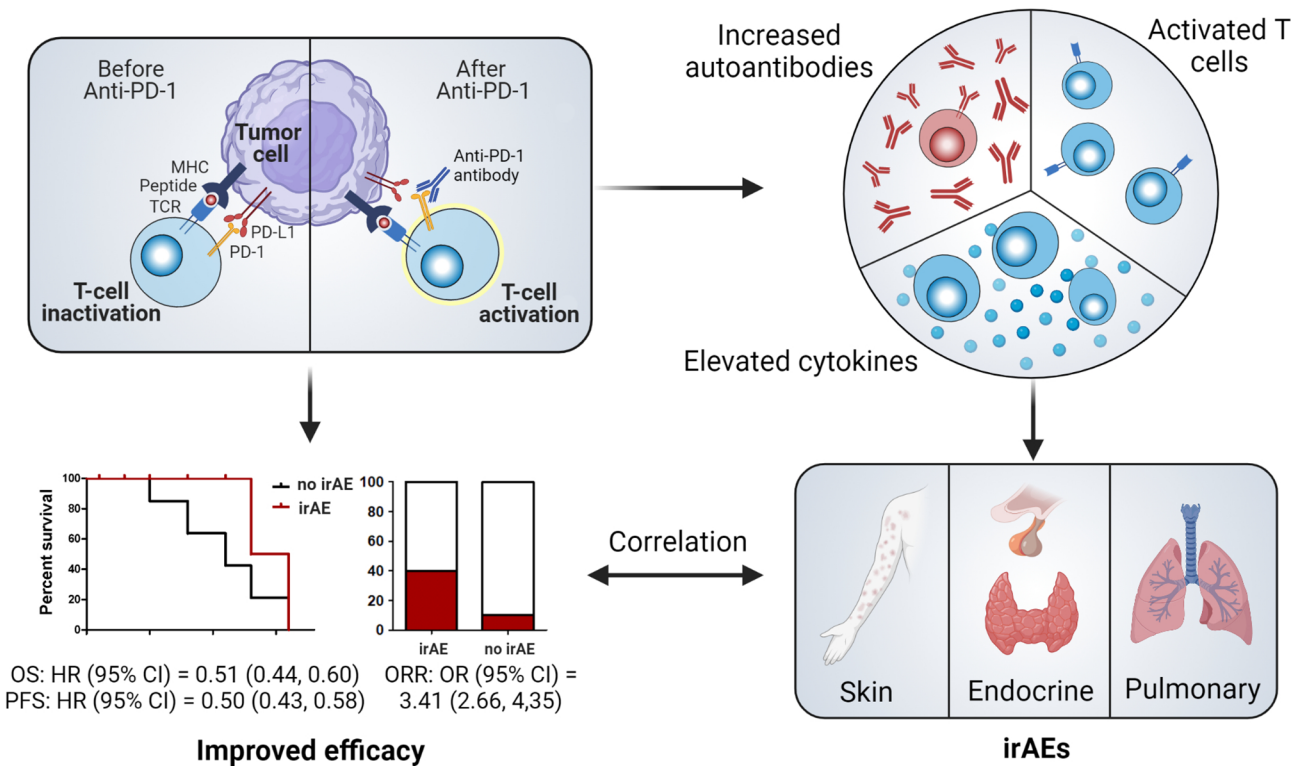

FIGURE 5 | Illustration of potential mechanisms of irAE occurrence and their relationship with the efficacy of immune checkpoint blockade. CI, confidence interval; MHC, major histocompatibility complex; HR, hazard ratio; irAE, immune-related adverse event; OR, odds ratio; ORR, objective response rate; PD-1, programmed cell death protein 1; PFS, progression-free survival; TCR, T-cell receptor.

exhibited better responses to immune checkpoint blockade. These data indicate that irAEs play a critical role in predicting the efficacy of PD-1 therapies in patients with NSCLC. Since these findings are concluded in a specific cancer, our current investigation is closer to clinical usage than existing studies.

We also analyzed the correlations of pulmonary, skin, and endocrine irAEs with survival data. Strikingly, skin and endocrine AEs predicted better survival, whereas pulmonary irAEs were only associated with prolonged PFS but not with OS. Another meta-analysis enrolling patients with various types of cancers showed that various AEs (except pneumonitis) were correlated with improved clinical outcomes (11). In addition, a recent systematic review calculated the correlations between ORRs after nivolumab treatment and incidences of different nivolumab-related irAEs in patients with different solid tumors, revealing that the ORRs were positively associated with skin ($r = 0.79$, $P < 0.001$) and endocrine ($r = 0.44$, $P = 0.05$) irAEs but not with pulmonary irAEs (12). These results confirm our findings from the subgroup analysis. Although antitumor immune responses in patients with lung cancer and pulmonary irAEs are similar, suggesting that pneumonitis may be a favorable biomarker for the efficacy of ICIs in NSCLC, the predictive effects of these AEs may be compromised by several reasons. First, the incidence rates of pulmonary irAEs are low in patients receiving PD-1 antibodies (53, 54) or other ICIs (55), which would cause a disparity between patients with and without immune-related pneumonitis, making it difficult to compare the two groups. Second, pulmonary irAEs are always associated with severe disease and mortality during treatment with ICIs (56), which might also be associated with poor outcomes after immune checkpoint blockade. Taken together, our analysis indicates that endocrine and skin irAEs might be effective predictors of improved outcomes after anti-PD-1 therapies in patients with NSCLC. However, more investigations are needed to determine the specific role of pulmonary irAEs in patients with NSCLC receiving ICIs.

The average incidence of an irAE in our analysis (excluding studies only reporting specific AEs) was 39.4% (ranging from 17.8% to 67.0%) for patients with NSCLC treated with PD-1 inhibitors, consistent with findings from other studies (11). Moreover, our study included both prospective and retrospective cohorts, which better approximate real-world data. All studies were carried out in North America, Asia, and Europe. Although more than half of these enrolled studies were conducted in Asia (15/26), the total number of patients in Asia was only 2,298, which is less than the number of patients in the European studies (5,184 patients). These results indicate that our analysis can be applied to patients with NSCLC receiving anti-PD-1 therapies worldwide. Furthermore, we performed some subgroup analyses based on the characteristics of the eligible studies to assess the impact of these features on the analysis. The results of subgroup analyses were consistent with the findings of all-inclusive meta-analyses, proving that the correlation is robust despite of the heterogeneity between the enrolled studies.

By identifying the correlations between irAEs and better immune responses to anti-PD-1 antibodies, our study emphasizes the significance of monitoring, detecting, and managing irAEs during the course of anti-PD-1 treatments. Patients with NSCLC with few or moderate AEs after treatment with anti-PD-1 antibodies may experience better outcomes than patients without any irAEs. However, the presence of severe irAEs might be unfavorable for patient survival, as these AEs are sometimes life-threatening and affected patients may need to discontinue their ICI therapy. Therefore, close monitoring and early detection of irAEs can help physicians accurately recognize less severe side effects, stratify patients with effective immune responses to PD-1 inhibitors, and prevent irAEs from progressing into more severe AEs. As described in the included studies, patients with common skin irAEs may develop some symptoms like immune-related pruritus, rash, and erythema (24, 34), which can be easy to identify. Some endocrine irAEs following anti-PD-1 therapies include hyper/hypothyroidism with two or more abnormal thyroid function tests (free thyroxine, free triiodothyronine, and thyroid stimulating hormone) (39), and adrenal insufficiency diagnosed by an adrenocorticotropic hormone stimulation test (57). Once irAEs are identified in a patient, appropriate and prompt management can be carried out in a timely manner to improve patient outcomes. Recently, guidelines for the management of irAEs were published (58, 59). Our study highlights the complex but crucial role of irAEs in the use of anti-PD-1 therapy in patients with NSCLC, which may contribute to the update of guideline for NSCLC.

To the best of our knowledge, this study is the first and most comprehensive systematic review and meta-analysis which summarizes and evaluates the correlation between irAE occurrence and clinical outcomes after receiving anti-PD-1 antibodies in NSCLC. Although some other systematic reviews have suggested the association between irAEs and improved clinical response of ICIs, they did not focus on a specific cancer type or a specific kind of ICIs. Therefore, they only summarized partial reports. Fausto et al. (11) included 10 studies regarding NSCLC patients receiving anti-PD-1 treatments in an overall systematic review of solid tumors. Besides, Park et al. (52) concluded the predictive effects of anti-PD-1/L1-associated irAEs for favorable clinical outcomes in a recent systematic review, which only covered 11 studies of NSCLC treated with anti-PD-1 regimens. Recently, Wang et al. (60) reported that irAEs in lung cancer might predict better ICI efficacy, in which 17 lung cancer cohorts treated with anti-PD-1 regimens were included. Compared to these published reviews, we added approximately 9 more cohorts for meta-analysis, making our review more comprehensive and persuasive. Since the effects of different ICIs in various cancers have totally different mechanisms and manifestations, those results concluded from other cancer categories or drugs can hardly be applicable for the cases discussed in our current study. Hence, our results are more important for personalized treatment for NSCLC patients who undergo anti-PD-1 therapies. However, our study still has some limitations. First, publication bias and heterogeneity existed in our analysis, which may be caused by the differences in the characteristics of the included studies. Nevertheless, our subgroup analyses based on these characteristics and sensitivity

analysis results suggest that heterogeneity between the included studies have little influence on our main conclusions. Second, most of the studies were retrospective cohort studies because of the scarce number of available prospective studies. Even so, the subgroup analyses for prospective studies suggest a significant correlation between irAE occurrence and better survival. Hence, we hope that our study encourages more prospective investigations of the relationship between irAE occurrence and ICI efficacy. Third, based on the available studies, our analysis demonstrates correlations rather than causal results. Other predictive biomarkers developed on the basis of tumor histological or genomic features may not affect our analysis and results. Nevertheless, the underlying mechanisms of how irAEs can predict outcomes after ICIs and whether other biomarkers have relationships with irAE occurrence require more investigation.

CONCLUSIONS

This study is the first meta-analysis to assess the predictive effects of irAE onset on clinical outcomes for patients with NSCLC receiving anti-PD-1 regimens. We demonstrate a significant correlation between the presence of irAEs and positive prognosis for patients with NSCLC after treatment with anti-PD-1 antibodies, suggesting that irAEs may be a clinical predictive biomarker for efficacy of anti-PD-1 therapy in NSCLC patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

Conceptualization, TY, ZH and CX. Writing—original draft preparation, ZZ and WX. Collection and curation of data, ZW and QJ. Revision of the manuscript, TY, ZW, QJ and CX. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by CAMS Innovation Fund for Medical Sciences (2017-I2M-1-010), The Drug Innovation Major Project (No. 2018ZX09711001-003, China), and CAMS & PUMC Innovation Fund for Graduate (No.2019-1007-23, China).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.708195/full#supplementary-material

REFERENCES

1. Wilky BA. Immune Checkpoint Inhibitors: The Linchpins of Modern Immunotherapy. *Immunol Rev* (2019) 290:6–23. doi: 10.1111/imr.12766
2. Wu X, Gu Z, Chen Y, Chen B, Chen W, Weng L, et al. Application of PD-1 Blockade in Cancer Immunotherapy. *Comput Struct Biotechnol J* (2019) 17:661–74. doi: 10.1016/j.csbj.2019.03.006
3. Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, et al. Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* (2015) 33:2004–12. doi: 10.1200/jco.2014.58.3708
4. Herbst RS, Baas P, Kim DW, Felip E, Pérez-Gracia JL, Han JY, et al. Pembrolizumab *Versus* Docetaxel for Previously Treated, PD-L1-Positive, Advanced Non-Small-Cell Lung Cancer (KEYNOTE-010): A Randomised Controlled Trial. *Lancet* (2016) 387:1540–50. doi: 10.1016/s0140-6736(15)01281-7
5. Rizvi NA, Mazières J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, et al. Activity and Safety of Nivolumab, an Anti-PD-1 Immune Checkpoint Inhibitor, for Patients With Advanced, Refractory Squamous Non-Small-Cell Lung Cancer (CheckMate 063): A Phase 2, Single-Arm Trial. *Lancet Oncol* (2015) 16:257–65. doi: 10.1016/s1470-2045(15)70054-9
6. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the Treatment of Non-Small-Cell Lung Cancer. *N Engl J Med* (2015) 372:2018–28. doi: 10.1056/NEJMoa1501824
7. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab *Versus* Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med* (2015) 373:1627–39. doi: 10.1056/NEJMoa1507643
8. Yu Y, Zeng D, Ou Q, Liu S, Li A, Chen Y, et al. Association of Survival and Immune-Related Biomarkers With Immunotherapy in Patients With Non-Small Cell Lung Cancer: A Meta-Analysis and Individual Patient-1Level Analysis. *JAMA Netw Open* (2019) 2:e196879. doi: 10.1001/jamanetworkopen.2019.6879
9. Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab Plus Ipilimumab in Lung Cancer With a High Tumor Mutational Burden. *N Engl J Med* (2018) 378:2093–104. doi: 10.1056/NEJMoa1801946
10. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated With Immune Checkpoint Blockade. *N Engl J Med* (2018) 378:158–68. doi: 10.1056/NEJMra1703481
11. Petrelli F, Grizzi G, Ghidini M, Ghidini A, Ratti M, Panni S, et al. Immune-Related Adverse Events and Survival in Solid Tumors Treated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. *J Immunother* (2020) 43:1–7. doi: 10.1097/cji.0000000000000300
12. Xing P, Zhang F, Wang G, Xu Y, Li C, Wang S, et al. Incidence Rates of Immune-Related Adverse Events and Their Correlation With Response in Advanced Solid Tumours Treated With NIVO or NIVO+IPI: A Systematic Review and Meta-Analysis. *J Immunother Cancer* (2019) 7:341. doi: 10.1186/s40425-019-0779-6
13. Cortellini A, Friedlaender A, Banna GL, Porzio G, Bersanelli M, Cappuzzo F, et al. Immune-Related Adverse Events of Pembrolizumab in a Large Real-World Cohort of Patients With NSCLC With a PD-L1 Expression ≥ 50% and Their Relationship With Clinical Outcomes. *Clin Lung Cancer* (2020) 21:498–508.e2. doi: 10.1016/j.cllc.2020.06.010
14. Cortellini A, Buti S, Agostinelli V, Bersanelli M. A Systematic Review on the Emerging Association Between the Occurrence of Immune-Related Adverse Events and Clinical Outcomes With Checkpoint Inhibitors in Advanced Cancer Patients. *Semin Oncol* (2019) 46:362–71. doi: 10.1053/j.seminoncol.2019.10.003
15. Higgins JP, Thompson SG. Quantifying Heterogeneity in a Meta-Analysis. *Stat Med* (2002) 21:1539–58. doi: 10.1002/sim.1186
16. Ahn BC, Pyo KH, Xin CF, Jung D, Shim HS, Lee CY, et al. Comprehensive Analysis of the Characteristics and Treatment Outcomes of Patients With Non-Small Cell Lung Cancer Treated With Anti-PD-1 Therapy in Real-

World Practice. *J Cancer Res Clin Oncol* (2019) 145:1613–23. doi: 10.1007/s00432-019-02899-y
17. Aso M, Toi Y, Sugisaka J, Aiba T, Kawana S, Saito R, et al. Association Between Skin Reaction and Clinical Benefit in Patients Treated With Anti-Programmed Cell Death 1 Monotherapy for Advanced Non-Small Cell Lung Cancer. *Oncologist* (2020) 25:e536–e44. doi: 10.1634/theoncologist.2019-0550
18. Baldini E, Lunghi A, Cortesi E, Turci D, Signorelli D, Stati V, et al. Immune-Related Adverse Events Correlate With Clinical Outcomes in NSCLC Patients Treated With Nivolumab: The Italian NSCLC Expanded Access Program. *Lung Cancer* (2020) 140:59–64. doi: 10.1016/j.lungcan.2019.12.014
19. Barlesi F, Dixmier A, Debieuvre D, Raspaud C, Auliac JB, Benoit N, et al. Effectiveness and Safety of Nivolumab in the Treatment of Lung Cancer Patients in France: Preliminary Results From the Real-World EVIDENS Study. *OncoImmunology* (2020) 9:1744898. doi: 10.1080/2162402X.2020.1744898
20. Barrón F, Sánchez R, Arroyo-Hernández M, Blanco C, Zatarain-Barrón ZL, Catalán R, et al. Risk of Developing Checkpoint Immune Pneumonitis and Its Effect on Overall Survival in Non-Small Cell Lung Cancer Patients Previously Treated With Radiotherapy. *Front Oncol* (2020) 10:570233. doi: 10.3389/fonc.2020.570233
21. Cortellini A, Chiari R, Ricciuti B, Metro G, Perrone F, Tiseo M, et al. Correlations Between the Immune-Related Adverse Events Spectrum and Efficacy of Anti-PD1 Immunotherapy in NSCLC Patients. *Clin Lung Cancer* (2019) 20:237–47.e1. doi: 10.1016/j.cllc.2019.02.006
22. Fujimoto D, Yoshioka H, Kataoka Y, Morimoto T, Kim YH, Tomii K, et al. Efficacy and Safety of Nivolumab in Previously Treated Patients With Non-Small Cell Lung Cancer: A Multicenter Retrospective Cohort Study. *Lung Cancer* (2018) 119:14–20. doi: 10.1016/j.lungcan.2018.02.017
23. Fukihara J, Sakamoto K, Koyama J, Ito T, Iwano S, Morise M, et al. Prognostic Impact and Risk Factors of Immune-Related Pneumonitis in Patients With Non-Small-Cell Lung Cancer Who Received Programmed Death 1 Inhibitors. *Clin Lung Cancer* (2019) 20:442–50.e4. doi: 10.1016/j.cllc.2019.07.006
24. Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non-Small-Cell Lung Cancer. *JAMA Oncol* (2018) 4:374–8. doi: 10.1001/jamaoncol.2017.2925
25. Hasan Ali O, Diem S, Markert E, Jochum W, Kerl K, French LE, et al. Characterization of Nivolumab-Associated Skin Reactions in Patients With Metastatic Non-Small Cell Lung Cancer. *Oncoimmunology* (2016) 5:e1231292. doi: 10.1080/2162402x.2016.1231292
26. Hosoya K, Fujimoto D, Morimoto T, Kumagai T, Tamiya A, Taniguchi Y, et al. Association Between Early Immune-Related Adverse Events and Clinical Outcomes in Patients With Non-Small Cell Lung Cancer Treated With Immune Checkpoint Inhibitors. *Clin Lung Cancer* (2020) 21:e315–e28. doi: 10.1016/j.cllc.2020.01.003
27. Kim HI, Kim M, Lee SH, Park SY, Kim YN, Kim H, et al. Development of Thyroid Dysfunction is Associated With Clinical Response to PD-1 Blockade Treatment in Patients With Advanced Non-Small Cell Lung Cancer. *OncoImmunology* (2018) 7:e1375642. doi: 10.1080/2162402X.2017.1375642
28. Ksienski D, Wai ES, Croteau N, Freeman AT, Chan A, Fiorino L, et al. Pembrolizumab for Advanced Nonsmall Cell Lung Cancer: Efficacy and Safety in Everyday Clinical Practice. *Lung Cancer* (2019) 133:110–6. doi: 10.1016/j.lungcan.2019.05.005
29. Lim SM, Kim SW, Cho BC, Kang JH, Ahn MJ, Kim DW, et al. Real-World Experience of Nivolumab in Non-Small Cell Lung Cancer in Korea. *Cancer Res Treat* (2020) 52:1112–9. doi: 10.4143/crt.2020.245
30. Lisberg A, Tucker DA, Goldman JW, Wolf B, Carroll J, Hardy A, et al. Treatment-Related Adverse Events Predict Improved Clinical Outcome in NSCLC Patients on KEYNOTE-001 at a Single Center. *Cancer Immunol Res* (2018) 6:288–94. doi: 10.1158/2326-6066.Cir-17-0063
31. Naqash AR, Ricciuti B, Owen DH, Florou V, Toi Y, Cherry C, et al. Outcomes Associated With Immune-Related Adverse Events in Metastatic Non-Small Cell Lung Cancer Treated With Nivolumab: A Pooled Exploratory Analysis From a Global Cohort. *Cancer Immunol Immunother* (2020) 69:1177–87. doi: 10.1007/s00262-020-02536-5
32. Noguchi S, Suminaga K, Kaki T, Kawachi H, Fukao A, Terashita S, et al. Correlation of Immune-Related Adverse Events and Effects of Pembrolizumab Monotherapy in Patients With Non-Small Cell Lung Cancer. *Lung Cancer (Auckl)* (2020) 11:53–7. doi: 10.2147/lctt.S254146
33. Osorio JC, Ni A, Chaft JE, Pollina R, Kasler MK, Stephens D, et al. Antibody-Mediated Thyroid Dysfunction During T-Cell Checkpoint Blockade in Patients With Non-Small-Cell Lung Cancer. *Ann Oncol* (2017) 28:583–9. doi: 10.1093/annonc/mdw640
34. Ricciuti B, Genova C, De Giglio A, Bassanelli M, Dal Bello MG, Metro G, et al. Impact of Immune-Related Adverse Events on Survival in Patients With Advanced Non-Small Cell Lung Cancer Treated With Nivolumab: Long-Term Outcomes From a Multi-Institutional Analysis. *J Cancer Res Clin Oncol* (2019) 145:479–85. doi: 10.1007/s00432-018-2805-3
35. Sato K, Akamatsu H, Murakami E, Sasaki S, Kanai K, Hayata A, et al. Correlation Between Immune-Related Adverse Events and Efficacy in Non-Small Cell Lung Cancer Treated With Nivolumab. *Lung Cancer* (2018) 115:71–4. doi: 10.1016/j.lungcan.2017.11.019
36. Suh KJ, Kim SH, Kim YJ, Kim M, Keam B, Kim TM, et al. Post-Treatment Neutrophil-to-Lymphocyte Ratio at Week 6 is Prognostic in Patients With Advanced Non-Small Cell Lung Cancers Treated With Anti-PD-1 Antibody. *Cancer Immunol Immunother* (2018) 67:459–70. doi: 10.1007/s00262-017-2092-x
37. Teraoka S, Fujimoto D, Morimoto T, Kawachi H, Ito M, Sato Y, et al. Early Immune-Related Adverse Events and Association With Outcome in Advanced Non-Small Cell Lung Cancer Patients Treated With Nivolumab: A Prospective Cohort Study. *J Thorac Oncol* (2017) 12:1798–805. doi: 10.1016/j.jtho.2017.08.022
38. Toi Y, Sugawara S, Kawashima Y, Aiba T, Kawana S, Saito R, et al. Association of Immune-Related Adverse Events With Clinical Benefit in Patients With Advanced Non-Small-Cell Lung Cancer Treated With Nivolumab. *Oncologist* (2018) 23:1358–65. doi: 10.1634/theoncologist.2017-0384
39. Zhou Y, Xia R, Xiao H, Pu D, Long Y, Ding Z, et al. Thyroid Function Abnormality Induced by PD-1 Inhibitors Have a Positive Impact on Survival in Patients With Non-Small Cell Lung Cancer. *Int Immunopharmacol* (2021) 91:107296. doi: 10.1016/j.intimp.2020.107296
40. Mueller DL, Jenkins MK, Schwartz RH. Clonal Expansion *Versus* Functional Clonal Inactivation: A Costimulatory Signalling Pathway Determines the Outcome of T Cell Antigen Receptor Occupancy. *Annu Rev Immunol* (1989) 7:445–80. doi: 10.1146/annurev.iy.07.040189.002305
41. Jain N, Nguyen H, Chambers C, Kang J. Dual Function of CTLA-4 in Regulatory T Cells and Conventional T Cells to Prevent Multiorgan Autoimmunity. *Proc Natl Acad Sci USA* (2010) 107:1524–8. doi: 10.1073/pnas.0910341107
42. Pedicord VA, Montalvo W, Leiner IM, Allison JP. Single Dose of Anti-CTLA-4 Enhances CD8+ T-Cell Memory Formation, Function, and Maintenance. *Proc Natl Acad Sci USA* (2011) 108:266–71. doi: 10.1073/pnas.1016791108
43. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced Expression of PD-1, a Novel Member of the Immunoglobulin Gene Superfamily, Upon Programmed Cell Death. *EMBO J* (1992) 11:3887–95. doi: 10.1002/j.1460-2075.1992.tb05481.x
44. Pauken KE, Wherry EJ. Overcoming T Cell Exhaustion in Infection and Cancer. *Trends Immunol* (2015) 36:265–76. doi: 10.1016/j.it.2015.02.008
45. Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of Immunotherapy for the Practitioner. *J Clin Oncol Off J Am Soc Clin Oncol* (2015) 33:2092–9. doi: 10.1200/JCO.2014.60.0379
46. Hua C, Boussemart L, Mateus C, Routier E, Boutros C, Cazenave H, et al. Association of Vitiligo With Tumor Response in Patients With Metastatic Melanoma Treated With Pembrolizumab. *JAMA Dermatol* (2016) 152:45–51. doi: 10.1001/jamadermatol.2015.2707
47. Teulings HE, Limpens J, Jansen SN, Zwinderman AH, Reitsma JB, Spuls PI, et al. Vitiligo-Like Depigmentation in Patients With Stage III-IV Melanoma Receiving Immunotherapy and Its Association With Survival: A Systematic Review and Meta-Analysis. *J Clin Oncol* (2015) 33:773–81. doi: 10.1200/jco.2014.57.4756
48. Attia P, Phan GQ, Maker AV, Robinson MR, Quezado MM, Yang JC, et al. Autoimmunity Correlates With Tumor Regression in Patients With Metastatic Melanoma Treated With Anti-Cytotoxic T-Lymphocyte Antigen-4. *J Clin Oncol* (2005) 23:6043–53. doi: 10.1200/jco.2005.06.205
49. Horvat TZ, Adel NG, Dang TO, Momtaz P, Postow MA, Callahan MK, et al. Immune-Related Adverse Events, Need for Systemic Immunosuppression, and Effects on Survival and Time to Treatment Failure in Patients With Melanoma Treated With Ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol* (2015) 33:3193–8. doi: 10.1200/jco.2015.60.8448

50. Verzoni E, Cartenì G, Cortesi E, Giannarelli D, De Giglio A, Sabbatini R, et al. Real-World Efficacy and Safety of Nivolumab in Previously-Treated Metastatic Renal Cell Carcinoma, and Association Between Immune-Related Adverse Events and Survival: The Italian Expanded Access Program. *J Immunother Cancer* (2019) 7:99. doi: 10.1186/s40425-019-0579-z
51. Hussaini S, Chehade R, Boldt RG, Raphael J, Blanchette P, Maleki Vareki S, et al. Association Between Immune-Related Side Effects and Efficacy and Benefit of Immune Checkpoint Inhibitors - A Systematic Review and Meta-Analysis. *Cancer Treat Rev* (2021) 92:102134. doi: 10.1016/j.ctrv.2020.102134
52. Park R, Lopes L, Saeed A. Anti-PD-1/L1-Associated Immune-Related Adverse Events as Harbinger of Favorable Clinical Outcome: Systematic Review and Meta-Analysis. *Clin Transl Oncol* (2021) 23:100–9. doi: 10.1007/s12094-020-02397-5
53. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients With Advanced Cancer: A Systematic Review and Meta-Analysis. *JAMA Oncol* (2016) 2:1607–16. doi: 10.1001/jamaoncol.2016.2453
54. Nishino M, Ramaiya NH, Awad MM, Sholl LM, Maattala JA, Taibi M, et al. PD-1 Inhibitor-Related Pneumonitis in Advanced Cancer Patients: Radiographic Patterns and Clinical Course. *Clin Cancer Res* (2016) 22:6051–60. doi: 10.1158/1078-0432.ccr-16-1320
55. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. *J Clin Oncol* (2017) 35:709–17. doi: 10.1200/jco.2016.68.2005
56. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. *JAMA Oncol* (2018) 4:1721–8. doi: 10.1001/jamaoncol.2018.3923
57. Hobbs KB, Yackzan S. Adrenal Insufficiency: Immune Checkpoint Inhibitors and Immune-Related Adverse Event Management. *Clin J Oncol Nurs* (2020) 24:240–3. doi: 10.1188/20.Cjon.240-243
58. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* (2018) 36:1714–68. doi: 10.1200/jco.2017.77.6385
59. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. NCCN Guidelines Insights: Management of Immunotherapy-Related Toxicities, Version 1.2020. *J Natl Compr Canc Netw* (2020) 18:230–41. doi: 10.6004/jnccn.2020.0012
60. Wang D, Chen C, Gu Y, Lu W, Zhan P, Liu H, et al. Immune-Related Adverse Events Predict the Efficacy of Immune Checkpoint Inhibitors in Lung Cancer Patients: A Meta-Analysis. *Front Oncol* (2021) 11:631949. doi: 10.3389/fonc.2021.631949

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Oncology

MINI REVIEW
published: 30 September 2021
doi: 10.3389/fonc.2021.720759

Management of Immune-Related Adverse Events in Patients With Non-Small Cell Lung Cancer

Michael Burke and Sawsan Rashdan *

Department of Internal Medicine, Division of Hematology and Oncology, University of Texas Southwestern Medical Center, Dallas, TX, United States

With proven efficacy of the use of immunotherapy in almost all stages of NSCLC, immunotherapy toxicity has become a very important topic that requires immediate recognition and management. The diagnosis of toxicities associated with immunotherapy in lung cancer can be very challenging and often requires multidisciplinary effort. This mini review gives an overview of the diagnosis and management of immune-related adverse events that arise from using immunotherapy in NSCLC, as well as the potential biomarkers for its early identification and future directions.

Keywords: lung cancer, immunotherapy, toxicity, adverse events, steroids, checkpoint inhibitor

OPEN ACCESS

Edited by:
Xuelei Ma,
Sichuan University, China

Reviewed by:
Gunes Esendagli,
Hacettepe University, Turkey
Mouldy Sioud,
Oslo University Hospital, Norway

***Correspondence:**
Sawsan Rashdan
sawsan.rashdan@utsouthwestern.edu

Specialty section:
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Oncology

Received: *04 June 2021*
Accepted: *31 August 2021*
Published: *30 September 2021*

Citation:
Burke M and Rashdan S (2021) Management of Immune-Related Adverse Events in Patients With Non-Small Cell Lung Cancer. Front. Oncol. 11:720759. doi: 10.3389/fonc.2021.720759

INTRODUCTION

With an estimated 228,820 new cases of lung cancer in 2020 and 135,720 anticipated lung cancer deaths comprising 22% of all cancer deaths in the United States, the burden of non-small cell lung cancer (NSCLC) as the most common type of lung cancer and its treatment has become extraordinary (1). Over the past two decades, the care of NSCLC has been revolutionized by the introduction of cancer immunotherapy. Since the initial publications in the management of progressive metastatic disease in Checkmate-057 (2), Checkmate-017 (3), and Keynote-010 (4), immunotherapy has increasingly dominated the management of NSCLC moving to the first-line setting in metastatic disease (5), then with the use in locally advanced disease after concurrent chemoradiation therapy (6) and now the anticipated involvement in the neoadjuvant space (7) (**Table 1**).

Currently approved agents for the management of NSCLC include an ever-growing list of immunomodulatory drugs such as pembrolizumab, atezolizumab, nivolumab, durvalumab, and ipilumumab. Unfortunately, the inevitable afterbirth of this revolution has been the recognition of immune-related adverse events (irAEs) of treatment and the need for management of this novel class of complications. Thankfully, the majority of these irAEs are of minor grade and may be treated symptomatically with continuation of treatment; however, due to the nature of immunotherapy, nearly every organ system may be affected and to lethal ends. As will be discussed in the following review, the incidence and severity of these effects in the management of NSCLC may vary depending on drug class, patient characteristics, combination with radiation therapy, and combination with targeted therapy as well as other immunomodulatory drugs.

TABLE 1 | FDA-approved immunotherapy in lung cancer without target mutation.

Trial	Population	Stage	IO combination	Subgroups	Mechanism	Reported irAE (>1%)
PACIFIC	NSCLC	III	Radiation + *durvalumab*		PD-1	Pneumonitis (4.8%)
IMpower150	NSCLC-non-squamous	IV	Carboplatin + bevacizumab + paclitaxel + *atezolizumab*		PD-L1	Dermatitis 29% Hypothyroid 13% Hyperthyroid 4.1% Pneumonitis 2.8% Colitis 2.3% Hepatitis 2%
CASPIAN	SCLC	ES	Carboplatin + etoposide + *durvalumab*		PD-1	Hypothyroid 9% Hyperthyroid 5% Pneumonitis 3% Hepatitis 3% Dermatitis 2% Colitis 2%
IMpower133	SCLC	ES	Carboplatin + etoposide + *atezolizumab*		PD-L1	Dermatitis 18.7% Hypothyroid 12.6% Hepatitis 7.1% Hyperthyroid 5.6% Pneumonitis 2.0% Colitis 1.5%
Checkmate-227	NSCLC	IV	*Ipilumumab* + *nivolumab* + platinum	PD-L1 >1% (Trend <1%)	CTLA-4 PD-1	Skin 34% Endocrine 23.8% Gastrointestinal 18.2% Hepatic 15.8% Pulmonary 8.3% Renal 4.3% Allergic 4.0%
Keynote-189	NSCLC-non-squamous	IV	Carboplatin + pemetrexed + *pembrolizumab*		PD-1	Hypothyroid 6.3% Pneumonitis 4.5% Hyperthyroid 2.7% Dermatitis 1.8%
Keynote-407	NSCLC-squamous	IV	Carboplatin + Taxol/Abraxane + *pembrolizumab*		PD-1	Hyperthyroid 9.2% Hypothyroid 6.4% Pneumonitis 6.4% Hepatitis 4.6% Colitis 2.8% Allergic 1.8% Dermatitis 1.8%
Keynote-042	NSCLC-non-squamous	IV	*Pembrolizumab*	PD-L1 >1% TPS	PD-1	Hypothyroid 12% Pneumonitis 8% Hyperthyroid 6% Dermatitis 2% Allergic 2% Thyroiditis 2% Hepatitis 1% Colitis 1%
EMPOWER-Lung 1 trial	NSCLC	IV	Cemiplimab-rwlc	PD-L1 >50%	PD-1	Dermatitis: grades 3/4: ≥2% Hyperthyroidism 3% Hypothyroidism 7% Colitis 2% Hepatitis 2% Pneumonitis 3%

ES, Extensive stage; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

DISCUSSION

Incidence

Pneumonitis

The reported incidence of immune-related adverse events has varied since initial observations depending on the immune modulating agent and the clinical setting. Checkpoint inhibitor pneumonitis (CIP) currently occurs in 3%–5% of all cases; however, that estimate rises to 7%–13% in the setting of NSCLC treatment (8). As demonstrated in Checkmate-012, Checkmate-227, and Checkmate-568 (9–11), this incidence worsens when dual checkpoint inhibitor therapy with anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) is used (12). Furthermore, the increased incidence in NSCLC patients is attributable to the increased association of

risk factors for immune-mediated pneumonitis in NSCLC patients including smoking, age >70 years, prior radiotherapy, prior lung disease (including chronic obstructive pulmonary disease), and exposure to the EGFR inhibitor osimertinib (8).

The interaction of checkpoint inhibitor therapy with osimertinib was first reported in the phase 1b TATTON trial assessing its tolerability in combination with durvalumab (13). The occurrence of clinically significant pneumonitis rose from 2.9% in the single agent arm to 38% in the combination arm resulting in the early termination of the trial. Interestingly, this observation remains to be replicated in the phase III multi-arm CAURAL trial (14). Furthermore, this interaction appears to be beyond concurrent treatment with an observed incidence of CIP with osimertinib administration during the first 3 months following checkpoint inhibitor treatment (15).

A similar interaction has been observed with concurrent or prior radiation treatment in NSCLC. In Keynote-001, 13% of patients treated with pembrolizumab and history of prior radiotherapy exposure were observed to develop radiation recall pneumonitis over only 1% incidence in patients without radiation exposure. Comparable numbers were reported in the phase 2 DETERRED trial of concurrent radiotherapy with atezolizumab with an incidence of grade 2 or higher pneumonitis of 10%. Additional observations suggest an association of checkpoint inhibitor pneumonitis with radiation dose with a nearly 9:1 ratio in patients treated with curative-intent radiotherapy over palliative-intent radiotherapy (16, 17).

Colitis

Inflammatory colitis following exposure to checkpoint inhibitor therapy represents another significant threat of morbidity and mortality in the management of NSCLC. A recent meta-analysis has demonstrated an overall incidence of 1.4% of colitis associated with immunomodulatory treatment, 0.89% for severe colitis, and 11.62% incidence of diarrhea in patients with NSCLC (18). Similar to the reports for CIP, the combination of CTLA-4 and anti-PD-1/PD-L1 treatment increased the incidence from 0.89% of grade 3 colitis to 3%–5% for combination therapy (9). Moreover, an increased severity is associated with anti-CTLA-4 therapy in addition to an increased incidence of all extraintestinal manifestations including mouth ulcers, anal fissures, and esophagitis/gastritis (19).

Interestingly, while CIP has been observed with increased frequency in the first-line setting, inflammatory colitis appears to increase in incidence with subsequent lines of treatment (18). Furthermore, unlike CIP, no association has been observed between colitis and patient age, sex, smoking, and history of controlled autoimmune disease.

Hepatitis

Inflammatory hepatitis is an uncommon cause of treatment interruption in the management of NSCLC with estimates <1% incidence of grade 3 hepatitis and 1%–3% of all grade hepatitis with the use of anti-PD-1/PD-L1 treatment in NSCLC (20, 21). The incidence has been shown to increase dramatically with combination therapy and/or the presence of liver metastases (10, 22).

Dermatitis

Dermatologic toxicities are among the most common immune-related adverse events encountered in daily practice when treating lung cancer with an estimated incidence of 44% following CTLA-4 inhibition and 34% with PD-1/PD-L1 targeting treatment (23). Early data have previously suggested that similarity between tumor antigen and somatic epitopes within the skin and fascia may provide a mechanistic explanation for the occurrence of dermatologic events (24). Manifestation of dermatologic adverse events can vary widely in presentation from pruritus and a mild maculopapular rash to bullous pemphigoid or psoriasis flare and even case reports of fulminant Stevens–Johnson syndrome (25). As such, recent National Comprehensive Cancer Network (NCCN) recommendations include a careful dermatologic exam on all patients with planned immunomodulatory treatment to detect and manage any mild or early grade disease before provocation to flare.

Endocrinopathy

In Keynote-001 (26), 21% of patients receiving pembrolizumab for the management of NSCLC experienced thyroid dysfunction requiring eventual supplementation. Subsequent clinical experience with immunotherapy of NSCLC has confirmed an estimated incidence of endocrine irAEs of less than 23% with the overwhelming majority involving the thyroid and rarely exceeding grade 2 (27, 28). Hypophysitis secondary to anti-PD-1/PD-L1 therapy is considered extremely rare and more frequently observed secondary to anti-CTLA-4 therapy (29–31). Interestingly, a recent meta-analysis of 38 randomized clinical trials comprising 7,551 patients who underwent checkpoint inhibitor immunotherapy found a consistent reduction in the incidence of thyroiditis and insulin-deficient diabetes for single-agent anti-PD-1/PD-L1 when compared with anti-CTLA-4 monotherapy (28–30, 32). As observed previously, the incidence of all immune-related endocrinopathies was higher with combination therapy (28, 33). Interestingly, the genetic risk for hypothyroidism was associated with risk of developing thyroid immune-related adverse events in NSCLC (34). Furthermore, the occurrence of gastrointestinal, dermatological, and endocrine irAEs in lung cancer patients has been proven to be a predictor of enhanced immune checkpoint inhibitor efficacy (35).

Diagnosis, Treatment, and Follow-Up

Checkpoint Inhibitor Pneumonitis

Diagnosis of checkpoint inhibitor pneumonitis requires a high index of suspicion given the lack of specificity in the presenting symptoms including dyspnea, chest pain, cough, and fever (36). As such, a broad differential diagnosis exists in lung cancer patients including pneumonia, progression of disease, COPD exacerbation, pulmonary embolism, and radiation recall pneumonitis (37). Accordingly, appropriate workup may vary depending on clinical presentation; however, high-resolution computed topography (CT) scan is often useful and is recommended as one of the initial diagnostic tests performed in this setting. In most cases, a multidisciplinary approach is

needed for accurate diagnosis. Pulmonary consultation for bronchoscopy with fungal and mycobacterial studies may be considered (38) (**Table 2**).

Regardless of the workup, CIP remains a diagnosis of exclusion, and a stepwise approach to empiric treatment guided by clinical presentation as defined by the CTCAE grading has gained favor (39). Grade 1 CIP presents asymptomatically involving less than 25% of available lung and discovered on surveillance imaging. Accordingly, for grade 1 CIP, a hold of immunotherapy for 3–4 weeks is recommended, and no steroid therapy is needed. Development of dyspnea without oxygen requirement is consistent with grade 2 CIP, and steroid therapy should be initiated with prednisone 1–2 mg/kg/day and tapered over 4–8 weeks. Severe dyspnea with associated hypoxia and involvement of >50% of lung volume on imaging or persistence of grade 2 symptoms for 48 h despite steroid treatment requires escalation of immunosuppressive treatment most commonly with anti-TNFα therapy of infliximab at 5 mg/kg at 0, 2, and 6 weeks (38, 40).

Data for alternative treatment of grade 3 CIP are limited; however, there are encouraging early data for the use of tocilizumab with a 79% response rate (36, 41). Additional discussion regarding the use of mycophenolate mofetil and pooled intravenous immunoglobulin persists, but supportive data remain elusive.

Colitis

Management of gastrointestinal toxicity of checkpoint inhibitor therapy often follows a similar algorithmic approach based on clinical presentation (42). Traditional inflammatory bowel disease markers including C-reactive protein (CRP), calprotectin, and albumin have similarly failed to demonstrate an ability to predict the course of immune colitis from checkpoint inhibitor therapy. Endoscopic and histological assessment in the form of Mayo (43), UCEIS (44), and Nancy scores (42) have shown early promise in predicting the need for aggressive immunosuppression to avoid eventual colectomy.

The differential diagnosis of diarrhea and colitis following initiation of checkpoint inhibitor therapy is largely restricted to inflammatory disease, ischemic colitis, and infectious colitis. Endoscopy and directed biopsy may assist in guided initial therapy; however, consideration of infectious etiologies is crucial and a limited workup including stool ova and parasite assay, *Clostridium difficile* polymerase chain reaction (PCR), stool culture, and cytomegalovirus (CMV) serology should be considered in all patients with moderate to severe diarrhea and colitis.

Early grade 1 diarrhea of <4 stools per day may be treated symptomatically with anti-diarrheal medication and fluid replacement. If diarrhea increases to 4–6 stools per day or persists for more than 14 days, immunomodulatory treatment should be held, oral prednisone started at 0.5–1 mg/kg/day, and referral placed for outpatient colonoscopy. Clinical worsening with diarrhea of more than 7 stools per day and/or severe abdominal pain with evidence of peritonitis necessitates hospitalization for resuscitation, intravenous corticosteroids, and initiation of infliximab. Administration of anti-tumor necrosis factor-α therapy has been a mainstay of grade 3–4 treatment; however, a recent case series of seven patients demonstrated effective treatment by targeting gastrointestinal specific integrin with vedolizumab with an observed response in all patients (45).

Hepatitis

A broad differential diagnosis exists for the onset of clinically significant transaminitis following initiation of cancer immunotherapy, including infection, autoimmune hepatitis, and drug-induced liver injury. To that end, an expansive workup should be entertained for CMV, herpes simplex virus (HSV), parvovirus, adenovirus, Epstein–Barr virus (EBV), anti-antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-liver kidney microsomal type 1 antibody (LKM-1), quantitative immunoglobulins, an abdominal ultrasound, and often liver biopsy (46, 47).

As the majority of cases are asymptomatic, early intervention is guided by laboratory findings of transaminitis. Of note, mild transaminitis with either AST or ALT below 3 times upper limit of normal (ULN) or total bilirubin below 1.5 times the ULN may be monitored with continuation of therapy. For grade 2 hepatitis with transaminases below 5 times ULN and total bilirubin below 3 times ULN, therapy is held and transaminases are monitored biweekly until levels return to grade 1 or below. Severe hepatitis with transaminases exceeding prior thresholds or evidence of liver failure requires immediate admission for intravenous corticosteroids of methylprednisolone 0.5–1.0 mg/kg/day and consideration of mycophenolate mofetil 500–1,000 mg Q12H if no improvement is observed within 72 h (46, 48).

Historically, anti-TNFα therapy has been discouraged in severe transaminitis secondary to immunomodulatory treatment with the standard escalation to mycophenolate for steroid refractory disease. Here, again, alternative treatments may be considered in the appropriate clinical context with common options including tacrolimus 0.1–0.15 mg/kg/day or anti-thymocyte globulin 1.5 mg/kg/day with consideration of hepatology consultation (49).

Dermatitis

Due to the wide variety in dermatologic presentation, an algorithmic approach should be taken in the majority of cases encountered in clinical practice with involvement of specialty care for additional workup and management (50). A mild rash involving <10% body surface area (BSA) with mild symptoms of burning or pruritus may be managed appropriately with medium- to high-potency topical corticosteroids and symptomatic care of oral anti-histamine treatment. Progression to grade 2 rash involving 10%–30% BSA with symptoms inhibiting instrumental activities of daily living would be a reasonable indication for the addition of systemic corticosteroids with prednisone 0.5–1 mg/kg/day with consideration of checkpoint inhibitor hold. Inpatient care and urgent dermatologic consultation may be considered for rashes involving more than 30% BSA depending on severity of symptoms. Provider discretion in addition to patient discussion is

TABLE 2 | Common irAE treatment algorithm.

Symptoms/grade	Workup	Treatment	Follow-up/monitoring
Pneumonitis			
Grade 1: Asymptomatic Involving <25% of the lungs	Labs: BNP, CPK, aldolase, CRP Imaging: CT chest WWO Other: EKG, echocardiography	Hold IO therapy 3–4 weeks. Clinical monitoring every 2–3 days.	If persistent, escalate treatment.
Grade 2: Cough/chest pain Dyspnea on exertion without hypoxia	Micro: sputum culture, *Mycoplasma*, *Legionella* If febrile*, consult pulmonary medicine for bronchoscopy and infectious workup including pneumocystis testing.	Start PO prednisone 1–2 mg/kg/day tapered over 4–8 weeks. Start broad spectrum antibiotics per local antibiogram.	If unimproved after 48 h, escalate treatment.
Grades 3–4: Dyspnea at rest with or without hypoxemia Involving >50% of the lungs		Transition prednisone to IV 1–2 mg/kg/day methylprednisolone.	If unimproved at 48 h, start infliximab at 5 mg/kg on days 0, 15, and 43. **Permanent discontinuation of immunotherapy.
	Alternative agents: **Mycophenolate mofetil BID** **IVIG** **Tocilizumab**		
Colitis			
Grade 1: <4 liquid stools above daily baseline	Labs: CBC, CMP, TFTs, CRP Other: fecal fat Micro: stool culture, ova/parasites, CMV PCR, Cdiff PCR, cryptosporidia *If persistent, consider GI referral for colonoscopy or hematochezia. **If peritoneal signs, low threshold CT abdomen WWO and urgent surgical consultation.	Continue IO with symptomatic treatment of loperamide and fluid repletion.	If persistent for >14 days or worsening escalate treatment.
Grade 2: 4–6 liquid stools above daily baseline or new abdominal pain/hematochezia		Start PO prednisone 0.5–1 mg/kg/day *do not wait for colonoscopy.	Clinical monitoring every 72 h, if worsening escalate treatment.
Grades 3–4: >7 liquid stools above daily baseline, life-threatening		Transition to IV methylprednisolone 1–2 mg/kg/daily. Urgent GI consultation.	If unimproved at 72 h, start infliximab at 5 mg/kg on days 0, 15, and 43. **Permanent discontinuation of immunotherapy.
	Alternative agents: **Mycophenolate mofetil BID** **Tacrolimus** ****Hold escalation of immunosuppression until colonoscopy/sigmoidoscopy is performed.**		
Hepatitis			
Grade 1: AST and ALT <3x ULN Total bilirubin <1.5x ULN	Labs: anti-ANA/SMA/LKM/SLA/LP, iron panel, quantitative Igs Micro: hepatitis A/B/C, HIV, parvovirus, CMV, HSV Other: Imaging: liver US W Doppler	Continue IO.	Repeat CMP weekly.
Grade 2: AST and/or ALT <5x ULN Total bilirubin <3x ULN		Start prednisone 1 mg/kg/day.	Monitor LFTs with INR and albumin biweekly. Escalate management if worsening.
Grades 3–4:	*Consider hepatology consult and imaging-guided biopsy if worsening with initial management.	Transition to IV methylprednisolone 2 mg/kg/day.	If no response or worsening at 48 h, start mycophenolate mofetil 500–1,000 mg BID.
	Alternative agents: ****Second-line agents for refractory disease include tacrolimus and anti-thymocyte globulin.**		
Dermatitis			
Grade 1: Mild rash involving <10% BSA	Physical examination and history excluding other common causes including viral exanthema and drug rash.	Avoid irritants. Consider mild strength topical corticosteroids and PRN oral antihistamine.	Resume routine monitoring.
Grade 2: Symptomatic involving 10%–30% BSA	*Consider urgent referral to dermatology and punch biopsy if refractory to moderate topical steroids or severe symptoms.	Escalation to moderate-/high-intensity topical corticosteroids and/or initiation of PO prednisone 0.5–1 mg/kg daily.	Weekly–biweekly physical exam.
Grade 3: Involving >30% BSA or severe symptoms.		Hold IO for severe symptoms and consider admission or IV methylprednisolone at 1–2 mg/kg/day and urgent dermatology evaluation.	
	Alternative agents: ****Pregabalin, gabapentin, and aprepitant can be considered for management of refractory pruritus.**		

Additional considerations:

**With prolonged steroid management, calcium/vitamin D supplementation, pneumocystis prophylaxis, and acid suppression.*

***Avoid infliximab if evidence of hepatic injury.*

critical as many grade 3 rashes with mild symptoms may be reasonably managed in the outpatient setting.

Special consideration should be given to alternative management of checkpoint inhibitor-induced pruritus with gabapentin, pregabalin, and/or aprepitant in cases refractory to antihistamine treatment (51). Consultation of dermatology and disease-directed care should be strongly considered for all cases of grade 4 adverse events including but not limited to drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, toxic epidermal necrolysis, and Steven–Johnson syndrome ahead of permanent discontinuation of checkpoint inhibitor therapy.

Endocrinopathies

With the availability of screening assays for many of the observed immune-related endocrine complications of treatment, many are caught early in disease course. Accordingly, in addition to vital signs, routine screening with a basic metabolic panel, calcium, parathyroid hormone (PTH), thyroid stimulating hormone (TSH), free T4, adrenocorticotropic hormone (ACTH), and/or AM cortisol should be obtained ahead of every cycle for the first 6 months and progressively spaced thereafter (33, 50). Otherwise, a high degree of clinical suspicion should be employed for patients undergoing immunotherapy with new or worsening symptoms including fatigue, headache, confusion, diplopia, nausea, vomiting, weakness, weight gain, constipation, diarrhea, sweating, weight loss, polyuria, polydipsia, paresthesia, muscle cramps, lightheadedness, tachycardia, bradycardia, and hypotension (50). Additional workup and management should be guided appropriately with endocrinology consultation for any patient found to be symptomatic or with a positive screen.

In contrast to many other immune-related adverse events, management of endocrinopathy is focused on hormone repletion rather than escalation of immunosuppression and reversal of disease course. Though rare, recognition and diagnosis of adrenal insufficiency is of critical importance for the prevention of adrenal crisis. In the absence of screening, these patients may present with headache, confusion, fatigue, nausea, vomiting, weight loss, and double vision with additional workup directed to explore primary and secondary adrenal insufficiency. With an elevated ACTH with or without hyponatremia and hyperkalemia indicative of primary adrenal insufficiency, additional workup should include an abdominal CT, plasma renin, and 21-hydroxylase antibody serology while administering empiric treatment. In the setting of a depressed ACTH, a pituitary magnetic resonance imaging (MRI), visual field exam, and laboratory workup including prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and testosterone should be entertained.

Asymptomatic or minimally symptomatic patients can be started on oral hydrocortisone 15–25 mg daily in two to three divided doses or oral fludrocortisone 100 mcg daily. Moderately to severely symptomatic patients should be hospitalized for intravenous glucocorticoids of hydrocortisone with 100 mg bolus upfront and then 50 mg every 6 h in addition to aggressive fluid resuscitation with normal saline and thyroid hormone repletion.

Rare

Inflammatory arthritis is an increasingly recognized complication of lung cancer immunotherapy with incidence ranging from 1% to 7% (52–54). When suspected, initial workup begins with physical exam and documentation of all involved inflamed joints in addition to laboratory workup of ANA, rheumatoid factor (RF), cyclic citrullinated peptide (CCP) antibodies, and human leukocyte antigen (HLA)-B27 as well as plain films of the involved joints. For mild cases without interruption of activities of daily living, symptomatic care can be pursued with oral prednisone 10–20 mg daily and non-steroidal anti-inflammatory drugs (NSAIDs) as needed for pain relief for 4–6 weeks of therapy with concurrent serial examinations (52). For more severe or refractory cases, additional workup and management should be pursued in coordination with rheumatology referral with consideration of immunotherapy hold.

The incidence of renal toxicity has been reported at <1% for single-agent therapy; however, it has been reported to be as high as 5% with the combination of CTLA-4 and PD-1/PD-L1 therapy (55). Mild elevations in serum creatinine less than 1.5× baseline can be observed with appropriate outpatient hydration; however, elevation above 1.5× baseline should prompt the hold of immunotherapy in addition to consideration for urgent resuscitation and workup with nephrology consultation depending on the degree of renal insufficiency (55). Immune-related neurologic, ophthalmic, and cardiac toxicities are exceedingly rare with reported incidences often <1% with management best guided by subspecialty consultation (50, 56).

Prediction Biomarker Research

Unfortunately, to date, there are no clinically useful predictive biomarkers to assess immune-related adverse event development in daily practice (57). The association of germline genetic variation with the risk for developing immune-related adverse events when using checkpoint inhibitors is still unclear. Variants in the major histocompatibility complex (MHC) locus were found to be strongly associated with autoimmune diseases in humans (58). Given the strong influence of these genetic variants on autoimmunity, looking at genome-wide single nucleotide polymorphism (SNP) data that are collected from patients treated with checkpoint inhibitors can help in recognizing variants that are associated with irAE. Furthermore, this can help in developing individual polygenic risk scores that can provide a personalized score that measures the genetic risk for an irAE (59). Several retrospective case series have identified discrete class II HLA alleles correlated with the development of several immune-related adverse events ranging from inflammatory arthritis to diabetes mellitus and adrenal insufficiency to colitis (60–65). While these alleles have been associated with the development of immune-related adverse events, they are not wholly predictive; accordingly, their clinical utility even when available remains uncertain.

Interestingly, early diversification of the circulating CD4+ and CD8+ T-cell repertoires following initiation of anti-CTLA-4 treatment has been associated with the onset of immune-related adverse events (66–69). Again, while hypothesis generating, the

practical utility of these data remains elusive and is likely outweighed by the burden of recurrent assessment to an uncertain end. Alternatively, serological markers such as surfactant protein, transforming growth factor β1, tumor necrosis factor-α, interleukin 1β, and interleukin 6 for the prediction of radiation-induced pneumonitis have been studied extensively, and their significance toward immunotherapy-induced pulmonary toxicity remains uncertain (70–72).

Rechallenge of CPI

One of the most pressing questions facing the management of cancer patients undergoing immunomodulatory treatment is the possibility of rechallenge following the occurrence of an immune-related adverse event. With the majority of immune-related adverse events manifesting as low severity grade 1–2 disease, a recent consensus statement from the Society for Immunotherapy of Cancer asserts that rechallenge is reasonable following resolution of event and completion of planned therapy (73). More controversial is the discussion of rechallenge in patients who have undergone a grade 3 event; here, guidance has been largely left to a personalized risk/benefit discussion between patient and provider.

Previously, in a retrospective study, 482 patients undergoing anti-PD-L1 immunomodulatory therapy and suffering treatment interruption secondary to a grade 2/3 immune-related adverse event were observed for possible recurrence on rechallenge (74). Interestingly, while 26% experienced recurrence of the same adverse event and 23% suffered an entirely new immune-related adverse event, 51% of patients did not suffer a recurrent event. A similar occurrence of subsequent events was observed regardless of grade on initial onset, but it did correlate time of initial onset with those events occurring with 3 months of treatment initial most likely to recur.

Further complicating the discussion of rechallenge is the correlation of immune-related adverse event occurrence with disease response. Despite early data suggesting that the occurrence of irAE was predictive of disease response, subsequent studies failed to confirm the initial observation (75–77). Recent data further suggest that early treatment of immune-related adverse events may improve overall survival of those undergoing immunomodulatory treatment by allowing rechallenge and prolonged disease control (74, 76, 78).

Pre-Existing Autoimmune Disease

Management of lung cancer patients with an indication for checkpoint inhibitor therapy and a history of pre-existing autoimmune disease is an additional point of ongoing debate (79). As a measure to minimize confounding bias, patients with a known history of active autoimmune disease have been excluded from large randomized control trials of immunomodulatory therapy limiting the availability of high-quality data in this population (57, 80). Available retrospective case series assessing anti-CTLA-4 treatment with pre-existing autoimmune disease has emerged in the melanoma literature with a trend toward increased occurrence and severity of irAE when compared with historical controls (81, 82).

Conversely, limited case series suggest that the risk of irAE occurrence with anti-PD-1/PD-L1 therapy in the setting of pre-existing autoimmune disease is comparable to those patients without known history and without identifiable compromise in efficacy (77, 83–85). While these data are encouraging, not all autoimmune conditions bear the same risk of morbidity and mortality on flare. As such, special consideration must be applied to patients with histories of life-threatening autoimmune diseases involving the neurologic and neuromuscular systems such as myasthenia gravis (57). Moreover, in a recent large retrospective cohort, immunosuppression with 10 mg or more of daily prednisone was associated with statistically significant decreases in response rate, progression-free survival, and overall survival for NSCLC patients on anti-PD-1 therapy (86).

Current summary recommendations from the NCCN suggest careful consideration of checkpoint inhibitor therapy in appropriate patients with well-controlled autoimmune disease requiring low to no immunosuppression in coordination with appropriate subspecialty care.

CONCLUSION

It is now clear that we need to understand and deal with the respiratory effects of a range of cancer treatments. Although much has been learned regarding the management of immune-related adverse events since their introduction into the NSCLC population, several outstanding questions remain. The lack of reliable, clinically deployable predictive biomarkers and patient characteristics to predict autoimmune development remains an area of active need. Such an assay would allow for the tailored treatment of every patient maximizing the probability of response while minimizing the occurrence of autoimmune phenomena and, thus, harm of treatment. Additional comparative work regarding the incidence of autoimmune events between immunomodulatory classes might partially address this need with lower barrier to entry. Currently, several active clinical trials are addressing this need investigating the correlation of autoantibody and other serological changes in immunotherapy patients with significant adverse event occurrence (NCT03984318, NCT03868046, NCT03409016).

Moreover, as discussed regarding the management of checkpoint inhibitor colitis, while many of the developed treatment algorithms stratify based on universal CTCAE criteria, this often has little correlation with eventual severity of disease, escalation of treatment, duration of treatment, and interruption of immunomodulatory therapy. Additional investigative collaboration across specialties will be required to address this need possibly by the translation of extant tools for the management of known autoimmune disease. Lastly, while anti-TNFα therapy in the form of infliximab has emerged as a rational and consensus standard of care for many forms of steroid refractory disease, often high-quality data remain lacking. To that end, trials investigating novel agents as well as traditional immunosuppressive therapy are ongoing (NCT04375228, NCT04552704).

Thankfully, the overwhelming majority of immune-related adverse events secondary to checkpoint inhibitor therapy appear to be of minor grade with only brief interruptions in treatment if any. Furthermore, with prompt recognition, an algorithmic approach as outlined here and by prior groups can achieve appropriate disease control.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version. UT Southwestern is aware of the submission and agrees to it. The corresponding author is responsible for submitting a competing financial interest statement on behalf of all authors of the paper.

REFERENCES

1. Data S. (2020).
2. Horn L, Spigel DR, Vokes EE, Holgado EH, Ready N, Steins M, et al. Nivolumab *Versus* Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). *J Clin Oncol* (2017) 35(35):3924–33. doi: 10.1200/JCO.2017.74.3062
3. Reck M, Taylor F, Penrod JR, DeRosa M, Morrissey L, Dastani H, et al. Impact of Nivolumab *Versus* Docetaxel on Health-Related Quality of Life and Symptoms in Patients With Advanced Squamous Non-Small Cell Lung Cancer: Results From the CheckMate 017 Study. *J Thorac Oncol* (2018) 13 (2):194–204. doi: 10.1016/j.jtho.2017.10.029
4. Herbst RS, Garon EB, Kim DW, Cho BC, Perez-Gracia JL, Han J-Y, et al. Long-Term Outcomes and Retreatment Among Patients With Previously Treated, Programmed Death-Ligand 1positive, Advanced NonSmall-Cell Lung Cancer in the KEYNOTE-010 Study. *J Clin Oncol* (2020) 38 (14):1580–90. doi: 10.1200/JCO.19.02446
5. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab *Versus* Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med* (2016) 375(19):1823–33. doi: 10.1056/NEJMoa1606774
6. Uemura T, Hida T. Durvalumab Showed Long and Durable Effects After Chemoradiotherapy in Stage III Non-Small Cell Lung Cancer: Results of the PACIFIC Study. *J Thorac Dis* (2018) 10(Suppl 9):S1108–12. doi: 10.21037/jtd.2018.03.180
7. Shu CA, Gainor JF, Awad MM, Chiuzan C, Grigg CM, Pabani A, et al. Neoadjuvant Atezolizumab and Chemotherapy in Patients With Resectable Non-Small-Cell Lung Cancer: An Open-Label, Multicentre, Single-Arm, Phase 2 Trial. *Lancet Oncol* (2020) 21(6):786–95. doi: 10.1016/S1470-2045(20)30140-6
8. Zhai X, Zhang J, Tian Y, Li J, Jing W, Guo H, et al. The Mechanism and Risk Factors for Immune Checkpoint Inhibitor Pneumonitis in non-Small Cell Lung Cancer Patients. *Cancer Biol Med* (2020) 17(3):599–611. doi: 10.20892/j.issn.2095-3941.2020.0102
9. Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, et al. Nivolumab Plus Ipilimumab as First-Line Treatment for Advanced Non-Small-Cell Lung Cancer (CheckMate 012): Results of an Open-Label, Phase 1, Multicohort Study. *Lancet Oncol* (2017) 18(1):31–41. doi: 10.1016/S1470-2045(16)30624-6
10. Reck M, Ciuleanu TE, Lee J-S, Schenker M, Audigier-Valette C, Zurawski B, et al. First-Line Nivolumab Plus Ipilimumab *Versus* Chemotherapy in Advanced NSCLC With 1% or Greater Tumor PD-L1 Expression: Patient-Reported Outcomes From CheckMate 227 Part 1. *J Thorac Oncol* (2021) 16 (4):665–76. doi: 10.1016/j.jtho.2020.12.019
11. Ready N, et al. First-Line Nivolumab Plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer (CheckMate 568): Outcomes by Programmed Death Ligand 1 and Tumor Mutational Burden as Biomarkers. *J Clin Oncol* (2019) 37 (12):992–1000. doi: 10.1200/JCO.18.01042
12. Cadranel J, Canellas A, Matton L, Darrason M, Parrot A, Naccache J-M, et al. Pulmonary Complications of Immune Checkpoint Inhibitors in Patients With Nonsmall Cell Lung Cancer. *Eur Respir Rev* (2019) 28(153):190058. doi: 10.1183/16000617.0058-2019
13. Oxnard GR, et al. TATTON: A Multi-Arm, Phase Ib Trial of Osimertinib Combined With Selumetinib, Savolitinib, or Durvalumab in EGFR-Mutant Lung Cancer. *Ann Oncol* (2020) 31(4):507–16. doi: 10.1016/j.annonc.2020.01.013
14. Yang JC, et al. Osimertinib Plus Durvalumab *Versus* Osimertinib Monotherapy in EGFR T790M-Positive NSCLC Following Previous EGFR TKI Therapy: CAURAL Brief Report. *J Thorac Oncol* (2019) 14(5):933–9. doi: 10.1016/j.jtho.2019.02.001
15. Schoenfeld AJ, Arbour KC, Rizvi H, Iqbal AN, Gadgeel SM, Girshman J, et al. Severe Immune-Related Adverse Events are Common With Sequential PD-(L)1 Blockade and Osimertinib. *Ann Oncol* (2019) 30(5):839–44. doi: 10.1093/annonc/mdz077
16. Voong KR, Hazell SZ, Fu W, Hu C, TingLin C, Ding K, et al. Relationship Between Prior Radiotherapy and Checkpoint-Inhibitor Pneumonitis in Patients With Advanced Non-Small-Cell Lung Cancer. *Clin Lung Cancer* (2019) 20(4):e470–9. doi: 10.1016/j.cllc.2019.02.018
17. Chen Y, Huang Z, Xing L, Meng X, Yu J. Radiation Recall Pneumonitis Induced by Anti-PD-1 Blockade: A Case Report and Review of the Literature. *Front Oncol* (2020) 10:561. doi: 10.3389/fonc.2020.00561
18. Lin LL, Lin G-F, Luo Q, Chen X-Q. The Incidence and Relative Risk of PD-1/PD-L1 Inhibitors-Related Colitis in non-Small Cell Lung Cancer: A Meta-Analysis of Randomized Controlled Trials. *Int Immunopharmacol* (2019) 77:105975. doi: 10.1016/j.intimp.2019.105975
19. Rocha M, Correia de Sousa J, Salgado M, Rocha A, Araújo I. Management of Gastrointestinal Toxicity From Immune Checkpoint Inhibitor. *GE Port J Gastroenterol* (2019) 26(4):268–74. doi: 10.1159/000494569
20. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, et al. Pembrolizumab *Versus* Docetaxel for Previously Treated, PD-L1-Positive, Advanced non-Small-Cell Lung Cancer (KEYNOTE-010): A Randomised Controlled Trial. *Lancet* (2016) 387(10027):1540–50. doi: 10.1016/S0140-6736(15)01281-7
21. Rizvi NA, Mazières J, Planchard D, Stinchcombe TE, Antonia MD, Horn MD, et al. Activity and Safety of Nivolumab, an Anti-PD-1 Immune Checkpoint Inhibitor, for Patients With Advanced, Refractory Squamous non-Small-Cell Lung Cancer (CheckMate 063): A Phase 2, Single-Arm Trial. *Lancet Oncol* (2015) 16(3):257–65. doi: 10.1016/S1470-2045(15)70054-9
22. Belli C, Bellia M, Zuin L, Mazzarella D, Trapani P, D'Amico E, et al. Liver Toxicity in the Era of Immune Checkpoint Inhibitors: A Practical Approach. *Crit Rev Oncol Hematol* (2018) 132:125–9. doi: 10.1016/j.critrevonc.2018.09.019
23. Si X, He C, Zhang L, Liu X, Li Y, Wang H, et al. Management of Immune Checkpoint Inhibitor-Related Dermatologic Adverse Events. *Thorac Cancer* (2020) 11(2):488–92. doi: 10.1111/1759-7714.13275
24. Tanaka R, Okiyama N, Okune M, Ishitsuka Y, Watanabe O, Furuta M, et al. Serum Level of Interleukin-6 is Increased in Nivolumab-Associated Psoriasiform Dermatitis and Tumor Necrosis Factor-Alpha Is a Biomarker of Nivolumab Recativity. *J Dermatol Sci* (2017) 86(1):71–3. doi: 10.1016/j.jdermsci.2016.12.019
25. Hwang SJE, Park JJW, Wakade W, Chou S, Byth K, Fernandez-Penas P, et al. Cutaneous Adverse Events of Anti-Programmed Death 1 Antibodies Combined With Anti-Cytotoxic T-Lymphocyte-Associated Protein 4 Therapy Use in Patients With Metastatic Melanoma. *Melanoma Res* (2019) 29(2):172–7. doi: 10.1097/CMR.0000000000000518
26. Leighl NB, Hellmann MD, Hui R, Carcereny E, Felip E, Ahn M-J, et al. Pembrolizumab in Patients With Advanced Non-Small-Cell Lung Cancer (KEYNOTE-001): 3-Year Results From an Open-Label, Phase 1 Study. *Lancet Respir Med* (2019) 7(4):347–57. doi: 10.1016/S2213-2600(18)30500-9
27. Dudzinska M, Szczyrek K, Wojas-Krawczyk J, Świrska I, Chmielewska A, Zwolak A. Endocrine Adverse Events of Nivolumab in Non-Small Cell Lung Cancer Patients-Literature Review. *Cancers (Basel)* (2020) 12(8):2314. doi: 10.3390/cancers12082314
28. Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, et al. Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-Analysis. *JAMA Oncol* (2018) 4(2):173–82. doi: 10.1001/jamaoncol.2017.3064

29. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved Survival With Ipilimumab in Patients With Metastatic Melanoma. *N Engl J Med* (2010) 363(8):711–23. doi: 10.1056/NEJMoa1003466
30. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med* (2015) 373(1):23–34. doi: 10.1056/NEJMoa1504030
31. Torino F, Corsello SM, Salvatori R. Endocrinological Side-Effects of Immune Checkpoint Inhibitors. *Curr Opin Oncol* (2016) 28(4):278–87. doi: 10.1097/CCO.0000000000000293
32. Mellati M, Eaton KD, Brooks-Worrell BM, Hagopian WA, Martins R, Palmer JP, et al. Anti-PD-1 and Anti-PDL-1 Monoclonal Antibodies Causing Type 1 Diabetes. *Diabetes Care* (2015) 38(9):e137–8. doi: 10.2337/dc15-0889
33. Stelmachowska-Banas M, Czajka-Oraniec I. Management of Endocrine Immune-Related Adverse Events of Immune Checkpoint Inhibitors: An Updated Review. *Endocr Connect* (2020) 9(10):R207–28. doi: 10.1530/EC-20-0342
34. Luo J, Martucci VL, Quandt Z, Groha S, Murray MH, Lovly CM, et al. Immunotherapy-Mediated Thyroid Dysfunction: Genetic Risk and Impact on Outcomes With PD-1 Blockade in Non-Small Cell Lung Cancer. *Clin Cancer Res* (2021). doi: 10.1158/1078-0432.CCR-21-0921
35. Wang D, Chen C, Gu Y, Lu W, Zhan P, Liu H, et al. Immune-Related Adverse Events Predict the Efficacy of Immune Checkpoint Inhibitors in Lung Cancer Patients: A Meta-Analysis. *Front Oncol* (2021) 11:631949. doi: 10.3389/fonc.2021.631949
36. Naidoo J, Wang X, Woo KM, Iyriboz D, Halpenny J, Cunningham JE, et al. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. *J Clin Oncol* (2017) 35(7):709–17. doi: 10.1200/JCO.2016.68.2005
37. Wang H, Guo X, Zhou J, Li Y, Duan L, Si X, et al. Clinical Diagnosis and Treatment of Immune Checkpoint Inhibitor-Associated Pneumonitis. *Thorac Cancer* (2020) 11(1):191–7. doi: 10.1111/1759-7714.13240
38. Rashdan S, Minna JD, Gerber DE. Diagnosis and Management of Pulmonary Toxicity Associated With Cancer Immunotherapy. *Lancet Respir Med* (2018) 6(6):472–8. doi: 10.1016/S2213-2600(18)30172-3
39. Naidoo J, Nishino M, Patel SP, Shankar B, Rekhtman N, Illei P, et al. Immune-Related Pneumonitis After Chemoradiotherapy and Subsequent Immune Checkpoint Blockade in Unresectable Stage III Non-Small-Cell Lung Cancer. *Clin Lung Cancer* (2020) 21(5):e435–44. doi: 10.1016/j.cllc.2020.02.025
40. Suresh K, RanhVoong K, Shankar B, Forde PM, Ettinger DS, Marrone KA, et al. Pneumonitis in Non-Small Cell Lung Cancer Patients Receiving Immune Checkpoint Immunotherapy: Incidence and Risk Factors. *J Thorac Oncol* (2018) 13(12):1930–9. doi: 10.1016/j.jtho.2018.08.2035
41. Stroud CR, Hegde A, Cherry C, Naqash AR, Sharma N, Addepalli S, et al. Tocilizumab for the Management of Immune Mediated Adverse Events Secondary to PD-1 Blockade. *J Oncol Pharm Pract* (2019) 25(3):551–7. doi: 10.1177/1078155217745144
42. Cheung VTF, Gupta T, Olsson-Brown A, Subramanian S, Sasson SC, Heseltine S, et al. Immune Checkpoint Inhibitor-Related Colitis Assessment and Prognosis: Can IBD Scoring Point the Way? *Br J Cancer* (2020) 123(2):207–15. doi: 10.1038/s41416-020-0882-y
43. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated Oral 5-Aminosalicylic Acid Therapy for Mildly to Moderately Active Ulcerative Colitis. A Randomized Study. *N Engl J Med* (1987) 317(26):1625–9. doi: 10.1056/NEJM198712243172603
44. Travis SP, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel J-F, et al. Developing an Instrument to Assess the Endoscopic Severity of Ulcerative Colitis: The Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gut* (2012) 61(4):535–42. doi: 10.1136/gutjnl-2011-300486
45. Bergqvist V, Hertervig E, Gedeon P, Kopljar M, Griph H, Kinhult S, et al. Vedolizumab Treatment for Immune Checkpoint Inhibitor-Induced Enterocolitis. *Cancer Immunol Immunother* (2017) 66(5):581–92. doi: 10.1007/s00262-017-1962-6
46. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino J, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* (2018) 36(17):1714–68. doi: 10.1200/JCO.2017.77.6385
47. Suzuki A, Brunt EM, Kleiner DE, Miquel R, Smyrk TC, Suzuki RJ, et al. The Use of Liver Biopsy Evaluation in Discrimination of Idiopathic Autoimmune Hepatitis *Versus* Drug-Induced Liver Injury. *Hepatology* (2011) 54(3):931–9. doi: 10.1002/hep.24481
48. Sanjeevaiah A, Kerr T, Beg MS. Approach and Management of Checkpoint Inhibitor-Related Immune Hepatitis. *J Gastrointest Oncol* (2018) 9(1):220–4. doi: 10.21037/jgo.2017.08.14
49. Tarhini A. Immune-Mediated Adverse Events Associated With Ipilimumab Ctla-4 Blockade Therapy: The Underlying Mechanisms and Clinical Management. *Scientifica (Cairo)* (2013) 2013:857519. doi: 10.1155/2013/857519
50. Haanen J, Carbonne F, Robert C, Kerr KM, Peters S, Larkin PJ, et al. Management of Toxicities From Immunotherapy: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. *Ann Oncol* (2017) 28(suppl_4):iv119–42. doi: 10.1093/annonc/mdx225
51. Ito J, Nakamura A, Nagano T, Ueharac K, Imaic Y, Tomiia K, et al. Aprepitant for Refractory Nivolumab-Induced Pruritus. *Lung Cancer* (2017) 109:58–61. doi: 10.1016/j.lungcan.2017.04.020
52. Naidoo J, Cappelli LC, Forde PM, Marrone KA, Lipson EJ, Hammers HJ, et al. Inflammatory Arthritis: A Newly Recognized Adverse Event of Immune Checkpoint Blockade. *Oncologist* (2017) 22(6):627–30. doi: 10.1634/theoncologist.2016-0390
53. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab *Versus* Ipilimumab in Advanced Melanoma. *N Engl J Med* (2015) 372(26):2521–32. doi: 10.1056/NEJMoa1503093
54. Hodi FS, Lee S, McDermott DF, Rao UN, Butterfield LH, Tarhini AA, et al. Ipilimumab Plus Sargramostim *vs* Ipilimumab Alone for Treatment of Metastatic Melanoma: A Randomized Clinical Trial. *JAMA* (2014) 312(17):1744–53. doi: 10.1001/jama.2014.13943
55. Sise ME, Seethapathy H, Reynolds KL. Diagnosis and Management of Immune Checkpoint Inhibitor-Associated Renal Toxicity: Illustrative Case and Review. *Oncologist* (2019) 24(6):735–42. doi: 10.1634/theoncologist.2018-0764
56. Johnson DB, Balko JM, Pharm D, Compton ML, Chalkias S, Gorham J, et al. Fulminant Myocarditis With Combination Immune Checkpoint Blockade. *N Engl J Med* (2016) 375(18):1749–55. doi: 10.1056/NEJMoa1609214
57. Kennedy LC, Bhatia S, Thompson JA, Grivas P. Preexisting Autoimmune Disease: Implications for Immune Checkpoint Inhibitor Therapy in Solid Tumors. *J Natl Compr Canc Netw* (2019) 17(6):750–7. doi: 10.6004/jnccn.2019.7310
58. Gutierrez-Arcelus M, Rich SS, Raychaudhuri S. Autoimmune Diseases - Connecting Risk Alleles With Molecular Traits of the Immune System. *Nat Rev Genet* (2016) 17(3):160–74. doi: 10.1038/nrg.2015.33
59. Torkamani A, Wineinger NE, Topol EJ. The Personal and Clinical Utility of Polygenic Risk Scores. *Nat Rev Genet* (2018) 19(9):581–90. doi: 10.1038/s41576-018-0018-x
60. Hasan Ali O, Berner F, Bomze D, Diem M, Cozzioe S, Jörger A, et al. Human Leukocyte Antigen Variation Is Associated With Adverse Events of Checkpoint Inhibitors. *Eur J Cancer* (2019) 107:8–14. doi: 10.1016/j.ejca.2018.11.009
61. Chowell D, Krishna C, Pierini F, Makarov V, Rizvi NA, Kuo F, et al. Evolutionary Divergence of HLA Class I Genotype Impacts Efficacy of Cancer Immunotherapy. *Nat Med* (2019) 25(11):1715–20. doi: 10.1038/s41591-019-0639-4
62. Chowell D, Morris LGT, Grigg CM, Weber JK, Samstein RM, Makarov V, et al. Patient HLA Class I Genotype Influences Cancer Response to Checkpoint Blockade Immunotherapy. *Science* (2018) 359(6375):582–7. doi: 10.1126/science.aao4572
63. Cappelli LC, Dorak MT, Bettinotti MP, Bingham COIII, Shah AA. Association of HLA-DRB1 Shared Epitope Alleles and Immune Checkpoint Inhibitor-Induced Inflammatory Arthritis. *Rheumatol (Oxford)* (2019) 58(3):476–80. doi: 10.1093/rheumatology/key358
64. Inaba H, Ariyasu H, Iwakura H, Ueda Y, Kurimoto C, Uraki S, et al. Comparative Analysis of Human Leucocyte Antigen Between Idiopathic and Anti-PD-1 Antibody Induced Isolated Adrenocorticotropic Hormone Deficiency: A Pilot Study. *Clin Endocrinol (Oxf)* (2019) 91(6):786–92. doi: 10.1111/cen.14082

65. Stamatouli AM, Quandt Z, Perdigoto AL, Clark PL, Kluger H, Weiss SA, et al. Collateral Damage: Insulin-Dependent Diabetes Induced With Checkpoint Inhibitors. *Diabetes* (2018) 67(8):1471–80. doi: 10.2337/dbi18-0002
66. Oh DY, Cham J, Zhang L, Fong G, Kwek SS, Klinger M, et al. Immune Toxicities Elicted by CTLA-4 Blockade in Cancer Patients Are Associated With Early Diversification of the T-Cell Repertoire. *Cancer Res* (2017) 77 (6):1322–30. doi: 10.1158/0008-5472.CAN-16-2324
67. Kato T, Tomiyama E, Koh Y, Matsushita M, Hayashi Y, Nakano K, et al. A Potential Mechanism of Anticancer Immune Response Coincident With Immune-Related Adverse Events in Patients With Renal Cell Carcinoma. *Anticancer Res* (2020) 40(9):4875–83. doi: 10.21873/anticanres.14490
68. Robert L, Tsoi J, Wang X, Emerson R, Homet B, Chodon T, et al. CTLA4 Blockade Broadens the Peripheral T-Cell Receptor Repertoire. *Clin Cancer Res* (2014) 20(9):2424–32. doi: 10.1158/1078-0432.CCR-13-2648
69. Subudhi SK, Aparicio A, Gao J, Zurita AJ, Araujo JC, Logothetis CJ, et al. Clonal Expansion of CD8 T Cells in the Systemic Circulation Precedes Development of Ipilimumab-Induced Toxicities. *Proc Natl Acad Sci USA* (2016) 113(42):11919–24. doi: 10.1073/pnas.1611421113
70. Rube CE, Palm J, Erren M, Fleckenstein J, König J, Remberger K, et al. Cytokine Plasma Levels: Reliable Predictors for Radiation Pneumonitis? *PloS One* (2008) 3(8):e2898. doi: 10.1371/journal.pone.0002898
71. Stenmark MH, Cai X-W, Shedden K, Hayman JA, Yuan S, Ritter T, Ten RK, et al. Combining Physical and Biologic Parameters to Predict Radiation-Induced Lung Toxicity in Patients With Non-Small-Cell Lung Cancer Treated With Definitive Radiation Therapy. *Int J Radiat Oncol Biol Phys* (2012) 84(2): e217–22. doi: 10.1016/j.ijrobp.2012.03.067
72. Takahashi H, Imai Y, Fujishima T, Shiratori M, Murakami S, Chiba H, et al. Diagnostic Significance of Surfactant Proteins A and D in Sera From Patients With Radiation Pneumonitis. *Eur Respir J* (2001) 17(3):481–7. doi: 10.1183/09031936.01.17304810
73. Puzanov I, Diab A, Abdallah K, Bingham COIII, Brogdon C, Dadu R, et al. Managing Toxicities Associated With Immune Checkpoint Inhibitors: Consensus Recommendations From the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* (2017) 5(1):95. doi: 10.1186/s40425-017-0300-z
74. Santini FC, Rizvi H, Plodkowski AJ, Ni A, Lacouture ME, Gambarin-Gelwan M, et al. Safety and Efficacy of Re-Treating With Immunotherapy After Immune-Related Adverse Events in Patients With NSCLC. *Cancer Immunol Res* (2018) 6(9):1093–9. doi: 10.1158/2326-6066.CIR-17-0755
75. Hua C, Boussemart L, Mateus C, Routier E, Boutros C, Cazenave H, et al. Association of Vitiligo With Tumor Response in Patients With Metastatic Melanoma Treated With Pembrolizumab. *JAMA Dermatol* (2016) 152(1):45–51. doi: 10.1001/jamadermatol.2015.2707
76. Horvat TZ, Adel NG, Dang T-O, Momtaz P, Postow MA, Callahan MK, et al. Immune-Related Adverse Events, Need for Systemic Immunosuppression, and Effects on Survival and Time to Treatment Failure in Patients With Melanoma Treated With Ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Oncol* (2015) 33(28):3193–8. doi: 10.1200/JCO.2015.60.8448
77. Leonardi GC, Gainor JF, Altan M, Kravets S, Dahlberg SE, Gedmintas L, et al. Safety of Programmed Death-1 Pathway Inhibitors Among Patients With Non-Small-Cell Lung Cancer and Preexisting Autoimmune Disorders. *J Clin Oncol* (2018) 36(19):1905–12. doi: 10.1200/JCO.2017.77.0305
78. Schadendorf D, Hodi F, Robert C, Weber JS, Margolin K, Hamid O, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. *J Clin Oncol* (2015) 33 (17):1889–94. doi: 10.1200/JCO.2014.56.2736
79. Khan SA, Pruitt SL, Xuan L, Gerber DE. Prevalence of Autoimmune Disease Among Patients With Lung Cancer: Implications for Immunotherapy Treatment Options. *JAMA Oncol* (2016) 2(11):1507–8. doi: 10.1001/jamaoncol.2016.2238
80. Coureau M, Meert A-P, Berghmans T, Grigoriu B. Efficacy and Toxicity of Immune -Checkpoint Inhibitors in Patients With Preexisting Autoimmune Disorders. *Front Med (Lausanne)* (2020) 7:137. doi: 10.3389/fmed.2020.00137
81. Lee B, Wong A, Kee D, Neeson N, Shackleton M, McArthur BG, et al. The Use of Ipilimumab in Patients With Rheumatoid Arthritis and Metastatic Melanoma. *Ann Oncol* (2016) 27(6):1174–7. doi: 10.1093/annonc/mdw056
82. Johnson DB, Sullivan RJ, Ott PA, Carlino MS, Khushalani NI, Ye F, et al. Ipilimumab Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders. *JAMA Oncol* (2016) 2(2):234–40. doi: 10.1001/jamaoncol.2015.4368
83. Menzies AM, Johnson DB, Atkinson VG, Wong ANM, Park JJ, McQuade JL, et al. Anti-PD-1 Therapy in Patients With Advanced Melanoma and Preexisting Autoimmune Disorders or Major Toxicity With Ipilimumab. *Ann Oncol* (2017) 28(2):368–76. doi: 10.1093/annonc/mdw443
84. Danlos FX, Voisin A-L, Dyevrec V, Michota J-M, Routierd E, Tailladee L, et al. Safety and Efficacy of Anti-Programmed Death 1 Antibodies in Patients With Cancer and Pre-Existing Autoimmune or Inflammatory Disease. *Eur J Cancer* (2018) 91:21–9. doi: 10.1016/j.ejca.2017.12.008
85. Gutzmer R, Koopa A, Meier F, Hassel JC, Terheyden P, Zimmere L, et al. Programmed Cell Death Protein-1 (PD-1) Inhibitor Therapy in Patients With Advanced Melanoma and Preexisting Autoimmunity or Ipilimumab-Triggered Autoimmunity. *Eur J Cancer* (2017) 75:24–32. doi: 10.1016/j.ejca.2016.12.038
86. Arbour KC, Mezquita L, Long N, Rizvi H, Auclin E, Ni A, et al. Impact of Baseline Steroids on Efficacy of Programmed Cell Death-1 and Programmed Death-Ligand 1 Blockade in Patients With Non-Small-Cell Lung Cancer. *J Clin Oncol* (2018) 36(28):2872–8. doi: 10.1200/JCO.2018.79.0006

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership