



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

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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.

1

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.

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

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.

(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 I² values together, which was suggested by Higgins and colleagues (15, 21). Heterogeneity was deemed to be low, moderate, or high according to I² 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). Fiftytwo 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, I² = 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.	NCT02684006	JAVELIN Benal 101	Avelumab	PD-L1	Avelumab + Axitinib vs. Sunitinib	NO		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	Ш	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	Ш	NSCLC	787
8	Paz-Ares et al. (29)	NCT02775435	KEYNOTE- 407	Pembrolizumab	PD-1	Pembrolizumab + CP vs. CP	NO	Ш	NSCLC	558
9	Barlesi et al. (30)	NCT02395172	JAVELIN Lung 200	Avelumab	PD-L1	Avelumab vs. Docetaxel	YES	Ш	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.	NCT02302807	IMvigor211	Atezolizumab	PD-L1	Atezolizumab vs. Vinflunine, Paclitaxel, or Docetaxel	YES	III	UC	902
12	(32) Hida et al.	NCT02008227	OAK	Atezolizumab	PD-L1	Atezolizumab vs. Docetaxel	YES	Ш	NSCLC	101
13	Bellmunt et al.	NCT02256436	KEYNOTE- 045	Pembrolizumab	PD-1	Pembrolizumab vs. Paclitaxel, Docetaxel, or Vinflunine	YES	Ш	UC	521
14	Rittmeyer et	NCT02008227	OAK	Atezolizumab	PD-L1	Atezolizumab vs. Docetaxel	YES	Ш	NSCLC	1187
15	Langer et al.	NCT02039674	KEYNOTE- 021	Pembrolizumab	PD-1	Pembrolizumab + PC vs. PC	NO	Ш	NSCLC	121
16	Reck et al.	NCT02142738	KEYNOTE- 024	Pembrolizumab	PD-1	Pembrolizumab vs. Platinum- based chemotherapy	NO	Ш	NSCLC	304
17	Ferris et al.	NCT02105636	CheckMate	Nivolumab	PD-1	Nivolumab vs. (Methotrexate, Docetaxel, or Cetuximab)	YES	Ш	HNSCC	347
18	Antonia et al.	NCT01928394	CheckMate	Nivolumab	PD-1	Nivolumab vs. Nivolumab +	YES	1/11	SCLC	213
19	Fehrenbacher	NCT01903993	POPLAR	Atezolizumab	PD-L1	Atezolizumab vs. Docetaxel	YES	П	NSCLC	277
20	Herbst et al.	NCT01905657	KEYNOTE- 010	Pembrolizumab	PD-1	Pembrolizumab vs. Docetaxel	YES	11/111	NSCLC	991
21	Hodi et al.	NCT01927419	CheckMate	Nivolumab	PD-1	Nivolumab + Ipilimumab vs. Ipilimumab	NO	Ш	Melanoma	140
22	Borghaei et al.	NCT01673867	CheckMate	Nivolumab	PD-1	Nivolumab vs. Docetaxel	YES	Ш	NSCLC	555
23	Brahmer et al.	NCT01642004	CheckMate	Nivolumab	PD-1	Nivolumab vs. Docetaxel	YES	Ш	NSCLC	260
24	Motzer et al.	NCT01668784	CheckMate 025	Nivolumab	PD-1	Nivolumab vs. Everolimus	YES	Ш	RCC	821
25	Kato et al.	NCT02569242	ATTRACTION-	Nivolumab	PD-1	Nivolumab vs. Paclitaxel or	YES	Ш	OSCC	417
26	Gandhi et al.	NCT02578680	KEYNOTE-	Pembrolizumab	PD-1	Pembrolizumab + PC vs. PC	NO	Ш	NSCLC	439
27	Ascierto et al.	NCT02130466	N/A	Pembrolizumab	PD-1	Pembrolizumab + DT vs. DT	NO	Ш	Melanoma	120
28	Paz-Ares et	NCT03043872	CASPIAN	Durvalumab	PD-L1	Durvalumab + EP vs. EP	NO	III	SCLC	431
29	Schmid et al.	NCT03036488	KEYNOTE-	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		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.



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), I² = 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 < 0.0001);



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 metaanalysis (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), $1^2 = 0\%$, Z = 0.83 (P = 0.40); Figure 6B) (28, 49). The corresponding funnel plot is provided in the supplement (S Figure 3B2) (28, 49).

Odds Ratio

M-H. Random, 95% Cl

Odds Ratio

0.10 (0.03, 0.34)

0.06 [0.01, 0.45]

0.06 (0.01. 0.25)

0.09 (0.03, 0.29

0.08 [0.04, 0.16]

0.0210.00.0.131

0.02 [0.00, 0.13]

0.02 (0.00, 0.33)

0.02 [0.00, 0.12]

0.02 [0.00, 0.09]

0.03 (0.00, 0.24)

0 1 2 10 0 3 0 5 2

0.05 [0.02, 0.17

0.06 [0.03, 0.14]

0.16 [0.02, 1.30]

0.06 (0.01, 0.52)

0.10 [0.02, 0.44]

0.07 [0.04, 0.13]

Odds Ratio

0.97 [0.71, 1.34] 2018

0.92 [0.68, 1.24] 2020 0.94 [0.76, 1.18]

 app(Lung Cancer)
 276
 45
 280
 16.5%
 1.35[0.87, 2.07]
 2018

 393
 122
 394
 20.1%
 1.41[1.05, 1.89]
 2018

 198
 4
 106
 2.4%
 1.50[0.42, 5.40]
 2018

 869
 870
 47.7%
 1.39[1.10, 1.77]
 1.01, 1.10, 1.77]

1697 100.0% 1.13 [0.93, 1.38]

0.001

-

-

01

PD-1/PD-L1+CI

Favours [experimental] Favours [control]

Odds Ratio

M-H, Random, 95% CI

hemotherapy Che

otherapy

10 4

Experimental

24

27

Heterogeneity: Tau² = 1.21; Chi² = 8.00, df = 2 (P = 0.02); I² = 75% Test for overall effect Z = 2.83 (P = 0.005) 1.1.2 PD-1 VS Docetaxel (NSCLC) Borghaei H,et al.2015

2 393

3 287 1 131

1 636

0 209

1 266 2 114

459 50 443 8.6%

839

482

4704

294 503

1

4

3

6

2

46

Heterogeneity: Tau² = 0.79; Chi² = 36.53, df = 14 (P = 0.0009); l² = 62%

Test for subaroup differences: Chi# = 5.45. df = 5 (P = 0.36). I# = 8.2% PD-1PD-L1+Chemotherapy Chemotherapy

57 152 6

Total events 215 17 Heterogeneity: Tau^a = 0.00; Chi^a = 0.04, df = 2 (P = 0.98); i^a = 0%

4.1.2 PD-1/PD-L1+Chemotherapy VS Chemotherapy(Breast Cancer)

Schema P, et al. 2020 154 761 6. Subtotal (95% CI) 1233 Total events: 252 175 Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); i² = 0%

98 154

467

Heterogeneity: Tau[#] = 0.01; Ch[#] = 5.59, df = 4 (P = 0.23); P = 28% Test for overall effect: Z = 1.22 (P = 0.22) Test for suboroue differences: Ch[#] = 5.49, df = 1 (P = 0.02), P = 81.8%

Test for overall effect Z = 2.70 (P = 0.007)

Test for overall effect Z = 0.51 (P = 0.61) Total (95% CI)

Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.56); I² = 0% Test for overall effect: Z = 3.03 (P = 0.002)

Test for overall effect Z = 8.48 (P < 0.00001)

Heterogeneity: Tau² = 0.00; Chi² = 1.21, df = 2 (P = 0.54); I² = 0% Test for overall effect: Z = 6.53 (P < 0.00001) 1.1.6 PD-1 VS Chemotherapy (HNSCC) Cohen EEW,et al. 2019 1 246 Ferris RL, et al. 2016 1 236

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); l² = 0% Test for overall effect Z = 4.86 (P < 0.00001) 1.1.5 PD-1/PD-L1 VS Chemotherapy (UC) Bellmunt J,et al.2017

2 339

3 343

0

Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 3 (P = 0.93); l² = 0% Test for overall effect: Z = 7.14 (P < 0.00001) 1.1.3 PD-1 VS Chemotherapy (NSCLC) Mok TSK,et al.2019

131

1100

636

142 609

1144

A1

Study or Subgroup

1.1.1 PD-L1 VS Docetaxel (NSCLC) Barlesi F.et al. 2018

Fehrenbacher L,et al.2016

Rittmeyer A.et al. 2017

Brahmer J,et al.2015

Herbst RS et al 2016A

Subtotal (95% CI)

Subtotal (95% CI)

Kato K.et al.2019

Total events

Shitara K,et al.2018 Subtotal (95% CI)

Powles Tet al 2018A

Powles T,et al.2018B

Subtotal (95% CI)

Subtotal (95% CI)

Total events

Total (95% CI)

Paz-Ares L,et al. 2018 Socinski MA,et al. 2018

Horn L, et al. 2018 Subtotal (95% CI) Total events

Schmid P. et al 2018

Schmid P at al 2020

Total events

Total events

B₁

Total events

Heterogeneity: Not applicable Test for overall effect Z = 3.98 (P < 0.0001) 1.1.4 PD-1 VS Docetaxel/Paclitaxel (OSCC)

Total events

Total events

Herbst RS,et al.2016B

Subtotal (95% CI)

Total events

Control

111

96

50

31 365 7.5%

15 135 5.3% 65 578 11.7%

25 268 8.5% 15 129 5.3%

28 309 7.4% 28 309 8.5% 1015 29.7%

50 615 5.5%

615 5.5%

22 208 3.5%

27 255 5.4%

15 112 7.2%

810 21.3%

6 234 5.0%

7 111 5.1%

345 10.1%

4347 100.0%

46 276 484 5.5% 8.9%

68

92

13

430

Study or Subgroup Events Total Events Total Weight M-H. Random, 95% CI Year 4.1.1 PD-1/PD-L1+Chemotherapy VS Chemotherapy(Lung Cancer)

171

452 97 438 25.6% 781 82 389 27.4% 1233 827 53.0%

179

350

2102

1078 24.4%

2	Study or Subgroup	Events Total	vents	Total	Weight	M-H, Ran	dom, 95% CI	Year	M-H, Random, 95% CI
	2.1.1 PD-L1 VS Docetaxe	I (NSCLC)							
	Rittmeyer A,et al.2017	0 609	7	578	8.0%	0.0	6 [0.00, 1.10]	2017	
	Barlesi F et al.2018	0 393	3	365	7.5%	0.1	3 [0.01, 2.56]	2018	
	Subtotal (95% CI)	1002		943	15.4%	0.09	9 [0.01, 0.70]		
	Total events	0	10						
	Heterogeneity: Tau ² = 0.01 Test for overall effect 7 = 1	0; Chi ² = 0.13, df = 2.30 (P = 0.02)	1 (P = 0.	72); I ² = I	0%				
		2.00 () - 0.02)							
	2.1.2 PD-1 VS Docetaxel Borghaei H.et al. 2015	(NSCLC) 0 287	3	268	7.4%	0.1	3 10 01 2 571	2015	
	Brahmer J.et al.2015	0 131	3	129	7.4%	0.1	4 [0.01, 2.69]	2015	
	Herbst RS.et al.2016A	0 339	1	309	6.4%	0.3	0 10.01.7.461	2016A	
	Herbst RS.et al.2016B	0 343	1	309	6.4%	0.3	0 [0.01, 7.38]	2016B	
	Subtotal (95% CI)	1100		1015	27.6%	0.20	0 [0.04, 0.91]		-
	Total events	0	8						
	Heterogeneity: Tau ^a = 0.00	0; Chi ² = 0.27, df =	3 (P = 0.	97); lª = l	0%				
	Test for overall effect Z = :	2.08 (P = 0.04)							
	2.1.3 PD-1 VS Chemother	rapy (NSCLC)							
	Mok TSK,et al.2019	0 636	5	615	7.8%	0.0	9 [0.00, 1.58]	2019	
	Subrotal (95% CI)	0.36		615	7.8%	0.05	10.00, 1.58]		
	i utal events	U	D						
	Test for overall effect: 7 =	able 1.65 (P = 0.10)							
	2.1.4 PD-1 VS Paclitaxel/	Docetaxel (OSCC)		370	7.00		7 10 00 1 00	2012	
	snitara K,et al.2018 Kata K et al.2018	0 294	6	276	7.9%	0.0	7 [0.00, 1.26]	2018	
	Natu K,81 al.2019 Subtotal (05% CD	0 209	1	208	0.4%	0.3	3 [0.01, 8.15]	2019	
	Sumotal (95% CI)	503	7	484	14.3%	0.14	· [0.02, 1.20]		
	rotal events	0	10-2	17.18	200				
	Test for overall effect Z =	1.79 (P = 0.07)	r (P = 0.	ar), r=1	0.70				
	2.1.5 PD-1/PD-L1 VS Cher	motherapy (UC)							
	Bellmunt J,et al.2017	0 266	2	255	7.1%	0.1	9 [0.01, 3.98]	2017	
	Powles T.et al. 2018A	1 114	3	112	12.6%	0.3	2 [0.03, 3.14]	2018A	
	Powles T.et al. 2018B	1 459	8	443	15.1%	0.1	2 10.01, 0.951	2018B	
	Subtotal (95% CI)	839	-	810	34.8%	0.19	9 [0.05, 0.74]		
	Total events	2	13						
	Heterogeneity: Tau ^a = 0.00	0; Chi ² = 0.41, df =	2 (P = 0.	82); I [#] = (0%				
	restion overall ellect 2 =	2.39 (P = 0.02)							
	Total (95% CI)	4080	10	3867	100.0%	0.15	5 [0.07, 0.34]		•
	Lutal events	2	43	000-18-	0%				
	Test for overall effect 7 -	4.54 /P = 0.00001	110-21		070				0.002 0.1 1 10
	Test for subaroup differen	ices: Chi#= 0.59. d	f= 4 (P=	= 0.96). P	°= 0%				PD-1/PD-L1 Chemothera
		D 10D I to Char -	heram	Chemot	barami		Odde Datio		Outrie Datie
	Study or Subgroup	Events	Total	Events	Total	Weight I	M-H, Random, S	95% CI	M-H, Random, 95% Cl
	Horn L,et al. 2018	erapy vs chemothe 2	198	ig cance 0	196	2.4%	5.00 [0.24, 1	04.82]	
	Paz-Ares L,et al.2018	3	278	2	280	6.9%	1.52 [0.25	, 9.15]	
	Socinski MA,et al. 2018	11	393	9	394	27.8%	1.23 [0.50	, 3.01]	
	Subtotal (95% CI)		869		870	37.0%	1.40 [0.65	, 3.04]	-
	Total events	16 Chill = 0.77 d/c 2.47	- 0.60	11					
	Test for overall effect: Z ≈ 0.8	cm ² = 0.77, df = 2 (P 36 (P = 0.39)	= 0.68); 1	- = U%					
	4.2.2 PD-1/PD-L1+Chemoth	erapy VS Chemothe	erapy(Bre	ast Cano	er)				
	Schmid P,et al. 2018	25	452	12	438	45.0%	2.08 [1.03	, 4.19]	
	Schmid P,et al. 2020	15	781	4	389	18.0%	1.88 [0.62	, 5.72]	
	Subtotal (95% CI)		1233		827	63.0%	2.02 [1.12	, 3.66]	-
	Heterogeneity: Tau ^a = 0.00; (Test for overall effect 7 = 0.2	40 Chi ^a = 0.02, df = 1 (P	= 0.88); I	16 *= 0%					
	Total (95% Cl)	13 (r = 0.02)	3463		1007	100.0%	17010 40	2 0 21	
	Total events	56	2102	27	1097	100.0%	1.76[1.10	, 2.82]	-
	Heterogeneity: Tau ^a = 0.00; (Chi ^a = 1.33, df = 4 (P	= 0.86);1	*= 0%					0.01 0.1 1 10
	Heterogeneity: Tau [#] = 0.00; Test for overall effect: Z = 2.3	Chi ^a = 1.33, df = 4 (P 37 (P = 0.02)	'= 0.86); I	*= 0%				1	0.01 0.1 1 10 Favours (experimental) Favours (contro

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.

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A 1 Study or Subg 1.1.1 PD-1 VS	PD-1/PD-L oup Events Tr locetaxel(NSCLC)	1 Chemoth	Total Weight	Odds Ratio M-H, Random, 95% Cl	Odds Year M-H, Rand	s Ratio Iom, 95% Cl	A 2	PD-1PD-L1 Chemotherapy Odds Ratio Odds Ratio <u>Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl Year M-H, Random, 95% Cl</u> 1.3.1 PD-1PD-L1 VS (vinflumine, pacificaxel, or docetaxel)(UC)
Herbst RS,et a Herbst RS,et a Subtotal (95% Total events Heterogeneity Test for overal	12016A 3 (2016B 3 CI) 6 Tau ^a = 0.00; Chi ^a = 0.0 effect Z = 3.70 (P = 0.0	339 14 343 14 682 28 0, df = 1 (P = 0, 0002)	309 15.0% 309 15.0% 618 30.1% 99); P=0%	0.19 [0.05, 0.66] 2 0.19 [0.05, 0.65] 2 0.19 [0.08, 0.45]	016A			Bellimurd, Jet al 2017 0 266 5 255 15 2% 0.09 [0.00, 1.56] 2017 Powles T, et al 2018A 0 114 3 112 14.5% 0.14 [0.01, 2.68] 2018A Powles T, et al 2018B 0 495 6 443 15.4% 0.07 [0.00, 1.21] 2018B Subtoal (495% CI) 875 810 45.1% 0.09 [0.02, 0.49] Total events 0 14 Heterogenetic, Tau* = 0.00, Chi* = 0.11, df = 2 (7 = 0.94); i* = 0%
1.1.2 PD-L1 V Hida T,et al.20 Barlesi F, et al. Subtotal (95% Total events Heterogeneity Test for overal	Docetaxel(NSCLC) 18 0 1018 0 CI) 0 Tau ² = 0.00; Chi ² = 0.0 effect Z = 3.96 (P < 0.0	56 14 393 26 449 40 1, df = 1 (P = 0. 0001)	45 3.5% 365 3.7% 410 7.2% 93); I ² = 0%	0.02 (0.00, 0.33) 0.02 (0.00, 0.27) 0.02 (0.00, 0.13)	2018			Test for overall effect Z = 2.7.8 (P = 0.005) 1.3.2 (PD-14PD-1.1 VS Docetaxel(NSCLC) Barlesi F, et al. 2016 0 99.3 1 365 12.5% 0.31 [0.01, 7.60] 2018 Subtrat (95% CI) 393 365 12.5% 0.31 [0.01, 7.60] Total events 0 1 1 Heterogeneity. Not applicable Test for anyelling of Z = 0.7.0 = 0.17)
1.1.3 PD-1 VS Shitara K,et al Kato K,et al.20 Subtotal (95% Total events Heterogeneity Test for overal	Paclitaxel(OSCC) 2018 0 19 1 Cl) 1 Tau# = 0.00; Chi# = 0.0 effect Z = 5.11 (P < 0.0	294 35 209 47 503 82 4, df = 1 (P = 0.) 00001)	276 3.7% 208 6.9% 484 10.6% 84); I#= 0%	0.01 [0.00, 0.19] 0.02 [0.00, 0.12] 0.01 [0.00, 0.07]	2018			1.3.3 PD.14PD.11 VS Chemotherapy 1.3.3 PD.14PD.11 VS Chemotherapy MokTSk,et al.2018 0.836 Statistical (59% CI) 636 615 15.4% Otal averts Total averts Festor overall det Z ± 17.6 (P = 0.0)
1.1.4 PD-1 VS Belimunt J.et a Subtotal (95% Total events Heterogeneity Test for overal	paclitaxel, docetaxel, 2017 2 CI) 2 Not applicable effect: Z = 3.78 (P = 0.0	or vinflunine)(1 266 28 266 28 28 0002)	UC) 255 12.0% 255 12.0%	0.06 [0.01, 0.26] 0.06 [0.01, 0.26]	2017			1.3.4 PD-1 VS Pacificace(IOSCC) Shilara K, et al. 2018 0 294 3 276 14.5% 0.13 [0.01, 256] 2018 Kata K, et al. 2019 0 209 1 208 12.4% 0.33 [0.01, 256] 2019 Statistical (65% CI) 503 484 27.0% 0.20 [0.02, 1.78] 0.20 [0.02, 1.78] Total events 0 4 441024764[C, 134" = 0.00; Chil" = 0.17; cf = 1 (P = 0.56); P = 0% 0%
1.1.5 PD-L1 V Powles T,et al Powles T,et al Subtotal (95% Total events Heterogeneity Test for overal	(vinflumine, paclitaxel 2018A 0 2018B 3 Cl) 3 Tau ^a = 0.00; Chi ^a = 0.1 effect Z = 4.97 (P < 0.0	, or docetaxel) 114 11 459 39 573 50 3, df = 1 (P = 0. 00001)	(UC) 112 3.6% 443 16.5% 555 20.1% 72); № = 0%	0.04 [0.00, 0.66] 2 0.07 [0.02, 0.22] 2 0.06 [0.02, 0.19]	0188			Test tor overall effect Z = 1.44 (P = 0.15) Total events 0 0 25 Heterogeneiby Tau" = 0.00, Ch" = 1.06, d'f 6 (P = 0.98); P = 0% Test for overall effect Z = 3.57 (P = 0.00.04) Test for overall effect Z = 0.57 (P = 0.00.04) Test for solverous differences - Ch" = 0.75, df = 3 (P = 0.86), P = 0% PD-1/PD-L1 Chemotherapy
1.1.6 PD-1 VS Cohen EEW,e Subtotal (95% Total events Heterogeneity Test for overal	metholrexate, doceta al.2019 0 CI) 0 Not applicable effect: Z = 1.67 (P = 0.1)	0xel, or cetuxir 246 5 246 5 5	nab)(HNSCC) 234 3.4% 234 3.4%	0.08 [0.00, 1.54] 0.08 [0.00, 1.54]	2019	-	B ₂	PD-1P0-L1+Chemotherapy Odds Ratio Dots Dots Study of Subjects Events Total Events Total Events N.H. Random, 95: C1 Year M.H. Random, 95: C1 Schmid P, et al. 2010 9 452 8 438 54: 458 1.09 (34, 24, 320) 2010 ————————————————————————————————————
1.1.7 PD-1 VS Mok TSK, et al. Subtotal (95% Total events Heterogeneity Test for overal	Chemotherapy(NSCLC 1019 3 CI) 3 Not applicable effect Z = 4.51 (P < 0.0) 636 41 636 41 00001)	615 16.6% 615 16.6%	0.07 [0.02, 0.22] 0.07 [0.02, 0.22]	2019			Гоменинания, Тшийн обос Снийн О.С., Снийн О.С., Снийн О.С., Снийн О.С., Снийн О.С., Слийн Слий
Total (95% CI) Total events Heterogeneity Test for overal Test for subar	3: 15 Tau ^a = 0.11; Chi ^a = 11, effect Z = 9.50 (P < 0.0 up differences: Chi ^a =	274 55, df = 10 (P = 00001) 10.18. df = 6 (P	3171 100.0% 0.32); I ² = 13% = 0.12). I ² = 41.1	0.07 [0.04, 0.12]	0.001 0.1 PD-1/PD-L1	1 10 1000 Chemotherapy		
1 <u>Study or Suboro</u> 2.1,1 PD-1/PD-1 Schmid P, et al.2 Schmid P, et al.2 Subtotal (95% CI Total events Heterogeneity: Test for overall e	PD-1/PD-1.1+Chen p Events •Chemother apy VS Chen 18 72 20 12 u ² = 0.01; Chi ² = 1.36, df = iect: Z = 1.18 (P = 0.24)	Total Execution Total Execution 452 781 1233 1 (P = 0.24); P =	entotherapy ents Total Wei 52 438 33 71 389 46 827 79 123 27%	Odds Ratio off M.H. Random, 95% CI Y 2% 1.41 [0.96, 2.06] 2 0% 1.05 [0.77, 1.43] 2 2% 1.19 [0.89, 1.59]	Odds ear M.H. Rand 118 120	Ratio mr. 95% Cl		
2.1.2 PD-1/PD-L1 Paz-Ares L et al. Subtotal (95% CI Total events Heterogeneity: N Test for overall e	+Chemotherapy VS Chem 018 33 33 t applicable lect: Z = 0.48 (P = 0.63)	notherapy(LC) 278 278	37 280 20 280 20 37	8% 0.88 [0.54, 1.46] 2 8% 0.88 [0.54, 1.46]	118	•		
Total (95% CI) Total events Heterogeneity: T Test for overall e	253 u#= 0.01; Chi#= 2.38, df= lect Z = 0.88 (P = 0.38) differences: Chi#= 1.00. i	1511 2 (P = 0.30); I ^a = df = 1 (P = 0.32). I	1107 100 160 16% *= 0%	0% 1.11 [0.88, 1.42]	0.01 0.1 1 PD-1/PD-L1+Chemotherapy	10 100 Chemotherapy		

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 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): 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): 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): subgroup analysis was put into practice based on tumor types in both groups.

_		00 400		Chamatha			Odde Patio		Odde P	tatio	_		PD 1+Chomot	thoramy	Chemether	2004		Odde Patio		Odde Patio	
Δ	Chucha or Casharoun	PD-1/PD	Total	Chemioure	Tetal	Maintel	M U Dandom OFF CL	Maar	M U Dander	allo	R	Study or Subgroup	Evente	Total	Evente	Total M/r	inter MI	I Dandom 05% Cl. Yes		U Bandom 05% Cl	
	124 PD 4 DD 14 VE Dee	Events	CL C)	Events	Total	vveigni	M-H, Kandom, 95% CI	rear	M-H, Kandor	n, 95% CI		2 1 1 DD 1+Chemother	any VS Chomot	thoranu/NS	CLCL	Total WW	agint_m-r	h runuoni, 35% ci 100	1 M	n, Nahuoni, 35% Ci	
	Berghani H at al 2016	eraxei(n3	207	25	260	10.49	0 1 7 10 06 0 461	2016				Langer C.Let al 2016	10	59	6	62 4	9%	1 90 00 65 5 621 201	6		
	Book Micticel 2016		154	15	200	2.40	0.00 (0.01, 0.46)	2015				Gandhi L. et al. 2018	33	294	10	145 10	1.6%	1.71 [0.82, 3.57] 201	8		
	Reck M,et al. 2016	1	154	15	150	2.4%	0.06 [0.01, 0.45]	2016				Subtotal (95% CI)		353	10	207 1	5.5%	1.77 [0.96, 3.25]	~	•	
	Herbst RS,et al. 2016A	-	339	10	309	8.1%	0.22 [0.07, 0.66]	2016A				Total events	43		16					-	
	Perpst RS,et al. 2016B	10	343	10	309	12.1%	0.38 [0.15, 0.94]	20168	_			Heterogeneity: Tau ² = 0	.00; Chi# = 0.03.	. df = 1 (P =	0.87); I# = 0	3%					
	Hitte T et el 2010	18	609	58	5/6	33.0%	0.27 [0.16, 0.47]	2017				Test for overall effect Z	= 1.83 (P = 0.07	7)	52						
	Filda 1,et al.2018 Subtotal (95% CD	- 2	1799	13	40	2.370	0.04 [0.01, 0.36]	2018	•												
	Subtotal (95% CI)	20	1/88		1029	08.8%	0.22 [0.14, 0.35]		•			2.1.2 PD-1/PD-L1+Chem	notherapy VS C	Chemothera	apy(BC)						
	I otal events	30	20 4	143		201						Schmid P,et al.2018	123	781	48	389 44	1.9%	1.33 [0.93, 1.90] 201	8	-	
	Heterogeneity: Tau- = 0.0	0, Chi = 0	20, 01=	5 (P = 0.2)	9), 1- = 11	576						Schmid P,et al.2020	62	452	60	438 39	3.5%	1.00 [0.68, 1.47] 202	0	.	
	Test for overall effect Z =	0.41 (P < (0.00001)								Subtotal (95% CI)		1233		827 8	4.5%	1.16 [0.88, 1.53]		•	
	12200 100 L1VE 640	flumino na	clitaval	or decete	volution							Total events	185	1992 - 1992 PM	108	0638					
	Deliment Let al 2017	riunnie, pa	ace	, or doceta	255	12.40	0.26 10 16 0.071	2017				Heterogeneity: Tau ^a = 0	.00; Chi [#] = 1.11,	, df = 1 (P =	0.29); I [#] = 1	10%					
	Beilmunt J,et al. 2017	2	200	10	200	12.4%	0.36 [0.15, 0.87]	2017				Test for overall effect Z	= 1.07 (P = 0.28	3)							
	Powles T et al 2019P	2	450	22	442	3.9%	0.27 [0.05, 1.32]	2010A				Tetal (OEV CD		4500		1024 40	0.01	1 24 10 00 4 501			
	Subtotal (95% CD	0	459	22	943	20 2%	0.25 [0.10, 0.63]	20166	•			Total (95% Cl)	220	1580	121	1034 10	0.076	1.24 [0.98, 1.58]			
	Total quanta	15	033	47	010	20.270	0.50 [0.10, 0.54]					Hotorogonoity Tou? = 0	00: Chil = 2.67	df = 2 /P =	0.453:18=0	196					
	Hotorogonoity Tour = 0.0	10: Chil = 0	20 df-	2/0 = 0.00	A) IF = 01	×						Test for overall effect 7	- 1 77 (P - 0.09	, ui = 5 (r =	0.45), 1 = 0	170			0.001 0.1	1 10	1000
	Tect for overall effect 7 =	A 02 /P = 0	29, 01-	2 (F = 0.00	0), 1 = 0	20						Test for subgroup differ	ences: Chi ² = 1	50 df=1 0	P = 0.22) P	= 33 5%			PD-1/PD-L1+Chemo	therapy Chemother	ару
	restion overall ellect 2 =	4.02 (F = (5.0001)									restion subarous amon	ences. em = 1.								
	1.2.3 PD.1 VS (methotre)	xate doce	taxel o	r cetuxima	b)(HNS)	C)															
	Cohen EEW et al. 2019	2	246	3	234	3.0%	0.63 (0.10.3.81)	2019													
	Subtotal (95% CI)		246	5	234	3.0%	0.63 [0.10, 3.81]	2010	-	-	-		PD-1/PD-L1+Ta	argeted	Targeted Th	herapy		Odds Ratio		Odds Ratio	
	Total events	2		3							C	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% C	
	Heterogeneity: Not applic	able		<u> </u>								Motzer RJ.et al. 2019	11	406	51	397	31.5%	0.19 (0.10, 0.37)	2019 -	-	
	Test for overall effect Z =	0.50 (P = 0	0.62)									Rini Bl.et al.2019	25	451	127	446	68.5%	0.15 [0.09, 0.23]	2019 -	-	
	Total (95% CI)		2873		2703	100.0%	0.26 [0.19, 0.35]		•			Total (95% CI)		857		843	100.0%	0.16 [0.11, 0.23]		×	
	Total events	53		193								Total events	36		178						
	Heterogeneity: Tau ² = 0.0	0; Chi ² = 7	.88, df=	9 (P = 0.5	5); P = 04	%		-		1 100		Heterogeneity: Tau ² = 0.	.00; Chi ² = 0.36,	df = 1 (P =	0.55); P= 0	9%			t de		+ +
	Test for overall effect: Z =	8.44 (P < 0	0.00001)				0.001	0.1 1	10 1000		Test for overall effect Z	= 9.61 (P < 0.00	0001)					0.01 0.1	1	10 100
	Test for subaroup differen	nces: Chi*	= 1.55.	df = 2 (P = 1	0.46). P=	= 0%			PD-1/PD-L1 (unemotherapy									PD-1/PD-L14	Targeted Targeted	Inerapy

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): 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.

Study or Subgroup	Events Tota	Events	Total	Weight	M-H, Random, 95% Cl	Yea	r M-H, Random, 95% Cl
1.1.1 PD-L1 VS (vinflun	ine, paclitaxel, or	docetaxel)	(UC)				
Powles T,et al.2018A	1 114	6	112	4.5%	0.16 [0.02, 1.32]	2018	A
Powles T,et al.2018B	7 459	25	443	28.7%	0.26 [0.11, 0.60]	2018	в —
Subtotal (95% CI)	573		555	33.3%	0.24 [0.11, 0.53]		•
Total events	8	31					
Heterogeneity: Tau ² = 0	0.00; Chi ² = 0.19, dt	= 1 (P = 0.	67); I ² = I)%			
Test for overall effect: Z	= 3.53 (P = 0.0004)					
1.1.2 PD-1 VS Docetax	el(NSCLC)						
Brahmer J,et al. 2015	2 131	7	129	8.2%	0.27 [0.06, 1.33]	201	5
Borghaei H,et al.2015	5 287	20	268	20.9%	0.22 [0.08, 0.59]	201	5
Herbst RS,et al. 2016A	3 339	17	309	13.5%	0.15 [0.04, 0.53]	2016	A
Herbst RS,et al.2016B	3 343	17	309	13.5%	0.15 [0.04, 0.52]	2016	B
Subtotal (95% CI)	1100		1015	56.1%	0.19 [0.10, 0.35]		•
Total events	13	61					
Heterogeneity: Tau ² = 0	.00; Chi ² = 0.52, dt	= 3 (P = 0.	92); I ^z = I)%			
Test for overall effect: Z	= 5.36 (P < 0.0000	1)					
1.1.3 PD-1 VS (methot	exate, docetaxel,	or cetuxin	nab)(HNS	SCC)			
Cohen EEW, et al. 2019	3 246	6	234	10.6%	0.47 [0.12, 1.90]	201	9
Subtotal (95% CI)	246		234	10.6%	0.47 [0.12, 1.90]		
Total events	3	6					
Heterogeneity: Not app	licable						
Test for overall effect: Z	= 1.06 (P = 0.29)						
Total (95% CI)	1919		1804	100.0%	0.23 [0.14, 0.36]		•
Total events	24	98					
Heterogeneity: Tau ² = 0	0.00; Chi ² = 2.10, df	= 6 (P = 0.	91); l ^z = I)%			0.001 0.1 1 10 10
Test for overall effect: Z	= 6.40 (P < 0.0000	1)					PD-1/PD-L1 Chemotherapy
Test for subaroup diffe	rences: Chi ² = 1.39	. df = 2 (P =	= 0.50). P	= 0%			
	PD-1/PD-L1+Chemot	ierapy Cl	nemother	ару	Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total E	vents	Total We	ight M-H, Random, 95% Cl	Year	M-H, Random, 95% CI
Socinski MA,et al.2018	42	393	37	394 75	.1% 1.15 [0.72, 1.84]	2018	-
Paz-Ares L,et al.2019	14	265	11	266 24	.9% 1.29 [0.58, 2.90]	2019	
Total (95% CI)		658		660 100	1.19 [0.79, 1.78]		+
Total events	56		48				
Heterogeneity: Tau ² = 0.00	Chi*= 0.06, df = 1 (P	= 0.81); I ² =	0%				0.01 0.1 1 10 1
rest for overall effect. Z = 0	.03 (P = 0.40)						PD-1/PD-L1+Chemotherapy 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).

random effect (RE) model (PD-1/PD-L1 + chemotherapy vs. chemotherapy).

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, I² = 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 allgrade 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 allgrade 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.

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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 vs. chemotherapy): subgroup analysis was put into practice based on 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): 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): 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 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): subgroup analysis was put into practice based on tumor types. 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 allgrade paraesthesia calculated by the fixed effect (FE) model (PD-1/PD-L1 + targeted by the fixed effect (FE) model (PD-1/PD-L1 + 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 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 + targeted vs. targeted therapy): subgroup analysis was put into practice based on PD-1/PD-L1 + targeted vs. targeted therapy): subgroup analysis was put into practice based on PD-1/PD-L1 + targeted vs. targeted therapy): subgroup analysis was put into practice based on PD-1/PD-L1 + targeted vs. targeted therapy): subgroup analysis was put into practice based on PD-1/PD-L1 + targeted vs. targeted therapy): subgroup analysis was put into practice based on PD-1/PD-L1 + targeted vs. targeted therapy): subgroup analysis was put into practice based on 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 + targeted vs. targeted therapy). **(D1)** The risk of all-grade headache 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 + targeted vs. targeted therapy). **(D1)** The risk of all-grade headache calculated by the random effect (RE) model (PD-1/PD-L1 + targeted vs. targeted therapy

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 vs. chemotherapy). **(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 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 + targeted vs. targeted therapy). **(D1)** The risk of all-grade headache 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).

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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).

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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.

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