Are anti-PD1 and anti-PD-L1 alike? The non-small-cell lung cancer paradigm

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Abstract

Anti-PD1 and anti-PD-L1 agents may have intrinsic and clinically relevant differences in the treatment of non-small cell lung cancer (NSCLC) patients. By reviewing currently available indirect evidence on these agents for NSCLC treatment, highlighting possible inter- and intra-class dissimilarities, anti-PD1 agents showed a higher response rate and a better outcome when combined with chemotherapy for the first-line treatment of patients with squamous and PD-L1 low advanced NSCLC, as compared to anti-PD-L1 agents. Conversely, anti-PD-L1 agents were responsible for less severe adverse events (AEs), particularly, immune-related AEs. These differences could be explained by their different specific properties. Considering possible differences between anti-PD1 and anti-PD-L1 agents could be clinically relevant for treatment tailoring and inspiring new investigational approaches.

Introduction

Immune-checkpoint inhibitors (ICIs) have hugely contributed to the outcome improvement of patients with lung cancer as several phases III clinical trials have shown (Table 1).[1-19]

Emerging evidence from published studies suggests that anti-programmed cell death 1 (PD1) and anti-programmed cell death ligand 1 (PD-L1) agents are very similar to each other from a clinical point of view.

As far as the treatment for the second and beyond-line of advanced non-small-cell lung cancer (aNSCLC) is concerned, both anti-PD1 and anti-PD-L1 demonstrated an overall survival (OS) advantage as compared to chemotherapy, despite the lack of a gain in progression-free survival (PFS).[12-15]

Long-lasting disease response rates were observed in approximately 14 to 20% of patients with immune-checkpoint inhibitors (ICIs) supporting an approximately 16% 5-year OS.[20]

Toxicity with ICIs was less severe than with chemotherapy and immune-related adverse events (irAE) did not represent a limiting or unmanageable toxicity when single-agent ICI was used.[21]

Several published results confirmed that the effect of ICIs is independent by the histology.[12-15,20]

The expression level of PD-L1 in tumor cells may matter in terms of benefits since high-PD-L1 patients show the best outcome.[14,14,20,22]

In the first-line setting, PFS may be increased alongside OS provided that an ICI is given to high-PD-L1 patients, or in combination with chemotherapy, or when ICIs with different mecha-

nisms of action are combined (*i.e.* anti-CTLA4 with anti-PD-L1). Furthermore, ICI combination treatments are effective on PFS and OS regardless of histology (*i.e.* squamous or non-squamous) and PD-L1 tumor cells expression level (*i.e.*, negative, low or high).[23]

In the unresectable stage III NSCLC not-progressing following concurrent chemoradiotherapy, the PFS benefit from the use of the anti-PD-L1 durvalumab compared to placebo was even more relevant than that reported for the OS.[16] Possible explanations for this effect could be: the selection of patients already responding to chemotherapy since immunotherapy tends to be more effective in those tumors with a high nonsynonymous mutational burden or DNA repair pathway mutations, which are also more sensitive to chemotherapy;[24-29] the pro-inflammatory effect of radiotherapy on the tumor microenvironment that could have reversed the primary resistance of *cold* tumors against immunotherapy;[30-32] the comparison of the anti-PD-L1 agent against placebo rather than to an active treatment.[33] From this general point of view, no relevant differences stand out between anti-PD1 and anti-PD-L1 agents.

In this narrative review, we will critically examine some clinical and preclinical data suggesting that some differences actually could exist in terms of efficacy, toxicity and biological properties based on their pharmacological profile.

Efficacy: possible differences

There is some evidence from indirect clinical trial comparisons and a meta-analysis which may suggest possible inter- and intra-class differences in terms of efficacy between anti-PD1 and anti-PD-L1 agents and are following examined.

Indirect trial comparisons suggesting possible ICI inter-class ORR differences

From an indirect comparison of phase III randomized clinical trials in the second- and beyond-line treatment of aNSCLC, a numerical difference in the absolute OS benefit in favor of the anti-PD-L1 agent (atezolizumab) as compared to the anti-PD1 agents (nivolumab and pembrolizumab) came to light, with 4.2 months of OS gain *versus* 1.9-3.2 months, respectively (Figure 1A).[12-15] However, this indirect comparison is biased by patients' selection. Indeed, patients in the OAK trial[15] with the anti-PD-L1 (atezolizumab) had more favorable characteristics than those of the Keynote 010 trial[14] with the anti-PD1 (pembrolizumab): with a higher proportion of patients with good performance status (36% *versus* 33%), non-squamous histology (74% *versus* 70%), never-smokers (20% *versus* 18%), EGFR/ALK-positive (11% *versus* 9%), higher PD-L1 expression (47% *versus* 40%) and ≥3 treatment lines (0 *versus* 8%).

Yet, as above mentioned, the OS benefit from ICIs is mainly driven by long-lasting disease responses and, for the second- and beyond-line treatment, the reported ORR with the anti-PD-L1 agent (atezolizumab) was lower than reported with the anti-PD1 agents (nivolumab and pembrolizumab), of 14% *versus* 18-20%, respectively, and the ORR gain was of 1% *versus* 7-11%, respectively (Figure 1B). Such small differences could be relevant since the 16% ORR observed with the anti-PD-L1 agent could not translate into the 5 year-OS of 16% and the 3-year 23% reported in the second- and beyond-line with the anti-PD1 agents (nivolumab and pembrolizumab, respectively).[20,22] Currently, data from the anti-PD-L1 atezolizumab are still limited to a 2-year OS of 31%[34] and longer follow-up OS data could clarify this issue.

Meta-analysis and other trial indirect comparisons suggesting possible ICI inter-class outcome differences

Another relevant evidence suggesting possible differences between anti-PD1 and anti-PD-L1 comes from a meta-analysis of trials combining ICIs with chemotherapy for the first-line treatment of aNSCLC. The HR for trials using the anti-PD1 agent (pembrolizumab) was 0.56 (95% CI, 0.46-0.67, p<0.00001) as compared to 0.85 (95% CI, 0.76-0.94, p=0.001) of those with the anti-PD-L1 (atezolizumab).[35]

Furthermore, by an indirect comparison of the two trials which investigated for the first-line treatment of aNSCLC with squamous histology the addition of the anti-PD1 (pembrolizumab) and the anti-PD-L1 (atezolizumab) agents (the Keynote 407 and ImPower 131 trials, respectively),[8,9] in combination with the same chemotherapy backbone (carboplatin-paclitaxel or carboplatin-nab-paclitaxel), the difference in the PFS gain varied from 0.7 to 1.6 months with the anti-PD-L1 (atezolizumab) and the anti-PD1 (pembrolizumab) agent as compared to chemotherapy alone, respectively. The difference in OS gain was even more considerable (0.1 *versus* 4.6 months, respectively) (Figure 1C). This difference in OS in favor of the anti-PD-1 *versus* the anti-PD-L1 was estimated with an HR of 0.67 (95% CI, 0.47-0.94, P=0.02) and was particularly relevant in the PD-L1 low population (HR of 0.43, 95% CI, 0.24-0.76, P<0.01).[36] In this regard, or for patients with aNSCLC with low-PD-L1 tumors cell expression, the above-mentioned meta-analysis has also reported a possible difference between the Keynote and Impower trials in favor of the anti-PD1 drug (pembrolizumab) as compared to the anti-PD-L1 (atezolizumab) when they were added to first-line chemotherapy.[35]

Indirect trial comparisons suggesting possible ICI intra-class outcome differences

Interestingly, in patients with high PD-L1 aNSCLC, either anti-PD1 (pembrolizumab, but not nivolumab)[1-3,37] and anti-PD-L1 agents (atezolizumab and durvalumab)[4,5] have shown a significant benefit in terms of OS as compared to the first-line chemotherapy, whilst a significant benefit in PFS has only been shown by pembrolizumab (by one of the two available studies)[1] and atezolizumab[5] (Table 1 and Figure 1D). The reason why the anti-PD1 nivolumab failed to show OS and PFS benefit in this patient subgroup is difficult to explain by possible differences between the different platforms and related antibodies used for the selection of high-PD-L1 patients[38] and might even suggest possible intrinsic intra-ICI class differences (Figure 1D).[1-5] Whereas, the different cut-off (of ≥25%) used for the identification of high-PD-L1 patients for durvalumab could at least partially explain the different OS and PFS benefit observed as compared to atezolizumab (Figure 1D), although intra-class ICI differences could also be considered.

Other factors against ICI inter-class outcome differences

Against possible intrinsic differences between the ICIs discussed below, it could be argued that a different trial follow-up duration or the assessment of PD-L1 expression could have affected these results. The longer the follow-up time of a trial is the lower the OS and PFS will be since more events will be observed.[39-41] The median follow-up time with the anti-PD1 agents nivolumab or pembrolizumab ranged from 7.7 to 25.2 (median, 12.0 months) as compared with 9.8 to 15.5 (median, 13.9 months) with the anti-PD-L1 atezolizumab.[2,3,6,8,9,11,37,42]

Table 1. Completed phase III randomized trials with ICIs in lung cancer.

Drug (Reference)	Histology	Trial	PDL1 expression	HR OS (95% CI) P value	HR PFS (95% CI) P value
aNSCLC - First-line single-agent					
Pembrolizumab (Reck et al., 2016)	NSCLC	KN-024	≥50%	0.60 (0.41-0.89) P=0.005	0.50 (0.37-0.68) P<0.001
Nivolumab (Carbone et al., 2017)	NSCLC	CM-026	≥5%	1.02 (0.80-1.30) NR	1.15 (0.91-1.45) P=0.25
Pembrolizumab (Mok et al., 2019)	NSCLC	KN-042	≥1%	0.81 (0.71-0.93) P=0.0018	1.07 (0.94-1.21) P=NR
Durvalumab (Reinmuth N et al., 2019)	NSCLC	MYSTIC	≥25%	0.66 (0.49-0.90) =0.002	NR
Atezolizumab (Spigel DR, et al., 2019)	NSCLC	IMPower110	≥50% (TC) or IC ≥10%	0.59 (0.40-0.89) P=0.0106	0.63 (0.45-0.88) P=0.007
aNSCLC - First-line combination					
Pembrolizumab + Chemotherapy (Gandhi et al., 2018)	NonSq	KN-189	any	0.49 (0.38-0.64) P<0.001	0.52 (0.43-0.64) P<0.001
Atezolizumab+ Bevacizumab- Chemotherapy (Socinski et al., 2018)	NonSq	IMPower150	any	0.78 (0.64-0.96) P=0.0164	0.59 (0.50-0.70) P<0.0001
Atezolizumab+ Chemotherapy (Jotte et al., 2018)	Sq	IMPower131	any	0.96* (0.78-1.18) P=0.69	0.71 (0.60-0.85) P=0.0001
Pembrolizumab+ Chemotherapy (Paz-Ares et al., 2018)	Sq	KN-407	any	0.64 (0.49-0.85) P=0.0008	0.56 (0.45-0.70) P<0.0001
Nivolumab+/- Platinum-Pem in NonSq Platinum-Gem in Sq (Borghaei et al., 2018) NonSq (273)	Sq (90)	CM-227	<1%	NR	0.74 (0.58-0.94) P=NR
Nivolumab+ Ipilimumab° (Hellmann et al., 2019)	NSCLC	CM-227	any	NR	0.58° (0.41-0.81) P<0.001
aNSCLC - Second- and beyond-line					
Nivolumab (Brahmer et al., 2015)	Sq	CM-017	NA	0.59 (0.44-0.79) P<0.001	0.62 (0.47-0.81) P<0.001
Nivolumab (Borghaei et al., 2015)	NonSq	CM-057	NA	0.73 (0.59-0.89) P=0.002	0.92 (0.77-1.11) P=0.39
Pembrolizumab (Rittmeyer et al., 2017)	NSCLC	KN-010	≥1%	0.71 (0.58-0.88) P=0.0008	0.88 (0.74-1.05) P=0.07
Atezolizumab (Herbst et al., 2016)	NSCLC	OAK	NA	0.73 (0.62-0.87) P=0.0003	0.95 (0.82-1.10) NR
Stage III NSCLC - Maintenance					
Durvalumab (Antonia et al., 2017; Gray et al., 2019)	NSCLC	PACIFIC	NA	0.69 (0.55-0.86) NR	0.52 (0.42-0.65) P<0.001

aNSCLC, advanced NSCLC; aSCLC, advanced SCLC; CM, Checkmate; ICIs, immune-checkpoint inhibitors; CTRT, chemo-rdiotherapy; KN, Keynote; IC, tumor-infiltrating immune cells; NonSq, non-squamous; NR, not reported; NSCLC, non-small cell lung cancer; SCLC, small-cell lung cancer; Sq, squamous; TC, tumor cells. *Results refer to first interim analysis; °Results refer only to patients with high tumor mutational burden, as defined by at least 10 mutations per megabase.

The longest follow-up with the anti-PD-L1 atezolizumab could, therefore, be considered as one of the possible explanations for the lower benefit observed in patients treated with this agent as compared with anti-PD1 ones in terms of OS or PFS but not of ORR.

Regarding the PD-L1 assessment, it is well known that possible differences between different platforms and related antibodies used, specifically the SP142-Ventana assay and the other ones, could exist.[38,43] Furthermore, other differences across clinical trials regarded the definition of PD-L1 positive tumors, which in studies with the anti-PD-L1 atezolizumab included not only PD-L1 positive tumor cells but also PD-L1 positive tumor-infiltrating immune cells. For instance, in the IMpower 110 trial, high PD-L1 patients were defined by ≥50% expression of PD-L1 on tumor cells (TC3) or ≥10% expression on tumor-infiltrating immune cells (IC3) (Table 1).[5] However, by a review of 400 samples of patients treated with second-line anti-PD-L1 atezolizumab, a significant OS difference between the ICI and chemotherapy was observed both in patients classified as negative or high PD-L1 by the SP142-Ventana and by the 22C3-Dako assay.[44] Similar findings, by a review of 503 samples, confirmed an OS benefit independently from the classification by the SP142-Ventana or SP263-Ventana assay for negative, low and high PD-L1 patients treated with first-line anti-PD-L1 atezolizumab in combination with bevacizumab

and chemotherapy as compared to bevacizumab and chemotherapy.[45] These results suggest that PD-L1 assessment should not be an issue for a possible difference in efficacy between anti-PD1 and anti-PD-L1 agents.

Summary of possible efficacy differences among anti-PD1 and anti-PD-L1 agents

Currently available evidence from indirect comparisons of phase III randomized trials and one metanalysis suggest possible ICI inter-class differences in terms of higher ORR and a better outcome for the first-line treatment in combination with the chemotherapy in favor of anti-PD1 agents, particularly for patients with squamous and low PD-L1 tumor expression. Possible ICI intra-class differences between the different anti-PD1 and anti-PD-L1 agents could also be considered.

Toxicity: possible differences

ICIs are characterized by lower and different toxicity than chemotherapy.[46] Particularly, irAEs, such as pneumonitis, hepatitis and colitis, could be an issue especially when ICIs are combined (*i.e.* anti-CTLA4 and anti-PD1 or anti-PD-L1).[46] Thus, recognizing possible different toxicity profiles between anti-PD1 and anti-
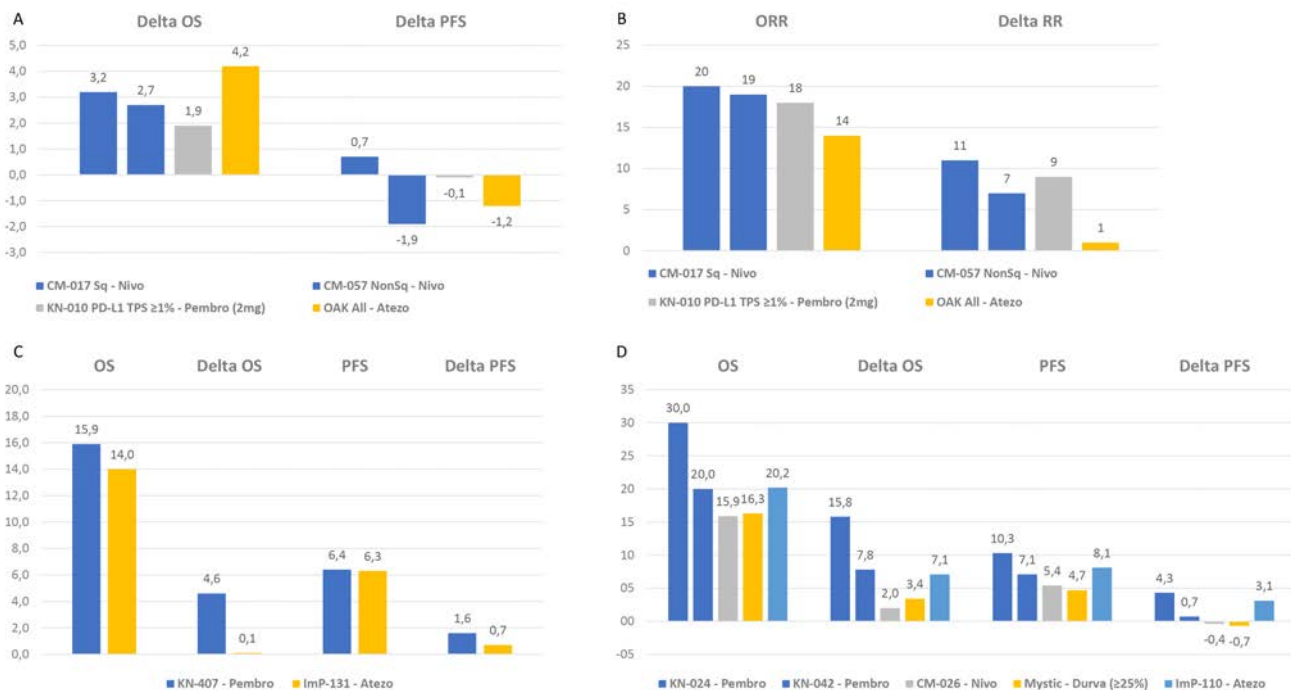
Figure 1. Indirect comparisons between anti-PD1 and anti-PD-L1 exploring possible clinical efficacy differences: A, indirect comparison of difference (Delta) in median months of OS and PFS between anti-PD1 and anti-PD-L1 agents and chemotherapy in the second- and beyond line treatment of aNSCLC by available phase III randomized trials; B, indirect comparison of ORR percentage between anti-PD1 and anti-PD-L1 agents and of gain in ORR (Delta) percentage between them and chemotherapy in the second- and beyond line treatment of aNSCLC by available phase III randomized trials; C, indirect comparison of median months of OS and PFS between anti-PD1 and anti-PD-L1 agents plus chemotherapy and of gain in OS and PFS (Delta) months between them and chemotherapy alone in the first-line treatment of squamous aNSCLC by available phase III randomized trials; D, indirect comparison of median months of OS and PFS between anti-PD1 and anti-PD-L1 agents and of gain in OS and PFS (Delta) months between them and chemotherapy in the first-line treatment of PD-L1 high aNSCLC by available phase III randomized trials. aNSCLC, advanced nonsmall-cell lung cancer; ADCC, antibody-dependent cell-mediated cytotoxicity (ADCC); Atezo, atezolizumab; CM, checkmate; G, grade; KN, keynote; Ig, immunoglobulin; ImP, ImPower; moAbs, monoclonal antibodies; Nivo, nivolumab; ORR, overall response rate; OS, overall survival; PD1, programmed cell death 1; PD-L1, programmed cell death ligand 1; Pembro, pembrolizumab; PFS, progressionfree survival; Sq, squamous.

PD-L1 could be clinically relevant for the safest ICI delivery, and investigational purposes, or to explore potential ICIs combinations within each other and with chemotherapy or other agents (*e.g.*, antiangiogenics or targeted treatments).

Indirect trial comparisons suggesting possible ICI inter-class toxicity differences

By an indirect comparison of the second- and beyond-line treatment clinical trials where single-agent anti-PD1 or anti-PD-L1 were compared with docetaxel,[12-15] the rate of overall-grade and severe (≥grade 3) toxicity seemed quite similar between the different ICIs, with the overall-grade toxicity ranging from 58 to 69% *vs*. 64% and the ≥ grade 3 toxicity from 7 to 13% *vs*. 15% for the anti-PD1 nivolumab and pembrolizumab *vs*. the anti-PD-L1 atezolizumab, respectively (Figure 2A). The rate of toxicity leading to treatment discontinuation was 3 to 5% *vs*. 8% for the anti-PD1 nivolumab and pembrolizumab *vs*. the anti-PD-L1 atezolizumab, respectively (Figure 2A). Yet, a possible difference in the most frequent irAEs in favour of the anti-PD-L1 atezolizumab as compared to the anti-PD1 nivolumab and pembrolizumab is detectable, with a rate of pneumonitis of 1 *vs*. 3-5%, hepatitis of 0.3 *vs*. 1-2% and colitis of 0.3 *vs*. 1%, respectively (Figure 2B).

Systematic- and meta-analysis suggesting possible ICI inter-class toxicity differences

By systematic analysis of 23 trials using anti-PD-1 (nivolumab and pembrolizumab) and anti-PD-L1 (atezolizumab, durvalumab, and avelumab) for 3284 patients and 2460 patients with NSCLC, respectively, investigating toxicity differences between the anti-PD-1 and anti-PD-L1 agents, their toxicity profiles appeared to be similar.[47] However, patients treated with anti-PD-1 agents were found to have a slightly increased rate of irAEs (16% *vs*. 11%; P=0.07) and pneumonitis (4% *vs* 2% P=0.01) compared to patients who received anti-PD-L1 agents.[47]

A recent systematic review and meta-analysis including 125 clinical trials and involving 20,128 patients reported 66% of any grade AEs, 14% of ≥ grade 3 AEs and 28% of treatment-related deaths due to pneumonitis with ICIs.[48] The anti-PD1 agents were associated with a higher mean incidence of ≥ grade 3 AE compared to anti-PD-L1 agents (odds ratio [OR], 1.58; 95%CI, 1.00-2.54). Furthermore, among anti-PD1 agents, nivolumab was associated with higher mean incidences of all-grade AEs compared with pembrolizumab (OR, 1.28; 95% CI, 0.97-1.79) and ≥ grade 3 AEs (OR, 1.30; 95% CI, 0.89-2.00).[48]
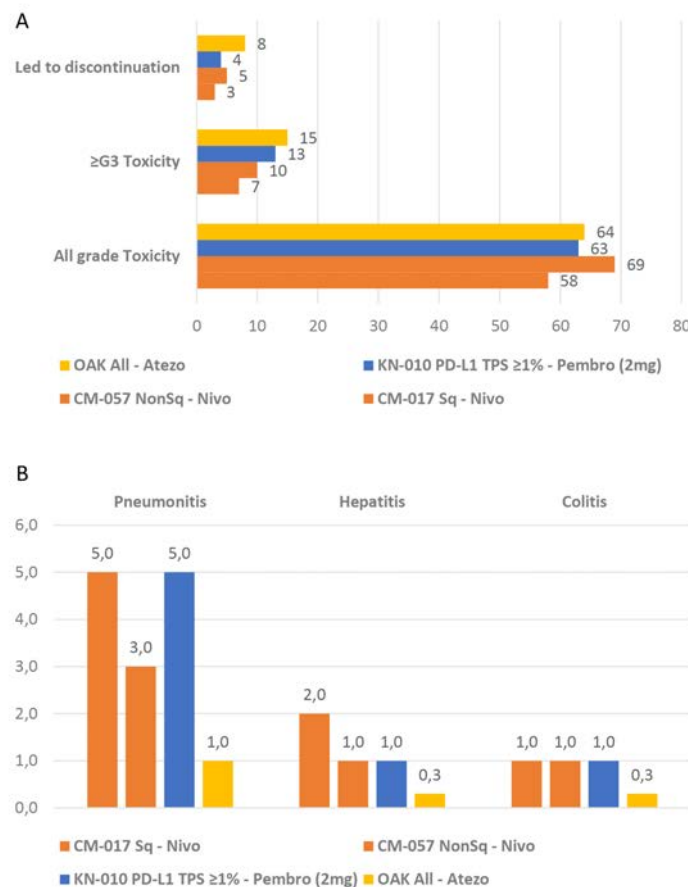
Figure 2. Indirect comparison between anti-PD1 and anti-PD-L1 exploring possible toxicity differences: A, indirect comparison of led to discontinuation, ≥ grade 3 and all grade toxicity percentages between anti-PD1 and anti-PD-L1 agents in the second- and beyond line treatment of aNSCLC by available phase III randomized trials; B, indirect comparison of immune-related adverse events percentages between anti-PD1 and anti-PD-L1 agents in the second- and beyond line treatment of aNSCLC by available phase III randomized trials. aNSCLC, advanced nonsmall-cell lung cancer; ADCC, antibody-dependent cell-mediated cytotoxicity (ADCC); Atezo, atezolizumab; CM, checkmate; G, grade; KN, keynote; Ig, immunoglobulin; ImP, ImPower; moAbs, monoclonal antibodies; Nivo, nivolumab; ORR, overall response rate; OS, overall survival; PD1, programmed cell death 1; PD-L1, programmed cell death ligand 1; Pembro, pembrolizumab; PFS, progressionfree survival; Sq, squamous.

Other evidence suggesting possible ICI intra-class toxicity differences

There could be different rates of infusion-related reactions (IRRs) with monoclonal antibodies (moAbs) inducing antibody-dependent cell-mediated cytotoxicity (ADCC) as compared to not-ADCC mAbs (Figure 3). For instance, avelumab, which is the only anti-PD-L1 triggering the ADCC, is associated with a higher rate of IRRs as compared to not-ADCC mAbs.[49]

Summary of possible toxicity differences among anti-PD1 and anti-PD-L1 agents

To sum up, current evidence suggests anti-PD1 agents could be associated with more frequent ≥ grade 3 AE, particularly irAEs (*e.g.*, pneumonitis, hepatitis and colitis), compared to anti-PD-L1 agents. The possible explanations for this difference are discussed below.

Action mechanisms: dissimilarities among anti-PD1 and anti-PD-L1

It is broadly known that immunotherapy could deliver therapeutic benefits through different mechanisms of action, firstly branching off on active and passive.

The former is designed to act by enhancing the immune response either via function empowerment of the whole immune cell spectrum, addressed by cytokines, or employing antigen–depending systems as therapeutic vaccines or antigen-independent ones as the T–cell function modulation. Proper immune-oncology (IO) stems from this latter and current drugs all funnel in the ICI subset, of which effectiveness currently lays on the blockage of immune suppression pathways as PD-1, PD-L1 and CTLA-4.[50]

Different target-related mechanisms

Although globally identified as ICIs, existing differences have to be focused and weighed.

For instance, anti-PD1 and anti-PD-L1 drugs prevent PD-L1 (and PD-L2) from interacting with PD-1, which would normally allow a decrease in T-cells function signaling and their activation against cells.[51]

Yet, the expression of these targets is not evenly spread: for a fact, PD1 belongs to T-cell membrane expression, and so anti-PD1 drugs perform a general undistinguished T-cell hyper-activation and a blockage of both PD-L1 and PD-L2. On one hand, this results in a possible higher efficacy even in low PD-L1 tumors, but this would potentially generate more severe irAEs than the anti-PD-L1 drugs.[51] Up-to-date examples listed in this class are the anti-PD1 nivolumab, pembrolizumab, pidilizumab, and AMP-224.

Instead, PD-L1 distribution regards tumor cells surface and is strictly tumor-associated. Therefore, the anti-PD-L1 effect is conveyed through dysregulation of tumor cell signaling and can give milder potential irAE.[51] Atezolizumab, durvalumab, avelumab and BMS-936559 are examples.

Molecular, pharmacodynamics and pharmacokinetics specifics assessment

Differences in molecular structure, in ADCC, affinity and engagement to the target, half-life, volume of distribution (Vd) and
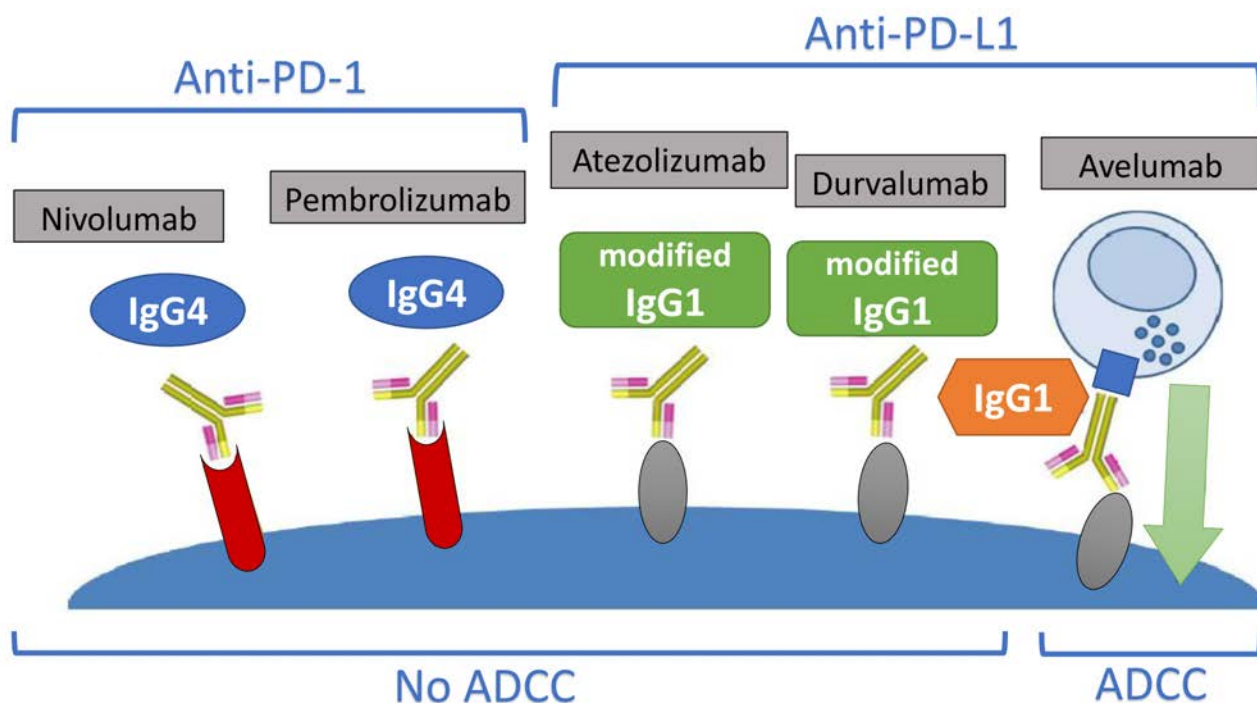
Figure 3. Anti-PD-1/PD-L1 isotypes. IgG1-moAbs containing an Fc region, which can bind cognate receptors on immune effector cells, could induce tumor cell lysis mediated by ADCC as compared to those with IgG4 or a mutated Fc region. aNSCLC, advanced non-small-cell lung cancer; ADCC, antibody-dependent cell-mediated cytotoxicity (ADCC); Atezo, atezolizumab; CM, checkmate; G, grade; KN, keynote; Ig, immunoglobulin; ImP, ImPower; moAbs, monoclonal antibodies; Nivo, nivolumab; ORR, overall response rate; OS, overall survival; PD1, programmed cell death 1; PD-L1, programmed cell death ligand 1; Pembro, pembrolizumab; PFS, progression-free survival; Sq, squamous.

clearance may exist between different anti-PD1 and anti-PD-L1 agents and even within the same group (Table 2).[52]

Possible inter- and intra-class differences between anti-PD1 and anti-PD-L1 in the half-maximal effective concentrations (EC50) to block the PD-1 signaling have also been demonstrated, *in vitro*.[53]

Furthermore, moAbs containing an Fc region which can bind cognate receptors on immune effector cells could induce tumour cell lysis mediated by ADCC as compared to those with IgG4 or a mutated Fc region, thus resulting in different efficacy and toxicity profiles (Figure 3).[54]

Anti-PD1 agents

Anti-PD-1 drugs are monoclonal antibodies (moAbs). Indeed, AMP-224 is a fusion protein, whilst nivolumab, pembrolizumab and pidilizumab belong to the Ig class, either of fully human (nivolumab, subclass IgG4) or humanized antibodies (pembrolizumab and pidilizumab, subclasses IgG4 and IgG1, respectively). Moreover, nivolumab and pembrolizumab do not boost ADCC and do not fix complement, mechanisms of action which both pidilizumab and AMP-224 are accountable for.

Affinity and engagement to their target vary as well. As to affinity, nivolumab has a low/intermediate affinity which is three times lower than pembrolizumab. Pidilizumab has a low affinity, while AMP-224 affinity is yet unknown.

Considering the engagement, a lower dose of pembrolizumab is required than of nivolumab (10 µg/mL [60%] *versus* 50 µg/mL [75%], respectively). Engagement in pidilizumab and AMP-224 is not known.

Half-lives, Vd and clearance are fairly comparable between nivolumab and pembrolizumab, with slight variations (half-life: 26.7 days *vs*. 26 days, Vd 8 L *vs*. 7.5 L and clearance 9.4 ml/h *vs*. 9.4 ml/h, respectively), while are not available for pidilizumab and AMP-224.[52]

Based on these properties, pembrolizumab seems to have the best affinity and engagement among the current anti-PD1 agents.

Anti-PD-L1 agents

Similar considerations can be done for anti-PD-L1 agents. They all belong to the Ig class. The only humanized one is atezolizumab (subclass IgG1 modified), while durvalumab, avelumab and BMS-936559 are all fully human (subclasses IgG1 modified,

IgG1 and IgG4, respectively). Avelumab only has a role in ADCC immune processes.

As long as affinity and engagement are concerned, the former is low/intermediate, intermediate and high for atezolizumab, durvalumab and avelumab, respectively. Engagement is ≥70% after 1 cycle, ≥70% after 1 cycle and up to a 95% for atezolizumab, durvalumab and avelumab, respectively. Engagement, half-life, Vd and clearance are unknown for BMS-936559.

Atezolizumab, durvalumab and avelumab has a half-life of 27 days *vs*. 12 days *vs*. 6.1 days, Vd of 6.9 L *vs*. 5.6 L *vs*. 4.72 L and clearance of 9.4 mL/h *vs*. 8.24 mL/h *vs*. 24.6 mL/h, respectively. Remarkably, atezolizumab half-life emerges among these, being further longer than the others.[52]

Thus, avelumab seems to have the best affinity and engagement among the current anti-PD-L1 agents and atezolizumab the longest half-life.

Resistance mechanisms

Primary and acquired resistance mechanisms to ICIs are key clinical barriers for further improvement in outcomes and each drug may cause different resistances and may involve the following immune response phases: antigen presentation and T-cell activation, T-cell trafficking and tumor infiltration and T-cell killing activity within the tumor microenvironment (TME).[55] Noteworthy, regarding the latter, the upregulation of PD-L1 is one of the possible mechanisms of primary and secondary tumors resistances.[55] Particularly, PD-L1 is upregulated in squamous cell carcinoma following the depletion of phosphatase and tensin homolog (PTEN) and serine-threonine kinase11 (Stk11). Under these circumstances, anti-PD-L1 agents could be less effective than anti-PD1, although a retrospective cohort comparison data suggested lack of benefit from the addition of the anti-PD1 pembrolizumab to first-line chemotherapy in patients' with tumors bearing Stk11 alterations.[56]

Conclusions

Based on this narrative review of available data on the use of anti-PD1 and anti-PD-L1 agents for NSCLC, we suggest possible differences may exist between these two groups of drugs in terms of efficacy and safety profiles. Particularly, anti-PD1 agents showed a higher response rate and better OS in the first-line treatment (in combination with chemotherapy) of squamous and PD-L1

Table 2. Biological differences among anti-PD1 and anti-PD-L1.

Parameter	Anti-PD-1				Anti-PD-L1			
	Nivolumab	Pembrolizumab	Pidilizumab	AMP-224	Atezolizumab	Durvalumab	Avelumab	BMS-936559
Humanized	-	✓	✓	-	✓	-	-	-
Fully human	✓	-	-	-	-	✓	✓	✓
Ig subclass	IgG4	IgG4	IgG1	Fusion protein	IgG1 mod.	IgG1 mod.	IgG1	IgG4
ADCC/CDC	--	--	✓	✓	-	-	✓	-
PD-1 affinity	+/++	+++	+	?	+/++	++	+++	++
PD-1 engagement	50 µg/mL (75%)	10 µg/mL (60%)	NA	NA	≥70%	≥70% after 1 cycle of 10 or 20 mg/kg Q2W	1 µg/mL after 1 cycle	NA (95%)
Half-life	26.7 days	26 days	-	-	27 days	12 days	6.1 days	-
Vd	8 L	7.5 L	-	-	6.9 L	5.6 L	4.72 L	-
Clearance	9.4 ml/h	9.2 mL/h	-	-	9.4 ml/h	8.24 ml/h	24.6 ml/h	-

ADCC/CDC, antibody dependent cell-mediated cytotoxicity/complement dependent cytotoxicity; Ig, immunoglobulin; mod., modified; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; Vd, volume of distribution.

low aNSCLC patients than anti-PD-L1 agents. Anti-PD-L1, as compared to anti-PD1 agents, could be responsible for less severe AEs and, particularly, irAEs. These differences could be explained by their different specific properties, mechanisms of actions and by tumor resistance mechanisms.

Considering possible differences between anti-PD1 and anti-PD-L1 agents could be clinically relevant for treatment tailoring based on patient's and tumor characteristics and could also inspire future investigations on therapeutic strategies based on their combination or switching aiming at overcoming primary and acquired immune-related resistance.

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