



Mini-review

PD-1/PD-L1 checkpoint blockades in non-small cell lung cancer: New development and challenges



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ABSTRACT

PD-1/PD-L1 checkpoint blockades have dramatically changed the landscape for second-line treatment of non-small cell lung cancer (NSCLC). Based on the promising results of Keynote-024 presented so far, pembrolizumab has been approved as first-line treatment for advanced PD-L1 positive NSCLC patients. However, overall response rate (ORR) is limited to PD-1/PD-L1 checkpoint blockades when used as single agent. Combining with chemotherapy, anti-CTLA-4 antibodies, targeted therapy, radiotherapy or other treatment options is perceived as an appealing method aimed at achieving higher efficacy. There are many clinical trials on going or finished assessing the efficacy and safety of the PD-1/PD-L1 blockades alone or combining with other approaches in first-line or second-line treatments. A lot of challenges need to be overcome before PD-1/PD-L1 checkpoint blockades are widely used in the patients with NSCLC including the identification of optimal combination, treatment-related adverse effects, the high cost and lack of effective predictive markers. In this review, we focus on outlining current clinical trials and challenges for future research of PD-1/PD-L1 pathway checkpoint blockades in NSCLC.

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Introduction

Immune-checkpoint blockades targeting programmed death-1 (PD-1) or programmed death ligand-1 (PD-L1) showed durable response rate and long-term survival in advanced non-small-cell lung cancer (NSCLC) [1–4]. Based on the prominent results, PD-1/PD-L1 checkpoint blockades become powerful new treatment

options. There are many clinical trials on going or finished assessing the efficacy and safety of the PD-1/PD-L1 blockades alone or combining with other approaches in first-line or second-line treatment. This review is focused on outlining current clinical trials and challenges for future research of PD-1/PD-L1 checkpoint blockades in NSCLC.

PD-1/PD-L1 blockades

PD-1 is a negative stimulatory receptor on the surface of activated T cells [5]. The binding of PD-1 to one of its ligands, PD-L1 or PD-L2 on tumor cells or tumor infiltrating immune cells, can inhibit a cytotoxic T-cell response and help tumor cells avoid T cell cytotoxicity and facilitate cancer formation [6,7]. Inhibiting the interaction of PD-1 and its ligands can significantly enhance T cell function, resulting in anti-tumor activity [8–10]. Anti-PD-1 antibodies, such as nivolumab and pembrolizumab, bind to PD-1 receptors with high-affinity and block PD-1/PD-L1 pathway to restore T-cell functions [9,11]. Anti-PD-L1 antibodies, such as atezolizumab (MPDL3280A), durvalumab (MEDI4736) and avelumab, bind to PD-L1 to block PD-1/PD-L1 pathway but do not bind to PD-L2, which

Abbreviations: PD-1, programmed death-1; PD-L1, programmed death ligand-1; NSCLC, Non-small cell lung cancer; ORR, overall response rate; DOR, duration of response; OS, overall survival; PFS, progression free survival; AE, adverse events; TC, tumor cells; IC, immune cells; FDA, Food and Drug Administration; Pembro, pembrolizumab; Nivo, nivolumab; Doce, docetaxel; Atezo, atezolizumab; Durva, durvalumab; BEV, Bevacizumab; SoC, standard of care; IC PT-DC, investigator's choice of platinum-based chemotherapy; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; CTLA-4, cytotoxic T-lymphocyte antigen 4; TKI, tyrosine kinase inhibitors; ILD, interstitial lung disease; CT, chemotherapy; RT, radiotherapy; PI3K- γ , gamma isoform of phosphoinositide 3-kinase.

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may help to avoid potential immune-related toxicity on immune homeostasis due to PD-L2 blockade [12]. PD-1/PD-L1 blockades achieved great success over chemotherapy in many kinds of tumors and were approved by U. S. Food and Drug Administration (FDA) for previously treated melanoma [13,14], Hodgkin lymphoma [15], urothelial carcinoma [16], metastatic head and neck squamous cell carcinoma [17]. PD-1/PD-L1 checkpoint blockades are investigated in current clinical trials in the first-line or second-line setting in NSCLC (Fig. 1).

PD-1/PD-L1 blockades in the second line

Clinical outcomes remain poor for patients with previously treated, advanced NSCLC [18]. PD-1/PD-L1 blockades were explored as an approach to improve the survival of those patients (Table 1). International, open-label, randomized trials showed superior survival and an improved safety profile versus standard docetaxel in patients with advanced, previously treated NSCLC [1–4].

In CheckMate 017 trial, the overall response rate (ORR) was 20% with nivolumab versus 9% with docetaxel ($p = 0.008$) in 272 patients with advanced, previously treated squamous NSCLC [1]. The median overall survival (OS) was 9.2 months with nivolumab versus 6.0 months with docetaxel. The median progression-free survival (PFS) was 3.5 months in the nivolumab group compared with 2.8 months in docetaxel group ($p < 0.001$). Treatment-related grade 3/4 adverse events (AEs) were 7% with nivolumab and 55% with docetaxel [1]. In CheckMate 057, OS, ORR, and safety profile were significantly better with nivolumab than with docetaxel in treating patients with advanced, previously treated non-squamous NSCLC [2]. On the contrary to the results of CheckMate 017, PFS did not favor nivolumab over docetaxel [2].

The efficacy and safety of pembrolizumab versus docetaxel were assessed in previously treated, PD-L1-positive, advanced NSCLC. Among patients with at least 50% of tumor cells expressing PD-L1, median OS was 14.9 months with 2 mg/kg pembrolizumab, 17.3 months with 10 mg/kg pembrolizumab, and 8.2 months with docetaxel ($p < 0.01$). Median PFS was 5.0 months for 2 mg/kg pembrolizumab, 5.2 months for 10 mg/kg pembrolizumab and 4.1 months for docetaxel ($p < 0.01$), respectively. Grade 3–5 AEs were less common in the patients of pembrolizumab group than docetaxel group [3].

Atezolizumab provided better OS benefit over docetaxel associated with PD-L1 expression in phase II POPLAR trial [4]. Phase III OAK study (including 1225 patients) offered more precise assessment of treatment effects in subgroups [19]. There was no

difference of ORR between two groups for overall population while the ORR was improved with atezolizumab (31%) versus docetaxel (11%) in TC3 (PD-L1 $\geq 50\%$ on tumor cells) or IC3 (PD-L1 $\geq 10\%$ tumor infiltrating immune cells) subgroups. Atezolizumab showed notably longer median DOR over docetaxel (16.3 months vs 6.2 months). The OS was improved with atezolizumab group (13.8 months) compared with docetaxel (9.6 months) regardless of PD-L1 expression.

Besides the above reported phase III trials, there is an ongoing phase III trial comparing the efficacy and safety of durvalumab versus the standard of care (erlotinib, gemcitabine, or vinorelbine) in previously treated advanced NSCLC patients with PD-L1 positive tumors ($\geq 25\%$ of tumor cells with membrane staining) [20]. Recruitment started in January 2015 and randomization targets of 250 patients will be enrolled from approximately 250 sites.

For prominent efficacy and safety profile, nivolumab [21] and atezolizumab were approved by FDA as second line therapy for NSCLC; pembrolizumab was approved for treating previously treated PD-L1 positive ($\geq 50\%$) advanced NSCLC patients [22]. PD-1/PD-L1 checkpoint blockades have dramatically changed the therapeutic landscape of NSCLC in second-line treatments. However, in these second-line studies, the control arms received single-agent docetaxel, which set a low bar to clear [23]. By contrast, in the first-line setting where chemotherapy has a greater survival advantage than in the second-line setting [18,24], it may be difficult for PD-1/PD-L1 checkpoint blockades to get more robust activity over standard platinum-based doublet chemotherapy.

PD-1/PD-L1 blockades in the first line

Platinum-based chemotherapy has been the standard first-line treatment for metastatic NSCLC without targetable mutations. However, the responses are rarely durable with moderate to severe toxicities [24]. A profound need exists for new treatment strategy to improve outcome with low toxicity. Nivolumab showed significant improvement of PFS and OS over dacarbazine and was approved by FDA in 2015 as a single agent for the first-line treatment of patients with BRAF^{V600} wild-type, unresectable or metastatic melanoma [25]. Due to the high efficacy of nivolumab as first-line treatment in melanoma and high efficacy of PD-1/PD-L1 inhibitors as single agent in second-line treatment of NSCLC, several trials were carried to investigate the efficacy of single PD-1/PD-L1 checkpoint blockade as first-line therapy for advanced NSCLC (Table 2).

Atezolizumab achieved an ORR of 19% for overall population and 27% for PD-L1 high expressing tumors with only 11% grade 3/4 AEs. Six-month PFS was 40% and six-month OS was 82% [26]. Durvalumab monotherapy showed 27% of ORR and a manageable safety profile (10% of grade ≥ 3 AEs) with early evidence [27]. In Checkmate 012 trial, the confirmed ORR of nivolumab was 23%, 28% and 14% for overall population, patients with tumor PD-L1 expression ($\geq 1\%$) and patients with no PD-L1 expression, respectively [28]. In Keynote-001 trial, the ORR for pembrolizumab was as high as 51.9% and the median PFS was 12.5 months for treatment-naïve stage IV NSCLC patients with PD-L1 expression on at least 50% cells in the tumor nest [29]. However the above trials were small-sized non-randomized studies lack of direct comparison with standard chemotherapy.

Phase III CheckMate 026 trial demonstrated that median PFS was 4.2 months with nivolumab and 5.9 months with platinum-based chemotherapy respectively in 423 stage IV/recurrent NSCLC patients with $\geq 5\%$ PD-L1 expression. OS was 14.4 months for nivolumab versus 13.2 months for chemotherapy [30]. There is no superiority of nivolumab compared with platinum-based chemotherapy in first-line setting.

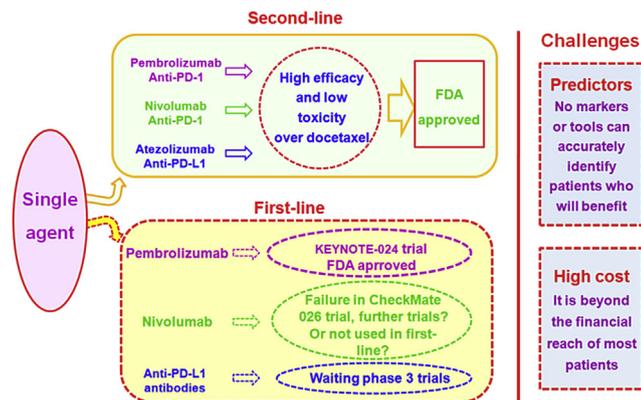


Fig. 1. PD-1/PD-L1 checkpoint blockade as a single agent in the first-line and second-line setting in NSCLC. Nivolumab and atezolizumab were approved by FDA as second line therapy for NSCLC; Pembrolizumab was approved for treating previously treated and treat-naïve PD-L1 positive NSCLC patients. However, PD-1/PD-L1 checkpoint blockades still face challenges before being widely used in the patients with NSCLC.

Table 1
Phase III clinical trials of PD-1/PD-L1 checkpoint blockade in previously treated NSCLC.

Trials	No	Arms	ORR	DOR	Median PFS	Median OS	AEs Grade3-5	PD-L1 efficacy and testing method	Ref.
Checkmate 017	272 (Sq)	Nivo 3 mg/kg, q2w	20%	NR	3.5mons	9.2mons	7%	No association; clone 28–8, Dako system	[1]
		Doce 75 mg/m ² q3w	9%	8.4mons	2.8mons	6.0mons	55%	Positive when ≥1%, ≥5%, or ≥10% TCs	
Checkmate 057	582 (Non-Sq)	Nivo 3 mg/kg q2w	19%	17.2mons	2.3mons	12.2mons	10%	Associated; clone 28–8, Dako system	[2]
		Doce 75 mg/m ² q3w	12%	5.6mons	4.2mons	9.4mons	54%	Positive when ≥1%, ≥5%, or ≥10% TCs	
Keynote 010	1034 (PD-L1 Positive)	Pem 2 mg/kg q3w	30%	NR	5.0mons	14.9mons	13%	Associated (PD-L1 ≥50%); 22C3, Dako system	[3]
		Pem 10 mg/kg q3w	29%	NR	5.2mons	17.3mons	16%	≥1% TCs enrolled, sub-population ≥50%	
		Doce 75 mg/m ² q3w	8%	8.0mons	4.1mons	8.2mons	35%		
OAK	1225	Atezo: 1200 mg q3w	14%	16.3mons	2.8mons	13.8mons	15%	Associated; SP142, Ventana Medical Systems	[19]
		Doce 75 mg/m ² q3w	13%	6.2mons	4.0mons	9.6mons	43%	TC 1/2/3, TC2/3, TC3: ≥1%, ≥5%, ≥50% TCs IC 1/2/3, TC2/3, TC3: ≥1%, ≥5%, ≥10% ICs	
ARCTIC	250 (sub-study A)	Durva: 10 mg/kg q2w One of three SoC	Ongoing	Coprimary endpoints: OS, PFS Secondary endpoints: ORR, Safety			Ongoing, SP263 Ventana Medical Systems ≥25% TCs	[21]	

Niv: nivolumab; Doce: docetaxel; Pem pembrolizumab; Atezo: atezolizumab; Durva: durvalumab; TC: tumor cells; IC: tumor infiltrating immune cells. SoC: standard of care including erlotinib, gemcitabine, or vinorelbine.

Table 2
Clinical trials of PD-1/PD-L1 checkpoint blockade alone in the first-line setting.

Trials	Stage/No.	Arms	PD-L1	ORR	Median PFS	Median OS	AEs Grade3-5	Ref.
BIRCH	II/142	Atezo 1200 mg q3w	SP142 ^a TC1/2/3, IC1/2/3	19% 27% for TC3/IC3	6-mon rate 40%	6-mon rate 82%	11%	[26]
NCT01693562	I/III/59	Durva 10 mg/kg q2w	SP263 ≥25% TCs	Overall: 27% PD-L1+: 28.6% PD-L1-: 11%	4.0 mons	21.0 mons	10%	[27]
CheckMate012	I/52	Nivo 3 mg/kg q2w	clone 28–8, ≥1%, 5% TCs	Overall: 23% PD-L1 ≥1%: 28% PD-L1 ≥5%: 31%	3.6mons	19.4mons	19%	[28]
Keynote-001	I/101	Pem 2 mg/kg q3w Pem 10 mg/kg q3w	22C3, ≥1% of all cells	Overall: 26.7% PD-L1 ≥50%: 51.9%	Overall: 6.2mons PD-L1 ≥50%: 12.5mons	Overall: 22.1mons PD-L1 ≥50%: not reached	11.9%	[29]
CheckMate 026	III/541	Nivo 3 mg/kg q2w IC PT-DC	clone 28–8, ≥1% TCs	26.1% 33.5%	4.2 mons 5.9 mons	14.4 mons 13.2 mons	18% 51%	[30]
Keynote-024	III/305	Pem 200 mg q3w IC PT-DC	22C3 ≥50% TCs	44.8% 27.8%	10.3 mons 6.0 mons	6-mons rate: 80.2% 72.4%	26.6% 53.3%	[31]
Keynote-042	III/1240	Pem 200 mg q3w IC PT-DC	22C3 ≥1% TCs	Ongoing Primary endpoint: OS in patients with PD-L1 ≥50% and ≥1% Secondary endpoint: OS, safety and tolerability				[33]
MYSTIC	III/675	Durva + tremeli Durva PT-DC	Not reported	Ongoing Primary endpoint: PFS Secondary endpoint: OS, ORR, DOR, safety and tolerability and so on				[34]

^a TC 1/2/3, TC2/3, TC3 were ≥1%, ≥5%, ≥50% TCs; IC 1/2/3, TC2/3, TC3 were ≥1%, ≥5%, ≥10% ICs.

Compared to nivolumab, pembrolizumab achieved greater success over platinum-based chemotherapy in patients with PD-L1 expression on at least 50% tumor cells ($n = 305$, Keynote-024 trial) [31]. The ORR was 44.8% with pembrolizumab and 27.8% with chemotherapy. Median PFS was 10.3 months in the pembrolizumab group versus 6.0 months in the chemotherapy group ($p < 0.001$). The estimated rate of OS at 6 months was 80.2% and 72.4% in the pembrolizumab group and chemotherapy group ($p = 0.005$) [31].

For both trials, patients with epidermal growth factor receptor (EGFR) activating mutations and anaplastic lymphoma kinase (ALK) translocations were excluded and crossover from the chemotherapy group to the pembrolizumab/nivolumab group was permitted in the event of disease progression. So what is the major reason for positive pembrolizumab results and negative nivolumab results? Patients enrolled in the CheckMate 026 study and Keynote-024 trial had PD-L1 expression on ≥5% [30] and ≥50% of tumor cells respectively [31]. CheckMate 026 trial may underscore the percentage of PD-L1 positivity because the ORR of nivolumab was as high as 50% in first-line use with PD-L1 expression ≥50% of tumor cells [32]. On the other hand, nivolumab showed a significant better PFS over docetaxel in squamous but not in the non-squamous NSCLC in the second-line setting [1,2]. In CheckMate 026, only 24% of enrolled patients were squamous NSCLC. Greater patient

selection may be needed for nivolumab to improve PFS and OS over chemotherapy or just be used in second line.

It should be noting that it remains unclear if pembrolizumab shows higher efficacy over chemotherapy in first-line treatment for advanced patients with 1%–49% PD-L1 expression. In Keynote-042 trial, a phase 3, open-label trial comparing the efficacy of pembrolizumab and platinum-based chemotherapy, the patients were eligible if they have PD-L1 expression in 1% of tumor cells [33]. The results will offer us the information if pembrolizumab could achieve longer survival over chemotherapy in wide range treatment-naïve NSCLC patients. MYSTIC (NCT02453282), a global phase 3 study, is ongoing. 675 treatment-naïve patients will be randomized (1:1:1) to receive durvalumab monotherapy; durvalumab + tremelimumab; or standard of care [34]. The results will confirm if durvalumab monotherapy can be used as first-line treatment for NSCLC patients.

Strategies to improve the efficacy

Up to date, the ORRs were limited to PD-1/PD-L1 checkpoint antibodies when used as single agent. Combining with other treatment was perceived as an appealing method aimed at achieving higher efficacy. Such a strategy would involve initiating

the immune response enhanced by checkpoint blockades, including cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors, chemotherapy, targeted therapy, radiotherapy or other treatment options (Table 3). The combinations demonstrated antitumor activity, but there are several limitations in the current trials (Fig. 2).

Combination with chemotherapy

Increasing evidence indicates that chemotherapy has immunological effects, such as reducing T-regulatory cell activity, selectively depleting immunosuppressive myeloid-derived suppressor cells and enhancing cross-presentation of tumor antigens [35–37]. Combining PD-1/PD-L1 checkpoint blockades with standard chemotherapy may have synergistic antitumor activity in NSCLC.

When pembrolizumab was added to three carboplatin based chemotherapy regimens, the ORR ranged from 52% to 71% [38]. The phase II randomized trial showed that ORR was 55% with pembrolizumab plus chemotherapy (carboplatin and pemetrexed), compared with 29% with chemotherapy alone as first-line therapy for advanced non-squamous NSCLC [39]. Nivolumab combined with chemotherapy showed 33%–47% of ORR in first-line advanced NSCLC in CheckMate 012 trial [40]. Atezolizumab (MPDL3280A) combined with platinum-based doublet chemotherapy showed promising activity (ORRs: 60%–75%) with no unexpected toxicities as first-line therapy for locally advanced or metastatic NSCLC [41].

Combining PD-1/PD-L1 blockades with chemotherapy appeared to be high responsive. It is notable that the sample sizes are small, most lack of comparison with chemotherapy, lack of data about PFS and OS improvement. Furthermore, treatment discontinuation related to AEs was greater (21%) with nivolumab and chemotherapy [40]. Despite those limitations, the results are really encouraging to be an effective treatment option to improve the outcomes of advanced NSCLC. We believe that further randomized, double-blind, large cohort, phase III studies would offer confirmed convinced data of the efficacy and safety of PD-1/PD-L1 checkpoint blockade plus platinum-doublet chemotherapy as first-line therapy for advanced NSCLC.

Combination with CTLA-4 checkpoint blockades

PD-1/PD-L1 and CTLA-4 checkpoints blockades enhance anti-tumor T-cell activity in different complementary mechanisms. Combining anti-PD-1/PD-L1 antibody with the anti-CTLA-4 antibody might have the potential to improve antitumor responses.

A multicenter phase Ib study assessed the combination of durvalumab and tremelimumab (anti-CTLA-4) in immunotherapy-naïve advanced NSCLC [42]. The ORR was only 23% in the combined tremelimumab 1 mg/kg cohort [42]. Combination pembrolizumab and ipilimumab yielded 25% of ORR and 13.8 months of DOR in second-line therapy for 45 NSCLC patients [43]. The ORRs were 38% and 47% for 3 mg/kg nivolumab q2w combination with ipilimumab (q6w and q12w, respectively) in first-line therapy for advanced NSCLC [44]. ORR was as high as 92% for patients with $\geq 50\%$ PD-L1 expression, 57% for patients with $\geq 1\%$ PD-L1 expression and 15% for patients without PD-L1 expression.

Owing to the limited follow-up period, the results should be carefully considered. The combination of durvalumab plus tremelimumab and pembrolizumab plus ipilimumab showed no better ORR but increased grade 3/4 AEs and discontinuation compared with single checkpoint inhibitors (Table 3). It is urgently need to develop a way that increases the efficacy and minimizes AEs about such combinations. The data from CheckMate 012 demonstrated encouraging response to nivolumab and ipilimumab, especially for high PD-L1 expression patients in first-line therapy. But the sample size was small and was not powered to compare safety and efficacy

with platinum-doublet chemotherapy. The results from phase III CheckMate 227 trial will offer the information whether nivolumab and ipilimumab can be a first-line treatment option for advanced NSCLC.

Combination with EGFR inhibitors

Randomized phase III trials have established the superiority of EGFR tyrosine kinase inhibitors (TKI) over chemotherapy as first-line therapy for EGFR mutation-positive NSCLC [45–48]. However nearly all patients will eventually experience disease progression resulting from acquired resistance [49]. It was reported that EGFR mutation/ALK rearrangement up-regulated PD-L1 expression [50]. Therefore EGFR-TKIs might indirectly enhance antitumor immunity through the down-regulation of PD-L1 [51,52]. Adding PD-1/PD-L1 checkpoint blockades to EGFR-TKIs may make treatment more effective in NSCLC.

The combination of nivolumab with erlotinib was evaluated in 21 patients with advanced, chemotherapy naïve, EGFR-mutated NSCLC [53]. The results showed an ORR of 19% (4/21) and 15% for 20 patients with acquired resistance to erlotinib. 24-week PFS rate was 51% and 1-year OS rate was 73%. Combination of durvalumab and gefitinib demonstrated 78.9% of ORR in EGFR-TKI treatment naïve NSCLC with EGFR mutation [54]. Among patients treated with osimertinib (AZD9291) and durvalumab, ORR was 57% in EGFR-TKI pretreated patients and 80% in EGFR-TKI treatment-naïve patients [55].

It is valuable that the combination showed anti-tumor activity in EGFR-TKI pretreated and treat-naïve patients. However, checkpoint blockades immunotherapy combining with TKIs face big challenge. EGFR-TKI is a strong standard therapy with high efficacy and low toxicity. ORRs of combinations were not obviously better than TKIs alone. The response may be durable and lead to survival benefit. All aforementioned reports are interim results. Long follow-up data may offer further information in survival improvement.

Combination with radiotherapy

Radiotherapy (RT) is a common and important nonsurgical treatment for NSCLC patients [56]. Besides the directly killing tumor cells by DNA damage, radiation can also trigger an immune responses and render the tumor microenvironment conducive to effective T-cell recruitment and function [57]. It is rare for radiotherapy to generate strong enough systemic anti-tumor immunity. Checkpoint blockades can enhance the response initiated by RT to systemic antitumor response, called abscopal effects [58,59]. Up to date, there is limited data investigating synergistic or abscopal effects about combining RT and anti-PD-1/PD-L1 antibodies in NSCLC.

RT to oligoprogressive sites during immune therapy is safe and offers excellent local control in NSCLC [60]. The 6- and 12-month actuarial local control rates of the radiated sites with RT were 91.7% and 85.2%. No abscopal effect was observed. Safety and tolerability of palliative RT to 29 unique osseous sites or 10 intrathoracic sites combining with immune checkpoint blockades was assessed in prospective trial using checkpoint blockades [61]. Symptomatic improvement either partial or full was noted in 20 lesions (77%).

Besides above studies, there are other ongoing trials to investigate the efficacy and safety of RT combined with checkpoint blockades in NSCLC. However, there are several considerations to be adequately addressed before they can be exported to routine clinical practice [62]. Firstly, the combination aims to improve clinical outcomes for patients with early stage NSCLC or to aim to improve the symptom for patients with metastatic disease. Second,

Table 3
Combining PD1/PD-L1 with other treatments.

Trails	Phase/No.	Arms	Condition	Efficacy	AEs	Ref.
Keynote 021 (A-C)	I/II/74	A Pembro, carboplatin, and paclitaxel; B Pembro, carboplatin, and paclitaxel + BEV C Pembro, carboplatin + pemetrexed	Chemonaive, advanced, EGFR/ALK (-) NSCLC	ORR: A 52% B 48% C 71% PFS: A 10.3mons B not reached C 10.2mons	G3/4/5 A 36%, B 46%, C 42%	[38]
Keynote 021	II/123	Pembro, carboplatin and pemetrexed Or carboplatin and pemetrexed	Chemonaive, stage IIIB/IV, non-sq- NSCLC	ORR: Combined 55% CT alone 29% PFS: Combined 13.0mons CT alone 8.9 mons	G3/4/5 Combined 23% CT alone 16%	[39]
CheckMate012	I/56	A Nivo, gemcitabine, cisplatin, B Nivo, pemetrexed, cisplatin, C Nivo, paclitaxel, carboplatin D Nivo, paclitaxel, carboplatin	Chemonaive, stage IIIB/IV	ORR: A 33%, B 47%, C 47%, D 43% 24-week PFS rates A 51%, B 71%, C 38%, D 51% 2-year OS rates A 25%, B 33%, C 27%, D 62%	G3/4/5: 45%; Discontinuation: 21%	[40]
NCT01633970	Ib/37	C Atezolizumab + carboplatin + paclitaxel D Atezolizumab + carboplatin + pemetrexed E carboplatin + nab-paclitaxel	Chemonaive locally advanced or metastatic NSCLC	ORR: C 60% D 75% E 62%	G 3/4: anemia (D & E, 7%), neutropenia (C, 13%; D, 7%) and thrombocytopenia (D & E, 7%); G5 candidemia	[41]
NCT02000947	Ib/102	Durvalumab and tremelimumab (anti-CTLA-4)	Immunotherapy-naive locally advanced or metastatic NSCLC.	ORR: 23% in the combined tremelimumab 1 mg/kg cohort ORR 24%; DOR:13.8 months Median PFS: 6 mons; Median OS: 17 mons	G 3/4: diarrhoea 11%, increased lipase 8%; colitis 9%, Discontinuation 28% G3/4/5: 24%; Discontinuation 9%	[42]
Keynote 021 (D,H)	I/II/45	Pembro + ipilimumab	Second-line advanced NSCLC with ≥1 prior regimen	ORR:38%–47% 57% (PD-L1 ≥1%); 92% (PD-L1 (≥50%); ORR 19% 24 wks PFS 51% 1-y-OS rate 73% ORR 78.9%	G3/4: 33%–37% Discontinuation 11%–13%;	[44]
CheckMate 012	I/78	Nivo + ipilimumab (q12w); Nivo + ipilimumab (q6w);	First-line: untreated advanced NSCLC	ORR 19% 24 wks PFS 51% 1-y-OS rate 73% ORR 78.9%	G3/4/5 24%	[53]
NCT01454102	I/21	Nivo + erlotinib	EGFR-mutated 20 pts progressed after TKI	ORR 19% 24 wks PFS 51% 1-y-OS rate 73% ORR 78.9%	G3/4/5 24%	[53]
NCT02088112	I/20	Durvalumab + gefitinib	EGFR-mutated EGFR-TKI naive	ORR 78.9%	Discontinuation: 20% for G3/4 AEs	[54]
TATTON	I B/31	Osimertinib + durvalumab	EGFR-mutated EGFR-TKI pretreated (A) or naive (B)	ORR A 57% B 80%	ILD 38% G3/4 ILD A 8% B 27% G3/4/5 10%	[55]
Not reported	I/21	RT + immune checkpoint blockades	Progressed during immunotherapy	6-month local control 91.7% Median PFS: 3.6 mons	G3/4/5 10%	[60]
Not reported	I/29	RT + immune checkpoint blockades	Metastatic NSCLC	Median OS: 8.7 mons Symptomatic improvement 77%. PFS: Nivo + BEV: 37.1 wks Nivo Squamous 16wks, Nivo non-squamous 21.4wks	G5 lung toxicity 1 pts.	[61]
NCT01454102	I/33	Nivo + BEV or Nivo alone	After first-line PT-based,	PFS: Nivo + BEV: 37.1 wks Nivo Squamous 16wks, Nivo non-squamous 21.4wks	G3/4/5 Nivo + BEV 25% Nivo 14%	[65]

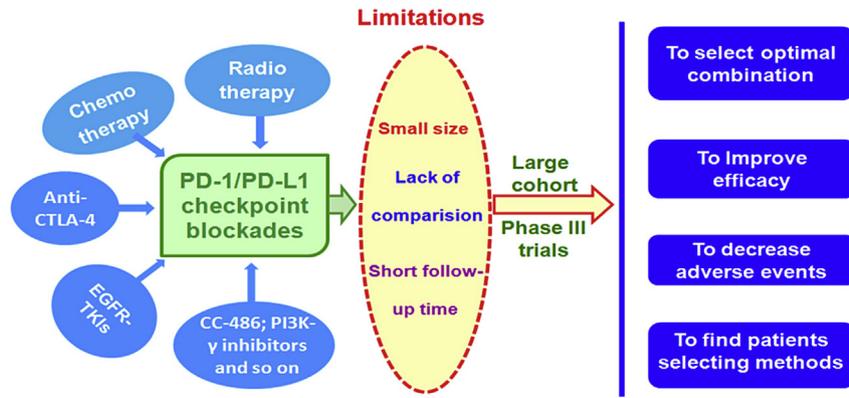


Fig. 2. PD-1/PD-L1 checkpoint blockades in combination with other treatment approaches in NSCLC. There are a lot of limitations in the current trials and a lot of challenges to overcome.

stereotactic ablative radiotherapy may be the radiotherapy modality most optimally combined with PD-1/PD-L1 blockade since it can achieve a more robust immune response than conventionally fractionated radiotherapy [63,64]. A final point, additive toxicities could potentially occur, which also requires consideration. One patient experienced possible treatment related grade 5 pulmonary toxicity when 10 patients received in intra-thoracic palliative RT during immunotherapy [61]. Most patients with NSCLC may receive intra-thoracic RT, so the pulmonary toxicity should be an important consideration for future clinical trials.

Combination with other treatments

Many mechanisms are found to be involved in the resistance to PD-1/PD-L1 blockades. So checkpoint blockades combined with other agents or treatment besides anti-CTLA antibodies, chemotherapy, EGFR inhibitors and radiotherapy are studied to overcome the resistance or enhance the efficacy.

Preliminary data demonstrated the prolonged PFS of nivolumab combined with bevacizumab over nivolumab alone with an acceptable side effect profile in maintenance of advanced NSCLC patients who did not progress after receiving first-line platinum-based chemotherapy [65]. A phase II multicenter, randomized study will assess the safety and efficacy of CC-486 (oral formulation of azacitidine) plus pembrolizumab vs pembrolizumab plus placebo in previously treated patients with locally advanced/metastatic NSCLC [66]. Inhibition of gamma isoform of phosphoinositide 3-kinase (PI3K- γ , highly expressed in immune-suppressive myeloid cells) by IPI-549 (PI3K- γ inhibitor) restored sensitivity to checkpoint blockades and inhibited tumor growth in mouse models [67]. Animal models demonstrated that significant tumor regression was observed when the vaccine combined with concurrently administered anti-PD-1 antibody [68,69].

Besides the above combinations, there are also other preliminary data that tried to enhance the efficacy or overcome the resistance of PD-1/PD-L1 blockades from different mechanism. Such combination may be a powerful approach for NSCLC treatment in future. But we need to consider the combinations carefully nowadays. First, the promising effects were reported from pre-clinical animal models. Whether the combinations work well in human-beings need to be confirmed. Second, PI3K- γ inhibitor, vaccine, azacitidine, entinostat and so on are not common treatment options in NSCLC. The efficacy and safety of such agents are not well-studied. Third, the clinical trials are just initiated in NSCLC. It takes long time to carry on phase III trial until safety and efficacy

are assessed in phase I/II trials. It is still a long way for such combination becoming into clinical use.

Challenges for future directions

PD-1/PD-L1 checkpoint blockade is rapidly becoming an effective therapeutic option for second line setting in NSCLC. Pembrolizumab showed promising results over standard chemotherapy in the first-line setting. However, there are a lot of challenges to be overcome before PD-1/PD-L1 checkpoint blockades are widely used in the patients with NSCLC.

Can immunotherapy replace first-line treatment for unresectable NSCLC?

In Keynote-024 trial, pembrolizumab showed better ORR, longer PFS and OS over platinum-based chemotherapy in treating previously untreated stage IV NSCLC with PD-L1 expression on at least 50% of tumor cells [31]. Based on the results, pembrolizumab was approved by FDA as first-line treatment for PD-L1 positive stage IV NSCLC patients. However, it should be noted that the response rate is only 44.8% and only 23–30.2% of all advanced NSCLC patients with at least 50% PD-L1 positive tumor cells [9,31]. The majority of advanced NSCLC cannot acquire benefit from pembrolizumab treatment. It may replace platinum-based chemotherapy as first-line treatment just in a little part NSCLC patients. For others, PD-1/PD-L1 blockades combining with chemotherapy are appealing, which have shown synergistic antitumor activity in first-line treatment for NSCLC patients [38–40]. But up to date, the sample size of reported trials was really small and treatment related grade ≥ 3 AEs was great in the combination group. For locally advanced NSCLC patients without EGFR mutation or ALK rearrangement, chemoradiotherapy is the first-line treatment choice. Randomized, double-blind, phase III studies are needed to compare the efficacy and safety of PD-1/PD-L1 checkpoint blockades and standard chemoradiotherapy as first-line therapy for locally advanced NSCLC.

Identification of optimal combination

The preliminary data showed efficacy of PD-1/PD-L1 blockades with other treatment in first-line setting or second-line setting in treating NSCLC. It is still a long way before those combinations are approved for clinical use. Firstly, the ORR is just modest in some combinations. The efficacy should be significant better with combination than single agents [42,43,53]. Secondly, it is a great challenge to identify the optimal combination strategy for NSCLC from

so many models of combinations in first-line setting and second-line setting. Thirdly, the sample sizes of the reported trials about combination treatments were small and lack of phase III trials. Finally, the sequence of combination is required to fully understand how to develop effective effects. Chemotherapy, anti-CTLA therapy, radiotherapy or EGFR inhibitors trigger different changes about immune cells and cytokines in tumor microenvironment. The best combination should be that the effects of PD-1/PD-L1 blockades coincide with other treatment-induced immunogenic tumor cell death, antigen presentation, trafficking, and T-cell engagement to trigger the most effective antitumor response.

Treatment related adverse events

PD-1/PD-L1 blockades showed promising safety when used as single agents in NSCLC. Treatment-related grade 3/4 AEs were only 7% for nivolumab alone in CheckMate 017, 10% in CheckMate 057 [1,2], 13% for pembrolizumab alone in Keynote-010 [3], 11% for atezolizumab alone in POPLAR in the second-line treatment for NSCLC [4]. However, the grade ≥ 3 AEs is higher when used in the first-line setting: 26.6% for pembrolizumab alone in Keynote-024 [31] and 18% for nivolumab in CheckMate 026 [30]. The toxic effects are further more frequent and severe when PD-1/PD-L1 checkpoint blockades are used in combination (Table 3). The grade 3/4 AEs were above 36% for pembrolizumab combining with chemotherapy [38] and 45% for nivolumab combining with chemotherapy [41]. Grade 3/4 interstitial lung disease occurred 38% with osimertinib in combination with durvalumab [55]. Discontinuations attributable to treatment-related AEs occurred in 28% patients treated with durvalumab plus tremelimumab [42] and 19% of patients treated with nivolumab and erlotinib [53]. Some AEs may occur after finishing treatment. So the adverse events must be a consideration both for physicians and patients when choosing the therapy model and the future trials should try to decrease the serious AEs.

Cost-effectiveness of PD-1/PD-L1 blockades

Some patients with NSCLC derived an enormous amount of benefit from PD-1/PD-L1 blockades. However most of such patients enrolled in clinical trials supported by the company, which means they used the antibodies for free. The assessment of benefit does not include the cost [70]. The average wholesale prices are to be \$28.78/mg for nivolumab and \$51.79/mg for pembrolizumab. The use of PD-1/PD-L1 blockades would cost more than 1 million for an individual patient [71]. The promise of PD-1/PD-L1 checkpoint blockade may be beyond the financial reach of most patients with NSCLC at the current price. It is not equitable that only very rich populations can avail of expensive therapeutics [72]. The price needs to be negotiated and the cost effectiveness of these agents needs careful consideration for routine clinical use.

Predictor of response to PD-1/PD-L1 blockades

Despite the activity of PD-1/PD-L1 blockades in NSCLC, it is urgently needed to find an effective predictor for response to PD-1/PD-L1 blockades considering cost, AEs and limited ORR. The PD-L1 immunohistochemistry is approved by FDA for selecting patients treated by pembrolizumab [22]. However, PD-L1 expression can be influenced by chemotherapy [73], EGFR-TKI [74] and immunotherapy [75]. In Keynote-010 trial, any tumor sample was initially permitted for PD-L1 testing. But the study protocol was later amended to require a new tumor sample for PD-L1 testing [3]. So PD-L1 testing should be taken at the point when immune

checkpoint therapy is considered except when attempting to take a biopsy would be too risky.

PD-L1 expression has been associated with higher efficacy to PD-1/PD-L1 blockades [2–4,31]. However, the responses have also been observed among PD-L1 negative patients [1,2,4]. PD-L1 expression is heterogeneous and dynamic [76]. Furthermore, different anti-PD-L1 antibodies and various scoring cutoffs were used without standardization (Tables 1 and 2) [2–4,31]. Given the limitation of PD-L1 in predictive function and testing, various other predictive tools have been explored. Somatic non-synonymous mutation burden testing by whole-exome sequencing is found to be associated with improved ORR, DCB and PFS of anti-PD-1 therapy in NSCLC [77]. Tumeh et al. established a predictive model based on CD8 expression and validated the model in an independent cohort of 15 patients to predict the response to PD-1 blockade [78]. It was also reported that the benefit of PD-L1 blockade in lung cancer associated with JAK3 activation [79] and enriched clonal neoantigens [80]. Up to date, no predictive markers or models can accurately identify patients who will benefit from PD-1/PD-L1 checkpoint blockades in NSCLC. To find a predictive biomarker or prediction model remains of paramount importance in clinical trials in NSCLC.

Specific challenges for NSCLC

The above mentioned challenges also exist in other tumor types. There are some specific challenges for NSCLC which are different from tumors of other types. First, NSCLC includes squamous carcinoma, adenocarcinoma and other non-small cell histology subgroups, which may cause difference of efficacy among various subhistologies. Nivolumab group achieved longer PFS compared with docetaxel group in squamous carcinoma [1] but PFS did not favor nivolumab over docetaxel in non-squamous carcinoma [2]. The PD-L1 expression could predict the response to nivolumab in the non-squamous NSCLC but not in squamous NSCLC [1,2]. Second, the treatment models for NSCLC are complicated, including surgery, chemotherapy, radiotherapy and targeted therapy. The PD-1/PD-L1 blockade could be assessed in neoadjuvant therapy and adjuvant therapy for early patients [81]; as single agents in second-line [1,2], first-line [31,33] or maintenance treatment [82] for unresected patients; in combination with other therapy for advanced NSCLC. Third, some patients possess EGFR mutation, KRAS mutation, and/or ALK rearrangement. It is difficult for PD-1/PD-L1 blockades to achieve as high ORR as erlotinib, gefitinib or crinitib does. Such gene mutations also influence the efficacy of PD-1/PD-L1 blockades [2,3,74]. Fourth, many NSCLC patients have smoking history. Tobacco exposure was reported to have effect on tumor immune microenvironment and immune therapy efficacy [3,83,84].

Conclusion

PD-1/PD-L1 checkpoint blockades have showed promising efficacy in NSCLC. Many trials are ongoing to assess the efficacy and safety of PD-1/PD-L1 checkpoint blockades combining with chemotherapy, anti-CTLA-4 antibodies, targeted therapy, radiotherapy or other approaches. However, there are a lot of considerations to be adequately addressed. First, nivolumab did not show better efficacy over chemotherapy and only a part of PD-L1 high expression patients benefit from pembrolizumab in first line. There is no research reported about PD-1/PD-L1 blockades versus chemoradiotherapy. Second, identifying the optimal combination and the sequence of combination is required to fully understand how to develop most effective effects. Third, decreasing the treatment-related AEs, especially when PD-1/PD-L1 checkpoint blockades are used in combination. Fourth, the high cost may be beyond the

reach of most patients with NSCLC at the current price. Finally, up to date, no predictive markers or tools can accurately identify patients who will benefit from PD-1/PD-L1 checkpoint blockades in NSCLC. PD-1/PD-L1 checkpoint blockade arising great interest of researchers, many trials are ongoing or just initiated. It is necessary to fully consider the above challenges in designing the clinical trials. Certain kinds of clinical trials are in urgent need: comparing the efficacy and safety of PD-1/PD-L1 blockades versus chemo-radiotherapy for locally advanced NSCLC, comparing directly the efficacy of various PD-1/PD-L1 blockades (especially pembrolizumab versus nivolumab), identifying a biomarker or model to predict and monitor the response. With the rapid development, we believe that PD-1/PD-L1 checkpoint blockades alone or in combination will be popular used to improve the outcomes and quality of life for patients with NSCLC.

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Conflicts of interest

None.

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