

PD-1/PD-L1 Blockade Therapy in Advanced Non-Small-Cell Lung Cancer: Current Status and Future Directions

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Immune checkpoint inhibitors • PD-1/PD-L1 • Non-small-cell lung cancer • Clinical trials • Combination therapy

ABSTRACT

The use of immune checkpoint inhibitors (ICIs) has become one of the most promising approaches in the field of cancer therapy. Unlike the current therapies that target tumor cells, such as chemotherapy, radiotherapy, or targeted therapy, ICIs directly restore the exhausted host antitumor immune responses mediated by the tumors. Among multiple immune modulators identified, the programmed cell death protein 1 (PD-1)/programmed cell death protein ligand 1 (PD-L1) axis leading to the exhaustion of T-cell immunity in chronic infections and tumors has been widely investigated. Therefore, blocking antibodies targeting PD-1 or PD-L1 have been developed and approved for the treatment of various advanced cancers, including non-small-cell lung cancer (NSCLC), making them the most successful ICIs. Compared with chemotherapy or radiotherapy, PD-1/PD-L1 blockade therapy significantly

improves the durable response rate and prolongs long-term survival with limited adverse effects in both monotherapy and combination therapy for advanced NSCLC. However, extensive challenges exist for further clinical applications, such as a small fraction of benefit population, primary and acquired resistance, the lack of predictive and prognostic biomarkers, and treatment-related adverse effects. In this article, we summarize the latest clinical applications of PD-1/PD-L1 blockade therapy in advanced NSCLC worldwide, as well as in China, and discuss the bottlenecks related to the use of this therapy in clinical practice. An exploration of the underlying mechanism of PD-1/PD-L1 blockade therapy and biomarker identification will maximize the application of ICIs in advanced NSCLC and facilitate bedside-to-bench studies in cancer immunotherapy as well. *The Oncologist* 2019;24(Special Issue):S31–S41

Implications for Practice: Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) and programmed cell death protein ligand 1 (PD-L1) display apparent benefits for the treatment of advanced non-small-cell lung cancer (NSCLC). However, the clinical applications of these therapies are challenged by the limited benefit population with additional high economic burden and adverse events. This review discusses the bottlenecks of ICI therapy in clinical practice and provides appropriate guidance in the development of predictive biomarkers, the establishment of the criteria for combining PD-1/PD-L1 blockade therapy with the existing therapies, and the management of adverse events observed both in monotherapy and combination therapy, which will help maximize the applications of ICIs in advanced NSCLC.

INTRODUCTION

The development of immune checkpoint inhibitor (ICI) agents targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1) or programmed cell death protein ligand 1 (PD-L1) has garnered tremendous interests in the field of immuno-oncology because of

the recent successful applications in multiple advanced cancers [1–3]. Although CTLA-4 is the first immune checkpoint molecule identified in 1987 [4], the PD-1/PD-L1 axis has been widely investigated because of the role in the exhaustion of CD8⁺ T cells [5]. Immuno-oncologists

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Table 1. Overview of anti-PD-1/PD-L1 antibodies approved by the FDA as of October 2017

Drug	Trademark	Manufacturer	Description	Approved by the FDA	Usage
Pembrolizumab	KEYTRUDA	Merck & Co	Humanized IgG4 anti-PD-1	September 4, 2014	Unresectable or metastatic melanoma Metastatic NSCLC Recurrent or metastatic head and neck squamous cell cancer Classical Hodgkin lymphoma
Nivolumab	OPDIVO	Bristol-Myers Squibb	Human IgG4 anti-PD-1	December 22, 2014	Metastatic melanoma Metastatic NSCLC Renal cell carcinoma Classical Hodgkin lymphoma Squamous cell carcinoma of the head and neck Urothelial carcinoma MSI-H or dMMR metastatic colorectal cancer Hepatocellular carcinoma
Atezolizumab	TECENTRIQ	Roche/Genentech	Humanized IgG1 anti-PD-L1	May 18, 2016	Advanced or metastatic urothelial carcinoma Metastatic NSCLC
Durvalumab	IMFINZI	AstraZeneca	Human IgG1 anti-PD-L1	May 1, 2017	Advanced or metastatic urothelial carcinoma
Avelumab	BAVENCIO	Merck KGaA/Pfizer	Human IgG1 anti-PD-L1	March 23, 2017	Metastatic Merkel cell carcinoma

Abbreviations: dMMR, mismatch repair deficient; FDA, U.S. Food and Drug Administration; MSI-H, microsatellite instability-high; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.

extended the concept to antitumor immunity, making PD-1/PD-L1 the most promising targets for drug development [6]. Therapeutic monoclonal antibodies targeting PD-1 or PD-L1 have demonstrated notable clinical efficacy in the treatment of various advanced cancers [6, 7]. Up to the end of 2017, five monoclonal antibodies targeting PD-1 or PD-L1 have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of various advanced cancers (Table 1), including melanoma [8], non-small-cell lung cancer (NSCLC) [9], head and neck squamous cell cancer [10], classical Hodgkin lymphoma [11], urothelial carcinoma [12], hepatocellular carcinoma [8], Merkel cell carcinoma [13], renal cell carcinoma [14], and colorectal cancer [15]. Immune checkpoint therapy, which was first approved as second-line treatment and has been extended to first-line treatment [16, 17], becomes an alternative option for cancer therapy. In this review, we introduce the development of PD-1/PD-L1 blockade therapy and its clinical applications in advanced NSCLC. The ongoing clinical trials of PD-1 and PD-L1 inhibitors in China are also introduced, which might contribute to a better understanding of ICI therapy in China.

MATERIALS AND METHODS

We searched in the PubMed database using the terms “PD-1, PD-L1, NSCLC, phase III trial, combination therapy” for articles published by August 2018. Original reports and systematic review articles were also reviewed to identify additional publications. Reports from recent conferences on cancer immunotherapy were included as well. Information regarding the relevant clinical trials was obtained from online databases (<https://www.chinadrugtrials.org.cn>; <https://www.clinicaltrials.gov>).

A BRIEF HISTORY OF CANCER IMMUNOTHERAPY

The successful treatment of an inoperable sarcoma using bacterial toxins reported by William Coley in 1910 [18] is recognized as the first example of immunotherapy. After Coley's success, researchers since the late 1990s have made great efforts to manipulate host immune responses for cancer immunotherapy, such as interleukin-2 (IL-2) [19], lymphokine-induced killer cells [20], tumor-infiltrating lymphocytes (TILs) [21], and the first therapeutic prostate cancer vaccine [22]. However, the clinical applications of these agents remain limited, mainly because of the low therapeutic effectiveness, high toxicity when used at a large dosage, and the cost of the treatments.

The successes of immune checkpoint blockade reagents and chimeric antigen receptor T-cells against multiple cancers made cancer immunotherapy the scientific breakthrough in 2013 according to *Science* journal [23]. CTLA-4 and PD-1/PD-L1 are among the targets that draw great attention in the field of cancer immunotherapy. CTLA-4 was first identified by screening mouse cytolytic-T-cell-derived cDNA libraries and is mainly expressed on activated T cells and regulatory T cells (Treg) [4]. CTLA-4 inhibits T-cell proliferation and IL-2 secretion by competing with CD28 for the B7 ligands [24, 25]. The blockade of CTLA-4 has been shown to potentiate T-cell responses in vitro [26] and cause tumor rejection in vivo in murine models [27]. The therapeutic CTLA-4-blocking antibody ipilimumab has been developed since 1999 and was approved in 2011 for the treatment of advanced melanoma [28, 29]. The development of CTLA-4 blocking antibody thus became the milestone of ICIs for cancer immunotherapy. Subsequently, ICIs targeting PD-1 and PD-L1, which were cloned in 1992 and 1999, respectively [30, 31], were developed. The antitumor efficacy of these ICIs observed in clinical trials is also encouraging for multiple advanced cancers [7, 32]. At present, five ICIs targeting PD-1

or PD-L1 have been approved by the FDA for the treatment of various cancers (Table 1), propelling cancer therapy into a new era.

MECHANISMS OF PD-1/PD-L1 BLOCKADE IN IMMUNOTHERAPY

It is widely accepted that activated T cells are key players in restraining cancer cells initiated by T-cell receptor (TCR) recognition of peptides presented by major histocompatibility complex molecule. PD-1 is mainly expressed on activated T cells and functions as a brake of T-cell activation through binding to the PD-1 ligands PD-L1 and PD-L2 [30, 33]. Upon binding with PD-L1 and PD-L2, PD-1 is phosphorylated by the protein tyrosine kinase Lck, leading to the recruitment of the tyrosine phosphatase Shp2 and the subsequent dephosphorylation of CD28, which in turn inhibits TCR/CD28 signaling and subsequent T-cell activation signal [34–37]. The PD-1 ligand PD-L1 is expressed on multiple normal tissues and malignant cells [38]. The expression of PD-L1 is upregulated on tumor cells when exposed to interferon- γ and other cytokines that are released by local activated T cells, resulting in the resistance of tumor cells to T-cell immunity, especially within the tumor microenvironment (TME) [39, 40]. After long exposure to tumor antigens in the TME, T cells infiltrated in the TME (named TILs) become exhausted, with characteristics of high expression of PD-1 and low antitumor function [40]. Therefore, antibodies blocking PD-1/PD-L1 interaction largely rescue the function of these exhausted T cells and result in enhanced antitumor immunity [41]. With high expression of PD-1 on Tregs, which play inhibitory roles in antitumor immunity [42, 43], interruption of PD-1/PD-L interaction can release antitumor responses by impairing the suppressive activity of Tregs [44]. In addition to T-cell immunity, antitumor effects can also be enhanced by redirecting the function of tumor-associated macrophages [45] and the natural killer cell-dendritic cell axis in the TME [46].

PD-1/PD-L1 BLOCKADE THERAPY IN ADVANCED NSCLC

Lung cancer is the leading cause of cancer mortality in China and worldwide [47–49]. Despite the availability of surgical resection, radiotherapy, platinum-based chemotherapy, and targeted therapies, the overall efficacies of the present therapies are still limited, with the 5-year survival rate at approximately 17.4% in NSCLC [50] accounting for approximately 80%–85% of lung cancer cases [49]. Therefore, there is still an urgent need for more clinical approaches with less toxicity and improved efficacy. Several ICIs targeting PD-1 or PD-L1 have been approved by the FDA for the clinical treatment of advanced NSCLC, demonstrating notable efficacy in clinical practice.

PD-1/PD-L1 Blockade as Second-Line Treatment in Advanced NSCLC

Nivolumab, a human anti-PD-1 monoclonal antibody, was the first PD-1/PD-L blockade agent for second-line treatment of advanced NSCLC. A series of international,

open-label, randomized phase III trials have been undertaken [51]. The results from the CheckMate 017 clinical trial demonstrated that nivolumab significantly improved the overall survival (OS), the overall response rate (ORR), and progression-free survival (PFS) with acceptable safety profiles such as treatment-related adverse events (TRAEs) and mortality in patients with previously treated advanced squamous NSCLC in comparison with docetaxel (Table 2) [51]. In nonsquamous NSCLC, although the median PFS did not favor nivolumab over docetaxel (2.3 months for nivolumab vs. 4.2 months for docetaxel), the OS and ORR were significantly improved for the patients treated with nivolumab according to the results from the CheckMate 057 trial [52]. Nivolumab thus became the first ICI targeting PD-1/PD-L1 approved by the FDA for metastatic NSCLC therapy in 2015 [9]. Importantly, a pooled analysis of the two studies revealed better 2-year OS rates (23% for nivolumab vs. 8% for docetaxel in squamous NSCLC and 29% with nivolumab vs. 16% with docetaxel in nonsquamous NSCLC), indicating that nivolumab provides a long-term clinical benefit and a favorable tolerability profile compared with docetaxel in advanced NSCLC [53]. Likewise, the results of the phase II/III clinical trial study KEYNOTE 010 demonstrated that compared with docetaxel, pembrolizumab, another anti-PD-1 antibody, significantly improved the OS, PFS, and ORR of the patients with advanced NSCLC who had PD-L1 expression on $\geq 50\%$ of tumor cells (Table 2) [54]. Furthermore, ICIs targeting PD-L1 also exhibit impressive benefits in the treatment of advanced NSCLC. Atezolizumab, a humanized anti-PD-L1 monoclonal antibody, significantly prolonged the OS of previously treated patients with advanced NSCLC with a favorable safety profile when compared with docetaxel treatment in both phase II (POPLAR) and phase III (OAK) clinical trials (Table 2) [55, 56].

Collectively, these results demonstrate that ICIs targeting PD-1 and PD-L1 significantly improve clinical efficacy in patients with advanced NSCLC with a favorable safety profile compared with chemotherapy [57], making anti-PD-1 and PD-L1 therapeutic antibodies a new option as second-line treatment in patients with advanced NSCLC.

PD-1/PD-L1 Blockade as First-Line Treatment in Advanced NSCLC

Based on the promising results of second-line treatment, the clinical efficacy of PD-1/PD-L1 blockade as first-line treatment for advanced NSCLC has been investigated. Results from the KEYNOTE 024 phase III trial demonstrated that compared with chemotherapy, the OS, PFS, and ORR were significantly improved by pembrolizumab in patients with PD-L1 expression on $\geq 50\%$ of tumor cells (Table 2) [58]. In 2016, these data led the FDA to permit pembrolizumab as a single agent for first-line treatment of patients with metastatic NSCLC [16]. Recently, results from the KEYNOTE 042 phase III trial showed that the OS of patients treated with pembrolizumab was significantly improved even in patients with PD-L1 expression on $\geq 1\%$ of tumor cells (Table 2) [59], indicating that more patients might benefit from pembrolizumab treatment. However, despite the favorable safety profile, nivolumab treatment exhibited no significant effects on improving the OS (median, 14.4 months

Table 2. Overview of phase III trials of PD-1/PD-L1 blockade therapy in advanced non-small-cell lung cancer as of August 2018

Trial name (line)	Number (selections)	Arms	Median OS (95% CI or <i>p</i> value), mo	Median PFS (95% CI or <i>p</i> value), mo	ORR (95% CI or <i>p</i> value), %	Grade 3–5 TRAEs, %	Ref.
CheckMate 017 (second)	272 (squamous)	Nivo 3 mg/kg every 2 wk	9.2 (7.3–13.3)	3.5 (2.1–4.9)	20 (14–28)	7	[51]
		Doce 75 mg/m ² every 3 wk	6.0 (5.1–7.3)	2.8 (2.1–3.5)	9 (5–15)	55	
CheckMate 057 (second)	582 (nonsquamous)	Nivo 3 mg/kg every 2 wk	12.2 (9.7–15.0)	2.3 (2.2–3.3)	19 (15–24)	10	[52]
		Doce 75 mg/m ² every 3 wk	9.4 (8.1–10.7)	4.2 (3.5–4.9)	12 (9–17)	54	
CheckMate 078 (second)	504	Nivo 3 mg/kg every 2 wk	12.0 (10.4–14.0)	2.8 (2.4–3.4)	16.6 (12.8–21.0)	10.0	[78]
		Doce 75 mg/m ² every 3 wk	9.6 (7.6–11.2)	2.8 (1.6–2.9)	4.2 (1.7–8.5)	48.0	
KEYNOTE 010 (second)	1,034 (PD-L1 ≥1%)	Pem 2 mg/kg every 2wk	10.4 (9.4–11.9)	3.9 (3.1–4.1)	18 (<i>p</i> = .005)	13	[54]
		Pem 10 mg/kg every 2wk	12.7 (10.0–17.3)	4.0 (2.7–4.3)	18 (<i>p</i> = .002)	16	
		Doce 75 mg/m ² every 3 wk	8.5 (7.5–9.8)	4.0 (3.1–4.2)	9	35	
OAK (second)	850	Atezo 1,200 mg every 3wk	13.8 (11.8–15.7)	2.8 (2.6–3.3)	14	15	[55]
		Doce 75 mg/m ² every 3 wk	9.6 (8.6–11.2)	4.0 (3.3–4.2)	13	43	
PACIFIC (consolidation)	709	Durva 10 mg/kg every 2 wk	23.2 (23.2–NR)	16.8 (13.0–18.1)	28.4	29.9	[76]
		Placebo	14.6 (10.6–18.6)	5.6 (4.6–7.8)	16.0 (<i>p</i> < .001)	26.1	
CheckMate 026 (first)	423 (PD-L1 ≥1%)	Nivo 3 mg/kg every 2 wk	14.4 (11.7–17.4)	4.2 (3.0–5.6)	26 (20–33)	18	[60]
		Chemo	13.2 (10.7–17.1)	5.9 (5.4–6.9)	33 (27–40)	51	
KEYNOTE 024 (first)	305 (PD-L1 ≥50%)	Pem 200 mg every 3 wk	NR	10.3 (6.7–NR)	44.8 (36.8–53.0)	26.6	[58]
		Chemo	NR (<i>p</i> = .005)	6.0 (4.2–6.2)	27.8 (20.8–35.7)	53.3	
KEYNOTE 042 (first)	1,274 (PD-L1 ≥1%)	Pem 200 mg every 3 wk	16.7 (13.9–19.7)	5.4 (4.3–6.2)	27.3	17.8	[59]
		Chemo	12.1 (11.3–13.3)	6.5 (6.3–7.0)	26.5	41.0	
CheckMate 227 (first)	1,739 (TMB high ^a)	Nivo + ipili		7.2 (5.5–13.2)	45.3 (36.9–54.0)	31.2	[69]
		Chemo		5.5 (4.4–5.8)	26.9 (20.2–34.4)	36.1	
IMpower 131 (first)	1,021	Atezo + chemo		6.3 (5.7–7.1)	59.4 ^b	68	[66]
		Chemo		5.6 (5.5–5.7)	51.3 ^b	56.9	
IMpower 150 (first)	692 (nonsquamous)	Atezo + BCP	19.2 (17.0–23.8)	8.3 (7.7–9.8)	63.5 (58.2–68.5)	58.5	[67]
		BCP	14.7 (13.3–16.9)	6.8 (6.0–7.1)	48.0 (42.5–53.6)	50.0	
KEYNOTE 407 (first)	560 (squamous)	Pem + chemo			58.4	64.4	[65]
		Chemo			35.0 (<i>p</i> = .0004)	74.5	
KEYNOTE 189 (first)	616 (nonsquamous)	Pem + chemo	NR	8.8 (7.6–9.2)	47.6 (42.6–52.5)	67.2	[64]
		Chemo	11.3 (8.7–15.1)	4.9 (4.7–5.5)	18.9 (13.8–25.0)	65.8	

^aTMB ≥10 mutations per megabase.^bData cutoff: January 22, 2018, unconfirmed.

Abbreviations: atezo, atezolizumab; BCP, bevacizumab plus carboplatin plus paclitaxel; chemo, chemotherapy; CI, confidence interval; doce, docetaxel; durva, durvalumab; ipili, ipilimumab; nivo, nivolumab; NR, not reached; OR, odds ratio; ORR, overall response rate; OS, overall survival; pem, pembrolizumab; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; TMB, tumor mutational burden; TRAE, treatment-related adverse event.

for nivolumab vs. 13.2 months for chemotherapy) or PFS (median, 4.2 months for nivolumab vs. 5.9 months for chemotherapy) in previously untreated patients at stage IV or recurrent patients with PD-L1 expression on at least 5% of tumor cells [60]. Even in patients with high PD-L1 positivity (PD-L1 expression on $\geq 50\%$ of tumor cells), no difference was demonstrated for nivolumab treatment compared with chemotherapy [60]. A retrospective analysis of the tumor mutational burden (TMB) in these studies showed that patients with a high TMB (≥ 243 missense mutations) had a higher ORR (47% vs. 28%) and longer PFS (median, 9.7 vs. 5.8 months) with nivolumab treatment. However, the OS was similar between two groups regardless of the TMB level [60]. The differences in patient characteristics, such as PD-L1 positivity, gender ratio, or TMB, might contribute to the conflicting results for the different efficacy of PD-1 blockade treatments [60]. The application of nivolumab as first-line treatment for advanced NSCLC warrants more supporting data before moving into clinical practice, even in combination therapy approaches. Similar to pembrolizumab, atezolizumab also achieved a high ORR (19%) with good tolerability in patients with advanced NSCLC in a phase II trial (BIRCH) [61]. Consequently, the efficacy of atezolizumab as first-line treatment in NSCLC will be tested in a phase III trial (IMpower110) through recruiting more patients.

Although ICIs targeting PD-1 and PD-L1 have been demonstrated with impressive benefits for advanced NSCLC in first-line treatment trials, there still exists a certain population of patients who do not respond to the therapy. To increase the response rate, combinations of PD-1 or PD-L1 blockade with other treatments, such as chemotherapy, targeted therapies, and other ICIs, have been investigated and show impressive improvements in first-line treatments. For instance, in the KEYNOTE 021 phase II study, the ORR for chemotherapy plus pembrolizumab (55%) was significantly higher than that for chemotherapy alone (29%), even in patients with PD-L1 expression levels less than 1% (57% vs. 13%) [62]. The incidence of grade 3 or 4 TRAEs was 39% in combination therapy and 26% in chemotherapy, indicating a tolerated safety profile for combination therapy [62]. Considering the promising efficacy and safety profiles of combination therapy, pembrolizumab plus chemotherapy is under an accelerated approval process by the FDA as first-line treatment for patients with metastatic nonsquamous NSCLC [63]. In the following phase III studies, pembrolizumab plus chemotherapy showed a higher response rate in both nonsquamous and squamous NSCLC (Table 2) [64, 65]. In addition, atezolizumab combined with chemotherapy got a longer median PFS (6.3 months vs. 5.6 months) compared with chemotherapy alone in the phase III trial IMpower 131 (Table 2) [66]. Combined with bevacizumab (a VEGF inhibitor) and chemotherapy, atezolizumab significantly improved PFS, OS, and ORR among patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression and EGFR or ALK mutations (Table 2) [67]. In addition, the combination of ICIs targeting two or more immune checkpoint molecules also leads to a synergistic response in clinical practice. In the CheckMate 227 phase III study, the combination of nivolumab and the anti-CTLA-4 antibody ipilimumab, which regulate immune

responses at different stages and through different mechanisms [68], demonstrated a longer PFS, higher ORR, and comparable adverse events compared with chemotherapy in advanced NSCLC with a high TMB (Table 2) [69]. In a phase Ib trial, the combination of durvalumab (an anti-PD-L1 blocking antibody) and the anti-CTLA-4 antibody tremelimumab has been used in a dose-escalation manner among 102 patients with advanced or metastatic NSCLC [70]. The ORR was 23% in durvalumab (10–20 mg/kg every 2 weeks or 4 weeks) treatment combined with tremelimumab (1 mg/kg) regardless of PD-L1 expression [70]. However, 36% of the 102 patients had TRAEs, and 28% discontinued treatment because of severe TRAEs, among which three deaths were related to the treatment [70]. The assessment of the safety and clinical activity of the combination of durvalumab and tremelimumab versus platinum-based chemotherapy is still ongoing [71, 72].

PD-1/PD-L1 Blockade as Third-Line Treatment in Advanced NSCLC

The BIRCH phase II trial investigated the clinical benefits of atezolizumab in first-line, second-line, and third-line treatments simultaneously in 667 patients with preselected advanced NSCLC [61]. The median OS was 23.5, 15.5, and 13.2 months in the first-line, second-line, and third-line cohorts, respectively [61]. The median PFS and ORR was comparable between the third-line (2.8 months, 18%) and second-line (2.8 months, 19%) cohorts [61]. These results suggested the efficacy of atezolizumab in the third-line treatment for patients with advanced NSCLC. In another phase II trial (ATLANTIC), the ORR of durvalumab in patients with NSCLC with EGFR and ALK positivity and $\geq 25\%$ of tumor cells expressing PD-L1 was 12.2%, which was lower than those with EGFR and ALK negativity (16.4%) or those with $\geq 90\%$ PD-L1 expression of tumor cells (30.9%) [73]. Because the clinical trials in this stage are limited, the efficacy of PD-1/PD-L1 blockade therapy might be warranted with more phase III trials.

PD-1/PD-L1 Blockade as Neoadjuvant and Consolidation Treatment in Advanced NSCLC

In patients with untreated and resectable early (stage I, II, or IIIA) NSCLC, nivolumab treatment exhibited few side effects (TRAE rate of any grade was 23%; of grade 3 or higher was 4.5%) and induced a major pathological response in 45% of resected tumors, demonstrating a good safety and feasibility of neoadjuvant role in early-stage NSCLC [74]. In advanced NSCLC, platinum-based doublet chemotherapy concurrent with radiotherapy is the standardized cure strategy. However, its efficacy is still poor [75]. PACIFIC is a phase III trial to compare the efficacy of durvalumab as consolidation treatment and placebo in patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy. The results indicated that the median OS (durvalumab, 23.2 months vs. placebo, 14.6 months), PFS (durvalumab, 16.8 months vs. placebo, 5.6 months), and ORR (durvalumab, 28.4% vs. placebo, 16.0%) were significantly improved in patients receiving durvalumab treatment [76]. Grade 3 or 4 adverse events occurred in

29.9% of patients treated with durvalumab versus 26.1% with placebo, indicating a safety profile for durvalumab (Table 2) [76]. The result suggests that durvalumab may become an effective adjuvant therapy in patients with stage III NSCLC after standard treatment. In addition, anti-PD-1/PD-L1 therapies are also under investigation in the neoadjuvant and consolidation settings for stage III NSCLC, which may provide treatment options in the management of stage III NSCLC [77].

PD-1/PD-L1 BLOCKADE THERAPY FOR ADVANCED NSCLC IN CHINA

Lung cancer is the most common cancer and the leading cause of cancer death in China [48] with a great need to improve clinical efficacy. Registered clinical trials of PD-1/PD-L1 blockade inhibitors against advanced NSCLC have been initiated since December 2015. CheckMate 078 is a randomized, open-label, and multinational phase III trial for nivolumab treatment in patients with advanced or metastatic NSCLC for whom platinum-based doublet chemotherapy has failed. This is the first Chinese study on PD-1/PD-L1 inhibitors in NSCLC. Results of CheckMate 078 showed that nivolumab significantly improved OS, ORR, and safety profiles in patients with advanced NSCLC without EGFR or ALK mutations in comparison with docetaxel (Table 2) [78]. The efficacy of nivolumab in CheckMate 078 is comparable to that in CheckMate 017 and CheckMate 057, indicating that Chinese patients with NSCLC benefit from nivolumab treatment similarly. Accordingly, nivolumab was approved by the Chinese Food and Drug Administration (CFDA) on June 15, 2018, as second-line treatment for advanced NSCLC without EGFR or ALK mutations and became the first commercialized ICI in China on August 28, 2018.

At present, several clinical trials of PD-1/PD-L1 inhibitors have been carried out to investigate the clinical efficacy in China [79]. Based on the Chinese drug trial registration website ([www://chinadrugtrials.org.cn](http://www.chinadrugtrials.org.cn)), 14 clinical trials concerning four FDA-approved drugs, nivolumab, pembrolizumab, durvalumab, and atezolizumab, are ongoing in China as of October 2017, particularly for patients with advanced NSCLC (Table 3). These include eight trials for first-line treatment (CTR20170340 for nivolumab, CTR20170044 and CTR20160097 for pembrolizumab, CTR20170012 and CTR20170158 for durvalumab, CTR20160510, CTR20160994, and CTR20170064 for atezolizumab) and six for second-line treatment (CTR20150767, CTR20170541, and CTR20171020 for nivolumab, CTR20160103 and CTR20160205 for pembrolizumab, CTR20160054 for atezolizumab; Table 3). Combination therapy is designed in 3 of 14 trials (nivolumab plus ipilimumab or chemotherapy in CTR20170541, atezolizumab plus chemotherapy in CTR20170064 and CTR20160994). Thirteen of 14 clinical trials are phase III trials, among which two trials have finished recruitment, three trials have no recruitment, and eight trials are currently recruiting patients in China (as of October 2017; Table 3).

The apparent clinical benefits of ICIs in cancer therapy have drawn great attention from Chinese pharmaceutical companies. Enormous efforts have been made to develop ICIs domestically. As indicated in the Chinese drug trial

registration database, eight anti-PD-1/PD-L1 antibodies (BGB-A317, JS001, SHR-1210, IBI308, GB226, and GLS-010 targeting PD-1; KN035 and CS1001 targeting PD-L1) developed by Chinese pharmaceutical companies have been approved by the CFDA for clinical trials up to October 2017. Four of these antibodies (BGB-A317 from BeiGene, Beijing, China; JS001 from Junshi Biosciences, Shanghai, China; SHR-1210 from Hengrui Medicine, Shanghai, China; IBI308 from Innovent Biologics, Jiangsu, China) are undergoing efficacy evaluation in seven clinical trials for patients with advanced NSCLC in particular, including two trials as first-line treatment (CTR20170322 for SHR-1210, CTR20170361 for BGB-A317) and five trials as second-line treatment (Table 3). SHR-1210 plus chemotherapy is designed as combination therapy in CTR20170322 for first-line treatment and in CTR20170090 for second-line treatment (Table 3). Among seven clinical trials, three are phase III studies (CTR20170380 for IBI308, CTR20170322 for SHR-1210, and CTR20171112 for BGB-A317). The trials CTR20170380 and CTR20170322 are currently recruiting patients in China.

CHALLENGES FOR PD-1/PD-L1 BLOCKADE THERAPY IN ADVANCED NSCLC

ICI therapy using antibodies targeting PD-1 or PD-L1 has demonstrated profound clinical efficacy for advanced NSCLC. However, the clinical applications of these antibodies are still limited because of certain unsolved challenges. First, there are few predictive biomarkers to identify patients who can benefit from ICI therapy. Tissue-based PD-L1 expression is the first criterion for the prediction of ICI treatment. The expression of PD-L1 on tumor cells has been demonstrated to be associated with the efficacy of PD-1/PD-L1 blockade therapy in NSCLC [54, 80, 81]. Nevertheless, the association is quite variable among different ICIs. For example, the improvement of the OS by nivolumab for squamous NSCLC and by durvalumab for NSCLC occurs regardless of PD-L1 expression [52, 76]. The expression levels of PD-L1 are heterogeneous and dynamic in immunohistochemistry assays with different detecting antibodies, as well as various scoring cutoffs, complicating the interpretation of the results [82–84]. Panels have been investigated to explore predictive biomarkers (Fig. 1), including nonsynonymous mutation burden and neoantigen prediction [85–89], defects of mismatch repair genes or high microsatellite instability [90, 91], microbiota [92, 93], and metabolic profiles [94]. However, these predictive biomarkers must be validated in more clinical samples. Importantly, the predictive models integrating multiplex factors show potential in predicting the clinical responses of ICI therapy [89, 95]. Considering the multifactorial properties of cancer-immune cross-talk [96], the determination of theoretical predictive models based on comprehensive biomarkers might be more feasible in future applications.

The second challenge is the occurrence of TRAEs. The incidence of grade 3 or 4 TRAEs ranges from 7% to 29.9% in anti-PD-1/PD-L1 monotherapy for advanced NSCLC, whereas the percentage ranges from 26.1% to 55% in the chemotherapy group, displaying the promising safety profiles of ICI treatments (Table 2). However, the TRAE incidence is much

Table 3. Summary of the registered clinical trials of PD-1/PD-L1 blockade therapy for lung cancer in China as of October 2017

Drug	Target	Manufacture	Trial	Phase	Indication	Design ^a	Enrollment	Treatment	Recruiting
Nivolumab	PD-1	Imported	CTR20150767	III	NSCLC	A	450	Second-line	Closed
Nivolumab	PD-1	Imported	CTR20170340	III	NSCLC	A	377	First-line	Yes
Nivolumab	PD-1	Imported	CTR20170541	III	NSCLC ^b	A	80	Second-line (com)	Not yet
Nivolumab	PD-1	Imported	CTR20171020	III	NSCLC	B	380	Second-line	Not yet
Pembrolizumab	PD-1	Imported	CTR20160097	III	NSCLC	A	350	First-line	Yes
Pembrolizumab	PD-1	Imported	CTR20160103	I	NSCLC	C	42	Second-line	Yes
Pembrolizumab	PD-1	Imported	CTR20160205	III	NSCLC	A	600	Second-line	Yes
Pembrolizumab	PD-1	Imported	CTR20170044	III	NSCLC (sq)	A	Undetermined	First-line	Yes
Durvalumab	PD-L1	Imported	CTR20170012	III	NSCLC	A	352	First-line	Yes
Durvalumab	PD-L1	Imported	CTR20170158	III	NSCLC	D	170	First-line (adj)	Not yet
Atezolizumab	PD-L1	Imported	CTR20160054	III	NSCLC	A	450	Second-line	Closed
Atezolizumab	PD-L1	Imported	CTR20160510	III	NSCLC	A	150	First-line (adj)	Yes
Atezolizumab	PD-L1	Imported	CTR20160994	III	NSCLC	A	150	First-line (com)	Yes
Atezolizumab	PD-L1	Imported	CTR20170064	III	NSCLC (non-sq)	A	170	First-line (com)	Yes
BGB-A317	PD-1	Domestic	CTR20170361	II	Lung cancer	E	60	First-line	Yes
BGB-A317	PD-1	Domestic	CTR20171112	III	NSCLC	C	640	Second-line	Not yet
JS001	PD-1	Domestic	CTR20171117	I	NSCLC	D	30	Second-line	Yes
SHR-1210	PD-1	Domestic	CTR20170090	II	NSCLC	D	118	Second-line (com)	Yes
SHR-1210	PD-1	Domestic	CTR20170299	II	NSCLC	D	120	Second-line	Yes
SHR-1210	PD-1	Domestic	CTR20170322	III	NSCLC	C	412	First-line (com)	Yes
IBI308	PD-1	Domestic	CTR20170380	III	NSCLC (sq)	C	266	Second-line	Yes

^aTrial designs: A, parallel-grouped, open-label, randomized, multinational; B, single-group, open-label, nonrandomized, multinational; C, parallel-grouped, open-label, randomized, domestic; D, parallel-grouped, open-label, nonrandomized, domestic; E, single-group, open-label, nonrandomized, domestic.

^bEGFR mutation positive and T790 M negative.

Abbreviations: adj, adjuvant; com, combined; non-sq, nonsquamous; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; sq, squamous.

higher in combination therapy (Table 2). For example, 68% of patients receiving atezolizumab plus chemotherapy treatment developed TRAEs, compared with 56.9% in the chemotherapy-alone group [66]. In the pembrolizumab-plus-chemotherapy treatment group, 67.2% of the patients developed TRAEs, which is comparable to chemotherapy [64]. In the combination of durvalumab and tremelimumab, 36% of the patients developed TRAEs, resulting in the discontinuation of the treatment in 28% of the patients and three deaths [70]. So TRAEs are still a great challenge for PD-1/PD-L1 blockade therapy, and efforts should be made to decrease and predict severe TRAEs in advance in the future.

The third challenge lies in how to choose optimal combination therapy for advanced NSCLC. Combination therapy of diverse ICIs has been demonstrated to be of great potential in increasing the response rates (Table 2) [69]. Apart from chemotherapy, inhibitors targeting IDO [97], VEGF [98], CTLA-4 [70, 99], lymphocyte activating 3 [100, 101], or T-cell immunoglobulin mucin 3 [102, 103] may provide more options for combination strategies in the future. Hence, with the improvement in combination therapy, establishing guiding principles to identify the optimal combination strategy for advanced NSCLC from these combination approaches will greatly extend the clinical applications of anti-PD-1/PD-L1 antibodies in the future.

CONCLUSION

In recent decades, the conceptual dissection of immunooncology has highlighted the important roles of immune checkpoints in the regulation of T-cell immunity. This understanding, in turn, has facilitated the development of ICIs for clinical applications against cancers. With the approval of ICIs as both second-line and first-line treatments in advanced NSCLC, PD-1/PD-L1-based immune checkpoint therapy has provided more options for the treatment of advanced NSCLC. However, considering the fact that the response rates of these ICIs range from 14% to 20% in unselected patients, it is crucial to identify predictive biomarkers for the selection of patients who are likely to benefit from the ICI treatments. The limited size of the population with clinical benefit also raises an interest in exploring the mechanism involved, especially concerning the immunological properties of the TME. In fact, a concept of “hot” and “cold” TME has been introduced with different levels of immune checkpoint expression in different local regions [104]. The immunological outcomes related to immune checkpoint expression in the TME are still difficult to investigate, although diverse treatment efficacy has been observed [83, 84]. Therefore, new techniques, such as single-cell sequencing and multiplex immunological imaging in the TME, can be adapted to better understand the complexity and dynamics of the local

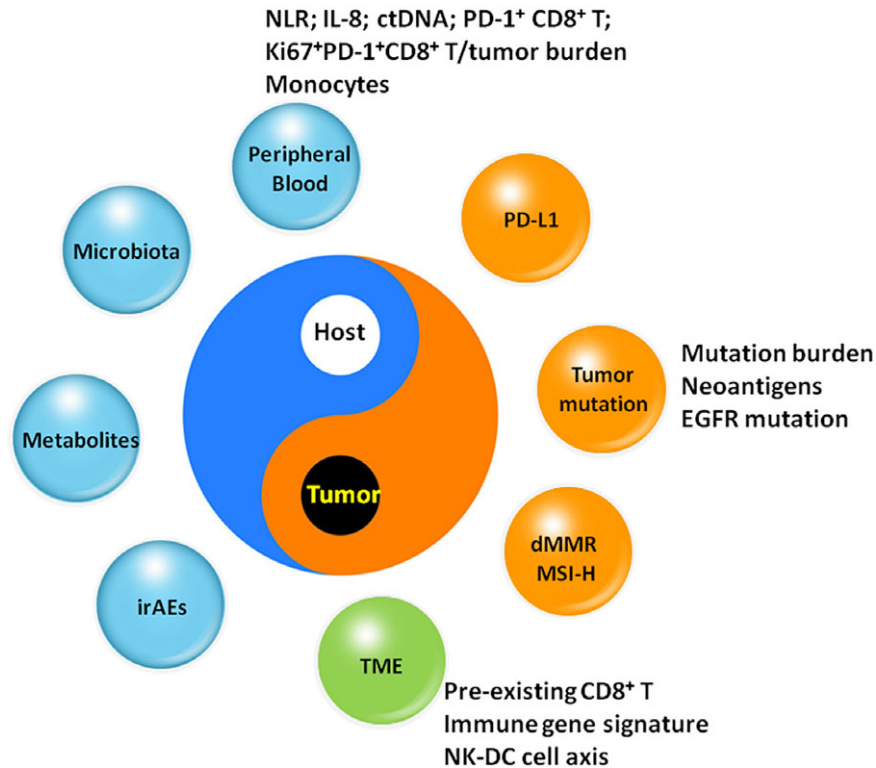


Figure 1. Biomarkers associated with the efficacy of PD-1/PD-L1 blockade therapy. Abbreviations and sources: ctDNA, circulating tumor DNA [116]; dMMR, mismatch repair deficient; IL-8, interleukin-8 [117]; irAE, immune-related adverse event [118]; Ki67⁺PD-1⁺CD8⁺T/tumor burden [119]; monocytes, CD14⁺CD16⁺HLA-DR^{hi} monocytes [105]; MSI-H, microsatellite instability-high; NK-DC axis, natural killer-dendritic cell axis [46]; NLR, neutrophil-to-lymphocyte ratio [120]; PD-1, programmed cell death protein 1; PD-1⁺CD8⁺T [121]; PD-L1, programmed cell death ligand 1; TME, tumor microenvironment [56, 122].

immune status [105, 106]. This might in turn guide the selection of patients for precise therapy by ICIs.

In addition, combination therapy of ICIs with conventional treatments must be optimized on a case-by-case principle. Combined with conventional chemotherapy or radiotherapy, ICI treatment might exhibit synergized clinical efficacy because of the enhanced cytotoxicity of T cells. This can be mediated by antigen release and presentation under a lower tumor burden. In addition, combination therapy of ICIs with other immunological activators such as TLR agonists [107] or supporting nutrition [108] are worthy of exploration when considering the complexity of antitumor immunity. Therefore, enriching the reservoirs of ICIs and defining the immune properties of patients with cancer will help realize the individualized treatment in advanced NSCLC.

In China, the clinical applications of ICI therapy started very recently and remain at an early stage. Clinical trials are ongoing to evaluate the effects of anti-PD-1/PD-L1 antibodies in Chinese patients. Importantly, genetic, biochemical, and microbiota-associated characteristics of Chinese populations must be considered in the evaluation of clinical efficacy. For instance, Chinese patients with NSCLC have high EGFR mutation rates (50% in the Chinese population vs. 20% in Western populations) [109–111]. EGFR mutations were previously considered to be associated with low response rates in anti-PD-1/PD-L1 treatments [57, 112, 113]. The Chinese population also harbors different

microbiota and microbiomes [114], as well as different biochemical and metabolic profiles [115], which may affect the efficacy of ICI treatments and biomarker profiles for the prediction and prognosis of the diseases. Therefore, together with the ongoing clinical trials, more retrospective or prospective investigations need to be carried out for the validation of treatment efficacy and exploration of biomarker determination, which will finally lead to durable control of the disease.

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