

PD-1/PD-L1 blockades in non-small-cell lung cancer therapy

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Abstract: Lung cancer is the leading cause of cancer death in males and the second leading cause of death in females worldwide. Non-small-cell lung cancer (NSCLC) is the main pathological type of lung cancer, and most newly diagnosed NSCLC patients cannot undergo surgery because the disease is already locally advanced or metastatic. Despite chemoradiotherapy and targeted therapy improving clinical outcomes, overall survival remains poor. Immune checkpoint blockade, especially blockade of programmed death-1 (PD-1) receptor and its ligand PD-L1, achieved robust responses and improved survival for patients with locally advanced/metastatic NSCLC in preclinical and clinical studies. However, with regard to PD-1/PD-L1 checkpoint blockade as monotherapy or in combination with other antitumor therapies, such as chemotherapy, radiotherapy (including conventional irradiation and stereotactic body radiotherapy), and target therapy, there are still many unknowns in treating patients with NSCLC. Despite this limited understanding, checkpoint blockade as a novel therapeutic approach may change the treatment paradigm of NSCLC in the future. Here we review the main results from completed and ongoing studies to investigate the feasibility of PD-1/PD-L1 inhibitors, as monotherapy or combinatorial agents in patients with locally advanced and metastatic NSCLC, and explore optimal strategy in such patients.

Keywords: immunotherapy, checkpoint, PD-1, PD-L1, NSCLC

Introduction

Lung cancer is the leading cause of cancer death in males, and the second leading cause of death in females worldwide. In 2008, a total of 1.6 million cases of lung cancer were diagnosed, and 1.4 million deaths occurred.¹ Approximately 85% of lung cancers are non-small-cell lung cancers (NSCLCs), which can be classified in two histological subgroups: squamous cell (Sq) and nonsquamous (non-Sq) cell lung cancer. Traditionally, surgery provides the best chance for cure, but unfortunately, the resection rate is as low as 25%–30%.² Emerging evidence suggested that efficacy of stereotactic body radiation therapy (SBRT) for operable NSCLC patients was comparable with surgery; however, the 3-year overall survival (OS) rate was only 76.0%.³ Most newly diagnosed NSCLC patients, approximately 85%, cannot undergo surgery because of locally advanced (Stage IIIB; 22%) or metastatic (Stage IV; 56%) disease.^{4–7} And according to data from SEER, the corresponding 5-year OS rates were 27.4% for regional and 4.2% for distant, even including partial small-cell lung cancer with a poorer prognosis.⁸ Platinum-based chemotherapy, with or without maintenance, was a standard treatment for most patients with advanced NSCLC, while for patients with sensitivity gene mutation, chemotherapy or targeted therapy was the standardized treatment. However, despite the major advances achieved for advanced or metastatic NSCLC over the past decade, survival remains poor, with median survival times of approximately 8–12 months and the 5-year survival rate being only 4%–5%.^{5,9,10}

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Thus, new therapeutic approaches to improve clinical outcomes are urgently needed.

Immunotherapy, especially immune checkpoint inhibition therapy, is a promising therapeutic approach currently being explored for treatment-naïve or treated patients. The goal of immunotherapy is to recognize and eradicate tumors by restoring the capacity of the host's immune. Effector T-cells played a pivotal role in immunotherapy progression by activation of naïve T-cells; to become fully activated, T-cells rely on two signals: one is the interaction of antigenic peptide–major histocompatibility complex (MHC) with the T-cell receptor (TCR), and the other is provided by the antigen-independent costimulatory signal, which consists of activating signals, such as the engagement of CD28 by B7-1 and B7-2, and inhibitory signals, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and programmed death-1 (PD-1) receptor pathways.¹¹ PD-1 ligand 1 (PD-L1) was highly expressed in many type of cancers or induced by high expression of the cytokine IFN- γ secreted by tumor cells (TCs). This engagement of PD-1 and its ligands inhibiting the activation of T-cells may be utilized by TCs to evade immune surveillance. Although PD-L2 blockade can inhibit the function of activated T-cells in theory, an *in vivo* study showed a greater effect was achieved by targeting the anti-PD-L1 blockade compared with anti-PD-L2 blockade.¹¹ So far, the targeted therapy on anti-PD-1 and anti-PD-L1 have greatly advanced the treatment of NSCLC.

A series of preclinical and clinical studies indicate that immunotherapy with PD-1/PD-L1 checkpoint blockades achieve robust immune responses and improved clinical outcomes. Checkpoint blockade is considered to be a promising tool for the treatment of lung cancer, combined with chemotherapy or radiotherapy, or combined with targeted therapy. However, there are still many unknowns involving the use of immune checkpoint inhibitors as monotherapy or in combination with other antitumor therapies in patients with NSCLC. Therefore, we reviewed several completed or ongoing trials to discuss the clinical impact of PD-1/PD-L1 blockade on patient outcomes and the potential role for PD-1/PD-L1 inhibitors as a monotherapy or in combination with other therapies.

Mechanism of PD-1 and its ligands in cancers and preclinical studies

The effector cells of tumor immune response mainly include cytotoxic T-lymphocytes, natural killer cells, and macrophages. T-cells are delivered by the binding of the TCR to the antigen peptide–MHC complex, thereby forming

an antigen–MHC–TCR complex. T-cells will be completely activated with the help of costimulatory signal, which consists of activating signals, such as the engagement of CD28 by B7-1 and B7-2, and inhibitory signals, such as CTLA-4 and PD-1 pathways. PD-1 is a Type I transmembrane protein and is expressed on T-cells, B-cells, nature killer cells, activated monocytes, and dendritic cells (DCs). PD-L1 and PD-L2, two ligands of PD-1, are also Type I transmembrane proteins and differ in their expression patterns. PD-L1 can be expressed on T-cells, B-cells, DCs, macrophages, a wide variety of nonhematopoietic cells, and also on TCs.^{11–13} PD-1 and its ligands consist of a signal sequence, immunoglobulin (Ig) domain and transmembrane domains, and a short cytoplasmic tail. PD-1 is phosphorylated on its two intracellular tyrosines after PD-1 binding to PD-L1 or PD-L2 based on their IgV-like domain. Then PD-1 binds two phosphatases, SHP-1 and SHP-2, which can bind to the ITIM and ITSM motifs of PD-1, which will downregulate antigen receptor signaling.^{11,14,15} The engagement of PD-1 by PD-L1 and PD-L2 inhibits the function of effector T-cells, while the engagement of B7-1/B7-2 and its ligand CD28 simulate T-cells proliferation. However, PD-L1, not PD-L2, is a binding partner for B7-1 and competitively binds B7-1 with an affinity greater than CD28, which reduces the function of B7-1-CD28 pathway-activated T-cells. Furthermore, both PD-L1 and PD-L2 do not bind to B7-2. In addition, PD-L2 expression was restricted to antigen-presenting cells and Th2 cells, and its impact on monitoring T-cells is not as well understood.^{11,16} All of these demonstrate that blocking PD-1 and PD-L1 pathways is more meaningful than blocking PD-L2 pathway.

Numerous preclinical studies showed PD-1/PD-L1 caused dysfunction of tumor-infiltrating lymphocytes (TILs). A preclinical study from Japan showed fewer TILs in PD-L1-positive tumor regions compared with PD-L1-negative tumor regions ($P=0.01$); moreover, the percentage of TILs expressing PD-1 in PD-L1-positive tumor regions was significantly lower than in PD-L1-negative tumor regions ($P=0.02$).¹³ Zhang et al¹⁷ detected PD-1 expression on CD8⁺ T-cells from normal control peripheral blood mononuclear cells (PBMCs) and the PBMCs of NSCLC patients. Results showed that CD8⁺ TIL had increased PD-1 expression and impaired immune function. Blockade of PD-1/PD-L1 partially restored the function of T-cells.¹⁷

Correlation between PD-1/PD-L1 expression and clinical activity

In the era of precision medicine, selection of patients most likely to benefit from specific treatments is vital. Therefore, it

is particularly important to screen for effective predictive biomarkers. Unfortunately, many questions regarding predictive biomarkers remain unanswered. It is uncertain whether it is the expression of PD-L1 on TCs or immune cells (ICs) that is associated with prognosis. In addition, the correlation of expression level of PD-L1 in TCs or ICs and prognosis is still not clear. Furthermore, the relationship of the efficacy of PD-L1/PD-1 blockade and the pathological types of lung cancer also remains to be determined. Studies regarding PD-L1 expression and associated with overall response rate (ORR) are summarized in Table 1.

Approximately 60% of NSCLC specimens tested demonstrate PD-L1 expression.¹⁸ In a recent Phase I study for nivolumab as first-line monotherapy to treat advanced NSCLC patients, the ORR was 31% in PD-L1-positive tumors, whereas it was 10% in PD-L1-negative tumors.¹⁹ Another Phase II study for nivolumab in SqNSCLC patients with greater than or equal to two prior regimens showed 24% of PD-L1-positive patients (expression more than 5%) and more than 14% in PD-L1-negative patients achieved a partial response.²⁰ Carbone et al²¹ analyzed data from 20 trials, including seven trials regarding NSCLC with 511 patients, and demonstrated higher ORR occurred in PD-L1-positive patients (23.2% versus 14.5%, $P=0.0216$). It seems that response varied with different PD-L1 inhibitors. For nivolumab and pembrolizumab, rather than MPDL3280A, ORR was significantly higher in PD-L1-positive tumors than that in PD-L1-negative tumors.

Another anti-PD-1 drug, pembrolizumab, in a Phase I trial, demonstrated the greatest anticancer efficacy in patients

with PD-L1 staining in $\geq 50\%$ of TCs, with an ORR of 45.2%.²² Updated data showed the ORR was 47% in the aforementioned group of patients, which was significantly higher than that in patients with PD-L1 staining in $< 50\%$ of TCs.²³ In a Phase Ia study of MPDL3280A in patients with locally advanced or metastatic solid tumors, including NSCLC, the correlation of ORR and PD-L1 expression on ICs or TCs was analyzed.²⁴ PD-L1 positivity was defined as $\geq 5\%$ of ICs or TCs staining for PD-L1 by immunohistochemistry (IHC). IHC score was ranked 0–3, which was defined as; PD-L1 positive in $< 1\%$, $\geq 1\%$ but $< 5\%$, $\geq 5\%$ but $< 10\%$, or $\geq 10\%$ of cells per area, respectively. For patients with NSCLC, PD-L1 positivity determined by IHC was significantly associated with response to MPDL3280A. Updated data presented at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting showed that the ORR was significantly higher in patients with PD-L1 expression of TC level 3 or IC level 3 (45%, $n=20$) than that in patients with PD-L1 expression of TC levels 0/1/2 and IC levels 0/1/2 (14%, $n=58$).²⁵ Another Phase II study (FIR) of MPDL3280A conducted in Stage IIIB/IV NSCLC also indicated that high PD-L1 expression was associated with a higher ORR.²⁶ An open-label, nonrandomized, multicenter Phase Ib study is being done to evaluate the safety and efficacy of pembrolizumab (MK-3475) in patients with PD-L1-positive advanced NSCLC.²⁷

It seems likely that PD-L1 expression is closely correlated with the curative efficacy of immune checkpoint inhibitors. However, CheckMate 017, a randomized, open-label, international Phase III study of nivolumab

Table 1 PD-L1 expression and association with ORR

Authors	ORR (%)		Agents	Pts (no)	Cutoff value for PD-L1 ⁺ (%)	Detection methods	Antibody	Evaluation criterion
	PD-L1 ⁺	PD-L1 ⁻						
Gettinger et al ¹⁹	31	10	Nivo	Treatment-naïve NSCLC (52)	5	IHC	Clone 28-8	RECIST v1.1
Rizvi et al ²⁰	24 (PR)	14 (PR)	Nivo	SqNSCLC; ≥ 2 prior regimens (117)	5	IHC	ND	Irc-RECIST v1.1
Carbone et al ²¹	23.2	14.5	Nivo Pembro	First-line or ≥ 2 prior regimens (511)	1 and 5	IHC	ND	RECIST
Rizvi et al ²³	47 ($\geq 50\%$) 19 (1%–49%)	14	MPDL3280A Pembro	Treatment-naïve NSCLC (101)	1	IHC	22C3	RECIST v1.1
Horn et al ²⁵	45 ($\geq 10\%$)	14 ($< 10\%$)	MPDL3280A	Locally advanced or metastatic NSCLC (88)	5	IHC	SP142	RECIST v1.1
Spigel et al ²⁶	29 ($\geq 10\%$) 27 ($\geq 10\%$) 25 ($\geq 10\%$)	NR	MPDL3280A	Treatment-naïve; $\geq 2L$ without BM $\geq 2L$ with treated asymptomatic BM (137)	5	IHC	SP142	RECIST v1.1

Abbreviations: ORR, overall response rate; PR, partial response; PD-L1^{+/−}, programmed death ligand 1 positive/negative; Nivo, nivolumab; Pembro, pembrolizumab; NR, not reported; Pts, patients; no, number of patients; Sq NSCLC, squamous non-small-cell lung cancer; 2L, second-line; BM, brain metastasis; Irc-RECIST, independent radiotherapy review committee-Response Evaluation Criteria in Solid Tumors; IHC, immunohistochemistry; ND, no data.

versus docetaxel for patients with advanced SqNSCLC during or after failed first-line chemotherapy, indicated that PD-L1 expression was neither prognostic nor predictive of benefit regardless of the expression levels of PD-L1 (1%, 5%, or 10%) as determined by OS and progression-free survival (PFS) rates.²⁸ Interestingly, however, in previously treated patients with advanced non-SqNSCLC, the study, CheckMate 057, indicated that ORR was significantly higher in the nivolumab arm (31%) than the docetaxel arm (12%) at PD-L1 expression level $\geq 1\%$.²⁹ This phenomenon was also observed between nivolumab and docetaxel arms at PD-L1 levels $\geq 5\%$ and $\geq 10\%$. Efficacy of nivolumab may be related to the pathological type of NSCLC, but this is not clear at present. The use of PD-L1 expression status and the expression level of PD-L1 as predictors of the response to checkpoint inhibitors or as biomarkers of prognosis remains controversial. Combined levels of PD-1 and PD-L1 probably predict the prognosis of SqNSCLC.³⁰ However, a meta-analysis to investigate correlation between PD-L1 expression and clinicopathological features of NSCLC showed that PD-L1 expression was not associated with histological type, except tumor differentiation.³¹ In another meta-analysis, the correlation between PD-L1 expression and the prognosis of patients with NSCLC was investigated.³² Pooled hazard ratio (HR) was 1.75 (95% confidence interval: 1.40–2.20, $P < 0.001$), with significant difference between positive and negative PD-L1 expressions. High level of PD-L1 was associated with increased mortality rates for NSCLC patients. However, this meta-analysis did not provide the correlation between the levels of PD-L1 expression and prognosis.

In addition, there appear to be many factors that may result in inconsistent results. The PD-L1 expression score is defined by IHC methods, which are influenced by subjective factors. In addition, different cutoff values, which were often defined as 1%, 5%, and 10%, may lead to inconsistent outcomes. In this era of precision medicine, highly selected patients to participate in these studies are urged. Choosing different biomarkers may be necessary to improve outcomes for different tumors. DNA mismatch repair (MMR) is a system for recognizing and repairing errors of bases that can arise during DNA replication and recombination, as well as repairing some forms of DNA damage. A recent study demonstrated that several immune checkpoint ligands, including PD-L1 and PD-1, were strongly expressed in the MMR-deficient (dMMR) tumor microenvironment.³³ A Phase II trial that enrolled 41 patients with treatment-refractory progressive metastatic cancer, including eleven patients with dMMR

colorectal cancer (CRC), 21 patients with MMR-proficient (pMMR) cancer, and nine patients with dMMR non-CRC, was designed to evaluate the clinical activity of pembrolizumab with a dose of 10 mg/kg of body weight every 14 days intravenously.³⁴ Results showed that the immune-related ORR was 40% for dMMR CRCs and 0% for pMMR CRCs; furthermore, the median PFS and OS were not reached in the cohort with dMMR CRC but 2.2 and 5.0 months, respectively, in the cohort with pMMR CRC (HR for death 0.22, $P = 0.05$). Some studies revealed that *MMR* gene polymorphisms were associated with lung cancer development.^{35,36} Those studies suggested that MMR may be an effective predictive biomarker of checkpoint inhibitors and a prognostic factor for clinical outcomes.

Response Evaluation Criteria in Solid Tumors (RECIST) was commonly used to evaluate response rate in many trials and was designed to assess solid tumors treated with chemoradiotherapy and targeted treatment. However, most studies have demonstrated that immune response is durable and maintained for a long period of time. RECIST may not accurately describe responses observed because of pseudoprogression.³⁷ New criteria have been developed to assess responses to immunotherapy.³⁸ Different diagnostic antibodies to assess PD-L1 or PD-1 expression may also impact the observation of ORR, and in addition, different technical staining platforms and different definitions of “positive” IHC staining can still have a significant influence on the analysis of outcomes.³⁹

PD-1/PD-L1 inhibitors as monotherapy in NSCLC

In this section, we summarized some Phase I–III clinical trial data that led to use of checkpoint inhibitors, such as nivolumab, pembrolizumab, MPDL3280A, and MEDI4736, as multi-, third-, second-, and first-line therapy. Lung cancer, the second major tumor type so targeted, is the subject of extensive immunotherapy research efforts after the first important and consequential breakthrough made in melanoma. Although lung cancer has been considered to be a nonimmunogenic tumor, the discovery of checkpoint inhibitors has created interest in using immunotherapy in NSCLC. These inhibitors of immune monitoring showed promising efficacy in multiple lines, second-line, and even first-line treatment. Checkpoint blockade research has generated a great deal of interest in the field of immunotherapy. Many monoclonal antibodies (mAbs) have been designed to block this immune checkpoint. Currently, the most commonly used PD-1 inhibitors are nivolumab

and pembrolizumab, and the major PD-L1 inhibitors are MPDL3280A and MEDI4736 (Table 2). Several clinical research studies have indicated promising efficacy and well-tolerated toxicities. Recently, a meta-analysis was conducted to evaluate the efficacy and safety of anti-PD-1 and anti-PD-L1 mAbs in the treatment of NSCLC.⁴⁰ For patients treated with anti-PD-1 agents, the higher ORR was observed in the median-dose cohort (3 mg/kg) than that in both low-dose (1 mg/kg) and high-dose (10 mg/kg) cohort with significant difference. Rates of common adverse events (AEs) of anti-PD-1 agents were acceptable, including 4.6% fatigue, 6.7% gastrointestinal disorders, 11.8% skin disorders, and 3.2% pneumonitis. Rates of Grade 3–4 AEs and drug-related death were 16.7% and 2.5% for patients with PD-1 inhibition therapy, respectively, whereas it was 31.7% and 1.8% for patients with PD-L1 inhibition therapy, respectively. These data indicated that blockade of PD-1/PD-L1 pathway was safe and effective.

A Phase I trial enrolled 122 advanced NSCLC patients who had received one to five systemic treatment regimens with nivolumab, which was administered at a dose of 1.0, 3.0, or 10.0 mg/kg.⁴¹ Results showed that the pooled ORR was 18.4% (14/76), using the modified RECIST. There was no dose-limiting toxicity (DLT), and the response of two patients lasted 1 year or more; for patients with a dose of 3.0 mg/kg, ORR was as high as 32%. Another Phase I, dose-escalation cohort expansion trial enrolled 129 advanced NSCLC patients with one to five prior regimens.⁴² For the entire group, median OS was 9.9 months, whereas it was 14.9 months in the 37 patients receiving 3 mg/kg nivolumab, 9.5 months in SqNSCLC patients, and 18.2 months in non-SqNSCLC patients. Only 14% of patients had Grade 3–4 treatment-related AEs, and the most common AE was fatigue (3%), and three patients (2%) died of pneumonitis.

As a third-line therapy for locally advanced or metastatic NSCLC, nivolumab has shown promising responses and acceptable toxicity levels. CheckMate 063, a Phase II, single-arm trial, enrolled 117 patients with advanced SqNSCLC who had been treated with greater than or equal to two agents

previously.²⁰ Nivolumab was administered as an intravenous infusion, 3 mg/kg every 2 weeks until disease progression or unacceptable AEs occurred. Finally, 17 of 117 patients were assessed for an objective response. At the time of analysis, 13 (77%) patients had an ongoing response and the median duration of response (mDOR) was not reached. Thirty (26%) of 117 patients had stable disease with a median duration of 6.0 months and the median OS was 8.2 months. Grade 3–4 treatment-related AEs occurred in 17% of patients; only two patients died of treatment-related pneumonia and ischemic stroke. Early data from CheckMate 153 also showed promising ORR and manageable immune-associated toxicities for those patients who had also been treated with at least two prior systemic regimens.⁴³

Nivolumab has also demonstrated significant effectiveness in patients with NSCLC as second-line monotherapy and has been discussed in this section and in the Correlation between PD-1/PD-L1 expression and clinical activity section. To evaluate the safety and efficacy of nivolumab as first-line monotherapy, a Phase I study was conducted; this study enrolled 52 chemotherapy-naïve patients with advanced NSCLC.¹⁹ At the time the abstract was published, the mDOR was not reached (range: 7.6+, 85.6+ weeks). The median OS was 98.3 weeks (range: 1.0, 104.4+ weeks); these data were encouraging, irrespective of whether tumor was PD-L1 positive or not. Updated OS and safety data will be presented in the future. As a result of improved outcomes with nivolumab treatment for NSCLC that has progressed while undergoing or after platinum-based chemotherapy, nivolumab became the first PD-1 inhibitor to be approved by the US Food and Drug Administration (FDA) for use in such patients.

Pembrolizumab, which was initially approved for the treatment of melanoma, has received the FDA's breakthrough therapy designation for advanced NSCLC patients without driver genes who have progressed while undergoing or after standard chemotherapy. The data from KEYNOTE-001, which enrolled 495 patients, showed promising outcomes and manageable toxicities.²² The pooled ORR was 19.4% with the use of RECIST version 1.1, with a response rate of 18.0% and

Table 2 Common PD-1/PD-L1 checkpoint inhibitors in clinical use for the treatment of NSCLC

Drug	Company	Description	Blockade site
Nivolumab	Bristol-Myers Squibb	Fully human IgG4 mAb	PD-1 on T-cells
Pembrolizumab	Merck Sharp & Dohme Corp	Humanized IgG4 mAb	PD-1 on T-cells
MPDL3280A	Roche	Human IgG1 mAb	PD-L1 on TCs
MEDI4736	AstraZeneca	Fully human IgG1 mAb	PD-L1 on TCs

Abbreviations: IgG, Immunoglobulin G; mAb, monoclonal antibody; NSCLC, non-small-cell lung cancer; PD-1, programmed death 1; PD-L1, programmed death ligand 1; TCs, tumor cells.

24.8% in the previously treated patients and untreated patients, respectively. Median PFS and OS were 3.0 and 9.3 months in treated patients, respectively, compared with 6.0 months and 16.2 months in previously untreated patients. Only 9.5% of AEs (47/495) less than or equal to Grade 3 were reported and evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Now, two randomized, open-label, Phase III studies, KEYNOTE-042 and KEYNOTE-024, were designed to evaluate pembrolizumab as first-line monotherapy compared to platinum-based chemotherapy in PD-L1-positive patients with locally advanced or metastatic NSCLC.^{44,45}

MPDL3280A, which was administered intravenously every 3 weeks as monotherapy in patients with incurable advanced NSCLC, also showed a promising ORR of 23% (12/53).²⁴ In POPLAR, a Phase II study comparing MPDL3280A and docetaxel in second-line/third-line NSCLC, reported in the 2015 ASCO meetings, the intention-to-treat interim analysis median OS was 11.4 months for the MPDL3280A group and higher than 9.5 months for the docetaxel group, but the difference was not statistically significant.⁴⁶ Results from subgroup analysis in those patients with PD-L1 expression level of TCs categorized as 1/2/3 or ICs categorized as 1/2/3 revealed that the interim median OS was not reached for the MPDL3280A group but was 9.1 months for the docetaxel group ($P=0.024$). Now, another Phase II study, the ATLANTIC, has been designed to evaluate the efficacy of MEDI4736 as a third-line therapy in patients with locally advanced or metastatic NSCLC.⁴⁷ A Phase III study, the OAK, is investigating MPDL3280A in comparison with docetaxel as second-line treatment, and a Phase II study, BIRCH, is recruiting participants to observe the response of MPDL3280A as first-, second-, and third-line therapy for PD-L1-positive patients with locally or metastatic NSCLC.⁴⁸ PD-1/PD-L1 inhibitors used as monotherapy to treat NSCLC showed the therapeutic effectiveness. Several studies that combine PD-1/PD-L1 with chemoradiotherapy and tyrosine kinase inhibitor (TKI)-targeted therapy also showed promising results, which will be discussed in subsequent sections. Completed Phase III and ongoing Phase II/III studies regarding PD-1/PD-L1 checkpoint inhibitors in NSCLC are summarized in Tables 3 and 4, respectively.

PD-1/PD-L1 in combination with chemotherapy in NSCLC

Platinum-based doublet chemotherapy was the standard of care for nononcogene-driven advanced NSCLC, with ORR approximately 30% and median OS of 8–10 months.

Table 3 Completed Phase III studies about PD-1/PD-L1 checkpoint inhibitors in NSCLC

Names	Authors	Agents	Phase	Pts (no)	Outcomes	Grade 3–4 treatment-related AEs	Evaluation criteria	Study identifier
CheckMate 063	Rizvi et al ²⁰	Nivo 3 mg/kg Q2W	II	≥2 prior agents; advanced/refractory SqNSCLC (117)	mDOR not reached (95% CI 8.31–not applicable) mPFS 1.9 mo (95% CI 1.8–3.2) mOS 8.2 mo (95% CI 6.1–10.9)	17% (20/117) Fatigue 4%, pneumonitis 3%, diarrhea 3%	RECIST v1.1	NCT01721759
CheckMate 017	Brahmer et al ²⁸	Nivo 3 mg/kg Q2W DOC 75 mg/m ² Q3W	III	Advanced SqNSCLC; failure of prior-platinum doublet-based chemotherapy (272)	Nivo versus DOC mOS 9.2 versus 6.0 mo mPFS 3.5 versus 2.8 mo	Nivo versus DOC 7% (9/131) versus 55% (71/129)	RECIST v1.1	NCT01642004
CheckMate 057	Paz-Ares ²⁹	Nivo 3 mg/kg Q2W DOC 75 mg/m ² Q3W	III	Non-SqNSCLC; failure of first-line treatment (582)	mDOR not reached versus 8.4 mo Nivo versus DOC ORR 19% versus 12% mDOR 17.2 mo versus 5.6 mo mOS 12.2 mo versus 9.4 mo $P=0.0015$ mPFS 2.3 mo versus 4.2 mo	Nivo versus DOC 10% versus 54%	RECIST v1.1	NCT01673867

Abbreviations: AEs, adverse events; Pts, patients; no, numbers; Nivo, nivolumab; DOC, docetaxel; Q^{2W}, every 2 weeks; non-SqNSCLC, nonsquamous non-small-cell lung cancer; mDOR, median duration of response; mo, months; mOS, median overall survival; mPFS, median progression-free survival; CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors; ORR, overall response rate.

Table 4 Ongoing Phase II/III studies about PD-1/PD-L1 checkpoint inhibitors in NSCLC

Agents	Phase	Pts setting (estimated enrollment)	Study design	Primary/secondary endpoints	Start date/estimated completion date	Evaluation criteria	Study identifier
Nivo	III	Locally advanced/metastatic NSCLC; ≥ 1 prior regimens (1,380)	Nivolumab 3 mg/kg Q2W	High-grade AEs	February 2014/March 2019	CTCAE v4.0	NCT02066636 ⁴³
Nivo as consolidated monotherapy	II	Stage III NSCLC; no progression after standard first-line chemoradiation (43)	Nivolumab 3 mg/kg	Grade ≥ 3 pneumonitis	August 2015/August 2019	CTCAE v4.0	NCT02434081 ⁵⁴
Pembro versus SOC	III	PD-L1+ chemotherapy-naïve locally advanced or metastatic NSCLC (1,240)	Pembrolizumab 200 mg IV D1 Q3W for up to 35 treatments Carboplatin: AUC5/6+ paclitaxel 200 mg/m ² /pemetrexed 500 mg/m ² D1 Q3W for a maximum of 6 cycles Pembrolizumab 200 mg IV D1 Q3W	OS/PFS	October 2014/July 2019	NR	NCT02220894 ⁴⁴
Pembro versus platinum-based chemotherapy	III	PD-L1 strong expressing treatment-naïve metastatic NSCLC (300)	Pembrolizumab 200 mg IV Q3W	PFS/OS, ORR	August 2014/May 2018	RECIST v1.1	NCT02142738 ⁴⁵
Pembro as consolidated monotherapy	II	Stage III NSCLC; No progression after concurrent chemoradiation (93)	Pembrolizumab 200 mg IV Q3W	Time to death or distant metastasis/PFS, OS, AEs	March 2015/January 2018	NR	NCT02343952 ⁵⁵
Pembro after SBRT versus Pembro alone	II	Metastatic NSCLC; ≥ 1 prior chemotherapy; ≥ 2 separate (metastatic) lesions (74)	Pembrolizumab 200 mg Q3W SBRT 3 \times 8Gy	ORR/percentage of CR, PR, SD, time to PD or death, toxicity	July 2015/October 2016	RECIST v1.1	NCT02492568 ⁷⁹
MEDI4736± tremelimumab versus SOC	III	Locally advanced/metastatic NSCLC; ≥ 2 prior regimens (900)	Substudy A: MEDI4736 versus SOC Substudy B: MEDI4736 versus MEDI4736+ tremelimumab versus tremelimumab versus SOC	OS, PFS/OS12, ORR, DOR	January 2015/November 2017	NR	NCT02352948 ⁶⁹
MPDL3280A versus DOC	II	Locally advanced/metastatic NSCLC; PD during or following 1 prior platinum-based regimen (287)	MPDL3280A 1,200 mg IV Q3W DOC 75 mg/m ² IV Q3W	OS/Pts Reported outcomes, OR, PFS, AEs	August 2013/February 2017	RECIST v1.1	NCT01903993 ⁴⁶
MEDI4736	II	Locally advanced/metastatic NSCLC; ≥ 2 prior regimens (453)	MEDI4736 IV D1 Q2W	ORR/DOR, PFS, DCR, OS, DSR, etc	February 2014/May 2017	RECIST v1.1	NCT02087423 ⁴⁷
MPDL3280A	II	PD-L1+ locally advanced or metastatic NSCLC (128)	MPDL3280A IV 1,200 mg D1 Q3W	ORR (mRECIST)/ORR, DOR, PFS, safety, pharmacokinetics	May 2013/June 2016	mRECIST v1.1	NCT01846416 ²⁶

Abbreviations: Pts, patients; PD-L1+, programmed death ligand 1 positive; Nivo, nivolumab; Pembro, pembrolizumab; SOC, standard of care; DOC, docetaxel; NSCLC, non-small-cell lung cancer; IV, intravenously; D1, day 1; Q*W, every * weeks; SBRT, stereotactic body radiotherapy; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; CR/PR, complete/partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; DSR, deep sustained response; AEs, adverse events; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CTCAE, Common Terminology Criteria for Adverse Events; NR, no report; AUC, area under the curve.

However, treatment options were limited for some patients, such as those with poor performance status. Furthermore, some agent-associated toxicities are so significant that some patients cannot tolerate this therapy. Immunotherapy is a novel therapeutic strategy for the treatment of lung cancer. Immunotherapy responses are slow but durable, whereas chemotherapy can rapidly shrink tumors. In theory, dual therapy that combined chemotherapy with a PD-1/PD-L1 blockade could achieve more long-term control of tumor growth through prolonging PFS, and possibly translate into increased OS. Major progress had been achieved by PD-1/PD-L1 inhibitors in patients with advanced NSCLC. As a result, checkpoint blockade therapy combined with chemotherapy brings new hope for improved outcomes for advanced lung cancer patients.

Some studies have demonstrated great response and good tolerance on combination therapy.^{49–51} The KEYNOTE 021 study evaluated the safety, tolerability, and clinical activity of pembrolizumab (2 or 10 mg/kg intravenously every 3 weeks) + carboplatin combined with paclitaxel (cohort A) and pemetrexed (cohort C).⁴⁹ The study enrolled 44 patients (20 in cohort A and 24 in cohort C) with treatment-naïve advanced NSCLC. The ORR was 30% and 58% in cohorts A and C, respectively. One case of DLT was observed. Rate of Grade 3–4 treatment-associated AEs was 27%, and no treatment-related deaths occurred. No data on the OS and PFS were reported. However, the data reported still indicated that pembrolizumab combined with chemotherapy as first-line therapy for advanced NSCLC showed an acceptable safety profile and is worth evaluating in a large cohort. MPDL3280A (15 mg/kg intravenously every 3 weeks) in combination with chemotherapy as first-line therapy also showed promising clinical activity in this setting, with well-tolerated toxicities.⁵⁰ ORR was 67% in the 37 patients evaluated. The major drug-related toxicities included Grade 3–4 AEs of anemia (7%), neutropenia (7%–13%), and thrombocytopenia (7%), while only one Grade 5 AE of candidemia was observed. Phase III studies are ongoing. Nivolumab, combined with chemotherapy, also showed similar outcomes. The results of the study “CheckMate 012”, which were reported at the 2014 ASCO Annual Meeting, were as follows: ORR 33%–47%, median PFS 21.0–31.0 weeks, and 1-year OS rate 50%–87%. No treatment-related deaths occurred, but a treatment-related toxicity rate of 45% at Grade 3/4 was reported.⁵¹

However, the efficacy of checkpoint inhibitors in combination with chemotherapy for advanced NSCLC was controversial, such as the dose of drugs, timing windows, and so on. Recently, numerous studies designed to evaluate

the efficacy of PD-1/PD-L1 inhibitors in combination with chemotherapy for advanced NSCLC patients have been conducted. Some Phase I/II studies are designed to observe pembrolizumab in combination with chemotherapy for patients with advanced NSCLC.^{52,53} A trial, which was designed to evaluate the feasibility of nivolumab consolidation in Stage IIIA/B NSCLC patients with disease progression after standard first-line chemoradiotherapy, is now recruiting participants.⁵⁴ Another study about consolidation therapy with pembrolizumab is recruiting participants with NSCLC who have received chemoradiation.⁵⁵ We hope those studies will generate data that will result in major progress for the treatment of NSCLC.

PD-1/PD-L1 in combination with targeted therapy in NSCLC

Targeted therapies were performed for a subpopulation of NSCLC patients. Epidermal growth factor receptor (EGFR) TKIs, such as gefitinib, erlotinib, and afatinib, were recommended as first-line treatment for patients with EGFR-mutant advanced NSCLC. Regardless of prolonged disease control, the 5-year survival rates remain poor for advanced NSCLC. The combination of a PD-1 pathway blockade and EGFR-TKIs might be a promising therapeutic treatment for patients with NSCLC, as data from preclinical studies have implied that EGFR activation upregulated PD-L1, which can contribute to immune evasion.^{56,57} Increasing evidence has demonstrated the correlation of genetic alterations in oncogenes and PD-L1 expression. However, there is still confusion regarding the correlation of PD-L1 status, driver genes (EGFR mutation or ALK rearrangement), and prognosis.

A retrospective study of 125 patients with NSCLC, including EGFR-mutant, KRAS-mutant, ALK-translocated or wild-type EGFR, ALK, and KRAS patients, and with confirmed PD-L1 expression, was correlated with EGFR mutations.⁵⁸ PD-1-positive (>5% of TCs) tumors were significantly associated with the presence of KRAS mutation ($P=0.006$), whereas PD-L1-positive tumors were significantly associated with the presence of EGFR mutation ($P=0.001$). Sensitivity to EGFR-TKIs was higher in PD-L1-positive patients than in PD-L1-negative patients in terms of the response rate ($P=0.01$). Of note, PD-L1-positive tumors were significantly associated with adenocarcinoma histology ($P=0.005$). Recently, a retrospective study of 56 patients with EGFR-mutant-positive advanced lung adenocarcinoma demonstrated a significantly greater disease-control rate ($P=0.004$), longer PFS ($P=0.001$), and OS ($P=0.004$) after TKIs therapy in PD-L1-positive patients.⁵⁹ Another retrospective study collected data on 170 patients

with advanced NSCLC treated with EGFR-TKIs in order to examine the correlation of PD-L1, clinicopathologic factors, and prognosis.⁶⁰ Subgroup analyses indicated that PD-L1 expression was associated with significantly shorter OS in EGFR wild-type patients ($P=0.029$) but not in EGFR-mutant patients ($P=0.932$) treated with EGFR-TKIs for lung adenocarcinoma.

On the other hand, EGFR-TKIs, in combination with PD-L1 blockade were well tolerated in patients with NSCLC. MEDI4736 (cohort A: 3 mg/kg every 2 weeks; cohort B: 10 mg/kg every 2 weeks) with gefitinib was utilized in an escalation Phase I study, and the data indicated that the maximum tolerated dose was not reached and no DLTs were observed; Grade 3–4 AEs were observed in three patients, including dyspnea/hypoxia, myalgia/fatigue, and elevated ALT.⁶¹ These data suggest a need to further evaluate the efficacy of combined therapies in patients with EGFR-sensitized, mutation-positive, TKI-naïve NSCLC.

Antiangiogenesis therapy is one of the most commonly used treatment strategies for advanced lung cancer. Bevacizumab (BEV) is a recombinant mAb that blocks the vascular endothelial growth factor, and is recommended, in combination with platinum-doublet chemotherapy, for locally advanced or metastatic non-SqNSCLC as first-line therapy or monotherapy maintenance. For patients who have responded (complete response [CR], partial response [PR], or stable disease [SD]) to previous chemotherapy with BEV, maintenance with BEV as monotherapy is recommended. Data from the recent AVAPERL study demonstrated that PFS and median OS for patients treated with single-agent BEV were 3.7 and 13.2 months, respectively.⁹ Recently, a Phase I study evaluated the efficacy of nivolumab ± BEV maintenance in patients with advanced NSCLC who did not progress during or after first-line platinum-based chemotherapy.⁶² Median PFS was 37.1 weeks with nivolumab + BEV, with the median OS not reached (range: 33.3, 86.7+ weeks). Few cases of Grade 3 treatment-related AEs occurred, and no Grade 4 AEs occurred in the nivolumab + BEV arms. These preliminary data support further evaluation of the efficacy of nivolumab ± BEV maintenance therapy in chemotherapy-treated patients. To compare the efficacy and safety of PD-1/PD-L1 blockade in combination with different treatment regimens, we have summarized that information in Table 5.

Necitumumab is a second-generation, recombinant human IgG1, EGFR mAb. Data from two randomized studies, INSPIRE and SQUIRE, indicated that necitumumab + gemcitabine and cisplatin, as a first-line therapy, could improve OS in treatment-naïve patients with advanced SqNSCLC (11.5 versus 9.9 months; $P=0.01$), but not in

non-SqNSCLC patients who are treated with necitumumab + pemetrexed and cisplatin.^{63,64} Necitumumab showed promising outcomes for patients with SqNSCLC. Recently, a Phase I study was designed to observe the safety and efficacy for necitumumab + pembrolizumab in advanced SqNSCLC and non-SqNSCLC patients.⁶⁵

PD-1/PD-L1 blockade in combination with CTLA-4 inhibitors in NSCLC

As mentioned, activation of T-cells requires antigen-specific stimulation via the TCR and a costimulatory signal. Among two coinhibitory signal model, CTLA-4 as the first identified coinhibitory pathway, a transmembrane glycoprotein with considerable homology to CD28, transmits an inhibitory signal to naïve T-cells and T-helper cells and enhances regulatory T-cell immunosuppressive activity. CTLA-4 inhibits T-cell activation by outcompeting CD28 in binding to CD80 and CD86. In contrast, PD-1 is primarily to inhibit activated T-cell function via its interaction with PD-L1 and PD-L2. It has been demonstrated that PD-1 ligation inhibited PI3K activity and downstream AKT activation, whereas CTLA-4 only inhibited AKT activation but did not influence PI3K activity. As CTLA-4 and PD-1 regulate immune response through a nonredundant distinct mechanism, it was possible to achieve superior antitumor effects by combined with dual blockade therapy. PD-1/PD-L1 blockades, in combination with anti-CTLA-4 mAb, as a dual checkpoint blockade has received increased attention due to the potential synergy effect. MEDI4736, an inhibitor of PD-L1, combined with tremelimumab (a selective human IgG2 mAb inhibitor of CTLA-4) has showed a promising response (PR and SD) with a manageable safety profile in solid tumors.⁶⁶ CheckMate 067 was conducted to evaluate the efficacy and safety of nivolumab ± ipilimumab in comparison with ipilimumab alone in patients with untreated metastatic melanoma.⁶⁷ Results showed the median PFS was 11.5 months with nivolumab + ipilimumab, which was significantly high when compared with 2.9 months with ipilimumab ($P<0.001$), and 6.9 months with nivolumab ($P<0.001$). However, treatment-related AEs of Grade 3–4 occurred 55.0% in the nivolumab + ipilimumab group, which were also higher compared with 16.3% in the nivolumab group and 27.3% in the ipilimumab group. So far, the dosage, timing, efficacy, and safety of the combination compared to standard of care are still unknown. Recently, a dose-escalation Phase I study was designed to evaluate safety/tolerability and to identify the maximum tolerated dose of MEDI4736 in combination with tremelimumab in advanced solid tumors including NSCLC.⁶⁸ A Phase III study, which is designed to evaluate the efficacy

Table 5 Efficacy and safety of immunotherapy with chemotherapy and targeted therapy in NSCLC patients

Agents	Authors	Pts	Regimens	ORR	PFS	OS	AEs
With chemotherapy	Papadimitrakopoulou et al ⁴⁹	Treatment-naïve Stage IIIB/IV NSCLC	Cohort A: Pembro: 2 or 10 mg/kg Q3W, Carboplatin: AUC 6 + paclitaxel 200 mg/m ² 4 cycles; pembro maintenance Cohort C: Pembro: 2 or 10 mg/kg Q3W, Carboplatin: AUC 5+ pemetrexed 500 mg/m ² 4 cycles; pembro + pemetrexed maintenance	Cohort A: 30% (pembro 10 mg/kg); 30% (pembro 2 mg/kg) Cohort C: 67% (pembro 10 mg/kg); 50% (pembro 2 mg/kg)	NR	NR	DLT 1 Grade 3 rash C 10 mg/kg Grade 3–4 treatment-related AE rate was 27% (15% in A, 38% in C); AEs were reversible transaminase elevation (n=3 in C), anemia (n=1 in A, 2 in C), rash (n=1 in A, 1 in C, colitis (n=2 in C) Grade 3–4: anemia 7% (arms D and E), neutropenia (arm C, 13%; arm D, 7%), thrombocytopenia (arms D and E, 7%)
	Liu et al ⁵⁰	Treatment-naïve Stage IIIB/IV NSCLC	Arm C: MPDL3280A 1,200 mg/m ² + paclitaxel 200 mg/m ² + carboplatin AUC 6, Q3W Arm D: MPDL3280A 1,200 mg/m ² + pemetrexed 500 mg/m ² + carboplatin AUC 6, Q3W Arm E: MPDL3280A 1,200 mg/m ² Q3W + nab-paclitaxel 100 mg/m ² Q1W + carboplatin AUC 6 Q3W	67% (all); 60% (in C) 75% (in D) 62% (in E)	NR	NR	
	Antonia et al ⁵¹	Chemotherapy-naïve patients with advanced NSCLC	Nivo 10 mg/kg + DDP 75 mg/m ² + GEM 1,250 mg/m ² (sq)/pemetrexed 500 mg/m ² (non-sq); Nivo 5 or 10 mg/kg Q3W + paclitaxel 200 mg/m ² + carboplatin AUC 6 (sq + non-sq); 4 cycles	33%–50%	36%–71% (24 wk)	59%–87% (1 yr)	25%–73% (Grade 3–4)
With targeted therapy	Rizvi et al ⁶²	Patients with advanced NSCLC without progression on first-line platinum-based chemotherapy	Nivo 5 mg/kg + BEV 15 mg/kg Q3W (non-sq); Nivo 3 mg/kg Q2W (sq, non-sq)	8% (Nivo + BEV); 10% (Nivo)	Nivo + BEV (8%) 37.1 wk; Nivo monotherapy: 16 wk (sq), 21.4 wks (non-sq)	Not reached (range: 33.3, 86.7+ weeks with Nivo + BEV; 2.1+56.3+ weeks with Nivo monotherapy)	No Grade 4 AEs

Abbreviations: Nivo, nivolumab; Pembro, pembrolizumab; DDP, cisplatin; GEM, gemcitabine; BEV, bevacizumab; non-sq, non-squamous; Q*W, every * week; PFS, progression-free survival; OS, overall survival; ORR, overall response rate; AEs, adverse events; Pts, patients; NR, not reported; DLT, dose-limiting toxicity; wk, week; yr, year; NSCLC, non-small-cell lung cancer; AUC, area under the curve.

and safety of MEDI4736 as third-line monotherapy (substudy A, PD-L1 positive) + tremelimumab (substudy B, PD-L1 negative) versus standard of care (including erlotinib, gemcitabine, or vinorelbine) in Stage IIIB/IV NSCLC patients, is currently recruiting participants.⁶⁹

PD-1/PD-L1 inhibitors in combination with radiotherapy in NSCLC

Radiotherapy has been recognized as a local therapy. Tumor immunogenicity relapse, mediated by irradiation, has been demonstrated in several models. Preclinical studies have indicated that tumor antigen-specific CD8⁺ T-cells increase following treatment of ablative single-dose local radiation. The complex local immune microenvironment induced by radiation enhances the host's capability of immune response to the tumor, which may result in a metastatic lesion regression. This process is the so-called abscopal effect or radiation-induced bystander effect.^{70,71} These complex molecular mechanisms allow combination therapy to become a possibility.⁷² As a result, radiotherapy combined with immunotherapy, in particular, a PD-1/PD-L1 pathway blockade, has generated a great deal of attention as a possible treatment regimen for NSCLC.

However, to date, no studies combining radiotherapy and immunotherapy have been completed for patients with NSCLC. Although it may be a new paradigm in cancer treatment, radiotherapy combined with immunotherapy still leaves a number of issues unresolved, such as the mechanism of combined therapy, the fraction model of irradiation, the time window for the combination of two treatments, and so on.⁷³

Currently, the main research focus in radioimmunotherapy is to determine the interaction of fraction regimens and immunotherapy. CTLA-4 is another checkpoint pathway that can attenuate the early activation of naïve and memory T-cells. An abscopal effect, mediated by radiotherapy and CTLA-4 inhibitors, has been reported in a treatment-refractory lung adenocarcinoma patient.⁷⁴ An immune-mediated abscopal effect has been observed with fractionated but not single-dose radiotherapy combined with anti-CTLA-4 antibody.⁷⁵ Schaeue et al⁷⁶ also demonstrated that radiation-mediated immune response varied with the size of dose per fraction. The medium-size radiation doses of 7.5 Gy/fraction gave the best tumor control rather than single-dose fractionated doses. PD-1 and PD-L1 act in a negative feedback loop to downregulate T-cell effector function and mediate apoptosis of infiltrating T-cells, leading to tumor immune evasion.^{12,77} We believe that irradiation combined

with anti-PD-L1 mAbs might also show similar results. Currently, a Phase I/II study has been designed to evaluate the safety and tolerability of pembrolizumab with SBRT in patients with NSCLC.⁷⁸ The goal of Phase II of this study is to validate the benefits from combination therapy for metastatic NSCLC. This study is not yet open for participant recruitment. Because of the abscopal effect, investigators believe that local SBRT to a single lesion for recurrent NSCLC in combination with checkpoint inhibitors could enhance the antitumor immune response, which could prolong patients' PFS or OS. However, as mentioned earlier, the model of irradiation in combination with checkpoint inhibitors has not been defined. A randomized Phase II, two-arm study was designed to observe ORR to pembrolizumab after SBRT versus pembrolizumab alone in patients with advanced NSCLC.⁷⁹ Another Phase I/II study was designed to evaluate the combination of pembrolizumab and SBRT in patients with metastatic NSCLC.⁸⁰

Conclusion

As a result of the success using anti-PD-1/PD-L1 mAbs in clinical studies, research in the field of immunotherapy has greatly increased in recent years. Anti-PD-1 and anti-PD-L1 mAbs, used as third-, second-, and even first-line therapy, have shown promising efficacy in patients with NSCLC and has consequently impacted upon the survival and quality of life. However, immunotherapy is not perfect and has a lot of unanswered questions, such as when and how to evaluate the efficacy, what are the effective biomarkers to predict response and prognosis, and so on. Additionally, it is critical to clarify the appropriate patients who will benefit from checkpoint blockade. Furthermore, investigations to determine the mechanisms of checkpoint pathways and the efficacy of combining immunotherapy with other antitumor agents are warranted.

Disclosure

The authors report no conflicts of interest in this work.

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