Review Article

Immunotherapy for advanced non-small cell lung cancer with negative programmed death-ligand 1 expression: a literature review

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Background and Objective: Lung cancer, mainly non-small cell lung cancer (NSCLC), is a serious threat to human life. In particular, the prognosis for advanced patients is poor, with the 5-year survival rate being exceedingly low. In recent years, immune checkpoint inhibition has changed the pattern of the treatment of a variety of cancers, including lung cancer; however, not all patients can benefit from immunotherapy, and thus finding the right biomarkers is particularly important for guiding precise treatment. Programmed death-ligand 1 (PD-L1) expression is one of the most valuable biomarkers for predicting the efficacy of lung cancer immunotherapy. Several studies have confirmed that patients with high PD-L1 expression are more likely to benefit from immunotherapy, but there is a high proportion of people with negative PD-L1 expression constituting a patient population that cannot be ignored. This article reviews the distribution of PD-L1 expression, the methods for evaluating PD-L1, and the effectiveness of immunotherapy for advanced NSCLC with negative PD-L1 expression.

Methods: We performed a literature review to identify relevant data published until September 2022. In order to organize related information, we searched for literature in PubMed; abstracts and reports published in the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), the World Conference on Lung Cancer (WCLC), and other congresses; and clinical trial information registered on ClinicalTrials.gov. Information on the distribution of PD-L1 expression, detection of PD-L1, and immunotherapy efficacy for NSCLC with negative PD-L1 expression was collated and reviewed.

Key Content and Findings: The incidence of PD-L1 expression in patients with stage IIIB/IV NSCLC is similar in all regions of the world, but PD-L1 expression level is associated with certain clinicopathological features. The expression of PD-L1 can be evaluated by various detecting methods. Some immunotherapy regimens have better efficacy than traditional chemotherapy in patients with negative PD-L1 expression.

Conclusions: Patients with NSCLC and negative PD-L1 expression can receive better survival benefits under some immunotherapy types, and these may represent a better treatment option for this relatively small patient population.

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Introduction

Lung cancer is a malignant tumor of major concern and threatens the health of populations worldwide. According to the data of the International Agency for Research on Cancer (IARC), there were about 2.207 million new cases of lung cancer and 1.796 million deaths worldwide in 2020, ranking it second in incidence and first in mortality (1). Among lung cancer cases, 85% are non-small cell lung cancer (NSCLC), and the 5-year survival is 26% for NSCLC overall, and only 8% for metastatic NSCLC (2,3). In early-stage patients, radical treatment can be achieved by operation, stereotactic body radiation therapy (SBRT) or radical concurrent chemoradiotherapy (cCRT), but almost half of patients are stage IV at the time of detection, and thus have already missed the chance of radical treatment. In addition, even in locally advanced stage patients who can be operated upon, the recurrence rate in the first year after surgery is as high as 41% (4). Therefore, systemic therapy, including chemotherapy, targeted therapy, and immunotherapy, has an important role in the treatment of lung cancer.

In recent years, immunotherapy, which mainly includes immune checkpoint inhibitors (ICIs), has changed the treatment of many cancers. The two most widely used immune checkpoints in NSCLC are programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1) and the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). CTLA-4 is commonly expressed in $CD4^+$ and $CD8^+$ T lymphocytes and provides an early inhibitory signal to prevent T-cell activation. PD-1 is expressed on T cells, B cells, and natural killer cells and plays a role in regulating central and peripheral immune tolerance. By overexpressing immune-checkpoint molecules, tumor cells (TCs) inhibit the response of the human immune system, escape from the surveillance and killing of human immune, and thus promote the growth of TCs (2). Anti-PD-1 antibodies include pembrolizumab, nivolumab, camrelizumab, tislelizumab, and sintilimab, among others. These are humanized or fully human immunoglobulin G4 (IgG4) type monoclonal antibodies. By binding PD-1 and blocking the binding of PD-L1 and PD-L2, it can relieve the immunosuppressive effect, activate the function of T cells, enhance the immune surveillance and killing ability of T cells to tumor, and generate tumor immune response. Anti-PD-L1 antibodies include atezolizumab, durvalumab, and sugemalimab, among others. They are monoclonal antibodies of human IgG1 or IgG4, which can block the binding of PD-L1 to PD-1 and CD80, in this way, T cells can recognize and kill TCs (5). Anti-CTLA-4 antibodies, including ipilimumab and tremelimumab, can bind to CTLA-4 and block the interaction between CTLA-4 and its ligand CD80/CD86. Blocking CTLA-4 has been shown to enhance the activation and proliferation of T cells, including tumor-infiltrating effector T cells. Inhibition of CTLA-4 signaling also attenuates regulatory T-cell function, which may contribute to a general increase in T-cell reactivity, including antitumor immune responses (6). ICIs, including anti-PD-1, PD-L1, and CTLA-4 antibodies, have shown promising efficacy and safety in the treatment of advanced NSCLC. Evaluating the economic impact of ICIs is of great importance due to escalating healthcare costs. A previous study (7) has shown that for a general cohort with NSCLC, nivolumab was not cost-effective, but increasing PD-L1 cutoffs resulted in acceptable cost-effectiveness (CE). On the other hand, pembrolizumab was found to be cost-effective for both previously treated and newly-diagnosed metastatic NSCLC. Overall, there are limitations to the CE of ICIs. More CE investigations and clinical trials are needed in the future.

Despite the significant and durable clinical efficacy of anti-PD-1/PD-L1 immune therapy in many cancer types, its use is also associated with high rates of skin, gastrointestinal, and endocrine adverse effects. Studies (8,9) have found that anti-PD-1 immune therapy increases the incidence of both high-grade and any-grade pneumonitis compared to chemotherapy, while there is no significant difference for anti-PD-L1 immune therapy. Although complications and cost issues exist with anti-PD-1/PD-L1 immune therapy, its tumor response rates, progression-free survival, and overall survival are significantly superior to those of chemotherapy.

However, there are still a large number of patients who do not benefit from immunotherapy. Therefore, the search for appropriate predictive biomarkers can help us further achieve the precise treatment of lung cancer.

PD-L1 expression is one of the most informative biomarkers for predicting the efficacy of lung cancer immunotherapy. Multiple studies have confirmed that patients with high PD-L1 expression are more likely to benefit from immunotherapy. However, there is a high proportion of patients with negative PD-L1 expression, and thus this patient population cannot be ignored. The PD-L1 tumor proportion score (TPS) is less than 1% in 41–57% of patients with NSCLC (10). Therefore, whether patients with negative PD-L1 expression can benefit from immunotherapy remains unclear. This review summarizes the literature concerning the distribution of PD-L1 expression, the detection of PD-L1, and discusses the current status of immunotherapy for patients with locally advanced or metastatic cancer and negative PD-L1 expression (*Tables 1*,*2*). We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-144/rc).

Methods

We performed a systematic literature review to identify all relevant data published until September 2022. In order to organize related information, we searched the literature published in PubMed; abstracts and reports published in the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), the World Conference on Lung Cancer (WCLC), and other congresses; and clinical trial information registered on ClinicalTrials.gov. Information on the distribution of PD-L1 expression, detection of PD-L1, and immunotherapy of advanced NSCLC with negative PD-L1 expression was collated and analyzed. *Table 3* summarizes the search strategy.

Distribution of PD-L1 expression

Distribution of PD-L1 expression in real world and trial cohorts

The PD-L1 immunohistochemistry (IHC) 22C3 was used to uniformly detect pretreatment tumor tissues from 2,617 patients with stage IIIB/IV NSCLC from 45 centers in 18 countries (10). Among 2,368 patients with detectable PD-L1 expression data, 1,136 (48%) patients had PD-L1 TPS <1% and 530 (22%) patients had PD-L1 TPS ≥50%. PD-L1 expression was slightly different in different regions of NSCLC patients: the proportion of PD-L1 TPS <1% and TPS ≥50% in Europe, was 48% and 22%, respectively, and was 47% and 22% in the Asia Pacific region, 53% and 21% in the Americas, and 45% and 24% in other regions, respectively. The prevalence of PD-L1 TPS <1% and TPS ≥50% in patients with stage IIIB/IV NSCLC is similar in all regions of the world, but the incidence of PD-L1 TPS <1% in the real world is higher than that in most populations screened in clinical trials (*Table 2*) (10). Similarly, in a real-world study in China, a total of 879 patients with NSCLC were included, of whom 424 (48.2%) had PD-L1 TPS <1% and 189 (21.5%) had PD-L1 TPS ≥50% (45). In another analysis of 6,295 NSCLC samples from China, PD-L1 TPS <1% and ≥50% were 57% and 14.3%, respectively (46). A PD-L1 22C3 IHC pharmDx assay from Canada found that among 1,713 patients with NSCLC, the proportion of patients with TPS less than 1% was 41.6%, and the proportion of patients with TPS ≥50% was 29.8% (47).

Clinicopathologic factors associated with PD-L1 expression

The distribution of PD-L1 expression varies with different clinicopathological features, including mutation type, histological type, and primary or metastatic lesions. In their study, Hwang *et al.* found that the expression rate of PD-L1 was higher in those with epidermal growth factor receptor (*EGFR*) wild type (WT), squamous cell carcinoma, and metastatic tumors (P<0.001) (47).

PD-L1 expression: biopsy vs. resected tissue

PD-L1 expression was higher in biopsy samples than in resected samples and higher in metastatic samples than in primary tissues. In adenocarcinoma, positive PD-L1 expression was associated with male sex, larger tumor size, metastasis to lymph nodes or other sites, lymphovascular invasion, and visceral pleural invasion (46). Biopsy specimens overall showed a higher expression rate of PD-L1 than did excised specimens. In addition, they found only moderate agreement (κ=0.67) between PD-L1-paired biopsy and resected specimens in 103 patients. Of the biopsied samples with TPS <1%, 52% (25/48) actually had TPS greater than 1% in the resected tumor, whereas 84.6% (22/26) of the samples with TPS greater than or equal to 50% in the resected tumor. The inconsistency rate between

Table 1 Major information from clinical trials of anti-PD-1/PD-L1 immunotherapy in NSCLC

Trials	Therapy line	CT number	Phase	Patients	Number of cases	Beginning and ending time	Therapy method	Primary end point
KEYNOTE-001 (11-13)	1, 2, 3	NCT01295827	I	NSCLC	101 treatment naive; 449 previously treated	Mar 4, 2011–Nov 5, 2018	Pembrolizumab	ORR
KEYNOTE-021G (14)	1	NCT02039674	I/II	Non-squamous NSCLC	123 (1:1)	Nov 25, 2014–Jan 25, 2016	Pembrolizumab + chemotherapy *vs.* chemotherapy	ORR
KEYNOTE-189 (15)	1	NCT02578680	III	Non-squamous NSCLC	616 (2:1)	Jan 15, 2016–Nov 8, 2017	Pembrolizumab + chemotherapy *vs.* chemotherapy	PFS, OS
KEYNOTE-407 (16)	1	NCT02775435	III	Squamous NSCLC	559 (1:1)	Jun 9, 2016–Apr 3, 2018	Pembrolizumab + chemotherapy *vs.* chemotherapy	OS, PFS
KEYNOTE-799 (17)	Immunotherapy combined with concurrent chemoradiotherapy	NCT03631784	II	NSCLC	112 (1:1)	Oct 19, 2018–Oct 18, 2021	Pembrolizumab + chemotherapy *vs.* chemotherapy	ORR, incidence of grade 3 or higher pneumonia
CheckMate-012 (18)	1	NCT01454102	I	NSCLC	17; 14	Dec 16, 2011–Jul 20, 2016	Nivolumab + ipilimumab, nivolumab	Safety
CheckMate-227 (19)	1	NCT02477826	III	NSCLC	1,189 (1:1:1); 550 (1:1:1)	Aug 5, 2015–Aug 29, 2024	Nivolumab *vs.* chemotherapy *vs.* nivolumab + ipilimumab	OS, PFS
CheckMate-9LA (20)	1	NCT03215706	III	NSCLC	1,150 (1:1)	Aug 24, 2017–Aug 16, 2019	Nivolumab + chemotherapy *vs.* chemotherapy	OS
CheckMate-017 (21)	2	NCT01642004	III	Squamous NSCLC	272 (1:1)	Oct 16, 2012–Nov 17, 2014	Nivolumab *vs.* docetaxel	OS
CheckMate-057 (22)	3	NCT01673867	III	non-squamous NSCLC	582 (1:1)	Nov 2, 2012–Feb 5, 2015	Nivolumab *vs.* docetaxel	OS
CheckMate-078 (23)	4	NCT02613507	III	NSCLC	504 (2:1)	Dec 11, 2015–Sep 15, 2017	Nivolumab *vs.* docetaxel	OS
CheckMate-870 (24)	5	NCT03195491	III	NSCLC	400	Dec 25, 2017–Jun 8, 2021	Nivolumab	Safety
Camel (25)	1	NCT03134872	III	Non-squamous NSCLC	412 (1:1)	May 12, 2017–Jul 27, 2019	Camrelizumab + chemotherapy *vs.* chemotherapy	PFS
Camel-sq (26)	1	NCT03668496	III	Squamous NSCLC	390 (1:1)	Nov 9, 2018–Nov 6, 2020	Camrelizumab + chemotherapy *vs.* chemotherapy	PFS
SHR-1210-II-201 (27)	2	NCT03085069	II	NSCLC	146	May 3, 2017–Aug 20, 2020	Camrelizumab	ORR
SHR-1210-II-202 (28)	1	NCT03083041	I/II	Non-squamous NSCLC	210	Mar 22, 2017–Apr 22, 2022	Camrelizumab + apatinib	Safety, ORR
RATIONALE 304 (29)	1	NCT03663205	III	Non-squamous NSCLC	332 (2:1)	Mar 22, 2017–Oct 26, 2020	Tislelizumab + chemotherapy *vs.* chemotherapy	PFS

Table 1 *(continued)*

Table 1 *(continued)*

Trials	Therapy line	CT number	Phase	Patients	Number of cases	Beginning and ending time	Therapy method	Primary end point
RATIONALE 307 (30)	1	NCT03594747	III	Squamous NSCLC	360 (1:1:1)	Jul 30, 2018–Sep 30, 2020	Tislelizumab plus paclitaxel/albumin paclitaxel and carboplatin *vs.* paclitaxel plus carboplatin	PFS
RATIONALE 303 (31,32)	2, 3	NCT03358875	III	NSCLC	805 (2:1)	Nov 30, 2017–Dec 30, 2022	Tislelizumab *vs.* docetaxel	OS
ORIENT-11 (33)	1	NCT03607539	III	Non-squamous NSCLC	397 (2:1)	Aug 23, 2018–Nov 15, 2019	Sintilimab + chemotherapy *vs.* chemotherapy	PFS
ORIENT-12 (34)	1	NCT03629925	III	Squamous NSCLC	357 (1:1)	Sep 28, 2018–Oct 15, 2019	Sintilimab + chemotherapy *vs.* chemotherapy	PFS
IMpower130 (35)	1	NCT02367781	III	Non-squamous NSCLC	724 (2:1)	Apr 16, 2015–Mar 15, 2018	Atezolizumab + chemotherapy *vs.* chemotherapy	PFS, OS
IMpower132 (36)	1	NCT02657434	III	Non-squamous NSCLC	578 (1:1)	Apr 30, 2016–Jul 18, 2019	Atezolizumab + chemotherapy *vs.* chemotherapy	PFS, OS
IMpower131 (37)	1	NCT02367794	III	Squamous NSCLC	343 (1:1)	Jun 11, 2015–Oct 3, 2018	Atezolizumab + chemotherapy *vs.* chemotherapy	OS
IMpower150 (38)	1	NCT02366143	III	Non-squamous NSCLC	1,202 (1:1:1)	Mar 31, 2015–Sep 13, 2019	ABCP/ACP *vs.* BCP	PFS, OS
POPLAR (39)	2	NCT01903993	II	NSCLC	287 (1:1)	Aug 6, 2013–Nov 19, 2015	Atezolizumab *vs.* docetaxel	OS
OAK (40)	2	NCT02008227	III	NSCLC	1,225	Mar 11, 2014–Jul 7, 2016	Atezolizumab *vs.* docetaxel	OS
PACIFIC (41)	Consolidation therapy followed chemoradiotherapy	NCT02125461	III	NSCLC	713	May 7, 2014–Feb 13, 2017	Durvalumab	PFS, OS
MYSTIC (42)	1	NCT02453282	III	NSCLC	1,118 (1:1:1)	Jul 21, 2015–Oct 4, 2018	D/D + T *vs.* CT	OS, PFS
POSEIDON (43)	1	NCT03164616	III	NSCLC	1,013 (1:1:1)	Jun 1, 2017–Mar 12, 2021	T + D + CT/D + CT *vs.* CT	PFS, OS
GEMSTONE-302 (44)	1	NCT03789604	III	NSCLC	479 (2:1)	Dec 13, 2018–Jun 8, 2020	Sugemalimab + chemotherapy *vs.* chemotherapy	PFS

PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; ABCP, atezolizumab combined with bevacizumab and carboplatin paclitaxel; ACP, atezolizumab combined with carboplatin and paclitaxel group; BCP, bevacizumab combined with carboplatin and paclitaxel group; D, duvalizumab; T, tremelimumab; CT, chemotherapy.

Table 2 Clinical trial end points of anti-PD-1/PD-L1 immunotherapy in NSCLC

Trials	PD-L1 positive	PD-L1 negative	PD-L1 negative rate	Therapy method	OS	PFS	ORR
KEYNOTE-001 (11-13)	385	102	0.21	Pembrolizumab	8.6 m		
KEYNOTE-021G (14)	79	44	0.36	Pembrolizumab + chemotherapy *vs.* chemotherapy	34.5 *vs.* 16.7 m		67% *vs.* 17%
KEYNOTE-189 (15)	388	190	0.33	Pembrolizumab + chemotherapy *vs.* chemotherapy	17.2 *vs.* 10.2 m	6.2 *vs.* 5.1 m	32.3% *vs.* 14.3%
KEYNOTE-407 (16)	353	194	0.35	Pembrolizumab + chemotherapy *vs.* chemotherapy	15 *vs.* 11 m	6.3 *vs.* 5.9 m	67.4% *vs.* 41.4%
KEYNOTE 799 (17)	106	49	0.32	Pembrolizumab + chemotherapy *vs.* chemotherapy			66.7% *vs.* 71.4%
CheckMate-012 (18,19)	76	31	0.29	Nivolumab + ipilimumab, nivolumab			18% *vs.* 14%
CheckMate-227 (19)	1,189	550	0.32	Nivolumab + ipilimumab *vs.* nivolumab *vs.* chemotherapy	17.2 *vs.* 15.2 *vs.* 12.2 m	5.1 *vs.* 5.6 *vs.* 4.7 m	27.3% *vs.* 37.9% *vs.* 23.1%
CheckMate-9LA (20)	407	264	0.39	Nivolumab + chemotherapy *vs.* chemotherapy	16.8 *vs.* 9.8 m		
CheckMate-017/057 (21,22)	364	316	0.46	Nivolumab *vs.* docetaxel	9.7 *vs.* 7.8 m		
CheckMate-078 (23)	252	205	0.45	Nivolumab *vs.* docetaxel	11.4 *vs.* 10.2 m		
CheckMate-870 (24)	169	174	0.51	Nivolumab	13.3 m		15%
Camel (25)	255	118	0.32	Camrelizumab + chemotherapy *vs.* chemotherapy		HR 0.76 (95% CI: 0.45–1.26)	
Camel-sq (26)	188	188	0.50	Camrelizumab + chemotherapy *vs.* chemotherapy	HR 0.62 (95% CI: 0.41–0.94)	HR 0.49 (95% CI: 0.35–0.68)	
SHR-1210-II-201 (27)	72	74	0.51	Camrelizumab		2.1 m	12.2%
SHR-1210-II-202 (28)	25	66	0.73	Camrelizumab + apatinib		11 m	40%
RATIONALE 304 (29)	190	144	0.43	Tislelizumab + chemotherapy *vs.* chemotherapy		HR 0.76 (95% CI: 0.47–1.22)	
RATIONALE 307 (30)	144	97	0.40	Tislelizumab + paclitaxel/carboplatin *vs.* tislelizumab + nab-paclitaxel/carboplatin *vs.* paclitaxel/carboplatin		HR 0.64 (95% CI: 0.37–1.10); HR 0.69 (95% CI: 0.41–1.18)	68.8% *vs.* 68.1% *vs.* 51.0%
RATIONALE 303 (31,32)	486	319	0.40	Tislelizumab *vs.* docetaxel	HR 0.74 (95% CI: 0.541–1.000)		
ORIENT-11 (33)	268	117	0.30	Sintilimab + chemotherapy *vs.* chemotherapy	HR 0.75 (95% CI: 0.48–1.19)	HR 0.60 (95% CI: 0.39–0.92)	

Table 2 *(continued)*

Table 2 *(continued)*

Trials	PD-L1 positive	PD-L1 negative	PD-L1 negative rate	Therapy method	OS	PFS	ORR
ORIENT-12 (34)	235	122	0.34	Sintilimab + chemotherapy *vs.* chemotherapy		HR 0.59 (95% CI: 0.41–1.09)	
IMpower130 (35)	323	356	0.52	Atezolizumab + chemotherapy *vs.* chemotherapy	15.2 *vs.* 12.0 m	6.2 *vs.* 4.7 m	
IMpower132 (36)	181	163	0.47	Atezolizumab + chemotherapy *vs.* chemotherapy	15.9 *vs.* 10.5 m	8.5 *vs.* 4.9 m	
IMpower131 (37)	518	331	0.39	Atezolizumab + chemotherapy *vs.* chemotherapy	14.0 *vs.* 12.5 m	5.7 *vs.* 5.6 m	
IMpower150 (38)	626	575	0.48	ABCP *vs.* ACP *vs.* BCP	16.9 *vs.* 14.8 *vs.* 14.1 m		
POPLAR (39)	195	92	0.32	Atezolizumab *vs.* docetaxel	9.7 *vs.* 9.7 m		
OAK (40)	306	215	0.41	Atezolizumab *vs.* docetaxel	9.9 *vs.* 7.0 m		
PACIFIC (41)	303	148	0.33	Durvalumab *vs.* placebo	33.1 *vs.* 43.0 m	10.7 *vs.* 5.6 m	
MYSTIC (42)	864	254	0.23	D *vs.* D + T *vs.* CT	10.1 *vs.* 11.9 *vs.* 10.3 m		
POSEIDON (43)	638	374	0.37	T + D + CT/D + CT *vs.* CT	14.0/13.3 *vs.* 11.7 m		
GEMSTONE-302 (44)	291	188	0.39	Sugemalimab + chemotherapy *vs.* chemotherapy		7.4 *vs.* 4.9 m	50.0% *vs.* 39.1%
Total	9,876	6,060	0.38				

PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; m, month; HR, hazard ratio; CI, confidence interval; ABCP, atezolizumab combined with bevacizumab and carboplatin paclitaxel; ACP, atezolizumab combined with carboplatin and paclitaxel group; BCP, bevacizumab combined with carboplatin and paclitaxel group; D, duvalizumab; T, tremelimumab; CT, chemotherapy.

Table 3 The summary of the search strategy

Items	Specification
Date of search	September 1, 2022
Databases and other sources searched	PubMed, ASCO, ESMO, WCLC, ClinicalTrials.gov
Search terms used	Non-small cell lung cancer; immunotherapy; negative PD-L1 expression
Time frame	2012–2023
Inclusion and exclusion criteria	Inclusion criteria: (I) literature types were randomized controlled trials, prospective or retrospective cohort studies, or systematic reviews and meta-analyses; (II) English-language articles
	Exclusion criteria: (I) literature types were editorial comments, case reports or series, guidelines, consensus statements, or study protocols; (II) language other than English
Selection process	Y.B. conducted the selection independently, and consensus was obtained by discussion and reaching a mutual agreement

ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; WCLC, World Conference on Lung Cancer; PD-L1, programmed death-ligand 1.

resection and biopsy with an area of less than 8 mm^2 was 71.4%, while the inconsistency rate between resection and biopsy with an area of greater than or equal to 8 mm^2 was 33.3% (P<0.026). In patients with primary tumor tissue samples, PD-L1 expression was higher in biopsy samples than in resected samples, and was highest in lymph nodes and lowest in bone (47).

PD-L1 expression: primary tumor vs. metastases

Negative PD-L1 expression was consistently more common in primary samples than in metastatic samples. In 27 paired primary lung and metastatic tumor biopsies, only a weak agreement was observed (κ=0.48) (47). In a systematic review of several studies, high PD-L1 expression was more associated with shorter survival than was low PD-L1 expression. In addition, the majority of evidence suggests that patients with high PD-L1 expression are more likely to benefit from anti-PD-1/PD-L1 agents (nivolumab, pembrolizumab, durvalumab, atezolizumab, and avelumab) than are patients with low PD-L1 expression in advanced NSCLC (48). In another study, PD-L1 expression was analyzed in tumor tissues of 80 patients with lung adenocarcinoma treated with tyrosine kinase inhibitor (TKI), of whom 71 had *EGFR* mutations and 9 had anaplastic lymphoma kinase (*ALK*) rearrangements. It was found that 45 patients (56.2%) had TPS <1% and 9 patients (11.3%) had TPS ≥50%. Among 71 *EGFR*-mutated tumors, 41 (57.7%) had TPS <1% and 7 (9.9%) had TPS ≥50%. Patients with TPS <1% had significantly better progression-free survival (PFS) than did patients with TPS ≥1% after initial TKI treatment (P=0.016) (49).

PD-L1 expression: association with tumour mutations

Next-generation sequencing showed that high PD-L1 expression was significantly associated with *KRAS*, *TP53*, and *MET* mutations, and WNT pathway changes were associated with negative PD-L1 expression. *EGFR* and *STK11* mutations were significantly associated with PD-L1 negativity and negated the predictive value of PD-L1 expression for ICI response (50).

PD-L1 expression: association with histological type

Zheng *et al.* used the PD-L1 (22C3) method to analyze the association of PD-L1 expression with clinicopathological features and driver mutations in 6,295 NSCLC specimens from 6 centers in China. They consistently found that PD-L1 expression was more common in squamous cell carcinoma and other histological types of NSCLC than in adenocarcinoma; meanwhile, PD-L1 expression was more common in *EGFR* and *ALK* WT translocations. Compared with other subtypes, lepidic, acinar, or papillary subtypes of adenocarcinoma were more likely to be PD-L1 negative (46). Schoenfeld *et al.* performed paired PD-L1 detection and next-generation sequencing in 1,586 patients with lung adenocarcinoma (50).

Detection of PD-L1

Tumor vs. immune vs. combined PD-L1 expression

PD-L1 expression on TCs and tumor-infiltrating immune cells (ICs), including lymphocytes, macrophages, dendritic cells, and neutrophils, can be detected by IHC (51,52). At present, there are a variety of assessment methods, including the TPS, TC, tumor-infiltrating ICs, and combined positive score (CPS). TPS or TC is obtained by detecting PD-L1 expression on TCs, which is defined as the percentage of viable TCs with partial or complete membranous PD-L1 staining relative to all viable TCs in the sample (53,54).

Most clinical trials of pembrolizumab or nivolumab in NSCLC have evaluated PD-L1 expression levels by TPS or TC (55,56). IC was obtained by measuring PD-L1 expression on tumor-infiltrating ICs and defined as the percentage of the number of tumor-associated ICs with positive PD-L1 staining at any intensity to the total number of tumor-associated ICs. Atezolizumab-related clinical trials were conducted to evaluate the expression level of PD-L1 by TC and IC (57). PD-L1 expression has also been assessed by CPS, which is defined as the sum of all PD-L1+ cells (TCs, lymphocytes, and macrophages) divided by the total number of surviving TCs, thus CPS is a scoring algorithm that combines tumor and ICs. For example, clinical trials of pembrolizumab in gastric cancer have used CPS to assess PD-L1 expression (58).

Some researchers have compared TPS and CPS and found that they have a high degree of consistency in assessing PD-L1 expression in NSCLC (59). In gastric cancer, TPS and CPS also have a high consistency. In fact, the heterogeneity and interobserver variability of PD-L1 expression are higher than those of PD-L1 IHC tests (60,61). In one study, pathologists also compared TC and IC and found TC to be more reliable, with an overall intraclass correlation coefficient (ICC) of 0.86–0.93;

however, the reliability of IC PD-L1 score was poor (overall ICC =0.18–0.19) (62).

Detection antibodies

In addition to different assessment modalities, there are a variety of antibodies used for PD-L1 IHC detection, including 22C3 (Merck & Co., Darmstadt, Germany; pembrolizumab), 28-8 (Bristol-Myers Squibb, New York, USA; nivolumab), SP142 (Genentech/Roche; atezolizumab), SP263 (AstraZeneca, London, UK; durvalumab), and 73-10 (Pfizer/Merck Serono, New York, USA; avelumab) assay. For example, the 22C3 assay was used to obtain PD-L1 TPS in the KEYNOTE-001 study (12); moreover, the CheckMate 017 study used the 28-8 assay to obtain PD-L1 TC or TPS (21); in the IMpower110 study, PD-L1 TC and IC were obtained by SP142 detection (63). In the PACIFIC study, SP263 detection was used to obtain PD-L1 TC (64). The Blueprint phase II study used real clinical lung cancer samples to compare the detection of PD-L1 with five antibodies and found that the staining measured by 22C3, 28-8, and SP263 showed similar sensitivity for the detection of PD-L1 expression on TC; meanwhile, the sensitivity of SP142 was lower and the sensitivity of 73-10 method was higher than 22C3, 28-8, and SP263 (62).

Utility as a predictive biomarker of ICI efficacy

PD-L1 expression as a prognostic and predictive marker remains a subject of debate and controversy. In the phase I Keynote-001 trial of pembrolizumab in patients with advanced NSCLC, patients with high PD-L1 expression experienced better treatment efficacy, so the Food and Drug Administration (FDA) accelerated the approval of pembrolizumab in patients with PD-L1 TPS >1% (13,65). Subsequent phase II/III study also confirmed further improvements in treatment outcomes observed in patients with TPS ≥50% (66). However, trials of nivolumab and atezolizumab failed to show a sufficiently strong association between PD-L1 status and treatment outcome to determine that some patients with PD-L1-negative tumors could also benefit from ICIs (21,67). This also requires us clinicians to dialectically view the therapeutic efficacy of PD-L1 expression across different clinical trials.

Factors affecting PD-L1 detection, quantification and interpretation

In addition, the interpretation and judgment of pathologists are also conflicting (68). PD-L1 test samples involve a multitude of factors that may affect the final results, including sample storage time, primary or metastatic status, selection of test time point, sample type, and pretest variables, and should thus be given their due attention (69). Despite several issues, pathologists have proposed some methods to improve the standardization level and accuracy of PD-L1. For example, cell lines were used to assess the differential sensitivity of PD-L1 assays; one or more cell lines were used as negative controls; and other suitable cell lines were included as low, medium, and high positive controls to validate the threshold for each assay (70). Although PD-L1 expression is a continuous variable, an emphasis on semiquantitative approaches that report TPS in 5% or 10% increments may provide treating clinicians with the best level of information (71). In addition, emerging technologies such as digital pathology multiplex imaging and automated image analysis have also contributed to the more accurate interpretation of PD-L1 expression (72).

Immunotherapy for negative PD-L1 expression

Anti-PD-1 inhibitors

Pembrolizumab

The KEYNOTE-001 study (11-13) (NCT01295827) was a multicohort, phase I, expanded clinical study that evaluated the efficacy and safety of pembrolizumab in advanced tumors at doses of 2 and 10 mg/kg in multitumor species and lines, and with the entire population lacking biomarker differentiation. The results of this study showed that pembrolizumab had acceptable side effects and showed certain antitumor efficacy. At 5-year follow-up of patients NSCLC, the median overall survival (mOS) was 22.3 months (m) in newly treated patients and 10.5 m in previously treated patients. The estimated 5-year overall survival (OS) rate was 23.2% for untreated patients and 15.5% for previously treated patients. Subgroup analyses showed that patients with PD-L1 TPS ≥50% had a better response to pembrolizumab. Among patients with PD-L1 TPS ≥50%, the mOS of newly treated (n=27) and treated (n=138) patients was 35.4 and 29.6 m, respectively, and the 5-year OS was 29.6% and 25.0%, respectively. The mOS of treated patients with TPS <1% (n=90) was only 8.6 m [95% confidence interval (CI): 5.5–10.6], and the 5-year survival rate was 3.5% (95% CI: 0.7–10.0%).

Based on the results of the KEYNOTE-001 trail, investigators initiated KEYNOTE-010 (66) for

treating patients with NSCLC and PD-L1 TPS ≥1%, KEYNOTE-024 for first-line treatment of those with NSCLC and PD-L1 ≥50% (73), and KEYNOTE-042 (74) for first-line therapy of those with NSCLC and PD-L1 ≥1%, all of which yielded positive results. Then expanded samples clinical trials include KEYNOTE-021, KEYNOTE-189, and KEYNOTE-407 were conducted, which incorporated all comers including patients with negative PD-L1 expression.

The KEYNOTE-021 study (14) (NCT02039674) compared the efficacy, safety, and outcome of pembrolizumab plus chemotherapy with chemotherapy alone as first-line treatments for advanced nonsquamous NSCLC without *EGFR* or *ALK* mutations in patients with different PD-L1 status. Cohort C was selected to enter Group G to participate in phase II trials after 3 cohorts of phase I trials. The results showed that pembrolizumab immunotherapy combined with chemotherapy significantly improved the objective response rate (ORR; 55% *vs.* 29%) and prolonged the time to tumor progression compared with chemotherapy alone. Based on these findings, the US FDA accelerated the approval of pembrolizumab in combination with pemetrexed and carboplatin as first-line therapy for metastatic nonsquamous NSCLC (regardless of PD-1 expression) in May 2017. Follow-up results published in the *Journal of Thoracic Oncology* in 2021 (75) showed that, regardless of PD-L1 status, compared immunotherapy combined with chemotherapy to chemotherapy alone, there were significant improvements in ORR (58% *vs.* 33%) and PFS [24.5 *vs.* 9.9 m; hazard ratio (HR) =0.54; 95% CI: 0.35–0.83]; the mOS was 34.5 and 21.1 m, respectively (HR =0.71; 95% CI: 0.45–1.12), although the crossover rate from chemotherapy alone to the PD-L1-treated group was 70%. Subgroup analysis showed that patients with TPS <1 (n=21 and 23) had an ORR of 67% and 17%, respectively, and an mOS of 34.5 and 16.7 m, respectively. There was no significant difference in efficacy between patients with TPS ≥1 and those with TPS <1. Based on the KEYNOTE-021 study, KEYNOTE-189 for nonsquamous cell carcinoma and KEYNOTE-407 for squamous cell carcinoma were conducted.

The KEYNOTE-189 study (15) (NCT02578680) evaluated the efficacy and safety of pembrolizumab combined with chemotherapy versus chemotherapy in patients with newly diagnosed *EGFR/ALK* WT nonsquamous NSCLC. The results showed that the median progression-free survival (mPFS) of the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group was 9.0 and 4.9 m, respectively (HR =0.48; 95% CI: 0.40–0.58), while the mOS was 22.0 and 10.7 m, respectively (HR =0.56; 95% CI: 0.45–0.70). In subgroup analysis, the OS and PFS of pembrolizumab combined with chemotherapy were better than those of chemotherapy alone, regardless of PD-L1 expression. Although patients with high PD-L1 expression benefited more, PD-L1-negative patients also obtained a clear benefit. Among patients with TPS <1 (n=127 and 63) in an immune-combination group and a chemotherapy-only group, the mPFS was 6.2 and 5.1 m (HR =0.64; 95% CI: 0.47–0.89), the mOS was 17. 2 and 10.2 m (HR =0.52; 95% CI: 0.36–0.74), and the ORR was 32.3% and 14.3%, respectively.

The KEYNOTE-407 study (16) (NCT02775435) evaluated the efficacy and safety of pembrolizumab combined with chemotherapy in the first-line treatment of patients with lung squamous cell carcinoma. Results showed that compared to placebo combined with chemotherapy, pembrolizumab combined with chemotherapy in previously untreated patients with metastatic lung squamous cell carcinoma improved PFS (8.0 *vs.* 5.1 m), OS (17.1 *vs.* 11.6 m), ORR (62.6% *vs.* 38.4%), and duration of response (DOR; 8.8 *vs.* 4.9 m), while demonstrating a controllable safety profile. On October 30, 2018, the FDA officially approved pembrolizumab plus chemotherapy for first-line treatment of metastatic squamous NSCLC based on KEYNOTE-407 findings and without consideration to PD-L1 expression levels. Subgroup analysis showed that among patients with TPS <1%, PFS was 6.3 in the immunochemotherapy group and 5.9 in the chemotherapy-only group (HR =0.67; 95% CI: 0.49–0.91), OS was 15 and 11 m (HR =0.79, 95% CI: 0.56–1.11), ORR was 67.4% and 41.4%, and DOR was 6.9 and 5.7 m, respectively. Although statistically, the efficacy of pembrolizumab combined with chemotherapy in patients with TPS <1 was not as good as that in patients with TPS ≥1, in patients with TPS <1, the efficacy of immune-combined group was still significantly better than that of chemotherapy alone group, and thus compared to chemotherapy alone, pembrolizumab combined with chemotherapy may be a better treatment option for patients with negative PD-L1 expression.

The combination of immunotherapy and cCRT for the treatment of unresectable stage III NSCLC is also currently being evaluated. The KEYNOTE-799 study (17) (NCT03631784) enrolled patients with previously untreated, unresectable, pathologically proven stage IIIA-C NSCLC into cohort A (squamous and nonsquamous,

n=112) and cohort B (nonsquamous cell carcinoma only, n=104). All were treated with pembrolizumab, chemotherapy, and radiotherapy. Results showed that the ORR and DCR of cohort A and B were 70.5% and 70.6%, respectively, and 88.4% and 93.1%, respectively. The 1-year PFS and 1-year OS rates were 67.1% and 71.6%, respectively, and 81.3% and 87.0%, respectively. In cohort A, the ORR of patients with PD-L1 <1% and ≥1% was 66.7% and 75.8%, respectively. In cohort B, the ORR of patients with PD-L1 <1% and ≥1% was 71.4% and 72.5%, respectively. Thus, regardless of PD-L1 TPS expression, pembrolizumab plus cCRT showed promising antitumor activity with a manageable safety profile. However, a larger sample of randomized controlled trials is needed for validation, and the ongoing phase III KEYNOTE-012 study (NCT04380636) may aid in this regard.

Nivolumab

The phase I CheckMate-012 (18) clinical trial (NCT01454102) evaluated the efficacy and safety of nivolumab in combination with ipilimumab in the first-line treatment of patients with advanced NSCLC. The results showed that nivolumab combined with ipilimumab in the first-line treatment of advanced NSCLC had good clinical benefit, and it was safe and well tolerated by patients. However, in patients with PD-L1 <1%, the ORR of nivolumab plus ipilimumab (n=17) was only 18%, and that of nivolumab (n=14) was 14%. The higher the expression of PD-L1 was, the more significant the benefit. In patients with PD-L1 ≥50%, the ORR of nivolumab combined with ipilimumab (n=13) was as high as 92%, and that of nivolumab (n=12) was 50%. Based on this clinical trial, the efficacy and safety of immune-monotherapy, immunochemotherapy, double immunotherapy, and double immunotherapy combined with sequential chemotherapy in the first-line treatment of NSCLC were investigated.

The phase III CheckMate-227 clinical trial (19) (NCT02477826) explored the efficacy and safety of immune-monotherapy, platinum-based chemotherapy, and dual immunotherapy as first-line treatment for advanced NSCLC, as well as the impact of biomarkers on efficacy. In 2019, the *New England Journal of Medicine* (*NEJM*) (19) published the results of 29.3 months' follow-up: in patients with PD-L1 ≥1%, the mOS of nivolumab + ipilimumab (O+Y) group and chemotherapy group were 17.1 and 14.9 m, respectively (HR =0.79; 97.72% CI: 0.65–0.96; P=0.007), while the 2-year OS rates were 40.0% and 32.8%, respectively. The OS benefit was also observed in patients with PD-L1 <1%, with an mOS of 17.2 m in the nivolumab + ipilimumab group and 12.2 m in the chemotherapy group (HR =0.62; 95% CI: 0.48–0.78), as well as 2-year OS rates of 40.4% and 23.0%, respectively. In 2022, the median follow-up of 54.8 months was published in the *Journal of Thoracic Oncology* (*JTO*) (76): for patients with PD-L1 <1%, O+Y double immunotherapy also significantly prolonged the survival of patients compared with chemotherapy. In addition, the efficacy of nivolumab combined with chemotherapy was also better than that of chemotherapy alone with an OS of 12.2 months. Compared to chemotherapy group, for O+Y group and nivolumab plus chemotherapy group, the OS are 17.2 and 15.2 months, respectively (HR =0.64, 95% CI: 0.51–0.81; HR =0.82, 95% CI: 0.65–1.02) and O+Y group and nivolumab plus chemotherapy group reduced the risk of death by 36% and 18%, respectively. For O+Y group, nivolumab plus chemotherapy group and chemotherapy group, the PFS was 5.1, 5.6, and 4.7 months (HR =0.75, 95% CI: 0.59–0.95; HR =0.72, 95% CI: 0.57–0.91); the ORR was 27.3%, 37.9%, and 23.1%; and the 4-year OS rates were 24%, 13%, and 10%, respectively. In addition, patients with squamous cell carcinoma who were negative for PD-L1 expression appeared to benefit more from double immunotherapy therapy than did patients who were positive, with a 47% lower risk of death. Among patients with nonsquamous cell carcinoma, PD-L1-positive expression was associated with longer survival than was PD-L1-negative expression, regardless of whether treatment was double immunotherapy or chemotherapy. For O+Y group, nivolumab plus chemotherapy group and chemotherapy group, the OS of nonsquamous cell carcinoma was 17.5, 17.7, and 13.1 months (HR =0.69, 95% CI: 0.53–0.89; HR =0.79, 95% CI: 0.61–1.02), and the OS of squamous cell carcinoma was 15.9, 11.3, and 8.5 months (HR =0.53, 95% CI: 0.44–0.84; HR =0.90, 95% CI: 0.58–1.38). In terms of safety, grade 3–4 treatment-related adverse events (TRAEs) were observed in 40% and 36% of patients in the dual immunotherapy and chemotherapy groups, respectively, with discontinuation rates of any grade of TRAEs in 22% and 13% of patients, respectively.

The CheckMate-9LA study (20) (NCT03215706) showed that nivolumab plus ipilimumab combined 2 two cycles of chemotherapy resulted in significantly longer survival and rapid disease control than did chemotherapy alone. After a median follow-up of 13.2 m, the mOS of the two groups was 15.6 and 10.9 m, respectively (HR =0.66; 95% CI: 0.55–0.80), and the 12-m OS rates were

63% and 47%, respectively. The mPFS was 6.7 and 5.0 m, respectively, (HR =0.68, 95% CI: 0.57–0.82), and the ORR of the two groups were 38.2% and 24.9%, respectively. Subgroup analysis showed that OS benefit was not associated with PD-L1 expression level. About 40% of patients had PD-L1 <1%, and the mOS was 16.8 and 9.8 m in the two groups, respectively (HR =0.62; 95% CI: 0.45–0.85). In patients with PD-L1 ≥1%, the mOS of the two groups was 15.8 and 10.9 m, respectively (HR =0.64; 95% CI: 0.50–0.82). However, there were more severe adverse reactions in the sequential immunochemotherapy group, and the incidence of grade 3–4 treatment-related adverse reactions in the two groups was 47% and 38%, respectively; meanwhile, the incidence of TRAEs was 30% and 18%, respectively, and resulted in treatment discontinuation in 19% and 7% of patients, respectively, with death due to TRAEs occurring in 2% of patients in both groups. Therefore, for the aim to avoid adverse reactions, patients with negative PD-L1 expression may also choose O+Y double immunotherapy or nivolumab combined with chemotherapy as first-line therapy.

The CheckMate 017 study (21) (NCT01642004) for second-line therapy demonstrated that patients with lung squamous cell carcinoma may benefit from nivolumab monotherapy regardless of PD-L1 expression. The results showed that the mOS of a nivolumab group reached 9.2 m, while the median survival time of a docetaxel group was only 6 m (HR =0.59; 95% CI: 0.44–0.79; P<0.001); the 1-year survival rates were 42% and 24% respectively, meanwhile, the PFS was 3.5 and 2.8 m, respectively (HR =0.62; 95% CI: 0.47–0.81; P<0.001). Subgroup analysis showed that PD-L1 expression was not associated with the efficacy of nivolumab in lung squamous cell carcinoma. Patients with negative PD-L1 expression (n=54 and 52) had similar OS, PFS, and ORR as did those with positive PD-L1 expression (n=63 and 56). In terms of safety, TRAEs (58% *vs.* 86%) and serious AEs (7% *vs.* 24%) were lower in the nivolumab group than in the docetaxel group. Based on this study, the FDA approved nivolumab as a second-line treatment for advanced squamous NSCLC. Therefore, patients with lung squamous cell carcinoma with negative PD-L1 expression may select nivolumab monotherapy as second-line therapy.

Similarly, the CheckMate 057 study (22) (NCT01673867) evaluated nivolumab as second-line therapy in nonsquamous NSCLC. The results showed that the mOS was 12.2 m in the nivolumab group and 9.4 m in the docetaxel group, which met the primary clinical end point. The 1-year survival rates were 51% and 39%, respectively, but the PFS was 2.3 and 4.2 m, respectively (P=0.3932; the PFS of nivolumab group was not superior to that of chemotherapy group). In nonsquamous cell carcinoma, the efficacy of nivolumab was correlated with the expression of PD-L1, and the efficacy of patients with positive PD-L1 expression was better than that of patients without PD-L1 expression. There was a strong predictive association between PD-L1 expression and clinical outcome at all expression levels for all efficacy end points. Nivolumab demonstrated improvements in OS, PFS, and ORR at prespecified PD-L1 expression levels of ≥1%, ≥5%, and ≥10%. Consistently, a subgroup analysis of PD-L1 expression levels based on the July 2015 database lock showed no significant difference in survival among patients with PD-L1 expression <1% (n=108 and 101), with an OS of 10.5 and 10.1 m, respectively for the nivolumab group and the docetaxel group (HR =0.90; 95% CI: 0.66–1.24). However, patients treated with nivolumab with PD-L1 ≥1% (n=123 and 123) had an OS prolongation of nearly 9 m compared to the docetaxel group (17.7 *vs.* 9.0 m; HR =0.59; 95% CI: 0.43–0.82). The OS of patients with PD-L1 ≥10 treated with nivolumab was 19.9 m, while that of patient treated with docetaxel was only 8 m (HR =0.40; 95% CI: 0.26–0.59). Interestingly, the median DOR (mDOR) was longer with nivolumab than with docetaxel at all PD-L1 expression levels: the mDOR for patients with PD-L1 expression <1% was 18.3 m (n=10) and 5.6 m (n=15), compared with 16 m (n=38) and 5.6 m (n=15) for patients with PD-L1 ≥1%. Based on this study, in October 2015, the FDA expanded the indication of nivolumab for NSCLC and approved nivolumab for second-line treatment in advanced nonsquamous NSCLC. Given the superior safety profile of nivolumab over docetaxel, nivolumab may also be a viable option for second-line treatment in patients with PD-L1-negative nonsquamous NSCLC.

The results of the CheckMate 017/057 trial, published in 2021 in *JCO*, included an OS rate of 13.4% for nivolumab group at 5-year follow-up (77). In the CheckMate 017 trial, the 5-year OS rate for nivolumab *vs.* docetaxel in patients with squamous cell carcinoma was 12.3% and 3.6%, respectively; meanwhile, in the CheckMate 057 trial, this was 14.0% *vs.* 2.1%, respectively for those with nonsquamous cell carcinoma: Superior OS was observed with nivolumab *vs.* docetaxel regardless of tumor PD-L1 expression (which may be related to the failure to distinguish between squamous cell carcinoma and adenocarcinoma), but

the benefit was more pronounced in patients with positive PD-L1 expression. Patients with PD-L1 ≥1% (n=185 and 179) treated with nivolumab *vs.* docetaxel had an OS of 13.4 and 8.5 m, respectively (HR =0.61; 95% CI: 0.49–0.76) and 5-year OS rates of 18.3% and 3.4%, respectively. The OS of patients with PD-L1 <1% (n=163 and 153) treated with nivolumab *vs.* docetaxel was 9.7 and 7.8 m (HR =0.76; 95% CI: 0.61–0.96), and the 5-year OS rates were 8.0% and 2.0%, respectively. Therefore, nivolumab can be used as second-line therapy in NSCLC patients with negative PD-L1 expression.

The China-based CheckMate 078 study (23) (NCT02613507) also achieved similar results to the CheckMate 017/057 study based on global population data. The 3-year follow-up data was released at the 2020 Chinese Society of Clinical Oncology (CSCO) meeting, and the 3-year OS rate was 19% in the nivolumab group, which was higher than the 12% in the docetaxel group. In addition, the mOS of the two groups was 11.9 and 9.5 m, respectively, and nivolumab reduced the risk of death by 25% (HR =0.75, 95% CI: 0.61–0.93), which was consistent with the global pooled population analysis (mOS: 11.1 *vs.* 8.1 m; HR =0.68). In addition, the results of the Asian analysis showed that nivolumab had a definite OS benefit compared with docetaxel in both the PD-L1-positive and PD-L1-negative patients. Furthermore, the CheckMate-870 study (NCT03195491) (24) evaluated the efficacy and safety of nivolumab in a real-world setting in China. The minimum follow-up time of 35.4 months was reported at the European Congress on Lung Cancer (ELCC) in 2022. The mOS in the PD-L1 ≥1% and <1% subgroups were 19.3 months (95% CI: 12.9–23.5) and 13.3 months (95% CI: 10.9–17.7), respectively. These results suggest that nivolumab can be used as second or third-line therapy for patients with advanced NSCLC and negative PD-L1 expression in the Chinese population.

Camrelizumab

The CameL study (25) (SHR-1210-III-303, NCT03134872) was the world's first phase III study of first-line immunotherapy combined with chemotherapy for patients with NSCLC in a Chinese population. The study showed that camrelizumab combined with pemetrexed/carboplatin had strong efficacy. The ORR in the camrelizumab group was 60.5%, which was significantly higher than the 38.6% in the chemotherapy group (P<0.0001). Meanwhile, mPFS in the camrelizumab group reached 11.3 m, which was significantly longer than 8.3 m in the chemotherapy group by 3 m (HR =0.60; 95% CI: 0.45–0.79; P=0.0001). The mOS of the camrelizumab group was 27.9 m, which was 2 years longer than that in the chemotherapy group. Compared with the 20.5 m of survival time in the chemotherapy group, the survival time of the patients was significantly prolonged by 7.4 m (HR =0.73; 95% CI: 0.55–0.96; P=0.0117). Subgroup analysis showed that regardless of PD-L1 expression level, PFS benefit could be seen in the immunotherapy plus chemotherapy group. When the PD-L1 TPS (<1% *vs.* ≥1%) was included as a covariate in the Cox model, a benefit in PFS was also observed in the camrelizumab plus chemotherapy group (HR =0.62; 95% CI: 0.46–0.84; P=0.001). However, patients with PD-L1 ≥1% (n=138, 117) seemed to benefit more from camrelizumab plus chemotherapy (HR =0.56; 95% CI: 0.39–0.82) compared with patients with PD-L1 <1% (n=49, 69; HR =0.76; 95% CI: 0.45–1.26). Concerning safety, the camrelizumab plus chemotherapy group had a higher rate of grade 3 TRAEs or higher than did the chemotherapy-only group [141 (69%) *vs.* 98 (47%)], with the most common TRAE being myelosuppression. Serious TRAEs occurred in 74 patients (36%) in the combination group and in 27 patients (13%) in the chemotherapy-only group. Based on the CameL study results, in June 2020, the National Medical Products Administration (NMPA) approved camrelizumab in combination with pemetrexed and carboplatin as first-line treatment for patients with *EGFR*/*ALK*-negative, unresectable locally advanced or metastatic nonsquamous NSCLC.

The CameL-sq study (26) (SHR-1210-III-307, NCT03668496) evaluated the efficacy and safety of camrelizumab combined with carboplatin and paclitaxel as first-line treatment for patients with advanced or metastatic squamous NSCLC. The results showed that as of November 6, 2020, camrelizumab combined with carboplatin and paclitaxel significantly improved patient outcomes. For camrelizumab combined with chemotherapy group and placebo combined with chemotherapy group, the PFS of the two groups was 8.5 and 4.9 m, respectively (HR =0.37; 95% CI: 0.29–0.47; P<0.001). Subgroup analysis showed that patients could benefit regardless of PD-L1 expression level. Compared to placebo combined with chemotherapy group, the HR of camrelizumab combined with chemotherapy group with PD-L1 <1% (n=91, 97) and ≥1% (n=95, 93) was 0.49 (95% CI: 0.35–0.68) and 0.34 (95% CI: 0.24–0.49), respectively. In both two groups, the mOS was not reached at 14.5 m (HR =0.55, P<0.001); Similarly, regarding PD-L1 expression, for both patients

with PD-L1 <1% and those with ≥1%, compared to placebo combined with chemotherapy group, the HR of camrelizumab combined with chemotherapy group was 0.62 (95% CI: 0.41–0.94) and 0.52 (95% CI: 0.31–0.86), respectively. The incidence of grade 3 and above TRAEs was 73.6% and 71.9% in the camrelizumab combined with chemotherapy group and placebo combined with chemotherapy group, respectively, and no unexpected adverse events (AE) occurred. Therefore, regardless of PD-L1 expression level, camrelizumab combined with chemotherapy in the first-line treatment of patients with advanced or metastatic squamous NSCLC can significantly prolong the PFS and OS with acceptable safety. Camrelizumab combined with carboplatin and pemetrexed has become the standard first-line treatment for patients with advanced/metastatic driver-negative nonsquamous NSCLC in China.

In addition to camrelizumab combined with chemotherapy, camrelizumab combined with antiangiogenic agents has also been evaluated as a first-line treatment for NSCLC. The SHR-1210-II-202 (28) (NCT03083041) multicenter phase I/II trial was designed to evaluate the efficacy and safety of camrelizumab combined with apatinib in the treatment of patients with advanced nonsquamous NSCLC. In cohort 4, a total of 25 patients with untreated advanced nonsquamous NSCLC with driver-negative genes were enrolled and received apatinib plus camrelizumab until disease progression or until toxicity became intolerable. The ORR was 40% (40% in both the PD-L1-positive and PD-L1-negative groups), the disease control rate (DCR) was 92%, the mPFS was 11.0 m (9.7 m in the PD-L1-positive group, 11.0 m in the PD-L1-negative group), and the mOS has not yet been reached as per the study results published in 2021 WCLC. In terms of safety, the incidence of grade 3/4 TRAEs was 20%, and the most common AEs were elevated alanine aminotransferase and aspartate aminotransferase, reactive cutaneous capillary endothelial proliferation (RCCEP), and hypertension, among others. Overall, the AE were controllable and manageable, with no new AE. The chemotherapy-free regimen of camrelizumab combined with low-dose apatinib can provide a better choice for patients with negative PD-L1 expression in clinical practice. Currently, SHR-1210-III-315 (NCT04203485), a phase III clinical study of camrelizumab plus apatinib for first-line treatment of advanced NSCLC for driver gene-negative patients, is underway.

The phase II clinical trial, SHR-1210-II-201 (27) (NCT03085069), explored the outcomes of second-line camrelizumab monotherapy in patients with different PD-L1 expression levels. The results showed an improvement in ORR, PFS, and OS with camrelizumab compared with previous data for second-line chemotherapy. The efficacy of PD-L1 <1% was similar to that of second-line monochemotherapy, with an ORR of 12.2%, a DCR of 44.6%, and a PFS of 2.1 m (95% CI: 1.9–3.2). Patients with higher PD-L1 expression were more likely to benefit from camrelizumab treatment. Patients with PD-L1 ≥50% (n=25) had an ORR of 28%, a DCR of 72%, and a PFS of 7.1 m (95% CI: 2.0–11.4), and camrelizumab was well tolerated. In terms of safety, TRAEs of any grade were reported in 87% of patients, including grade ≥3 TRAEs in 17.1%, severe TRAEs in 13.7%, dose adjustment or interruption due to TRAEs in 13.7%, and treatment discontinuation due to TRAEs in 4.8% of patients.

Tislelizumab

In the phase II RATIONALE 206 study, tislelizumab plus chemotherapy significantly prolonged PFS and improved response rates. On this basis, the phase III RATIONALE 304 study (29) (NCT03663205) compared the efficacy and safety of pemetrexed plus a platinum-based regimen with tislelizumab to those of chemotherapy alone in patients with untreated nonsquamous NSCLC. The study reported a median follow-up of 9.8 m as of January 23, 2020, with the PFS of tislelizumab plus chemotherapy being significantly longer than that of chemotherapy alone (mPFS: 9.7 *vs.* 7.6 m; HR =0.645; 95% CI: 0.462–0.902; P=0.0044). In addition, tislelizumab plus chemotherapy had higher ORR (57% *vs.* 37%) and longer mDOR (8.5 *vs.* 6.0 m) than did chemotherapy alone. Subgroup analysis showed that the PFS benefit was more obvious in patients with PD-L1 ≥1% (n=190) compared to patients with PD-L1 <1% (n=144; HR =0.758; 95% CI: 0.469–1.224), especially in patients with PD-L1 ≥50% (n=110; HR =0.308; 95% CI: 0.167–0.567). However, statistical significance regarding benefit was not reached. Overall, the regimen of tislelizumab combined with chemotherapy was well tolerated and showed good antitumor activity. On June 22, 2021, based on the RATIONALE 304 study, the NMPA approved tislelizumab plus chemotherapy as first-line treatment for driver-negative patients with unresectable locally advanced or metastatic nonsquamous NSCLC without differentiating types of PD-L1 expression. Therefore, tislelizumab plus pemetrexed and platinum-based regiments may be attempted in patients with negative PD-L1 expression.

Tislelizumab plus chemotherapy also showed significant

efficacy in nonsquamous cancers. The RATIONALE 307 study (30) (NCT03594747) evaluated the efficacy and safety of tislelizumab plus paclitaxel/albumin paclitaxel and carboplatin versus paclitaxel plus carboplatin as first-line treatment for advanced (stage IIIB/IV) squamous NSCLC. A total of 360 patients were randomly assigned to three groups: 120 patients in group A (tislelizumab plus paclitaxel/carboplatin), 119 patients in group B (tislelizumab plus nab-paclitaxel/carboplatin), and 121 patients in group C (paclitaxel/carboplatin). Results showed that up to December 2019, the median follow-up was 8.6 m. In groups A, B, and C, the PFS was 7.6, 7.6, and 5.5 m, respectively. The ORR was 73%, 75%, and 50%, respectively. Subgroup analysis showed that tislelizumab combined with paclitaxel/carboplatin prolonged PFS (Independent Review Committee assessment) compared with paclitaxel/carboplatin alone, regardless of PD-L1 expression status. However, patients with PD-L1 ≥1% (n=144) had a more significant benefit (HR =0.45; 95% CI: 0.29–0.70) compared to patients with PD-L1 <1% (n=97; HR =0.64; 95% CI: of 0.37–1.10). Similar results were obtained in the tislelizumab plus albumin-paclitaxel/carboplatin group. In patients with PD-L1 <1%, the ORR of group A (n=42), group B (n=42), and group C (n=41) was 68.8%, 68.1%, and 51.0%, respectively. In patients with PD-L1 ≥50%, the ORR of immune-chemotherapy combined with chemotherapy was 78.6%, 88.1%, and 53.7% in group A (n=48), group B (n=47), and group C (n=49), respectively. The incidence of any treatment termination due to AE was 12.5%, 29.7%, and 15.4% in these three groups, respectively. The most common grade ≥3 AE in all groups was a decrease in neutrophil count, which is consistent with known chemotherapy toxicity. TRAEs of grade ≥3 were similar in the three groups (85.8%, 83.9%, and 80.3%, respectively). Based on this study, in January 2021, tislelizumab combined with chemotherapy was officially approved by the NMPA for first-line treatment of locally advanced or metastatic squamous NSCLC. Therefore, tislelizumab plus paclitaxel/carboplatin regimen may also be attempted in patients with squamous cell carcinoma and negative PD-L1 expression.

Tislelizumab alone has also shown better efficacy and safety than has docetaxel in second- or third-line therapy. The RATIONALE 303 study (31,32) (NCT03358875) reported that with a median follow-up of 19 m, the mOS of the tislelizumab and docetaxel groups were 17.2 *vs.* 11.9 m, respectively (HR =0.64; 95% CI: 0.527–0.778) in the intention-to-treat (ITT) population. In patients with PD-L1 TC ≥25% (n=343), the mOS was 19.1 and 11. 9 m (HR =0.52; 95% CI: 0.384–0.713), the mPFS was 4.1 and 2.6 m (HR =0.64), the PFS was 12 m 23.3% and 5.7%, and the ORR was 21.9% and 7.0%, respectively. In patients with PD-L1 TC <1% (n=319), the HR of mOS was 0.74 (95% CI: 0.541–1.000). These results suggest that tislelizumab can be used in second- or third-line treatment for PD-L1-negative patients with NSCLC.

Sintilimab

Sintilimab combined with chemotherapy has also shown promising efficacy in the first-line treatment of NSCLC. The ORIENT-11 study (33) (NCT03607539) published mOS data with a median follow-up of 30.8 m in the 2022 ELCC. The results showed that sintilimab combined with chemotherapy significantly prolonged the survival of patients compared with chemotherapy alone, with an mOS of 24.2 and 16.8 m (HR =0.65; 95% CI: 0.50–0.85), respectively. Subgroup analysis showed that in patients with TPS <1%, sintilimab combined with chemotherapy reduced the risk of death by 25% (HR =0.75; 95% CI: 0.48–1.19), but the CI crossed 1, and thus a statistically significant difference was not reached. In patients with TPS ≥1%, the HR was 0.56 (95% CI: 0.40–0.77), and sintilimab significantly prolonged survival. The combination of sintilimab was well tolerated, with a low frequency of discontinuation (6%) and death (2.3%) due to AEs. Grade ≥3 AEs occurred in 164 patients (61.7%) in the sintilimab group and in 77 patients (58.8%) in the placebo group. Based on this study, the NMPA approved sintilimab in combination with pemetrexed and platinum-based chemotherapy for first-line treatment of nonsquamous NSCLC in February 2021. Therefore, PD-L1-negative patients with nonsquamous NSCLC may consider sintilimab plus chemotherapy as first-line treatment.

Consistent results from the ORIENT-12 study (34) of squamous cell carcinoma (NCT03629925) showed that compared with a placebo group, a sintilimab group had significantly prolonged mPFS as assessed by immune-related response criteria (irRC; 5.5 *vs.* 4.9 m; HR =0.536; P<0.00001), while the investigator-assessed mPFS was 6.7 and 4.9 m, respectively (HR =0.532; P<0.00001), and the prespecified primary end point was reached. mOS was not achieved in either group, but there was a tendency toward a benefit in OS in the sintilimab group compared with the placebo group (HR 0.567; P=0.01701). In subgroup analysis, a significant prolongation of PFS was seen regardless of PD-L1 expression level, with an HR of 0.548 (95% CI: 0.406–1.086) in patients with PD-L1 TPS <1%

(n=59, 63). In patients with PD-L1 TPS ≥1% (n=120, 115), the HR was 0.526 (95% CI: 0.392–0.704). The incidence of grade 3 or higher AEs was similar in the sintilimab group and the placebo group (86.6% *vs.* 83.1%), and no new safety issues were observed. On June 3, 2021, based on ORIENT-12 results, the NMPA approved sintilimab plus gemcitabine plus platinum-based chemotherapy as first-line treatment for unresectable locally advanced or metastatic squamous NSCLC. Therefore, PD-L1-negative patients with squamous cell carcinoma may consider sintilimab plus chemotherapy as first-line treatment.

Anti-PD-L1 inhibitors

Atezolizumab

Atezolizumab plus carboplatin and an albumin-paclitaxel regimen can significantly improve the survival of patients with nonsquamous NSCLC. The IMpower130 study (35) (NCT02367781) showed that immunochemotherapy (carboplatin + albumin-paclitaxel) significantly improved outcomes compared with chemotherapy, with an mPFS of 7.0 *vs.* 5. 5 m (HR =0.64; 95% CI: 0.54–0.77; P<0.0001) and an mOS of 18.6 *vs.* 13.9 m (HR =0.79; 95% CI: 0.64–0.98; P=0.033), respectively. In the analysis of the ITT population, atezolizumab still provided benefit, with a PFS of 7.0 *vs.* 5.6 m (HR =0.65) and an OS of 18.1 *vs.* 13.9 m (HR =0.80) in the two groups, respectively. The incidence of grade 3/4 AEs was 81% *vs.* 71% in the two groups, and the incidence of immune-related AEs was 45%, most of which were grade 1–2. Common AEs included rash, hypothyroidism, and hepatitis. Subgroup analysis showed that PFS was significantly prolonged in the combined immunochemotherapy group regardless of PD-L1 expression level. In patients with PD-L1 TC ≥50% or IC ≥10% (n=88, 42), the mPFS was 6.4 and 4.6 m, respectively (HR =0.51; 95% CI: 0.34–0.77), while in patients with negative PD-L1 expression (n=235, 121), the mPFS was 6.2 and 4.7 m, respectively (HR =0.72; 95% CI: 0.56–0.91). However, OS was not statistically significant in any PD-L1 subgroup. In patients with high PD-L1 expression, the mOS was 17.3 and 16.9 m, respectively (HR =0.84; 95% CI: 0.51–1.39). In patients with negative PD-L1 expression, the mOS was 17.3 and 16.9 m, respectively. The mOS was 15.2 and 12.0 m (HR =0.81; 95% CI: 0.61–1.08), respectively for the combined immunochemotherapy group and the chemotherapy group. This may be due to the large number of patients in the chemotherapy group (nearly 60%) who switched over to anti-PD-1 or anti-PD-L1 therapy after progression. Overall, this evidence suggests that atezolizumab plus carboplatin and albumin-paclitaxel may also be attempted for first-line therapy in patients with nonsquamous NSCLC who have negative PD-L1 expression.

Atezolizumab plus pemetrexed and platinum (APP) has also been evaluated, and the IMpower 132 study (36) (NCT02657434) showed that APP significantly improved PFS but did not prolong OS as compared with pemetrexed platin (PP). The mPFS was 7.6 and 5.2 m in the two treatment groups (HR =0.60; 95% CI: 0.49–0.72; P<0.0001). In subgroup analysis, patients with PD-L1 TC ≥50% or IC ≥10% (n=25, 20) had a mPFS of 10.8 and 6.5 m (HR =0.46; 95% CI: 0.22–0.96), and patients with negative PD-L1 expression (n=88, 75) had an mPFS of 8.5 and 4.9 m (HR =0.45; 95% CI: 0.31–0.64), respectively. Interestingly, in patients with low PD-L1 expression (n=63, 73), there was no difference in PFS between the two groups, with an mPFS of 6.2 and 5.7 m, respectively (HR =0.80; 95% CI: 0.56–1.16). Unfortunately, although APP prolonged survival by nearly 4 m compared with PP, it did not achieve statistical significance, with an mOS of 17. 5and 13.6 m in the two groups (HR =0.86; 95% CI: 0.71–1.06; P=0.1546). In subgroup analysis, only PD-L1-negative patients had significantly longer survival, with an mOS of 15.9 and 10.5 m (HR =0.67; 95% CI: 0.46–0.96; P=0.1546). These results suggest that the AP regimen could be used as a first-line therapy for patients with PD-L1-negative nonsquamous NSCLC.

In addition to different regimens combining immunotherapy with chemotherapy, atezolizumab combined with targeted therapy and chemotherapy has also been developed as a treatment option. The IMpower150 study (38) (NCT02366143) investigated the safety and efficacy of atezolizumab combined with bevacizumab and carboplatin paclitaxel (ABCP) in first-line treatment of advanced nonsquamous cell NSCLC. The results indicated a median follow-up of about 40 m, with the mOS in the atezolizumab combined with carboplatin and paclitaxel group (ACP group; 19.0 m) being 4.3 m longer than that in the bevacizumab combined with carboplatin and paclitaxel group (BCP group; 14.7 m; HR =0.84; 95% CI: 0.71–1.00; P=0.05) in the ITT-WT (*EGFR* and *ALK* wild) population. The mOS of the BCP group was 19.5 m, while that of the ABCP group was and 14.7 m (HR =0.80; 95% CI: 0.67–0.95; P=0.01). Stratified analysis of PD-L1 expression in the ITT-WT population showed that in patients with TC1/3 or IC1/3 as detected with the SP142 (n=185, 165), the ACP

regimen had a significant clinical benefit compared with the BCP regimen (24.4 *vs.* 16.0 m; HR =0.71; 95% CI: 0.55–0.91); in patients with negative PD-L1 expression (TC0 and IC0; n=164, 173), there was no significant difference in OS between ACP and BCP (14.8 *vs.* 14.1 m; HR =0.96; 95% CI: 0.76–1.22). Similarly, among patients with positive PD-L1 expression (n=192, 165), the ABCP group had a significant improvement in OS compared with the BCP group (22.5 *vs.* 16.0 m; HR =0.73; 95% CI: 0.57–0.94). Patients with negative PD-L1 expression (n=164, 173) showed no significant difference in OS between the ABCP and BCP regimens (16.9 *vs.* 14.1 m; HR =0.9; 95% CI: 0.71–1.14). In the biomarker-evaluable WT (BEP-WT) population, similar results were obtained between ACP and ABCP compared with BCP regardless of whether the SP142 or SP263 was used. These results suggest that the ACP and ABCP regiments are new clinical treatment options for PD-L1-positive patients. Bevacizumab combined with chemotherapy is still the cornerstone of first-line nonsquamous NSCLC treatment in patients with negative PD-L1 expression.

For patients with squamous cell carcinoma, the results of the IMpower 131 study (37) (NCT02367794) showed that atezolizumab combined with chemotherapy [carboplatin + albumin paclitaxel (A+CnP)] significantly improved PFS compared with chemotherapy alone, with an mPFS of 6.3 *vs.* 5.6 m, respectively (HR =0.71; P=0.0001); unfortunately, the OS was not as expected, at 14.2 *vs.* 13.5 m (HR =0.88; P=0.16). However, subgroup analysis showed that in the TC3/IC3 group with high PD-L1 expression (n=47, 44), the benefit of A+CnP regimen was significant, with an mPFS of 10.1 *vs.* 5.1 m (HR =0.41, 95% CI: 0.25–0.68), respectively, while the mOS was 23.4 *vs.* 10.2 m (HR =0.48; 95% CI: 0.29–0.81). In PD-L1-negative patients (n=160, 171), there was no significant difference in PFS or OS, with a PFS of 5.7 and 5.6 m (HR =0.82; 95% CI: 0.65–1.04) and an OS of 14.0 and 12.5 m (HR =0.87; 95% CI: 0.67–1.13), respectively.

Atezolizumab also showed better efficacy and safety than did docetaxel in second-line therapy. The phase II POPLAR study (39) (NCT01903993) showed that in the ITT population, the mOS was 12.6 *vs.* 9.7 m (HR =0.73; P=0.04) for the atezolizumab group and the docetaxel group, respectively, but there was no significant difference in PFS or ORR. Subgroup analysis showed that patients with high PD-L1 expression benefited more from atezolizumab, while PD-L1-negative patients (n=92) did not see a survival difference between the two treatment types, which may be related to the small sample size. In the safety evaluation, atezolizumab was well tolerated and had a better safety profile than did chemotherapy. In addition to POPLAR, the phase III OAK study (67) with an expanded sample (NCT02008227) reported an mOS of 13.8 *vs.* 9.6 m in the ITT population (HR =0.73; P=0.0003). There still was no significant difference in PFS or ORR. Subgroup analysis showed that although the benefit was more pronounced with higher PD-L1 expression, the benefit was also seen in patients with negative PD-L1 expression. In TC0/IC0 patients (n=379), atezolizumab and docetaxel increased survival by 3.7 m, with an mOS of 12.6 *vs.* 8.9 m, respectively (HR =0.75; 95% CI: 0.59–0.96; P=0.0215). In PD-L1-positive patients, the mOS was 15.7 *vs.* 10.3 m, respectively (HR =0.74; 95% CI: 0.58–0.93; P=0.0102). The maximum benefit was found in the highest PD-L1 expression group (TC3/IC3), with an mOS of 20.5 *vs.* 8.9 m, respectively. On May 18, 2016, atezolizumab received FDA approval for patients with NSCLC after platinum-based chemotherapy progression based on the POPLAR and OAK study. Later, the NMPA also approved this indication for atezolizumab. Survival at 4 years in the OAK study (40) was 15.5% in the atezolizumab group and 8.7% in the docetaxel group. A long-term OS benefit with atezolizumab was observed in each PD-L1 expression subgroup. In patients with TC0/IC0 (n=103, 112), the mOS was 9.9 and 7.0 m, respectively (HR =0.66; 95% CI: 0.49–0.89). In patients with TPS <1% (n=154, 152), the mOS was 10.6 and 7.5 m (HR =0.75; 95% CI: 0.59–0.97). These results suggest that atezolizumab is an option for second-line treatment of patients with advanced NSCLC with negative PD-L1 expression.

Durvalumab

The PACIFIC study (41) (NCT02125461) was the first randomized, controlled, phase III trial to evaluate the efficacy of ICIs in patients with unresectable stage III NSCLC. Durvalumab was used as consolidation therapy in patients with stage III unresectable NSCLC who did not develop disease progression after standard platinum-based cCRT and was compared with placebo after standard cCRT. At 5-year follow-up, in patients with PD-L1 TC ≥1%, the OS was 63.1 and 29.6 m (HR =0.61; 95% CI: 0.44–0.85), 5-year OS rate was 50.1% and 36.9%, and the PFS was 24.9 and 5.5 m, respectively (HR =0.47, 95% CI: 0.35–0.64). However, in patients with PD-L1 TC <1%, no survival benefit was seen for patients with NSCLC who received durvalumab maintenance therapy: the OS was 33.1 and

43.0 m (HR =1.15; 95% CI: 0.75–1.75), the 5-year OS rates was 29.7% and 37.2%, and the PFS was 10.7 and 5.6 m (HR =0.80; 95% CI: 0.53–1.20), respectively.

Durvalumab alone or durvalumab in combination with tremelimumab has failed in first-line treatment of NSCLC. The MYSTIC study (42) (NCT02453282) explored durvalumab alone (PD-L1 inhibitor) or durvalumab and tremelimumab (CTLA-4 inhibitor) in combination with standard chemotherapy in the first-line treatment of locally advanced or metastatic *EGFR/ALK* WT NSCLC. A total of 1,118 patients were enrolled and divided into the durvalumab alone (20 mg/kg, Q4W), durvalumab (20 mg/kg, q4W) + tremelimumab (1 mg/kg Q4W, 4 cycles), or chemotherapy group at a ratio of 1:1:1, and the main end points were OS and PFS. By October 2018, at a median follow-up of 30.2 m, no significant improvement in OS was observed between the 2 immunotherapy modalities compared with chemotherapy in patients with PD-L1 TC ≥25% (16.3 *vs.* 12.9 m; 11.9 *vs.* 12.9 m; HR =0.76, 97.54% CI: 0.56–1.02; HR =0.85, 98.77% CI: 0.61–1.17), but the 2-year survival rate in the immunotherapy group was significantly better than that in the conventional chemotherapy group (38.3% *vs.* 35.4% *vs.* 22.7%). In patients with PD-L1 TC <1%, there was also no benefit of immunotherapy (OS, 10.1, 11.9, 10.3 m; HR =1.18, 95% CI: 0.86–1.62; HR =0.73, 95% CI: 0.51–1.04). From this study, it can be seen that chemotherapy is still the cornerstone of first-line treatment for NSCLC. On this basis, the POSEIDON study was carried out.

The POSEIDON study (43) (NCT03164616) evaluated the efficacy and safety of duvalizumab with or without tremelimumab, plus chemotherapy, as compared with chemotherapy alone in untreated metastatic NSCLC. A total of 1,013 patients with *EGFR/ALK* WT were enrolled and randomly divided into three groups (1:1:1): duvalizumab plus tremelimumab plus chemotherapy, duvalizumab plus therapy, and chemotherapy alone. The primary end points were PFS and OS, and the secondary end points were ORR and safety. The results published by WCLC in 2021 showed the following: Compared with chemotherapy alone, the 3-drug combination regimen significantly improved OS (14.0 *vs.* 11.7 m; HR =0.77; 95% CI: 0.65–0.92; P=0.00304) and PFS (6.2 *vs.* 4.8 m; HR =0.72; 95% CI: 0.60–0.86; P=0.00031). However, there was no statistically significant improvement in OS with dual-agent therapy compared with chemotherapy alone. In the subgroup analysis, the HR of PD-L1 TC <1% was 0.77 as compared with chemotherapy. Although this was not as good as the HR of 0.65 for TC ≥50%, a survival benefit was demonstrated, thus providing a treatment option for PD-L1-negative patients. Consistent with the results for the overall population, the HR was 0.99 in patients with PD-L1 TC <1% compared with chemotherapy, with no survival benefit. TRAEs and discontinuation due to TRAEs were numerically higher in the 3-drug combination group than in the chemotherapy-alone group. The incidence of grade 3/4 AEs was 53.3%, 54.8%, and 51.7% for three groups, respectively, and the incidence of serious adverse reactions was 44.2%, 40.1% and 35.1%, respectively. The rate of treatment interruption due to adverse reactions (22.1%, 20.4%, and 15.3%) and the mortality due to adverse reactions (12.4%, 10.2%, and 9.0%) were also higher in 3-drug and 2-drug combination groups than in the chemotherapy-alone. Therefore, the 3-drug combination can be considered for PD-L1-negative patients, but adverse reactions should also carefully monitored.

Sugemalimab

The GEMSTONE-302 study (44) on sugemalimab combined with chemotherapy has shown promising clinical efficacy and safety in the first-line treatment of metastatic NSCLC. The results published in 2022 in *Lancet Oncology* indicated that the mPFS of the sugemalimab group versus that of the placebo group was 9 and 4.9 m, respectively (HR =0.48; 95% CI: 0.39–0.60; P<0.0001). Subgroup analysis showed that sugemalimab treatment significantly prolonged PFS compared with placebo regardless of PD-L1 expression level. Among patients with PD-L1 TPS <1% (n=124, 64), the mPFS was 7.4 *vs.* 4.9 m (HR =0.56; 95% CI: 0.40–0.77). In patients with PD-L1 TPS ≥1% (n=196, 95), the mPFS was 10.9 and 4.9 m (HR =0.46, 95% CI: 0.35–0.62), the ORR was 61.4% and 39.2% (P<0.0001), and the mDOR was 9.69 *vs.* 3.68 m, respectively. Better tumor response rates were observed according to different levels of PD-L1 expression and in different tissues. In those with PD-L1 TPS <1%, the ORR was 50.0% *vs.* 39.1%; in patients with TPS of 1–49%, the ORR was 66.7% *vs.* 35.4%; and in patients with TPS ≥50%, the ORR was 70.6% *vs.* 43.5%, respectively. OS analysis showed that mOS was 22.8 *vs.* 17.7 m in the sugemalimab group versus the placebo group (HR =0.67; 95% CI: 0.50–0.90; P=0.0064). However, the results were not sufficiently mature for PD-L1 stratification analysis. The safety profile of sugemalimab combined with chemotherapy was favorable, with AEs of grade 3 or higher occurring in 61.9% of patients treated with sugemalimab versus

61.6% of patients treated with placebo. Although the benefit of sugemalimab plus chemotherapy was greater in patients with high PD-L1 expression, significant PFS and ORR benefits were also seen in patients with negative PD-L1 expression, supporting the use of sugemalimab plus chemotherapy as antitumor therapy in these patients.

Conclusions

The prevalence of PD-L1 expression in patients with stage IIIB/IV NSCLC is similar across all regions of the world, but PD-L1 expression level is associated with certain clinicopathological features. Adenocarcinoma, primary tumor, resected samples, and the outcome of longer survival are associated with low PD-L1 expression. *EGFR* and *STK11* mutations, along with WNT pathway changes, have been significantly associated with negative PD-L1 expression, while *KRAS*, *TP53*, and *MET* mutations have been significantly associated with high PD-L1 expression was.

The expression of PD-L1 can be evaluated by various methods. TPS/TC and CPS have high consistency, while the reliability of IC is slightly worse. Among the antibodies used for PD-L1 IHC, 22C3, 28-8, and SP263 staining have shown considerable sensitivity for the detection of PD-L1 expression on TC. However, the sensitivity of SP142 is low, while the sensitivity of the 73-10 method is higher. Although there are still many doubts and challenges regarding PD-L1 expression as a marker, experts and researchers have also proposed several solutions in terms of detection technology.

Clinically, we are more concerned about whether PD-L1 can predict the efficacy of immunotherapy to guide treatment. In fact, in many immunotherapies, it has been observed that patients with high PD-L1 expression experience better immunotherapy efficacy, but for patients with negative PD-L1 expression, some immuno-combined chemotherapy regimens are also better than chemotherapy alone. PD-L1 is a relatively popular biomarker at present. A meta-analysis of seven trials involving 1,132 patients with PD-L1 negative and driver gene negative advanced non squamous NSCLC showed that compared to chemotherapy alone, immunotherapy combined with chemotherapy as a first-line treatment for patients with PD-L1 negative advanced non squamous NSCLC achieved better ORR (odds ratio 2.81, 95% CI: 1.69–4.65), PFS (HR 0.63, 95% CI: 0.55–0.74, P<0.001) and OS (HR 0.68, 95% CI: 0.56–0.82, P<0.001) (78). In addition, nearly half of the NSCLC population has PD-L1-negative expression, and thus we need to understand how to choose immunotherapy for these PD-L1-negative patients.

In the treatment of locally advanced NSCLC, the classic PACIFIC study (cCRT followed by durvalumab) significantly prolonged the survival of patients. Unfortunately, the PFS and OS were not prolonged in patients with negative PD-L1 expression. In contrast, the phase II KEYNOTE-799 trial of pembrolizumab plus concurrent chemotherapy showed promise in patients with negative PD-L1 expression, with an ORR of 66.7% and 71.4% in the cohort A (squamous/nonsquamous) and cohort B (nonsquamous), respectively, which was similar to that in patients with positive PD-L1 expression. However, both PFS and OS have not been achieved, and verification by randomized controlled phase III clinical trials is still needed.

In the first-line treatment, the efficacy of single immune agents in patients with negative PD-L1 expression is not ideal. The efficacy of immunotherapy combined with chemotherapy, double immunotherapy combined with chemotherapy, and immunotherapy combined with targeted therapy is more effective. In patients with nonsquamous NSCLC, pembrolizumab combined with pemetrexed and platinum is a good choice. In the KEYNOTE-189 study, a significant survival benefit was seen for this regiment, with an extension of 7.0 m of survival compared with chemotherapy alone. In patients with squamous cell carcinoma, pembrolizumab combined with carboplatin and paclitaxel or paclitaxel albumin was proven to be a viable option, and in the KEYNOTE-407 trial, immunochemotherapy significantly prolonged both PFS and OS by 4.0 m.

Patients with negative PD-L1 expression can also select O+Y double immunotherapy or nivolumab plus chemotherapy as first-line therapy. In the CheckMate-227 study, O+Y double immunotherapy extended OS by 5.0 m compared with standard chemotherapy, and nivolumab plus chemotherapy extended survival by 3.0 m compared with chemotherapy alone. In subgroup analysis, patients with nonsquamous cell cancer had an OS increase of 4.4 m with double immunotherapy compared with standard chemotherapy, and an OS increase of 4.6 m with nivolumab plus chemotherapy. Patients with PD-L1-negative squamous cell carcinoma had a 7.4-m increase in survival under dual immunotherapy, but the increase was slightly weaker with nivolumab plus chemotherapy at only 2.8 m and did not reach statistical significance. Therefore, patients with nonsquamous cell carcinoma could undergo both O+Y double immunotherapy and nivolumab plus chemotherapy, and patients with squamous cell

carcinoma should perhaps prefer double immunotherapy. In attempting to compensate for the deficiency of slow immune response and pseudoprogression, the CheckMate-9LA study demonstrated that first-line dual immunotherapy combined with limited cycles of chemotherapy could significantly prolong the survival of patients with NSCLC. Nivolumab plus ipilimumab combined with two cycles of chemotherapy extended survival by 7.0 m compared with chemotherapy alone. However, it is clear that the AEs in the sequential immunochemotherapy group are more severe and should be selected carefully.

In nonsquamous NSCLC, the CameL study showed that camrelizumab combined with chemotherapy increased PFS by 3.0 m compared with chemotherapy alone regardless of PD-L1 expression. However, the HR of the PD-L1-negative subgroup was 0.76, and the CI was over 1, and thus this still needs to be verified by a larger sample. For patients with nonsquamous cell carcinoma with negative PD-L1 expression, tislelizumab combined with pemetrexed and platinum only demonstrated a nonsignificant PFS benefit compared with chemotherapy alone (RATIONALE 304 study), and no OS data were reported. Sintilimab plus chemotherapy significantly prolonged PFS and reduced the risk of death by 25% compared with placebo plus chemotherapy, although the CI crossed 1. Therefore, patients with PD-L1-negative nonsquamous NSCLC should consider sintilimab plus chemotherapy as first-line therapy (ORIENT-11 study). Initial efficacy was also seen in PD-L1-negative patients with camrelizumab plus the targeted drug apatinib (SHR-1210-II-202 study), with an ORR of 40% and an mPFS of 11.0 m, but fewer patients were enrolled, and further phase III trials are needed. Atezolizumab plus carboplatin and albumin-paclitaxel significantly prolonged PFS (6.4 and 4.6 m) and OS by 3.2 m in patients with negative PD-L1 expression compared with chemotherapy alone, although the CI crossed 1 (IMpower130). Atezolizumab plus pemetrexed platin did not prolong PFS compared with chemotherapy alone, but significantly prolonged OS (15.9 and 10.5 m), suggesting that a regimen of atezolizumab plus pemetrexed and platinum-based (IMpower132) should be used as a first-line treatment for nonsquamous NSCLC patients with negative PD-L1 expression. Interestingly, no significant OS benefit was seen with this regimen in patients with positive PD-L1 expression. In patients with negative PD-L1 expression, atezolizumab plus bevacizumab plus carboplatin paclitaxel (ABCP) and ACP did not significantly prolong OS compared with BCP, and bevacizumab plus chemotherapy remains the cornerstone of first-line nonsquamous NSCLC treatment.

In squamous cell carcinoma, the CameL-sq study showed that camrelizumab combined with chemotherapy could significantly prolong the PFS and OS of patients with negative PD-L1 expression, but the follow-up time was short and there was no mature OS data. Compared with chemotherapy alone, tislelizumab combined with chemotherapy prolonged PFS and reduced the risk of disease progression by 36%. However, when CI exceeded 1, this regimen also achieved a higher ORR, which makes us suspect that this regimen can bring long-term benefits to patients. In the ORIENT-12 study, the combination of sintilimab and chemotherapy prolonged PFS and reduced the risk of disease progression by 45%, but again, OS was not reached. Moreover, in the IMpower131 study, atezolizumab plus carboplatin plus albumin-paclitaxel did not significantly prolong PFS and OS compared with chemotherapy alone.

In the MYSTIC study, durvalumab alone or in combination with tremelimumab failed as first-line treatment for NSCLC, including in patients with negative PD-L1 expression, and no additional survival benefit was seen compared with chemotherapy. Considering that chemotherapy remains the cornerstone of first-line treatment for NSCLC, the POSEIDON study of durvalumab with or without tremelimumab, plus chemotherapy versus chemotherapy alone, showed a 23% reduction in the risk of death in the tremelimumab + durvalumab + chemotherapy compared with the chemotherapy-alone group. This regimen provides an option for PD-L1-negative patients, but this group experienced a higher number of AEs, and thus this regimen should be administered with caution. Sugemalimab combined with chemotherapy was also found to be a potential treatment option for PD-L1-negative patients with NSCLC. Compared with chemotherapy alone, it prolonged PFS by 2.5 m (7.4 *vs.* 4.9 m) and improved ORR (50.0% *vs.* 39.1%). OS results have not been stratified for PD-L1.

Nivolumab alone is an option for second-line therapy in patients with negative PD-L1 expression, and the results of Checkmate-017 showed that nivolumab increased OS by 3.2 m compared with docetaxel in lung squamous cell carcinoma. However, in nonsquamous cell cancer, the CheckMate-057 subgroup analysis showed no significant survival benefit for nivolumab compared with docetaxel. As histological types were not differentiated at 5 years of follow-up, second-line nivolumab was seen to extend OS by 1.9 m in patients with NSCLC with negative PD-L1

expression. Therefore, patients with PD-L1-negative lung squamous cell carcinoma could be treated with nivolumab in second-line therapy, while patients with nonsquamous cell carcinoma should also be considered to be treated with nivolumab in second-line therapy. The CheckMate-078 (23) and CheckMate-870 (24) studies both suggest that nivolumab should also be attempted in second- and third-line therapy for patients with advanced NSCLC with negative PD-L1 expression in the Chinese population. The value of camrelizumab in second-line therapy in patients with negative PD-L1 expression remains to be considered. The single-arm phase II study of SHR-1210-II-201 showed efficacy similar to that of single-agent chemotherapy, but the results of large randomized controlled trials are not yet available. Tislelizumab compared with docetaxel was found to prolong survival and reduce the risk of death by 26% in second- or third-line treatment and represents an alternative treatment option for PD-L1-negative patients with NSCLC (RATIONALE 303 study). In OAK study, atezolizumab was shown to significantly prolong OS compared with docetaxel in both patients with TC0/IC0 (9.9 and 7.0 m) and in those with TPS <1% (10.6 and 7.5 m).

This review found that even patients with NSCLC who are negative for PD-L1 expression can receiver better survival benefits with some immunotherapies, which thus represent a better treatment option for this relatively small patient population. However, since most clinical trials of immunotherapy have not targeted PD-L1-negative patients with NSCLC, only the results of subgroup analysis with limited statistical power are available and should be carefully considered. Therefore, the immunotherapy of patients with NSCLC and PD-L1-negative expression needs to be further explored in real-world studies. In addition, some regimens significantly benefited patients with high PD-L1 expression, but showed less benefit for patients with negative PD-L1 expression, while some regimens showed good benefit in both PD-L1-negative and PD-L1-positive patients; in the IMpower132 study, patients with negative PD-L1 expression were even shown to experience more significant OS benefit than those with positive PD-L1 expression. The mechanism behind this is still unclear and further studies in this direction are needed.

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Footnote

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