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EDITORIAL

First-line immunotherapy for advanced non-small cell lung cancer: current progress and future prospects

Jingyi Wang[1,2], Lin Wu[1]

[1]The Second Department of Thoracic Oncology, Hunan Cancer Hospital/The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha 410013, China; [2]Xiangya Lung Cancer Center, Xiangya Hospital, Central South University, Changsha 410008, China

Global Cancer Statistics 2022 reported the prevalence and high mortality rate of lung cancer. Notably, non-small cell lung cancer (NSCLC) accounts for the majority of the histologic types[1]. Precision therapy for lung cancer has progressed rapidly and immune checkpoint inhibitors (ICIs) have become a leading research topic. Indeed, ICI therapy has been shown to improve the prognosis of lung cancer patients. ICI monotherapy or combination therapy has now become the first-line standard treatment option for patients with driver gene-negative advanced NSCLC[2]. Despite the clear progress being made in immunotherapy, many issues still need to be further explored, such as the selection of optimization strategies and the identification of efficacy-related biomarkers. Herein we will summarize the current status of first-line immunotherapy for NSCLC, discuss the research progress with respect to immunotherapy biomarkers, and clarify the challenges and future directions of first-line immunotherapy for NSCLC.

Mechanism of action underlying ICIs

The ICIs that have been studied intensively include programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors. PD-L1 is a co-regulatory molecule expressed on tumor cells and inhibits T cell-mediated cell death. T-cells express PD-1 (a negative regulator), which binds to ligands, including PD-L1 (CD274) and PD-L2 (CD273). PD-1/PD-L1 is a negatively regulated signaling pathway for T-cell activation. By blocking this pathway PD-1/PD-L1 inhibitors reactivate suppressed T-cells, enhance recognition of tumor antigens and kill tumor cells. CTLA-4 is another co-stimulatory molecule that negatively regulates T-cell activation. CTLA-4 inhibitors effectively block the binding of CTLA-4 to B7 molecules and restore the activity of the co-stimulatory CD28-B7 signaling pathway. Thus, the inhibitory effect on T cell activation is weakened and the infiltration of tumor-specific T cells is increased[2,3].

Correspondence to: Lin Wu
E-mail: wulin-calf@vip.163.com
ORCID ID: https://orcid.org/0000-0001-7078-7767
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Current status of first-line immunotherapy for advanced NSCLC

Immunotherapy has changed the landscape of first-line treatment for patients with advanced NSCLC. We have summarized immunotherapy regimens approved by the U.S. Food & Drug Administration (FDA) and/or the Chinese National Medical Products Administration (NMPA) for first-line treatment of advanced NSCLC.

ICI monotherapy

Currently, pembrolizumab, atezolizumab, or cemiplimab monotherapy is recommended as first-line treatment for advanced NSCLC with high PD-L1 expression and negative driver genes regardless of histologic type (squamous or non-squamous; **Table 1**)[2].

Evidence for monotherapy with the PD-1 inhibitor, pembrolizumab, comes primarily from the KEYNOTE-024 and KEYNOTE-042 studies. The KEYNOTE-024 study included

Table 1 Summary of clinical trials of first-line ICIs monotherapy for advanced NSCLC

Study	Patient	Arm	ORR, %	DOR, median, months	PFS		OS		Grade ≥ 3 TRAEs, %
					Median, months	HR (95% CI)	Median, months	HR (95% CI)	
KEYNOTE-024	PD-L1 TPS ≥ 50% advanced NSCLC	Pembrolizumab *vs.* chemotherapy	44.8 *vs.* 27.8	NR *vs.* 6.3	10.3 *vs.* 6.0	0.50 (0.37–0.68)	26.3 *vs.* 13.4	0.62 (0.48–0.81)	26.6 *vs.* 53.3
KEYNOTE-042	PD-L1 TPS ≥ 1% advanced NSCLC	Pembrolizumab *vs.* chemotherapy	27 *vs.* 27	20.2 *vs.* 8.3	5.4 *vs.* 6.5	1.07 (0.94–1.21)	16.7 *vs.* 12.1	0.81 (0.71–0.93)	18 *vs.* 41
IMpower110	PD-L1 TC ≥ 50%/IC ≥ 10% advanced NSCLC	Atezolizumab *vs.* chemotherapy	38.3 *vs.* 28.6	NE	8.1 *vs.* 5.0	0.63 (0.45–0.88)	20.2 *vs.* 13.1	0.59 (0.40–0.89)	NE
EMPOWER-Lung 1	PD-L1 TPS ≥ 50% advanced NSCLC	Cemiplimab *vs.* chemotherapy	39 *vs.* 20	16.7 *vs.* 6.0	8.2 *vs.* 5.7	0.54 (0.43–0.68)	NR *vs.* 14.2	0.57 (0.42–0.77)	14 *vs.* 39

ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; TPS, tumor proportion score; TC, tumor cell; IC, immune cell; ORR, objective response rate; DOR, duration of response; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; NE, not evaluable; NR, not reached; TRAE, treatment-related adverse event.

305 patients with advanced NSCLC and a PD-L1 tumor proportion score (TPS) ≥ 50%. The study showed that pembrolizumab significantly improves the objective response rate [ORR (44.8% *vs.* 27.8%)], prolongs progression-free survival [PFS (median, 10.3 *vs.* 6.0 months; HR = 0.50)], and overall survival [OS (median, 26.3 *vs.* 13.4 months; HR = 0.62)] compared to chemotherapy[4]. The KEYNOTE-042 study expanded the enrollment criteria to PD-L1 TPS ≥ 1%, the results of which suggested that pembrolizumab significantly reduces the risk of death compared to chemotherapy. The subgroup analysis, however, suggested that patients with PD-L1 and a TPS ≥ 50% were the primary population to benefit[5].

The IMpower110 study showed that among advanced NSCLC patients with high PD-L1 expression [tumor cell (TC) ≥ 50% or tumor-infiltrating immune cell (IC) ≥ 10%], the PD-L1 inhibitor, atezolizumab, significantly improved the ORR (38.3% *vs.* 28.6%), PFS (median, 8.1 *vs.* 5.0 months; HR = 0.63), and OS (median, 20.2 *vs.* 13.1 months; HR = 0.59)[6]. In 2020 the U.S. FDA approved atezolizumab for first-line monotherapy in metastatic NSCLC with a PD-L1 TC ≥ 50% or an IC ≥ 10%.

The PD-1 inhibitor, cemiplimab, was approved by the U.S. FDA for first-line treatment of metastatic NSCLC with a PD-L1 TPS ≥ 50% based on the EMPOWER-Lung 1 study. Specifically, cemiplimab significantly improved the ORR (39% *vs.* 20%) and prolonged the PFS (median, 8.2 *vs.* 5.7 months; HR = 0.54) and OS [median, not reached (NR) *vs.* 14.2 months; HR = 0.57] compared to chemotherapy[7].

In conclusion, for patients with advanced NSCLC and high PD-L1 expression, ICI monotherapy provides significant clinical benefits and changes the treatment pattern; however, the clinical benefits of immune monotherapy in NSCLC patients with low or no PD-L1 expression are not significant. Therefore, immuno-combination therapy is vital for further expanding the population that will benefit and optimizing the efficacy of immunotherapy.

ICIs combined with chemotherapy

ICIs, in combination with chemotherapy, are the guideline-recommended first-line standard for driver gene-negative advanced NSCLC independent of the level of PD-L1 expression (**Table 2**).

The KEYNOTE-189 study enrolled patients with advanced non-squamous NSCLC who were treated with pembrolizumab in combination with pemetrexed and platinum. Compared to

Table 2 Summary of clinical trials of first-line ICIs combined with chemotherapy for advanced NSCLC

Study	Patient	Arm	ORR, %	DOR, median, months	PFS		OS		Grade ≥ 3 TRAEs, %
					Median, months	HR (95% CI)	Median, months	HR (95% CI)	
KEYNOTE-189	Advanced non-squamous NSCLC	Pembrolizumab + chemotherapy *vs.* chemotherapy	48.3 *vs.* 19.9	12.5 *vs.* 7.1	9.0 *vs.* 4.9	0.49 (0.41–0.59)	22.0 *vs.* 10.6	0.56 (0.46–0.69)	NE
KEYNOTE-407	Advanced squamous NSCLC	Pembrolizumab + chemotherapy *vs.* chemotherapy	62.2 *vs.* 38.8	9.0 *vs.* 4.9	8.0 *vs.* 5.1	0.62 (0.52–0.74)	17.2 *vs.* 11.6	0.71 (0.59–0.85)	57.2 *vs.* 55.7
IMpower130	Advanced non-squamous NSCLC	Atezolizumab + chemotherapy *vs.* chemotherapy	49.2 *vs.* 31.9	8.4 *vs.* 6.1	7.0 *vs.* 5.5	0.64 (0.54–0.77)	18.6 *vs.* 13.9	0.79 (0.64–0.98)	24 *vs.* 13
EMPOWER-Lung 3	Advanced NSCLC	Cemiplima + chemotherapy *vs.* chemotherapy	43.3 *vs.* 22.7	15.6 *vs.* 7.3	8.2 *vs.* 5.0	0.56 (0.44–0.70)	21.9 *vs.* 13.0	0.71 (0.53–0.93)	43.6 *vs.* 31.4
CameL	Advanced non-squamous NSCLC	Camrelizumab + chemotherapy *vs.* chemotherapy	60.5 *vs.* 38.6	17.6 *vs.* 9.9	11.3 *vs.* 8.3	0.60 (0.45–0.79)	NR *vs.* 20.9	0.73 (0.53–1.02)	69 *vs.* 47
CameL-sq	Advanced squamous NSCLC	Camrelizumab + chemotherapy *vs.* chemotherapy	64.8 *vs.* 36.7	13.1 *vs.* 4.4	8.5 *vs.* 4.9	0.37 (0.29–0.47)	NR *v.s* 14.5	0.55 (0.40–0.75)	74 *vs.* 72
ORIENT-11	Advanced non-squamous NSCLC	Sintilimab + chemotherapy *vs.* chemotherapy	51.9 *vs.* 29.8	NR *vs.* 5.5	8.9 *vs.* 5.0	0.482 (0.362–0.643)	NR *vs.* NR	0.609 (0.400–0.926)	61.7 *vs.* 58.8
ORIENT-12	Advanced squamous NSCLC	Sintilimab + chemotherapy *vs.* chemotherapy	44.7 *vs.* 35.4	6.1 *vs.* 5.1	5.5 *vs.* 4.9	0.536 (0.422–0.681)	NR *vs.* NR	0.567 (0.353–0.909)	86.6 *vs.* 83.1
RATIONALE 304	Advanced non-squamous NSCLC	Tislelizumab + chemotherapy *vs.* chemotherapy	57.4 *vs.* 36.9	8.5 *vs.* 6.0	9.7 *vs.*7.6	0.645 (0.462–0.902)	NR *vs.* NR	NE	67.6 *vs.* 53.6
RATIONALE 307	Advanced squamous NSCLC	Tislelizumab + chemotherapy *vs.* chemotherapy	72.5 *vs.* 49.6	8.2 *vs.* 4.2	7.6 *vs.* 5.5	0.524 (0.370–0.742)	NR *vs.* NR	NE	88.3 *vs.* 83.8
GEMSTONE-302	Advanced NSCLC	Sugemalimab + chemotherapy *vs.* chemotherapy	63.4 *vs.* 40.3	9.8 *vs.* 4.4	9.0 *vs.* 4.9	0.48 (0.39–0.60)	22.8 *vs.* 17.7	0.67 (0.50–0.90)	56 *vs.* 57
CHOICE-01	Advanced NSCLC	Toripalimab + chemotherapy *vs.* chemotherapy	65.7 *vs.* 46.2	8.4 *vs.* 4.2	8.4 *vs.* 5.6	0.49 (0.39–0.61)	NR *vs.* 17.1	0.69 (0.53–0.92)	78.6 *vs.* 82.1
AK105-302	Advanced squamous NSCLC	Penpulimab + chemotherapy *vs.* chemotherapy	71.4 *vs.* 44.0	8.25 *vs.* 2.96	7.6 *vs.* 4.2	0.44 (0.34–0.56)	NR *vs.* 19.8	0.55 (0.40–0.75)	63.6 *vs.* 62.9

ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; TPS, tumor proportion score; ORR, objective response rate; DOR, duration of response; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; NE, not evaluable; NR, not reached; TRAE, treatment-related adverse event.

the chemotherapy-only group, the combination therapy group had improved ORR (48.3% *vs.* 19.9%), PFS (median, 9.0 *vs.* 4.9 months; HR = 0.49), and OS (median, 22.0 *vs.* 10.6 months; HR = 0.56)[8]. The KEYNOTE-407 study further established the efficacy of pembrolizumab in combination with paclitaxel/nanoparticle albumin-bound (nab)-paclitaxel and carboplatin as first-line therapy in patients with advanced squamous NSCLC[9]. In combination with chemotherapy, pembrolizumab is recommended as the preferred first-line treatment option for non-squamous and squamous NSCLC[2].

The IMpower130 study compared atezolizumab with chemotherapy and chemotherapy alone as a first-line treatment option in patients with advanced non-squamous NSCLC. The combination therapy group had significant improvement in PFS (median, 7.0 *vs.* 5.5 months; HR = 0.64) and OS (median, 18.6 *vs.* 13.9 months; HR = 0.79). Therefore, the U.S. FDA approved atezolizumab in combination with nab-paclitaxel plus carboplatin for first-line treatment of metastatic non-squamous NSCLC[10].

The EMPOWER-Lung 3 study evaluated the efficacy of cemiplimab in combination with platinum-doublet chemotherapy in advanced NSCLC as first-line treatment. The study showed that the median PFS and OS were significantly longer in the cemiplimab combination chemotherapy group than the chemotherapy alone group [median (m)PFS, 8.2 *vs.* 5.0 months, HR = 0.56; mOS: 21.9 *vs.* 13.0 months, HR = 0.71][11]. The U.S. FDA approved cemiplimab plus platinum-doublet chemotherapy as a first-line treatment option for patients with advanced NSCLC.

In addition, Chinese self-developed PD-1/PD-L1 inhibitors have achieved remarkable success in clinical studies of ICIs combined with chemotherapy for the first-line treatment of advanced NSCLC. Based on the CameL[12] and CameL-sq[13] studies, the NMPA approved the PD-1 inhibitor, camrelizumab, in combination with pemetrexed/paclitaxel and carboplatin for first-line treatment of advanced non-squamous/squamous NSCLC. Camrelizumab combined with chemotherapy significantly improved the ORR (non-squamous, 60.5% *vs.* 38.6%; squamous, 64.8% *vs.* 36.7%) and prolonged the PFS (non-squamous: median, 11.3 *vs.* 8.3 months, HR = 0.60; squamous: median, 8.5 *vs.* 4.9 months, HR = 0.37) and OS (non-squamous: median, NR *vs.* 20.9 months, HR = 0.73; squamous: median, NR *vs.* 14.5 months, HR = 0.55). Based on the ORIENT-11[14] and ORIENT-12[15] studies, the NMPA approved the PD-1 inhibitor, sintilimab, in combination with pemetrexed/paclitaxel and carboplatin for first-line treatment of advanced non-squamous/squamous NSCLC. The sintilimab/chemotherapy combination group significantly prolonged the PFS compared to the chemotherapy group (non-squamous: median, 8.9 *vs.* 5.0 months; HR = 0.482; squamous: median, 5.5 *vs.* 4.9 months; HR = 0.536). Based on the RATIONALE 304[16] and RATIONALE 307[17] studies, the NMPA approved the PD-1 inhibitor, tislelizumab, in combination with pemetrexed/gemcitabine and carboplatin for first-line treatment of advanced non-squamous/squamous NSCLC. Tislelizumab in combination with chemotherapy met the primary study endpoint, i.e., a significant prolongation of the PFS compared to standard chemotherapy alone (non-squamous: median, 9.7 *vs.* 7.6 months; HR = 0.645; squamous: median, 7.6 *vs.* 5.5 months; HR = 0.524). The NMPA approved the PD-L1 inhibitor, sugemalimab, in combination with pemetrexed/paclitaxel and carboplatin for first-line treatment of metastatic non-squamous/squamous NSCLC based on the GEMSTONE-302 study[18]. Sugemalimab in combination with chemotherapy significantly improved the ORR (63.4% *vs.* 40.3%) and prolonged the PFS (median, 9.0 *vs.* 4.9 months; HR = 0.48) and OS (median, 22.8 *vs.* 17.7 months; HR = 0.67) compared to chemotherapy alone. The NMPA approved the PD-1 inhibitor, toripalimab, in combination with pemetrexed and carboplatin for first-line treatment of advanced non-squamous NSCLC based on the CHOICE-01 study[19]. Compared to chemotherapy alone, toripalimab in combination with chemotherapy significantly improved the ORR (65.7% *vs.* 46.2%) and prolonged the PFS (median, 8.4 *vs.* 5.6 months; HR = 0.49) and OS (median, not reached *vs.* 17.1 months; HR = 0.69). The NMPA approved the PD-1 inhibitor, penpulimab, in combination with paclitaxel and carboplatin for first-line treatment of advanced squamous NSCLC based on the AK105-302 study[20]. Specifically, immune combination therapy significantly prolonged the PFS compared to the chemotherapy-only group (median, 7.6 months *vs.* 4.2 months; HR = 0.44).

ICIs combined with anti-angiogenic therapy

ICIs combined with anti-angiogenic therapy have also shown promising applications in first-line treatment of advanced NSCLC (**Table 3**).

The IMpower150 study showed that patients with advanced non-squamous NSCLC treated with atezolizumab plus BCP (ABCP) had significant improvement in the PFS (median, 8.3 *vs.* 6.8 months; HR = 0.62), OS (median, 19.2 *vs.* 14.7 months; HR = 0.78), and ORR (63.5% *vs.*

Table 3 Summary of clinical trials of first-line ICIs combined with anti-angiogenic therapy or dual ICI combination therapy for advanced NSCLC

Study	Patient	Arm	ORR, %	DOR, median, months	PFS		OS		Grade ≥ 3 TRAEs, %
					Median, months	HR (95% CI)	Median, months	HR (95% CI)	
ICIs combined with antiangiogenic therapy									
IMpower150	Advanced non-squamous NSCLC	Atezolizumab + bevacizumab + chemotherapy *vs.* Bevacizumab + chemotherapy	63.5 *vs.* 48.0	9.0 *vs.* 5.7	8.3 *vs.* 6.8	0.62 (0.52–0.74)	19.2 *vs.* 14.7	0.78 (0.64–0.96)	58.5 *vs.* 50
Dual ICI combination therapy									
CheckMate 227	Advanced NSCLC	Nivolumab + ipilimumab *vs.* chemotherapy	33.1 *vs.* 27.8	19.6 *vs.* 5.8	5.1 *vs.* 5.5	0.79 (0.69–0.91)	17.1 *vs.* 13.9	0.73 (0.64–0.84)	32.8 *vs.* 36
CheckMate 9LA	Advanced NSCLC	nivolumab + ipilimumab+ chemotherapy *vs.* chemotherapy	38.2 *vs.* 24.9	11.3 *vs.* 5.6	6.7 *vs.* 5.0	0.68 (0.57–0.82)	15.6 *vs.* 10.9	0.66 (0.55–0.80)	47 *vs.* 38
POSEIDON	Advanced NSCLC	Tremelimumab + durvalumab + chemotherapy *vs.* chemotherapy	38.8 *vs.* 24.4	9.5 *vs.* 5.1	6.2 *vs.* 4.8	0.72 (0.60–0.86)	14.0 *vs.* 11.7	0.77 (0.65–0.92)	51.8 *vs.* 44.4

ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; TPS, tumor proportion score; ORR, objective response rate; DOR, duration of response; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; TRAE, treatment-related adverse event.

48.0%) compared to bevacizumab plus carboplatin plus paclitaxel (BCP). The ABCP four-drug combination regimen was approved by the U.S. FDA for first-line treatment of metastatic non-squamous NSCLC based on the results of IMpower150[21].

Dual ICI combination therapy

Studies have reported positive results related to the first-line treatment of advanced NSCLC with dual ICI combination therapy (PD-1/PD-L1 inhibitors combined with CTLA-4 inhibitors; **Table 3**).

The CheckMate 227 study compared the efficacy and safety of the PD-1 inhibitor, nivolumab, plus the CTLA-4 inhibitor, ipilimumab, with chemotherapy alone for first-line treatment of advanced NSCLC. Specifically, a significant median OS benefit of nivolumab plus ipilimumab over chemotherapy alone in patients with a PD-L1 ≥ 1% (17.1 *vs.* 14.9 months; HR = 0.79, $P = 0.007$) was reported, which met the primary study endpoint[22]. The U.S. FDA approved nivolumab plus ipilimumab for first-line treatment of advanced NSCLC with a PD-L1 TPS ≥ 1%.

The CheckMate-9LA study was a phase III clinical study that determined the efficacy and safety of first-line nivolumab plus ipilimumab combined with two cycles of chemotherapy versus chemotherapy alone for advanced NSCLC. Combination treatment significantly prolonged the PFS (median, 6.7 months *vs.* 5.0 months; HR = 0.68) and OS (median, 15.6 months *vs.* 10.9 months; HR = 0.66) compared to chemotherapy[23]. The U.S. FDA approved nivolumab plus ipilimumab combined with chemotherapy (2 cycles) for first-line treatment of advanced NSCLC.

The efficacy and safety of the PD-L1 inhibitor, durvalumab, plus the CTLA-4 inhibitor, tremelimumab, in combination with chemotherapy and chemotherapy alone in first-line treatment of metastatic NSCLC were compared in the POSEIDON study. Dual immunotherapy combined with chemotherapy significantly prolonged the PFS (median, 6.2 months *vs.* 4.8 months; HR = 0.72) and OS (median, 14.0 months *vs.* 11.7 months; HR = 0.77) compared to chemotherapy alone. Subgroup analyses showed that OS was similar in the squamous cell histology group and other subgroups[24]. The U.S. FDA approved the tremelimumab plus durvalumab regimen in combination with platinum-based chemotherapy as first-line treatment option for patients with metastatic NSCLC.

Novel immunotherapy

A series of emerging ICIs are currently under development. The ICIs will become an important direction for future research and include inhibitors targeting novel immune checkpoints, such as the T cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT), lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin and mucin domain-containing protein (TIM-3), bi-/tri-specific antibody-targeted therapy, and tumor vaccines[25].

Research progress of biomarkers for immunotherapy

PD-L1

The NCCN guidelines recommend that all patients with advanced NSCLC undergo immunohistochemistry (IHC) testing for PD-L1 expression prior to receiving first-line therapy if clinically feasible to assess the availability of an ICI regimen[2]. Several prospective clinical trials have demonstrated a correlation between high PD-L1 expression and the efficacy of first-line immunotherapy. Based on the Keynote 024 study, pembrolizumab was approved for first-line treatment of patients with advanced NSCLC and a PD-L1 TPS ≥ 50%. The Keynote 042 study expanded the indication for pembrolizumab to include patients with a PD-L1 TPS ≥ 1%, but subgroup analyses suggested that the primary population of benefit would be PD-L1 patients with a TPS ≥ 50%. The subsequent IMpower110 and EMPOWER-Lung 1 studies obtained similar results. PD-L1 expression has been shown to have predictive value in exploratory analyses of many NSCLC clinical trials. Some patients with negative PD-L1 expression also benefit from PD-1/PD-L1 inhibitor therapy. With the advent of immunologic combination therapy strategies, the predictive value of PD-L1 has decreased. Subgroup analyses of several clinical studies have shown that patients with advanced NSCLC benefit from first-line immunocombination therapy independent of PD-L1 expression status[8-21,23,24]. Imperfections in PD-L1 as a biomarker can be attributed to various factors. PD-L1 expression is heterogeneous, varies within tumors, may be inconsistent in sections of the same tumor sample, and may even change with treatment. Differences in assay methods and interpretation of results exist across assays and need to be standardized[26]. Although PD-L1 is not a perfect biomarker, PD-L1 expression is currently the best available biomarker for assessing a patient's suitability for receiving a PD-1/PD-L1 inhibitor, and remains an essential guide.

Tumor mutational burden (TMB)

The TMB is the number of somatic non-synonymous mutations per MByte occurring in a specific genomic region and reflects the neoantigenic load. Evidence for the use of TMB as an immune-associated biomarker in NSCLC has been derived primarily from subgroup analyses of clinical trials. In the CheckMate 227 study, first-line nivolumab in combination with ipilimumab was superior to chemotherapy in NSCLC patients with a high TMB (≥ 10 mut/MB) with respect to PFS independent of PD-L1 expression. Long-term follow-up data, however, showed that the TMB level was not associated with OS. Furthermore, combining the TMB with PD-L1 expression did not predict OS[22]. There is still a lack of sufficient clinical data to support use of the TMB as a biomarker and many studies have shown conflicting results. The TMB is also difficult to quantify and standardize. Therefore, this diagnostic and predictive method has not received regulatory approval and the NCCN guidelines do not recommend measuring the TMB level for immunotherapy decision-making.

Others

In recent years, emerging blood-based biomarkers based on liquid biopsies have attracted much attention in the investigation of biomarkers for predicting immune efficacy in NSCLC, including circulating free tumor DNA (ctDNA), circulating non-coding RNAs (microRNAs), and peripheral blood immune cell populations. The evolution of epigenetic biomarkers and the gut microbiota are also receiving attention[27].

Challenges and future directions of first-line immunotherapy for NSCLC

Immunotherapy has changed the landscape of first-line treatment for advanced NSCLC, but also faces many challenges. There are no head-to-head comparative studies between immunotherapy regimens, and the optimal treatment paradigm remains to be clarified. The effective management of immune-related adverse events (irAEs) must be emphasized independent of the type of immunotherapy. Although various

biomarkers, including PD-L1 and the TMB, have some predictive value in many clinical trials, neither are ideal biomarkers with respect to efficacy. Fewer irAEs have been identified as predictive biomarkers. Although first-line immunotherapy has improved the survival prognosis of patients with advanced NSCLC, only a fraction of patients have experienced long-term benefits after receiving immunotherapy. The mechanism of acquired resistance to immunotherapy remains unclear and the mode of treatment after resistance warrants further study. In addition, the higher treatment cost of ICIs is a current problem.

Emerging ICIs should be further developed in the future and additional optimal combination therapy modalities should be validated. For example, immunotherapy combined with anti-angiogenic therapy and de-chemotherapy modalities have good prospects for application in the first-line treatment of patients with advanced NSCLC. Immunotherapy combined with radiotherapy in advanced NSCLC also deserves further exploration, especially the choice of radiotherapy modality, the optimal dose, and the sequence of radiotherapy and immunotherapy need to be clarified. In addition, the search for the best biomarkers to predict ICI efficacy and irAEs should continue. Comprehensive prediction and dynamic monitoring models should be further constructed to achieve individualized precision immunotherapy. Furthermore, elucidating the mechanism underlying immune resistance and exploring strategies to overcome immune resistance are also directions for future research.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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