Current and future drug combination strategies based on programmed death-1/programmed death-ligand 1 inhibitors in non-small cell lung cancer

Ying Cheng[1], Hui Li[2], Liang Zhang[1], Jing-Jing Liu[1], Chang-Liang Yang[1], Shuang Zhang[1]

[1]Department of Thoracic Oncology, Jilin Cancer Hospital, Changchun, Jilin 130012, China;
[2]Translational Oncology Research Lab, Jilin Provincial Key Laboratory of Molecular Diagnostics for Lung Cancer, Jilin Cancer Hospital, Changchun, Jilin 130012, China.

Abstract

In recent years, immune checkpoint inhibitors (ICIs) have made breakthroughs in the field of lung cancer and have become a focal point for research. Programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor monotherapy was the first to break the treatment pattern for non-small cell lung cancer (NSCLC). However, owing to the limited benefit of ICI monotherapy at the population level and its hyper-progressive phenomenon, it may not meet clinical needs. To expand the beneficial range of immunotherapy and improve its efficacy, several research strategies have adopted the use of combination immunotherapy. At present, multiple strategies, such as PD-1/PD-L1 inhibitors combined with chemotherapy, anti-angiogenic therapy, cytotoxic T-lymphocyte-associated protein 4 inhibitors, and radiotherapy, as well as combined treatment with new target drugs, have been evaluated for clinical practice. To further understand the current status and future development direction of immunotherapy, herein, we review the recent progress of ICI combination therapies for NSCLC.

Keywords: Non-small cell lung cancer; Programmed death-1/programmed death-ligand 1; Immune checkpoint inhibitor; Combination therapy

Introduction

Lung cancer is associated with the highest morbidity and mortality rates worldwide.[1] In recent years, programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors have made breakthroughs in the treatment of lung cancer. PD-1/PD-L1 inhibitors were initially used as second-line treatments but were upgraded as first-line treatments for advanced lung cancer and unresectable locally advanced non-small cell lung cancer (NSCLC). Now, immunotherapy is moving toward neoadjuvant and adjuvant treatments for early-stage NSCLC.[2-9] Immunotherapy strategies include single-agent immune checkpoint inhibitors (ICIs) in monotherapy and combination therapies. Several studies have shown that the population that benefits from single-agent ICI therapy is limited and may have a hyper-progressive response pattern.[10] An immune combination strategy not only further improves treatment efficacy but also expands the population that benefits from immunotherapy, thereby covering the entire patient population without driver gene mutations. Therefore, more clinical studies are currently adopting immune combination therapies based on PD-1/PD-L1 inhibitors, such as ICIs combined with chemotherapy, anti-angiogenic agents, dual immune blockades, and radiotherapy, which have become research hotspots. Numerous studies have also preliminarily explored the combination therapy of PD-1/PD-L1 inhibitors and novel immune target drugs. Herein, we review the current status of and future trends in ICIs used in combination therapies for NSCLC.

Current Status of Combined Immunotherapy Strategies for NSCLC

Combination therapies for advanced NSCLC

ICIs in combination with chemotherapy

Platinum-based doublet chemotherapy was the first-line standard of care for patients with advanced NSCLC without driver oncogene mutations before the availability of ICIs. Adding immunotherapy with chemotherapy was the earliest and most commonly used combination therapy. An increasing number of studies have reported

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Correspondence to: Prof. Ying Cheng, Department of Thoracic Oncology, Jilin Cancer Hospital, No. 1018 Hu Guang Road, Changchun, Jilin 130012, China
E-Mail: jl.cheng@163.com

that chemotherapy has a positive effect on the immune microenvironment of tumors, and this enhances the antitumor activity through cellular mechanisms that include the reduction in T-regulatory cell (Tregs) activity, depletion of myeloid-derived suppressor cells (MDSCs), and induction of antigen-presenting cell maturation.[11,12] Therefore, combining ICIs with chemotherapy could result in synergistic antitumor activity.

The phase II randomized controlled study, KEYNOTE-021 cohort G, evaluated pembrolizumab combined with pemetrexed plus carboplatin *vs.* pemetrexed plus carboplatin as a first-line treatment in patients with advanced non-squamous NSCLC without epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) gene mutations. The results showed that the ICI plus chemotherapy group had a significant improvement in objective response rate (ORR), prolonged progression-free survival (PFS), and overall survival (OS). These findings indicated that patients can benefit regardless of the PD-L1 expression level.[13] Therefore, the Food and Drug Administration (FDA) accelerated the approval of the use of pembrolizumab in combination with pemetrexed plus carboplatin as a first-line treatment of non-squamous NSCLC. The KEYNOTE-189 study also reported that the combination of pembrolizumab and chemotherapy significantly prolonged the OS and PFS compared with chemotherapy alone in patients with metastatic NSCLC.[14] The updated data show that the 3-year OS rate of the two groups was 31.3% and 17.4%, respectively. Similarly, the results of the IMpower130 study showed atezolizumab plus carboplatin and nab-paclitaxel significantly improved the OS and PFS compared with chemotherapy treatment alone.[15] However, in the IMpower132 study, atezolizumab plus pemetrexed and cisplatin or carboplatin only reached the co-primary endpoint for PFS but not the OS compared with chemotherapy alone [Table 1].[16]

The emergence of immunotherapy has also improved the treatment of advanced lung squamous cell carcinoma. The KEYNOTE-407 study was a phase III study that evaluated the efficacy and safety of pembrolizumab combined with paclitaxel or albumin–paclitaxel and carboplatin. The results showed that combined immunotherapy significantly improved the PFS and OS in patients with advanced squamous NSCLC.[17,18] The FDA approved the use of pembrolizumab in combination with chemotherapy as a first-line treatment of metastatic squamous NSCLC based on the results of the KEYNOTE 407 study. The updated data showed that the 3-year OS rate of the two groups was 29.7% and 18.2%, respectively. Another phase III study, IMpower131, also evaluated the efficacy of atezolizumab combined with chemotherapy; however, the study only reached the PFS endpoint, and no OS benefit was observed with the addition of atezolizumab.[19] The IMpower131 study had different rates of subsequent treatment between the groups. The subsequent treatment ratio in the ICI combination group was 36.2%, whereas the subsequent treatment ratio in the chemotherapy group was 58.2%. The higher subsequent treatment ratio in the chemotherapy group may affect the OS.

Several phase III studies that evaluated the combined use of chemotherapy and PD-1 inhibitors developed in China, such as camrelizumab, sintilimab, and tislelizumab have also reported that the combination treatment can improve PFS and that all of them have good tolerance [Table 1].[20-25] ICIs combined with chemotherapy apply to patients with advanced NSCLC without driver gene mutations, regardless of PD-L1 expression or the histological type (*ie*, non-squamous cell carcinoma or squamous cell carcinoma). Hence, ICIs combined with chemotherapy have become a standard first-line treatment for advanced NSCLC.

ICIs in combination with anti-angiogenic agents and chemotherapy

Tumor angiogenesis is the development of abnormal tumor blood vessels that promote tumor growth and an important hallmark of cancer. Anti-angiogenic agents can normalize and remodel the blood vessels of tumors that increase immune cell infiltration into the tumor and promote the killing activity of immune effector cells. Immunotherapy can regulate remodeling and normalization of tumor vasculature through immune stimulation, motivate activated effector cells to secrete interferon, and act synergistically with anti-angiogenic agents.[26] Generally, anti-angiogenesis drugs include large-molecule monoclonal antibodies, such as bevacizumab and ramucirumab, and small-molecule tyrosine kinase inhibitors (TKIs), such as lenvatinib and anlotinib.

The IMpower150 was the first phase III study to report the use of ICIs in combination with chemotherapy and bevacizumab. The study evaluated atezolizumab combined with paclitaxel and carboplatin (ACP), atezolizumab combined with bevacizumab plus paclitaxel and carboplatin (ABCP), and bevacizumab combined with paclitaxel and carboplatin (BCP) as a first-line treatment of non-squamous NSCLC. The results showed that compared with the BCP group, the ABCP group significantly prolonged the OS [19.2 months *vs.* 14.7 months, hazard ratio (HR) 0.78, 95% confidence interval (CI) 0.64–0.96].[27] Based on the results of this study, the FDA approved the use of atezolizumab in combination with bevacizumab plus paclitaxel and carboplatin as a first-line treatment for patients with advanced non-squamous NSCLC without *EGFR* or *ALK* gene mutations. The IMpower150 study also explored the beneficial populations of the combination therapy. The updated results showed that the patients with liver metastasis, large tumor size, and *EGFR* mutation were more likely to benefit when ICIs are combined with chemotherapy and bevacizumab.[28-30] The retrospective analysis of biomarkers showed that the OS of the ABCP, ACP, and BCP groups comprising patients with *KRAS* mutation was 19.81 months, 11.73 months, and 9.86 months, respectively. These results suggested that patients with *KRAS* mutations could benefit from this combination treatment.[31] Another phase III study evaluated nivolumab combined with bevacizumab plus paclitaxel and carboplatin *vs.* placebo combined with bevacizumab plus paclitaxel and carboplatin. The nivolumab combination

Table 1: ICIs used in combination with chemotherapy as first-line treatment for NSCLC.

Study	Arms	Phase	Histology	Primary endpoint	ORR	PFS	OS
KEYNOTE 021G	Pembrolizumab + carboplatin + pemetrexed vs. carboplatin + pemetrexed	II	Non-squamous NSCLC	ORR	56.7% vs. 30.2%	13.0 vs. 8.3 (HR 0.53, 95% CI 0.31–0.91)	NR vs. 21.1 (HR 0.56, 95% CI 0.32–0.95)
KEYNOTE 189	Pembrolizumab + platinum + pemetrexed vs. platinum + pemetrexed	III	Non-squamous NSCLC	PFS, OS	47.6% vs. 18.9%	9.0 vs. 4.9 (HR 0.49, 95% CI 0.41–0.59)	22.0 vs. 10.6 (HR 0.56, 95% CI 0.46–0.69)
IMPOWER130	Atezolizumab + carboplatin + nab-paclitaxel vs. carboplatin + nab-paclitaxel	III	Non-squamous NSCLC	PFS, OS	49.2% vs. 31.9%	7.0 vs. 5.5 (HR 0.64, 95% CI 0.54–0.77)	18.6 vs. 13.9 (HR 0.79, 95% CI 0.64–0.98)
IMPOWER132	Atezolizumab + platinum + pemetrexed vs. platinum + pemetrexed	III	Non-squamous NSCLC	PFS, OS	47% vs. 32%	7.6 vs. 5.2 (HR 0.60, 95% CI 0.49–0.72)	18.1 vs. 13.6 (HR 0.81, 95% CI 0.64–1.03)
KEYNOTE 407	Pembrolizumab + carboplatin + paclitaxel/ nab-paclitaxel vs. carboplatin + paclitaxel/nab-paclitaxel	III	Squamous NSCLC	PFS, OS	58.4% vs. 35.0%	6.4 vs. 4.8 (HR 0.56, 95% CI 0.45–0.60)	15.9 vs. 11.3 (HR 0.64, 95% CI 0.49–0.85)
IMPOWER131	Atezolizumab + carboplatin + paclitaxel (arm A) or atezolizumab + carboplatin + nab-paclitaxel (arm B) vs. carboplatin + nab-paclitaxel (arm C)	III	Squamous NSCLC	PFS, OS	Arm B vs. arm C: 49% vs. 41%	Arm B vs. arm C: 6.3 vs. 5.6 (HR 0.71, 95% CI 0.60–0.85)	Arm B vs. arm C: 14.0 vs. 13.9 (HR 0.96, 95% CI 0.78–1.18)
CAMEL	Camrelizumab + carboplatin + pemetrexed vs. carboplatin + pemetrexed	III	Non-squamous NSCLC	PFS	60% vs. 39.1%	11.3 vs. 8.3 (HR 0.61, 95% CI: 0.46–0.80)	27.9 vs. 20.5 (HR 0.73, 95% CI 0.55–0.96)
ORIENT-11	Sintilimab + platinum + pemetrexed vs. platinum + pemetrexed	III	Non-squamous NSCLC	PFS	51.9% vs. 29.8%	8.9 vs. 5.0 (HR 0.48, 95% CI: 0.36–0.64)	Not mature
RATIONAL-304	Tislelizumab + carboplatin + pemetrexed vs. carboplatin + pemetrexed	III	Non-squamous NSCLC	PFS	57.4% vs. 36.9%	9.7 vs. 7.6 (HR 0.645, 95% CI 0.462–0.902)	Not mature
ORIENT-12	Sintilimab + platinum + gemcitabine vs. platinum + gemcitabine	III	Squamous NSCLC	PFS	44.7% vs. 35.4%	5.5 vs. 4.9 (HR 0.536, 95% CI 0.422–0.681)	Not mature
RATIONAL-307	Tislelizumab + carboplatin + paclitaxel (arm A) or tislelizumab + carboplatin + nab-paclitaxel (arm B) vs. carboplatin + paclitaxel (arm C)	III	Squamous NSCLC	PFS	72.5% vs. 74.8% vs. 49.6%	7.6 vs. 5.5 (HR 0.524, 95% CI 0.370–0.742, HR 0.478, 95% CI 0.336–0.679)	Not mature
CAMEL-sq	Camrelizumab + carboplatin + paclitaxel vs. carboplatin + paclitaxel	III	Squamous NSCLC	PFS	64.8% vs. 36.7%	8.5 vs. 4.9 (HR 0.37, 95% CI 0.29–0.47)	NR vs. 14.5 (HR 0.55, 95% CI 0.40–0.75)

CI: Confidence interval; HR: Hazard ratio; ICIs: Immune checkpoint inhibitors; NR: Not reached; NSCLC: Non-small cell lung cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival.

group presented significantly improved PFS compared with the placebo combination group (12.1 months *vs.* 8.1 months; HR 0.56, 95% CI: 0.43–0.71), which confirmed the efficacy of combination therapy of ICIs plus chemotherapy and bevacizumab.[32]

The LEAP-006 study was a phase III study of ICIs combined with small-molecule TKI and chemotherapy. It evaluated the preliminary efficacy and safety of lenvatinib combined with pembrolizumab plus pemetrexed and carboplatin in the first-line treatment of advanced NSCLC. The first stage was safety introduction in which 13 patients were enrolled. The ORR of the combination therapy was 69.2% and the incidence of adverse events (AEs) of ≥3 was 53.5%, which preliminarily confirmed that lenvatinib combined with pembrolizumab plus chemotherapy had good antitumor activity and appropriate safety levels.[33] The second stage of the randomized controlled study is ongoing. A phase Ib study evaluated the efficacy of sintilimab combined with anlotinib in the first-line treatment of NSCLC. The ORR was 72.7% and the disease control rate (DCR) was 100%. The median PFS was 15 months. ICIs combined with small-molecule anti-angiogenesis drugs may be a promising treatment strategy, which needs further verification in phase III studies.[34]

Double-immune checkpoint blockades

Both PD-1/PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) checkpoint inhibitors can enhance T-cell activity against tumors with different complementary mechanisms. A preclinical study suggested that CTLA-4 and PD-1 pathway blockade produced synergistic antitumor activity.[35]

The CheckMate 227 was the first phase III study of dual immunotherapy for patients with advanced NSCLC with positive results. The study mainly evaluated the efficacy of nivolumab combined with ipilimumab compared with platinum-based chemotherapy in the first-line treatment of patients with advanced NSCLC without *EGFR* and *ALK* mutations. In 2018, the data from part I of this study were released. Compared with chemotherapy, nivolumab combined with ipilimumab significantly improved the PFS and ORR of patients with a high mutational burden of NSCLC. Data from part I of the final analysis were reported in 2019. The OS of patients with PD-L1 ≥1% who received nivolumab combined with ipilimumab was 17.1 months, which was significantly higher than the OS of the chemotherapy group, at 14.9 months (HR 0.79, 97.72% CI 0.65–0.96).[36] Based on the results of this study, the FDA approved the use of nivolumab combined with ipilimumab as a first-line treatment for patients with PD-L1 ≥1% and *EGFR* and *ALK*-negative NSCLC, providing a new chemo-free first-line treatment program. However, in the phase III MYSTIC study, the median OS of patients with PD-L1 ≥25% was 16.3 months *vs.* 12.9 months for durvalumab *vs.* chemotherapy (HR 0.76, 97.54% CI 0.564–1.019) and 11.9 months *vs.* 12.9 months for durvalumab plus tremelimumab *vs.* chemotherapy (HR 0.85, 98.77% CI 0.611–1.173). The median PFS was 3.9 months *vs.* 5.4 months for durvalumab plus tremelimumab *vs.* chemotherapy (HR 1.05,

99.5% CI 0.722–1.534; *P* = 0.705). Single-agent durvalumab or durvalumab plus tremelimumab did not improve the OS or PFS compared with chemotherapy in patients with PD-L1 ≥25%.[37] Both the CheckMate227 and the MYSTIC studies changed the study endpoints several times during the course of the study. The final primary endpoint of the CheckMate227 study was OS in the population with PD-L1 ≥1%, whereas the primary endpoint of the MYSTIC study was PFS (durvalumab + tremelimumab *vs.* chemotherapy), OS (durvalumab *vs.* chemotherapy), and OS (durvalumab + tremelimumab *vs.* chemotherapy) in the population with PD-L1 ≥25%. The different choice of study endpoints may be one of the reasons for the failure of MYSTIC study.

Despite the success of the CheckMate 227 study, the two survival curves of the double-immune combination group and the chemotherapy group showed a crossover, suggesting that the double-immune combination therapy group involved patients who experienced early progression and death. The CheckMate 9LA study was based on dual immunotherapy plus two cycles of platinum-based chemotherapy, which overcame the disadvantages of early disease progression in dual immunotherapy. The results confirmed that the median OS of nivolumab combined with ipilimumab and chemotherapy was significantly higher than that of standard chemotherapy (15.6 months and 10.9 months; HR 0.66, 95% CI 0.55–0.80).[38] Based on these results, the FDA also approved the use of nivolumab combined with ipilimumab and two-cycle chemotherapy as the first-line treatment of advanced NSCLC without driver gene mutations. In terms of safety, the incidence of all AEs in the CheckMate 227 and CheckMate 9LA studies was 77% and 92%, respectively; the incidence of grade 3–4 AEs was 33% and 47%, respectively.[36,38] Although dual-immunity combined chemotherapy increased toxicity in patients to a certain extent, the overall toxicity was controllable.

Nivolumab plus ipilimumab and nivolumab plus ipilimumab plus two cycles of chemotherapy have become new options for the first-line treatment of advanced NSCLC. However, compared with ICIs combined with chemotherapy, these two regimens have not shown an improved curative effect. Considering the economic cost of dual immunotherapy and the adverse effects of dual immunotherapy combined with chemotherapy, it may be necessary to explore the appropriate population for these two regimens in the future.

ICIs in combination with targeted therapies

Targeted therapy using EGFR-TKI and ALK-TKI is the standard treatment for advanced NSCLC patients with *EGFR* mutations or *ALK* rearrangements. Some studies have shown that targeted therapy could release neo-antigens, enhance antitumor immune responses, and improve ICIs' antitumor activity. To further improve the efficacy of targeted therapies, the combination of targeted and immunotherapies has been explored.[39-43]

The phase I CheckMate 012 trial reported the efficacy and safety of the combination of nivolumab and erlotinib.

Twenty-one advanced NSCLC patients with *EGFR* mutations had an ORR of 19%, but the incidence of grade 3–4 AEs was 24%.[44] In another phase I trial, atezolizumab combined with erlotinib was used to treat locally advanced or metastatic NSCLC. The duration of response (DOR) was 9.7 months and the ORR was 75%. However, 39% of the patients had grade 3–4 AEs, with the most common AEs being pyrexia and elevated alanine aminotransferase (ALT).[45] The TATTON trial was a phase I study that evaluated the efficacy of durvalumab and osimertinib in patients with *EGFR* mutations. Although the efficacy was encouraging, this combination seems to strongly increase the risk of interstitial lung disease. The incidence of interstitial pneumonia in EGFR TKI-resistant patients was 26% and that in EGFR TKI-naïve patients was 64%. Therefore, the trial was terminated due to the significant toxicity of the treatments.[46]

The E group of the CheckMate 370 study aimed to evaluate the safety of nivolumab combined with crizotinib in the treatment of *ALK*-positive patients with newly diagnosed NSCLC. Although 5 of 13 patients (38%) had partial response (PR), 5 of 13 patients (38%) had severe hepatotoxicity and the treatment was discontinued; 2 patients also died, and therefore, the study was terminated.[47] In a phase Ib clinical trial, atezolizumab combined with alectinib was used to treat patients who had *ALK*-positive NSCLC. Among 22 patients who were initially treated with ALK TKIs, the ORR was 81%, median PFS was 21.7 months, and DOR was 20.3 months. However, the incidence of treatment-related AEs above grade 3 was 62%.[48] The JAVELIN Lung 101 was a phase Ib/II study that evaluated 28 patients with *ALK*-positive NSCLC who received avelumab plus lorlatinib treatment. These patients were previously treated with ALK TKIs and had disease progression. The median PFS was 9.3 months and ORR was 46.4%; however, grade 3–4 AEs occurred in 53.6% of the patients.[49]

Numerous studies have shown that ICIs combined with targeted therapies can cause serious adverse effects. Therefore, in patients with *EGFR* and *ALK* mutations, this combined treatment strategy may not be a feasible option.

Combination immunotherapy strategies for unresectable locally advanced NSCLC

Radiotherapy plays an important role in unresectable locally advanced lung cancer. Numerous studies have shown that ICIs combined with radiotherapy have a synergistic mechanism. Tumor-associated antigens re-leased after radiotherapy can generate the activated T cells in the tumor microenvironment,[50] promote the antigen presentation of activated dendritic cells, upregulate the expression of PD-L1 on tumor cells,[51] promote the release of cytokines that attract activated T cells to the tumor, enhance the ability of immune effector cells to attack tumor cells, and increase the number of activated antigen-presenting cells in draining lymph nodes.[52-55]

The PACIFIC study was the first phase III study to report that ICI treatment results in locally advanced NSCLC. The study evaluated the efficacy of durvalumab or placebo in patients with locally advanced unresectable NSCLC who did not progress after concurrent radiochemotherapy. The PFS of durvalumab and placebo was 17.2 months and 5.6 months,[56] with updated OS of 47.5 months and 29.1 months, respectively.[57] Based on these results, durvalumab consolidation therapy after concurrent radio-chemotherapy for the treatment of unresectable locally advanced NSCLC became standard treatment. However, the PACIFIC study administered ICIs after concurrent radiochemotherapy, and the mode of simultaneous application of radiochemotherapy and immunotherapy is also being explored.

The KEYNOTE 799 was a phase II study of ICIs combined with concurrent radiotherapy and chemotherapy. The purpose of this study was to determine whether the simultaneous use of ICI and radiochemotherapy had a synergistic mechanism that could further improve treatment efficacy. The results showed that the ORR of the two cohorts (pembrolizumab + paclitaxel + carboplatin + radiotherapy *vs.* pembrolizumab + pemetrexed + cisplatin + radiotherapy) was 69.6% and 70.5%, respectively. ICIs combined with concurrent radiotherapy and chemotherapy were preliminarily confirmed to have good antitumor activity; however, the incidence of interstitial pneumonia caused by ICIs combined with radiotherapy was a clinical concern. The study showed that the incidence of pneumonia grade ≥3 was only 8.0% and 7.9%, suggesting that the toxicity of this combination therapy was within an acceptable range.[58] Therefore, the phase III study based on the KEYNOTE-799 findings is currently ongoing.

Combination immunotherapy strategies for early-stage NSCLC

Immunotherapy has changed the treatment pattern of advanced NSCLC and unresectable locally advanced stage III NSCLC. Whether it can be applied to early-stage NSCLC has become a research hotspot. Lemmon *et al*[59] reported a significant tumor immunosuppressive microen-vironment in stage I lung cancer tumor tissues that are characterized by the depletion of dendritic cells and natural killer cells, and changes in tumor-infiltrating myeloid cells. These findings suggest that the immune system is disrupted in early-stage lung cancer and provide a theoretical basis for the application of immunotherapy in early-stage NSCLC.

Although the CheckMate 159 was a clinical study of immune monotherapy, the study was a milestone in the field of neoadjuvant immunotherapy. The study involved 21 patients with untreated, resectable, and stages I–IIIa NSCLC who received two cycles of neoadjuvant treatment with nivolumab. The results showed that 45% of the patients underwent radical surgery with a major pathological response (MPR) and none of the patients delayed surgery.[60] The results of this study preliminarily confirmed the antitumor activity and safety of neoadjuvant immunotherapy, and since then introduced an era of neoadjuvant immunotherapy.

To further improve the efficacy of neoadjuvant immuno-therapy, multiple immunotherapy strategies have been

explored for early-stage NSCLC treatment, including dual immunotherapy, ICIs and chemotherapy, and ICIs and concurrent radiochemotherapy. The NEOSTAR study was a phase II study of dual immune combination therapy to evaluate the efficacy of nivolumab (N) or nivolumab combined with ipilimumab (NI) neoadjuvant treatment of NSCLC. Forty-four patients were enrolled in the study, with 23 and 21 patients in the N and NI groups, respectively. The MPR in the N and NI groups was 20% and 43%, and the complete pathological response (pCR) was 9% and 21%, respectively. These results suggested that the neoadjuvant treatment of nivolumab combined with ipilimumab had a better curative effect than nivolumab alone.[61] The NADIM study was a phase II study of ICI combined with chemotherapy to evaluate the efficacy of nivolumab combined with paclitaxel and carboplatin in the treatment of stage IIIA NSCLC. Among the 41 patients underwent surgical treatment, 34 (83%) achieved MPR, of which 26 (63%) achieved pCR. At 24 months, the PFS was 77.1% and the ICI combined with chemotherapy significantly improved the efficacy of the neoadjuvant therapy. In addition, ICI combined with chemotherapy was well tolerated. The incidence of treatment-related grade ≥3 AEs was 30%; however, these AEs were not related to surgical delays or death.[62]

The research results reviewed here show that the strategy of using ICIs with chemotherapy is potentially a new development in neoadjuvant immunotherapies. The CheckMate 816 met a primary endpoint of improved pathologic complete response. This is the first time, an ICI-based combination has demonstrated superior efficacy *vs.* chemotherapy as neoadjuvant therapy in a phase III trial of patients with resectable NSCLC. Several phase III clinical studies of ICIs combined with chemotherapy are still ongoing, including KEYNOTE 617 (NCT: 03425643), IMpower030 (NCT: 03456063), and AEGEAN (NCT: 03800134).

Future of Combined Immunotherapy Strategies

ICIs combined with novel immune target drugs

In recent years, new immune target drugs have become a hotspot in cancer treatment research, including drugs targeting co-inhibitory receptors, co-stimulatory molecular receptors, and immunosuppressive cells.[63] Therapies that use PD-1/PD-L1 inhibitors combined with these new immune target drugs are in the early stages of clinical research. Rodriguez-Abreu et al[64] reported a phase II study that verified whether a T cell immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) inhibitor combined with atezolizumab could affect the TIGIT receptor that normally binds to highly expressed CD155 on cancer cells and inhibits cytotoxic T cells and natural killer cell-mediated tumor attack. Additionally, inhibiting the TIGIT and PD-1 receptors can cooperate with immune cells that kill tumors to enhance the antitumor immune response.[65,66] This study evaluated the efficacy of the TIGIT antibody tiragolumab combined with atezolizumab compared with placebo plus atezolizumab in the first-line treatment of patients with PD-L1 expression ≥1% in NSCLC. A total of 135 subjects were enrolled and the

results showed that the ORR of the combined treatment was 31.3%, whereas the ORR of placebo plus atezolizumab was only 16.2%, respectively; the PFS was 5.4 months and 3.6 months, respectively. The study showed that the incidence of grade ≥3 AEs was similar in the two groups, suggesting that tiragolumab combined with atezolizumab improved the ORR and PFS and it was well tolerated.[64] At present, several new immune target drugs are in early clinical studies.[67-75]

Bispecific antibodies are a unique combination therapy strategy. Bispecific antibodies can simultaneously bind with two antigen epitopes, block or activate dual-target signaling pathways, and mediate immune cells to kill tumor cells. M7824 is a dual-function fusion protein that targets PD-L1 and transforming growth factor β (TGF-β), which improves the effect of antitumor treatment by simultaneously antagonizing PD-L1 and trapping TGF-β.[76] In a phase I study, the ORR of the second-line treatment of NSCLC with M7824 (1200 mg every 2 weeks) was 27.5%, the median DOR was 18 months, and the median OS was 17.1 months; these results indicated that M7824 had good antitumor activity.[77] Clinical studies testing M7824 in the treatment of unresectable, locally advanced NSCLC, and first-line treatment of advanced NSCLC are ongoing.[78,79] Several types of bispecific antibodies are in the early stages of a clinical study.

Precisely combined immunotherapy based on cancer immune phenotypes

The tumor microenvironment can affect the efficacy of immunotherapy, and the current combined treatment strategies mostly involve stacking of several drugs, rather than precise combination therapy adopted for tumor microenvironment factors. Due to the infiltration of immune cells into the tumor microenvironment, anticancer immunity in humans can be classified by three main phenotypes: the immune-desert phenotype, immune-excluded phenotype, and inflamed phenotype.[80,81] Each of these phenotypes is associated with specific underlying biological mechanisms that may prevent the host immune response from eradicating cancer. In the future, precise and individualized immune combination therapeutic strategies will be adopted according to cancer immune phenotypes.[12,82,83] The immune-desert phenotype can be the result of immunological ignorance and the induction of tolerance or a lack of appropriate T-cell priming or activation. Treatment of this phenotype has to adopt a combined strategy to promote the release of tumor antigens so that cold tumors can be transformed into hot tumors. Combination therapy strategies used for such tumors include chemotherapy, radiotherapy, DNA repair-based therapies, and cancer vaccines. The immune-excluded phenotype may reflect a specific chemokine state, the presence of particular vascular factors or barriers, or specific stromal-based inhibition. ICIs combined with anti-angiogenesis drugs, epigenetic regulators, and soluble factor inhibitors, such as TGF-β inhibitors, can be used to change the characteristics of the tumor microenvironment and inhibit tumor growth. The inflamed phenotype can demonstrate infiltration by several

subtypes of immune cells; the cells in inflamed tumors can also express inhibitory factors. ICIs can be used in combination with immunosuppressive receptor inhibitors or in combination with co-stimulatory receptor agonists to further increase the antitumor immunity.[81]

Conclusions

ICI combination therapies have changed the history of lung cancer treatment, and they show great clinical promise. In the field of advanced NSCLC, ICIs combined chemotherapy, ICIs combined anti-angiogenesis and chemotherapy, nivolumab plus ipilimumab, and nivolumab plus ipilimumab plus two cycles of chemotherapy have become standard first-line treatments for driver gene negative advanced NSCLC. Combined immunotherapies have been used to treat patients with advanced NSCLC, and they have enriched treatment options. In the field of unresectable locally advanced NSCLC, ICIs consolidation therapy after concurrent radiochemotherapy has also become the standard treatment, and more optimized immune combination strategies are still being evaluated. In the neoadjuvant treatment of early-stage NSCLC, ICIs combined with chemotherapy have shown promising efficacy and safety, and potential as an improved therapeutic strategy in the future. Drugs that target novel immune candidates are an emerging field. The combination of PD-1/PD-L1 inhibitors and new target drugs is still in the early stages of a clinical study, and it may further contribute to the development of immunotherapy for NSCLC. In the future, patients with NSCLC will be classified according to their tumor microenvironment factors, and individualized and precise immune combination therapy strategies will be implemented.

Funding

Conflicts of interest

None.

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