Novel therapeutic strategies for non-small cell lung cancer: Combination therapies with immune checkpoint inhibitors (Review)

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Abstract. The treatment of non-small cell lung cancer (NSCLC) has been notably improved by the use of immune checkpoint inhibitors (ICIs). Although ICIs have been authorized by the United States Food and Drug Administration for the clinical treatment of NSCLC, concerns remain regarding resistance and adverse reactions. Chemotherapy, targeted therapy and other immunotherapies for cancer have the potential to impact cancer immunity, thereby boosting the ability of the body to kill the tumor cells. This provides preliminary evidence for combined therapy, which has been reported to be effective in numerous clinical trials, resulting in the approval of ICIs for use in combination with chemotherapy. Ongoing studies concentrate on novel approaches that can enhance immune responses against tumors through combined strategies. The present review primarily outlines the key mechanisms of combined treatment and the strategies for combining ICIs in NSCLC, demonstrating the viability of combined therapy.

Contents

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1. Introduction

Lung cancer remains the leading cause of cancer-related death worldwide, making it the second most common type of cancer, with 226,650 new cases and 124,730 deaths predicted for 2025. The risk factors for lung cancer include smoking, second-hand smoke, other combustible tobacco products, occupational exposure, radon, air pollution and other environmental exposures. Lung cancer also has a poor prognosis, with a 5-year survival of <27% (1). Moreover, ~85% of all new cases of lung cancer are attributed to non-small cell lung cancer (NSCLC) (2). This comprises non-squamous carcinoma and squamous carcinoma, and frequently manifests in the advanced stages, leading to a low rate of survival.

The treatment strategy for NSCLC has gradually evolved from traditional chemotherapy and radiotherapy to personalized targeted therapy and immunotherapy. Chemotherapy, particularly platinum-based combination chemotherapy, remains the cornerstone of NSCLC treatment, but its efficacy is limited and accompanied by marked toxic side effects (3). Furthermore, the emergence of targeted therapy has profoundly transformed the treatment landscape of NSCLC. Through tumor genotyping, patients identified with driver gene mutations, such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements, can be treated with the corresponding targeted drugs, thereby avoiding unnecessary chemotherapy (4). Although certain patients can benefit from targeted therapies, these benefits are limited to those with EGFR mutations, ALK rearrangements or other sensitive driver gene alterations, which occur in only a minority of patients (5). Additionally, resistance to targeted therapies remains an inevitable challenge (6). Therefore, novel therapeutic strategies are needed to improve the survival rates in NSCLC.

Immunotherapy has emerged as a novel approach for treating tumors, in addition to radiotherapy, chemotherapy and targeted medications. Immune checkpoint inhibitors (ICIs) have been reported to be notably effective in the treatment of specific types of cancer, and ICIs have received clinical approval for use in NSCLC therapy (7). Inhibitors targeting programmed cell death-1 (PD-1), programmed cell death-ligand 1 (PD-L1) and cytotoxic T lymphocytes cell antigen-4 (CTLA-4) are the main components of ICIs. However, whilst ICIs have shown marked clinical efficacy in the treatment of NSCLC, not all patients benefit. A study has indicated that only 20-30% of patients with NSCLC respond to ICIs, meaning that most patients do not achieve the expected therapeutic effects after treatment (8). Moreover, even patients who initially respond to ICIs inevitably develop resistance over time, leading to disease progression and a decline in treatment efficacy (9). To address this challenge, researchers are exploring several strategies to enhance the efficacy of ICIs and extend the progression-free survival (PFS) of patients. For example, certain studies suggest incorporating chemotherapy or anti-angiogenic drugs into therapies with ICIs to boost treatment outcomes (10,11). This combination therapy has shown promise in clinical trials, particularly in patients who do not respond well to monotherapy with ICIs (12). Furthermore, the United States Food and Drug Administration has approved the use of atezolizumab in combination with chemotherapy for treating both squamous and non-squamous NSCLC (13,14).

Therefore, the aim of the present review was to provide a summary of the collective utilization of ICIs alongside other treatments for NSCLC and outline the primary mechanisms of combined ICIs.

2. ICIs combined with chemotherapy

Mechanism of ICIs combined with chemotherapy. Typically, ICIs are ineffective against tumors as immune cells are absent from the tumor microenvironment (TME; referred to as 'immune-desert' or 'immune-excluded') or because they cannot penetrate the tumor (15,16). Chemotherapy drugs can influence the immunogenicity of cancer cells through multiple mechanisms. First, chemotherapy drugs can alter the immune microenvironment of the tumor, thereby enhancing antitumor immune responses. For example, certain chemotherapy drugs can induce immune-mediated cell death in tumor cells, a form of cell death that activates adaptive immune responses and promotes the activation and proliferation of antitumor T cells (17). Additionally, chemotherapy drugs can improve the immune state of the TME by inhibiting the function of immunosuppressive cells and enhancing the activity of immune effector cells (18). Secondly, chemotherapeutic drugs can enhance antigen presentation by promoting the recruitment and activation of dendritic cells (DCs), thereby improving the ability of the immune system to recognize and attack tumor antigens. A study has reported that chemotherapeutic drugs can induce tumor cells to release pro-inflammatory factors, which promote the migration and maturation of DCs, thus enhancing T-cell activation (19). This mechanism not only enhances the direct cytotoxic effects of chemotherapeutic drugs but also improves their antitumor efficacy through immune modulation. Finally, chemotherapy drugs can enhance the effectiveness of immunotherapy by modulating immune suppression circuits in the TME. Chemotherapy drugs can disrupt immune suppression mechanisms in the TME, for example, by reducing the number of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), thereby enhancing the function of effector T cells and natural killer (NK) cells (20). This immune regulatory effect provides a theoretical basis for the combined use of chemotherapy and immunotherapy, potentially improving the overall efficacy of cancer treatment.

A multicenter retrospective study showed that among patients with NSCLC who received ICIs, the prevalence of HPD was ~14%, whereas it was ~5% among those treated with chemotherapy. Within the initial 3-month period following ICI treatment, tumor progression accounted for ~15% of deaths. HPD was significantly associated with >2 metastatic sites before ICI treatment (62.5 vs. 42.6%; P=0.006) (21). Moreover, the Checkmate 227 trial reported that patients with PD-L1 expression of <1% experienced a lower progression risk with nivolumab combined with chemotherapy than nivolumab plus ipilimumab therapy at the early 3-month timepoint (22). The KEYNOTE-062 trial also reported that survival rates during the first 6-9 months were lower for patients treated with pembrolizumab monotherapy than for those treated with chemotherapy (23). These data suggest that patients at high risk of HPD may find it advantageous to receive both chemotherapy plus ICIs or to rapidly switch to chemotherapy after ICI therapy (24). In summary, the effectiveness of ICIs is enhanced by chemotherapeutic medications through their impact on the immunogenicity of cancer cells (Fig. 1).

Clinical study of ICIs combined with chemotherapy. The effectiveness of combining ICIs with chemotherapy has been previously reported. In the KEYNOTE-189 study, the effectiveness of pemetrexed in combination with platinum-based medications or a placebo, was evaluated for the treatment of non-squamous metastatic NSCLC in a double-blind phase III trial. The pembrolizumab plus pemetrexed-platinum arm achieved an objective response rate (ORR) of 48.3%, whereas the placebo plus pemetrexed-platinum arm only achieved 19.9%. In the pembrolizumab-combination group, the 5-year overall survival (OS) rate was 19.4%, whereas in the placebo-combination group, the 5-year OS rate was 11.3%. The 5-year PFS rates were 7.5 and 0.6%, respectively (25,26).

According to another study, patients in the ICIs plus chemotherapy group had significantly improved OS [not reached (NR) vs. 18.3 months; P=0.011] and PFS (14.9 vs. 6.3 months; P<0.001) times compared with those in the bevacizumab plus chemotherapy group. Moreover, as a first-line treatment, ICIs combined with chemotherapy was a more beneficial treatment for patients with adenocarcinoma who did not have driver gene alterations compared with bevacizumab combined with chemotherapy (27). Additionally, Tsai *et al* (28) reported that the combination of pembrolizumab with chemotherapy or radiotherapy results in a notably improved PFS for patients with treatment-naïve advanced NSCLC.

Furthermore, the efficacy of atezolizumab plus carboplatin plus paclitaxel (ACP group), atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (ABCP group) or bevacizumab plus carboplatin plus paclitaxel (BCP group) was

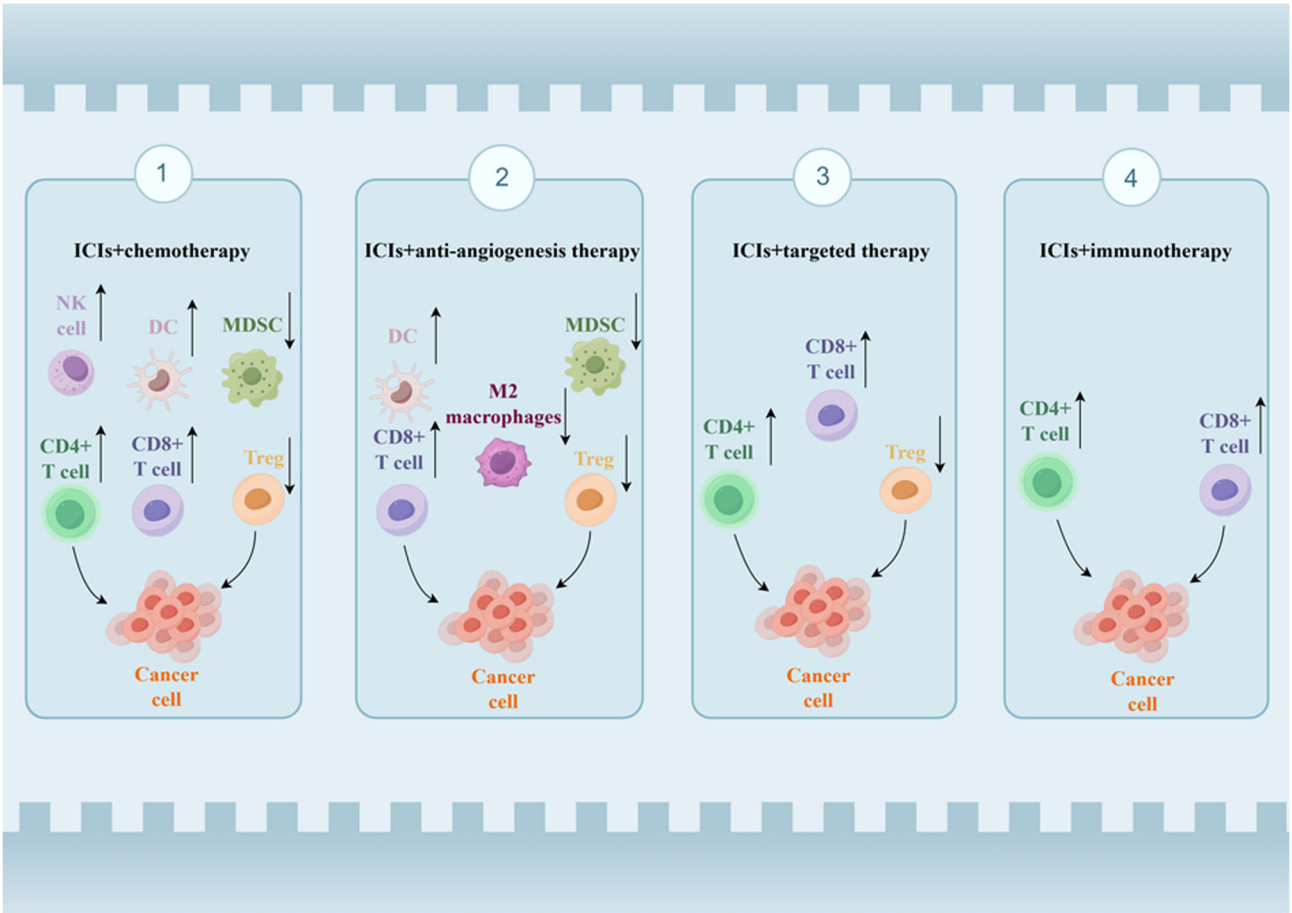

Figure 1. Mechanism of combination therapies. 1) Chemotherapeutic drugs can reduce the number of Tregs and MDSCs, thereby enhance the function of T cells, NK cells and DCs. 2) Anti-angiogenesis therapy enhances the infiltration of $CD8^+$ T cells and the function of DC cells; it reduces the number of immunosuppressive cells such as MDSCs, Tregs and M2-like TAMs. 3) Targeted therapy impacts the immune response against tumors by inducing a decrease in immunosuppressive cells (such as Tregs) and an enhancement in the infiltration and activity of T cells. 4) Immunotherapy promotes $CD4^+$ and $CD8^+$ T cell activation. Figdraw was used to construct this figure. Treg, regulatory T cell; MDSC, myeloid-derived suppressor cell; NK, natural killer; DC, dendritic cell; TAMs, tumor-associated macrophages.

assessed in patients with metastatic non-squamous NSCLC by Impower150. The conclusive findings indicated that the median OS time for the ACP group was 19.0 months compared with 15.0 months for the BCP group [hazard ratio (HR), 0.86; 95% confidence interval (CI), 0.73-1.01] in patients with NSCLC lacking EGFR or ALK genomic abnormalities (29).

The KEYNOTE-407 study randomly divided patients with untreated metastatic squamous NSCLC into two groups: One group received pembrolizumab plus carboplatin and either paclitaxel or nab-paclitaxel, whilst the other group received a saline placebo plus carboplatin and the choice of paclitaxel or nab-paclitaxel. In the study, the OS and PFS rates were improved with pembrolizumab plus chemotherapy (HR, 0.71; 95% CI, 0.59-0.85) compared with placebo plus chemotherapy (HR, 0.62; 95% CI, 0.52-0.74), with 5-year OS rates of 18.4 and 9.7%, respectively (30,31). Numerous clinical studies have reported the efficacy of chemotherapy plus ICIs (12,13,32-35) (Tables I and SI).

3. ICIs combined with anti-angiogenesis therapy

Mechanism of ICIs combined with anti-angiogenesis therapy. The entry of immune cells into the tumor is facilitated by blood vessels. VEGF can induce tumor neovascularization and abnormal angiogenesis and promote the occurrence of an immunosuppressive TME (36). The presence of VEGF in circulation hinders the development and effectiveness of DCs, aiding the tumor in evading immune detection (36). Additionally, abnormal blood vessel formation leads to a reduction in the quantity and effectiveness of lymphocytes that combat tumors. When there is an increase in oxygen consumption, the neo-vasculature is unable to form, leading to direct impairment of tumor-infiltrating lymphocyte (TIL) functions due to hypoxia (37). The M2-like phenotype of tumor-associated macrophages is facilitated by the hypoxic environment within the tumor (38). Based on the immunomodulatory role of VEGF-A in different cancer types, ICIs have been combined with anti-angiogenic drugs in therapy (39). Blocking VEGF-A pharmacologically results in an augmentation of intratumoral $CD8^+$ cells and a decrease in tumor growth (40). The use of anti-VEGF/VEGFR2 medications facilitates the normalization of blood vessels, leading to enhanced infiltration of cytotoxic T cells and aiding in the transportation of drugs inside tumors. Additionally, it reduces immunosuppressive cells such as MDSCs and Tregs, demonstrating a notable synergistic impact when combined with PD-1/PD-L1 inhibition (41,42) (Fig. 1).

Table I. Clinical trials of ICIs in combination with chemotherapy in NSCLC.

Clinical trial	Setting	Intervention	Outcome, months	(Refs.)
NCT02657434 (IMpower132)	Chemotherapy-naive and with stage IV NSCLC	Arm A: Atezolizumab + carboplatin or cisplatin + pemetrexed; Arm B: Carboplatin or cisplatin + pemetrexed	mOS: 17.5 vs. 13.6; mPFS: 7.6 vs. 5.2	(12)
NCT02367781 (IMpower130)	Stage IV non-squamous NSCLC	Arm A: Atezolizumab + nab-paclitaxel + carboplatin; Arm B: Nab-paclitaxel + carboplatin	mOS:18.6 vs. 13.9; mPFS: 7.0 vs. 5.5	(13)
NCT02578680 (KEYNOTE-189)	Advanced or metastatic non-squamous NSCLC	Arm A: Pembrolizumab + chemotherapy; Arm B: Placebo + chemotherapy	mOS: 22.0 vs. 10.7; mPFS: 9.0 vs. 4.9	(26)
NCT02366143 (IMpower150)	Stage IV NSCLC	Arm A: Atezolizumab + paclitaxel + carboplatin; Arm B: Bevacizumab + paclitaxel + carboplatin	mOS: 19.0 vs. 14.7	(29)
NCT02775435 (KEYNOTE-407)	First-line metastatic squamous NSCLC	Arm A: Pembrolizumab + chemotherapy; Arm B: Placebo + chemotherapy	mOS: 17.1 vs. 11.6; mPFS: 8.0 vs. 5.1	(31)
NCT02367794 (IMpower131)	Stage IV squamous NSCLC	Arm A: Atezolizumab + paclitaxel + carboplatin; Arm B: Atezolizumab + nab-paclitaxel + carboplatin; Arm C:nab-paclitaxel + carboplatin	mOS: 12.6 vs. 14.2 vs. 13.5; mPFS: 5.6 vs. 6.3 vs. 5.6	(32)
NCT03663205	Advanced non-squamous NSCLC	Arm A: Tislelizumab + platinum + pemetrexed; Arm B: Platinum + pemetrexed	mOS: 21.4 vs. 20.1; mPFS: 9.7 vs. 7.6	(33)
NCT03515837 (KEYNOTE-789)	TKI-resistant, EGFR-mutated, metastatic non-squamous NSCLC	Arm A: Pembrolizumab + pemetrexed + chemotherapy; Arm B: Placebo + pemetrexed + chemotherapy	mOS: 15.9 vs. 14.7; mPFS: 5.6 vs. 5.5	(34)
NCT03664024 (KEYNOTE-782)	Stage IV non-squamous NSCLC without prior systemic treatment	Pembrolizumab + platinum-doublet chemotherapy	mOS: 18.1; mPFS: 7.2	(35)

NCT, National Clinical Trial; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ICIs, immune checkpoint inhibitors.

Clinical study of ICIs combined with anti-angiogenesis therapy. In the CheckMate 012 phase I study, it was reported that the combination of nivolumab and bevacizumab resulted in a median PFS time of 37.1 weeks in patients with non-squamous cell carcinoma (n=12). Moreover, among patients with non-squamous cell carcinoma (n=13) and squamous cell carcinoma (n=8) treated with nivolumab monotherapy, the median PFS times were 21.4 and 16 weeks, respectively (43).

Furthermore, the impact of a combination treatment involving atezolizumab and bevacizumab was evaluated in the IMpower150 phase III trial for patients with previously untreated metastatic non-squamous NSCLC. According to the Kaplan-Meier analysis, it was reported that the ABCP group had notably extended PFS and OS times compared with the BCP group, with a median PFS time of 8.4 months for ABCP and 6.8 months for BCP (HR, 0.57; 95% CI, 0.48-0.67) and a median OS time of 19.5 months for ABCP

Table II. Clinical trials of ICIs in combination with anti-angiogenesis therapy in NSCLC.

Clinical trial	Setting	Intervention	Outcome, months	(Refs.)
NCT02366143 (IMpower150)	Stage IV non-squamous NSCLC	Arm B: Atezolizumab + bevacizumab + carboplatin + paclitaxel; Arm C: bevacizumab + carboplatin + paclitaxel	mOS: 19.5 vs. 14.7; mPFS: 8.4 vs. 6.8	(29)
NCT02443324	Advanced treatment-naive NSCLC	Pembrolizumab + ramucirumab	mPFS: 9.3	(44)

NCT, National Clinical Trial; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer.

and 14.7 months for BCP (HR, 0.8; 95% CI, 0.67-0.95) (29). Additionally, in the NCT02443324 phase I trial, the combination of ramucirumab and pembrolizumab demonstrated manageable safety and favorable antitumor efficacy in patients diagnosed with advanced gastric or gastroesophageal junction adenocarcinoma, NSCLC and urothelial cancer (44).

Another study reported that the combination of anti-PD-1/PD-L1 therapy and anti-angiogenesis therapy markedly enhanced the effectiveness of treatment in patients with advanced lung adenocarcinoma who did not respond to initial or advanced treatment. The disease control rate (DCR) was significantly greater in the group receiving both anti-PD-1/L1 and anti-angiogenesis treatment compared with the group receiving only anti-PD-1/L1 therapy (92.0 vs. 46.9%; P=0.0004). The median PFS time was 5.1 months compared with 2.0 months (HR, 0.551; 95% CI, 0.337-0.902; P=0.002), whilst the median OS time was 14.3 months compared with 8.4 months (HR, 0.549; 95% CI, 0.305-0.990; P=0.046), respectively (45).

Finally, according to a retrospective study, the combination of ICIs and low-dose anlotinib was reported to be a viable treatment choice for advanced NSCLC in the second-line setting (46) (Tables II and SI).

4. ICIs combined with targeted therapy

Mechanism of ICIs combined with targeted therapy. Previous research has indicated that NSCLC with EGFR mutations possesses a distinct TME (47). The alteration of EGFR and EGFR-tyrosine kinase inhibitors (TKIs) could potentially impact the TME, consequently influencing the effectiveness of immunotherapy. Immunologically cold tumors, typically NSCLCs with EGFR mutations, are characterized by lower levels of $CD8^+$ TILs and impaired function, leading to reduced cytotoxicity and inherent resistance to ICIs (48,49). The TME of patients with NSCLC may be modified by EGFR or ALK inhibitors, leading to an increase in $CD8^+$ TILs and a decrease in immunosuppressive cells (such as Tregs). This suggests the potential for the use of PD-1/PD-L1 antibodies (50).

In addition, the use of BRAF and MEK inhibitors impacts the immune response against tumors by inducing an increase in the immune-stimulating cytokine levels, a reduction in the immunosuppressive cytokine levels and an enhancement in the infiltration and activity of T cells. BRAF and MEK inhibitors allow the immune system to identify cancerous growths and improve the response of TILs (51). KRAS-mutant patients have been reported to exhibit a higher PD-L1 tumor proportion score and tumor mutational burden, as observed in the KEYNOTE-042 study (52). Stimulating effector T-lymphocyte activation and reducing the proliferation of immunosuppressive cells are the primary mechanisms of action for other targeted therapy medications (53,54). In summary, the aforementioned mechanisms provide a theoretical basis for combining these targeted therapies with ICIs (Fig. 1).

Clinical study of ICIs combined with targeted therapy. The combination of erlotinib and atezolizumab in the treatment of advanced NSCLC has attracted significant attention. In this study, the results indicated that the combination exhibited tolerable safety and showed promising clinical activity in patients with EGFR-mutated NSCLC. The combination therapy achieved an ORR of 75%, with a median PFS of 15.4 months, while median OS was NR (55). Furthermore, the TATTON trial (NCT02143466) assessed the efficacy of osimertinib in combination with selumetinib, savolitinib or durvalumab in patients with advanced NSCLC harboring EGFR mutations. In the selumetinib, savolitinib and durvalumab arms, the ORR was 42% (95% CI, 26-59%), 44% (95% CI, 22-69%) and 43% (95% CI, 23-66%), respectively. For TKI pretreatment and TKI-naïve patients, osimertinib plus durvalumab demonstrated encouraging results. Nevertheless, the therapy led to a rise in drug-related interstitial lung disease, resulting in the discontinuation of the combined treatment regimen in this particular cohort (56).

According to a cohort study, patients in the ICIs plus anlotinib group exhibited a significantly longer median PFS compared with those in the ICIs monotherapy group (6.37 vs. 3.90 months; P<0.001) (57). Furthermore, in the study performed by He *et al* (58), the study group (anlotinib combined with ICIs) exhibited considerably higher DCR and ORR values compared with the control group (62.50 vs. 36.11 and 81.25 vs. 55.56, respectively; P<0.05).

In addition, in the KEYNOTE-021 clinical trial, the combination of pembrolizumab and erlotinib resulted in an ORR of 41.7%, whilst the combination of pembrolizumab and gefitinib resulted in an ORR of 14.3%. The median PFS time for pembrolizumab plus erlotinib was 19.5 months (95% CI, 3.0-19.5), whilst for pembrolizumab plus gefitinib

Table III. Clinical trials of ICIs in combination with targeted therapy in NSCLC.

Clinical trial	Target	Setting	Intervention	Outcome	(Refs.)
NCT02039674 (KEYNOTE-021)	EGFR/ALK	Newly diagnosed stage IIIB/IV NSCLC, progression >1 year after adjuvant therapy for stages I-IIIA NSCLC	Cohort E: Pembrolizumab + erlotinib;	ORR: 41.7%	(59)
NCT03157089	EGFR	Pretreated stage IIIB/IV squamous NSCLC	Afatinib + pembrolizumab	mOS: 29.3 months; mPFS: 13.1 months	(61)

NCT, National Clinical Trial; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

it was 1.4 months (95% CI, 0.2-13.0). The median OS time was not achieved and 13.0 months, respectively (95% CI, 0.2-NR) (59).

There are also combination therapies for other gene mutation inhibitors under study, with the JASPER study phase II (NCT04475939) reporting that niraparib, a poly-ADP ribose polymerase-1/2 inhibitor taken orally and combined with pembrolizumab, exhibited positive clinical outcomes (60). The NCT03157089 have investigated the use of afatinib plus ICIs in the treatment of NSCLC (61) (Tables III and SI).

5. ICIs combined with immunotherapy

Mechanism of ICIs combined with immunotherapy. Elements of the immune system, such as immune checkpoints, and the diverse and intricate alterations in cytokine levels, serve a role in regulating the immune response of the body against tumors in the TME (62). The impact of a PD-1/PD-L1 blockade is also affected by these variables (63). Compared with single use, the combined use of ICIs has a greater blocking effect and lower rate of drug resistance. Numerous research studies are currently assessing several combinations of cancer immunotherapy medications (64). Several checkpoint inhibitors possess distinct modes of operation. CTLA-4 inhibitors mainly act in the lymph nodes by restoring the induction and proliferation of activated T cells, and inhibitors of PD-1 function by acting on the outer region of the tumor location to hinder the neutralization of cytotoxic T cells (65). Moreover, research on cytokine therapy has reported that the administration of cytokine agonists results in the proliferation and activation of $CD4^+$ and $CD8^+$ T cells and NK cells (66). In addition to immunotherapy, alternative treatment options such as chimeric antigen receptor (CAR)-T cell therapy, tumor vaccines and other emerging therapies are also necessary. The immunosuppressive effect within the tumor may be decreased, and the simultaneous use of ICIs may impact the growth and stimulation of T cells, resulting in a synergistic effect (67,68). Inhibitors of co-stimulatory or co-inhibitory receptors function as co-stimulatory molecules, promoting $CD4^+$ and $CD8^+$ T-cell activation, clonal expansion, survival, cytokine synthesis and the formation of T-cell memory (69).

The growth of cancer cells relies heavily on nutrients, leading to depletion in the TME. To adapt to the conditions of limited nutrients, immune cells are prompted to modify their glucose, amino acid and lipid metabolism (70). Cancer is characterized by the emerging phenomenon of metabolic reprogramming (71). Throughout the process of metabolic reprogramming, the effectiveness of the antitumor response is undermined by immune cells as they undergo differentiation or polarization into phenotypes that suppress the immune system (72). Therefore, the malfunctioning metabolisms may impact the immune response against tumors and trigger an immunosuppressive TME to evade immune detection (Fig. 1).

Clinical study of ICIs combined with immunotherapy. T-cell immunoglobulin and mucin domain-containing 3, T-cell immunoglobulin and ITIM domain (TIGIT), lymphocyte activation gene 3, CD47 and V-domain Ig suppressor of T-cell activation are part of the upcoming wave of immune checkpoints (73-77). Furthermore, the combination of additional types of ICIs have demonstrated a synergistic impact in clinical investigations. The results of the CheckMate 227 trial indicated that the combination of nivolumab and ipilimumab exhibited lasting effectiveness in individuals with advanced NSCLC. The median OS time was 17.1 months (95% CI, 15.0-20.1) and 15.7 months (95% CI, 13.3-18.7) when receiving nivolumab plus ipilimumab and nivolumab, respectively, in patients with a tumor PD-L1 expression of ≥1%. In patients with a PD-L1 of <1%, the OS time was 17.2 months (95% CI, 12.8-22.0) for nivolumab plus ipilimumab compared with 12.2 months (95% CI, 9.2-14.3) for chemotherapy (78). A phase Ia/Ib non-randomized controlled trial evaluated the safety and antitumor activity of the anti-TIGIT antibody, tiragolumab, and its combination with atezolizumab in patients with advanced solid tumors. In the metastatic NSCLC cohort, the ORR was 46% and the DCR was 77%. The median response duration was 24.2 months (95% CI, 9.7-NR) (79). Additionally, in the CITYSCAPE clinical trial, the median PFS time was 5.4 months (95% CI, 4.2-not estimable) in the tiragolumab

plus atezolizumab group compared with 3.6 months (95% CI, 2.7-4.4) in the placebo plus atezolizumab group (HR, 0.57; 95% CI, 0.37-0.90; P=0.015) (80). Numerous clinical trials have validated the effectiveness and safety characteristics of several combinations of ICIs (81-83).

Within the TME, high levels of adenosine (ADO), an immunosuppressive metabolite, have been reported to regulate tumor immunity. According to the existing evidence, ADO inhibits the production of cytokines and the growth of $CD8^+$ and $CD4^+$ T cells, as well as the cytotoxic activity of $CD8^+$ cells (84). CD39 and CD73 are the principal enzymes involved in ADO generation and are expressed on cells within the TME. CD39 and CD73 impact the immune response by inhibiting the function of effector T cells and maintaining the stability of immunosuppressive regulatory cells (85). Moreover, the NCT02503774 study is testing a combination of oleclumab (anti-CD73) with durvalumab in NSCLC. However, the inhibitors of CD39 have yet to progress into clinical development. An ongoing study, NCT04148937, is evaluating the effectiveness of LY3475070 (a CD-73 inhibitor) in combination with pembrolizumab for clinical purposes. There are currently four main ADO receptors available: A1R, A2AR, A2BR and A3R (86). Several ongoing clinical trials are assessing the efficacy of ADO receptor inhibitors plus ICIs. OX40, also known as CD134 or TNF receptor (TNFR)SF4, belongs to the super-family of TNFR. OX40 is expressed by activated T cells, including $CD4^+$ and $CD8^+$ T cells (87,88). In several preclinical models, tumor regression was observed when using anti-OX40 monoclonal antibodies and OX40L-Fc fusion proteins (89,90). Ongoing clinical investigations are assessing the therapeutic potential of humanized anti-OX40 agonists combined with ICIs against diverse advanced solid tumors, including NSCLC.

Cancer cells have the ability to secrete diverse immune-modulating cytokines to inhibit T cells and create an environment of immune suppression (91). The interaction between TGF-β, the most crucial cytokine for suppressing the immune system, and epithelial-mesenchymal transition (EMT), along with its impact on the TME, could potentially serve as a resistance mechanism to ICIs (92). TGF-β mediates EMT by activating both the Smad signaling pathway and non-Smad signaling pathways. The Smad signaling pathway is a classic pathway of TGF-β signaling, where TGF-β activates Smad2/3 through its receptor, which then forms a complex with Smad4 and enters the nucleus to regulate gene expression (93). Additionally, TGF-β further promotes EMT through non-Smad signaling pathways, such as the PI3K/AKT and MAPK pathways (94). Several types of inhibitors exist for the TGF-β pathway, such as antibodies that hinder the binding of TGF-β to receptors, molecules that impede TGF-β receptor kinases and TGF-β ligand traps. Both galunisertib and vactosertinib are inhibitors of small-molecular receptor kinases. These inhibitors hinder ATP binding to TGF-β receptors, effectively obstructing the activation of Smad2 and Smad3 in response to TGF-β (95,96). Ongoing clinical trials (NCT02423343 and NCT04515979) are being performed to evaluate the efficacy of galunisertib combined with nivolumab and vactosertinib combined with pembrolizumab in NSCLC.

BEMPEG, also known as NKTR-214, is an IL-2 pathway agonist that specifically targets CD122 and can be attached to several detachable polyethylene glycol chains. NKTR-214 has the potential to enhance the growth and stimulation of $CD8^+$ T cells and NK cells. Multiple clinical trials have investigated the utilization of NKTR-214 in conjunction with ICIs for several advanced solid malignancies (66,97).

The use of CAR-T cell treatment has been increasingly utilized in different types of solid tumor (98). The NCT03060343 trial is involving the administration of autologous CAR-T cells that targeted PD-L1 and CD80/CD86 to assess the safety, tolerability and engraftment potential for the treatment of recurrent or refractory NSCLC during its initial stage. During a phase I clinical trial (NCT03330834), the safety and effectiveness of anti-PD-L1 CAR-T cell therapy is being evaluated in patients with advanced NSCLC who had a positive PD-L1 status.

Cancer vaccines represent an exciting approach for cancer immunotherapy. In the NCT02897765 phase Ib trial, the combination of a personalized neoantigen-based vaccine termed NEO-PV-01 and a PD-1 inhibitor was reported to be effective in treating patients with advanced melanoma, NSCLC or bladder cancer. No negative responses associated with the therapy were identified in the study, and the combined application was reported to be safe. Neoantigen-specific $CD4^+$ and $CD8^+$ T-cell responses were triggered by the combination (99). Furthermore, in the NCT02823990 phase II study, the effectiveness of TG4010 (a vaccine consisting of modified vaccinia virus Ankara, human mucin 1 and IL-2) combined with nivolumab is being assessed in individuals with NSCLC who had received previous treatment.

Furthermore, oncolytic virus is a promising tumor immunotherapy agent. The oncolytic virus has the potential to selectively kill tumors and activate innate and adaptive immune responses in the host (100). The use of oncolytic virotherapy has been reported to enhance the infiltration of T cells within the tumor and result in an improvement in anti-PD-1 immunotherapy (101). Currently, ongoing clinical trials aim to investigate the combination of oncolytic virus and ICIs in solid tumors, such as NSCLC.

Finally, through the activation of T cells mediated by the T-cell receptor, zoledronic acid (ZA) has been reported to enhance antitumor immunity. In a mouse model of LL2 lung cancer, the combination of ZA and ICIs resulted in an increase in $CD8^+$ IFN-γ^+ T cells and γδ T cells, as well as a decrease in CD11b cells in both the circulation and TILs. The combination group exhibited markedly inhibited tumor growth (102) (Tables IV and SI).

6. Immune-related adverse events (irAEs) in combination therapy

Auto irAEs can manifest following the administration of ICIs (103). The main causes of irAEs are primarily due to increased T cell responsiveness and the activation of self-reactive T cells (104). irAEs may manifest as autoimmune diseases affecting the endocrine, dermatological, respiratory, gastrointestinal, hepatic, renal, neurological, cardiac and hematological systems (105,106). Fatigue, cutaneous toxicities, colitis and endocrine dysfunctions have been reported most frequently, followed by hepatitis and pneumonitis (107). Patients treated with ICIs have experienced a notable incidence of acute and chronic illness, as well as death. In NSCLC, the overall

Table IV. Clinical trials of ICIs in combination with immunotherapy in NSCLC.

Clinical trial	Target or combination regimen	Setting	Intervention	Outcome, months	(Refs.)
CheckMate 227	PD-1, CTLA-4	Advanced NSCLC	Arm A: nivolumab + ipilimumab Arm B: nivolumab	mOS: 17.1 vs. 15.7; mPFS: 5.1 vs. 4.2	(78)
NCT03563716	PD-L1, TIGIT	Advanced or metastatic NSCLC	Arm A: Tiragolumab + atezolizumab; Arm B: Placebo + atezolizumab	mPFS: 5.4 vs. 3.6	(80)
NCT02352948	PD-1	Advanced or metastatic NSCLC (Stage IIIB-IV)	Arm A: Durvalumab; Arm B: Durvalumab + tremelimumab	mOS:11.7 vs. 11.5; mPFS: 3.8 vs. 3.5	(81)
NCT03302234	PD-1, CTLA-4	Untreated metastatic NSCLC	Arm A: Pembrolizumab + ipilimumab; Arm B: Pembrolizumab + placebo	mOS: 21.4 vs. 21.9; mPFS: 8.2 vs. 8.4	(82)
NCT02453282	PD-L1, CTLA-4	NSCLC	Arm A: Durvalumab + tremelimumab; Arm B: Durvalumab	mOS: 11.9 vs. 16.3;	(83)

NCT, National Clinical Trial; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T lymphocytes cell antigen-4; TIGIT, T cell immunoglobulin and ITIM domain.

occurrence of irAEs observed with anti-PD-1 and anti-PD-L1 therapy has been reported to be 22% (95% CI, 17-28%) for all grades, whilst for high grades, it was 4% (95% CI, 2-6%) (108). Despite the higher likelihood of organ-specific irAEs associated with ICIs compared with conventional therapies, the overall occurrence rate remains minimal (109). Furthermore, evaluating the safety of combination therapy remains challenging.

Currently, available data on irAEs associated with combination therapy are limited. A previous study demonstrated that, in the combined application of chemotherapeutic drugs and ICIs, the adverse reaction rate was slightly increased. Moreover, a comprehensive examination and backward-looking analysis revealed that the combination of chemotherapy and ICIs exhibited a greater incidence of unfavorable incidents compared with monotherapy, primarily due to the inclusion of adverse events traditionally associated with chemotherapy in addition to those events reported with combination therapy (110). In addition, ICIs can cause a severe adverse reaction known as immune-related pneumonitis (IRP), with Long *et al* (111) reporting that the combination of chemotherapy and PD-1 inhibitors results in a decreased incidence of IRP compared with the use of PD-1 inhibitors alone.

Furthermore, another study reported that, in the group where ICIs were combined with anti-angiogenesis drugs, the occurrence rate of grade 1-2 irAEs was 80%, whilst in the ICI monotherapy group, it was 73%. Additionally, the occurrence rate of grade 3-4 adverse events was 12 and 6%, respectively. In the combination therapy group, the grade 3-4 irAEs included high blood pressure (4%), tiredness (4%), adrenal insufficiency, low red blood cell count and diarrhea (45). The most common related serious irAEs of ramucirumab plus pembrolizumab were asthenia and myocardial infarction, observed in 2/27 patients (7%) with NSCLC. In general, the combination of ICIs with anti-angiogenesis demonstrated a tolerable safety profile and beneficial antitumor effects in patients with NSCLC (112).

Drug-induced interstitial lung disease has been the most severe irAE reported when ICIs are used in conjunction with targeted therapy. The TATTON and CAURAL trials had to be terminated due to drug-induced interstitial lung disease (113). According to research findings, the combination of pembrolizumab and gefitinib was deemed impractical as it resulted in severe liver toxicity (grade 3/4) in 71.4% of individuals, ultimately causing 4 patients to permanently halt their treatment. Rashes, acne-like skin inflammation, diarrhea, underactive thyroid and itching were the most common adverse events observed with the combination of pembrolizumab and erlotinib (59). However, further research is required to ascertain the effectiveness and security of ICIs in conjunction with targeted treatment, particularly for EGRF-altered NSCLC.

Research indicates that the combination of nivolumab and ipilimumab can indeed lead to a higher incidence of treatment-related serious side effects in the treatment of certain cancers. Previous research has demonstrated that the occurrence of treatment-related severe side effects of any level was higher in the nivolumab plus ipilimumab group compared with chemotherapy (24.5 vs. 13.9%), as well as the discontinuation of treatment due to these side effects (18.1 vs. 9.1%). The most frequent treatment-related severe adverse events in patients

administered nivolumab plus ipilimumab were skin reactions (34.0%) and endocrine events (23.8%) (22). In the combination of ICIs and chemotherapy, assessing the risk of ophthalmic treatment-related adverse events is a critical area of research. According to a systematic review and meta-analysis, the combined use of PD-1 and CTLA-4 inhibitors may increase the incidence of ophthalmic treatment-related adverse events and irAEs (114). According to a meta-analysis, ICIs also primarily cause myocarditis during initial administration and the combination of dual ICIs results in a higher incidence of cardiac irAEs compared with monotherapies or ICIs combined with chemotherapy (115). Furthermore, according to a retrospective cohort study performed at a single center, the use of CTLA-4 and combination ICI regimens increases the likelihood of admissions due to irAEs, which occur at an earlier stage after the initiation of drug treatment (116). Neurological irAEs in a clinical study exhibited considerable variability and severity, with patients receiving combination ICIs experiencing more severe irAEs (117). Whilst the occurrence of systemic, immunohematological and rheumatic diseases is relatively lower in ICI therapy, their prevalence increases when two ICIs are used in combination (118).

Assessing the presence of immune-related side effects poses a challenging issue when administering ICIs. A previous study identified initial quantities of particular cytokines (such as angiopoietin 1, CD40L, IL-17 and granulocyte colony-stimulating factor) associated with specific irAEs in individuals with melanoma who received ICI treatment (119). However, further investigation is needed to determine if the dynamic identification of cytokines can be utilized to forecast the onset of unfavorable immune reactions. Moreover, in the event of a substantial rise in adverse immune reactions following combination therapy, there is a possibility of heightened toxicity leading to grade 3-4 irAEs, and thus, the treatment plan should not be implemented. Therefore, further investigations are necessary to determine an appropriate combination therapy regimen and identify biomarkers that can accurately forecast its effectiveness in treating NSCLC. If the TME, lymphocyte subsets, immune checkpoint expression and cytokine content changes before and after treatment can be dynamically analyzed, it will help choose a reasonable immunotherapy combination application plan and reduce the occurrence of grade 3-4 irAEs.

7. Conclusion

ICIs have achieved notable advancements in the management of cancer and can be utilized for the treatment of NSCLC. However, ICIs have the challenge of resistance. The combination of ICIs with chemotherapy and anti-angiogenesis therapy has shown promising efficacy and safety in treating NSCLC. This combined therapy not only improves patient survival rates but also offers new treatment options for those who do not respond to single treatments. The clinical application of ICIs in combination with chemotherapy and anti-angiogenic medications has been progressively implemented. ICIs combined with targeted therapy and immunotherapy have shown marked improvements in cancer treatment efficacy, but this is accompanied by an increase in irAEs. Therefore, future research should evaluate the effectiveness and security of the combined treatment.

The present review did not describe the biomarkers associated with combination therapy. Advancing biomarker discovery is critical for predicting which patients will derive optimal benefits from these treatments. By analyzing the TME and gene expression characteristics of patients, researchers hope to develop more precise treatment regimens, thereby enhancing the overall efficacy of ICIs. These efforts not only help improve patient outcomes but also provide crucial scientific evidence for the development of personalized treatment strategies.

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Material preparation and data collection were performed by SM, XX, MQ and GS. SM and RH wrote the first draft of the manuscript and all authors commented on subsequent versions of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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The authors declare that they have no competing interests.

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