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REVIEW ARTICLE

# Research progress in immunotherapy of advanced non-small cell lung cancer

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## ABSTRACT

Non-small cell lung cancer (NSCLC) poses a serious threat to people's health. Its morbidity and mortality are among the highest among all malignant tumors, and there is an urgent need for more effective new treatment methods. In recent years, NSCLC immunotherapy has made great progress, the first PD-1 inhibitor nivolumab (Nivolumab, O drug) was approved by the US Food and Drug Administration (FDA) in March 2015, applying to the patients who progressed or has received platinum chemotherapy drugs in the past. Immunotherapy of advanced NSCLC has entered a new era. This article reviews the current research progress of NSCLC immunotherapy.

***Keywords:*** Non-small Cell Lung Cancer (NSCLC); Immunotherapy; Chemotherapy; Radiotherapy; Targeted Therapy

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## 1. Introduction

The incidence rate and mortality of Lung cancer are very high. According to the world cancer statistics 2018, the incidence rate of lung cancer ranks first (2.1 million) in all malignant tumors, and the mortality rate is second (1.8 million), which seriously endangers people's health. Non-small cell lung cancer (NSCLC) is the most common clinical type of lung cancer, accounting for about 85% of all lung cancer types[1]. Most NSCLC patients are in the advanced stage at the time of treatment, and the treatment prognosis is poor. Therefore, it is of great clinical significance to explore new treatment methods for advanced NSCLC to improve the prognosis of patients[2]. In the past, the main treatment of advanced NSCLC was radiotherapy and chemotherapy, and the 5-year survival rate was less than 15%[3]. In recent 10 years, studies have confirmed that the driver gene mutation was positive in advanced NSCLC patients can get significant survival benefits through targeted therapy[4]. Nowadays, tumor immunotherapy has pushed the treatment of NSCLC to a climax again, and some have proved to be beneficial to patients. However, only 20% of patients benefit from immunotherapy, and up to 50% of patients have experienced adverse events[5]. How to choose immunotherapy to maximize the survival benefit of patients with advanced NSCLC has become an urgent clinical problem to be solved.

## 2. Immunotherapy of tumor

The human immune system plays an important role in the process

of tumor development. There is an interactive relationship between the two. The human immune system not only can promote tumor growth but also inhibit tumor growth, which is called "immune editing" of cancer[6]. The immune system clears tumor cells by recognizing tumor-specific antigens and related antigens and generating T cell immune response. It mainly includes the following processes. Firstly, dendritic cells migrate to tumor cells and are activated by new antigens released during carcinogenesis. Secondly, dendritic cells present antigens on major histocompatibility complex (MHC) I and II molecules and capture activated antigens on T cells specific T cells. Finally, activated cytotoxic T lymphocytes (CTL) are transported to the tumor site to produce effective immune surveillance, and finally kill cancer cells and prevent tumorigenesis[7]. At present, the research of tumor immunotherapy mainly focuses on tumor vaccines and immune checkpoint inhibitors.

### 2.1 Tumor vaccine

The tumor vaccine is a newly developed vaccine to prevent tumors. Its principle is to activate the patient's autoimmune system, induce the body's specific cellular and humoral immune response by using tumor cells or tumor antigen substances, so that enhance the body's anti-cancer ability, and prevent the growth, diffusion, and recurrence of tumor, to achieve the purpose of eliminating or controlling the tumor. Immune checkpoint inhibitors are mainly effective for patients with immunogenic tumors, such as tumor-infiltrating lymphocytes (TILs), of which antigens are closely related. New antigens are produced by gene mutations in the process of tumorigenesis, represented by tumor mutation burden (TMB). High TMB tumors have been proved to be the most immunogenic and sensitive tumor inhibitors to immune checkpoints. However, in patients with non-immunogenic tumors, TILs have weak or no infiltration, and they are not active. Therefore, a key problem in immune-oncology is: how to transform non-immunogenic tumors into immunogenic tumors? One way to achieve this goal is to use cancer vaccines. Among the developed cancer vaccines, the Provenge vaccine for prostate cancer proved ineffective in phase III clinical trials, and other cancers, including NSCLC, showed certain clinical benefits[8]. In a randomized, double-blind, phase IIB trial, NSCLC patients with HLA-A*201 positive and TERT expression who did not progress after first-line platinum chemotherapy were randomly divided into groups and treated with Vx-001 or placebo. The results showed that the study did not reach its primary endpoint (the median OS of placebo and Vx-001 were 11.3 and 14.3 months, respectively; P = 0.86)[9]. A study of the docetaxel autologous tumor-derived autophagy vaccine in patients with advanced NSCLC showed that the GM-CSF drop vaccine could induce the immune response of tumor cells, and it did not observe obvious immunotoxicity, although this study does not continue due to its poor prognosis. However, the research on tumor vaccine for patients with advanced NSCLC has made further development[10]. Although studies have shown that the tumor vaccine can benefit some patients, the Ctumor vaccine is still in the stage of laboratory research and has not been put into clinical use. We still need to do more prospective trials to study it.

### 2.2 Application of immune checkpoint inhibitors in NSCLC

#### 2.2.1 Cytotoxic T cell lymphocyte antigen-4 (CTLA-4)

Cytotoxic T cell lymphocyte-associated antigen-4 (CTLA-4), also known as CD152, is a protein receptor that acts as an immune checkpoint and can down-regulate the immune response. Previous studies have shown that the activation of T lymphocytes is considered to require at least two signals: one is transmitted by T cell receptor complex after antigen recognition, and the other is transmitted by costimulatory receptors (such as CD28). CTLA-4 is expressed on activated T cells, about 30% is homologous to CD28, can bind to CD28 ligands (such as CD80 and CD86), and has high affinity, indicating that when CTLA-4 is up-regulated in activated T cells, it may preferentially interact with CD80 and CD86. Ipilimumab is an immunoglobulin monoclonal antibody against CTLA-4. It was approved by FDA in 2011 for the treatment of metastatic malignant melanoma[11]. Therefore, clinical

studies on the therapeutic efficacy and toxicity of CTLA-4 inhibitors are mostly carried out in melanoma patients. A phase III, randomized, open, multicenter Arctic trial was conducted to evaluate the efficacy and safety of immunotherapy in patients with advanced NSCLC after multi-line treatment. The results showed that in patients with PD-L1 ≥ 25%, Dorvalumab (drug I) alone improved PFS and OS compared with standard treatment; in patients with PD-L1 ≤ 25%, Dorvalumab combined with CTLA-4 inhibitor Tremeliumab can only improve PFS and OS numerically, but there is no significant difference. The safety is the same as that of previous treatment[12]. There is still a long way to go to study the therapeutic efficacy or adverse reactions of CTLA-4 inhibitors in NSCLC.

#### 2.2.2 Programmed death 1(PD-1) and programmed cell death ligand 1(PD-L1)

Blocking PD-1/PD-L1 tumor immunotherapy has been proved to improve the ability to kill tumor cells by blocking the PD-1/PD-L1 signal pathway, restoring the immune activity of T cells in NSCLC, and enhancing immune response[5]. At present, several PD-1 and PD-L1 inhibitors have been approved by FDA and European Medicines Agency (EMA) approved and recommended as the standard therapeutic drug for NSCLC. For example, EMA and FDA recommend pembrolizumab as a first-line treatment for advanced lung squamous cell carcinoma with negative driver gene and PD-L1 expression ⩾ 50%. Pembrolizumab is also approved for locally advanced or metastatic NSCLC patients with PD-L1 expression > 1%. In addition, for unresectable locally advanced NSCLC, durvalumab was approved by FDA and EMA as monotherapy for NSCLC patients whose condition did not progress after radiotherapy and chemotherapy regardless of PD-L1 expression level (FDA approval)[13,14]. At present, the expression of tumor cell PD-L1 is considered to be the best molecular marker for the dominant population in anti-PD-1/PD-L1 treatment. Many clinical studies have found that the positive expression of tumor cell PD-L1 is related to its curative effect and prognosis[15,16]. However, a large number of studies show that only about 20% of patients can benefit from immunotherapy. Given the high cost of immunotherapy, how to select the dominant population of immunotherapy and realize the precise treatment of NSCLC is also an important direction for us to explore in the future.

## 3. Immunotherapy for NSCLC

### 3.1 Combined immunochemotherapy

The synergistic effect of immunotherapy combined with chemotherapy has been confirmed in clinical trials. A large number of studies have confirmed that chemotherapy combined with immunotherapy can benefit patients more than chemotherapy alone[17,18]. In 2017, FDA approved pembrolizumab combined with pemetrexed and carboplatin treatment of advanced non-small cell lung cancer[19]. In 2018, FDA approved pembrolizumab combined with paclitaxel and carboplatin as a first-line treatment for metastatic squamous cell carcinoma, regardless of PD-L1 expression. A meta-analysis included 14 relevant randomized controlled trials (RCTs). A total of 8081 newly diagnosed patients with advanced NSCLC were included in the study. The results showed that in terms of tumor response and long-term survival, immunotherapy combined with first-line chemotherapy showed stronger advantages than chemotherapy alone, but also increased grade 3–5 toxic and side effects. The meta-analysis also showed that although combination therapy was superior to single chemotherapy in tumor response and long-term survival, combination therapy increased grade 3–5 toxicity[20]. Based on a large number of studies, the combination of immunotherapy can enhance the recognition and clearance of tumor cells by the immune system, to produce a lasting and effective anti-tumor immune response. It is particularly important to formulate an accurate administration plan, obtain the maximum anti-tumor immune response and disease control rate, and minimize adverse reactions. Wu *et al.* proposed “medium dose intermittent chemotherapy (MEDIC)” and the main purpose of the regimen is to increase the anti-tumor immunogenicity and produce a sustained anti-tumor immune response by initiating repeated cytotoxic injury. In addition to the formulation of dose, the use sequence of each regimen also plays an important role in obtaining an

effective anti-tumor response. Some studies have shown that the response rate of immunosuppressants is 23%–25%, while chemotherapy is the first 18%–20%. However, up to now, there is no sufficient evidence to confirm what kind of administration sequence can maximize the survival benefit of patients. How to select the optimal combination scheme, administration sequence, dosage, and how to select the dominant population will be an important direction for our exploration in the future.

### 3.2 Immunocombined radiotherapy

In recent years, with the understanding of the immune stimulation characteristics of local radiotherapy and its impact on the cell cycle, as well as the understanding of the immune regulation mechanism at the molecular and cellular levels, changes have taken place. The traditional viewpoint on the anticancer effect of ionizing radiation is. Among all newly diagnosed cancer patients, more than 60% will receive radiotherapy with curative purpose or palliative treatment[21]. More and more evidence shows that tumor cell death induced by local radiation can also act on the distal non-radiation tumor site through injury signal cascade, immunogenic cell death, or both at the same time, to achieve the systemic anti-tumor effect, to activate the immune system. These findings have led to the transformation of the application of radiotherapy in the treatment of various malignant tumors[22]. Many pieces of evidence show that the combination of radiotherapy and immunotherapy can increase the cellular immune response in patients with advanced solid tumors, including lung cancer, and has a synergistic effect when combined with immune checkpoint blocking therapy[23]. However, the current research data on immune combined radiotherapy are limited to small sample size, short follow-up period, or lack of randomized controlled trials, or some trials use different immunotherapy, different radiation doses, or grades. Nevertheless, the results of these early clinical trials show that in patients with advanced NSCLC, the clinical effect of combined radiotherapy and immune checkpoint blocking therapy is better than that of treatment alone. The success lies in that the combination of radiotherapy and immunotherapy can make the slow response tumors more sensitive to immunotherapy.

### 3.3 Combined immune targeted therapy

The mutation rate of epidermal growth factor receptor (EGFR) in patients with advanced NSCLC is 40.3%–64.5%. Tyrosine kinase inhibitor(TKI) can work on the EGFR gene directly and inhibit tumor development. Studies have shown that the current three generations of EGFR-TKI can significantly prolong the progression-free survival (PFS) of patients. However, drug resistance is inevitable in patients with advanced NSCLC receiving targeted therapy, and about 50% of patients have EGFR-T790M mutation[25]. Previous studies have confirmed that the EGFR gene can play the role of oncogene through the non-cellular autonomous mechanism and may promote other oncogenes to play the function of immune escape, while EGFR-TKI can improve the antitumor ability of immunotherapy by upregulating PD-L1 expression of tumor cells[26]. A phase Ib multicenter clinical study was conducted to study the safety of necitumumab combined with pembrolizumab in the treatment of stage IV NSCLC. The results showed that the safety of the combination of the two drugs was tolerable and had no additional toxicity compared with the single drug[24]. Therefore, the treatment of EGFR-TKI combined with immunosuppressants may become a new treatment strategy for patients with EGFR mutant NSCLC.

### 3.4 Immune combination against blood vessels

From the traditional platinum-containing dual drug therapy to the molecular targeted therapy in recent 10 years, and then to the rise of the latest immunotherapy, the treatment of advanced NSCLC is no longer limited to radiotherapy and chemotherapy. In 2006, FDA approved the anti-angiogenesis drug bevacizumab as the first-line treatment of advanced SCLC, which provides new decision-making for patients with advanced NSCLC. A large number of experiments have shown that anti-angiogenic drugs combined with chemotherapy, targeting, and immunotherapy can produce synergistic effects[27]. In a study conducted by Rizvi in 2015, the efficacy and safety of nivolumab alone

and nivolumab combined with bevacizumab were evaluated for patients with advanced NSCLC. The results of nivolumab combined with bevacizumab in the treatment of simple adenocarcinoma and nivolumab alone in the treatment of squamous cell carcinoma and adenocarcinoma showed that both groups did not reach the main endpoint of the study, and the overall survival (OS). The median PFS of patients is 37.1 weeks; the median PFS of patients with squamous cell carcinoma in the single drug group is 16 weeks, and the median PFS of patients with adenocarcinoma is 21.4 weeks. Both drugs are safe[28]. Although antiangiogenic drugs can bring some clinical benefits, there are still many problems needed our attention. For example, the combined treatment of multi-target antiangiogenic drugs has just started, and biomarkers are not yet available. Therefore, further researches need to explore the best combination therapy and effective biomarkers.

### 3.5 Double immune therapy

Immune checkpoint inhibitor is the mainstream direction of immunotherapy for lung cancer at present. Since CTLA-4 and PD-L1 act on the activation and effect stages of immune regulation respectively, blocking the key points of these two steps at the same time can play a synergistic role and bring unexpected effects[29,30]. In 2020, the American Society of Clinical Oncology (ASCO) published the 3-year follow-up data of CheckMate-227 and the results of CheckMate-9LA, the first double immunotherapy study. The data confirmed that PD-1 combined with CTLA-4 double immunotherapy is expected to bring lasting benefits to specific patients. CheckMate-227 brings a new first-line "de chemotherapy" scheme to patients. The three-year follow-up data show that first-line nivolumab combined with low-dose ipilimumab shows more lasting OS benefits than chemotherapy regardless of PD-L1 expression. In terms of safety, the addition of low-dose ipilimumab increases immune-related adverse events, However, the incidence of grades 3–4 is equivalent to that of chemotherapy[31]. CheckMate 9LA study showed that, regardless of PD-L1 expression and histological changes, in the first-line treatment of NSCLC patients, nivolumab (360 mg, Q3W) combined with low-dose ipilimumab (1 mg·kg$^{-1}$, Q6W) showed clinical benefits in all efficacy evaluations compared with chemotherapy alone (up to 4 cycles), and 2-cycle chemotherapy was well tolerated for the vast majority of patients[32]. CheckMate-227 and CheckMate-9LA provide treatment options of "de chemotherapy" and "less chemotherapy" for patients with gene negative advanced NSCLC, which may be one of the trends of future research. We should continue to strengthen the ability to prevent and manage adverse reactions of immunotherapy, accumulate more experience, make better use of immunotherapy, and bring greater clinical benefits to patients.

## 4. Summary and prospect

In recent years, the treatment of NSCLC has provided new treatment strategies for patients with advanced NSCLC, from the first platinum-containing dual drug to the later targeted therapy, until the emergence of immunotherapy. Although more and more data show that a large number of patients benefit from immunotherapy, immunotherapy is expensive and the effective rate is no more than 45%. How to determine the dominant population and how to make rational use of immunotherapy and combination programs have become an urgent problem for us to breakthrough. Moreover, the subjects included in many clinical studies are patients with relatively young age, no autoimmune diseases, and good PS score, which is different from the real cases we have seen in the actual clinic. Therefore, further researches need for immunotherapy.

## Conflict of interest

The authors declare no potential conflicts of interest.

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