Immune Checkpoint Inhibitors in Lung Cancer

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Abstract. With the fast increase in morbidity and mortality, lung cancer has become one of the greatest threats to physical health in some countries. Immune checkpoint inhibitors (ICIs) have a significant influence on the treatment landscape of lung cancer, including non-small cell lung cancer (NSCLC). This review highlights the most important ICIs used in lung cancer at present, anti-CTLA-4 and PD-1/L1. The application status, efficacy, shortcomings and prospect of each drug, including Ipilimumab (CTLA-4), Nivolumab, Pembrolizumab, and Durvalumab (PD-1/L1), are listed to show the drug indication in the current market. By comparing different drugs, the direction of ICI drug development can be more precise, which can have an important influence on choosing drugs for lung cancer treatment.

Keywords: Lung Cancer, Immune Checkpoint Inhibitors, NSCLC, PD-1/L1, CTLA-4.

1. Introduction

Lung cancer is a malignant tumor originating from lung bronchial mucosa or gland. Because the growth of cells in lung tissue is out of control, the epithelial cells of the lung undergo carcinogenesis. The main tumor mass forms gradually over time, then expand and invades adjacent tissues, eventually spreading to the lung and other parts of the body. The American Cancer Association estimated that by 2022, there will be 1918030 new cancer cases and 609360 cancer deaths in the United States, of which about 350 die of lung cancer every day, the leading cause of cancer death [1]. Lung cancer has a five-year survival rate of only 18 percent, with the fastest increase in morbidity and mortality [2]. Lung cancer is the most commonly diagnosed cancer in the Global Cancer burden report 2018, according to the 2018 Global Cancer Mortality and Mortality estimates report prepared by the International Agency for Cancer Research [3]. The etiology of lung cancer is very complex, and there are many types. The two most common types of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Among them, non-small cell lung cancer is more common type, accounting for more than 80% of the total cases of lung cancer, while small cell lung cancer accounts for only 10% to 15% of lung cancer cases. The most common types of NSCLC are squamous cell carcinoma, large cell carcinoma and adenocarcinoma. Other subtypes, including sarcomatous carcinoma and adeno-squamous cell carcinoma, are less common. Lung cancer's high incidence and death have imposed significant threats on human life and health, which is the reason why scientists have never stopped the exploration of new treatments.

Traditional lung cancer treatments include surgery, chemotherapy, radiotherapy, or a combination of these treatments. However, with the development of science and technology, new treatments have emerged, such as targeted therapy. Targeted therapy is an anti-cancer treatment that utilizes medications or other substances to target and destroys specific cancer cells. It is less harmful to normal cells than chemotherapy or radiotherapy. Among them, ICIs are widely used in targeted therapy of lung cancer. By blocking the negative regulatory information of cancer cells, cutting off the escape mechanism of the tumor, recognizing the anti-tumor T cell reaction of tumor antigen, to achieve the effect of cancer treatment.
Compared with other traditional treatments, the advantages of immune checkpoint inhibitors are apparent. ICIs are no longer limited to only one targeted drug, but more research is done in combination. There are many ICI drugs in progress, and the combined use of them can improve the progression-free survival rate and overall survival rate [4]. ICIs are now used as first-line treatments for tumor metastases, consolidation after radiotherapy and chemotherapy for unresectable locally advanced diseases, and adjuvant therapy after surgical resection and chemotherapy for resectable diseases. Studies have shown that immunosuppressive site inhibitors significantly prolong OS in patients compared with chemotherapy [5]. ICIs are promising drugs, which have a broad prospect in the treatment of lung cancer, and are worth the time and effort of scientists and researchers to develop.

Cytotoxicity T-lymphocyte associated protein-4 (CTLA-4), anti-programmed death protein-1, and its ligand 1 (PD-1/L1) are the most important antibodies inhibitors used in lung cancer at present. In this paper, we will focus on these two ICIs, and introduce the advantages and disadvantages of antibodies inhibitor in the treatment of lung cancer and the development status of clinical research.

2. CTLA-4

CTLA-4 is the first immunological site used in targeted immunotherapy. The principle of CTLA-4 inhibitor is to regulate T cell activation through a variety of external mechanisms, bind to CTLA-4 protein, block CTLA-4 mediated immunosuppression, and activate cytotoxicity T lymphocytes to participate in anti-tumor immune response [6]. Several studies have reported its overexpression in several cancers, including breast and esophageal cancer. Human antibodies against CTLA-4 have shown significant anticancer potential for a variety of melanoma and tumor types [7].

At the moment, the clinical application of CTLA-4 inhibitors, such as AstraZeneca's ipilimumab and tremelimumab, has been widely used in tumor immunotherapy and has accumulated a lot of clinical application experience. After successful trials on metastatic melanoma, the FDA approved ipilimumab as the first ICI in 2011 [8]. Ipilimumab is the most important research on the use of CTLA-4 in lung cancer.

2.1. Ipilimumab

Ipilimumab is a full human IgG monoclonal antibody. This novel treatment for immune checkpoint molecules swept the world after the FDA approved ipilimumab for sale. Many studies have recently and are currently looking into the use of ipilimumab in conjunction with other drugs, as well as the long-term survival rate of patients who have previously received treatment. The FDA initially granted it approval for the treatment of malignant melanoma, for example, unresectable or metastatic melanoma. [9]. However, it has been approved for a variety of other malignant tumors. In recent years, researchers have been exploring its applications in, specifically, lung cancers.

2.1.1 Efficacy

Compared with other mAbs, ipilimumab was the earliest to be studied and developed. It is found that the effect of ipilimumab in combination with other drugs is better than that of using ipilimumab alone. Studies have shown that nivolumab plus ipilimumab shows delayed deterioration and numerical improvements in health-related quality of living. In CheckMate 227 (NCT02477826), patients with untreated stage IV or recurrent NSCLC and 1% or a higher expression of PD-L1 significantly improved the overall survival rate compared with chemotherapy. In first-line treatment, immunotherapy combined with chemotherapy is gradually replacing the therapeutic status of chemotherapy alone over the past two or three years. A new scheme of bispecific antibody was ushered in for late NSCLC. In the release of CheckMate227 long-term follow-up data, double immunotherapy allowed 1/3 patients with late-stage NSCLC to survive for three years. Previous data showed that the first-line treatment + low dose ipilimumab monoclonal antibody was superior to the traditional chemotherapy, no matter whether PD-L1 expression was positive or negative [9].

In addition, the latest data of the Phase III CheckMate 9LA experiment showed that the median follow-up time was 30.7 months. Compared with chemotherapy, nivolumab and ipilimumab
combined with chemotherapy continued to prolong the OS. In most subgroups, including PD-L1 and histology, the therapeutic results of both the experimental and control groups were observed to improve. During a follow-up of at least 2 years, the two cycles of chemotherapy with nivolumab and ipilimumab provided lasting therapeutic advantages and safety and were still an effective first-line treatment for advanced non-small-cell lung cancer [10].

2.1.2 Adverse reactions

Ipilimumab causes excessive T cell activation. Therefore, unpleasant effects are common. Immune-mediated reactions are common and can influence any organ system and are usually controllable. However, they may display major, life-threatening problems. Ipilimumab causes excessive T-cell activation, which contributes to the main causes of side effects. Immune-mediated reactions are common and can influence multiple organ systems, but they are normally under control. However, they may display major, fatal problems.

The gastrointestinal and integumentary systems are the most commonly afflicted systems, often characterized by pruritus rash, diarrhea, or colitis. The less common adverse reactions include conjunctivitis, uveitis, inflammatory hepatitis, hypothyroidism, hypophysitis, adrenal insufficiency, hypogonadal dysfunction, intestinal perforation, severe enteroocolitis, Stevens-Johnson syndrome, toxic epidermolysis, and liver failure [12].

Although its related adverse reactions and toxicity were found, the effect is still much better than that of treatment alone. There has not been an antidote against the toxicity of ipilimumab overdose. Therefore, appropriate doses and adverse reactions must be carefully monitored. If there is a severe adverse reaction or a rapid exasperation of patients’ conditions, treatment providers should consider discontinuing.

2.1.3 Prospects

At present, it is mainly combined with the PD-1 antibody, which plays an important role in amplifying the tumor inhibition effect of the latter. According to statistics, more than 300 clinical trials are registered with ipilimumab, and the main subjects are tumors sensitive to PD-1 antibody, such as melanoma, renal clear cell carcinoma, and NSCLC with high tumor mutation burden (TMB) [13]. It can be predicted that the main research hotspots of new indications of CTLA-4 inhibitors in the future will turn to the combination of PD-1/PD-L1 drugs and clinical chemotherapy to a certain extent.

3. PD-1/PD-L1

PD-1 / PD-L1 immune checkpoint inhibitors have similar effects to CTLA-4 immune checkpoint inhibitors. But the principle is not completely the same, as shown in Figure 1. Its research is several years later than CTLA-4 immune checkpoint inhibitor, but its application now shows the potential to treat many types of tumors and substantially improve the overall survival of patients. Studies have shown that anti-PD-1 / PD-L1 ICI shows promising efficacy (about a 30% remission rate) [15]. Based on the great success achieved in clinical trials, PD-1 inhibitors aim to fight tumors through the human body's own immune system and have a variety of tumor indications. 10 kinds of α-PD-1 and 3 α-PD-L1 antibodies have been approved for various types of cancer. Targeted PD-1 / PD-L1 immune checkpoint inhibitors have shown unprecedented clinical efficacy in a variety of tumors. At present, what are familiar to people are nivolumab, pembrolizumab, and durvalumab.
Figure 1. Pd-1/PD-L1 interaction with T cell immunological response [16]. The MHC molecule on Antigen-presenting cells (APC) binds to Tumor cell receptor (TCR) on the tumor cell surfaces, activating T cell’s immune response against tumor cells through a cascade of events. This signal is inhibited by PD-1/PD-L1 on the tumor cell surface, which deactivates T cells. Nivolumab’s function is to bind PD-L1, preventing co-signaling of PD-1 and PD-L1, by which guarantee T-cell is activated.

3.1. Nivolumab

Nivolumab is a human PD-1 monoclonal antibody that has been genetically modified. Antibody-dependent cellular cytotoxicity (ADCC) was eliminated by engineering the IgG4 isotype [16]. Since PD-1 is expressed on T effector cells and other immune cells, an intact ADCC has the ability to exhaust activated T cells and tumor-infiltrating lymphocytes, as well as reducing activity. Nivolumab was the first PD-1 inhibitor used in advanced squamous NSCLC after chemotherapy had been applied.

3.1.1 Efficacy

(1) In Non-small Cell Lung Cancer

Patients with late-stage NSCLC have limited choices of treatments after first-line chemotherapy. However, nivolumab has brought hope to them.

Nivolumab is generally advantageous in different aspects, including improved OS and PFS. In the CheckMate 017 trial, intravenous nivolumab 3 mg/kg per two weeks was linked with noticeable improvement in OS and PFS and a considerably higher rate of response than treatment with second-line docetaxel therapy for advanced squamous cell NSCLC. Nivolumab also showed better tolerability than docetaxel in CheckMate 017, and its adverse events were more controllable. To summarize, nivolumab marked a significant leap in treatment for previously-treated advanced squamous cell NSCLC [17].

Nivolumab's effectiveness and safety were assessed in another randomized, open-label, multinational phase III trial. [25]. Median OS was 6.0 months with docetaxel, whilst 9.2 months with nivolumab. The rate of one-year OS was 42% with nivolumab versus 24% with docetaxel at one year. The rate of response in respective groups was 20% and 9% for nivolumab and docetaxel, respectively. The median PFS with nivolumab was 3.5 months compared with the docetaxel group’s 2.8 months. Grade 3 or 4 trAEs were observed in 7% of the individuals using nivolumab vs 55% of those taking docetaxel. [18].

Other clinical trials also confirmed the better performance of nivolumab than docetaxel in previously treated patients. Specifically, in treating advanced squamous and non-squamous NSCLC, two phase III studies have revealed its long-term overall clinical benefit compared with docetaxel.
(2) In small cell lung cancer

In small cell lung cancer (SCLC), there have also been implications of nivolumab for different stages (limited/extensive) of SCLC, and as treatment of different lines (First, second, third line and further). Though the performances are less favorable compared with those of NSCLC, they are still eligible choices for treatment.

The reaction of nivolumab, ipilimumab combination, and nivolumab monotherapy in the maintenance therapy of extensive-disease SCLC (ED-SCLC) after first-line chemotherapy was examined in CheckMate 451, a phase III trial. A minimum of 8.9 months of follow-up was required. In patients with a tumor mutational burden of fewer than 13 mutations per mega-base, nivolumab with ipilimumab showed a trend toward improved OS [22]. For patients who did not advance following first-line chemotherapy, there were no signs of a longer survival time.

The results of CheckMate 032, a phase II and III multicenter study that discovered nivolumab's efficacy in recurrent SCLC, were as follows: For 109 patients who received nivolumab monotherapy as their third or later-line treatment, the ORR and median DOR were found to be 11.9% and 17.9 months, and 61.5% of patients with an objective response had a DOR of at least 12 months. The median PFS time for patients treated with nivolumab monotherapy as a third or later-line treatment was 1.4 months, and the median OS duration was 5.6 months, with a 12-month OS rate of 28.3% and an 18-month OS rate of 20.0% 11.9% of patients experienced treatment-related side events ranging from grade 3 to 4 [23]. It is thus confirmed that nivolumab monotherapy was also well tolerated and showed sustained responses as a third or later-line therapy for recurrent SCLC.

3.1.2 Safety

Safety issues concerning nivolumab use are non-specific and classified as a series of immune-related adverse events (irAE). Their leading to drug discontinuance or death is rare. Compared with docetaxel, nivolumab had shown a lower rate of both hematologic and nonhematologic toxic events. Adverse events of any grade were observed in 58–85 percent of patients treated with nivolumab in trials, whereas grade 3–4 toxicities were reported in 5.7–17 percent of patients. Fatigue (in 16% of the patients), loss of appetite (in 11% of the patients), and asthenia (10% of patients) made up the most frequently reported treatment-related adverse events [18]. The common side effects included fatigue (16–33%), anorexia (11%), diarrhea (8–10%) and endocrinopathies [19]. In a separate phase III study, 58% of patients in the nivolumab group experienced any grade of event, 7% had grade 3 or 4 events, and no grade 5 events were recorded; 86 % in the docetaxel group had any grade of the incident, and the incidence of 3 or 4 grade events was 55%. Lastly, 2% of patients had grade 5 events [18].

In a five-year phase Ib trial carried out in Japan, good safety results were obtained. There were no treatment-related deaths, and dose-limiting toxicity (DLT) was only observed in one participant. For irAEs, hepatic irAEs were observed in thirteen patients. Interstitial lung disease occurred in three patients. Renal irAEs were observed in two patients. Only two patients from two different groups encountered severe irAEs [24].

3.1.3 Prospects

In conclusion, nivolumab has produced exciting and favorable results. Nivolumab's reduction in death with better tolerability, enhanced efficacy, greater response rate and more importantly, improved survival rates were found in numerous trials of different phases. Nivolumab has shown controllable long-term safety, which supports the implementation of controlled phase III trials. Currently, multiple trials inspecting nivolumab's efficacy in advanced NSCLC are ongoing. The combination of different ICI, such as nivolumab and ipilimumab or even with more ICIs, is of the most significant interest to scientists.

3.2. Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody directed against PD-1 on lymphocytes, as well as an IgG4 kappa antibody directed against human cell surface PD-1. The PD-1 receptor
functions as a key immune checkpoint that prevents the self-attacking of the immune system. [25]. In 2014, the FDA granted it expedited approval for advanced refractory melanoma. It has now been approved to treat a variety of different neoplastic disorders in the United States. Merck is said to have submitted a prospective pembrolizumab application to the FDA as early as January 2014. Since pembrolizumab was able to show significant improvements over existing treatment drugs in early clinical studies, the FDA gave it priority consideration.

3.2.1 Efficacy

The results of the effectiveness and safety of pembrolizumab were announced at the ASCO conference in June 2014 by the University of California School of Medicine and other study teams. Pembrolizumab was shown to be effective in treating NSCLC in clinical studies, with most patients experiencing PFS of more than two years. Pembrolizumab was well tolerated in this study. Pharmacokinetic properties typical of monoclonal antibodies with long-lasting anticancer effects in solid tumors have been observed in phase 1 clinical studies in patients with advanced solid tumors [26].

In NSCLC, pembrolizumab is commonly used. Pembrolizumab added to regular chemotherapy has been shown in several studies to have improved OS and PFS when compared to chemotherapy alone. Pembrolizumab with chemotherapy (pemetrexed and carboplatin) was used as a first-line treatment for patients with metastatic non-squamous NSCLC. Furthermore, pembrolizumab combined chemotherapy (pemetrexed and carboplatin) showed that in advanced metastatic NSCLC patients without EGFR or ALK gene mutations who had not received chemotherapy, pembrolizumab combined chemotherapy treatment resulted in a significantly higher remission rate than chemotherapy (55%) and a disease control rate of 88%. Furthermore, regardless of whether patients have high or low PD-1 expression, this effect persists [27]. Other evidence suggests that adding pembrolizumab to standard chemotherapy with pemetrexed and platinum drugs, rather than chemotherapy alone, significantly improved overall and progression-free survival in patients with previously untreated metastatic non-squamous NSCLC without EGFR or ALK mutations. [28].

In other studies, Pembrolizumab improved overall survival and had an excellent risk-benefit ratio in patients with advanced NSCLC who had previously been treated with PD-L1. In metastatic NSCLC with tumor PD-L1 expression greater than 1% and progression after platinum-based chemotherapy, single agents were used. (Patients with EGFR / ALK tumor abnormalities progress after receiving targeted therapy for their respective tumor abnormalities.) In patients with advanced NSCLC who had previously been treated with a PD-1 inhibitor, the median survival with pembrolizumab (10 mg/kg) was 17.3 months compared to 8.2 months in the docetaxel group [29]. The data presented above clearly show that pembrolizumab treatment improves overall survival in patients with NSCLC.

Pembrolizumab is not only studied in NSCLC but also in SCLC. Studies have shown that metastatic SCLC after platinum-based chemotherapy and at least one other therapy has an objective response rate, when treated with pembrolizumab, of 18.7% and a median OS of 9.1 months [30].

3.2.2 Adverse reactions

Pembrolizumab causes adverse reactions in patients during treatment, and its toxicity may harm the fetus [36], according to a large study. Women who are able to conceive should be counseled on the possibility of fetal injury and the use of effective contraception. Animal studies have shown that certain infections, such as mycobacterium tuberculosis, lymphocytic choriomeningitis, and hepatitis B, become more severe. Nonetheless, pembrolizumab has yet to be tested for latent oncogenicity or genotoxicity. Pembrolizumab had a terminal elimination half-life of 27 days [32]. Pembrolizumab is a newer biological agent. Although it is effective, its safety needs extra attention. There are numerous studies aiming at its safety currently being conducted in clinical research.

3.3. Durvalumab

Durvalumab is a full human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody, which inhibits the interaction between PD-L1 and PD-1 or CD80, enhancing anti-tumor immune responses
and activating T-cell functions [33]. It was proven that the addition of durvalumab to chemotherapy can prolong OS and PFS of the previously untreated patients with unresectable NSCLC significantly when compared to the chemotherapy alone in the Phase-III-CASPIAN trial. Advantages are obvious while it also has shortcomings and unsolved issues blocking its way to reach the market. It has a promising development to be further explored.

USA, Australia, Canada, Japan, Singapore, and India have approved durvalumab consolidation treatment added in chemoradiation therapy for patients with unresectable stage III NSCLC, while in the EU, only the patients with tumors expressing PD-L1≥1% can use durvalumab [33, 34].

3.3.1 Properties and Clinical efficacy

Durvalumab is predominantly removed by protein catabolism in the reticuloendothelial system or through target-mediated disposition. No clinically meaningful differences are found between its usage as either monotherapy or combination therapy with chemotherapy in terms of the pharmacokinetics (PK) of durvalumab, which proves the feasibility of the consolidation treatment [33].

Randomly selecting 713 placebo-controlled patients with unresectable NSCLC, PACIFIC Study evaluated the efficacy of durvalumab. With a 4-year follow-up analysis, durvalumab showed significant improvement in OS and PFS compared to placebo.

Randomly selecting 805 untreated ES-SCLC patients suitable to receive as first-line treatment for SCLC, CASPIAN Study evaluated the efficacy of durvalumab with or without combination with chemotherapy. Improvements in OS were found in patients receiving both durvalumab and chemotherapy compared to those receiving chemotherapy alone.

3.3.2 The advantages

Currently, durvalumab is one of the scanty approved immunotherapies for the first-line treatment of ES-SCLC, combined with cisplatin or carboplatin (plus etoposide) [33]. It can significantly prolong the OS and PFS of patients and the benefits can be sustained for a longer time. It is shown that the tolerability of durvalumab is relatively manageable since AEs were mostly low grade.

Moreover, durvalumab consolidation treatment is proved cost-effective compared to chemotherapy alone [34].

3.3.3 Shortcomings and unsolved issues

Durvalumab has a limitation on certain mutations. Not all patients can benefit from durvalumab, especially for patients with ERBB2/EGFR-mutant tumors, which are important drivers in NSCLC. A retrospective analysis of patients with unresectable stage III NSCLC receiving durvalumab consolidation treatment selected 36 patients, among which 14 had ERBB2/EGFR-mutant tumors to evaluate the efficacy, with a result showing shorter DFS on them. Although PD-L1 expression is high, limited responses to durvalumab are still obvious in ERBB2/EGFR-mutant tumors [35].

Although AEs are manageable, the toxicity is still a non-eligible issue, which needs special attention. The safety of durvalumab as monotherapy and in combination with chemotherapy is based on 3006 patients with multiple tumor types and 265 patients with SCLC respectively. Among which neutropenia is the most frequent for combination treatment and cough appears as the most common one in monotherapy.

Pneumonitis occurs both in monotherapy and in combination treatment, presenting as immune-related pneumonitis bilaterally with a larger area and radiation pneumonitis unilaterally with smaller areas respectively. Corticosteroid therapy can be a kind of management for immune-mediated pneumonitis, which can’t be used before the treatment but after the process [34].

Based on the MoA, durvalumab has a potential to impact pregnancy, which is proven in a mouse model finally resulting in fetal loss but hasn’t been examined whether it is true for humans. It is not expected to have metabolic drug-drug interactions with durvalumab but currently, no studies have been conducted in terms of the formal pharmacokinetic interaction [34].

The uses of durvalumab in pregnant women, children, adolescents aged below 18 years of age, elderly patients, and patients with renal, kidney, or hepatic impairment have not enough data to show
the efficacy [33]. Although the combination treatment is cost-effective, the access to durvalumab is limited [34].

3.3.4 Comparison with other ICI drugs

In patients with ES-SCLC, there are no remarkable diversities in PFS or OS between atezolizumab, durvalumab, pembrolizumab, and nivolumab as first-line treatment. Durvalumab has been shown to improve ORR more than atezolizumab, but it has a higher risk of immune-related AEs than atezolizumab and pembrolizumab [36].

3.3.5 Further prospective

Durvalumab has a promising development space, including several directions to further explore. To tackle the unaddressed issue—optimal duration of the treatment, is one of the requirements since ICI treatment has just a fixed duration of 1-2 years currently. Moreover, limiting long-term toxicity and controlling certain AEs are still in great need, which may somehow need a multidisciplinary team to participate in [33]. More researches are necessary to get enough data in terms of the eligible patients, especially those with no data mentioned above. Drug-drug interaction still needs to be explored further. The feasibility of combination treatment for EGFR mutant patients should be examined and ensured in the future.

Currently, the combination of durvalumab and tremelimumab shows oncological advantages in comparison with chemotherapy, but is not better than durvalumab monotherapy. But combination therapy is a better way to tackle more tumors [37]. Thus, the combination therapy could be a future goal as well.

In conclusion, durvalumab has shown unique advantages in NSCLC but still has its shortcomings and unsolved issues. Thus, more Phase III trials are in need to further develop this promising drug for lung cancer.

4. Conclusions

Lung cancers remain to be the type of cancer with the largest and fastest growing number of patients around the world. Human beings have been developing therapies against lung cancers. Immune Checkpoint Inhibitors are new pathways of therapies towards lung cancers. Several ICI drugs, including nivolumab, pembrolizumab, ipilimumab and durvalumab were summarized in terms of their efficacies, safety issues and prospects in this paper. There have been great amounts of trials on these drugs that explored their applications in both NSCLC and SCLC, bringing out new statistics and revelation of new combined therapeutics. For all the drugs, in either monotherapy or combined therapy they performed generally better in terms of OS, PFS and safety issues than drugs developed in previous years. The current generation of ICI drugs has provided encouraging curative effects for lung cancers patients.

From the beginning of immune monotherapy to combination therapy, research has made great progress. Combination therapies are critical in enhancing the performances of immunotherapy, surmounting drug resistance, and enlarging the beneficiary population. Nowadays, clinical combination therapy is developing faster. Combination therapy is not only the combination of two drugs (dual immunotherapy) but also the combination of other treatments, such as the combination of immunotherapy and chemotherapy, immunotherapy and radiotherapy, immunotherapy and targeted therapy. Biomarkers for anticipating the effectiveness of ICI should be developed in future years using epigenetic analysis and whole-genome sequencing, as part of a comprehensive prediction model that includes various biomarkers and monitoring technologies, comprehensively evaluating the tumor immune status of patients, and formulating personalized and accurate combination therapy strategies. Moreover, researchers should continue to explore new targets of ICIs and the drug resistance mechanism, develop new drugs and realize the specific immunotherapy for lung cancer patients. Undoubtedly, this field of ICI drugs development in lung cancers is still demanding and prospective.
References


