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Immunotherapy for Small Cell Lung Cancer

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Abstract

Small cell lung cancer (SCLC) is a poorly differentiated, highly malignant neuroendocrine tumor characterized by rapid growth, aggressiveness, and easy recurrence. It is usually found in late clinical stage and the opportunity for surgery is lost. Therefore, surgery is often not used in clinical treatment. Although it is sensitive to chemoradiotherapy, it has a high recurrence rate and lacks effective treatment methods at present. Following chemotherapy and radiotherapy, immunotherapy for small cell lung cancer has become the mainstream research direction. Immunotherapy is profoundly changing the approach to cancer treatment due to its tolerable safety profile, sustained treatment response due to the production of immune memory, and effectiveness in a broad patient population. Immunotherapy for small cell lung cancer is one of the effective treatment methods for small cell lung cancer, and relevant studies are not rare, but there are still shortcomings such as intolerance of side effects and inaccurate evaluation of treatment timing. This article reviews the history of immunotherapy, the mechanism of action of immunodrugs, and the current immunodrugs used in the first-line treatment of extensive small cell lung cancer.

Keywords

Small Cell Lung Cancer, Immunotherapy, PD-L1 Inhibitor, PD-1 Inhibitor

1. Introduction

The incidence of lung cancer ranks first in the world. In 2020, nearly one-third of lung cancer cases and cancer-related deaths worldwide will occur in China [1]. Compared with other tumors, lung cancer has a poorer prognosis. Small cell lung cancer, a smoking-related invasive subtype of lung cancer with neuroendocrine differentiation, belongs to low-differentiation and high-grade neuroendocrine carcinoma. [2] More than 150,000 people worldwide are diagnosed with

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small cell lung cancer each year. [3] It accounts for about 15% of all lung cancers, with a 5-year survival rate of less than 7% and medium-extensive SCLC (ES-SCLC) accounts for about two-thirds of all SCLC cases. [4] Extensive stage SCLC (ES-SCLC) accounts for about two-thirds of all SCLC cases. SCLC is characterized by rapid tumor growth and early metastatic spread, requiring systemic treatment at all stages of the disease. However, the survival rate of both NSCLC and SCLC types of metastatic lung cancer is very low, with a 5-year survival rate of only about 4%. [5] Overall treatment for small cell lung cancer (SCLC) progresses more slowly than for non-small cell lung cancer. In fact, the standard treatment regimen for SCLC has not changed significantly in more than 20 years. [6] Although SCLC is very sensitive to systemic chemotherapy at the time of initial diagnosis, local and systemic recurrence occurs most often after completion of the appropriate treatment regimen, even in cases where the stage is early. Drug resistance is one of the important reasons for complex metastasis and short survival of patients. Therefore, it is necessary to select a suitable regimen to delay tumor progression and drug resistance.

The development of programmed cell death protein 1 (PD-1)/Programmed death ligand 1 (PD-L1) checkpoint inhibitors has significantly changed the treatment strategy for ES-SCLC. In a pivotal phase 3 trial, adding atrilizumab to chemotherapy extended progression-free survival (PFS) and overall survival. Therefore, chemoimmunotherapy, in which PD-L1 inhibitors are added to a combination of platinum drugs and etoposides, has become the standard first-line treatment option for ES-SCLC. [7] [8]

2. Immune Checkpoint

2.1. The Role of Immune Checkpoints

A large number of recent studies have shown that tumors can be treated by enhancing the immune response to tumor cells, and considerable progress has been made. Patients who do not benefit from targeted therapy or are resistant to chemotherapy can improve survival with immunotherapy regardless of tissue type and mutation type. [9] The most ideal way to destroy tumors is to selectively destroy tumor cells by using the cellular immune pathway mediated by the body's own immune cells, especially T cells.

This brings us to immune checkpoints. Immune checkpoints are a kind of immunosuppressive molecule, which is expressed on immune cells and can regulate the degree of immune activation. They play an important role in preventing the occurrence of autoimmunity and attacking normal cells, maintaining normal immune function in the human body, and preventing excessive damage of peripheral tissue. The popular understanding is the small protein molecules produced by immune cells to regulate their own immune function. Immune checkpoints are thought to be negative modulators of the immune response, preventing excessive peripheral tissue damage. But cancer cells can also use this mechanism to circumvent the human immune system from elimination, in-

cluding: evading immune cell recognition, increasing resistance to apoptotic pathways, or immunosuppressive conditions. [10]

Immune checkpoints (PD-L1 and PD-1) are membrane protein receptors with classical IG (immunoglobulin-like) extracellular domains that bind to intracellular domains to transmit signals to them. Monocytes, T cells, natural killer T cells, B cells and dendritic cells express CD 279 (type I transmembrane receptor PD-1). PD-1 has two natural ligands: PD-L1 (B7-H1, CD 274) and PD-L2 (B7-DC, CD 273). Given that PD-L1 is expressed more widely in normal and tumor cells than PD-L2, more research has focused on the physiological and pathological functions that PD-1/PD-L1 is involved in and how to interfere with their interactions for tumor therapy. [11] The PD-1/PD-L1 system reduces T lymphocyte proliferation, cytokine production, and cytotoxicity of cancer cells, causes tumor-specific T cell fatigue and apoptosis, and allows cancer cells to evade the immune response. The immune checkpoints pathway is described below.

2.2. Discovery of Immunonegative Regulation of PD-1/PD-L1 Pathway and CTLA-4 Pathway

We all know that T cells are normally in an immune surveillance state and can only function when they are activated. The complete activation of T cells is regulated by a "two-signal" system: the first signal comes from the specific binding of TCR to the antigen peptide-MHC complex, that is, T cells recognize the antigen; The second signal comes from a costimulator molecule, that is, a signal mediated by the interaction of a costimulator molecule expressed by an antigen-presenting cell (APC) with the corresponding receptor or ligand on the surface of the T cell. In order to avoid T cells from being over-stimulated, there are negative co-stimulatory molecules that regulate T cells, mainly PD-1/PD-L1 pathway and CTLA4-B7 pathway.

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kines by binding to PD-1. It should be added that Professor Shiping is also engaged in the research of B7 family proteins, and first published a patent in December 1999 to publish the gene and protein sequence of PD-L1, but in the published article, the name of PD-L1 is B7H1. 7 path. [12] And he didn't actually find a ligand for B7H1. Prof Shohei's article was published 10 months earlier than Honjo's, but the related patent was published three months later. Therefore, in terms of the timing of the PD-L1 sequence published on the patent, the two teams are almost simultaneous.

James P. Allison's main research direction is the development and activity mechanism of T cells. In 1996, Professor James P. Allison first discovered that the surface receptor B7 of "cancer cells" can inhibit the immune response of "T cells" by binding to the transmembrane receptor CTLA-4 on the surface of "T cells" to achieve immune escape.

Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4; Also known as CD152) and programmed cell death protein 1 (PD-1; Also known as CD 279), both receptors are inhibitory receptors of the immune response, but they regulate the immune response at the same level and through different mechanisms. So does this mean that blocking either of these pathways can have an anti-tumor effect?

On October 1, 2018, James P. Allison James P. Allision of the University of Texas MD Anderson Cancer Center and Japanese immunologist Tasuku Honjo were awarded the Nobel Prize in Physiology or Medicine for their discovery of cancer therapies that inhibit negative immune regulation. The immunotherapy of tumor has officially entered the stage of tumor treatment.

2.2.1. The Development of Immune Checkpoint Modulators

On October 1, 2018, the Karolinska Medical Institute of Sweden announced in Stockholm that the 2018 Nobel Prize in Physiology or Medicine has been awarded to James Allison of the United States and Jo Yuke of Japan for their discovery of "immune checkpoint therapy", a cancer therapy that inhibits negative immune regulation. Not only because immunotherapy is now a hot research spot at home and abroad, but also because its emergence will push the history of anti-cancer to a new milestone.

Unlike radiation and chemotherapy, which are designed to directly interfere with tumor cell growth and survival, immunotherapy indirectly targets tumors by enhancing anti-tumor immune responses that occur spontaneously in many patients.

Cancer therapy targeting negative immune regulation has developed rapidly in recent years from the perspective of the medical field, which makes the treatment of tumor more and more optimistic. Immune checkpoint inhibitors Three immune checkpoint regulators, namely CTLA-4, PD-1, and PD-L1. Immune checkpoint antibodies as promising cancer therapies are based on their natural role as co-suppressor receptors for T cell activation. Therefore, T cell co-stimulatory and co-inhibitory receptors play an important role in the treatment of PD-1/PD-L1

immune checkpoint inhibitors.

2.2.2. CTLA-4 Pathway and Drug Development

Except for constitutively expressed CTLA-4 on regulatory T cells (TREGs), only a small amount of CTLA-4 can be detected on the cell surface of resting T cells, and most CTLA-4 molecules are located in the intracellular compartments of nuclear Golgi vesicles, endosomes, and lysosomes. CTLA-4 plays a critical role in the control of T cell activation and tolerance: on the one hand, it mediates the immunosuppressive capacity of regulatory T cells (TREGs) in general; On the other hand, the expression of CTLA-4 after activation of resting T cells acts as a feedback control mechanism to balance the strength of the adaptive immune response by regulating the production of cytokines such as IFN-γ, T cell differentiation, expansion, cell contact and migration.

The idea of CTLA-4 target druggability is mainly based on the high-affinity binding of anti-CTLA-4 antibodies to CTLA-4 molecules. CTLA-4 is mainly expressed by T cells, and has a close relationship with the co-stimulatory molecular receptor (CD28) on T cells in gene structure, chromosome localization, sequence homology and gene expression. Ctla-4 can bind to the co-stimulatory molecule (B7) on the surface of antigen-presenting cells (APC). However, unlike CD28, CTLA-4 inhibits T cell activation by binding to B7 molecules, acting as a competitive ligand in its extracellular domain, occupying the B7 ligand of APC, thereby blocking CD28 signaling, or inhibiting T cell activation by mediating a negative signal in its intracellular domain. Exogenous antigens and tumor-specific related target antigens stimulate anti-tumor immunity. In the initial stage, due to the limited CTLA-4 level, B7 and CD28 play a dominant role, and T cells are activated to secrete IL-2 and other cytokines, and expand and differentiate effectively T cells. With the increase of CTLA-4 expression in activated T cells, CTLA-4 and CD28 competitively bind to B7 molecules in the late stage of the immune response, inhibiting T cells from the G phase to the s phase and the activity of IL-2 transcription factors, thereby downregulating or terminating T cell response. This provided the basis for the development of CTLA-4 inhibitor ipilimumab. [13]

Pilimumab was developed as the first ICI (immune checkpoint inhibitor), which was approved by the FDA after a successful trial in metastatic melanoma. Later, it also showed a good therapeutic effect in the treatment of other tumors, such as non-small cell lung cancer, and the CheckMate227 clinical trial proved the effectiveness of ipilimumab combined with other immune agents in the treatment of non-small cell lung cancer. [14]

2.2.3. PD-1/PD-L1 Pathway and Drug Development

The primary function of PD-1 (as opposed to CTLA-4) is to inhibit T cell activation in peripheral tissues and prevent autoimmunity during the inflammatory response to infection. In the tumor microenvironment, this corresponds to key immune resistance mechanisms. T cell activation is a complex regulatory pro-

cess, and its activation mainly depends on dual signaling. The first signal consists of the binding of an MHC presenting antigen to a T cell receptor (TCR). CD4 and CD8 can bind to MHC molecules and play a promoting role in the activation process of T cells, so they are called co-receptors of TCR. At the same time, the polypeptide-MHC complex is recognized, and the binding of TCR complex and antigen presenting cell (APC) is enhanced. When TCR is specifically bound to the polypeptide-MHC complex, CD4 and CD8 are subsequently bound to MHC molecules, triggering a series of downstream pathways in T cells, providing the initial signal for T cells to recognize the antigen after TCR. But this signal is not enough to activate the dormant T cells. Only in the case of the second co-stimulatory signal provided by CD28 and its receptor, the RNA and protein related to T cell activation will be synthesized, the key cytokine IL-2 will be secreted, and the cell will enter the G1 phase from the G0 phase, which is the second signal, also known as T cell co-stimulatory signal.

When T cells are stimulated, PD-1 expression is induced. PD-L1 is one of the PD-1 ligands. When one of its ligands binds to it, PD-1 inhibits kinases associated with T cell activation through the phosphatase SHP 250. However, other signaling pathways may be triggered, and since PD-1 blocks the "TCR stop signal," this pathway has the potential to alter the duration of T-cell-APC or T-cell-target cell contact. PD-1 is strongly expressed in Treg cells (similar to CTLA-4) and increases its proliferation in the presence of ligands. PD-1 is more widely expressed than CTLA-4: It is induced on other activated subpopulations of non-T lymphocytes, such as B cells and natural killer (NK) cells, limiting their lysing activity.

In other words, the interaction between PD-1 on T cells and PD-L1 on tumor cells or APC can effectively inhibit T cell activation, and even lead to T cell apoptosis, reduced cytokine production, T cell lysis and induction of antigen tolerance, so that tumors evade immune surveillance. [15] PD-1/PD-L1 inhibitors bind to PD-1 or PD-L1 respectively, preventing the interaction between PD-1 and PD-L1, thereby restoring the recognition and killing effect of immune cells, and avoiding immune escape of tumor cells.

T cell activation is a complex regulatory process involving T-cell receptor (TCR) and co-stimulatory signaling of peptide-major histocompatibility complex (MHC) conjugations (1). After T cell activation, cosuppression immune checkpoint proteins, such as programmed cell death protein 1 (PD-1), are induced and act as a brake for activation (2). Cancer cells use immune checkpoint proteins to avoid and suppress anti-tumor immune responses. The binding of PD-1 to ligand programmed death 1 (PD-L1), which is expressed on the surface of cancer cells, leads to T cell depletion and immunosuppression.

3. Clinical Application of Several Immune Drugs

3.1. Humanized Monoclonal Antibodies Atezolizumab and Durvalumab

In March 2019, the U.S. Food and Drug Administration (FDA) approved ate-

zolizumab (Attezumab, Tecentriq) in combination with carboplatin and etoposide for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC). 5-year survival in patients with es-SCLC treated with Attilizumab in impower133, a randomized, double-blind, Phase I/III study. Demonstrated that the addition of atezolizumab (plus carboplatin plus etoposide (CP/ET) compared with placebo plus CP/ET for the treatment of extensive small cell lung cancer (ES-SCLC) significantly improved overall survival (OS) and progression-free survival (PFS). Median follow-up for overall survival (OS) was 13.9 months, and atezolizumab was associated with a significant improvement in OS, with a median OS of 12.3 months in the atezolizumab + CP/ET group and 10.3 months in the placebo + CP/ET group (hazard ratio [HR], 0.70; 95% CI, 0.54 - 0.91; P 5.007). The median progression-free survival (PFS) was 5.2 months in the atezolizumab plus CP/ET group and 4.3 months in the placebo plus CP/ET arm (HR, 0.77; 95% CI, 0.62 to 0.96; $P < 0.05$). [16]

In 2019, China's National Medical Products Administration (NMPA) officially approved a new indication application for the PD-L1 inhibitor durvalumab (I drug) for the first-line treatment of extensive-stage small cell lung cancer (SCLC), which also became the second after Attilizumab. The second immunodrug for SCLC is listed in China. On March 30, 2020, the FDA also approved valiuzumab in combination with etoposide plus carboplatin or cisplatin for the first-line treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC). Duvaliumab was able to gain first-line treatment in small cell lung cancer patients based on the results of a Phase III CASPIAN clinical study in which Duvaliumab combined with EP compared with EP increased the proportion of people with long-term benefit: 12-month PFS rate of 17.9% vs 5.3% and 24-month OS rate of 22.2% vs 14.4%. The 2021ESMO CASPIAN study further published 3-year OS rate data, showing that the 3-year OS rate in the Duvaliuzumab combined EP group was 17.6%, while the 3-year OS rate in the EP group was only 5.8%. [17]

Based on the research CASPIAN, IMpower133, etc. The median OS (mOS) in immunotherapy combined with platinum-etoposide group was significantly longer than that in platinum-etoposide monotherapy group (CASPIAN: 13 [95% CI 11.5 - 14.8] vs. 10.3 [95% CI 9.3 - 11.2] months; IMpower 133:12.3 [95% CI 10.8 - 15.9] vs. 10.3 [95% CI 9.3 - 11.3] months) Similarly, progression-free survival (PFS) benefits were observed. IMpower 133 showed that the median PFS (mPFS) was longer in the combination treatment group (5.2 months [95% CI 4.4 - 5.6]) than in the monotherapy group (4.3 months [95% CI 4.2 - 4.5]). In the CASPIAN trial, although mPFS were not significant, 1-year progression-free survival (18% [95% CI 13.1 - 22.5]) was significantly higher in the combination treatment group than in the chemotherapy alone group (5% [95% CI 2.4 - 8.0]). This indicated that 1-year progression-free survival was significantly higher in the combination treatment group (18% [95% CI 13.1 - 22.5]) than in the chemotherapy alone group (5% [95% CI 2.4 - 8.0]). [16]

3.2. The PD-L1 Inhibitor Adebrelimab

Adebrelimab is the first self-developed PD-L1 inhibitor approved for small cell lung cancer indication in China. CAPSTONE-1 was a multicenter, randomized, placebo-controlled Phase III study conducted in 47 tertiary hospitals in China. In this study, Adebrelimab combined with chemotherapy significantly improved overall survival (mOS: 15.3 months vs 12.8 months), reduced the risk of death by 28%, and achieved a 2-year survival rate of 31.3% (vs chemotherapy 17.2%), with good safety, and the incidence of grade 3 irAE did not exceed 1.8%. [18]

3.3. The PD-L1 Inhibitor Toripalimab

Toripalimab was independently developed in China, and the State Drug Administration conditionally approved the first domestic PD-1 monoclonal antibody. In 2019, EXTENTORCH, a randomized, double-blind, placebo-controlled, multicenter, Phase III clinical study, was officially launched to compare the efficacy and safety of the PD-1 inhibitor Toripalimab or placebo combined with etoposide and platinum in the first-line treatment of ES-SCLC. At the PFS data cutoff date (February 28, 2022), the median follow-up was 11.8 months. The chemotherapy alone group and the Toripalimab combined chemotherapy group achieved 87% and 77% of PFS events, respectively, with a significant improvement in PFS in the Toripalimab combined chemotherapy group compared to the chemotherapy alone group (5.8 months vs. 5.6 months, HR = 0.667, P = 0.0002). Even more promising, the 1-year PFS rate was higher in the Toripalimab combined chemotherapy group (18.1% vs. 4.9%), which was nearly 4 times higher than that in the chemotherapy alone group, and nearly one-fifth of patients achieved 1-year progression-free survival. In the 2024 CSCO small cell Lung Cancer Guidelines, the addition of Toripalimab in combination with etoposide plus carboplatin or cisplatin after 4 - 6 cycles of Toripalimab maintenance therapy is a Level III recommendation. [19]

3.4. PD-L1 Inhibitor Tislelizumab

RATIONALE-312 is a multi-center, double-blind, placebo-controlled, randomized phase III clinical trial comparing Tislelizumab + platinum and etoposide with placebo + platinum and etoposide as first-line treatment for extensive SCLC. The trial enrolled 457 patients from July 2019 to April 2021 and were randomly assigned to tislelizumab (n = 227) or placebo (n = 230) plus chemotherapy. As of April 2023, Tislelizumab + chemotherapy showed a statistically significant OS benefit compared with placebo + chemotherapy (stratified hazard ratio < $0.75 [95% confidence interval (CI): 0.61 - 0.93); Unilateral P < $0.0040; The median was 15.5 [95% CI: 13.5 - 17.1] vs 13.5 months [95% CI: 12.1 - 14.9]. Progression-free survival was significantly improved in the tislelizumab group compared with placebo (stratified hazard ratio 1/4 0.64 [95% CI: 0.52 to 0.78]; P < 0.0001; The median was 4.7 [95% CI: 4.3 - 5.5] vs 4.3 months [95% CI: 4.2 - 4.4]. Although 86% of patients in all treatment groups reported grade 3 or great-

er treatment-related adverse events, the majority were more manageable hematological adverse events. It can be concluded that Tislelizumab + chemotherapy as first-line treatment for patients with advanced ES-SCLC shows a statistically significant clinical benefit and a manageable safety profile compared with placebo + chemotherapy. [20]

3.5. The PD-1 Inhibitor Serplulimab

Since its launch in March 2022, Serplulimab has been successively approved in China for the treatment of microsatellite highly unstable solid tumors, squamous non-small cell lung cancer, and extensive small cell lung cancer.

The ASTRO-005 study is an international double-blind Phase 3 randomized clinical trial that enrolled 894 screened patients in six countries from September 12, 2019 to April 27, 2021, and randomized 585 patients with major stage SCLC who had not previously received systemic therapy. Follow-up will be conducted until October 22, 2021. As of the data deadline for the interim analysis (October 22, 2021), the median follow-up was 12.3 months (range 0.2 - 24.8 months). Median overall survival (15.4 months [95% CI, 13.3 months-not evaluable]) was significantly higher in the Serplulimab group than in the placebo group (10.9 months [95% CI, 10.0 - 14.3 months]) (hazard ratio, 0.63 [95% CI, 0.49 - 0.82]; $P < 0.001$). Median progression-free survival was also longer in the serplulimab group (5.7 months [95% CI, 5.5 - 6.9 months]) than in the placebo group (4.3 months [95% CI, 4.2 - 4.5 months]) (hazard ratio, 0.48 [95% CI, 0.38 - 0.59]). Only about one-third of patients in both the serplulimab and placebo groups experienced grade 3 or higher treatment-related adverse events. Thus, in patients with previously untreated extensive stage SCLC, serplulimab combined with chemotherapy significantly improved overall survival compared with chemotherapy alone. [21] Support serplulimab in combination with chemotherapy as the first-line treatment for this patient population. Srulizumab is also the world's first and to date only anti-PD-1 monoclonal antibody approved for use in small cell lung cancer.

3.6. The PD-L1 Inhibitor Envafolimab

Envafolimab is the first approved PD-L1 inhibitor in China, which has good preliminary antitumor activity in advanced solid tumors. The 2022CSCO (Chinese Society of Clinical Oncology) conference included a clinical study on the first-line treatment of ES-SCLC with Envafolimab combined with chemotherapy—a Phase II clinical study exploring the first-line treatment of ES-SCLC with Envafolimab combined with carboplatin/cisplatin and etoposide. The study included 22 patients from September 2021 to June 2022. Sixteen patients received at least one efficacy evaluation, of which 14 achieved partial response (PR, 87.5%) and 2 stable disease (SD, 12.5%), with an objective response rate of 87.5% and a disease control rate (DCR) of 100%. Envafolimab brought tumor remission to more patients. Among the 11 patients who received follow-up, 1 had

been followed up for 7 months, and no endpoint disease progression (PD) event occurred in 5 patients, and the longest progression-free survival (PFS) reached 7.7 months. Prof. Jiao Shunchang affirmed the efficacy and safety of Envafolimab, and said that Envafolimab combined with chemotherapy will bring a new choice for first-line treatment of patients with ES-SCLC.

Envafolimab combined with chemotherapy has also achieved good efficacy in the treatment of mixed small-cell lung cancer. Combined small cell lung cancer (C-SCLC) is a special subtype of small cell lung cancer, which is relatively rare, aggressive, prone to early metastasis, and poor prognosis. At present, the research on C-SCLC is limited, and there is no unified standard treatment, especially for extensive C-SCLC. Liu reported a patient with early adrenal, rib, and mediastinal lymph node metastases in C-SCLC who was treated with carboplatin and etoposide while envafolimab was initiated. After 6 cycles of chemotherapy, the lung lesions were significantly reduced, and the comprehensive efficacy evaluation showed partial remission. No serious drug-related adverse events occurred during treatment, and the drug regimen was well tolerated. [22] We look forward to more comprehensive and convincing clinical studies of Envafolimab in the treatment of small cell lung cancer, or it can be included in the treatment guidelines of small cell lung cancer in the future.

3.7. CTLA-4 Inhibitor Ipilimumab

From September 2011 to April 2014, 42 patients who had not previously received systemic treatment for SCLC were enrolled in this study at 6 research centers in the United Kingdom. The baseline demographics and disease characteristics of the evaluable population (n = 38). Most patients were male (66%), had a physical status (PS) of 1 (66%), and involved the lungs, lymph nodes, and liver. The presence of autoantibodies at baseline was studied in 38 patients. Seventeen patients (45%) were positive for at least one proven autoimmune antibody at baseline. At the time of the final database lock (November 3, 2015), no patients remained on treatment after at least 6.8 months of follow-up (median 8.5 months). The main reason for stopping treatment was toxicity (10/39 [26%]). Even treatment delay was associated with ipilimumab-related toxicity. Even five deaths (13%) were associated with ipilimumab.

Of 38 patients (efficacy analysis population), 6 (15.8% [95% CI: 7.4% - 30.4%]) were progression-free at 1 year based on RECIST. The median PFS was 6.9 months (95% CI: 5.5 - 7.9). The median irPFS was 7.3 months (95% CI: 5.5 - 8.8) and 12.6% (95% CI: 4.0 - 26.3) at 1 year. The median OS was 17.0 months (95% CI: 7.9 - 24.3). Responses were available for 29 and 33 patients, respectively, of whom 21 (72.4%) achieved objective responses based on RECIST and 28 (84.8%) achieved objective responses based on irRC. Supplementary compares the two response patterns. Patients who underwent PCI had numerically better OS (median OS of 18.5 and 12.3 months, respectively), but the difference did not reach statistical significance. [23]

4. Conclusion and Prospect

In recent decades, more and more immune agents have been developed and applied to the clinic. So far, immunological agents have had a considerable place in the treatment guidelines of small cell lung cancer, and even single-drug immune maintenance therapy can be used in the later stage. However, immunotherapy still has many limitations in the treatment of small cell lung cancer. Some progress has been made in the neoadjuvant therapy of immunotherapy for non-small cell lung cancer. It has been reported that patients with early non-small cell lung cancer after immunotherapy have no pathological tissue after surgery, achieving the same effect as surgery, and the damage is less than that of surgery. However, due to the popularity of radical surgery and the high cost of preoperative immunotherapy without authoritative indications and medical insurance, such clinical trials are difficult to carry out and the data are insufficient to draw conclusions. However, from the current theory, immunotherapy for the treatment of small cell lung cancer is clear and effective, and immunosuppressive therapy for small cell lung cancer has broad prospects.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

PD-1:	Programmed cell death protein 1
PD-L1:	Programmed cell death-Ligand 1
ES-SCLC:	Extensive-stage small-cell lung cancer
C-SCLC:	Combined small cell lung cancer
CTLA-4:	T-lymphocyte-associated protein 4
CSCO:	Chinese Society of Clinical Oncology