Review Article

Advances and challenges in immunotherapy of small cell lung cancer

Hanfei Guo, Lingyu Li, Jiuwei Cui

Cancer Center, The First Hospital of Jilin University, Changchun 130021, China

Correspondence to: Jiuwei Cui, PhD, MD. Cancer Center, The First Hospital of Jilin University, 71 Xinmin Street, Changchun 130021, China. Email: cuijw@jlu.edu.cn.

Abstract

Small cell lung cancer (SCLC) is a highly lethal disease, characterized by early metastasis and rapid growth, and no effective treatment after relapse. Etoposide-platinum (EP) combination has been the backbone therapy of SCLC over the past 30 years. It is extremely urgent and important to seek new therapies for SCLC. In the past 5 years, immunotherapy, such as immune checkpoint inhibitors programmed cell death protein-1 (PD-1), cytotoxic T lymphocyte associatedprotein-4 (CTLA-4), has made remarkable achievements in the treatment of patients with SCLC, and it has become the first-line option for the treatment of some patients. Some traditional chemotherapeutic drugs or targeted drugs, such as alkylating agent temozolomide and transcription inhibitor lurbinectedin, have been found to have immunomodulatory effects and are expected to become new immunotherapeutic agents. In this study, we aimed to review the efficacy of new treatments for SCLC and discuss the current challenges and application prospect in the treatment of SCLC patients.

Keywords: Small cell lung cancer (SCLC); immunotherapy; immune checkpoint inhibitors

Submitted Sep 06, 2019. Accepted for publication Dec 31, 2019.
doi: 10.21147/j.issn.1000-9604.2020.01.13
View this article at: https://doi.org/10.21147/j.issn.1000-9604.2020.01.13

Introduction

Small cell lung cancer (SCLC) is a poorly differentiated and high-grade neuroendocrine tumor, which accounts for 10%–15% of all lung cancers (1,2). SCLC is characterized by short tumor doubling time (TDT) and metastasis at an early stage. More than half of the patients were diagnosed at extensive disease (ED) (2,3). Chemotherapy combined with chest radiotherapy has been considered as a standard treatment for SCLC patients for the past 50 years (4). Although SCLC patients are still sensitive to current therapy, with an objective response rate (ORR) of 70%, quite a lot of patients develop drug resistance or disease relapse rapidly after remission (4). The median overall survival (OS) is 15–20 months with limited disease (LD)-SCLC and 8–13 months with ED-SCLC (3,5,6).

Current research suggests that the immune system plays a key role in controlling tumor growth and progression, a process known as cancer immune surveillance. Tumors can escape from immune surveillance by inducting regulatory T cells (Tregs) to promote dysfunctions of T cells and natural killer (NK) cells (7). Such immunosuppressive state is observed in patients with SCLC, which can influence the prognosis of these patients (8). For example, inflammation reduction in pre-existent T-cell occurs more commonly in SCLC than in non-SCLC (NSCLC) (9). Immunotherapy may be a new hope for SCLC patients by reversing the immunosuppressive status. Preclinical and clinical trials on immune checkpoint inhibitors and adoptive cell therapy have heralded a new era in the treatment of SCLC. Cellular immunotherapy (CIT), tumor vaccines, and immunomodulators are also being studied. However, there are still challenges that need to be addressed. Seeking biomarkers to achieve precise treatment is also underway (*Figure 1*).

Immune checkpoint inhibitors

Cytotoxic T lymphocytes (CTLs) is the main force in anti-cancer immune response (10). In the tumor micro-

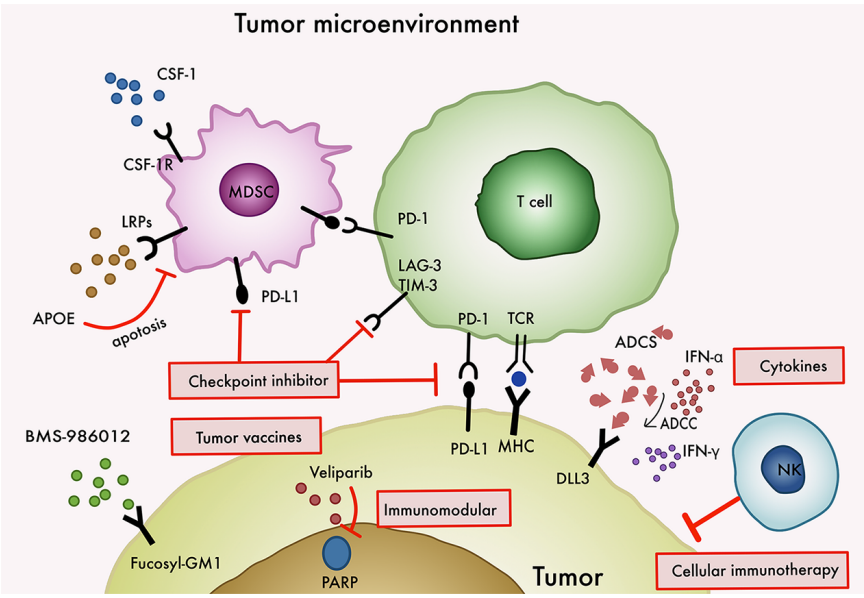

Figure 1 Advances in immunotherapy of small cell lung cancer. CSF-1, colony stimulating factor 1; MDSC, myeloid-derived suppressor cells; PD-L1, programmed cell death 1 ligand 1; PD-1, programmed-death 1; LRPs, low-density lipoprotein-related receptors; APOE, apolipoprotein E; PARP, Poly (ADP-ribose) polymerase; LAG-3, lymphocyte activation gene-3; TIM-3, T-cell immunoglobulin and mucin domain-containing protein 3; TCR, T cell receptor; MHC, major histocompatibility complex; ADCC, antibody-dependent cell-mediated cytotoxicity; DLL3, delta-like protein 3; INF-α, interferon-α; NK, natural killer.

environment, the immune checkpoint pathway is often overactive and then contributes to an immunosuppressive state. The receptors of immune checkpoint on immune cells, such as the CTL-associated protein 4 (CTLA-4) (11), and programmed-death 1 (PD-1), when engaged by their ligands, CD80/CD86 and PD-L1/PD-L2, respectively, can transmit an inhibitory signal, maintain self-tolerance, and discontinue anti-tumor immune responses (12). The aberrant expression of PD-L1 was reported in 72% of patients with SCLC, which was significantly correlated with LD, and was shown to be an independent predictor for favorable outcome (13). The utilization of immune checkpoint inhibitors can effectively restore and augment CTLs responses, leading to potential anti-tumor immune responses, which is of intriguing interest (14).

Clinically, seven immune checkpoint inhibitor antibodies have been approved by the United States Food and Drug Administration (FDA) for the treatment of a variety of tumors: ipilimumab that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4), and six antibodies that block PD-1/PD-L1 including pembrolizumab, nivolumab, atezolizumab, durvalumab, cemiplimab and avelumab. To date, the immune checkpoint inhibitors have achieved a promising result in the treatment of recurrent SCLC (*Table 1*).

Checkpoint inhibitor as first-line treatment for SCLC

IMpower133 is an international, double-blind, randomized, placebo-controlled phase III study that recruited 403 patients from 22 countries to evaluate the efficacy and safety of carboplatin and etoposide combined with atezolizumab as a first-line treatment of ED-SCLC. The median OS was 12.3 months in the atezolizumab group and 10.3 months in the placebo group [hazard ratio (HR)], 0.70; 95% confidence interval (95% CI), 0.54–0.91; P=0.007], while the median progression-free survival (PFS) was 5.2 months and 4.3 months, respectively (HR, 0.77; 95% CI, 0.62–0.96; P=0.02) (15). In the IMpower133 trail, atezolizumab group extended the median OS by 2 months and the median PFS by 0.9 months, immune-related adverse effects (AEs) were more common in the atezolizumab group compared with the placebo group (39.9% *vs.* 24.5%), including rash, hepatitis, fluid-related reactions, pneumonia and colitis. It is the only FDA-approved treatment of SCLC for more than 20 years and is a landmark development in the history of SCLC treatment. However, we need to be aware that the data of OS and PFS gained in IMpower133 were very limited, though significant. In this study the crossover was not allowed and the experimental arm received post-induction maintenance.

Table 1 Completed clinical trials of immune checkpoint inhibitors in SCLC

Clinical trial	Phase	Agent	No.	ORR (%)	DOR (month)	Median PFS (month)	Median OS (month)	Reference
First-line								
IMpower133	III	Atezolizumab *vs.* placebo	201 *vs.* 202	62.7 *vs.* 65.4	4.2 *vs.* 3.9	5.2 *vs.* 4.3	12.3 *vs.* 10.3	(15)
CA184-041	II	Ipilimumab	130	32 *vs.* 57 *vs.* 49	–	5.2 *vs.* 3.9 *vs.* 5.2	9.1 *vs.* 12.9 *vs.* 9.9	(16)
NCT01331525	II	Ipilimumab	42	72.4	–	6.9	17.0	(17)
CA184-156	III	Ipilimumab	566 *vs.* 566	62 *vs.* 62	4.01 *vs.* 3.45	4.6 *vs.* 4.4	11 *vs.* 10.9	(18)
Second-line and beyond								
NCT01375842	Ia	Atezolizumab 15 mg/kg *vs.* 1,200 mg	17	6 *vs.* 24	–	1.5	5.9	(19)
KEYNOTE-028	Ib	Pembrolizumab	24	33.3	19.4	1.9	9.7	(9)
KEYNOTE-158	II	Pembrolizumab	107	18.7	–	2.0	8.7	(20)
CheckMate-032	I/II	Nivolumab *vs.* Nivo+ipili	149 *vs.* 96	11.6 *vs.* 21.9	15.8 *vs.* 10.0	1.5 *vs.* 1.4	4.7 *vs.* 5.7	(21,22)
NCT02261220	I/II	Durvalumab + tremelimumab	30	13.3	–	1.8	7.9	(23)
Switch maintenance treatment								
NCT02359019	II	Pembrolizumab	45	11.1	–	1.4	9.6	(24)

SCLC, small cell lung cancer; ORR, objective response rate; DOR, duration of response; PFS, progression-free survival; OS, overall survival.

A phase II study (CA184-041), which enrolled 130 patients, evaluated the safety and efficacy of ipilimumab in combination with paclitaxel and carboplatin: the median PFS of control, concurrent, and ipilimumab group were 5.2, 3.9 and 5.2 months, respectively; the median OS for all three cohorts were 9.9, 9.1 and 12.9 months, respectively (16). In another phase II study (NCT01331525), which enrolled 42 patients, ipilimumab in combination with carboplatin and etoposide was used as a first-line treatment for patients with ED-SCLC; the median PFS was 6.9 months, while the median OS was 17.0 months (17). A confirmatory phase III study (CA184-156) showed that ipilimumab in combination with chemotherapy (EP regimen) as a first-line treatment for ED-SCLC, failed to improve OS, PFS, and ORR compared with chemotherapy alone (18).

A phase III trial CASPIAN (NCT03043872) showed that first-line durvalumab plus platinum-etoposide significantly improved OS in patients with ES-SCLC *vs.* a clinically relevant control group (HR, 0.73; 95% CI, 0.59–0.91; P=0.0047). Safety findings were consistent with the known safety profiles of all drugs received (25).

Radiation can lead to apoptosis of tumor cells, and it can expose the immune system to additional antigens and partially reshape the tumor microenvironment by reducing the number of mesenchymal-derived suppressor cells (26,27), thereby activating the local anti-tumor immune response. Therefore, combination of immunotherapy and radiotherapy is a reasonable strategy for the cancer therapy.

A number of clinical studies have been conducted to further determine the safety and clinical activity of immune checkpoint inhibitors as a first-line treatment for SCLC, including pembrolizumab (KEYNOTE-604, KEYNOTE-011, and REACTION/NCT02580994) and atezolizumab (NCT02748889). The results have not yet been announced, and we are looking forward to their findings.

Checkpoint inhibitor as second-line therapy and beyond for SCLC

According to research data, the ORR of SCLC patients receiving various third-line therapy is 21.3%; the duration of response (DOR) is 2.6 months; the median OS is 4.4 months; and the 1-year survival rate is only 11% (28). For SCLC therapy, it is important to follow up the regimen. The checkpoint inhibitors used as second-line therapy and beyond have achieved a promising result in recurrent SCLC with chemotherapy tolerable. FDA has approved nivolumab in the treatment of recurrent SCLC in 2018, and immunotherapy has become an accessible treatment option for SCLC.

Checkpoint inhibitor as monotherapy

As part of the phase Ia study (NCT01375842), 17 patients with ED-SCLC received atezolizumab at 15 mg/kg or

1,200 mg via intravenous infusion every three weeks. The ORR of the two groups is 6% and 24%, respectively; the median PFS and OS of all these patients are 1.5 months and 5.9 months, respectively, suggesting that atezolizumab is safe and effective as a monotherapy for SCLC patients (19).

KEYNOTE-028 is a phase Ib trial, which as a monotherapy evaluated the efficacy of pembrolizumab in 24 patients with PD-L1-positive, platinum-refractory ED-SCLC, demonstrated an ORR of 33% (95% CI, 16%−55%) and a median PFS of 1.9 months (9). In another trial, KEYNOTE-158, pembrolizumab demonstrated an ORR of 18.7% (95% CI, 11.8−27.4), median PFS of 2.0 months and median OS of 8.7 months (20). A checkpoint inhibitor as monotherapy for SCLC can provide long-term clinical benefits and causes less toxicity.

A phase III clinical trial, Checkmate-331, reported that nivolumab was ineffective, and thus the administration of this drug was discontinued prematurely. A series of clinical trials have been conducted to compare the efficacy of pembrolizumab and topotecan in patients with recurrence SCLC (NCT02963090). Further studies have also been performed to examine the effectiveness of durvalumab as a first-line treatment for SCLC (MEDIOLA/NCT 02734004).

Double checkpoint inhibitor combination

CTLA-4 acts in T cell activation at an early stage, whereas PD-1/PD-L1 acts in the later stages of T cell activation in tumor immune responses. The combination of these two inhibitors is more effective than either of the two alone.

In a basket phase I/II study, Checkmate-032, dual blockade of PD-1 and CTLA-4 was used to treat patients with relapsed SCLC: the nivolumab at 1 mg/kg plus ipilimumab 3 mg/kg arm achieved an ORR of 23%; and the nivolumab monotherapy arm achieved 10% (21). The results of the expanded cohort of recurrent SCLC patients showed that ipilimumab (3 mg/kg) combined with nivolumab (1 mg/kg) resulted in higher ORR (21.9% *vs*. 11.6%) and long-term OS (5.7 months *vs*. 4.7 months) than nivolumab alone (22). Based on the above results, the National Comprehensive Cancer Network guidelines recommend the combination of nivolumab and ipilimumab as a second-line choice for patients with SCLC, while nivolumab was approved by the FDA as a salvage treatment for SCLC.

In a phase I study in 2017, 30 patients with ED-SCLC were enrolled to evaluate the safety and clinical activity of durvalumab in combination with tremelimumab (NCT02261220). The results exhibited an ORR of 13.3%, a median PFS of 1.8 months (95% CI, 1.0−1.9), and a median OS of 7.9 months (95% CI, 3.2−15.8), indicating that durvalumab combined with tremelimumab had a tolerable safety and activity in pretreated ED-SCLC patients who are both platinum sensitive and platinum resistant (23).

CTLA-4 and PD-1 negatively regulate T-cell activation in different ways; thus, dual blockade of CTLA-4 and PD-1 enhances antitumor activity (21,23). However, the risk of developing serious immune-related cardiotoxicity is also increased greatly (29). Approximately 82% of patients who used more than two kinds of immune checkpoint inhibitors developed treatment-related AEs, while only 60% of patients who used one type of immune checkpoint inhibitor developed treatment-related AEs (21). Other immune checkpoint molecules such as lymphocyte-activation gene 3, T-cell immunoglobulin mucin-3, and V-domain immunoglobulin suppressor of T-cell activation have been explored (30).

Checkpoint inhibitor as switch maintenance treatment in patients with SCLC

Pembrolizumab delays drug resistance and is used as a switch maintenance therapy. A single-arm phase II trial investigated pembrolizumab as the switch maintenance therapy for 12 months in ED-SCLC patients after completion of standard therapy (NCT02359019). Of the 45 patients enrolled in this study, 5 achieved an objective response, resulting in an ORR of 11.1%. The median PFS was 1.4 months, while the median OS was 9.6 months. Patients treated with pembrolizumab developed AEs including fatigue, nausea, cough, and dyspnea. One patient developed atrioventricular block, while another patient developed type 1 diabetes (24).

The CheckMate-451 study evaluated the effect of nivolumab as switch maintenance therapy. The study included 834 patients with ED-SCLC who did not progress after four cycles of chemotherapy. Results showed no significant increase in OS (31).

Study on prognostic biomarkers of immune checkpoint inhibitors

PD-L1 expression level has been investigated as a potential biomarker to predict response to anti-PD-1/PD-L1 therapy (32,33); however, its effectiveness in SCLC

patients remained controversial due to the differences in the positive cutoff level, diagnostic kits, staining antibodies, difficulty in obtaining specimens, and fixation techniques (13,34). An exploratory analysis of biomarkers was conducted in the KEYNOTE-158 trail; the positive rate of PD-L1 in this study was 39% (42/107), and the PD-L1-positive patients had higher ORR (35.7% *vs*. 6.0%) and longer OS (14.9 months *vs*. 5.9 months) than PD-L1-negative patients. In CheckMate-032 study, PD-L1 expression was detected by Dako28-8 mAb assay; results showed that approximately 17% of patients were positive for PD-L1. However, the therapeutic effect of nivolumab with or without ipilimumab was independent of the state of PD-L1 expression. In the CheckMate-032 study, an exploratory analysis of tumor mutation burden (TMB) and nivolumab efficacy was conducted, and the results were published on World Conference on Lung Cancer (WCLC) in 2017. A total of 211 patients were evaluated for TMB; the results showed that patients with high TMB showed higher ORR. Moreover, patients with complete response/partial response had higher TMB than those with stable diseases/progressive diseases. In the nivolumab + ipilimumab treatment group, the PFS and OS of patients with high TMB were 7.8 months and 22.0 months, respectively. The study concluded that immunotherapy and high TMB are associated with better clinical benefit, and TMB is a potentially helpful marker to predict response to immunotherapy (35). Due to the small number of SCLC cases and difficulties in sample collection, exploratory studies primarily focus on investigating the potential predictive biomarkers. However, only a few studies used screening criteria. Hence, further studies determining the prognostic biomarkers of SCLC may be beneficial in future clinical practice.

CIT

Patients with SCLC are found to have functional deficiency in a variety of immunocytes (36), such as NK cells, lymphokine-activated killer cells, tumor-infiltrating lymphocytes (TILs), CTLs, cytosine induced killer (CIK) cells, and gamma delta-positive T lymphocytes (γδT). CIT transforms and amplifies immune cells *in vitro* through cell engineering. For example, the expression of C-X-C motif chemokine receptor 2 (CXCR2) on the surface of T cells is conducive to the delivery of T cells to tumor, and chimeric antigen receptor-engineered T cells (CART) can target tumor-associated antigens (TAAs) to kill tumor cells without human leukocyte antigen (HLA) presentation.

A prospective cohort study of CIT with autologous NK, γδT, and CIK cells as a maintenance therapy for SCLC patients showed that OS was extended to 8.5 months in the study group *vs.* the control group (20 and 11.5 months, P=0.005) (37). Another study indicated that chemotherapy combined with CIK-cell therapy significantly improved the ORR of patients with ED-SCLC (40.9% and 9.1%), and the PFS of the combined treatment group was also longer than that of the control group (8 *vs*. 4 months, P=0.005) (38). None of these studies have observed severe side effects, indicating that CIT might provide a safe and effective treatment for patients with SCLC.

By specifically identifying the tumor cell surface proteins with major histocompatibility complex, CAR-T cell immunotherapy has shown long-lasting and potential therapeutic effects on patients with malignant hematopathy and has been approved in the treatment of B-cell acute lymphoblastic leukemia (39). Some cell surface molecules are highly expressed in SCLC and are potential targets of CART therapy, such as delta-like protein 3 (DLL3), CD56, and CD47. DLL3 is expressed in about 80% of SCLC patients according to previous studies, while almost nonexistent in normal people (40). A phase I, first-in-human study was conducted to evaluate the safety and tolerability of AMG 119, a CAR-T cell therapy targeting DLL3 in patients with relapsed/refractory SCLC (NCT03392064). CD56R-CAR-T cells were able to inhibit SCLC tumor cells growth *in vivo* (41). CD47 is overexpressed in SCLC and plays an important role in blocking phagocytosis, improving tumor survival, metastasis, and angiogenesis (42). CD47-CAR-T cells can effectively kill a variety of cells with high expression of CD47. Therefore, CD47-CAR-T cells are expected to be a potential treatment for SCLC (43).

CIT is an effective anti-tumor immune method, but its efficiency against SCLC is still under investigation due to the difficulty in achieving the efficiency and standardization of immune cell amplification and preparation *in vitro* (44). Immunosuppressive factors in the tumor microenvironment can also limit its clinical application: impenetrable of T cells due to tumor capsule, outer fibrosis (45) and activation of immune checkpoint pathway (46). Combination of radiofrequency or chemotherapy and CIT was also associated with improvements in clinical outcomes of patients with solid tumors (47,48). This finding has demonstrated that the combination of CIT with other therapies may have a promising effect. Moreover, the

results of multi-center, large-sample clinical studies will be used as reference in the future research.

Tumor vaccines

Tumor vaccines can bind to tumor antigen to stimulate dendritic cells (DC) and activate CD8 T cells, induce cellular and humoral immune responses (49,50), and enhance the effect of antibody-dependent cell-mediated cytotoxicity (ADCC). TAA is a protein expressed by unmutated genes, which is significantly overexpressed in tumor cells but rarely expressed in normal cells. Several TAAs have been found in SCLC cells, such as the fucosyl-GM1 (51), ganglioside GD3, polysialic-acid (52), and P53 protein (53).

As an anti-fucosyl-GM1 antibody, BMS-986012 inhibits SCLC growth *in vitro* when used alone or in combination with chemotherapeutic or immunomodulatory agents (51). A phase I/II trial is ongoing to evaluate the safety and efficiency of BMS-986012 in combination with platinum and etoposide as first-line therapy for ED-SCLC (NCT02815592).

INGN-225 is a p53 vaccine based on adenovirus-tranduced DC (DC-Ad-p53 vaccine), which can yield a substantial T-cell response and enhance the chemotherapeutic effect in 40%−57% of patients with ED-SCLC (53). However, a phase II clinical trial showed that DC-Ad-p53 vaccine failed to improve ORRs to the second-line chemotherapy (54). As its safety profile and therapeutic immune potential remain, combination with the other immunotherapeutic agents are reasonable options, and another phase II clinical study examined the efficiency of INGN-225 combined with chemotherapy in patients with SCLC (NCT00617409).

However, most clinical trials on tumor vaccines based on TAAs have failed to improve the OS of patients (55-58). TAA may be not an ideal therapeutic antigen as these antigens are expressed in normal cells and are likely to lead to autoimmune phenomena and serious side effects, and the immune system is usually highly tolerant to an antigen of its own origin. Therefore, it is difficult to stimulate the response of the patients' immune system (59). The use of a combination of therapies may enhance the effect of tumor vaccines.

Antibody-drug conjugates (ADC)

A monoclonal antibody has high specificity of binding to antigen and displays good molecular targeting function. ADCs can kill tumor cells by specifically identifying TAAs in tumor cells (60).

By conjugating toxin tesirine to DLL3 monoclonal antibody, rovalpituzumab tesirine (Rova-T) can specifically identify and target SCLC cells. In a phase I study, disease control rate (DCR) of 68% was detected in recurrent or refractory SCLC patients treated with Rova-T monotherapy, and it was higher (88%) in the high DLL3 subgroup (DLL3 expression >50%) (61). In a phase II study (TRINITY), the effects of Rova-T as first-line or second-line treatment in DLL3 positive (≥25% tumor cells expressing DLL3 by immunohistochemistry) SCLC patients were detected, the results showed that Rova-T was more effective in third-line treatment in patients with high expression of DLL3 (≥75%), but the ORR is only 18% in the overall population (62).

A phase III study MERU (NCT03033511) is ongoing to evaluate the efficacy of Rova-T as maintenance therapy for patients with SCLC following first-line chemotherapy. Another phase III study TAHOE (NCT03061812) in ongoing to compare Rova-T *vs.* topotecan in subjects with advanced or metastatic SCLC.

Sacituzumab govitecan (IMMU-132) is another ADC that conjugates the active metabolite of the topoisomerase-1 inhibitor camptothecin (irinotecan) into an antibody that binds to Trop-2, a calcium-transducing transmembrane glycoprotein widely expressed in SCLC (63). In a phase II trial, IMMU-132 for the treatment of patients with recurrent metastatic SCLC, reported an ORR of 14% and a DCR of 35%, respectively, and a median OS of 7.5 months (64). Based on this study, IMMU-132 has received FDA Fast Track Designation in SCLC. ADC treatment has brought hope to the SCLC, which would also be a pioneer in the individualized treatment of SCLC.

Immunotherapy with immunomodulators

Immunomodulator regulation consists of positive immune regulation, including some cytokines, and negative immune regulation, such as immune checkpoints, which have been described in the previous paragraphs and will not be repeated here. In recent years, some monoclonal antibodies attached to a chemotherapeutic drug targeting signaling pathways or gene replication have been found to have immunomodulatory effects, which may provide new strategies for immunotherapy.

Cytokines

Widely used in CIT to induce and amplify lymphocytes, cytokines can directly stimulate immune cells and enhance their cytotoxicity. Several cytokines have been approved by FDA for cancer treatment, such as high-dose IL-2 for melanoma and renal cell carcinoma, and interferon-α (IFN-α) for adjuvant therapy for stage III melanoma (65).

IFN-α can enhance ADCC and antigen presentation, inhibit angiogenesis and induce tumor apoptosis (66). In two phase II trials conducted on patients with LD-SCLC or ED-SCLC, both studies showed statistically significant survival benefit ($P<0.05$) in patients treated with IFN-α plus chemotherapy *vs.* chemotherapy alone (67,68). By contrast, a phase II study showed the addition of IFN-α and 13-cis-retinoic to paclitaxel did not improve the outcomes of patients with recurrent SCLC (69).

IFN-γ is mainly produced by NK and NKT cells, which has several anti-tumor and immunomodulatory effects (70). However, the anti-tumor role of IFN is complex and controversial. IFN-γ can activate the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway by phosphorylating JAK1 and JAK2 proteins, and the sustained type II interferon signaling promotes epigenomic changes associated with STAT1 in tumors (71). *In vivo* studies, IFN-γ increased the expression of HLA and reduced the expression of gBK protein; cells treated with IFN-γ then were killed by the CTL more effectively (67). However, earlier trials of IFN-γ were discontinued due to lack of statistically significant results or dose-dependent toxicity. However, IFN remains a potential auxiliary therapy in patients with SCLC, and further trials are needed to identify its effect.

Immunotherapy targeting macrophage-stimulating agent

RRx-001 is a macrophage-stimulating agent with the ability to partially reverse resistance to chemotherapy in SCLC patients by epigenetic effects. RRx-001 can synergize with chemotherapy, radiotherapy and immunotherapy (72), as well as protect normal tissues against cisplatin-induced toxicities (73).

A phase II clinical study, QUADRUPLE THREAT (NCT02489903), showed that the SCLC patients who had undergone RRx-001 treatment and restarted etoposide-platinum (EP) treatment showed an ORR of 26.9% in the intention-to-treat population, median OS were 8.6 months. RRx-001 followed by re-challenge with platinum plus etoposide chemotherapy is effective and tolerable, the most common treatment-emergent adverse event from RRx-001 was mild discomfort at the infusion site (23%) (74).

Immunotherapy targeting myeloid-derived suppressor cells (MDSCs)

MDSCs can inhibit the functions of T cells and other immune cells. Pre-clinical studies have found that the co-culture of T cells and MDSC from patients with SCLC can induce the apoptosis of T cells (75), and the content of MDSC in peripheral blood is related to the prognosis of SCLC patients (76). Apolipoprotein E (ApoE) binds to MDSC cell surface receptor LRP8 and induces apoptosis of MDSC (77). RGX-104 (GW3965) is an agonist of nuclear hormone receptor (LXR), which can induce the transcription and expression of ApoE. RGX-104 combined with PD-1 inhibitor showed a synergistic effect on activating anti-tumor immunity in animal models (78). Research on the treatment of recurrent solid tumors (including SCLC) by RGX-104+/− Nivo is also under way (NCT02922764).

Toll-like receptor 9 (TLR9) agonist

TLRs are mainly expressed in B cells and DC; activation of TLR9 can activate the innate and acquired immunity. Lefitolimod (MGN1703) is a TLR9 agonist, which can connect to DCs, then release IFN-α, and activate mononuclear cells, NK cells, T cells and NKT cells, thereby producing chemokines IP-10. Lefitolimod can also promote the secretion of various inflammatory factors by binding to TLR9 expressing B cells, and promote the differentiation of B cells into plasma cells to produce antibodies (79). In the previous phase I and II studies, lefitolimod was found to activate anti-tumor immune response and demonstrated early signs of immunotherapy efficacy, as well as tolerability (80,81).

In a phase II IMPULSE study on patients with ED-SCLC, subgroup analysis indicated that immunotherapeutic maintenance treatment combined with lefitolimod reduced the risk of death in patients with low frequency of activated CD86+ B cells (HR, 0.53; 95% CI, 0.26−1.08) and in patients with chronic obstructive pulmonary disease (HR, 0.48; 95% CI, 0.20−1.17) (82).

New role of traditional drugs in immune moderation

An increase in genomic aberrations and rapid cell proliferation in SCLC resulted in DNA damage and

genomic instability. Poly (ADP-ribose) polymerase (PARP) is a family of enzymes involved in DNA repair. The expression of PARP enzyme in SCLC cells was significantly higher than that of normal lung epithelial cells and other lung cancer tissue subtypes (83). By inhibiting DNA repair and promoting apoptosis of tumor cells, PARP inhibitors can enhance the efficacy of radiotherapy, alkalinizing agents and platinum drug chemotherapy (84). They are able to promote CCL5 secretion, activate type I IFN, and induce PD-L1 expression; DNA damage also triggers the release of various molecular signals, which can enhance the anti-tumor immune response (85).

Temozolomide (TMZ) is an oral alkylating agent that causes apoptosis as its cytotoxic effect. A phase II study in patients with recurrent SCLC showed a significantly higher ORR in the TMZ + veliparib group compared with the TMZ group (39% *vs*. 14%; P=0.016). However, there was no significant difference in the median PFS and OS between the two groups (86). Another phase II study evaluating the combination of cisplatin and etoposide with or without veliparib in ED-SCLC patients also demonstrated modest improved efficacy; the ORR of veliparib and placebo groups was 71.9% *vs*. 65.6%, respectively. Median PFS was 6.1 and 5.5 months, while the median OS was 10.3 and 8.9 months, respectively (87).

Lurbinectedin (PM1183), a transcription inhibitor, blocks transcription and induces DNA double-strand breakage, leading to aberration and apoptosis of tumor cells during mitosis (88). In the preclinical model, lurbinectedin can reduce tumor-related macrophages and inflammatory tumor microenvironment (89). In a phase I study, results from lurbinectedin and doxorubicin in relapsed SCLC have shown remarkable activities with manageable tolerance, with an ORR of 57.7% and a DCR of 69.2%. As a second-line treatment, it showed durable response rates of 91.7% and 33.3% in patients with sensitive diseases and resistant diseases, respectively (90).

Conclusions and expectation

Immunotherapy is the most promising treatment for SCLC in recent years. Nivolumab is the first FDA-approved third-line immunotherapy for SCLC (35). In the IMpower133 study, atzolizumab combined with chemotherapy as first-line therapy also showed improvement in OS (15). Tumor vaccines, immunomodulators, cellular immunity and other immunotherapy methods play an increasingly important role in comprehensive tumor therapy. Reasonable treatment timing and optimal combined strategy are the hotspots of SCLC immunotherapy (*Table 2*).

Immune checkpoint inhibitors have brought changes in the treatment mode of SCLC, but they are only limited to a small number of patients with limited efficacy (20). Their development also strongly promotes the development of biomarkers. Several immune-based biomarkers have been evaluated, including TILs in tumor cells (44), secretion of immune factors (e.g., cytokines), expression of cell surface molecules (e.g., PD-L1), and gene signatures/patterns (dMMR, MSI-H) (35). Efforts are underway to identify predictive immune-based biomarkers that may help select patients who may benefit from immunotherapy (91). Personalized medicine will be used in the therapeutic management of SCLC patients in the near future.

Immunotherapy, targeted therapy and chemotherapy act on different targets and cells, and the combination of these drugs is expected to achieve greater therapeutic effects. The PACIFIC trial of NSCLC showed that PFS and OS were significantly longer in the radiotherapy + durvalumab group, especially in PD-L1 positive patients (92). SCLC is sensitive to radiotherapy (2); immunotherapy combined with radiotherapy is expected to further improve the survival benefit of SCLC patients (26,27). In addition, various therapeutic combinations of novel drugs are being explored, some of which have provided a strong theoretical basis for further clinical trials of SCLC.

In addition, more traditional targeted therapies have been found to have immunomodulatory effects. For example, DNA repair inhibitors (such as PARP inhibitors) have been found to have immunomodulatory effects while improving the efficacy of chemotherapy (85), which can open up new strategies for combined therapy. In addition to these emerging drugs and clinical studies, several new drugs and therapeutic combinations have been evaluated in preclinical studies or are at the early stage of clinical development.

Overall, therapeutic strategies for SCLC have made breakthroughs in recent years. However, the tumor immune microenvironment is dynamic and complex, and the tumor cells can escape immune surveillance in various ways, leading to the immune tolerance and poor efficacy of the immunotherapy (93). Research on biomarkers to screen effective population, improve treatment response rate, and combine with other therapies needs to be further explored (94). Large randomized phase III trials are still needed to

Table 2 Ongoing clinical trials of immune checkpoint inhibitors in SCLC

Clinical trial gov. identifier	Phase	Treatment arms	Population	Primary endpoint	Primary completion
First-line					
REACTION/ NCT02580994	II	Pembrolizumab+chemotherapy *vs*. chemotherapy	ED-SCLC	PFS	August 2020
CASPIAN/ NCT03043872	III	Durvalumab+tremelimumab+ chemotherapy *vs*. Durvalumab+chemotherapy *vs*. chemotherapy	ED-SCLC	OS	September 30, 2019
STIMULI/ NCT02046733	II	chemotherapy followed by nivolumab+ipilimumab *vs*. chemotherapy	LD-SCLC	OS, PFS	October 2019
KEYNOTE-604/ NCT03066778	III	Pembrolizumab+chemotherapy *vs*. Placebo+chemotherapy	SCLC	PFS, OS	December 16, 2019
KEYNOTE-011/ NCT01840579	I	Pembrolizumab *vs*. pembrolizumab+chemotherapy *vs*. Pembrolizumab+Ipilimumab *vs*. Pembrolizumab+chemotherapy+G-CSF	Solid tumor, SCLC, NSCLC	DLTs*, AE	June 30, 2020
Second-line and beyond					
CheckMate-331/ NCT02481830	I/II	Nivolumab *vs*. chemotherapy topotecan *vs*. chemotherapy amrubicin	Lung cancer	OS	August 17, 2018
AFT-17/ NCT02963090	II	Pembrolizumab *vs*. topotecan	SCLC	PFS	May 20, 2019
MEDIOLA/ NCT02734004	I/II	MEDI4736 (anti-PD-L1 antibody) +Olaparib (PARP inhibitor)	Ovarian, breast, SCLC, gastric cancers	DCR, safety and tolerability	August 5, 2022
CA001-030/ NCT02247349	II	BMS-986012 (anti-fucosyl-GM1) *vs*. BMS-986012+nivolumab	SCLC	AE	October 24, 2019
NCT02701400	II	Tremelimumab+durvalumab *vs*. Tremelimumab+durvalumab+radiation	Relapsed SCLC	PFS, ORR	January 2020
Maintance treatment					
CheckMate-451	III	Nivolumab *vs*. Nivolumab+ipilimumab *vs*. placebo	Lung cancer	OS, PFS	October 1, 2018

*, Number of participants experiencing dose-limiting toxicities; SCLC, small cell lung cancer; ED-SCLC, extensive stage small cell lung cancer; LD-SCLC, limited disease small cell lung cancer; PFS, progression-free survival; OS, overall survival; DLT, dose-limiting toxicity; AE, adverse effect; DCR, disease control rate; ORR, objective response rate.

determine the effectiveness and optimal combination strategy of those therapies (95).

Acknowledgements

This study was supported by the Ministry of Science and Technology Foundation (No. 2016YFC1303804) and the National Natural Science Foundation of China (No. 81672275).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2019. CA Cancer J Clin 2019;69:7-34.
2. Rudin CM, Giaccone G, Ismaila N. Treatment of small-cell lung cancer: American Society of Clinical Oncology Endorsement of the American College of Chest Physicians Guideline. J Oncol Pract 2016; 12:83-86.
3. Jett JR, Schild SE, Kesler KA, et al. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines.

Chest 2013;143:e400S-e419S.
4. Ramalingam SS. Small-Cell Lung Cancer: New Directions for Systemic Therapy. J Oncol Pract 2016; 12:119-20.
5. Asai N, Ohkuni Y, Kaneko N, et al. Relapsed small cell lung cancer: treatment options and latest developments. Ther Adv Med Oncol 2014;6:69-82.
6. Fiegl M, Pircher A, Waldthaler C, et al. Small steps of improvement in small-cell lung cancer (SCLC) within two decades: a comprehensive analysis of 484 patients. Lung Cancer 2014;84:168-74.
7. Savage PA, Leventhal DS, Malchow S. Shaping the repertoire of tumor-infiltrating effector and regulatory T cells. Immunol Rev 2014;259:245-58.
8. Becker JC, Andersen MH, Schrama D, et al. Immune-suppressive properties of the tumor microenvironment. Cancer Immunol Immunother 2013;62: 1137-48.
9. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in patients with extensive-stage small-cell lung cancer: Results from the phase Ib KEYNOTE-028 Study. J Clin Oncol 2017;35:3823-9.
10. Mcgranahan N, Furness AJ, Rosenthal R, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science 2016;351:1463-9.
11. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12: 252-64.
12. Haanen JB, Robert C. Immune checkpoint inhibitors. Prog Tumor Res 2015;42:55-66.
13. Ishii H, Azuma K, Kawahara A, et al. Significance of programmed cell death-ligand 1 expression and its association with survival in patients with small cell lung cancer. J Thorac Oncol 2015;10:426-30.
14. Barsoum IB, Smallwood CA, Siemens DR, et al. A mechanism of hypoxia-mediated escape from adaptive immunity in cancer cells. Cancer Res 2014;74:665-74.
15. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018;379: 2220-9.
16. Reck M, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. Ann Oncol 2013;24:75-83.
17. Arriola E, Wheater M, Galea I, et al. Outcome and biomarker analysis from a multicenter phase 2 study of ipilimumab in combination with carboplatin and etoposide as first-line therapy for extensive-stage SCLC. J Thorac Oncol 2016;11:1511-21.
18. Reck M, Luft A, Szczesna A, et al. Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. J Clin Oncol 2016;34:3740-8.
19. Sequist LV, Chiang A, Gilbert J, et al. Clinical activity, safety and predictive biomarkers results from a phase Ia atezolizumab (atezo) trial in extensive-stage small cell lung cancer (ES-SCLC). Ann Oncol 2016:27.
20. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 study. J Clin Oncol 2020;38:1-10.
21. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol 2016;17:883-95.
22. Ready NE, Ott PA, Hellmann MD, et al. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: Results from the CheckMate 032 randomized cohort. J Thorac Oncol 2019:pii:S1556-0864(19)33531-2.
23. Cho DC, Mahipal A, Dowlati A, et al. Safety and clinical activity of durvalumab in combination with tremelimumab in extensive disease small-cell lung cancer (ED-SCLC). J Clin Oncol 2018;36:8517-8517.
24. Gadgeel SM, Pennell NA, Fidler MJ, et al. Phase II study of maintenance pembrolizumab in patients with extensive-stage small cell lung cancer (SCLC). J Thorac Oncol 2018;13:1393-9.
25. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019;394:1929-39.

26. Kroemer G, Galluzzi L, Kepp O, et al. Immunogenic cell death in cancer therapy. Annu Rev Immunol 2013;31:51-72.
27. Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest 2014; 124:687-95.
28. Coutinho AD, Shah M, Lunacsek OE, et al. Real-world treatment patterns and outcomes of patients with small cell lung cancer progressing after 2 lines of therapy. Lung Cancer 2019;127:53-8.
29. Heinzerling L, Ott PA, Hodi FS, et al. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. J Immunother Cancer 2016;4:50.
30. Nirschl CJ, Drake CG. Molecular pathways: coexpression of immune checkpoint molecules: signaling pathways and implications for cancer immunotherapy. Clin Cancer Res 2013;19:4917-24.
31. Owonikoko TK, Kim HR, Govindan R, et al. Nivolumab (nivo) plus ipilimumab (ipi), nivo, or placebo (pbo) as maintenance therapy in patients (pts) with extensive disease small cell lung cancer (ED-SCLC) after first-line (1L) platinum-based chemotherapy (chemo): Results from the double-blind, randomized phase III CheckMate 451 study. Ann Oncol 2019;30:ii77-80.
32. Taube JM, Klein A, Brahmer JR, et al. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin Cancer Res 2014;20:5064-74.
33. Patel SP, Kurzrock R. PD-L1 expression as a predictive biomarker in cancer immunotherapy. Mol Cancer Ther 2015;14:847-56.
34. Schultheis AM, Scheel AH, Ozretić L, et al. PD-L1 expression in small cell neuroendocrine carcinomas. Eur J Cancer 2015;51:421-6.
35. Hellmann MD, Callahan MK, Awad MM, et al. Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in small-cell lung cancer. Cancer Cell 2018;33:853-61.e4.
36. Wang W, Hodkinson P, Mclaren F, et al. Small cell lung cancer tumour cells induce regulatory T lymphocytes, and patient survival correlates negatively with FOXP3+ cells in tumour infiltrate. Int J Cancer 2012;131:E928-37.
37. Ding X, Cao H, Chen X, et al. Cellular immunotherapy as maintenance therapy prolongs the survival of the patients with small cell lung cancer. J Transl Med 2015;13:158.
38. Huang J, Kan Q, Lan, et al. Chemotherapy in combination with cytokine-induced killer cell transfusion: An effective therapeutic option for patients with extensive stage small cell lung cancer. Int Immunopharmacol 2017;46:170-7.
39. Arabi F, Torabi-Rahvar M, Shariati A, et al. Antigenic targets of CAR T Cell Therapy. A retrospective view on clinical trials. Exp Cell Res 2018;369:1-10.
40. Tanaka K, Isse K, Fujihira T, et al. Prevalence of Delta-like protein 3 expression in patients with small cell lung cancer. Lung Cancer 2018;115:116-20.
41. Crossland DL, Denning WL, Ang S, et al. Antitumor activity of CD56-chimeric antigen receptor T cells in neuroblastoma and SCLC models. Oncogene 2018;37:3686-97.
42. Weiskopf K, Jahchan NS, Schnorr PJ, et al. CD47-blocking immunotherapies stimulate macrophage-mediated destruction of small-cell lung cancer. J Clin Invest 2016;126:2610-20.
43. Golubovskaya V, Berahovich R, Zhou H, et al. CD47-CAR-T cells effectively kill target cancer cells and block pancreatic tumor growth. Cancers (Basel) 2017;9:pii:E139.
44. Schalper KA, Brown J, Carvajal-Hausdorf D, et al. Objective measurement and clinical significance of TILs in non-small cell lung cancer. J Natl Cancer Inst 2015;107:pii:dju435.
45. Kakarla S, Gottschalk S. CAR T cells for solid tumors: armed and ready to go? Cancer J 2014;20: 151-5.
46. Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: Mechanisms, response biomarkers, and combinations. Sci Transl Med 2016;8:328rv324.
47. Cui J, Wang N, Zhao H, et al. Combination of radiofrequency ablation and sequential cellular immunotherapy improves progression-free survival for patients with hepatocellular carcinoma. Int J Cancer 2014;134:342-51.
48. Cui J, Li L, Wang C, et al. Combined cellular

immunotherapy and chemotherapy improves clinical outcome in patients with gastric carcinoma. Cytotherapy 2015;17:979-88.
49. Sahin U, Derhovanessian E, Miller M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature 2017;547:222-6.
50. Ott PA, Hu Z, Keskin DB, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. Nature 2017;547:217-21.
51. Ponath P, Menezes D, Pan C, et al. A Novel, fully human anti-fucosyl-GM1 antibody demonstrates potent *in vitro* and *in vivo* antitumor activity in preclinical models of small cell lung cancer. Clin Cancer Res 2018;24:5178-89.
52. Gong L, Zhou X, Yang J, et al. Effects of the regulation of polysialyltransferase ST8SiaII on the invasiveness and metastasis of small cell lung cancer cells. Oncol Rep 2017;37:131-8.
53. Antonia SJ, Mirza N, Fricke I, et al. Combination of p53 cancer vaccine with chemotherapy in patients with extensive stage small cell lung cancer. Clin Cancer Res 2006;12:878-87.
54. Chiappori AA, Williams CC, Gray JE, et al. Randomized-controlled phase II trial of salvage chemotherapy after immunization with a TP53-transfected dendritic cell-based vaccine (Ad.p53-DC) in patients with recurrent small cell lung cancer. Cancer Immunol Immunother 2019;68:517-27.
55. Dickler MN, Ragupathi G, Liu NX, et al. Immunogenicity of a fucosyl-GM1-keyhole limpet hemocyanin conjugate vaccine in patients with small cell lung cancer. Clin Cancer Res 1999;5:2773-9.
56. Bottomley A, Debruyne C, Felip E, et al. Symptom and quality of life results of an international randomised phase III study of adjuvant vaccination with Bec2/BCG in responding patients with limited disease small cell lung cancer. Eur J Cancer 2008; 44:2178-84.
57. Giaccone G, Debruyne C, Felip E, et al. Phase III study of adjuvant vaccination with Bec2/bacille Calmette-Guerin in responding patients with limited-disease small-cell lung cancer (European Organisation for Research and Treatment of Cancer 08971-08971B; Silva Study). J Clin Oncol 2005;23:6854-64.
58. Krug LM, Ragupathi G, Hood C, et al. Immunization with N-propionyl polysialic acid-KLH conjugate in patients with small cell lung cancer is safe and induces IgM antibodies reactive with SCLC cells and bactericidal against group B meningococci. Cancer Immunol Immunother 2012;61:9-18.
59. Cecco S, Muraro E, Giacomin E, et al. Cancer vaccines in phase II/III clinical trials: state of the art and future perspectives. Curr Cancer Drug Targets 2011;11:85-102.
60. Perez HL, Cardarelli PM, Deshpande S, et al. Antibody-drug conjugates: current status and future directions. Drug Discov Today 2014;19:869-81.
61. Bauer TM, Spigel D, Ready N, et al. ORAL02.01: Safety and efficacy of single-agent rovalpituzumab tesirine, a DLL3-targeted ADC, in recurrent or refractory SCLC: Topic: Medical Oncology. J Thorac Oncol 2016;11:S252-3.
62. Carbone DP, Morgensztern D, Moulec SL, et al. Efficacy and safety of rovalpituzumab tesirine in patients With DLL3-expressing, ≥ 3rd line small cell lung cancer: Results from the phase 2 TRINITY study. J Clin Oncol 2018;36:8507-8507.
63. Starodub A, Camidge DR, Ronald J, et al. Trop-2 as a therapeutic target for the antibody-drug conjugate (ADC), sacituzumab govitecan (IMMU-132), in patients (pts) with previously treated metastatic small-cell lung cancer (mSCLC). J Clin Oncol 2016; 34:8559-8559.
64. Gray JE, Heist RS, Starodub AN, et al. Abstract CT155: Phase 2 study of sacituzumab govitecan (IMMU-132), an anti-Trop-2/SN-38 antibody-drug conjugate (ADC), in patients with pretreated metastatic small-cell lung cancer (mSCLC). Cancer Research 2017;77:CT155-CT155.
65. Diller ML, Kudchadkar RR, Delman KA, et al. Complete response to high-dose IL-2 and enhanced IFNγ+Th17: ?TREG ratio in a melanoma patient. Melanoma Res 2016;26:535-9.
66. Tomescu C, Tebas P, Montaner LJ. IFN-α augments natural killer-mediated antibody-dependent cellular cytotoxicity of HIV-1-infected autologous CD4+ T cells regardless of major histocompatibility complex class 1 downregulation. AIDS 2017;31:613-22.
67. Hoa NT, Ge L, Tajhya RB, et al. Small cell lung

cancer cells express the late stage gBK tumor antigen: a possible immunotarget for the terminal disease. Am J Transl Res 2014;6:188-205.
68. Zarogoulidis K, Ziogas E, Boutsikou E, et al. Immunomodifiers in combination with conventional chemotherapy in small cell lung cancer: a phase II, randomized study. Drug Des Devel Ther 2013;7: 611-7.
69. Pillai RN, Aisner J, Dahlberg SE, et al. Interferon alpha plus 13-cis-retinoic acid modulation of BCL-2 plus paclitaxel for recurrent small-cell lung cancer (SCLC): an Eastern Cooperative Oncology Group study (E6501). Cancer Chemother Pharmacol 2014; 74:177-83.
70. Overacre-Delgoffe AE, Chikina M, Dadey RE, et al. Interferon-γ drives T_{reg} fragility to promote anti-tumor immunity. Cell 2017;169:1130-41.
71. Zaretsky JM, Garcia-Diaz A, Shin DS, et al. Mutations associated with acquired resistance to PD-1 blockade in melanoma. N Engl J Med 2016;375: 819-29.
72. Oronsky B, Paulmurugan R, Foygel K, et al. RRx-001: a systemically non-toxic M2-to-M1 macrophage stimulating and prosensitizing agent in Phase II clinical trials. Expert Opin Investig Drugs 2017; 26:109-19.
73. Oronsky B, Reid TR, Larson C, et al. RRx-001 protects against cisplatin-induced toxicities. J Cancer Res Clin Oncol 2017;143:1671-7.
74. Morgensztern D, Rose M, Waqar SN, et al. RRx-001 followed by platinum plus etoposide in patients with previously treated small-cell lung cancer. Br J Cancer 2019;121:211-7.
75. Iclozan C, Antonia S, Chiappori A, et al. Therapeutic regulation of myeloid-derived suppressor cells and immune response to cancer vaccine in patients with extensive stage small cell lung cancer. Cancer Immunol Immunother 2013;62:909-18.
76. Tian T, Gu X, Zhang B, et al. Increased circulating $CD14^{+}HLA\text{-}DR^{-/low}$ myeloid-derived suppressor cells are associated with poor prognosis in patients with small-cell lung cancer. Cancer Biomark 2015; 15:425-32.
77. Veglia F, Perego M, Gabrilovich D. Myeloid-derived suppressor cells coming of age. Nat Immunol 2018; 19:108-19.
78. Tavazoie MF, Pollack I, Tanqueco R, et al. LXR/ApoE activation restricts innate immune suppression in cancer. Cell 2018;172:825-40.e818.
79. Corrales L, Matson V, Flood B, et al. Innate immune signaling and regulation in cancer immunotherapy. Cell Res 2017;27:96-108.
80. Weihrauch MR, Richly H, von Bergwelt-Baildon MS, et al. Phase I clinical study of the toll-like receptor 9 agonist MGN1703 in patients with metastatic solid tumours. Eur J Cancer 2015;51:146-56.
81. Schmoll HJ, Wittig B, Arnold D, et al. Maintenance treatment with the immunomodulator MGN1703, a Toll-like receptor 9 (TLR9) agonist, in patients with metastatic colorectal carcinoma and disease control after chemotherapy: a randomised, double-blind, placebo-controlled trial. J Cancer Res Clin Oncol 2014;140:1615-24.
82. Thomas M, Ponce-Aix S, Navarro A, et al. Immunotherapeutic maintenance treatment with toll-like receptor 9 agonist lefitolimod in patients with extensive-stage small-cell lung cancer: results from the exploratory, controlled, randomized, international phase II IMPULSE study. Ann Oncol 2018;29: 2076-84.
83. Byers LA, Wang J, Nilsson MB, et al. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. Cancer Discov 2012;2:798-811.
84. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science 2017;355:1152-8.
85. Chabanon RM, Muirhead G, Krastev DB, et al. PARP inhibition enhances tumor cell-intrinsic immunity in ERCC1-deficient non-small cell lung cancer. J Clin Invest 2019;129:1211-28.
86. Pietanza MC, Waqar SN, Krug LM, et al. Randomized, double-blind, phase II Study of temozolomide in combination with either veliparib or placebo in patients with relapsed-sensitive or refractory small-cell lung cancer. J Clin Oncol 2018;36:2386-94.
87. Owonikoko TK, Dahlberg SE, Sica GL, et al. Randomized phase II Trial of cisplatin and etoposide in combination with veliparib or placebo for extensive-stage small-cell lung cancer: ECOG-

ACRIN 2511 study. J Clin Oncol 2019;37:222-9.
88. Foy V, Schenk MW, Baker K, et al. Targeting DNA damage in SCLC. Lung Cancer 2017;114:12-22.
89. Belgiovine C, Bello E, Liguori M, et al. Lurbinectedin reduces tumour-associated macrophages and the inflammatory tumour microenvironment in preclinical models. Br J Cancer 2017;117:628-38.
90. Calvo E, Moreno V, Flynn M, et al. Antitumor activity of lurbinectedin (PM01183) and doxorubicin in relapsed small-cell lung cancer: results from a phase I study. Ann Oncol 2017;28:2559-66.
91. Yuan J, Hegde PS, Clynes R, et al. Novel technologies and emerging biomarkers for personalized cancer immunotherapy. J Immunother Cancer 2016;4:3.
92. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 2017;377:1919-29.
93. Chang CH, Qiu J, O'Sullivan D, et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. Cell 2015;162:1229-41.
94. Tang W, Peng Q, Lyu Y, et al. Risk prediction models for lung cancer: Perspectives and dissemination. Chin J Cancer Res 2019;31:316-28.
95. Song M, Chen X, Wang L, et al. Future of anti-PD-1/PD-L1 applications: combinations with other therapeutic regimens. Chin J Cancer Res 2018; 30:157-72.

Cite this article as: Guo H, Li L, Cui J. Advances and challenges in immunotherapy of small cell lung cancer. Chin J Cancer Res 2020;32(1):115-128. doi: 10.21147/j.issn.1000-9604.2020.01.13

