Received: 29 April 2022 | Accepted: 29 June 2022

DOI: 10.1002/cai2.23

REVIEW

CANCER INNOVATION

Opportunities and challenges of immune checkpoint inhibitors for extensive-stage small-cell lung cancer

Jing Zhao[1,2] | **Xiaoli Zhuo**[1,2] | **Lei Liu**[1,2] | **Zhe Yang**[1,3] | **Guobin Fu**[1,3]

[1]The Department of Oncology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China

[2]The Department of Oncology, The College of Clinical Medicine, Shandong First Medical University (Shandong Academy of Medical Sciences), Jinan, China

[3]The Department of Oncology, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China

Correspondence
Zhe Yang and Guobin Fu, The Department of Oncology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan 250021, China.
Email: dslyyyz@sina.com and fgbs@sina.com

Funding information

Taishan Scholar Foundation of Shandong Province, Grant/Award Number: tsqn202103179; National Natural Science Foundation of China, Grant/Award Number: 81802284; Science and Technology Development Plans of Shandong Province, Grant/Award Number: 2014GSF118157; Scientific Research Foundation of Shandong Province of Outstanding Young Scientists, Grant/Award Number: BS2013YY058; 2021 Shandong Medical Association Clinical Research Fund, Grant/Award Number: YXH2022ZX02176

Abstract

Small-cell lung cancer (SCLC) accounts for 15%–20% of primary lung cancers, and it is characterized by low differentiation, rapid proliferation, and early metastasis. At least two-thirds of SCLC patients present with the extensive stage (ES) at the time of initial clinical diagnosis. Over the last 2 decades, platinum-based combination chemotherapy has remained the standard first-line treatment for SCLC. With the introduction of the immunotherapy era, immunotherapy plus chemotherapy has replaced conventional chemotherapy as the first-line treatment option for ES-SCLC and is recommended by National Comprehensive Cancer Network clinical guidelines. Therefore, in this review, we present the latest research advances in SCLC treatment, predictive biomarkers, and other topics of high interest to provide options for patients with SCLC.

KEYWORDS

small-cell lung cancer, immune checkpoint inhibitors, molecular typing, targeted therapy

Abbreviations: ADCs, antibody-drug conjugates; AE, adverse event; CAR, chimeric antigen receptor; CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte antigen-4; DLL3, delta-like protein 3; EP, etoposide plus platinum; ES-SCLC, extensive-stage small-cell lung cancer; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitors; LDH, lactate dehydrogenase; NCCN, National Comprehensive Cancer Network; ORR, objective response rate; OS, overall survival; PD-1, programmed death molecule-1; PD-L1, programmed death molecule ligand-1; PFS, progression-free survival; SCLC, small-cell lung cancer; TMB, tumor mutational burden.

Jing Zhao and Xiaoli Zhuo contributed equally to this study.

1 | BACKGROUND

Lung cancer is the malignant tumor with the highest morbidity and mortality worldwide [1]. Small-cell lung cancer (SCLC), a neuroendocrine tumor, is a subtype of lung cancer that accounts for 15%–20% of lung cancers and has a large biological phenotypic difference compared with non-small-cell lung cancer (NSCLC) [2]. Approximately two-thirds of patients are diagnosed with extensive-stage small-cell lung cancer (ES-SCLC), which presents as lesions that extend beyond one side of the chest at the time of diagnosis and exhibits distinct clinicopathological characteristics, such as low differentiation, rapid proliferation, and early metastasis [3]. Although the first-line objective response rate (ORR) of patients treated with etoposide plus platinum (EP) chemotherapy can be as high as 70%, short-term recurrence due to drug resistance has become a research bottleneck in the treatment of SCLC [4, 5]. Immunotherapy with immune checkpoint inhibitors (ICIs) has achieved significant clinical benefit in the treatment of various solid tumors in recent years, including SCLC, replacing the platinum-based first-line chemotherapy regimen used for nearly 2 decades in ES-SCLC. The National Comprehensive Cancer Network (NCCN) has approved EP with simultaneous or sequential atezolizumab/durvalumab as the current first-line treatment for ES-SCLC following results from the IMpower133 and CASPIAN trials [4]. In addition to ICIs, various antigen-specific immunotherapies, including chimeric antigen receptor (CAR)-T cells, tumor vaccines, antibody-drug conjugates (ADCs), and immunomodulators, are anticipated to offer new hope for patients with SCLC.

Immunotherapy involves artificially enhancing or suppressing the immune function of the body in patients with low or hyperactive immune function. The main approaches to immunotherapy are ICIs, including anti-programmed death molecule-1 (PD-1)/programmed death molecule ligand-1 (PD-L1) antibodies, immunomodulators targeting T cells, pericyte therapy, and bispecific antibodies [6]. Immunotherapy has provided the first great breakthrough in 2 decades in the treatment of ES-SCLC and has become the main research direction for SCLC treatment. ICIs function by regulating the interaction between immune cells and tumor cells, thereby inhibiting tumor cell growth and proliferation. The main ICIs currently available are PD-1/PD-L1 inhibitors and cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors. Researchers have conducted a series of clinical trials to improve patient treatment efficacy. Accordingly, the opportunities and challenges related to the treatment of ES-SCLC patients in recent years are reviewed below.

2 | ICI MONOTHERAPY FOR ES-SCLC

2.1 | Success of ICI monotherapy in backline therapy

Nivolumab is a fully human monoclonal immunoglobulin G4 anti-PD-1 antibody that has been approved for the treatment of a variety of cancers, including ES-SCLC. CheckMate032 [7] is a trial evaluating the effectiveness and safety of nivolumab in patients with SCLC or other solid tumors who have progressed after ≥1 line of platinum-based chemotherapies. A total of 147 eligible patients were included, the ORR was 11.6%, the progression-free survival (PFS) was 1.4 months, and the median overall survival (OS) was 5.7 months. Keeping et al. [8] conducted a meta-analysis in association with this study, analyzing the effectiveness of nivolumab versus the standard of care in ≥3 lines of treatment for SCLC. They concluded that in CheckMate032, the median OS for SCLC patients receiving nivolumab monotherapy was 5.7 months (95% confidence interval [CI]: 3.5–8.0), with a 1-year OS estimate of 28%. The median OS for patients in the Flatiron cohort was 3.8 months (95% CI: 2.8–4.9), with an estimated 1-year OS of 4%. The unadjusted comparison showed that nivolumab monotherapy provided durable responses and was well tolerated as a ≥first-line treatment for recurrent SCLC. These findings indicate that nivolumab monotherapy may be a viable ≥first-line therapeutic option for these patients. The researchers conducted a subgroup analysis of the results to further identify patients who benefit from ICIs. Unlike in NSCLC and malignant melanoma, the level of PD-L1 expression was not a prognostic predictor for ICI efficacy in SCLC. Subgroup analysis of tumor mutational burden (TMB) revealed that patients with a high TMB had a 16.5% increase in the ORR compared with those with a low TMB, implying that determining the TMB may be a possible strategy to identify patients who will benefit from ICIs for the treatment of SCLC. The Food and Drug Administration (FDA) approved nivolumab for patients with SCLC who progressed after platinum-based chemotherapy and at least one other line of therapy based on the outcomes of CheckMate032 and other trials. However, these trials had some shortcomings. First, the study was not trial-controlled, and it was unclear whether patients benefited from the treatment compared with standard chemotherapy. Second, the trial enrolled ethnically homogeneous patients, and it was unknown whether there were differences in efficacy across patients of other races. Finally, the study did not analyze baseline metastases in the patients included, and its influence on efficacy is unclear.

To further investigate the effect of nivolumab on the efficacy of SCLC treatment, the researchers performed a similar trial, CheckMate331 [9]. They randomly assigned patients who relapsed following first-line platinum-based chemotherapy to receive nivolumab 240 mg every 2 weeks or chemotherapy (chemotherapy agents: topotecan or amrubicin) until disease progression or unacceptable toxicity. The primary endpoint was OS. In the nivolumab treatment arm versus chemotherapy arm, the ORR was 13.7% versus 16.5%, the median PFS was 1.4 versus 3.8 months, and the median OS was 7.5 versus 8.4 months, respectively. Those who were platinum-resistant to first-line therapy benefited more from immunotherapy, whereas those with high-lactate dehydrogenase (LDH) levels and baseline liver metastases benefited less. The reason for this may be that LDH is a marker of tumor load, and elevated LDH levels can impair the effectiveness of ICIs via different mechanisms, such as altered nutrient metabolism and tumor immunity. Moreover, the liver's microenvironment of relative immune tolerance may limit the effectiveness of immune checkpoints in patients with liver metastases, thereby impairing immunotherapy efficacy [10, 11]. As a result, the investigators postulated that both LDH levels and liver metastases may be used to predict immunotherapy efficacy in SCLC [12, 13]. The former occurs likely because the onset of platinum resistance in SCLC is associated with a switch to the I molecular subtype, whereas SCLC-I may benefit more from treatment with ICIs. As with CheckMate032, patients with high PD-L1 expression in this study's subgroup analysis did not obtain more clinical benefit after immunotherapy, implying that PD-L1 expression levels in SCLC tumor tissue are not a reliable predictor of immunotherapy efficacy.

Pembrolizumab, a PD-1 monoclonal antibody, has demonstrated beneficial biological activity and significantly prolonged PFS in patients with ES-SCLC who progressed after platinum-based chemotherapy and at least one other line of therapy. The KEYNOTE-028 and KEYNOTE-158 [14] studies evaluated the effectiveness and safety of pembrolizumab in patients with recurrent or metastatic SCLC after ≥2 lines of therapy. The ORR was 19.3%, PFS was 2.0 months, and OS was 7.7 months. Pembrolizumab demonstrated therapeutic benefit in patients with ES-SCLC who received ≥2 lines of therapy, regardless of the patient's PD-L1 expression level. Pembrolizumab was also approved for third-line therapy in SCLC by the FDA and NCCN in 2019 based on the results of the KEYNOTE-028 and KEYNOTE-158 trials. Subsequently, a series of studies, such as KEYNOTE-604 investigating pembrolizumab or placebo plus chemotherapy as first-line treatment for ES-SCLC, were conducted.

2.2 | Failure of ICI monotherapy in first-line therapy

Researchers have investigated the efficacy and safety of ICIs in the first-line treatment of ES-SCLC on the basis of a number of post-line treatments. CheckMate451 [15] evaluated the efficacy and safety of nivolumab monotherapy as a maintenance treatment option after first-line chemotherapy for ES-SCLC. The primary study endpoint was OS. The results of the study showed that the ORR in the nivolumab monotherapy group versus placebo group was 11.5% versus 4.2%, the median PFS was 1.9 versus 1.4 months, and the median OS was 10.4 versus 9.6 months, respectively. After first-line standard chemotherapy, nivolumab monotherapy did not significantly prolong OS compared with placebo. As a result of the CheckMate331 and CheckMate451 trials, the FDA withdrew nivolumab in the treatment of ES-SCLC for this indication; the NCCN still recommends it as one of the optional strategies. However, an analysis of the results found that nivolumab improved PFS and ORR in patients with <5 weeks from last chemotherapy to nivolumab treatment and high TMB (≥13 mut/Mb) compared with the placebo and provided a persistent clinical benefit in patients treated effectively with ICIs. These results indicate that nivolumab may be an effective treatment for SCLC, particularly in patients who previously benefited significantly from ICI treatment. Difficulties in the therapeutic application of PD-1 inhibitors in ES-SCLC, such as achieving significant clinical benefit in second-line treatment but failing in first-line treatment, suggest that selecting the optimal timing of intervention for application in subsequent clinical treatment is essential. Therefore, in the treatment of ES-SCLC, the application of PD-1 agents should be analyzed individually, and for those who benefit from ICIs, the application in ≥2 lines can be considered. For those who do not benefit, the application of PD-L1 inhibitors or PD-1 inhibitors in combination with other drugs can be considered. Concurrently, the development of new PD-1 drugs should be accelerated. The discovery of novel PD-1 agents should be accelerated to enhance the efficacy of SCLC treatment and increase patient life expectancy.

On the basis of the above results, we summarized the initial exploration of the clinical use of ICIs in SCLC.

In the above study, there was a significant clinical benefit in ES-SCLC patients treated with PD-1 inhibitors in the backline, but there was only a clinical benefit in PFS and no statistical difference in OS between PD-1 inhibitors and placebo in maintenance therapy after first-line chemotherapy, indicating a new option for the treatment of SCLC. However, this trial had some limitations, such as the small number of patients and

generally similar trial protocol type. The influence on SCLC patients has to be validated by future investigations. The majority of the patients analyzed had relapsed following first-line therapy, and the study's impartiality and correctness need to be evaluated further. Moreover, the study discussed above focused on PD-1 inhibitors, and the efficacy of PD-L1 inhibitors in SCLC remains uncertain. As a result, future research should focus on the effect of different ICIs on SCLC efficacy, development of efficacy prediction biomarkers, and optimization of combination and dose regimens to extend the PFS benefit to the final OS benefit.

3 | ICI COMBINATION THERAPY IN ES-SCLC

3.1 | ICIs plus chemotherapy

As the treatment of malignant tumors continues to develop, researchers have discovered that the combined use of chemotherapy and ICIs can have a synergistic effect, and the specific mechanism may be connected to the following aspects. First, chemotherapeutic drugs can reduce tumor volume to a greater extent, thereby decreasing the production of immunosuppressive substances in tumor tissues and improving the killing ability of the autoimmune system against tumor cells. Simultaneously, the death of tumor cells releases a large amount of immunogenic substances, thereby further stimulating the function of the immune system [16, 17]. The increased number of myeloid-derived suppressor cells and regulatory T cells in patients with malignant tumors can have an immunosuppressive effect, while their sensitivity to chemotherapeutic treatments is significant. Chemotherapeutic medications reduce the number of myeloid-derived suppressor cells and regulatory T cells and improve patients' immunological function [18, 19]. In addition, it has been demonstrated that variations in intestinal flora affect the therapeutic efficacy of ICIs. Recent studies have also shown that chemotherapeutic drugs disrupt the normal functions of intestinal epithelial cells, thereby allowing bacteria and certain microorganisms to enter the sterile tissue of the intestinal epithelium; colonization by such microorganisms can have anticancer and immune-enhancing effects [20].

Reck et al. [21] conducted a phase III clinical study comparing ipilimumab plus EP versus placebo plus EP for the treatment of ES-SCLC. Ipilimumab, a completely human immunoglobulin G1 monoclonal antibody that inhibits the binding of the checkpoint protein CTLA-4 to its ligands, dramatically increased OS in a variety of tumor types. The primary outcome of the research was patient OS, with a median OS of 11.0 months for chemotherapy plus ipilimumab and 10.9 months for chemotherapy plus placebo. The chemotherapy plus ipilimumab group had a median PFS of 4.6 months compared with 4.4 months in the chemotherapy plus placebo group. In the safety analysis, most severe adverse events (AEs) were not significantly different between the two treatment groups, but the rates of diarrhea and colitis were significantly increased in the chemotherapy plus ipilimumab arm. Treatment-related AEs led to discontinuation in 18% of patients treated with chemotherapy plus ipilimumab and 2% of those treated with chemotherapy plus placebo. Chemotherapy plus ipilimumab versus chemotherapy plus placebo, the immune-related AEs with an incidence of ≥5% were diarrhea (25% versus 10%), rash (19% versus 3%), pruritus (12% versus 2%), colitis (6% versus 1%), and alopecia (5% versus 7%) [21]. The analysis of outcomes revealed an increased rate of discontinuation due to serious AEs in the chemotherapy plus ipilimumab arm; however, the overall incidence of immune-related AEs did not change significantly from the previous study, and the majority of AEs were manageable, indicating a good safety profile. The results of the trial indicated that the combination of ipilimumab and etoposide did not extend OS in patients with ES-SCLC. The researchers next examined more ICIs.

Atezolizumab is the first FDA-approved ICI for the first-line therapy of ES-SCLC. It is an anti-PD-L1 monoclonal antibody that binds to PD-L1 and inhibits its interaction with PD-1 and the B7.1 receptor [22, 23]. IMpower133 is a phase I/III randomized, double-blind clinical trial that demonstrated the efficacy of adding atezolizumab to first-line treatment in patients with ES-SCLC [24]. Patients were randomly assigned to one of two groups and received atezolizumab/placebo plus chemotherapy for four cycles, followed by maintenance treatment with atezolizumab/placebo alone until patients experienced unacceptable toxic effects, disease progression, or no additional clinical benefit. The findings indicated that the ORR was 60.2% in the atezolizumab plus chemotherapy group compared with 64.4% in the placebo plus chemotherapy group; the median PFS was 5.2 versus 4.3 months, and the median OS was 12.3 versus 10.3 months, respectively. In the atezolizumab plus chemotherapy arm, 20.2% of patients who developed immune-related AEs required treatment with glucocorticoids, while in the chemotherapy arm, 5.6% of patients with AEs needed treatment. The most common AEs were rash (20.2% versus 10.7%), hypothyroidism (12.6% versus 0.5%), hepatitis (7.6% versus 4.6%), and infusion-related reactions (5.6% versus 5.1%). Patients improved after atezolizumab plus chemotherapy

regardless of their PD-L1 or blood TMB levels, with a tolerable safety profile following treatment, confirming that atezolizumab plus chemotherapy can be used as a first-line therapeutic option for ES-SCLC. However, unlike the CheckMate032 study, patients with high blood TMB levels in IMpower133 did not demonstrate a discernible therapeutic benefit compared with those with low blood TMB levels. This may be because of inconsistencies in the specimens studied and the testing methodologies used; thus, the relationship between TMB and the efficacy of ICI therapy requires further validation. In IMpower133, treatment with atezolizumab in combination with chemotherapy failed to benefit patients with asymptomatic baseline brain metastases, revealing the inefficacy of ICIs in patients with SCLC who develop organ metastases, such as those to the brain or liver. However, because carboplatin was the only platinum-based medication used in this study, it is unknown whether additional platinum-based therapies will be as beneficial. Several of the study's weaknesses will be addressed in the next CASPIAN trials.

CASPIAN [25, 26] is a phase III clinical trial evaluating the efficacy and safety of durvalumab in ES-SCLC, another anti-PD-L1 monoclonal antibody [27]. This trial randomized previously untreated ES-SCLC patients and compared the differences of efficacy and safety following treatment with durvalumab plus chemotherapy versus chemotherapy. The findings indicated that the ORR was 74% in the durvalumab plus chemotherapy group versus 71% in the chemotherapy group; the median PFS was 5.1 versus 5.4 months, and the median OS was 12.9 versus 10.5 months. Similar rates of serious AEs were observed in the durvalumab plus chemotherapy arm compared with the chemotherapy arm alone, demonstrating an acceptable safety profile for therapeutic application. This implies that adding durvalumab to first-line treatment for ES-SCLC may significantly enhance patient outcomes. Moreover, the newest NCCN recommendations permitted the inclusion of atezolizumab or durvalumab in the standard first-line treatment arm for ES-SCLC based on the outcomes of the IMpower133 and CASPIAN trials. For platinum-based therapy combinations, CASPIAN is more clinically relevant than IMpower133. Additionally, subgroup analyses demonstrated that durvalumab combined with chemotherapy may confer significant therapeutic benefit for patients with baseline brain metastases and improved benefit for Asian patients.

To further research the use of pembrolizumab in SCLC, the KEYNOTE-604 study of pembrolizumab or placebo plus chemotherapy as first-line treatment for ES-SCLC was conducted on the basis of KEYNOTE-028 and KEYNOTE-158. The KEYNOTE-604 [28] results concluded that the ORR in the pembrolizumab plus chemotherapy group compared with the placebo plus chemotherapy group was 70.6% versus 61.8%; the median PFS was 4.5 versus 4.3 months, and the median OS was 10.8 versus 9.7 months. In the pembrolizumab plus EP and placebo plus EP groups, any-cause AEs were Grade 3–4 in 76.7% and 74.9%, Grade 5 in 6.3% and 5.4%, and led to the discontinuation of any drug in 14.8% and 6.3%, respectively. Analysis of the results showed a statistically significant improvement in PFS in the pembrolizumab plus chemotherapy group with no unanticipated treatment-related AEs, but no statistically significant benefit in patient OS. Accordingly, it is speculated that this may be related to the inclusion of a higher proportion of patients with baseline metastases and high LDH expression in the KEYNOTE-604 study, further confirming that the above factors may be associated with the poor prognosis of patients on immunotherapy. On the basis of the KEYNOTE-604 results, the FDA withdrew pembrolizumab for the indication of ≥3 lines of SCLC treatment (Table 1).

We summarized the data from the current clinical studies of ICIs for the treatment of major SCLC (Table 2).

Drug resistance has become an inevitable problem in the follow-up of immunotherapy-treated SCLC patients, and the rechallenge of immunotherapy is now a viable option for disease progression after ICIs. In a study by Giaj Levra et al. [29] on the “rechallenge” of nivolumab following treatment resistance in NSCLC, some patients benefited from ICIs despite a significant decrease in the ORR relative to the initial dose. In addition, there are a number of considerations to consider when rechallenging after ICI resistance, such as the need for intercalation before rechallenge, choice of drug for rechallenge, and influence of initial therapy on rechallenge expectations. The influence of initial therapy on re-treatment anticipation must be investigated further. Immunotherapy rechallenge is a potential option for patients with ES-SCLC who have progressed on ICIs, but only if sufficient data exist to justify a tailored treatment strategy for each patient.

3.2 | ICIs plus targeted therapy

In the treatment of NSCLC, several studies have demonstrated that the combination of ICIs and targeted therapies improves therapeutic efficacy without increasing safety risks and provides a greater clinical benefit for patients. Numerous preclinical and clinical investigations have demonstrated a synergistic impact of ICIs and targeted antiangiogenic treatments. On the one hand,

TABLE 1 ICI monotherapy in ES-SCLC

Trial name	CheckMate032	KEYNOTE-028 and KEYNOTE-158	CheckMate331		CheckMate451	
			EG	CG	EG	CG
Lines	≥3	≥2	2		1	
Arm	Nivolumab	Pembrolizumab	Nivolumab	Chemotherapy	Nivolumab	Placebo
Number	147	83	284	285	280	275
ORR (%)	11.6	19.3	13.7	16.5	11.5	4.2
PFS (m)	1.4	2.0	1.4	3.8	1.9	1.4
HR	–	–	1.41		0.67	
OS (m)	5.7	7.7	7.5	8.4	10.4	9.6
HR	–	–	0.86		0.84	
p	–	–	0.110		–	

Note: The series of studies conducted to date in ES-SCLC, and several PD-1 agents have shown potential antitumor activity in the backline treatment of ES-SCLC, with varying degrees of prolongation of PFS and OS in ES-SCLC.

Abbreviations: CG, control group; EG, experimental group; ES-SCLC, extensive-stage small-cell lung cancer; HR, hazard ratio; ICI, immune checkpoint inhibitor; ORR, objective response rate; OS, overall survival; PD-1, programmed death molecule-1; PFS, progression-free survival.

TABLE 2 ICIs plus chemotherapy in ES-SCLC

Trial name	Martin reck		IMpower133		CASPIAN		KEYNOTE-604	
	EG	CG	EG	CG	EG	CG	EG	CG
Lines	1		1		1		1	
Arm	Ipilimumab	Placebo	Atezolizumab	Placebo	Durvalumab	Placebo	Pembrolizumab	Placebo
Number	478	476	201	202	268	269	228	225
ORR (%)	62	62	60.2	64.4	74	71	70.6	61.8
PFS (m)	4.6	4.4	5.2	4.3	5.1	5.4	4.5	4.3
HR	0.85		0.77		0.80		0.73	
p	0.0161		–		–		0.0023	
OS (m)	11	10.9	12.3	10.3	12.9	10.5	10.8	9.7
HR	0.94		0.70		0.75		0.80	
p	0.378		0.015		0.003		0.016	

Note: Results of studies on PD-1 versus PD-L1 immune checkpoint inhibitors in the first-line treatment of ES-SCLC, in which the regimen of atezolizumab in combination with CE extended patients' PFS by 0.9 months and OS by 2.0 months, thus opening a new era of SCLC treatment. The regimen of durvalumab in combination with EP extended patients OS by 2.4 months, further extending patients' survival time.

Abbreviations: CE, carboplatin plus etoposide; CG, control group; EG, experimental group; EP, etoposide plus platinum; ES-SCLC, extensive-stage small-cell lung cancer; HR, hazard ratio; ICI, immune checkpoint inhibitor; ORR, objective response rate; OS, overall survival; PD-1, programmed death molecule-1; PD-L1, programmed death molecule ligand-1; PFS, progression-free survival.

antiangiogenic agents suppress inhibitory immune signaling by increasing the ratio of antitumor immune cells and decreasing the expression of various immunological checkpoints [30]. On the other hand, ICI therapy restores the immune-supportive microenvironment and normalizes the vascular system, facilitating medication delivery [31]. The PASSION [32] study enrolled 59 patients with ES-SCLC who were treated with apatinib plus camrelizumab and achieved an ORR of 34.0%, a median PFS of 3.6 months, and a median OS of 8.4 months. Apatinib plus camrelizumab demonstrated potential antitumor activity in chemotherapy-sensitive and chemotherapy-resistant ES-SCLC patients without causing additional treatment-related side effects, providing optimism for the future treatment of SCLC. However, the combination of immunotherapy and antiangiogenic agents in the treatment of SCLC is still in the exploratory stage, with multiple studies underway in China, and there is an

urgent need to address the issue of further optimizing the regimen and selecting the optimal treatment dose, sequence, and timing.

4 | OTHER IMMUNOTHERAPY APPROACHES IN SCLC THERAPY

Owing to the significant progress in the treatment of ICIs, such as anti-PD-1 antibodies, researchers have investigated additional immunotherapies, including CAR-T cells, tumor vaccines, ADCs, and immunomodulators. Various cell surface molecules, such as CD56, delta-like protein 3 (DLL3), and CD47, are highly expressed in SCLC and may be targeted with CAR-T cell therapy. Drugs targeting related proteins, such as DLL-3, are expected to provide new hope for patients with SCLC. DLL-3 is expressed in 87% of SCLC and is related to the expression of ASH-1, a critical component in the formation of SCLC that is expressed at low levels in normal tissues [33]. On the basis of a previous phase III clinical trial of the ADC Rova-T targeting DLL-3 antibodies by Blackhall et al. [34], which was discontinued due to a shorter OS than that for conventional chemotherapy and a high risk of AEs. Giffin et al. [33] conducted a study of the bispecific T-cell activator AMG757 targeting DLL-3 in an SCLC preclinical model, demonstrating antitumor activity. AMG757 activates T cells, instructs them to lyse tumor cells, and greatly accelerates tumor regression in mice with patient-derived xenografts of SCLC [33, 35]. Chen et al. [36] produced DLL-3-targeted bispecific antibodies and CAR-modified T cells for in vitro and in vivo tests of tumor cell growth inhibition with/without a PD-L1 antibody. The results indicated that the bispecific antibody targeting DLL-3 and CAR-T cells exhibited significant antitumor activity both in vitro and in vivo, and the bispecific antibody targeting DLL-3 in combination with the PD-L1 antibody exhibited synergistic action. From a pharmacological standpoint, ADCs targeting DLL-3 have the potential to become significant agents in the treatment of SCLC, and they are already widely applied in the treatment of other types of solid tumors [36]. To further optimize treatment efficacy and prognosis in patients with SCLC, confirming the combination of ADC medications with tyrosine kinase inhibitors and ICIs on the basis of further optimizing ADC drug structure is required. Additionally, diverse immunological agents are currently being explored clinically in China for the treatment of SCLC, and we anticipate that they may provide new therapeutic breakthroughs.

5 | PREDICTIVE BIOMARKERS FOR THE EFFICACY OF ICIS IN SCLC

5.1 | Programmed death molecule ligand-1

PD-L1 is a tumor cell surface molecule widely used in the clinical setting as a predictive marker for the efficacy of ICIs in a variety of solid tumors, and with the widespread use of ICIs in patients with ES-SCLC, its predictive value in SCLC has been investigated. Sun et al. [37] analyzed the surgical tissues of 102 SCLC patients after immunohistochemistry and concluded that PD-L1 expression levels were low in the tumor tissues of SCLC, and the level of PD-L1 expression in the tumor tissues of SCLC patients was not significantly correlated with the efficacy of immunotherapy in the Impower133, KEYNOTE-604, and CASPIAN studies. Therefore, PD-L1 expression levels cannot be used as a predictive marker for the efficacy of ICIs in SCLC patients.

5.2 | Tumor mutational burden

SCLC is a tumor with extensive gene loss and mutations and is characterized by a high TMB. In the CheckMate032 study, investigators divided patients into three groups according to differences in TMB levels: low, medium, and high. The results showed that the ORR, PFS, and OS were significantly increased in the high TMB group compared with those in the low TMB group. However, in the Impower133 study, patients were grouped according to their blood TMB levels to investigate its effect on the efficacy of ICIs, and the results showed no correlation between blood TMB levels and the efficacy of ICIs in SCLC patients. Therefore, further research on TMB as a predictive marker for the efficacy of immunotherapy in SCLC is needed.

In addition to PD-L1 and TMB, which are currently widely used, clinical studies of SCLC have also found that patient baseline metastases, Eastern Cooperative Oncology Group scores, and LDH levels affect the efficacy of ICIs and that it is difficult to obtain tissue from SCLC patients.

6 | CHALLENGES IN ICI THERAPY AND MOLECULAR TYPING IN SCLC

6.1 | Challenges in ICI therapy in SCLC

Both PD-1 checkpoint inhibitors were rapidly approved for clinical use in SCLC based on their efficacy in

relapsed-progressive ES-SCLC backline treatment studies, but neither PD-1 inhibitor met the expected study endpoints in subsequent first-line exploration. In contrast, atezolizumab and durvalumab, two PD-L1 inhibitors in ES-SCLC, have excelled in the first-line treatment of ES-SCLC. Increasing the median OS after SCLC treatment has achieved some milestones, providing patients with a chance of long-term survival, but in comparison with other types of lung cancer and the majority of solid tumors, the duration of PFS following disease remission in SCLC patients is brief, with a median OS improvement of only 2 months following first-line chemotherapy plus immunotherapy, which was significantly less than clinical expectations. Various clinical trials evaluating numerous PD-1 inhibitors have failed, and PD-L1 inhibitors have been shown to be clinically ineffective in a subgroup of patients with baseline liver metastases and elevated LDH expression. ICIs, such as PD-L1 agents, are only useful in the first-line therapy of ES-SCLC patients, and there is no standardized and effective treatment for patients with unresectable LS-SCLC who have relapsed or advanced following first-line treatment. These are the critical clinical concerns that remain to be addressed in the treatment of SCLC, resulting in a bottleneck in current clinical research on SCLC, and further investigation of how to increase the efficacy of SCLC treatment will be the primary focus of future research. Additionally, researchers have been actively investigating the possibility of adapting combination therapy regimens, providing induction chemotherapy, expediting the development of potential new drugs, and precisely defining the molecular typing of SCLC to select immune-preferred treatment patients.

6.2 | Molecular typing of SCLC

Therapeutic research on SCLC has several limitations, with few clinical benefits for patients and poor PFS and OS improvement. With the introduction of the era of precision treatment, accurate molecular typing of SCLC to identify patients who will benefit from ICIs may become a critical component of tailored ES-SCLC treatment.

Rudin et al. [38] classified SCLC into four subtypes, SCLC-A, SCLC-N, SCLC-Y, and SCLC-P, according to pathologic tissue data on the expression levels of *ASCL1, NEUROD1, YAP1*, and *POU2F3* genes in SCLC patients and mouse models. Gay et al. [39] performed another statistical analysis of RNA-sequencing data from 81 SCLC patients previously published by Skoulidis et al. [40] and defined four subtypes, SCLC-A, SCLC-N, SCLC-P, and SCLC-I, according to their tissue *ASCL1, NEUROD1*, and *POU2F3* gene expression levels. A subgroup analysis of patients in the IMpower133 trial found that patients with SCLC-I achieved a median OS of 18.2 months, significantly longer than that for patients with other subtypes who benefited from treatment with ICIs. Analysis showed that SCLC-I lacked expression of the three genes mentioned above and displayed strong epithelial-to-mesenchymal transition and immune cell infiltration, resulting in increased tumor antigen presentation, which may also explain why it is the most sensitive subtype to treatment with ICIs.

6.3 | Opportunities for China-Made PD-1 antibodies

Most foreign PD-1 antibody studies have been discontinued owing to the lack of clinical benefit from first-line treatment with atezolizumab and durvalumab in combination with chemotherapy for ES-SCLC. However, the application of ICIs in combination with chemotherapy in the treatment of SCLC is currently being studied in China, and certain clinical results from China regarding PD-1 antibody treatment provide new hope for the treatment of SCLC. BGB-A317-312, a phase II clinical study evaluating the efficacy and safety of tislelizumab plus chemotherapy in the first-line treatment of SCLC, demonstrated positive clinical benefits with an ORR of 67%, median PFS of 6.9 months, and median OS of 15.6 months in SCLC patients [41]. Along with the JS001-0280-III-SCLC, SHR-1316-III-301, and HLX10-005-SCLC301 studies, we anticipate that Chinese ICIs combined with chemotherapy will yield favorable results in the near future, greatly improving the therapeutic options for SCLC patients.

7 | CONCLUSION

The results of IMpower133 and CASPIAN have altered the first-line chemotherapy regimen for ES-SCLC. Targeted therapy for improved treatment results is being driven by the refinement of SCLC molecular types, optimization of therapeutic regimens, and development of innovative medicines. Although the first-line treatment of ES-SCLC has achieved success, several issues remain, including how to select the most effective therapeutic drugs for each patient, how to identify patients who benefit more from immunotherapy, how to improve immunotherapy efficacy in ES-SCLC patients, whether immunotherapy plays a role in relapsed refractory SCLC, and the active exploration of additional

immunotherapy methods in clinical application. We anticipate that additional research into efficacy-predicting biomarkers based on accurate molecular types and ultimately personalized diagnostic and therapy regimens for SCLC patients will instill new hope in patients. SCLC therapy still faces several challenges that need to be addressed in the future, but we believe that with the progress of modern medicine, researchers will be able to solve them.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Jing Zhao, Xiaoli Zhuo, and Lei Liu analyzed data and edited the manuscript. Zhe Yang and Guobin Fu made substantial contributions to the study design and revision of the manuscript. All authors critically reviewed the manuscript, and all approved the final version submitted for publication.

ACKNOWLEDGMENTS

We sincerely thank Jingjiang Lai, Fengxian Jiang, Jingliang Wang, and Wei Xu for their help in data collection and manuscript editing.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest except Professor Guobin Fu, who is member of *Cancer Innovation* Editorial Board. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this study for publication.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding authors upon request.

ETHICS STATEMENT

The studies collected for this review were obtained from public repositories through legal means, and the studies cited were ethically reviewed and do not violate any ethical principles.

INFORMED CONSENT

Not applicable.

ORCID

Jing Zhao http://orcid.org/0000-0002-1883-6661
Guobin Fu http://orcid.org/0000-0003-0893-7714

REFERENCES

1. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115–32. https://doi.org/10.3322/caac.21338
2. Torre LA, Siegel RL, Jemal A. Lung cancer statistics. Adv Exp Med Biol. 2016;893:1–19. https://doi.org/10.1007/978-3-319-24223-1_1
3. Byers LA, Rudin CM. Small cell lung cancer: where do we go from here? Cancer. 2015;121(5):664–72. https://doi.org/10.1002/cncr.29098
4. Ganti AKP, Loo BW, Bassetti M, Blakely C, Chiang A, D'Amico TA, et al. Small cell lung cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2021;19(12):1441–64. https://doi.org/10.6004/jnccn.2021.0058
5. Kalemkerian GP, Schneider BJ. Advances in small cell lung cancer. Hematol Oncol Clin North Am. 2017;31(1):143–56. https://doi.org/10.1016/j.hoc.2016.08.005
6. Steven A, Fisher SA, Robinson BW. Immunotherapy for lung cancer. Respirology. 2016;21(5):821–33. https://doi.org/10.1111/resp.12789
7. Ready NE, Ott PA, Hellmann MD, Zugazagoitia J, Hann CL, de Braud F, et al. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: results from the Checkmate 032 randomized cohort. J Thorac Oncol. 2020;15(3):426–35. https://doi.org/10.1016/j.jtho.2019.10.004
8. Keeping ST, Cope S, Chan K, Wilson FR, Jansen JP, Penrod JR, et al. Comparative effectiveness of nivolumab versus standard of care for third-line patients with small-cell lung cancer. J Comp Eff Res. 2020;9(18):1275–84. https://doi.org/10.2217/cer-2020-0134
9. Spigel DR, Vicente D, Ciuleanu TE, Gettinger S, Peters S, Horn L, et al. Second-line nivolumab in relapsed small-cell lung cancer: Checkmate 331☆. Ann Oncol. 2021;32(5):631–41. https://doi.org/10.1016/j.annonc.2021.01.071
10. Warner AB, Postow MA. Bigger is not always better: tumor size and prognosis in advanced melanoma. Clin Cancer Res. 2018;24(20):4915–17. https://doi.org/10.1158/1078-0432.Ccr-18-1311
11. Botticelli A, Salati M, Di Pietro FR, Strigari L, Cerbelli B, Zizzari IG, et al. A nomogram to predict survival in non-small cell lung cancer patients treated with nivolumab. J Transl Med. 2019;17(1):99. https://doi.org/10.1186/s12967-019-1847-x
12. Hermes A, Gatzemeier U, Waschki B, Reck M. Lactate dehydrogenase as prognostic factor in limited and extensive disease stage small cell lung cancer—a retrospective single institution analysis. Respir Med. 2010;104(12):1937–42. https://doi.org/10.1016/j.rmed.2010.07.013
13. Nakazawa K, Kurishima K, Tamura T, Kagohashi K, Ishikawa H, Satoh H, et al. Specific organ metastases and survival in small cell lung cancer. Oncol Lett. 2012;4(4):617–20. https://doi.org/10.3892/ol.2012.792
14. Chung HC, Piha-Paul SA, Lopez-Martin J, Schellens J, Kao S, Miller WH Jr, et al. Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: results from the KEYNOTE-028 and KEYNOTE-158 studies. J Thorac Oncol. 2020;15(4):618–27. https://doi.org/10.1016/j.jtho.2019.12.109
15. Owonikoko TK, Park K, Govindan R, Ready N, Reck M, Peter S, et al. Nivolumab and ipilimumab as maintenance therapy in extensive-disease small-cell lung cancer: checkmate 451. J Clin Oncol. 2021;39(12):1349–59. https://doi.org/10.1200/jco.20.02212

16. Rabinovich GA, Gabrilovich D, Sotomayor EM. Immunosuppressive strategies that are mediated by tumor cells. Annu Rev Immunol. 2007;25:267–96. https://doi.org/10.1146/annurev.immunol.25.022106.141609
17. Russ AJ, Wentworth L, Xu K, Rakhmilevich A, Seroogy CM, Sondel PM, et al. Suppression of T-cell expansion by melanoma is exerted on resting cells. Ann Surg Oncol. 2011;18(13):3848–57. https://doi.org/10.1245/s10434-011-1667-6
18. Welters MJ, van der Sluis TC, van Meir H, Loof NM, van Ham VJ, van Duikeren S, et al. Vaccination during myeloid cell depletion by cancer chemotherapy fosters robust T cell responses. Sci Transl Med. 2016;8(334):334ra352. https://doi.org/10.1126/scitranslmed.aad8307
19. Melief CJM, Welters MJP, Vergote I, Kroep JR, Kenter GG, Ottevanger PB, et al. Strong vaccine responses during chemotherapy are associated with prolonged cancer survival. Sci Transl Med. 2020;12(535):eaaz8235. https://doi.org/10.1126/scitranslmed.aaz8235
20. Salas-Benito D, Pérez-Gracia JL, Ponz-Sarvisé M, Rodriguez-Ruiz ME, Martínez-Forero I, Castañón E, et al. Paradigms on immunotherapy combinations with chemotherapy. Cancer Discov. 2021;11(6):1353–67. https://doi.org/10.1158/2159-8290.Cd-20-1312
21. Reck M, Luft A, Szczesna A, Havel L, Kim S-W, Akerley W, 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(31):3740–48. https://doi.org/10.1200/jco.2016.67.6601
22. Blair HA. Atezolizumab: a review in previously treated advanced non-small cell lung cancer. Target Oncol. 2018;13(3):399–407. https://doi.org/10.1007/s11523-018-0570-5
23. Ishii H, Azuma K, Kawahara A, Kinoshita T, Kage M, Hoshino T, 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(3):426–30. https://doi.org/10.1097/jto.0000000000000414
24. Liu SV, Reck M, Mansfield AS, Mok T, Scherpereel A, Reinmuth N, et al. Updated overall survival and pd-l1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (impower133). J Clin Oncol. 2021;39(6):619–30. https://doi.org/10.1200/jco.20.01055
25. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, 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(10212):1929–39. https://doi.org/10.1016/s0140-6736(19)32222-6
26. Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2021;22(1):51–65. https://doi.org/10.1016/s1470-2045(20)30539-8
27. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med. 2017;377(20):1919–29. https://doi.org/10.1056/NEJMoa1709937
28. Rudin CM, Awad MM, Navarro A, Gottfried M, Peters S, Csőszi T, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. J Clin Oncol. 2020;38(21):2369–79. https://doi.org/10.1200/jco.20.00793
29. Giaj Levra M, Cotté FE, Corre R, Calvet C, Gaudin AF, Penrod JR, et al. Immunotherapy rechallenge after nivolumab treatment in advanced non-small cell lung cancer in the real-world setting: a national data base analysis. Lung Cancer. 2020;140:99–106. https://doi.org/10.1016/j.lungcan.2019.12.017
30. Lupo G, Caporarello N, Olivieri M, Cristaldi M, Motta C, Bramanti V, et al. Anti-angiogenic therapy in cancer: downsides and new pivots for precision medicine. Front Pharmacol. 2016;7:519. https://doi.org/10.3389/fphar.2016.00519
31. Huang Y, Kim BYS, Chan CK, Hahn SM, Weissman IL, Jiang W. Improving immune-vascular crosstalk for cancer immunotherapy. Nat Rev Immunol. 2018;18(3):195–203. https://doi.org/10.1038/nri.2017.145
32. Fan Y, Zhao J, Wang Q, Huang D, Li X, Chen J, et al. Camrelizumab plus apatinib in extensive-stage SCLC (PASSION): a multicenter, two-stage, phase 2 trial. J Thorac Oncol. 2021;16(2):299–309. https://doi.org/10.1016/j.jtho.2020.10.002
33. Giffin MJ, Cooke K, Lobenhofer EK, Estrada J, Zhan J, Deegen P, et al. AMG 757, a half-life extended, DLL3-targeted bispecific t-cell engager, shows high potency and sensitivity in preclinical models of small-cell lung cancer. Clin Cancer Res. 2021;27(5):1526–37. https://doi.org/10.1158/1078-0432.CCR-20-2845
34. Blackhall F, Jao K, Greillier L, Cho BC, Penkov K, Reguart N, et al. Efficacy and safety of rovalpituzumab tesirine compared with topotecan as second-line therapy in DLL3-high SCLC: results from the phase 3 TAHOE study. J Thorac Oncol. 2021;16(9):1547–58. https://doi.org/10.1016/j.jtho.2021.02.009
35. Taromi S, Firat E, Simonis A, Braun LM, Apostolova P, Elze M, et al. Enhanced AC133-specific Car T cell therapy induces durable remissions in mice with metastatic small cell lung cancer. Cancer Lett. 2021;520:385–99. https://doi.org/10.1016/j.canlet.2021.08.012
36. Chen X, Amar N, Zhu Y, Wang C, Xia C, Yang X, et al. Combined DLL3-targeted bispecific antibody with pd-1 inhibition is efficient to suppress small cell lung cancer growth. J Immunother Cancer. 2020;8(1):e000785. https://doi.org/10.1136/jitc-2020-000785
37. Sun C, Zhang L, Zhang W, Liu Y, Chen B, Zhao S, et al. Expression of PD-1 and PD-L1 on tumor-infiltrating lymphocytes predicts prognosis in patients with small-cell lung cancer. Onco Targets Ther. 2020;13:6475–83. https://doi.org/10.2147/ott.S252031
38. Rudin CM, Poirier JT, Byers LA, Dive C, Dowlati A, George J, et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. Nat Rev Cancer. 2019;19(5):289–97. https://doi.org/10.1038/s41568-019-0133-9
39. Gay CM, Stewart CA, Park EM, Diao L, Groves SM, Heeke S, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with

distinct therapeutic vulnerabilities. Cancer Cell. 2021;39(3):346–60. https://doi.org/10.1016/j.ccell.2020.12.014

40. Skoulidis F, Byers LA, Diao L, Papadimitrakopoulou VA, Tong P, Izzo J, et al. Co-occurring genomic alterations define major subsets of KRAS-mutant lung adenocarcinoma with distinct biology, immune profiles, and therapeutic vulnerabilities. Cancer Discovery. 2015;5(8):860–77. https://doi.org/10.1158/2159-8290.cd-14-1236
41. Wang Z, Zhao J, Ma Z, Cui J, Shu Y, Liu Z, et al. A phase 2 study of tislelizumab in combination with platinum-based chemotherapy as first-line treatment for advanced lung cancer in Chinese patients. Lung Cancer. 2020;147:259–68. https://doi.org/10.1016/j.lungcan.2020.06.007

How to cite this article: Zhao J, Zhuo X, Liu L, Yang Z, Fu G. Opportunities and challenges of immune checkpoint inhibitors for extensive-stage small-cell lung cancer. Cancer Innovation. 2022;1:183–193. https://doi.org/10.1002/cai2.23