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Review Article

Current status and future perspectives of immune checkpoint inhibitors in extensive-stage small cell lung cancer

Xingyu Liu[1*], Huifang Xing[2*], Baoxing Liu[1]

[1]*Department of Thoracic Surgery, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou 45008, P. R. China;* [2]*Department of Geriatric Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, P. R. China.* [*]*Equal contributors.*

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Abstract: Small-cell lung cancer (SCLC) is a type of neuroendocrine neoplasms with high aggressiveness and poor prognosis. Chemotherapy has been the standard first-line therapy for SCLC over the past several decades. In recent years, results of randomized phase III CASPIAN and IMpower-133 trials indicated that the combination of immune checkpoint inhibitors (ICIs) with platinum-etoposide chemotherapy improved the overall survival (OS) of patients with extensive stage small-cell lung cancer (ES-SCLC), which has transformed the treatment model for ES-SCLC. ICIs combined with chemotherapy has become the new first-line standard treatment of ES-SCLC with the latest research results from CASPIAN and ASTRUM-005 studies. This review summarizes the recent progress of ICIs in the treatment of ES-SCLC and expounds the mode and efficacy of immunotherapy for ES-SCLC. Future research focused on exploring basic SCLC biology and identifying novel predictive biomarkers in response to ICIs in ES-SCLC is essential. Double-ICIs treatment strategies, bispecific antibodies, and ICIs combined with other therapies, such as chemotherapy, radiotherapy, and targeted therapy, represent a new modality and show great promise for the treatment of ES-SCLC, which should achieve greater therapeutic effects through multiple synergistic mechanisms.

Keywords: Immune checkpoint inhibitors, extensive-stage small cell lung cancer, immunotherapy, combination therapy, chemotherapy

Introduction

Lung cancer is one of the most common malignant tumors as well as the most lethal malignancy [1]. Unlike non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) belongs to neuroendocrine neoplasms and exhibits rapid growth, high invasiveness, early regional and distant metastasis, and poor prognosis. SCLC accounts for around 10%-15% of all lung cancer cases and approximately 70% newly diagnosed cases are in the extensive stage when first confirmed, by which stage the disease has spread beyond one hemithorax and cannot be limited to one radiation field [2].

Over the past several decades, chemotherapy has been the most important therapeutic strategy for extensive-stage small cell lung cancer (ES-SCLC). Currently, etoposide combined with platinum remains the standard first-line therapy. On the one hand, cancer cells of SCLC patients are hypersensitive to chemotherapy and radiotherapy, yet patients often suffer rapid relapses and poor prognosis. The median overall survival (OS) of ES-SCLC patients is about 10 months, with 2-year survival rate at less than 5% and 5-year survival rate only 2% [3, 4].

In the last few years, the arrival of the immunotherapy era has brought about new ideas and innovations in treating SCLC. Clinical studies such as those of Impower133 and CASPIAN have made a significant breakthrough in first-line therapies of ES-SCLC [2, 5-7]. During the 2021 European Society for Medical Oncology (ESMO) Congress that took place from September 16 to 21, the phase 3 CASPIAN trial published its latest research results on the three-

year overall survival (OS) of ES-SCLC patients [7]. Compared with chemotherapy monotherapy, combination immuno-chemotherapy can improve one-year progression-free survival (PFS) and three-year OS by more than 3 times. Immuno-checkpoint inhibitors (ICIs) combined with chemotherapy drugs have become the new first-line standard of ES-SCLC. ICIs also exhibited some anti-tumor activity in third-line or follow-up treatment of patients with disease recurrence. This article summarizes the much-anticipated emerging ICI research results in the field of ES-SCLC treatment, and elaborates on the rationale and therapeutic strategy of immunotherapy.

Normally our immune system can identify new cancer cells via immune surveillance and attack and eliminate the tumor cells [8]. First, innate immune responses are activated, where natural killer cells recognize the antigens on the surface of cancer cells and deflake malignant cells to activate antigen-presenting cells (APCs) such as macrophages and dendritic cells [9]. Second, APCs can present the cancer cell ligand to B cells, and CD4+ or CD8+ T cells after absorbing, processing, and presenting lysed cells, and release the tumor necrosis factor (TNF) [10]. These effector cells would express antibody which can bind to the specific antigens on the surface of cancer cells to attack malignant cells [11, 12]. This dual signaling regulatory mechanism plays an important role in the activation of effector T cells. Positive co-stimulatory molecules, such as CD28/B7, can enhance effector T cell activation [13]. The CTLA4 or PD-1/PD-L1 signaling pathway components, which can help tumor cells escape attacks from immune cells, are negative molecules [14, 15]. Tumor cells may go dormant to maintain the balance between cancer cells and the immune system. Under persistent pressure from the immune system, a series of gene mutations may occur in cancer cells [16, 17]. The negative molecules and gene mutations will result in the immune escape of tumors.

SCLC is characterized by high tumor mutational load [18, 19], which was thought to enhance the activation of the immune system [20-22]. However, SCLC actually suppresses immune effects. Effector and regulatory T cells play an important role in specific anti-tumor immune response pathways. In particular, regulatory T cells help tumor cells escape the attack of effector cells by downregulating immune responses [23]. High levels of regulatory T cells were observed in the peripheral blood of ES-SCLC patients, but the level is low in long-term ES-SCLC survivors, which was thought to be a mechanism to downregulate anti-tumor immune responses [24, 25]. High levels of tumor-infilltrating lymphocytes (TILs) in the tumor microenvironment in SCLC patients are associated with better survival benefits, where paranormal T cells, CD8+ cells, and CD45+ T cells can be found in long-term SCLC survivors [26-28]. Decreased TILs and a lack of major histocompatibility complex (MHC) proteins might be a potential mechanism that helps SCLC cells escape being eliminated by the immune system [29, 30].

Currently, ICIs such as anti-CTLA-4 and anti-PD-(L) 1 are the most advantageous and widely used immuno-drugs and target programmed death-(L) 1 and cytotoxic T-lymphocyte associated protein 4 signaling pathways. ICIs combined with PD-(L) 1 or CTLA-4 could inhibit the negative co-stimulatory signals and activate effector T cells to restore anti-tumor immune responses [31, 32]. A list of clinical trials of immune checkpoint inhibitors are shown in **Tables 1-3**.

Anti-PD-L1 inhibitors

The two phase 3 clinical trials for IMpower133 and CASPIAN have pioneered the safety and efficacy of immunotherapy combined with chemotherapy as first-line treatment of ES-SCLC [2, 3, 5, 6].

The CASPIAN study

The phase 3 CASPIAN study updated its three-year overall survival in the 2021 ESMO congress in September [6]. As a global, randomized, open-label and multicenter clinical study, the CASPIAN trial recruited treatment-naïve ES-SCLC patients (n=805), with asymptomatic or treated and stable brain metastases permitted to be involved. Patients were divided into three groups to receive EP, durvalummab + EP (D+EP), and durvalummab + tremelimumab + EP (D+T+EP) respectively. Compared with EP monotherapy, the OS of the D+EP group leads by a vast margin. The median overall survival

Table 1. Summary of clinical trials about anti-PD-L1 in ES-SCLC

Trial	Phase	No. of Patients	Treatment	FDA Approval	OS	PFS	ORR (%)	AEs (%)
CASPIAN	III	537	Durvalumab + chemotherapy vs. chemotherapy	Yes	12.9 vs. 10.5 months (HR, 0.71; 95% CI: 0.60-0.86; P=0.0003)	5.1 vs. 5.4 months (HR, 0.78; 95% CI: 0.65-0.94; p=0.0003)	68 vs. 58	Serious AEs 32.5 vs. 36.5
IMpower133	III	403	Atezolizumab + chemotherapy vs. chemotherapy	Yes	12.3 vs. 10.3 months (HR, 0.70; 95% CI: 0.54-0.91; P=0.007)	5.2 vs. 4.3 months (HR, 0.77; 95% CI: 0.62-0.96; p=0.02)	60.2 vs. 64.4	Grade 3/4 AEs 56.6 vs. 56.1
IFCT-1603	II	73	Atezolizumab vs. chemotherapy	Yes	9.5 vs. 8.7 months (HR, 0.84; 95% CI: 0.45-1.58; P=0.60)	1.4 (95% CI: 1.2-1.5) vs. 4.3 (95% CI: 1.5-5.9)	2.3 (95% CI: 0.0-6.8)	Grade 3/4 AEs 4.2 vs. 75

OS: overall survival; PFS: progression-free survival; ORR: objective response rate; AEs: adverse events.

Table 2. Summary of clinical trials about anti-PD-1 in ES-SCLC

Trial	Phase	No. of Patients	Treatment	FDA Approval	OS	PFS	ORR (%)	AEs (%)
ASTRUM-005	III	585	Serplulimab + chemotherapy vs. chemotherapy	No	15.38 vs. 11.0 months (HR, 0.62; 95% CI, 0.48-0.80; p<0.001)	n.r.	n.r.	n.r.
KEYNOTE-604	III	453	Pembrolizumab + chemotherapy vs. chemotherapy	No	10.8 vs. 9.7 months (HR, 0.80; 95% CI, 0.64-0.98; p=0.0164)	4.5 vs. 4.3 months (HR 0.75, 95% CI 0.61-0.91, p=0.0023)	70.6 vs. 61.8	Grade 3/4 AEs 76.7 vs. 74.9
CheckMate-451	III	834	Nivolumab vs. Nivolumab plus Ipilimumab vs. Placebo	No	10.4 months (9.5 to 12.1) vs. 9.2 months (8.2 to 10.2) vs. 9.6 months (8.2 to 11.0)	1.9 months (1.6 to 2.6) vs. 1.7 months (1.5 to 2.6) vs. 1.4 months (1.4 to 1.5)	11.5 vs. 9.1 vs. 4.2	Grade 3/4 AEs 11.5 vs. 52.2 vs. 8.4
CheckMate-331	III	569	Nivolumab vs. Topotecan or amrubicin	No	7.5 months vs. 8.4 months (HR, 0.86; 95% CI, 0.72-1.04)	1.4 months (95% CI: 1.4-1.5) vs. 3.8 months (95% CI: 3.0-4.2)	13.7 vs. 16.5	Grade 3/4 AEs 13.8 vs. 73.2
PASSION	II	47	camrelizumab plus apatinib	No	8.4 months *(9.6 months vs. 8.0 months)	3.6 months *(3.6 months vs. 2.7 months)	34 (95% CI: 20.9-49.3) *(37.5% versus 32.3%)	Grade 3 or higher AEs 72.9
KEYNOTE 158	II	107	Pembrolizumab	No	9.1 months (95% CI, 5.7-14.6)	2 months (95% CI: 1.9-2.1)	18.7 (95% CI: 11.8-27.4)	Treatment-related AEs 59
A phase II study	II	45	Pembrolizumab	No	9.6 months (95% CI, 7.0-12.0)	1.4 months (95% CI: 1.3-2.8)	11.1 (95% CI: 4.8-23.5)	All grades AEs. 10 or higher
CheckMate-032	I/II	243	Nivolumab vs. Nivolumab + Ipilimumab	No	5.7 months (3.8-7.6) vs. 4.7 months (3.1-8.3)	1.4 months (1.3-1.4) vs. 1.5 months (1.4-2.2)	11.6 vs. 21.9	Grade 3/4 AEs 12.9 vs. 37.5
KEYNOTE 028	IB	24	Pembrolizumab	No	9.7 months (95% CI, 4.1-n.r.)	1.9 months (95% CI: 1.7-5.9)	33.3	Grade 3 or higher AEs 8.3

OS: overall survival; PFS: progression-free survival; ORR: objective response rate; AEs: adverse events; n.r.: not reported. *Chemotherapy-sensitive and chemotherapy-resistant patients.

Table 3. Summary of clinical trials about anti-CTLA-4 in ES-SCLC

Trial	Phase	No. of Patients	Treatment	FDA Approval	OS	PFS	ORR (%)	AEs (%)
CheckMate 451	III	834	Nivolumab plus Ipilimumab vs. Nivolumab vs. placebo	No	9.2 months vs. 9.6 months (HR, 0.92; 95% CI: 0.75-1.12; P=0.37)	1.7 months (1.5-2.6) vs. 1.9 months (1.6-2.6) vs. 1.4 months (1.4-1.5)	9.1 vs. 11.5 vs. 4.2	Grade 3/4 AEs 52.2 vs. 11.5 vs. 8.4
CASPIAN trial	III	537	Durvalumab + Tremelimumab + chemotherapy vs. chemotherapy	Yes	10.4 months vs. 10.5 months (HR, 0.81; 95% CI, 0.67-0.97; P=0.02)	16.9% (95% CI: 12.6-21.7) vs. 5.3% (95% CI: 2.9-8.8)	58 vs. 58	Serious AEs 47.4 vs. 36.5
CA184-156	III	1132	Ipilimumab + chemotherapy vs. chemotherapy	No	11 months vs. 10.9 months (HR 0.94; 95% CI: 0.81-1.09; P=0.3775)	4.6 months vs. 4.4 months (HR 0.85; 95% CI: 0.75-0.97; P=0.0161)	62 vs. 62	Grade 3/4 AEs 48 vs. 45
CheckMate-032	I/II	243	Nivolumab vs. Nivolumab + Ipilimumab	No	5.7 months (3.8-7.6) vs. 4.7 months (3.1-8.3)	1.4 months (1.3-1.4) vs. 1.5 months (1.4-2.2)	11.6 vs. 21.9	Grade 3/4 AEs 12.9 vs. 37.5

OS: overall survival; PFS: progression-free survival; ORR: objective responserate; AEs: adverse events.

(mOS) of the D+EP group was extended by two months (12.9 months vs. 10.5 months, HR, 0.71; 95% CI: 0.60-0.86; P=0.0003) [6]. The two-year OS rate of the D+EP group to EP group was 22.9% vs. 13.9% and the three-year OS rate of the D+EP group to the EP group was 17.6% vs. 5.8% [2, 6]. The significant long-term OS benefit of the D+EP group showed long survival-smearing of immunotherapy. However, patients of the D+T+EP did not acquire any improved mOS benefits (10.4 months vs. 10.5 months; HR, 0.81; 95% CI: 0.67-0.97; P=0.02).

In the CASPIAN study, the rate of serious adverse events (AEs) of the D+EP and EP group were 32.5% and 36.5% respectively, and the rates of AEs leading to death were 5.3% and 6.0% respectively. This significant phenomenon means that adverse events were not increased by durvalummab. On the one hand, the three-year OS of the D+EP group proved overwhelmingly advantageous and was more than three times compared with the EP group. On the other hand, 1, 1.5, and 2-year PFS were also superior than the EP group by more than 3 times. All these data confirm that durvalummab combined with chemotherapy has not only remarkable efficacy but also favorable safety, and its adverse events can be tolerated.

The IMpower133 study

Another similar phase III study on IMpower133 also recruited 403 treatment-naïve ES-SCLC patients. The patients were divided into 2 groups who received EP or atezolizumab (an anti-PD-L1 inhibitor)+EP [5]. The major endpoints OS and PFS evaluated. Results showed that the mOS of patients who received atezolizumab+EP (A+EP) was two months longer than patients who received EP (12.3 months vs. 10.3 months, HR, 0.70; 95% CI: 0.54-0.91; P=0.0096), and the median PFS of patients who received A+EP was one month longer than patients who received EP (5.2 months vs. 4.3 months, HR, 0.77; 95% CI: 0.62-0.96; P=0.017). A+EP treatment yielded significant 1-year OS (51.7% vs. 38.2%) and PFS benefits (12.6% vs. 5.4%) and reduced the risk of death by 30%.

As the first clinical study on immunotherapy in SCLC that showed two significant endpoints benefits simultaneously, OS and PFS, atezolizumab was approved for first-line treatment of ES-SCLC by the FDA in March, 2019.

However, there were no statistical difference in the objective response rate (ORR) between combined treatment and chemotherapy in the 2 phase III trials. Survival curves suggest that the advantage of immunotherapy combined with chemotherapy only became apparent 6 months later. Compared with NSCLC, 2-months OS benefits of combined therapy are too short, which may be related to the fact that some SCLC patients cannot benefit from immunotherapy. Therefore it is important to identify the patients who can actually benefit from immunotherapy.

The IFCT-1603 trial

The efficacy of atezolizumab versus chemotherapy in the treatment of SCLC has been explored in IFCT-1603 trial [33]. A total of 73 patients were divided randomly (2:1) into the atezolizumab (n=49) and chemotherapy groups (n=24). No median OS benefit was observed in the atezolizumab group versus chemotherapy (9.5 months vs. 8.7 months; HR, 0.84; 95% CI: 0.45-1.58; P=0.60). The median PFS of the atezolizumab group was 1.4 months (95% CI: 1.2-1.5), and the median PFS of the chemotherapy group was 4.3 months (95% CI: 1.5-5.9). The IFCT-1603 trial did not find any significant therapy efficacy for atezolizumab.

In those studies of PD-L1 inhibitors, the two phase 3 clinical trials for IMpower133 and CASPIAN have pioneered the safety and efficacy of immunotherapy combined with chemotherapy as first-line treatment of ES-SCLC. Atezolizumab and Durvalumab have been approved for first-line treatment of ES-SCLC by the Food and Drug Administration (FDA). However, in IFCT-1603 trial no OS benefit was observed in the atezolizumab group versus chemotherapy. The IFCT-1603 trial did not find any significant therapy efficacy for atezolizumab.

Anti-PD-1 inhibitors

The ASTRUM-005 study

In December 2021, interim analysis of the ASTRUM-005 trial, an international multi-center phase III study that explores the efficacy and safety of serplulimab, was disclosed in Shanghai. The primary endpoint of the ASTRUM-005 trial is OS, and the secondary endpoints included PFS, ORR, DOR, and safety.

Until October 22, 2021, a total of 585 eligible patients had been enrolled in the study with 389 patients receiving serplulimab plus EP and 196 patients receiving placebo plus EP. The median OS of the serplulimab group and placebo group was 15.38 months vs. 11.10 months (HR, 0.62; 95% CI: 0.48-0.80; P< 0.001). The rates of 2-year OS were 43.2% and 8.0% respectively. In the Asian subgroup, the median OS of the serplulimab group vs. placebo group was 16.03 months vs. 11.10 months (HR, 0.59; 95% CI: 0.44-0.79; P<0.001).

Results of the ASTRUM-005 trial indicated that serplulimab in combination with chemotherapy could improve OS significantly in first-line treatment of ES-SCLC with good performance on safety. Such favorable survival benefits are expected to make serplulimab the first PD-1 drug for first-line treatment of ES-SCLC.

The KEYNOTE-604 study

Compared with the significant achievements of the CASPIAN and IMpower133 trials aimed at anti-PD-L1 inhibitors, results from the KEYNOTE-604 study for the anti-PD-1 inhibitor pembrolizumab did not go as well [34]. Although pembrolizumab combined with chemotherapy improved mPFS (HR=0.75; 95% CI: 0.61-0.91; P=0.0023), immunotherapy did not obtain a good OS benefit (10.8 months vs. 9.7 month; HR=0.75; 95% CI: 0.61-0.91; P=0.0023).

The CheckMate-451 trial

In the CheckMate 451 trial, nivolumab or nivolumab plus ipilimumab as maintenance therapy after chemotherapy, did not improve mOS (HR, 0.92; 95% CI: 0.75-1.12; P=0.3693) or mPFS versus placebo either [35]. Compared with the placebo, OS was not statistically improved with nivolumab combined with ipilimumab (9.2 vs. 9.6 months; HR, 0.92; 95% CI: 0.75-1.12; P=5.37), as well as nivolumab (10.4 vs. 9.6 months; HR, 0.84; 95% CI: 0.69-1.02). Significant benefits were also not observed regarding PFS in patients with nivolumab (HR, 0.72; 95% CI: 0.60-0.87) or nivolumab plus ipilimumab (HR, 0.67; 95% CI: 0.56-0.81). In the nivolumab group, grade 3-4 AE was 11.5%, which was superior to the placebo group (8.4%). In summary, anti-PD-L1 inhibitors are superior to anti-PD-1 inhibitors treating ES-SCLC patients.

The CheckMate-331 trial

The randomized and open-label clinical CheckMate 331 trial was intended to explore the function of nivolumab versus chemotherapy in patients with relapsed SCLC [36]. Compared with chemotherapy monotherapy, patients in the nivolumab group had no observable better OS (7.5 months vs. 8.4 months; HR, 0.86; 95% CI: 0.72-1.04; P=0.11) or PFS benefits (1.4 months vs. 3.8 months; HR, 1.41; 95% CI: 0.50-1.27). The rates of grade 3-4 AEs were 13.8% and 73.2%. Overall, nivolumab did not provide significant survival benefits and brought about more adverse events in the treatment of relapsed SCLC compared to chemotherapy.

The PASSION trial

The phase 2 PASSION trial explored the efficacy of camrelizumab plus apatinib in second-line ES-SCLC treatment after chemotherapy [37]. In the initial stage of this study, patients were randomized to receive camrelizumab every 2 weeks plus once daily apatinib (QD), with 5 days on/2 days off or 7 days on/7 days off. Then one cohort was expanded to 45 patients according to the first cycle (28 days) data. In 47 patients of the QD cohort, mOS were 8.4 months, mPFS 3.6 months and ORR 34.0% (95% CI: 20.9-49.3). The rates of grade 3-4 or higher AEs were 72.9%. The PASSION trial showed that camrelizumab combined with apatinib had the potential to be an anti-tumor strategy for second-line ES-SCLC treatment.

The CheckMate-032 trial

The multicenter, open-label, phase 1/2 CheckMate-032 trial explored the application of nivolumab plus ipilimumab in third-line treatment of ES-SCLC [38]. Patients were randomized to the nivolumab group (n=147) or the nivolumab plus ipilimumab group (n=96). Nivolumab plus ipilimumab could increase ORR compared to the nivolumab group (21.9% vs. 11.6%; odds ratio, 2.12; 95% CI: 1.06-4.26; P=0.03), with median OS of 5.7 months (95% CI: 3.8-7.6) and 4.7 months (95% CI: 3.1-8.3), respectively. The rates of 24-month OS were 17.9% (nivolumab) and 16.9% (nivolumab plus ipilimumab). The rates of grade 3-4 AEs were 12.9% (nivolumab) and 37.5% (nivolumab plus ipilimumab). Combination therapy appeared to have higher toxicity compared to nivolumab

monotherapy. Despite ORR of nivolumab plus ipilimumab group being higher, OS benefits were similar between the two groups.

Keynote 028/158

The Keynote 028 and 158 trials investigated the anti-tumor activity of pembrolizumab in several different cancer types. Patients with cancer progression after standard therapy or those not suitable to receive standard treatment met the recruitment criteria of the SCLC group. In the phase Ib KEYNOTE 028 trial [39], 24 patients with SCLC were enrolled to receive pembrolizumab (10 mg/Kg) every 2 weeks. The mPFS of the SCLC group was 1.9 months (95% CI: 1.7 to 5.9 months) and mOS was 9.7 months (95% CI: 4.1 months to not reached). The ORR was 33.3% and 6 and 12-month OS were 66.0% and 37.7% respectively. In the 24 patients of the SCLC group, 16 experienced treatment-related AEs and grade 5 colitis/intestinal ischemia occurred in one of them. In the phase II Keynote 158 trial [40], 107 patients with ES-SCLC were enrolled to receive pembrolizumab every 3 weeks. The ORR of the SCLC group was 18.7% (95% CI: 11.8-27.4). The median PFS was 2 months (95% CI: 1.9-2.1) and median OS was 9.1 months (95% CI: 8.7-14.6). It is worth noting that the mPFS in PD-L1 positive and negative patients were 2.1 months and 1.9 months respectively, and the mOS was 14.6 months and 7.7 months respectively. About 59% of the patients experienced adverse events, which resulted in the treatment being halted in 4 patients and one patient died due to pneumonia. Another study summarized and analyzed data from the two trials in which ORR was the primary endpoint and PFS, OS, and safety were the secondary endpoints [41]. In the 131 patients of the two trials, 83 patients who had experienced two lines of chemotherapy previously were included. Aggregated mOS was 7.7 months (95% CI: 5.2-10.1) and mPFS was 2.0 months (95% CI: 1.9-3.4). The 12-month and 24-month OS was 34.3% and 20.7% respectively. Aggregated ORR was 19.3 (95% CI: 11.4-29.4). The rate of AEs was 61.4% and rate of grade 3-5 AEs was 9.6%.

A phase 2 study

In a phase 2 clinical trial, patients with ES-SCLC received pembrolizumab (200 mg) every 3 weeks after chemotherapy [42]. A total of 45 patients meeting the recruitment standard were enrolled. The mOS was 9.6 months (95% CI: 7.0-12.0) with 12-month OS of 37% and the mPFS was 1.4 months (95% CI: 1.3-2.8) with 12-month PFS of 13%. The ORR of all patients enrolled was 11.1% (95% CI: 4.8-23.5). The incidence of all grade AEs with a frequency was 10% or higher.

In those studies of PD-1 inhibitors, ASTRUM-005 trial indicated that serplulimab could improve OS significantly in first-line treatment of ES-SCLC with good performance on safety. Such favorable survival benefits are expected to make serplulimab the first PD-1 drug for first-line treatment of ES-SCLC. The PASSION trial showed that camrelizumab combined with apatinib have potential to be an anti-tumor strategy for second-line ES-SCLC treatment. However, in other clinical trials, pembrolizumab and nivolumab did not provide significant survival benefits and brought about more adverse events in the treatment of ES-SCLC.

Anti-CTLA-4 inhibitors

The CASPIAN trial

The CASPIAN trial also investigated the effects of durvalummab plus tremelimumab (D+T) in addition to durvalummab, the single immune checkpoint inhibitor, in ES-SCLC treatment [7]. The median OS of the D+T+EP group did not obtain significant benefits (10.4 months vs. 10.5 months; HR, 0.81; 95% CI: 0.67-0.97; P=0.02) versus EP monotherapy, and the same was true compared with the D+EP group. In the D+T+EP group, the rate of 36-month OS was 15.3%, and 5.8% for the EP group and 17.6% for the D+EP group. The rates of serious adverse AE (all causes) were 47.4% (126/266) for the D+T+EP group and 36.5% (97/266) for the EP group, and the rates of AE leading to death (all causes) were 10.9% (97/266) for the D+T+EP group and 6.0% (12/266) for the EP group, which means that combination therapy of double immune checkpoint inhibitors increased the risks of adverse events on the basis of EP chemotherapy. Therefore, we concluded that combination therapy of double immune checkpoint inhibitors was not beneficial to ES-SCLC patients and had a poorly tolerated safety profile compared to EP and D+EP after >3 years of median follow-up.

The CheckMate 451 trial

The phase III CheckMate 451 trial compared the effects of nivolumab or nivolumab plus ipilimumab as maintenance therapy after inductive chemotherapy versus placebo [35]. Patients in the nivolumab plus ipilimumab (N+I) group did not obtain significant OS benefit versus placebo (9.2 months vs. 9.6 months; HR, 0.92; 95% CI: 0.75-1.12; P=5.37). The PFS HR of the N+I group versus placebo was 0.72 (95% CI: 0.60-0.87). The rates of grade 3-4 AEs were 52.2% for the N+I group and 8.4% for the placebo. The study demonstrated that combination therapy of nivolumab plus ipilimumab did not improve mOS or mPFS of ES-SCLC patients.

The CA184-156 trial

The CA184-156 trial evaluated the efficacy and safety of chemotherapy plus ipilimumab or placebo in patients with ES-SCLC [43]. A total of 1,132 eligible patients were randomized to receive ipilimumab or placebo after induction chemotherapy. No survival benefits were found in terms of OS with a median OS of 11 versus 10.9 months (HR, 0.94; 95% CI: 0.81-1.09; P=0.3775). And the PFS was 4.6 versus 4.4 months for placebo and ipilimumab arm, respectively (HR, 0.85; 95% CI: 0.75-0.97). The combination of ipilimumab and chemotherapy was associated with a higher frequency of grade 3/4 AEs (48% vs. 45%).

The CheckMate-032 trial

The CheckMate-032 trial explored the application of nivolumab plus ipilimumab in third-line treatment of ES-SCLC [38]. Patients were randomized into the nivolumab group (n=147) or nivolumab plus ipilimumab group (n=96). The median OS was 5.7 months (95% CI: 3.8-7.6) and 4.7 months (95% CI: 3.1-8.3) respectively and median PFS was 1.4 months (95% CI: 1.3-1.4) and 1.5 months (95% CI: 1.4-2.2) respectively. Anti-CTLA-4 combined with anti-PD-1 failed to improve survival time. And the combination therapy appeared to have higher toxicity compared to nivolumab monotherapy.

In those trials of CTLA-4 inhibitors, all studies indicated that CTLA-4 inhibitors combined with ICIs or chemotherapy failed to improve survival time, and the combination therapy appeared to have higher toxicity.

We have performed a statistical meta-analysis about ICI in treatment of SCLC previous [44]. An improvement of OS in patients who were administered ICIs (HR, 0.83; 95% CI: 0.79-0.91; z=3.80, P<0.001) was observed, and the pooled statistical analysis did not show any obvious heterogeneity (I^2=31.7%, P=0.210). Similarly, the PFS for SCLC patients was significantly better (HR, 0.78; 95% CI: 0.72-0.85; z=5.93, P<0.001), with a lower between-study heterogeneity (I^2=20.3%, P=0.286). In subgroup meta-analyses, ES-SCLC patients who received anti-PD 1/L1 obtained an advantage of OS (HR, 0.77; 95% CI: 0.68-0.87; P<0.001; heterogeneity, P=0.472). In the subgroup of anti-CTLA-4, the benefit in the OS was not obvious (HR, 0.92; 95% CI: 0.80-1.06; P=0.266; heterogeneity, P=0.389). Next, in anti-PD 1/L1 subgroup, superior outcomes for OS were observed only in patients who received anti-PD L1 (HR, 0.72; 95% CI: 0.61-0.85; P<0.001; heterogeneity, P=0.808), and the HR of the anti-PD 1 subgroup was 0.84. In summary, PD-L1 inhibitor led to a statistically longer OS. The result is s consistent with this manuscript.

Other combination therapies

It is imperative to improve the efficacy of immunotherapy in ES-SCLC treatment further. Except for chemotherapy, other combination therapy strategies are being explored to improve OS and PFS.

ICIs combined with radiotherapy

In addition to chemotherapy, radiotherapy is another important treatment for ES-SCLC. Although relevant statistics concerning radiotherapy plus ICIs is lacking, the combination therapy is expected to obtain a synergistic effect. Therefore many clinical trials are under way to evaluate the role of ICIs plus radiotherapy in patients with SCLC. For example, as a phase II/III study, the NCT04402788 trial would evaluate the efficacy of the combination therapy including ICIs plus standard chemotherapy followed by consolidation radiation in ES-SCLC patients with OS and PFS as endpoints. More relevant clinical trials are presented in **Tables 3** and **4**.

ICIs combined with angiogenesis inhibitors

Two phase II trials involving ES-SCLC patients found certain clinical benefits from bevacizum-

Table 4. Other potential combination therapy strategies of ICIs in ES-SCLC

Therapy strategies	Summary
Radiotherapy	NCT04402788 trial would evaluate the efficacy of the combination therapy including ICIs plus standard chemotherapy followed by consolidation radiation in ES-SCLC patients with OS and PFS as endpoints.
Angiogenesis inhibitors	Two phase II trials involving ES-SCLC patients found certain clinical benefits from bevacizumab. Another commonly used angiogenesis inhibitor is anlotinib, which has improved the PFS and OS for second/third-line treatment of ES-SCLC.
Targeted therapy	Relevant trials of PARP or DLL3 inhibitors combined with ICIs are on-going, such as the NCT04624204, NCT03958045, and NCT03026166 studies.
Bispecific antibodies	The blockade of TIM-3, DLL-3, or LAG-3 signaling pathways can enhance the anti-tumor function of T cells theoretically. Currently relevant clinical trials on anti-TIM-3 and anti-LAG-3 combined with anti-PD-1/L1 in recurrent SCLC are on-going, such as NCT03708328 and NCT03365791.

PARP: poly ADP-ribose polymerase; DLL3: Delta-Like Ligand 3; TIM-3: T cell immunoglobulin and mucin domain 3; LAG-3: Lymphocyte-activation gene 3.

ab [45, 46]. However, the OS of another phase III trial in which patients with ES-SCLC received EP plus bevacizumab did not improve significantly [47]. Another commonly used angiogenesis inhibitor is anlotinib, which has improved the PFS and OS for second/third-line treatment of ES-SCLC [48]. In a single-arm phase II study, the median PFS of patients who received anlotinib plus EP strategy was 11.43 month [49]. Base on the efficacy of anlotinib, several clinical trials are under way to explore ICIs in combination with anlotinib, such as the NCT04055792 trial whose therapy strategy is sintilimab plus anlotinib, the NCT04620837 trial whose therapy strategy is tislelizumab plus anlotinib, and the NCT04731909 trial whose therapy strategy is toripallmab in combination with anlotinib.

ICIs combined with targeted therapy

The targeted therapy aimed at PARP (poly ADP-ribose polymerase) and DLL3 (Delta-Like Ligand 3) showed good anti-tumor activities in pre-clinical observations [50-52]. In the treatment of breast cancer, PARP inhibitors can enhance patients' response to ICIs [53]. A preclinical trial about SCLC indicated that the survival of tumor-bearing mice which received olaparib (a PARP inhibitor) was significantly longer than those receiving olaparib or PD-L1 [54]. PARP inhibitor can not only promote immune response activation, but also up-regulate the expression of PD-L1, so that PARP inhibitors combined with ICIs are promising in the treatment of SCLC. DLL3 is highly expressed on the surface of SCLC tumor cells and linked to SCLC progression [52, 55]. As an inhibitory treatment for DLL3, Rova-T monotherapy showed significant anti-tumor activities and good safety in some clinical trials for recurrent SCLC [56, 57]. Relevant trials of PARP or DLL3 inhibitors combined with ICIs are on-going, such as the NCT04624204, NCT03958045, and NCT03026166 studies.

Bispecific antibodies

Apart from PD-1/L1 and CTLA-4 trials, other immune checkpoints are also being investigated, such as TIM-3 (T cell immunoglobulin and mucin domain 3) and LAG-3 (Lymphocyte-activation gene 3). TIM-3 is an inhibitory membrane molecule on T cells, which can inhibit the activation of innate immune response when TIM-3 binds to the high mobility group box 1 protein (HMGB1). The Biocytogen Biotechnology Center has published an experimental report on combination therapy of PD-1 and TIM-3 inhibitors in B-hPD-1/hTIM3 mice. Results showed that the combination group obtained more obvious tumor inhibition effects, and its anti-tumor efficacy was superior to PD-1 alone. LAG-3, another inhibitory immune checkpoint of T cell, can regulate the proliferation, activation and homeostasis of T cells. A phase II study (NCT03365791) evaluated the efficacy of LAG-525 combined with Spartalizumab in the treatment of advanced solid tumors and hematological malignancies. The results showed good anti-tumor activities, especially in neuroendocrine tumors, SCLC, and DLBCL, with clinical benefit rate at 24 weeks (CBR-24) being 0.86, 0.27, and 0.804, respectively, which met the primary endpoint. In the AMG757 (NCT03319940) study, a delta-like

Table 5. Predictive biomarkers of ICIs in ES-SCLC

Biomarkers	Summary
PD-L1	In CASPIAN and IMPower study, PD-L1 expression had no significant correlation with OS. However, a meta-analysis indicated that positive PD-L1 expression demonstrated a trend towards longer OS.
TMB	In CheckMate 032 trial, Results indicated that the OS and PFS of high TMB group who received nivolumab or nivolumab plus ipilimumab were superior to medium TMB group and low TMB group which reminded us that SCLC patients with high TMB could obtain more survival benefits.
TIL and GEP	In the phase Ib Keynote 028 trial, the patient group with SCLC showed an ORR of 33% after treatment with pembrolizumab. The study showed that tumor T cell-inflamed GEPs were a potential predictive biomarker of pembrolizumab response.
CTC	The study of Tamminga, which involved 104 NSCLC patients received immunotherapy, showed patients with decreased CTC levels were more likely to benefit from immunotherapy.
Metastasis sites	In KEYNOTE-158 study, OS benefits wasn't observed in patients with hepatic metastases compared to patients without metastases. In IMPower133 study, SCLC patients with brain metastases did not appear to benefit from ICI in combination with chemotherapy.

TMB: tumor mutation burden; TIL: tumor infiltrating lymphocyte; GEN: gene-expression profifile; CTC: circulating tumor cells.

ligand 3 (DLL-3)-targeting and half-life extended BiTE (bispecific T-cell engager) immuno-oncology therapy in SCLC, 28 patients (44%) had previously been treated with PD-1/PD-L1 inhibitors. Results showed that the confirmed ORR was 14%, DCR was 37%. AMG 757 had an acceptable safety profile at doses up to 100 mg, with rapid and long-lasting responses. Hence the blockade of TIM-3, DLL-3, or LAG-3 signaling pathways can enhance the anti-tumor function of T cells theoretically. Currently relevant clinical trials on anti-TIM-3 and anti-LAG-3 combined with anti-PD-1/L1 in recurrent SCLC are on-going, such as NCT03708328 and NCT03365791.

Biomarkers

Impower 133 and CASPIAN studies indicated that the OS of patients who received ICIs only had minimal benefit of 2 months, indicating that a significant percentage of patients cannot benefit from ICIs. Hence, how to select patients who can benefit from immunotherapy is crucial (**Table 5**).

PD-L1

PD-L1 is only expressed in 18%-32% of SCLC patients, in contrast to 60% in NSCLC patients [58]. In 277 appreciable samples of the CASPIAN study, the PD-L1 tumor proportion score (TPS) in 95% of the patients is less than 1% and there was no correlation between PD-L1 and the survival index [3]. In 137 samples from the Impower study, regardless if 1% or 5% was chosen as the threshold for PD-L1 TPS, there was no significant correlation with OS [5]. The above results indicated that PD-L1 cannot predict the efficacy of ICIs plus chemotherapy in first-line treatment of ES-SCLC.

Some clinical trials that explored second-line treatment in ES-SCLC and higher seem to show inconsistent results. The results of CheckMate 032 indicated that PD-L1 had no significant correlation with ORR [38]. The combined positive score (CPS) was used to evaluate the expression of PD-L1. In the KEYNOTE-028 study, the ORR of patients with relapsed SCLC whose CPS was ≥1% was 33% (8/24) [39]. In the KEYNOTE 158 study, compared with patients whose CPS was <1%, the ORR (35.7% vs. 6%), PFS (28.5% vs. 8.2%), and OS (53.1% vs. 30.7%) of patients whose CPS was ≥1% performed better [40]. It is worth our consideration that CPS may have advantages over TPS in evaluating PD-L1 expression. The predictive value of CPS in immunotherapy needs to be further explored in more clinical trials.

TMB

In general, higher TMB has correlation with greater OS and PFS and SCLC is a type of solid tumor with high TMB [59]. In the CheckMate 032 trial, researchers performed whole exomesequencing (WES) on tumor tissues and divided these samples into high, medium, and low TMB groups. Results indicated that the OS and PFS of the high TMB group who received nivolumab or nivolumab plus ipilimumab were superior to medium and low TMB groups, which suggests that SCLC patients with high TMB may obtain more survival benefits [60]. The predictive value of TMB based on blood (bTMB)

was evaluated in the IMpower133 study. When 10 mut/Mb was used as the cut-off value of bTMB, patients in both high and low bTMB groups who received immunotherapy plus chemotherapy could achieve statistically significant OS benefits. When 16 mut/Mb was used as the cut-off value, there were no statistical differences in the OS between the immunotherapy and chemotherapy groups. Based on these opposite statistical results, we think that bTMB is not an appropriate index to predict the treatment efficacy of ICIs combined with chemotherapy in first-line treatment in ES-SCLC [5].

TIL and T-cell–inflamed GEP

The infiltration degree of tumor-infiltrating lymphocytes (TIL) is also a prognostic indicator of immunotherapy efficacy. Some studies have suggested that SCLC patients with a high number of TILs have better prognosis before immunotherapy [61-64]. In the KEYNOTE-028 study, TILs were found to be associated with ORR and mPFS [39]. The T-cell–inflamed gene-expression profile (GEP) was shown to predict the clinical efficacy with pembrolizumab therapy across a diverse set of 20 solid tumors [65]. GEP, as an inflammatory marker of the inflammatory tumor microenvironment, showed a moderate correlation with TMB and could predict patient clinical responses independently. Patients with high GEP and PD-L1 expression or TMB could obtain more clinical benefit. These indicators together may serve as potential biomarkers to identify patients who likely would benefit from ICIs.

CTC

Some studies have shown that the increase in circulating tumor cells (CTC) predicts the poor effect of immunotherapy [66, 67]. The study of Tamminga, which involved 104 NSCLC patients receiving immunotherapy, showed that the PFS and OS of patients without detectable CTCs were significantly better than those with detectable CTCs. In addition, by comparing CTCs before and after immunotherapy, it was found that patients with decreased CTC levels were more likely to benefit from immunotherapy [68]. Hence CTCs are considered an independent predictor of immunotherapy efficacy.

Basic clinical parameters

In addition to the above biomarkers, we cannot ignore the possible influence of basic clinical parameters such as metastatic sites. In the phase II KEYNOTE-158 study, similar OS benefits were not observed in patients with hepatic metastases compared to patients without metastases [69]. In the IMPower133 study, SCLC patients with brain metastases were also admitted but did not appear to benefit from ICIs in combination with chemotherapy [5]. Medication history, age, gender, and ethnicity may also have an impact on outcome prediction. However, due to the limitations of clinical data, using clinical characteristics as predictors remains to be seen and needs to be confirmed by carefully controlled studies.

Discussion

Etoposide plus platinum treatment has been the standard first-line ES-SCLC therapy strategy for decades [70]. Almost all treated patients relapse within one year, with a median OS of about 10-11 months. The emergence of ICIs has brought new hope to treating ES-SCLC patients in recent years. Impower 133 was the first clinical trial to significantly prolong OS and PFS, and CASPIAN further confirmed that ICIs could improve the survival prognosis of ES-SCLC patients [2, 3, 5, 7]. The two trials established the importance of ICIs to ES-SCLC therapies, and made ICIs plus chemotherapy the new standard in the first-line treatment of ES-SCLC. The three-year survival data of CASPIAN were updated during the 2021 ESMO congress, with three-year OS rates of durvalumab plus chemotherapy overwhelmingly favorable compared to chemotherapy group [7]. In December 2021, interim analysis of the ASTRUM-005 trial, an international multi-center phase III serplulimab study was revealed in Shanghai. The favorable survival benefits are expected to make serplulimab the first PD-1 drug for the first-line treatment of ES-SCLC. Although ICIs plus chemotherapy improved OS of patients with ES-SCLC, the benefits observed so far with ICIs do not represent a breakthrough. To further improve the efficacy of ICIs, finding more suitable predictive biomarkers and exploring different combination treatment strategies are urgently needed.

Using biomarkers to identify SCLC patients who respond to ICIs

Neither PD-L1 nor TMB seems appropriate as predictive factors for the efficacy of ICIs in first-line treatments in ES-SCLC, possibly because

SCLS is a highly aggressive, proliferative, and unstable solid tumor. TIL, Gen, and CTC may be taken as new predictive biomarkers. However, due to limited clinical data, their predicative value needs to be confirmed by additional studies. Other potential predictive indices could be considered, such as mutations in the TP53 and RB1 genes, and the schlafen family member 11 (SLFN11) gene that was considered a biomarker of PFS and OS [71]. Existing clinical trials suggested limited predictive values of these indicators. It is necessary to explore PD-L1 combined with TMB, tumor-infiltrating immune cells, and other comprehensive factors as well as their correlation with the efficacy of ICIs to determine the beneficiaries and improve efficacy.

Combination therapy

Previous studies have shown that ICIs have favorable toxicity profiles and durable responses in the treatment of ES-SCLC, while ICI monotherapy shows a relatively low response rate. ICIs combined with chemotherapy had made small progress in first and third-line treatment of ES-SCLC. Hence combination therapy strategies such as radiotherapy, targeted therapy, and bispecific antibodies might be the more eutherapeutic treatment strategy with better prospects. Bispecific antibodies or double ICIs, such as anti-PD-1/L1 and anti-CTLA-4, may work synergistically due to the non-redundant pathways. Radiotherapy and chemotherapy may enhance the immunogenicity of tumor cells by inducing rapid tumor lysis and the subsequent release of tumor antigens. In addition, ICIs combined with target therapy may obtain better therapeutic effects due to their different targets.

Does anti-PD-L1 have more favorable effects on ES-SCLC than anti-PD-1?

Currently only two PD-L1 inhibitors, atezolizumab and durvalumab, have been approved for first-line treatment in patients with SCLC. Does anti-PD-L1 have more favorable effects on ES-SCLC than anti-PD-1? It appears that no statistical significance has been observed with PD-1 inhibitors in clinical trials. In the KEYNOTE-604 trial, pembrolizumab failed to improve ES-SCLC patient OS. However, patients who received pembrolizumab plus chemotherapy showed a significant PFS benefit and durable responses. Compared to the IMpower 133 and CASPIAN trials, patients with more brain metastases (≥65 years), ECOG (PS=1), larger tumors, and more than three metastatic sites were recruited in the KEYNOTE-604 trial. The subgroup with brain metastases was the only one in which patients with ES-SCLC did not obtain OS benefit from immunotherapy combined with chemotherapy. Hence these recruited patients with poorer prognostic factors in the KEYNOTE-604 trial could explain the lack of OS benefits in experimental arm compared to the other two clinical trials.

The duration and course of ICIs in the treatment of ES-SCLC

Another problem is how to decide on the course and duration of ICIs in treating ES-SCLC. In the IMpower 133 study, atezolizumab or placebo was administered on the first day of each cycle with carboplatin and etoposide, and continued for 4 cycles. Then atezolizumab or placebo was followed until disease progression or unacceptable toxicity. In the CASPIAN trial, durvalumab or durvalumab-tremelimumab plus EP was also administered on the first day of each cycle for 4 cycles. And then durvalumab was followed every four weeks as maintenance treatment. In the Keynote-604 trial, pembrolizumab combined with EP was given on the first day of each three weeks for four cycles, followed by 31 cycles. These clinical trials were designed to use ICIs with chemotherapy drugs on the same day. But in treating other types of tumors, sequential therapies of immunotherapy after chemotherapy appear more effective, probably because some ICI-activated T cells would be damaged by chemotherapy drugs. Sequential therapy can minimize T cell killing by chemotherapy and extend the effect of ICIs the furthest [72].

Another question is how to determine the dosage of chemotherapy drugs in combination with immunotherapy. The maximum tolerated dose (MTD) usually causes cell death of immune cells. Therefore it is also necessary to consider whether the full dose of chemotherapy drugs should be used for combination therapy. An animal experiment found that low-dose chemotherapy drugs combined with ICIs could obtain better therapeutic efficacy compared with the MTD strategy, especially when administered 24

hours before immunotherapy [2]. Low-dose strategies can not only reduce the toxicity of chemotherapy, but also provide sufficient time to activate the tumor immune microenvironment.

Future and perspectives

The results of Caspian and Impower133 studies showed that with favorable toxicity profiles and durable responses, ICIs have made a breakthrough in single-treatment strategies of ES-SCLC and led to considerations about the future of first-line treatment for SCLC. Combination therapy shows great promise and should be researched further. The double-ICI treatment strategy, bispecific antibodies, and ICIs combined with other therapy such as chemotherapy, radiotherapy, and targeted therapy, represent a new modality for the treatment of ES-SCLC, achieving greater therapeutic effects through multiple synergistic mechanisms. Future research focused on exploring the basic biology of SCLC and identifying novel predictive biomarkers in response to ICIs in SCLC is essential. Currently, the prognostic biomarkers for SCLC are still unclear, the exploration of more sensitive and effective biomarkers, scientific guidance, and individualized treatment of patients remain the direction towards which we strive for. It is hoped that with the development of clinical trials about ICIs for SCLC, more effective treatment strategies will come to fruition for the treatment of ES-SCLC.

At present, there is no agreement with regard to the dose and cycles of ICIs combined with chemotherapy. Previous studies suggest that the clinical efficacy of combination therapy may be affected by the dosage, drug frequency, cycle, and the order of chemotherapy and ICIs, which should be the focus of future research on combination therapy.

Conclusion

In conclusion, ICIs in combination with chemotherapy including durvalumab or atezolizumab plus platinum-etoposide have been approved as the standard therapy strategy for first-line treatment of ES-SCLC. The favorable OS benefits of ASTRUM-005 trial are expected to make serplulimab the first PD-1 drug for first-line treatment of ES-SCLC. Therefore, the role of ICIs in limited-stage SCLC (LS-SCLC) is much anticipated. It is believed that as we gain more understanding of the complex mechanisms of the immune system and molecular characteristics of SCLC immune microenvironment, precise immunotherapy will help overcome the treatment bottleneck of SCLC and improve the survival of patients with SCLC.

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Address correspondence to: Baoxing Liu, Department of Thoracic Surgery, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou 45008, P. R. China. E-mail: liu15238670795@163.com

References

[1] Siegel RL, Miller KD, Fuchs HE and Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021; 71: 7-33.

[2] Saltos A, Shafique M and Chiappori A. Update on the biology, management, and treatment of small cell lung cancer (SCLC). Front Oncol 2020; 10: 1074.

[3] Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, Hochmair MJ, Özgüroğlu M, Ji JH, Voitko O, Poltoratskiy A, Ponce S, Verderame F, Havel L, Bondarenko I, Kazarnowicz A, Losonczy G, Conev NV, Armstrong J, Byrne N, Shire N, Jiang H and Goldman JW; CASPIAN investigators. 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: 1929-1939.

[4] Mathieu L, Shah S, Pai-Scherf L, Larkins E, Vallejo J, Li X, Rodriguez L, Mishra-Kalyani P, Goldberg KB, Kluetz PG, Theoret MR, Beaver JA, Pazdur R and Singh H. FDA approval summary: atezolizumab and durvalumab in combination with platinum-based chemotherapy in extensive stage small cell lung cancer. Oncologist 2021; 26: 433-438.

[5] Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, Huemer F, Losonczy G, Johnson ML, Nishio M, Reck M, Mok T, Lam S, Shames DS, Liu J, Ding B, Lopez-Chavez A, Kabbinavar F, Lin W, Sandler A and Liu SV;

IMpower133 Study Group. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018; 379: 2220-2229.

[6] Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, Hochmair MJ, Ozguroglu M, Ji JH, Garassino MC, Voitko O, Poltoratskiy A, Ponce S, Verderame F, Havel L, Bondarenko I, Kazarnowicz A, Losonczy G, Conev NV, Armstrong J, Byrne N, Thiyagarajah P, Jiang H and Paz-Ares L; CASPIAN investigators. 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: 51-65.

[7] Paz-Ares L, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, Hochmair M, Ozguroglu M, Ji JH, Voitko O, Poltoratskiy A, Verderame F, Havel L, Bondarenko I, Losonczy G, Conev N, Broadhurst HL, Dalvi T, Jiang H and Goldman JW. LBA61 Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the phase III CASPIAN study. Annals of Oncology 2021; 32: S1338.

[8] Vesely MD, Kershaw MH, Schreiber RD and Smyth MJ. Natural innate and adaptive immunity to cancer. Annu Rev Immunol 2011; 29: 235-271.

[9] Diefenbach A and Raulet DH. The innate immune response to tumors and its role in the induction of T-cell immunity. Immunol Rev 2002; 188: 9-21.

[10] Mittal D, Gubin MM, Schreiber RD and Smyth MJ. New insights into cancer immunoediting and its three component phases-elimination, equilibrium and escape. Curr Opin Immunol 2014; 27: 16-25.

[11] Finn OJ. Cancer immunology. N Engl J Med 2008; 358: 2704-2715.

[12] Finn OJ. Immuno-oncology: understanding the function and dysfunction of the immune system in cancer. Ann Oncol 2012; 23 Suppl 8: viii6-9.

[13] Lesokhin AM, Callahan MK, Postow MA and Wolchok JD. On being less tolerant: enhanced cancer immunosurveillance enabled by targeting checkpoints and agonists of T cell activation. Sci Transl Med 2015; 7: 280sr1.

[14] Selby M, Engelhardt J, Quigley M, Henning K, Chen T, Srinivasan M and Korman A. Anti-CTLA-4 Antibodies of IgG2a Isotype enhance antitumor activity through reduction of intratumoral regulatory T cells. Cancer Immunol Res 2013; 1: 32-42.

[15] Wolchok JD and Saenger Y. The mechanism of anti-CTLA-4 activity and the negative regulation of T-cell activation. Oncologist 2008; 13 Suppl 4: 2-9.

[16] Callahan MK and Wolchok JD. At the bedside: CTLA-4- and PD-1-blocking antibodies in cancer immunotherapy. J Leukoc Biol 2013; 94: 41-53.

[17] Butt AQ and Mills KH. Immunosuppressive networks and checkpoints controlling antitumor immunity and their blockade in the development of cancer immunotherapeutics and vaccines. Oncogene 2014; 33: 4623-4631.

[18] George J, Lim JS, Jang SJ, Cun Y, Ozretic L, Kong G, Leenders F, Lu X, Fernandez-Cuesta L, Bosco G, Muller C, Dahmen I, Jahchan NS, Park KS, Yang D, Karnezis AN, Vaka D, Torres A, Wang MS, Korbel JO, Menon R, Chun SM, Kim D, Wilkerson M, Hayes N, Engelmann D, Putzer B, Bos M, Michels S, Vlasic I, Seidel D, Pinther B, Schaub P, Becker C, Altmuller J, Yokota J, Kohno T, Iwakawa R, Tsuta K, Noguchi M, Muley T, Hoffmann H, Schnabel PA, Petersen I, Chen Y, Soltermann A, Tischler V, Choi CM, Kim YH, Massion PP, Zou Y, Jovanovic D, Kontic M, Wright GM, Russell PA, Solomon B, Koch I, Lindner M, Muscarella LA, la Torre A, Field JK, Jakopovic M, Knezevic J, Castanos-Velez E, Roz L, Pastorino U, Brustugun OT, Lund-Iversen M, Thunnissen E, Kohler J, Schuler M, Botling J, Sandelin M, Sanchez-Cespedes M, Salvesen HB, Achter V, Lang U, Bogus M, Schneider PM, Zander T, Ansen S, Hallek M, Wolf J, Vingron M, Yatabe Y, Travis WD, Nurnberg P, Reinhardt C, Perner S, Heukamp L, Buttner R, Haas SA, Brambilla E, Peifer M, Sage J and Thomas RK. Comprehensive genomic profiles of small cell lung cancer. Nature 2015; 524: 47-53.

[19] Peifer M, Fernandez-Cuesta L, Sos ML, George J, Seidel D, Kasper LH, Plenker D, Leenders F, Sun R, Zander T, Menon R, Koker M, Dahmen I, Muller C, Di Cerbo V, Schildhaus HU, Altmuller J, Baessmann I, Becker C, de Wilde B, Vandesompele J, Bohm D, Ansen S, Gabler F, Wilkening I, Heynck S, Heuckmann JM, Lu X, Carter SL, Cibulskis K, Banerji S, Getz G, Park KS, Rauh D, Grutter C, Fischer M, Pasqualucci L, Wright G, Wainer Z, Russell P, Petersen I, Chen Y, Stoelben E, Ludwig C, Schnabel P, Hoffmann H, Muley T, Brockmann M, Engel-Riedel W, Muscarella LA, Fazio VM, Groen H, Timens W, Sietsma H, Thunnissen E, Smit E, Heideman DA, Snijders PJ, Cappuzzo F, Ligorio C, Damiani S, Field J, Solberg S, Brustugun OT, Lund-Iversen M, Sanger J, Clement JH, Soltermann A, Moch H, Weder W, Solomon B, Soria JC, Validire P, Besse B, Brambilla E, Brambilla C, Lantuejoul S, Lorimier P, Schneider PM, Hallek M, Pao W, Meyerson M, Sage J, Shendure J,

Schneider R, Buttner R, Wolf J, Nurnberg P, Perner S, Heukamp LC, Brindle PK, Haas S and Thomas RK. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat Genet 2012; 44: 1104-1110.

[20] Efremova M, Finotello F, Rieder D and Trajanoski Z. Neoantigens generated by individual mutations and their role in cancer immunity and immunotherapy. Front Immunol 2017; 8: 1679.

[21] Sabari JK, Lok BH, Laird JH, Poirier JT and Rudin CM. Unravelling the biology of SCLC: implications for therapy. Nat Rev Clin Oncol 2017; 14: 549-561.

[22] Yarchoan M, Johnson BA 3rd, Lutz ER, Laheru DA and Jaffee EM. Targeting neoantigens to augment antitumour immunity. Nat Rev Cancer 2017; 17: 209-222.

[23] Hiura T, Kagamu H, Miura S, Ishida A, Tanaka H, Tanaka J, Gejyo F and Yoshizawa H. Both regulatory T cells and antitumor effector T cells are primed in the same draining lymph nodes during tumor progression. J Immunol 2005; 175: 5058-5066.

[24] Onizuka S, Tawara I, Shimizu J, Sakaguchi S, Fujita T and Nakayama E. Tumor rejection by in vivo administration of anti-CD25 (interleukin-2 receptor alpha) monoclonal antibody. Cancer Res 1999; 59: 3128-3133.

[25] Shimizu J, Yamazaki S and Sakaguchi S. Induction of tumor immunity by removing CD25+CD4+ T cells: a common basis between tumor immunity and autoimmunity. J Immunol 1999; 163: 5211-5218.

[26] Eerola AK, Soini Y and Pääkkö P. A high number of tumor-infiltrating lymphocytes are associated with a small tumor size, low tumor stage, and a favorable prognosis in operated small cell lung carcinoma. Clin Cancer Res 2000; 6: 1875-1881.

[27] Muppa P, Parrilha Terra SBS, Sharma A, Mansfield AS, Aubry MC, Bhinge K, Asiedu MK, de Andrade M, Janaki N, Murphy SJ, Nasir A, Van Keulen V, Vasmatzis G, Wigle DA, Yang P, Yi ES, Peikert T and Kosari F. Immune cell infiltration may be a key determinant of long-term survival in small cell lung cancer. J Thorac Oncol 2019; 14: 1286-1295.

[28] Wang W, Hodkinson P, McLaren F, Mackean MJ, Williams L, Howie SEM, Wallace WAH and Sethi T. Histologic assessment of tumor-associated CD45(+) cell numbers is an independent predictor of prognosis in small cell lung cancer. Chest 2013; 143: 146-151.

[29] He Y, Rozeboom L, Rivard CJ, Ellison K, Dziadziuszko R, Yu H, Zhou C and Hirsch FR. MHC class II expression in lung cancer. Lung Cancer 2017; 112: 75-80.

[30] Schalper K, Carvajal-Hausdorf D, McLaughlin J, Altan M, Chiang A, Velcheti V, Kaftan E, Zhang J, Lu L, Rimm D, Han B, Lu H, Zhao H and Herbst R. Objective measurement and significance of PD-L1, B7-H3, B7-H4 and TILs in small cell lung cancer (SCLC). J Clin Oncol 2016; 34: 8566-8566.

[31] Fife BT and Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. Immunol Rev 2008; 224: 166-182.

[32] Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T and Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A 2002; 99: 12293-12297.

[33] Pujol JL, Greillier L, Audigier-Valette C, Moro-Sibilot D, Uwer L, Hureaux J, Guisier F, Carmier D, Madelaine J, Otto J, Gounant V, Merle P, Mourlanette P, Molinier O, Renault A, Rabeau A, Antoine M, Denis MG, Bommart S, Langlais A, Morin F and Souquet PJ. A randomized non-comparative phase II study of anti-programmed cell death-ligand 1 atezolizumab or chemotherapy as second-line therapy in patients with small cell lung cancer: results from the IFCT-1603 trial. J Thorac Oncol 2019; 14: 903-913.

[34] Rudin CM, Awad MM, Navarro A, Gottfried M, Peters S, Csoszi T, Cheema PK, Rodriguez-Abreu D, Wollner M, Yang JC, Mazieres J, Orlandi FJ, Luft A, Gumus M, Kato T, Kalemkerian GP, Luo Y, Ebiana V, Pietanza MC and Kim HR; KEYNOTE-604 Investigators. 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: 2369-2379.

[35] Owonikoko TK, Park K, Govindan R, Ready N, Reck M, Peters S, Dakhil SR, Navarro A, Rodriguez-Cid J, Schenker M, Lee JS, Gutierrez V, Percent I, Morgensztern D, Barrios CH, Greillier L, Baka S, Patel M, Lin WH, Selvaggi G, Baudelet C, Baden J, Pandya D, Doshi P and Kim HR. Nivolumab and ipilimumab as maintenance therapy in extensive-disease small-cell lung cancer: CheckMate 451. J Clin Oncol 2021; 39: 1349-1359.

[36] Spigel DR, Vicente D, Ciuleanu TE, Gettinger S, Peters S, Horn L, Audigier-Valette C, Pardo Aranda N, Juan-Vidal O, Cheng Y, Zhang H, Shi M, Luft A, Wolf J, Antonia S, Nakagawa K, Fairchild J, Baudelet C, Pandya D, Doshi P, Chang H and Reck M. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331☆. Ann Oncol 2021; 32: 631-641.

[37] Fan Y, Zhao J, Wang Q, Huang D, Li X, Chen J, Fang Y, Duan J, Zhou C, Hu Y, Yang H, Hu Y, Zhou J, Lin X, Wang L, Wang Z, Xu Y, Zhang T, Shi W, Zou J and Wang J. Camrelizumab plus apatinib in extensive-stage SCLC (PASSION): a multicenter, two-stage, phase 2 trial. J Thorac Oncol 2021; 16: 299-309.

[38] Ready NE, Ott PA, Hellmann MD, Zugazagoitia J, Hann CL, de Braud F, Antonia SJ, Ascierto PA, Moreno V, Atmaca A, Salvagni S, Taylor M, Amin A, Camidge DR, Horn L, Calvo E, Li A, Lin WH, Callahan MK and Spigel DR. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: results from the CheckMate 032 randomized cohort. J Thorac Oncol 2020; 15: 426-435.

[39] Ott PA, Elez E, Hiret S, Kim DW, Morosky A, Saraf S, Piperdi B and Mehnert JM. Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the phase Ib KEYNOTE-028 study. J Clin Oncol 2017; 35: 3823-3829.

[40] Chung HC, Lopez-Martin JA, Kao SC-H, Miller WH, Ros W, Gao B, Marabelle A, Gottfried M, Zer A, Delord JP, Penel N, Jalal SI, Xu L, Zeigenfuss S, Pruitt SK and Piha-Paul SA. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158. J Clin Oncol 2018; 36: 8506-8506.

[41] Chung HC, Piha-Paul SA, Lopez-Martin J, Schellens JHM, Kao S, Miller WH Jr, Delord JP, Gao B, Planchard D, Gottfried M, Zer A, Jalal SI, Penel N, Mehnert JM, Matos I, Bennouna J, Kim DW, Xu L, Krishnan S, Norwood K and Ott PA. 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: 618-627.

[42] Gadgeel SM, Pennell NA, Fidler MJ, Halmos B, Bonomi P, Stevenson J, Schneider B, Sukari A, Ventimiglia J, Chen W, Galasso C, Wozniak A, Boerner J and Kalemkerian GP. Phase II study of maintenance pembrolizumab in patients with extensive-stage small cell lung cancer (SCLC). J Thorac Oncol 2018; 13: 1393-1399.

[43] Reck M, Luft A, Szczesna A, Havel L, Kim SW, Akerley W, Pietanza MC, Wu YL, Zielinski C, Thomas M, Felip E, Gold K, Horn L, Aerts J, Nakagawa K, Lorigan P, Pieters A, Kong Sanchez T, Fairchild J and Spigel D. 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: 3740-3748.

[44] Liu X, Xing H, Zhang H, Liu H and Chen J. Immunotherapy versus standard chemotherapy for treatment of extensive-stage small-cell lung cancer: a systematic review. Immunotherapy 2021; 13: 989-1000.

[45] Horn L, Dahlberg SE, Sandler AB, Dowlati A, Moore DF, Murren JR and Schiller JH. Phase II study of cisplatin plus etoposide and bevacizumab for previously untreated, extensive-stage small-cell lung cancer: eastern cooperative oncology group study E3501. J Clin Oncol 2009; 27: 6006-6011.

[46] Ready NE, Dudek AZ, Pang HH, Hodgson LD, Graziano SL, Green MR and Vokes EE. Cisplatin, irinotecan, and bevacizumab for untreated extensive-stage small-cell lung cancer: CALGB 30306, a phase II study. J Clin Oncol 2011; 29: 4436-4441.

[47] Tiseo M, Boni L, Ambrosio F, Camerini A, Baldini E, Cinieri S, Brighenti M, Zanelli F, Defraia E, Chiari R, Dazzi C, Tibaldi C, Turolla GM, D'Alessandro V, Zilembo N, Trolese AR, Grossi F, Riccardi F and Ardizzoni A. Italian, multicenter, Phase III, randomized study of cisplatin plus etoposide with or without bevacizumab as first-line treatment in extensive-disease small-cell lung cancer: the GOIRC-AIFA FARM6PM-FJM trial. J Clin Oncol 2017; 35: 1281-1287.

[48] Cheng Y, Wang Q, Li K, Shi J, Liu Y, Wu L, Han B, Chen G, He J, Wang J, Lou D, Yu H, Qin H and Li XL. 173800verall survival (OS) update in ALTER 1202: anlotinib as third-line or further-line treatment in relapsed small-cell lung cancer (SCLC). Annals of Oncology 2019; 30.

[49] Han B, Zhang W, Zhang B, Chen Y, Zhang Y, Lou Y, Dong Y, Qian F, Zhou W and Yang Z. P48.09 anlotinib plus etoposide and carboplatin as first-line treatment for extensive-stage small cell lung cancer: a single arm phase II trial. J Thorac Oncol 2021; 16: S503.

[50] Chabanon RM, Muirhead G, Krastev DB, Adam J, Morel D, Garrido M, Lamb A, Henon C, Dorvault N, Rouanne M, Marlow R, Bajrami I, Cardenosa ML, Konde A, Besse B, Ashworth A, Pettitt SJ, Haider S, Marabelle A, Tutt AN, Soria JC, Lord CJ and Postel-Vinay S. PARP inhibition enhances tumor cell-intrinsic immunity in ERCC1-deficient non-small cell lung cancer. J Clin Invest 2019; 129: 1211-1228.

[51] Jiang Y, Dai H, Li Y, Yin J, Guo S, Lin SY and McGrail DJ. PARP inhibitors synergize with gemcitabine by potentiating DNA damage in non-small-cell lung cancer. Int J Cancer 2019; 144: 1092-1103.

[52] Owen DH, Giffin MJ, Bailis JM, Smit MD, Carbone DP and He K. DLL3: an emerging target in small cell lung cancer. J Hematol Oncol 2019; 12: 61.

[53] Jiao S, Xia W, Yamaguchi H, Wei Y, Chen MK, Hsu JM, Hsu JL, Yu WH, Du Y, Lee HH, Li CW, Chou CK, Lim SO, Chang SS, Litton J, Arun B, Hortobagyi GN and Hung MC. PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression. Clin Cancer Res 2017; 23: 3711-3720.

[54] Sen T, Rodriguez BL, Chen L, Corte CMD, Morikawa N, Fujimoto J, Cristea S, Nguyen T, Diao L, Li L, Fan Y, Yang Y, Wang J, Glisson BS, Wistuba II, Sage J, Heymach JV, Gibbons DL and Byers LA. Targeting DNA damage response promotes antitumor immunity through STING-mediated T-cell Activation in small cell lung cancer. Cancer Discov 2019; 9: 646-661.

[55] Furuta M, Sakakibara-Konishi J, Kikuchi H, Yokouchi H, Nishihara H, Minemura H, Harada M, Yamazaki S, Akie K, Fujita Y, Takamura K, Kojima T, Harada T, Minami Y, Watanabe N, Oizumi S, Suzuki H, Nishimura M, Dosaka-Akita H and Isobe H; Hokkaido Lung Cancer Clinical Study Group. Analysis of DLL3 and ASCL1 in surgically resected small cell lung cancer (HOT1702). Oncologist 2019; 24: e1172-e1179.

[56] Rudin CM, Pietanza MC, Bauer TM, Ready N, Morgensztern D, Glisson BS, Byers LA, Johnson ML, Burris HA 3rd, Robert F, Han TH, Bheddah S, Theiss N, Watson S, Mathur D, Vennapusa B, Zayed H, Lally S, Strickland DK, Govindan R, Dylla SJ, Peng SL and Spigel DR; SCRX16-001 investigators. Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. Lancet Oncol 2017; 18: 42-51.

[57] Morgensztern D, Besse B, Greillier L, Santana-Davila R, Ready N, Hann CL, Glisson BS, Farago AF, Dowlati A, Rudin CM, Le Moulec S, Lally S, Yalamanchili S, Wolf J, Govindan R and Carbone DP. Efficacy and safety of rovalpituzumab tesirine in third-line and beyond patients with DLL3-expressing, relapsed/refractory small-cell lung cancer: results from the phase II TRINITY study. Clin Cancer Res 2019; 25: 6958-6966.

[58] Yu H, Boyle TA, Zhou C, Rimm DL and Hirsch FR. PD-L1 expression in lung cancer. J Thorac Oncol 2016; 11: 964-975.

[59] Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, Borresen-Dale AL, Boyault S, Burkhardt B, Butler AP, Caldas C, Davies HR, Desmedt C, Eils R, Eyfjord JE, Foekens JA, Greaves M, Hosoda F, Hutter B, Ilicic T, Imbeaud S, Imielinski M, Jager N, Jones DT, Jones D, Knappskog S, Kool M, Lakhani SR, Lopez-Otin C, Martin S, Munshi NC, Nakamura H, Northcott PA, Pajic M, Papaemmanuil E, Paradiso A, Pearson JV, Puente XS, Raine K, Ramakrishna M, Richardson AL, Richter J, Rosenstiel P, Schlesner M, Schumacher TN, Span PN, Teague JW, Totoki Y, Tutt AN, Valdes-Mas R, van Buuren MM, van't Veer L, Vincent-Salomon A, Waddell N and Yates LR; Australian Pancreatic Cancer Genome Initiative; ICGC Breast Cancer Consortium; ICGC MMML-Seq Consortium; ICGC PedBrain, Zucman-Rossi J, Futreal PA, McDermott U, Lichter P, Meyerson M, Grimmond SM, Siebert R, Campo E, Shibata T, Pfister SM, Campbell PJ and Stratton MR. Signatures of mutational processes in human cancer. Nature 2013; 500: 415-421.

[60] Antonia SJ, Lopez-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, Jager D, Pietanza MC, Le DT, de Braud F, Morse MA, Ascierto PA, Horn L, Amin A, Pillai RN, Evans J, Chau I, Bono P, Atmaca A, Sharma P, Harbison CT, Lin CS, Christensen O and Calvo E. 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: 883-895.

[61] Bonanno L, Pavan A, Dieci MV, Di Liso E, Schiavon M, Comacchio G, Attili I, Pasello G, Calabrese F, Rea F, Favaretto A, Rugge M, Guarneri V, Fassan M and Conte PF. The role of immune microenvironment in small-cell lung cancer: Distribution of PD-L1 expression and prognostic role of FOXP3-positive tumour infiltrating lymphocytes. Eur J Cancer 2018; 101: 191-200.

[62] Berghoff AS, Ricken G, Wilhelm D, Rajky O, Widhalm G, Dieckmann K, Birner P, Bartsch R and Preusser M. Tumor infiltrating lymphocytes and PD-L1 expression in brain metastases of small cell lung cancer (SCLC). J Neurooncol 2016; 130: 19-29.

[63] Iams WT, Shiuan E, Meador CB, Roth M, Bordeaux J, Vaupel C, Boyd KL, Summitt IB, Wang LL, Schneider JT, Warner JL, Zhao Z and Lovly CM. Improved prognosis and increased tumor-infiltrating lymphocytes in patients who have SCLC with neurologic paraneoplastic syndromes. J Thorac Oncol 2019; 14: 1970-1981.

[64] Wang H, Li Z, Dong B, Sun W, Yang X, Liu R, Zhou L, Huang X, Jia L and Lin D. Prognostic significance of PD-L1 expression and CD8+ T cell infiltration in pulmonary neuroendocrine tumors. Diagn Pathol 2018; 13: 30.

[65] Ott PA, Bang YJ, Piha-Paul SA, Razak ARA, Bennouna J, Soria JC, Rugo HS, Cohen RB, O'Neil BH, Mehnert JM, Lopez J, Doi T, van Brummelen EMJ, Cristescu R, Yang P, Emancipator K, Stein K, Ayers M, Joe AK and Lunceford JK. T-cell-inflamed gene-expression profile, programmed death ligand 1 expression, and tumor mutational burden predict efficacy in patients treated with pembrolizumab across 20 cancers: KEYNOTE-028. J Clin Oncol 2019; 37: 318-327.

[66] Guibert N, Delaunay M, Lusque A, Boubekeur N, Rouquette I, Clermont E, Mourlanette J, Gouin S, Dormoy I, Favre G, Mazieres J and Pradines A. PD-L1 expression in circulating tu-

mor cells of advanced non-small cell lung cancer patients treated with nivolumab. Lung Cancer 2018; 120: 108-112.

[67] Castello A, Carbone FG, Rossi S, Monterisi S, Federico D, Toschi L and Lopci E. Circulating tumor cells and metabolic parameters in NSCLC patients treated with checkpoint inhibitors. Cancers (Basel) 2020; 12: 487.

[68] Tamminga M, de Wit S, Hiltermann TJN, Timens W, Schuuring E, Terstappen LWMM and Groen HJM. Circulating tumor cells in advanced non-small cell lung cancer patients are associated with worse tumor response to checkpoint inhibitors. J Immunother Cancer 2019; 7: 173.

[69] Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, Chung HC, Kindler HL, Lopez-Martin JA, Miller WH Jr, Italiano A, Kao S, Piha-Paul SA, Delord JP, McWilliams RR, Fabrizio DA, Aurora-Garg D, Xu L, Jin F, Norwood K and Bang YJ. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020; 21: 1353-1365.

[70] Yang S, Zhang Z and Wang Q. Emerging therapies for small cell lung cancer. J Hematol Oncol 2019; 12: 47.

[71] Pietanza MC, Waqar SN, Krug LM, Dowlati A, Hann CL, Chiappori A, Owonikoko TK, Woo KM, Cardnell RJ, Fujimoto J, Long L, Diao L, Wang J, Bensman Y, Hurtado B, de Groot P, Sulman EP, Wistuba, II, Chen A, Fleisher M, Heymach JV, Kris MG, Rudin CM and Byers LA. 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: 2386-2394.

[72] Zhao L, Xing W, Yang Y, Zhang Y, Ma B, Fu X, Liang G, Shang Y, Wang Z, Lin H and Gao Q. The sequence of chemotherapy and anti-PD-1 antibody influence the efficacy of neoadjuvant immunochemotherapy in locally advanced esophageal squamous cell cancer: a phase II study. J Clin Oncol 2021; 39: 4051-4051.