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Combination therapy: Future directions of immunotherapy in small cell lung cancer

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ABSTRACT

Small cell lung cancer (SCLC), an aggressive and devastating malignancy, is characterized by rapid growth and early metastasis. Although most patients respond to first-line chemotherapy, the majority of patients rapidly relapse and have a relatively poor prognosis. Fortunately, immunotherapy, mainly including antibodies that target the cytotoxic T lymphocyte antigen-4 (CTLA-4), checkpoints programmed death-1 (PD-1), and programmed death-ligand 1 (PD-L1) to block immune regulatory checkpoints on tumor cells, immune cells, fibroblasts cells and endothelial cells, has achieved the milestone in several solid tumors, such as melanoma and non-small-cell lung carcinomas (NSCLC). In recent years, immunotherapy has made progress in the treatment of patients with SCLC, while its response rate is relatively low to monotherapy. Interestingly, the combination of immunotherapy with other therapy, such as chemotherapy, radiotherapy, and targeted therapy, preliminarily achieve greater therapeutic effects for treating SCLC. Combining different immunotherapy drugs may act synergistically because of the complementary effects of the two immune checkpoint pathways (CTLA-4 and PD-1/PD-L1 pathways). The incorporation of chemoradiotherapy in immunotherapy may augment antitumor immune responses because chemoradiotherapy can enhance tumor cell immunogenicity by rapidly inducing tumor lysis and releasing tumor antigens. In addition, since immunotherapy drugs and the molecular targets drugs act on different targets and cells, the combination of these drugs may achieve greater therapeutic effects in the treatment of SCLC. In this review, we focused on the completed and ongoing trials of the combination therapy for immunotherapy of SCLC to find out the rational combination strategies which may improve the outcomes for SCLC.

Contents

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Introduction

Small cell lung cancer (SCLC), which represents 10% to 20% of total lung cancers [1], is known as an highly aggressive cancer with dismal outcomes closely related to tobacco use and has a high mutation burden without known tumorigenic drivers [2]. SCLC has traditionally been divided into limited stage small cell lung cancer (LS-SCLC) and extensive stage small cell lung cancer (ES-SCLC). The platinum–etoposide doublet has remained the first-line standard chemotherapy, with topotecan as the second-line therapy over three decades [3]. While response with first line chemotherapy is achieved in about 70% for SCLC patients, relapse occurs rapidly in most cases (80% of patients with LS-SCLC and almost all patients with ES-SCLC recur or experience disease progression), and the outcomes of the second-line treatment (single-agent topotecan) are poor [4,5]. Approximately 20–40% of LS-SCLC patients and 5% of ES-SCLC patients survive for 2 years [6]. In addition, there are not yet third-line treatment for SCLC. And although recent results from targeted therapy trials are encouraging, most SCLC patients demonstrate rapid acquired resistance [7]. Thus, more effective treatments are urgently needed.

In the past few years, immune checkpoint inhibitors (ICIs) activating anti-tumor immunity to target and kill cancer cells have made unprecedented progress [8,9]. It is a common therapeutic approach to use antibodies whose chief targets include the immune checkpoints programmed death-1 (PD-1), PD-1 ligand (PD-L1), and cytotoxic T lymphocyte antigen-4 (CTLA-4) to block immune regulatory checkpoints on tumor and immune cells [10]. Due to the obvious effect of ICIs in several tumors, such as non-small cell lung cancer (NSCLC) and melanoma, several ICIs, including anti-CTLA-4 (tremelimumab and ipilimumab), anti-PD1 (nivolumab and pembrolizumab), and anti-PD-L1 (durvalumab and atezolizumab), have been approved by the US Food and Drug Administration (FDA) to treat patients with some advanced cancers [11,12]. Based on some improvements in clinical outcomes, immunotherapy has indicated a great therapeutic potential for the treatment of SCLC.

Although SCLC has a high mutation rate (tumor mutational burden (TMB), a biomarker of sensitivity to immunotherapy in SCLC) [13], only a small percentage of patients respond to ICIs (approximately 10% with anti-PD-1 monotherapy and 23% with anti-PD-1/anti-CTLA4 combination) [14,15], because of low expression of PD-L1, major histocompatibility complex-1 (MHC-1) as well as the excess of regulatory T cells (Tregs) which can inhibit activation, expansion and effector functions of other T cells [16]. The low expression of MHC-1 will result in a decrease of cytotoxic T-lymphocytes (TILs) infiltrating in SCLC tumor, which is a negative factor in the immunotherapy response [17]. Recently, many studies showed that the combinations (multi-ICIs, immunotherapy/chemoradiotherapy and immunotherapy/ targeted therapy) have obvious effect in the treatment of SCLC [14,18–21]. Thus, it is of vital importance to find out the promising combination treatment strategies to acquire better effects for the treatment of SCLC.

Monotherapy and combination therapy for immunotherapy

The CTLA-4 and PD-1/PD-L1 immune checkpoint pathways can maintain peripheral tolerance by downregulating T cell activation, which can be utilized by tumors to form an immunosuppressive state whereby the tumors continue to grow without being recognized and eliminated by the autoimmune system. Therefore, it is a promising method to restore antitumor immune responses for the treatment of SCLC through the inhibition of CTLA-4 and PD-1/PD-L1 pathways. Interestingly, some studies have reported that the presence of paraneoplastic syndromes, such as Lambert-Eaton syndrome, most commonly accompanied by SCLC, is associated with a better prognosis for SCLC [22,23]. Moreover, tumor tissue from SCLC patients with neurologic paraneoplastic syndromes presented with increased tumor infiltrating lymphocytes [24]. These immune-mediated neurologic syndromes can be induced by ICIs, which suggest that the SCLC patients might be response highly to immunotherapy with ICIs [25].

Monotherapy

Nivolumab (a fully human monoclonal antibody against PD-1), in a phase I/II, multicenter, open-label trial, was proven the safety and efficacy in the third-line therapy for recurrent SCLC [26]. There are 109 patients receiving nivolumab (3 mg/kg every 2 weeks) as third- or later-line treatment, until disease progression or intolerable toxicity. At the median follow-up time (28.3 months), the overall response rate (ORR) was 11.9% (95% confidence interval (CI): 6.5–19.5) and the median duration of response (DOR) was 17.9 months (95% CI: 7.9–42.0). The median progression free survival (PFS) was 1.4 months (95% CI: 1.3–1.6) and 17.2% of patients, at 6 months, were progression-free. The median overall survival (OS) was 5.6 months (95% CI: 3.1–6.8) and the 12-month and 18-month OS rates were 28.3% (95% CI: 20.0–37.2) and 20.0% (95% CI: 12.7–28.6), respectively. The treatment-related adverse events (TRAEs) of grade 3 or 4 occurred in 11.9% of the treated patients. Three patients discontinued because of TRAEs. Based on these results, nivolumab monotherapy was approved by the FDA as the third-line treatment of advanced SCLC. Unfortunately, a global, open-label, randomized phase III trial (Checkmate 331) reported that single-agent treatment of nivolumab was not as expected compared to chemotherapy with topotecan or amrubicin in SCLC patients that relapsed after platinum-based therapy [27]. In this trial, nivolumab did not improve survival compared to chemotherapy: the median OS were 7.5 months and 8.4 months, respectively. Both the response rate (13.7% vs. 16.5%) and PFS (1.4 months vs. 3.8 months) supported chemotherapy in numerical values. However, in the China cohort, the median OS in patients treated with nivolumab was longer, 11.5 months and 7.0 months (HR = 0.70; 95%CI: 0.42–1.17), respectively, compared with chemotherapy, and the ORR of the two groups was 20.6% and 4.7%, respectively. Perhaps there is a difference in the efficacy of nivolumab in different subgroups, which needs further clinical trials in different subgroups.

Pembrolizumab, an anti-PD1 humanized IgG4 antibody, was initially explored in relapsed ES-SCLC with positive expression of PD-L1 in a phase Ib basket study (KEYNOTE 028) [15]. In this study, PD-L1 positive was defined as membranous PD-L1 expression ≥1% of tumor and associated inflammatory cells or positive staining in the stroma. Twenty-four patients with PD-L1-positive were enrolled and received the treatment of pembrolizumab (10 mg/kg every 2 weeks). As a result, though the median PFS was 1.9 months, the ORR was 33.3% with the median DOR (19.4 months) and the median OS was 9.7 months. Among the 24 patients, the most common adverse events (AEs) were fatigue (n = 7), asthenia (n = 7), and cough (n = 6). Moreover, a multicenter, open label, single group assignment phase II trial was conducted to evaluate the effect of pembrolizumab in 107 patients with recurrent SCLC. The ORR was 18.7% for the overall cohort. The median PFS was 2.0 months with the OS of 9.1 months, regardless of the status of PD-L1 expression. In this study, the tumor PD-L1 level was evaluated through the PD-L1 IHC 22C3 pharmDx assay, and samples with a PD-L1 combined positive score of at least 1 were considered positive. The combined positive score was the ratio of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) to the total number of tumor cells multiplied by 100. In PD-L1 positive patients (n = 42), the anti-cancer effect was more promising than those (n = 50) with PD-L1 negative expression. The ORR was 35.7% and 6%; the

median OS was 14.9 months and 5.9 months; and the median PFS was 2.1 months and 1.9 months, respectively. 63 patients occurred TRAEs, mainly including fatigue, pruritus, hypothyroidism, decreased appetite and nausea [28]. A single-arm phase II study conducted by Gadgeel et al. [29] evaluated the effect of pembrolizumab for the maintenance therapy in ES-SCLC patients with a response or stable disease after completion of first-line chemotherapy (etoposide-platinum). For all enrolled patients treated with pembrolizumab at a dosage of 200 mg every 3 weeks, the response rate was 11.1% (95% CI: 4.8–23.5). The median PFS was 1.4 months (95% CI: 1.3–2.8). The 6-month and 12-month PFS rates were 20% and 13%, respectively. The median OS was 9.6 months (95% CI: 7.0–12). Although maintenance pembrolizumab did not improve median PFS compared with the historical data, based on PD-L1 expression at the stromal interface (tumor PD-L1 status was assessed by using the DAKO 22C3 antibody and PD-L1 positive was considered if a lichenoid pattern of PD-L1 membrane-stained cells surrounding the tumor nests was identified at low power), the PD-L1-positive patients ($n = 8$) had longer median PFS compared with the patients with negative PD-L1 ($n = 12$): 6.5 (95% CI: 1.1–12.8) months vs. 1.3 (95% CI: 0.6–2.5) months. This PD-L1 expression renders tumor-specific T cells inactive and, therefore, may serve as an immune escape mechanism in cancer immunotherapy. Because the binding of PD-1 and PD-L1 renders CTLs inactive and increases the infiltration of Tregs into tumor, which serves as an immune escape mechanism in cancer, pembrolizumab can block this bond to act against tumor. Therefore, pembrolizumab might benefit a subset of SCLC patients with positive expression of PD-L1.

Atezolizumab, a humanized monoclonal anti-PD-L1 antibody, can promote activation and proliferation of T cells through the inhibition of the binding of PD-L1 to PD-1 and B7–1 receptors (also known as CD80) [30]. A phase I study demonstrated that atezolizumab single-agent presented promising DOR without serious side effects in patients with relapsed SCLC [31]. In this study, all 17 patients with ES-SCLC who receive treatment of atezolizumab (15 mg/kg or 1200 mg every 3 weeks) were evaluated. The ORR was 6%; the median OS was 5.9 (95% CI 4.3–20.1) months; the median PFS was 1.5 (95% CI 1.2–2.7) months. Grade > 2 toxicity was observed in 2 patients. Grade 5 hepatic failure was seen in one patient and one patient experienced a grade 3 pneumonitis, resulting in treatment discontinuation. However, the IFCT-1603 study, a randomized non-comparative phase II study, showed that atezolizumab monotherapy failed to show significant efficacy in the second-line treatment for SCLC [32]. At 6 weeks, 1 of 43 eligible patients who experienced a relapse after first-line chemotherapy (platinum and etoposide) treated with atezolizumab achieved an objective response (OR), whereas 8 others had stable disease (SD) (20.9%). Compared to chemotherapy, the median PFS was significantly shorter with atezolizumab: 1.4 (CI 1.2–1.5) months versus 4.2 (CI 1.5–5.9) months, respectively. The median OS did not significantly differ between the atezolizumab group and the chemotherapy group (9.5 months vs. 8.7 months, respectively). In this study, PD-L1 expression was assessed in tumor samples according to previously published scoring criteria using the Ventana SP142 PD-L1 immuno-histochemistry assay. Among 53 evaluable specimens, only 1 (2%) was proven positive for PD-L, which may be the reason for the failure of this clinical trial. Moreover, another reason for this result may be the small number of patients investigated, which is the main limitation of the study. Therefore, whether PD-L1 expression affects the efficacy of atezolizumab in SCLC must await analysis in a larger population.

Combination immunotherapy

As mentioned above, although a single agent of immunotherapy has potential efficacy in SCLC, its response rate is relatively low. One approach appears to solve this problem by combining CTLA4 inhibitor with PD-1 inhibitor or PD-L1 inhibitor to enhance the immune activity over either therapy alone, which were observed in patients with some other tumors, such as melanoma [33]. The CTLA-4 can suppress the T cells proliferation at the initial stage of an immune response, mainly in lymph nodes, while PD-1 can inhibit previously activated T cells at the later stages of this response, typically in peripheral tissue, including tumors tissue [34]. The anti-CTLA4 antibody can activate antigen-specific T cells and clear Tregs in the tumor microenvironment. The blocking of PD-L1 or PD-1 can restore the killing effect of T cells on tumors [35]. In addition, a study (in vivo) disclosed that anti-CTLA-4 agents induced a proliferative signal primarily in a subset of transitional memory T cells, while anti-PD-1 agents can lead to changes in genes involved in cytolysis and natural killer cells (NK cells) function [36]. Combination therapy will result in nonredundant changes in the expression of genes associated with the proliferation of tumor and expression of chemokine [36]. Due to the differences in timing, location, and nonoverlapping effects of the two immune checkpoint pathways, the combination of anti-CTLA-4 agents and anti-PD-1 or anti-PD-L1 drugs may have the potential synergistic effects in the immunotherapy of SCLC.

Nivolumab in combination with ipilimumab. Checkmate-032, a multicenter, multi-arm, phase I/II trial, was performed to evaluate the safety and effect of nivolumab alone and nivolumab plus ipilimumab in SCLC patients who progressed after at least one platinum-based chemotherapy. In this trial, 216 enrolled patients received nivolumab (3 mg/kg ($n = 98$)) every 2 weeks or nivolumab plus ipilimumab (1 mg/kg plus 1 mg/kg ($n = 3$), 1 mg/kg plus 3 mg/kg ($n = 61$), or 3 mg/kg plus 1 mg/kg ($n = 54$)) every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg every 2 weeks, until disease progression or intolerable toxicity. The ORR was 10% in the nivolumab monotherapy cohort, 33% in the nivolumab 1 mg/kg plus ipilimumab 1 mg/kg cohort, 23% in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort, and 19% in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort. And the median PFS was 1.4 months (nivolumab), 2.6 months (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg), and 1.4 months (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg). The median OS was 4.4, 7.7, and 6.0 months, respectively. However, the combination of nivolumab and ipilimumab also increased the rate of the grade 3/4 TRAEs compared to nivolumab alone: 13/98 (13%) for the nivolumab 3 mg/kg group, 18/ 61 (30%) for the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg group, and 10/ 54 (19%) for the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg group, respectively [14]. The above results, from the initial treatment arms, revealed the tolerability and efficacy of nivolumab plus ipilimumab, promoting the addition of a randomized expansion cohort to further assess the effect of the combination of nivolumab and ipilimumab on advanced SCLC. In this expansion cohort, 242 patients were divided randomly 3:2 to nivolumab alone or nivolumab plus ipilimumab. The response patterns were consistent with the initial (non-randomized) trial: 12% (nivolumab monotherapy) and 21% (nivolumab plus ipilimumab) [18]. CheckMate 451, a global, double-blind, phase III study, enrolled 834 patients with ES-SCLC who did not progress on the first-line platinum-based chemotherapy, to evaluate the safety and activity of nivolumab plus ipilimumab vs. nivolumab vs. placebo as maintenance therapy. These patients were randomized 1:1:1 to receive nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (every 3 weeks for four cycles followed by maintenance nivolumab 240 mg every 2 weeks, $n = 279$), nivolumab 240 mg (every 2 weeks, $n = 280$) or placebo ($n = 275$), until progression or unacceptable toxicity. The primary endpoint (OS) was not significantly prolonged with nivolumab plus ipilimumab as compared to placebo, with a median OS of 9.2 and 9.6 months, respectively. OS was also not improved for nivolumab vs. placebo. PFS was marginally improved with nivolumab plus ipilimumab vs. placebo (1.7 months vs. 1.4 months, HR 0.72, 95% CI 0.60–0.87). Safety profiles of nivolumab plus ipilimumab and nivolumab were consistent with previous reports at this dose/schedule in SCLC [37]. Therefore, based on the above data analysis, nivolumab plus ipilimumab might benefit the recurrent SCLC patients after at least one platinum-based chemotherapy. However, nivolumab in combination with ipilimumab, as the maintenance therapy after the first-line platinum-based chemotherapy, did not show the expected effect for the patients with SCLC.

Durvalumab in combination with tremelimumab. A phase I clinical trial was performed to evaluate the safety profile and activity of dual checkpoint inhibition with the durvalumab (a human IgG1 monoclonal antibody targeting PD-L1) in combination with the tremelimumab (a fully human

IgG2 monoclonal antibody targeting CTLA-4) in the patients with ES-SCLC [38]. In this study, 30 patients were enrolled in the expansion phase and received dual-agent treatment (durvalumab 20 mg/kg plus tremelimumab 1 mg/kg every four weeks for 7 doses, then every 12 weeks for 2 doses, followed by durvalumab 10 mg/kg every two weeks for up to 12 months). 20/30 (67%) patients reported ≥1 TRAEs, among which the most common TRAEs were pruritus (n = 7 (23%)) and fatigue (n = 7 (23%)). Seven patients experienced Grade 3 or 4 TRAEs. Confirmed ORR was 13.3% (95% CI 3.8–30.7); the median DOR was 18.9 months (95% CI: 16.3–18.9). At 16 weeks, disease control rate (DCR) was 20.0% (95% CI: 7.7–38.6). The median OS was 7.9 months (95% CI: 3.2–15.8), and 12-month OS rate was 41.7% (95% CI: 23.3–59.2). Besides, the median PFS was 1.8 months (95% CI 1.0–1.9). This study indicates that combination therapy (durvalumab plus tremelimumab) exhibited an acceptable safety and promising efficacy for the pretreated patients with ES-SCLC. Further large clinical trials (phase II / III) of combination therapy (durvalumab in combination with tremelimumab) should be warranted to better understand its safety profile and activity in the patient with SCLC. At present, several clinical trials are ongoing to evaluate the effect of combination immunotherapy in the treatment of patients with SCLC (**Table 1**, Table 2).

Immunotherapy in combination with chemoradiotherapy

Currently, etoposide or irinotecan with platinum plus concurrent or sequential thoracic radiotherapy is a recommended standard treatment for LS-SCLC, Unfortunately, with the shortage of specific symptoms and rapid tumor growth, ES- SCLC accounts for the majority of new cases (approximately 65%) [39]. In the extensive stage, first-line standard chemotherapy is the mainstay treatment. Despite sensitivity to the initial treatment, the majority of SCLC patients rapidly develop recurrent disease, often with additional sites of metastasis. Fortunately, studies have revealed an unexpected ability that chemotherapy and radiotherapy can promote immune responses by enhancing tumor cell immunogenicity, enhancing MHC-I expression, directly activating immune effectors such as NK cells and targeting immunosuppressive cells such as Tregs defined as an essential mediator of immune tolerance [40–42]. In addition, there is increasing evidence that chemotherapy or radiation can decrease the immunosuppressive properties of cancer via reducing the tumor mass (debulking) and create an environment more suitable for T-cell activation [43,44]. Therefore, the treatment efficacy of immunotherapy may be optimized through concomitant treatment with chemoradiotherapy in SCLC.

Combining chemotherapy

Due to the aggressive course of SCLC and the low response, immunotherapy alone, as a first-line therapy, is too risky in an unselected population. If no responses were observed, patients with SCLC would lose the reliable benefit of chemotherapy. Interestingly, there is an unexpected interplay between the chemotherapy and immune system. On the one hand, chemotherapy enhances the immunogenicity of tumor cells through cell-surface calreticulin exposure on tumor cells, autophagy induction, mobility group box 1 protein and ATP release [45–47]. On the other hand, chemotherapy can activate immune effectors such as NK cells and prevent tumor-induced immunosuppression. For example, cisplatin, the common drug in the treatment of SCLC, can activate NK cells by triggered the expression of ligands of the activating NK cells receptor NKG2D [48]. In addition to this effect, cisplatin can disrupt signal transducer and activator of transcription 6 and then reduce expression of the programmed death receptor-ligand 2 on both dendritic cells (DCs) and tumor cells, leading to decrease of the immunosuppressive capability of tumor cells [49]. Thus, it is expected that combinations of chemotherapy and immunotherapy can be used to achieve long-lasting anticancer responses in the treatment of SCLC.

The IMpower 133, a double-blind, placebo-controlled, phase III trial, was performed to evaluate the efficacy of adding atezolizumab to first-line treatment with etoposide and carboplatin in patients with ES-SCLC who had not previously received treatment [19]. In a 1:1 ratio, 403 enrolled patients were randomly assigned to receive atezolizumab (n = 201, at a dose of 1200 mg on day 1 of each cycle) or placebo (n = 202) combined with four cycles of etoposide (100 mg/m2 on days 1–3) plus carboplatin (area under the curve (AUC) 5 on day 1) every 3 weeks, followed by maintenance atezolizumab or placebo until the occurrence of unacceptable toxic effects or disease progression. At a median follow-up of 13.9 months, the addition of atezolizumab significantly improved overall survival. Median OS was 12.3 months (atezolizumab) versus 10.3 months (placebo), with stratified hazard ratio (HR) of 0.70 (95% CI, 0.54 to 0.91; P = 0.007), and the 1-year OS was improved from 38.2% to 51.7%. A significant improvement in PFS was also found in the atezolizumab group compared to the placebo group (median, 5.2 (95% CI, 4.4–5.6) months vs. 4.3 (95% CI, 4.2 to 4.5) months; HR, 0.77 (95% CI, 0.62 to 0.96); P = 0.02) (Table 3, NCT02763579). The side effects were similar in the two groups, and immune-related adverse events were consistent with the previously reported adverse events of atezolizumab monotherapy. This study indicated a significant amelioration in efficacy for patients with SCLC treated with atezolizumab in combination with the standard carboplatin-etoposide regimen, making it the FDA-approved frontline treatment for ES- SCLC.

There were two phase II trials and a phase III clinical trial to examine the safety and efficacy of ipilimumab in combination with chemotherapy in newly diagnosed patients with ES-SCLC (Table 3).

In a multicenter, double-blind, randomized phase II trial (CA184-041) [20], patients (n = 130) with previously untreated ES-SCLC were randomized (1: 1: 1) to receive control cohort (6 doses of placebo plus paclitaxel plus carboplatin), concurrent-ipilimumab cohort (4 doses of ipilimumab plus paclitaxel plus carboplatin followed by 2 doses of placebo plus paclitaxel plus carboplatin) and phased-ipilimumab cohort (2 doses of placebo plus paclitaxel plus carboplatin followed by 4 doses of ipilimumab plus paclitaxel plus carboplatin). Treatment, carboplatin (AUC = 6) plus paclitaxel (175 mg/m2) in addition to ipilimumab (10 mg/kg) or placebo, was administered every 3 weeks for 6 cycles, followed by placebo (control cohort) or ipilimumab (phased and concurrent cohort) as maintenance treatment every 12 weeks, until progression, intolerance or death. Phased ipilimumab

Table 1
Ongoing studies of combination immunotherapy in SCLC.

Design	Phase	Condition	n	Endpoint	ClinicalTrials.gov identifier
Nivolumab + Ipilimumab	II	Recurrent ES-SCLC who have previously received platinum-based chemotherapy	40	Primary: change in the ratio of Teff/Treg Secondary: RR; DOR; PFS	NCT03670056
Nivolumab + Ipilimumab + Ad.p53-DC	II	Recurrent SCLC who received at least one prior treatment with a platinum containing regimen	41	Primary: DCR Secondary: PFS; OS; ORR; IR	NCT03406715
Nivolumab vs. Nivolumab + Ipilimumab vs. Placebo	III	ES-SCLC after completion of platinum-based first line chemotherapy	1327	Primary: OS Secondary: PFS;	NCT02538666

Abbreviations Ad.p53-DC: dendritic Cell based p53 Vaccine; DCR: disease control rate; DOR: duration of response; ES-SCLC: extensive-stage small cell lung cancer; IR: immune response; ORR: overall response rate; PFS: progression-free survival; RR: response rate; SCLC: small cell lung cancer; Teff: effector T cells; Treg: regulatory T cells.

Table 2
Ongoing studies of combining immunotherapy with chemotherapy and combining immunotherapy with radiotherapy ± chemotherapy in SCLC.

Treatment	Phase	Condition	n	Endpoint	ClinicalTrials.gov identifier
IM + CT					
Durvalumab + tremel-imumab + CE vs. Durvalumab + CE	I	Untreated ES-SCLC	18	Primary: safety and tolerability	NCT03963414
Avelumab + CE	II	Advanced SCLC	55	Primary: 1-year PFS rate Secondary: OS; BOR; ORR;	NCT03568097
Nivolumab + CE vs. CE	II	ES-SCLC	150	Primary: PFS Secondary: OS; BOR; AEs	NCT03382561
Durvalumab + tremel-imumab + CE vs. durvalumab + CE vs. CE	III	Untreated ES-SCLC	988	Primary: OS Secondary: PFS; ORR	NCT03043872
Atezolizumab + CE	IIIB	Untreated ES-SCLC	150	Primary: safety Secondary: OS; PFS; ORR; DOR	NCT04028050
Pembrolizumab + CE vs. Placebo + CE	III	ES-SCLC	453	Primary: PFS; OS Secondary: ORR; DOR; AEs	NCT03066778
IM + RT					
ipilimumab + nivolu-mab + TRT	I / II	ES-SCLC after CT	21	Primary: recommended phase II dose (Phase I); PFS (Phase II) Secondary: OS	NCT03043599
Atezolizumab + SHRT	II	Recurrent SCLC	35	Primary: OS Secondary: PFS	NCT03262454
Tremelimumab + dur-valumab vs. Tremelimumab + dur-valumab + SBRT or HRT	II	Recurrent SCLC	28	Primary: PFS; ORR Secondary: IrORR; OS	NCT02701400
IM + CT + RT					
LS-SCLC, pembrolizumab + CT + RT ES-SCLC, pembrolizumab + RT	I	• LS-SCLC; ES-SCLC;	80	Primary: side effects and best dose of pembrolizumab Secondary: RR; PFS; OS; Biomarker response	NCT02402920
Atezolizumab after concurrent chemoradiation vs. chemoradiation alone	II	• LS-SCLC	212	Primary: 2 years survival Secondary: PFS; BRR; TRAEs;	NCT03540420
Concurrent RT + CT + durvalumab, followed by consolidation durvalumab	II	LS-SCLC After chemoradiation	51	Primary: PFS Secondary: OS; safety	NCT03585998
Nivolumab + ipilim-umab vs. no intervention	II	LS-SCLC after chemoradiation	264	Primary: OS; PFS Secondary: OR; Time to treatment failure; Toxicity	NCT02046733
Pembrolizumab + co-ncurrent CT ± RT	II	ES-SCLC.	60	Primary: PD-L1 expression Secondary: PFS; OS	NCT02934503
Atezolizumab + CE + 3D-CRT or IMRT vs. CE + 3D-CRT or IMRT	II/ III	LS-SCLC	506	Primary: PFS (Phase II); OS (Phase III) Secondary: PFS (phase III); AE; ORR	NCT03811002

Abbreviations AEs: adverse events; BOR: best overall response; BRR: best response rate; CE: cisplatin/carboplatin + etoposide; CT: chemotherapy; DOR: duration of response; ES-SCLC: extensive-stage small cell lung cancer; HRT: hypofractionated radiotherapy; IMRT: Intensity-Modulated Radiotherapy; irORR: Immune-related objective response rate; IT: immunotherapy; LE-SCLC: limited-stage small cell lung cancer; OR: objective response; ORR: objective response rate; OS: overall survival; PFS: progression free survival; RR: response rate; RT: radiotherapy; SBRT: stereotactic body radiotherapy; SCLC: small cell lung cancer; SHRT: sequential hypofractionated radiotherapy; TRT: thoracic radiotherapy; TRAEs: treatment-related adverse events; 3D-CRT: 3-Dimensional Conformal Radiotherapy;

regimen, but not concurrent ipilimumab, improved immune-related (ir) PFS compared with control (HR, 0.64; $P = 0.03$). The median irPFS was 6.4 months (phased ipilimumab), 5.7 months (concurrent-ipilimumab), and 5.3 months (control), and median PFS is 5.2, 3.9 and 5.2 months, respectively. The median OS was 9.9 months for control, 9.1 months for concurrent ipilimumab, and 12.9 months for phased ipilimumab (HR = 0.95, 0.75; $P = 0.41$, 0.13). Control, phased ipilimumab, and concurrent ipilimumab, respectively, were associated with the best overall response rate (BORR) of 49, 57 and 33%, while the irBORR of 53%, 49%, and 71%. Grade 3/4 TRAEs appeared higher in ipilimumab containing cohort (phased, 50%; concurrent, 43%) than in the control cohort (30%). The overall incidence of immune-related grade 3/4 AEs were 9, 17 and 21% for control, phased ipilimumab and concurrent ipilimumab, respectively. The results indicated that ipilimumab plus chemotherapy might improve outcomes and their sequencing may affect clinical outcomes for patients with untreated ES-SCLC.

Table 3
Completed clinical trials of combining immunotherapy with chemotherapy in ES-SCLC.

ClinicalTrials.gov identifier	phase	Treatment arms	PFS (month)	OS (month)
NCT01331525	II	Ipi/Pac/Car ($n = 42$)	6.9 (95% CI: 5.5–7.9)	17.0 (95% CI 7.9–24.3)
NCT00527735	II	6 doses of Pla/Pac/Car ($n = 45$) vs. 4 doses of Ipi/Pac/Car followed by 2 doses of Pla/Pac/Car ($n = 43$) vs. 2 doses of Pla/Pac/Car followed by 4 doses of Ipi/Pac/Car (n = 42)	5.3 vs. 5.7 vs. 6.4 [HR = 0.75 (95% CI, 0.48–1.19), $P = 0.11$; HR = 0.64(95% CI, 0.40–1.02), $P = 0.03$)]	9.9 vs. 9.1 vs. 12.9 [HR = 0.95, (95% CI, 0.59–1.54), $P = 0.41$; HR = 0.75(95% CI, 0.46–1.23), $P = 0.13$]
NCT02763579	III	Pla/Eto/Car, maintained with Pla ($n = 202$) vs. Ate/Eto/Car maintained with Ate ($n = 201$)	4.3 vs. 5.2 [HR = 0.77 (95% CI, 0.62–0.96), $P = 0.02$]	10.3 vs. 12.3 [HR = 0.70(95% CI, 0.54–0.91), $P = 0.007$]
NCT01450761	III	Pla/Eto/Plat ($n = 476$) vs. Ipi/Eto/Plat ($n = 478$)	4.4 vs. 4.6 [HR = 0.85(95% CI, 0.75–0.97), $P = 0.016$]	10.9 vs. 11.0 [HR = 0.94(95% CI, 0.81–1.09), $P = 0.3775$]

Abbreviations Ate: atezolizumab; Car: carboplatin; CI: confidence interval; ES-SCLC: extensive-stage small cell lung cancer; Eto: etoposide; HR: hazard ratio; Ipi: ipilimumab; Pac: paclitaxel; PFS: progression-free survival; Pla: placebo; Plat: platinum; OS: overall survival.

Another multicenter phase II study was conducted to explore the efficacy of ipilimumab (10 mg/kg, was given every 12 weeks for 3 to 6 cycles) combined with standard first-line chemotherapy (paclitaxel / carboplatin for up to 6 cycles) for patients with ES-SCLC [50]. This study enrolled 42 patients, and the OR by RECIST and the immune-related response criteria is 72.4% and 84.8%, respectively, in the patients evaluable for response. 15.8% of patients achieved PFS at 1-year by RECIST. The median PFS was 6.9 months (95% CI: 5.5–7.9) and the median irPFS was 7.3 months (95% CI: 5.5–8.8). The median OS was 17.0 months (95% CI: 7.9–24.3). All patients experienced at least one AEs, and at least one ≥grade 3 toxicity appeared in 35/39 (89.7%) of patients, 69.2% related to ipilimumab. Additionally, 5 deaths were thought to be associated with ipilimumab.

CA184-156 study, a randomized, double-blind phase III clinical trial, was carried out to evaluate the combination of ipilimumab (10 mg/kg) with etoposide / platinum vs. placebo combined with etoposide/platinum in patients with newly diagnosed ES-SCLC [51]. Of the 1132 enrolled patients, 213 patients receiving at least one dose of blinded study therapy were evaluable (ipilimumab plus chemotherapy (n = 478); placebo plus chemotherapy (n = 476)). However, no difference was seen in median OS between chemotherapy plus ipilimumab group and chemotherapy plus placebo group (11.0 vs. 10.9 months; HR, 0.94; 95% CI, 0.81 to 1.09; P = 0.3775). The median PFS was also not significantly improved (4.6 vs. 4.4 months; HR, 0.85; 95% CI, 0.75 to 0.97; P = 0.016). BORR were similar in the two group. Rates of TRAEs were similar between the arms, 82% with chemotherapy plus ipilimumab and 76% with chemotherapy plus placebo. Diarrhea, rash, and colitis were more frequent in chemotherapy plus ipilimumab. The rate of treatment-related discontinuation in ipilimumab plus chemotherapy was higher than the placebo cohort (18% v 2%). There were 5 treatment-related deaths in the chemotherapy plus ipilimumab, while 2 treatment-related deaths in the chemotherapy plus placebo.

It is worth noting these two clinical trials (The IMpower 133 and CA184-156 study). it's not hard to find that atezolizumab plus first-line chemotherapy (carboplatin-etoposide), compared with chemotherapy alone, significantly improve the OS and PFS in the treatment of patients with SCLC, but ipilimumab plus first-line chemotherapy (platinum- etoposide) do not improve the OS and PFS. One possible explanation is that ipilimumab can stimulate peripheral T-cell activation but does not activate T cells in the tumor microenvironment [9]. In contract, atezolizumab be able to activate intratumoral T lymphocytes [9]. In addition, carboplatin and etoposide may decrease peripheral T-cell activation and proliferation, but not deplete the intratumoral T-cell population. Therefore, it is rational that atezolizumab in addition to first-line chemotherapy can benefit the SCLC patients.

Combining a promising chemotherapeutic drug: arsenic trioxide

Arsenic trioxide (As_2O_3), the most active single drug in the treatment of acute promyelocytic leukemia (APL), has been approved by the US FDA for treating APL [52]. As_2O_3 can cure APL through degradation of PML-RARa fusion protein, which is the main mechanism in the treatment of APL [53]. In recent years, the immunoregulation role of As_2O_3 has been proved by numerous studies in the treatment of tumors. In APL NB4 cell line, low doses of As_2O_3 (1 μM) can increased cytolytic activity of NK cells against APL by increasing the expression of activating receptors (NKP30, NKG2D, and KIR2DS4), decreasing expression of inhibitory receptors KIR3DL1/DL2, and increasing expression of activating ligand (MICA/B, DNAM-1 ligand and HLA class I) [54]. Moreover, a study examined the effect of ATO administration on myeloid-derived suppressor cells (MDSCs) from mice bearing either the melanoma B16 or hepatoma H22 cells, and revealed that the immunoregulatory effects of As_2O_3 was achieved by inhibiting the activity of MDSCs and by enhancing T-cell function [55]. In addition, several studies have shown that As_2O_3 might serve as an immune adjuvant by the depletion of Tregs to enhance antitumor immune responses in the treatment of several solid tumors, such as colon cancer and liver cancer [56–58]. Interestingly, some previous researches indicated that As_2O_3 can inhibit the growth of SCLC. Pettersson HM et al. reported that low doses of As_2O_3 could induce SCLC cells death by inducing a mixed necrotic and apoptotic cell death. And SCLC cells were more sensitive than NSCLC cells to As_2O_3, with lower IC_{50} values (1 to 2 Amol/L vs. 2 to 5 Amol/L) [58]. In a word, As_2O_3 can significantly inhibit SCLC through various mechanisms as follow: 1) induces cytotoxicity via altered redox homeostasis and mitochondrial integrity [59]; 2) inhibits tumor growth through antiangiogenesis through the blockade of Notch signaling [60]; 3) inhibits the metastasis by blocking calcineurin-nuclear factor of activated T cells signaling [61]. However, the results from a phase II clinical trial of As_2O_3 for the treatment of patients with relapsed SCLC are frustrating. Of 17 evaluable patients, no complete or partial responses were observed. 2 (12%) patients acquired stable disease and 15 (88%) patients developed progressive disease. The median time to progression was 7 weeks (1–17 weeks) and the median OS was 4.5 months (2–7 months) [62]. There was a study demonstrating that As_2O_3 may induce cancer immunoresistance by up-regulation of PD-L1 surface expression in human HL-60 leukemia cells [63]. However, there is a lack of research on the combination of As_2O_3 with ICIs, such as anti-PD-1/anti-PD-L1, in the treatment of SCLC.

Combining radiotherapy

Radiotherapy is critical for the treatment of patients with SCLC, both in curative and palliative settings. Although, in patients with LS-SCLC, the optimal radiation dose and optimal timing (sequential or concurrent) is still not clear, the addition of thoracic radiotherapy to platinum-based chemotherapy is recommended [64]. Besides, some studies demonstrate that the combination of thoracic radiotherapy and chemotherapy seems to benefits to patients with ES-SCLC [65]. In addition, in a phase III trial [66], prophylactic cranial irradiation provided a survival benefit and was recommended for responders with either LS- or ES-SCLC [67].

Current evidence demonstrates that radiotherapy can trigger both local and systemic immune responses via diverse mechanisms to promote tumor cell death. What is most noteworthy is that the abscopal effect, which is described as the regression and rejection of non-irradiated and distant tumor lesions induced by radiation [68], have been reported in some tumors, such as lung adenocarcinoma [69]. Although the mechanism involved has remained unclear, this phenomenon is proposed to be associated with the systemic immune responses induced by radiation. With the advent of immunotherapy, the interaction of radiotherapy and immune system has gained particular interest. Interestingly, some studies have shown that immunotherapy can boost the abscopal effect and radiotherapy is able to intensify the effect of immunotherapy [70,71]. And this interaction between radiation and immunotherapy has been increasingly reported in several tumors, such as NSCLC [72], melanoma [73], intrahepatic cholangiocarcinoma [74]. The mechanism might be as follows.

On the one hand, the immune system can recognize damaged cells induced by ionizing radiation via identifying some specific molecules, such as oxidized DNA, heat shock proteins (HSPs), and ATP etc. released by radiation damage [75,76]. These specific molecules function as an alarm for the immune system. These alarms can be recognized by antigen presentation cells (APCs) through binding to some receptors on the surface of APCs and presented to $CD4^+$ and CTLs. For example, oxidized DNA originating from the nucleus or mitochondria is able to bind to toll-like receptor 9 (TLR9), resulting in the induction of inflammatory responses through the activation of inflammasome [77]. HSP70 can also engage with TLR4 and CD91, leading to the activation of both NK cells and CTLs [78]. In response to these alarms, CTLs release inflammatory cytokines including TNF-α and IFN-γ. These cytokines are able to activate CTLs and induce the transformation of $CD4^+$ to CTLs [79]. In addition, these cytokines can suppress mesenchymal derived suppressor cells and Tregs [80]. Furthermore, radiation can promote the release of chemokines that recruit inflammatory cells, such as DCs, macrophages and CTLs into the tumor microenvironment,

augmenting immune responses against tumor [81]. Therefore, based on the above mechanisms, radiotherapy can trigger the immune system against cancer cells. On the other hand, immunotherapy can strengthen these effects by stimulating the APCs and effector cytotoxic T cells and depleting intratumoral Tregs [82].

Hence, it is rational that the combination of radiotherapy with immunotherapy can strengthen the anti-tumor immune response locally and systemically. At present, there are several ongoing clinical trials that employ immunotherapy in combination with radiotherapy to exploit its synergistic effects in the patients with SCLC (Table 2). In addition, several trials utilizing ICIs to maintain an immune response after chemoradiation treatment are ongoing (Table 2). However, there are not completed trials combining radiotherapy with ICB for SCLC so far.

Combining immunotherapy and targeted therapy

Molecular targeted therapy, a revolutionary treatment that inhibits the growth, progression, and metastasis of cancer by interfering with specific molecules, has shown significant clinical success in treating NSCLC [83]. In recent years, with the deeper unravelling of the molecular mechanisms underlying the carcinogenesis of SCLC, there is new hope that some molecular targeted drugs might achieve adequate clinical benefits by inhibiting poly ADP-ribose polymerase (PARP), delta-like protein 3 (DLL3) pathway, and vascular endothelial growth factor (VEGF) pathway [84] (Fig. 1). In addition, there are some studies that reported positive outcomes by the combination of molecular targeted agents and immunotherapy drugs. We will discuss the current evidence focusing on immunotherapy combining with targeted therapy and outline the important views that might hopefully change the poor prognosis of patients with SCLC.

ICIs in combination with PARP inhibition

PARP acts as a DNA repair protein and the transcription factor adenovirus E2 promoter-binding factor-1 (E2F1) co-activator, which suggests that its inhibition not only directly blocks the repair of double-strand DNA breaks and controls the cell cycle, but regulates other E2F1-regulated DNA repair proteins [85–87]. Compared to other histologic subtypes of lung cancer, SCLC highly expresses the PARP [85,88]. In addition, clinical trials utilizing PARP inhibitors in ovarian and breast cancer have shown potential, especially in patients with potential defects in DNA repair or platinum-sensitive, which makes PARP inhibitors an attractive candidate for the treatment of SCLC because of the high sensitivity to platinum-based treatment [89,90]. In other cancer types, such as breast cancer, PARP inhibitors can enhance response to ICIs [91]. Because the DNA damage induced by PARP inhibitors not only can promote immune priming through a range of molecular mechanisms, but upregulate the expression of PD-L1, the combination of PARP inhibitors and ICIs is promising in SCLC patients [92]. Triparna Sen et al. [21] conducted a preclinical study to detect whether PARP inhibitors could enhance the anti-tumor effect of anti-PD-L1 in SCLC cell lines. In this study, 50 mg/kg olaparib (PARP inhibitors) or 10 mg/kg anti-PD-L1 alone had no significant anti-tumor activity in an immunocompetent SCLC model. However, striking tumor regressions occurred in animals treated with the olaparib and anti-PD-L1 combination. All combined groups had a complete regression as early as day 7 and the effect lasted until day 80, and the OS of the olaparib plus anti-PD-L1 group was obviously higher than the olaparib or anti-PD-L1 groups ($p < 0.001$). Further investigation indicated that PARP inhibition activates the STING-TBK1-IRF3 innate immune response pathway by inducing DNA damage in SCLC models, leading to the upregulation of Type 1 interferon IFNβ expression. The upregulated IFNβ leads to the upregulation of PDL1

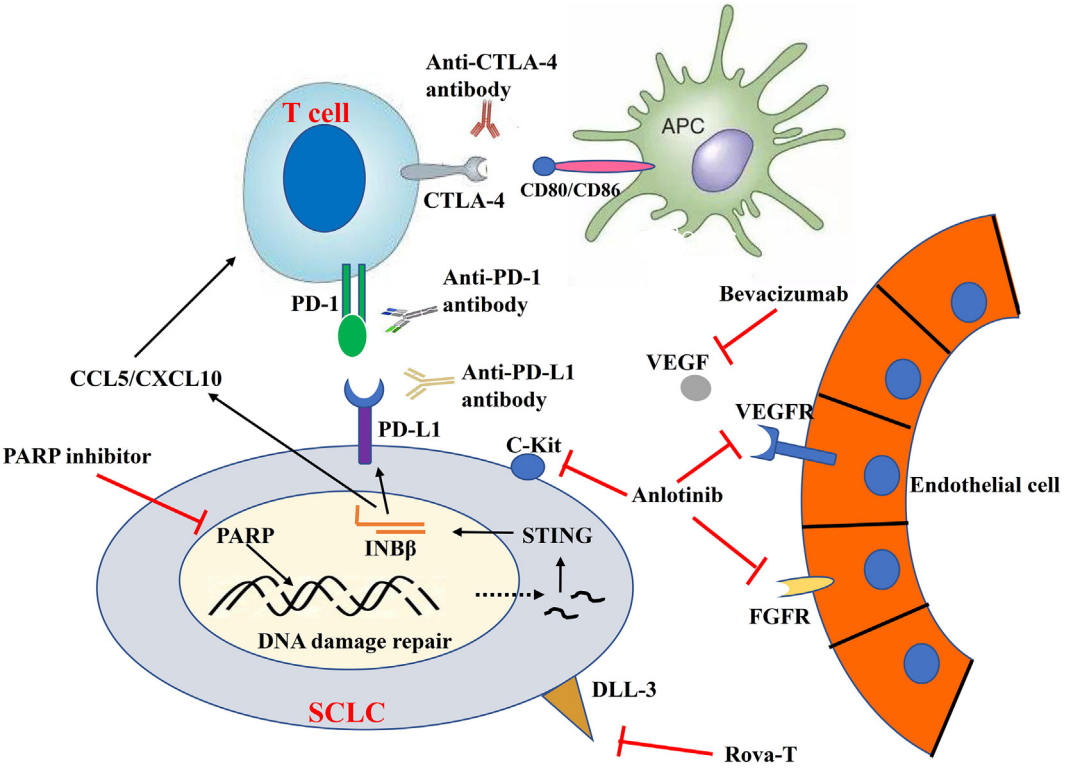

Fig. 1. Mechanisms of immune checkpoint blockade in combination with targeted therapy drugs for the treatment of small cell lung cancer. APC: Antigen-presenting cell; CCL5: Chemokine (CC motif) ligand 5; CTLA-4: Cytotoxic T-lymphocyte antigen-4; CXCL10: Chemokine (C-X-C motif) ligand; DLL3: Delta-like protein 3; FGFR: Fibroblast growth factor receptor; IFNβ: Interferon-beta; PARP: Poly ADP-ribose polymerase; PD-1: Programmed death-1; PD-L1: Programmed death-ligand1; Rova-T: Rovalpituzumab tesirine; SCLC: Small cell lung cancer; STING: Stimulator of interferon genes; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth receptor;

expression and enhances the expression of chemokines CXCL10 and CCL5, which can induce activation of cytotoxic T-lymphocytes [21] (Fig. 1). These results partly elucidated the synergistic effect of these combinations in SCLC. Recently, several clinical trials with PARP inhibitors and ICIs are ongoing in order to rapidly translate this combination into the clinic application to improve the prognosis of patients with SCLC (Table 4).

ICIs in combination with rovalpituzumab tesirine (Rova-T)

DLL3, an inhibitory ligand of the Notch signaling pathway, highly expressed on the surface of SCLC tumor cells, is correlated with tumor progression of SCLC [93–95]. Rova-T is known as a humanized monoclonal antibody directed against DLL3. An open-label, phase I clinical trial reported that Rova-T shows substantial anti-tumor effect with a manageable safety profile in recurrent SCLC. The confirmed OR is 18% (11 of 60 assessable patients), and the most frequent ≥3 TRAEs were thrombocytopenia (11%), pleural effusion (8%), and increased lipase (7%) [96]. Results of phase II clinical studies of Rova-T in patients with DLL3-expressing SCLC, who progressed after at least two prior lines of therapy indicated that, with a median follow-up of 19.1 weeks, the best OR was 18.0% (95% CI, 14.1–22.5). The median PFS was 4.1 months. The median OS was 6.7 months with toxicities which was consistent with the findings of the phase I study [97]. Unfortunately, the phase III trial comparing Rova-T to topotecan as second-line therapy for patients with SCLC was halted due to shorter OS in the Rova-T arm than the topotecan arm. In another study, it reported that DLL3 is of importance in the immune system to regulate T-cell development. The absence of DLL3 could induce the activity of the Notch signaling and this could synergize with TCR signals to promote T-cell differentiation [98]. A phase I clinical study concerning the combination of ipilimumab/nivolumab or Rova-T/nivolumab/ipilimumab in SCLC is ongoing (Table 4). The combination of Rova-T and immunotherapy might have a synergistic effect in SCLC, which gives hope to conduct more relevant research.

Anti-angiogenesis and immunotherapy

Angiogenesis is important in tumor growth, invasion, and metastases [99]. To support the high proliferation rate of tumor cells, tumors need to rapidly develop a new vascular network characteristic of disorganized, immature and permeable blood vessels, which impair their functionality. The dysfunction of tumor vascular would cause profound consequences for the tumor microenvironment, resulting in hypoxia, increased risks of metastatic dissemination as well as decreased immune cell infiltration and activity [100]. Vascular endothelial growth factor (VEGF), as the most important mediators of angiogenesis, is thought to be related to poor prognosis of SCLC, which made the VEGF pathway an attractive target in SCLC patients [101].

Bevacizumab, an anti-VEGFA antibody, seems to have some benefit for patients with ES-SCLC in several phase II clinical studies [102–105] (Fig. 1). Given the promising results in phase II studies, a large phase III trial was designed to evaluate the efficacy of adding bevacizumab to standard chemotherapy of cisplatin/etoposide for the treatment of ES-SCLC. The results were disappointing: PFS was improved, but OS had not a statistically significant increase [106]. Besides bevacizumab, another anti-angiogenetic agent, anlotinib, targeting the vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), C-Kit and other targets, has been under studying in phase II clinical trials in SCLC with promising results (Fig. 1). Anlotinib significantly prolonged median FFS compared with placebo: 4.3 vs. 0.7 months (HR = 0.19, $P < 0.0001$). The median OS was 7.3 months in the anlotinib arm vs. 4.9 months in the placebo arm. DCR was superior for the anlotinib group at 71.6% vs. 13.2% in the placebo group [107]. Moreover, trials with other anti-angiogenetic agents (vandetanib, thalidomide, and sunitinib) have shown controversial results [108–110]. Interestingly, in an autochthonous mouse model of SCLC, Meder L et al. found that the combination of anti-VEGF and anti-PD-L1-targeted therapy synergistically improves treatment effect compared to monotherapy. The study indicated that VEGF enhances expression of the inhibitory receptor TIM-3 on T cells, resulting in resistance to anti-PD-1 treatment in SCLC. Therefore, the addition of anti-VEGF to anti-PD-1 targeted treatment could be a potential treatment strategy in SCLC [111].

Conclusion and perspectives

In summary, previous clinical trials have shown that immunotherapy, with favorable toxicity profile and durable responses, has made some little breakthroughs in the treatment of patients with SCLC, while immunomonotherapy shows a relatively low response rate. Thereby, combination immunotherapy and combination of immunotherapy with other therapy, such as chemotherapy, radiotherapy, and targeted therapy, represent a new modality for treating SCLC, which can achieve greater therapeutic effects through multiple synergistic mechanisms. Combining different ICIs may act synergistically due to the nonredundant effects of the two immune checkpoint pathways (CTLA-4 and PD-1/PD-L1 pathways), despite potentially with a higher rate of toxicity than monotherapy. The addition of chemoradiotherapy to immunotherapy may augment antitumor immune responses because chemoradiotherapy can enhance tumor cell immunogenicity by rapidly inducing tumor lysis and releasing tumor antigens. In addition, given that ICIs and molecular targets drugs act upon different targets

Table 4
Ongoing studies incorporating immunotherapy and targeted therapy in SCLC.

Drug	Phase	Patient (n)	Study design	Endpoint	ClinicalTrials.gov identifier
ICB + PARP inhibitor					
Nivolumab Rucaparib	II	ES-SCLC (36)	Open label, single group assignment: nivolumab + rucaparib as maintenance after induction therapy with platinum doublet	Primary: PFS Secondary: DCR; OS; ORR;	NCT03958045
Durvalumab Tremelimumab Olaparib Thoracic radiotherapy	I	ES-SCLC (54)	Open label, non-randomized, parallel assignment: thoracic radiotherapy + durvalumab vs. thoracic radiotherapy + durvalumab + tremelimumab vs. thoracic radiotherapy + durvalumab + olaparib	Primary: safety (Phase 1); PFS (Phase IB) Secondary: mPFS; OS	NCT03923270
ICB + Rova-T					
Ipilimumab Nivolumab Rova- T	I/ II	ES-SCLC (42)	Open label, non-randomized, parallel assignment: Rova- T + nivolumab vs. Rova- T + nivolumab + ipilimumab (1 mg/kg) vs. Rova- T + nivolumab + ipilimumab (3 mg/kg)	Primary: safety Secondary: CBR; DOR; PFS; ORR; OS	NCT03026166

Abbreviations CBR: clinical benefit rate; DCR: disease control rate; DOR: duration of response; ES-SCLC: extensive stage small cell lung cancer; ICB: immune checkpoint blockade; mPFS: median PFS; ORR: objective response rate; OS: overall survival; PARP: poly ADP-ribose polymerase; PFS: progression-free survival; Rova- T: Rovalpituzumab Tesirine; SCLC: small cell lung cancer.

and cells, the combination of these drugs may achieve greater therapeutic effects in the treatment of SCLC. Especially, some emerging targeted therapy drugs, such as olaparib, Rova-T and anlotinib, have shown some potentials for improving outcomes in SCLC, which is regarded as the first choice for targeted therapy in combined with immunotherapy.

Compared with the other combination therapies, combining immunotherapy with chemotherapy is expected to become the most promising therapy for SCLC, since the combination of immunotherapy with chemotherapy has been intensively studied and has achieved much more satisfying results. As previously mentioned, maintenance pembrolizumab did not improve PFS and OS in ES-SCLC patients after completion of first-line chemotherapy compared with the historical data, but the combination of atezolizumab with chemotherapy as first-line treatment showed a significant improvement in PFS and OS [19,29]. In addition, the result from the Checkmate-032 and CheckMate 451 trials showed that nivolumab plus ipilimumab was beneficial for the recurrent SCLC patients after at least one platinum-based chemotherapy, while this combination, as the maintenance therapy after the first-line chemotherapy, did not show the expected effect for the patients with SCLC [14,37]. This suggests that combining immunotherapy with chemotherapy during induction may be more beneficial than the standard chemotherapy for SCLC patients, and it may be a preferred treatment approach over maintenance immunotherapy alone.

CRediT authorship contribution statement

Wei Huang: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Jia-Jia Chen:** Investigation, Visualization. **Rui Xing:** Software, Validation, Supervision. **Yue-Can Zeng:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Salem A, Mistry H, Hatton M, Locke I, Monnet I, Blackhall F and Faivre-Finn C (2018). Association of Chemoradiotherapy With Outcomes Among Patients With Stage I to II vs Stage III Small Cell Lung Cancer: Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol e185335.

[2] F. Blackhall, K.K. Frese, K. Simpson, E. Kilgour, G. Brady, C. Dive, Will liquid biopsies improve outcomes for patients with small-cell lung cancer? Lancet Oncol 19 (2018) e470–e481.

[3] N. Hanna, P.A. Bunn Jr., C. Langer, L. Einhorn, T. Guthrie Jr., T. Beck, R. Ansari, P. Ellis, M. Byrne, M. Morrison, et al., Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer, J. Clin. Oncol. 24 (2006) 2038–2043.

[4] M. Puglisi, S. Dolly, A. Faria, J.S. Myerson, S. Popat, M.E. O'Brien, Treatment options for small cell lung cancer - do we have more choice? Br. J. Cancer 102 (2010) 629–638.

[5] A. Rossi, M. Di Maio, P. Chiodini, R.M. Rudd, H. Okamoto, D.V. Skarlos, M. Früh, W. Qian, T. Tamura, E. Samantas, et al., Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data, J. Clin. Oncol. 30 (2012) 1692–1698.

[6] B.E. Lally, J.J. Urbanic, A.W. Blackstock, A.A. Miller, M.C. Perry, Small cell lung cancer: have we made any progress over the last 25 years? Oncologist 12 (2007) 1096–1104.

[7] A.Z. Abidin, M.C. Garassino, R. Califano, A. Harle, F. Blackhall, Targeted therapies in small cell lung cancer: a review, Ther Adv Med Oncol 2 (2010) 25–37.

[8] A. Ribas, J.D. Wolchok, Cancer immunotherapy using checkpoint blockade, Science 359 (2018) 1350–1355.

[9] D.M. Pardoll, The blockade of immune checkpoints in cancer immunotherapy, Nat. Rev. Cancer 12 (2012) 252–264.

[10] S.L. Topalian, C.G. Drake, D.M. Pardoll, Immune checkpoint blockade: a common denominator approach to cancer therapy, Cancer Cell 27 (2015) 450–461.

[11] J.D. Wolchok, V. Chiarion-Sileni, R. Gonzalez, P. Rutkowski, J.J. Grob, C.L. Cowey, C.D. Lao, J. Wagstaff, D. Schadendorf, P.F. Ferrucci, et al., Overall survival with combined nivolumab and ipilimumab in advanced melanoma, N. Engl. J. Med. 377 (2017) 1345–1356.

[12] M. Reck, D. Rodriguez-Abreu, A.G. Robinson, R. Hui, T. Csoszi, A. Fulop, M. Gottfried, N. Peled, A. Tafreshi, S. Cuffe, et al., Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer, N. Engl. J. Med. 375 (2016) 1823–1833.

[13] J. George, J.S. Lim, S.J. Jang, Y. Cun, L. Ozretic, G. Kong, F. Leenders, X. Lu, L. Fernandez-Cuesta, G. Bosco, et al., Comprehensive genomic profiles of small cell lung cancer, Nature 524 (2015) 47–53.

[14] S.J. Antonia, J.A. López-Martin, J. Bendell, P.A. Ott, M. Taylor, J.P. Eder, D. Jäger, M.C. Pietanza, D.T. Le, F. de Braud, et al., Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial, Lancet Oncol 17 (2016) 883–895.

[15] P.A. Ott, E. Elez, S. Hiret, D.W. Kim, A. Morosky, S. Saraf, B. Piperdi, J.M. Mehnert, Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the phase Ib KEYNOTE-028 study, J. Clin. Oncol. 35 (2017) 3823–3829.

[16] G. Hamilton, B. Rath, Immunotherapy for small cell lung cancer: mechanisms of resistance, Expert. Opin. Biol. Ther. 19 (2019) 423–432.

[17] A. Doyle, W.J. Martin, K. Funa, A. Gazdar, D. Carney, S.E. Martin, I. Linnoila, F. Cuttitta, J. Mulshine, P. Bunn, et al., Markedly decreased expression of class I histocompatibility antigens, protein, and mRNA in human small-cell lung cancer, J. Exp. Med. 161 (1985) 1135–1151.

[18] M.D. Hellmann, P.A. Ott, J. Zugazagoitia, N.E. Ready, C.L. Hann, F.G. De Braud, S.J. Antonia, P.A. Ascierto, V. Moreno, A. Atmaca, et al., Nivolumab (nivo) ± ipilimumab (ipi) in advanced small-cell lung cancer (SCLC): First report of a randomized expansion cohort from CheckMate 032, J. Clin. Oncol. 35 (2017) 8503.

[19] L. Horn, A.S. Mansfield, A. Szczęsna, L. Havel, M. Krzakowski, M.J. Hochmair, F. Huemer, G. Losonczy, M.L. Johnson, M. Nishio, et al., First-line Atezolizumab plus chemotherapy in extensive-stage small-cell lung Cancer, N. Engl. J. Med. 379 (2018) 2220–2229.

[20] M. Reck, I. Bondarenko, A. Luft, P. Serwatowski, F. Barlesi, R. Chacko, M. Sebastian, H. Lu, J.M. Cuillerot, T.J. Lynch, Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial, Ann. Oncol. 24 (2013) 75–83.

[21] T. Sen, B.L. Rodriguez, L. Chen, C.M.D. Corte, N. Morikawa, J. Fujimoto, S. Cristea, T. Nguyen, L. Diao, L. Li, et al., Targeting DNA damage response promotes antitumor immunity through STING-mediated T-cell activation in small cell lung cancer, Cancer Discov 9 (2019) 646–661.

[22] A.F. Lipka, M.I. Boldingh, E.W. van Zwet, M.W.J. Schreurs, J.B.M. Kuks, C.M. Tallaksen, M.J. Titulaer, J. Verschuuren, Long-term follow-up, quality of life, and survival of patients with Lambert-Eaton myasthenic syndrome, Neurology 94 (2020) e511–e520.

[23] T. Ivanovski, F. Miralles, Lambert-Eaton Myasthenic syndrome: early diagnosis is key, Degener Neurol Neuromuscul Dis 9 (2019) 27–37.

[24] W.T. Iams, E. Shiuan, C.B. Meador, M. Roth, J. Bordeaux, C. Vaupel, K.L. Boyd, I.B. Summitt, L.L. Wang, J.T. Schneider, et al., Improved prognosis and increased tumor-infiltrating lymphocytes in patients who have SCLC with neurologic paraneoplastic syndromes, J. Thorac. Oncol. 14 (2019) 1970–1981.

[25] F. Graus, J. Dalmau, Paraneoplastic neurological syndromes in the era of immune-checkpoint inhibitors, Nat. Rev. Clin. Oncol. 16 (2019) 535–548.

[26] N. Ready, A.F. Farago, F. de Braud, A. Atmaca, M.D. Hellmann, J.G. Schneider, D.R. Spigel, V. Moreno, I. Chau, C.L. Hann, et al., Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032, J. Thorac. Oncol. 14 (2019) 237–244.

[27] M. Reck, D. Vicente, T. Ciuleanu, S. Gettinger, S. Peters, L. Horn, C. Audigier-Valette, N. Pardo, O. Juan-Vidal, Y. Cheng, et al., LBA5Efficacy and safety of nivolumab (nivo) monotherapy versus chemotherapy (chemo) in recurrent small cell lung cancer (SCLC): results from CheckMate 331, Ann. Oncol. 29 (2018).

[28] H.C. Chung, J.A. Lopez-Martin, S.C.-H. Kao, W.H. Miller, W. Ros, B. Gao, A. Marabelle, M. Gottfried, A. Zer, J.-P. Delord, et al., Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158, J. Clin. Oncol. 36 (2018) 8506.

[29] S.M. Gadgeel, N.A. Pennell, M.J. Fidler, B. Halmos, P. Bonomi, J. Stevenson, B. Schneider, A. Sukari, J. Ventimiglia, W. Chen, et al., Phase II study of maintenance pembrolizumab in patients with extensive-stage Small Cell Lung Cancer (SCLC), J. Thorac. Oncol. 13 (2018) 1393–1399.

[30] H. West, M. McCleod, M. Hussein, A. Morabito, A. Rittmeyer, H.J. Conter, H.G. Kopp, D. Daniel, S. McCune, T. Mekhail, et al., Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial, Lancet Oncol. 20 (2019) 924–937.

[31] L.V. Sequist, A. Chiang, J. Gilbert, M. Gordon, P.R. Conkling, D. Thompson, J.P. Marcoux, S.J. Antonia, B. Liu, D.S. Shames, et al., Clinical activity, safety and predictive biomarkers results from a phase Ia atezolizumab (atezo) trial in extensive-stage small cell lung cancer (ES-SCLC), Ann. Oncol. 27 (2016).

[32] J.L. Pujol, L. Greillier, C. Audigier-Valette, D. Moro-Sibilot, L. Uwer, J. Hureaux, F. Guisier, D. Carmier, J. Madelaine, J. Otto, et al., 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. 14 (2019) 903–913.
[33] J.D. Wolchok, H. Kluger, M.K. Callahan, M.A. Postow, N.A. Rizvi, A.M. Lesokhin, N.H. Segal, C.E. Ariyan, R.A. Gordon, K. Reed, et al., Nivolumab plus ipilimumab in advanced melanoma, N. Engl. J. Med. 369 (2013) 122–133.
[34] B.T. Fife, J.A. Bluestone, Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways, Immunol. Rev. 224 (2008) 166–182.
[35] D.S. Chen, I. Mellman, Oncology meets immunology: the cancer-immunity cycle, Immunity 39 (2013) 1–10.
[36] R. Das, R. Verma, M. Sznol, C.S. Boddupalli, S.N. Gettinger, H. Kluger, M. Callahan, J.D. Wolchok, R. Halaban, M.V. Dhodapkar, et al., Combination therapy with anti-CTLA-4 and anti-PD-1 leads to distinct immunologic changes in vivo, J. Immunol. 194 (2015) 950–959.
[37] Owonikoko T, Kim H, Govindan R, Ready N, Reck M, Peters S, Dakhil S, Navarro A, Rodriguez-Cid J and Schenker M J A o O (2019). LBA1_PR Nivolumab (nivo) plus ipilimumab (ipi), nivo, or placebo (pbo) as maintenance therapy in patients (pts) with extensive disease small cell lung cancer (ED-SCLC) after first-line (1L) platinum-based chemotherapy (chemo): Results from the double-blind, randomized phase III CheckMate 451 study. 30, mdz094.
[38] D.C. Cho, A. Mahipal, A. Dowlati, W.A. Chow, N.H. Segal, K.Y. Chung, B.J. Schneider, J.J. Nemunaitis, A.R. Abdul Razak, F.Y.-C. Tsai, et al., Safety and clinical activity of durvalumab in combination with tremelimumab in extensive disease small-cell lung cancer (ED-SCLC), J. Clin. Oncol. 36 (2018) 8517.
[39] E.B. Bernhardt, S.I. Jalal, Small cell lung cancer, Cancer Treat. Res. 170 (2016) 301–322.
[40] F. Ghiringhelli, L. Apetoh, The interplay between the immune system and chemotherapy: emerging methods for optimizing therapy, Expert. Rev. Clin. Immunol. 10 (2014) 19–30.
[41] E.A. Reits, J.W. Hodge, C.A. Herberts, T.A. Groothuis, M. Chakraborty, E.K. Wansley, K. Camphausen, R.M. Luiten, A.H. de Ru, J. Neijssen, et al., Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy, J. Exp. Med. 203 (2006) 1259–1271.
[42] L. Aymeric, L. Apetoh, F. Ghiringhelli, A. Tesniere, I. Martins, G. Kroemer, M.J. Smyth, L. Zitvogel, Tumor cell death and ATP release prime dendritic cells and efficient anticancer immunity, Cancer Res. 70 (2010) 855–858.
[43] L. Zitvogel, L. Apetoh, F. Ghiringhelli, F. Andre, A. Tesniere, G. Kroemer, The anticancer immune response: indispensable for therapeutic success? J. Clin. Invest. 118 (2008) 1991–2001.
[44] A. Bang, J.D. Schoenfeld, Immunotherapy and radiotherapy for metastatic cancers, Ann Palliat Med 8 (2019) 312–325.
[45] M. Obeid, A. Tesniere, F. Ghiringhelli, G.M. Fimia, L. Apetoh, J.L. Perfettini, M. Castedo, G. Mignot, T. Panaretakis, N. Casares, et al., Calreticulin exposure dictates the immunogenicity of cancer cell death, Nat. Med. 13 (2007) 54–61.
[46] L. Apetoh, F. Ghiringhelli, A. Tesniere, M. Obeid, C. Ortiz, A. Criollo, G. Mignot, M.C. Maiuri, E. Ullrich, P. Saulnier, et al., Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy, Nat. Med. 13 (2007) 1050–1059.
[47] M. Michaud, I. Martins, A.Q. Sukkurwala, S. Adjemian, Y. Ma, P. Pellegatti, S. Shen, O. Kepp, M. Scoazec, G. Mignot, et al., Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice, Science 334 (2011) 1573–1577.
[48] S. Gasser, S. Orsulic, E.J. Brown, D.H. Raulet, The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor, Nature 436 (2005) 1186–1190.
[49] W.J. Lesterhuis, C.J. Punt, S.V. Hato, D. Eleveld-Trancikova, B.J. Jansen, S. Nierkens, G. Schreibelt, A. de Boer, C.M. Van Herpen, J.H. Kaanders, et al., Platinum-based drugs disrupt STAT6-mediated suppression of immune responses against cancer in humans and mice, J. Clin. Invest. 121 (2011) 3100–3108.
[50] E. Arriola, M. Wheater, I. Galea, N. Cross, T. Maishman, D. Hamid, L. Stanton, J. Cave, T. Geldart, C. Mulatero, et al., Outcome and biomarker analysis from a multicenter phase 2 study of ipilimumab in combination with carboplatin and etoposide as first-line therapy for extensive-stage SCLC, J. Thorac. Oncol. 11 (2016) 1511–1521.
[51] M. Reck, A. Luft, A. Szczesna, L. Havel, S.W. Kim, W. Akerley, M.C. Pietanza, Y.L. Wu, C. Zielinski, M. Thomas, 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. 34 (2016) 3740–3748.
[52] T.D. Zhang, G.Q. Chen, Z.G. Wang, Z.Y. Wang, S.J. Chen, Z. Chen, Arsenic trioxide, a therapeutic agent for APL, Oncogene 20 (2001) 7146–7153.
[53] V. Lallemand-Breitenbach, J. Zhu, Z. Chen, H. de Thé, Curing APL through PML/RARA degradation by As2O3, Trends Mol. Med. 18 (2012) 36–42.
[54] A.A. Alex, S. Ganesan, H.K. Palani, N. Balasundaram, S. David, K.M. Lakshmi, U.P. Kulkarni, P.N. Nisham, A. Korula, A.J. Devasia, et al., Arsenic trioxide enhances the NK cell cytotoxicity against acute promyelocytic leukemia while simultaneously inhibiting its bio-genesis, Front. Immunol. 9 (2018) 1357.
[55] Q. Gao, J. Jiang, Z. Chu, H. Lin, X. Zhou, X. Liang, Arsenic trioxide inhibits tumor-induced myeloid-derived suppressor cells and enhances T-cell activity, Oncol. Lett. 13 (2017) 2141–2150.
[56] A. Thomas-Schoemann, F. Batteux, J. Alexandre, A new strategy to target regulatory T cells in solid tumors, Oncoimmunology 2 (2013), e23338, .
[57] A. Thomas-Schoemann, F. Batteux, C. Mongaret, C. Nicco, C. Chereau, M. Annereau, A. Dauphin, F. Goldwasser, B. Weill, F. Lemare, et al., Arsenic trioxide exerts antitumor activity through regulatory T cell depletion mediated by oxidative stress in a murine model of colon cancer, J. Immunol. 189 (2012) 5171–5177.
[58] L. Wang, R. Wang, L. Fan, W. Liang, K. Liang, Y. Xu, G. Peng, Q. Ye, Arsenic trioxide is an immune adjuvant in liver cancer treatment, Mol. Immunol. 81 (2017) 118–126.
[59] C.Y. Zheng, S.K. Lam, Y.Y. Li, J.C. Ho, Arsenic trioxide-induced cytotoxicity in small cell lung cancer via altered redox homeostasis and mitochondrial integrity, Int. J. Oncol. 46 (2015) 1067–1078.
[60] M.H. Yang, K.J. Chang, B. Li, W.S. Chen, Arsenic trioxide suppresses tumor growth through antiangiogenesis via notch signaling blockade in small-cell lung cancer, Biomed. Res. Int. 2019 (2019) 4647252.
[61] J.C. Zheng, K.J. Chang, Y.X. Jin, X.W. Zhao, B. Li, M.H. Yang, Arsenic trioxide inhibits the metastasis of small cell lung cancer by blocking calcineurin-Nuclear Factor of Activated T cells (NFAT) signaling, Med. Sci. Monit. 25 (2019) 2228–2237.
[62] T.K. Owonikoko, G. Zhang, H.S. Kim, R.M. Stinson, R. Bechara, C. Zhang, Z. Chen, N.F. Saba, S. Pakkala, R. Pillai, et al., Patient-derived xenografts faithfully replicated clinical outcome in a phase II co-clinical trial of arsenic trioxide in relapsed small cell lung cancer, J. Transl. Med. 14 (2016) 111.
[63] X. Wang, J. Li, K. Dong, F. Lin, M. Long, Y. Ouyang, J. Wei, X. Chen, Y. Weng, T. He, et al., Tumor suppressor miR-34a targets PD-L1 and functions as a potential immunotherapeutic target in acute myeloid leukemia, Cell. Signal. 27 (2015) 443–452.
[64] A. Sun, L.D. Durocher-Allen, P.M. Ellis, Y.C. Ung, J.R. Goffin, K. Ramchandar, G. Darling, Guideline for the initial management of small cell lung cancer (limited and extensive stage) and the role of thoracic radiotherapy and first-line chemotherapy, Clin Oncol (R Coll Radiol) 30 (2018) 658–666.
[65] B.J. Slotman, H. van Tinteren, J.O. Praag, J.L. Knegjens, S.Y. El Sharouni, M. Hatton, A. Keijser, C. Faivre-Finn, S. Senan, Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial, Lancet 385 (2015) 36–42.
[66] B. Slotman, C. Faivre-Finn, G. Kramer, E. Rankin, M. Snee, M. Hatton, P. Postmus, L. Collette, E. Musat, S. Senan, Prophylactic cranial irradiation in extensive small-cell lung cancer, N. Engl. J. Med. 357 (2007) 664–672.
[67] Fruh M, De Ruysscher D, Popat S, Crino L, Peters S and Felip E (2013). Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 24 Suppl 6, vi99-105.
[68] F.G. Herrera, J. Bourhis, G. Coukos, Radiotherapy combination opportunities leveraging immunity for the next oncology practice, CA Cancer J. Clin. 67 (2017) 65–85.
[69] A. Kuroda, T. Tabuchi, E. Iwami, K. Sasahara, T. Matsuzaki, T. Nakajima, Y. Tsutsumi, K. Eguchi, T. Terashima, Abscopal effect of radiation on multiple lung metastases of lung adenocarcinoma: a case report, BMC Cancer 19 (2019) 336.
[70] W. Ngwa, O.C. Irabor, J.D. Schoenfeld, J. Hesser, S. Demaria, S.C. Formenti, Using immunotherapy to boost the abscopal effect, Nat. Rev. Cancer 18 (2018) 313–322.
[71] B. Frey, Y. Rubner, L. Kulzer, N. Werthmöller, E.M. Weiss, R. Fietkau, U.S. Gaipl, Antitumor immune responses induced by ionizing irradiation and further immune stimulation, Cancer Immunol. Immunother. 63 (2014) 29–36.
[72] G.S. Herter-Sprie, S. Koyama, H. Korideck, J. Hai, J. Deng, Y.Y. Li, K.A. Buczkowski, A.K. Grant, S. Ullas, K. Rhee, et al., Synergy of radiotherapy and PD-1 blockade in Kras-mutant lung cancer, JCI Insight 1 (2016), e87415, .
[73] L.W. Pfannenstiel, C. McNeilly, C. Xiang, K. Kang, C.M. Diaz-Montero, J.S. Yu, B.R. Gastman, Combination PD-1 blockade and irradiation of brain metastasis induces an effective abscopal effect in melanoma, Oncoimmunology 8 (2019), e1507669, .
[74] X. Liu, J. Yao, L. Song, S. Zhang, T. Huang, Y. Li, Local and abscopal responses in advanced intrahepatic cholangiocarcinoma with low TMB, MSS, pMMR and negative PD-L1 expression following combined therapy of SBRT with PD-1 blockade, J Immunother Cancer 7 (2019) 204.
[75] J. Krombach, R. Hennel, N. Brix, M. Orth, U. Schoetz, A. Ernst, J. Schuster, G. Zuchtriegel, C.A. Reichel, S. Bierschenk, et al., Priming anti-tumor immunity by radiotherapy: dying tumor cell-derived DAMPs trigger endothelial cell activation and recruitment of myeloid cells, Oncoimmunology 8 (2019), e1523097, .
[76] M. McLaughlin, E.C. Patin, M. Pedersen, A. Wilkins, M.T. Dillon, A.A. Melcher, K.J. Harrington, Inflammatory microenvironment remodelling by tumour cells after radiotherapy, Nat. Rev. Cancer 20 (2020) 203–217.
[77] G. Ward, K. McGraw, A. McLemore, N. Lam, H.-A. Hou, B. Meyer, A. List, Oxidized mitochondrial DNA engages TLR9 to activate the NLRP3 inflammasome in myelodysplastic syndromes, Blood 134 (2019) 774.
[78] E. Garelli, A. Rittmeyer, P.M. Putora, M. Glatzer, R. Dressel, S. Andreas, Abscopal effect in lung cancer: three case reports and a concise review, Immunotherapy 11 (2019) 1445–1461.
[79] M.E. Hoekstra, L. Bornes, F.E. Dijkgraaf, D. Philips, I.N. Pardieck, M. Toebes, D.S. Thommen, J. van Rheenen, T.N.M. Schumacher, Long-distance modulation of bystander tumor cells by CD8(+) T cell-secreted IFNγ, Nat Cancer 1 (2020) 291–301.
[80] S. Najafi, A. Mirshafiey, The role of T helper 17 and regulatory T cells in tumor microenvironment, Immunopharmacol. Immunotoxicol. 41 (2019) 16–24.
[81] R.R. Weichselbaum, H. Liang, L. Deng, Y.X. Fu, Radiotherapy and immunotherapy: a beneficial liaison? Nat. Rev. Clin. Oncol. 14 (2017) 365–379.
[82] M.E. Rodriguez-Ruiz, C. Vanpouille-Box, I. Melero, S.C. Formenti, S. Demaria, Immunological mechanisms responsible for radiation-induced abscopal effect, Trends Immunol. 39 (2018) 644–655.
[83] F.R. Hirsch, K. Suda, J. Wiens, P.A. Bunn Jr., New and emerging targeted treatments in advanced non-small-cell lung cancer, Lancet 388 (2016) 1012–1024.
[84] S.M. Gadgeel, Targeted therapy and immune therapy for small cell lung cancer, Curr. Treat. Options in Oncol. 19 (2018) 53.
[85] L.A. Byers, J. Wang, M.B. Nilsson, J. Fujimoto, P. Saintigny, J. Yordy, U. Giri, M. Peyton, Y.H. Fan, L. Diao, et al., Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1, Cancer Discov 2 (2012) 798–811.
[86] C.M. Simbulan-Rosenthal, D.S. Rosenthal, R. Luo, R. Samara, L.A. Espinoza, P.O. Hassa, M.O. Hottiger, M.E. Smulson, PARP-1 binds E2F-1 independently of its DNA binding and catalytic domains, and acts as a novel coactivator of E2F-1-mediated transcription during re-entry of quiescent cells into S phase, Oncogene 22 (2003) 8460–8471.

[87] A. Kumari, T. Iwasaki, S. Pyndiah, E.K. Cassimere, C.D. Palani, D. Sakamuro, Regulation of E2F1-induced apoptosis by poly(ADP-ribosyl)ation, Cell Death Differ. 22 (2015) 311–322.
[88] M. Santarpia, M.G. Daffina, N. Karachaliou, M. Gonzalez-Cao, C. Lazzari, G. Altavilla, R. Rosell, Targeted drugs in small-cell lung cancer, Transl Lung Cancer Res 5 (2016) 51–70.
[89] P.C. Fong, D.S. Boss, T.A. Yap, A. Tutt, P. Wu, M. Mergui-Roelvink, P. Mortimer, H. Swaisland, A. Lau, M.J. O'Connor, et al., Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers, N. Engl. J. Med. 361 (2009) 123–134.
[90] P.C. Fong, T.A. Yap, D.S. Boss, C.P. Carden, M. Mergui-Roelvink, C. Gourley, J. De Greve, J. Lubinski, S. Shanley, C. Messiou, et al., Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval, J. Clin. Oncol. 28 (2010) 2512–2519.
[91] S. Jiao, W. Xia, H. Yamaguchi, Y. Wei, M.K. Chen, J.M. Hsu, J.L. Hsu, W.H. Yu, Y. Du, H.H. Lee, et al., PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression, Clin. Cancer Res. 23 (2017) 3711–3720.
[92] R.A. Stewart, P.G. Pilie, T.A. Yap, Development of PARP and immune-checkpoint inhibitor combinations, Cancer Res. 78 (2018) 6717–6725.
[93] D.H. Owen, M.J. Giffin, J.M. Bailis, M.D. Smit, D.P. Carbone, K. He, DLL3: an emerging target in small cell lung cancer, J. Hematol. Oncol. 12 (2019) 61.
[94] K. Tanaka, K. Isse, T. Fujihira, M. Takenoyama, L. Saunders, S. Bheddah, Y. Nakanishi, I. Okamoto, Prevalence of Delta-like protein 3 expression in patients with small cell lung cancer, Lung Cancer 115 (2018) 116–120.
[95] M. Furuta, H. Kikuchi, T. Shoji, Y. Takashima, E. Kikuchi, J. Kikuchi, I. Kinoshita, H. Dosaka-Akita, J. Sakakibara-Konishi, DLL3 regulates the migration and invasion of small cell lung cancer by modulating snail, Cancer Sci. 110 (2019) 1599–1608.
[96] C.M. Rudin, M.C. Pietanza, T.M. Bauer, N. Ready, D. Morgensztern, B.S. Glisson, L.A. Byers, M.L. Johnson, H.A. Burris 3rd, F. Robert, et al., 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 18 (2017) 42–51.
[97] D.P. Carbone, D. Morgensztern, S. Le Moulec, R. Santana-Davila, N. Ready, C.L. Hann, B.S. Glisson, A. Dowlati, C.M. Rudin, S. Lally, et al., Efficacy and safety of rovalpituzumab tesirine in patients with DLL3-expressing, ≥3rd line small cell lung cancer: Results from the phase 2 TRINITY study, J. Clin. Oncol. 36 (2018) 8507.
[98] G.F. Hoyne, G. Chapman, Y. Sontani, S.E. Pursglove, S.L. Dunwoodie, A cell autonomous role for the Notch ligand Delta-like 3 in alphabeta T-cell development, Immunol. Cell Biol. 89 (2011) 696–705.
[99] C. Viallard, B. Larrivee, Tumor angiogenesis and vascular normalization: alternative therapeutic targets, Angiogenesis 20 (2017) 409–426.
[100] P. Carmeliet, R.K. Jain, Principles and mechanisms of vessel normalization for cancer and other angiogenic diseases, Nat. Rev. Drug Discov. 10 (2011) 417–427.
[101] G. Fontanini, P. Faviana, M. Lucchi, L. Boldrini, A. Mussi, T. Camacci, M.A. Mariani, C.A. Angeletti, F. Basolo, R. Pingitore, A high vascular count and overexpression of vascular endothelial growth factor are associated with unfavourable prognosis in operated small cell lung carcinoma, Br. J. Cancer 86 (2002) 558–563.
[102] D.R. Spigel, P.M. Townley, D.M. Waterhouse, L. Fang, I. Adiguzel, J.E. Huang, D.A. Karlin, L. Faoro, F.A. Scappaticci, M.A. Socinski, Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: results from the SALUTE trial, J. Clin. Oncol. 29 (2011) 2215–2222.
[103] L. Horn, S.E. Dahlberg, A.B. Sandler, A. Dowlati, D.F. Moore, J.R. Murren, J.H. Schiller, 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. 27 (2009) 6006–6011.
[104] N.E. Ready, A.Z. Dudek, H.H. Pang, L.D. Hodgson, S.L. Graziano, M.R. Green, E.E. Vokes, Cisplatin, irinotecan, and bevacizumab for untreated extensive-stage small-cell lung cancer: CALGB 30306, a phase II study, J. Clin. Oncol. 29 (2011) 4436–4441.
[105] D.R. Spigel, F.A. Greco, J.D. Zubkus, P.B. Murphy, R.A. Saez, C. Farley, D.A. Yardley, H.A. Burris 3rd, J.D. Hainsworth, Phase II trial of irinotecan, carboplatin, and bevacizumab in the treatment of patients with extensive-stage small-cell lung cancer, J. Thorac. Oncol. 4 (2009) 1555–1560.
[106] M. Tiseo, L. Boni, F. Ambrosio, A. Camerini, E. Baldini, S. Cinieri, M. Brighenti, F. Zanelli, E. Defraia, R. Chiari, et al., 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 FARM6PMFJM trial, J. Clin. Oncol. 35 (2017) 1281–1287.
[107] Y. Cheng, Q. Wang, K. Li, J. Shi, L. Wu, B. Han, G. Chen, J. He, J. Wang, H. Qin, et al., OA13.03 Anlotinib as third-line or further-line treatment in relapsed SCLC: a multicentre, randomized, double-blind phase 2 trial, J. Thorac. Oncol. 13 (2018) S351–S352.
[108] A.M. Arnold, L. Seymour, M. Smylie, K. Ding, Y. Ung, B. Findlay, C.W. Lee, M. Djurfeldt, M. Whitehead, P. Ellis, et al., Phase II study of vandetanib or placebo in small-cell lung cancer patients after complete or partial response to induction chemotherapy with or without radiation therapy: National Cancer Institute of Canada Clinical Trials Group Study BR.20, J. Clin. Oncol. 25 (2007) 4278–4284.
[109] S.M. Lee, P.J. Woll, R. Rudd, D. Ferry, M. O'Brien, G. Middleton, S. Spiro, L. James, K. Ali, M. Jitlal, et al., Anti-angiogenic therapy using thalidomide combined with chemotherapy in small cell lung cancer: a randomized, double-blind, placebo-controlled trial, J. Natl. Cancer Inst. 101 (2009) 1049–1057.
[110] N.E. Ready, H.H. Pang, L. Gu, G.A. Otterson, S.P. Thomas, A.A. Miller, M. Baggstrom, G.A. Masters, S.L. Graziano, J. Crawford, et al., Chemotherapy with or without maintenance Sunitinib for untreated extensive-stage small-cell lung cancer: a randomized, double-blind, placebo-controlled phase II study-CALGB 30504 (Alliance), J. Clin. Oncol. 33 (2015) 1660–1665.
[111] L. Meder, P. Schuldt, M. Thelen, A. Schmitt, F. Dietlein, S. Klein, S. Borchmann, K. Wennhold, I. Vlasic, S. Oberbeck, et al., Combined VEGF and PD-L1 blockade displays synergistic treatment effects in an autochthonous mouse model of small cell lung cancer, Cancer Res. 78 (2018) 4270–4281.