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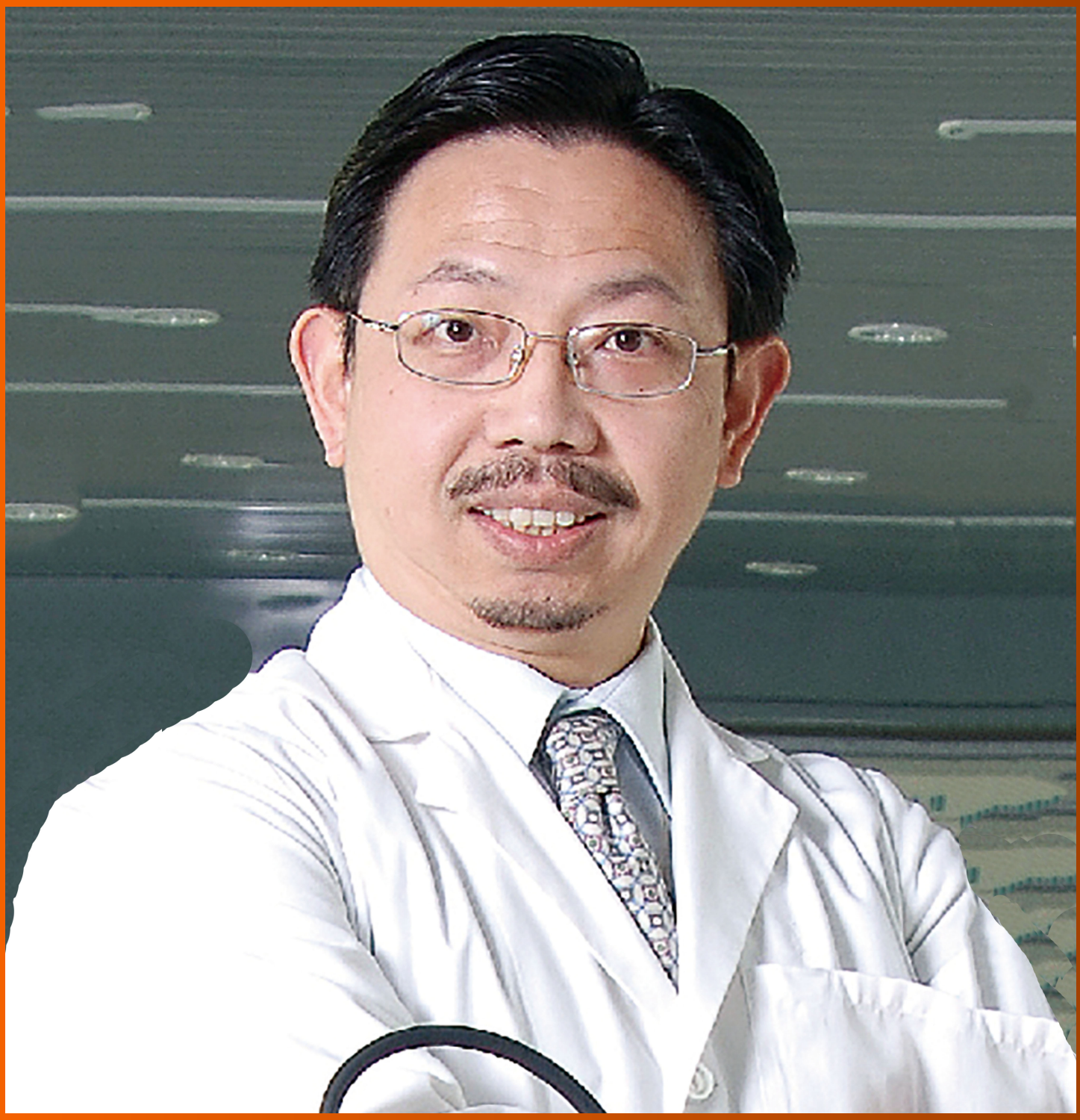

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MINIREVIEWS

Progress in immunotherapy for small cell lung cancer

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Abstract

Small-cell lung cancer (SCLC) is a special type of lung cancer that belongs to highly aggressive neuroendocrine tumors. At present, radiotherapy and chemotherapy remain the mainstay of treatment for SCLC. Progress in targeted therapies for SCLC with driver mutations has been slow, and these therapies are still under investigation in preclinical or early-phase clinical trials, and research on antiangiogenic tyrosine kinase inhibitors (*e.g.*, anlotinib) has achieved some success. Immunotherapy is becoming an important treatment strategy for SCLC after radiotherapy and chemotherapy. In this article we review the recent advances in immunotherapy for SCLC.

Key words: Small-cell lung cancer; Programmed death-1 inhibitors; Cytotoxic T lymphocyte-associated antigen-4 inhibitors; Poly adenosine diphosphate ribose polymerase inhibitors

Core tip: Small-cell lung cancer (SCLC) is a special type of lung cancer that belongs to highly aggressive neuroendocrine tumors. Classical radiotherapy and chemotherapy have a plateauing effect. Immunotherapy is becoming an important treatment strategy for SCLC. In this article, we review the recent advances in immunotherapy for SCLC.

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INTRODUCTION

Small-cell lung cancer (SCLC) accounts for 13%-15% of all lung cancers. In the past two decades, little progress has been made in the treatment of SCLC, and radiotherapy and chemotherapy remain the mainstay of treatment. However, disease relapse or drug resistance can occur in almost all patients, and currently available options are limited. Most SCLC cases are still incurable[1]. Although many studies have explored gene mutations in SCLC, molecularly targeted therapies for SCLC gene abnormalities are still under investigation. Small-molecule antiangiogenic drugs (*e.g.*, anlotinib) have made some progress in treating SCLC but with limited efficacy. Immunotherapy with checkpoint inhibitors for SCLC has lagged behind that for non-small cell lung cancer. Nevertheless, the role of immunotherapy in SCLC has been increasingly recognized.

In this review, we summarize the current status of nonspecific immunotherapy, vaccines, and immune checkpoint inhibitors (ICIs) in the treatment of SCLC.

NONSPECIFIC IMMUNOTHRAPY

Interferons

Interferons (IFNs) are a group of proteins and glycoproteins produced by cells in response to viral stimuli. They have a wide range of regulatory effects on normal cells, tumor cells, and host immune defense cells by inhibiting cell growth and changing the structure, surface antigen expression, and differentiation/function of cells[2]. Early clinical studies have shown that IFN-α monotherapy may halt the growth of lung cancer[3]. In a multicenter randomized Phase III study on chemotherapy plus IFN-α treatment for SCLC, 209 patients were randomly divided into three groups: Group A was treated with chemotherapy alone (intravenous injection of cisplatin 70 mg/m^2 on day 1 and intravenous injection of etoposide 100 mg/m^2 on days 1, 2 and 3, every 28 d); Group B received chemotherapy + natural IFN-α (3 MU, three times/wk, intramuscularly); and Group C received chemotherapy + recombinant IFNα-2a (3 MU, three times/wk, intramuscularly). The results of the study showed that survival did not significantly differ among these three groups[4]. It is still unclear which combinations between IFN-α and other treatments can achieve better outcomes.

Interleukin-2

Interleukin-2 (IL-2) is a cytokine that can bind to specific receptors that are constitutively expressed on T cells and natural killer cells and mediate their immunostimulating effects[5]. Some studies have shown that the level of IL-2 secretion in SCLC patients at diagnosis may be related to prognosis[6,7]. A clinical study showed that exogenous IL-2 may be effective in SCLC patients[8]. Meazza *et al*[9] found that *IL-2* gene transfection in IL-2R-negative SCLC cell lines might activate nonspecific effector cells and thus eliminate tumorigenicity in nude mice, and IL-2-transfected cells produce a local bystander effect on the growth of wild-type tumor cells[9]. However, another study found that the expression of Fas-ligand (CD95L) is upregulated in a variety of epithelial tumors including SCLC. As a result, cytotoxic T cells do not enter the tumor microenvironment and thus do not exert their effects[10]. To date, the role of IL-2 in the treatment of SCLC has not been fully recognized.

VACCINES

The p53 tumor suppressor gene plays a pivotal role in controlling cell growth and differentiation. More than 90% of SCLC patients have *p53* gene mutations and p53 protein overexpression[11], which are mainly due to a single site mutation or abnormal degradation of wild-type (wt) p53. In a Phase I/II clinical trial, INGN-225 was generated in SCLC patients after infection with wt-*p53*-containing adenovirus constructs, and the result confirmed the safety of INGN-225. Furthermore, more than 40% of patients showed an immune response. It was also found that the response rate was higher in patients who had just completed chemotherapy[12]. A similar conclusion was reached in a clinical trial that used the combination of p53 cancer vaccine with chemotherapy in 29 patients with extensive-stage (ES)-SCLC[13]. Since the role of the p53 vaccine for SCLC is still under investigation in clinical trials, more high-level evidence is still needed. A Phase II study on personalized peptide vaccination (PPV) in 46 patients with advanced SCLC revealed immune enhancement without severe adverse events and overall survival (OS) benefits after PPV, suggesting that the combination of PPV with chemotherapy may be a promising strategy for treating

SCLC[13]. Phase III randomized controlled clinical trials are needed.

iCIs

Immune microenvironment of SCLC

Most SCLC cases are associated with smoking. Quitting smoking and low tar inhalation can lower the incidence of SCLC[14]; in contrast, long-term exposure to carcinogens in tobacco smoke may increase the tumor mutation burden (TMB)[15]. In addition, tobacco exposure causes high-frequency inactive mutations of *TP53* and *RB1*, and their deletion can lead to high instability of the genome[16]. Studies have confirmed that, compared with other lung cancers, SCLC is associated with higher expression of DNA damage response (DDR) pathway mediators[17-19]. These genes are associated with high TMB in SCLC patients, which sheds new light on the research and development of DDR pathway-targeted drugs and on immunosuppression through a cascade of interactions. There are still negative immune factors in the microenvironment. For example, tumor-infiltrating lymphocytes (TILs) in SCLC are significantly correlated with the low expression of major histocompatibility complex class I (MHC-I) molecules and antigen presentation of cytotoxic T lymphocytes. Studies have shown absent or reduced MHC-I antigen expression and low TIL levels in SCLC patients; additionally, most lymphocytes are distributed at the edge rather than center of the tumor. Thus, low MHC-I antigen expression leads to reduced T-cell recruitment, resulting in decreased TIL infiltration inside the tumor, which is a negative predictive factor for outcome to immunotherapy. The proportions of $CD3^+$ and $CD8^+$ infiltrating lymphocytes are markedly decreased in the tumor microenvironment of SCLC. During biopsies performed before and after treatment, immunophenotype characterization has shown that 64% were immune-excluded phenotype, 21% were inflamed, and 14% were immune desert[20].

Cytotoxic T lymphocyte-associated antigen 4 inhibitors

Cytotoxic T lymphocyte-associated (CTLA) antigen is present in regulatory T cells and its expression is dependent on forkhead box P3. Mice with regulatory T cells that lack CTLA-4 protein expression were recently shown to develop lethal autoimmunity, revealing that regulatory T cell expression of CTLA-4 is necessary for immune suppression and prevention of *in vivo* autoimmunity[21].

CTLA-4 is a member of the CD28-B7 superfamily; it can be expressed on activated T cells and plays a role in downregulating T-cell activity. It is a key negative regulator in the early stage of T-cell activation[22,23]. CTLA-4 inhibitors block CTLA-4-driven inhibitory signaling pathways and prevent the interactions of this receptor with its ligands CD80 and CD86 on antigen-presenting cells, leading to activation and proliferation of tumor-specific T cells and restriction of immune escape[24]. In a Phase II trial that compared ipilimumab plus paclitaxel with carboplatin and paclitaxel monotherapy in patients with ES-SCLC, programmed death ligand (PD-L) 1 expression level was not stratified. Immune-related response criteria were used to assess the treatment response. Ipilimumab plus chemotherapy improved the immune-related progression-free survival (PFS)[25] compared with chemotherapy alone. However, in a randomized Phase III trial (CA184-156) that compared the efficacy of ipilimumab plus etoposide and platinum *vs* etoposide and platinum in treating ES-SCLC, the median OS was 11.0 mo (95% confidence interval [CI]: 10.45–11.33) in patients treated with ipilimumab plus chemotherapy and 10.9 mo (95%CI: 10.02–11.50) in the chemotherapy plus placebo group, showing no significant improvement (hazard ratio [HR]: 0.94; 95%CI: 0.81–1.09; P = 0.3775). Ipilimumab combined with standard chemotherapy does not improve OS and PFS of patients with ES-SCLC. The possible explanation may be that ipilimumab combined with standard chemotherapy does not activate T cells in the tumor microenvironment, and peripheral T-cell activation alone may not be effective in eliciting a sufficiently potent antitumor response in SCLC. Chemotherapy may also limit the proliferation and activation of T cells[26].

PD-1 inhibitors

PD-1 is a receptor on T cells. It can counter T-cell proliferation under the action of either one of its ligands, PD-L1 or PD-L2, enabling tumor cells to escape immune eradication and achieve proliferation and metastasis[27]. PD-1 inhibitors block the binding of PD-L1 and PD-L2 to the PD-1 receptor of T cells, thereby activating T cells to recognize and kill tumor cells and eventually achieve an antitumor immune response[28].

Nivolumab

In a nonrandomized Phase I/II multicenter, open-label trial (CheckMate 032), ES-SCLC patients who had previously received second-line or higher chemotherapy were treated with the PD-1 inhibitor nivolumab in different ways or in combination with ipilimumab. A total of 216 patients were divided into four groups: Nivolumab 3 mg/kg (n = 98); ipilimumab 1 mg/kg + nivolumab 1 mg/kg (n = 3); ipilimumab 3 mg/kg + nivolumab 1 mg/kg (n = 61); ipilimumab 1 mg/kg + nivolumab 3 mg/kg (n = 54). After four cycles of treatment, maintenance treatment with nivolumab 3 mg/kg was applied. Objective response rate (ORR) was the primary endpoint, which was 4% (10/98 patients), 33% (1/3), 23% (14/61), and 19% (10/54) in these four groups, respectively[29]. Notably, in the pooled cohort, the ORR was 22.3% in patients with high TMB (248 mutations) and only 4.8% in patients with low TMB (< 143 mutations)[30]. No correlation was found between PD-L1 expression and treatment response. Based on data from the Phase I/II CheckMate-032 basket trial, nivolumab was granted accelerated approval by the United States Food and Drug Administration as third-line and later-line treatment for SCLC. Another Phase III CheckMate 451 study (NCT02538666) analyzed the efficacy of nivolumab monotherapy (240 mg), nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg), and placebo in maintenance therapy[30]. The study did not reach its primary endpoint (comparison of OS between the combination and placebo groups). OS in these two groups was 9.2 and 9.6 mo, respectively (HR: 0.92, 95%CI: 0.75–1.12; P = 0.37), and the 1-year OS rate was 41% and 40%, respectively[31]. Another large-scale Phase III trial (CheckMate 331; NCT02481830) enrolled 569 patients and explored the efficacy of nivolumab monotherapy *versus* chemotherapy as second-line treatment for ES-SCLC. Platinum-sensitive relapse was noted in 56% of these patients, but OS showed no significant difference between these two groups (7.5 mo *vs* 8.4 mo, HR: 0.86, 95%CI: 0.72-1.04; P = 0.11)[32].

Pembrolizumab

The KEYNOTE-158 study (NCT02628067) was a Phase II trial involving 11 solid tumors and included 107 treated ES-SCLC patients. The primary endpoint ORR was 18.7%, and the median PFS and OS were 2 and 9.1 mo, respectively[33]. Similarly, the KEYNOTE-028 study analyzed the effectiveness and safety of pembrolizumab in patients with previously treated SCLC; however, in this study, PD-L1 expression level ≥ 1% was used as a screening condition, and the therapeutic dose was increased to 10 mg/kg every 2 wk. The ORR and OS were 33.3% and 9.7 mo, respectively[33,34]. The study was limited by its Phase I design and small sample size.

PD-L1

PD-L1 is a fully human anti-PD-L1 monoclonal antibody that competes with B7-1 and PD-1 on T cells to activate T cells, overcome tumor cell escape, and restore tumor-specific T-cell immunity[35]. A multination, randomized, double-blind, placebo-controlled Phase III trial IMpower-133 (NCT02763579) was performed to evaluate the therapeutic effect of atezolizumab plus carboplatin and etoposide in treatment-naïve patients with ES-SCLC. A total of 403 treatment-naïve ES-SCLC patients were included and randomized into two groups in a 1:1 ratio: Chemotherapy + placebo and chemotherapy + atezolizumab (1200 mg every 3 wk)[36]. The two primary endpoints were PFS and OS. PFS was 5.2 mo in the atezolizumab group and 4.3 mo in the placebo group (HR: 0.77; 95%CI: 0.62-0.96; P = 0.02); OS was 12.3 mo in the atezolizumab group and 10.3 mo in the placebo group (HR: 0.7, 95%CI: 0.54-0.91; P = 0.007); and 1-year survival rate was 51.7% and 38.2%, respectively[37]. Notably, the OS curves began to separate after about 7 mo, which indicated the superiority of the atezolizumab group. Such separation continued after a median follow-up of 13.9 mo. The ORR between these two groups was 60.2% and 64.4%, respectively, suggesting that some patients may achieve longer benefits. However, chemotherapy + atezolizumab also resulted in more adverse reactions, and the rate of drug discontinuation due to adverse reactions was 11.1% and 3.1%, respectively, in these two groups[37]. IMpower133 is the first Phase III study with an immunotherapy-based combination to show improvement in PFS and OS in the initial treatment of ES-SCLC. Accordingly, the National Comprehensive Cancer Network guidelines list EC combined with atezolizumab as a Level I recommendation[38]. Another Phase II trial (IFCT-1603; NCT03059667) compared the effectiveness and safety of atezolizumab (1200 mg every 3 wk) with those of chemotherapy (topotecan or the original treatment regimen). Among the 73 patients enrolled, 64.4% had platinum-sensitive recurrence. The primary endpoint was ORR at 6 wk, which was 2.3% and 10% in the atezolizumab and chemotherapy groups; and PFS was 4.3 and 1.4 mo, respectively (HR: 2.26; 95%CI: 1.3-3.93; P = 0.004). However, the OS showed no significant difference between these two groups (9.5 mo *vs* 8.7 mo, HR: 0.84, 95%CI: 0.45-1.58; P = 0.6)[39].

Durvalumab

CASPIAN is the second study that proved the effectiveness of PD-L1 monoclonal antibody as the first-line treatment for ES-SCLC. A total of 805 patients were randomly assigned to durvalumab + platinum-etoposide (n = 268), durvalumab + tremelimumab + platinum–etoposide (n = 268), and platinum-etoposide alone (n = 269). According to the preliminary data, the PFS of the durvalumab combination group was 5.1 mo (95%CI: 4.7-6.2 mo), PFS of the chemotherapy-only group was 5.4 mo (95%CI: 4.8-6.2 mo), the 6-mo PFS rate was 45% (95%CI: 39.3%-51.3%) and 46% (95%CI: 39.3%-51.7%), the 12-mo PFS rate was 18% (95%CI: 13.1%-22.5%) and 5% (95%CI: 2.4%-8.0%), and the OS was 13.0 mo with durvalumab plus platinum + etoposide and 10.3 mo with platinum + etoposide[40].

ICIs combined with poly (ADP ribose) polymerase inhibitors

Sen *et al*[41] characterized the increased expression of DDR protein in SCLC by using reverse phase protein array, a functional proteomics technique[41]. They found strong synergy between immune-checkpoint blockade and DDR inhibitors; these agents increased the levels of TILs through innate immune responses and showed synergistic effects with anti-PD-L1 therapy in multiple SCLC models. Further studies showed that the antitumor immune response targeting poly (ADP ribose) polymerase (PARP) developed through the STING-TBK1-IRF3 pathway in SCLC, which offers theoretical support for the combination of PARP inhibitors with anti-PD-L1 antibodies[42]. A Phase II clinical trial (Registration No: NCT02484404) explored the combination of a PARP inhibitor with anti-PD-L1 monoclonal antibody for SCLC. A total of 20 patients with recurrent SCLC were included. The median age was 64 years, and the diseases were platinum refractory or resistant in 60% of the patients. After enrollment, they were treated with durvalumab (anti-PD-L1 monoclonal antibody) + olaparib (a PARP inhibitor). Of 19 evaluable patients, the ORR was 10.5% (n = 2). Clinical benefit was observed in four patients (21.1%, 95%CI, 6.1%-45.6%) with confirmed responses or prolonged stable disease (≥ 8 mo)[43]. Notably, biopsy specimens during their study suggested that tumor immune phenotypes might be relevant for SCLC responses to immune checkpoint blockade combinations. The most common treatment-related adverse events were anemia (80%), lymphopenia (60%), and leukopenia (50%)[43].

ICIs combined with radiotherapy

Radiotherapy can influence the immune system and its interactions with cancer cells and tumors, producing cytokines that recruit anti-tumor immune cells, increasing the exposure of tumor antigens[44]. The use of radiotherapy may enhance efficacy of inmunotherapy.

Hendriks *et al*[44] evaluated in a Phase I 3 plus 3 design increasing doses of pembrolizumab (maximum 200 mg) every 3 wk combined with thoracic radiotherapy (45 Gy per 15 daily fractions) administered sequentially after induction of platinum-etoposide chemotherapy in extensive-stage SCLC. The results showed that the patients were generally well tolerated, with median PFS (6.1 mo) and median OS (8.4 mo). The combination treatment did not appear to improve survival[45]. Therefore, there is still a need for more exploration and research on the combined treatment model.

CONCLUSION

Immunotherapy for SCLC has included IFN, IL, immune adjuvants, and vaccines in recent decades (several important studies are summarized in Table 1). However, their applications lack support from high-level evidence, and most of these therapies are still under investigation in clinical trials. SCLC is typically featured by high TMB, unstable *TP53* and *RB1* genes, and high mutation rate of DDR pathway. It has a lower expression level of PD-LI than other lung cancers. Certain advances have been made in the use of ICIs. Combination of first-line ICIs with chemotherapy for ES-SCLC has been confirmed by two large prospective studies, and is recommended by the National Comprehensive Cancer Network guidelines. However, the role of ICIs when used as later-line drugs warrants further study. Although both PD-L1 and TMB are still not useful biomarkers, further investigations on the immune microenvironment may be helpful in estimating the prognosis of immunotherapy. As we are in an era of Immune 2.0, there are theoretical bases for combination of immunotherapy and radiotherapy and for combinations of antiangiogenic drugs targeting the DDR pathway, although more clinical research is needed. In general, advances in immunotherapy and combinations of different treatment strategies have shed new light on the treatment of ES-SCLC.

Table 1 Immune checkpoint inhibitors and relevant clinical studies

		Ref.	Method	PFS	OS	ORR (%)
Ipilimumab	CA184-156	[26]	Ipilimumab plus Etoposide and Platinum *vs* Placebo plus Etoposide and Platinum	4.6 mo *vs* 4.4 mo	11.0 mo *vs* 10.9 mo	-
Nivolumab	CheckMate 032	[29]	(1) Nivolumab 3 mg/kg; (2) Ipilimumab 1 mg/kg + Nivolumab 1 mg/kg; (3) Ipilimumab 3 mg/kg + Nivolumab 1 mg/kg; and (4) Ipilimumab 1 mg/kg + Nivolumab 3 mg/kg	1.4 mo	5.6 mo	(1) 10; (2) 33; (3) 23; and (4) 19
	CheckMate 451	[31]	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg q3w *vs* Nivolumab 240 mg q2w *vs* Placebo	-	9.2 mo *vs* 10.4 mo *vs* 9.6 mo	-
	CheckMate 331	[32]	Nivolumab 240 mg q2w *vs* Topotecan	-	7.5 mo *vs* 8.4 mo	13.7 *vs* 16.5
Pembrolizumab	KEYNOTE-158	[33]	Pembrolizumab 200 mg q3w	2 mo	9.1 mo	18.7
Atezolizumab	IMpower-133	[37]	Atezolizumab + Etoposide and Carboplatin *vs* Placebo + Etoposide and Carboplatin	5.2 mo *vs* 4.3 mo	12.3 mo *vs* 10.3 mo	-
Durvalumab	CASPIAN	[40]	Durvalumab plus Etoposide and Platinum *vs* Etoposide and Platinum	5.1 mo *vs* 5.4 mo	13.0 mo *vs* 10.3 mo	-

PFS: Progression-free survival; OS: Overall survival; ORR: Objective response rate.

REFERENCES

1 **Ihde DC**. Small cell lung cancer. State-of-the-art therapy 1994. *Chest* 1995; **107**: 243S-248S [PMID: 7781401 DOI: 10.1378/chest.107.6_supplement.243s]
2 **Prior C**, Oroszy S, Oberaigner W, Schenk E, Kummer F, Aigner K, Hausmaninger H, Peschel C, Huber H. Adjunctive interferon-alpha-2c in stage IIIB/IV small-cell lung cancer: a phase III trial. *Eur Respir J* 1997; **10**: 392-396 [PMID: 9042638 DOI: 10.1183/09031936.97.10020392]
3 **Mattson K**, Holsti LR, Niiranen A, Kivisaari L, Iivanainen M, Sovijärvi A, Cantell K. Human leukocyte interferon as part of a combined treatment for previously untreated small cell lung cancer. *J Biol Response Mod* 1985; **4**: 8-17 [PMID: 2984340]
4 **Ruotsalainen TM**, Halme M, Tamminen K, Szopinski J, Niiranen A, Pyrhönen S, Riska H, Maasilta P, Jekunen A, Mäntylä M, Kajanti M, Joensuu H, Sarna S, Cantell K, Mattson K. Concomitant chemotherapy and IFN-alpha for small cell lung cancer: a randomized multicenter phase III study. *J Interferon Cytokine Res* 1999; **19**: 253-259 [PMID: 10213464 DOI: 10.1089/107999099314180]
5 **Taniguchi T**. Structure and function of IL-2 and IL-2 receptors. *Behring Inst Mitt* 1992; 87-95 [PMID: 1524574]
6 **Fischer JR**, Schindel M, Bülzebruck H, Lahm H, Krammer PH, Drings P. Long-term survival in small cell lung cancer patients is correlated with high interleukin-2 secretion at diagnosis. *J Cancer Res Clin Oncol* 2000; **126**: 730-733 [PMID: 11153147 DOI: 10.1007/pl00008479]
7 **Fischer JR**, Schindel M, Bülzebruck H, Lahm H, Krammer PH, Drings P. Decrease of interleukin-2 secretion is a new independent prognostic factor associated with poor survival in patients with small-cell lung cancer. *Ann Oncol* 1997; **8**: 457-461 [PMID: 9233525 DOI: 10.1023/a:1008242000431]
8 **Clamon G**, Herndon J, Perry MC, Ozer H, Kreisman H, Maher T, Ellerton J, Green MR. Interleukin-2 activity in patients with extensive small-cell lung cancer: a phase II trial of Cancer and Leukemia Group B. *J Natl Cancer Inst* 1993; **85**: 316-320 [PMID: 8381188 DOI: 10.1093/jnci/85.4.316]
9 **Meazza R**, Marciano S, Sforzini S, Orengo AM, Coppolecchia M, Musiani P, Ardizzoni A, Santi L, Azzarone B, Ferrini S. Analysis of IL-2 receptor expression and of the biological effects of IL-2 gene transfection in small-cell lung cancer. *Br J Cancer* 1996; **74**: 788-795 [PMID: 8795583 DOI: 10.1038/bjc.1996.437]
10 **Niehans GA**, Brunner T, Frizelle SP, Liston JC, Salerno CT, Knapp DJ, Green DR, Kratzke RA. Human lung carcinomas express Fas ligand. *Cancer Res* 1997; **57**: 1007-1012 [PMID: 9067260]

11 **D'Amico D**, Carbone D, Mitsudomi T, Nau M, Fedorko J, Russell E, Johnson B, Buchhagen D, Bodner S, Phelps R. High frequency of somatically acquired p53 mutations in small-cell lung cancer cell lines and tumors. *Oncogene* 1992; **7**: 339-346 [PMID: 1312696]

12 **Chiappori AA**, Soliman H, Janssen WE, Antonia SJ, Gabrilovich DI. INGN-225: a dendritic cell-based p53 vaccine (Ad.p53-DC) in small cell lung cancer: observed association between immune response and enhanced chemotherapy effect. *Expert Opin Biol Ther* 2010; **10**: 983-991 [PMID: 20420527 DOI: 10.1517/14712598.2010.484801]

13 **Antonia SJ**, Mirza N, Fricke I, Chiappori A, Thompson P, Williams N, Bepler G, Simon G, Janssen W, Lee JH, Menander K, Chada S, Gabrilovich DI. Combination of p53 cancer vaccine with chemotherapy in patients with extensive stage small cell lung cancer. *Clin Cancer Res* 2006; **12**: 878-887 [PMID: 16467102 DOI: 10.1158/1078-0432.CCR-05-2013]

14 **Ettinger DS**, Aisner J. Changing face of small-cell lung cancer: real and artifact. *J Clin Oncol* 2006; **24**: 4526-4527 [PMID: 17008688 DOI: 10.1200/JCO.2006.07.3841]

15 **Peifer M**, Fernández-Cuesta L, Sos ML, George J, Seidel D, Kasper LH, Plenker D, Leenders F, Sun R, Zander T, Menon R, Koker M, Dahmen I, Müller C, Di Cerbo V, Schildhaus HU, Altmüller J, Baessmann I, Becker C, de Wilde B, Vandesompele J, Böhm D, Ansén S, Gabler F, Wilkening I, Heynck S, Heuckmann JM, Lu X, Carter SL, Cibulskis K, Banerji S, Getz G, Park KS, Rauh D, Grütter 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, Sänger 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, Büttner R, Wolf J, Nürnberg P, Perner S, Heukamp LC, Brindle PK, Haas S, Thomas RK. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nat Genet* 2012; **44**: 1104-1110 [PMID: 22941188 DOI: 10.1038/ng.2396]

16 **Drapkin BJ**, Farago AF. Unexpected Synergy Reveals New Therapeutic Strategy in SCLC. *Trends Pharmacol Sci* 2019; **40**: 295-297 [PMID: 30975441 DOI: 10.1016/j.tips.2019.03.005]

17 **Byers LA**, Wang J, Nilsson MB, Fujimoto J, Saintigny P, Yordy J, Giri U, Peyton M, Fan YH, Diao L, Masrorpour F, Shen L, Liu W, Duchemann B, Tumula P, Bhardwaj V, Welsh J, Weber S, Glisson BS, Kalhor N, Wistuba II, Girard L, Lippman SM, Mills GB, Coombes KR, Weinstein JN, Minna JD, Heymach JV. Proteomic profiling identifies dysregulated pathways in small cell lung cancer and novel therapeutic targets including PARP1. *Cancer Discov* 2012; **2**: 798-811 [PMID: 22961666 DOI: 10.1158/2159-8290.CD-12-0112]

18 **Sen T**, Tong P, Stewart CA, Cristea S, Valliani A, Shames DS, Redwood AB, Fan YH, Li L, Glisson BS, Minna JD, Sage J, Gibbons DL, Piwnica-Worms H, Heymach JV, Wang J, Byers LA. CHK1 Inhibition in Small-Cell Lung Cancer Produces Single-Agent Activity in Biomarker-Defined Disease Subsets and Combination Activity with Cisplatin or Olaparib. *Cancer Res* 2017; **77**: 3870-3884 [PMID: 28490518 DOI: 10.1158/0008-5472.CAN-16-3409]

19 **Doerr F**, George J, Schmitt A, Beleggia F, Rehkämper T, Hermann S, Walter V, Weber JP, Thomas RK, Wittersheim M, Büttner R, Persigehl T, Reinhardt HC. Targeting a non-oncogene addiction to the ATR/CHK1 axis for the treatment of small cell lung cancer. *Sci Rep* 2017; **7**: 15511 [PMID: 29138515 DOI: 10.1038/s41598-017-15840-5]

20 **Carvajal-Hausdorf D**, Altan M, Velcheti V, Gettinger SN, Herbst RS, Rimm DL, Schalper KA. Expression and clinical significance of PD-L1, B7-H3, B7-H4 and TILs in human small cell lung Cancer (SCLC). *J Immunother Cancer* 2019; **7**: 65 [PMID: 30850021 DOI: 10.1186/s40425-019-0540-1]

21 **Tai X**, Van Laethem F, Pobezinsky L, Guinter T, Sharrow SO, Adams A, Granger L, Kruhlak M, Lindsten T, Thompson CB, Feigenbaum L, Singer A. Basis of CTLA-4 function in regulatory and conventional CD4(+) T cells. *Blood* 2012; **119**: 5155-5163 [PMID: 22403258 DOI: 10.1182/blood-2011-11-388918]

22 **Salama AK**, Hodi FS. Cytotoxic T-lymphocyte-associated antigen-4. *Clin Cancer Res* 2011; **17**: 4622-4628 [PMID: 21467163 DOI: 10.1158/1078-0432.CCR-10-2232]

23 **Greenwald RJ**, Freeman GJ, Sharpe AH. The B7 family revisited. *Annu Rev Immunol* 2005; **23**: 515-548 [PMID: 15771580 DOI: 10.1146/annurev.immunol.23.021704.115611]

24 **Pentcheva-Hoang T**, Corse E, Allison JP. Negative regulators of T-cell activation: potential targets for therapeutic intervention in cancer, autoimmune disease, and persistent infections. *Immunol Rev* 2009; **229**: 67-87 [PMID: 19426215 DOI: 10.1111/j.1600-065X.2009.00763.x]

25 **Reck M**, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, Sebastian M, Lu H, Cuillerot JM, Lynch TJ. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. *Ann Oncol* 2013; **24**: 75-83 [PMID: 22858559 DOI: 10.1093/annonc/mds213]

26 **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, 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 [PMID: 27458307 DOI: 10.1200/JCO.2016.67.6601]

27 **Freeman GJ**, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, Fitz LJ, Malenkovich N, Okazaki T, Byrne MC, Horton HF, Fouser L, Carter L, Ling V, Bowman MR, Carreno BM, Collins M, Wood CR, Honjo T. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med* 2000; **192**: 1027-1034 [PMID: 11015443 DOI: 10.1084/jem.192.7.1027]

28 **Dong H**, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, Roche PC, Lu J, Zhu G, Tamada K, Lennon VA, Celis E, Chen L. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med* 2002; **8**: 793-800 [PMID: 12091876 DOI: 10.1038/nm730]

29 **Ready N**, Farago AF, de Braud F, Atmaca A, Hellmann MD, Schneider JG, Spigel DR, Moreno V, Chau I, Hann CL, Eder JP, Steele NL, Pieters A, Fairchild J, Antonia SJ. Third-Line Nivolumab Monotherapy in Recurrent SCLC: CheckMate 032. *J Thorac Oncol* 2019; **14**: 237-244 [PMID: 30316010 DOI: 10.1016/j.jtho.2018.10.003]

30 **Hellmann MD**, Callahan MK, Awad MM, Calvo E, Ascierto PA, Atmaca A, Rizvi NA, Hirsch FR, Selvaggi G, Szustakowski JD, Sasson A, Golhar R, Vitazka P, Chang H, Geese WJ, Antonia SJ. Tumor Mutational Burden and Efficacy of Nivolumab Monotherapy and in Combination with Ipilimumab in Small-Cell Lung Cancer. *Cancer Cell* 2018; **33**: 853-861.e4 [PMID: 29731394 DOI:

10.1016/j.ccell.2018.04.001]
31 **Owonikoko TK**, Kim HR, 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, Fairchild J, Baudelet C, Park K. Nivolumab (nivo) plus ipilimumab (ipi), nivo, or placebo (pbo) as maintenance therapy in patients (pts) with extensive disease small cell lung cancer (ED-SCLC) after first-line (1L) platinum-based chemotherapy (chemo): Results from the double-blind, randomized phase III CheckMate 451 study. *Ann Oncol* 2019; **30** Suppl 2: ii77 [DOI: 10.1093/annonc/mdz094]
32 **Reck M**, Vicente D, Ciuleanu T, Gettinger S, Peters S, Horn L, Audigier-Valette C, Pardo N, Juan-Vidal O, Cheng Y, Zhang H, Shi M, Wolf J, Antonia SJ, Nakagawa K, Selvaggi G, Baudelet C, Chang H, Spigel DR. Efficacy and safety of nivolumab (nivo) monotherapy versus chemotherapy (chemo) in recurrent small cell lung cancer (SCLC): Results from CheckMate 331. *Ann Oncol* 2018; **29** suppl10: x39-x43 [DOI: 10.1093/annonc/mdy511]
33 **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, 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 [PMID: 31870883 DOI: 10.1016/j.jtho.2019.12.109]
34 **Ott PA**, Elez E, Hiret S, Kim DW, Morosky A, Saraf S, Piperdi B, 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 [PMID: 28813164 DOI: 10.1200/JCO.2017.72.5069]
35 **Herbst RS**, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN, Kohrt HE, Horn L, Lawrence DP, Rost S, Leabman M, Xiao Y, Mokatrin A, Koeppen H, Hegde PS, Mellman I, Chen DS, Hodi FS. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 2014; **515**: 563-567 [PMID: 25428504 DOI: 10.1038/nature14011]
36 **Horn L**, Mansfield AS, Szczęsna 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, 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 [PMID: 30280641 DOI: 10.1056/NEJMoa1809064]
37 **Mansfield AS**, Każarnowicz A, Karaseva N, Sánchez A, De Boer R, Andric Z, Reck M, Atagi S, Lee JS, Garassino M, Liu SV, Horn L, Wen X, Quach C, Yu W, Kabbinavar F, Lam S, Morris S, Califano R. Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small-cell lung cancer (IMpower133): a randomized phase I/III trial. *Ann Oncol* 2020; **31**: 310-317 [PMID: 31959349 DOI: 10.1016/j.annonc.2019.10.021]
38 **National Comprehensive Cancer Network (NCCN)**. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Small Cell Lung Cancer. Version 1. 2019. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx
39 **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, 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 [PMID: 30664989 DOI: 10.1016/j.jtho.2019.01.008]
40 **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, 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 [PMID: 31590988 DOI: 10.1016/S0140-6736(19)32222-6]
41 **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, 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 [PMID: 30777870 DOI: 10.1158/2159-8290.CD-18-1020]
42 **Thomas A**, Vilimas R, Trindade C, Erwin-Cohen R, Roper N, Xi L, Krishnasamy V, Levy E, Mammen A, Nichols S, Chen Y, Velcheti V, Yin F, Szabo E, Pommier Y, Steinberg SM, Trepel JB, Raffeld M, Young HA, Khan J, Hewitt S, Lee JM. Durvalumab in Combination with Olaparib in Patients with Relapsed SCLC: Results from a Phase II Study. *J Thorac Oncol* 2019; **14**: 1447-1457 [PMID: 31063862 DOI: 10.1016/j.jtho.2019.04.026]
43 **Nesbit EG**, Leal TA, Kruser TJ. What is the role of radiotherapy for extensive-stage small cell lung cancer in the immunotherapy era? *Transl Lung Cancer Res* 2019; **8**: S153-S162 [PMID: 31673520 DOI: 10.21037/tlcr.2019.05.01]
44 **Hendriks LEL**, Menis J, De Ruysscher DKM, Reck M. Combination of Immunotherapy and Radiotherapy-The Next Magic Step in the Management of Lung Cancer? *J Thorac Oncol* 2020; **15**: 166-169 [PMID: 32127183 DOI: 10.1016/j.jtho.2019.12.106]

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