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The incidences of adverse events in small-cell lung cancer patients after radiotherapy and immunotherapy treatment: a systematic review and meta-analysis

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Abstract. – Immunotherapy is important in treating small-cell lung cancer (SCLC), and its anti-tumor effects are better when combined with radiotherapy. However, the toxicity of this combination is little known. This study assessed the incidences of adverse events when adding radiotherapy to ICIs in patients with SCLC. We searched the online databases to identify eligible studies and included nine references. For extensive-stage SCLC patients, the median PFS ranged from 4.5 to 12.5 months, and median OS ranged from 8.4 to NR months, respectively. The incidences of grade 3 or higher pneumonitis, lung infection, diarrhea, and fatal adverse events were 8.7% (95% CI: 5%-14.7%), 6.7% (95% CI: 2.5%-16.5%), 12.6% (95% CI: 7.6%-20%), and 5.1% (95% CI: 2.1%-11.6%), respectively. Our findings suggest that radiotherapy plus ICIs may provide acceptable safety and favorable efficacy for SCLC patients.

Key Words:
Radiotherapy, Immune checkpoint inhibitor, Small cell lung cancer, Survival, Meta-analysis.

Introduction

Small cell lung cancer (SCLC) accounts for 10%-15% of lung cancers[1]. About two-thirds of these patients have metastatic disease at diagnosis and resulting in a poor prognosis[1,2]. For a long period, the first-line treatment for SCLC is platinum-based chemotherapy, such as etoposide plus cisplatin (EP) or irinotecan plus cisplatin (IP)[3]. For patients with limited-stage SCLC (LS-SCLC) and extensive-stage SCLC (ES-SCLC), these treatment regimens can effectively control the disease after several treatment cycles[3]. However, most patients develop recurrent disease after initial treatment, and there is a lack of effective treatment strategy for these patients[3,4]. Therefore, it is urgent to find novel treatment strategies for these patients.

In recent years, immune checkpoint inhibitors (ICIs) have exhibited remarkable efficacy in treating various cancers[5]. And it shows progress in immunotherapy for SCLC [6]. Several studies used ICIs monotherapy in the first line and subsequent line treatment of SCLC, which had different treatment outcomes[7]. For pre-treated SCLC, durable responses after ICIs treatment are observed with acceptable toxicity[8]. Based on the findings from the recent studies, nivolumab and pembrolizumab were approved for subsequent line treatment of relapsed SCLC[9]. For first-line treatment of SCLC, the IMpower133 study found that the median overall survival (OS) of the EP combined with Atezolizumab group was 2 months longer than that of the chemotherapy group alone[10,11]. The benefits of OS and progression-free survival (PFS) were also consistent. It showed that adding Atezolizumab to EP could significantly prolong the OS of SCLC patients, and this combination regimen was approved by the National Comprehensive Cancer Network (NCCN) guidelines and the U.S. Food and Drug Administration (FDA) as the first-line treatment option for ES-SCLC

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patients in 2019[12]. These studies prove the feasibility of immunotherapy contained combination therapy for SCLC.

Radiotherapy is one of the most important treatment options for SCLC[13-15]. Evidence from meta-analyses suggested that adding thoracic radiation (TRT) to chemotherapy improved the tumor control rate and survival rate[14]. Thereafter, several studies focused on the radiation dose and fraction, which made notable progress in recent years[16,17]. Despite these improvements, the overall prognosis of SCLC remains unsatisfactory, with limited OS[17]. Recently, the combination of ICIs and radiotherapy shows promising outcomes in stage III non-small cell lung cancer (NSCLC)[18]. The PACIFIC trial assessed the advances of combining ICIs with radiotherapy for NSCLC and found that chemoradiotherapy followed by adjuvant durvalumab treatment improved both FPS and OS with well-tolerated toxicity in patients with stage III NSCLC[17]. A retrospective study included 6 SCLC patients treated with combined ICIs following radiation, which found this combination was associated with severe immune-related toxicity in relapsed SCLC patients[19]. It is not well estimated whether this combination can be applied to the treatment of SCLC with remarkable efficacy and acceptable toxicity.

In the present study, we searched online databases to identify clinical studies on radiotherapy plus ICIs therapy in treating SCLC, aimed to summarize the efficacy and safety of this combination strategy in SCLC patients.

Search Strategy

Online databases including PubMed and Embase were searched to retrieve clinical studies of SCLC patients with ICIs and radiation treatment. The preprint databases, such as bioRxiv, were also included to search studies on the above topic. We also checked references from relevant reviews to identify potential eligible studies if necessary. The deadline for primary searching was April 2021. There was no language limitation during the search process. The search terms used for the search were: 'small cell lung cancer', 'SCLC', 'radiation', 'radiotherapy', 'stereotactic body radiation therapy ', 'SBRT', 'anti-pd-1', 'pd-1 inhibitor', 'CTLA-4 inhibitor', 'immune checkpoint inhibitor', 'immunotherapy', 'nivolumab', 'pembrolizumab', 'aterolizumab' 'durvalumab', and 'ipilimumab'. The search strategy of PubMed is shown in **Supplementary Table I**. This study was performed based on the PRISMA checklist (**Supplementary Table II**).

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) patients with histopathological or cytological diagnosis of small cell lung cancer; (2) randomized controlled trials, prospective studies, or retrospective studies; (3) SCLC patients received radiation and immune checkpoint inhibitors, regardless of timing and doses; (4) reported outcomes, such as overall response rate (ORR), disease control rate (DCR), progression-free survival, overall survival, and adverse events. Duplicate references and studies without sufficient endpoint data were discarded. Expert opinion, comments, and reviews were also discarded.

Literature Screening and Data Extraction

The references were screened by two reviewers (Qiong Wang and Aihua Liu), independently. And disagreement about inclusion of a specific study was resolved through discussion with a third reviewer. According to the previously designed table, the basic characteristics of the included studies (first author, publication year, gender, age, disease type, intervention, efficacy, and safety) and methodological quality evaluation indicators (random method, allocation concealment, blinding, with or without withdrawal or loss to follow-up) were extracted and recorded.

Quality Evaluation

For randomized controlled trials (RCTs), the Cochrane Handbook was used to evaluate the methodological quality of the included studies, including random method, allocation concealment, blinding, with, or without withdrawal or lost to follow-up[20]. High-quality studies have to meet the above 4 items (low risk of bias), moderate quality ones need to meet one or more of the above standards (moderate risk of bias), and low-quality study means that none of the above methods are satisfied (high risk of bias).

For retrospective studies, the Newcastle-Ottawa Scale (NOS) quality assessment scale was used to assess the quality of the included studies[21]. NOS introduces 'star system' to qualify the studies, and there are three broad perspectives: study groups selection, comparability of the groups, and ascertainment of exposure or outcome, respectively. According to the total

score (0-9 points), studies could be divided into the following groups: poor quality (0-3 points), moderate quality (4-6 points), and high quality (7-9 points).

Statistical Analysis

The percentage of occurrence and its 95% CI were used to present the overall effect of radiotherapy plus ICIs on survival and toxicity in SCLC. The hazard ratio (HR) and its 95% CI were used to evaluate the relationship between combination treatment and survival in SCLC if possible. The odds ratio (OR) and its 95% CI were used to evaluate the efficacy and safety of ICIs combined with radiotherapy if possible. If the chi-square test $p<0.1$ or $I^2>50\%$, it was considered heterogeneous[22]. If heterogeneity existed, the random-effects model was used to reduce the impact of heterogeneity on the results. Otherwise, the fixed-effects model was used[22]. Egger's and Begg's tests are used to assess publication bias if possible. The Comprehensive meta-analysis and GraphPad Prism 8 software (La Jolla, CA, USA) were used for statistical analysis.

Results

Literature Screening Results

309 relevant references were retrieved after the systematic search. Studies that were duplicated or did not provide sufficient data were excluded. After screening the titles and abstracts, 288 studies were excluded. After reading the full text of the remaining 21 articles, 12 articles were discarded. Finally, 9 references[8,23-30] were included (Figure 1). These studies included 666 patients, with an average age ranging from 62 to 70 years.

Baseline Characteristics and Methodological Quality of the Studies

The basic characteristics of the included studies are shown in Table I. There were six studies with eight reports. The subjects of two references[25,27] were limited-stage SCLC patients, four references[24,26,28,30] were about extensive-stage SCLC, and two references[8,23] included relapsed SCLC patients. Four studies[23,24,28,30] were performed in America, two study[8,29] were in Europe, and three studies[25-27] were performed in multiple regions.

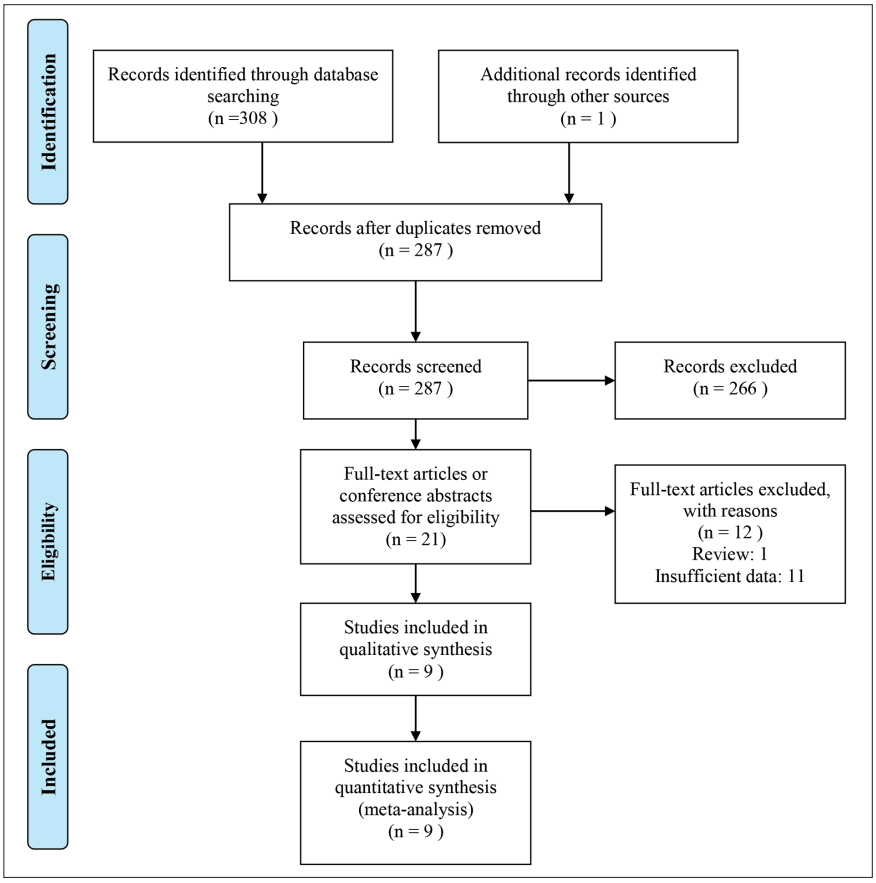

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram.

Table I. Baseline characteristics of included studies.

Authors	Year	Design	Number	Region	Age	Male, n (%)	Patient type	Treatment	Outcomes
Schmid et al[8]	2020	Retrospective	45	Europe	63	33 (73.3%)	Relapsed SCLC	Nivolumab, nivolumab+ ipilimumab, or atezolizumab with radiotherapy	ORR, OS, PFS, safety
Pakkala et al[23]	2020	RCT	18	America	67.8	11 (61.1)	Relapsed SCLC	Tremelimumab and durvalumab with radiation	ORR, OS, PFS, safety
Perez et al[24]	2021	Prospective	21	America	66	13 (62)	Extensive-stage SCLC	Ipilimumab and nivolumab with thoracic radiotherapy	ORR, OS, PFS, safety
Peters et al[25]	2022	RCT	153	Multiple	62	92 (60.0)	Limited-stage SCLC	Ipilimumab and nivolumab with thoracic radiotherapy	OS, PFS, safety
Welsh et al[26]	2019	Prospective	38	Multiple	65	20 (61)	Extensive-stage SCLC	Pembrolizumab with thoracic radiation therapy	ORR, OS, PFS, safety
Welsh et al[27]	2020	Prospective	45	Multiple	64	16 (40)	Limited-stage SCLC	Pembrolizumab was started concurrently with CRT and continued for up to 16 cycles	ORR, OS, PFS, safety
Elegbede et al[28]	2021	Retrospective	67	America	65	33 (49.3)	Extensive-stage SCLC	Atezolizumab, chemotherapy and radiation	ORR, OS, PFS, safety
Galuba et al[29]	2021	Retrospective	35	Europe	NR	NR	SCLC	Atezolizumab, chemotherapy and radiation	PFS
Gross et al[30]	2021	Retrospective	244	America	65	NR	Extensive-stage SCLC	Immunotherapy, chemotherapy and radiation	OS

List of Abbreviations: RT, radiotherapy; RCT, randomized controlled trials; SCLC, small cell lung cancer; SBRT, stereotactic body radiation therapy; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; CRT, chemoradiotherapy; IMRT, Intensity modulated radiation therapy; TRT, thoracic radiation therapy.

Table II. The quality assessment of the included studies.

Study	Random	Allocation	Blinding	Withdrawal	Lost to follow-up
Pakkala et al[23]	Y	N	N	N	N
Peters et al[25]	Y	N	N	NR	NR

	Selection				Comparability	Outcome			Score
	A	B	C	D	E	F	G	H	
Schmid et al[8]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Perez et al[24]	☆		☆	☆	☆	☆	☆	☆	7
Welsh et al[26]	☆		☆	☆	☆	☆	☆	☆	7
Welsh et al[27]	☆		☆	☆	☆	☆	☆	☆	7
Elegbede et al[28]	☆	☆	☆	☆	☆	☆	☆	☆	8
Galuba et al[29]	☆	☆	☆		☆	☆	☆		6
Gross et al[30]	☆	☆	☆	☆	☆	☆	☆	☆	8

NOS criteria: Selection (**A**: representativeness of cases, **B**: selection of controls, **C**: exposure ascertainment, and **D**: no death when investigation begin); Comparability (**E**: comparable on confounders); Outcome (**F**: outcome assessment, **G**: adequate follow-up, and **H**: loss to follow-up rate). The total score is equal to the total number of stars.

Two studies[23,25] were RCTs, three studies[24,26,27] were prospective studies, and four[8,28-30] were retrospective studies.

Two[23,25] of the 9 reports were RCTs. All the RCTs were clear about the allocation concealment and blinding method, and there was limited information about patients who withdrew or lost to follow-up. The quality of the single-arm studies was assessed by NOS method. Overall, six[8,24,26-28,30] of the studies were considered as high quality, and the rest one[29] was evaluated as moderate quality, which ensured the reliability of the meta-analysis of adverse events. The results of methodological quality assessment are shown in Table II.

Main Results

Summary of PFS and OS

All the studies reported PFS and OS in patients with different stage SCLC. The study of Peters et al[25] showed that for patients with limited-stage SCLC, those who were treated with ICIs and radiotherapy had a longer PFS than those without ICIs (14.5 *vs.* 10.7 months). Another single-arm study by Welsh et al[27] showed that the PFS was 19.7 months for limited-stage SCLC patients who received both ICIs and radiotherapy (Figure 2A). The PFS for extensive-stage SCLC patients ranged from 4.47 to 12.5 months when treated

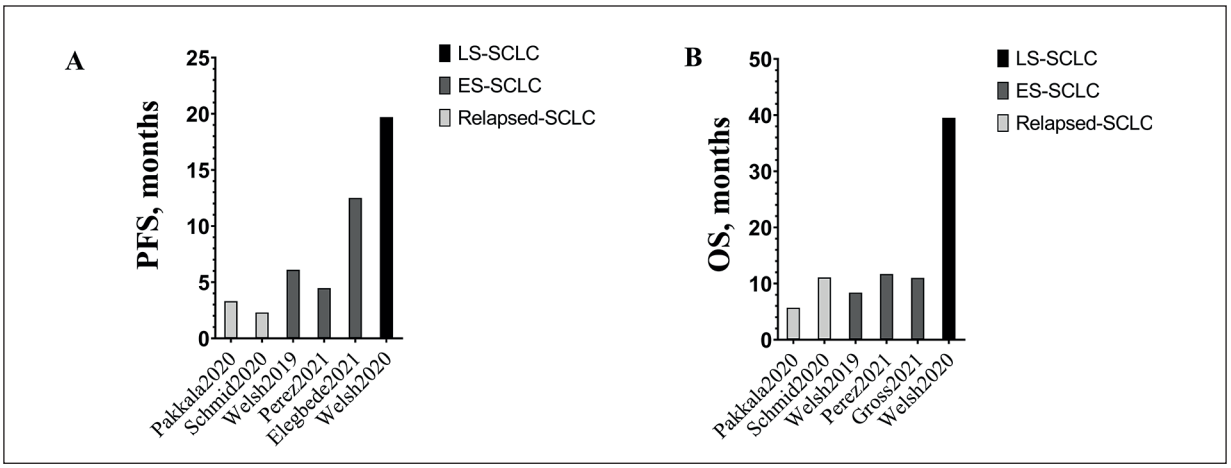

Figure 2. The summarized progression-free survival and overall survival in SCLC with different stages. **A,** progression-free survival; **B,** overall survival.

with ICIs and thoracic radiation (Figure 2A). For patients with relapsed SCLC, the PFS was between 2.3 months to 3.3 months (Figure 2A).

As shown in Figure 2B, the OS of patients with limited-stage SCLC was 39.5 to NR months when receiving ICIs and radiotherapy treatment, and between 8.4 months to 11.7 months for extensive-stage SCLC. In the study by Pakkala et al[26], the OS was 5.7 months *vs*. 2.6 months for relapsed SCLC patients who received ICIs with and without radiotherapy. However, in the setting of the real world, the study of Schmid et al[8] showed that those who received both ICIs and radiotherapy had a longer OS than those with ICIs only (11.1 months *vs*. 6.5 months).

We also explored the association between PFS and OS, aiming to assess whether PFS could be a potential surrogate for OS in SCLC patients after treatments of ICIs and radiotherapy. The correlation analysis result (Figure 3) showed that the Pearson's r was 0.96 (95% CI: 0.53-0.99; p=0.009) with an R square of 0.93 (OS= 0.4998*PFS-0.4564).

Survival Rate

Limited-Stage SCLC

There were a few studies[25,27] that reported the survival rates of limited-stage SCLC patients at different time points. Because of the heterogeneity of the related studies, we used the descriptive method in this section. The analysis of survival rates was performed based on the single-arm design of the included studies. The survival rate for patients who received radiotherapy and ICIs is presented in **Supplementary Figure 1**. Briefly, in the study of Welsh et al[26], the PFS rates of limited-stage SCLC patients treated with pembrolizumab, and RT were 97.7%, 77.6%, 66.9%, and 43.8% at 3 months, 6 months, one year, and two years, respectively (**Supplementary Figure 1**). Peters et al[25] reported that the 2-year PFS rate was 43.0% for limited-stage SCLC patients treated with a combination of ipilimumab, nivolumab, and RT (**Supplementary Figure 1**). The study of Welsh et al[27] reported that the overall survival rates of limited-stage SCLC patients at 6 months and 12 months were 95.0% and 75.7%, respectively (**Supplementary Figure 1**). Similarly, the 12-month OS rate for limited-stage SCLC patients treated with a combination of ipilimumab, nivolumab, and RT was 79.0% (**Supplementary Figure 1**).

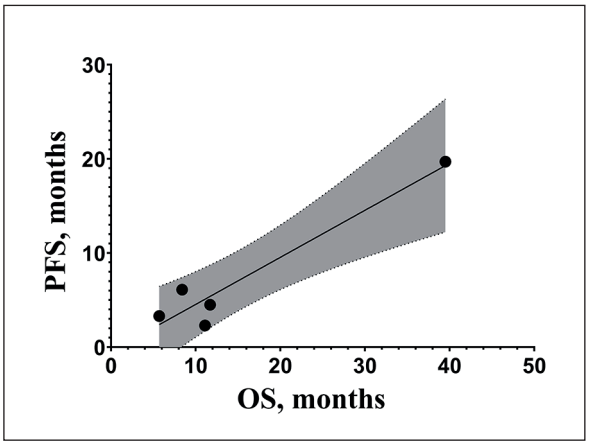

Figure 3. Correlation analysis of PFS and OS in SCLC patients treated with ICIs and radiotherapy.

Extensive-Stage SCLC

For extensive-stage SCLC patients, the analyses were performed using the outcomes from single-arm studies[24,26,31]. For extensive-stage SCLC patients who were treated with combined therapy of ipilimumab, nivolumab, and RT, the PFS rates at 3 months, 6 months, 12 months, and 24 months were 71.4%, 24.0%, 14.0%, and 9.3%, respectively (**Supplementary Figure 2**). For those treated with pembrolizumab and radiotherapy, the PFS rates at 3 months, 6 months, and 12 months were 78.0%, 50.2%, and 19.7%, respectively (**Supplementary Figure 2**). Next, we also evaluated the impact of radiotherapy and immunotherapy on OS. For extensive-stage SCLC patients who received ipilimumab, nivolumab, and RT therapy, the OS rates at 6 months and 12 months were 62.0% and 48.0%, respectively (**Supplementary Figure 2**). For those treated with pembrolizumab and radiotherapy, although there were more patients were alive at 6 months (76.5%) after treatment, the OS rate (29.7%) at 12 months was lower than that of the above group (48.0%) (**Supplementary Figure 2**). The indirect comparison of these survival results suggested that a combination of ipilimumab, nivolumab, and radiotherapy may be associated with better overall survival than that of the single ICI and radiotherapy therapy.

Relapsed SCLC

The survival rates at various time points were also assessed in relapsed SCLC patients. Two studies[8,23] reported the PFS and OS in relapsed SCLC patients after combination treat-

ment of ICIs and radiotherapy. As reported in the study of Schmid et al[8], patients received either nivolumab, nivolumab and ipilimumab, or atezolizumab with radiotherapy. 35.0% of these patients were alive without disease progression at 3 months, and it was 28.0% at 6 months (**Supplementary Figure 3**). Another study by Pakkala et al[23] showed that the PFS rate at 3 months was 57.5% after treated with tremelimumab, durvalumab, and radiotherapy (**Supplementary Figure 3**). Regarding OS, the percentages of patients were 59.9% and 40.0% at 6 months and 12 months for those treated with radiotherapy in combination with nivolumab±ipilimumab, or atezolizumab (**Supplementary Figure 3**). In the study of Pakkala et al[23], the OS rates at 6 months and 12 months for relapsed SCLC patients after treatment of radiotherapy and tremelimulab and durvalumab were 42.9% and 28.6%, respectively (**Supplementary Figure 3**).

Meta-Analysis Results of Adverse Events

The incidences of overall and specific adverse events were evaluated based on the reported cases from the included studies[8,23-30]. The summarized incidence of any ≥grade 3 adverse events was 59.8% (95% CI: 49.9%-69%) for SCLC patients who received ICIs and radiotherapy, regardless of disease stage (Figure 4A). Concerning specific adverse events, the event rates of < grade 3 and ≥grade 3 pneumonitis were 14.9% (95% CI: 8.8%-24.3%) and 8.7% (95% CI: 5%-14.7%) for SCLC patients with combination treatment, respectively (Figure 4B). For the incidences of lung infection, 4.9% (95% CI: 1.6%-14.2%) of these patients had ≤ grade 2 lung infection after treatment, while a slightly higher rate (6.7% (95% CI: 2.5%-16.5%)) of ≥ grade 3 lung infection was observed (Figure 4C). Percentages of patients with ≤ grade 2 and ≥ grade 3 diarrhea were 16.8% (95% CI: 11.3%-24.2%) and 12.6% (95% CI: 7.6%-20%), respectively (Figure 4D). Two studies reported fatal adverse events after treatment, and the overall rate was 5.1% (95% CI: 2.1%-11.6%) for SCLC patients (Figure 4E).

Publishing Bias Assessment

The publication bias assessment was not performed as there was insufficient number of studies after grouping them by disease stage. Due to the limited number of studies and the summarized safety and efficacy data, we presume that the risk of publication bias could be high.

Discussion

The treatment landscape of SCLC has changed rapidly since the administration of immunotherapy[32,33]. Whether the combination of radiotherapy and ICIs is associated with better treatment efficacy and survival outcome for SCLC patients, is not well determined. In the present study, we collected published evidence in clinical studies reporting ICI+RT *vs.* ICI/RT to treat SCLC patients, and the results based on disease stage showed that this combination resulted in different PFS and OS outcomes and toxicity. To our knowledge, this is the first meta-analysis assessing the efficacy and safety of radiation and immunotherapy in patients with LS-SCLC, ES-SCLC, and relapsed SCLC. Based on the pooled data, this combination may be worth further investigation, especially for patients with LS-SCLC.

For LS-SCLC patients, recent research progress mainly focuses on the optimal fraction and dosing of radiation[13]. A meta-analysis[13] of five RCTs reported that the one-year and two-year PFS and OS rates for LS-SCLC patients who received once daily radiotherapy during concurrent chemoradiotherapy treatment were 67.2% and 75.2%, 38.9%, and 47.1%, respectively. The median OS was 21.6 months for the once-daily group, and it was 25.6 months for the twice-daily group[13]. The incidences of grade 3-5 AEs were 68.7% for the once-daily group and 75.9% for the twice-daily radiation group[13]. In the prospective, single-arm trial of Welsh et al[27], the effect of ICIs plus chemoradiotherapy on efficacy and survival was evaluated in LS-SCLC patients. The results showed that the median OS was 39.5 months, the median PFS was 19.7 months, and the two-year OS rate was 65.8%[27]. In another study by Peters et al[25], the median OS was not reached in LS-SCLC patients who were treated with both ICIs and chemoradiotherapy, while it was 31.6 months for patients who received chemoradiotherapy. With regards to PFS, they were 14.5 months *vs.* 10.7 months for LS-SCLC patients with and without ICIs[25]. In the study of Welsh et al[27], the six-month, one-year, and two-year PFS rates for patients who received combination treatment were 77.6%, 66.9%, and 43.8%, respectively. The one-year OS rate was 75.7%, which was slightly higher than that of the once-daily radiotherapy group without immunotherapy. However, the two-year OS rate of LS-SCLC was 65.8% for ICI plus chemoradio-

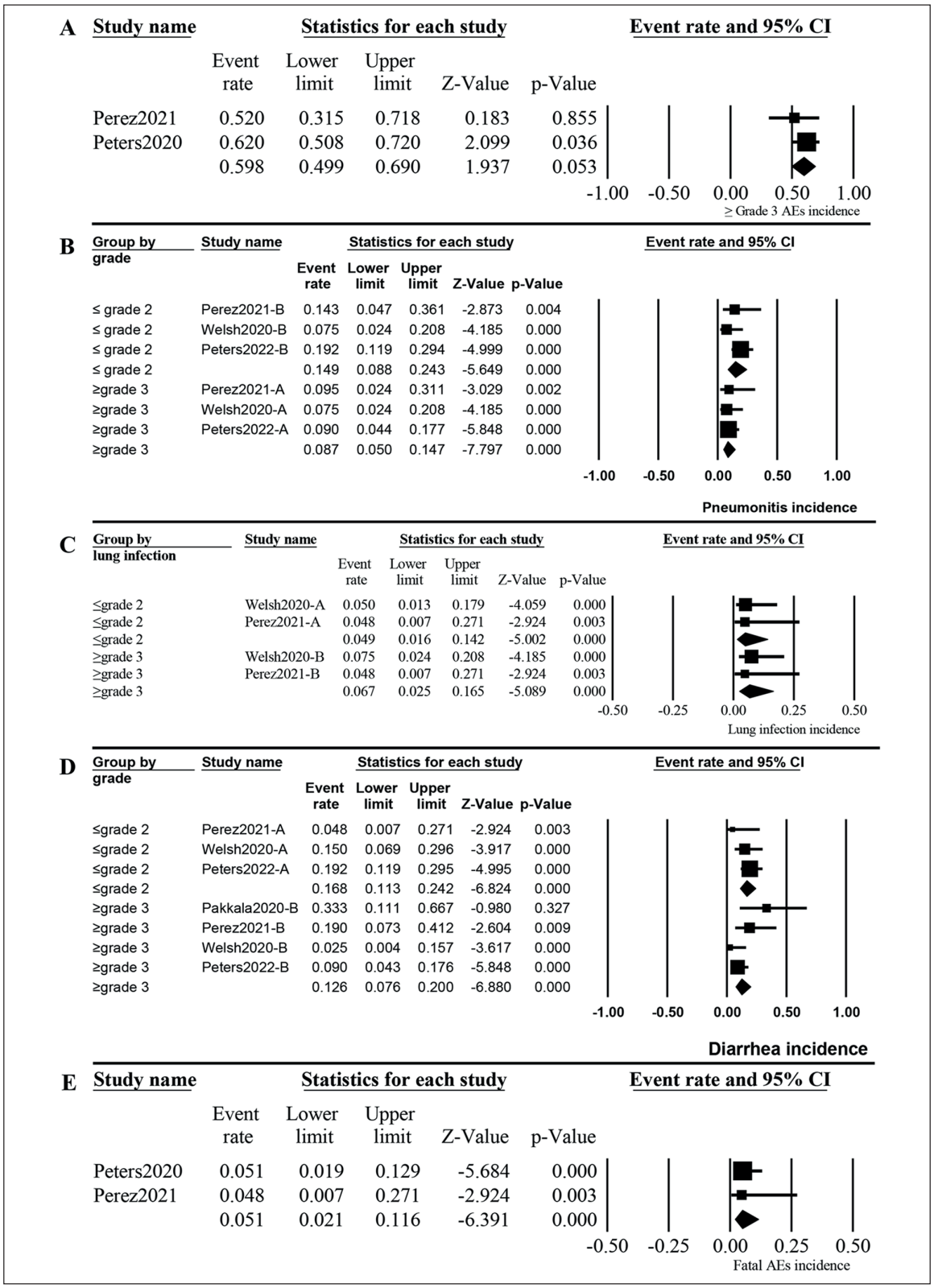

Figure 4. The meta-analyses of adverse events for SCLC patients, regardless of disease stage. **A,** The incidence of grade 3 or higher adverse events for SCLC patients treated with both ICIs and radiotherapy. **B,** The incidence of pneumonitis in SCLC patients treated with both ICIs and radiotherapy. **C,** The incidence of lung infection in SCLC patients with the combination treatment. **D,** Diarrhea incidence in SCLC patients. **E,** Rate of fatal adverse events in SCLC patients who received ICIs plus radiation.

therapy group, and it was 47.1% for the chemoradiotherapy group[13]. These results suggested that adding ICIs to radiation may prolong the median OS and PFS.

For patients with ES-SCLC, adding ICIs to first-line chemotherapy has been evaluated in several clinical trials, and several meta-analyses on the above topic have been published[6,7,34,35]. In the meta-analysis performed by Facchinetti et al[36], four RCTs were included and the pooled survival analyses showed that the one-year, and two-year OS rates for ICI plus chemotherapy group were 50.2%, and 22.3%, respectively[36]. The six-month, one-year, and 1.5-year PFS rates for ICIs combined with chemotherapy group were 38.7%, 16.1%, and 13.0%, respectively[36]. In our study, the impact of combination of chemoradiotherapy and ICIs on PFS and OS were evaluated, and the median OS ranged from 8.4 months to 11.7 months for the radiation involved group, and they were between 10.8 and 12.9 months in the ICIs plus chemotherapy group. As suggested by these data, the PFS rates were similar between ICIs and chemotherapy group with and without radiation. However, the one-year OS rate was higher in the dual ICI plus radiotherapy group when indirectly compared to that of the single ICI and radiotherapy group. This difference may be explained by the following reasons. First, the sample size was relatively small in the radiation group. Secondly, the study types varied. In our meta-analysis, the included studies were prospective single-arm ones to assess the safety and efficacy of ICIs and radiotherapy, while it was a meta-analysis of RCTs[36] to evaluate the outcome of ES-SCLC patients after chemotherapy and ICIs treatment. Thirdly, the duration of treatment and follow-up varied between these studies[24,26,36]. Therefore, further trials with a larger sample size and longer follow-up are recommended.

For relapsed SCLC, the administration of ICIs shows different effects on survival when compared to second or subsequent line chemotherapy. In CheckMate 331 trial[37], the nivolumab was used in relapsed SCLC, and the results did not find a significant improvement in OS when compared to chemotherapy (median OS: 7.5 *vs.* 8.4 months). The median PFS for nivolumab *vs.* chemotherapy group was 1.4 *vs.* 3.8 months. The six-month and one-year OS rates were 54.5% and 59.9%, 36.6%, and 34.1% for patients in the nivolumab and chemotherapy groups, respectively[37]. The PFS rates were 19.7% *vs.* 26.5% at 6 months and 10.9% *vs.* 10.0% at 12 months for nivolumab *vs.* chemotherapy groups, respectively[37]. In another study, the clinical activity of atezolizumab was evaluated in a small cohort of patients with relapsed SCLC[38]. The results showed that the median PFS based on immune-related response criteria was 2.9 months and the median OS was 5.9 months[38]. As reported by the studies included in our analysis, the reported median OS ranged from 5.7 to 11.1 months for relapsed SCLC patients with ICIs and radiotherapy, while they were between 2.6 and 6.5 months for those who received ICIs without radiotherapy. The six-month and one-year OS rates were 42.9% and 28.6% for relapsed SCLC patients treated with dual ICI and radiotherapy, respectively. The above data suggest that the survival outcomes were similar in relapsed SCLC patients who received ICIs with and without radiotherapy. The site, timing, and doses of radiation may be the reasons for the moderate efficacy of this novel regimen in relapsed SCLC patients.

With regards to safety, the combination of radiotherapy and ICIs is associated with acceptable toxicity. In this study, the overall rate of grade 3 or higher AEs in the combination group was 59.8%, and the incidence of fatal AEs was 5.1%. In the study of Ready et al[39], the combination of two ICIs resulted in 37.5% of patients with grade 3 and 4 AEs, and three (3.1%) treatment-related death were observed in this group. In the meta-analysis by Wu et al[13], the combined incidence of grade 3-5 AEs for LS-SCLC patients with concurrent chemoradiotherapy was 72.3%, which was higher than that of our results. Therefore, adding radiotherapy to ICIs is associated with acceptable safety profiles.

There are several limitations in our study. As most of the studies were RCTs or prospective designs, the sample sizes of these studies were small. Besides, some of them were single-arm trials, making it impossible to perform regular meta-analyses comparing the outcomes of two groups. Second, the stage and ICIs treatment regimen of the patients, as well as the timing and doses of radiation used in the included studies of our meta-analysis varied, and this may increase the risk of intervention bias. Thus, more clinical trials are needed to further determine the combination of ICIs and radiotherapy in SCLC patients with different stages.

Conclusions

Taken together, the application of radiotherapy with ICIs does not exhibit increased toxicities for SCLC patients, and the effect of this combination

on survival warrants further investigation, especially for LS-SCLC patients.

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Authors' Contribution
Huilin Xu and Wei Hu worked as the supervisor and participated in processes of study design, study selection, data extraction and analysis, writing, and quality evaluation.
Anbing He worked as the supervisor, and evaluated the writing of the manuscript.
Qiong Wang, Aihua Liu and Huilin Xu performed the study selection, data extraction, and writing.
Qiong Wang and Huijun Fan participated in the process of study quality evaluation and data extraction.
Wei Hu, Aihua Liu, and Dedong Cao participated in the process of quality control.

Data Availability Statement
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate
This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest
The Authors declare that they have no conflict of interests.

References

1) Lum C, Alamgeer M. Technological and Therapeutic Advances in Advanced Small Cell Lung Cancer. Cancers (Basel) 2019; 11: 1570.
2) Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7-30.
3) Drapkin BJ, Minna JD. A rational targeted therapy for platinum-resistant small-cell lung cancer. Cancer Cell 2021; 39: 453-456.
4) Ai X, Pan Y, Shi J, Yang N, Liu C, Zhou J, Zhang X, Dong X, He J, Li X, Chen G, Li X, Zhang H, Liao W, Zhang Y, Ma Z, Jiang L, Cui J, Hu C, Wang W, Huang C, Zhao J, Ding C, Hu X, Wang K, Gao B, Song Y, Liu X, Xiong J, Liu A, Li J, Liu Z, Li Y, Wang M, Zhang B, Zhang D, Lu S. Efficacy and Safety of Niraparib as Maintenance Treatment in Patients With Extensive-Stage SCLC After First-Line Chemotherapy: A Randomized, Double-Blind, Phase 3 Study. J Thorac Oncol 2021; 16: 1403-1414.
5) Meric-Bernstam F, Larkin J, Tabernero J, Bonini C. Enhancing anti-tumour efficacy with immunotherapy combinations. Lancet 2021; 397: 1010-1022.
6) Zhang S, Li S, Cheng Y. Efficacy and safety of PD-1/PD-L1 inhibitor plus chemotherapy versus chemotherapy alone as first-line treatment for extensive-stage small cell lung cancer: A systematic review and meta-analysis. Thorac Cancer 2020; 11: 3536-3546.
7) Zhou T, Zhang Z, Luo F, Zhao Y, Hou X, Liu T, Wang K, Zhao H, Huang Y, Zhang L. Comparison of First-Line Treatments for Patients With Extensive-Stage Small Cell Lung Cancer: A Systematic Review and Network Meta-analysis. JAMA Netw Open 2020; 3: e2015748.
8) Schmid S, Mauti LA, Friedlaender A, Blum V, Rothschild SI, Bouchaab H, Frosch P, Britschgi C, Konig D, Wannesson L, Janthur WD, Schar S, Demmer I, Addeo A, Jochum W, Fruh M. Outcomes with immune checkpoint inhibitors for relapsed small-cell lung cancer in a Swiss cohort. Cancer Immunol Immunother 2020; 69: 1605-1613.
9) Zhou F, Zhao W, Gong X, Ren S, Su C, Jiang T, Zhou C. Immune-checkpoint inhibitors plus chemotherapy versus chemotherapy as first-line treatment for patients with extensive-stage small cell lung cancer. J Immunother Cancer 2020; 8: e001300.
10) Huang C, Gan GN, Zhang J. IMpower, CASPIAN, and more: exploring the optimal first-line immunotherapy for extensive-stage small cell lung cancer. J Hematol Oncol 2020; 13: 69.
11) Mansfield AS, Liu SV, Szczesna A, Havel L, Kzrakowski M, Hochmair MJ, Huemer F, Losonczy G, Johnson ML, Nishio M, Reck M, Mok TS, Lam S, Shames DS, Liu J, Kabbinavar F, Sandler A, Horn L. IMpower133: Primary efficacy and safety + CNS-related adverse events in a Ph1/3 study of first-line (1L) atezolizumab (atezo) + carboplatin + etoposide in extensive-stage SCLC (ES-SCLC). Cancer Res 2019; CT199.
12) Wang BC, Xiao BY, Li PC, Kuang BH, Chen WB, Li PD, Lin GH, Liu Q. Efficacy and Safety of First-Line Immunotherapy in Combination with Chemotherapy for Patients with Extensive-Stage Small Cell Lung Cancer: A Systematic Review and Network Meta-Analysis. J Oncol 2020; 2020: 2368164.
13) Wu Q, Xiong Y, Zhang S, Chen X, Yi F, Wei Y, Zhang W. A Meta-Analysis of the Efficacy and Toxicity of Twice-Daily vs. Once-Daily Concurrent Chemoradiotherapy for Limited-Stage Small Cell Lung Cancer Based on Randomized Controlled Trials. Front Oncol 2019; 9: 1460.
14) Rathod S, Jeremic B, Dubey A, Giuliani M, Bashir B, Chowdhury A, Liang Y, Pereira S, Agarwal J, Koul R. Role of thoracic consolidation

radiation in extensive stage small cell lung cancer: A systematic review and meta-analysis of randomised controlled trials. Eur J Cancer 2019; 110: 110-119.

15) Li AM, Zhou H, Xu YY, Ji XQ, Wu TC, Yuan X, Jiang CC, Zhu XX, Zhan P, Shen ZT. Role of thoracic radiotherapy in extensive stage small cell lung cancer: a systemic review and meta-analysis. Ann Transl Med 2021; 9: 299.
16) Gronberg BH, Killingberg KT, Flotten O, Brustugun OT, Hornslien K, Madebo T, Langer SW, Schytte T, Nyman J, Risum S, Tsakonas G, Engleson J, Halvorsen TO. High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial. Lancet Oncol 2021; 22: 321-331.
17) Daly ME, Ismaila N, Decker RH, Higgins K, Owen D, Saxena A, Franklin GE, Donaldson D, Schneider BJ. Radiation Therapy for Small-Cell Lung Cancer: ASCO Guideline Endorsement of an ASTRO Guideline. J Clin Oncol 2021; 39: 931-939.
18) Paz-Ares L, Spira A, Raben D, Planchard D, Cho BC, Ozguroglu M, Daniel D, Villegas A, Vicente D, Hui R, Murakami S, Spigel D, Senan S, Langer CJ, Perez BA, Boothman AM, Broadhurst H, Wadsworth C, Dennis PA, Antonia SJ, Faivre-Finn C. Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial. Ann Oncol 2020; 31: 798-806.
19) Gilmore B, Batus M, Fidler MJ, Marwaha G, Bonomi P. Significant Tumor Regression and Toxicity with Nivolumab Plus Ipilimumab in Small Cell Lung Cancer Patients Following Radiation. J Thorac Oncol 2018; 13: S797.
20) Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons, 2019.
21) Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-605.
22) Cooper H, Hedges LV, Valentine JC. The handbook of research synthesis and meta-analysis. Russell Sage Foundation, 2019.
23) Pakkala S, Higgins K, Chen Z, Sica G, Steuer C, Zhang C, Zhang G, Wang S, Hossain MS, Nazha B, Beardslee T, Khuri FR, Curran W, Lonial S, Waller EK, Ramalingam S, Owonikoko TK. Durvalumab and tremelimumab with or without stereotactic body radiation therapy in relapsed small cell lung cancer: a randomized phase II study. J Immunother Cancer 2020; 8: e001302.
24) Perez BA, Kim S, Wang M, Karimi AM, Powell C, Li J, Dilling TJ, Chiappori A, Latifi K, Rose T, Lannon A, MacMillan G, Saller J, Grass GD, Rosenberg S, Gray J, Haura E, Creelan B, Tanvetyanon T, Saltos A, Shafique M, Boyle TA, Schell MJ, Conejo-Garcia JR, Antonia SJ. Prospective Single-Arm Phase 1 and 2 Study: Ipilimumab and Nivolumab With Thoracic Radiation Therapy After Platinum Chemotherapy in Extensive-Stage Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2021; 109: 425-435.
25) Peters S, Pujol JL, Dafni U, Dómine M, Becker A, Andrade J, Curioni-Fontecedro A, Molinier O, Moro-Sibilot D, Nackaerts K, Mollá AI, López Vivanco G, Madelaine J, Popat S, Reck M, Roschitzki-Voser H, Mitchell P, De Ruysscher D, Le Pechoux C, Stahel R. Consolidation ipilimumab and nivolumab vs. observation in limited stage SCLC after chemo-radiotherapy: Results from the ETOP/IFCT 4-12 STIMULI trial. Ann Oncol 2020; 31: S1211.
26) Welsh JW, Heymach JV, Chen D, Verma V, Cushman TR, Hess KR, Shroff G, Tang C, Skoulidis F, Jeter M, Menon H, Nguyen QN, Chang JY, Altan M, Papadimitrakopoulou VA, Simon GR, Raju U, Byers L, Glisson B. Phase I Trial of Pembrolizumab and Radiation Therapy after Induction Chemotherapy for Extensive-Stage Small Cell Lung Cancer. J Thorac Oncol 2020; 15: 266-273.
27) Welsh JW, Heymach JV, Guo C, Menon H, Klein K, Cushman TR, Verma V, Hess KR, Shroff G, Tang C, Skoulidis F, Jeter M, Comeaux N, Patel RR, Chen D, Ozgen T, Nguyen QN, Chang JY, Altan M, Zhang J, Papadimitrakopoulou VA, Simon GR, Byers LA, Glisson B. Phase 1/2 Trial of Pembrolizumab and Concurrent Chemoradiation Therapy for Limited-Stage SCLC. J Thorac Oncol 2020; 15: 1919-1927.
28) Elegbede AA, Gibson AJ, Fung AS, Cheung WY, Dean ML, Bebb DG, Pabani A. A Real-World Evaluation of Atezolizumab Plus Platinum-Etoposide Chemotherapy in Patients With Extensive-Stage SCLC in Canada. JTO Clin Res Rep 2021; 2: 100249.
29) Galuba JM, Imke S, Koziorowski A, Bölükbas S, Nilius G, Christoph DC. Efficacy and safety of simultaneously performed radiotherapy in patients with small-cell lung cancer undergoing atezolizumab treatment. Oncol Res Treat 2021; 44: 173-174.
30) Gross AJ, Kharouta MZ, Podder TK, Choi S, Biswas T. Role of Thoracic Radiotherapy in Extensive Stage Small Cell Lung Cancer (ES-SCLC) in the Immunotherapy Era: A National Hospital-Based Registry Analysis. Int J Radiat Oncol Biol Phys 2021; 111: e466.
31) Perez BA, Kim S, Dilling TJ, Latifi K, Rose T, Lannon A, Macmillan G, Grass GD, Chiappori A, Haura EB, Creelan B, Gray J, Tanvetyanon T, Shafique M, Saltos AN, Rosenberg SA, Schell M, Antonia SJ. A Prospective Single Arm Phase I/II Study: Consolidative Ipilimumab and Nivolumab with Thoracic Radiotherapy after Platinum Based Chemotherapy for Patients with Extensive-Stage Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2019; 105: S36.
32) Dawe DE, Harlos CH, Juergens RA. Immuno-oncology—the new paradigm of lung cancer treatment. Curr Oncol 2020; 27: 78-86.

33) Konala VM, Madhira BR, Ashraf S, Graziano S. Use of Immunotherapy in Extensive-Stage Small Cell Lung Cancer. Oncology 2020; 98: 749-754.

34) Zhang S, Bi M. The efficiency and safety of immune checkpoint inhibitors in the treatment of small cell lung cancer: a meta-analysis. Ann Palliat Med 2020; 9: 4081-4088.

35) Landre T, Chouahnia K, Des Guetz G, Duchemann B, Assie JB, Chouaid C. First-line immune-checkpoint inhibitor plus chemotherapy versus chemotherapy alone for extensive-stage small-cell lung cancer: a meta-analysis. Ther Adv Med Oncol 2020; 12: 1758835920977137.

36) Facchinetti F, Di Maio M, Tiseo M. Adding PD-1/PD-L1 Inhibitors to Chemotherapy for the First-Line Treatment of Extensive Stage Small Cell Lung Cancer (SCLC): A Meta-Analysis of Randomized Trials. Cancers (Basel) 2020; 12: 2645.

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

38) Chiang AC, Sequist LVD, Gilbert J, Conkling P, Thompson D, Marcoux JP, Gettinger S, Kowanetz M, Molinero L, O'Hear C, Fasso M, Lam S, Gordon MS. Clinical Activity and Safety of Atezolizumab in a Phase 1 Study of Patients With Relapsed/Refractory Small-Cell Lung Cancer. Clin Lung Cancer 2020; 21: 455-463. e454.

39) Ready NE, Ott PA, Hellmann MD, Zugazagoitia J, Hann CL, de Braud F, Antonia SJ, Ascierto PA, Moreno V, Atmaca A, Salvagni S, Taylor M, Amin A, Camidge DR, Horn L, Calvo E, Li A, Lin WH, Callahan MK, Spigel DR. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: Results From the CheckMate 032 Randomized Cohort. J Thorac Oncol 2020; 15: 426-435.