

Immune-checkpoint inhibitors plus chemotherapy versus chemotherapy as first-line treatment for patients with extensive-stage small cell lung cancer

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ABSTRACT

We performed a meta-analysis to comprehensively investigate the efficacy and safety of immune-checkpoint inhibitors (ICIs) plus chemotherapy in patients with extensive-stage small cell lung cancer (ES-SCLC). The primary outcome was overall survival (OS). The secondary outcomes included progression-free survival (PFS), objective response rate (ORR) and \geq grade 3 adverse events (AEs). A total of six studies involving 2905 patients were identified, including 469 patients receiving program death ligand 1 (PD-L1) inhibitor plus chemotherapy, 308 receiving PD-1 inhibitors plus chemotherapy, 563 receiving CTLA-4 inhibitors plus chemotherapy, 268 receiving PD-L1/CTLA-4 inhibitors plus chemotherapy, and 1297 receiving chemotherapy alone. 10.8% (283/2615) patients had baseline brain metastases (BMs). Notably, ICIs plus chemotherapy was associated with significantly improved OS (HR, 0.82; 95% CI, 0.75 to 0.89). Subgroup analyses revealed that PD-1 inhibitors (HR, 0.77; 95% CI, 0.64 to 0.92) and PD-L1 inhibitors (HR, 0.73; 95% CI, 0.63 to 0.85) plus chemotherapy yielded a statistically significant improvement in OS while CTLA-4 inhibitors did not (HR, 0.92; 95% CI, 0.81 to 1.06). In patients with baseline BMs, ICIs plus chemotherapy showed no survival benefits over chemotherapy alone (HR, 1.23; 95% CI, 0.92 to 1.64). ICIs plus chemotherapy also significantly prolonged PFS (HR, 0.81; 95% CI, 0.75 to 0.87) while the pooled ORRs were comparable between ICIs plus chemotherapy and chemotherapy alone (RR, 1.04; 95% CI, 0.99 to 1.10). Patients treated with CTLA-4 inhibitors (relative risk (RR), 1.12; 95% CI, 0.99 to 1.28) experienced more \geq grade 3 AEs than those treated with PD-1/PD-L1 inhibitors (RR, 1.03; 95% CI, 0.96 to 1.11). The addition of PD-1/PD-L1 inhibitors to chemotherapy resulted in significant improvements in both PFS and OS for patients with treatment-naïve ES-SCLC, not at the cost of increased AEs.

INTRODUCTION

Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers, characterized by a highly invasive and lethal disease.¹ Huge efforts have been made to improve the survival of this population. However, they were almost annihilated and etoposide and platinum (EP) remains standard-of-care

first-line therapy for extensive-stage (ES) SCLC for the past 30 years.²

SCLC has high tumor mutational burden (TMB),³ which is associated with more tumor neoantigens and improved efficacy of immune-checkpoint inhibitors (ICIs). Currently, PD-1 inhibitors, including nivolumab or pembrolizumab, have been approved by Food Drug and Administration (FDA) as a third-line or later-line therapy for patients with ES-SCLC. However, the objective response rates (ORRs) were only 10%–19.3% as monotherapy,^{4–5} which was lower than expected response rate and may be partially attributed to the low program death ligand 1 (PD-L1) expression on tumor cells in SCLC.⁴ Recent success of ICIs in combination with chemotherapy in both lung adenocarcinoma and lung squamous cell carcinoma propelled this therapeutic strategy into ES-SCLC.^{6,7} Theoretically, chemotherapy, including EP, could result in immunogenic tumor cell death, increase presentation of tumor-associated antigens, promote the maturation of dendritic cells and therefore activate the cytotoxic T-cell response.⁸ Encouragingly, recent two landmark trials, IMpower133 and CASPIAN,^{9,10} demonstrated a synergetic antitumor effect of ICIs and EP and found that the addition of PD-L1 inhibitors (atezolizumab or durvalumab) to EP could significantly improve overall survival (OS) compared with EP alone for patients with ES-SCLC. Although the absolute improvements of progression-free survival (PFS) were moderate, a higher 12-month PFS rates were observed in patients treated with PD-L1 inhibitors plus chemotherapy (12.6% in IMpower133% and 18% in CASPIAN vs 5.4% and 5.0% in controls), reflecting that the PFS benefit was durable in a subset of patients.

Nevertheless, some disparities regarding study end points have been observed. For instance, the recent KEYNOTE-604 study reported that pembrolizumab plus EP could only statistically improve PFS compared with placebo plus EP (4.5 vs 4.3 months) for patient with ES-SCLC, the significance threshold for OS differences was not met (10.8 vs 9.7 months, HR, 0.80; 95% CI, 0.64 to 0.98).¹¹ Meanwhile, in another phase 2 randomized study, nivolumab plus EP significantly improved both PFS and OS compared with EP alone.¹² Such disparities arose concerns about the role of different ICIs in ES-SCLC. Therefore, we performed this meta-analysis to comprehensively investigate the efficacy and safety of ICIs plus EP in patients with ES-SCLC.

METHODS

We identified eligible trials that compared ICIs plus chemotherapy against chemotherapy alone or plus placebo in first-line setting of patients with ES-SCLC from MEDLINE, EMBASE, PubMed and the Cochrane Central Register of Controlled Trials databases with the following search terms: small cell lung cancer/carcinoma, immune checkpoint inhibitor, CTLA-4, PD-1, PD-L1, ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab and randomized/controlled clinical trial. The abstracts from proceedings of the American Society of Clinical Oncology, the European Society for Medical Oncology, the American Association for Cancer Research and the World Conference on Lung Cancer were also reviewed. Studies were restricted to English language published or presented before June 1, 2020.

The primary outcome was OS. The secondary outcomes included PFS, ORR and \geq grade 3 adverse events (AEs). The HRs with 95% CIs for OS and PFS, and dichotomous data for ORR were extracted. Other items included the study name, first author, year of publication, study design, study phase, number of patients, study drugs, comparators, tumor assessment criteria, follow-up time. Data were extracted independently by two authors (FZ and WZ), with discrepancies resolved by consensus.

A fixed-effect or random-effect model was adopted depending on between-study heterogeneity. Publication bias was assessed by visual inspection of a funnel plot, Begg's and Egger's tests. All data were analyzed using Review Manager V. 5.3 (RevMan; Cochrane Collaboration). Statistical significance was defined as a two-sided $p < 0.05$.

RESULTS

In total, six studies involving 2905 patients were identified (online supplementary figure 1).^{9–15} The main characteristics of the included trials are presented in table 1. Two trials compared ipilimumab plus chemotherapy with chemotherapy, two trials compared PD-1 inhibitors (pembrolizumab and nivolumab) plus chemotherapy versus chemotherapy, while two trials compared PD-L1

inhibitors (atezolizumab and durvalumab) plus chemotherapy versus chemotherapy. Additionally, the CASPIAN study was a three-arm randomized trial that investigated durvalumab with or without tremelimumab (CTLA-4 inhibitor) plus chemotherapy versus chemotherapy alone. In brief, 469 patients received PD-L1 inhibitor plus chemotherapy, 308 received PD-1 inhibitors plus chemotherapy, 563 received CTLA-4 inhibitors plus chemotherapy, 268 received PD-L1/CTLA-4 inhibitors plus chemotherapy and 1297 received chemotherapy alone. Moreover, 10.8% (283/2615) patients had baseline brain metastases (BMs). The median follow-up time ranged from 10.5 to 25.1 months. All of the six trials provided OS, PFS, ORR and AE information. The assessment of risk of bias is presented in online supplementary figure 2.

ICIs plus chemotherapy was associated with a statistically significant 18% reduction in the hazard for death (HR, 0.82; 95% CI, 0.75 to 0.89; $p < 0.001$; online supplementary figure 3a). Subgroup analyses revealed that PD-1 inhibitors (HR, 0.77; 95% CI, 0.64 to 0.92; $p = 0.005$) and PD-L1 inhibitors (HR, 0.73; 95% CI, 0.63 to 0.85; $p < 0.001$) plus chemotherapy yielded a statistically significant improvement in OS while CTLA-4 inhibitors did not (HR, 0.92; 95% CI, 0.81 to 1.06; $p = 0.26$) (figure 1a). There were no significant differences between PD-1 inhibitors and PD-L1 inhibitors in terms of OS (test for subgroup difference: $p = 0.71$) but patients treated with PD-1/PD-L1 inhibitors derived more OS benefits than those treated with CTLA-4 inhibitors (test for subgroup difference: $p = 0.02$). We further stratified patients according to baseline BMs. Notably, in patients with baseline BMs, ICIs plus chemotherapy showed no survival benefits over chemotherapy alone (HR, 1.23; 95% CI, 0.92 to 1.64; $p = 0.17$). While, in patients without baseline BMs, PD-1/PD-L1 inhibitors (HR, 0.75; 95% CI, 0.64 to 0.87; $p = 0.0001$) rather than CTLA-4 inhibitors (HR, 1.03; 95% CI, 0.88 to 1.20; $p = 0.71$) plus chemotherapy significantly prolonged OS (online supplementary figure 4).

ICIs plus chemotherapy also significantly prolonged PFS compared with chemotherapy alone (HR, 0.81; 95% CI, 0.75 to 0.87; $p < 0.001$) (online supplementary figure 3b). Subgroup analyses showed that all of PD-1 inhibitors (HR, 0.72; 95% CI, 0.61 to 0.86; $p = 0.0002$), PD-L1 inhibitors (HR, 0.79; 95% CI, 0.68 to 0.91; $p = 0.001$), CTLA-4 inhibitors plus chemotherapy (HR, 0.86; 95% CI, 0.76 to 0.97; $p = 0.01$) yielded a statistically significant improvement in PFS (figure 1b). There were no significant differences among PD-1 inhibitors, PD-L1 inhibitors and CTLA-4 inhibitors regarding PFS.

The pooled ORRs were comparable between ICIs plus chemotherapy and chemotherapy alone (RR, 1.04; 95% CI, 0.99 to 1.10; $p = 0.15$) (online supplementary figure 3c). Subgroup analyses suggested that none of PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors improved ORRs (figure 1c).

ICIs plus chemotherapy was associated with increased \geq grade 3 AEs compared with chemotherapy alone (RR, 1.07; 95% CI, 1.01 to 1.14; $p = 0.02$) (online supplementary

Table 1 Characteristics of patients with ES-SCLC in included trials

Study name, year	Phase	No. of total patients	Intervention arm	No. of patients	Control arm	No. of patients	Baseline BM, No, (%)	ORR (%)	mPFS (months)	HR for PFS (95% CI)		mOS (months)	HR for OS (95% CI)	Tumor assessment criteria	NCI CTCAE	Median follow-up time (months)
										(95% CI)	(95% CI)					
Reck <i>et al.</i> , 2012 ³	2	130	Phased ipi/concurrent ipi+PC	42/43	PC	45	NR	*57 vs 33 vs 49	*5.2 vs 5.2 vs 5.2	0.93 to 1.45	12.1 vs 9.9 vs 9.9	0.75 to 1.23 to 0.95	mWHO/irRC	3.0	11.1	
Reck <i>et al.</i> , 2016 ¹⁴	3	954	Ipi+EP	478	EP	476	55 (12) vs 45 (10)	62 vs 62	4.6 vs 4.4	0.85 to 0.97	11.0 vs 10.9	0.94 to 1.09	mWHO	3.0	10.5	
IMpower133, 2016 ⁹	3	403	Atezo+EC	201	EC	202	17 (8.5) vs 18 (8.9)	60.2 vs 64.4	5.2 vs 4.3	0.77 to 0.96	12.3 vs 10.3	0.70 to 0.91	RECIST V.1.1	4.0	13.9	
CASPAIN, 2019, 2020 ^{10,15}	3	805	D+EP/D+T+EP	268/268	EP	269	28 (10.4) vs 38 (14.2) vs 27 (10.0)	67.9 vs 58.4 vs 58.0	5.1 vs 4.9 vs 5.4	0.80 to 0.96	12.9 vs 10.4 vs 10.5	0.75 to 0.91	RECIST V.1.1	4.03	25.1	
KEYNOTE-60 4 to 2020 ¹¹	3	453	Pem+EP	228	EP	225	33 (14.5) vs 22 (9.8)	70.6 vs 61.8	4.5 vs 4.3	0.75 to 0.91	10.8 vs 9.7	0.78 to 0.97	RECIST V.1.1	4.0	21.6	
EAS161, 2020 ²	2	160	Nivo+EP	80	EP	80	NR	52.0 vs 47.0	5.5 vs 4.7	0.65 to 0.91	11.3 vs 8.5	0.67 to 0.98	RECIST V.1.1	5.0	NR	

*According to mWHO criteria.

ES-SCLC, extensive-stage small cell lung cancer; BM, brain metastases; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; NCI CTCAE, National Cancer Institute common terminology criteria for adverse events; ipi, ipilimumab; Atezo, atezolizumab; D, durvalumab; T, tremelimumab; Nivo, nivolumab; Pem, pembrolizumab; EC, carboplatin and etoposide; EP, cisplatin/carboplatin and deoposide; PC, paclitaxel and carboplatin; NR, not reported; No, numbers; mWHO, modified WHO criteria; irRC, immune-related response criteria; RECIST, Response Evaluation Criteria in Solid Tumors.

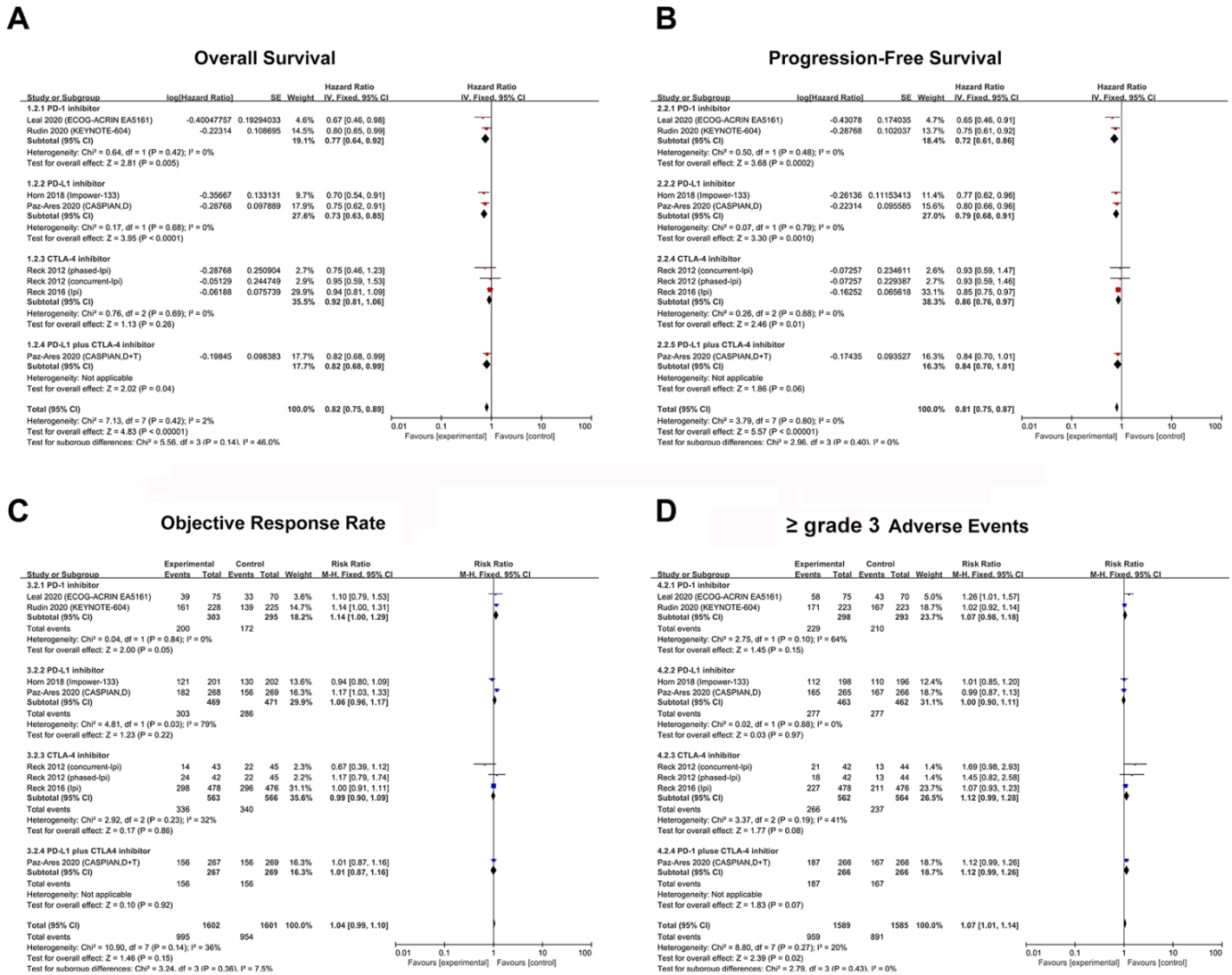


Figure 1 Subgroup analyses of immune-checkpoint inhibitors plus chemotherapy vs chemotherapy alone. (A) Overall survival, (B) progression-free survival, (C) objective response rate and (D) ≥grade 3 adverse events.

figure 3d). Generally, patients treated with CTLA-4 inhibitors (RR, 1.12; 95% CI, 0.99 to 1.28; p=0.08) experienced more ≥grade 3 AEs than those treated with PD-1 inhibitors (RR, 1.07; 95% CI, 0.98 to 1.18; p=0.15) or PD-L1 inhibitors (RR, 1.00; 95% CI, 0.90 to 1.11; p=0.97), but lack of statistical significance (test for subgroup difference: p=0.25) (figure 1d).

Visual inspection of the funnel plots for OS and PFS revealed no asymmetry (online supplementary figure 5), suggesting no publication bias. Begg's (p=0.536 for OS; p=0.536 for PFS) and Egger's (p=0.270 for OS; p=0.707 for PFS) tests results were not significant.

DISCUSSION

To our knowledge, this was the first meta-analysis to investigate the impact of ICIs plus chemotherapy versus chemotherapy alone or plus placebo on clinical outcomes in patients with ES-SCLC. Our study demonstrated that PD-1/PD-L1 inhibitors plus chemotherapy significantly improved both PFS and OS compared with chemotherapy

alone, without significantly increased ≥grade 3 AEs. Despite CTLA-4 inhibitors plus chemotherapy prolonged PFS, no OS benefits were observed. In addition, the ORRs were similar between ICIs plus chemotherapy and chemotherapy alone.

The success of IMpower133 study shows the first reddening of dawn for the treatment of ES-SCLC.⁹ Consistent with the findings of atezolizumab plus chemotherapy in non-squamous non-small cell lung cancer (NSCLC) (IMpower130),¹⁶ atezolizumab combined with chemotherapy also resulted in a significant improvement in terms of OS (12.3 vs 10.3 months; HR, 0.70, 95% CI, 0.54 to 0.91) and PFS (5.2 vs 4.3 months; HR, 0.77; 95% CI, 0.62 to 0.96). The CASPIAN study also demonstrated that durvalumab plus EP significantly improved OS (13.0 vs 10.3 months; HR 0.73; 95% CI, 0.59 to 0.91).¹⁰ Our pooled analysis revealed a statistically significant and clinically meaningful improvement in OS for patients who received PD-L1 inhibitors plus chemotherapy (HR, 0.73; 95% CI, 0.63 to 0.85), not at the cost of increased AEs

(RR, 1.00; 95% CI, 0.90 to 1.11), further supporting first-line use of PD-L1 inhibitors plus chemotherapy in patients with ES-SCLC. These results demonstrated the flexibility of PD-L1 inhibitors plus chemotherapy for patients with ES-SCLC. Currently, these two combinations have been approved by FDA as first-line treatment in patients with ES-SCLC.

Despite the KEYNOTE-604 study failed to meet the prespecified efficacy boundary for OS (HR, 0.80; 95% CI, 0.64 to 0.98, $p=0.0164$; significance threshold $p=0.0128$), our pooled analysis demonstrated that the addition of PD-1 inhibitors to chemotherapy also significantly improved both OS (HR, 0.77; 95% CI, 0.64 to 0.92; $p=0.005$) and PFS (HR, 0.72; 95% CI, 0.61 to 0.86; $p=0.0002$), suggesting PD-1 inhibitors plus chemotherapy as first-line treatment for patients with ES-SCLC deserves further investigation. In addition, our meta-analysis found that patients with baseline BMs did not derive survival benefits from PD-1/PD-L1 inhibitors plus chemotherapy. In KEYNOTE-604 study, more patients had baseline BMs than those in IMpower133 and CASPIAN studies (14.5% vs 8.5% vs 10%) and imbalance existed between the pembrolizumab arm and placebo arm regarding baseline BMs (14.5% vs 9.8%), which may partially explain the failure of KEYNOTE-604 study. Notably, ICIs have been demonstrated to be active and result in similar clinical outcomes in advanced NSCLC patients with BMs versus those without.^{17,18} Therefore, the findings regarding the efficacy of ICIs in ES-SCLC patients with BMs should be interpreted with caution, as these results were based on subset analyses.

In addition, although a previous mirror meta-analysis found that PD-1 inhibitors exhibited better survival outcomes than PD-L1 inhibitors in patients with solid tumors,¹⁹ our meta-analysis demonstrated no significant differences between PD-1 and PD-L1 inhibitors plus chemotherapy for patients with ES-SCLC, in terms of ORR, PFS and OS. However, the findings were obtained from indirect analysis. Nevertheless, the HRs for OS (0.77 vs 0.73) and PFS (0.72 vs 0.79) were comparable between the two groups, suggesting similar efficacy of PD-1 inhibitors and PD-L1 inhibitors in patients with ES-SCLC.

Our meta-analysis found no significant OS improvement in patients treated with CTLA-4 inhibitors plus chemotherapy (HR, 0.92; 95% CI, 0.81 to 1.06), which was similar with the results of ipilimumab plus chemotherapy in advanced squamous NSCLC.²⁰ One possible explanation was that ipilimumab, which stimulates early-stage T-cell activation, may not generate an effective antitumor response in local tumor environment without corresponding effector T-cell activation. Notably, updated results from the CASPIAN study demonstrated that tremelimumab plus durvalumab and chemotherapy also failed to improve ORR, PFS and OS over chemotherapy alone.¹⁵ In contrast, AEs leading to discontinuation (21.4% vs 10.2% vs 9.4%) occurred more frequently in durvalumab and tremelimumab arm compared with durvalumab arm and chemotherapy-only arm. Predictive

biomarkers, such as TMB,²¹ may be helpful to identify patients who may benefit from these combinations.

In conclusion, the current meta-analysis demonstrated that the addition of PD-1/PD-L1 inhibitors to chemotherapy resulted in significant improvements in both PFS and OS for patients with treatment-naïve ES-SCLC, not at the cost of increased AEs.

Contributors FZ, WZ and TJ contributed to data acquisition, data interpretation and statistical analysis and drafting of the manuscript. XG and CZ contributed to the study design, data acquisition, data interpretation and statistical analysis. All the authors contributed to critical revision of the manuscript.

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