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First-line immune-checkpoint inhibitor plus chemotherapy *versus* chemotherapy alone for extensive-stage small-cell lung cancer: a meta-analysis

Thierry Landre, Kader Chouahnia, Gaëtan Des Guetz, Boris Duchemann, Jean-Baptiste Assié and Christos Chouaïd

Abstract

Introduction: Platin-based chemotherapy (CT) has long been the first-line standard-of-care for patients with extensive-stage small-cell lung cancer (ES–SCLC). Adding immune-checkpoint inhibitor(s) to CT (ICI+CT) in this setting is an option of interest, although its benefit is apparently modest.

Methods: This meta-analysis was conducted on randomized trials comparing first-line ICI+CT *versus* CT alone for ES–SCLC. Outcomes included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), response at 12 months and adverse events (AEs). Subgroup analyses were computed according to the immunotherapy used, performance status (PS), age, platinum salt, liver metastases and brain metastases at diagnosis.

Results: The literature search identified one randomized phase II (ECOG-ACRIN-5161) and four phase III trials (CASPIAN, IMPOWER-133, KEYNOTE-604 and Reck *et al.* 2016) that included 2775 patients (66% males, 95% smokers, median age: 64 years, PS = 0 or 1). ICI+CT was significantly associated (hazard ratio [95% confidence interval]) with prolonged OS [0.82 (0.75–0.89); $p < 0.00001$] and PFS [0.81 (0.75–0.87); $p < 0.00001$], with OS benefits for anti-PD-L1 [0.73 (0.63–0.85); $p < 0.0001$] or anti-PD-1 [0.76 (0.63–0.93); $p < 0.006$] but not for anti-CTLA-4 [0.90 (0.80–1.01), $p = 0.07$]. ORRs for ICI+CT or CT alone were comparable [odds ratio 1.12 (0.97–1.00); $p = 0.12$], but responses at 12 months favored ICI+CT [4.16 (2.81–6.17), $p < 0.00001$]. Serious grade-3/4 AEs were more frequent with ICI+CT [odds ratio 1.18 (1.02–1.37); $p = 0.03$]. Compared with CT, no ICI+CT benefit was found for ES–SCLC with brain metastases at diagnosis [HR 1.14 (0.87–1.50); $p = 0.34$].

Conclusions: First-line ICI+CT appears to be superior to CT alone for ES–SCLC except for patients with brain metastases at diagnosis.

Keywords: chemotherapy, immunotherapy, meta-analysis, small-cell lung cancer

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Introduction

Small-cell lung cancer (SCLC), a highly malignant tumor, represents approximately 13–16% of annual lung cancer diagnoses worldwide.[1] The ability of SCLC tumor cells to disseminate early explains why ~70% of the cases were diagnosed at a metastatic stage. The prognosis is dismal, with 5-year overall survival (OS) less than 7%.[2] In that recent study, SCLC was found to be a heterogeneous disease, in which several transcriptional regulators define emerging subtypes, likely impacting clinical outcomes. Nevertheless, in therapeutic terms, little decisive progress has been made in the first-line management of extended-stage SCLC (ES–SCLC). Over the past 30 years, the first-line standard-of-care has

been etoposide and cisplatin (or carboplatin).[3,4] In Asia, the irinotecan-plus-platin combination has been an alternative regimen.[5] But, generally speaking, results have remained disappointing. Although most patients' SCLCs respond initially to platin-based chemotherapy (CT), 95% of them rapidly develop resistance.

Immune-checkpoint inhibitors (ICIs), such as monoclonal antibodies targeting T-cell checkpoint programmed cell-death protein-1 (PD-1) or its ligand (PD-L1), or pathways inhibiting cytotoxic T-lymphocyte antigen-4 (CTLA-4), unleash T-cell responses to eliminate tumor cells. However, despite having one of the highest mutational burdens, SCLC overall response rates (ORRs) to ICI(s) have been only modest. ICI efficacies against refractory SCLCs or tumors that had relapsed after platin-based chemotherapy were studied first.[6,7] More recently, first-line atezolizumab in combination with carboplatin+etoposide CT for ES–SCLC showed an OS gain compared with CT alone, and atezolizumab was recently approved in several countries. In a very short time, several randomized studies, using very similar methodologies to compare ICI+platin-based–CT combinations with CT alone, were published.[8] Even for those yielding positive findings, ICI+CT efficacy appeared to be modest. The objective of this meta-analysis was to evaluate the efficacies and safety profiles of ICI+CT *versus* CT alone, as first-line ES–SCLC therapy, based on all the randomized-trial data published or presented in abstracts.

Methods

Research strategy

The literature search screened the PubMed and Cochrane electronic databases, accessed until 30 September 2020 and was completed by a manual search on this topic in AACR, ASCO, ESMO, WLCC and ELCC congress abstracts until 10 October 2020. The search terms used were: "immune checkpoint inhibitor or immunotherapy," "nivolumab or pembrolizumab or atezolizumab or avelumab or durvalumab or ipilimumab or tremelimumab," "advanced or metastatic," "small-cell lung cancer or SCLC," "PD-1 or PD-L1 or CTLA-4," and "randomized controlled trial." Only randomized trials or phase II or III studies comparing first-line ICI+CT *versus* CT alone were retained. The search details in PubMed and a PRISMA flowchart depicting the study selection process are shown in Supplemental File S1.

Data extraction

All the studies were analyzed by two independent readers (T.L., K.C.), using a predefined protocol. Discrepancies were resolved by discussion with a third reader (C.C.). The following information was collected: patients' characteristics including sex, age, Eastern Cooperative Oncology Group performance status (PS), smoking status, brain metastases at diagnosis and type of immunotherapy. The principal evaluation criteria's were OS and progression-free survival (PFS). Secondary criteria were ORR, response rate at 12 months and safety. Subgroup analyses were computed according to the type of immunotherapy combined with CT, carboplatin or cisplatin use, PS (0 or 1), brain or liver metastases at diagnosis and smoking status.

Statistical analyses

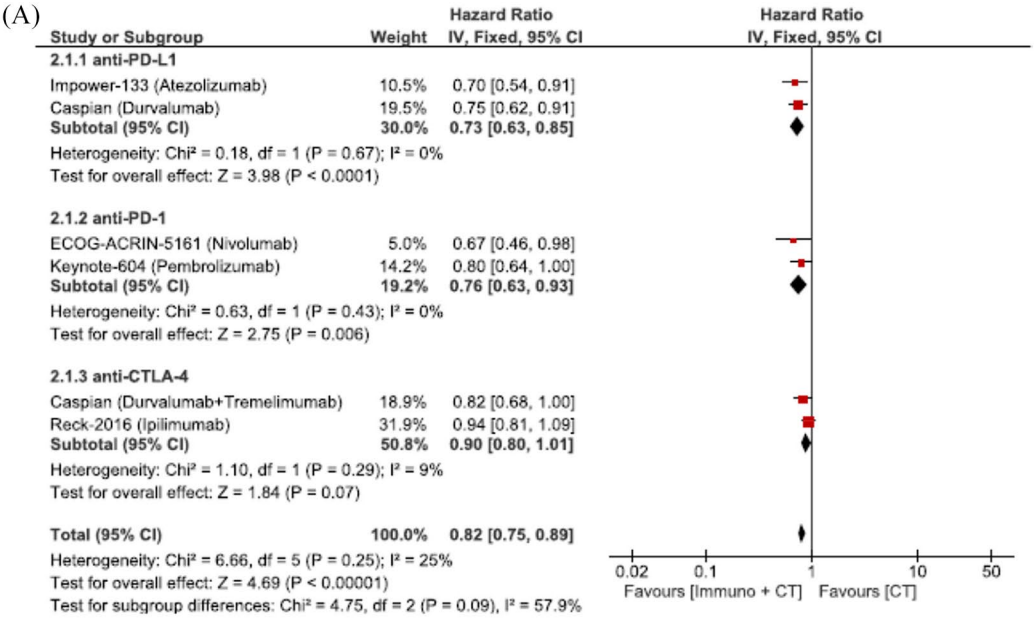
Analyses were computed using the Cochrane method of collaboration for meta-analyses, with Review Manager software (RevMan version 5.3; Oxford, UK). Statistical heterogeneity was assessed with χ^2 tests and I^2 statistics, with $p < 0.10$ in a χ^2 test defining the presence of heterogeneity. The I^2 statistic indicates heterogeneity among studies, with values of 30–60% representing moderate heterogeneity.

A fixed-effect model was used to calculate the cumulative hazard ratio (HR), when among-study heterogeneity was weak, and a randomized model when it was marked. The meta-analysis results are reported as odds ratios (ORs) for ORRs, and HRs for OS and PFS with their [95% confidence interval (CI)]. All tests were two-sided and $p < 0.05$ defined significance. A Begg's funnel plot was used to analyze the heterogeneity among the studied populations (Supplemental Figure 1).

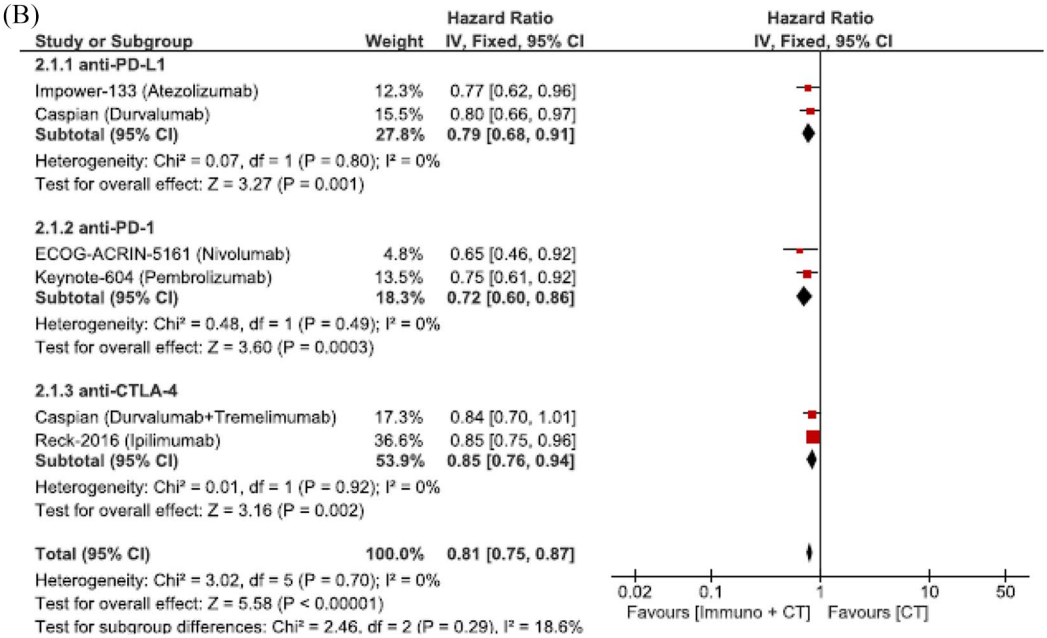
Results

In the first step, six phase III and two phase II randomized trials were selected,[9–17] but the study evaluating nivolumab+CT for relapsed ES–SCLC was not retained[12] as well as CHECKMATE-451 with maintenance immunotherapy starting at the end of CT.[16] A randomized phase II evaluating pembrolizumab+CT (EORTC-1417-REACTION)

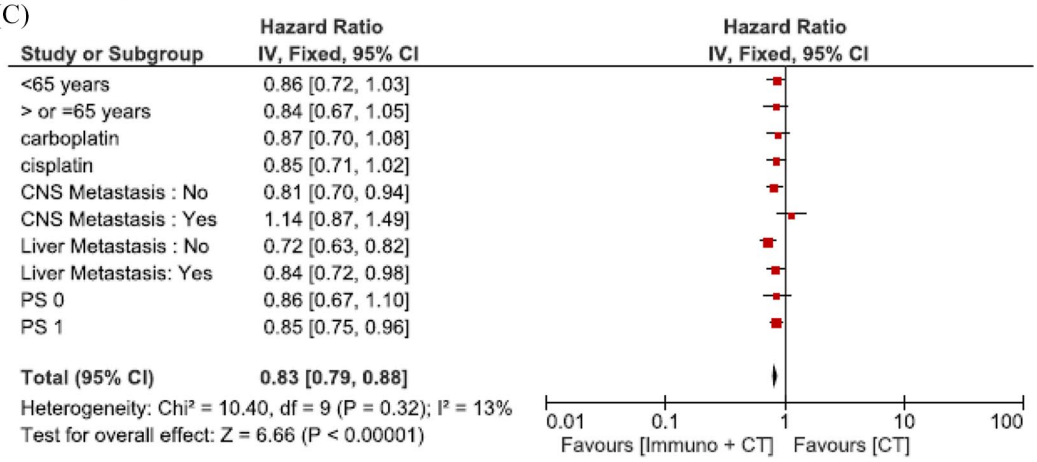
(A)


Study or Subgroup | Weight | Hazard Ratio IV, Fixed, 95% CI
2.1.1 anti-PD-L1
Impower-133 (Atezolizumab) 10.5% 0.70 [0.54, 0.91]
Caspian (Durvalumab) 19.5% 0.75 [0.62, 0.91]
Subtotal (95% CI) 30.0% 0.73 [0.63, 0.85]
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 3.98 (P < 0.0001)
2.1.2 anti-PD-1
ECOG-ACRIN-5161 (Nivolumab) 5.0% 0.67 [0.46, 0.98]
Keynote-604 (Pembrolizumab) 14.2% 0.80 [0.64, 1.00]
Subtotal (95% CI) 19.2% 0.76 [0.63, 0.93]
Heterogeneity: Chi² = 0.63, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 2.75 (P = 0.006)
2.1.3 anti-CTLA-4
Caspian (Durvalumab+Tremelimumab) 18.9% 0.82 [0.68, 1.00]
Reck-2016 (Ipilimumab) 31.9% 0.94 [0.81, 1.09]
Subtotal (95% CI) 50.8% 0.90 [0.80, 1.01]
Heterogeneity: Chi² = 1.10, df = 1 (P = 0.29); I² = 9%
Test for overall effect: Z = 1.84 (P = 0.07)
Total (95% CI) 100.0% 0.82 [0.75, 0.89]
Heterogeneity: Chi² = 6.66, df = 5 (P = 0.25); I² = 25%
Test for overall effect: Z = 4.69 (P < 0.00001)
Test for subgroup differences: Chi² = 4.75, df = 2 (P = 0.09), I² = 57.9%
Hazard Ratio IV, Fixed, 95% CI
0.02 0.1 1 10 50
Favours [Immuno + CT] Favours [CT]

(B)


Study or Subgroup | Weight | Hazard Ratio IV, Fixed, 95% CI
2.1.1 anti-PD-L1
Impower-133 (Atezolizumab) 12.3% 0.77 [0.62, 0.96]
Caspian (Durvalumab) 15.5% 0.80 [0.66, 0.97]
Subtotal (95% CI) 27.8% 0.79 [0.68, 0.91]
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 3.27 (P = 0.001)
2.1.2 anti-PD-1
ECOG-ACRIN-5161 (Nivolumab) 4.8% 0.65 [0.46, 0.92]
Keynote-604 (Pembrolizumab) 13.5% 0.75 [0.61, 0.92]
Subtotal (95% CI) 18.3% 0.72 [0.60, 0.86]
Heterogeneity: Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 3.60 (P = 0.0003)
2.1.3 anti-CTLA-4
Caspian (Durvalumab+Tremelimumab) 17.3% 0.84 [0.70, 1.01]
Reck-2016 (Ipilimumab) 36.6% 0.85 [0.75, 0.96]
Subtotal (95% CI) 53.9% 0.85 [0.76, 0.94]
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 3.16 (P = 0.002)
Total (95% CI) 100.0% 0.81 [0.75, 0.87]
Heterogeneity: Chi² = 3.02, df = 5 (P = 0.70); I² = 0%
Test for overall effect: Z = 5.58 (P < 0.00001)
Test for subgroup differences: Chi² = 2.46, df = 2 (P = 0.29), I² = 18.6%
Hazard Ratio IV, Fixed, 95% CI
0.02 0.1 1 10 50
Favours [Immuno + CT] Favours [CT]

(C)


Study or Subgroup | Hazard Ratio IV, Fixed, 95% CI
<65 years 0.86 [0.72, 1.03]
> or =65 years 0.84 [0.67, 1.05]
carboplatin 0.87 [0.70, 1.08]
cisplatin 0.85 [0.71, 1.02]
CNS Metastasis : No 0.81 [0.70, 0.94]
CNS Metastasis : Yes 1.14 [0.87, 1.49]
Liver Metastasis : No 0.72 [0.63, 0.82]
Liver Metastasis: Yes 0.84 [0.72, 0.98]
PS 0 0.86 [0.67, 1.10]
PS 1 0.85 [0.75, 0.96]
Total (95% CI) 0.83 [0.79, 0.88]
Heterogeneity: Chi² = 10.40, df = 9 (P = 0.32); I² = 13%
Test for overall effect: Z = 6.66 (P < 0.00001)
Hazard Ratio IV, Fixed, 95% CI
0.01 0.1 1 10 100
Favours [Immuno + CT] Favours [CT]

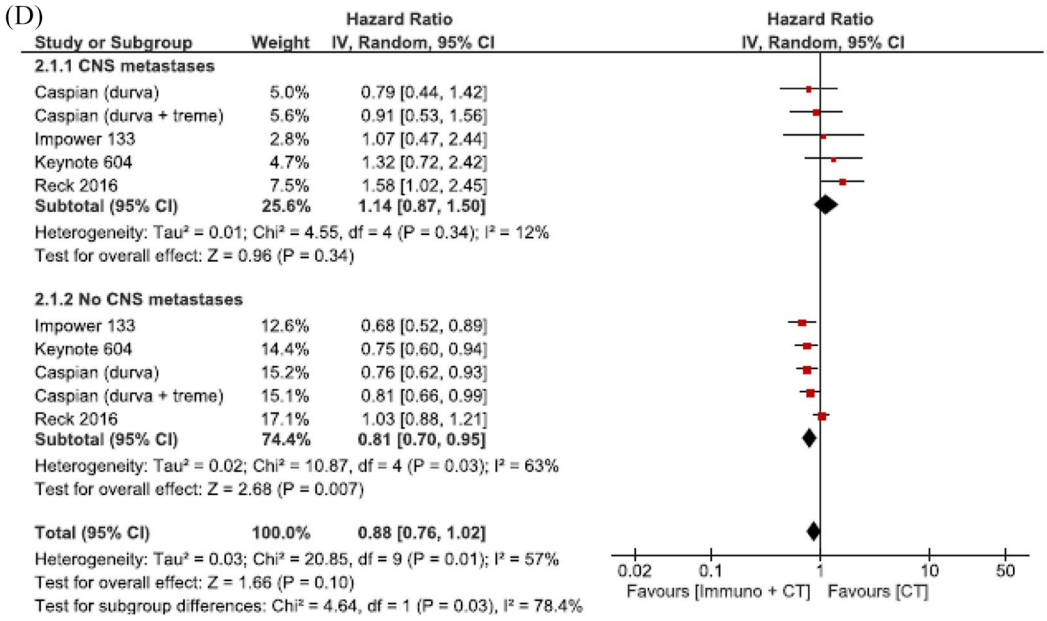


Figure 1. Meta-analysis results for (*A*) overall survival and (*B*) progression-free survival for the entire study population and according to used immunotherapy molecule(s) and (C) overall survival according to subgroups. Meta-analysis for OS in patients with or without CNS metastases at diagnosis (D).

was also excluded because it can be considered as a maintenance study.[17]

The meta-analysis was conducted on five studies. The immunotherapy agent combined with CT was ipilimumab,[9] pembrolizumab,[13] nivolumab,[14] atezolizumab[11] or durvalumab alone or combined with tremelimumab.[10,15]

The main characteristics of the studies are reported in Table 1. The meta-analysis regrouped 2775 patients (median age: 64 year; 66% men; 95% smokers; 34% and 66% patients had a PS of 0 or 1; and 10% had brain metastases at diagnosis).

Compared with CT alone, ICI+CT achieved a significant OS gain ($p < 0.00001$). Heterogeneity was found among the different immunotherapy classes, with anti-PD-L1 ($p < 0.0001$) and anti-PD-1 ($p < 0.006$) being beneficial, but no such advantage was found for anti-CTLA4 (HR = 0.90; 95% CI: 0.80–1.01) (Figure 1A). The ICI+CT combination also obtained, compared with CT alone, a significant PFS gain ($p < 0.00001$). That PFS advantage was found for all immunotherapy types, with no significant difference among anti-PD-1, anti-PD-L1 and anti-CTLA-4 subgroups (Figure 1B). The OS benefit was found for all patients, regardless of age (<65 or ⩾65) or PS (0 or 1), carboplatin or cisplatin use and for those with liver metastases at diagnosis. In contrast, analysis of OS as a function of brain metastases at diagnosis, based on the available data from four studies[9,11,13,15] found no benefit for those patients (Figure 1C, D). The low number of nonsmokers precluded calculation of ICI+CT efficacy with acceptable accuracy.

Based on the ORRs available for the five studies,[9,11,13–15] ICI+CT and CT alone were comparable ($p = 0.12$) (Figure 2A). However, the response rate at 12 months obtained with the ICI+CT combination showed a clear and significant difference ($p < 0.00001$) (Figure 2B).

Concerning safety, ICI+CT recipients experienced more frequent grade-3/4 adverse events ($p < 0.03$), compared with CT alone (Figure 3).

Discussion

This meta-analysis, based on published data in selected randomized trials comparing first-line ICI+CT *versus* CT alone to treat ES-SCLCs in patients with PS 0 or 1, showed that the combination significantly prolonged OS and PFS but with differences according to the molecules used: anti-PD-L1 (durvalumab and atezolizumab) seemed

Table 1. Summaries of the trials of etoposide–platin chemotherapy plus different classes of immunotherapy to treat ES-SCL.

Reference	Experimental arm: Etoposide–Platin+	*n*	Median age	Males	Smokers	PS 0/1 (%)	BM	Median follow-up	Primary outcome, months: experimental *versus* control
KEYNOTE-604 Rudin[13]	Pembrolizumab (200 mg)	453	65	65%	96%	26/74	12%	21.6 months	OS: 10.8 *versus* 9.7
CASPIAN Paz-Ares[10]	Durvalumab (1500 mg)	805	63	70%	92%	35/65	10%	25.1 months	OS: 12.9 *versus* 10.5
CASPIAN Paz-Ares[15]	Durvalumab (1500 mg)–Tremelimumab (75 mg)	–	63	70%	92%	37/63	10%	25.1 months	OS: 10.4 *versus* 10.5
IMPOWER-133 Horn[11]	Atezolizumab (1200 mg)	403	64	64%	97%	35/65	9%	22.9 months	OS: 12.3 *versus* 10.3
NCT01450761 Reck[9]	Ipilimumab (10 mg/kg)	954	63	67%	92%	30/70	11%	NR	OS: 11 *versus* 10.9
EA-5161* Leal[14]	Nivolumab (360 mg)	160	65	45%	NR	49/51	NR	NR	PFS: 5.5 *versus* 4.7

*Randomized phase II.
BM, percentage of patients with brain metastases at diagnosis; ES-SCLC, extended-stage small-cell lung cancer; NR, not reported; PS, Eastern Cooperative Oncology Group performance status.

to give better results. The advantage for anti-PD-L1 and anti-PD-1 agents was clear. However, for anti-PD-1 agents, results were based on a small randomized phase II study[14] and the Keynote-604 trial, which yielded numerically superior but non-significant OS, which was the principal criterion.[13] The anti-CTLA-4 (ipilimumab and tremelimumab) agents alone or in combination with an anti-PD-1/PD-L1 did not apparently provide a benefit. Moreover, no ICI+CT advantage was found for patients with brain metastases at diagnosis.

Clinical benefit differences among the different immunotherapy classes were reported previously for the treatment of advanced non-small-cell lung cancer (NSCLC) but gave the anti-PD-1 agents an advantage.[18–20] Notably, according to that indirect comparison, for the treatment of advanced squamous NSCLC, pembrolizumab+taxane–platin achieved significantly better OS [HR 0.67 (95% CI: 0.47–0.94); $p=0.02$] and prolonged PFS [HR 0.79 (95% CI: 0.60–1.04); $p=0.10$] *versus* atezolizumab+taxane–platin. Analysis as a function of PD-L1 expression showed that the difference remained significant for patients with low/negative PD-L1, but not those with >50% PD-L1 status. Hence, differences between the actions of anti-PD-1 and anti-PD-L1 still exist; they are poorly understood and will probably remain so in the absence of biological markers. It must be emphasized that this difference among immunotherapy classes was not observed for PFS, for which ICI+CT was always significantly better, regardless of the immunotherapy class used.

The median OS benefit obtained with ICI+CT was modest (~2–3 additional months), without any ORR difference, probably reflecting the high chemosensitivity of SCLCs and, consequently, high response rates in the reference arm. However, the response levels at 12 months were significantly higher for the ICI+CT combinations, showing that a subgroup of patients obtained a nonnegligible benefit from them.

The impact of tumor mutational burden (TMB) has not been studied in our meta-analysis. However, survival analysis of IMPOWER-133 with a cut-off of 10 or 16 mut/Mb suggests that TMB is not a discriminating biomarker.

Finally, confirming the results of pivotal trials, grade-3/4 toxicity was significantly higher for the ICI+CT arm.

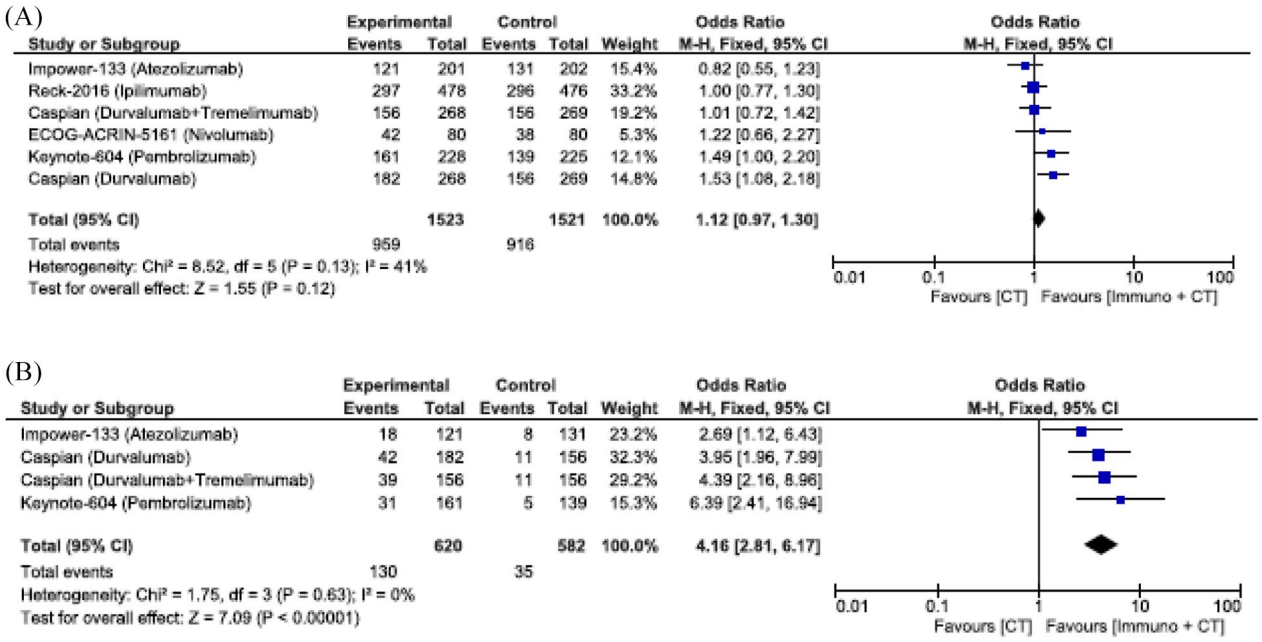


Figure 2. Meta-analysis results for (A) overall response rates and (B) overall responses at 12 months

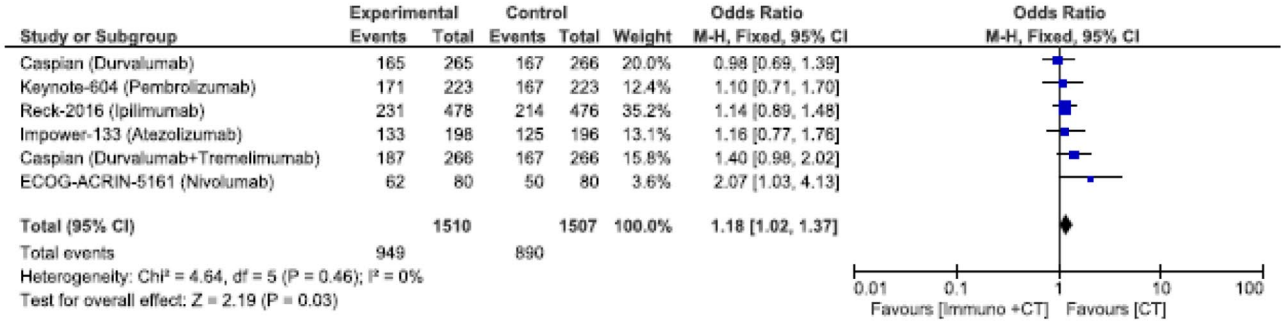


Figure 3. Meta-analysis results for the rate of grade-3/4 adverse events according to first-line immunotherapy.

Our study has several limitations:

First, it was a meta-analysis on trial data rather than individual patients' information. Second, the CASPIAN and the IMPOWER-133 studies, although both randomized phase III trials, have different design as one is open-label and the other is placebo-controlled. The same applies to the ECOG-ACRIN-5161 and the KEYNOTE-604, respectively. Moreover, the inclusion criteria for patients with brain metastases are slightly different across trial (e.g. in the CASPIAN study untreated asymptomatic patients were eligible while in the other studies with anti-PD-1/L1 agents brain metastases should have been treated). Finally, by evaluating the design of the studies, differences are present. In the CASPIAN and IMPOWER-133 studies, treatment beyond progression with durvalumab was allowed if the patients were experiencing clinical benefit. The same did not apply to the KEYNOTE-604 study or the ipilimumab trial.

Conclusion

This meta-analysis identified OS and PFS benefits for ES–SCLC patients given first-line ICI+CT compared with CT alone. The advantage for anti-PD-L1 and anti-PD-1 agents was clear, while the benefit was not found for anti-CTLA-4 alone or in combination. In addition, that benefit was not found for patients with brain

metastases at diagnosis but apparently did not depend on PS (0 or 1), age, platinum salt, or the presence of liver metastases; and grade-3/4 adverse events were more frequent with ICI+CT compared with CT alone.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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