

Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133)

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abstract

PURPOSE IMpower133 (ClinicalTrials.gov identifier: [NCT02763579](https://clinicaltrials.gov/ct2/show/study/NCT02763579)), a randomized, double-blind, phase I/III study, demonstrated that adding atezolizumab (anti-programmed death-ligand 1 [PD-L1]) to carboplatin plus etoposide (CP/ET) for first-line (1L) treatment of extensive-stage small-cell lung cancer (ES-SCLC) resulted in significant improvement in overall survival (OS) and progression-free survival (PFS) versus placebo plus CP/ET. Updated OS, disease progression patterns, safety, and exploratory biomarkers (PD-L1, blood-based tumor mutational burden [bTMB]) are reported.

PATIENTS AND METHODS Patients with untreated ES-SCLC were randomly assigned 1:1 to receive four 21-day cycles of CP (area under the curve 5 mg per mL/min intravenously [IV], day 1) plus ET (100 mg/m² IV, days 1-3) with atezolizumab (1,200 mg IV, day 1) or placebo, and then maintenance atezolizumab or placebo until unacceptable toxicity, disease progression, or loss of clinical benefit. Tumor specimens were collected; PD-L1 testing was not required for enrollment. The two primary end points, investigator-assessed PFS and OS, were statistically significant at the interim analysis. Updated OS and PFS and exploratory biomarker analyses were conducted.

RESULTS Patients received atezolizumab plus CP/ET (n = 201) or placebo plus CP/ET (n = 202). At the updated analysis, median follow-up for OS was 22.9 months; 302 deaths had occurred. Median OS was 12.3 and 10.3 months with atezolizumab plus CP/ET and placebo plus CP/ET, respectively (hazard ratio, 0.76; 95% CI, 0.60 to 0.95; descriptive *P* = .0154). At 18 months, 34.0% and 21.0% of patients were alive in atezolizumab plus CP/ET and placebo plus CP/ET arms, respectively. Patients derived benefit from the addition of atezolizumab, regardless of PD-L1 immunohistochemistry or bTMB status.

CONCLUSION Adding atezolizumab to CP/ET as 1L treatment for ES-SCLC continued to demonstrate improved OS and a tolerable safety profile at the updated analysis, confirming the regimen as a new standard of care. Exploratory analyses demonstrated treatment benefit independent of biomarker status.

J Clin Oncol 39:619-630. © 2021 by American Society of Clinical Oncology

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INTRODUCTION

Nearly two-thirds of patients with small-cell lung cancer (SCLC) have extensive-stage (ES) disease at diagnosis, which is associated with poor prognosis and a 5-year survival rate of < 7%.¹ Platinum chemotherapy (carboplatin [CP] or cisplatin) with etoposide (ET) has remained the standard treatment for > 2 decades.^{2,3} Despite initial high response rates, median survival is limited to approximately 10 months.⁴ Recently, immune checkpoint inhibitors have demonstrated

improved outcomes in patients with extensive-stage small-cell lung cancer (ES-SCLC).⁵⁻⁷ Based on the double-blinded, randomized phase III IMpower133 study,⁵ the programmed death-ligand 1 (PD-L1) inhibitor atezolizumab, in combination with CP and ET (CP/ET), was approved for the first-line (1L) treatment of ES-SCLC by the US Food and Drug Administration (FDA)⁸ and the European Medicines Agency.⁹ Results from the randomized, phase III CASPIAN study also recently led to the FDA approval of the combination

ASSOCIATED CONTENT

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on November 5, 2020 and published at ascopubs.org/journal/jco on January 13, 2021: DOI <https://doi.org/10.1200/JCO.20.01055>

CONTEXT

Key Objective

Based on results of the pivotal IMpower133 study, atezolizumab (anti-programmed death-ligand 1 [anti-PD-L1]) in combination with carboplatin and etoposide (CP/ET) was approved for the first-line treatment of extensive-stage small-cell lung cancer (ES-SCLC). Updated findings at a preplanned overall survival (OS) analysis of IMpower133, representing an additional 9 months of follow-up from the primary analysis, are reported.

Knowledge Generated

With a median follow up of 22.9 months, updated results from IMpower133 continued to show OS improvement with atezolizumab plus CP/ET and a safety profile comparable to that of placebo plus CP/ET. Exploratory analyses also suggest that clinical benefit was seen in atezolizumab plus CP/ET-treated patients with ES-SCLC independent of biomarker (blood-based tumor mutational burden or PD-L1) status.

Relevance

Updated analyses from IMpower133 further support atezolizumab plus CP/ET as a new standard of care for untreated ES-SCLC.

of the PD-L1 inhibitor, durvalumab, plus platinum and ET for the 1L treatment of ES-SCLC.⁷ In addition, based on durable responses observed in nonrandomized studies, the programmed death-1 (PD-1) inhibitors nivolumab⁶ and pembrolizumab^{10,11} both received US FDA accelerated approval for the third-line treatment of ES-SCLC.

Atezolizumab is a humanized monoclonal anti-PD-L1 antibody that inhibits PD-L1 engagement with PD-1 and B7.1.¹² In the landmark IMpower133 study, 1L treatment with either atezolizumab or placebo plus CP/ET was compared in patients with ES-SCLC.^{5,13} At the primary analysis, with a median follow-up for overall survival (OS) of 13.9 months, atezolizumab was associated with a significant improvement in OS with a median of 12.3 months in the atezolizumab plus CP/ET arm and of 10.3 months in the placebo plus CP/ET arm (hazard ratio [HR], 0.70; 95% CI, 0.54 to 0.91; $P = .007$).⁵ The median progression-free survival (PFS) was 5.2 months in the atezolizumab plus CP/ET and 4.3 months in the placebo plus CP/ET arm (HR, 0.77; 95% CI, 0.62 to 0.96; $P = .02$).⁵

A preplanned updated OS analysis with an additional 9 months of follow-up was conducted; median follow-up for OS was 22.9 months. Updated analyses of safety and OS by blood-based tumor mutational burden (bTMB) levels, as well as exploratory analyses of OS according to PD-L1 expression levels and patterns of disease progression, are reported.

PATIENTS AND METHODS

Study Design and Patients

IMpower133 was a global, phase I/III double-blind, randomized, placebo-controlled trial, whose design and primary results have been previously reported (ClinicalTrials.gov identifier: [NCT02763579](https://clinicaltrials.gov/ct2/show/study/NCT02763579)).⁵ The trial was conducted in

accordance with Good Clinical Practice and the Declaration of Helsinki. Protocol approval was obtained from independent review boards or ethics committees for each site. All patients provided written informed consent.

Briefly, eligible patients had histologically or cytologically confirmed chemotherapy-naïve ES-SCLC. A computed tomography or magnetic resonance imaging scan of the head was required at screening. Patients with treated asymptomatic brain metastases were eligible, and those with active or untreated CNS metastases were excluded from the study.

Patients were stratified by sex, Eastern Cooperative Oncology Group performance status (0 v 1), and presence of brain metastases (yes v no) at enrollment. Available tumor specimens retrieved using any method (eg, fine needle aspirations, tissue biopsies, bronchoscopy, or cytological samples) were collected. Exploratory biomarker analyses according to PD-L1 expression levels on both tumor cells (TCs) and tumor-infiltrating immune cells (ICs) were conducted in the biomarker-evaluable population (BEP). Prespecified secondary analyses according to bTMB status were conducted in the BEP.

Procedures

Eligible patients were randomly assigned in a 1:1 ratio to receive four 21-day cycles of CP/ET (CP: area under the curve of 5 mg/mL/min, intravenous [IV] on day 1 of each cycle; ET: 100 mg/m² of body surface area, IV on days 1-3 of each cycle) plus either IV atezolizumab 1,200 mg (atezolizumab plus CP/ET) or IV placebo (placebo plus CP/ET) on day 1 of each cycle (induction phase), followed by the same dose of IV atezolizumab or placebo during a maintenance phase until unacceptable toxicity or disease progression. Treatment beyond disease progression was allowed if patients experienced clinical benefit.

End Points, Assessments, and Statistical Analysis

The two primary end points were OS and investigator-assessed PFS per RECIST version 1.1 (RECIST 1.1) in the intention-to-treat (ITT) population. Key secondary end points were investigator-assessed overall response rate (ORR) per RECIST 1.1, duration of response (DOR), and safety.

Exploratory end points included assessment of efficacy based on PD-L1 expression levels and bTMB as previously described.⁵ PD-L1 testing was performed using the PD-L1 immunohistochemical (SP263) assay on a Ventana BenchMark ULTRA automated staining platform according to the manufacturer's instructions.¹⁴ Tumor tissue slides (slide age \leq 1 year) were used for the SP263 analyses. For these exploratory analyses, including updated analyses of OS and PFS, results are considered descriptive in nature.

Samples were considered to be positive for PD-L1 expression if the percentage of TC expressing PD-L1 at any intensity was \geq 1% or if the proportion of tumor area occupied by IC expressing PD-L1 at any intensity was \geq 1%. As there are no PD-L1 immunohistochemistry (IHC)-validated cutoffs in SCLC, PD-L1 prevalence was evaluated in a stepwise fashion in line with non-SCLC (NSCLC) PD-L1 IHC cutoffs: \geq 1%, \geq 5%, \geq 25%, and \geq 50% TC or IC. Because of the limited PD-L1 prevalence observed in the study, exploratory OS by PD-L1 status was evaluated at the \geq 1% and \geq 5% TC or IC cutoffs, whereas PFS and ORR were assessed at the \geq 1% TC or IC cutoff.

Tumor assessments and statistical analyses were previously described⁵; a brief description is included in the Data Supplement (online only).

Patients who received at least one dose of study treatment were included in the safety analysis. Adverse events (AEs) were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The investigator determined whether AEs were related to the trial regimen.

Patterns of disease progression were evaluated in the ITT population. Patients with disease progression were evaluated for sites of progression, including at existing lesions (target and nontarget lesions) and new lesions.

RESULTS

Baseline Characteristics

At the data cutoff for this preplanned analysis (clinical cutoff date: January 24, 2019), follow-up had continued for an additional 9 months after the primary analysis. The median duration of follow-up for OS was 23.1 months (range, 0-29.5 months) in the atezolizumab plus CP/ET arm and 22.6 months (range, 0-30.7 months) in the placebo plus CP/ET arm. Patient disposition and reasons for study discontinuation are shown in Figure 1. Patient baseline characteristics were previously described and were generally well-balanced between the treatment arms.⁵

Efficacy

Updated Kaplan-Meier estimates for OS in the ITT population are shown in Figure 2A. The median OS was 12.3 months (95% CI, 10.8 to 15.8) in the atezolizumab plus CP/ET arm and 10.3 months (95% CI, 9.3 to 11.3) in the placebo plus CP/ET arm (HR, 0.76; 95% CI, 0.60 to 0.95). OS at 12 months demonstrated a survival increase of 12.9% in the atezolizumab plus CP/ET arm (51.9%) compared with the placebo plus CP/ET arm (39.0%). Similarly, at 18 months, 13.0% more patients were alive in the atezolizumab plus CP/ET arm (34.0%) than with placebo plus CP/ET (21.0%). Consistent with results observed at the primary analysis,⁵ the addition of atezolizumab was associated with consistent OS benefit across the majority of subgroups (Fig 2B). At the updated analysis, confirmed ORRs in the ITT population were 60.2% in the atezolizumab plus CP/ET arm (95% CI, 53.1 to 67.0) versus 64.4% (95% CI, 57.3 to 71.0; descriptive $P = .3839$) in the placebo plus CP/ET arm. The median DOR was 4.2 months (95% CI, 4.1 to 4.5) in the atezolizumab plus CP/ET arm versus 3.9 months (95% CI, 3.1 to 4.2) in the placebo plus CP/ET arm (HR, 0.67; 95% CI, 0.51 to 0.88; descriptive $P = .0037$).

At the updated analysis, 181 patients (90.0%) in the atezolizumab plus CP/ET arm and 194 patients (96.0%) in the placebo plus CP/ET arm had RECIST-defined disease progression. Median PFS in the ITT population at the updated analysis was 5.2 months (95% CI, 4.4 to 5.6) in the atezolizumab plus CP/ET arm and 4.3 months (95% CI, 4.2 to 4.5) in the placebo plus CP/ET arm (HR, 0.77; 95% CI, 0.63 to 0.95). Disease progression occurred with the following patterns in the atezolizumab plus CP/ET and placebo plus CP/ET arms, respectively: 57.7% and 64.9% at existing lesions, 42.8% and 49.0% at new lesions, and 20.9% and 28.2% at both new and existing lesions. The patterns of progression in specific organs were generally similar between arms (Data Supplement). The most common sites of new lesions (occurring in \geq 10% of patients) were the CNS, lung, lymph nodes, and liver; the incidence of new lesions at these sites was similar between arms (Data Supplement). Among patients treated with PCI in the atezolizumab plus CP/ET ($n = 22$) and placebo plus CP/ET ($n = 22$) arms, respectively, disease progression occurred in 68.2% and 77.3% at existing lesions, 45.5% and 54.5% at new lesions, and 27.3% and 31.8% at both new and existing lesions. The patterns of progression in specific organs in patients treated with or without PCI are shown in the Data Supplement. Among the patients who received PCI, one patient in each arm developed new brain lesions. Among patients who did not receive PCI, 21.1% and 22.2% developed new brain lesions in the atezolizumab plus CP/ET and placebo plus CP/ET arms, respectively.

Safety

Similar to the findings in the primary analysis, the median duration of treatment was 4.7 months (range, 0-29 months)

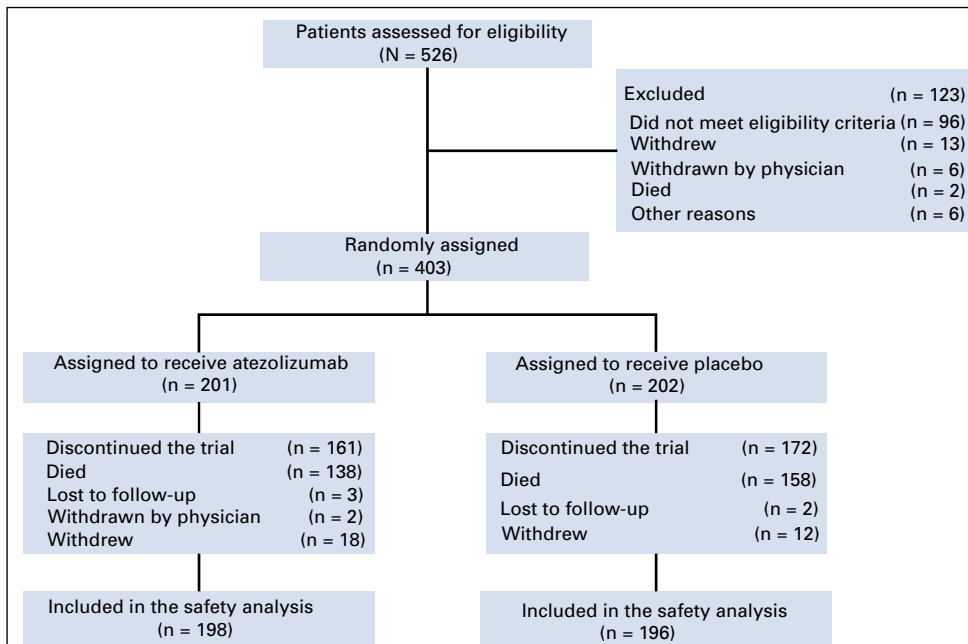


FIG 1. Patient flow diagram in IMpower133. All patients who underwent random assignment were included in the intention-to-treat analysis. Patients were assigned to receive either atezolizumab plus carboplatin plus etoposide or placebo plus carboplatin plus etoposide. One patient assigned to the placebo group received a dose of atezolizumab and was included in the atezolizumab group in the safety analyses. Clinical cutoff date: January 24, 2019.

with atezolizumab and 4.1 months (range, 0-26 months) with placebo (Table 1). Patients received a median of 7.0 doses (range, 1-39 doses) of atezolizumab and 6.0 doses (range, 1-38 doses) of placebo. AEs, including treatment-related AEs, are listed in Table 1 and were comparable with safety reported at the primary analysis.⁵ Immune-related AEs that were consistent with an immune-mediated mechanism of action and required treatment with systemic corticosteroids occurred in 40 patients (20.2%) in the atezolizumab plus CP/ET arm versus 11 patients (5.6%) in the placebo plus CP/ET arm (Table 1). The most common immune-related AEs, irrespective of treatment given for the event, in the atezolizumab plus CP/ET and placebo plus CP/ET arms were rash (20.2% v 10.7%), hypothyroidism (12.6% v 0.5%), hepatitis (7.6% v 4.6%), and infusion-related reactions (5.6% v 5.1%). Immune-related pneumonitis occurred in five patients (2.5% v 2.6%) in each arm.

Exploratory Biomarker Analyses

The PD-L1 IHC BEP comprised 34% of the ITT population: 64 patients (32%) from the atezolizumab plus CP/ET arm and 73 patients (36%) from the placebo plus CP/ET arm (Data Supplement). Baseline characteristics in the BEP are summarized in Table 2 and were generally well balanced. The prevalence for PD-L1 expression levels was 47.4% (n = 65) for PD-L1 expression on < 1% of TC and IC, 52.6% (n = 72) for PD-L1 expression on ≥ 1% on TC or IC, and 21.2% (n = 29) for PD-L1 expression on ≥ 5% TC or IC

(Data Supplement). PD-L1 expression was observed mostly on IC, with limited expression on TC (Data Supplement). Because of the limited number of patients whose tumors had PD-L1 expression ≥ 5%, exploratory analysis of OS by PD-L1 status was evaluated only at the 1% and 5% TC or IC cutoffs. In the subgroup of patients with PD-L1 expression < 1% TC and IC, an OS benefit was observed with atezolizumab plus CP/ET (median OS, 10.2 months; 95% CI, 7.9 to 15.7) compared with placebo plus CP/ET (8.3 months; 95% CI, 6.9 to 9.1; HR, 0.51; 95% CI, 0.30 to 0.89; Figs 3A-3C). The median OS in patients with PD-L1 expression ≥ 1% TC or IC was 9.7 months (95% CI, 7.6 to 17.4) in the atezolizumab plus CP/ET arm compared with 10.6 months (95% CI, 8.3 to 14.7) in the placebo plus CP/ET arm (HR, 0.87; 95% CI, 0.51 to 1.49) (Figs 3A-3C). An OS benefit was observed in patients with tumors containing PD-L1 expression ≥ 5% TC or IC (Figs 3A-3C). In this subgroup, the median OS was 21.6 months (95% CI, 9.4 to not evaluable) with atezolizumab plus CP/ET compared with 9.2 months (95% CI, 6.1 to 15.7) with placebo plus CP/ET (HR, 0.60; 95% CI, 0.25 to 1.46).

Similarly, a PFS benefit with atezolizumab plus CP/ET (median PFS, 5.4 months; 95% CI, 4.5 to 5.6) compared with placebo plus CP/ET (4.2 months; 95% CI, 4.0 to 4.2) was observed in patients with tumors containing PD-L1 expression < 1% TC or IC (HR, 0.52; 95% CI, 0.31 to 0.88; Figs 3B-3C). The median PFS in patients with tumors containing PD-L1 expression ≥ 1% TC or IC was

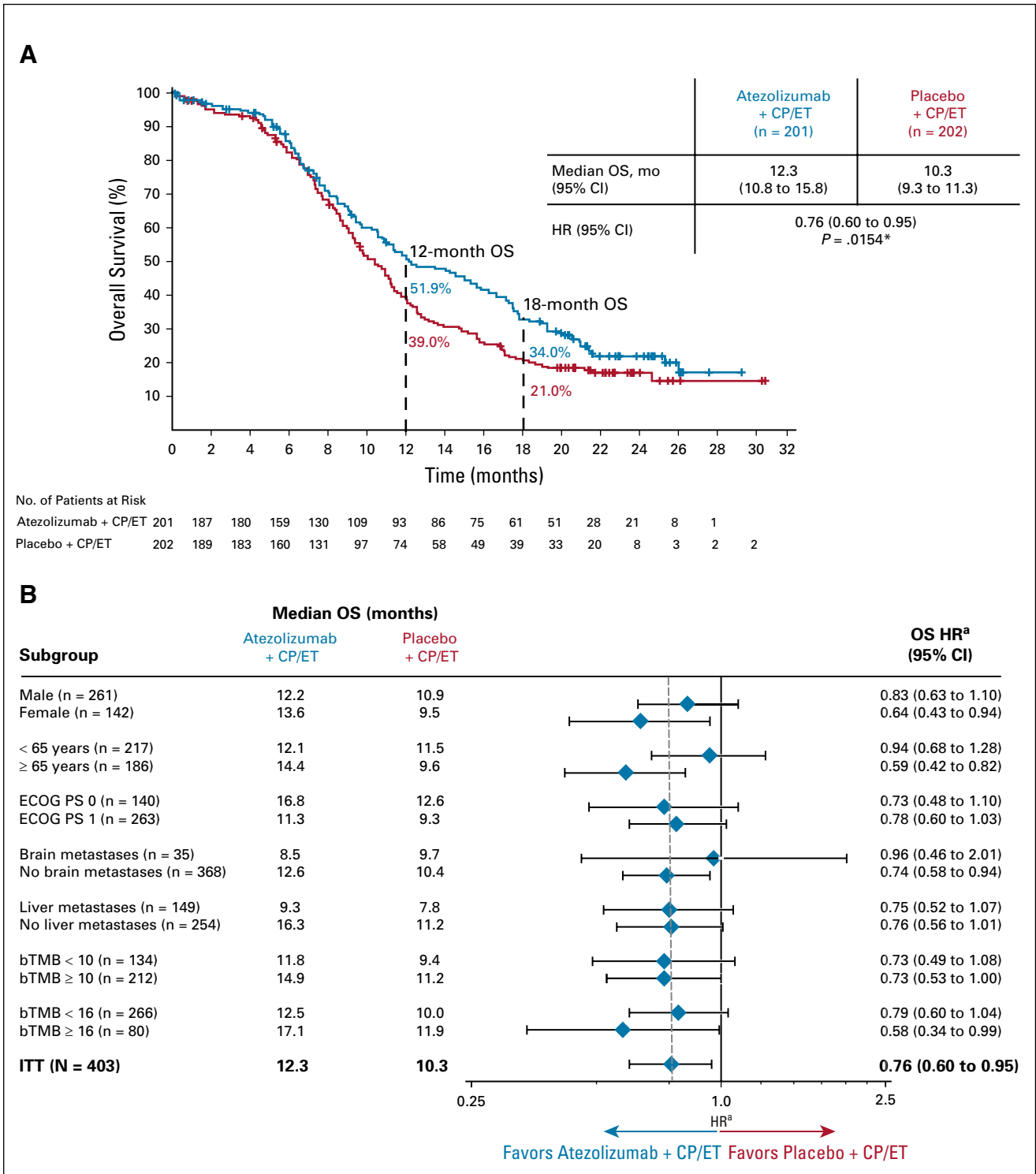


FIG 2. (A) Kaplan-Meier analysis of overall survival (OS) at the updated analysis of the intention-to-treat (ITT) population and (B) OS by baseline characteristics. A total of 57 patients had unknown bTMB score. These patients comprised the nonbiomarker evaluable population, which included 28 patients who had a bTMB result with a maximum somatic allele frequency < 1%, 15 patients who had a sample that either failed quality control at the testing vendor or had median exon coverage < 800, and 14 patients who did not submit a plasma sample at baseline. *P value used for descriptive purposes only. ^aHazard ratios (HRs) are unstratified for patient subgroups and are stratified for the ITT population. Clinical cutoff date: January 24, 2019. bTMB, blood-based tumor mutational burden; CP/ET, carboplatin plus etoposide; ECOG PS, Eastern Cooperative Oncology Group performance status.

TABLE 1. Safety Summary and Drug Exposure

Category	Atezolizumab Plus CP/ET (N = 198)	Placebo Plus CP/ET (N = 196)
Number of AEs, n	2291	1919
All-cause AEs, n (%)		
Any-grade AEs	198 (100)	189 (96.4)
Grade 3 or 4	134 (67.7)	124 (63.3)
Grade 5	4 (2.0)	11 (5.6)
Serious AEs	77 (38.9)	69 (35.2)
Leading to any treatment withdrawal	24 (12.1)	6 (3.1)
Leading to any dose modification or interruption	139 (70.2)	119 (60.7)
Atezolizumab or placebo	118 (59.6)	102 (52.0)
Treatment-related AEs, n (%)		
Any-grade AEs	188 (94.9)	181 (92.3)
Atezolizumab or placebo-related	130 (65.7)	100 (51.0)
Grade 3 or 4	113 (57.1)	110 (56.1)
Grade 5	3 (1.5)	3 (1.5)
AESIs, n (%) ^a		
Any-grade	82 (41.4)	48 (24.5)
Grade 3 or 4	16 (8.1)	5 (2.6)
Serious	14 (7.1)	7 (3.6)
Treatment-related	66 (33.3)	36 (18.4)
Grade 3 or 4	14 (7.1)	4 (2.0)
Serious	12 (6.1)	5 (2.6)
Leading to any treatment withdrawal	8 (4.0)	2 (1.0)
Leading to any dose modification or interruption	24 (12.1)	11 (5.6)
Treated with steroids or hormone replacement therapy ^b	40 (20.2)	11 (5.6)
AESIs ≥ 1.5% in either group, n (%)		
Immune-mediated rash	40 (20.2)	21 (10.7)
Immune-mediated hypothyroidism	25 (12.6)	1 (0.5)
Immune-mediated hepatitis ^c	15 (7.6)	9 (4.6)
Infusion-related reactions	11 (5.6)	10 (5.1)
Immune-mediated hyperthyroidism	11 (5.6)	5 (2.6)
Immune-mediated pneumonitis	5 (2.5)	5 (2.6)
Immune-mediated adrenal insufficiency	0	3 (1.5)
Immune-mediated colitis	3 (1.5)	0
Atezolizumab or placebo treatment		
Treatment duration, median (range), mo	4.7 (0-29)	4.1 (0-26)
Dose intensity, median (range), %	94.9 (16-100)	94.7 (60-102)
Number of doses received, median (range)	7.0 (1-39)	6.0 (1-38)
Total cumulative dose, median (range), mg	8,400 (80-46,800)	0
Carboplatin treatment		
Treatment duration, median (range), mo	2.3 (0-4)	2.2 (0-4)
Dose intensity, median (range), %	92.3 (48-101)	93.3 (60-102)
Number of doses received, median (range)	4.0 (1-6)	4.0 (1-5)
Total cumulative dose, median (range), mg	2062.5 (380-3,670)	2175.0 (341-3,691)

(continued on following page)

TABLE 1. Safety Summary and Drug Exposure (continued)

Category	Atezolizumab Plus CP/ET (N = 198)	Placebo Plus CP/ET (N = 196)
Etoposide treatment		
Treatment duration, median (range), mo	2.3 (0-4)	2.2 (0-4)
Dose intensity, median (range), %	89.4 (32-99)	90.3 (59-99)
Number of doses received, median (range)	12.0 (1-18)	12.0 (2-15)
Total cumulative dose, median (range), mg	2055.2 (8-3,492)	2131.7 (294-3,240)

NOTE. Clinical cutoff date: January 24, 2019.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; CP/ET, carboplatin plus etoposide.

^aAs defined by the study sponsor.

^bAn event consistent with an immune-mediated mechanism of action requiring treatment with systemic corticosteroids or hormone replacement therapy.

^cBased on diagnosis and laboratory abnormalities.

5.1 months (95% CI, 4.2 to 5.6) in the atezolizumab plus CP/ET arm compared with 5.5 months (95% CI, 4.2 to 5.6) in the placebo plus CP/ET arm (HR, 0.86; 95% CI, 0.51 to 1.46) (Figs 3B-3C). Confirmed ORRs in the PD-L1 negative subgroup (defined by PD-L1 expression < 1% TC and IC) were 75.0% and 62.2% with atezolizumab plus CP/ET and

TABLE 2. Baseline Characteristics in the ITT Population and PD-L1 IHC BEP

Characteristic	ITT Population ⁵		PD-L1 IHC BEP	
	Atezolizumab Plus CP/ET (n = 201)	Placebo Plus CP/ET (n = 202)	Atezolizumab Plus CP/ET (n = 64)	Placebo Plus CP/ET (n = 73)
Age < 65 years, n (%)	111 (55.2)	106 (52.5)	41 (64.1)	43 (58.9)
Male, n (%)	129 (64.2)	132 (65.3)	39 (60.9)	46 (63.0)
ECOG performance status, n (%)				
0	73 (36.3)	67 (33.2)	21 (32.8)	24 (32.9)
1	128 (63.7)	135 (66.8)	43 (67.2)	49 (67.1)
Tobacco use history, n (%)				
Never	9 (4.5)	3 (1.5)	5 (7.8)	1 (1.4)
Current	74 (36.8)	75 (37.1)	24 (37.5)	31 (42.5)
Former	118 (58.7)	124 (61.4)	35 (54.7)	41 (56.2)
Brain metastasis at enrollment, n (%)				
Yes	17 (8.5)	18 (8.9)	3 (4.7)	4 (5.5)
No	184 (91.5)	184 (91.1)	61 (95.3)	69 (94.5)
SLD at baseline, median (range), mm	113.0 (12.0-325.0)	105.5 (15.0-353.0)	125.5 (12.0-325.0)	123 (26.0-353.0)
Blood-based tumor mutational burden, n (%)				
< 10	71/173 (41.0)	68/178 (38.2)	22 (37.9)	30 (44.1)
≥ 10	102/173 (59.0)	110/178 (61.8)	36 (62.1)	38 (55.9)
< 16	133/173 (76.9)	138/178 (77.5)	43 (74.1)	55 (80.9)
≥ 16	40/173 (23.1)	40/178 (22.5)	15 (25.9)	13 (19.1)
PD-L1 expression, n (%)				
TC or IC ≥ 5%	N/A	N/A	15 (23.4)	14 (19.2)
TC or IC ≥ 1%	N/A	N/A	36 (56.3)	36 (49.3)
TC and IC < 1%	N/A	N/A	28 (43.8)	37 (50.7)

NOTE. Clinical cutoff date (ITT): April 4, 2018. Clinical cutoff date (PD-L1 IHC BEP): January 24, 2019.

Abbreviations: BEP, biomarker-evaluable population; CP/ET, carboplatin plus etoposide; ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cell; IHC, immunohistochemistry; ITT, intention-to-treat; N/A, not available; PD-L1, programmed death-ligand 1; SLD, sum of longest diameter; TC, tumor cell.

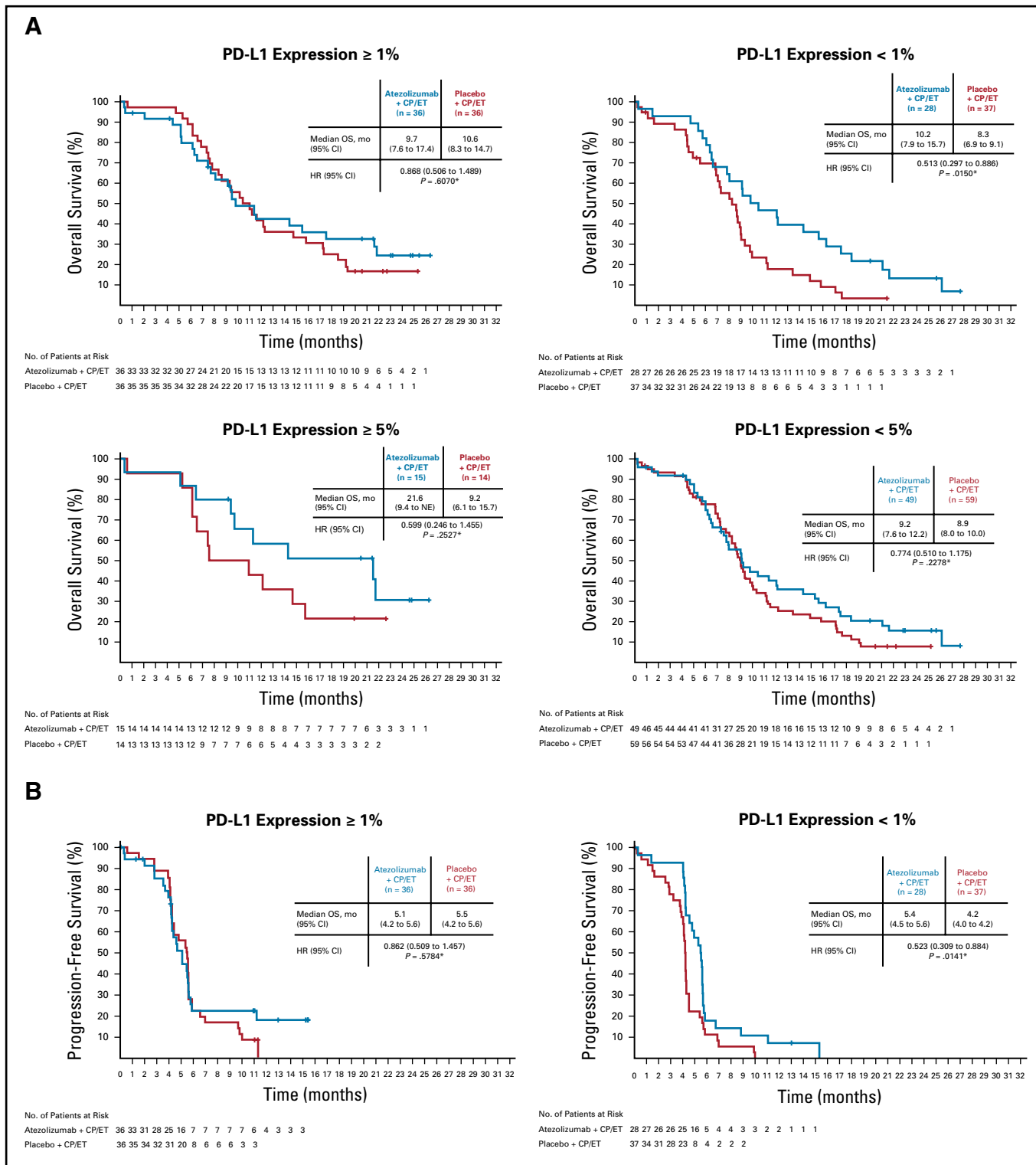


FIG 3. Kaplan-Meier analysis of (A) overall survival (OS) and (B) progression-free survival (PFS) and (C) subgroup analysis of PFS (clinical cutoff date: April 4, 2018) and OS (clinical cutoff date: January 24, 2019) by programmed death-ligand 1 (PD-L1) expression in the biomarker-evaluable population (BEP). **P* values used for descriptive purposes only. ^aHazard ratios (HRs) are unstratified for patient subgroups and stratified for the intention-to-treat (ITT) population. CP/ET, carboplatin plus etoposide; NE, not evaluable.

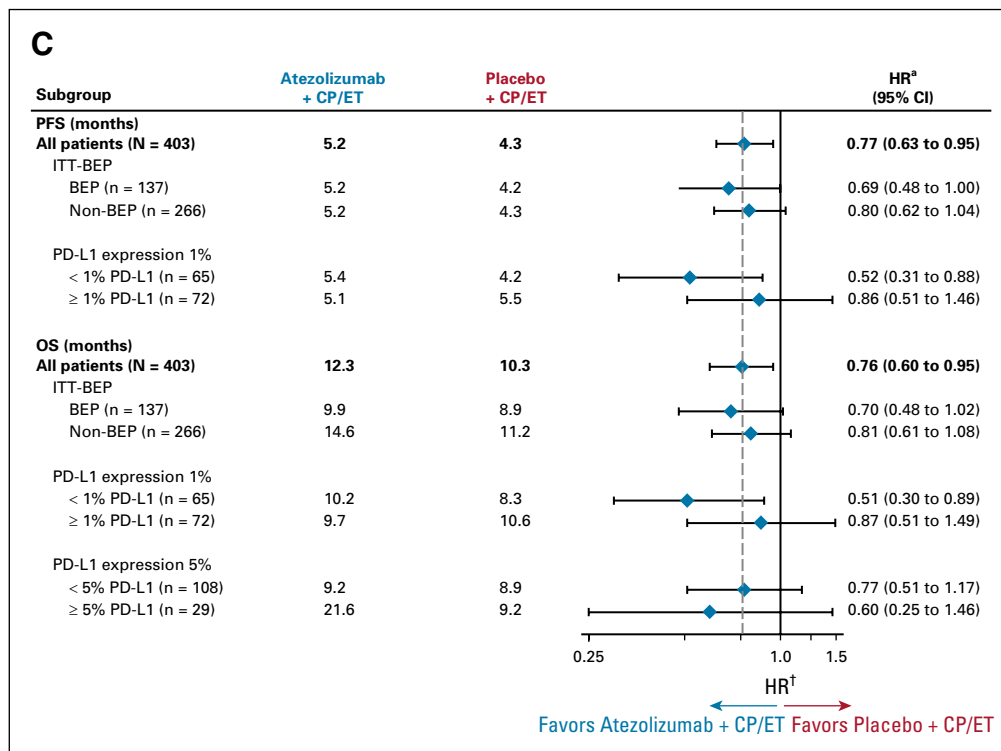


FIG 3. (Continued).

placebo plus CP/ET, respectively. Responses in the PD-L1 positive subgroup (defined by PD-L1 expression $\geq 1\%$ TC or IC) were 52.8% and 69.4% with atezolizumab plus CP/ET and placebo plus CP/ET, respectively (Table 3).

Consistent with the previously reported bTMB results, updated analyses showed an OS benefit in both the bTMB high and low subgroups using the prespecified bTMB cutoffs of 10 and 16, respectively (Fig 2B).⁵ The overlap of patients with bTMB high and PD-L1 high was limited, as 55.9% (n = 38/68) of PD-L1 positive patients (defined by a PD-L1 IHC result of $\geq 1\%$ TC or IC) were also bTMB high (defined by a bTMB score ≥ 10) (Data Supplement).

DISCUSSION

IMpower133 was the first randomized study in > 3 decades to show improved survival in patients with untreated ES-SCLC, leading to regulatory approvals of atezolizumab plus CP/ET in the 1L setting in the United States⁸ and European Union.⁹ The updated OS results, after an additional 9 months of follow-up, continued to demonstrate improved clinical benefit of atezolizumab plus CP/ET compared with placebo plus CP/ET. At both 12 and 18 months, 13% more patients were alive in the atezolizumab plus CP/ET arm than in the placebo plus CP/ET arm. The OS benefit was observed in most patient subgroups.

TABLE 3. Overall Response Rates in the PD-L1 BEP

Patient Population	Atezolizumab Plus CP/ET (n = 64)	Placebo Plus CP/ET (n = 73)
TC or IC $\geq 1\%$		
Evaluable patients, n	36	36
Confirmed OR, n (%)	19 (52.8)	25 (69.4)
Unconfirmed OR, n (%)	27 (75.0)	29 (80.6)
TC and IC < 1%		
Evaluable patients, n	28	37
Confirmed OR, n (%)	21 (75.0)	23 (62.2)
Unconfirmed OR, n (%)	23 (82.1)	26 (70.3)

NOTE. Clinical cutoff date: January 24, 2019.

Abbreviations: BEP, biomarker-evaluable population; CP/ET, carboplatin plus etoposide; IC, tumor-infiltrating immune cells; OR, objective response; PD-L1, programmed death-ligand 1; TC, tumor cells.

Consistent with previously reported results,⁵ there appeared to be an imbalance in OS benefit among patients with baseline brain metastases compared with patients without baseline brain metastases. The number of patients enrolled in the study with brain metastases was small, which may be because of the requirement that brain metastases be treated prior to enrollment; further trials are needed to investigate the role of immunotherapy in patients with SCLC who have brain metastases.

There continued to be fewer patients in the atezolizumab plus CP/ET arm than in the placebo plus CP/ET arm with radiographic progression. Patterns of progression were similar between arms, with no difference in the incidence of new brain metastases. However, it should be noted that evaluation of the patterns of progression considered metastatic sites individually rather than the combination(s) of patterns at sites (eg, isolated v diffused progression or unique visceral involvement). With longer follow-up, the safety profile of atezolizumab plus CP/ET remained consistent with that previously reported. Improvements in health-related quality of life in patients in the atezolizumab plus CP/ET arm compared with patients in the placebo plus CP/ET arm were previously reported¹³ and suggest that the addition of atezolizumab did not increase toxicity related to CP/ET or adversely contribute to symptom burden.

PD-L1 expression in SCLC is highly variable, and published results indicate that expression ranges from 2% to 83%, depending on the assay and scoring algorithm used.¹⁵ In this study, using the SP263 assay, the prevalence of PD-L1 expression \geq 1% on TC or IC within the BEP was 53%, whereas the prevalence of PD-L1 expression \geq 5% on TC or IC was 21%. Furthermore, PD-L1 expression was more frequently observed on IC than on TC; this finding differs from that for NSCLC, for which PD-L1 expression is observed on both TC and IC.¹⁶ The pattern of PD-L1 expression primarily on IC in SCLC was also seen in the phase III CASPIAN (ClinicalTrials.gov identifier: NCT03043872) study, which also demonstrated an improvement in OS similar to that observed in IMpower133 when the anti-PD-L1 antibody durvalumab was added to platinum plus etoposide (EP) versus placebo plus EP in patients with untreated ES-SCLC.^{7,17} The data from both IMpower133 and CASPIAN suggest that the immune biology of SCLC may be more similar to that of diseases such as triple-negative breast cancer¹⁸ and urothelial carcinoma,¹⁹ for which PD-L1 expression is primarily on IC (limited PD-L1 expression on TC).

In the exploratory analysis in IMpower133, an OS benefit was observed across PD-L1 subgroups. These findings

were also noted in other similar phase III studies. In CASPIAN, durvalumab plus EP demonstrated improved OS compared with placebo plus EP across PD-L1 subgroups.¹⁷ In KEYNOTE-604, analyses of OS by PD-L1 subgroup appeared to show a similar benefit in OS with pembrolizumab plus EP compared with placebo plus EP across PD-L1 subgroups.²⁰ Results from these studies suggest that PD-L1 expression does not appear to be a predictive biomarker for PD-L1/PD-1 checkpoint inhibitor plus chemotherapy in 1L ES-SCLC. An updated exploratory analysis by bTMB in IMpower133 continued to demonstrate that atezolizumab plus CP/ET resulted in improved benefit over placebo plus CP/ET, independent of bTMB levels. However, similar to NSCLC and other indications,²¹ in ES-SCLC, bTMB and PD-L1 IHC appear to identify distinct patient populations. Together, these data suggest that bTMB and PD-L1 status should not be used for patient treatment decisions for the atezolizumab plus CP/ET regimen, as currently neither biomarker appears to be predictive of outcomes.

A caveat with the exploratory biomarker PD-L1 IHC analysis was the limited size of the BEP, with only 34% of the enrolled study population included in the PD-L1 analyses. This limitation can be partially attributed to poor tissue quality (including crush artifact) and sample collection methods (eg, fine needle aspirates) that destroy tissue architecture and limit IHC analyses.²² Various sample collection methods were allowed with the intention of making the study population more reflective of the general population of patients with ES-SCLC, given how diagnoses are made in clinical practice (bronchoscopy, cytological samples, and fine needle aspiration).

Given the limitations of the PD-L1 IHC analyses and the current lack of identification of a biomarker for checkpoint inhibitors in SCLC, additional studies are necessary to further evaluate potential biomarkers and associations with outcomes.^{17,23,24}

In conclusion, with a follow-up of 22.9 months, updated results continued to demonstrate an improvement in OS with atezolizumab plus CP/ET and a similar safety profile compared with placebo plus CP/ET in patients with ES-SCLC. Although the PD-L1 analyses were limited to a subset of the ITT population, no numerical difference in efficacy outcomes was observed across the PD-L1 IHC subgroups. Overall, the data suggest that clinical benefit was observed in patients with ES-SCLC treated with 1L atezolizumab plus CP/ET, independent of bTMB or PD-L1 biomarker status.

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PRIOR PRESENTATION

Presented at the European Society for Medical Oncology 2019 Congress, Barcelona, Spain, September 27 - October 1, 2019 (abstract 2374).

SUPPORT

Sponsored by F. Hoffmann-La Roche Ltd/Genentech, Inc, a member of the Roche Group.

CLINICAL TRIAL INFORMATION

NCT02763579

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the author are available with this article at DOI <https://doi.org/10.1200/JCO.20.01055>.

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ACKNOWLEDGMENT

We thank the patients participating in this trial and their families and the nurses, research coordinators, data managers, and clinical study site investigators. Medical writing assistance for this manuscript was provided by Preshita Gadkari, PhD, of Health Interactions, Inc, and funded by F. Hoffmann-La Roche, Ltd.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133)**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/nccn or ascopubs.org/jco/authors/author-center.

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No other potential conflicts of interest were reported.

