ORIGINAL ARTICLE

IMpower150 Final Overall Survival Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in First-Line Metastatic Nonsquamous NSCLC

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ABSTRACT

Introduction: We report the final overall survival (OS) analyses of atezolizumab-carboplatin-paclitaxel (ACP [experimental arm]) and OS data with approximately 39.8 months of median follow-up with atezolizumab-bevacizumab-carboplatin-paclitaxel (ABCP) versus bevacizumab-carboplatin-paclitaxel (BCP) in chemotherapy-naive patients with metastatic nonsquamous NSCLC in the phase 3 IMpower150 study (NCT02366143).

Methods: In this randomized, open-label study (N = 1202), coprimary end points included investigator-assessed progression-free survival and OS in intention-to-treat (ITT) wild-type (WT; no *EGFR* or *ALK* alterations) patients. Secondary and exploratory end points included OS in ITT and programmed death-ligand 1 (PD-L1) subgroups defined by the VENTANA SP142 and SP263 immunohistochemistry assays.

Results: At the final analysis with ACP versus BCP (data cutoff: September 13, 2019; minimum follow-up: 32.4 mo), ACP had numerical, but not statistically significant, improvements in OS (ITT-WT: median OS = 19.0 versus 14.7 mo; hazard ratio = 0.84; 95% confidence interval: 0.71–1.00). OS benefit was sustained with ABCP versus BCP (ITT-WT: 19.5 versus 14.7 mo; hazard ratio = 0.80; 95% confidence interval: 0.67–0.95). Exploratory analyses in the SP142-defined PD-L1 subgroups revealed longer median OS with ABCP and ACP versus BCP in PD-L1–high and PD-L1–positive subgroups; in the PD-L1–negative subgroups, median OS was similar with ACP and ABCP versus BCP. Safety was consistent with that in earlier analyses (data cutoff: January 22, 2018).

Conclusions: At the final IMpower150 OS analysis, ACP had numerical, but not statistically significant, OS improvement versus BCP. Updated data with an additional 20 months of follow-up revealed continued OS improvement with ABCP versus BCP in all patients.

Keywords: Non–small cell lung cancer; Atezolizumab; Bevacizumab; Chemotherapy; IMpower150

Introduction

Lung cancer is the most common cause of cancer mortality worldwide.[1] NSCLC represents more than 80% of the lung cancer cases,[2] with most having nonsquamous histology.[3] Current first-line treatment options in metastatic nonsquamous NSCLC without oncogenic driver alterations include checkpoint inhibitor monotherapy in patients with high programmed death-ligand 1 (PD-L1) expression and checkpoint inhibitor therapy in combination with platinum-doublet chemotherapy with or without bevacizumab.[2,4–7] Despite the available standard-of-care first-line treatments, clinical outcomes have remained suboptimal and additional therapeutic options are needed.

Atezolizumab is an anti–PD-L1 antibody that restores tumor-specific immunity by preventing the binding of PD-L1 to the programmed death-1 (PD-1) and B7.1 receptors.[8,9] Inhibition of vascular endothelial growth factor (VEGF) by bevacizumab confers immune modulatory effects that, when combined with chemotherapy, may further enhance the T-cell–mediated killing of cancer cells by atezolizumab through reversal of VEGF-mediated immunosuppression and chemotherapy-induced cell death.[10,11] The phase 3 IMpower150 study evaluated the efficacy of atezolizumab-bevacizumab-carboplatin-paclitaxel (ABCP) or atezolizumab-carboplatin-paclitaxel (ACP) versus bevacizumab-carboplatin-paclitaxel (BCP) in an all-comer patient population with metastatic nonsquamous NSCLC.[12] ABCP versus BCP had statistically significant and clinically meaningful progression-free survival (PFS; $p < 0.001$) and overall survival (OS; $p = 0.02$) benefit regardless of PD-L1 expression and numerical improvements irrespective of *EGFR* or *ALK* genetic alteration status[12,13]; with ACP versus BCP, a similar benefit was not observed.[13] On the basis of these results, ABCP has been approved in the United States for the first-line treatment of metastatic nonsquamous NSCLC without *EGFR* or *ALK* genetic alterations,[14] whereas in Europe and Japan, this combination is also approved in patients with *EGFR* or *ALK*-positive NSCLC after failure with tyrosine kinase inhibitors previously.[15]

We report the final OS analysis from the experimental ACP arm of the IMpower150 trial and updated exploratory OS data with an additional follow-up of approximately 20 months with ABCP versus BCP. In addition to evaluating assay concordance, we present OS outcomes in PD-L1 subgroups defined by the VENTANA SP142 and SP263 PD-L1 immunohistochemistry (IHC) assays.

Materials and Methods

Study Design and Patients

IMpower150 was an international, open-label, randomized, phase 3 trial conducted at 240 study centers in 26 countries (NCT02366143).[12,13] The study was

performed according to the Good Clinical Practice guidelines and the Declaration of Helsinki, with study protocol approval provided by independent ethics committees at each of the participating sites.

Eligible patients were chemotherapy naive and had stage IV metastatic nonsquamous NSCLC, measurable disease at baseline per Response Evaluation Criteria in Solid Tumors version 1.1, a baseline Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and available tumor tissue for biomarker testing. Patients with any PD-L1 expression status, as assessed by the VENTANA SP142 IHC assay (Ventana Medical Systems), were included in the study. Patients with *EGFR* or *ALK* genomic alterations were included if they had experienced disease progression or unacceptable side effects with one or more tyrosine kinase inhibitors previously. Additional patient eligibility criteria and study design information have been published previously.[12,13] All patients provided written informed consent.

Treatment

Patients were randomly assigned to ACP, ABCP, or BCP, with randomization stratified by sex, baseline liver metastases, and PD-L1 expression. Induction chemotherapy was administered for four or six cycles every 21 days (the number of cycles was determined by the investigator before randomization). The number of chemotherapy cycles patients actually received may have differed on the basis of factors such as toxicity and disease progression. Study treatment was given intravenously on day 1 of each 21-day cycle and comprised atezolizumab 1200 mg, bevacizumab 15 mg/kg, area under the concentration-time curve of 6 mg/mL per min carboplatin, and 200 mg/m^2 paclitaxel (patients of Asian ethnicity received 175 mg/m^2). After the induction phase, patients continued atezolizumab, bevacizumab, or both treatments until unmanageable toxicity or disease progression (per Response Evaluation Criteria in Solid Tumors). After disease progression, continuation of atezolizumab was allowed if clinical benefit was evident. Crossover to atezolizumab was not permitted.

Outcomes

The coprimary end points of PFS and interim OS were previously reported for ABCP versus BCP in the intention-to-treat (ITT)-wild-type (WT) population (excluding patients with *EGFR* or *ALK* genomic alterations) and among key subgroups in ITT patients.[12,13] In the present analyses, we report the final OS and PFS for ACP versus BCP and updated OS and PFS for ABCP versus BCP in the ITT-WT population. Exploratory analyses, including OS across all treatment arms in the PD-L1 subgroups in the ITT-WT population and SP263 biomarker-evaluable WT population (SP263 BEP-WT), are also included.

PD-L1 expression was assessed in archival or fresh tumor tissue (or both), stored under appropriate conditions, and evaluated at a central laboratory using the VENTANA SP142 or SP263 IHC assays.[16,17] For the SP263 assay, staining was conducted on all available tumor tissue samples, irrespective of other biomarker results. PD-L1 cutoff values were based on the proportion of tumor area occupied by PD-L1–expressing tumor-infiltrating immune cells (ICs) of any intensity or the percentage of PD-L1–expressing tumor cells (TCs) of any intensity as follows: (1) PD-L1 positive: greater than or equal to 1% TC or IC by SP142 (TC1/2/3 or IC1/2/3) or TC greater than or equal to 1% by SP263; (2) PD-L1 high: greater than or equal to 50% TC or greater than or equal to 10% IC by SP142 (TC3 or IC3) or TC greater than or equal to 50% by SP263; and (3) PD-L1 negative: less than 1% TC and IC by SP142 (TC0 and IC0) or TC less than 1% on SP263.

Adverse events (AEs) in the safety-evaluable ITT population, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0), are also reported.

Statistical Analysis

Details of the statistical analysis plan have been reported previously.[12,13] To control for overall type I error, a two-sided significance level of 0.05 was allocated to PFS in the tumor gene expression-WT population, PFS in the ITT-WT population, and OS in the ITT-WT population in a 3:3:19 ratio. The final analyses of PFS and OS were planned when approximately 516 PFS events and 507 OS events had occurred in the ABCP and BCP arms combined in the ITT-WT population. If the OS analysis for the ABCP versus BCP arm was significant, formal testing of PFS and OS was planned for the ACP versus BCP arm. If the OS analysis for the ACP versus BCP arm was significant, formal testing of PFS and OS for the ABCP versus BCP arm and the ACP versus BCP arm in the ITT population was planned.

Medians for OS in ITT, ITT-WT, and SP263 BEP-WT patients were estimated from Kaplan-Meier analyses. Corresponding hazard ratios (HRs) and 95% confidence interval (CI) for treatment comparisons were calculated from stratified and unstratified Cox regression models and the Brookmeyer-Crowley method, respectively. Subgroup analyses were conducted using unstratified HRs estimated from a Cox proportional hazards model. Concordance between SP142- and SP263-defined PD-L1 subgroups was visualized using Venn diagrams.

Statistical tests were performed with Statistical Analysis System version 9.4, R version 3.6.1, and Spotfire version 7.7.

Results

Patient Populations

Between March 31, 2015, and December 30, 2016, 1202 patients (ITT) were enrolled into the study (all biomarker-evaluable for the SP142 assay). Baseline characteristics were generally well balanced between the treatment arms (Table 1). PD-L1–positive tumors evaluated by the SP142 assay were identified in 213 of 402 patients (53%) in the ACP arm, 209 of 400 patients (52.3%) in the ABCP arm, and 195 of 400 patients (48.8%) in the BCP arm. The ITT-WT population comprised 1047 patients; of these, 774 patients were deemed biomarker-evaluable for the SP263 assay (SP263 BEP-WT). The baseline characteristics of the SP263 BEP-WT population are found in Supplementary Table 1.

Final and Updated Survival Analyses

At the final OS analysis (data cutoff, September 13, 2019), the minimum duration of follow-up in the ITT-WT population was 32.4 months (median, 39.8 mo in the ABCP arm, 38.8 mo in the ACP arm, and 40.0 mo in the BCP arm). As of the data cutoff date, OS events had occurred in 250 (ACP), 258 (ABCP), and 265 (BCP) patients in the ITT-WT population and 290 (ACP), 284 (ABCP), and 309 (BCP) patients in the ITT population. In the ITT-WT population, median OS was 19.0 months in the ACP arm compared with 14.7 months in the BCP arm, with an OS HR estimate of 0.84 (95% CI: 0.71–

Table 1. Baseline Demographic Characteristics (ITT, Final Analysis)

Characteristic	ACP (n = 402)	ABCP (n = 400)	BCP (n = 400)
Median age (range), y	63.0 (32-85)	63.0 (31-89)	63 (31-90)
Sex, n (%)			
Male	241 (60.0)	240 (60.0)	239 (59.8)
Female	161 (40.0)	160 (40.0)	161 (40.3)
Age group, n (%)			
<65 y	223 (55.5)	215 (53.8)	226 (56.5)
65-74 y	152 (37.8)	149 (37.3)	132 (33.0)
75-84 y	26 (6.5)	33 (8.3)	39 (9.8)
≥85 y	1 (0.2)	3 (0.8)	3 (0.8)
Race, n (%)			
American Indian or Alaskan Native	0	3 (0.8)	1 (0.3)
Asian	48 (11.9)	56 (14.0)	46 (11.5)
Black or African American	9 (2.2)	3 (0.8)	12 (3.0)
White	331 (82.3)	322 (80.5)	335 (83.8)
Multiple	4 (1.0)	3 (0.8)	0
Unknown	10 (2.5)	13 (3.3)	6 (1.5)
ECOG performance status, n (%)			
0	180 (44.8)	159 (40.1)	179 (45.1)
1	222 (55.2)	238 (59.9)	218 (54.9)
Tobacco use history, n (%)			
Never	77 (19.2)	82 (20.5)	77 (19.3)
Current	98 (24.4)	91 (22.8)	92 (23.0)
Previous	227 (56.5)	227 (56.8)	231 (57.8)
PD-L1 (SP142) status			
TC3 or IC3	68 (16.9)	75 (18.8)	73 (18.3)
TC1/2/3 or IC1/2/3	213 (53.0)	209 (52.3)	195 (48.8)
TC0 and IC0	188 (46.8)	191 (47.8)	205 (51.3)
PD-L1 (SP263) status			
N	299	295	279
≥50%	71 (23.7)	72 (24.4)	63 (22.6)
≥1% and <50%	107 (35.8)	89 (30.1)	76 (27.2)
<1%	121 (40.5)	134 (45.4)	140 (50.2)
Intended cycles of treatment			
4	224 (55.7)	214 (53.5)	217 (54.3)
6	178 (44.3)	186 (46.5)	183 (45.8)
Baseline target tumor SLD, median (range)	70.00 (10.0-299.0)	72.42 (10.4-243.0)	71.00 (10.0-251.0)

ABCP, atezolizumab-bevacizumab-carboplatin-paclitaxel; ACP, atezolizumab-carboplatin-paclitaxel; BCP, bevacizumab-carboplatin-paclitaxel; ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intention to treat; PD-L1, programmed death-ligand 1; SLD, sum of longest diameter; TC, tumor cells.

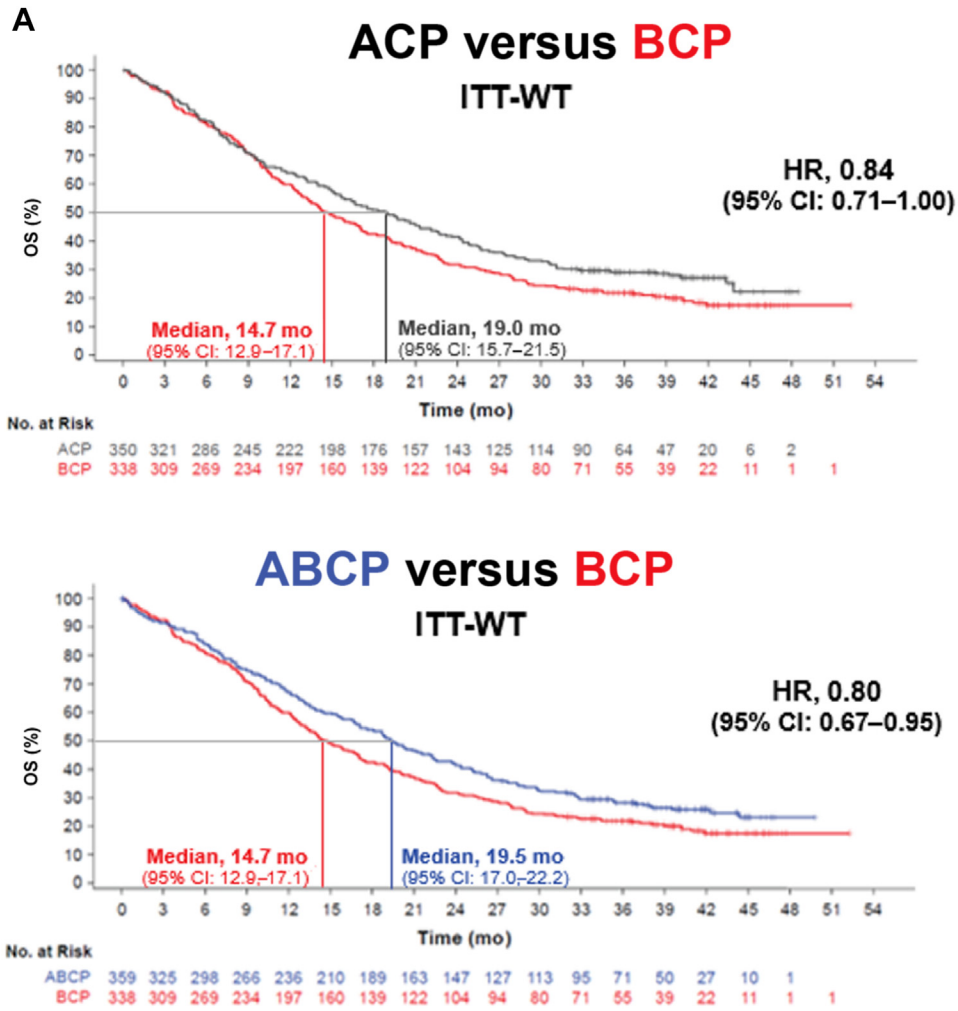


Figure 1. OS in the ITT and ITT-WT populations. Kaplan-Meier analyses of OS and forest plots of HRs in key subgroups with ACP or ABCP versus BCP in the ITT-WT (*A* and *C*) and ITT (*B* and *D*) populations. [a]Stratified analysis; [b]one patient in the ACP arm and two in the BCP arm were greater than or equal to 85 years of age. [c]Three patients in the ABCP arm and two in the BCP arm were greater than or equal to 85 years of age. [d]One patient in the ACP arm and three in the BCP arm were greater than or equal to 85 years of age. [e]Three patients in the ABCP arm and three in the BCP arm were greater than or equal to 85 years of age. HR for OS was therefore not evaluable in these patients. ABCP, atezolizumab-bevacizumab-carboplatin-paclitaxel; ACP, atezolizumab-carboplatin-paclitaxel; BCP, bevacizumab-carboplatin-paclitaxel; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention to treat; NE, not evaluable; OS, overall survival; WT, wild-type.

1.00, $p = 0.05$) (Fig. 1*A*). In the ITT population, median OS was 19.0 months in the ACP arm compared with 15.0 months in the BCP arm, with an OS HR estimate of 0.86 (95% CI: 0.73–1.01, $p = 0.07$) (Fig. 1*B*), although this comparison was not formally tested given the testing hierarchy. OS rates at 1 and 2 years in the ITT-WT population were 64% and 41% in the ACP arm versus 60% and 32% in the BCP arm, respectively. In the ITT population, the corresponding OS rates were 66% and 42% in the ACP arm versus 60% and 34% in the BCP arm, respectively.

In an updated exploratory analysis at the same clinical cutoff date, median OS in the ITT-WT population was 19.5 months in the ABCP arm versus 14.7 months in the BCP arm (HR = 0.80, 95% CI: 0.67–0.95) (Fig. 1*A*). Similar improvements were found in ITT patients, with a median OS of 19.8 months in the ABCP arm compared with 15.0 months in the BCP arm (HR = 0.80, 95% CI: 0.68–0.95) (Fig. 1*B*). In the ITT-WT population, 1- and 2-year OS rates were 67% and 42% in the ABCP arm versus 60% and 32% in the BCP arm, respectively; in the ITT population, these rates were 68% and 43% in the ABCP arm and 60% and 34% in the BCP arm, respectively.

OS benefit with ACP was observed in key patient subgroups compared with BCP in the ITT-WT and ITT populations, including males, those with ECOG PS of 0, and current or previous smokers (Fig. 1*C* and *D*). Median

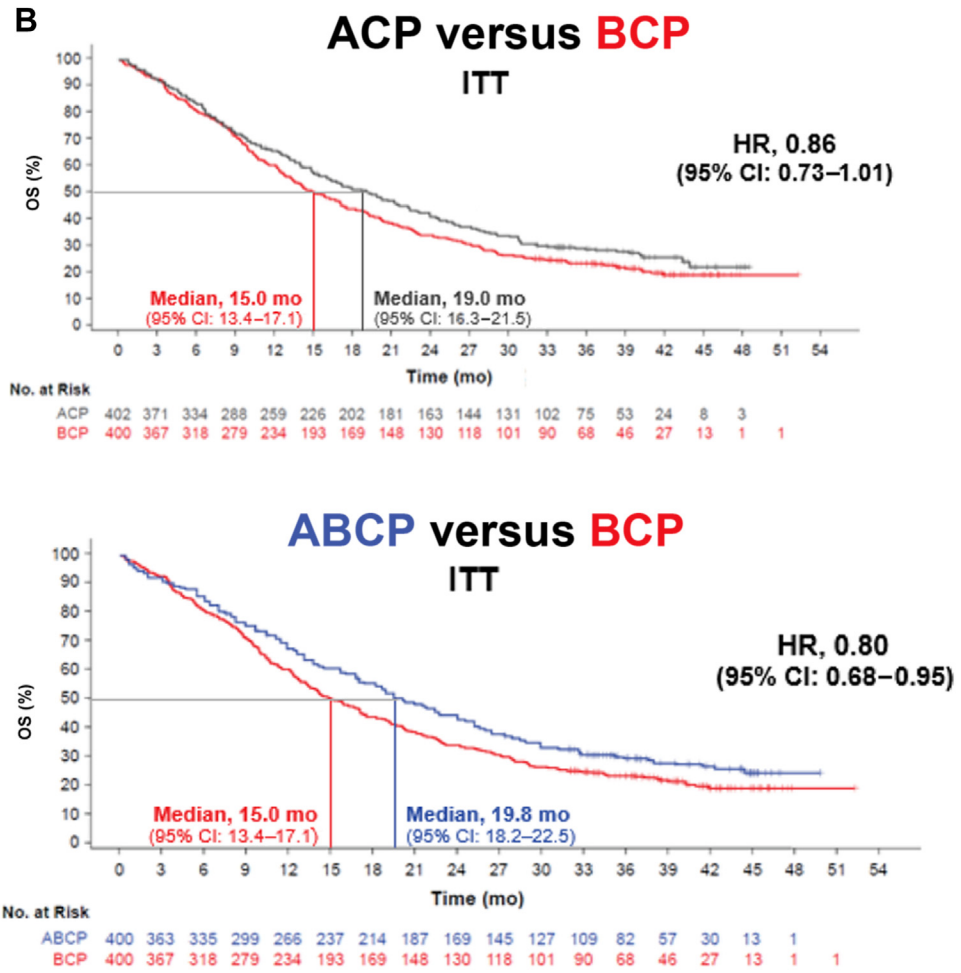


Figure 1. (*continued*).

OS was longer in the ABCP versus BCP arm in key ITT-WT and ITT subgroups, including males, patients aged less than 65 years or 65 to 74 years, white patients, patients with ECOG PS of 1, and current or previous smokers (Fig. 1*C* and *D*).

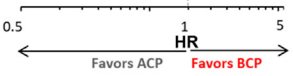
In the ITT-WT population, 49.7% of the ACP arm, 46.8% of the ABCP arm, and 63.0% of the BCP arm received subsequent nonprotocol anticancer therapy, with 8.3%, 10.3%, and 46.4%, respectively, having received subsequent nonprotocol immunotherapy (Supplementary Table 2). In the ITT population, 52.7% of the ACP arm, 47.8% of the ABCP arm, and 64.5% of the BCP arm received subsequent nonprotocol anticancer therapy, with 8.2%, 9.8%, and 42.0%, respectively, having received subsequent nonprotocol immunotherapy (Supplementary Table 3). The most often used immunotherapy agents across the study arms in the ITT-WT and ITT populations were nivolumab, pembrolizumab, and atezolizumab. At the final OS analysis in the ACP arm, PFS events had occurred in 307 (ACP), 312 (ABCP), and 325 (BCP) patients in the ITT-WT population. Median PFS in the ITT-WT population was 6.3 months in the ACP arm and 8.4 months in the ABCP arm versus 6.8 months in the BCP arm (ACP versus BCP, HR = 0.82, 95% CI: 0.70–0.97; ABCP versus BCP, HR = 0.57, 95% CI: 0.48–0.67 with ABCP versus BCP) (Supplementary Fig. 1). PFS rates at 1 and 2 years were 26% and 14% in the ACP arm and 38% and 19% in the ABCP arm versus 20% and 3% in the BCP arm, respectively, in the ITT-WT population.

Survival by PD-L1 Status

Exploratory analysis in the PD-L1 subgroups defined by SP142 revealed that among ITT-WT patients with PD-L1–high tumors (TC3 or IC3), median OS was longer in the ACP arm (median = 26.3 mo, HR = 0.76, 95% CI: 0.49–1.17) and the ABCP arm (median = 30.0 mo, HR = 0.70, 95% CI: 0.46–1.08, respectively) than in the BCP arm (median = 15.0 mo) (Figs. 2*A* and 3). Among patients in the ITT-WT population with SP142-defined

C

Subgroups	ITT-WT ACP, n (%)	ITT-WT BCP, n (%)	OS HR (95% CI)	Median OS (mo) ACP	Median OS (mo) BCP
All patients	350 (100)	338 (100)	0.84 (0.71–1.00)[a]	19.0	14.7
Sex					
Male	221 (63.1)	209 (61.8)	0.79 (0.64–0.98)	17.6	14.0
Female	129 (36.9)	129 (38.2)	0.84 (0.63–1.12)	21.0	16.7
Age group, years[b]					
< 65	195 (55.7)	185 (54.7)	0.81 (0.64–1.02)	19.4	14.3
65-74	130 (37.1)	118 (34.9)	0.85 (0.64–1.14)	17.9	15.8
75-84	24 (6.9)	33 (9.8)	0.70 (0.39–1.27)	17.8	14.1
Race					
Asian	27 (7.7)	23 (6.8)	0.84 (0.40–1.80)	43.8	28.8
Black or African American	9 (2.6)	11 (3.3)	1.06 (0.34–3.31)	19.0	17.5
White	300 (85.7)	298 (88.2)	0.83 (0.69–1.00)	17.1	14.3
Baseline ECOG					
0	156 (44.6)	143 (42.3)	0.72 (0.54–0.96)	27.0	21.6
1	194 (55.4)	192 (56.8)	0.91 (0.73–1.13)	13.0	12.3
Tobacco use history					
Never	45 (12.9)	50 (14.8)	0.76 (0.48–1.20)	21.3	18.2
Current/Previous	305 (87.1)	288 (85.2)	0.83 (0.68–1.00)	18.9	14.1
Intended cycles at induction					
4	193 (55.1)	180 (53.3)	0.80 (0.63–1.02)	20.2	14.1
6	157 (44.9)	158 (46.7)	0.83 (0.65–1.06)	16.3	15.6



Subgroups	ITT-WT ABCP, n (%)	ITT-WT BCP, n (%)	OS HR (95% CI)	Median OS (mo) ABCP	Median OS (mo) BCP
All patients	359 (100)	338 (100)	0.80 (0.67–0.95)[a]	19.5	14.7
Sex					
Male	219 (61.0)	209 (61.8)	0.72 (0.58–0.90)	19.5	14.0
Female	140 (39.0)	129 (38.2)	0.92 (0.70–1.22)	19.5	16.7
Age group, years[c]					
< 65	191 (53.2)	185 (54.7)	0.83 (0.65–1.04)	18.9	14.3
65-74	133 (37.0)	118 (34.9)	0.72 (0.54–0.97)	22.9	15.8
75-84	32 (8.9)	33 (9.8)	0.97 (0.58–1.62)	16.7	14.1
Race					
Asian	43 (12.0)	23 (6.8)	1.18 (0.61–2.28)	24.1	28.8
Black or African American	3 (0.8)	11 (3.3)	0.60 (0.07–5.00)	NE	17.5
White	296 (82.5)	298 (88.2)	0.79 (0.65–0.94)	18.9	14.3
Baseline ECOG					
0	140 (39.0)	143 (42.3)	0.81 (0.61–1.08)	24.7	21.6
1	216 (60.2)	192 (56.8)	0.78 (0.63–0.97)	15.3	12.3
Tobacco use history					
Never	59 (16.4)	50 (14.8)	0.75 (0.49–1.14)	22.3	18.2
Current/Previous	300 (83.6)	288 (85.2)	0.81 (0.67–0.98)	18.9	14.1
Intended cycles at induction					
4	188 (52.4)	180 (53.3)	0.86 (0.68–1.09)	20.9	14.1
6	171 (47.6)	158 (46.7)	0.74 (0.58–0.95)	18.6	15.6

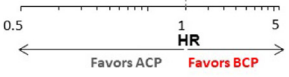
Figure 1. (*continued*).

PD-L1–positive tumors (TC1/2/3 or IC1/2/3), median OS was longer in the ACP arm (24.4 mo, HR = 0.71, 95% CI: 0.55–0.91) and the ABCP arm (22.5 mo, HR = 0.73, 95% CI: 0.57–0.94) than in the BCP arm (16.0 mo) (Figs. 2*B* and 3). Among patients in the ITT-WT population with SP142-defined PD-L1–negative tumors (TC0

D

ITT

Subgroups	ACP, n (%)	BCP, n (%)	OS HR (95% CI)	Median OS (mo) ACP	Median OS (mo) BCP
All patients	402 (100)	400 (100)	0.86 (0.73–1.01)[a]	19.0	15.0
Sex					
Male	241 (60.0)	239 (59.8)	0.82 (0.67–1.01)	17.7	14.1
Female	161 (40.0)	161 (40.3)	0.88 (0.68–1.13)	21.2	17.1
Age group, years[b]					
< 65	223 (55.5)	226 (56.5)	0.79 (0.64–0.98)	19.7	14.1
65-74	152 (37.8)	132 (33.0)	0.93 (0.71–1.22)	17.7	15.9
75-84	26 (6.5)	39 (9.8)	0.82 (0.47–1.42)	17.8	14.1
Race					
Asian	48 (11.9)	46 (11.5)	0.92 (0.55–1.56)	31.4	28.8
Black or African American	9 (2.2)	12 (3.0)	1.03 (0.35–3.09)	19.0	22.3
White	331 (82.3)	335 (83.8)	0.85 (0.71–1.01)	17.0	14.2
Baseline ECOG					
0	180 (44.8)	179 (44.8)	0.80 (0.62–1.04)	27.0	23.3
1	222 (55.2)	218 (54.5)	0.87 (0.71–1.07)	13.6	12.2
Tobacco use history					
Never	77 (19.2)	77 (19.3)	0.92 (0.64–1.32)	20.7	18.9
Current/Previous	325 (80.8)	323 (80.8)	0.83 (0.69–0.99)	19.0	14.1
Intended cycles at induction					
4	224 (55.7)	217 (54.3)	0.82 (0.66–1.03)	19.5	14.4
6	178 (44.3)	183 (45.8)	0.86 (0.68–1.09)	17.0	15.6



ITT

Subgroups	ABCP, n (%)	BCP, n (%)	OS HR (95% CI)	Median OS (mo) ABCP	Median OS (mo) BCP
All patients	400 (100)	400 (100)	0.80 (0.68–0.95)[a]	19.8	15.0
Sex					
Male	240 (60.0)	239 (59.8)	0.76 (0.62–0.94)	19.2	14.1
Female	160 (40.0)	161 (40.3)	0.86 (0.67–1.11)	21.0	17.1
Age group, years[c]					
< 65	215 (53.8)	226 (56.5)	0.79 (0.64–0.99)	19.5	14.1
65-74	149 (37.3)	132 (33.0)	0.76 (0.57–1.00)	22.9	15.9
75-84	33 (8.3)	39 (9.8)	1.10 (0.67–1.82)	16.6	14.1
Race					
Asian	56 (14.0)	46 (11.5)	1.03 (0.63–1.70)	25.0	28.8
Black or African American	3 (0.8)	12 (3.0)	0.54 (0.07–4.44)	NE	22.3
White	322 (80.5)	335 (83.8)	0.79 (0.66–0.94)	19.1	14.2
Baseline ECOG					
0	159 (39.8)	179 (44.8)	0.85 (0.65–1.11)	25.2	23.3
1	238 (59.5)	218 (54.5)	0.74 (0.60–0.91)	15.8	12.2
Tobacco use history					
Never	82 (20.5)	77 (19.3)	0.75 (0.52–1.07)	23.8	18.9
Current/Previous	318 (79.5)	323 (80.8)	0.82 (0.69–0.98)	18.9	14.1
Intended cycles at induction					
4	214 (53.5)	217 (54.3)	0.83 (0.66–1.03)	22.6	14.4
6	186 (46.5)	183 (45.8)	0.78 (0.62–0.99)	18.2	15.6

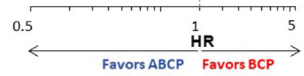


Figure 1. (*continued*).

and IC0), median OS was similar in the ACP arm versus the BCP arm (median = 14.8 mo versus 14.1 mo, HR = 0.96, 95% CI: 0.76–1.22), and limited OS improvement was found in the ABCP arm versus the BCP arm (median = 16.9 mo versus 14.1 mo, HR = 0.90, 95% CI: 0.71–1.14) (Figs. 2*C* and 3). PFS trends were similar to those observed for OS across SP142-defined PD-L1 subgroups (Supplementary Fig. 1).

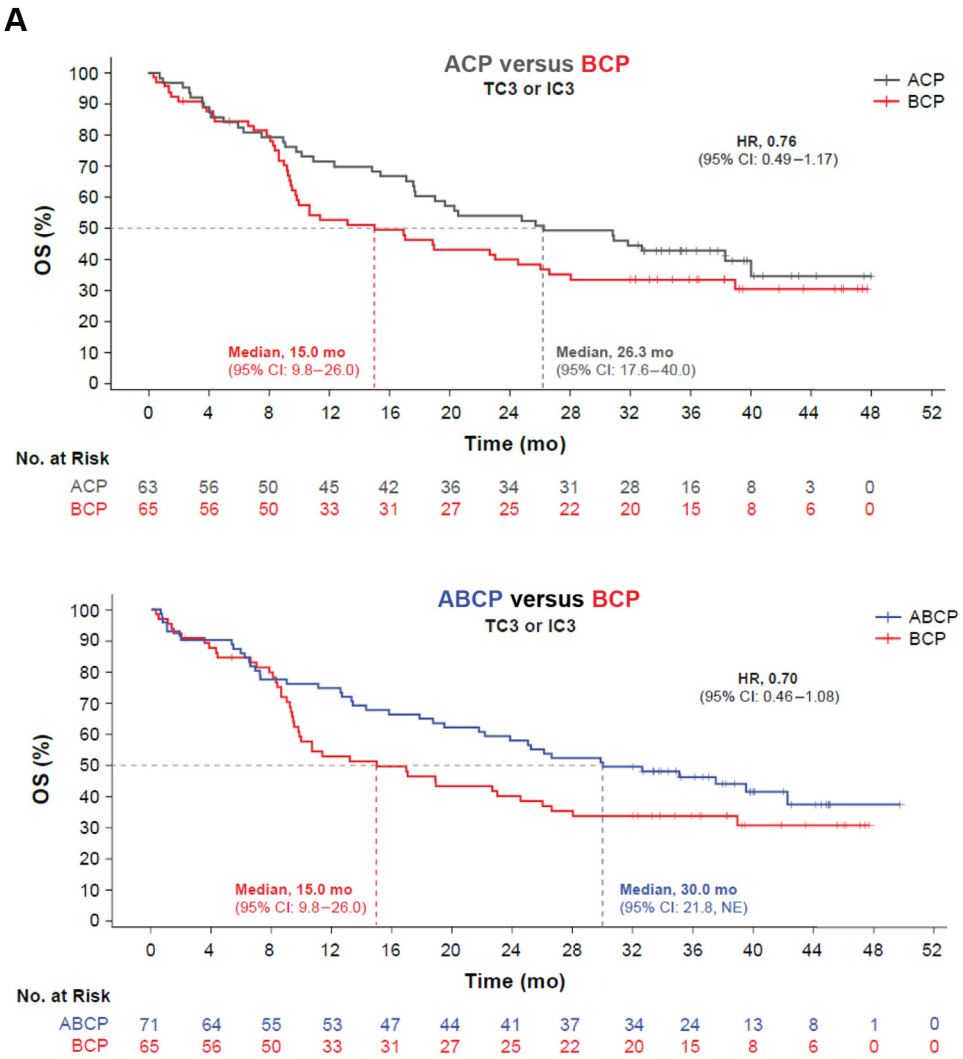


Figure 2. Survival outcomes in SP142 PD-L1 subgroups within the ITT-WT population. Kaplan-Meier analyses of overall survival with ACP or ABCP versus BCP according to SP142-defined PD-L1 status in the ITT-WT population: (*A*) PD-L1 high as greater than or equal to 50% TC or greater than or equal to 10% IC (TC3 or IC3). (*B*) PD-L1 positive as greater than or equal to 1% TC or IC (TC1/2/3 or IC1/2/3). (*C*) PD-L1 negative as less than 1% TC and IC (TC0 and IC0). ABCP, atezolizumab-bevacizumab-carboplatin-paclitaxel; ACP, atezolizumab-carboplatin-paclitaxel; BCP, bevacizumab-carboplatin-paclitaxel; CI, confidence interval; HR, hazard ratio; IC, tumor-infiltrating immune cells; ITT, intention to treat; NE, not evaluable; PD-L1, programmed death-ligand 1; TC, tumor cells; WT, wild-type.

Within the SP263 BEP-WT population, the prevalence rates of patients with SP142-defined PD-L1–positive tumors (TC1/2/3 or IC1/2/3) were 54.8% in the ACP arm, 54.4% in the ABCP arm, and 51.9% in the BCP arm, whereas 58.5% in the ACP arm, 55.1% in the ABCP arm, and 50.6% in the BCP arm had PD-L1–positive tumors by the SP263 assay (TC $\geq$1%). Results for the SP142-defined PD-L1 subgroups within the SP263 BEP-WT population are provided in Figure 3 and Supplementary Figure 2 to illustrate general consistency with the SP263-defined subgroups. OS benefits were found in SP263-defined PD-L1–positive (TC $\geq$1%) subgroups within the SP263 BEP-WT population in the ACP arm (HR = 0.66, 95% CI: 0.50–0.87; Fig. 3*A*) and ABCP arm (HR = 0.69, 95% CI: 0.52–0.91; Fig. 3*B*) compared with the BCP arm. Within the SP263 BEP-WT population, median OS was longer in the ACP arm versus the BCP arm in PD-L1–high subgroups as assessed by the SP263 assay (TC $\geq$50%: 23.3 versus 11.2 mo, HR = 0.59, 95% CI: 0.39–0.90). OS improvements were also found in the ABCP arm versus the BCP arm in the SP263-defined PD-L1–high (TC $\geq$50%) subgroup within the SP263 BEP-WT population (median OS = 21.8 versus 11.2 mo, HR = 0.62, 95% CI: 0.40–0.94). In the PD-L1–negative subgroups within the SP263 BEP-WT population, median OS in the ACP, ABCP, and BCP arms was 15.4 months in the ACP arm, 18.6 months in the ABCP arm, and 14.0 months in the BCP arm when defined by SP263; limited benefits were found with ACP and ABCP versus the BCP (SP142 TC0 and IC0: ACP versus BCP, HR = 0.87, 95% CI: 0.66–

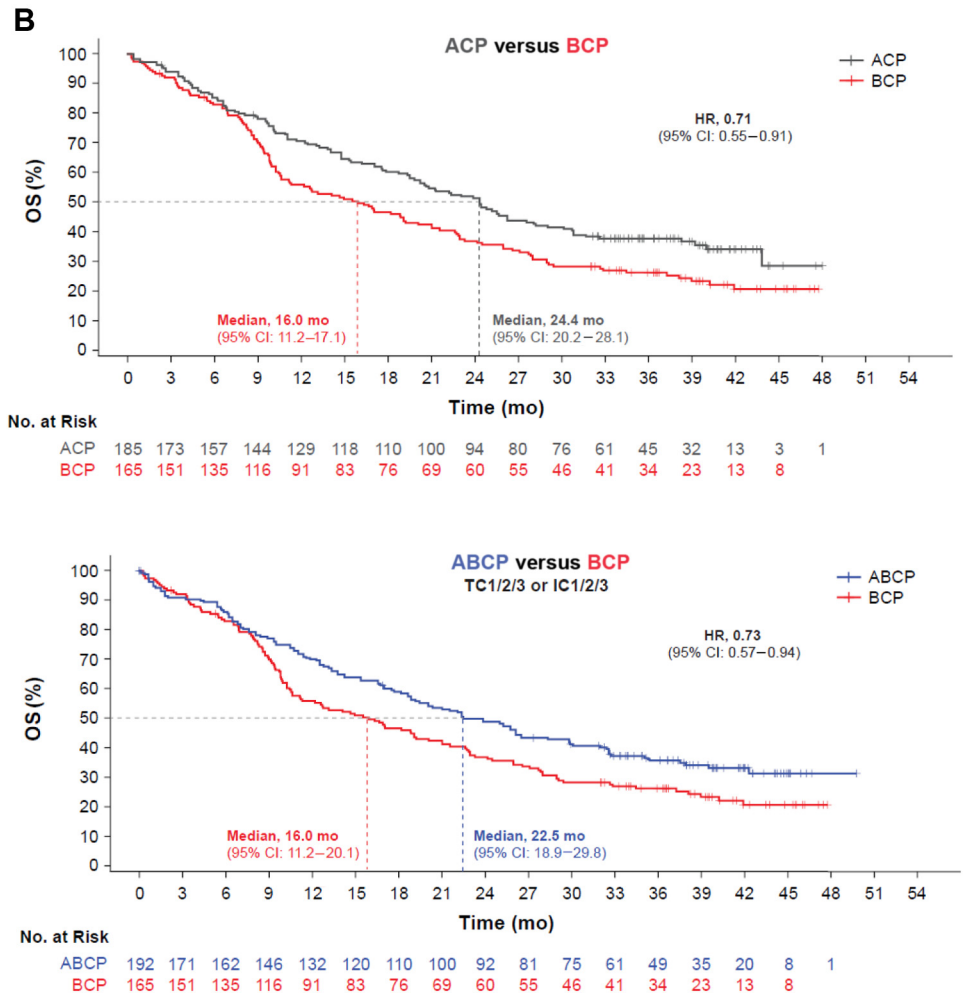


Figure 2. (*continued*).

1.16 and ABCP versus BCP, HR = 0.81, 95% CI: 0.61–1.07; SP263 TC <1%: ACP versus BCP, HR = 0.90, 95% CI: 0.68–1.19 and ABCP versus BCP, HR = 0.82, 95% CI: 0.62–1.08). Trends in PFS similar to those in OS were found with ACP and ABCP compared with BCP across PD-L1 subgroups defined by SP142 or SP263 in the SP263 BEP-WT population (Supplementary Fig. 1).

Interassay Concordance Analyses

Concordance analysis between the SP142 and SP263 assays found that there were overlapping and unique populations identified at each corresponding cutoff. Within the PD-L1–positive subgroups, 76% (317 of 416) of SP142-defined patients (TC1/2/3 or IC1/2/3) were also positive (TC ≥1%) by the SP263 assay (Fig. 4*A*). Conversely, within SP263-defined patients (TC ≥1%), 75% (317 of 425) of patients were also positive (TC1/2/3 or IC1/2/3) by the SP142 assay. Within the PD-L1–high subgroups, 76% (114 of 150) of SP142-defined patients (TC3 or IC3) were also PD-L1 high (TC ≥50%) by the SP263 assay (Fig. 4*B*). Conversely, within the SP263-defined high subgroup (TC ≥50%), 59% (114 of 194) of patients were also high (TC3 or IC3) by the SP142 assay.

Safety

At data cutoff, 1187 ITT patients received treatment (ACP, 400 patients; ABCP, 393; BCP, 394) and were included in the safety evaluation (Table 2).

The mean and median duration of carboplatin were similar across the three arms respectively: 2.3 and 2.1 months in the ACP arm, 2.4 and 2.2 months in the ABCP arm, and 2.4 and 2.2 months in the BCP arm. Overall, 94.3%, 94.1%, and 95.9% of patients in the ACP, ABCP, and BCP arms, respectively, experienced a treatment-related AE. Of these patients, 43.0% (172 of 400 patients) in the ACP arm, 57.3% (225 of 393) in the ABCP arm, and 49.0% (193 of 394) in the BCP arm were reported as having a grade 3/4 event. Treatment-related grade 5 AEs occurred in four patients (1.0%) who

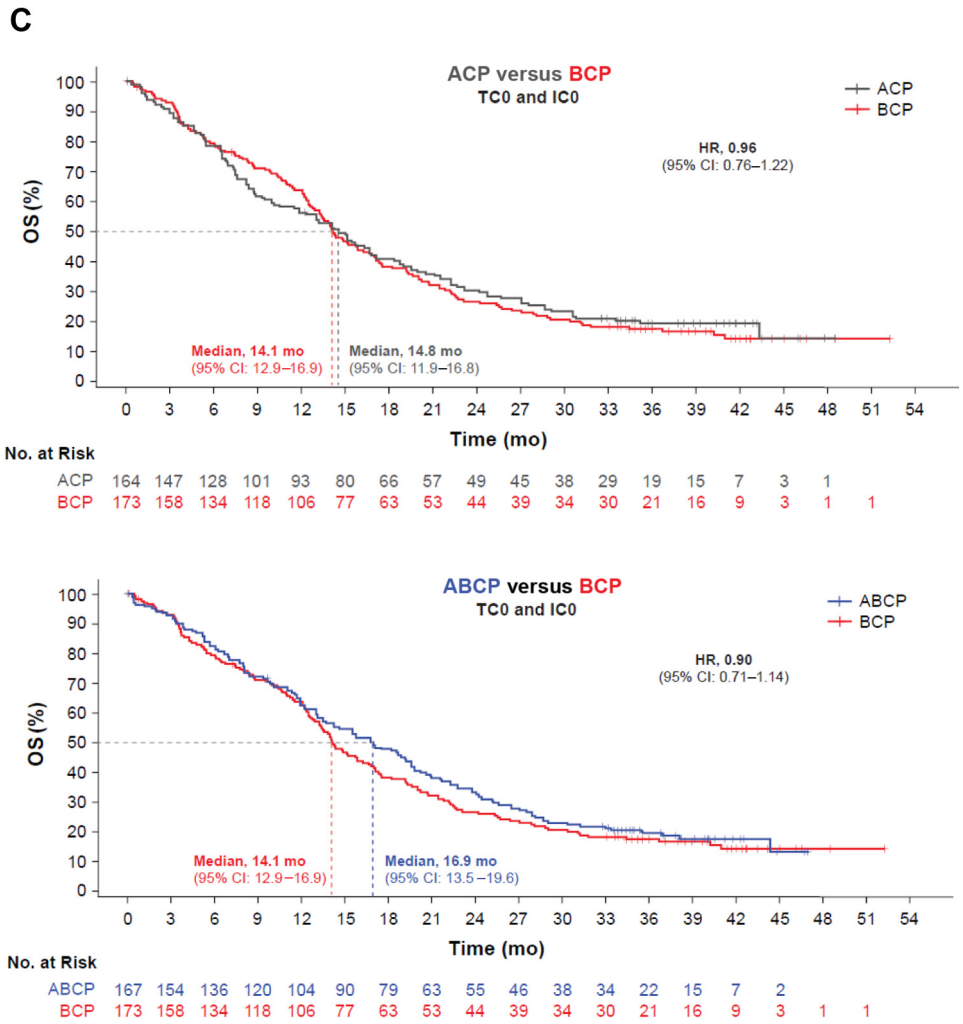


Figure 2. (*continued*).

received ACP, 12 patients (3.1%) who received ABCP, and 10 patients (2.5%) who received BCP.

AEs led to withdrawal of study treatment in 14.5% of the ACP arm, 41.2% of the ABCP arm, and 26.4% of the BCP arm.

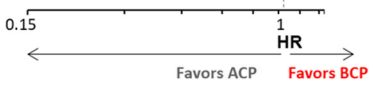
Discussion

IMpower150 met its coprimary PFS and OS end points and revealed significant improvement in survival with ABCP versus BCP in patients with chemotherapy-naive NSCLC.[12,13] In this final IMpower150 OS analysis in the ACP arm, results revealed numerical but not statistically significant OS improvement in the ACP arm versus the BCP arm. Furthermore, updated exploratory data with an additional 20 months of follow-up have revealed continued OS improvement with ABCP versus BCP. When analyzed by PD-L1 status, OS benefit with ACP or ABCP versus BCP was observed in PD-L1–positive subgroups regardless of IHC assay used, and similar results were found in PD-L1–high subgroups with both atezolizumab-containing regimens versus BCP. In the PD-L1–negative subgroups, no difference in OS was observed with ABCP and ACP versus BCP depending on the IHC assay used.

Overall, the OS benefit with ACP versus BCP was numerically similar to that with ABCP versus BCP in the ITT-WT population, suggesting the efficacy of ACP may be similar to that of the ABCP regimen. Nevertheless, this study was not designed to formally test a comparison of ABCP versus ACP, as both experimental arms were tested versus BCP only to build on approved and widely used regimens at the time of the study design.[18] The statistical analysis plan was designed in hierarchical fashion to maximize statistical power, in that the treatment arms were tested hierarchically. The ABCP arm was tested first, followed by the ACP arm, with the rationale that if the addition of atezolizumab to BCP (ABCP) did not provide significant benefit, the substitution of atezolizumab for bevacizumab (ACP) was unlikely to reveal significant benefit over BCP.[12]

A

Subgroup	ACP, n (%)	BCP, n (%)	OS HR (95% CI)	Median OS, mo ACP	Median OS, mo BCP
ITT-WT	350 (100)	338 (100)	0.84 (0.71–1.00)[a]	19.0	14.7
SP142					
TC3 or IC3	63 (18)	65 (19)	0.76 (0.49–1.17)	26.3	15.0
TC1/2/3 or IC1/2/3	185 (53)	165 (49)	0.71 (0.55–0.91)	24.4	16.0
TC0 and IC0	164 (47)	173 (51)	0.96 (0.76–1.22)	14.8	14.1
SP263 BEP-WT	270 (100)	241 (100)	0.73 (0.6–0.89)	19.0	14.0
SP142					
TC3 or IC3	49 (18.1)	51 (21.2)	0.61 (0.37–0.99)	30.9	10.7
TC1/2/3 or IC1/2/3	148 (54.8)	125 (51.9)	0.64 (0.48–0.85)	23.1	12.3
TC0 and IC0	122 (45.2)	116 (48.1)	0.87 (0.66–1.16)	14.0	14.3
SP263					
TC ≥50%	68 (25.2)	61 (25.3)	0.59 (0.39–0.9)	23.3	11.2
TC ≥1%	158 (58.5)	122 (50.6)	0.66 (0.5–0.87)	23.1	13.5
TC <1%	112 (41.5)	119 (49.4)	0.9 (0.68–1.19)	15.4	14.0

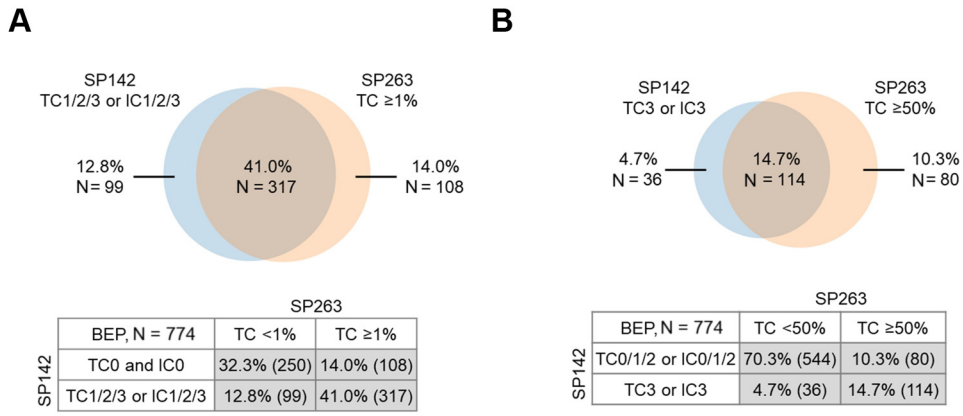


B

Subgroup	ABCP, n (%)	BCP, n (%)	OS HR (95% CI)	Median OS, mo ABCP	Median OS, mo BCP
ITT-WT	359 (100)	338 (100)	0.80 (0.67–0.95)[a]	19.5	14.7
SP142					
TC3 or IC3	71 (20)	65 (19)	0.7 (0.46–1.08)	30.0	15.0
TC1/2/3 or IC1/2/3	192 (53)	165 (49)	0.73 (0.57–0.94)	22.5	16.0
TC0 and IC0	167 (47)	173 (51)	0.9 (0.71–1.14)	16.9	14.1
SP263 BEP-WT	263 (100)	241 (100)	0.74 (0.61–0.91)	18.9	14.0
SP142					
TC3 or IC3	50 (19.0)	51 (21.2)	0.64 (0.39–1.04)	28.2	10.7
TC1/2/3 or IC1/2/3	143 (54.4)	125 (51.9)	0.69 (0.52–0.92)	20.3	12.3
TC0 and IC0	120 (45.6)	116 (48.1)	0.81 (0.61–1.07)	16.8	14.3
SP263					
TC ≥50%	65 (24.7)	61 (25.3)	0.62 (0.4–0.94)	21.8	11.2
TC ≥1%	145 (55.1)	122 (50.6)	0.69 (0.52–0.91)	18.9	13.5
TC <1%	118 (44.9)	119 (49.4)	0.82 (0.62–1.08)	18.6	14.0

Figure 3. HRs for OS in PD-L1 subgroups. Forest plots of OS in the ACP arm versus the BCP arm (*A*) and the ABCP arm versus the BCP arm (*B*) according to SP142-defined PD-L1 status in the ITT-WT population and SP142- and SP263-defined PD-L1 expression in the SP263 BEP-WT. [a]Stratified analysis. ABCP, atezolizumab-bevacizumab-carboplatin-paclitaxel; ACP, atezolizumab-carboplatin-paclitaxel; BCP, bevacizumab-carboplatin-paclitaxel; BEP, biomarker-evaluable population; CI, confidence interval; HR, hazard ratio; IC, tumor-infiltrating immune cells; ITT, intention to treat; OS, overall survival; PD-L1, programmed death-ligand 1; TC, tumor cells; WT, wild-type.

Separation of the Kaplan-Meier survival curves between the ABCP and BCP arms occurred earlier than the separation of the ACP and BCP arms. Furthermore, although both ABCP and ACP seem to provide benefit over BCP and the Kaplan-Meier survival curves qualitatively look similar, bevacizumab seems to contribute additional benefit. At the final analysis, the separation in Kaplan-Meier survival curves between the ACP arm versus the BCP arm was not sufficient to cross the boundary for significance. Landmark analyses can



SP142	SP263		
	BEP, N = 774	TC <1%	TC ≥1%
	TC0 and IC0	32.3% (250)	14.0% (108)
	TC1/2/3 or IC1/2/3	12.8% (99)	41.0% (317)

SP142	SP263		
	BEP, N = 774	TC <50%	TC ≥50%
	TC0/1/2 or IC0/1/2	70.3% (544)	10.3% (80)
	TC3 or IC3	4.7% (36)	14.7% (114)

Figure 4. Concordance between SP142 and SP263 PD-L1–defined subgroups. Venn diagrams of overlapping and unique populations for SP142 and SP263 according to (*A*) PD-L1 positive and (*B*) PD-L1 high expression status. BEP, biomarker-evaluable population; IC, tumor-infiltrating immune cells; PD-L1, programmed death-ligand 1; TC, tumor cells.

be performed to account for the possibility of a delayed clinical effect with immunotherapy[19] and have revealed long-term OS benefits with immune checkpoint inhibitors over follow-up durations of up to 5 years in patients with NSCLC.[20–22] Interestingly, the IMpower130 trial evaluating the addition of first-line atezolizumab to platinum-based chemotherapy (carboplatin/nab-paclitaxel) reported similar magnitudes of OS benefit versus chemotherapy alone within the ITT-WT population with advanced, nonsquamous NSCLC.[23] In this IMpower150 study, ACP compared with BCP revealed favorable OS benefit in the PD-L1–positive subgroups but median OS was similar between arms in the PD-L1–negative subgroups, indicating the OS benefit with ACP in the overall ITT-WT population is mainly driven by the PD-L1–positive patients.

The BCP arm in this study outperformed (median OS = 14.7 mo) other similar study populations and historic controls for nonsquamous NSCLC (e.g., KEYNOTE-189 with a median OS of 10.7 mo and CheckMate 9LA with a median OS of 11.9 mo for pemetrexed in combination with a platinum-based chemotherapy).[7,24] In both the ITT-WT and ITT populations, more patients in the BCP arm received subsequent nonprotocol therapy and immunotherapy (ITT-WT: 63.0% and 46.4%; ITT: 64.5% and 42.0%) than in the ACP arm (ITT-WT: 49.7% and 8.3%; ITT: 52.7% and 8.2%) and ABCP arm (ITT-WT: 46.8% and 10.3%; ITT: 47.8% and 9.8%). The higher incidence of subsequent nonprotocol anticancer therapy, including immunotherapy, in the BCP arm may have affected OS outcomes. Nevertheless, findings from this analysis of IMpower150 together with earlier and updated IMpower150 analyses in overall and difficult-to-treat NSCLC patient groups, such as those with *EGFR* mutations and liver metastases,[12,13] highlight the sustained benefits of the combination of bevacizumab and atezolizumab added to carboplatin-paclitaxel over BCP. However, along with these benefits, clinicians also need to consider the patient eligibility criteria and known risks of bevacizumab.[25] Nevertheless, these findings lend support to

Table 2. Overview of Safety in the Safety-Evaluable Population

AE, n (%)	ACP (n = 400)	ABCP (n = 393)	BCP (n = 394)
Total number of patients with ≥1 AE	391 (97.8)	386 (98.2)	390 (99.0)
Treatment-related AE	377 (94.3)	370 (94.1)	378 (95.9)
Grade 3/4 AE	241 (60.3)	255 (64.9)	234 (59.4)
Treatment-related grade 3/4 AE	172 (43.0)	225 (57.3)	193 (49.0)
Grade 5 AE	11 (2.8)	26 (6.6)	22 (5.6)
Treatment-related grade 5 AE	4 (1.0)	12 (3.1)	10 (2.5)
Serious AE	169 (42.3)	187 (47.6)	142 (36.0)
Treatment-related serious AE	81 (20.3)	105 (26.7)	80 (20.3)
AE of special interest	195 (48.8)	219 (55.7)	112 (28.4)
Treatment-related AE of special interest	158 (39.5)	189 (48.1)	70 (17.8)
AE leading to withdrawal from any treatment	58 (14.5)	162 (41.2)	104 (26.4)
AE leading to dose modification/interruption	209 (52.3)	256 (65.1)	190 (48.2)

ABCP, atezolizumab-bevacizumab-carboplatin-paclitaxel; ACP, atezolizumab-carboplatin-paclitaxel; AE, adverse event; BCP, bevacizumab-carboplatin-paclitaxel.

an underlying synergistic action of the atezolizumab and bevacizumab with chemotherapy combination in the tumor microenvironment, in which reversal of VEGF-mediated immunosuppression by bevacizumab and chemotherapy-induced cell death potentiate T-cell–mediated killing by atezolizumab.[10,11] However, the specific actions of atezolizumab and bevacizumab within the ABCP regimen require further investigation.

OS benefits found in PD-L1–positive subgroups from this unselected NSCLC population align with findings with first-line monotherapy in PD-L1–high tumors. In multiple clinical trials of patients with NSCLC who received first-line monotherapy with PD-L1/PD-1 checkpoint inhibitors, high PD-L1 expression was a predictor of beneficial effects of treatment.[4,5,26] Furthermore, the benefit of PD-L1/PD-1 checkpoint inhibitors in combination with chemotherapy versus chemotherapy alone as first-line treatment for patients with NSCLC with no *EGFR* or *ALK* genetic alterations, independent of PD-L1 status, has been found in phase 3 clinical trials and subsequently approved by the U.S. Food and Drug Administration and European Medicines Agency. In addition to the results in IMpower150,[12] the IMpower130 trial of atezolizumab in combination with chemotherapy (nab-paclitaxel and carboplatin) and the KEYNOTE-189 trial of pemetrexed in combination with a platinum-based drug plus either pembrolizumab or placebo revealed that the combination of checkpoint inhibitor and chemotherapy conferred OS benefits in unselected NSCLC populations and across PD-L1 subgroups versus chemotherapy.[23,27] OS findings in the PD-L1–negative subgroup observed at this analysis of IMpower150 differ from those found in IMpower130 or KEYNOTE-189[23,27]; the underlying factors contributing to the disparate OS data in this patient subgroup across the studies are unknown but could include differences in sample size, PD-L1 expression, and treatment regimens, as the control arm of IMpower150 contained an additional active agent (bevacizumab).

Interassay comparisons revealed overlapping and uniquely positive patient populations between SP142 and SP263. Variations in assay sensitivities and scoring algorithms between these assays have been found to translate to the analytical differences reported in the Blueprint PD-L1 IHC Assay Comparison Project.[28,29] Nevertheless, both assays seem to predict similar OS and PFS clinical sensitivity to atezolizumab across corresponding PD-L1 subgroups in this study, despite identifying modestly different patient populations.

New safety signals were not identified in this analysis. In addition, safety profiles of the treatment regimens were consistent with the safety data reported at the second interim OS analysis[13] and with current knowledge of the individual medicines. Of note, the occurrence of AEs leading to any treatment withdrawal was substantially lower in the ACP arm versus the BCP arm.

Formal statistical tests were not performed in biomarker subgroups owing to the small sample populations for some subgroups, the SP263-BEP sample size compared with the ITT-WT population, and the exploratory nature of the analyses. These factors should be taken into consideration when interpreting the findings from this subanalysis.

This report confirms and extends earlier analyses supporting ABCP as an efficacious first-line treatment option in patients with metastatic nonsquamous NSCLC on the basis of its strong OS benefit versus BCP, which led to its regulatory approval and inclusion as a standard-of-care in the guidelines of the National Comprehensive Network and the European Society of Medical Oncology.[2,14,15,30] Although ACP had only a numerical improvement in OS compared with BCP, both atezolizumab-containing regimens indicated an OS benefit in PD-L1–positive populations.

CRediT Authorship Contribution Statement

Mark A. Socinski, Robert M. Jotte, Shengchun Kong, Mark McCleland, Martin Reck, Geetha Shankar: Conception and design.

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Shengchun Kong, Wei Zou: Software.

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Data Sharing

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology at* www.jto.org and at https://doi.org/10.1016/j.jtho.2021.07.009.

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