ORIGINAL ARTICLE

IMpower150 Final Exploratory Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in Key NSCLC Patient Subgroups With *EGFR* Mutations or Metastases in the Liver or Brain

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ABSTRACT

Introduction: Final overall survival (OS) analyses are presented for *EGFR* mutations and liver or brain metastases subgroups in the phase 3 IMpower150 study (NCT02366143) evaluating atezolizumab plus bevacizumab plus carboplatin and paclitaxel (ABCP) or atezolizumab plus carboplatin and paclitaxel (ACP) versus bevacizumab plus carboplatin and paclitaxel (BCP).

Methods: Overall, 1202 patients (intention-to-treat population) with chemotherapy-naive, metastatic, nonsquamous NSCLC were randomized to ABCP, ACP, or BCP. Patients with treated, stable brain metastases were permitted. OS was evaluated in *EGFR* mutations and baseline liver metastases subgroups; rate and time to development of new brain metastases were evaluated in the intention-to-treat patients.

Results: At data cutoff (September 13, 2019; median follow-up, 39.3 mo), OS improvements were sustained with ABCP versus BCP in sensitizing *EGFR* mutations (all: hazard ratio [HR] = 0.60; 95% confidence interval [CI]: 0.31–1.14; previous tyrosine kinase inhibitor [TKI]: HR = 0.74; 95% CI: 0.38–1.46) and baseline liver metastases (HR = 0.68; 95% CI: 0.45–1.02) subgroups. ACP did not have survival benefit versus BCP in sensitizing *EGFR* mutations (all: HR = 1.0; 95% CI: 0.57–1.74; previous TKI: HR = 1.22; 95% CI: 0.68–2.22) or liver metastases (HR = 1.01; 95% CI: 0.68–1.51) subgroups. Overall, 100 patients (8.3%) developed new brain metastases. Although not formally evaluated, an improvement toward delayed time to development was found with ABCP versus BCP (HR = 0.68; 95% CI: 0.39–1.19).

Conclusions: This final exploratory analysis revealed OS benefits for ABCP versus BCP in patients with sensitizing *EGFR* mutations, including those with previous TKI failures, and with liver metastases, although these results should be interpreted with caution. The impact of ABCP on delaying the development of new brain lesions requires further investigation.

Keywords: Nonsquamous NSCLC; Atezolizumab; Bevacizumab; IMpower150; *EGFR* mutation

Introduction

Advances in first-line treatment options, such as the inclusion of immune checkpoint inhibitors (anti–programmed death-ligand 1 [PD-L1]/programmed death-1 [PD-1]), have improved the clinical outcomes of patients with metastatic nonsquamous NSCLC.[1] The anti–PD-L1 antibody atezolizumab restores tumor-specific immunity by blocking PD-L1 from binding to its PD-1 and B7.1 receptors.[2,3] Atezolizumab, as monotherapy and in combination with chemotherapy, was found to have efficacy in patients with NSCLC.[4–8] The recombinant humanized vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab was found to substantially improve overall survival (OS) when combined with chemotherapy versus chemotherapy alone in patients with advanced NSCLC.[9] It has

been proposed that bevacizumab plus chemotherapy enhances the T-cell–mediated cancer-cell killing action of atezolizumab by reversing VEGF-mediated immunosuppression and chemotherapy-induced cell death.[10,11] The global phase 3 IMpower150 study evaluated atezolizumab plus bevacizumab plus carboplatin and paclitaxel (ABCP) chemotherapy and revealed significant and clinically meaningful improvements in progression-free survival ($p < 0.001$) and OS ($p = 0.02$) versus bevacizumab plus carboplatin and paclitaxel (BCP) in the intention-to-treat (ITT) wild-type (WT) population with chemotherapy-naive metastatic nonsquamous NSCLC without *EGFR/ALK* genetic alterations.[12] Furthermore, study results revealed greater survival in the ABCP versus BCP arm irrespective of PD-L1 expression and *EGFR/ALK* status.[12]

Despite treatment advances in metastatic NSCLC, patients with sensitizing *EGFR* mutations inevitably fail treatment with first-line standard-of-care tyrosine kinase inhibitors (TKIs).[1,13,14] Although immune checkpoint inhibitor (anti–PD-L1/PD-1) monotherapy was found to have no superior survival versus chemotherapy in patients with previously treated *EGFR*-mutant NSCLC, PD-L1/PD-1 inhibitors are a recommended second-line option post-TKI failure.[15,16] Prognosis can also be poor among patients who develop liver or brain metastases[17,18]: 13% to 22% or 46% to 57% of NSCLC cases, respectively.[19–22] Therefore, definitive treatment options are needed to improve outcomes among these difficult-to-treat patient subgroups with NSCLC. Patients who develop liver metastases have been found to have poorer outcomes than those with metastases to other sites,[23] and monoimmunotherapies and chemotherapies have mostly been ineffective in these patients.[24–26] In a previous study, patients with baseline liver metastases were found to have improved OS with bevacizumab plus carboplatin and paclitaxel.[9] Therefore, we hypothesized that the poor treatment outcomes with immunotherapy in patients with liver metastases could be attributed to tissue-specific immunoregulation, which might be reversed by combination treatment with bevacizumab.

In subgroup analyses from the IMpower150 study, OS benefits were found for ABCP versus BCP in patients with sensitizing *EGFR* mutations and baseline liver metastases.[27] The sustained benefit of immunotherapy is debatable in such subgroups because of the lack of randomized studies, particularly those reporting long-term data. Therefore, we present final exploratory OS data with an additional approximately 20 months of follow-up (for a total median follow-up of 39.3 mo at the data cutoff [September 13, 2019]) for the ABCP, atezolizumab plus carboplatin and paclitaxel (ACP) chemotherapy, and BCP arms in key *EGFR* mutation and liver metastases subgroups from the IMpower150 trial. Bevacizumab was previously found to delay or prevent progression of brain metastases in NSCLC.[28,29] Therefore, we also present results from exploratory post hoc analyses evaluating the rate and time to development of new lesions in the brain in the ABCP or ACP arm versus the BCP arm, regardless of the presence of brain metastases at baseline.

Materials and Methods

Study Design and Patients

IMpower150 was an international, open-label, randomized, phase 3 trial conducted across 240 study centers in 26 countries (NCT02366143).[12,27] The study was performed in line with Good Clinical Practice guidelines and the Declaration of Helsinki, and the study protocol was approved by independent ethics committees at each site.

Chemotherapy-naive patients with stage IV metastatic nonsquamous NSCLC, measurable disease at baseline per Response Evaluation Criteria in Solid Tumors version 1.1,[30] a baseline Eastern Cooperative Oncology Group performance status of 0 or 1, available tumor tissue for biomarker testing, and any PD-L1 immunohistochemistry status were eligible for inclusion. Patients with sensitizing *EGFR* mutations (exon 19 deletion and Leu858Arg mutations) or *ALK* translocations were required to have disease progression or treatment intolerance with at least one approved TKI therapy. In cases in which patients with sensitizing *EGFR* mutations did not receive an approved TKI therapy (13 of 91 patients [14%]), this was noted within the study. All patients underwent a computed tomography or magnetic resonance imaging scan of the head at screening for study eligibility determination. Untreated brain metastases led to study exclusion. Detailed information on patient eligibility criteria and study design methods was previously published.[12,27] All patients provided informed written consent.

Treatment

Patients were randomized to ACP, ABCP, or BCP and stratified according to sex, baseline liver metastases, and PD-L1 expression on tumor cells (TC) and tumor-infiltrating immune cells (IC; evaluated by the VENTANA SP142 immunohistochemistry assay [Ventana Medical Systems, Inc., Tucson, AZ]). PD-L1 expression on SP142-stained TC and IC was based on the percentage of PD-L1–expressing TC of any intensity or the proportion of tumor area occupied by PD-L1–expressing IC of any intensity.[31] PD-L1 expression status was defined as follows: (1) PD-L1 low: greater than or equal to 1% of TC and IC and less than 50% of TC or less than 10% of IC (TC1/2 or IC1/2); (2) PD-L1 high: greater than or equal to 50% TC or greater than or equal to 10% of IC (TC3 or

Table 1. Baseline Demographic and Clinical Characteristics by Key Patient Subgroups

Characteristics	ABCP	ACP	BCP
Patients with *EGFR* mutations			
N	34	45	44
Median age (range), y	64.0 (37-76)	63.0 (38-82)	61.5 (31-81)
Sex, n (%)			
Male	18 (52.9)	17 (37.8)	20 (45.5)
Female	16 (47.1)	28 (62.2)	24 (54.5)
Race, n (%)			
Asian	12 (35.3)	20 (44.4)	18 (40.9)
Black or African American	0	0	1 (2.3)
White	21 (61.8)	25 (55.6)	24 (54.5)
Unknown	1 (2.9)	0	1 (2.3)
ECOG PS, n (%)			
0	18 (52.9)	20 (44.4)	27 (61.4)
1	16 (47.1)	25 (55.6)	17 (38.6)
Tobacco use history, n (%)			
Never	20 (58.8)	29 (64.4)	20 (45.5)
Previous	8 (23.5)	12 (26.7)	20 (45.5)
Current	6 (17.6)	4 (8.9)	4 (9.1)
Liver metastases at enrollment, n (%)	4 (11.8)	9 (20.0)	7 (15.9)
Positive *EML4-ALK* rearrangement status, n (%)	1 (2.9)	0	0
Positive *KRAS* mutation status, n (%)	1 (2.9)	1 (2.2)	2 (4.5)
PD-L1 expression, n (%)[a]			
TC3 or IC3	4 (11.8)	4 (8.9)	5 (11.4)
TC1/2 or IC1/2	10 (29.4)	18 (40.0)	11 (25.0)
TC0 and IC0	20 (58.8)	23 (51.1)	28 (63.6)
Patients with baseline liver metastases			
N	52	52	57
Median age (range), y	64.5 (39-79)	59.0 (41-81)	63.0 (48-83)
Sex, n (%)			
Male	26 (50.0)	28 (53.8)	35 (61.4)
Female	26 (50.0)	24 (46.2)	22 (38.6)
Race, n (%)			
Asian	1 (1.9)	2 (3.8)	1 (1.8)
Black or African American	1 (1.9)	1 (1.9)	1 (1.8)
American Indian or Alaskan Native	1 (1.9)	0	0
White	46 (88.5)	48 (92.3)	54 (94.7)
Unknown	3 (5.8)	1 (1.9)	1 (1.8)
ECOG PS, n (%)			
0	16 (30.8)	22 (42.3)	22 (39.3)
1	36 (69.2)	30 (57.7)	34 (60.7)
Positive *EGFR* mutation status, n (%)	4 (7.7)	9 (17.3)	7 (12.3)
Positive *EML4-ALK* rearrangement status, n (%)	1 (1.9)	2 (3.8)	3 (5.3)
Positive *KRAS* mutation status, n (%)	8 (15.4)	4 (7.7)	6 (10.5)
PD-L1 expression, n (%)[a]			
TC3 or IC3	5 (9.6)	5 (9.6)	9 (15.8)
TC1/2 or IC1/2	17 (32.7)	20 (38.5)	18 (31.6)
TC0 and IC0	30 (57.7)	27 (51.9)	30 (52.6)
Patients with new metastases in the brain			
N	28	48	24
Median age (range), y	62.0 (47-77)	64.5 (32-79)	57.5 (43-81)
Sex, n (%)			
Male	16 (57.1)	25 (52.1)	13 (54.2)
Female	12 (42.9)	23 (47.9)	11 (45.8)
Race, n (%)			
Asian	8 (28.6)	9 (18.8)	5 (20.8)
White	19 (67.9)	38 (79.2)	19 (79.2)
Unknown	1 (3.6)	1 (2.1)	0

(continued)

Table 1. Continued

Characteristics	ABCP	ACP	BCP
ECOG PS, n (%)			
0	11 (39.3)	21 (43.8)	11 (45.8)
1	17 (60.7)	27 (56.3)	13 (54.2)
Tobacco use history, n (%)			
Never	7 (25.0)	10 (20.8)	7 (29.2)
Previous	15 (53.6)	29 (60.4)	12 (50.0)
Current	6 (21.4)	9 (18.8)	5 (20.8)
Liver metastases at enrollment, n (%)	6 (21.4)	6 (12.5)	5 (20.8)
Positive *EGFR* mutation status, n (%)	5 (17.9)	7 (14.6)	5 (20.8)
Positive *EML4-ALK* rearrangement status, n (%)	1 (3.6)	1 (2.1)	0
Positive *KRAS* mutation status, n (%)	3 (10.7)	7 (14.6)	5 (20.8)
PD-L1 expression, n (%)			
TC3 or IC3	2 (7.1)	9 (18.8)	5 (20.8)
TC1/2 or IC1/2	8 (28.6)	21 (43.8)	6 (25.0)
TC0 and IC0	18 (64.3)	18 (37.5)	13 (54.2)

***Note*:** A total of 123 patients had *EGFR*-mutated disease, including 91 whose tumors had a sensitizing mutation.
[a]Per testing with the SP142 PD-L1 assay. TC3 or IC3 equal to TC greater than or equal to 50% or IC greater than or equal to 10%; TC1/2 or IC1/2 equal to TC or IC greater than or equal to 1% and TC less than 50% or IC less than 10%; TC0 and IC0 equal to TC and IC less than 1%.
ABCP, atezolizumab plus bevacizumab plus carboplatin and paclitaxel; ACP, atezolizumab plus carboplatin and paclitaxel; BCP, bevacizumab plus carboplatin and paclitaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, tumor-infiltrating immune cell; PD-L1, programmed death-ligand 1; TC, tumor cell.

IC3); and (3) PD-L1 negative: less than 1% of TC and IC (TC0 and IC0).

Patients received induction chemotherapy for four or six cycles every 21 days, with cycle number determined by the investigator before randomization. Study treatments were administered intravenously on day 1 of each 21-day cycle at the following doses: atezolizumab 1200 mg, bevacizumab 15 mg/kg of body weight, area under the concentration–time curve of 6 mg/mL per min carboplatin, and 200 mg/m^2 paclitaxel (patients of Asian ethnicity were given 175 mg/m^2). Patients continued atezolizumab, bevacizumab, or both treatments until unmanageable toxicity or disease progression (per Response Evaluation Criteria in Solid Tumors version 1.1[30]). Atezolizumab continuation was permitted after disease progression if eligibility criteria were met, including clinical benefit as assessed by the investigator. Crossover to atezolizumab was not allowed.

Outcomes

Results from the primary analysis of the co-primary end points of progression-free survival and OS were previously reported in the ABCP versus BCP arm in the ITT-WT population (excluding patients with *EGFR* or *ALK* genomic alterations) and among key patient subgroups in the ITT population.[12,27] Final OS was analyzed for all treatment arms in the following ITT patient subgroups: *EGFR* mutations, sensitizing *EGFR* mutations (in the overall subgroup and in patients receiving TKI therapy previously), and baseline liver metastases. Additional exploratory end points were the rate and time to development of new brain metastases in the ITT population, regardless of the presence of baseline treated and stable brain metastases.[32] Brain scans (computed tomography or magnetic resonance imaging, with or without contrast) were performed as clinically indicated, with analyses of new lesion development on the basis of investigator assessments.

The incidence, severity, and nature of adverse events (AEs) in the safety-assessable population and key patient subgroups were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Statistical Analysis

The statistical analysis plan was reported previously.[12,27] OS was defined as the time from randomization to death from any cause. Data for patients who were not reported as having died at the time of analysis were censored at the date last known to be alive. Data for patients who did not have postbaseline information were censored at the date of randomization plus one day. Analyses of the rate and time to development of new brain metastases were post hoc analyses. Time to development of new brain metastases was defined as the time from randomization to the time of observed newly developed brain lesions in brain scans. Median OS and time to development of new brain metastases in ITT patients were estimated from survival curves generated by the Kaplan-Meier method; corresponding 95% confidence intervals (CIs) were derived using the Brookmeyer-Crowley method. Hazard ratios (HRs) comparing the treatment effect between two treatment arms were calculated from unstratified Cox regression models, and 95% CIs were provided.

Safety results are presented descriptively. Statistical tests were conducted with SAS version 9.4, R version 3.3.1, and Spotfire version 7.7.

Results

Patient Populations

Overall, 1202 patients were enrolled in the ITT population between March 31, 2015, and December 30, 2016. At data cutoff (September 13, 2019), the median duration of follow-up in the ITT population was 39.3 months (Supplementary Fig. 1).

Overall, 123 patients had *EGFR* mutations in the ITT population: ABCP (n = 34), ACP (n = 45), and BCP (n = 44). In the subgroup with *EGFR* mutations, 26 patients in the ABCP arm, 33 patients in the ACP arm, and 32 patients in the BCP arm had sensitizing *EGFR* mutations. Of those with sensitizing *EGFR* mutations, 78 had received previous TKI therapy: ABCP (n = 22), ACP (n = 28), and BCP (n = 28). A total of 161 patients had baseline liver metastases: 52 patients each in the ABCP and ACP arms and 57 patients in the BCP arm. In the ITT population, 100 patients (8.3%) developed new brain metastases across the ABCP (7.0%, 28 of 400 patients), ACP (11.9%, 48 of 402 patients), and BCP (6.0%, 24 of 400 patients) arms.

Baseline characteristics were generally balanced between treatment arms in patient subgroups (Table 1). Numerical differences in PD-L1 status were observed between arms. In patients with *EGFR* mutations, 40% of patients in the ACP arm had tumors with PD-L1–low expression (TC1/2 or IC1/2) versus 29.4% in the ABCP arm and 25% in the BCP arm. Among patients with baseline liver metastases, 9.6% each in the ABCP and ACP arms had PD-L1–high tumors compared with 15.8% in the BCP arm. In patients who developed new brain metastases, 7.1% in the ABCP arm had tumors with PD-L1–high expression (TC3 or IC3) compared with 18.8% in the ACP arm and 20.8% in the BCP arm. In the ACP arm, 37.5% of patients had PD-L1–negative tumors (TC0 and IC0) versus 64.3% and 54.2% in the ABCP and BCP arms, respectively.

Updated Exploratory Analyses of OS

Results of exploratory OS analyses are found in Figures 1 and 2 for the subgroups of ITT patients.

In patients with *EGFR* mutations, median OS was 26.1 months in the ABCP arm and 20.3 months in the BCP arm; the HR point estimate for the treatment comparison was 0.91 (95% CI: 0.53–1.59) (Fig. 1*A*). In this subgroup, OS improvement was not found in the ACP arm versus the BCP arm (median = 21.4 versus 20.3 mo, HR = 1.16, 95% CI: 0.71–1.89) (Fig. 1*A*).

In patients with sensitizing *EGFR* mutations, median OS was longer in the ABCP arm (29.4 mo) than in the BCP arm (18.1 mo) (HR = 0.60, 95% CI: 0.31–1.14) (Fig. 1*B*). In this subgroup, median OS was similar between the ACP (19.0 mo) and BCP (18.1 mo) arms (HR = 1.00, 95% CI: 0.57–1.74) (Fig. 1*B*). The 3-year OS rates in patients with sensitizing *EGFR* mutations were 41.9% (95% CI: 22.1–61.6) in the ABCP arm, 25.6% (95% CI: 10.4–40.8) in the ACP arm, and 24.6% (95% CI: 9.5–39.7) in the BCP arm. Among patients with sensitizing *EGFR* mutations who had received previous TKI therapy, median OS was longer in the ABCP (27.8 mo) than in the BCP (18.1 mo) arm; the HR point estimate was 0.74 for ABCP versus BCP (95% CI: 0.38–1.46) (Fig. 1*C*). No OS benefit was found for ACP compared with BCP in patients with sensitizing *EGFR* mutations who had received previous TKI therapy (14.9 versus 18.1 mo, HR = 1.22, 95% CI: 0.68–2.22) (Fig. 1*C*). At 3 years, OS rates in patients with sensitizing *EGFR* mutations who had received previous TKI therapy were 35.3% (95% CI: 14.3–56.2) with ABCP, 15.4% (95% CI: 1.6–29.2) with ACP, and 24.5% (95% CI: 8.4–40.6) with BCP.

Median OS was 13.2 months in the ABCP arm and 9.1 months in the BCP arm in ITT patients with baseline liver metastases (Fig. 2*A*). The corresponding HR point estimate was 0.68 for ABCP versus BCP (95% CI: 0.45–1.02). No OS benefit was observed in the ACP arm compared with the BCP arm (median = 7.7 versus 9.1 mo, HR = 1.01, 95% CI: 0.68–1.51) in the baseline liver metastases subgroup (Fig. 2*B*). Similar results to those of the ITT population were found in the ITT-WT patients with baseline liver metastases in the ABCP (HR = 0.69, 95% CI: 0.45–1.08) and ACP (HR = 1.02, 95% CI: 0.65–1.60) arms versus the BCP arm.

Time to Development of New Brain Metastases

Among the 100 patients who developed new brain metastases at data cutoff, median time to development was not reached in the ABCP (range: 0–45.9 mo), ACP (range: 0–46.9 mo), or BCP (range: 0–42.3 mo) arm (Fig. 3A and Fig. 3B). The HR point estimates for time to development of new brain metastases were 0.68 for ABCP (95% CI: 0.39–1.19) and 1.55 for ACP (95% CI: 0.95–2.55) versus BCP.

Safety

Overall, 120 patients with *EGFR* mutations, 154 patients with baseline liver metastases, and 100 patients with new lesions in the brain were included in the safety evaluation at data cutoff (Table 2).

In patients with *EGFR* mutations, 100% in the ABCP arm, 88.6% in the ACP arm, and 95.3% in the BCP arm reported a treatment-related AE. Overall, grade 3/4

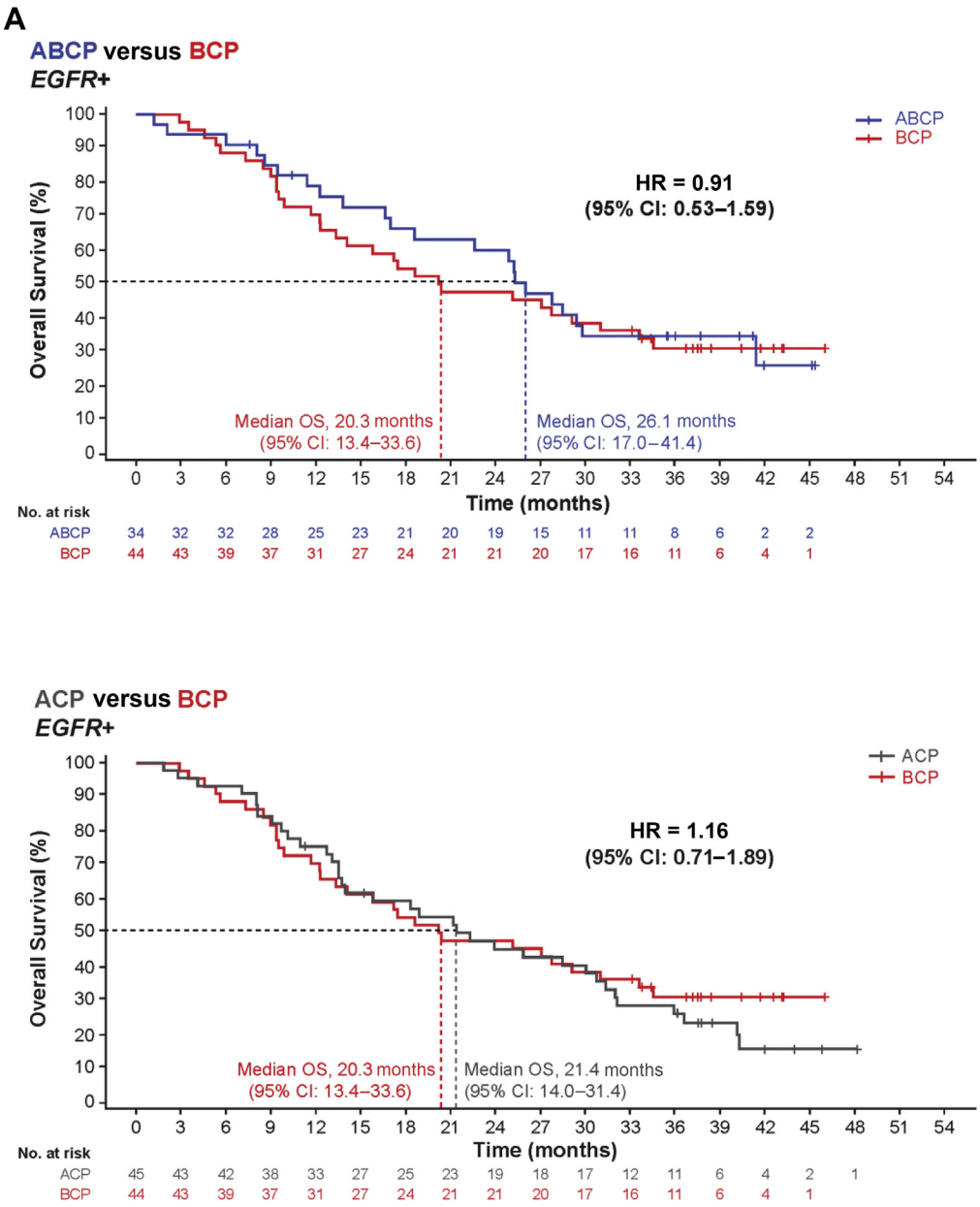

Figure 1. OS in patients with *EGFR* mutations. Kaplan-Meier analyses of OS in the ABCP or ACP arm versus the BCP arm in (*A*) patients with *EGFR* mutations, (*B*) patients with sensitizing *EGFR* mutations, and (*C*) patients with sensitizing *EGFR* mutations who had received previous TKI therapy. ABCP, atezolizumab plus bevacizumab plus carboplatin and paclitaxel; ACP, atezolizumab plus carboplatin and paclitaxel; BCP, bevacizumab plus carboplatin and paclitaxel; CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; TKI, tyrosine kinase inhibitor.

treatment-related AEs were reported in 66.7% (22 of 33 patients) of the patients in the ABCP arm, 56.8% (25 of 44) in the ACP arm, and 55.8% (24 of 43) in the BCP arm. One patient (2.3%) in the BCP arm and no patient in the atezolizumab arms experienced a treatment-related grade 5 AE. AEs led to treatment withdrawal in 42.4% of the patients in the ABCP arm, 13.6% in the ACP arm, and 16.3% in the BCP arm.

Most patients in the baseline liver metastases subgroup reported at least one treatment-related AE (ABCP, 100%; ACP, 94.1%; BCP, 100%); treatment-related grade 3/4 AEs were experienced by 52.1% of the patients (25 of 48) in the ABCP arm, 37.3% (19 of 51) in the ACP arm, and 54.5% (30 of 55) in the BCP arm. Treatment-related grade 5 AEs occurred in three patients (6.3%) in the ABCP arm, one (2%) in the ACP arm, and two (3.6%) in the BCP arm. Overall, 33.3% of patients in the ABCP arm, 11.8% of patients in the ACP arm, and 36.4% of patients in the BCP arm discontinued owing to AEs.

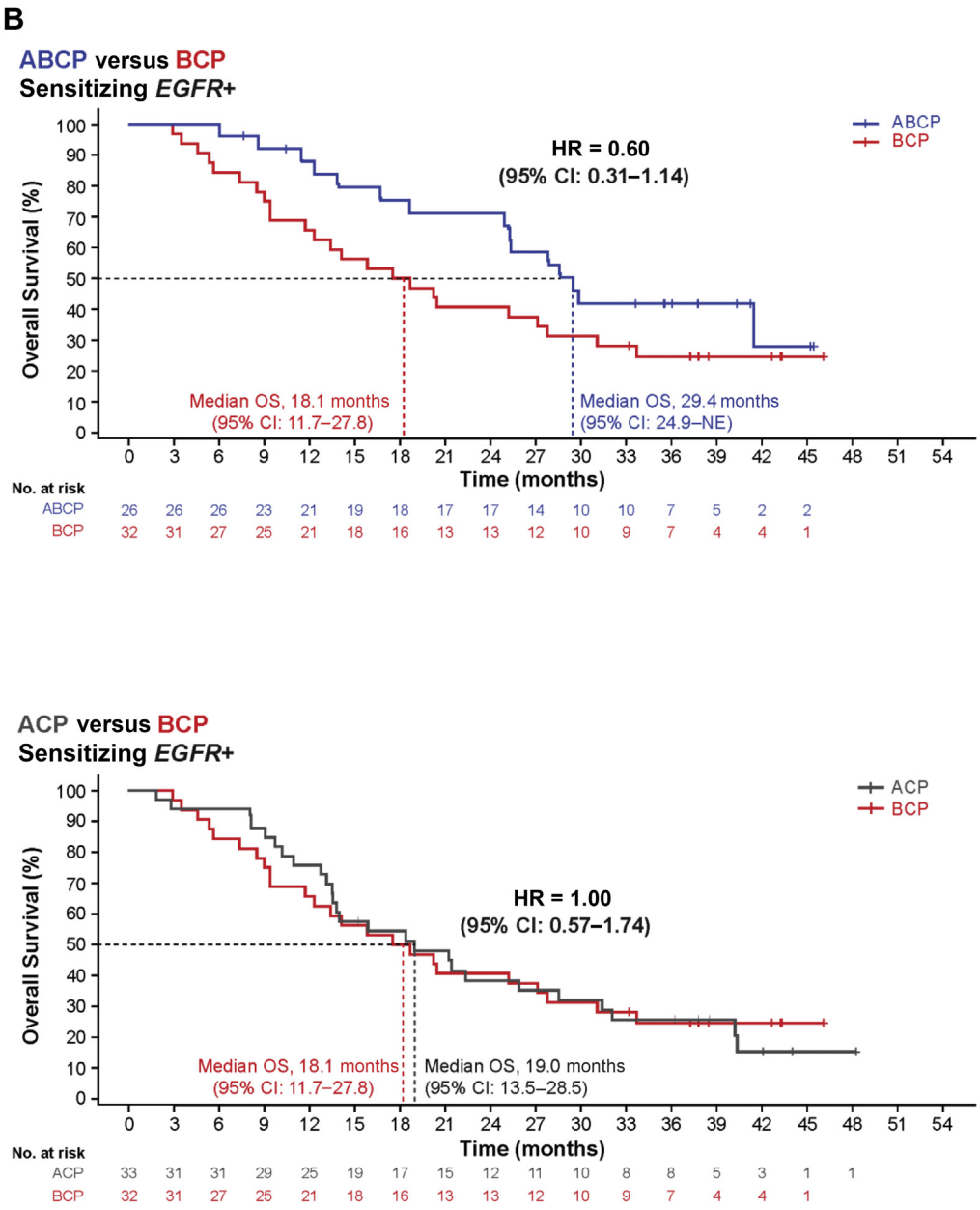

Figure 1. (*continued*).

In the brain metastases subgroup, at least one treatment-related AE was experienced by 96.4%, 95.8%, and 95.8% of the patients in the ABCP, ACP, and BCP arms, respectively. Grade 3/4 treatment-related AEs occurred in 64.3% (18 of 28 patients) of the ABCP arm, 35.4% (17 of 48) of the ACP arm, and 41.7% (10 of 24) of the BCP arm. No treatment-related grade 5 AEs were reported in any treatment arm among patients with brain metastases. Treatment withdrawal owing to AEs was reported in 42.9% of the patients in the ABCP arm, 10.4% in the ACP arm, and 33.3% in the ACP arm.

Discussion

On the basis of IMpower150, ABCP has become a standard-of-care regimen and is approved for the first-line treatment of metastatic nonsquamous NSCLC without *EGFR/ALK* genetic alterations (United States and Europe)[33,34] or for *EGFR/ALK*-positive NSCLC after failure with TKIs (Europe).[34] In this analysis, updated final data with longer follow-up for key patient subgroups continued to reveal OS benefits in the ABCP arm versus the BCP arm among patients with sensitizing *EGFR* mutations (including those with previous TKI failure) and baseline liver metastases, although the analyses in these

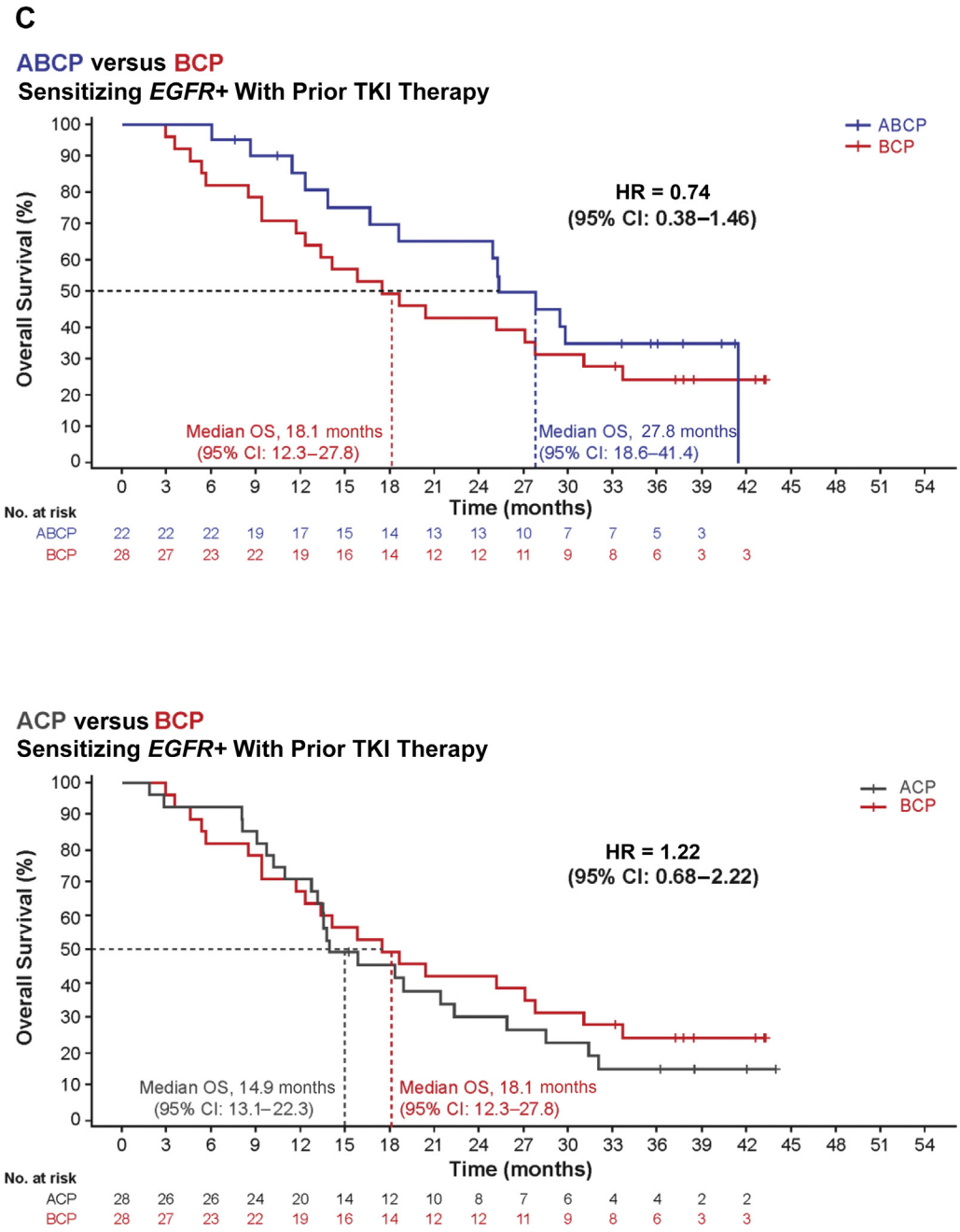

Figure 1. (*continued*).

subgroups were exploratory and not powered to draw definitive conclusions.

The ABCP regimen was found to have unique benefit among the available evidence for checkpoint inhibitors in the *EGFR*-mutant NSCLC patient subgroup with poor outcomes and limited treatment options. Despite a greater proportion of patients with PD-L1–positive tumors in the ACP arm than in the ABCP or BCP arm, OS was not significantly different between the ACP and BCP arms. The findings in favor of the ABCP regimen support the reported synergistic action of this combination.[10,11] It remains to be determined how this interaction confers the benefits observed with the ABCP regimen in the key subgroups analyzed here. Nevertheless, it may be speculated that increased sensitivity to bevacizumab through promotion of VEGF expression in *EGFR*-mutant tumors[35] or reversal of immune suppression by bevacizumab against a background of reduced $CD8^+$ T-cell infiltration in patients with *EGFR* mutations or liver metastases[26,36] may further enhance T-cell–mediated killing by atezolizumab. Moreover, low PD-L1 prevalence rates across treatment arms suggest that the observed

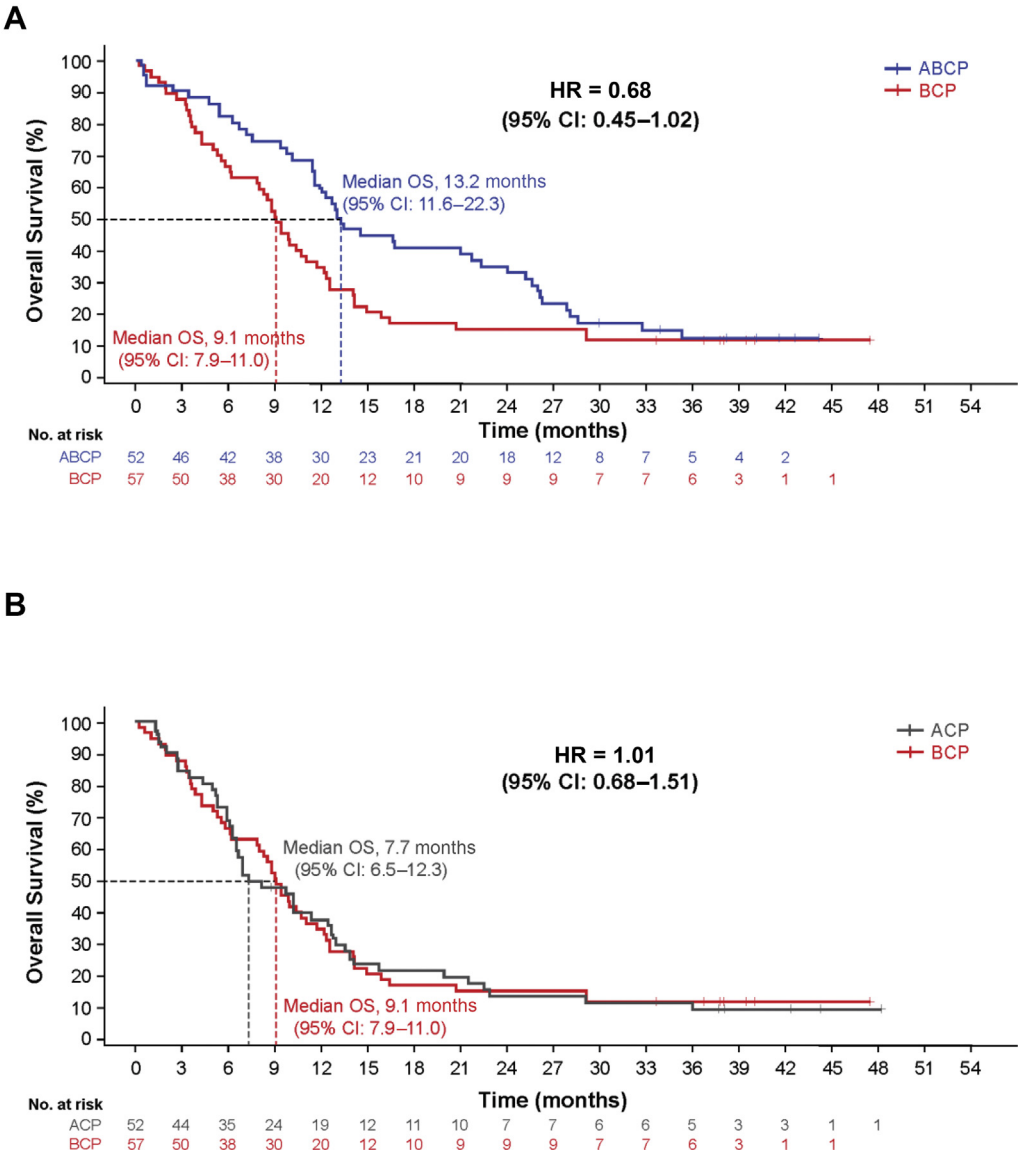

Figure 2. OS in patients with baseline liver metastases. Kaplan-Meier analyses of OS in the (*A*) ABCP versus the BCP arm and (*B*) in the ACP arm versus the BCP arm in patients with baseline liver metastases. ABCP, atezolizumab plus bevacizumab plus carboplatin and paclitaxel; ACP, atezolizumab plus carboplatin and paclitaxel; BCP, bevacizumab plus carboplatin and paclitaxel; CI, confidence interval; HR, hazard ratio; OS, overall survival.

clinical benefit of ABCP was not solely driven by PD-L1–high expression and is consistent with previous evidence suggesting PD-L1 expression does not predict benefit in *EGFR*-mutant NSCLC.[37] In this context, both enhanced T-cell priming through tumor-draining lymph node–targeted PD-L1 blockade by atezolizumab and interferon gamma–mediated induction of PD-L1 expression through reprogramming of the tumor microenvironment to an immune stimulatory state by bevacizumab may result in increased tumor sensitivity to PD-L1 inhibition.[5,38–43] The observed activity of ABCP in patients with liver metastases in this study is further supported by findings from the phase 3 IMbrave150 trial evaluating atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma.[44] Liver metastases from lung cancer have been found to respond to treatment in a manner more similar to liver cancer than lung cancer.[26,45]

In this updated exploratory analysis of IMpower150, the bevacizumab-containing ABCP and BCP arms had comparable, lower rates of new brain lesion development on the study versus the ACP arm, supporting the previously reported benefit of bevacizumab plus chemotherapy in reducing the risk of brain metastases development.[29] Furthermore, our analyses revealed an improvement toward delayed time to development of new brain lesions with ABCP versus BCP, which is unlikely to be PD-L1 driven given the lower frequency

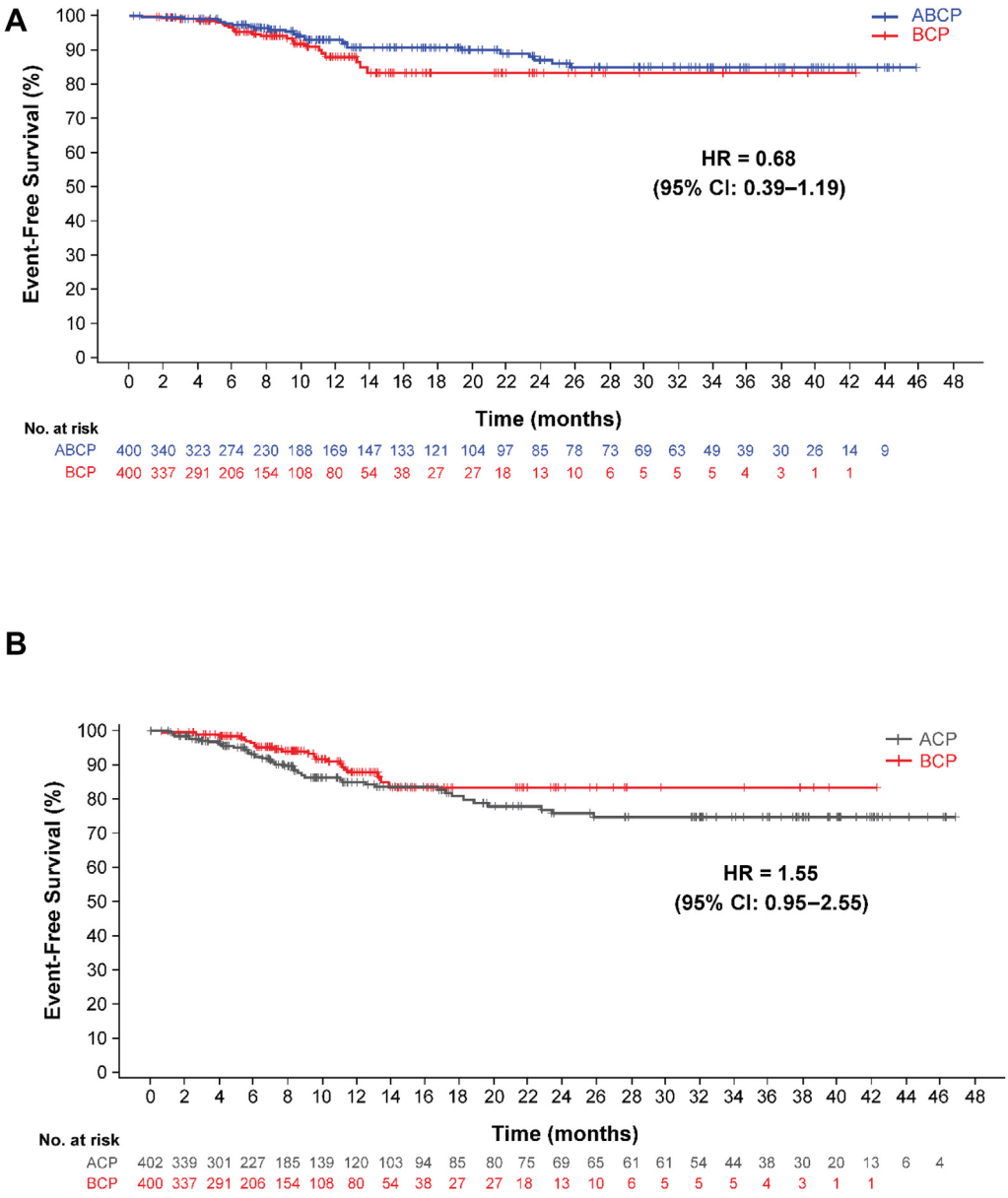

Figure 3. Kaplan-Meier curves revealing the time to development of new brain lesions in the ITT population. Kaplan-Meier analyses of time to development of new brain metastases in (*A*) the ABCP versus the BCP arm and (*B*) the ACP arm versus the BCP arm in the ITT population. ABCP, atezolizumab plus bevacizumab plus carboplatin and paclitaxel; ACP, atezolizumab plus carboplatin and paclitaxel; BCP, bevacizumab plus carboplatin and paclitaxel; CI, confidence interval; HR, hazard ratio; ITT, intention to treat.

of patients with PD-L1–high tumors in the ABCP arm versus the other arms. Notably, immune checkpoint blockade has been proposed to enhance T-cell migration to brain tumors,[46] which may provide a mechanistic explanation for the observation that adding atezolizumab to BCP, while not reducing the rate of brain lesion development, delayed the time to development of new lesions. Given the small sample size and the exploratory nature of the analyses, these preliminary findings require further confirmation within a study design incorporating routine brain imaging assessments.

No new safety signals were identified in this exploratory analysis. Safety profiles of the treatment regimens among the patient subgroups were consistent with safety data reported at the second interim OS analysis[27] and with current experience with each medicine.

Small sample sizes between subgroups and the exploratory nature of the subanalyses, although prespecified, did not allow for formal statistical testing. Therefore, the current findings should be interpreted with caution. In addition to *EGFR* and *ALK* genetic alterations, *ROS1*, *BRAF*, *RET*, and *KRAS* mutations or

Table 2. Safety Summary in Key Patient Subgroups

Safety Characteristic	ABCP	ACP	BCP
Patients with *EGFR* mutations			
N	33	44	43
Median treatment duration (range), mo			
Atezolizumab	9.7 (0-45)	6.4 (0-43)	—
Bevacizumab	8.8 (0-45)	—	5.5 (0-28)
Patients with ≥1 AE, n (%)			
Any AE	33 (100)	43 (97.7)	43 (100)
Grade 3/4	22 (66.7)	31 (70.5)	27 (62.8)
Grade 5	0	0	1 (2.3)
Treatment-related AE, n (%)[a]	33 (100.0)	39 (88.6)	41 (95.3)
Grade 3/4	22 (66.7)	25 (56.8)	24 (55.8)
Grade 5[b]	0	0	1 (2.3)
Serious AE, n (%)	14 (42.4)	16 (36.4)	9 (20.9)
Treatment related	8 (24.2)	9 (20.5)	4 (9.3)
AE leading to any treatment discontinuation, n (%)	14 (42.4)	6 (13.6)	7 (16.3)
AE leading to any dose modification/interruption, n (%)	23 (69.7)	23 (52.3)	21 (48.8)
Patients with baseline liver metastases			
N	48	51	55
Median treatment duration (range), mo			
Atezolizumab	7.8 (0-44)	4.9 (0-44)	—
Bevacizumab	6.5 (0-44)	—	3.5 (0-19)
Patients with ≥1 AE, n (%)			
Any AE	48 (100)	48 (94.1)	55 (100)
Grade 3/4	28 (58.3)	28 (54.9)	35 (63.6)
Grade 5	7 (14.6)	1 (2.0)	4 (7.3)
Treatment-related AE, n (%)[a]	43 (89.6)	44 (86.3)	51 (92.7)
Grade 3/4	25 (52.1)	19 (37.3)	30 (54.5)
Grade 5	3 (6.3)	1 (2.0)	2 (3.6)
Serious AE, n (%)	24 (50.0)	25 (49.0)	27 (49.1)
Treatment related	7 (14.6)	12 (23.5)	18 (32.7)
AE leading to any treatment discontinuation, n (%)	16 (33.3)	6 (11.8)	20 (36.4)
AE leading to any dose modification/interruption, n (%)	28 (58.3)	21 (41.2)	26 (47.3)
Patients with new metastases in the brain			
N	28	48	24
Median treatment duration (range), mo			
Atezolizumab	8.4 (1-35)	7.3 (0-43)	—
Bevacizumab	6.1 (1-23)	—	5.7 (1-13)
Patients with ≥1 AE, n (%)			
Any AE	28 (100.0)	48 (100.0)	24 (100.0)
Grade 3/4	21 (75.0)	27 (56.3)	14 (58.3)
Grade 5	0	1 (2.1)	1 (4.2)
Treatment-related AE, n (%)[a]	27 (96.4)	46 (95.8)	23 (95.8)
Grade 3/4	18 (64.3)	17 (35.4)	10 (41.7)
Grade 5	0	0	0
Serious AE, n (%)	15 (53.6)	20 (41.7)	4 (16.7)
Treatment related	7 (25.0)	8 (16.7)	0
AE leading to any treatment discontinuation, n (%)	12 (42.9)	5 (10.4)	8 (33.3)
AE leading to any dose modification/interruption, n (%)	21 (75.0)	28 (58.3)	16 (66.7)

[a]Related to any study treatment.
[b]Pulmonary hemorrhage.
ABCP, atezolizumab plus bevacizumab plus carboplatin and paclitaxel; ACP, atezolizumab plus carboplatin and paclitaxel; AE, adverse event; BCP, bevacizumab plus carboplatin and paclitaxel.

rearrangements, among others, have been identified as oncogenic drivers that can coexist in NSCLC tumors.[47,48] Until recently, TKIs targeting these driver mutations were not part of the treatment landscape; therefore, further studies may be warranted to elucidate clinical benefits with the ABCP regimen after targeted therapy in patients with tumors harboring oncogenic drivers, such as *ROS1*, *BRAF*, *RET*, and *KRAS*.

ABCP is advocated as a standard-of-care regimen for the first-line treatment of metastatic nonsquamous NSCLC.[1,15] This updated analysis reveals possible survival gains with ABCP in key patient subgroups, highlighting this regimen as a potential new treatment option for difficult-to-treat patients with poor prognostic outcomes, such as those with liver metastases or sensitizing *EGFR* mutations for whom TKIs have failed.

CRediT Authorship Contribution Statement

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Fabrice Barlesi, Christian A. Thomas, Joachim G. Aerts, Francisco Orlandi, Daniil Stroyakovskiy: Investigation, resources, writing—review and editing.

Mark A. Socinski, Robert M. Jotte, Delvys Rodríguez-Abreu: Conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing—original draft, writing—review and editing, visualization, supervision, project administration.

Martin Reck: Conceptualization, investigation, resources, writing—review and editing, visualization.

Federico Cappuzzo: Investigation, resources, writing—review and editing, visualization.

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Liza C. Villaruz: Resources, writing—review and editing, visualization.

Darren Wan-Teck Lim: Investigation, resources, data curation writing—original draft, writing—review and editing, visualization, supervision, project administration.

David Merritt: Conceptualization, methodology, investigation, writing—original draft, writing—review and editing, visualization, supervision.

Shelley Coleman: Investigation, resources, data curation, writing—original draft, writing—review and editing, visualization, supervision.

Anthony Lee: Investigation, resources, data curation, writing—original draft, writing—review and editing, visualization.

Geetha Shankar: Conceptualization, methodology, investigation, data curation, writing—original draft, writing—review and editing, visualization.

Wei Yu: Conceptualization, methodology, software, validation, formal analysis, data curation, writing—original draft, writing—review and editing, visualization.

Ilze Bara: Resources, investigation, writing—original draft, writing—review and editing, visualization, supervision.

Makoto Nishio: Resources, writing—review and editing.

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.2021.09.014.

References

1. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(suppl 4):iv192–iv237.
2. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity*. 2013;39:1–10.
3. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature*. 2014;515:563–567.
4. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet*. 2016;387:1837–1846.
5. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389:255–265.
6. Horn L, Gettinger SN, Gordon MS, et al. Safety and clinical activity of atezolizumab monotherapy in metastatic non-small-cell lung cancer: final results from a phase I study. *Eur J Cancer*. 2018;101:201–209.

7. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1–selected patients with NSCLC. *N Engl J Med*. 2020;383:1328–1339.
8. West H, McCleod M, Hussein M, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:924–937.
9. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*. 2006;355:2542–2550.
10. Hegde PS, Wallin JJ, Mancao C. Predictive markers of anti-VEGF and emerging role of angiogenesis inhibitors as immunotherapeutics. *Semin Cancer Biol*. 2018;52:117–124.
11. Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. *Immunity*. 2013;39:74–88.
12. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288–2301.
13. Takeda M, Nakagawa K. First- and second-generation EGFR-TKIs are all replaced to osimertinib in chemo-naive EGFR mutation-positive non-small cell lung cancer? *Int J Mol Sci*. 2019;20:146.
14. Mu Y, Hao X, Yang K, et al. Clinical modality of resistance and subsequent management of patients with advanced non-small cell lung cancer failing treatment with osimertinib. *Target Oncol*. 2019;14:335–342.
15. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer, version 7.2021. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed September 18, 2021.
16. Lee CK, Man J, Lord S, et al. Checkpoint inhibitors in metastatic EGFR-mutated non-small cell lung cancer—a meta-analysis. *J Thorac Oncol*. 2017;12:403–407.
17. Sperduto PW, Yang TJ, Beal K, et al. Estimating survival in patients with lung cancer and brain metastases: an update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). *JAMA Oncol*. 2017;3:827–831.
18. Ren Y, Dai C, Zheng H, et al. Prognostic effect of liver metastasis in lung cancer patients with distant metastasis. *Oncotarget*. 2016;7:53245-53253.
19. Villano JL, Durbin EB, Normandeau C, Thakkar JP, Moirangthem V, Davis FG. Incidence of brain metastasis at initial presentation of lung cancer. *Neuro Oncol*. 2015;17:122–128.
20. Chang YP, Chen YM, Lai CH, et al. The impact of de novo liver metastasis on clinical outcome in patients with advanced non-small-cell lung cancer. *PLoS One*. 2017;12:e0178676.
21. Lee DS, Kim YS, Kay CS, et al. Distinctive patterns of initially presenting metastases and clinical outcomes according to the histological subtypes in stage IV non-small cell lung cancer. *Medicine (Baltimore)*. 2016;95:e2795.
22. Tamura T, Kurishima K, Nakazawa K, et al. Specific organ metastases and survival in metastatic non-small-cell lung cancer. *Mol Clin Oncol*. 2015;3:217–221.
23. Riihimaki M, Hemminki A, Fallah M, et al. Metastatic sites and survival in lung cancer. *Lung Cancer*. 2014;86:78–84.
24. Li S, Sun S, Xiang H, Yang J, Peng M, Gao Q. Liver metastases and the efficacy of the PD-1 or PD-L1 inhibitors in cancer: a meta-analysis of randomized controlled trials. *Oncoimmunology*. 2020;9:1746113.
25. Pillai RN, Kamphorst AO, Owonikoko TK, et al. Liver metastases and sensitivity to checkpoint inhibition in patients with non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2016;34(suppl 15):e20665–e20665.
26. Tumeh PC, Hellmann MD, Hamid O, et al. Liver metastasis and treatment outcome with anti-PD-1 monoclonal antibody in patients with melanoma and NSCLC. *Cancer Immunol Res*. 2017;5:417–424.
27. Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. *Lancet Respir Med*. 2019;7:387–401.
28. Fu Y, Hu J, Du N, et al. Bevacizumab plus chemotherapy versus chemotherapy alone for preventing brain metastasis derived from advanced lung cancer. *J Chemother*. 2016;28:218–224.
29. Ilhan-Mutlu A, Osswald M, Liao Y, et al. Bevacizumab prevents brain metastases formation in lung adenocarcinoma. *Mol Cancer Ther*. 2016;15:702–710.
30. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version1.1). *Eur J Cancer*. 2009;45:228–247.
31. Vennapusa B, Baker B, Kowanetz M, et al. Development of a PD-L1 complementary diagnostic immunohistochemistry assay (SP142) for atezolizumab. *Appl Immunohistochem Mol Morphol*. 2019;27:92–100.
32. Cappuzzo F, Reck M, Socinski MA, et al. IMpower150: exploratory analysis of brain metastases development. *J Clin Oncol*. 2020;38(suppl 15):9587–9587.
33. TECENTRIQ *(atezolizumab) [package insert]. South San Francisco, CA*. Genentech, Inc; 2020.
34. TECENTRIQ *(atezolizumab) [summary of product characteristics]. Grenzach-Wyhlen*. Germany: Roche Registration GmbH; 2020.
35. Hung MS, Chen IC, Lin PY, et al. Epidermal growth factor receptor mutation enhances expression of vascular endothelial growth factor in lung cancer. *Oncol Lett*. 2016;12:4598–4604.
36. Gainor JF, Shaw AT, Sequist LV, et al. EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer: a retrospective analysis. *Clin Cancer Res*. 2016;22:4585–4593.
37. Jin R, Zhao J, Xia L, et al. Application of immune checkpoint inhibitors in EGFR-mutant non-small-cell lung cancer: from bed to bench. *Ther Adv Med Oncol*. 2020;12:1758835920930333.

38. Butte MJ, Keir ME, Phamduy TB, Sharpe AH, Freeman GJ. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. *Immunity*. 2007;27:111–122.
39. Yang J, Riella LV, Chock S, et al. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. *J Immunol*. 2011;187:1113–1119.
40. Paterson AM, Brown KE, Keir ME, et al. The programmed death-1 ligand 1:B7-1 pathway restrains diabetogenic effector T cells in vivo. *J Immunol*. 2011;187:1097–1105.
41. Park JJ, Omiya R, Matsumura Y, et al. B7-H1/CD80 interaction is required for the induction and maintenance of peripheral T-cell tolerance. *Blood*. 2010;116:1291–1298.
42. Kudo M. Scientific rationale for combined immunotherapy with PD-1/PD-L1 antibodies and VEGF inhibitors in advanced hepatocellular carcinoma. *Cancers (Basel)*. 2020;12:1089.
43. Dammeijer F, van Gulijk M, Mulder EE, et al. The PD-1/PD-L1-checkpoint restrains T cell immunity in tumor-draining lymph nodes. *Cancer Cell*. 2020;38:685–700:e8.
44. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382:1894–1905.
45. Pao W, Ooi CH, Birzele F, et al. Tissue-specific immunoregulation: a call for better understanding of the "Immunostat" in the context of cancer. *Cancer Discov*. 2018;8:395–402.
46. Lorger M, Andreou T, Fife C, James F. Immune checkpoint blockade—how does it work in brain metastases? *Front Mol Neurosci*. 2019;12:282.
47. Zhuang X, Zhao C, Li J, et al. Clinical features and therapeutic options in non-small cell lung cancer patients with concomitant mutations of EGFR, ALK, ROS1, KRAS or BRAF. *Cancer Med*. 2019;8:2858–2866.
48. Skoulidis F, Heymach JV. Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. *Nat Rev Cancer*. 2019;19:495–509.