ORIGINAL ARTICLE

Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC

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ABSTRACT

BACKGROUND

The cancer-cell–killing property of atezolizumab may be enhanced by the blockade of vascular endothelial growth factor–mediated immunosuppression with bevacizumab. This open-label, phase 3 study evaluated atezolizumab plus bevacizumab plus chemotherapy in patients with metastatic nonsquamous non–small-cell lung cancer (NSCLC) who had not previously received chemotherapy.

METHODS

We randomly assigned patients to receive atezolizumab plus carboplatin plus paclitaxel (ACP), bevacizumab plus carboplatin plus paclitaxel (BCP), or atezolizumab plus BCP (ABCP) every 3 weeks for four or six cycles, followed by maintenance therapy with atezolizumab, bevacizumab, or both. The two primary end points were investigator-assessed progression-free survival both among patients in the intention-to-treat population who had a wild-type genotype (WT population; patients with *EGFR* or *ALK* genetic alterations were excluded) and among patients in the WT population who had high expression of an effector T-cell (Teff) gene signature in the tumor (Teff-high WT population) and overall survival in the WT population. The ABCP group was compared with the BCP group before the ACP group was compared with the BCP group.

RESULTS

In the WT population, 356 patients were assigned to the ABCP group, and 336 to the BCP group. The median progression-free survival was longer in the ABCP group than in the BCP group (8.3 months vs. 6.8 months; hazard ratio for disease progression or death, 0.62; 95% confidence interval [CI], 0.52 to 0.74; P<0.001); the corresponding values in the Teff-high WT population were 11.3 months and 6.8 months (hazard ratio, 0.51 [95% CI, 0.38 to 0.68]; P<0.001). Progression-free survival was also longer in the ABCP group than in the BCP group in the entire intention-to-treat population (including those with *EGFR* or *ALK* genetic alterations) and among patients with low or negative programmed death ligand 1 (PD-L1) expression, those with low Teff gene-signature expression, and those with liver metastases. Median overall survival among the patients in the WT population was longer in the ABCP group than in the BCP group (19.2 months vs. 14.7 months; hazard ratio for death, 0.78; 95% CI, 0.64 to 0.96; P=0.02). The safety profile of ABCP was consistent with previously reported safety risks of the individual medicines.

CONCLUSIONS

The addition of atezolizumab to bevacizumab plus chemotherapy significantly improved progression-free survival and overall survival among patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression and *EGFR* or *ALK* genetic alteration status. (Funded by F. Hoffmann–La Roche/Genentech; IMpower150 ClinicalTrials.gov number, NCT02366143.)

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*A complete list of investigators in the IMpower150 study is provided in the Supplementary Appendix, available at NEJM.org.

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The standard of care for patients with metastatic non–small-cell lung cancer (NSCLC) who have not previously received treatment includes platinum-doublet chemotherapy with or without bevacizumab for those with nonsquamous cancer,[1-3] targeted therapies for those with oncogenic alterations, anti–programmed death 1 (PD-1) monotherapy for those with programmed death ligand 1 (PD-L1) expression on at least 50% of tumor cells,[4] and anti–PD-1 plus platinum-doublet chemotherapy for those with nonsquamous cancer.[5] However, the prognosis remains poor.

The anti–PD-L1 antibody atezolizumab (Tecentriq, F. Hoffmann–La Roche/Genentech)[6,7] has been shown to provide an overall survival benefit in patients with previously treated metastatic NSCLC regardless of PD-L1 expression[8] and has shown promising efficacy and an acceptable safety profile when combined with platinum-doublet chemotherapy in patients who have not previously received chemotherapy for NSCLC.[9]

Trials of second-line or later treatments for NSCLC have shown that patients with *EGFR*-mutant tumors do not benefit from checkpoint inhibition.[8,10,11] Identifying effective treatments for these patients after treatment failure or the occurrence of unacceptable side effects from tyrosine kinase inhibitor therapy presents a clinical problem.

Bevacizumab combined with chemotherapy is approved for the treatment of metastatic nonsquamous NSCLC.[1,12,13] In addition to the known antiangiogenic effects of bevacizumab,[14] the inhibition of vascular endothelial growth factor (VEGF) has immunomodulatory effects.[15-26] The efficacy of atezolizumab may be enhanced through the addition of bevacizumab to reverse VEGF-mediated immunosuppression.[26,27]

In the IMpower150 study, we asked two questions: does VEGF blockade enhance the efficacy of immunotherapy, and does immunotherapy combine effectively with chemotherapy? We addressed the first question by evaluating the effect of adding atezolizumab to the combination of bevacizumab and chemotherapy, and the second by assessing the effect of replacing bevacizumab with atezolizumab in the combination with chemotherapy (results not shown). We report the final analysis of progression-free survival and the interim analysis of overall survival.

Methods

Study Oversight

F. Hoffmann–La Roche/Genentech sponsored the IMpower150 study, provided the study drugs, and collaborated with the academic authors on the design of the study and on the collection, analysis, and interpretation of the data. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and with the principles of the Declaration of Helsinki. All patients provided written informed consent. An independent data monitoring committee reviewed safety data. The protocol, available with the full text of this article at NEJM.org, was approved by independent ethics committees at each participating site. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol. All the authors or a delegate from the authors' institutions signed a confidentiality agreement with the sponsor. All earlier versions of the manuscript were prepared by the authors, with editorial and writing assistance funded by the sponsor.

Patients

Patients were eligible for inclusion in the study if they had stage IV or recurrent metastatic nonsquamous NSCLC (classified according to criteria for measurable disease in Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST]) for which they had not previously received chemotherapy, a baseline Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability), and tumor tissue available for biomarker testing and if they were eligible to receive bevacizumab (see the protocol); patients with any PD-L1 immunohistochemistry status were eligible. Patients with *EGFR* or *ALK* genomic alterations were included if they had had disease progression with or unacceptable side effects from treatment with at least one approved tyrosine kinase inhibitor. Patients were excluded if they had untreated metastases of the central nervous system, if they had autoimmune disease, or if they had received previous immunotherapy or anti–CTLA-4 therapy within 6 weeks before randomization or systemic immunosuppressive medications within 2 weeks before

randomization. Patients who had received previous adjuvant or neoadjuvant chemotherapy were eligible if the last treatment was at least 6 months before randomization.

STUDY DESIGN AND TREATMENT

In this international, open-label, phase 3 study, patients were randomly assigned, in a 1:1:1 ratio, to receive atezolizumab plus carboplatin plus paclitaxel (ACP group), atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (ABCP group), or bevacizumab plus carboplatin plus paclitaxel (BCP group). Randomization was stratified according to sex, presence or absence of liver metastases at baseline, and PD-L1 tumor expression (as assessed by immunohistochemical analysis). PD-L1 expression on tumor cells or tumor-infiltrating immune cells was analyzed in archival or freshly collected tumor tissue (or both) and scored as described previously (Table S1 in the Supplementary Appendix, available at NEJM.org).[28] PD-L1 expression was evaluated at a central laboratory with the use of the SP142 PD-L1 immunohistochemistry assay (Ventana Medical Systems).

Induction treatment was administered for four or six 21-day cycles (with the number of cycles determined at the discretion of the investigator before randomization); treatment was administered on day 1 of each cycle. Atezolizumab was administered at a dose of 1200 mg, bevacizumab at a dose of 15 mg per kilogram of body weight, paclitaxel at a dose of 200 mg per square meter of body-surface area (175 mg per square meter for Asian patients), and carboplatin at an area under the concentration–time curve of 6 mg per milliliter per minute. After the induction phase, patients continued to receive atezolizumab, bevacizumab, or both until the occurrence of unmanageable toxic effects or disease progression (as determined according to RECIST criteria). Continuation of atezolizumab after the occurrence of disease progression was allowed if evidence of clinical benefit existed. No crossover to atezolizumab was allowed.

END POINTS AND ASSESSMENTS

The two primary end points were progression-free survival (as assessed by investigators according to RECIST criteria) both among patients in the intention-to-treat population who had a wild-type genotype (WT population; patients with *EGFR* or *ALK* genomic alterations were excluded) and among patients in the WT population who had high expression of an effector T-cell (Teff) gene signature in the tumor (Teff-high WT population) and overall survival in the WT population. The Teff gene signature was defined as the expression of *PD-L1*, *CXCL9*, and *IFN-γ* messenger RNA, as determined with the use of RNA that was isolated from macrodissected tumor tissue obtained at baseline and measured with a clinical trial assay (real-time quantitative polymerase-chain-reaction assay performed at Roche Molecular Systems) (further information on the Teff gene signature is provided in the Supplementary Appendix).

A protocol amendment during the study changed the primary-analysis populations from the intention-to-treat population as a whole (which included both the WT population and patients with *EGFR* or *ALK* genomic alterations) and the population of patients with PD-L1 expression, as assessed by immunohistochemical analysis, to the WT population and the Teff-high WT population. The decision to exclude patients with *EGFR* or *ALK* genomic alterations from the primary analysis was based on data showing that with respect to progression-free and overall survival, the benefits of monotherapy with PD-L1 inhibitors or PD-1 inhibitors as second-line or later therapy were similar to the benefits with chemotherapy in these patients.[8,10,11] Expression of a Teff gene signature was added as a primary progression-free survival end point on the basis of data from the phase 3 OAK trial showing that Teff gene-signature expression is a more sensitive biomarker for progression-free survival benefit with atezolizumab than PD-L1 expression.[29]

Key secondary end points included progression-free survival, as assessed by the investigators, and overall survival in the intention-to-treat population, which comprised all enrolled patients, including those with *EGFR* or *ALK* genomic alterations. In addition, the following end points were assessed in the WT population: progression-free survival, as assessed at an independent review facility; investigator-assessed progression-free survival in the PD-L1 expression subgroups; and the rate of objective response (defined as complete response or partial response, as assessed by the investigators according to RECIST criteria), as well as the duration of response among the patients who had an objective response. Safety

was assessed in all patients who received at least one dose of a study drug.

Patients underwent tumor assessments during screening, every 6 weeks from day 1 of cycle 1 for the first 48 weeks, and every 9 weeks thereafter until the occurrence of disease progression (according to RECIST criteria) or until the loss of clinical benefit among patients who continued to receive atezolizumab after initial disease progression. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

STATISTICAL ANALYSIS

Full details of the statistical analysis plan are provided in the protocol. In the primary endpoint analyses, the ABCP group was compared with the BCP group before the ACP group was compared with the BCP group, as shown in the alpha-spending algorithm (Fig. S1 in the Supplementary Appendix). This study design was implemented to maximize statistical power, with the consideration that if the addition of atezolizumab to the BCP regimen did not provide significant benefit over BCP alone, it would be highly unlikely that substituting atezolizumab for bevacizumab in the BCP regimen would provide significant benefit. To strictly control for the overall type 1 error rate at a two-sided significance level of 0.05, a two-sided alpha value of 0.012 was allocated to progression-free survival (split equally into 0.006 for each primary-analysis population [i.e., the WT population and the Teff-high WT population]), and a two-sided alpha value of 0.038 was allocated to overall survival in the WT population. If the result of any comparison of progression-free survival between the ABCP group and the BCP group was significant, the alpha value would then be recycled for the comparison of overall survival between the ABCP group and the BCP group. If the result of the comparison of overall survival between the ABCP group and the BCP group was significant, the remaining alpha value would be passed down to compare both progression-free survival and overall survival between the ACP group and the BCP group. If the result of the comparison of overall survival between the ACP group and the BCP group was significant, testing would be extended to the intention-to-treat population, including those with *EGFR* or *ALK* genomic alterations.[30,31]

The final analyses of progression-free survival and overall survival were to be performed when approximately 516 instances of disease progression or death and 507 deaths, respectively, had occurred in the ABCP and BCP groups combined in the WT population. An interim analysis of overall survival was planned when approximately 370 deaths had occurred in the ABCP and BCP groups combined in the WT population.

The primary analyses of progression-free survival and overall survival in the WT population were performed with the use of a stratified log-rank test, in which the stratification factors were those used during randomization (i.e., sex, presence or absence of liver metastases at baseline, and PD-L1 tumor expression). The stratification factors used in the analysis of progression-free survival in the Teff-high WT population were sex and the presence or absence of liver metastases at baseline.

Hazard ratios were estimated with the use of a stratified Cox regression model, and the Brookmeyer–Crowley method was used to calculate 95% confidence intervals. The Kaplan–Meier method was used to estimate medians. We performed prespecified subgroup analyses to assess the consistency of the treatment effect, using unstratified hazard ratios that were estimated from a Cox proportional-hazards model.

RESULTS

PATIENTS

From March 2015 through December 2016, a total of 1202 patients (intention-to-treat population) were enrolled at 240 sites in 26 countries and were randomly assigned to the ACP group (402 patients), the ABCP group (400 patients), or the BCP group (400 patients) (Fig. 1). The WT population comprised 1040 of these patients (86.5%): 348 in the ACP group, 356 in the ABCP group, and 336 in the BCP group. Teff gene-signature expression could be evaluated in 95.6% of the patients in the WT population. A total of 445 of the 1040 patients in the WT population (42.8%) had high Teff gene-signature expression (Teff-high WT population): 161 in the ACP group, 155 in the ABCP group, and 129 in the BCP group.

Baseline characteristics were generally balanced between the ABCP group and the BCP group in the intention-to-treat population as a whole (Table 1), in the WT population, and in

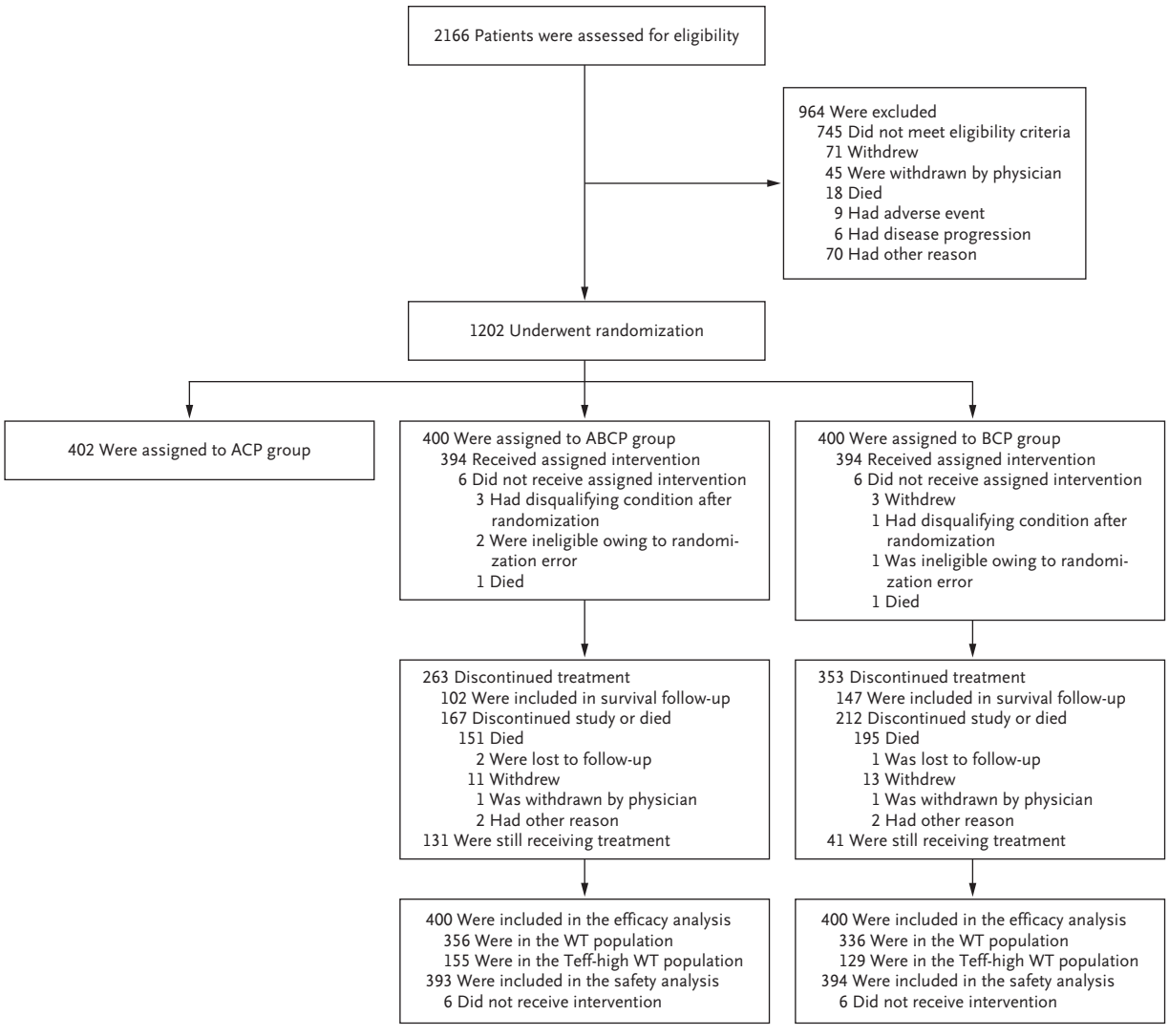


Figure 1. Eligibility, Randomization, and Analysis.

Patients were randomly assigned to receive atezolizumab plus carboplatin plus paclitaxel (ACP group), atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (ABCP group), or bevacizumab plus carboplatin plus paclitaxel (BCP group); treatments were administered every 3 weeks for four or six cycles, after which the patients received maintenance therapy with atezolizumab, bevacizumab, or both. One patient who was randomly assigned to the ABCP group did not receive bevacizumab and was assigned to the ACP group in the safety analysis. The WT population comprised patients in the intention-to-treat (ITT) population who had a wild-type (WT) genotype (patients with *EGFR* or *ALK* genetic alterations were excluded); the Teff-high WT population comprised patients in the WT population who had high expression of an effector T-cell (Teff) gene signature in the tumor. This figure shows the efficacy and safety populations as of the data-cutoff date of September 15, 2017.

the Teff-high WT population. Three patients (12.0%) in the ABCP group and four (12.5%) in the BCP group who had *EGFR* mutations did not report receipt of previous tyrosine kinase inhibitor therapy, predominantly because of a lack of accessibility to approved EGFR inhibitor therapy in their countries. Patients with PD-L1–negative tumors (PD-L1 expression on <1% of tumor cells and tumor-infiltrating immune cells, as determined by immunohistochemical analysis) composed approximately half of each treatment group in both the intention-to-treat population as a

Table 1. Baseline Characteristics of All Enrolled Patients (Intention-to-Treat Population).*

Characteristic	ABCP Group (N = 400)	BCP Group (N = 400)
Median age (range) — yr	63 (31–89)	63 (31–90)
Age group — no. (%)		
<65 yr	215 (53.8)	226 (56.5)
65–74 yr	149 (37.2)	132 (33.0)
75–84 yr	33 (8.2)	39 (9.8)
≥85 yr	3 (0.8)	3 (0.8)
Male sex — no. (%)	240 (60.0)	239 (59.8)
Liver metastases absent at enrollment — no. (%)	347 (86.8)	343 (85.8)
Race or ethnic group — no. (%)†		
White	322 (80.5)	335 (83.8)
Asian	56 (14.0)	46 (11.5)
Black	3 (0.8)	12 (3.0)
American Indian or Alaska Native	3 (0.8)	1 (0.2)
Multiple	3 (0.8)	0
Unknown	13 (3.2)	6 (1.5)
ECOG performance-status score — no./total no. (%)‡		
0	159/397 (40.1)	179/397 (45.1)
1	238/397 (59.9)	218/397 (54.9)
History of tobacco use — no. (%)		
Never	82 (20.5)	77 (19.2)
Current	90 (22.5)	92 (23.0)
Previous	228 (57.0)	231 (57.8)
Nonsquamous histologic subtype — no. (%)		
Adenocarcinoma	378 (94.5)	377 (94.2)
Other§	19 (4.8)	17 (4.2)
Unknown or not assessed	3 (0.8)	6 (1.5)
EGFR mutation status — no. (%)¶		
Positive	35 (8.8)	45 (11.3)
Negative	352 (88.0)	345 (86.3)
EML4-ALK rearrangement status — no. (%)‖		
Positive	13 (3.2)	21 (5.2)
Negative	383 (95.8)	375 (93.8)
KRAS mutation status — no. (%)**		
Positive	47 (11.8)	38 (9.5)
Negative	59 (14.8)	77 (19.2)

* The date of data cutoff was September 15, 2017. ABCP denotes atezolizumab plus bevacizumab plus carboplatin plus paclitaxel, and BCP bevacizumab plus carboplatin plus paclitaxel. Percentages may not sum to 100 because of rounding.
† Race and ethnic group were reported by the participants.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability. Three patients in each treatment group had a missing ECOG performance status score at baseline.
§ Other subtypes include adenocarcinoma with neuroendocrine features, adenosquamous carcinoma, bronchioloalveolar carcinoma, large-cell carcinoma, sarcomatoid carcinoma, and undifferentiated carcinoma.
¶ A total of 13 patients (3.2%) in the ABCP group and 10 (2.5%) in the BCP group had unknown *EGFR* mutation status.
‖ A total of 4 patients (1.0%) in the ABCP group and 4 (1.0%) in the BCP group had unknown *EML4-ALK* rearrangement status.
** A total of 294 patients (73.5%) in the ABCP group and 285 (71.2%) in the BCP group had unknown *KRAS* mutation status.

whole and the WT population. (Additional details on baseline characteristics are provided in Tables S2 and S3 in the Supplementary Appendix.)

PRIMARY ANALYSES OF PROGRESSION-FREE SURVIVAL

At the time of data cutoff (September 15, 2017), the minimum duration of follow-up was 9.5 months (median duration of follow-up in the WT population, 15.4 months in the ABCP group and 15.5 months in the BCP group). In the WT population, among the 692 patients in the ABCP and BCP groups combined, 517 (74.7%) had disease progression or died. Progression-free survival was significantly longer in the ABCP group than in the BCP group (median, 8.3 months vs. 6.8 months; stratified hazard ratio for disease progression or death, 0.62; 95% confidence interval [CI], 0.52 to 0.74; P<0.001); 241 of 356 patients (67.7%) in the ABCP group had disease progression or died as compared with 276 of 336 patients (82.1%) in the BCP group (Fig. 2A). At 6 months, the rate of progression-free survival was higher in the ABCP group than in the BCP group (66.9% vs. 56.1%); the corresponding rates at 12 months were 36.5% and 18.0%. The results were confirmed by central independent review (Fig. S2A in the Supplementary Appendix).

In the Teff-high WT population, among the 284 patients in the ABCP and BCP groups combined, 200 (70.4%) had disease progression or died. Progression-free survival was significantly longer in the ABCP group than in the BCP group (median, 11.3 months vs. 6.8 months; stratified hazard ratio, 0.51; 95% CI, 0.38 to 0.68; P<0.001); 97 of 155 patients (62.6%) in the ABCP group had disease progression or died as compared with 103 of 129 patients (79.8%) in the BCP group (Fig. S3A in the Supplementary Appendix). At 6 months, the rate of progression-free survival was 71.7% in the ABCP group as compared with 57.0% in the BCP group; the corresponding rates at 12 months were 46.0% and 18.0%. The results were confirmed by central independent review (Fig. S2B in the Supplementary Appendix).

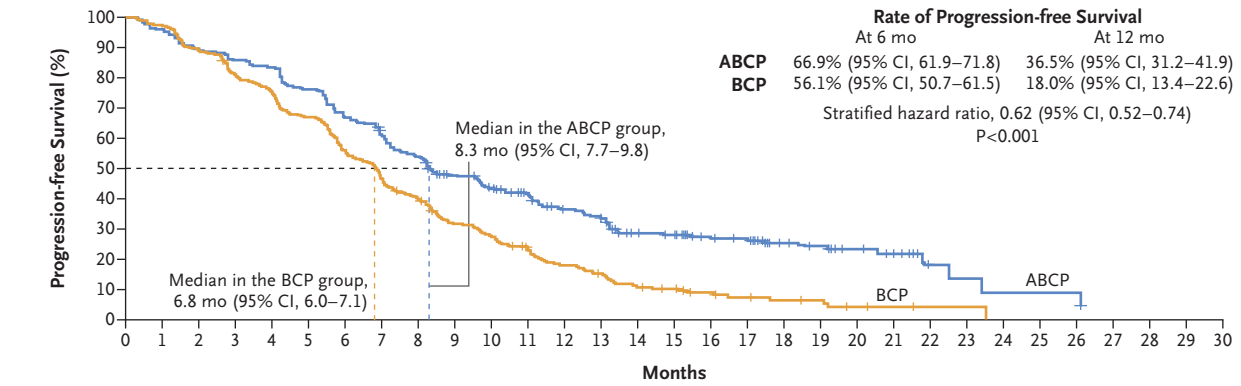
SECONDARY AND EXPLORATORY ANALYSES OF PROGRESSION-FREE SURVIVAL

Progression-free survival among patients with *EGFR* mutations or *ALK* translocations was longer with ABCP than with BCP (median, 9.7 months vs. 6.1 months; unstratified hazard ratio, 0.59; 95% CI, 0.37 to 0.94) (Fig. 2B). Progression-free survival was also longer with ABCP than with BCP in the entire intention-to-treat population, including patients with *EGFR* mutations or *ALK* translocations (median, 8.3 months vs. 6.8 months; stratified hazard ratio, 0.61; 95% CI, 0.52 to 0.72) (Fig. 2B, and Fig. S4 in the Supplementary Appendix).

In the subgroup of patients with low or negative PD-L1 expression (PD-L1 expression on <50% of tumor cells and <10% of tumor-infiltrating immune cells), progression-free survival was longer with ABCP than with BCP (median, 8.0 months vs. 6.8 months; unstratified hazard ratio, 0.68; 95% CI, 0.56 to 0.82); progression-free survival was also longer with ABCP in the subgroup with high PD-L1 expression (median, 12.6 months vs. 6.8 months; unstratified hazard ratio, 0.39; 95% CI, 0.25 to 0.60) (Fig. 2B). Prolonged progression-free survival was observed regardless of PD-L1 status (Fig. 2B), including in the PD-L1–negative subgroup (median, 7.1 months with ABCP vs. 6.9 months with BCP; unstratified hazard ratio, 0.77; 95% CI, 0.61 to 0.99) and the PD-L1–low subgroup (median, 8.3 months vs. 6.6 months; unstratified hazard ratio, 0.56; 95% CI, 0.41 to 0.77), as well as in the subgroup of patients with low expression of a Teff gene signature (median, 7.3 months vs. 7.0 months; unstratified hazard ratio, 0.76; 95% CI, 0.60 to 0.96). A benefit with respect to progression-free survival was observed with ABCP in key clinical and biomarker subgroups, including patients with liver metastases (median, 7.4 months with ABCP vs. 4.9 months with BCP; unstratified hazard ratio, 0.42; 95% CI, 0.26 to 0.66) and patients with *KRAS* mutations (median, 8.1 months vs. 5.8 months; unstratified hazard ratio, 0.50; 95% CI, 0.29 to 0.84). (Additional details are provided in Fig. S3B and Figs. S5 through S7 in the Supplementary Appendix.)

INTERIM ANALYSIS OF OVERALL SURVIVAL

At the time of the interim analysis of overall survival in the WT population (data cutoff, January 22, 2018; the minimum duration of follow-up was approximately 14 months, and the median duration of follow-up was approximately



B Hazard Ratios for Disease Progression or Death in Biomarker Subgroups

Population	No. of Patients (%)	Median Progression-free Survival (mo)		Hazard Ratio (95% CI)
		ABCP	BCP	
ITT population	800 (100)	8.3	6.8	0.61 (0.52–0.72)
Patients with *EGFR* or *ALK* genetic alternations	108 (14)	9.7	6.1	0.59 (0.37–0.94)
WT population	692 (87)	8.3	6.8	0.62 (0.52–0.74)
PD-L1 subgroups (in the WT population)				
TC3 or IC3	135 (20)	12.6	6.8	0.39 (0.25–0.60)
TC1/2/3 or IC1/2/3	354 (51)	11.0	6.8	0.50 (0.39–0.64)
TC1/2 or IC1/2	224 (32)	8.3	6.6	0.56 (0.41–0.77)
TC0/1/2 and IC0/1/2	557 (80)	8.0	6.8	0.68 (0.56–0.82)
TC0 and IC0	338 (49)	7.1	6.9	0.77 (0.61–0.99)
Teff subgroups (in the WT population)				
High gene-signature expression	284 (43)	11.3	6.8	0.51 (0.38–0.68)
Low gene-signature expression	374 (57)	7.3	7.0	0.76 (0.60–0.96)

Figure 2. Investigator-Assessed Progression-free Survival in the ABCP Group and the BCP Group.

Panel A shows the Kaplan–Meier estimates of progression-free survival among the patients in the WT population. Panel B shows the hazard ratios (with 95% confidence intervals) for investigator-assessed progression-free survival in biomarker subgroups. Stratified hazard ratios are given for the ITT population (all enrolled patients, including those with *EGFR* or *ALK* genetic alterations), the WT population, and the Teff-high WT population; unstratified hazard ratios are given for the patients with *EGFR* or *ALK* genetic alterations, all programmed death ligand 1 (PD-L1) subgroups, and the subgroup of patients with low Teff gene-signature expression. The PD-L1 subgroups comprised 692 patients, and the Teff subgroups 658 patients; PD-L1 status and Teff gene-signature expression were evaluated among the patients in the WT population. PD-L1 status was determined by immunohistochemical analysis: TC3 or IC3 indicates PD-L1 expression on at least 50% of tumor cells or at least 10% of tumor-infiltrating immune cells (high PD-L1 expression); TC1/2/3 or IC1/2/3, PD-L1 expression on at least 1% of tumor cells or tumor-infiltrating immune cells (PD-L1–positive); TC1/2 or IC1/2, PD-L1 expression on at least 1% of tumor cells or tumor-infiltrating immune cells and less than 50% of tumor cells or less than 10% of tumor-infiltrating immune cells (low PD-L1 expression); TC0/1/2 and IC0/1/2, PD-L1 expression on less than 50% of tumor cells and less than 10% of tumor-infiltrating immune cells (low or negative PD-L1 expression); and TC0 and IC0, PD-L1 expression on less than 1% of tumor cells and tumor-infiltrating immune cells (PD-L1–negative). Patients with a sensitizing *EGFR* mutation or *ALK* translocation were included in the study if they had had disease progression or the occurrence of unacceptable side effects with at least one approved targeted therapy. The date of data cutoff was September 15, 2017.

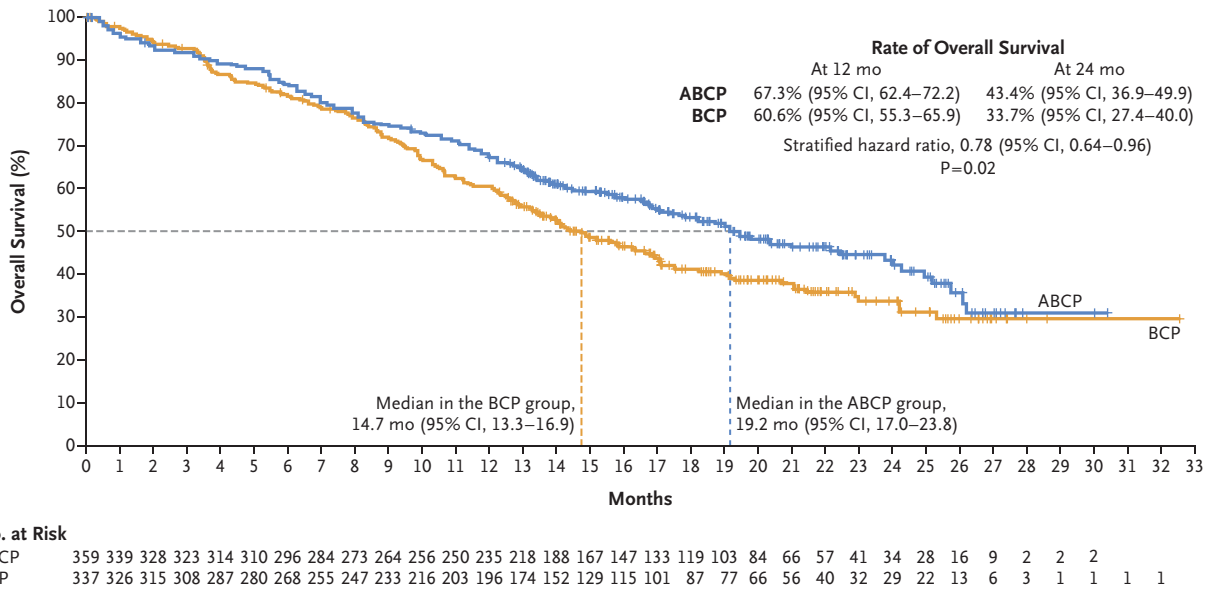


Figure 3. Interim Analysis of Overall Survival in the ABCP Group and the BCP Group.

Shown are Kaplan–Meier estimates of overall survival among the patients in the WT population. The date of data cutoff was January 22, 2018. At the earlier cutoff date of September 15, 2017, four patients were initially reported as having an *EGFR* mutation or an *ALK* translocation and were later confirmed to have WT genotype; this has been corrected in the analysis with the data cutoff at January 22, 2018.

20 months), a total of 376 of the 696 patients in the ABCP and BCP groups combined (54.0%) had died. Overall survival was significantly longer in the ABCP group than in the BCP group (median, 19.2 months vs. 14.7 months; stratified hazard ratio for death, 0.78; 95% CI, 0.64 to 0.96; P=0.02), with 179 deaths occurring among 359 patients in the ABCP group (49.9%), as compared with 197 deaths occurring among 337 patients in the BCP group (58.5%) (Fig. 3). The efficacy boundary for overall survival in the ACP group as compared with the BCP group has not yet been crossed, and therefore data are not shown.

RATE OF OBJECTIVE RESPONSE AND DURATION OF RESPONSE

In the WT population, the rate of investigator-assessed unconfirmed objective response (data cutoff, September 15, 2017) was 63.5% in the ABCP group and 48.0% in the BCP group; 3.7% of the patients in the ABCP group had complete responses, as compared with 1.2% of the patients in the BCP group. The results were similar in the Teff-high WT population (Table 2). In the WT population, the median duration of response was 9.0 months in the ABCP group and 5.7 months in the BCP group; in the Teff-high WT population, the median duration of response was 11.2 months in the ABCP group and 5.7 months in the BCP group (Table 2).

SAFETY

At the final analysis of progression-free survival (data cutoff, September 15, 2017) in the ABCP and BCP groups, a total of 787 patients had received treatment (393 patients had received ABCP and 394 had received BCP) and were included in the safety analysis. Among the patients in the ABCP group, the median duration of treatment with atezolizumab was 8.2 months (range, 0 to 26; median number of doses, 12 [range, 1 to 38]), and the median duration of treatment with bevacizumab was 6.7 months (range, 0 to 26; median number of doses, 10 [range, 1 to 38]). Among the patients in the BCP group, the median duration of treatment with bevacizumab was 5.1 months (range, 0 to 22; median number of doses, 8 [range 1 to 33]). The median duration of chemotherapy in the ABCP group and the BCP group was 2.2 months (range, 0 to 5). Subsequent nonprotocol immunotherapy was administered in 31.7% of patients in the BCP group.

Table 2. Investigator-Assessed Response Rate and Duration of Response.*

Variable	ABCP Group	BCP Group
Response†		
WT population — no. of patients	353	331
Objective response — no. (% [95% CI])	224 (63.5 [58.2–68.5])	159 (48.0 [42.5–53.6])
Complete	13 (3.7 [2.0–6.2])	4 (1.2 [0.3–3.1])
Partial	211 (59.8 [54.5–64.9])	155 (46.8 [41.4–52.4])
Stable disease — no. (% [95% CI])	77 (21.8 [17.6–26.5])	115 (34.7 [29.6–40.1])
Progressive disease — no. (% [95% CI])	18 (5.1 [3.1–7.9])	27 (8.2 [5.4–11.7])
Patients with missing data or who could not be evaluated — no. (%)	34 (9.6)	30 (9.1)
Teff-high WT population — no. of patients	153	127
Objective response — no. (% [95% CI])	106 (69.3 [61.3–76.5])	68 (53.5 [44.5–62.4])
Complete	6 (3.9 [1.5–8.3])	3 (2.4 [0.5–6.8])
Partial	100 (65.4 [57.3–72.9])	65 (51.2 [42.2–60.2])
Stable disease — no. (% [95% CI])	23 (15.0 [9.8–21.7])	39 (30.7 [22.8–39.5])
Progressive disease — no. (% [95% CI])	6 (3.9 [1.5–8.3])	10 (7.9 [3.8–14.0])
Patients with missing data or who could not be evaluated — no. (%)	18 (11.8)	10 (7.9)
Duration of response‡		
WT population — no. of patients	224	159
Median duration of response (range) — mo	9.0 (0.4–24.9§)	5.7 (0.0§–22.1)
Patients with ongoing response at the data-cutoff date — no. (%)	91 (40.6)	32 (20.1)
Teff-high WT population — no.	106	68
Median duration of response (range) — mo	11.2 (0.5–24.9§)	5.7 (0.0§–22.1)
Patients with ongoing response at the data-cutoff date — no. (%)	49 (46.2)	16 (23.5)

* The date of data cutoff was September 15, 2017. The WT population comprised patients in the intention-to-treat (ITT) population who had a wild-type (WT) genotype (patients with *EGFR* or *ALK* genetic alterations were excluded); the Teff-high WT population comprised patients in the WT population who had high expression of an effector T-cell (Teff) gene signature in the tumor.

† Objective response was defined as unconfirmed complete response or partial response, as determined by the investigators according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST). Only patients with measurable disease at baseline and at least one postbaseline tumor assessment were included in the analysis of objective response rate (in the WT population, three patients in the ABCP group and five patients in the BCP group did not have a postbaseline assessment, and in the Teff-high WT population, two patients in each treatment group did not have a postbaseline assessment).

‡ Duration of response was assessed among patients who had an objective response, as determined by the investigator according to RECIST.

§ Data from the patients at the lower or upper range of duration of response were censored.

Adverse events related to any treatment (as determined by the investigator) occurred in 94.4% of the patients in the ABCP group and in 95.4% of the patients in the BCP group (Table 3). Incidence rates of grade 1 or 2 treatment-related adverse events were 35.9% in the ABCP group and 45.4% in the BCP group. The most common grade 3 or 4 treatment-related adverse events were neutropenia, decreased neutrophil count, febrile neutropenia, and hypertension. The incidences of rash, stomatitis, febrile neutropenia, and hemoptysis were higher by less than 10 percentage points among the patients in the ABCP group than among those in the BCP group.

Treatment-related deaths occurred in 11 patients (2.8%) in the ABCP group and in 9 patients (2.3%)

Table 3. Incidence of Treatment-Related Adverse Events.*

Event	ABCP Group (N=393)			BCP Group (N=394)		
	Grade 1–2	Grade 3–4	Grade 5	Grade 1–2	Grade 3–4	Grade 5
	number of patients (percent)					
Treatment-related adverse events	141 (35.9)	219 (55.7)	11 (2.8)	179 (45.4)	188 (47.7)	9 (2.3)
Treatment-related adverse events with an incidence of ≥10%†						
Alopecia	183 (46.6)	0	0	173 (43.9)	0	0
Peripheral neuropathy	141 (35.9)	11 (2.8)	0	113 (28.7)	9 (2.3)	0
Nausea	119 (30.3)	15 (3.8)	0	101 (25.6)	8 (2.0)	0
Fatigue	88 (22.4)	13 (3.3)	0	79 (20.1)	10 (2.5)	0
Anemia	70 (17.8)	24 (6.1)	0	71 (18.0)	23 (5.8)	0
Decreased appetite	77 (19.6)	10 (2.5)	0	56 (14.2)	3 (0.8)	0
Diarrhea	70 (17.8)	11 (2.8)	0	58 (14.7)	2 (0.5)	0
Neutropenia	18 (4.6)	54 (13.7)	0	24 (6.1)	44 (11.2)	0
Hypertension	50 (12.7)	25 (6.4)	0	42 (10.7)	25 (6.3)	0
Arthralgia	63 (16.0)	3 (0.8)	0	55 (14.0)	4 (1.0)	0
Constipation	65 (16.5)	0	0	45 (11.4)	0	0
Asthenia	52 (13.2)	5 (1.3)	0	53 (13.5)	11 (2.8)	0
Epistaxis	50 (12.7)	4 (1.0)	0	68 (17.3)	0	0
Vomiting	50 (12.7)	6 (1.5)	0	51 (12.9)	5 (1.3)	0
Decreased platelet count	34 (8.7)	20 (5.1)	0	35 (8.9)	9 (2.3)	0
Myalgia	51 (13.0)	2 (0.5)	0	46 (11.7)	1 (0.3)	0
Thrombocytopenia	36 (9.2)	16 (4.1)	0	28 (7.1)	17 (4.3)	0
Proteinuria	41 (10.4)	10 (2.5)	0	37 (9.4)	11 (2.8)	0
Decreased neutrophil count	14 (3.6)	34 (8.7)	0	10 (2.5)	25 (6.3)	0
Rash	47 (12.0)	5 (1.3)	0	20 (5.1)	0	0
Stomatitis	43 (10.9)	4 (1.0)	0	20 (5.1)	1 (0.3)	0
Paresthesia	42 (10.7)	0	0	36 (9.1)	1 (0.3)	0
Febrile neutropenia	2 (0.5)	33 (8.4)	3 (0.8)	0	23 (5.8)	0

* The incidence of treatment-related adverse events from any component of the treatment is shown. The date of data cutoff was September 15, 2017.
† For grade 3–4 events, treatment-related adverse events with an incidence of 5% or higher are listed.

in the BCP group (Table 3). Five deaths with ABCP were due to pulmonary hemorrhage or hemoptysis, four of which occurred in patients with potential high-risk features (e.g., tumor infiltration of great vessels or cavitation).[1,32] These events occurred early in the study and led to changes in the education provided to the investigators and study staff to improve the early identification and care of patients with high-risk features. Treatment-related serious adverse events were noted in 25.4% of the patients in the ABCP group and in 19.3% of those in the BCP group.

A total of 77.4% of the immune-related adverse events that occurred in the ABCP group were grade 1 or 2 and none were grade 5. The most common immune-related adverse events were rash, hepatitis, hypothyroidism, hyperthyroidism, pneumonitis, and colitis. (Additional information on adverse events are provided in Tables S4 through S7 in the Supplementary Appendix.)

DISCUSSION

The results of this phase 3 randomized trial showed a significant improvement in progression-free survival and overall survival with the addition of atezolizumab to BCP as first-line treatment for nonsquamous metastatic NSCLC. The rate of progression-free survival at 12 months was twice as high with ABCP as with BCP (36.5% vs. 18.0%), and the risk of death was lower (by 22%) and the rate of objective response higher (63.5% vs. 48.0%) with ABCP than with BCP.

ABCP induced longer progression-free survival across all tested subgroups of patients according to PD-L1 expression and according to Teff gene-signature expression, including patients with low or negative PD-L1 expression and those with low Teff gene-signature expression. High Teff gene-signature expression — a surrogate marker of PD-L1 expression and preexisting immunity[29] — conferred a greater progression-free survival benefit; however, the degree of benefit was similar to that for high PD-L1 expression. These findings in unselected patients with metastatic NSCLC are particularly relevant because the use of PD-1 inhibitors as first-line monotherapy is currently limited to patients with high PD-L1 expression, and most patients with metastatic NSCLC have tumors with low, negative, or unknown PD-L1 expression.[33]

The benefit of ABCP with respect to progression-free survival was consistent across all clinical subgroups analyzed, including patients with liver metastases at baseline, a population that had previously had limited therapeutic benefit with checkpoint-inhibitor monotherapy.[34-36] The benefit observed in patients with *EGFR* or *ALK* genetic alterations is notable, given that clinical trials that have investigated the use of PD-L1 or PD-1 inhibitors as monotherapy after the failure of tyrosine kinase inhibitor therapy have not shown that these therapies are more effective than standard chemotherapy in these patients.[8,10,11] Furthermore, such patients have limited proven treatment options, and data are lacking from phase 3 trials investigating the effectiveness of platinum-based regimens with or without PD-L1 or PD-1 inhibitors in this patient population.[37]

A benefit with respect to progression-free survival was not observed in phase 2 and 3 trials comparing atezolizumab with docetaxel in patients who had previously received treatment for NSCLC.[8,28] The results of the current trial may have differed from the findings in those trials because of our addition of atezolizumab to bevacizumab and chemotherapy, both of which have immunomodulatory effects that may augment the efficacy of atezolizumab[26,27] or because the patients in our trial received an earlier line of therapy (since our eligibility criteria included no previous receipt of chemotherapy for NSCLC).

The Kaplan–Meier curves of progression-free survival among the patients who received ABCP were nonproportional with respect to the treatment effect of ABCP and BCP. The progression-free survival benefit with ABCP was delayed and increased substantially after the median was reached, as evidenced by a rate of progression-free survival in the ABCP group that was double that in the BCP group at 12 months. Similarly, in the interim analysis of overall survival, a benefit was observed among the patients who received ABCP, as compared with those who received BCP, regardless of the nonproportionality of the Kaplan–Meier curves.

The safety profile of ABCP was consistent with safety profiles of the individual medicines,[1,8] including the rate of hemorrhagic events caused by bevacizumab; no new safety signals were identified with the combination. The frequency of treatment-related serious adverse events was similar to that in previously reported studies of chemotherapy combined with checkpoint inhibitors.[5] The incidence and nature of immune-related adverse events in the ABCP group were similar to those with atezolizumab monotherapy.[8,28,38] Most adverse events were transient and were limited to the chemotherapy induction phase. The rate of serious adverse effects during maintenance treatment with atezolizumab, bevacizumab, or both was low, a finding that is clinically relevant, given that induction represents a short time (approximately 2.2 months), whereas maintenance treatment can be prolonged.

The large population size of the IMpower150 study and the inclusion criteria allowed for testing of ABCP in clinically relevant subgroups (e.g., patients with *EGFR* or *ALK* genomic alterations and those with low PD-L1 expression). However, because this was a large multinational study, the reporting of data on previous treatments was dependent on individual study sites. This

study tests only the efficacy of atezolizumab plus bevacizumab in combination with one chemotherapy regimen. Other trials are investigating atezolizumab with different chemotherapy combinations (the IMpower130 study [ClinicalTrials.gov number, NCT02367781], the IMpower131 study [NCT02367794], and the IMpower132 study [NCT02657434]).

In summary, the phase 3 IMpower150 study showed that the addition of atezolizumab to bevacizumab plus chemotherapy as first-line treatment for nonsquamous metastatic NSCLC resulted in a significant improvement in progression-free survival and overall survival, regardless of PD-L1 expression and *EGFR* or *ALK* genetic alteration status.

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APPENDIX

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