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Clinical Trials: Immunotherapy

Clinical Cancer Research

Efficacy and Safety of the Biosimilar ABP 215 Compared with Bevacizumab in Patients with Advanced Nonsquamous Non–small Cell Lung Cancer (MAPLE): A Randomized, Double-blind, Phase III Study

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Abstract

Purpose: This phase III study compared clinical efficacy and safety of the biosimilar ABP 215 with bevacizumab reference product (RP) in patients with advanced nonsquamous non–small cell lung cancer (NSCLC).

Patients and Methods: Patients were randomized 1:1 to ABP 215 or bevacizumab 15 mg/kg every three weeks for 6 cycles. All patients received carboplatin and paclitaxel every three weeks for ≥4 and ≤6 cycles. The primary efficacy endpoint was risk ratio of objective response rate (ORR); clinical equivalence was confirmed if the 2-sided 90% confidence interval (CI) of the risk ratio was within the margin of 0.67 to 1.5. Secondary endpoints included risk difference of ORR, duration of response (DOR), progression-free survival (PFS), and overall survival (OS); pharmacokinetics, adverse events (AEs), and incidence of antidrug antibodies (ADAs) were monitored.

Results: A total of 820 patients were screened; 642 were randomized to ABP 215 ($n = 328$) and bevacizumab ($n = 314$). Overall, 128 (39.0%) and 131 (41.7%) patients in the ABP 215 and bevacizumab groups, respectively, had objective responses [ORR risk ratio: 0.93 (90% CI, 0.80–1.09)]. In the ABP 215 and bevacizumab group, 308 (95.1%) and 289 (93.5%) patients, respectively, had at least 1 AE; 13 (4.0%) and 11 (3.6%) experienced a fatal AE. Anti-VEGF toxicity was low and comparable between treatment groups. At week 19, median trough serum drug concentration was 132 μg/mL (ABP 215 group) and 129 μg/mL (bevacizumab group). No patient tested positive for neutralizing antibodies.

Conclusions: ABP 215 is similar to bevacizumab RP with respect to clinical efficacy, safety, immunogenicity, and pharmacokinetics. The totality of evidence supports clinical equivalence of ABP 215 and bevacizumab.

Introduction

Non–small cell lung cancer (NSCLC) is the leading cause of cancer-related death in both men and women in the United States and the European Union. Bevacizumab is approved in the United States, European Union, and elsewhere for first-line treatment in patients with advanced or recurrent nonsquamous NSCLC in combination with platinum-based chemotherapy. Bevacizumab is also approved in the United States and European Union for the treatment of patients with glioblastoma (United States only); metastatic colorectal cancer; metastatic renal cell carcinoma; persistent, recurrent, or metastatic cervical cancer; recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer; and metastatic breast cancer (European Union only) (1, 2). ABP 215 [U.S.: MVASI (bevacizumab-awwb); EU: MVASI (bevacizumab)] has been approved as the first biosimilar to bevacizumab (Amgen Inc.).

Similarity between ABP 215 and bevacizumab has been demonstrated in multiple, rigorous nonclinical and preclinical evaluations. ABP 215 has been shown to have the same primary and higher-order structure as bevacizumab (3). In addition, high similarity between ABP 215 and bevacizumab has been demonstrated with respect to biological functions in molecular studies and pharmacokinetic parameters in healthy volunteers (3, 4). Here, we report the results of a phase III randomized study (MAPLE; registered at ClinicalTrials.gov, NCT01966003) comparing the efficacy, safety, immunogenicity,

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Translational Relevance

Analytic, functional, and phase I clinical pharmacokinetic studies have demonstrated that ABP 215 is similar to bevacizumab and there was no evidence of increased immunogenicity in the phase I study. This randomized, double-blind, phase III comparative trial (MAPLE Study) was conducted to assess the clinical similarity of ABP 215 to bevacizumab reference product in patients with advanced non–small cell lung cancer. In the ABP 215 and bevacizumab group, 128 (39.0%) and 131 (41.7%) patients had objective responses, respectively [objective response rate risk ratio, 0.93; 90% confidence interval (CI), 0.80–1.09]. Adverse events were low and comparable and no patient tested positive for neutralizing antibodies. The results of this study add to the growing body of evidence supporting the clinical value of the biosimilar ABP 215. Bevacizumab biosimilars offer the potential to expand treatment options, mitigate cost barriers for payers, and increase patient access to this important therapy in oncology.

and pharmacokinetic profiles of ABP 215 and bevacizumab reference product (RP) in patients with advanced nonsquamous NSCLC.

Patients and Methods

Study design and treatments

This study was conducted in compliance with the International Council for Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. The study was reviewed and approved by an independent ethics committee or institutional review board. Written informed consent was obtained from all patients before any study-related procedures were performed.

This study was a randomized, double-blind, active-controlled study in adult patients with nonsquamous NSCLC receiving first-line chemotherapy with carboplatin and paclitaxel. The study was conducted at 101 study centers in 17 countries in Asia/Pacific, Europe, North America, and Latin America. The primary objective was to compare the efficacy of ABP 215 with bevacizumab RP. The secondary objectives included assessment of safety, including events of interest (including those associated with anti-VEGF toxicities), pharmacokinetics, and immunogenicity of ABP 215 compared with bevacizumab RP.

Eligible patients included males and females $\geq$18 and <80 years of age with histologically or cytologically confirmed, stage IV or recurrent metastatic nonsquamous NSCLC with measurable disease according to the modified RECIST v1.1. For patients with recurrent disease, at least 12 months had to have elapsed since completing adjuvant chemotherapy. Patients had to have a baseline CT or MRI scan of the chest and abdomen to assess disease burden before enrolling in the study and receiving first-line chemotherapy for NSCLC. If the scan was performed more than 28 days before randomization, an additional scan was obtained. First-line carboplatin/paclitaxel chemotherapy had to be initiated within 8 days after randomization, and patients had to be expected to receive at least 4 cycles of chemotherapy. Patients had to have adequate bone marrow, hepatic, and renal function and a life expectancy >6 months.

Exclusion criteria included patients with small-cell lung cancer or mixed small-cell lung cancer and NSCLC; mixed adenosquamous carcinomas with a predominantly squamous component; history or known presence of central nervous system metastases; malignancy other than NSCLC within 5 years (except adequately treated *in situ* cervical cancer, or squamous or basal cell carcinoma of the skin); or planned major surgical procedure during the treatment phase.

Patients were randomly assigned 1:1 to receive intravenous ABP 215 or bevacizumab 15 mg/kg administered every three weeks for 6 cycles. All patients received carboplatin and paclitaxel chemotherapy every three weeks for $\geq$4 and $\leq$6 cycles. All doses of investigational product (IP) were administered as an intravenous infusion; the first dose was administered over 90 minutes. If the first IP administration was well tolerated, the second infusion could be administered over 60 minutes. If infusion over 60 minutes was tolerated, all subsequent infusions were administered over 30 minutes.

Patients remained on the treatment phase until 21 days after the last dose of IP or study-specified chemotherapy. Patients were followed for disease progression and overall survival (OS) after completing the end-of-treatment visit until the end of the clinical study, withdrawal of consent, lost to follow-up, death, or receipt of prescribed therapy, including nonstudy anticancer treatment.

Randomization and masking

All patients who entered into the screening period received a unique patient identification number before any study procedures were performed. Upon completion of screening, the site contacted an interactive voice and web response system (IXRS) to receive a unique patient randomization number to randomize the patient centrally to treatment. Randomization was stratified by geographic region (Eastern Europe vs. Western Europe vs. Asia Pacific/Other vs. North America), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1), and sex.

Schedule of assessments and procedures

Medical history, physical examination, vital signs, concommitant medications, electrocardiography, adverse events (AEs), laboratory assessments, and ECOG performance were performed at screening. Physical examination, vital signs, concommitant medications, AEs, and laboratory evaluation, including serum chemistry, hematology, urine protein, pharmacokinetic sampling, and antidrug antibodies (ADAs), were performed at baseline. Vital signs, AEs, concomitant medication, serum chemistry, hematology, and urine protein were assessed at weeks 4, 7, 10, 13, 16, and at the end of treatment (week 19).

Patients underwent a CT scan or MRI at screening, week 7, week 13, and at the end of treatment. After completing the end-of-treatment visit, patients were followed for disease progression and OS every 9 weeks until the end of the clinical study, withdrawal of consent, lost to follow-up, death, or receipt of prescribed therapy (e.g., commercial bevacizumab, nonstudy anticancer treatment). Disease assessments were performed by the investigator and by central, independent, blinded radiologists.

Pharmacokinetic (predosing) and ADA sampling were performed at baseline, weeks 4 (pharmacokinetics only), 7, 13, and at the end of treatment. ADA sampling was also performed 6 months after the end of treatment for patients still on study. Patients with positive binding ADA results were assessed for neutralizing antibodies.

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Primary and secondary endpoints

The primary efficacy endpoint was the risk ratio of objective response rate (ORR), defined as the rate of the best overall response of either complete response (CR) or partial response (PR) according to RECIST v1.1 during study. The primary analysis was based on the central, independent, blinded radiologists' review of radiographic images in the intent-to-treat (ITT) population. All patients who did not meet the criteria for CR or PR by the end of the study were considered nonresponders.

Secondary efficacy endpoints included risk difference of ORR, duration of response (DOR), and progression-free survival (PFS). PFS was defined as the time from randomization until the first occurrence of disease progression per RECIST v1.1 or death. For patients alive and progression-free at the close of study, PFS was censored at the date of the last tumor evaluation demonstrating lack of progression. DOR was calculated as time from the first objective response (PR or CR) to disease progression according to RECIST v1.1. For responders not meeting the criteria for progression by the end of the study, DOR was censored at the date of the last evaluable tumor assessment.

Safety endpoints included incidence of AEs, AEs of interest (including anti-VEGF–related AEs), OS, changes in clinical laboratory tests and vital signs, and incidence of ADAs.

Here, we report the results of the primary endpoint of RR of ORR, and secondary endpoints including RD of ORR, OS, DOR, PFS, AEs, pharmacokinetics, and incidence of ADAs.

Statistical analysis

The sample size was chosen to achieve >90% power to demonstrate equivalence between ABP 215 and bevacizumab on the primary efficacy endpoint (risk ratio of ORR) with a margin of 0.67 to 1.5 at a 2-sided significance level of 0.05. It was assumed that the ORR would be approximately 38% in both the ABP 215 and bevacizumab arms (5).

The ITT population consisted of all randomized patients. The tumor analysis set consisted of all randomized patients who were treated with IP and had measurable disease at screening as determined by the central radiology review. The per protocol population was a subset of the tumor analysis set that included patients who completed the treatment period or who discontinued IP or chemotherapy before completing 6 cycles of IP and at least 4 cycles of chemotherapy due to reasons allowed per protocol (i.e., disease progression, AEs, and death), and did not experience a protocol deviation that affected their evaluation for the primary objective of the study. The protocol deviations that affect evaluation for the primary objective were determined on the basis of a blinded data review prior to database lock. Analyses for the per protocol population were based on actual treatment received. The safety population included all randomized patients who were treated with IP.

Clinical equivalence of the primary endpoint was demonstrated by comparing the 2-sided 90% CI of the risk ratio in ORR between ABP 215 and bevacizumab with the prespecified equivalence margin of 0.67 to 1.5. The primary analysis was based on response determined by independent, blinded radiologists, and the ITT population consisted of all randomized patients. The 90% CIs for risk ratio were estimated using a generalized linear model adjusted for stratification factors. A sensitivity analysis was also performed, including the following baseline covariates in the model, in addition to the randomization stratification factors: weight loss in the last 6 months, age group, stage IV/recurrent disease at baseline, race, smoking history, EGFR mutation status, and ALK status. The linear model and sensitivity analyses were prospectively defined. The 90% CIs for risk difference of ORR were also determined. Descriptive 90% CIs on the HR for PFS in the ITT population were estimated using Cox models stratified by the stratification factors. Kaplan–Meier (KM) estimates of quartiles are provided for time-to-event endpoints. Analysis of DOR included patients in the ITT population who had an objective response and based on the response determined by the central, independent, blinded radiologists.

All reported AEs were coded according to MedDRA v18, and the severity of each AE was graded by the investigator according to CTCAE v4.03 criteria.

Results

Patients and exposure

Patient disposition is shown in Fig. 1; 820 patients were screened and 642 patients were randomized to ABP 215 (n = 328) and bevacizumab (n = 314). Of the randomized patients, 324 (98.8%) and 309 (98.4%) patients in the ABP 215 and bevacizumab group, respectively, received at least 1 dose of IP and were included in the safety analysis population; 317 (96.6%) and 305 (97.1%) patients, respectively, received at least 1 dose of IP and had measurable disease at baseline. In general, the 2 treatment arms were balanced with respect to demographic characteristics and baseline disease characteristics (Table 1). The median time since original diagnosis with NSCLC was 4.0 weeks in both groups.

Exposure to IP in the 2 treatment arms was comparable; the mean (SD) number of IP doses was 4.8 (1.76) and 5.0 (1.61) in the ABP 215 and bevacizumab group, respectively. The number of patients completing at least 6 doses of IP was 192 (59.0%) and 202 (65.4%) in the ABP 215 and bevacizumab group, respectively. One patient in the ABP 215 arm received 7 doses of IP. Similar numbers of patients in the 2 treatment arms had at least 1 dose delay [72 (22.2%) patients and 70 (22.7%) patients], doses withheld at least once [6 (1.9%) patients and 10 (3.2%) patients], and a least 1 dose interruption [3 (0.9%) patients and 0 patients], in the ABP 215 and bevacizumab group, respectively. Most dose delays, doses withheld, and dose interruptions were due to AEs. No more than 2 patients had a partial dose of IP at any time point. The mean (SD) numbers of paclitaxel doses were 4.5 (1.69) and 4.7 (1.56) in the ABP 215 and bevacizumab arms, respectively. The mean (SD) numbers of carboplatin doses were 4.6 (1.67) and 4.7 (1.57) in ABP 215 and bevacizumab, respectively. Most dose delays, doses withheld, and dose changes were due to AEs.

Efficacy

A total of 128 (39.0%) and 131 (41.7%) in the ABP 215 and bevacizumab group, respectively, had objective responses (CR or PR); PFS and OS were comparable in both treatment groups (Table 2A). The risk ratio (ABP 215 to bevacizumab) for ORR was 0.93 (90% CI, 0.80–1.09). The 2-sided 90% CI for ORR was within the prespecified equivalence margin of 0.67 to 1.5 (Fig. 2). Two patients (0.6%) in each treatment arm had complete responses; the remaining responders [126 (38.4%) and 129 patients (41.1%) in the ABP 215 and bevacizumab group, respectively] had partial responses.

The results were consistent in all secondary and sensitivity analyses of the primary endpoint. The RR of ORR based on the

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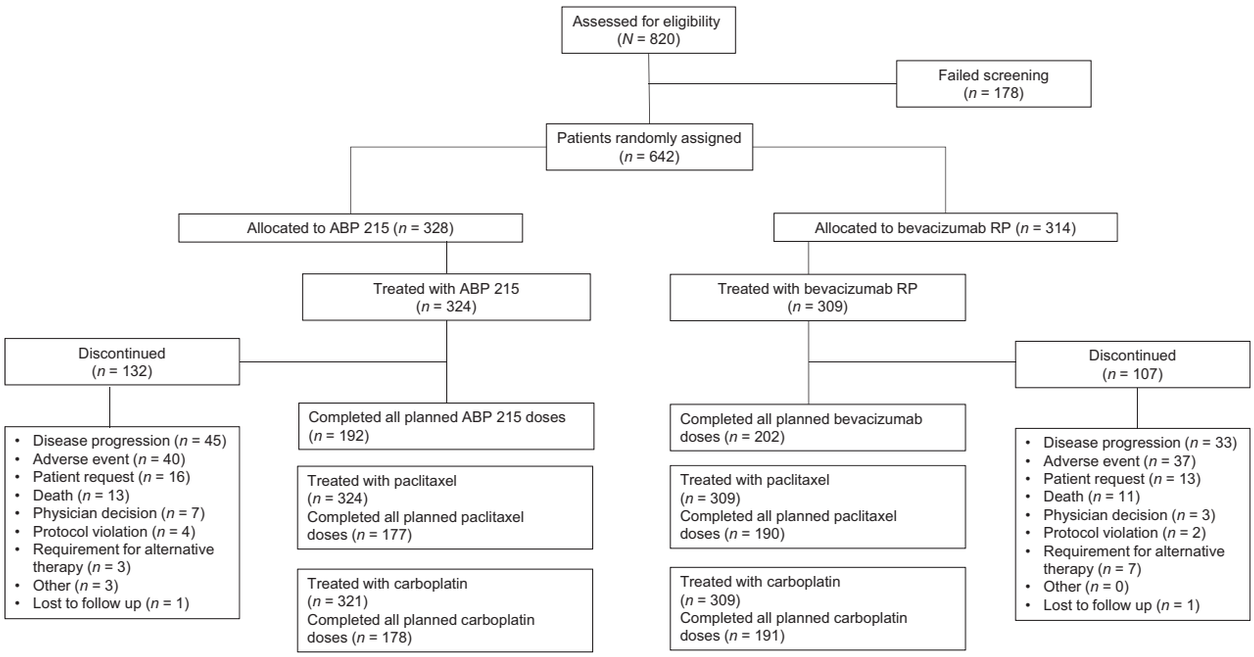

Figure 1.
Patient disposition.

Table 1. Patient demographics and baseline characteristics (ITT population)

	ABP 215 (*N* = 328)	Bevacizumab (*N* = 314)
Age, mean (SD)	61.6 (9.09)	61.6 (8.88)
< 65 years, *n* (%)	199 (60.7)	191 (60.8)
≥ 65 years, *n* (%)	129 (39.3)	123 (39.2)
Weight, mean (SD)	71.2 (14.7)	73.5 (15.3)
Race, *n* (%)		
White	315 (96.0)	300 (95.5)
Black	2 (0.6)	5 (1.6)
Asian	6 (1.8)	7 (2.2)
Other	7 (2.1)	2 (0.6)
Sex		
Male	196 (59.8)	188 (59.9)
Geographic region, (%)		
Eastern Europe	189 (57.6)	186 (59.2)
Western Europe	78 (23.8)	76 (24.2)
North America	31 (9.5)	26 (8.3)
Asia Pacific/ Other	30 (9.1)	26 (8.3)
Smoking status, *n* (%)		
Never	65 (19.8)	76 (24.2)
Former	163 (49.7)	158 (50.3)
Current	100 (30.5)	80 (25.5)
Staging of original diagnosis, *n* (%)		
≤ Stage IIIA	23 (7.0)	25 (8.3)[a]
Stage IIIB	2 (0.6)	7 (2.2)
Stage IV	303 (92.4)	281 (89.5)
Disease stage at baseline, *n* (%)		
Stage IV	309 (94.2)	290 (92.4)
Recurrent disease	19 (5.8)	24 (7.6)
Weight loss in past 6 months, *n* (%)		
0%–5%	289 (88.1)	276 (87.9)[a]
> 5%–10%	39 (11.9)	37 (11.8)
ECOG performance status, *n* (%)		
Grade 0	127 (38.7)	117 (37.3)
Grade 1	201 (61.3)	197 (62.7)

[a]One patient with missing data.

central, independent, blinded radiologists' review in the PP population was 0.94 (90% CI, 0.80–1.10), and the RR in the tumor response set was 0.93 (90% CI, 0.80–1.09). The RR of ORR based on the investigator assessment in the ITT population was 1.01 (90% CI, 0.88–1.16), and the RR of ORR based on the central, independent, blinded radiologists' review in the ITT population when including additional covariates in the model was 0.90 (90% CI, 0.77–1.05).

Clinical equivalence was also supported by comparing the risk difference (RD) of ORR between ABP 215 and bevacizumab RP. The RD between the treatment arms was −2.90% (90% CI, −9.26%–3.45%) in the ITT population based on central, independent, blinded radiologists' review. The results were similar in the secondary and sensitivity analyses in both the PP population (−2.82%; 90% CI, −9.73%–4.10%) and in the tumor response set (−2.78%; 90% CI, −9.27%–3.71%), and also when using the investigator's assessment of response in the ITT population (−0.68%; 90% CI, −7.11%–5.76%).

Table 2A. Summary of primary efficacy results (ITT Population)

	ABP 215 (*N* = 328)	Bevacizumab (*N* = 314)
Best overall response, *n* (%)		
Complete response	2 (0.6)	2 (0.6)
Partial response	126 (38.4)	129 (41.1)
Stable disease	144 (43.9)	137 (43.6)
Progressive response	21 (6.4)	18 (5.7)
Not evaluable	35 (10.7)	28 (8.9)
ORR, *n* (%)[a]	128 (39.0)	131 (41.7)
PFS, *n* (%)[b]	197 (60.1)	189 (60.2)
OS, *n* (%)	281 (86.7)	273 (88.3)

[a]On the basis of RECIST v1.1.
[b]Patients who were alive and progression-free at the end of the study.

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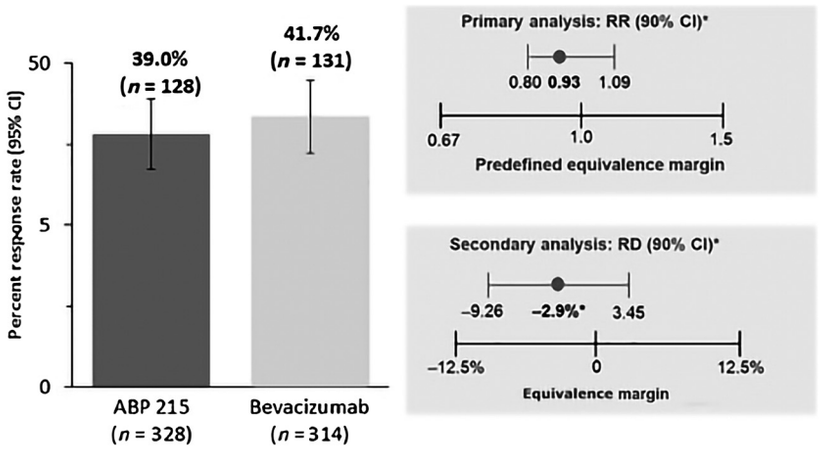

Figure 2.
Response rate and risk ratio of ORR.
ORR, objective response rate (defined as complete or partial response based on RECIST V1.1); RR, risk ratio (based on a generalized linear model adjusted for randomization stratification factors geographic region, ECOG performance status, and sex); RD, risk difference.

The KM curves for DOR, PFS, and OS are presented in Fig. 3. ABP 215 and bevacizumab were similar with regard to PFS; 131 (39.9%) patients in the ABP 215 arm and 125 (39.8%) patients in the bevacizumab arm had progressed or died before they ended the study. The estimated hazard ratio (HR) was 1.03 (90% CI, 0.83–1.29). The estimated DOR medians were 5.8 months (95% CI, 4.9–7.7) and 5.6 months (95% CI, 5.1–6.3 months).

Safety

A summary of AEs is shown in Table 2B; only treatment-emergent AEs are included in the summaries. Most AEs were grade 1 or 2 in severity. AEs grade ≥3 were commonly associated with anti-VEGF toxicities including hypertension, gastrointestinal perforations, pulmonary hemorrhage, wound-healing complications, and proteinuria, and were comparable between treatment groups (Fig. 4).

In the ABP 215 and bevacizumab group, respectively, 85 (26.2%) and 71 (23.0%) patients had serious AEs, including febrile neutropenia [11 (3.4%) and 8 (2.6%)], neutropenia [6 (1.9%) and 3 (1.0%)], pneumonia [6 (1.9%) and 5 (1.6)], pulmonary embolism [5 (1.5%) and 6 (1.9%)], anemia [3 (0.9%) and 6 (1.9%)], dyspnea [3 (0.9%) and 4 (1.3%)], and hemoptysis [3 (0.9%) and 5 (1.6%)].

Twenty-four patients, including 13 (4.0%) and 11 (3.6%) patients in the ABP 215 and bevacizumab groups, respectively, experienced a fatal AE during the treatment phase. AEs with fatal outcomes in more than 1 patient included death (not otherwise specified), hemoptysis, and rectal hemorrhage in the ABP 215 group ($n = 2$ each) and hemoptysis ($n = 2$) in the bevacizumab group.

Table 2B. Overall summary of AEs

AE category, *n* (%)	ABP 215 (*N* = 324)	Bevacizumab (*N* = 309)
Any AE	308 (95.1)	289 (93.5)
Any grade ≥ 3 AE	139 (42.9)	137 (44.3)
Any fatal AE	13 (4.0)	11 (3.6)
Any serious AE	85 (26.2)	71 (23.0)
Any AE leading to discontinuation of IP	61 (18.8)	53 (17.2)
Any AE leading to discontinuation of any component of chemotherapy	74 (22.8)	59 (19.1)
Any AE leading to dose delay of IP	73 (22.5)	69 (22.3)
Any AE leading to dose delay of any component of chemotherapy	86 (26.5)	83 (26.9)
Any AE leading to dose reduction of any component of chemotherapy	48 (14.8)	49 (15.9)

NOTE: Only treatment-emergent AEs are summarized. For each category, patients are included only once, even if they had multiple events in that category.

Pharmacokinetics

Median trough serum concentration values were similar between ABP 215 and bevacizumab at all pharmacokinetic sample collection time points. At week 19, median trough serum concentration was 131.8 μg/mL and 129.0 μg/mL in the ABP 215 and bevacizumab group, respectively.

Immunogenicity

Four (1.4%) and 7 (2.5%) patients in the ABP 215 and bevacizumab group, respectively, developed binding ADAs during the study, of which 3 patients (1.0% and 1.1%) in each arm had transient binding ADAs, that is, they were negative at the patient's last time point tested within the study period. No patient in either treatment arm tested positive for neutralizing antibodies.

Discussion

This phase III study compared the efficacy, safety, and immunogenicity of the biosimilar ABP 215 and bevacizumab RP. The study met its primary endpoint. The risk ratio of ORR and 90% CI between ABP 215 and bevacizumab RP based on the central, independent, blinded radiologists' review of radiographic images were within the prespecified equivalence margin, indicating that clinical efficacy in ABP 215 and bevacizumab RP is similar. Analysis of risk difference of ORR also supports clinical equivalence. DOR, PFS, and pharmacokinetic profiles were also similar between treatment groups. The results in all secondary and sensitivity analyses of the primary endpoint further support similarity in clinical efficacy.

The frequency, type, and severity of AEs and AEs of interest were comparable between ABP 215 and bevacizumab RP and were within the expected range of type and severity described for bevacizumab. Moreover, the incidence of AEs commonly associated with anti-VEGF toxicities was comparable between groups. This finding has important clinical implications because biosimilars are usually approved across all indications for the originator product, and these anti-VEGF toxicities are common across bevacizumab indications. Immunogenicity was similar; few patients developed binding ADAs in either group and no patients developed neutralizing antibodies.

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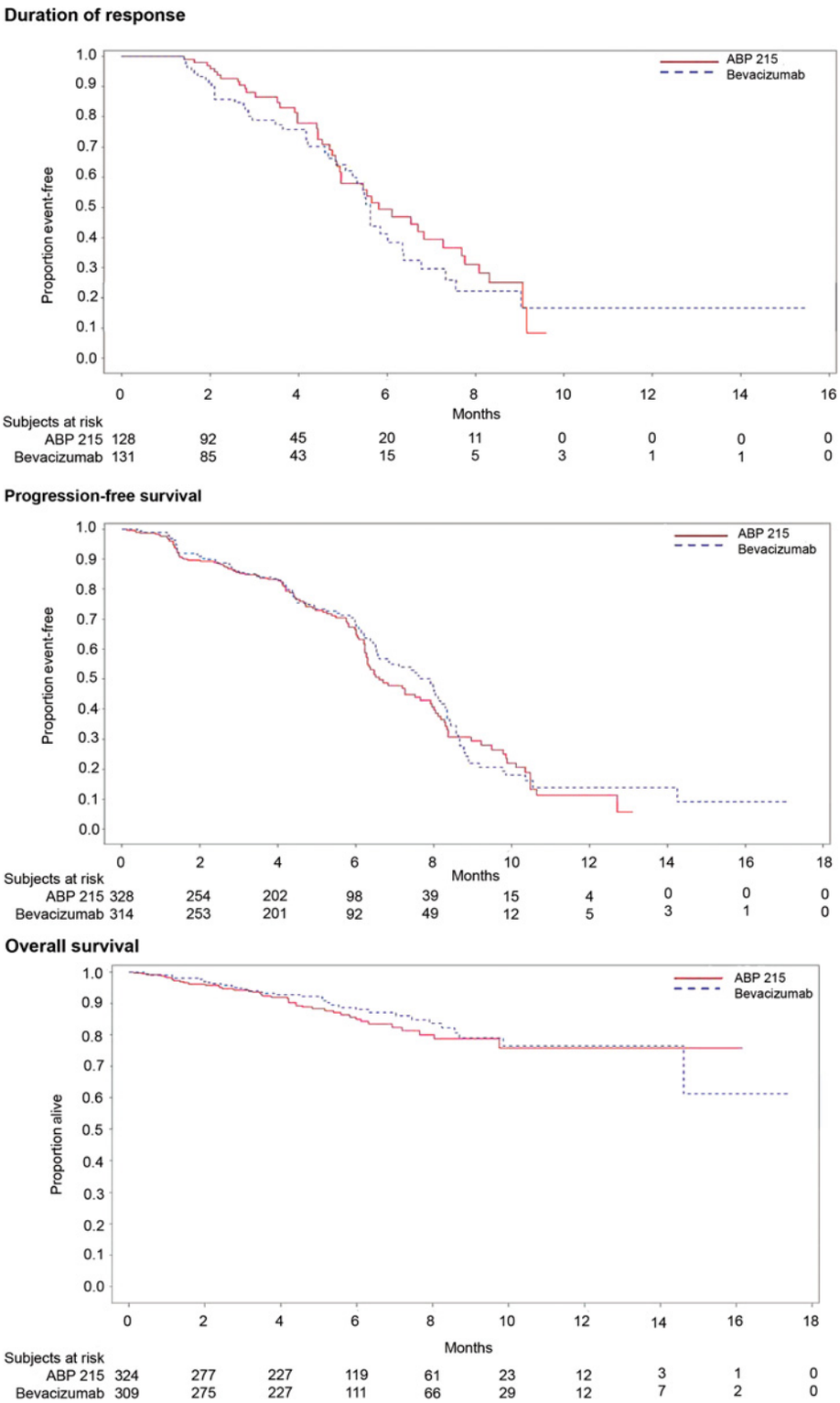

Figure 3.
KM plot of DOR, PFS, and OS.

The patient population was selected based in part on the size of the expected treatment effect with bevacizumab in patients with NSCLC. Based on the results of a meta-analysis of 4 randomized bevacizumab studies in NSCLC, it was assumed that the ORR would be approximately 38% in both the ABP 215 and bevacizumab arms (5). In addition, this patient population represents a sensitive and homogenous population chosen to minimize potential confounding factors. The response to

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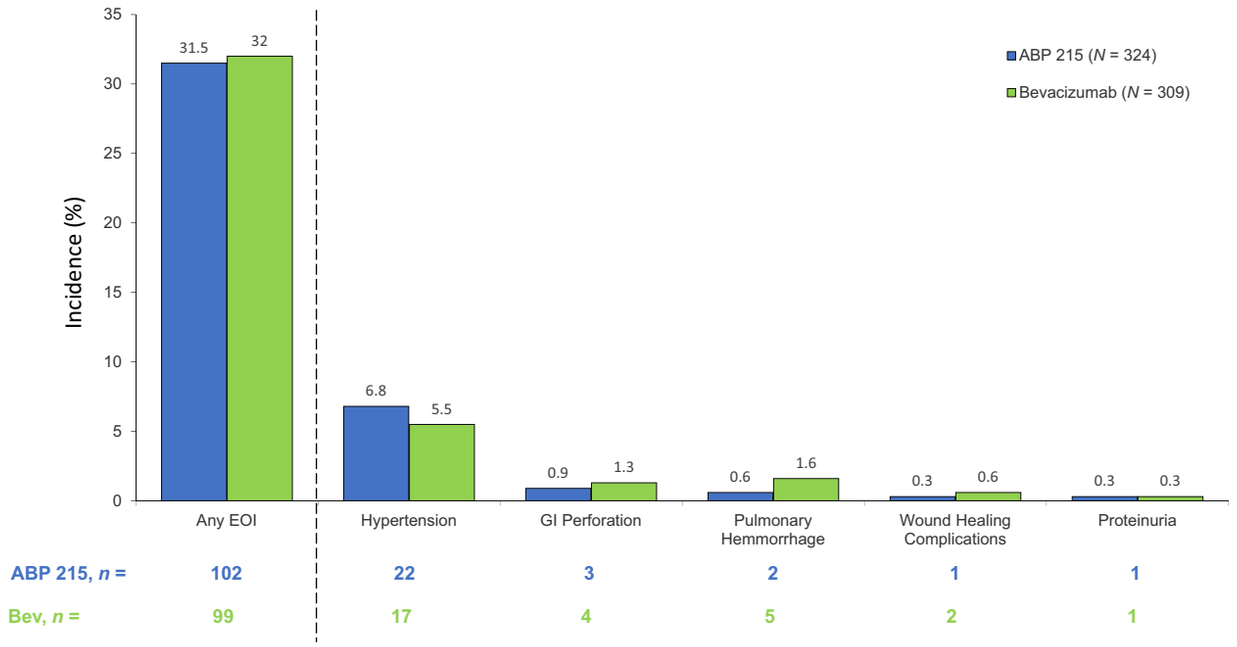

Figure 4.
Grade ≥3 adverse events of interest and anti-VEGF toxicities. EOI, event of interest; GI, gastrointestinal.

bevacizumab observed in this study is representative of that which could be expected in clinical practice; and the similarity of ABP 215 and bevacizumab in this study can be expected to predict clinical similarity.

Two potential limitations of this study are the choice of response rate as a primary endpoint and the lack of a maintenance phase to determine DOR and long-term safety. However, it is important to understand the distinction between biosimilar studies and noninferiority studies. A noninferiority study is designed to assess whether the difference in response between an investigational product and the active control is less than a prespecified margin. If the difference is less than the prespecified margin, the new treatment is confirmed not to be less effective than the active control. In contrast, in similarity studies, a prespecified 2-sided CI defines both the lower and upper margins for similarity. Therefore, the proposed biosimilar can be neither inferior nor superior to the comparative RP. At least 1 comparative clinical study with predefined upper and lower margins is required by regulatory agencies as part of the evaluation of a biosimilar. The aim of clinical studies for biosimilars is to determine clinical equivalence between 2 very similar products, not to reestablish clinical benefit per se. An important consideration in this respect is the choice of primary endpoint. Although OS is often considered the standard for demonstrating clinical benefit in oncology innovators studies, it is not a sensitive endpoint for studies of oncology biosimilars. Therefore, response rate is an appropriate endpoint, provided it is of sufficient magnitude to detect any clinical difference, with prespecified equivalence margins determined on the basis of the sum of evidence available for the RP (6). In this patient population, the maximum objective response is usually observed during the first 3 to 4 cycles, and AEs typically manifest during the first 2 to 3 months. Also, there are no randomized studies of maintenance therapy, only *ad hoc* examinations suggesting that patients who receive maintenance therapy do better than those who do not, and there is no way to determine prespecified equivalence criteria during a maintenance phase. Therefore, the value of including a maintenance phase in this study would have been limited and would have yielded little additional information regarding biosimilarity.

In conclusion, this phase III equivalence study comparing ABP 215 and bevacizumab completes the totality of evidence recommended by regulatory agencies for biosimilars development (7–10). Together with results of previous studies, the results of this study show that ABP 215 is similar to bevacizumab RP (3, 4).

Disclosure of Potential Conflicts of Interest

L. P.-A. Rodriguez reports receiving speakers bureau honoraria from Roche, Lilly, Novartis, Pfizer, Boehringer, AstraZeneca, Amgen, MSD, and Bristol-Myers Squibb, and is a consultant/advisory board member for Roche, Lilly, Novartis, Pfizer, Boehringer, Astra Zeneca, Amgen, MSD, and Bristol-Myers Squibb.

N. Thatcher reports receiving speakers bureau honoraria from Roche, Boehringer Ingelheim, and Amgen and is a consultant/advisory board member for Roche and Amgen.

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M. Schenker is an Associate Professor at the University of Medicine and Pharmacy in Craiova, reports receiving commercial research grants from Bristol-Myers Squibb, Roche, Novartis, Amgen, Pfizer, Eli Lilly, Abbvie, Astellas, AstraZeneca, Merck Serono, MSD, Mylan, Pharma Mar, Bayer, and Gilead, and is a consultant/advisory board member for Bristol-Myers Squibb, Roche, Eli Lilly, Astellas, and MSD.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Thomas, Z. Pan, V. Hanes, L. P.-A. Rodriguez, N. Thatcher
Writing, review, and/or revision of the manuscript: M. Thomas, Z. Pan, V. Breder, G. Ostoros, V. Hanes, M. Schenker, L. P.-A. Rodriguez, N. Thatcher
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Z. Pan
Study supervision: J.H. Goldschmidt, V. Hanes, N. Thatcher

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Amgen Data Sharing Statement

There is a plan to share data. This may include deidentified individual patient data for variables necessary to address the specific research question in an approved data-sharing request; also related data dictionaries, study protocol, statistical analysis plan, informed consent form, and/or clinical study report. Data sharing requests relating to data in this manuscript will be considered after the publication date and (i) this product and indication (or other new use) have been granted marketing authorization in both the United States and Europe, or (ii) clinical development discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for these data. Qualified researchers may submit a request containing the research objectives, the Amgen product(s) and Amgen study/studies in scope, endpoints/outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Amgen does not grant external requests for individual patient data for the purpose of reevaluating safety and efficacy issues already addressed in the product labeling. A committee of internal advisors reviews requests. If not approved, a Data Sharing Independent Review Panel may arbitrate and make the final decision. Requests that pose a potential conflict of interest or an actual or potential competitive risk may be declined at Amgen's sole discretion and without further arbitration. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymized individual patient data and/or available supporting documents, containing fragments of analysis code provided in analysis specifications. Further details are available at the following: http://www.amgen.com/datasharing.

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Clinical Cancer Research

Correction: Efficacy and Safety of the Biosimilar ABP 215 Compared with Bevacizumab in Patients with Advanced Nonsquamous Non–small Cell Lung Cancer (MAPLE): A Randomized, Double-blind, Phase III Study

Nicholas Thatcher, Jerome H. Goldschmidt, Michael Thomas, Michael Schenker, Zhiying Pan, Luis Paz-Ares Rodriguez, Valery Breder, Gyula Ostoros, and Vladimir Hanes

In the original version of this article (1), Fig. 1 was incomplete and the "Methods" sections of both the abstract and the article stated that patients received drugs thrice weekly instead of every three weeks. These errors have been corrected in the latest online HTML and PDF versions of the article. The authors regret these errors.

Reference

1. Thatcher N, Goldschmidt JH, Thomas M, Schenker M, Pan Z, Paz-Ares Rodriguez L, et al. Efficacy and safety of the biosimilar ABP 215 compared with bevacizumab in patients with advanced non-squamous non–small-cell lung cancer (MAPLE): a randomized, double-blind, phase III study. Clin Cancer Res 2019;25:2088–95.

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