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A phase III, randomized, double-blind, multicenter study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB8 (proposed bevacizumab biosimilar) and reference bevacizumab in patients with metastatic or recurrent nonsquamous non-small cell lung cancer

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ABSTRACT

Objectives: Efficacy, safety, pharmacokinetics (PK), and immunogenicity of the biosimilar candidate SB8 was compared to its reference product bevacizumab (BEV) in patients with metastatic or recurrent nonsquamous non—small cell lung cancer.

Methods: Patients were randomized (1:1) in a phase III, double-blind study to receive intravenous SB8 or BEV 15 mg/kg with paclitaxel/carboplatin every 3 weeks for 24 weeks, followed by SB8 or BEV maintenance monotherapy. The primary endpoint was best overall response rate (ORR) by 24 weeks. Secondary endpoints included survival outcomes, safety, PK, and immunogenicity.

Results: 763 patients (SB8, $n = 379$; BEV, $n = 384$) were randomized; baseline characteristics were well balanced. Best ORR in the FAS was 47.6% and 42.8%, and best ORR in the PPS was 50.1% and 44.8% for SB8 and BEV, respectively. The risk ratio of best ORR was 1.11 (90% CI, 0.975 − 1.269), and the risk difference in best ORR was 5.3% (95% CI, −2.2%–12.9%). Median survival outcomes were comparable between SB8 and BEV: progression-free survival was 8.50 vs 7.90 months, respectively (HR [95% CI], 0.99 [0.83–1.18]; $p = 0.9338$); overall survival was 14.90 vs 15.80 months, respectively (HR [95% CI], 1.03 [0.83–1.28]; $p = 0.7713$); and duration of response was 7.70 vs 7.00 months, respectively (HR [95% CI], 1.05 [0.81–1.37]; $p = 0.6928$). Severity and incidence of treatment-emergent adverse events, PK, and immunogenicity were comparable between SB8 and BEV.

Conclusion: This study demonstrated equivalence between SB8 and BEV in terms of best ORR risk ratio, with comparable safety, PK, and immunogenicity.

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1. Introduction

Angiogenesis is important for tumor cell growth, proliferation, and metastasis of many cancer types [1,2], including non—small cell lung cancer (NSCLC) [3]. Vascular endothelial growth factor (VEGF), a key regulator of vascular growth [4], is overexpressed in many cancer types and is associated with tumor cell proliferation, increased microvessel density, and poor prognosis [1,5–10]. Bevacizumab, a humanized monoclonal antibody that targets VEGF, has shown clinical benefit in many types of cancers and is approved as first-line treatment for patients with nonsquamous NSCLC when administered in combination with paclitaxel and carboplatin (United States) [11] or with platinum-based chemotherapy (European Union) [12].

SB8 is a proposed biosimilar of the reference product bevacizumab (BEV). Biosimilars are biological products that are highly similar to an already authorized, medicinal reference product, with no clinically meaningful differences in purity, safety, or potency [13,14]. Physicochemical and functional characteristics of SB8 and BEV were shown to be similar (data on file). Pharmacokinetic (PK) profiles of SB8 and BEV were also shown to be similar in a phase I study in healthy men (NCT02453672) [15].

The objective of this study was to demonstrate the equivalence of SB8 to BEV in terms of best overall response rate (ORR) by 24 weeks of chemotherapy in patients with metastatic or recurrent nonsquamous NSCLC. Secondary endpoints, including survival outcomes, safety, PK, and immunogenicity, were also evaluated.

2. Methods

2.1. Patients

Adults (≥18 years) were eligible if they had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; histologically and/or cytologically confirmed metastatic [16] or recurrent nonsquamous NSCLC or NSCLC not otherwise specified; ≥1 measurable lesion as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1); and ≥3-months life expectancy. Patients were excluded if they had epidermal growth factor receptor (EGFR) gene mutations or anaplastic lymphoma kinase (ALK) gene rearrangements; symptomatic brain metastasis and/or leptomeningeal disease; or history of first-line systemic anticancer treatment for metastatic or recurrent NSCLC, systemic neoadjuvant/adjuvant chemotherapy ≤12 months before randomization, or treatments that targeted VEGF receptor or EGFR signaling pathways. Additional enrollment criteria are provided in the Supplementary Material.

2.2. Study design

This phase III, randomized, double-blind, multicenter, equivalence study (ClinicalTrials.gov identifier, NCT02754882; EudraCT, 2015-004026-34) was conducted at 100 sites in 13 countries. All patients provided written consent, and trial conduct complied with the Declaration of Helsinki. Each study center's independent ethics committee or institutional review board reviewed and approved the protocol, study, and informed consent forms before enrollment.

Patients were randomly assigned (1:1) to receive SB8 or BEV concurrent with paclitaxel/carboplatin. Randomization was stratified by age group (< 70, ≥70 years) and gender. During the induction period, SB8 15 mg/kg or BEV 15 mg/kg was administered intravenously (IV) with paclitaxel 200 mg/m^2 and carboplatin area under the curve 6 every 3 weeks (Q3W) for 4–6 cycles (Supplementary Fig. 1). Patients with complete response (CR), partial response (PR), or stable disease after induction period completion were enrolled in the maintenance period; SB8 15 mg/kg or BEV 15 mg/kg was administered IV Q3W until progressive disease (PD), unacceptable toxicity, death, or end of study (EOS), whichever occurred first. Dose reductions for toxicity were not permitted; however, schedule modifications were allowed. A stepwise dose reduction was permitted for paclitaxel/carboplatin.

2.3. Randomization and masking

Automated random assignment of patient numbers to randomization numbers linked to study medication was generated by the Interactive Web Recognition System. Patients, investigators, and site personnel were blinded to medication assignment; however, unblinding could occur if medically necessary.

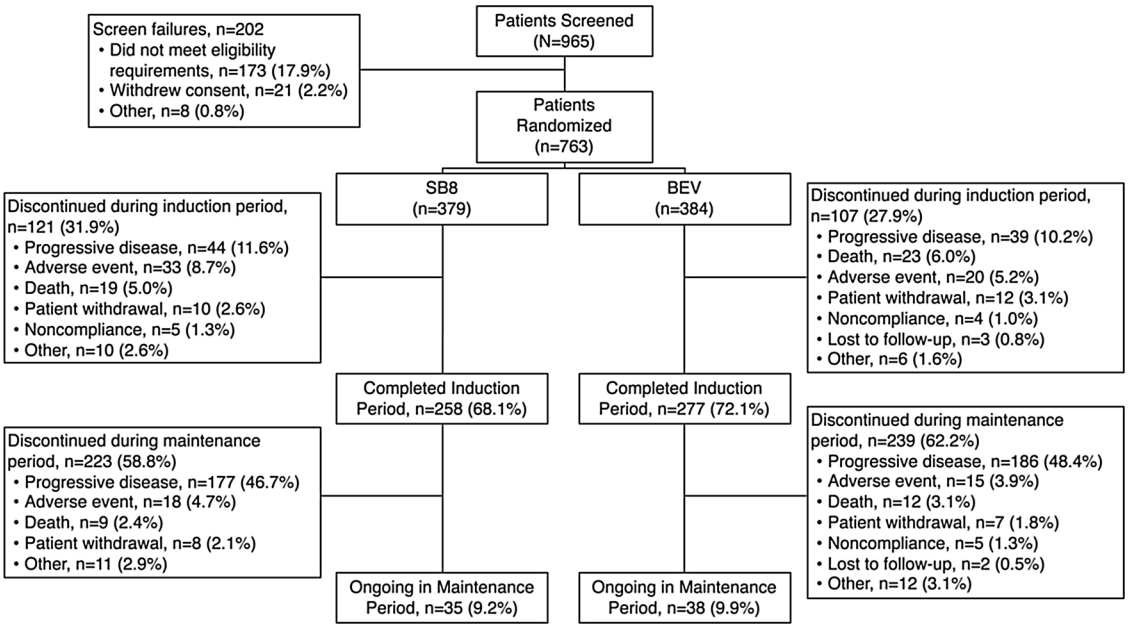

Fig. 1. Patient disposition.
BEV, reference bevacizumab.

Table 1
Patient demographics and baseline disease characteristics (Randomized Set[a]).

	SB8 (*N* = 379)	BEV (*N* = 384)	Total (*N* = 763)
Men, *n* (%)	252 (66.5)	256 (66.7)	508 (66.6)
Age, mean (SD), years	60.2 (8.95)	60.0 (9.18)	60.1 (9.06)
< 65	255 (67.3)	269 (70.1)	524 (68.7)
≥65	124 (32.7)	115 (29.9)	239 (31.3)
< 70	326 (86.0)	334 (87.0)	660 (86.5)
≥70	53 (14.0)	50 (13.0)	103 (13.5)
Race, *n* (%)			
White	347 (91.6)	348 (90.6)	695 (91.1)
Asian	32 (8.4)	35 (9.1)	67 (8.8)
Black	0	1 (0.3)	1 (0.1)
Region, *n* (%)			
European Union	77 (20.3)	78 (20.3)	155 (20.3)
Non-European Union	302 (79.7)	306 (79.7)	608 (79.7)
BMI, median (range), kg/m^2	24.9 (15.8 – 46.7)	24.8 (13.5 – 42.2)	24.9 (13.5 – 46.7)
ECOG, *n* (%)			
0	106 (28.0)	107 (27.9)	213 (27.9)
1	272 (71.8)	277 (72.1)	549 (72.0)
≥2	1 (0.3)	0	1 (0.1)
Smoking history, *n* (%)			
Never smoked	143 (37.7)	148 (38.5)	291 (38.1)
Former smoker	100 (26.4)	102 (26.6)	202 (26.5)
Current smoker	136 (35.9)	134 (34.9)	270 (35.4)
Cancer type, *n* (%)			
Adenocarcinoma	364 (96.0)	363 (94.5)	727 (95.3)
Adenosquamous carcinoma	2 (0.5)	2 (0.5)	4 (0.5)
Large cell carcinoma	2 (0.5)	7 (1.8)	9 (1.2)
Spindle cell carcinoma	1 (0.3)	0	1 (0.1)
Large cell neuroendocrine carcinoma	0	2 (0.5)	2 (0.3)
Pleomorphic carcinoma	0	1 (0.3)	1 (0.1)
Not otherwise specified	10 (2.6)	9 (2.3)	19 (2.5)
Stage of disease, *n* (%)			
IB	1 (0.3)	1 (0.3)	2 (0.3)
IIA/IIB	1 (0.3)	2 (0.5)	3 (0.4)
IIIA/IIIB	0	1 (0.3)	1 (0.1)
IV	375 (98.9)	380 (99.0)	755 (99.0)
Not categorized	2 (0.5)	0	2 (0.3)
EGFR mutation, *n* (%)			
Yes	0	1 (0.3)	1 (0.1)
No	98 (25.9)	92 (24.0)	190 (24.9)
Unknown	281 (74.1)	291 (75.8)	572 (75.0)
ALK alteration, *n* (%)			
Yes	0	0	0
No	65 (17.2)	67 (17.4)	132 (17.3)
Unknown	314 (82.8)	317 (82.6)	631 (82.7)
Duration of disease, median (range), months	1.1 (0.1 – 214.5)	1.1 (0.2 – 121.5)	1.1 (0.1 – 214.5)

ALK, anaplastic lymphoma kinase; BEV, reference bevacizumab; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor.
[a] All patients who received a randomization number at the time of randomization based on assigned treatment.

Table 2
Summary of primary efficacy endpoints (Full analysis set and per protocol set).

	SB8	BEV
Full Analysis Set	(*N* = 379)	(*N* = 383)
Best overall response,[a] *n* (%)		
Complete response (CR)	0	1 (0.3)
Partial response (PR)	172 (45.4)	151 (39.4)
Stable disease (SD)	136 (35.9)	151 (39.4)
Progressive disease (PD)	27 (7.1)	21 (5.5)
Not evaluable	43 (11.3)	58 (15.1)
Best ORR (CR + PR),[b] *n* (%)	181 (47.6)	164 (42.8)
Risk ratio (90% CI[c])	1.11 (0.975 – 1.269)	
Risk difference (95% CI[d])	4.8% (–2.3%–11.9%)	
Per Protocol Set	(*N* = 337)	(*N* = 328)
Best overall response, *n* (%)		
Complete response (CR)	0	1 (0.3)
Partial response (PR)	169 (50.1)	146 (44.5)
Stable disease (SD)	134 (39.8)	149 (45.4)
Progressive disease (PD)	25 (7.4)	20 (6.1)
Not evaluable	9 (2.7)	12 (3.7)
Best ORR (CR + PR),[e] n (%)	169 (50.1)	147 (44.8)
Risk ratio (90% CI[c])	1.12 (0.978 – 1.280)	
Risk difference (95% CI[d])	5.3% (–2.2%–12.9%)	

BEV, reference bevacizumab; CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a] Two patients were excluded: 1 had an assessment that did not belong to the induction period and 1 had no best ORR owing to the absence of a target lesion at baseline by central review.
[b] The best ORR was defined as the proportion of patients whose best overall response was either CR or PR, according to RECIST v1.1, during the induction treatment period by 24 weeks, with imputation for missing data. Missing data from patients who withdrew due to disease progression and adverse events without any tumor assessment resulted in them being categorized as non-responders. Missing data from patients who withdrew for reasons other than disease progression or adverse events and remained in the study without any tumor assessment were imputed using the multiple imputation method.
[c] Equivalence margin (0.737–1.357). [d]Equivalence margin (—12.5%–12.5%).
[e] The best ORR was defined as the proportion of patients whose best overall response was either CR or PR, according to RECIST v1.1, during the induction treatment period by 24 weeks.

2.4. Assessments

Radiographic imaging with computed tomography or magnetic resonance imaging was performed per RECIST v1.1 [17] after treatment at cycles 2, 4, and 6; before day 1 of cycles 3, 5, and 7; and every 4 cycles thereafter until PD, unacceptable toxicity, death, or EOS, whichever occurred first. Physical examination, vital signs, ECOG performance status, clinical laboratory assessment, and study medication compliance were assessed at each cycle.

2.5. Endpoints

The primary efficacy endpoint was best ORR, defined as the proportion of patients whose best overall response was either CR or PR during the induction treatment period by 24 weeks, based on independent central review per RECIST v1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), duration of response (DOR), adverse events (AEs), PK, and immunogenicity.

PFS was defined as the time from date of randomization to date of PD or death; patients who did not progress at the time of analysis were censored at the end of treatment (EOT) visit or last tumor assessment. OS was defined as the time from date of randomization to death; patients alive at the time of analysis were censored at the date they were last known to be alive. DOR, evaluated for patients with CR or PR, was defined as the time from first documented evidence of tumor response until PD.

AEs were collected after study enrollment until the EOT visit; serious AEs were followed until event resolution or stabilization. Treatment-emergent AEs (TEAEs) had an onset date on or after study medication initiation or started before treatment, with an increase in severity during treatment. AEs were coded using the Medical Dictionary for Regulatory Activities version 20.0 and graded by severity according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Trough concentration (C_{trough}) was determined before IV infusion at cycles 1, 3, 5, and 7; maximum concentration (C_{max}) was determined after IV infusion at cycles 1, 3, 5, and 7. Incidence of antidrug antibodies (ADA) was determined before IV infusion at cycles 1, 3, 5, and 7 and at EOT.

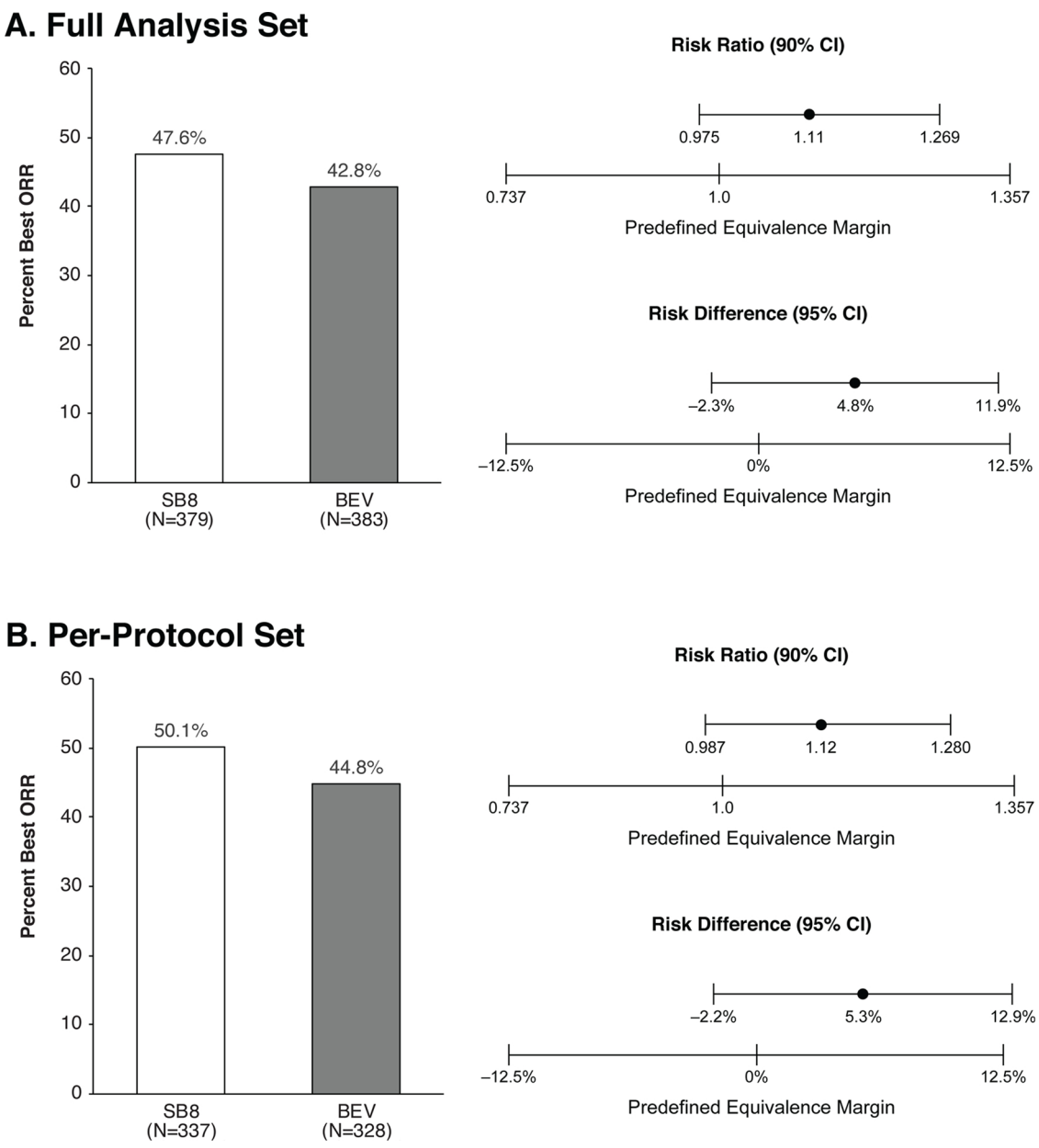

Fig. 2. Best ORR (CR + PR), risk ratio, and risk difference in the (A) full analysis set and (B) per- protocol set.
BEV, reference bevacizumab; CR, complete response; ORR, overall response rate; PR, partial response.

2.6. Statistical analyses

Efficacy was evaluated in the full analysis set (FAS; all randomized patients by intention-to-treat principle, without incorrect randomization) and the per-protocol set (PPS; patients completing at least the first 2 cycles of combination chemotherapy with tumor assessment, without major protocol deviations affecting the primary efficacy assessment). Safety and immunogenicity were evaluated in the safety set (SAF; patients receiving ≥1 dose of study medication). PK was evaluated in the PK population (patients having ≥1 measured serum concentration of BEV).

Regulatory agency's guideline recommends an equivalence design with symmetric inferiority and superiority margins, which should be pre-specified based on both statistical and clinical grounds by using the data of the reference product, would be used for biosimilar's Phase III to establish statistical evidence that the proposed biosimilar is neither inferior nor superior to the reference product [18,19].

For calculation of the equivalence margin for the risk ratio of best ORR by 24 weeks, a meta-analysis published by Botrel et al., 2011 [20] using four trials of BEV evaluating the effect of BEV in combination with chemotherapy in recurrent or advanced non-squamous NSCLC was considered.

To demonstrate equivalence of best ORR between treatment groups, the risk ratio of best ORR was analyzed in the FAS, and risk difference of best ORR was analyzed in the PPS for the primary analysis. Equivalence was declared if the 2-sided 90% CI of the best ORR risk ratio between treatment groups was contained within the predefined equivalence margin (FAS, 0.737-1.357) or if the 2-sided 95% CI of the best ORR risk difference was contained within the equivalence range (PPS, –12.5–12.5%). A sample size of 339 patients per treatment group was determined based on the assumption of the equivalence margin that satisfied the primary analysis for ratio and difference and a 10% drop-out rate with 80% power and best ORR of 35% in both treatment groups.

Primary efficacy analysis was performed using log-binomial regression and binomial regression models, with treatment group as an

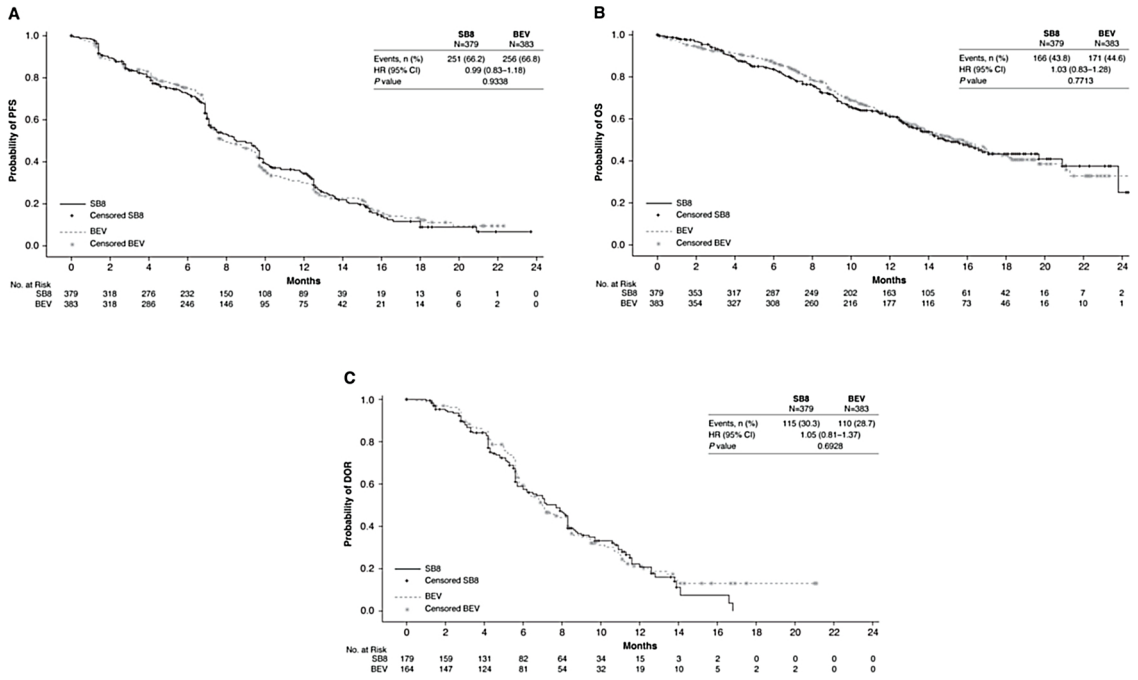

Fig. 3. Kaplan–Meier plot for (A) PFS, (B) OS, and (C) DOR in the full analysis set.
BEV, reference bevacizumab; DOR, duration of response; OS, overall survival; PFS, progression-free survival.

explanatory variable. Data from patients with missing tumor assessments in the FAS were imputed using the multiple imputation method. Sensitivity analyses were performed using log-binomial regression and binomial regression models, with covariates of age group (< 70 years, ≥70 years), sex (male, female), region (EU, non-EU), and treatment groups to explore robustness of the primary efficacy result.

Secondary endpoints of PFS, OS, and DOR were analyzed for the FAS using the Kaplan–Meier method. A Cox proportional hazard model, with treatment group as an explanatory variable, was used to report hazard ratios (HRs) and 95% CIs. Additionally, the overall changes in tumor burden by 24 weeks of the induction treatment period for SB8 and BEV treatment groups was performed in the FAS using the waterfall plot. Safety, PK, and immunogenicity were summarized using descriptive statistics.

3. Results

3.1. Patients

Of 965 patients screened, 763 were randomized (SB8, n = 379; BEV, n = 384) (Fig. 1). Most patients (SB8, n = 258 [68.1%]; BEV, n = 277 [72.1%]) completed the induction period. At the time of analysis, 35 (9.2%) patients in the SB8 group and 38 (9.9%) patients in the BEV group were ongoing in the maintenance period. At EOS, median (range) follow-up duration was 15.2 (0–24.4) months.

During the induction period, mean (SD) cycles of SB8 and BEV were 4.8 (1.55) and 4.8 (1.61), respectively; mean (SD) cycles of paclitaxel treatment were 4.8 (1.55) and 4.8 (1.63), respectively; and mean (SD) cycles of carboplatin treatment were 4.9 (1.55) and 4.8 (1.62), respectively. During the maintenance period, mean (SD) cycles of SB8 and BEV were 9.3 (6.64) and 9.1 (6.21), respectively.

Baseline demographics and disease characteristics were well balanced between treatment groups. The mean (SD) age of patients was 60.2 (8.95) years in the SB8 group and 60.0 (9.18) years in the BEV group, and the proportions of men were 66.5% and 66.7%, respectively (Table 1).

3.2. Efficacy

In the FAS, the proportion of patients achieving best ORR was 47.6% and 42.8% in the SB8 and BEV groups, respectively. The risk ratio of best ORR was 1.11 (90% CI, 0.975 − 1.269) and was contained within the predefined equivalence margin (0.737–1.357) (Table 2, Fig. 2A). In the PPS, the proportion of patients achieving best ORR was 50.1% and 44.8% in the SB8 and BEV groups, respectively. The risk difference in best ORR was 5.3% (95% CI, −2.2–12.9%); the lower margin was contained within the predefined equivalence margin, and the upper margin was outside this margin (−12.5–12.5%) (Table 2, Fig. 2B). Sensitivity analyses reflected the primary analysis and supported the robustness of the primary analysis.

In the FAS, at EOS, 251 (66.2%) and 256 (66.8%) patients in the SB8 and BEV groups, respectively, had disease progression or died. Median PFS in the SB8 and BEV groups was 8.50 (95% CI, 7.40–9.70) and 7.90 (95% CI, 7.40–9.50) months, respectively; the estimated HR was 0.99 (95% CI, 0.83–1.18). The 12-month PFS rate was 34% (95% CI, 29–40%) in the SB8 group and 30% (95% CI, 25–35%) in the BEV group (Fig. 3A). In the FAS, at EOS, 166 (43.8%) and 171 (44.6%) patients in the SB8 and BEV groups, respectively, had died. Median OS in the SB8 and BEV groups was 14.90 (95% CI, 13.30–17.10) and 15.80 (95% CI, 13.60–17.10) months, respectively; the estimated HR was 1.03 (95% CI, 0.83–1.28). The 12-month OS rate was 61% (95% CI, 56–66%) in the SB8 group and 62% (95% CI, 57–67%) in the BEV group (Fig. 3B). Median (95% CI) DOR in the FAS was 7.70 (6.00–8.30) and 7.00 (6.10–8.30) months in the SB8 and BEV groups, respectively (Fig. 3C); the estimated HR was 1.05 (95% CI, 0.81–1.37). PFS, OS, and DOR results in the PPS were consistent with those in the FAS. The overall changes in tumor burden by 24 weeks of the induction treatment period for the FAS were comparable between the SB8 and BEV treatment groups (Supplementary Fig. 2).

3.3. Safety

The SAF consisted of 758 patients (SB8, n = 378; BEV, n = 380). AEs accidentally entered into the electronic data capture system after

Table 3
Summary of Adverse Events (Safety Set).

Patients, n (%)	SB8 (N = 378)	BEV (N = 380)
Patients with ≥1 TEAE	348 (92.1)	346 (91.1)
Grade 1 TEAE	47 (12.4)	57 (15.0)
Grade 2 TEAE	127 (33.6)	134 (35.3)
Grade ≥3 TEAE	174 (46.0)	155 (40.8)
Serious TEAE	75 (19.8)	81 (21.3)
TEAEs leading to study medication discontinuation	50 (13.2)	36 (9.5)
Death	22 (5.8)	27 (7.1)
TEAEs occurring in ≥5% of patients		
Alopecia	184 (48.7)	183 (48.2)
Anemia	92 (24.3)	90 (23.7)
Nausea	74 (19.6)	80 (21.1)
Neutropenia	74 (19.6)	71 (18.7)
Thrombocytopenia	58 (15.3)	46 (12.1)
Asthenia	49 (13.0)	44 (11.6)
Arthralgia	46 (12.2)	46 (12.1)
Fatigue	46 (12.2)	48 (12.6)
Hypertension	46 (12.2)	36 (9.5)
Leukopenia	40 (10.6)	24 (6.3)
Peripheral neuropathy	38 (10.1)	54 (14.2)
Decreased weight	37 (9.8)	28 (7.4)
Decreased appetite	36 (9.5)	34 (8.9)
Increased aspartate aminotransferase	32 (8.5)	24 (6.3)
Paresthesia	32 (8.5)	32 (8.4)
Diarrhea	31 (8.2)	25 (6.6)
Increased alanine aminotransferase	29 (7.7)	30 (7.9)
Blood urea increased	28 (7.4)	18 (4.7)
Headache	26 (6.9)	27 (7.1)
Increased alkaline phosphatase	26 (6.9)	27 (7.1)
Myalgia	24 (6.3)	35 (9.2)
Peripheral sensory neuropathy	24 (6.3)	35 (9.2)
Dysphonia	24 (6.3)	16 (4.2)
Vomiting	24 (6.3)	22 (5.8)
Cough	23 (6.1)	20 (5.3)
Dyspnea	22 (5.8)	30 (7.9)
Constipation	21 (5.6)	18 (4.7)
Epistaxis	20 (5.3)	14 (3.7)
Musculoskeletal pain	19 (5.0)	16 (4.2)
Decreased platelet count	18 (4.8)	19 (5.0)
Proteinuria	17 (4.5)	24 (6.3)
TEAEs of special interest[a]	31 (8.2)	20 (5.3)
Hypertension	29 (7.7)	16 (4.2)
Proteinuria	2 (0.5)	7 (1.8)
Other important TEAEs by SMQ		
Hypersensitivity reactions/infusion reactions	48 (12.7)	47 (12.4)
Bleeding/hemorrhage	43 (11.4)	45 (11.8)
Pulmonary hemorrhage	13 (3.4)	17 (4.5)
Venous thromboembolic events	12 (3.2)	14 (3.7)
Congestive heart failure	8 (2.1)	9 (2.4)
Arterial thromboembolic events	6 (1.6)	2 (0.5)
Wound healing complications	1 (0.3)	3 (0.8)
Gastrointestinal perforations	1 (0.3)	0
Embryo-fetal development disturbance	1 (0.3)	0
Ovarian failure	0 (0.0)	1 (0.3)

BEV, reference bevacizumab; SMQ, standardized Medical Dictionary for Regulatory Activities queries; TEAE, treatment-emergent adverse event.

[a] Hypertension of grade ≥3; ≥2+ proteinuria on urine dipstick (or other ways of urinalysis) and 24-h urine protein excretion ≥1 g or protein/creatinine ratio in spot urine ≥1 g/g creatinine (or ≥226.0 mg/mmol creatinine).

the EOT visit were not excluded from analyses. TEAEs were reported in 348 (92.1%) and 346 (91.1%) patients in the SB8 and BEV groups, respectively; most were grade 1 or 2 (Table 3). The most frequently occurring TEAEs were alopecia (SB8, 48.7%; BEV, 48.2%), anemia (SB8, 24.3%; BEV, 23.7%), and nausea (SB8, 19.6%; BEV, 21.1%). The most frequently occurring severe (grade ≥ 3) TEAEs were neutropenia (SB8, 8.7%; BEV, 9.5%), hypertension (6.3%; 3.7%), anemia (4.8%; 5.5%), and decreased neutrophil count (4.0%; 3.2%). Incidences of TEAEs of special interest (hypertension grade ≥ 3; ≥2+ proteinuria on urine dipstick/urinalysis and 24-h urine protein excretion ≥1 g or protein/creatinine ratio in spot urine ≥1 g/g creatinine [or ≥226.0 mg/mmol creatinine]) were comparable between treatment groups (SB8, 8.2%; BEV, 5.3%), as were incidences of serious TEAEs (19.8%; 21.3%, respectively) and deaths, regardless of cause (5.8%; 7.1%, respectively). The incidence of other important TEAEs (including bleeding/hemorrhage, thromboembolic events, and wound healing complications) was also comparable (Table 3).

3.4. Pharmacokinetics

The PK population consisted of 341 patients (SB8, n = 161; BEV, n = 180). Mean C_{trough} and C_{max} were comparable between treatment groups for cycles 1 through 7, with similar variability in cycles 3 through 7 (Supplementary Fig. 3).

3.5. Immunogenicity

The incidences of an overall positive ADA result were comparable between the SB8 and BEV groups in the SAF throughout the study, including up to cycle 7 (SB8, n = 46/341 [13.5%]; BEV, n = 34/337 [10.1%]) and EOT (n = 55/341 [16.1%]; n = 37/337 [11.0%]).

4. Discussion

This phase III study compared the efficacy, safety, PK, and immunogenicity of SB8 with BEV in patients with metastatic or recurrent nonsquamous NSCLC. Equivalence of efficacy between SB8 and BEV was shown in terms of best ORR risk ratio. Safety, PK, and immunogenicity results were comparable between SB8 and BEV.

The aim of the clinical development of a biosimilar, according to the guiding principle, is to compare its efficacy with the reference product and not to determine patient benefit per se [13]. Best ORR was selected as the primary endpoint of this study since ORR is a more sensitive endpoint that enables precise comparisons of relevant therapeutic effects. Survival outcomes are important to establish efficacy of novel anticancer therapeutics but are less suitable in establishing biosimilarity because factors outside of product performance can influence survival outcomes [13].

Based on communications with the US Food and Drug Administration and European Medicines Agency, NSCLC was chosen to assess biosimilarity of SB8 with BEV as the most sensitive indication for measuring difference in response rate. Best ORR was 47.6% for SB8 and 42.8% for BEV, which was within the range of ORRs (31.5–60.7%) reported in clinical trials that established the efficacy and safety profile of bevacizumab in combination with paclitaxel and carboplatin in patients with recurrent or metastatic NSCLC [21–23]. Additionally, survival outcomes were evaluated as secondary endpoints and were comparable between groups.

The safety profile of SB8 was comparable to that of BEV with regard to the type, incidence, or severity of TEAEs. TEAEs of special interest and anti-VEGF toxicities (eg, hemorrhage, thromboembolism) were similar between the SB8 and BEV groups and were similar to previous clinical studies that evaluated bevacizumab in NSCLC [21–23]. The PK profiles and immunogenicity were comparable between SB8 and BEV. The efficacy, safety, and PK results were comparable between the SB8 and BEV groups among patients who had an overall positive or negative ADA result up to cycle 7 or EOT.

A step-wise approach to establishing biosimilarity began with functional and analytical analyses; a previous phase I study [15] supported these analyses by evaluating the safety, PK, and immunogenicity in healthy participants. This study was the final step in this process and established equivalence between SB8 and BEV in regard to efficacy and further supported comparable safety, PK, and immunogenicity.

5. Conclusion

Equivalence was demonstrated between SB8 and BEV in terms of

best ORR risk ratio; noninferiority was demonstrated in terms of risk difference, but nonsuperiority was not conclusive. Additional efficacy endpoints, safety, PK, and immunogenicity were comparable between SB8 and BEV. The totality of evidence demonstrates the biosimilarity of SB8 to its reference product BEV.

Disclosures

Martin Reck has an honorarium and is an advisor/consultant for Samsung Bioepis Co., Ltd., AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Lilly, Merck, MSD, Novartis, Pfizer, and Roche. Jihye Choi and Donghoon Shin are employees of Samsung Bioepis Co., Ltd. All other authors have no conflicts of interest to declare.

Data statement

Upon request, and subject to certain criteria, conditions, and exceptions, Samsung Bioepis will provide access to individual de-identified participant data to researchers whose proposals meet the research criteria and other conditions and for which an exception does not apply. Proposals should be directed to the corresponding author. For access, data requestors must enter into a data access agreement with Samsung Bioepis.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2020.05.027.

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