Efficacy and safety of proposed bevacizumab biosimilar BE1040V in patients with metastatic colorectal cancer: A phase III, randomized, double-blind, noninferiority clinical trial

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ABSTRACT

Purpose: The purpose of this study was to compare the efficacy and safety of a proposed bevacizumab biosimilar to those of the reference product in patients with metastatic colorectal cancer (mCRC).

Methods: This Phase III, multicenter, randomized, double-blind (patient- and assessor-blind), active-controlled, 2-armed, parallel-group, noninferiority trial was conducted in patients with histologically verified colorectal cancer with evidence of at least 1 metastasis. Patients with mCRC were randomized 2:1 to receive 5 mg/kg IV of either study drug plus FOLFIRI-3 (with repeated irinotecan 100 mg/m^2 60- min infusion on day 3) or the reference drug plus FOLFIRI-3 every 2 weeks for 1 year. Progression-free survival (PFS) was the primary end point, and overall survival, objective response rate, and time to treatment failure as well as safety and immunogenicity were secondary end points. The population assessable for PFS was per protocol, and

the intention-to-treat population was used for sensitivity analysis. Safety was assessed based on reports of adverse events, laboratory test results, and vital sign measurements.

Findings: A total of 126 patients were enrolled; PFS values in the biosimilar and reference arms were 232 days (7.7 months) and 210 days (7 months), respectively (P = 0.47). The hazard ratio of the biosimilar arm versus the reference arm was 0.79 in the per-protocol population (90% CI, 0.46−1.35; P = 0.47). The upper limit for the 2-sided 90% CI was lower than the margin of 1.44, indicating that the biosimilar drug was noninferior to the reference drug. The hazard ratio for overall survival in the intent-to-treat population was 0.99 (95% CI, 0.55−1.80; P = 0.99). The difference between other efficacy end points among the groups was not statistically significant. No significant difference was observed in the comparison of the two arms for safety. The antidrug antibody was positive in 1 patient in each arm.

Implications: The proposed biosimilar BE1040V was noninferior to the reference product in terms of efficacy in the treatment of mCRC, and tolerability was comparable between the 2 drugs. ClinicalTrials.gov identifier: NCT03288987. (*Clin Ther.* xxxx;xxx:xxx) © 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key words: bevacizumab, biosimilar, metastatic colorectal cancer, noninferiority, randomized clinical trial.

INTRODUCTION

Colorectal cancer (CRC) is the third-most commonly diagnosed cancer and the second-leading cause of cancer deaths all over the world.[1] CRC can metastasize to distant sites through lymphatic, hematogenous, direct, and transperitoneal routes.[2] Metastatic CRC (mCRC) accounts for 20%−25% of all CRCs.[3,4] The liver is the most common identified dissemination site of mCRC since the majority of the intestinal drainage is via the hepatic portal system. The lungs are the second-most common site, mostly coinciding with nervous system metastases.[3,5,6]

Peritoneal metastases are reported to be more common in Signet-ring-cell CRC and mucinous CRC.[3]

Although there have been significant improvements in treatment protocols, mCRC still has a high mortality rate; the 5-year relative survival rate in mCRC is currently 14%.[7] Diagnosis of CRC is through regular screening tests or on presentation of symptoms. Most patients, however, are diagnosed after the onset of symptoms and have more advanced disease than do those who are diagnosed by screening.[8] In cases in which the tumor is not eligible for resection or conversion to a resectable state, systemic therapy may be considered as the first-line treatment.[9] The overall survival (OS) rate with systemic chemotherapy in clinical trials in past decades has improved significantly; the median OS has risen from 11 months with fluorouracil (5-FU) monotherapy in the 1990s to 30 months in recent trials.[9,10] This increase is partly due to the use of new chemotherapeutic agents, such as oxaliplatin and irinotecan (IRI) alongside 5-FU, and biologic agents.[11,12] Combination regimens such as FOLFOX and FOLFIRI have been the cornerstone in the treatment of metastatic disease.[12] Targeted therapy with drugs such as epidermal growth factor receptor and vascular endothelial growth factor monoclonal antibodies can also be used alongside combination therapies. In fact, only trials that have incorporated the use of biologic agents into regimens of combination therapies have consistently reported a median survival rate of over 24 months.[9]

Bevacizumab works by inhibiting vascular endothelial growth factor-A, an angiogenic factor known to be overexpressed in tumors.[13] Although it is not clear what subset of patients will benefit from bevacizumab due to the lack of a validated predictive biomarker, it is recommended that this biologic agent be added to the combination chemotherapies.[9] Bevacizumab has approved indication for first- or second-line treatment of mCRC in concurrent use with 5-FU−based doublets. It also has been approved for the second-line treatment of mCRC after progression on a first-line treatment regimen containing bevacizumab.[14]

Biosimilars are biologic products that are highly similar to reference products, without clinically significant differences with regard to tolerability and efficacy.[15]

The main purpose of expanding the development of biosimilars is to increase patients' access to biologic therapies. Biologic medicines are well established in clinical practice and are vital for the treatment of serious and chronic conditions such as cancer, diabetes, and autoimmune diseases. By demonstrating biosimilarity between a reference medicine that has already been approved and a proposed, highly similar medicine, patients would have more access to essential biologic drugs with more affordability. Furthermore, biosimilars offer benefits to health care professionals and health care systems as well; by delivering the same outcomes, biosimilars have the potential of imposing significantly less health care–related financial burden.[15,16] AryoGen Pharmed (Alborz, Iran)[13] is a biopharmaceutical company that manufactures biosimilar drugs.[17,18] As mentioned earlier, due to the considerable cost of the reference product bevacizumab and also the high mortality rate of mCRC in Iran, BE1040V was developed as a biosimilar of the reference product bevacizumab. This study aimed to evaluate the efficacy, safety, and immunogenicity of BE1040V versus reference bevacizumab in patients with mCRC.

PATIENTS AND METHODS
Design

This Phase III, multicenter, randomized, double-blind (patient- and assessor-blind), active-controlled, 2-armed, parallel-group, noninferiority study was conducted in 22 centers across 9 cities of Iran. Patients were randomly assigned in a 2:1 ratio using block randomization (block size, 6) to receive 5 mg/kg IV of either the test drug* or the reference product† alongside FOLFIRI-3 every 2 weeks for a total of 1 year.

The study was conducted in congruence with the Declaration of Helsinki and Good Clinical Practice principles across all centers. All of the study protocols were approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.REC.1395.4) and Ahvaz Jundishapur

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* Trademark: Stivant(AryoGen Pharmed, Alborz, Iran).[17,18]

† Trademark: Avastin (F. Hoffmann-La Roche, Basel, Switzerland).

University of Medical Sciences (IR.AJUMS.REC.1395.351), and the study was registered at ClinicalTrials.gov (NCT03288987). Each participant signed a written informed-consent form before the initiation of the trial.

Intervention

The FOLFIRI-3 regimen comprised IRI 100 mg/m^2 as a 60-min infusion and leucovorin (LV) 400 mg/m^2 on day 1, 5-FU 2000 mg/m^2 as a 46-h infusion on day 1 after administration of the previous drugs, and repeated IRI 100 mg/m^2 60-min infusion on day 3.[19,20] Bevacizumab 5 mg/kg IV was also administered intravenously on day 1 before FOLFIRI administration. Bevacizumab dosing and intervals were based on the National Comprehensive Cancer Network guidelines.[21] This cycle was repeated every 2 weeks.

Participants
Inclusion Criteria

Patients who met the following criteria were included in the study: male or female between 18 to 75 years old; histologically-confirmed CRC with evidence of metastasis; 1 or more bi-dimensionally measurable lesion(s) based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1); and not amenable to curative resection. Other inclusion criteria were an Eastern Cooperative Oncology Group performance status of 0 or 1, an estimated life expectancy of >3 months, and adequate organs and bone marrow function.

Patients may have received prior adjuvant chemotherapy for primary CRC provided that at least 6 months had passed from the time the adjuvant therapy was concluded, and recurrent disease was documented. In patients with hypertension, blood pressure had to be controlled (≤150/100 mmHg) with a stable antihypertensive therapy.

Exclusion Criteria

Exclusion criteria were as follows: prior targeted therapy for mCRC; radiotherapy or surgery for mCRC within 4 weeks before the random assignment; significant traumatic injury within 28 days before study entry; history or presence of CNS metastasis; and/or major surgery or open biopsy within 28 days before the initiation of study

treatment. Other exclusion criteria were pregnancy or breastfeeding; proteinuria exceeding 500 mg/24 h; history of allergic reaction to chemical or biologic structures similar to bevacizumab, IRI, 5-FU, and/or LV; presence of serious nonhealing wound or ulcer or active bone fracture; history of myocardial infarction or stroke within 6 months prior to enrollment; current or recent use of therapeutic doses of anticoagulant and/or thrombolytic drugs; and/or long-term, daily treatment with aspirin at a dose of >325 mg/d. However, the use of a preventive dose of low-molecular-weight heparin was permitted. Patients with symptomatic and unstable arrhythmia requiring pharmacotherapy; clinically significant peripheral vascular disease; uncontrolled diabetes; serious, active, or uncontrolled infection; and an inability to comply with study or follow-up procedures were also excluded.

Randomization and Allocation Concealment

The randomization plan of the patients was carried out using an on-line system. Permuted block randomization was made, for a total of 126 patients (with 2:1 allocation ratio). The assigned code was denoted by 4 initials (corresponding to the first 2 letters of the patients' first name and the first 2 letters of the first surname) and 3 numbers (center code). Each drug package for the course of a patient's treatment had a 3-digit number similar to the randomization code, as long as the random code was unique, each patient had a unique drug package that was completely identified with the randomized process.

The randomization process was not exposed to those who were conducting the study and was provided via telephone call for each consecutive eligible patient after the identification characteristics were recorded by the randomization center. Since the randomization code was unique, the next sequence was not predictable for site personnel. Randomization codes were allocated after all inclusion criteria and none of the exclusion criteria were met and the informed consent form was signed.

End Points

The primary end point was *progression-free survival* (PFS), defined as the time from the date of randomization to the first date of documented progression or death as a result of any cause.

Secondary end points were overall survival (OS), objective response rate (ORR), and time to treatment failure (TTF). OS was described as the time from randomization to date of death due to any cause. ORR was defined as the sum of partial tumor responses (PRs) and complete responses (CRs) according to RECIST 1.1 and was assessed every 3 months by computed tomography scan. TTF was defined as the time from randomization to progression, death from any cause, or treatment discontinuation.

Other secondary end points included safety and immunogenicity evaluations. Safety was assessed based on adverse events (AEs) reports, laboratory test results, and vital-sign measurements. AEs were ranked according to the Common Terminology Criteria for AEs version 5.0.[22]

Enzyme-linked immunosorbent assay (ELISA) was used for the measurement of antidrug antibodies (ADAs), and samples for immunogenicity assessment were collected at baseline and before bevacizumab administration at every other cycle.

Statistical Analysis

The primary efficacy (PFS) hypothesis was that BE1040V would be noninferior to the reference drug. PFS was assumed to be 10.6 months in the reference group. The planned sample size of 126 was calculated to provide at least 80% power to show noninferiority with margins of –2 months and a 1-sided 0.05 significance level.

The population assessable for PFS was per protocol, and the intention-to-treat (ITT) population was used for sensitivity analysis. Patients receiving at least 1 dose of study drugs were included in the safety population. ITT analysis of the secondary end points was performed as well.

Noninferiority was declared by comparing the 90% CI for the hazard ratio (HR) of BE1040V to the reference product to the point-estimate margin and was based on the synthesis method. The proportional hazard assumption was checked based on scaled Schoenfeld residuals. Furthermore, estimated HRs with their CIs were calculated by Cox Proportional Hazards Regression. The survival curves (PFS, OS, and TTF) were plotted using the Kaplan–Meier

method. In patients who were lost to follow-up, survival data were censored from the time of the last contact. The proportions were assessed for statistical significance by the Fisher's exact test to compare ORR in the 2 treatment groups. Baseline characteristics were summarized by percentage or mean and standard deviation (SD).

Safety was assessed based on reports of AEs, laboratory test results, and vital-sign measurements. Intensity, seriousness, and causality assessment of AEs were reported in the 2 groups. The analysis was carried out using Stata version 14 (StataCorp, College Station, TX) and a forest plot was graphed by Rstudio software version R 3.1.0 (RStudio, rstudio.com).

RESULTS

The study was conducted between October 2016 and July 2018, during which a total of 186 patients were screened. A total of 126 patients were enrolled and randomly assigned to receive either BE1040V (n = 82) or the reference drug (n = 44). Patients' disposition scheme is illustrated in Figure 1, and their baseline characteristics by treatment group are shown in Table I.

We also assessed KRAS and NRAS mutation status, although it was not a determining factor for the treatment choice; 34.15% and 20.45% of patients in the BE1040V and reference groups had wild-type KRAS, respectively. Also, 64.63% and 52.27% of the BE1040V and reference groups had wild-type NRAS, respectively.

Efficacy

Primary End Point

In the analysis of the per-protocol population, PFS values with BE1040V and the reference product were 232 days (7.7 months) and 210 days (7 months), respectively ($P = 0.47$). The HR of BE1040V versus the comparator was calculated to be 0.79 (90% CI, 0.46−1.35; $P = 0.47$) (Figure 2). Therefore, since the upper limit of 2-sided 90% CI was lower than the noninferiority margin of 1.44, BE1040V was considered to be noninferior to the reference drug.

The ITT population was also analyzed (n = 126), and HR was 0.84 (90% CI, 0.50−1.41; $P = 0.59$).

Forest plots of PFS in both treatment populations were also plotted and can be seen in Figure 3.

Secondary End Points

OS

Figure 4 depicts the OS in the treatment groups. The plot was analyzed using the log-rank test, and the variation between the 2 groups was not statistically meaningful. The HR for OS in the ITT population was 0.99 (95% CI, 0.55−1.80) (Figure 4), and the difference between the 2 groups was not statistically significant ($P = 0.99$).

TTF

Median TTF with BE1040V was 73±9.39 days versus 73±9.12 days for the reference product, and the difference between the 2 groups was not statistically significant ($P = 0.59$). The respective Kaplan−Meier curves of TTF were plotted and can be seen in Figure 5.

ORR

ORR values were reported to be 17 (40.48%) and 5 (21.74%) with BE1040V and the reference drug, respectively; and 1 patient in the BE1040V group had a CR. The difference between the 2 groups was not statistically significant (difference = 0.19; 95% CI, –0.04 to 0.41; $P = 0.173$).

Safety

Adverse Events

A total of 124 patients were analyzed for AEs (2 patients did not receive study medication and were not included in the safety population); the prevalences of AEs by treatment group are shown in Table II. No significant differences were observed in the comparison of the 2 arms.

Immunogenicity

Positive ADA was reported in 2 patients (1 in BE1040V group at the third visit; 1 in the bevacizumab group at the 11th visit). Due to the low rate of ADA, statistical analysis could not be performed for the correlation between the ADA status and safety.

DISCUSSION

In this Phase III, randomized, noninferiority study, we compared the efficacy of the proposed biosimilar BE1040V with that of the reference drug bevacizumab in terms of PFS as the primary end
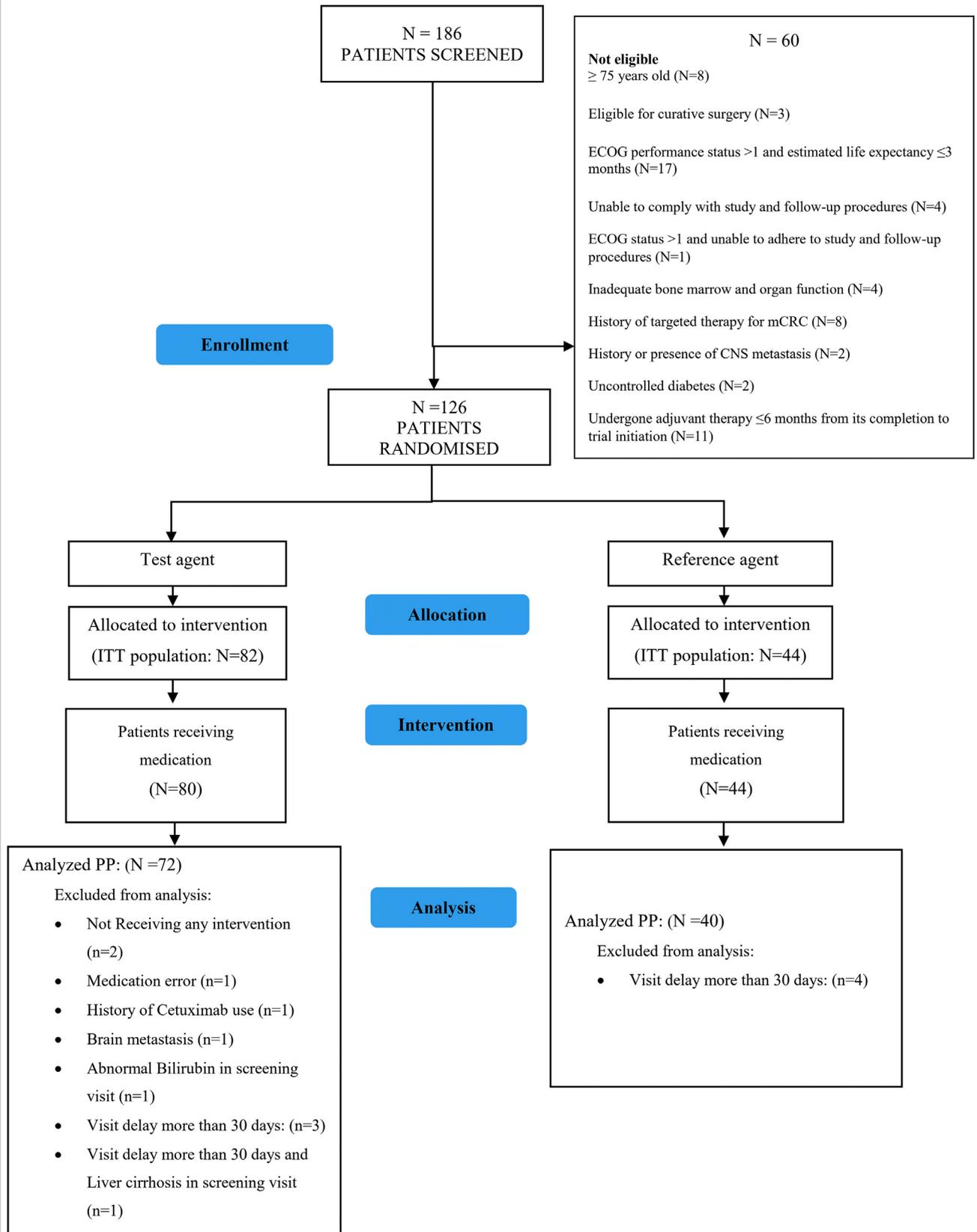
N = 186
PATIENTS SCREENED

N = 60

Not eligible
≥ 75 years old (N=8)

Eligible for curative surgery (N=3)

ECOG performance status >1 and estimated life expectancy ≤3 months (N=17)

Unable to comply with study and follow-up procedures (N=4)

ECOG status >1 and unable to adhere to study and follow-up procedures (N=1)

Inadequate bone marrow and organ function (N=4)

History of targeted therapy for mCRC (N=8)

History or presence of CNS metastasis (N=2)

Uncontrolled diabetes (N=2)

Undergone adjuvant therapy ≤6 months from its completion to trial initiation (N=11)

Enrollment

N =126
PATIENTS RANDOMISED

Test agent

Reference agent

Allocation

Allocated to intervention
(ITT population: N=82)

Allocated to intervention
(ITT population: N=44)

Intervention

Patients receiving medication
(N=80)

Patients receiving medication
(N=44)

Analysis

Analyzed PP: (N =72)

Excluded from analysis:

- Not Receiving any intervention (n=2)
- Medication error (n=1)
- History of Cetuximab use (n=1)
- Brain metastasis (n=1)
- Abnormal Bilirubin in screening visit (n=1)
- Visit delay more than 30 days: (n=3)
- Visit delay more than 30 days and Liver cirrhosis in screening visit (n=1)

Analyzed PP: (N =40)

Excluded from analysis:

- Visit delay more than 30 days: (n=4)

Figure 1. Patient disposition. PP = per protocol; ECOG = Eastern Cooperative Oncology Group; mCRC = metastatic colorectal cancer; ITT = intention to treat; PP = per protocol.

Table I. Patients' baseline characteristics.

Characteristic	BE1040V (n = 82)	Reference Drug (n = 44)
Sex, %		
Male	37.80	34.09
Female	62.20	65.91
Age, mean (SD)	56.26 (11.94)	56.27 (13.12)
Weight, mean (SD)	66.15 (12.09)	65.33 (10.39)
Site of primary tumor, %*		
Colon	66.67	51.52
Rectum	27.27	39.39
Colorectal	6.06	9.09
No. of metastatic sites, %*		
1	60.76	56.41
>1	39.24	43.59

There is no imputation for missing values.
*Valid percent: Missing data were excluded from the calculations.

point and OS, ORR, TTF, safety, and immunogenicity as the secondary end points in the treatment of mCRC. We found PFS to be 7.7 months in the BE1040V arm and 7 months in the reference arm in the analysis in the per-protocol population, and the difference was not statistically meaningful between the 2 groups; similar results were seen in the ITT population. Moreover, noninferiority was declared by analysis the CI of the HR.

In our study, PFS was relatively lower than that in most landmark Phase III clinical trials of chemotherapy plus bevacizumab for the treatment of mCRC. For instance, in the pivotal study of Hurwitz et al,[23] in which bevacizumab was administered alongside IRI 125 mg/m^2, 5-FU 500 mg/m^2, and LV 20 mg/m^2, PFS as a secondary end point was reported to be 10.6 months versus 6.2 months with chemotherapy plus placebo ($P < 0.001$). Heinemann et al[24] administered bevacizumab plus IRI 180 mg/m^2, LV 400 mg/m^2, and 5-FU 400 mg/m^2 and then 2400 mg/m^2. PFS, as a secondary end point, was 10.3 months (95% CI, 9.8–11.3).

In another study, conducted by Pasarrdi et al,[25] 41.5% of patients received FOLFIRI while others received FOLFOX4, and PFS, the primary end point, was 9.6 months with chemotherapy plus bevacizumab (95% CI, 8.2–10.3). In a study of Saltz et al,[26] bevacizumab was combined with oxaliplatin-based chemotherapy for the first-line treatment of mCRC. Median PFS as the primary study end point was 9.4 months versus 8.0 months in the bevacizumab plus placebo group (HR = 0.83; 97.5%
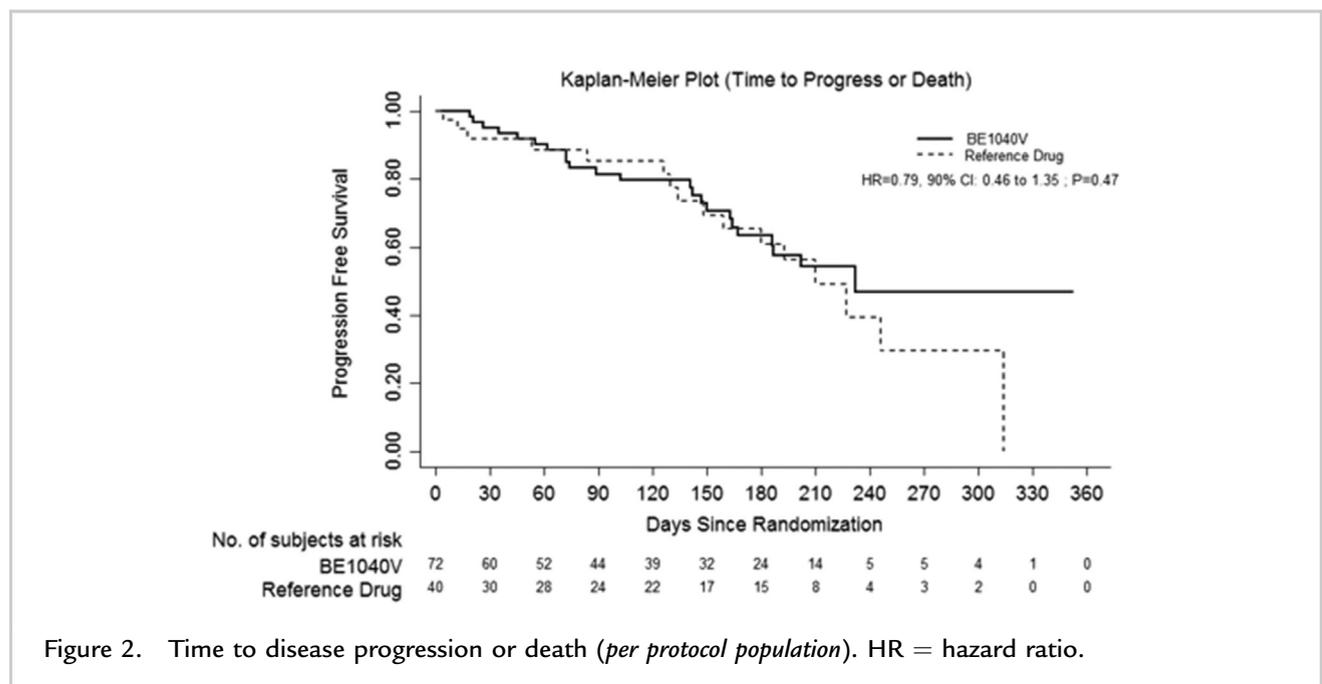

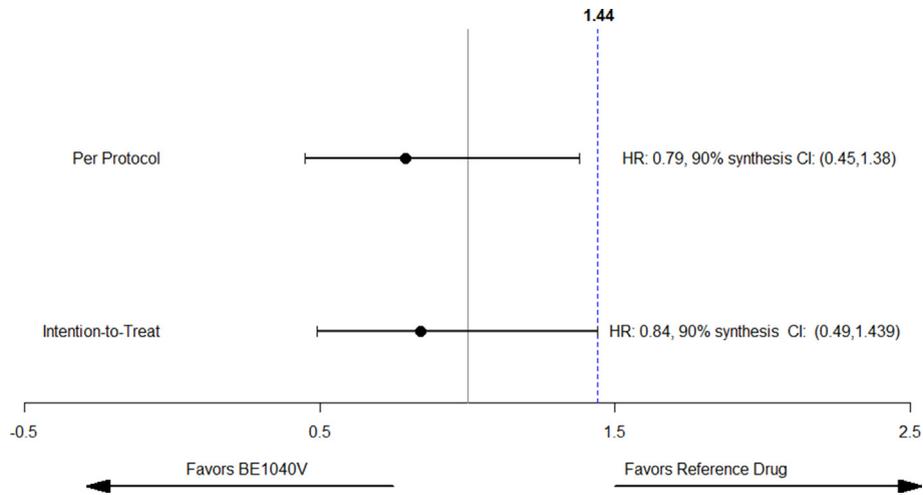Figure 2. Time to disease progression or death (*per protocol population*). HR = hazard ratio.

Figure 3. Forest plot of progression-free survival. HR = hazard ratio.

CI, 0.72−0.95; P = 0.0023). In a randomized, open-label study by Guan et al,[27] bevacizumab plus IRI 125 mg/m^2 on day 1, followed by LV 20 mg/m^2 and 5-FU 500 mg/m^2 weekly for 4 weeks, was administered; PFS as the secondary end point was reported to be 8.3 months (95% CI, 7.4−8.9). Reported PFS for that study was the closest to our

finding among the trials, especially in the BE1040V group, with 7.7 months. Another study of a treatment regimen similar to that chemotherapy backbone in the present study, was conducted by Saltz et al.[28] It should be mentioned that the treatment setting in that article consisted of induction therapy with FOLFIRI-3 until disease progression,
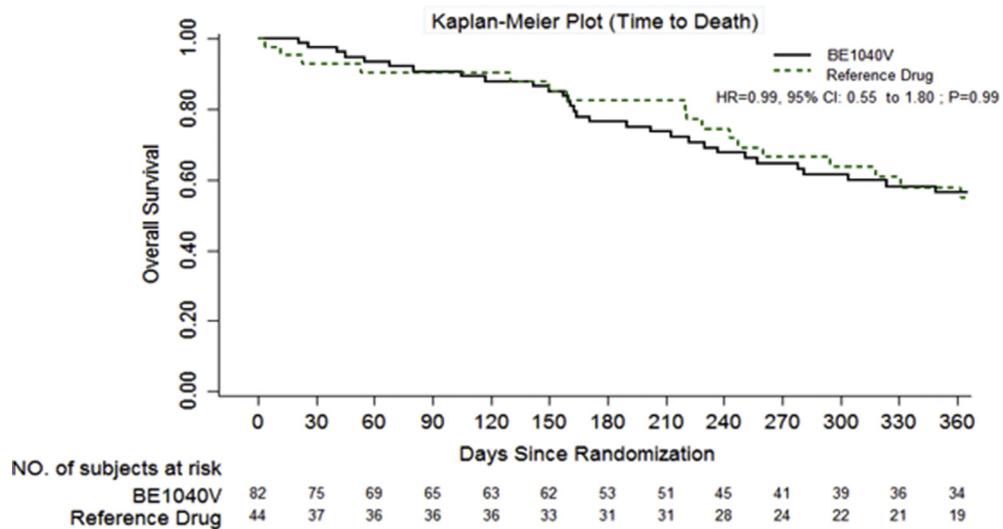
Figure 4. Time to death. HR = hazard ratio.

Figure 5. Time to treatment failure. HR = hazard ratio.
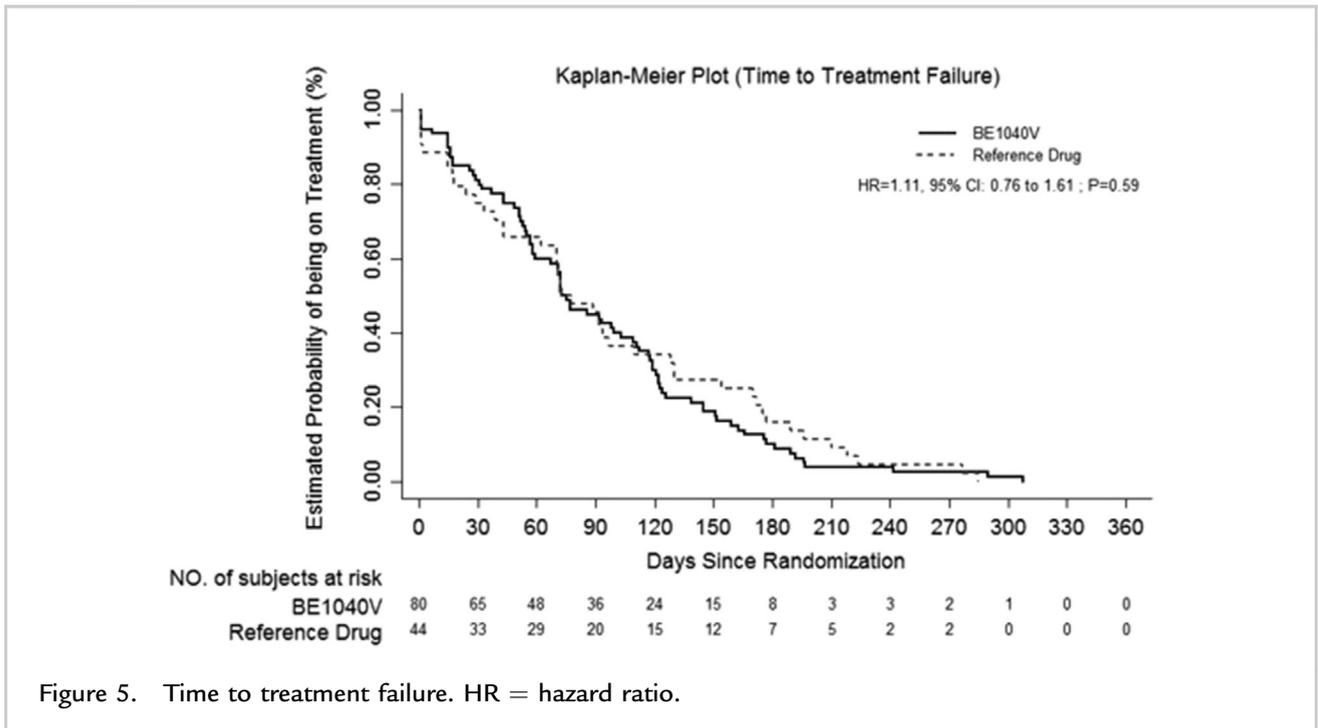
unacceptable toxicities, surgical intervention, or withdrawal of consent (for a maximum of 12 weeks) and maintenance therapy with bevacizumab and capecitabine until tumor progression, unacceptable toxicity, or withdrawal of consent. While in our study, patients were all treated with FOLFIRI-3 therapy until disease progression or death for a maximum of 1 year (52 weeks).

One reason for the relatively lower PFS time in our study may have been the number of patients who were discontinued from the treatment because of investigators' decision after a PR. The reasons for the investigator's decision of treatment discontinuation were patient noncompliance and intolerance, as patients refused to continue their treatment after partial remission and response to chemotherapy.

It seems that other causes of shorter PFS can be differences in public health care between countries, so CRC may be diagnosed later and in the advanced stage, and life expectancy would be shorter. In addition, genetics and environmental factors affect life expectancy in different countries.

Also, it should be noted that PFS and other end points are not directly comparable since our chemotherapy regimen in which repeated IRI was administered was different from those in these trials.

There are, however, some trials in which the reported PFS was lower than 7 months. For example, in a biosimilarity study published by Apsangikar et al,[29] the FOLFIRI regimen consisting of IRI 180 mg/m^2, LV 400 mg/m^2, and 5-FU 400 mg/m^2 followed by 2400 mg/m^2 was administered. PFS values as a secondary end point were 3.58 and 3.63 months at week 25 ($P = 0.444$) and 3.64 and 4.18 months at year 1 ($P = 0.922$) in the biosimilar group and the reference group, respectively.

In another study, carried out by Bennouna et al,[30] the continuation of bevacizumab along with IRI-based or oxaliplatin-based chemotherapy after disease progression was investigated. The choice of chemotherapy was based on the previous treatment regimen, and of 407 patients, 16% received FOLFIRI. Median PFS, a secondary end point, was 5.7 months in the bevacizumab plus chemotherapy group in the total population (95% CI, 5.2−6.2). In general, it could be argued that the PFS, as the primary end point of our study, falls within a range of approximately 3.5−10.6 months, as reported in prior trials.

The analysis of OS did not reveal a statistically significant difference between the 2 groups (HR = 0.99; 95% CI, 0.55−1.80; $P = 0.99$). We

Table II. Adverse events (AEs) in patients who received at least 1 dose of study drug.

Parameter	BE1040V (n = 80)	Reference drug (n = 44)
AE grade 3/4*	19 (23.75)	12 (27.27)
AE led to hospitalization*	4 (5.00)	0 (0.00)
Any AE*	76 (95.00)	44 (100.00)
AEs of special interest		
Hemorrhage*	3 (3.75)	1 (2.27)
Hypertension*	11 (13.75)	5 (11.36)
Embolism*	1 (1.25)	0 (0)
Proteinuria*	18 (22.5)	12 (27.27)
GI perforation*	1 (1.25)	0 (0.00)

Data are given as number (%) of patients.
*P > 0.05.

could not report the median OS, as one of the limitations of our study was the short follow-up duration. We treated patients up to 1 year, and patients were censored if they had not experienced progression or death by the time of the cutoff.

In our study, the analysis of ORR showed no statistically meaningful difference between the 2 sets (P = 0.173); CR was seen in 1 patient (2.38%) in the BE1040V group. Also, findings for ORR were consistent with those from other trials in which ORR was reported to be between 28% to 66%. Hurwitz et al[23] measured ORR to be 44.8% in the bevacizumab arm, in which CR was 3.7%, and PR was 41.0%.

Guan et al[27] reported 28%–44% for ORR, where CR was 2.9%, and PR was 32.4%. In the study of Heinemann et al,[24] ORR, the primary end point, was 58% (95% CI, 52.1–63.7); 57% of patients achieved PR and 1% achieved CR. In the study of Stathopoulos et al,[31] patients were administered LV 200 mg/m^2, 5-FU 500 mg/m^2 plus IRI 135 mg/m^2 and bevacizumab 7.5 mg/kg every 3 weeks, and PR was reported to be 36.8%, but no CR was seen.[31] Apsangikar et al[29] reported 60.53% and 66.67% for the ORR in the biosimilar group and reference group, respectively (P = 0.622), and 3 CRs (7.9%)

were seen in the biosimilar group. Lastly, Bennouna et al[30] reported 5% for the ORR (CR, <1%; PR, 5%).

As for the safety evaluation, the rate of any grade 3/4 AE were 23.75% and 27.27% in the BE1040V and reference drug groups, respectively, in our study. This finding seems consistent with the results from Saltz et al[26] study (21%) although a much higher result was published by Hurwitz et al[23] (84.9%), which may have been related to the difference in the administration of combination therapy.

AEs of special interest that are related to bevacizumab were also similar to those from previous clinical trials. For example, other trials reported a range of up to 2% for gastrointestinal perforation and 2%–11% for hypertension. Also, Saltz et al[23,26,27] reported a prevalence of 2% for pulmonary embolism, which is in line with 1.25% reported in our trial.

In the immunogenicity assessment, since there were only 2 reports of a positive result, statistical analysis could not be performed; nonetheless, it seems unlikely that these positive results had a meaningful impact on the study end points. This result is in line with the 0.6% positive report in clinical trials of adjuvant treatment of a solid tumor with bevacizumab.[32]

CONCLUSION
This Phase III, multicenter, randomized, double-blind study has demonstrated the noninferior efficacy and comparable tolerability of the biosimilar drug BE1040V compared to the bevacizumab reference drug in mCRC treatment.

CONFLICTS OF INTEREST
N.A. is the head of medical department of Orchid Pharmed Company, an AryoGen partner in conducting clinical trials. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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