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Original Article

Comparison of Efficacy and Safety of a Bevacizumab Biosimilar, in Combination with Chemotherapies, in Nonresectable Metastatic Colorectal Cancer and in Advanced Nonsquamous Non–Small Cell Lung Cancer: A Randomized, Double-Blind, Phase III Study

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Abstract


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The objective of this study was to compare the efficacy, safety, pharmacokinetics, and immunogenicity of a proposed bevacizumab biosimilar (DRL_BZ) with the innovator Avastin (reference medicinal product [RMP]) in patients with nonresectable metastatic colorectal cancer (mCRC) over a period of 9 months and advanced nonsquamous non–small cell lung cancer (NSCLC) over 6 months. The study was planned as a randomized, double-blind trial. In part A, a total of 117 mCRC patients were intended to receive 5 mg/kg of bevacizumab every 2 weeks along with mFOLFOX6 chemotherapy for a maximum of 18 cycles. In part B, 60 NSCLC patients were to receive 15 mg/kg of bevacizumab every 3 weeks along with pemetrexed and carboplatin for the initial four cycles, followed by pemetrexed for another four cycles. The primary endpoint was the progression-free survival rate at 6 months (PFS6) in both subparts. The anticipated sample size was 106 evaluable mCRC patients to achieve 85% statistical power for concluding noninferiority with a margin of half the difference (18.8%) between DRL_BZ and Avastin, along with a pilot study involving 60 evaluable NSCLC patients. Safety comparison included assessing adverse events (AEs),

Keywords

- bevacizumab
- biosimilar
- colorectal cancer
- non–small cell lung cancer
- oncology

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infusion reactions, and lab abnormalities. Immunogenicity comparison involved the incidence of antidrug antibodies (ADAs) and neutralizing antibodies (NAbs). Pharmacokinetic comparison was planned after the first and fourth dosing cycles of treatment in 24 NSCLC patients. The PFS6 for mCRC patients treated with DRL_BZ and RMP was 57.8% and 50% respectively, with a difference in efficacy of 7.8 (–8.7, 23.7). The PFS9 was 31.1% and 22.9%, with a difference of 8.2% (–6.9%, 22.9%). The objective response rate (ORR) for DRL_BZ and RMP was 28.8% and 22.4%, while the disease control rate (DCR) was 44.2% and 37.9% respectively. For NSCLC patients, the PFS6 was 44% and 45%, showing a difference of –1.0 (–4.2, 22.1). The ORR was 41.4% and 48.1%, and the DCR was 62.1% and 63%. The frequency, type, and severity of AEs were similar in both indications. Blood levels during the first and fourth dosing cycles exhibited comparable values. All NSCLC patients tested negative for ADA, while no mCRC patients on DRL_BZ tested positive for ADA. Low incidences of ADA (8%) and NAbs (4.0%) were reported in patients on RMP. Overall, the efficacy, safety, immunogenicity, and pharmacokinetic parameters of DRL_BZ and RMP were found to be comparable.

Clinical Trial Registration For BZ-01-002: CTRI/2016/01/006481

Introduction

Bevacizumab is a humanized immunoglobulin G1 (IgG1) used in antiangiogenic therapies. Many human tumors show upregulation of vascular endothelial growth factor (VEGF) and high expression of its receptors. VEGF plays a key role in tumor growth by regulating angiogenesis. Bevacizumab blocks the VEGF activity resulting in reduction of angiogenesis, thereby inhibiting tumor growth, and plays an imperious role in tumor treatment.[1,2] Bevacizumab is approved for the treatment of a range of cancers, including metastatic or recurrent nonsquamous non–small cell lung cancer (NSCLC), metastatic colorectal cancer (mCRC), metastatic renal cell carcinoma, cervical cancer, and platinum-resistant or platinum-sensitive recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancers.[1,2] Numerous trials have shown the significant clinical benefits in terms of prolonged PFS and/or overall survival (OS) in cancer patients with the treatment combining bevacizumab with standard chemotherapy.[3]

Given the high cost of innovator biologics, treatment is often inaccessible to most patients. The American Society of Clinical Oncology and the European Society for Medical Oncology have emphasized on the importance of biosimilars in improving patient access to anticancer therapies and supporting the sustainable cancer care. An urgent need exists for enabling patient access to good-quality affordable treatments. A lower cost bevacizumab biosimilar with its demonstrated efficacy and safety in specific tumor types could address the unmet needs of patients and physicians worldwide.[4] Bevacizumab biosimilar (DRL_BZ) is being developed as a biosimilar to the reference medicinal product (RMP) bevacizumab Avastin.

Patients and Methods

Study Design

This is a randomized, multicenter, double-blind study conducted as parts A and B. The part A study is planned in patients with mCRC and part B in patients with NSCLC (►Fig. 1). The study was approved by an independent ethics committee or an institutional review board at different study centers and conducted in accordance with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, and applicable local regulations. Each patient provided written informed consent before they were included in the study.

In part A, the efficacy and safety of DRL_BZ and RMP in combination with mFOLFOX6 (a combination therapy of oxaliplatin, leucovorin, and 5-flourouracil [5FU]) were planned to be compared in patients who were getting treatment for the first time for mCRC. The study was randomized equally to the treatments arms and further stratified based on exposure to prior adjuvant oxaliplatin therapy, Eastern Cooperative Oncology Group (ECOG) status (0–1, and 2), and region (country). A block, stratified randomization schedule was generated by the independent personnel, and the central randomization procedure was implemented and the treatment groups were assigned via the Interactive Web Response System (IWRS). A patient was considered randomized when the patient met all eligibility criteria and received randomization number from IWRS. The total duration of an individual patient participation was up to 40 weeks. In part B, the efficacy and safety of DRL_BZ and RMP in combination with pemetrexed and carboplatin were planned to be compared in patients with recurrent or advanced (stage IV) nonsquamous NSCLC, who were not previously treated with chemotherapy. The total duration of an individual patient participation was up to 28 weeks. The study was randomized equally to the treatments arms and further stratified based on gender.

The study was conducted between January 2016 and February 2019 across 24 sites in India and 3 sites in Russia.

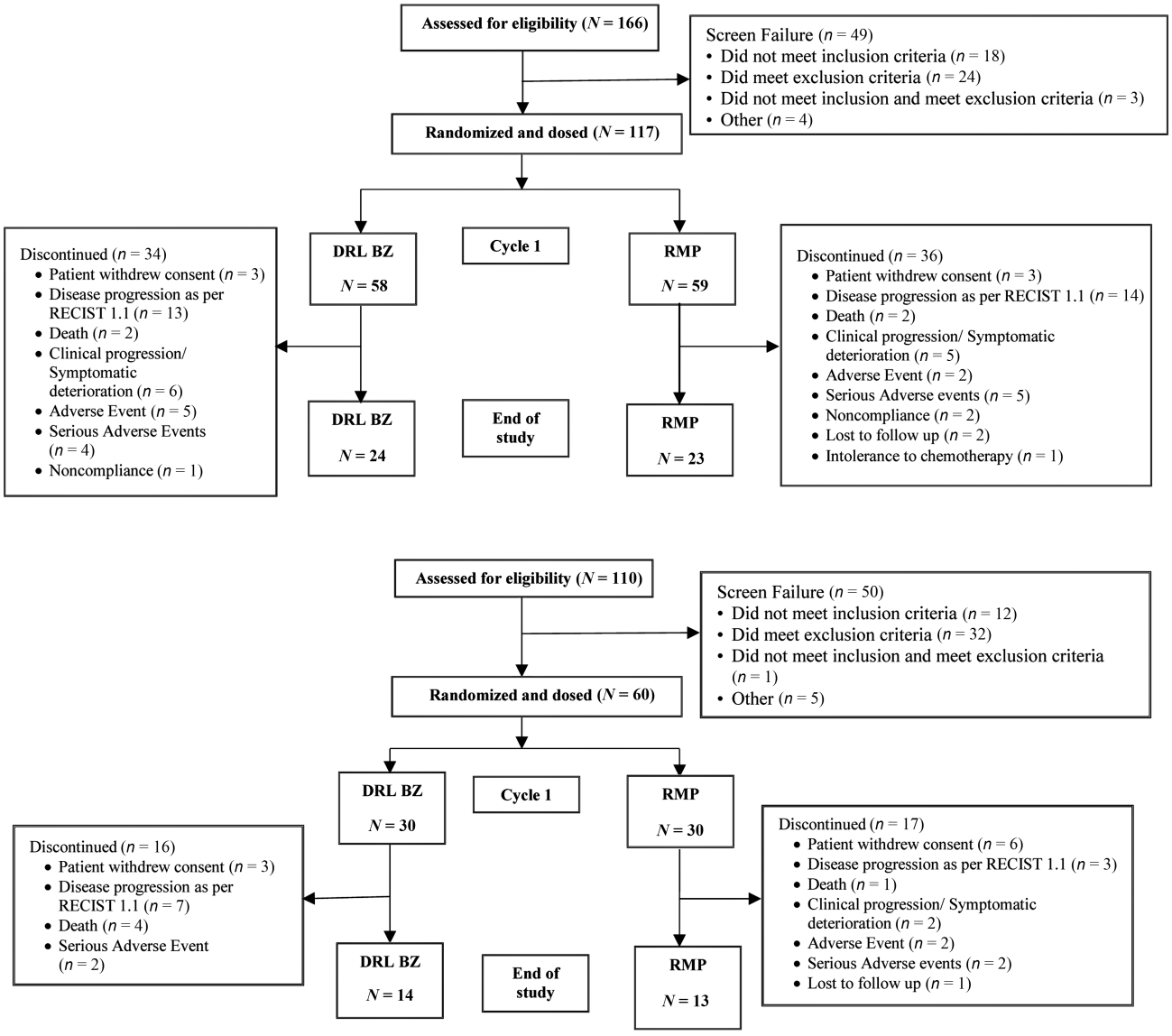

Fig. 1 (A) Patient disposition for metastatic colorectal cancer (mCRC). (B) Patient disposition for non–small cell lung cancer (NSCLC). DRL_BZ, bevacizumab biosimilar; RECIST, Response Evaluation Criteria in Solid Tumors; RMP, reference medicinal product.

Patients

Selection Criteria for mCRC

Patients of either gender, aged 18 to 75 years, with histologically or cytologically confirmed (stage IV) mCRC with ECOG performance status of 0 to 2 and life expectancy of more than 3 months were included in part A of the study. The patients were expected to have no clinically relevant abnormality in their hematology, liver function, renal function, and coagulation function assessment to qualify for the study. Women of child-bearing potential were fit, provided they were taking suitable contraceptive measures.

Patients who had previously used bevacizumab and any other monoclonal antibodies within the last 6 months, underwent chemotherapy or other systemic therapies (prior adjuvant therapy was allowed if it was earlier than 12 months), had resectable metastatic disease, had central nervous system metastasis, allergic to active treatments planned in the study, history of other malignancies in the last 5 years (except nonmelanoma skin cancer or carcinoma in situ of the cervix, or resected intraductal breast cancer), dihydropyrimidine dehydrogenase deficiency, those needing nonsteroidal anti-inflammatory drugs (NSAIDs) during the study, or those who had been part of another clinical trial were excluded from the study. Patients with any other clinically relevant diseases that can affect their safety as assessed by the investigator were also excluded. Patients scheduled for radiation therapy or surgery during the course of the study and those who underwent radiotherapy within 14 days of screening and had not recovered from all toxicities of radiotherapy were considered unsuitable. If a patient had undergone any surgery within 28 days of screening, they were not fit for the study.

Selection Criteria for NSCLC

Patients of either gender, aged 18 to 75, with histologically or cytologically confirmed relapsed or advanced (stage IV)

NSCLC of nonsquamous histology for which they have not received systemic therapies with ECOG performance status (ECOG-PS) of 0 or 1 and life expectancy of more than 3 months were included in part B of the study. The patients were expected to have no clinically relevant abnormality in their hematology, liver function, renal function, and coagulation function assessment to qualify for the study. Women of child-bearing potential were fit provided they were taking suitable contraceptive measures. Patients whose radiation therapy did not include more than 25% of the bone marrow or the whole pelvis, provided it was completed 2 weeks earlier to screening and have recovered from all acute adverse effects of radiotherapy, could be included in the study.

Patients who have previously used bevacizumab, carboplatin, pemetrexed, any other monoclonal antibodies within the last 6 months, have evidence of squamous cell lung cancer, central nervous system metastasis, allergic to treatments planned in the study (bevacizumab, pemetrexed, carboplatin, vitamin B12, folic acid or dexamethasone, or to any of their excipients), history of other malignancies within the last 5 years (except nonmelanoma skin cancer or carcinoma in situ of the cervix, or resected intraductal breast cancer), those needing NSAIDs during the study, or those who have been part of another clinical trial were unfit. Patients with any other clinically relevant diseases that can affect their safety as assessed by the investigator were excluded. If a patient had undergone any surgery within 28 days of screening, they were excluded from the study.

Treatment

Metastatic Colorectal Cancer

Patients assigned to the DRL_BZ or RMP arms received 5 mg/kg of bevacizumab every 2 weeks with mFOLFOX6. For any patient, maximum planned cycles were 18. For first 12 cycles, DRL_BZ or RMP + mFOLFOX6 chemotherapy was administered, while for the next 6 cycles, based on the investigator's risk–benefit assessment, the patient could receive DRL_BZ or RMP as monotherapy or with mFOLFOX6.

Non–Small Cell Lung Cancer

Patients assigned to the DRL_BZ and RMP arms received 15 mg/kg of bevacizumab with pemetrexed + carboplatin chemotherapy every 3 weeks for four cycles, that is, 12 weeks. After four cycles, chemotherapy was continued with only pemetrexed for the subsequent four cycles.

Endpoints

The primary endpoint was progression-free survival rate at 6 months (PFS6) in the mCRC and NSCLC arms. Secondary endpoints included objective response rate (ORR) and disease control rate (DCR) assessed using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) 1.1. The PFS9 was assessed additionally for mCRC. The pharmacokinetic (PK) parameters were analyzed for a subset of NSCLC patients. Safety was assessed as incidence of adverse events (AEs), infusion reactions, and laboratory parameter abnormalities, and the immunogenicity was assessed as incidence of antidrug antibodies (ADAs) and neutralizing antibodies (NAbs). Tumor response was evaluated using computed tomography/magnetic resonance imaging (CT/MRI). Immunogenicity assessment and blood level assessment were performed using validated methods.

Statistical Analysis

Metastatic Colorectal Cancer

The sample size calculation was based on the general observation that effects of bevacizumab alone versus bevacizumab in combination with chemotherapy backbones differ the most when measured in terms of PFS, and the most sensitive point was at 6 months following initiation of treatment. The noninferiority margin and the overall design were based on the results reported in the Avastin and Irinotecon in first line metastatic colorectal cancer (ARTIST) trial.[5] It was reported that the addition of bevacizumab to the modified Irinotecan, Fluorouracil and Leucovorin (IFL) regimen (mIFL) as the first-line treatment significantly improved the PFS6 (25.0% with mIFL vs. 62.6% with mIFL plus bevacizumab; $p < 0.001$). A sample size of 106 evaluable patients per study arm could provide a statistical power of 85% to conclude noninferiority with a margin of half of the difference (18.8%) of DRL_BZ as compared to Avastin. The anticipated approximate sample size for the study was up to 280 patients after accommodating for dropouts and withdrawals.

There were no available data for modern chemotherapy standards like mIFL when co-administered with bevacizumab. Since the chemotherapy backbone used in this study differed from the chemotherapy backbone that was used to estimate the sample size, a sample size recalculation was planned on the basis of the availability of the PFS6 data of approximately 100 patients. The sample size reestimation targeted a statistical power of 85% to conclude noninferiority with a margin of half of the difference (18.8%) of DRL_BZ as compared to Avastin under these assumptions.

The sample size reestimation done using outcome data of 101 patients ensured the earlier planned statistical estimates and, hence, it was concluded that the recruited number of patients were sufficient to test the hypothesis of noninferiority between the two treatment arms. Since few patients were undergoing treatment while sample size reestimation was ongoing, the final number of patients included in the mCRC study were 117.

Non–Small Cell Lung Cancer

A sample size of 30 patients per arm was expected to provide an approximate assessment of gross differences of therapeutic outcomes between both treatment arms, empirically. The NSCLC study was included to generate efficacy and safety data in another indication, which was expected to benefit subsequent regulatory marketing approval.

A total of 24 patients (12 patients per treatment arm) on treatment for NSCLC were identified and were expected to provide blood samples after the first and fourth infusion cycles, for estimation of the drug level.

Analysis Populations

Efficacy was evaluated based on the modified intent-to-treat (mITT; included patients who received at least one dose of medication and who had at least one postbaseline efficacy assessment from CT scan/MRI available); intent-to-treat (ITT; this population included all randomized patients who received at least one dose of medication); and per protocol (PP; this population included patients who had at least one postbaseline efficacy assessment from CT scan/MRI available after week 24 and did not have any major protocol deviations that impact efficacy analysis) population. The analysis of efficacy performed using mITT population was considered the primary analysis. Safety population included patients who received at least one dose of medication, irrespective of whether they completed the rest of the evaluations. Immunogenicity population included patients for whom the preinfusion, and at least one postdose immunogenicity sample with valid results was available. The PK population included all patients in the PK subset of part B of the study, who received at least one dose of medication and had at least one measured postdose blood sample at a scheduled time point after the start of the infusion, with no major protocol deviations or violations that can significantly affect the blood level of the study drug as determined before unblinding

Results

Patient Disposition

Of the 166 patients screened, 117 patients were found suitable for the mCRC study and randomized. Among these, 58 patients were randomized to DRL_BZ, of which 24 patients completed the study and 23 of 59 patients who were randomized to Avastin completed the study (►Fig. 1A). Of the 110 patients screened, 60 patients were found suitable for the NSCLC study and randomized. Among these, 30 patients were randomized to DRL_BZ, of which 14 patients completed the study and 13 of 30 patients who were randomized to Avastin completed the study (►Fig. 1B).

Patient Demographics and Baseline Characteristics

The demographic and clinical characteristics of the study patients were balanced (►Table 1). The mean age was 52.99 years for the mCRC population and 55.80 years for the NSCLC population. The majority were males in both the treatment populations (74 and 49) and the majority had ECOG-PS of 0 to 1 in both the mCRC (116) and NSCLC (60) population. Very few received prior treatment for colorectal cancer (13) and prior systemic therapies for NSCLC (1).

Table 1 Patient demographics and baseline characteristics (safety population)

Characteristics	mCRC		NSCLC	
	DRL_BZ ($N = 58$)	RMP ($N = 59$)	DRL_BZ ($N = 30$)	RMP ($N = 30$)
Mean age in years (±SD)	53.74 (±13.13)	52.25 (±13.55)	56.80 (±8.65)	54.80 (±11.93)
Male, *n* (%)	40 (69.0)	34 (57.6)	25 (83.3)	24 (80.0)
Female, *n* (%)	18 (31.0)	25 (42.4)	5 (16.7)	6 (20.0)
Asian, *n* (%)	51 (87.9)	51 (86.4)	30 (100.0)	30 (100.0%)
White/Caucasian/European Heritage, *n* (%)	7 (12.1)	8 (13.6)	–	–
ECOG performance status (*n*)	58	59	30	30
Grade 0, *n* (%)	7 (12.1)	8 (13.6)	4 (13.3)	2 (6.7)
Grade 1, *n* (%)	51 (87.9)	50 (84.7)	26 (86.7)	28 (93.3)
Grade 2, *n* (%)	0	1 (1.7)	0	0
Grade 3, *n* (%)	0	0	0	0
Grade 4, *n* (%)	0	0	0	0
Prior treatment received for colorectal cancer, *n* (%)	5 (8.6)	8 (13.6)	NA	NA
Prior systemic therapies for nonsquamous NSCLC, *n* (%)	NA	NA	1 (3.3)	0
Prior systemic therapies for metastatic nonsquamous NSCLC, *n* (%)	NA	NA	0	0
Subjects given prior radiation therapy, *n* (%)	4 (6.9)	4 (6.8)	0	0
Colorectal cancer stage IV M1, *n* (%)	58 (100.0)	59 (100.0)	NA	NA
Nonsquamous NSCLC of advanced stage IV, *n* (%)	NA	NA	30 (100.0)	30 (100.0)

Abbreviations: DRL_BZ, bevacizumab biosimilar; ECOG, Eastern Cooperative Oncology Group; mCRC, metastatic colorectal cancer; NSCLC, non–small cell lung cancer; RMP, reference medicinal product; SD, standard deviation.

Table 2 Efficacy outcomes in mCRC patients (mITT population)

Progression-free survival rate at 6 mo (PFS6)						
	mITT		**PP**		**ITT**	
	DRL_BZ (*N* = 52)	**RMP (*N* = 58)**	**DRL_BZ (*N* = 47)**	**RMP (*N* = 50)**	**DRL_BZ (*N* = 58)**	**RMP (*N* = 59)**
No. of patients evaluable for PFS6 (*n*)	45	52	45	50	45	52
Nonprogressing patients, *n* (%)	26 (57.8)	26 (50.0)	26 (57.8)	24 (48.0)	26 (44.8)	26 (44.1)
Two-sided 90% CI[a]	(45.6, 69.1)	(38.9, 61.1)	(45.6, 69.1)	(36.8, 59.4)	(34.6, 55.6)	(33.9, 54.7)
Difference in percentage[b], % (90% CI)	7.8 (–8.7 to 23.7)		9.8 (–6.9 to 25.7)		0.8 (–14.0 to 15.5)	
Progression-free survival rate at 9 mo (PFS9)						
	mITT					
	DRL_BZ			RMP		
No. of patients evaluable for PFS9 (*n*)	45			48		
Nonprogressing patients, *n* (%)	14 (31.1)			11 (22.9)		
Two-sided 90% CI[a]	21.1–43.3)			14.5–34.2		
Difference in percentage[b], % (90% CI)	8.2 (–6.9 to 22.9)					
Response rates at the EOS						
No. of patients evaluable (*n*)	50			55		
Complete response, *n* (%)	0			0		
Partial response, *n* (%)	15 (28.8)			13 (22.4)		
Stable disease, *n* (%)	8 (15.4)			9 (15.5)		
Progressive disease, *n* (%)	27 (51.9)			33 (56.9)		
Overall response rate, *n* (%) 90% CI	15 (28.8) 19.8–40.0			13 (22.4) 14.8–32.5		
Disease control rate, *n* (%) 90% CI	23 (44.2) 33.5–55.6]			22 (37.9) 28.2–48.7		

Abbreviations: CI, confidence interval; DRL_BZ, bevacizumab biosimilar; EOS, end of the study; mITT, modified intent-to-treat; mCRC, metastatic colorectal cancer; PP, per protocol; RMP, reference medicinal product; SD, standard deviation.

Note: For the ITT population, percentages are calculated using the number of patients present in the ITT population.

For the mITT and PP population, percentages are calculated out of the number of patients evaluable for PFS6 and PFS9.

EOS: End of study assessment of any parameter is defined as the latest nonmissing assessment of the parameter after administration of the first dose of DRL_BZ and RMP. Thus, in addition to scheduled visit assessments, early termination assessments and unscheduled visit assessments are used to derive EOS assessment.

The percentages are calculated using the number of patients present in the mITT population.

[a]Two-sided 90% CIs for one sample proportion are estimated using the Wilson score method.

[b]Two-sided 90% CIs for difference in two independent proportions are estimated using the Wilson score method.

Efficacy with mCRC Treatment

In the mCRC arm, the efficacy percentage noted for PFS6 in the mITT population analysis was 57.8 and 50% with DRL_BZ and RMP, respectively (►Table 2). The lower limit of the 90% confidence interval (CI) for the difference in efficacy between the DRL_BZ and RMP arms for nonprogressing patients was –8.7%, and it was within the noninferiority margin of 18.8% as inferred based on the ARTIST trial. The equivalent number as per the PP population analysis was –6.9%.

The efficacy percentage noted in the mITT population analysis for PFS9 was 31.1 and 22.9% and the percentage difference between the DRL_BZ and RMP arms after treatment was 8.2% (–6.9 to 22.9%; ►Table 2). The efficacy percentage noted for ORR for the two arms was 28.8 and 22.4%, and the DCR was 44.2 and 37.9% (►Table 2). At the end of the study (EOS), no patients showed a complete response (CR) in any treatment arms. The percentage of patients with partial response, stable disease, and progressive disease was similar in both arms.

Efficacy with NSCLC Treatment

The efficacy percentage noted for PFS6 in the mITT population analysis was 44 and 45% with DRL_BZ and RMP, respectively (►Table 3). The difference in efficacy between the DRL_BZ and RMP arms for the nonprogressing patients was –1.0%. The equivalent number as per the PP population analysis was –5.0%.

The efficacy percentage noted for the ORR was 41.4 and 48.1% and that for the DCR was 62.1 and 63% (►Table 3). At the EOS, no patients showed CR in any treatment arms. The percentage of patients with partial response, stable disease, and progressive disease was similar in both arms.

Pharmacokinetics

The PK parameters, $C_{max,}$ AUC_{0-t}, and AUC_{0-tau}, at the first and fourth cycles were compared during the study in the PK subset population identified within the NSCLC patient group (►Table 4). The parameters were overall comparable between the treatment arms. The results corroborated with the findings of a previously reported phase I study where the PK of DRL_BZ was similar to that of the reference products.[6]

Safety with mCRC Treatment

A total of 1,246 treatment-emergent AEs (TEAEs) were reported (DRL_BZ, $n = 572$; RMP, $n = 674$), of which 67 were serious TEAEs (DRL_BZ, $n = 27$; RMP, $n = 40$; ►Table 5). Forty-six and 41 patients in the DRL_BZ and RMP groups, respectively, had at least one TEAE of grade 3/4. Thirty patients (DRL_BZ, $n = 16$; RMP, $n = 14$) discontinued study participation because of TEAEs. A total of eight (6.8%) patients (4 patients in each

Table 3 Efficacy outcomes in NSCLC patients (mITT population)

Progression-free survival rate at 6 mo (PFS6)				
	mITT		PP	
	DRL_BZ ($N = 29$)	RMP ($N = 27$)	DRL_BZ ($N = 20$)	RMP ($N = 20$)
No. of patients evaluable for PFS6	25	20	20	20
Nonprogressing patients, *n* (%)	11 (44.0)	9 (45.0)	8 (40.0)	9 (45.0)
Two-sided 90% CI[a]	(29.1–60.1)	(28.4–62.8)	(24.2–58.1)	(28.4–62.8)
Difference in percentage[b] (90% CI)	–1.0 (–24.2 to 22.1)		–5.0 (–28.8 to 19.6)	
	DRL_BZ ($N = 29$)		RMP ($N = 27$)	
No. (%) of subjects in mITT population achieving best overall response at the EOS				
No. of patients evaluable	28		27	
Complete response, *n* (%)	0		0	
Partial response, *n* (%)	12 (41.4)		13 (48.1)	
Stable disease, *n* (%)	6 (20.7)		4 (14.8)	
Progressive disease, *n* (%)	10 (34.5)		10 (37.0)	
Overall response rate, *n* (%) 90% CI	12 (41.4) 27.7–56.5		13(48.1) 33.2–63.4	
Disease control rate, *n* (%) 90% CI	18 (62.1) 46.8–75.3		17 (63.0) 47.2–76.4	

Abbreviations: CI, confidence interval; DRL_BZ, bevacizumab biosimilar; EOS, end of the study; mITT, modified intent-to-treat; NSCLC, non–small cell lung cancer; PP, per protocol; RMP, reference medicinal product.

Note: For ITT population, percentages are calculated using the number of patients present in the ITT population.

For mITT and PP population, percentages are calculated out of the number of patients evaluable for PFS6.

EOS: End of study assessment of any parameter is defined as the latest nonmissing assessment of the parameter after administration of the first dose of DRL_BZ and Avastin. Thus, in addition to scheduled visit assessments, early termination assessments and unscheduled visit assessments are used to derive end of study assessment.

The percentages are calculated using the number of patients present in the mITT population.

[a]Two-sided 90% CIs for one sample proportion are estimated using the Wilson score method.

[b]Two-sided 90% CIs for the difference in two independent proportions are estimated using the Wilson score method.

Table 4 Comparison of PK parameters after cycle 1 and 4 dosing (PK population)

PK parameters	Treatment	N^a	Mean (±SD)	N^a	Mean (±SD)
		C1		C4	
C_{max} (μg/mL)	DRL_BZ	11	365.45 (±92.11)	5	464.40 (±57.03)
	RMP	10	336.60 (±118.79)	7	406.00 (±68.50)
$AUC_{0\text{-}t}$ (μg*h/mL)	DRL_BZ	10	55,518.47 (±18,363.73)	5	88,560.13 (±10,127.80)
	RMP	9	41,374.00 (±18,848.72)	6	74,293.18 (±39,516.68)
$AUC_{0\text{-}tau}$ (μg*h/mL)	DRL_BZ	10	55,518.47 (±18,363.73)	5	88,560.13 (±10,127.80)
	RMP	9	41,374.00 (±18,848.72)	6	74,293.18 (±39,516.68)

Abbreviations: DRL_BZ, bevacizumab biosimilar; PK, pharmacokinetic; RMP, reference medicinal product; SD, standard deviation.
[a]PK population received at least one dose of DRL_BZ or RMP and had at least one measurable postdose PK sample at a scheduled time point after the start of the infusion.

Table 5 Overall summary of AEs

	mCRC		NSCLC	
	DRL_BZ (*N* = 58) *n* (%), *E*	RMP (*N* = 59) *n* (%), *E*	DRL_BZ (*N* = 30) *n* (%), *E*	RMP (*N* = 30) *n* (%), *E*
At least one TEAE	57 (98.3), 572	56 (94.9), 674	28 (93.3), 214	23 (76.7), 174
At least one related TEAE	25 (43.1), 97	26 (44.1), 114	8 (26.7), 17	9 (30.0), 11
At least one treatment emergent SAE	17 (29.3), 27	20 (33.9), 40	12 (40.0), 15	5 (16.7), 9
At least one treatment emergent fatal SAE	4 (6.9), 4	4 (6.8), 4	4 (13.3), 4	2 (6.7), 2
Mild	52 (89.7), 315	49 (83.1), 357	23 (76.7), 101	16 (53.3), 93
Moderate	44 (75.9), 150	47 (79.7), 216	24 (80.0), 86	18 (60.0), 47
Severe	36 (62.1), 86	30 (50.8), 78	13 (43.3), 19	16 (53.3), 30
Life threatening	10 (17.2), 17	11 (18.6), 19	3 (10.0), 4	2 (6.7), 2
Overall summary of TEAE and SAEs				
	mCRC		NSCLC	
	DRL_BZ (*N* = 58) *n* (%), *E*	RMP (*N* = 59) *n* (%), *E*	DRL_BZ (*N* = 30) *n* (%), *E*	RMP (*N* = 30) *n* (%), *E*
Any SAE	17 (29.3), 27	20 (33.9), 40	12 (40.0), 15	5 (16.7), 9
Grade 1	52 (89.7), 315	49 (83.1), 357	23 (76.7), 101	16 (53.3), 93
Grade 2	44 (75.9), 150	47 (79.7), 216	24 (80.0), 86	18 (60.0), 47
Grade 3	36 (62.1), 86	30 (50.8), 78	13 (43.3), 19	16 (53.3), 30
Grade 4	10 (17.2), 17	11 (18.6), 19	3 (10.0), 4	16 (53.3), 93
Grade 5	4 (6.9), 4	4 (6.8), 4	4 (13.3), 4	2 (6.7), 2

Abbreviations: AEs, adverse events; DRL_BZ, bevacizumab biosimilar; mCRC, metastatic colorectal cancer; NSCLC, non–small cell lung cancer; RMP, reference medicinal product; SAE, serious adverse event; TEAEs, treatment-emergent adverse events.

arm) reported TEAEs resulting in death; none of them were related to the study drug except for one fatal event of acute myocardial infarction in the DRL_BZ arm. The most common TEAEs (≥10% in either/both groups) were anemia, neutropenia, thrombocytopenia, and diarrhea (►Table 6).

Safety with NSCLC Treatment

A total of 388 TEAEs were reported (DRL_BZ, $n = 214$; RMP, $n = 174$), of which 24 were serious TEAEs (DRL_BZ, $n = 15$; RMP, $n = 9$; ►Table 5). Sixteen and 32 patients in the DRL_BZ and RMP groups, respectively, had at least one TEAE of grade 3/4. Twelve patients (6 in each arm) discontinued study participation because of TEAEs. A total of six (10%) patients (DRL_BZ, $n = 4$; RMP, $n = 2$) reported TEAEs resulting in death; of these, one event in the DRL_BZ arm was considered as related to the study drug. During the study, five (59%) and two (58%) cases of hypertension were noted with RMP and DRL_BZ for mCRC; and four (59%) and one (58%) cases of proteinuria were noted with RMP and DRL_BZ for mCRC, respectively. In the NSCLC patients, one (30%) case each of hypertension was noted in the RMP and DRL_BZ arms; and one (30%) and two (30%) cases of proteinuria were noted with RMP and DRL_BZ. The most common

Table 6 TEAEs with ≥10% incidence in any group by preferred term in safety population

In mCRC safety population		
TEAE	**DRL_BZ (*N* = 58) *n* (%), *E***	**RMP (*N* = 59) *n* (%), *E***
Anemia	19 (32.8), 41	21 (35.6), 31
Leukopenia	10 (17.2), 26	10 (16.9), 18
Neutropenia	18 (31.0), 33	22 (37.3), 36
Thrombocytopenia	19 (32.8), 51	19 (32.2), 53
Abdominal pain	8 (13.8), 9	10 (16.9), 13
Diarrhea	21 (36.2), 34	21 (35.6), 39
Nausea	14 (24.1), 20	12 (20.3), 13
Vomiting	13 (22.4), 23	13 (22.0), 24
Asthenia	16 (27.6), 20	14 (23.7), 16
Mucosal inflammation	4 (6.9), 4	8 (13.6), 10
Pyrexia	11 (19.0), 18	11 (18.6), 18
Urinary tract infection	5 (8.6), 7	8 (13.6), 8
Increased alanine aminotransferase	4 (6.9), 4	7 (11.9), 11
Increased aspartate aminotransferase	6 (10.3), 9	8 (13.6), 14
Increased blood alkaline phosphatase	3 (5.2), 3	7 (11.9), 9
Decreased appetite	9 (15.5), 10	8 (13.6), 11
Hyperglycemia	1 (1.7), 1	7 (11.9), 7
Hypokalemia	3 (5.2), 6	9 (15.3), 14
Headache	9 (15.5), 12	4 (6.8), 5
Neuropathy peripheral	7 (12.1), 9	8 (13.6), 11
Paresthesia	8 (13.8), 8	9 (15.3), 11
Peripheral sensory neuropathy	8 (13.8), 8	6 (10.2), 7
Alopecia	11 (19.0), 11	5 (8.5), 5
Palmar–plantar erythrodysesthesia syndrome	10 (17.2), 10	7 (11.9), 7
Skin hyperpigmentation	8 (13.8), 8	17 (28.8), 17
In NSCLC safety population		
TEAE	**DRL_BZ (*N* = 30) *n* (%), *E***	**RMP (*N* = 30) *n* (%), *E***
Anemia	15 (50.0), 29	14 (46.7), 26
Neutropenia	2 (6.7), 4	4 (13.3), 4
Thrombocytopenia	4 (13.3), 5	5 (16.7), 11
Constipation	4 (13.3), 5	7 (23.3), 9
Diarrhea	4 (13.3), 4	6 (20.0), 8
Nausea	6 (20.0), 8	7 (23.3), 10
Stomatitis	4 (13.3), 7	4 (13.3), 9
Vomiting	7 (23.3), 8	3 (10.0), 3
Asthenia	11 (36.7), 12	11 (36.7), 12
Pain	2 (6.7), 2	5 (16.7), 5
Pyrexia	8 (26.7), 9	5 (16.7), 9
Increased alanine aminotransferase	5 (16.7), 6	2 (6.7), 2
Decreased creatinine renal clearance	5 (16.7), 7	1 (3.3), 2
Decreased appetite	5 (16.7), 6	5 (16.7), 6
Cough	9 (30.0), 11	3 (10.0), 3
Alopecia	4 (13.3), 4	4 (13.3), 4

Abbreviations: DRL_BZ, bevacizumab biosimilar; mCRC, metastatic colorectal cancer; NSCLC, non–small cell lung cancer; RMP, reference medicinal product; TEAEs, treatment-emergent adverse events.

TEAEs (≥10% in either/both groups) were anemia, asthenia, cough, and pyrexia (►Table 6).

Immunogenicity

All 58 mCRC patients exposed to DRL_BZ were negative for ADAs, while of the 59 RMP treated patients, 8.0% where positive for ADAs and 4.0% were positive for Nabs. All NSCLC patients were negative for ADAs.

Discussion

The present study was conducted to compare the efficacy, safety, and immunogenicity of a proposed DRL_BZ with innovator Avastin in patients with nonresectable mCRC over 9 months. The planned and identified endpoint was PFS6 based on the observation that it was sensitive and could compare efficacy more sensitively, that is, in limited number of patients. Since new chemotherapeutic agents are getting approved on a regular basis, there is lack of data on combination therapies of earlier-approved medications with new medications—in our case, there is limited information on mFOLFOX6 chemotherapy In combination. The present study explored the efficacy of the combination of bevacizumab with mFOLFOX6 chemotherapy. Taking into consideration the possibility of the difference in efficacy, an interim analysis was planned after efficacy data of approximately 100 patients were available to relook at the power of the study. The interim analysis concluded sufficient statistical power to terminate the study and ensured conclusive evidence for efficacy comparison. Thus, this randomized, multicenter, double-blind study could conclude similar efficacy, safety, and immunogenicity including 117 mCRC patients. The efficacy percentage noted in the study was 57.8 and 50% with DRL_BZ and RMP, respectively. The difference in efficacy observed between the treatment arms was 7.8 (–8.7, 23.7), and it was within the noninferiority margin of 18.8% as inferred to conclude biosimilarity. The PFS9 observed in the study with DRL_BZ and RMP, respectively, was 31.1 and 22.9% and the difference in efficacy was 8.2% (–6.9%, 22.9%). The secondary end points, ORR was 28.8 and 22.4% and DCR was 44.2 and 37.9% for

DRL_BZ and RMP respectively. The ORR and DCR were comparable between the treatment arms, which further substantiates the noninferiority of DRL_BZ in comparison with RMP. The results observed in the study was comparable with the ARTIST trial evaluating bevacizumab in mCRC patients where the PFS6 was 62.6% (95% CI: 54.5–70.6%) and ORR was 35%.[5] A metanalysis including 3,178 patients with advanced colorectal cancer found an objective response rate (odds ratio = 3.15; 95% CI: 2.25–4.40) and cancer control rate (OR = 2.73, 95% CI: 1.91-3.90) favoring the combination of bevacizumab with the FOLFOX regimen over the group with FOLFOX regimen alone.[7] Another study reported a disease-free survival hazard ratio for bevacizumab with FOLFOX4 versus FOLFOX4 as 1.17 (95% CI: 0.98–1.39; $p = 0{\cdot}07$). The OS hazard ratio for bevacizumab with FOLFOX4 versus FOLFOX4 alone was noted as 1.27 (1.03–1.57; $p = 0.02$).[8]

The present study also included a part B that compared the efficacy, safety, PK, and immunogenicity of DRL_BZ with innovator Avastin in 60 patients with advanced NSCLC over 6 months. The data for this pilot study were generated to compare the efficacy directly with Avastin and also with historic controls. A PFS6 of 44 and 45% was observed with DRL_BZ and RMP, respectively. The difference in efficacy was negligible at –1.0 (–24.2, 22.1) although the confidence interval was wide, which is anticipated to be due to the small sample size. The ORR observed was 41.4 and 48.1% and the DCR observed was 62.1 and 63%. The median OS for bevacizumab in combination with paclitaxel and carboplatin compared with those receiving chemotherapy alone was found to be 12.3 versus 10.3 months (HR: 0.80; 95% CI: 0.68–0.94).[1]

C_{max}, AUC_{0-t}, and AUC_{0-tau} in the PK subset of NSCLC patients were comparable between the arms and were in line with the PK similarity between DRL_BZ and RMP demonstrated in a prior study.[6]

The frequency, type, and severity of AEs were comparable between DRL_BZ and RMP. The most frequently observed AEs in the study were anemia, neutropenia, thrombocytopenia, and diarrhea. Moreover, the incidence of AEs commonly associated with anti-VEGF toxicities was comparable between the two arms in both mCRC and NSCLC patients. The most common grade 3 to 5 AEs observed in an earlier published trial with a combination of bevacizumab and FOLFOX were neutropenia (36%), diarrhea (12%), and hypertension (11%). A metanalysis concluded that the incidence of gastrointestinal adverse reactions was observed to be significantly high with the addition of bevacizumab to the FOLFOX regimen.[7] No patients developed binding ADAs in the DRL_BZ arm.

A positive benefit–risk profile of biosimilars is based on the totality of the evidence rather than solely on comparative efficacy and safety studies in each approved indication.[9] The comparable efficacy proved in the adequately powered mCRC patient study, comparable numerical efficacy observed in the pilot NSCLC study, comparable safety and lack of any unique AEs, comparable immunogenicity, and numerically comparable PK parameters in the limited number of patients along with earlier proof of healthy volunteer bioequivalence demonstrated, taken together, indicate that DRL_BZ is a biosimilar to Avastin.

Limitations

The study recruited and randomized lesser number of mCRC patients in the DRL_BZ and Avastin arms than it was originally planned (280). The NSCLC study was a pilot study with 60 patients and was inadequately powered for efficacy comparison.

Conclusion

The phase III study comparing the efficacy, safety, PK parameters, and immunogenicity between DRL_BZ and RMP in combination with chemotherapy in patients with mCRC and NSCLC showed a similar efficacy. Safety, immunogenicity, and PK were comparable between the DRL_BZ and RMP treatment arms. DRL_BZ was found to be a biosimilar to Avastin.

Author Contributions

S.K., R.K., P.R., and N.M. conceptualized and designed the manuscript. They were also involved in the study conduct and data analysis and interpretation. G.M., A.A., K.H., N.M., A.D., M.G., G.P., S.B.J., and M.V.D. actively participated in patient recruitment, clinical assessment, and management. All the authors read and approved the final manuscript.

Statement of Ethical Conduct of Research

The study was approved by an independent ethics committee or an institutional review board at different study centers and conducted in accordance with the Declaration of Helsinki, International Council for Harmonization Good Clinical Practice guidelines, and applicable local regulations. Each patient provided written informed consent before they were included in the study.

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Dr. Narendra Maharaj is an employee of and owns stock options in Dr. Reddy's Lab. Ltd.

Conflict of Interest

All the authors received support from Dr. Reddy's Laboratories Ltd.

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