ORIGINAL ARTICLE

# A Prospective, Randomized, Multiple-Dose, Multi-Center, Comparative Clinical Study to Evaluate the Efficacy, Safety, Immunogenicity of a biosimilar Bevacizumab (Test product, Hetero) and Reference Medicinal Product (Bevacizumab, Roche) in Patients of Metastatic Colorectal Cancer

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## Abstract

**Objective:** To compare efficacy and safety of a biosimilar, Bevacizumab (Hetero) *vs* reference medicinal product (Bevacizumab, Roche) as first line therapy in patients with metastatic colorectal cancer (mCRC) in combination with chemotherapy.

**Methods:** Patients of aged 18 to 65 with histologically pre-confirmed mCRC and treatment naïve with unresectable metastatic disease or distant metastases were enrolled and randomized to receive either Hetero-Bevacizumab or RMP-Bevacizumab along with chemotherapy (XELOX or FOLFOX-4) regimen over a period of 24 weeks (up to 8 cycles of Hetero-Bevacizumab/RMP-Bevacizumab+ XELOX regimen (each cycle of 3 weeks) or up to 12 cycles of Hetero-Bevacizumab/ RMP-Bevacizumab + FOLFOX-4 regimen (each cycle of 2 weeks). Bevacizumab was administered at 7.5 mg/kg as an IV infusion over 60-90 minutes on Day 1 of each treatment cycle. The efficacy endpoints were the overall response rate (CR+PR) and disease control rate (DCR) according to RECIST 1.1. The safety endpoints included assessments of treatment emergent adverse events and immunogenicity.

**Results:** 160 patients were screened; 111 patients were randomized in the study. No statistical significant difference in overall response rate between both the treatment groups (HB-MAB vs. RB-MAB: 35.56 % vs. 20%, P=0.28 at Week 6; 37.50 % vs. 30.77 %, P=0.73 at Week 12). Similar trend was observed for disease control rate (HB-MAB vs. RB-MAB: 100% vs. 96%, P=0.36 at Week 6; 95.83 vs. 100%, P=1.00 at Week 12).

**Conclusion:** Herero's Bevacizumab was found to be comparable to reference medical product, Bevacizumab in terms of efficacy and tolerability for the Indian patients with metastatic colorectal cancer.

## Introduction

Colorectal cancer (CRC) is the 3rd most common cancer in men and the 2nd in women worldwide. The burden of CRC has risen rapidly in some economically developed Asian countries.[1] Despite advances in screening procedures and the use of adjuvant therapy, approximately 50% of patients with colorectal cancer eventually develop metastatic disease.[2] The treatment of colorectal cancer has become increasingly complex over recent years.[3] With the emergence of new chemotherapy drugs and targeted agents, there has been great improvement in the prognosis of patients with metastatic colorectal cancer.[3]

Angiogenesis plays an important role in progression of CRC. Evidence from preclinical and clinical studies indicates that vascular endothelial growth factor (VEGF) is the predominant angiogenic factor in CRC. VEGF is expressed in approximately 50% of CRCs, with minimal to no expression in normal colonic mucosa and adenomas.[4] It had been observed that VEGF family members control several aspects of physiological and tumoral angiogenesis. Amongst other anti-angiogenesis therapies, anti-VEGF antibody was shown to have potent inhibitory effect on growth of several preclinical tumor models.[5] Therefore, anti-angiogenesis was proposed as a possible strategy for anti-cancer therapy.[6]

Bevacizumab is the first anti-angiogenesis therapy approved by USFDA in 2004 for first line therapy of metastatic colorectal cancer (mCRC).[7,8] Bevacizumab is a humanized anti-VEGF Immunoglobulin G1 (IgG1) monoclonal antibody, which binds and neutralizes all isoforms of the VEGF-A and bioactive proteolytic fragments .[9] Bevacizumab inhibits binding of VEGF to its receptors VEGFR-1 and VEGFR-2. Bevacizumab was approved for several other indications: non-squamous non-small cell lung cancer (NSCLC), metastatic renal cell carcinoma, ovarian cancer and advanced epithelial, ovarian, fallopian tube and primary peritoneal cancer. Metastatic colorectal cancer was the most commonly prescribed indication for bevacizumab owing

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to more consistent improvement in progression free survival and overall survival in this cancer.[10,11] Bevacizumab-containing regimens have been shown to be superior in the first-line treatment of colorectal cancer.[2] However, the cost of bevacizumab is unaffordable for majority of the population in the developing countries. Bio-similar drug development has recently been identified as a priority by all major regulatory authorities to make them affordable, the efforts in this direction is evident from recent release of guidelines for establishing bio-similarity.

Reference Medicinal Product (RMP)-Bevacizumab was approved in mCRC based on encouraging data from two pivotal studies using IFL (irinotecan, leucovorin (folinic acid), and fluorouracil) and FOLFOX-4 (Oxaliplatin, Folinic Acid and 5-Fluorouracil) chemotherapy combination.[7,8] Capecitabine plus oxaliplatin (XELOX) was also shown to be non-inferior to FOLFOX-4 in a large study.[12] Overall survival and progression free survival were comparable between FOLFOX-4 and XELOX arms in combination with Bevacizumab. RMP-Bevacizumab had been approved earlier at doses, either 5 mg/kg or 10 mg/kg with IFL or FOLFOX-4 chemotherapy respectively. However, National Comprehensive Cancer Network (NCCN) guidelines[13] recommended using 5 mg/kg along with FOLFOX-4 regimen for up to 12 cycles. In a pivotal clinical study with XELOX chemotherapy, RMP-Bevacizumab was administered at a dose of 7.5 mg/kg[14] for up to 8 cycles. The efficacy and safety data of Bevacizumab usage in Indian patients is limited.

Therefore, in view of the above considerations, the objective of this study was to provide clinical evidence for bio-similarity of Hetero's Bevacizumab in comparison to RMP-Bevacizumab (Roche's bevacizumab) in combination with concomitant XELOX/FOLFOX-4 chemotherapy, in a randomized, active controlled, parallel design study in Indian patients of mCRC.

## Methods

### Ethics

The study was conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the applicable Indian regulatory guidelines e.g., Guidelines on similar biologics- regulatory requirements for marketing authorization in India 2012, guidelines governing biomedical research in human patients which were in consistent with the Ethical Guidelines outlined in Declaration of Helsinki, (64th WMA General Assembly, Fortaleza, Brazil, October 2013), thus ensuring greater protection to the patient. The study was initiated after obtaining approval of the competent authority (CDSCO) and IRB/IEC of each participating study center. Prior to any study-related screening procedures, written informed consent was obtained from each patient before enrolling in the study. The study was registered with clinical trial registry of India (CTRI: CTRI/2015/05/005757) before enrollment of first patient in the study.

### Patients and study design

This study was conducted at 24 different oncology study centers across India from May 2015 to Apr 2016. This was a randomized, active controlled, parallel group design study in patients with metastatic colorectal cancer (mCRC). The primary objective of this study was to compare the efficacy of Hetero-Bevacizumab with RMP-Bevacizumab (Bevacizumab, Roche) as first line treatment of patients with mCRC. Secondary objectives were to compare immunogenic potential (measured titers of anti-bevacizumab antibodies) of two formulations of Bevacizumab at screening, at the end of cycle 4 or cycle 6, and at the EOT of XELOX or FOLFOX-4 regimen respectively and to compare Quality of Life (QoL) as assessed by functional assessment of Cancer Therapy–Colorectal score (FACT-C) and Treatment Outcome Index Scores. The efficacy endpoints were overall response rate (CR+PR) and disease control rate (DCR) according to RECIST 1.1 and evaluation of incidence and titres of anti-bevacizumab antibodies in all patients of both the groups. This study consisted of a screening period of up to 21 days and treatment period of 24 weeks (either up to 8 cycles of Hetero-Bevacizumab/RMP-Bevacizumab+ XELOX regimen (each cycle of 3 weeks) or up to 12 cycles of Hetero-Bevacizumab/RMP-Bevacizumab + FOLFOX-4 regimen(each cycle of 2 weeks). No dose adjustment for bevacizumab was permitted in this study.

Male and female patients with histologically pre-confirmed metastatic colorectal cancer, and not suitable for radical surgery, or radiotherapy who were treatment naïve with unresectable metastatic disease or distant metastases; non-responder with adjuvant therapy for their primary cancer; at least one measurable lesion according to RECIST criteria (version 1.1) and aged 18 to 65 years (both inclusive) were included in study. Patients with drug allergy, hypersensitivity or intolerance; presence of a serious non-healing wound, ulcer, or bone fracture; history of previous abdominal fistula or gastrointestinal perforation; history of intestinal inflammatory disease; hemorrhagic diathesis or coagulopathy were excluded. Non-menopausal women with pregnancy or lactation or with positive pregnancy test were also excluded.

Eligible patients were randomly assigned to receive either Hetero-Bevacizumab or RMP-Bevacizumab (2:1) along with XELOX or FOLFOX-4 regimen, chemotherapy based on investigator's discretion. Bevacizumab was administered at 7.5 mg/kg in 3 weekly cycles (XELOX) and 5 mg/kg in 2 weekly cycles (FOLFOX-4) until the occurrence of unacceptable toxicity, disease progression, death or end of cycle 8 or cycle 12 in XELOX and FOLFOX-4 regimen respectively.). Bevacizumab was given as an intravenous (IV) infusion over 60-90 minutes on Day 1 of each treatment cycle. Infusion was targeted to 90 minutes at Cycle 1 and to 60 minutes at other cycles if infusion is tolerated at cycle 1. XELOX regimen consisted of Capecitabine (1,000 mg/m2/twice daily) taken orally on Days 1-14 and Oxaliplatin (130 mg/m$^2$) was administered intravenously on Day 1 of each treatment cycle. This was followed by bevacizumab treatment on Day 1 of all active cycles. XELOX regimen (XELOX + Hetero-Bevacizumab or XELOX + RMP-Bevacizumab) was administered every three weeks until the occurrence of unacceptable toxicity, disease progression, death or end of cycle 8. Leucovorin (LV) 200 mg/m$^2$/day as a 2-hour infusion followed by bolus 5-FU 400 mg/m2/day and a 22-hour infusion of 5-FU 600 mg/m2/

**Table 1: Demographic Characteristics (Safety Population)**

| Variable | Statistics | HB-MAB (N=72) | RB-MAB (N=37) | p-value HB-MAB vs. RB-MAB |
|---|---|---|---|---|
| Gender n (%) | Male | 44 (61.11) | 18 (48.65) | 0.2277 |
| | Female | 28 (38.89) | 19 (51.35) | |
| Age (years) | n | 72 | 37 | 0.2105 |
| | Mean ± SD | 48 ± 10 | 46 ± 11 | |
| Height (cm) | n | 72 | 37 | 0.2376 |
| | Mean ± SD | 158.89 ± 8.16 | 156.86 ± 8.93 | |
| Weight (kg) | n | 72 | 37 | 0.4684 |
| | Mean ± SD | 54.99 ± 11.25 | 53.23 ± 13.20 | |
| BSA ($m^2$) | n | 72 | 37 | 0.3448 |
| | Mean ± SD | 1.55 ± 0.17 | 1.51 ± 0.20 | |

Abbrevitions: N = number of subjects in specified treatment; n = number of subjects at specified category; HB-MAB: Bevacizumab, Hetero; RB-MAB: Bevacizumab, Roche; For parameters Age, Height, Weight and BSA, p-values are calculated using Independent t test; For parameters Gender, p-value is calculated using Fisher's exact test.

**Table 4: Analysis of change from Visit 1 (Screening) to EOT (Day 169 ± 3) in quality of life assessment (FACT-C and Treatment Outcome Index) among the treatment groups (ITT population)**

| | | Least Square Mean of change from Visit 1 (Screening) | | | | |
|---|---|---|---|---|---|---|
| Questionnaire | Treatment | Mean ± SD | Estimate | Standard Error | 95% Confidence Intervals | p-value HB-MAB Vs. RB-MAB |
| Physical well-being | HB-MAB | -1.25 ± 4.27 | -0.96 | 1.73 | (-4.83, 2.90) | 0.4112 |
| | RB-MAB | 2.00 ± 5.29 | 1.54 | 2.23 | (-3.43, 6.51) | |
| Social/Family well-being | HB-MAB | -3.75 ± 3.81 | -5.12 | 1.21 | (-7.81, -2.43) | 0.0161 |
| | RB-MAB | -1.00 ± 4.30 | 1.19 | 1.60 | (-2.37, 4.75) | |
| Emotional well-being | HB-MAB | -0.63 ± 2.62 | -0.79 | 0.88 | (-2.76, 1.18) | 0.7079 |
| | RB-MAB | -1.60 ± 4.04 | -1.34 | 1.12 | (-3.84, 1.16) | |
| Functional well-being | HB-MAB | 1.63 ± 8.57 | 1.78 | 2.01 | (-2.70, 6.27) | 0.2016 |
| | RB-MAB | -2.40 ± 4.88 | -2.66 | 2.55 | (-8.33, 3.02) | |
| Additional concerns | HB-MAB | -1.00 ± 3.85 | -0.94 | 1.51 | (-4.31, 2.42) | 0.2419 |
| | RB-MAB | -4.00 ± 4.18 | -4.09 | 1.94 | (-8.41, 0.23) | |

**Abbreviations**: N = number of subjects in specified treatment; n = number of subjects having non-missing values at specified visits. **HB-MAB**: Bevacizumab, Hetero; **RB-MAB**: Bevacizumab, Roche; [#]p-value are calculated with Shapiro-Wilk test (i.e. Normality test.; Note: p-values calculated with ANCOVA Model: change from baseline = baseline + treatment

day, repeated for 2 consecutive days of each treatment cycle. Oxaliplatin 85 mg/$m^2$on day 1 only given as a 2-hour infusion in 250 mL of dextrose 5%, concurrent with LV.

The independent review of all the Computed Tomography (CT)/ Magnetic Resonance Imaging (MRI) images were done by a trained and experienced team of radiologists as per RECIST 1.1 guidelines. The radiologists were blinded to the study treatments and were not made aware about the treatment allocation. Computed Tomography/MRI scan was performed at baseline (screening), at the end of cycle 2, at the end of cycle 4, at the end of cycle 6, and at the End of Treatment (EOT) visit for patients randomized to Hetero-Bevacizumab/ RMP-Bevacizumab + XELOX regimen whereas CT scan was performed at baseline (screening), at the end of cycle 3, at the end of cycle 6, at the end of cycle 9, and at the EOT visit for patients randomized to Hetero-Bevacizumab/ RMP-Bevacizumab RMP+ FOLFOX-4 regimen. Safety was evaluated by monitoring of adverse events (AEs) including significant clinical signs symptoms and laboratory abnormalities observed during treatment. All randomized patients in whom at least one dose of bevacizumab (test or reference) had been administrated were eligible for data analysis of safety endpoints. The immunogenicity tests were performed by assessing serum for the presence of anti-bevacizumab antibodies in all patients of both groups at screening visit, at the end of cycle 4 (XELOX) or cycle 6 (FOLFOX-4), and at the EOT visit.

## Statistical considerations

For efficacy analysis, at least 66 subjects in test product and 33 subjects in reference product were required to show non-inferiority of test product to reference product with 80% power and 2.5% level of significance. Published literature shows disease control rate

**Table 2: Disease control rate (DCR) at the week 6 (Day 43 ± 3), week 12 (Day 85 ± 3), week 18 (Day 127 ± 3) and end of treatment [EOT] (Day 169 ± 3) visit among the ITT population**

| Week | Responder* | HB-MAB (N=45) n (%) | RB-MAB (N=25) n (%) | 95% Confidence Interval | p-value HB-MAB vs. RB-MAB |
|---|---|---|---|---|---|
| Week 6 (Day 43 ± 3) | n | 45 | 25 | | |
| | Yes | 45 (100.00) | 24 (96.00) | (-11.68, 3.68) | 0.3571 |
| | No | 0 (0.00) | 1 (4.00) | | |
| Week 12 (Day 85 ± 3) | n | 24 | 13 | | |
| | Yes | 23 (95.83) | 13 (100.00) | (-3.83, 12.16) | 1.0000 |
| | No | 1 (4.17) | 0 (0.00) | | |
| Week 18 (Day 127 ± 3) | n | 14 | 5 | | |
| | Yes | 14 (100.00) | 5 (100.00) | (0.00, 0.00) | - |
| | No | 0 (0.00) | 0 (0.00) | | |
| EOT (Day 169 ± 3) | n | 8 | 5 | | |
| | Yes | 7 (87.50) | 3 (60.00) | (-76.17, 21.17) | 0.5105 |
| | No | 1 (12.50) | 2 (40.00) | | |

Abbreviations: N = number of subjects in specified treatment; n = number of subjects at specified category; HB-MAB: Bevacizumab, Hetero; RB-MAB: Bevacizumab, Roche; *Patients with CR (complete response) or PR (partial response) or SD (stable disease) are considered as Responder (Yes) and patients with other responses are considered as Non-responder (No); p-values are calculated with Fisher's exact test; Note: All the subjects reported as Responder at Week 12 (Day 85 ± 3) and Week 18 (Day 127 ± 3). During calculation of the p-value, 2 cells frequency is Zero; hence p-value cannot be calculated.

**Table 3: Overall response rate (ORR) at the week 6 (Day 43 ± 3), week 12 (Day 85 ± 3), week 18 (Day 127 ± 3) and end of treatment [EOT] (Day 169 ± 3) visit among the treatment-ITT population**

| Week | Responder* | HB-MAB (N=45) n (%) | RB-MAB (N=25) n (%) | 95% Confidence Interval | p-value HB-MAB vs. RB-MAB |
|---|---|---|---|---|---|
| Week 6 (Day 43 ± 3) | n | 45 | 25 | | |
| | Yes | 16 (35.56) | 5 (20.00) | (-36.57, 5.46) | 0.2761 |
| | No | 29 (64.44) | 20 (80.00) | | |
| Week 12 (Day 85 ± 3) | n | 24 | 13 | | |
| | Yes | 9 (37.50) | 4 (30.77) | (-38.43, 24.97) | 0.7343 |
| | No | 15 (62.50) | 9 (69.23) | | |
| Week 18 (Day 127 ± 3) | n | 14 | 5 | | |
| | Yes | 6 (42.86) | 0 (0.00) | (-68.78, -16.93) | 0.1280 |
| | No | 8 (57.14) | 5 (100.00) | | |
| EOT (Day 169 ± 3) | n | 8 | 5 | | |
| | Yes | 4 (50.00) | 0 (0.00) | (-84.65, -15.35) | 0.1049 |
| | No | 4 (50.00) | 5 (100.00) | | |

Abbreviations: N = number of subjects in specified treatment; n = number of subjects at specified category; HB-MAB: Bevacizumab, Hetero; RB-MAB: Bevacizumab, Roche; *Patients with CR (complete response) or PR (partial response) or SD (stable disease) are considered as Responder (Yes) and patients with other responses are considered as Non-responder (No); p-values are calculated with Fisher's exact test

(DCR) ranging from 80% to 90%. We assumed disease control rate (primary endpoint) of 75% with non-inferiority margin of 25%, and no difference between test and reference product. Considering 10% dropout rate due to subject withdrawal and protocol deviations, a total 111 subjects were needed to be enrolled in to the study with 2:1 treatment allocation ratio. i.e. (74-Test: 37-Reference).

Evaluable patients for efficacy included the subject's data who have received at least three cycles of FOLFOX-4 regimen or two cycles of XELOX regimen and completed at least first post baseline radiological assessment. All patients who received at least one dose of assigned study medication were included for safety. Categorical data was presented as absolute number/percentage of patients while quantitative data was presented as mean ± standard deviation (SD) or median (range). Depending on the distribution of data appropriate parametric or non-parametric test was used to find p value. Unpaired "t"/ Man Whitney test was used to analyze the quantitative data for between group comparisons. Chi-square test or Fisher's exact test was used to compare the categorical or qualitative data (DCR, ORR and incidence and titers of anti-bevacizumab antibodies) of both the treatment groups. Comparison of QoL scores (FACT-C and Treatment Outcome Index) in both the groups was made using ANCOVA model or Wilcoxon-signed rank test based on distribution of data. Assumptions of the normality were assessed using Shapiro-Wilk test. P value of less than 0.05 was considered as statistical significant difference. Statistical analysis was performed using SAS® software Version 9.1.3 or higher (SAS Institute Inc., NC, USA) or any other appropriate software.

## Results

### Patient disposition and demographic characteristic

A total of 160 patients were screened and 111 patients were randomized in the study. Of these, data of 109 patients were included in this analysis. All the demographic variables (gender, age, height, weight, BSA and race) were comparable between both the treatment arms (Table 1).

### Efficacy results

There was no statistical significant difference in disease control rate (DCR) among both the treatment groups (Hetero-Bevacizumab vs. RMP-Bevacizumab: 100% vs. 96%, P=0.36) at the Week 6 (Day 43 ± 3). Similar trend was observed at the Week 12 (95.83 vs. 100%, P=1.00). At the end of Week 18 (Day 127 ± 3), however, there was no statistical significant difference in DCR was found between both the treatment groups (87.50 % vs. 60%, P=0.51) (Table 2).

Overall response rate (ORR) was numerically higher in Hetero-Bevacizumab group as compared to RMP-Bevacizumab, however, there was no statistical significant difference in ORR was found between both the treatment groups (Hetero-Bevacizumab vs. RMP-Bevacizumab: 35.56 % vs. 20%, P=0.28) at Week 6 (Day 43 ± 3). Improvement in ORR was observed in both the treatment group at the end of Week 12 (37.50 % vs. 30.77 %, P=0.73) as compared to Week 6 [Table 3]. Overall, both the study groups were found comparable in terms of efficacy endpoints after treatment. One patient in Hetero-Bevacizumab with FOLFOX-4 arm had achieved complete response at the end of the study. Total two patients in RMP-Bevacizumab with FOLFOX-4 arm and one patient in Hetero-Bevacizumab with FOLFOX-4 arm had progressive disease as per RECIST 1.1 criteria during end of study. No patient in XELOX arm had progressive disease or complete response as per RECIST 1.1 (Table 3).

Overall, improvement in quality of life (QOL) was found comparable between both the study groups for all the parameters of FACT-C and Treatment Outcome Index questionnaire except for Social/Family well-being. Improvement in 'Social/Family well-being' was statistically superior with Hetero-Bevacizumab (3.75) as compared with RMP-Bevacizumab (1.00) at the end of study. There was no statistical significant difference observed in physical, emotional, and functional well-being among both the treatment groups ($p<0.05$). Also there was no statistical significant difference observed in additional concerns item of QOL ($p<0.05$) (Table 4).

### Immunogenicity results

Of total of 141 samples were analyzed for anti-drug antibodies/ immunogenicity in a three tier immunogenicity assay, 3 samples showed anti-drug antibodies positive with very low titer levels. Out of these, 1 sample was from Hetero-Bevacizumab and 2 samples were from RMP-Bevacizumab treated patients and with FOLFOX regimen. Immunogenicity assay results are highly influenced by several factors including sample handling, timing of sample collection, concomitant medications, underlying disease.

### Safety results

A total of 182 treatment emergent adverse events (TEAEs) were reported in 48 patients during the study. A total of seven serious adverse events (SAEs) were reported including two deaths. A total of 5 patients reported 6 SAEs (one case of Intestinal Obstruction; one case of diarrhea; one case of Rectal Hemorrhage; one case of Lower Respiratory Tract Infection; One case of Pneumonia and Sepsis and one case of death-cause unknown) with Hetero-Bevacizumab. One case of sudden death was reported with RMP-Bevacizumab group.

In Hetero-Bevacizumab group, a total of 109 AEs were reported in 30 patients (41.67%). Sixty seven AEs in 16 (22.22%) patients were mild, 33 AEs in 9 (12.50%) patients were moderate, 7 AEs in 3 (4.17%) patients were severe, 1 AE in 1 (1.39%) patient was life threatening and 1 AE in 1 (1.39%) patient was death. At least 1 (1.39%) patient reported a certainly related AE; 7 (9.72%) patients reported a probable/likely related AE; 7 (9.72%) patients reported a possibly related AE; 15 (20.83%) patients reported an unlikely related AE; two patients were withdrawn due to AE. In RMP-Bevacizumab group, a total of 73 AEs were reported in 18 (48.65%) patients. Forty nine AEs in 10 (27.03%) patients were mild in severity; 19 AEs in 3 (8.11%) patients were moderate in severity; 4 AEs in 4(10.81%) patients were severe in severity; and 1(2.70%) death was reported. At least 1(2.70%) patient reported a certainly related AE; 4(10.81%) patients reported a probable/likely related AE; 3(8.11%) patients reported a possibly related AE; 10 (27.03%) patients reported an unlikely related AE. One patient was discontinued due to death.

## Discussion

Bevacizumab is a recombinant, humanized monoclonal antibody against vascular endothelial growth factor (VEGF) that is used to inhibit VEGF function in vascular endothelial cells and thereby inhibit tumour angiogenesis, upon which solid tumours depend for growth and metastasis. The addition of bevacizumab to fluoropyrimidine-based chemotherapy, with or without irinotecan or oxaliplatin, in both the first- and second-line treatment of metastatic colorectal cancer, significantly increased median progression-free survival or time to disease progression in most randomized controlled trials. Bevacizumab was generally associated with a survival advantage. Bevacizumab had acceptable tolerability, with the majority of adverse events being generally mild and clinically manageable.[15] The addition of bevacizumab to fluorouracil-based chemotherapy is a standard of care for previously untreated mCRC.[16] The disease control rates (DCR) reported in published clinical studies of bevacizumab ranges from 55-100%,[16-18] whereas the overall response rates were 30-40%,[16-22] depending on the regimen used. In this study, all the randomized patients were confirmed cases of mCRC. The efficacy was comparable in the patients who received Hetero-Bevacizumab or RMP-Bevacizumab along with concomitant FOLFOX-4 or XELOX chemotherapy regimen. The efficacy endpoints, i.e., DCR (87.5-100% vs 60-96%) and ORR (37.50 % vs. 30.77 % at week 12) were numerically higher in patients administered Hetero-Bevacizumab as compared to RMP- Bevacizumab, however, these differences were not statistically significant. Overall, the efficacy of both the study groups were comparable with each other and that reported in published literature.

It was also observed that the quality of life (QOL) after Hetero-Bevacizumab treatment was greater among patients of mCRC. Although, there was no statistical significant difference observed in physical, emotional, and functional well-being among the treatment groups, however, improvement in 'Social/Family well-being' was statistically superior with Hetero-Bevacizumab as compared to RMP-Bevacizumab at the end of study. This improvement in QOL with usage of bevacizumab as the first anti-angiogenesis therapy by the FDA in 2004 for first line therapy of mCRC with concomitant chemotherapy is consistent with that reported in published literature, as well.[7-8, 23-25]

Bio-similar drug development has recently been identified as a priority by all major regulatory authorities to provide affordable, safe and effective alternative to potent biological therapies and comparative clinical studies help generate evidence in that direction. The results in this study provides a clinical evidence for the bio-similarity of Hetero-Bevacizumab compared to RMP-Bevacizumab based on efficacy, safety and immunogenicity data in patients of metastatic colorectal cancer (mCRC), suggesting a possibility for interchangeability of usage.

### Conclusion

Based on study results, it can be concluded that Hetero's Bevacizumab was comparable in terms of efficacy and safety and can be used interchangeably for the management of patients with metastatic colorectal cancer.

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