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A Real-World Study of Safety, Immunogenicity and Efficacy of Bevacizumab in Patients with Solid

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1. Abstract

1.1. Objective: The aim of this study was to evaluate the post-marketing safety, tolerability, immunogenicity and efficacy of Bevacizumab (manufactured by Hetero Biopharma) in a broader population of patients with solid tumors.

1.2. Patients & Methods: This phase IV, prospective, multi-centric clinical study was carried out in Indian patients with solid malignancies (metastatic colorectal cancer, non-squamous non-small-cell lung cancer, metastatic renal cell carcinoma) indicated for treatment with Bevacizumab between Apr 2018 and Jul 2019. This study included 203 patients from 15 tertiary care oncology centres across India for safety assessment, of which a subset of 115 patients were also evaluated for efficacy and immunogenicity. This study was conducted after approval from the competent au-

thority (CDSCO) and registered in the Clinical Trial Registry of India (CTRI).

1.3. Results: Out of the 203 enrolled patients, 121 (59.6%) patients reported 336 adverse events (AEs) during this study. Of 336 reported AEs, 14 serious adverse events (SAEs) were reported by 13 patients. Of these SAEs, six deaths were reported which were assessed as unrelated to the study medication. The remaining non-fatal SAEs were resolved.

Most adverse events reported in this study (32.5%) were general disorders and administration site conditions, followed by gastrointestinal disorders (30%). The most frequently reported adverse events were diarrhoea (11.3%), asthenia (10.3%), headache (9.04%), pain (7.4%), vomiting (7.9%), and neutropenia (5.9%). At the end of the study, 2 (1.75%) of 69 patients reported antibodies to bevacizumab. At the end of 12 months, no patient had reported antibodies to bevacizumab. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were reported in 18.3%, 22.6%, 9.6%, and 8.7% of patients, respectively. The overall response rate (CR+PR) was reported in 40.9% of patients at the end of the study. Disease control rate (DCR), also known as the clinical benefit rate (CBR) was reported in 50.4% of patients.

1.4. Conclusion: Bevacizumab (Cizumab, Hetero Biopharma) was observed to be safe, well tolerated, lacking immunogenicity, and efficacious in the treatment of solid tumors. The findings of this Phase-IV study of bevacizumab, primarily as a combination therapy regimen suggest its suitability and rationality for usage in multiple solid malignancies.

1.5. Clinical Trail Registry Number: CTRI/2018/04/013371 [Registered on CTRI

http://ctri.nic.in/Clinicaltrials/advsearch.php: 19/04/2018]; Trial Registered Prospectively.

2. Introduction

Bevacizumab, an angiogenesis inhibitor targeting vascular endothelial growth factor (VEGF), was approved by the US Food and Drug Administration (FDA) on February 2004 [1,2]. It is a recombinant humanized monoclonal antibody that binds to, and neutralizes all isoforms of VEGF A and prevents VEGF from binding to its VEGFR-1 and VEGFR-2 receptors, thereby inhibiting angiogenesis and tumour growth, normalization of remaining tumour vasculature, and inhibition of further tumour angiogenesis reflecting a key targeting strategy in cancer therapy [3,4]. Neutralization of VEGF prevents neovascularization as well as remodels existing tumour vasculature by decreasing vessel diameter, density, and permeability [5,6]. Bevacizumab was approved initially for the treatment of metastatic colorectal cancer (mCRC) and subsequently approved for the treatment of multiple recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC), metastatic renal cell carcinoma (mRCC), metastatic cervical cancer, recurrent glioblastoma (GBM), hepatocellular carcinoma (HCC) epithelial ovarian, fallopian tube and primary peritoneal cancers by the Food and Drug Administration (FDA) [7] in the United States [8,9].

Colorectal cancer (CRC) remains a major public health problem in most developed countries. A global incidence of approximately 1.2 million was reported in 2008. Based on currently available data, the incidence rates of CRC in India for males and females are 4.3 per 100, 000 population and 3.4 per 1, 00, 000 population, respectively. While the incidence rate of CRC among native Indians has been slowly rising over many decades, the incidence of CRC in immigrant Indians living in the UK and USA has raised rapidly. The absolute burden of CRC has also increased in India during the last 3 decades [10]. NSCLC accounts for over 85% of lung cancer diagnoses, the most leading cause of cancer-related death worldwide [11,12], and most patients present with advanced stage at the time of diagnosis, resulting in a poor prognosis [13]. Currently, results of large-scale randomized trials and real-world studies have placed bevacizumab[14] in combination with platinum-based chemotherapy as the standard first-line therapy for non-squamous (NS)-NSCLC [15]. However, the cost of bevacizumab was unaffordable for the majority of the population in developing countries. Hence, Hetero has developed a biosimilar of bevacizumab to reduce the cost and to reach the needy at an affordable cost. Subsequently, Hetero conducted a phase-3 clinical trial to evaluate the efficacy, safety and immunogenicity in metastatic colorectal cancer patients. In our phase 3 study, the results of efficacy endpoints, i.e. disease control rate (DCR [87.5-100% vs. 60-96%] and overall response (ORR) [37.50% vs. 30.77%] at week 12) showed numerically higher values in patients receiving Hetero-Bevacizumab compared to the reference drug bevacizumab, Roche (RMP bevacizumab); however, these differences were not statistically significant. In the safety endpoints, the quality of life (QOL) was greater after treatment with Hetero-Bevacizumab in patients with mCRC. Although no statistically significant difference in physical, emotional, and functional well-being was observed between the treatment groups, the improvement in “social/family well-being” in Hetero-Bevacizumab was statistically superior- compared to RMP-bevacizumab [16]. As per the Guidelines for Similar Biologics 2016, India,[16] this phase-IV post marketing safety, tolerability, immunogenicity, and efficacy study of bevacizumab therapy was organised and conducted in patients with multiple indications such as metastatic colorectal cancer, non-squamous non–small cell lung cancer, glioblastoma, metastatic renal cell carcinoma, and persistent, recurrent, or metastatic carcinoma of the cervix; in oncology tertiary care centres in India, to provide detailed information that may help physicians to optimize the therapeutic management of these patients.

3. Material and Methods

3.1. Study Design: This was phase IV, prospective, open-label, multi-centre, post-marketing study of the marketed formulation of

Hetero-Bevacizumab (Cizumab) in patients with solid malignancies, conducted from April 2018 to July 2019 at 16 sites in India to evaluate the safety, efficacy, and long-term immunogenicity of bevacizumab in daily medical practice conditions. It was approved by CDSCO on 13/5/2016 and the phase IV trial was registered with the CTRI on 19/04/2018 (CTRI/2018/04/013371). This study was planned to collect data from at least 200 patients with solid malignancies. Assuming a loss to follow up, 214 patients were screened to enrol 203 patients. All 203 patients were included in the safety evaluation and 115 patients were included in the efficacy and immunogenicity evaluations. The study included adult male or female patients of 18 years or older, with solid malignancies who were prescribed bevacizumab by their treating physicians constituted the target patient population (mCRC, NSCLC, GBM, mRCC, metastatic breast cancer and persistent, recurrent, or metastatic carcinoma of the cervix). Hetero-Bevacizumab was administered in the dosage and for the duration, as recommended in the package insert and as per the inclusion and exclusion criteria. The first infusion was administered over 90 minutes to check whether it was well tolerated then subsequently, the second infusion was administered over 60 minutes. All the subsequent infusions were administered over 30 minutes if infusion over 60 minutes was well tolerated. Criteria for study drug discontinuation were gastrointestinal perforations, fistula formation involving an internal organ, wound dehiscence and wound healing complications requiring medical intervention, serious haemorrhage, severe arterial or venous thromboembolic events, hypertensive crisis, posterior reversible encephalopathy syndrome (PRES), nephrotic syndrome. Bevacizumab was required to be temporarily suspended in the following situations: at least 4 weeks prior to elective surgery/ severe hypertension not controlled with medical management/ moderate to severe proteinuria or severe infusion reactions.

3.2. Inclusion and Exclusion Criteria: Patients judged to be at low risk for intestinal obstruction or perforation, adequate haematological function: ANC ≥ 1.5 x 109/L; platelets ≥ 100 x 109/L, Hb ≥ 9 g/dl were enrolled in the study. Patients were included only if a gap of 4 weeks were maintained from any major surgery, open surgical biopsy, or significant traumatic injury or if post-operative, at least 4 weeks' time after surgery and until the surgical wound is fully healed, prior to randomization. Patients with a clinical history of allergy/ hypersensitivity to murine proteins or components of Hetero-Bevacizumab; patients with serious hemorrhage or recent haemoptysis; presence of a serious, non-healing wound; ulcer; or bone fracture; history of hemorrhagic diathesis or coagulopathy; significant vascular disease or recent peripheral arterial thrombosis within 6 months prior to dosing or any peripheral vascular disease; or venous thrombo-embolic events within the past 3 months were excluded. Pregnant or lactating patients were not allowed in this study.

3.3. Study Assessments: Safety assessments were conducted in all patients (screening, at the end of up to 8 cycles or end of study) while a subset of approximately 100 patients were also scheduled for immunogenicity and efficacy assessments (screening, at the end of 6-8 cycles or end of the study). During study treatment, all patients were monitored for significant clinical signs and symptoms, as well as laboratory abnormalities. Immunogenicity assessments were repeated at the end of 12 months from baseline. Treatment emergent clinical & laboratory adverse events (TEAEs) were assessed as safety endpoints. Adverse events were evaluated based on their causality, expectedness, seriousness, incidence, severity, outcome, duration, action taken. Immunogenicity was evaluated by assessing the presence of anti-bevacizumab antibodies in serum by using a validated bioanalytical method at Hetero Biopharma Limited. The immunogenicity assessment for the anti-bevacizumab antibody is performed by the affinity capture and elution (ACE) method by enzyme linked immunosorbent assay (ELISA). The method follows sequential steps to detect anti-drug antibody (ADA) in the presence of high levels of free drug (bevacizumab). First, the ADA-Free drug complex was dissociated with acid treatment followed by neutralization in the presence of solid–phase drug giving the ADA an opportunity to be affinity captured. After washing away excess free drug, bound ADA were eluted with acid and subsequently bound to a fresh solid surface upon neutralization. Bound ADA was subsequently detected by biotin labelled drug and streptavidin Horseradish Peroxidase (HRP). Tetramethylbenzidine (TMB) substrate is used to generate a response. The Optical Density (OD) of the wells is measured using an ELISA plate reader and it is directly proportional to the amount of anti-Bevacizumab antibody present in the sample [17]. Efficacy assessments in terms of radiological assessments of ORR and DCR were assessed by the investigator according to RECIST 1.1 criteria. The possible lack of efficacy was also evaluated in the case of immunogenic reactions and also a positive change in response rates for improved efficacy.

3.4. Statistical Analysis: All patients who completed at least one cycle of study drug treatment were included in the intent to treat (ITT) population and patients who completed the study treatment as per the protocol without any major protocol deviations were included in per protocol (PP) population. Baseline summary statistics, including mean, and standard deviation for age, height, weight, BMI, and proportion of male:female were compared using Fisher's exact test. The variables measured on a continuous scale were compared using a t-test and the proportion of males/ females was compared using Fisher's exact test. All statistical testings were performed using two-tailed tests at a 5% level of significance. Efficacy endpoints at baseline and subsequent visits were analysed using Logistic Regression (or) Fisher's exact test. The 95% confidence interval for the mean change was also estimated. Safety variables including AEs, clinical laboratory parameters, vital signs, ECG parameters, and complete physical examinations were listed and summarized with descriptive statistics as appropri-

ate. Adverse events were coded using version 22.0 of the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of serious adverse events was compared across the treatment groups using Fisher's exact test. All statistical tests were performed using SAS® (version 9.4 or higher) system software (SAS Institute Inc.; USA).

3.5. Ethical Approval: This study was conducted in accordance with the ethical guidelines set out in the Declaration of Helsinki, 1964 (revised in 2013), Post Authorization Safety Studies (Phase IV study), Schedule Y, Drug & Cosmetic Act 201, and Guidelines for Similar Biologics 2016, India along with subsequent amendments and Indian regulatory laws governing biomedical research involving human patients. The study was approved by the Drugs Controller General, India (DCGI), CDSCO and subsequently registered with the clinical trial registry (CTRI/2018/04/013371) prospectively. Institutional ethics committee approvals were obtained from each participating study centre before initiating the study and written informed consent was obtained from each study participant before any protocol-driven tests or evaluations were performed

4. Results

4.1. Patient Characteristics: A total of 214 patients were screened to enrol 203 patients in this study. All 203 patients received at least one cycle of study treatment. Therefore, data from all 203 patients are included in the safety population. Out of 203 patients, 115 patients were also evaluated for efficacy and immunogenicity during the study. Of 115 patients evaluated for efficacy, only 56 patients completed the study. Therefore, 115 patients are included in the ITT population and 56 patients in the PP population (Table 1).

4.2. Safety Evaluation: A total of 121 patients (59.6%) reported at least one adverse event during the treatment. Overall, 336 adverse events were reported at the end of the study. 102 (32.5%) AEs were reported in general disorders and administration site conditions, 65 (30%) AEs were reported in gastrointestinal disorders, 54 (17.7%) AEs were reported in blood and lymphatic system disorders, 28 (12.8%) AEs were reported in nervous system disorders, and 23 (9.4%) AEs were reported in investigations (Table 2). The most frequently reported AEs were diarrhoea, asthenia, headache, pain, neutropenia, and vomiting.

Most AEs were mild to moderate in intensity. 77 (19.7%) AEs were certainly related, and 259 (39.9%) AEs were not related to the study drug as assessed by the treating doctor. Out of the 336 AEs, 14 serious adverse events (SAEs) were reported by 13 patients. Of these SAEs, 06 deaths were reported that were not related to study medication and all remaining SAEs were resolved. No consistent or clinically significant vital signs, laboratory, physical findings, or other observations related to the safety of the study drug were recorded for patients in this study.

4.3. Immunogenicity Analysis: At the end of the study, 2 (1.75%) of the 69 patients reported anti-bevacizumab antibodies. At the end of 12 months, no patient reported anti-bevacizumab antibodies (Table 3).

4.4. Efficacy Analysis: In the ITT population (n=115), Complete Response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD) were reported in 21 (18.3%), 26 (22.6%), 11(9.6%) and 10 (8.7%) patients, respectively. ORR was reported in 17(40.9%) patients at the end of the study. The DCR was reported in 58 (50.4%) patients. Tumour response data was not available for analysis in 47 (40.9%) patients. In the PP population (n=56), CR, PR, SD, and PD were reported in 18 (32.1%), 23 (41.1%), 9 (16.1%), and 6 (10.7%) patients, respectively. The ORR was reported in 41 (73.21%) patients and DCR was reported in 50 (89.29%) patients at the end of the study (Table 4).

Table 1: Demographic & Baseline Characteristics (Safety Population)

Variable	**Statistics**	**Bevacizumab (Hetero) N=203**
Gender, n (%)	Female	116 (57.14)
	Male	87 (42.86)
Age (years)	Mean ± SD	50.2 ± 11.1
Height (cm)	Mean ± SD	157.0 ± 8.9
Weight (Kg)	Mean ± SD	55.2 ± 11.7
BMI(kg/m2)	Mean ± SD	22.4 ± 4.7
Race, n (%)		
Indian		203(100.00)
Baseline disease		
Metastatic Colorectal Cancer (mCRC)	84	
Metastativ carcinoma of the cervix	56	
Non-Squamous Non-Small Cell Lung Cancer (NSCLC)	47	
Metastatic Renal Cell Carcinoma (mRCC)	11	
Glioblastoma	3	
Carcinoma of sigmoid colon, ovary & rectum	2	

N = number of subjects in specified treatment; 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 2: List of Adverse events occurred in Patients with solid tumours treated with Bevacizumab

Adverse Events	Bevacizumab		
	N=203	% of AE	No of AE's
Any Treatment-Emergent Adverse Event	121	59.6	336
Blood and lymphatic system disorders			
Anaemia	10	4.9	17
Autoimmune neutropenia	4	2	7
Febrile neutropenia	1	0.5	1
Hypochromic anaemia	1	0.5	3
Leukopenia	3	1.5	3
Neutropenia	12	5.9	14
Thrombocytopenia	5	2.5	9
Cardiac disorders			
Haemoptysis	1	0.5	1
Ear and labyrinth disorders			
Ear pain	1	0.5	1
Vertigo	1	0.5	1
Eye disorders			
Dry eye	2	1	2
Eye pain	4	2	4
Lacrimation increased	3	1.5	3
Gastrointestinal disorders			
Large intestinal obstruction	1	0.5	1
Abdominal discomfort	1	0.5	1
Abdominal distension	1	0.5	1
Abdominal pain	2	1	3
Abdominal pain upper	1	0.5	1
Constipation	3	1.5	3
Death	3	1.5	3
Diarrhoea	23	11.3	23
Dry mouth	6	3	6
Haematochezia	2	1	2
Hiccups	1	0.5	1
Intestinal obstruction	1	0.5	1
Mouth ulceration	1	0.5	1
Vomiting	16	7.9	19
General disorders and administration site conditions			
Asthenia	21	10.3	24
Burning sensation	3	1.5	3
Chest Pain	2	1	2
Chills	1	0.5	1
Death	3	1.5	3
Fatigue	8	3.9	20
Mucosal inflammation	1	0.5	1
Pain	15	7.4	35
Pyrexia	11	5.4	12
Tenderness	1	0.5	1
Infections and infestations			
Nasopharyngitis	4	2	4

Pulmonary tuberculosis	1	0.5	1
Investigations			
Blood creatinine increased	1	0.5	1
Blood pressure increased	6	3	7
Blood test abnormal	1	0.5	1
Haemoglobin decreased	6	3	8
Neutrophil count decreased	1	0.5	1
Platelet count decreased	1	0.5	1
Protein total abnormal	1	0.5	2
White blood cell count decreased	2	1	2
Metabolism and nutrition disorders			
Decreased appetite	5	2.5	5
Hyponatraemia	1	0.5	1
Musculoskeletal and connective tissue disorders			
Arthralgia	1	0.5	1
Flank pain	1	0.5	1
Muscle spasms	1	0.5	1
Neck pain	1	0.5	1
Pain in extremity	2	1	2
Nervous system disorders			
Cognitive disorder	1	0.5	1
Dizziness	1	0.5	2
Dysphonia	1	0.5	1
Headache	18	8.9	18
Neuropathy peripheral	1	0.5	1
Tremor	1	0.5	1
Vertigo	3	1.5	4
Psychiatric disorders			
Insomnia	5	2.5	5
Renal and urinary disorders			
Dysuria	1	0.5	2
Micturition disorder	1	0.5	1
Urinary tract infection	1	0.5	1
Reproductive system and breast disorders			
Vaginal fistula	1	0.5	1
Vaginal haemorrhage	1	0.5	2
Respiratory, thoracic and mediastinal disorders			
Cough	2	1	2
Dysphonia	1	0.5	1
Dyspnoea	3	1.5	4
Dyspnoea exertional	1	0.5	1
Epistaxis	1	0.5	1
Productive cough	1	0.5	1
Skin and subcutaneous tissue disorders			
Alopecia	5	2.5	5
Pruritus	1	0.5	1
Vascular disorder			
Haemorrhage	1	0.5	1
Haemorrhoids	1	0.5	1
Hypertension	4	2	5

Adverse events are classified by System Organ Class and Preferred Term as defined by the Medical Dictionary of Regulatory Affairs (MedDRA) v23.0.

Table 3: Summary of Immunogenicity Assessment

Visit	Response (anti-bevacizumab antibodies)	Hetero Bevacizumab N=114
Screening	Positive	0 (0)
	Negative	114(100.0)
End of Study	Positive	2 (1.75)
	Negative	67 (58.77)
End of 12 Months	Positive	0 (0)
	Negative	22 (19.30)

Table 4: Subject discontinued status based on indication wise

Indication/ Status	Reason	Total
Glioblastoma-N(3)		
Completed		1
Not Completed	Investigators or Sponsors Medical Monitor Discretion	1
	Lost to Follow-up	1
Metastatic Carcinoma of the Cervix-N(56)		
Completed		26
Not Completed	Death	2
	Disease progression	3
	Due to AE according to Investigator	1
	Investigators or Sponsors Medical Monitor Discretion	1
	Lost to Follow-up	13
	Withdrew Consent	10
Metastatic Renal Cell Carcinoma-N(11)		
Completed		6
Not Completed	Investigators or Sponsors Medical Monitor Discretion	1
	Lost to Follow-up	3
	Withdrew Consent	1
Metastatic colorectal cancer-N(84)		
Completed		44
Not Completed	Death	1
	Disease progression	6
	Due to AE according to Investigator	1
	Investigators or Sponsors Medical Monitor Discretion	1
	Lost to Follow-up	23
	Withdrew Consent	8
Non-Squamous Non–Small Cell Lung Cancer-N(47)		
Completed		22
Not Completed	Death	2
	Disease progression	3
	Due to AE according to Investigator	1
	Investigators or Sponsors Medical Monitor Discretion	1
	Lost to Follow-up	15
	Withdrew Consent	3
Other-N(2)		
Completed		2

5. Discussion

Vascular endothelial growth factor receptors (VEGFRs) play a key role in tumour angiogenesis. Bevacizumab was approved as the first anti-angiogenesis therapy by the FDA in 2004 for first-line therapy of metastatic colorectal cancer (mCRC) and later on for other solid tumours [18,19]. Anti-angiogenic targeted therapy is one of the major treatment modalities in patients with solid tumours. Bevacizumab (manufactured by Hetero) is a recombinant, humanized anti-VEGF monoclonal antibody that inhibits VEGF function in vascular endothelial cells and thereby inhibits tumour angiogenesis, upon which solid tumours depend for growth and metastasis. This study aimed to assess the safety, tolerability, immunogenicity, and efficacy of Hetero-Bevacizumab in Indian patients with solid tumours in the post-marketing phase. The results of our phase IV post-marketing study confirm the manageable safety profile, efficacy, and immunogenicity of bevacizumab (Hetero) and support the use of bevacizumab in both the first- and second-line treatment of solid tumours in the approved indications by the FDA, and also establish the relevance of findings of our randomized Phase III studies [20]. The addition of bevacizumab to the chemotherapy regimen (standard of care) for solid tumours was associated with a survival benefit, acceptable tolerability, and most adverse events were generally mild to moderate and clinically manageable. In our study, the overall response rate is 40.9%, which is comparable to our Phase III study (ORR was 37.50%) and to previously published clinical studies which reported ORR as 30-40%, depending on the prescribed regimen [21-27]. The development of biosimilars offers an affordable, safe, and effective alternative to potent biological therapies and comparative clinical studies help generate evidence in that direction. The results of this study provide clinical evidence for the biosimilar Hetero-Bevacizumab in relation to the efficacy, safety, and immunogenicity data in patients with solid tumours, suggesting a possibility for interchangeability of usage.

6. Conclusion

Based on study results, it can be concluded that Herero's Bevacizumab (Cizumab) was comparable in terms of safety, tolerability, and efficacy and can be used interchangeably with approved and available Bevacizumab brands for the management of patients with approved indications in solid tumours. This data provides a trend of its safety profile and efficacy of bevacizumab in real-world scenarios of prescribed settings and is consistent with our phase-III study and published literature.

7. Availability of Data and Materials

Data supporting the findings are presented within the manuscript and additional datasets used are available from the corresponding author on request.

8. Conflict of Interest

None declared.

9. Funding

This study, study related material and study drugs were sponsored by Hetero Biopharma. The study was designed and executed by Hetero Biopharma in line with local and international regulatory requirement.

10. Authors' Contributions

Concept and design of trial, regulatory approvals: S.S., S.C., B.R.; Project management: S.K. and P.T.; Manuscript drafting and revision, statistical analysis, data interpretation and conclusion analysis: S.S., S.C., L.T. and R.V. All the investigators in bevacizumab investigator group were responsible for conducting trial as per study protocol, site SOPs and relevant applicable regulations. All authors contributed to the study and approved the final manuscript.

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