



Ramucirumab in Indian Patients with Advanced Gastric Cancer—Does Borderline Performance Status and Heavy Burden of Disease in Real World Practice Impact Clinical Benefit?

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Abstract



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Background Ramucirumab is considered a standard of care as second-line therapy (CT2) in advanced gastric cancers (AGCs). The aim of this study was to assess practice patterns and outcomes with ramucirumab among Indian patients with AGCs.

Materials and Methods A computerized clinical data entry form was formulated by the coordinating center's (Tata Memorial Hospital) medical oncologists and disseminated through personal contacts at academic conferences as well as via email for anonymized patient data entry. The data was analyzed for clinical characteristics, response rates, and survival outcomes.

Results A total of 26 physicians contributed data, resulting in 55 patients receiving ramucirumab and being available for analysis. Median age was 53 years (range: 26–78), 69.1% of patients had greater than two sites of disease, and baseline Eastern Cooperative Oncology Group's performance score (ECOG PS) ≥ 2 was seen in 61.8% of patients. Ramucirumab was used as monotherapy in 10.9% of patients, while the remaining 89.1% received ramucirumab combined with chemotherapy. Median event-free survival (EFS) and median overall survival (OS) with ramucirumab were 3.53 months (95% CI: 2.5–4.57) and 5.7 months (95% CI: 2.39–9.0), respectively. Common class specific grade adverse events seen with ramucirumab included gastrointestinal (GI) hemorrhage (9.1% - all grades) and uncontrolled hypertension (Grade 3/4 - 3.6%).

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Keywords

- ▶ Ramucirumab
- ▶ ECOG PS \geq 2
- ▶ advanced gastric cancer
- ▶ India

Conclusions Ramucirumab appears to have similar efficacy in Indian AGC patients when compared with real-world data from other countries in terms of median EFS, but OS appears inferior due to more patients having borderline ECOG PS and high metastatic disease burden. GI hemorrhages appear more common than published data, although not unequivocally related to ramucirumab.

What is Already Known?

Ramucirumab is a recombinant human monoclonal immunoglobulin G1 antibody against human vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2) and is the only anti-VEGF agent approved for use in advanced gastric cancers (AGCs) in the second-line setting.

What is New in this Study?

A collaborative study of patients with AGC, who were treated by 26 clinicians with ramucirumab across India, which is a reasonably efficacious and safe option, especially with Eastern Cooperative Oncology Group's performance score (ECOG PS) 2 and heavy disease burden.

What are the Future Clinical and Research Implications of the Study Findings?

We need more studies looking at patients with AGCs with poor performance status and extensive disease burden, as immunotherapy is unlikely to help beyond a small chunk of patients.

Introduction

Treatment modalities and regimens have gradually improved overall survival (OS) in AGCs over the last decade. Approximately 30 to 65% of patients progressing on first-line chemotherapy (CT1) in AGC received second-line chemotherapy as per trial data (CT2).¹⁻³ Checkpoint inhibitors agents in the form of nivolumab, pembrolizumab and avelumab have further increased treatment options in AGC, although the benefits are modest (pembrolizumab and nivolumab).⁴⁻⁶

One of the current standards of care as CT2 in AGC is the combination of paclitaxel plus ramucirumab or ramucirumab monotherapy, based on the RAINBOW and REGARD phase III trials.^{7,8} The combination as well as monotherapy showed an OS benefit when compared with paclitaxel monotherapy (9.6 vs. 7.4 months; $p = 0.017$) and supportive care alone (5.2 vs. 3.8 months; $p = 0.047$). Besides the OS benefit, ramucirumab appears well-tolerated with a maintained quality of life (QoL) as reported in these studies, when compared with standard chemotherapeutic regimens like irinotecan, docetaxel, paclitaxel and FOLFIRI used as CT2 in AGC.^{3,9}

While the phase III studies with ramucirumab have established it as standard of care as CT2, the use of this drug in clinical practice may vary compared with respect to prior

chemotherapeutic regimens used, companion chemotherapy backbone, and patient factors like PS and tolerance profile. Available real-world data from the RAMoss study and the expanded access program cohort by the Korean Cancer Study Group (KCSG) suggests similar outcomes in nontrial scenarios.^{10,11} The potential prohibitory cost of the drug may also play a factor in limiting its use as opposed to chemotherapeutic agents.

With these factors in mind, we conducted a study with an objective of evaluating how oncologists in India used ramucirumab in their setting in AGC and whether practice patterns and outcomes differed from published data.

Materials and Methods**Clinical Record Form (CRF)**

A CRF for anonymized patient data entry was created by the medical oncologists (AR and VO) of the coordinating center. The entry form was divided into the following eight domains:

1. Physician details.
2. Demographic patients' details.
3. Baseline disease information.
4. Prior treatment history (brief).
5. Prior treatment (detailed).
6. Details of ramucirumab-based treatment.
7. Temporal profile of potential class-related adverse events—not reported in manuscript.
8. Practice related questions—not reported in manuscript.

Distribution of CRF

The CRF was distributed online for anonymized patient data entry. The form was designed on Google forms (Google, Mountain View, CA). Clinicians were identified from a database maintained in the GI medical oncology information system (MOIS) as well as via personal contacts. Individual and group emails with a link to the online CRF were sent to these physicians, and they were requested to reply from April 11, 2018 onward to November 21, 2018.

All responses were recorded electronically and translated into a Google spreadsheet, which was used for analysis. In case of missing data, clinicians were requested to supply the same where available by email responses.

Ethics

The data collection and handling were conducted as per the ethical guidelines of the declaration of Helsinki.¹² It was a retrospective analysis of anonymized patient data and consent was not required.

Statistical Analysis

Data was converted for entry in SPSS software (IBM) version 21 and used for analysis. Descriptive statistics, including median, frequency, and percentage for categorical variables, is used. Event-free survival (EFS) was calculated from the date of starting treatment with ramucirumab to date of permanent cessation of ramucirumab, irrespective of cause of cessation. This was considered as a surrogate for progression-free survival. Overall survival (OS) was calculated from date of starting ramucirumab-based treatment to the date of death or loss to follow-up. Median EFS and OS was calculated using Kaplan–Meier estimates.

Results

Baseline Demographic and Clinical Characteristics

A total of 63 patients had their data entered, of which data was found inadequate for analysis for eight entries (→Table 1). The median age of the remaining 55 patients eligible for analysis was 53 years (range: 26–78), 38 patients (69.1%) were male, 27.3% had signet ring histology, and 7.3% were human epidermal growth factor receptor 2 (HER2) positive. Clinically, 40% of patients had undergone a prior curative resection, 69.1% had greater than two sites of metastatic disease, and ECOG PS ≥ 2 was seen in 61.8% of patients (ECOG PS 2–56.4%; ECOG PS 3–5.5%) when starting ramucirumab. Patients had commonly received a triplet docetaxel-based regimen (38.2%) or epirubicin-based triplet (29.1%) as CT1 before starting on second-line treatment.

Characteristics of Therapy with Ramucirumab

As much as 10.9% of patients received monotherapy, while the remaining 89.1% patients received ramucirumab in combination with a chemotherapy backbone (→Table 2). Paclitaxel (81.6%; n = 49) was the most common chemotherapy backbone used. As much as 81.8% of patients were started with a ramucirumab dose of 8 mg/kg.

As much as 10.2% of patients required dose modifications of the chemotherapy backbone while on ramucirumab-based treatment, while dose reductions of ramucirumab were not required in any patient. Common grade 3 and grade 4 adverse events seen were neutropenia (11%), anemia (7.3%), and febrile neutropenia (5.5%). Class-specific grade 3/4 adverse events relatable to ramucirumab which were noted included uncontrolled hypertension (3.6%) and gastrointestinal (GI) bleeding/hemorrhage (9.1%; inclusive of primary tumor bleeds and all grades). No instances of GI perforation or thromboembolism were reported. An increased requirement of antihypertensives was noted in 14.5% of patients.

Response Rates and Outcomes

As much as 20% of patients had a partial response (PR), 25.5% of patients had stable disease (SD), and 38.2% of patients had progressive disease (PD) as best response to ramucirumab (→Table 2). As of cutoff date for analysis, 43.6% of patients had PD, 10.9% had ceased treatment due to adverse events, while 25.5% of patients were still continuing on

Table 1 Baseline demographic and clinical characteristics

Characteristics	Number (percentage where feasible)
Median age (years)	53 (26–78)
• ≥ 65	11 (20)
• < 65	44 (80)
Gender	
• Male	38 (69.1)
• Female	17 (30.9)
Pathological details	
Degree of differentiation	
• Adenocarcinoma NOS	10 (18.1)
• Well differentiated adenocarcinoma	01 (1.8)
• Moderately differentiated carcinoma	06 (10.9)
• Poorly differentiated carcinoma	38 (69.1)
Signet ring histology	
• Yes	15 (27.3)
• No	30 (54.5)
• Not available	10 (18.2)
HER2 status	
• Positive	04 (7.3)
• Negative	43 (78.1)
• Not tested	08 (14.5)
Microsatellite status	
• Stable	19 (34.5)
• High	04 (7.3)
• Not tested	32 (58.2)
Disease status	
Prior curative resection	
• Yes	22 (40)
• No	33 (60)
Sites of disease	
• Primary stomach (including locoregional recurrences)	39
• Liver	28
• Peritoneal/omental	27
• Pulmonary	13
• Nonregional nodes	31
• Osseous	07
• Soft tissue	03
• Ovarian deposits (including Krukenberg's)	03
Number of metastatic sites	
• > 2 sites	38 (69.1)
• ≥ 2 sites	17 (30.9)
Prior treatment history	
Median number of prior lines of therapy	1 (0–5)
Prior first-line treatment	
• Docetaxel-based triplet	21 (38.2)
• Paclitaxel-based triplet	01 (1.8)
• Epirubicin-based triplet	16 (29.1)
• Doublet regimens	14 (25.5)
• Monotherapy	01 (1.8)
• Ramucirumab-based first-line therapy	02 (3.6)
ECOG PS	
• 0/1	21 (38.2)
• 2	31 (56.4)
• 3	03 (5.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; epidermal growth factor receptor 2 (HER2); NOS, not otherwise specified; PS, performance status.

treatment. Five patients died while on treatment, with one patient having died possibly due to ramucirumab-related GI hemorrhage.

Table 2 Characteristics of therapy with ramucirumab

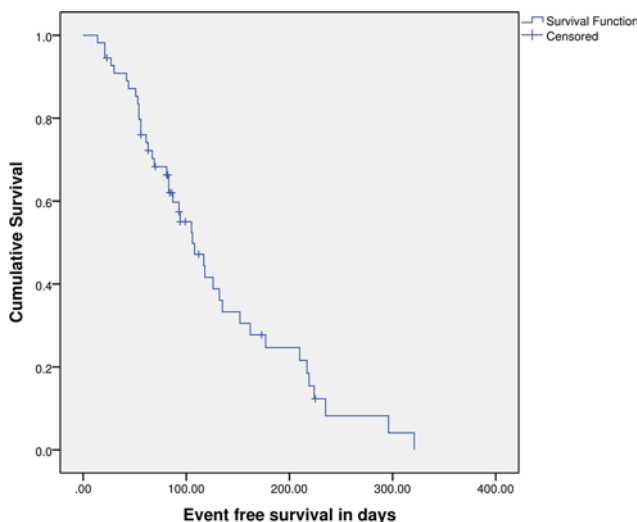
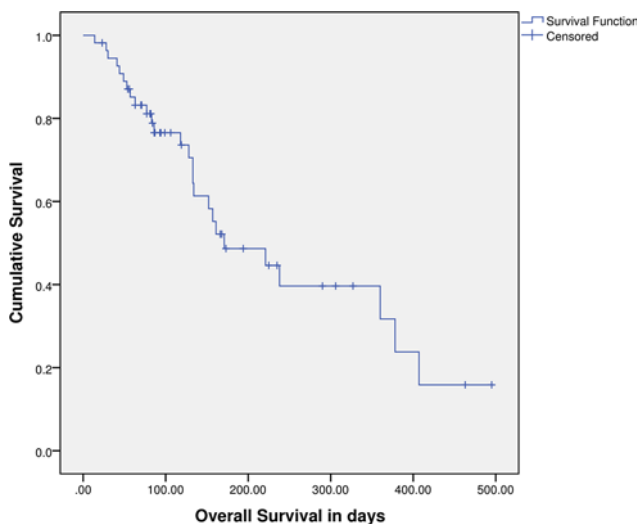
Characteristics	Number (percentage)
Ramucirumab use	
Ramucirumab monotherapy/combination	
• Monotherapy	06 (10.9)
• Combination	49 (89.1)
1. Paclitaxel	40
2. FOLFIRI	05
3. FOLFOX	01
4. Paclitaxel-carboplatin	01
5. Irinotecan	01
6. 5 Fluorouracil	01
Schedule of ramucirumab used	
• Biweekly	48 (87.3)
• Weekly	06 (10.9)
• Every 3 weeks	01 (1.8)
Dosage of ramucirumab used	
• 8 mg/kg	45 (81.8)
• 6 mg/kg	05 (9.1)
• 4 mg/kg	05 (9.1)
Treatment-related events with ramucirumab	
Dose reduction/modifications	
• Chemotherapy backbone (<i>n</i> = 49)	5 (10.2)
• Ramucirumab	0
Class-related grade \geq 3/4 adverse events	
• Gastrointestinal bleeding/hemorrhage (all grades)	05 (9.1)
• Uncontrolled hypertension	02 (3.6)
• Thromboembolic events	0
• Gastrointestinal perforation	0
Increased requirement of antihypertensives	
• Yes	08 (14.5)
• No	44 (80)
• No data	03 (5.5)
Requirement of cardiac evaluation for suspected cardiac dysfunction Grade \geq 3/4 adverse events	05 (9.1)
• Anemia	04 (7.3)
• Neutropenia	06 (11)
• Febrile neutropenia	03 (5.5)
• Thrombocytopenia	03 (5.5)
• Non neutropenic infections	03 (5.5)
• Diarrhea	02 (3.6)
• Vomiting	02 (3.6)
Response rates	
• Partial response	11 (20)
• Stable disease	14 (25.5)
• Progressive disease	21 (38.2)
• Not available	09 (16.4)
Reasons for cessation of ramucirumab	
• Progressive disease	24 (43.6)
• Toxicities	06 (10.9)
• Cost constraints	03 (5.5)
• Death while on ramucirumab (progression/adverse events)	05 (9.1)
1. Drug related	01
2. Drug unrelated	04
• Lost to follow-up	03 (5.5)
• On treatment	14 (25.5)

With a median follow-up of 4.8 months, median EFS (→Fig. 1) was 3.53 months (95% CI: 2.5–4.57) and median estimated OS (→Fig. 2) was 5.7 months (95% CI: 2.39–9.0). Twenty-three patients had died, while 3 patients were lost to follow-up at the time of analysis.

Discussion

Ramucirumab is a recombinant human monoclonal immunoglobulin G1 antibody against human VEGF receptor 2 (VEGFR2) and is the only anti-VEGF agent approved for use in AGC, albeit in the second-line setting. Besides having a very modest OS benefit when compared with placebo alone in the REGARD study, ramucirumab also showed a trend toward improved global QoL. The RAINBOW study also showed that QoL was maintained on treatment with paclitaxel plus ramucirumab along with an acceptable safety profile. This possibly allows its use in patients with a precarious ECOG PS (ECOG PS \geq 2), although this has not been examined in a trial setting.

The current study in Indian patients with AGC had the primary aim of ensuring collaboration between Indian medical oncologists in evaluating the clinical presentation and outcomes in patients receiving ramucirumab. The cohort of 55 patient data examined in this study showed a few points of interest requiring elucidation. Most patients received paclitaxel as the chemotherapy backbone with ramucirumab,

**Fig. 1** Event-free survival (EFS).**Fig. 2** Overall survival (OS).

but a few patients also received other accompanying regimens (10.9%). These percentages will likely rise in the near future, considering the increasing use of the docetaxel-based docetaxel, oxaliplatin, fluorouracil, and leucovorin (FLOT) regimens in the perioperative setting and a possible reluctance in using a potentially cross-resistant agent, i.e., paclitaxel on recurrence.¹³ FOLFIRI or irinotecan are possible options in such a scenario and their feasibility in combination with ramucirumab has already been shown in colorectal cancers.¹⁴

A significant proportion of patients had signet ring histology (27.3%), which is equivocally considered as a poor prognostic marker in AGC.^{15,16} A majority of patients had ECOG PS ≥ 2 , which would be expected in patients who have progressed post-CT1 in AGC. ECOG PS 2 has also been shown to be a strong predictor of inferior outcomes in AGC from large well-conducted retrospective studies.^{17,18} However, data on the efficacy of ramucirumab in patients with inferior ECOG PS is lacking, as such patients are usually systematically excluded from clinical trials. Again, the current study cohort had patients with a high metastatic disease burden (69.1% of patients had > 2 sites of metastatic disease). When a cohort with such unfavorable characteristics (high proportion of signet ring histology, predominantly ECOG PS ≥ 2 , high metastatic burden) is evaluated, outcomes would be expected to be inferior to published data. Thus, as expected, the median OS in the current study is 5.7 months, which is less than the survival seen in the RAINBOW trial (9.6 months). A more

relevant comparison with the real-world RAMoss study and the data from the expanded access program in Korea (EAP-KCSG) is shown in **Table 3**. As can be evinced, the patients in both these studies had baseline characteristics, which approximated patients being considered for trials (predominantly ECOG PS 0/1, less metastatic burden of disease) and expectedly had a similar OS (RAMoss—8.6 months for combination arm; EAP-KCSG—8.6 months for combination arm). However, the PFS across the studies is similar (RAMoss—4.4 months for combination arm; EAP-KCSG—3.8 months for combination arm; current study [EFS]—3.53 months), suggesting that ramucirumab is reasonably efficacious even in patients with ECOG PS 2 and heavy metastatic burden of disease.

Patients profiled in the study appeared to have tolerated ramucirumab well with no new safety signals seen. There were no instances of GI perforation or thromboembolic events in the study. GI hemorrhages appeared to be significantly more common (9.1%) but was reported by physicians as being tumor-related bleed, with only one instance of the bleed being attributable to ramucirumab causing death. There was a slightly increased incidence of hypertension, and requirement of increased antihypertensives was seen (14.5%), but grade $\frac{3}{4}$ hypertension was only marginally high (3.6%).

The current collaborative study comprises a cohort of patients with AGC who have been treated by 26 clinicians with ramucirumab across India and is an accurate representation of practice patterns employed by them. The number of

Table 3 Comparison of real-world studies evaluating ramucirumab in advanced gastric cancer

Characteristic	EAP-KCSG	RAMoss	Current study
Number of patients	265	167	55
Region	South Korea	Italy	India
ECOG PS			
• 0/1	94.6	88.7	38.2
• ≥ 2	5.4	11.3	61.2
Number of metastatic sites			
• 0–2	73	–	30.9
• ≥ 3	27	–	69.1
Ramucirumab use			
• Monotherapy	13.7	10.2	10.9
• Combined with chemotherapy	86.4	89.8	89.1
Response rates (%)			
• Complete response	0.4	1.3	0
• Partial response	14.7	18.9	20
• Stable disease	47.2	39.2	25.5
• Progressive disease	30.2	40.6	38.2
• Clinical benefit rate	61.9	58.1	45.5
• NA	7.5	–	16.4
Class specific grade $\frac{3}{4}$ toxicities (%)			
• GI hemorrhage (all grades)	1.3	7.7 (bleeding)	9.1
• GI perforation	2.3	0	0
• Thromboembolic events	0.8	0	0
• Uncontrolled hypertension	1.1	0.6	3.6
Median PFS (months)	1.8 (mono) 3.8 (combination)	2.7 (mono) 4.4 (combination)	3.53 (EFS)
Median OS (months)	6.4 (mono) 8.6 (combination)	4.8 (mono) 8.6 (combination)	5.7

Abbreviations: EAP-KCSG, expanded access program in Korean Cancer Study Group ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; GI, gastrointestinal; NA, not available; OS, overall survival; PS, performance status; PFS, progression-free survival.

patients accrued in the study is also indicative of the small numbers of patients who are potentially feasible for this drug, based on logistic and financial constraints in India, although a further discussion on this aspect is beyond the scope of this study. The strengths of the current study lie in showing that ramucirumab is a reasonably efficacious and safe option as second-line therapy in Indian patients with AGC, especially with ECOG PS 2 and heavy disease burden. It also provides limited evidence that patients with poor ECOG PS (PS 2) can be treated with ramucirumab-based therapy, although outcomes are expectedly inferior. However, multiple caveats exist when reporting outcomes in such small data cohorts. Physicians entered data online and hence there may be bias in reporting and recall of patient-related details. We are unable to evaluate any prognostic or predictive factors with regard to outcomes as the small numbers preclude any such relevant statistical analysis. Decisions on whether ramucirumab should be used in patients with poor PS still remains unanswered, although answers are unlikely to be forthcoming, given the nature of patient selection in clinical trials.

In conclusion, ramucirumab appears to have similar efficacy in Indian gastric cancer patients when compared with real-world data from other countries in terms of median PFS, but OS appears to be lower due to the treatment of more patients with ECOG PS \geq 2 and higher metastatic burden of disease. GI hemorrhages appear more common than published data, although it is possibly related to tumor hemorrhage than ramucirumab.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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