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ORIGINAL ARTICLE

Ramucirumab for the treatment of patients with gastric or gastroesophageal junction cancer in community oncology practices

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Abstract

Background Limited real-world research has investigated ramucirumab for the treatment of patients with gastric or gastroesophageal junction (GEJ) cancer. This study was designed to describe ramucirumab monotherapy or combination therapy use in a community oncology practice setting.

Methods This was a retrospective observational cohort study to describe the treatment of adult patients with gastric or GEJ cancer who initiated ramucirumab treatment between 4/21/14 and 6/30/16 within the US Oncology Network. Kaplan–Meier method and Cox proportional hazards regression analyses were used to assess clinical outcomes. Multivariable logistic regression models were used to assess patient-level predictors of ramucirumab monotherapy or combination therapy.

Results A total of 505 patients (mean age 64.4 years; 75.1% male) were included in the analysis; subgroups included: monotherapy (22.8%; $n = 115$), combination therapy (77.2%; $n = 390$). Monotherapy patients were significantly older (67.7 vs. 63.4 years; $P = 0.0006$), received ramucirumab approximately 3 months later after diagnosis (16.9 vs. 14.1 months; $P = 0.0318$) and more frequently initiated ramucirumab in the third or later lines of treatment (38.3 vs. 8.2%; $P<0.0001$) than patients receiving combination therapy. Median overall survival (OS) for monotherapy and combination therapy from the start of second-line therapy was 5.5 months (confidence interval [CI] 4.3, 7.8) and 7.4 months (CI 6.6, 8.8), respectively.

Conclusions The results showed that patients who received ramucirumab monotherapy started ramucirumab therapy later after diagnosis and were older than those who received ramucirumab in combination. Additionally, survival data suggest that outcomes observed in community oncology practices are similar to data from phase 3 clinical trials.

Keywords Gastric cancer · Gastroesophageal junction cancer · Ramucirumab · Outcomes research · Overall survival

Introduction

In the United States (US), approximately 28,000 patients are diagnosed with gastric or gastroesophageal junction (GEJ) cancer annually and 10,960 deaths were estimated in 2017 [1]. The majority of these cases (~ 90%) present with adenocarcinoma, which originates from the mucosa of the stomach [2]. While mortality rates have declined, gastric cancer is the second leading cause of global cancer-related death after lung cancer [2]. The prognosis for this disease is poor, with an overall estimated 5-year survival of about 30% in the US [3]. Although patients with localized disease have a reasonable prognosis through surgical intervention and perioperative treatment, over 60% of patients are diagnosed at an advanced stage, with an estimated 5-year survival rate of only 5% for patients with distant metastases.

Chemotherapy and targeted treatments are recommended for patients with advanced or metastatic gastric or GEJ cancer [4]. Systemic, multi-agent chemotherapy is associated with improved survival in the first-line setting [5]. Preferred second-line treatment options recommended by the National Comprehensive Care Network (NCCN) include cytotoxic agents (i.e., docetaxel, paclitaxel, irinotecan, fluorouracil/irinotecan), as well as the anti-angiogenic, ramucirumab (used alone or in combination with paclitaxel) [4]. The

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introduction of targeted therapies, such as ramucirumab, has provided patients with advanced or metastatic gastric or GEJ cancer with additional treatment options, yet there is uncertainty in routine clinical practice about the outcomes of these therapies outside of a clinical trial setting. Additional evidence would benefit patients and healthcare providers navigate this emerging and complex treatment landscape and identify the most appropriate course of therapy.

Ramucirumab is a human IgG1 monoclonal antibody vascular endothelial growth factor receptor (VEGFR) 2 antagonist [6]. Through blocking activation of VEGFR-2 by VEGF-A and the other VEGF ligands, ramucirumab inhibits the angiogenesis pathways involved in the development and progression of gastric cancer [7]. The safety and efficacy of ramucirumab were demonstrated in two Phase 3 multicenter, international, randomized, double-blind, placebo-controlled trials of patients with advanced or metastatic gastric or GEJ adenocarcinoma who experienced disease progression on or following fluoropyrimidine- or platinum-containing chemotherapy [8, 9]. In the REGARD trial, ramucirumab monotherapy was associated with significantly improved overall survival (OS) compared to best supportive care (5.2 vs. 3.8 months; hazard ratio [HR] 0.776 [95% CI 0.603–0.998]; $P = 0.047$) [8]. Similarly, patients randomized to ramucirumab and paclitaxel in the RAINBOW trial had significantly longer OS compared to those who received paclitaxel alone (9.6 vs. 7.4 months; HR 0.807 [95% CI 0.678–0.962]; $P = 0.017$) [9]. In both trials, ramucirumab, either alone or in combination, was generally well tolerated [8, 9].

Based on these results, the US Food & Drug Administration (FDA) approved ramucirumab as a monotherapy (April 21, 2014) and in combination with paclitaxel (November 5, 2014) for the treatment of advanced or metastatic gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy [6, 10].

The objective of this study was to assess demographic and clinical characteristics as well as treatment patterns and outcomes associated with ramucirumab alone or in combination with cytotoxic agents (e.g., paclitaxel) for the treatment of gastric or GEJ adenocarcinoma. The treatment patterns and survival outcomes among patients who received either ramucirumab monotherapy or in combination were investigated. Additionally, factors associated with monotherapy and combination therapy utilization were explored.

Methods

Study Design

This was a retrospective observational cohort study that examined patient profiles, treatment patterns and outcomes for patients with gastric or GEJ cancer treated with ramucirumab who received healthcare services at US Oncology Network (USON) clinics. The date of initiation of a ramucirumab-containing regimen was defined as the index date. Eligible patients were 18 years of age or older at the index date who had a documented diagnosis of gastric or GEJ cancer, initiated ramucirumab between April 21, 2014 and June 30, 2016, received care at USON sites utilizing the full electronic healthcare record (EHR) capacities at the time of treatment and had ≥ 2 office visits during the study observation period. Patients enrolled in clinical trials at any time during the study period were excluded because they had clinical scenarios that deviated from the population of interest.

The EHR of the USON, iKnowMed (iKM), was used in this study. iKM is an oncology-specific EHR system that captures outpatient practice encounter history for patients who receive care within the USON, including, but not limited to laboratory tests, diagnosis, therapy administration, line of therapy (LOT), cancer stage, comorbidities and performance status. iKM captures data on outpatient medical oncology care for patients treated across the US (19 states). Overall, the iKM EHR system captures data on approximately 10% of newly diagnosed cancer patients in the US.

To supplement available vital status information in iKM, the Social Security Death Index (SSDI) was used to estimate OS. OS was defined as the interval between the index date and the date of death as documented in the SSDI and iKM EHR database. Patients alive at the end of the database were censored on the study end date or the last visit date available in the database, whichever occurred first. Because the study derived data mainly from the iKM database to meet the objectives, an intent-to-treat perspective was applied.

Statistical analysis

Patient profiles, treatment patterns and outcomes were assessed for all patients identified in the iKM database who met inclusion criteria, as well as for the subgroups of patients receiving monotherapy or combination therapy. Classification of patients into the monotherapy and combination subgroups was based on their initial ramucirumab regimen. For example, if a patient began ramucirumab monotherapy and advanced to a new LOT with a combination ramucirumab regimen, that patient was considered to be a monotherapy subgroup member.

Demographic, clinical and treatment characteristics were summarized for the entire patient cohort and subgroups. Continuous variables were described by mean, standard deviation, median and interquartile range (IQR). Categorical variables

Table 1 Baseline and clinical characters characteristics of gastric or GEJ cancer patients receiving ramucirumab

Analysis variable	Total study cohort (N = 505)	Monotherapy subgroup (n = 115)	Combination therapy subgroup (n = 390)	P value
Monotherapy use at index, *n* (%)	115 (22.77%)			
Combination therapy use at index, *n* (%)	390 (77.23%)			
Age at index (years)				0.0006[d]
Mean (SD)	64.41 (11.42)	67.74 (11.63)	63.42 (11.19)	
Median (IQR)	65.06 (57.39,72.31)	67.50 (60.42,75.81)	64.11 (56.97,70.95)	
Gender, *n* (%)				0.7486[e]
Female	126 (24.95%)	30 (26.09%)	96 (24.62%)	
Male	379 (75.05%)	85 (73.91%)	294 (75.39%)	
Race, *n* (%)				0.9558[e]
Black	32 (6.34%)	8 (6.96%)	24 (6.15%)	
White	407 (80.59%)	93 (80.87%)	314 (80.51%)	
Other	25 (4.95%)	6 (5.22%)	19 (4.87%)	
Not documented	41 (8.12%)	8 (6.96%)	33 (8.46%)	
Ethnicity, *n* (%)				0.2817[e]
Hispanic or Latino	75 (14.85%)	13 (11.30%)	62 (15.90%)	
Not Hispanic or Latino	392 (77.62%)	90 (78.26%)	302 (77.44%)	
Not documented	38 (7.53%)	12 (10.44%)	26 (6.67%)	
Geographic region, *n* (%)				0.0037[e]
Midwest	64 (12.67%)	19 (16.52%)	45 (11.54%)	
Northeast	19 (3.76%)	7 (6.09%)	12 (3.08%)	
South	289 (57.23%)	49 (42.61%)	240 (61.54%)	
West	133 (26.34%)	40 (34.78%)	93 (23.85%)	
Payer information, *n* (%)				0.0220[c]
Medicaid	22 (4.36%)	3 (2.61%)	19 (4.87%)	
Medicare	197 (39.01%)	54 (46.96%)	143 (36.67%)	
Private	174 (34.46%)	30 (26.09%)	144 (36.92%)	
Other	18 (3.56%)	1 (0.87%)	17 (4.36%)	
Not documented	94 (18.61%)	27 (23.48%)	67 (17.18%)	
Physician specialty, *n* (%)				0.7943[c]
Hematology and medical oncology	450 (89.11%)	104 (90.44%)	346 (88.72%)	
Internal medicine	1 (0.20%)	0 (0.00%)	1 (0.26%)	
Not documented	54 (10.69%)	11 (9.57%)	43 (11.03%)	
Physician patient volume, *n* (%)				0.0205[c]
< 100 patients/year	374 (74.06%)	96 (83.48%)	278 (71.28%)	
100–199 patients/year	121 (23.96%)	17 (14.78%)	104 (26.67%)	
200 + patients/year	10 (1.98%)	2 (1.74%)	8 (2.05%)	
BMI category at baseline, *n* (%)				0.6063[c]
Normal	216 (42.77%)	53 (46.09%)	163 (41.80%)	
Obese	95 (18.81%)	18 (15.65%)	77 (19.74%)	
Overweight	114 (22.57%)	27 (23.48%)	87 (22.31%)	
Underweight	74 (14.65%)	14 (12.17%)	60 (15.39%)	
Not documented	6 (1.19%)	3 (2.61%)	3 (0.77%)	
Smoking status at baseline, *n* (%)				0.4618[c]
Current	76 (15.05%)	15 (13.04%)	61 (15.64%)	
Former	238 (47.13%)	60 (52.17%)	178 (45.64%)	
Never	186 (36.83%)	39 (33.91%)	147 (37.69%)	
Not documented	5 (0.99%)	1 (0.87%)	4 (1.03%)	
Histological subtype, *n* (%)				0.4091[c]

Table 1 (continued)

Analysis variable	Total study cohort ($N = 505$)	Monotherapy subgroup ($n = 115$)	Combination therapy subgroup ($n = 390$)	P value
Adenocarcinoma	30 (5.94%)	3 (2.61%)	27 (6.92%)	
Signet ring cell carcinoma	4 (0.79%)	1 (0.87%)	3 (0.77%)	
Not documented	471 (93.27%)	111 (96.52%)	360 (92.31%)	
Time from initial gastric or GEJ cancer diagnosis to start of ramucirumab (m)				0.0318[d]
Patients with available data	503	115	388	
Mean (SD)	14.70 (14.69)	16.86 (15.81)	14.06 (14.29)	
Median (IQR)	10.09 (5.78,18.13)	12.55 (6.57,22.73)	9.69 (5.50,17.56)	
Time since prior therapy to start of ramucirumab (m)				0.1151[d]
Patients with available data	433	90	343	
Mean (SD)	2.07 (2.62)	1.42 (1.22)	2.24 (2.86)	
Median (IQR)	0.99 (0.69,2.33)	0.92 (0.69,1.71)	0.99 (0.69,2.63)	
Primary tumor locations, *n* (%)				0.5943[f]
Greater curvature	11 (2.18%)	5 (4.35%)	6 (1.54%)	
Lesser curvature of stomach, unspecified	13 (2.57%)	3 (2.61%)	10 (2.56%)	
Cardio-esophageal junction	14 (2.77%)	3 (2.61%)	11 (2.82%)	
Antrum of stomach NOS	23 (4.55%)	5 (4.35%)	18 (4.62%)	
Lower thoracic esophagus	25 (4.95%)	4 (3.48%)	21 (5.38%)	
Body of stomach	26 (5.15%)	6 (5.22%)	20 (5.13%)	
Lower third of esophagus	46 (9.11%)	6 (5.22%)	40 (10.26%)	
Gastroesophageal junction	93 (18.42%)	19 (16.52%)	74 (18.97%)	
Other	41 (8.12%)	10 (8.70%)	31 (7.95%)	
Not documented	213 (42.18%)	54 (46.96%)	159 (40.77%)	
Stage at initial gastric or GEJ cancer diagnosis, *n* (%)				0.9717[c]
I	19 (3.76%)	4 (3.48%)	15 (3.85%)	
II	72 (14.26%)	16 (13.91%)	56 (14.36%)	
III	99 (19.60%)	24 (20.87%)	75 (19.23%)	
IV	285 (56.44%)	62 (53.91%)	223 (57.18%)	
Not documented	30 (5.94%)	9 (7.83%)	21 (5.39%)	
Prior cancer diagnosis, *n* (%)				0.5587[e]
No	451 (89.31%)	101 (87.83%)	350 (89.74%)	
Yes	54 (10.69%)	14 (12.17%)	40 (10.26%)	
Prior cancer diagnosis location (if applicable), *n* (%)				
Pancreas	5 (0.99%)	1 (0.87%)	4 (1.03%)	1.000[c]
Prostate	5 (0.99%)	0 (0.00%)	5 (1.28%)	0.2224[c]
Cancer, unknown primary	8 (1.58%)	2 (1.74%)	6 (1.54%)	1.000[c]
Breast cancer, female	9 (1.78%)	4 (3.48%)	5 (1.28%)	0.1247[c]
Other	31 (6.14%)	7 (6.09%)	24 (6.15%)	0.9790[e]
Use of ramucirumab before/after November 2014 combination therapy approval, *n* (%)				< 0.0001[e]
Monotherapy prior to November 2014 FDA approval	71 (53.79%)			
Combination therapy prior to November 2014 FDA approval	61 (46.21%)			
Monotherapy after November 2014 FDA approval	44 (11.80%)			
Combination therapy after November 2014 FDA approval	329 (88.20%)			
Number of agents used in line of therapy prior to ramucirumab (excluding mesna and leucovorin)				< 0.0001[d]
Patients with available data	432	90	342	

Table 1 (continued)

Analysis variable	Total study cohort ($N = 505$)	Monotherapy subgroup ($n = 115$)	Combination therapy subgroup ($n = 390$)	P value
Mean (SD)	2.38 (0.79)	2.01 (0.79)	2.47 (0.76)	
Median (IQR)	2 (2,3)	2 (1,3)	3 (2,3)	
Number of prior LOTs, *n* (%)				0.2155[c]
1	338 (66.93%)	75 (65.22%)	263 (67.44%)	
2	79 (15.64%)	11 (9.57%)	68 (17.44%)	
3 +	15 (2.97%)	4 (3.48%)	11 (2.82%)	
No prior treatment documented in EHR[a]	72 (14.26%)	25 (21.74%)	47 (12.05%)	
Number of prior LOTs undefined[b]	1 (0.20%)	0 (0.00%)	1 (0.26%)	
Prior treatments for gastric or GEJ cancer prior to ramucirumab initiation, *n* (%)	433 (85.74%)	90 (78.26%)	343 (87.95%)	0.0090[e]
Anti-angiogenic-containing	1 (0.20%)	0 (0.00%)	1 (0.26%)	1.000[c]
Antineoplastic-containing	6 (1.19%)	0 (0.00%)	6 (1.54%)	0.1809[c]
Irinotecan-containing	48 (9.51%)	17 (14.78%)	31 (7.95%)	0.0281[e]
Anthracycline-containing	67 (13.27%)	8 (6.96%)	59 (15.13%)	0.0232[e]
Trastuzumab-containing	75 (14.85%)	16 (13.91%)	59 (15.13%)	0.7474[e]
Taxane-containing	146 (28.91%)	38 (33.04%)	108 (27.69%)	0.2660[e]
Platinum-containing	316 (62.57%)	47 (40.87%)	269 (68.97%)	< 0.0001[e]
Fluoropyrimidine-containing	334 (66.14%)	49 (42.61%)	285 (73.08%)	< 0.0001[e]
Evidence of metastatic disease at baseline, *n* (%)				0.5435[c]
No	16 (3.17%)	2 (1.74%)	14 (3.59%)	
Yes	489 (96.83%)	113 (98.26%)	376 (96.41%)	
Location of metastases (if applicable), *n* (%)				
Brain	14 (2.77%)	7 (6.09%)	7 (1.80%)	0.0138[e]
Bone	60 (11.88%)	16 (13.91%)	44 (11.28%)	0.4435[e]
Lung	63 (12.48%)	12 (10.44%)	51 (13.08%)	0.4511[e]
Peritoneum	96 (19.01%)	21 (18.26%)	75 (19.23%)	0.8158[e]
Liver	152 (30.10%)	38 (33.04%)	114 (29.23%)	0.4334[e]
Other	110 (21.78%)	17 (14.78%)	93 (23.85%)	0.0385[e]
Not documented	289 (57.23%)	67 (58.26%)	222 (56.92%)	
ECOG performance score at initiation of ramucirumab use, *n* (%)				0.4136[c]
0	25 (4.95%)	3 (2.61%)	22 (5.64%)	
1	182 (36.04%)	41 (35.65%)	141 (36.15%)	
2 +	51 (10.10%)	13 (11.30%)	38 (9.74%)	
Not documented	247 (48.91%)	58 (50.44%)	189 (48.46%)	
Weight loss (3 months prior to initiation of ramucirumab), *n* (%)				0.5878[c]
< 10%	124 (24.55%)	31 (26.96%)	93 (23.85%)	
≥ 10%	10 (1.98%)	1 (0.87%)	9 (2.31%)	
No weight loss	371 (73.47%)	83 (72.17%)	288 (73.85%)	
Comorbidities at initiation of ramucirumab, *n* (%)				
Liver	5 (0.99%)	1 (0.87%)	4 (1.03%)	1.000[c]
Renal	9 (1.78%)	3 (2.61%)	6 (1.54%)	0.4323[c]
Diabetes	21 (4.16%)	1 (0.87%)	20 (5.13%)	0.0587[c]
Pulmonary	36 (7.13%)	6 (5.22%)	30 (7.69%)	0.3647[e]
Neuropathy	43 (8.52%)	6 (5.22%)	37 (9.49%)	0.1494[e]
Cardiovascular	45 (8.91%)	7 (6.09%)	38 (9.74%)	0.2265[e]
Hematological	120 (23.76%)	34 (29.57%)	86 (22.05%)	0.0962[e]
Other	223 (44.16%)	43 (37.39%)	180 (46.15%)	0.0963[e]

Table 1 (continued)

Analysis variable	Total study cohort (N = 505)	Monotherapy subgroup (n = 115)	Combination therapy subgroup (n = 390)	P value
Toxicity/symptoms at initiation of ramucirumab (60-day period before index event), n (%)				
Neutropenia	22 (4.36%)	8 (6.96%)	14 (3.59%)	0.1201[e]
Edema	24 (4.75%)	7 (6.09%)	17 (4.36%)	0.4440[e]
Abdominal pain/bloating	24 (4.75%)	2 (1.74%)	22 (5.64%)	0.1306[c]
Neuropathy	25 (4.95%)	7 (6.09%)	18 (4.62%)	0.5226[e]
Diarrhea	28 (5.55%)	7 (6.09%)	21 (5.39%)	0.7724[e]
Nausea	102 (20.20%)	13 (11.30%)	89 (22.82%)	0.0069[e]
Other	46 (9.11%)	9 (7.83%)	37 (9.49%)	0.5864[e]

[a]These patients may have prior treatment outside of the US Oncology Network (USON)

[b]This patient had evidence of prior treatment within the USON but the number of LOTs was not defined in the EHR database

[c]P value calculated based on a Fisher's Exact test

[d]P value calculated based on a Kruskal–Wallis test

[e]P value calculated based on a χ^2 test

[f]Monte Carlo estimate

were defined by patient count and percentage. To make statistical comparisons between the subgroups, Pearson χ^2 or Fisher's exact test were used to analyze categorical variables and Kruskal–Wallis tests were conducted for continuous variables.

An alpha level of 0.05 was the primary criterion for statistical significance of this study. Results were reported in aggregate using SAS® 9.4 (SAS Institute Inc., Cary, NC, US).

Stepwise multivariable logistic regression models were used to evaluate predictors for the use of ramucirumab monotherapy versus combination therapy. Predictors, consisting of baseline demographic and clinical factors, found to be significant at the 0.25 level were entered into the model, while final predictors retained in the model had to be significant at the 0.10 level. To increase statistical power, predictors identified in the final model were refitted in a logistic regression model to avoid exclusion of patients with missing data due to unselected predictors.

Kaplan–Meier curves were constructed for the monotherapy and combination therapy subgroups to illustrate OS and time to treatment discontinuation (TTTD) profiles and medians with their respective 95% confidence intervals (CIs). Survival rates were calculated at 6, 9, 12 and 18 months for OS. Conversely, treatment discontinuation rates for TTTD were calculated at 3-, 6-, 9- and 12-month periods.

Similar to evaluating baseline and clinical predictive factors in the multivariable logistic regression models, the same was done for univariate and multivariable Cox proportional hazards regression analyses for OS and TTTD. That is, stepwise multivariable Cox proportional hazards regression models utilized a 0.25 significance level for predictors to be entered into the model and a 0.10 level for them to remain in the model.

Demographic and clinical confounding factors were included in the multivariable logistic regression and Cox proportional hazards regression models based on their clinical relevance and/or the univariate significance level.

Results

Patient demographic and clinical characteristics

A total of 505 patients (mean age 64.4 years; 75.1% male; 80.6% White; 57.2% treated in Southern US; Table 1) were included in the analysis; subgroups included: monotherapy (22.8%; n = 115) and combination therapy (77.2%; n = 390; Fig. 1). The majority of the study population, 73.5%, had either Medicare (39.0%) or private (34.5%) insurance (Table 1). Healthcare services received in hematological and medical oncology settings were the primary source for this study population (89.1%). Physicians treating less than 100 patients annually represented almost three-fourths of the care administered (74.1%). Of the overall study population, 42.8% had normal weight, while 22.6% and 18.8% were overweight and obese, respectively. Histology was infrequently documented, with a record of adenocarcinoma for 5.9% of patients, signet ring carcinoma for 0.8% of patients and missing information for 93.3%. Compared to those who received combination therapy, the monotherapy subgroup was significantly older (67.7 vs. 63.4 years; P = 0.0006).

Patients had been diagnosed with gastric or GEJ cancer for an average of 14.7 months (± 14.7) at the index date, with a mean of 2.1 months (± 2.6) between their prior therapy and the start of ramucirumab treatment (Table 1). Most

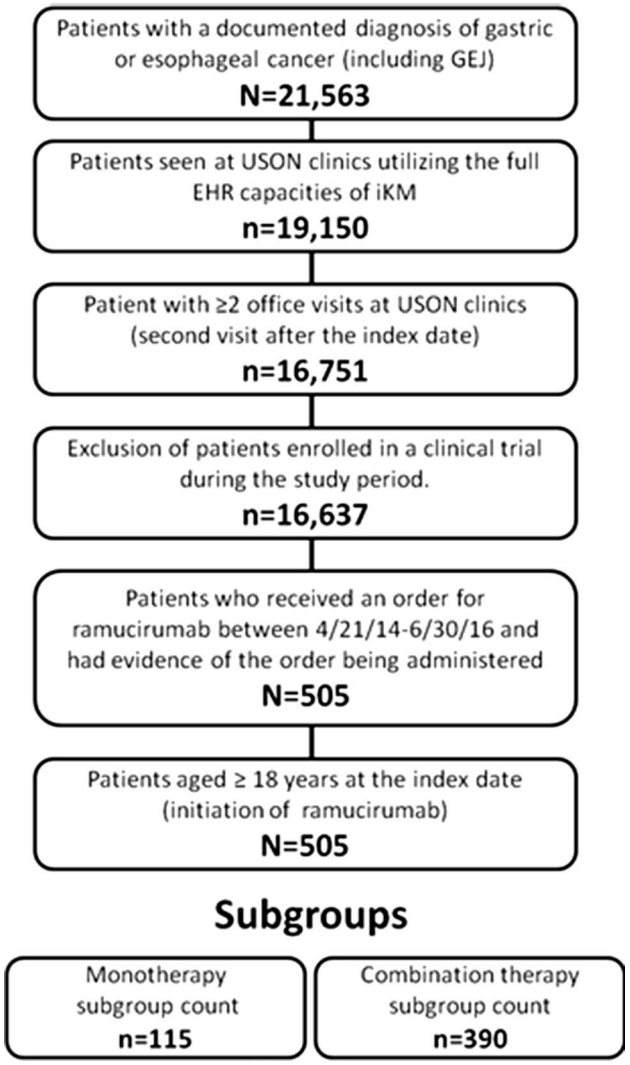


Fig. 1 CONSORT Diagram

patients (56.4%) were diagnosed with Stage IV disease and did not have a prior cancer diagnosis documented in the EHR (89.3%). Prior to starting treatment with ramucirumab, approximately 85% of patients had received prior lines of therapy. On average, patients received 2.4 (±0.8) agents in the LOT prior to the ramucirumab-containing regimen (median 2; IQR 2, 3).

Compared to patients in the combination therapy subgroup, the duration between diagnosis and ramucirumab initiation was approximately 3 months longer for those who receivedmonotherapy (mean 16.9 [± 15.8] vs. 14.1 [14.3] months; $P = 0.0318$; Table 1). A significantly higher number of patients who received ramucirumab in combination received prior therapy compared to the monotherapy subgroup (88.0 vs. 78.3% with prior therapies; $P = 0.009$). Furthermore, a difference of prior regimens was observed between the treatment groups. A higher use of irinotecan-, anthracycline-, platinum- and fluoropyrimidine-containing regimens were observed in the combination subgroup compared to patients receiving monotherapy ($P = 0.0281$, $P = 0.0232$, $P < 0.0001$ and $P < 0.0001$, respectively).

Treatment patterns

The majority (80.6%) of patients began ramucirumab treatment in the second-line setting (Table 2). Approximately 70% of patients did not receive a subsequent treatment following discontinuation of ramucirumab. Ramucirumab dose modifications occurred among 14 (2.8%) patients; 12 (3.1%) who received combination therapy and 2 (1.7%) who received monotherapy. A significantly higher proportion of monotherapy patients initiated ramucirumab in the third-line setting or beyond, than those who received ramucirumab in combination (38.3 vs. 8.2%, respectively; $P < 0.0001$). While most patients (53.8%) received monotherapy following the approval of ramucirumab as a single agent (April 2014–November 2014), only 11.8% of patients received monotherapy after the FDA approval of ramucirumab plus paclitaxel in November 2014 (Table 1). Throughout the study period, 5 patients switched from ramucirumab monotherapy to combination therapy, while 4 switched from combination therapy to monotherapy.

Clinical outcomes

The mean overall follow-up time from the index diagnosis to the last contact date, end of study period or date of death, whichever came first, was 11.1 months (± 6.4; Table 2). The mean duration of follow-up was significantly greater among patients who received combination therapy compared to those who received monotherapy (11.8 [± 6.3] vs. 8.8 [± 6.3] months; $P < 0.0001$).

Among patients who received ramucirumab in the second-line setting, the median OS durations for the monotherapy and combination therapy subgroups were 5.5 months (CI 4.3, 7.8) and 7.4 months (CI 6.6, 8.8), respectively (Fig. 2). The multivariable Cox proportional hazard model identified several predictors of OS for patients who received ramucirumab monotherapy (Table 3). Hispanic or Latino ethnicity, location of clinic (Northeast vs. South) and diarrhea were associated with a decreased risk of death. In contrast, patients with liver or peritoneal metastases had an increased risk of death than those without.

Among patients who received combination therapy, Hispanic or Latino ethnicity and body mass index (BMI; obese vs. normal) appeared to have a protective effect on OS (Table 3). Patients with an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or greater, hematological and pulmonary comorbidities, lung

Table 2 Treatment patterns of gastric or GEJ cancer patients receiving ramucirumab

Analysis variable	Total study cohort ($N = 505$)	Monotherapy subgroup ($n = 115$)	Combination therapy subgroup ($n = 390$)	P value
Regimen used for index, *n* (%)				
Ramucirumab monotherapy	115 (22.77%)			
Ramucirumab + paclitaxel	381 (75.45%)			
Ramucirumab + other combination agents	9 (1.78%)			
Switched ramucirumab regimen, *n* (%)				
Combination to monotherapy	4 (44.44%)			
Monotherapy to combination	5 (55.56%)			
First LOT with ramucirumab, *n* (%)				< 0.0001[a]
LOT1	15 (2.97%)	4 (3.48%)	11 (2.82%)	
LOT2	407 (80.59%)	65 (56.52%)	342 (87.69%)	
LOT3	58 (11.49%)	31 (26.96%)	27 (6.92%)	
LOT4+	18 (3.56%)	13 (11.30%)	5 (1.28%)	
LOT unknown	7 (1.39%)	2 (1.74%)	5 (1.28%)	
Duration of follow-up (months)				< 0.0001[b]
Mean (SD)	11.13 (6.43)	8.77 (6.28)	11.83 (6.32)	
Median (IQR)	9.86 (6.28,15.19)	6.90 (3.78,12.23)	10.64 (7.00,15.68)	
Treatment immediately following ramucirumab discontinuation, *n* (%)				
Subsequent treatment	145 (28.71%)	35 (30.44%)	110 (28.21%)	0.6423[c]
Anthracycline-containing	6 (1.19%)	1 (0.87%)	5 (1.28%)	1.000[a]
Antineoplastic-containing	9 (1.78%)	4 (3.48%)	5 (1.28%)	0.1247[a]
Trastuzumab-containing	17 (3.37%)	7 (6.09%)	10 (2.56%)	0.0657[c]
Platinum-containing	23 (4.55%)	8 (6.96%)	15 (3.85%)	0.1598[c]
Taxane-containing	23 (4.55%)	7 (6.09%)	16 (4.10%)	0.3697[c]
Irinotecan-containing	41 (8.12%)	6 (5.22%)	35 (8.97%)	0.1949[c]
Fluoropyrimidine-containing	51 (10.10%)	13 (11.30%)	38 (9.74%)	0.6254[c]
Duration of ramucirumab therapy (months)[d]				0.2378[b]
Mean (SD)	3.13 (3.23)	2.91 (3.31)	3.20 (3.21)	
Median (IQR)	2.10 (0.95,4.24)	1.87 (0.95,4.24)	2.30 (0.95,4.6)	
Number of ramucirumab infusions across all LOTs				0.6329[b]
Patients with available data	511	117	394	
Number of ramucirumab infusions	3507	791	2716	
Mean (SD)	6.86 (6.11)	6.76 (6.69)	6.89 (5.94)	
Median (IQR)	5 (3,9)	5 (3,7)	5 (3,10)	
LOT1				0.5109[b]
Patients with available data[f]	15	4	11	
Number of ramucirumab infusions	83	22	61	
Mean (SD)	5.53 (4.19)	5.50 (2.08)	5.55 (4.82)	
Median (IQR)	5 (3,8)	5.5 (4,7)	4 (2,8)	
LOT2				0.4358[b]
Patients with available data[f]	408	65	343	
Number of ramucirumab infusions	2898	500	2398	
Mean (SD)	7.10 (6.33)	7.69 (7.62)	6.99 (6.07)	
Median (IQR)	5 (3,10)	5 (4,8)	5 (3,10)	
LOT3				0.6567[b]
Patients with available data[f]	61	33	28	
Number of ramucirumab infusions	366	200	166	
Mean (SD)	6.00 (4.98)	6.06 (4.66)	5.93 (5.42)	
Median (IQR)	5 (3,6)	5 (3,6)	4.5 (2.5,6.5)	

Table 2 (continued)

Analysis variable	Total study cohort ($N = 505$)	Monotherapy subgroup ($n = 115$)	Combination therapy subgroup ($n = 390$)	P value
LOT4+				0.0190[b]
Patients with available data[f]	19	13	6	
Number of ramucirumab infusions	104	64	40	
Mean (SD)	5.47 (6.08)	4.92 (7.10)	6.67 (3.08)	
Median (IQR)	4 (2,7)	2 (2,4)	6 (4,8)	
LOT Unknown				0.0651[b]
Patients with available data[f]	8	2	6	
Number of ramucirumab infusions	56	5	51	
Mean (SD)	7 (5.29)	2.50 (0.71)	8.50 (5.32)	
Median (IQR)	4.5 (3,11.5)	2.5 (2,3)	7.5 (4,13)	
Ramucirumab dose modifications (cycles)[e]				0.2216[b]
Patients with available data	14	2	12	
Mean (SD)	3.29 (1.90)	5 (2.83)	3.00 (1.71)	
Median (IQR)	3 (2,4)	5 (3,7)	3 (2,3.5)	

[a] P value calculated based on a Fisher's Exact test

[b] P value calculated based on a Kruskal–Wallis test

[c] P value calculated based on a χ^2 test

[d] Patients with ongoing treatment were censored for overall follow-up, duration of therapy and survival estimates. In total, 100 patients were censored due to ongoing treatment. Ongoing treatment was defined as a treatment administration between 5 May 2016 and 30 June 2016

[e] Patients with ongoing treatment were not censored for calculations of the number of dose modifications or infusions

Patients may have received ramucirumab in multiple LOTs

metastases or edema during prior therapy had a higher risk of death.

Across all lines of therapy, the median time to ramucirumab discontinuation was higher among patients who received combination therapy than those who received it as monotherapy (2.8 months [CI 2.4, 3.3] and 1.9 months [CI 1.4, 2.4], respectively; Fig. 3). There were no statistically significant differences in TTTD by line of therapy in which ramucirumab was initiated. Patients in the monotherapy subgroup with metastases to the peritoneum or liver were observed have an increased risk of treatment discontinuation (Table 3). In contrast, patients of Hispanic or Latino ethnicity were found to were observed to have a longer TTTD.

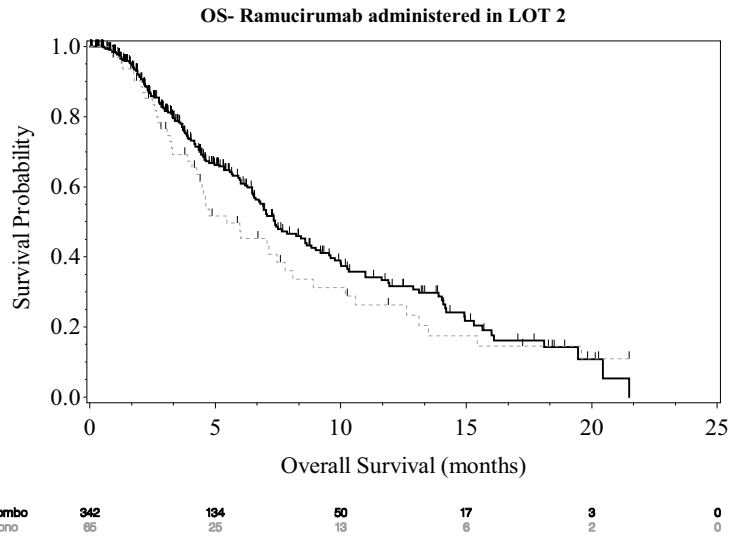
Several factors were found to be predictive of TTTD among patients treated with combination therapy (Table 3). Hispanic or Latino patients, non-White patients, as well as obese or overweight had lower risk of discontinuation. Those with hematological or pulmonary comorbidities, prior irinotecan-containing treatment and weight loss of over 10% were associated with increased risk of discontinuation.

Predictive factors associated with monotherapy versus combination therapy

Patients with prior use of a fluoropyrimidine-containing therapy were less likely to receive monotherapy (odds ratio [OR], 0.33; $P < 0.0001$; Table 4). Initiation of ramucirumab by LOT was also a predictor of receiving monotherapy, and patients with an index date in the fourth-line setting were almost ten times more likely to receive monotherapy than patients who received it in the first-line setting (OR 9.82; $P < 0.0047$). Additionally, patients with an index date in LOT3 were 4.39 ($P = 0.0244$) times more likely to receive monotherapy compared to patients with first-line ramucirumab treatment. No other factors were consistently predictive of ramucirumab use, including age, gender, race, ethnicity, BMI, stage, comorbidities, histology, metastatic sites, toxicity or prior treatment.

Discussion

Real-world evidence has increasingly become a critical component of product development in a variety of therapeutic areas including oncology. There is increasing interest among providers, patients, industry, the FDA and other



Variable	Level	# of patients	Median survival (95% CI; months)	Survival rate (95% CI)			
				6-month	9-month	12-month	18-month
Group	Monotherapy	65	5.45 (4.27,7.79)	47.44 (33.60, 60.06)	31.28 (18.80,44.55)	26.25 (14.58,39.49)	14.58 (5.73,27.34)
	Combination therapy	342	7.40 (6.60,8.84)	61.99 (55.44, 67.86)	42.56 (35.43,49.49)	31.65 (24.59,38.94)	16.11 (9.67, 24.00)

CI, confidence interval; Combo, combination therapy; Mono, monotherapy

Fig. 2 Overall survival for patients receiving ramucirumab as monotherapy and combination therapy in the second-line setting

stakeholders to leverage real-world data outside of the traditional controlled, clinical trial setting to assist in the development of new drugs or expand labeled indications. Broader clinical effectiveness and safety data could impact quality, delivery of care and outcomes by accelerating our understanding of how to optimally incorporate treatments into everyday clinical practice. Importantly, real-world outcomes can also confirm the results of clinical trial data in the community practice setting. This has become particularly relevant for oncology treatments in a variety of tumor types, including gastric and GEJ cancers and treatments such as ramucirumab.

While the safety and efficacy of ramucirumab have been demonstrated in clinical trials, there is limited evidence of its use in real-world practice. To the best of our knowledge, this is the first study to examine patient characteristics, treatment patterns and clinical outcomes of ramucirumab for gastric or GEJ cancer in a community oncology setting. This information provides critical insight into providers' decision-making processes and, consequently, how ramucirumab is being used in real-world clinical practice. Moreover, this is the first study to demonstrate that clinical outcomes of patients receiving ramucirumab in the community oncology setting are comparable to those of patients in clinical trials.

In this study, the demographic and patient characteristics of gastric or GEJ cancer patients treated in the community setting appear to be similar to data reported in other clinical trials [8, 9]. Overall survival estimates were also consistent with trends found in ramucirumab clinical trials. Among patients who initiated ramucirumab in the second-line setting, the median OS was 5.5 and 7.4 months for monotherapy and combination patients, respectively. In comparison, Fuchs et al. [10] found a median OS of 5.2 months among patients who received ramucirumab monotherapy in the REGARD clinical trial (over 90% of this patient population represented Western countries). Likewise, Wilke et al. [9] observed a median OS of 8.5 months among patients from North America, Australia, Israel and Europe who received ramucirumab in combination with paclitaxel in the RAINBOW clinical trial.

Predictors of OS and TTTD were explored through Cox proportional hazard analyses. Hispanic ethnicity was

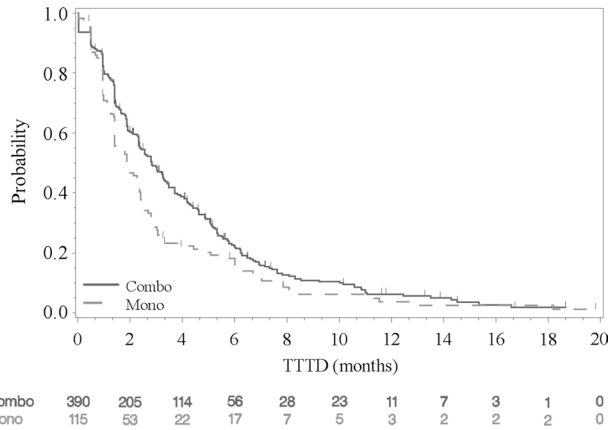
Table 3 Cox proportional hazard models for predictors of overall survival and time to treatment discontinuation

Variable	Level	Hazard ratio	95% Lower CI	95% Upper CI	Individual effect *P* value	Overall effect *P* value
Overall survival, monotherapy subgroup						
Ethnicity	Not Hispanic or Latino (ref)	–	–	–	–	0.0086
	Hispanic	0.283	0.110	0.725	0.0086	
Practice region	South (reference)	–	–	–	–	0.0071
	Midwest	1.636	0.843	3.176	0.1459	
	Northeast	0.142	0.032	0.628	0.0101	
	West	0.685	0.380	1.234	0.2075	
Liver metastasis	No (reference)	–	–	–	–	0.0523
	Yes	1.674	0.995	2.818	0.0523	
Peritoneal metastasis	No (reference)	–	–	–	–	0.0018
	Yes	2.932	1.494	5.755	0.0018	
Prior therapy toxicity: diarrhea	No (reference)	–	–	–	–	0.0541
	Yes	0.423	0.177	1.015	0.0541	
Overall survival, combination therapy subgroup						
Race	White (reference)	–	–	–	–	0.0638
	Black	0.509	0.264	0.982	0.0441	
	Other	0.501	0.231	1.086	0.0800	
Ethnicity	Not Hispanic or Latino (reference)	–	–	–	–	0.0014
	Hispanic or Latino	0.468	0.294	0.745	0.0014	
BMI status	Normal (reference)	–	–	–	–	0.0033
	Obese	0.544	0.351	0.842	0.0063	
	Overweight	1.086	0.731	1.613	0.6833	
	Underweight	1.525	0.994	2.339	0.0531	
ECOG status	0/1 (reference)	–	–	–	–	0.0018
	2 +	2.144	1.330	3.456	0.0018	
Hematological comorbidities	No (reference)	–	–	–	–	0.0063
	Yes	1.609	1.144	2.263	0.0063	
Pulmonary comorbidities	No (reference)	–	–	–	–	0.0144
	Yes	1.916	1.138	3.227	0.0144	
Lung metastasis	No (reference)	–	–	–	–	0.0797
	Yes	1.506	0.953	2.382	0.0797	
Prior fluoropyrimidine-containing treatment	No (reference)	–	–	–	–	0.0791
	Yes	1.365	0.965	1.931	0.0791	
Prior therapy toxicity: edema	No (reference)	–	–	–	–	0.0132
	Yes	2.059	1.163	3.646	0.0132	
Time to treatment discontinuation, monotherapy subgroup						
Ethnicity	Not Hispanic or Latino (reference)	–	–	–	–	0.0047
	Hispanic or Latino	0.361	0.178	0.732	0.0047	
Peritoneal metastasis	No (reference)	–	–	–	–	0.0059
	Yes	2.041	1.229	3.392	0.0059	
Liver metastasis	No (reference)	–	–	–	–	0.0283
	Yes	1.613	1.052	2.472	0.0283	
Time to treatment discontinuation, combination therapy subgroup						
Race	White (reference)	–	–	–	–	0.0468
	Black	0.791	0.481	1.299	0.3540	
	Other	0.697	0.407	1.194	0.1887	
Ethnicity	Not Hispanic or Latino (reference)	–	–	–	–	< 0.0001
	Hispanic or Latino	0.484	0.341	0.687	<0.0001	

Table 3 (continued)

Variable	Level	Hazard ratio	95% Lower CI	95% Upper CI	Individual effect *P* value	Overall effect *P* value
BMI	Normal (reference)	–	–	–	–	0.0003
	Obese	0.638	0.455	0.894	0.0090	
	Overweight	0.984	0.722	1.340	0.9177	
	Underweight	1.563	1.120	2.181	0.0086	
Weight loss	<10% (reference)	–	–	–	–	0.0383
	≥10%	2.356	1.047	5.302	0.0383	
	No weight loss vs. <10%	0.792	0.591	1.060	0.1171	0.1171
Stage	I (reference)	–	–	–	–	0.0300
	II	1.559	0.747	3.253	0.2365	
	III	1.685	0.815	3.484	0.1590	
	IV	2.197	1.100	4.390	0.0258	
Hematological comorbidities	No (reference)	–	–	–	–	0.0872
	Yes	1.277	0.965	1.691	0.0872	
Pulmonary comorbidities	No (reference)	–	–	–	–	0.0387
	Yes	1.604	1.025	2.511	0.0387	
Prior antineoplastic-containing treatment	No (reference)	–	–	–	–	0.0673
	Yes	2.607	0.934	7.278	0.0673	
Prior irinotecan-containing treatment	No (reference)	–	–	–	–	0.0313
	Yes	1.628	1.045	2.537	0.0313	
Prior taxane-containing treatment	No (reference)	–	–	–	–	0.0584
	Yes	1.295	0.991	1.693	0.0584	

BMI body mass index, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group



Variable	Level	# of patients	Median DOT (95% CI; months)	Discontinuation rate (95% CI)			
				3- month	6-month	9-month	12-month
Group	Monotherapy	115	1.87 (1.41, 2.37)	71.29 (62.75, 79.34)	81.76 (73.96, 88.38)	93.87 (87.75, 97.56)	96.32 (92.47, 99.51)
	Combination therapy	390	2.83 (2.37, 3.29)	51.29 (46.11,56.68)	77.70 (72.78, 82.28)	89.12 (84.93, 92.57)	93.81 (90.21, 96.42)

DOT, duration of therapy; CI, confidence interval; Combo, combination therapy; Mono, monotherapy; TTTD, time to treatment discontinuation

Fig. 3 Time to ramucirumab treatment discontinuation among patients receiving ramucirumab as a monotherapy or combination therapy

Table 4 Multivariable logistic regression for predictors of receiving ramucirumab as a monotherapy vs. combination therapy

Variable	Level	*N* (monotherapy subgroup)	Monotherapy ramucirumab odds ratio	95% Lower CI	95% Upper CI	Individual effect *P* value	Overall effect *P* value
Prior treatments for gastric or GEJ cancer prior to ramucirumab initiation: fluoropyrimidine	No (reference)	171 (66)	–	–	–	–	< 0.0001
	Yes	334 (49)	0.332	0.207	0.532	< 0.0001	
Line of therapy of ramucirumab initiation	1 (reference)	15 (4)	–	–	–	–	< 0.0001
	2	407 (65)	0.894	0.267	2.997	0.8565	
	3	58 (31)	4.385	1.210	15.883	0.0244	
	4+	18 (13)	9.820	2.015	47.846	0.0047	

CI confidence interval, *GEJ* gastroesophageal junction

associated with a lower risk of death and discontinuation for both the monotherapy and combination therapy subgroups. No other consistent predictors were identified in this study, although individual model results were similar to previous literature that reported performance status, liver and peritoneal metastases as prognostic factors [11, 12]. While several factors were statistically correlated with these clinical endpoints for the individual treatment subgroups (monotherapy vs. combination therapy), the clinical interpretations of these results are not definitive.

Examination of key demographic and clinical characteristics of study patients did not yield any unexpected predictors of monotherapy or combination therapy use. Instead, as anticipated, patients received ramucirumab in accordance with label indications. Following the November 2014 approval, combination therapy was received by more than 88% of all patients treated with ramucirumab. Patients previously treated with combination fluoropyrimidine- and platinum-containing regimens were more likely to receive ramucirumab monotherapy.

Expansion of the label indications during the study observation period are reflected by the differences in the proportion of patients receiving monotherapy or combination therapy. The overrepresentation of monotherapy that occurred during the April–November 2014 time period may have influenced the overall findings from this study, as both regimens were not FDA approved during this time.

These results demonstrate the real-world use of ramucirumab according to the label indications within the USON. In collaboration with the National Comprehensive Cancer Network (NCCN) and McKesson Specialty Health, the USON has developed treatment pathways to deliver evidence-based and standardized care to patients within the clinical workflow. The lack of other predictive factors associated with ramucirumab observed in this study, besides those supported by the label, suggests adherence to these treatment pathways. By decreasing variation in practice patterns and focusing on high-quality, cost-effective care, USON's treatment pathways have benefited patients' clinical outcomes.

The results of this study suggest the USON's iKM EHR provides a valuable source of real-world information about use of ramucirumab among a gastric or GEJ cancer patient population. This EHR system was designed by oncologists to advance the science of cancer care. With more than 975,000 patient records; 6800 concurrent users; and nearly 1000 provider users, the system provides insight into quality patient care and serves as a decision support tool at the point of care by providing staging and diagnosis suggestions according to criteria from the NCCN.

This was a retrospective assessment. The iKM data, despite its wealth of information about community-based oncology, is limited to clinics that are part of the USON; thus, results in this study cannot be generalized to the US population. There was the potential for documentation bias if there were omissions or errors. In addition, several key variables had a high proportion of missing structured data, which limits the conclusions that can be made.

Conclusions

Overall, the results confirm treatment pattern expectations—that is, patients who received ramucirumab monotherapy did so prior to November 2014 and tended to be more heavily pre-treated than those who received it in combination. Moreover, based on these findings, it appears that clinical outcomes in the community oncology practices are similar to clinical outcomes as observed in clinical trials. The results of this study suggest the USON's iKM EHR provides a valuable source of real-world information about use of ramucirumab among a gastric or GEJ cancer patient population. Future research can expand upon these finding to explore other factors associated with use of ramucirumab and associated clinical outcomes.

Compliance with ethical standards

Funding This study was funded Eli Lilly and Company.

Conflict of Interest Dr. Paulson has advisory board roles at Taiho, Merrimack, Bristol Myers Squibb, and Advanced Accelerator Application, as well as owns stock in Juno and Immunomedics. Dr. Hess is employed by Eli Lilly and Company. Dr. Liepa is employed by and owns stock in Eli Lilly and Company. Dr. Cui is employed by and owns stock in Eli Lilly and Company. Ms. Aguilar is employed by McKesson Specialty Health and provided research consulting services to Eli Lilly and Company. Ms. Clark is employed by McKesson Specialty Health, owns stock in McKesson and provided research consulting services to Eli Lilly and Company. Dr. Schelman is employed by and owns stock in Eli Lilly and Company.

Ethical standards Institutional Review Board and Compliance/Privacy approval was gained prior to initiation of the retrospective research. Since this project involved the analysis of existing data and records, study information was analyzed in such a manner that research participants could not be directly identified. Patient informed consent was not required due to the nature of the study design. Thus, exemption status and a waiver of informed consent were approved by The US Oncology, Inc. Institutional Review. Data was handled in compliance with HIPAA and Health Information Technology for Economic and Clinical Health (HITECH).

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