Journal of Cancer Research and Clinical Oncology (2019) 145:2365–2373
https://doi.org/10.1007/s00432-019-02971-7

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Weight loss and body mass index in advanced gastric cancer patients treated with second-line ramucirumab: a real-life multicentre study

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Received: 28 April 2019 / Accepted: 2 July 2019 / Published online: 6 July 2019

Abstract

Aims and methods This multicenter retrospective study aims to evaluate the correlations between Body Weight Loss (BWL), Body Mass Index (BMI) and clinical outcomes (ORR, PFS, and OS) of advanced gastric cancer (aGC) patients treated with second-line ramucirumab-based therapy in a "real-life" setting.

Results From December 2014 to October 2018, 101 consecutive aGC patients progressed to a first-line chemotherapy were treated with ramucirumab alone (10.9%) or in combination with paclitaxel (89.1%). Median BMI was 21.2 kg/m^2 and mBWL since first-line treatment commencement was 4.5%. Among 53 patients who underwent primary tumor resection (PTR), 73.6% experienced BWL, while 26.4% did not experience BWL ($p=0.0429$). Patients who underwent PTR had a significantly higher probability of experiencing BWL (yes vs no) [OR = 2.35 (95% CI 1.02–5.42), $p=0.0439$]. Among the 89 evaluable patients, ORR was 26.9% (95% CI 17.2–40.1). At a median follow-up of 17.3 months, mPFS was 5.4 months (95% CI 3.6–6.8) and mOS was 8.7 months (95% CI 7.3–11.9). In the multivariate analysis, only ECOG-PS and BMI were confirmed independent predictors for shorter PFS [HR = 1.69 (95% CI 1.01–2.82), $p=0.04$] [HR = 1.97 (95% CI 1.12–3.46), $p=0.01$] and OS [HR = 1.69 (95% CI 1.01–2.83), $p=0.04$] [HR = 2.08 (95% CI 1.17–3.70), $p=0.01$].

Conclusion Efficacy of ramucirumab is confirmed in this "real-life" analysis. BWL seems not to have correlations with clinical outcomes in these patients, while BMI and ECOG-PS remain major prognostic factors. A possible explanation for the lack of prognostic effect of BWL might be the proportion of patients subjected to PTR in this series (52.5%).

Keywords Advanced gastric cancer · Ramucirumab · Body mass index · Body weight loss · Prognostic factors · Second-line chemotherapy

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Introduction

Gastric cancer (GC) is the fourth most common cancer and the second leading cause of cancer-related mortality (Ferro et al. 2014). Surgery remains the only curative approach and perioperative treatments have improved the prognosis of resectable disease (Macdonald et al. 2001; Ychou et al. 2011). Despite this, less than 30% of localized GC patients are cured and most of them relapse after a prior curative surgery or present a metastatic disease at diagnosis (Van Cutsem et al. 2016). Standard first-line treatment comprehends a combination of fluoropyrimidines and a platinum-containing regimen (Cunningham et al. 2008; Janmaat et al. 2017), while a triplet including an anthracycline or a taxane is restricted to locally advanced disease or carefully selected patients with distant metastases (Al-Batran et al. 2016; Shah et al. 2015; Cortellini et al. 2018). The addition of trastuzumab to chemotherapy in HER2-positive disease prolonged overall survival versus chemotherapy alone (Bang et al. 2010).

Ramucirumab is a human IgG1 monoclonal antibody that selectively targets vascular endothelial growth factor receptor (VEGFR)-2 and was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) based on two positive randomized, double-blind, placebo-controlled phase III trials (Fuchs et al. 2014; Wilke et al. 2014).

Western (Paulson et al. 2018; Di Bartolomeo et al. 2018) and Eastern (Matsumoto et al. 2018; Jung et al. 2018; Murahashi et al. 2018) Expanded Access Programs (EAP) confirmed the safety and the efficacy of Ramucirumab with or without paclitaxel as second-line treatment of inoperable locally advanced or metastatic gastroesophageal junction or gastric tumors in the "real-life".

Pre- and/or post-operative body weight loss (BWL) and body mass index (BMI) have been widely investigated as prognostic (Kubo et al. 2016; Komatsu et al. 2018; Moriwaki et al. 2003; Lee et al. 2016; Lin et al. 2013; Jun et al. 2016; Kulig et al. 2010; Ejaz et al. 2015; Lee et al. 2012) or predictive (Aoyama et al. 2017) factors in early gastric cancer after curative gastrectomy, with controversial results.

BWL and BMI seem to have a prognostic role for advanced gastric cancer (aGC) patients with peritoneal dissemination (Chen et al. 2017) and in general for all aGC patients treated with a first-line chemotherapy (Takayoshi et al. 2017; Ock et al. 2016).

Against this background we conducted a "real life" study of aGC patients, treated with second-line ramucirumab-based therapy. The aims of this study were to further confirm clinical efficacy and safety of ramucirumab-based second-line treatment in a "real life" setting and to evaluate the relationships between BMI, BWL and clinical outcomes in this setting of patients.

Materials and methods

This retrospective analysis evaluated consecutive aGC patients, treated with ramucirumab, alone or combined with paclitaxel, at medical oncology department of 7 Italian institutions (Supplementary file 1), from December 2014 to October 2018. Patients were eligible if they had histologically confirmed diagnosis of measurable aGC and provided an informed consent.

The measured clinical outcomes were objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). ORR was defined as the portion of patients experiencing an objective response (complete response, CR, or partial response, PR) as best response. Responses to treatment were evaluated according to RECIST criteria (version 1.1), according to clinicians' evaluation in their clinical practice (Eisenhauer et al. 2009). PFS was defined as the length of time from the beginning of treatment to disease progression or death resulting from any cause or to the last contact; OS as the length of time between the beginning of treatment to death resulting from any cause or to last contact. Cumulative toxicity was registered according to National Cancer Institute Common Terminology Criteria (NCI-CTC) for Adverse Events (AEs) (version 4 up to January 2018, version 5 from January 2018). Median received dose intensities (rDI) were calculated as per cycle mg/mq/week and mg/kg/week for paclitaxel and ramucirumab, respectively. Data cutoff period was January 2019. Median PFS and median OS were evaluated using the Kaplan–Meier method (Kaplan and Meier 1958). Median period of follow-up was calculated according to the reverse Kaplan–Meier method (Schemper and Smith 1997).

Weight and height were obtained from patients' medical records; BMI was calculated using the formula of weight/height^2 (kilograms per square meter) and categorized according to the World Health Organization categories: underweight, BMI < 18.5; normal, 18.5 ≤ BMI ≤ 24.9; overweight, 25 ≤ BMI ≤ 29.9; obese, BMI ≥ 30.

Baseline clinical factors used as covariates were: sex (male vs female), age (< 70 years old vs ≥ 70 years old), ECOG-PS (0 vs ≥ 1), presence of ascites (yes vs no), BMI (underweight vs non-underweight), primary tumor resection (yes vs no) and BWL since first-line treatment commencement (< the median value vs ≥ the median value); given the lack of established cutoffs for BWL in this setting, we used the median value as threshold in this study. In our opinion, BWL during first-line treatment might be considered a "nutritional surrogate factor" for second-line treatment. Moreover, in the pooled analysis of REGARD and

RAINBOW studies, BWL within the previous 3 months was considered as a baseline covariate/prognostic factor (Cox 1972).

As ramucirumab dosage is weight-based, baseline weight (at the moment of ramucirumab commencement) was also used as a continuous covariate in all the analyses, considering the possible dose-depending confounding effect on clinical outcomes.

Chi square test was used to evaluate the correlations between ORR a baseline clinical factors. To weigh the possible influence of ascites on body weight, Chi square was also used to evaluate the correlation between baseline ascites, and BMI and BWL. Cox proportional hazards regression was used to evaluate predictor variables in univariate and multivariate analysis for median PFS and median OS (Cox 1972). Only factors significant at univariate analysis were used for the multivariate analysis. Chi square test was also used to evaluate the correlation between BWL since the first-line treatment commencement (yes vs no) and surgical resection of the primary tumor (yes vs no). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the logistic regression model, to estimate the influence of the surgical resection of the primary tumor (yes vs no) on the weight loss since the first-line treatment commencement (yes vs no). All statistical analyses were performed using MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Being a retrospective study of clinical practice, this collection was not considered a clinical trial. Therefore, approval by institutional review boards was not required, although a notification was sent (normative ref. Gazzetta Ufficiale della Repubblica Italiana n. 76 of 31-3-2008). All patients provided written, informed consent to the proposed treatment option. The procedures followed were in accordance with the precepts of Good Clinical Practice and the ethical standards of the local responsible committee on human experimentation (Comitato Etico per le province di L'Aquila e Teramo).

Results

Patient characteristics

101 consecutive aGC patients progressed to a first-line chemotherapy were treated with ramucirumab as monotherapy (10.9%) or in combination with paclitaxel (89.1%). Patients and disease characteristics are summarized in Table 1.

Median BMI was 21.2 kg/m^2 (range 14.6–37.2) with 50.5% of normal weight patients and 22.8% of underweight patients. Median BWL since first-line treatment commencement was 4.5%. Among 58 patients (57.4%) who underwent primary tumor surgical resection, 39 (73.6%) experienced a BWL since the first-line treatment commencement, while 14 (26.4%) did not experience a BWL ($p=0.0429$). Logistic regression revealed that patients who underwent primary tumor surgical resection had a significantly higher probability of experiencing weight loss since the first-line treatment commencement [OR = 2.35 (95% CI 1.02–5.42), $p=0.0439$). There were no significant correlation between baseline ascites and BWL since first-line treatment commencement and BMI ($p=0.4272$ and $p=0.0862$, respectively).

Clinical outcomes analysis

Eighty-nine patients (88.1%), who underwent at least one radiological reassessment, were considered eligible for ORR analysis. In the overall population ORR was 26.9% (95% CI 17.2–40.1); as Table 2 shows, none of the variables revealed to be significant associated to ORR.

The median follow-up was 17.3 months; in the overall population median PFS was 5.4 months (95% CI 3.6–6.8; 76 progression events) and median OS was 8.7 months (95% CI 7.3–11.9; 36 censored patients). At the univariate analysis, the presence of ascites, BMI and ECOG-PS were significantly related with shorter PFS and OS, while no significant associations were found with BWL since first-line treatment commencement. At the multivariate analysis, only ECOG-PS and BMI were confirmed independent predictors for shorter PFS [HR = 1.69 (95% CI 1.01–2.82), $p=0.04$] [HR = 1.97 (95% CI 1.12–3.46), $p=0.01$] and shorter OS [HR = 1.69 (95% CI 1.01–2.83), $p=0.04$] [HR = 2.08 (95% CI 1.17–3.70), $p=0.01$] (Tables 3, 4).

Table 5 summarized all the registered AEs. No G4 toxicity was observed. Global incidence of G3 toxicity was 23.9%, mainly neutropenia (13.9%). The most frequent AEs were G1-2 neuropathy (23.8%), G1-2 fatigue (16.8%), G1-2 neutropenia (13.9%) and G1-2 anemia (13.9%). Overall, 10 patients (9.9%) experienced at least one ramucirumab-related AE, particularly G1-2 (7.9%) or G3 (2%) hypertension. There were no treatment-related deaths. Dose reductions of paclitaxel due to AEs were required for 17.8% of patients. No ramucirumab dose reduction was reported. Median rDIs of paclitaxel and ramucirumab were 60 mg/mq/week and 4 mg/kg/week, respectively.

Eleven patients (10.9%) underwent a "maintenance" treatment with ramucirumab alone after an induction therapy with paclitaxel, discontinued due to cumulative haematological or neurological toxicity. Reasons for treatment discontinuation were: disease progression (86.1%), toxicity (1%) or patient refusal (1%). Thirty-eight patients (37.6%) underwent a third-line treatment: 23 patients (22.8%) received an irinotecan-based mono- or doublet therapy, 1 patient (1%) received a taxane-based mono- or doublet therapy, 6 patients (6%) received a fluoropyrimidine-based monotherapy, 5

Table 1 Patient characteristics

Characteristic	No. (%)
Overall	101
Age	
Median	68
Range	38–83
Elderly (≥ 70)	42 (41.6)
Sex	
Male	60 (59.4)
Female	41 (40.6)
ECOG-PS	
0	57 (56.4)
1	39 (38.6)
2	5 (5)
Site	
Gastric body/fundus	39 (38.6)
Antropylorus	22 (21.8)
Gastro-oesophageal junction/cardia	29 (28.7)
NA	11 (10.9)
Histology (Lauren classification)	
Intestinal	54 (53.5)
Diffuse	31 (30.7)
Other/NA	16 (15.8)
Grading	
G1–G2	35 (34.7)
G3	50 (49.5)
NA	16 (15.8)
HER2 status	
Negative	84 (83.2)
Positive	14 (13.9)
NA	3 (3)
Stage at diagnosis	
I–II	6 (6)
III	29 (28.7)
IV	66 (65.3)
No. of metastatic sites	
< 2	59 (58.4)
≥ 2	42 (41.6)
Locations of metastases	
Lymph nodes	53 (52.5)
Liver	39 (38.6)
Peritoneum or ovary	39 (38.6)
Lung	14 (13.9)
Bone	5 (5)
Ascites	
Yes—high level, symptomatic	15 (14.9)
Not—low level, asymptomatic	86 (85.1)
Primary tumor resection	
Total gastrectomy	31 (30.7)
Subtotal gastrectomy	22 (21.8)
Not	48 (47.5)
Previous regimen	
Mono therapy	3 (3)
Doublet therapy	49 (48.5)
Triplet therapy	35 (34.7)
Combination with trastuzumab	14 (13.9)
Previous setting	
Adjuvant treatment	18 (17.8)
First-line treatment	83 (82.2)
Treatment	
Paclitaxel/ramucirumab	90 (89.1)
Ramucirumab	11 (10.9)
Time to progression on first-line (adjuvant) treatment	
< 6 months	49 (48.5)
> 6 months	52 (51.5)
BMI (kg/m^2)	
Median (range)	21.2 (14.6–37.2)
Underweight (BMI ≤ 18.5)	23 (22.8)
Normal weight (BMI 18.5 < BMI ≤ 24.9)	51 (50.5)
Overweight (25 < BMI ≤ 29.9)	23 (22.8)
Obese (BMI ≥ 30)	4 (3.9)
Weight loss since first-line commencement	
Yes	65 (64.4)
No	36 (35.6)
Median (%) (range)	4.5 (− 37.3– + 13.3%)

Table 2 Activity analysis

Variable	Response/ratio	ORR (95% CI)	*p* value
Overall	24/89	26.9 (17.2–40.1)	–
Sex			
Female	11/35	31.4 (15.7–56.2)	0.4476
Male	13/54	24.1 (12.8–41.1)	
Age			
Elderly	12/38	31.5 (16.3–55.2)	0.4000
Non-elderly	12/51	23.5 (12.2–41.1)	
Ascites			
Yes	2/13	15.3 (1.8–55.5)	0.3113
No	22/76	28.9 (18.1–43.8)	
BMI			
Non-underweight	20/73	27.4 (16.7–42.3)	0.8457
Underweight	4/16	25 (6.8–64)	
ECOG-PS			
0	17/52	32.7 (19–52.3)	0.1513
≥ 1	7/30	23.3 (9.3–48.1)	
Weight loss ≥ 4.5%			
Yes	12/45	26.7 (13.8–46.6)	0.9489
No	12/44	27.2 (14.1–47.6)	
Primary tumor resection			
Yes	14/34	41.2 (22.5–69.1)	0.6148
No	10/41	24.4 (11.7–44.8)	

Table 3 Univariate and multivariate analysis for PFS

Variable (comparator)	Progression free survival			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Sex (male vs female)	1.13 (0.71–1.81)	0.5912	–	–
Age (elderly vs non-elderly)	0.76 (0.48–1.22)	0.2583	–	–
Ascites (yes vs no)	2.66 (1.41–5.03)	0.0024	1.73 (0.86–3.52)	0.1236
BMI (underweight vs non-underweight)	2.17 (1.27–3.71)	0.0418	1.97 (1.12–3.46)	0.0175
ECOG-PS (≥ 1 vs 0)	1.89 (1.18–3.04)	0.0080	1.69 (1.01–2.82)	0.0446
Weight (continuous)	0.98 (0.97–1.01)	0.0665	–	–
BWL ≥ 4.5% (yes vs no)	0.94 (0.61–1.48)	0.7984	–	–
Primary tumor resection (no vs yes)	1.25 (0.79–1.98)	0.3371	–	–

Table 4 Univariate and multivariate analysis for OS

Variable (comparator)	Overall survival			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Sex (male vs female)	1.31 (0.79–2.16)	0.2963	–	–
Age (elderly vs non-elderly)	1.09 (0.66–1.81)	0.7282	–	–
Ascites (yes vs no)	2.16 (1.12–4.22)	0.0239	1.72 (0.85–3.47)	0.1300
BMI (underweight vs non-underweight)	2.21 (1.24–3.89)	0.0065	2.08 (1.17–3.70)	0.0131
ECOG-PS (≥ 1 vs 0)	1.92 (1.17–3.15)	0.0096	1.69 (1.01–2.83)	0.0457
Weight (continuous)	0.99 (0.7– 1.01)	0.2941		
Weight loss ≥ 4.5% (yes vs no)	0.77 (0.47–1.27)	0.3114	–	–
Primary tumor resection (no vs yes)	1.51 (0.93–2.48)	0.1007	–	–

Table 5 Adverse events

CTCAE grade	101 patients—*N* (%)			
	G1	G2	G3	G4
Nausea (%)	7 (6.9)	4 (4)	–	–
Vomiting (%)	3 (3)	–	–	–
Diarrhea (%)	9 (8.9)	3 (3)	–	–
Stomatitis/mucositis (%)	3 (3)	1 (1)	–	–
Anorexia (%)	2 (2)	5 (5)	–	–
Fatigue (%)	10 (9.9)	7 (6.9)	2 (2)	–
Peripheral sensory neuropathy (%)	14 (13.9)	10 (9.9)	2 (2)	–
Hypertransaminasemia (%)	3 (3)	1 (1)	–	–
Proteinuria (%)	2 (2)	–	–	–
Hypertension (%)	6 (5.9)	2 (2)	2 (2)	–
Leukopenia (%)	5 (5)	5 (5)	2 (2)	–
Neutropenia (%)	5 (5)	9 (8.9)	14 (13.9)	–
Anemia (%)	9 (8)	6 (5.9)	2 (2)	–
Thrombocytopenia (%)	3 (3)	1 (1)	1 (1)	–

patients (5%) received trifluridine-tipiracil and 3 patients (3%) received other regimens. Fourteen patients (13.9%) underwent a fourth-line treatment: 10 patients (10%) received an irinotecan-based mono- or doublet therapy, 3 patients (3%) received a platinum-based mono- or doublet therapy and 1 patient (1%) received an anthracycline-based regimen.

Discussion

RAINBOW and REGARD trials established ramucirumab, with or without paclitaxel, as a relevant option for second-line treatment of aGC patients (Fuchs et al. 2014; Wilke et al. 2014). Safety and efficacy data of ramucirumab were confirmed outside of clinical trials in retrospective analysis of both Western and Eastern EAP populations (Paulson et al. 2018; Di Bartolomeo et al. 2018; Matsumoto et al. 2018; Jung et al. 2018; Murahashi et al. 2018).

Our cohort of patients is a true representation of clinical practice; the median age (68 years) was higher than what was reported in the above-mentioned studies (60–62 years) (Fuchs et al. 2014; Wilke et al. 2014; Paulson et al. 2018;

Table 6 Comparison with phase III and real-world studies

Study	Regard (Fuchs et al. 2014)	Rainbow (Wilke et al. 2014)	RAMoss (Di Bartolomeo et al. 2018 Apr)	KCSG (Jung et al. 2018 Sep)	Present study
Type	Phase III randomized study	Phase III randomized study	EAP	EAP	Retrospective study
Treatment (only RAM-based arm)	RAM	PTX-RAM	PTX-RAM/RAM	PTX-RAM/RAM	PTX-RAM/RAM
Population	West/east	West/east	West	East	West
Number of patients	238	330	167	265	101
Median age (years)	60	61	61	57-62	68
PS-ECOG 0-1-2 (%)	28-72-0	35-65-0	53.9-39.5-11.3	21.8-74.8-3.4	56.4-38.6-6.5
Diffuse histology (%)	40	35	25.7	–	30.7
G3 (%)	–	56	57.4	59.2	49.5
HER2 + status (%)	< 5%	< 5%	26.9	12.1	13.9
PTR (%)	27	37	44.9	48.7	52.5
Peritoneal metastases (%)	27	49	43.2	NE	38.6
Ascites (%)	–	–	NV	27.5	14.9
mOS (mo)	5.2	9.6	8	8.6–6.4	8.7
mPFS (mo)	2.1	4.4	4.3	3.8–1.8	5.4
ORR (%)	3	28	20.2	16.6–5.4	26.9
G1–2 neutropenia (%)	–	14	14.9	20.5–13.5	13.9
G1–2 neurotoxicity (%)	–	38	26.3	37.5–24.3	23.8
G1–2 fatigue (%)	–	45	27.5	35.8–29.7	16.8
G1–2 hypertension (%)	8	10	3.5	13.6–7.4	7.9
G3–4 neutropenia (%) (included febrile neutropenia)	–	41	5.4	53.9–10.8	13.9
G3–G4 neurotoxicity (%)	–	8	–	4.4–0	2
G3–4 fatigue (%)	–	12	0.6	3–2.7	2
G3–4 hypertension (%)	8	14	0.6	1.2–3.7	2

EAP expanded access programm, *RAM* ramucirumab, *RAM-PTX* ramucirumab-paclitaxel, *PTR* primary tumor resection

Di Bartolomeo et al. 2018; Matsumoto et al. 2018; Jung et al. 2018; Murahashi et al. 2018), and prognostically disadvantaged categories of patients are well represented (with poorly differentiated/diffuse histotype/HER-2 tumors, with unresected primary tumor, with peritoneal involvement or symptomatic ascites, patients rapidly progressed to first-line treatment). Nevertheless our efficacy results seem aligned to what was previously reported in the REGARD and RAINBOW trials as well as in the EAP studies, with a more than acceptable safety profile (Table 6).

BMI and BWL are both known as potential prognostic factors in curative and first-line settings (Murahashi et al. 2018; Kubo et al. 2016; Komatsu et al. 2018; Moriwaki et al. 2003; Lee et al. 2016; Lin et al. 2013; Jun et al. 2016; Kulig et al. 2010; Ejaz et al. 2015; Aoyama et al. 2017; Chen et al. 2017; Takayoshi et al. 2017), but less studied in second-line setting, especially in patients treated with ramucirumab-based therapy. In a retrospective series of approximately 2000 Asian patients, BWL and perioperative BMI proved to be important prognostic survival factors (Park et al. 2018). Baseline body weight (with the median value as threshold), and BWL > 10% within the previous 3 months have been already investigated in the pooled analysis of the RAINBOW and REGARD studies (Fuchs et al. 2017). Indeed, at the univariate analysis they were both significantly related to a shorter OS (but were not included in the multivariate model), but baseline BMI was not evaluated (Fuchs et al. 2017). Unexpectedly, in our cohort BWL and weight were not related to PFS nor OS, and the BMI (underweight vs non-underweight) remained the major surrogate of the

nutritional status (and prognostic parameter). As the BMI, also ECOG-PS (≥ 1 vs 0) proved to be predictive of PFS and OS, while none of the other covariates seemed to be predictive of survival.

A possible explanation for the lack of prognostic effect of BWL might be the proportion of patients subjected to PTR in this series (52.5%). Indeed in this population we found a significant association between BWL and PTR, and patients who underwent PTR had a significantly higher probability of experiencing BWL, as logistic regression analysis evidenced.

Most patients undergoing curative gastrectomy experience BWL due to reduced food intake after surgery, and postoperative body weight is maintained throughout the entire life after surgery (Kim et al. 2017). In the metastatic setting the potential prognostic disadvantage related to BWL could be compensated by the advantage linked to the relief of symptoms such as obstruction, perforation or bleeding (Izuishi and Mori 2016) as well as to the increasing evidence of prognostic advantage of PTR in overall survival (Hartgrink et al. 2002; Ebinger et al. 2016), although this last factor has not been confirmed as such in this series. Moreover, looking to the hazard ratios of BWL and PTR for both PFS and OS, we can noticed that they have an opposite sense; despite the absence of statistical significance we can speculate that being significantly related to each other, they might oppositely affect clinical outcomes.

Among limitations of this study we must recognize the retrospective nature, which expose to selection biases, the lack of centralized data review and the sample size, which was considerable for aGC second-line setting, but might have been insufficient for proper prognostic considerations.

Conclusion

This analysis confirms the safety and the efficacy of ramucirumab in a "real life" setting. BWL since first-line treatment beginning seems not to have correlations with clinical outcomes in these patients, while BMI and ECOG-PS remain major prognostic factors at the beginning of a second-line ramucirumab-based treatment.

Acknowledgements This work was supported by the Consorzio Interuniversitario Nazionale per la Bio-Oncologia (CINBO).

Authors' contributions All authors contributed to the publication according to the ICMJE guidelines for the authorship. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work is appropriately investigated and resolved.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials The data sets used during the present study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest Dr Alessio Cortellini received grants as speaker by MSD, Astra-Zeneca and Boehringer Ingelheim, gran consultancies by BMS, Roche, Novartis, Istituto Gentili and Ipsen.

Informed consent All patients provided informed consent to participate in this observational non-interventional study.

Ethical statement The procedures followed were in accordance with the precepts of Good Clinical Practice and the Declaration of Helsinki. The study was conducted following the rules of the local bioethical committee competent on human experimentation (Comitato etico per le province di L'Aquila e Teramo).

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