Original article

THE IMPACT OF CLINICAL FEATURES ON EFFICACY AND SAFETY OF THE COMBINATION OF RAMUCIRUMAB AND PACLITAXEL FOR METASTATIC GASTRO-OESOPHAGEAL JUNCTION/ GASTRIC CANCER: DATA OF A REAL LIFE EXPERIENCE IN AN ITALIAN INSTITUTION.

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Abstract: The RAINBOW Phase III study established the efficacy of the combination of paclitaxel and ramucirumab, a monoclonal antibody targeting VEGF receptor-2 (VEGF-R2), as second-line therapy. We retrospectively analyzed the data of patients treated with ramucirumab plus paclitaxel at our Institution to evaluate the impact of clinical heterogeneous figures on the efficacy and safety of this combination paclitaxel/ramucirumab in a real- life cohort of patients. After a median follow-up of 10.74 months, the median progression-free survival (PFS) was 5.8 months (95% CI: 3.04 - 5,63). Disease control rate (DCR) was 61% and the median duration of response (DOR) was 5.8 months. Median overall survival (OS) was 8.3 months. A trend toward better outcome was observed in HER2 positive patients. In multivariate analysis, nutritional status (p = 0.0001) and number of metastatic sites (p = 0.0266) resulted significantly related with longer PFS. Our analysis confirmed the efficacy and safety of the combination of ramucirumab with paclitaxel also in the real-life practice and the median PFS is significantly longer than that reported for Western population in previous studies. Subgroup analysis confirms the key-role of nutritional status as prognostic factor and suggests a possible interaction between EGF and angiogenesis pathways that deserves further investigations.

Keywords: gastric cancer; ramucirumab; paclitaxel; second line therapy; vascular endothelial growth factor receptor 2; targeted therapy; nutrition

1. Introduction

Gastric cancer is a leading cause of cancer mortality worldwide, ranking the fourth in Italy, where it was responsible for 9557 deaths in 2014 [1, 2]. In 2017, 12800 new diagnoses of gastro-oesophageal junction and gastric cancer have been estimated in Italy; most patients are diagnosed in advanced/metastatic stage or develop a relapse after surgery with curative intent. A combination of platinum compounds (oxaliplatin and cisplatin) and fluoropyrimidines (fluorouracil, capecitabine, and S1) is generally considered as the standard-of-care for first line treatment; targeted therapy is limited to HER-2 positive disease that is treated with trastuzumab, in addition to chemotherapy [3]. For patient who progressed after first-line CT and have good clinical conditions, the association of paclitaxel and ramucirumab, a monoclonal antibody targeting VEGF receptor-2 (VEGF-R2), is currently the preferred therapy, based on the result of the RAINBOW trial that showed significant survival benefits in comparison to chemotherapy alone. Moreover, in the REGARD trial ramucirumab alone has produced a statistically significant improvement of life expectancy over placebo in second line setting, proving to be a useful option for patient who are unfit for chemotherapy [4,5].

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On the basis of this background, we report our experience with the combination of PACLITAXEL and RAMUCIRUMAB in pre-treated metastatic gastric (mGC) ad gastro-oesophageal cancer (mGOC), in order to assess the safety and efficacy of this regimen in the daily clinical practice.

2. Results

2.1 Patients' characteristics

All patients received at least 1 cycle (28 days) of the drug combination and have at least a 2 months follow-up. The longest treatment period was 15 cycles and it is still ongoing. The characteristics of patients and their tumors are summarized in table 1. The primary tumor site was stomach in 34 patients (72,3 %) or gastro-oesophageal junction in 13 patients (27,7 %), respectively. The histology subtype according to Lauren classification was intestinal or adenocarcinoma NOS in 33 cases and diffuse with signet ring cells in 14 cases. Primary tumor was previously resected in twenty-five patients, including five cases of palliative surgery due to bleeding, and twenty cases of radical surgery, associated with neoadjuvant/perioperative therapy (5 cases), intraoperative HIPEC (1 case) or adjuvant therapy (10 cases). Forty-four patients were previously treated with platinum and fluoropyrimidine doublets, including twelve cases of HER-2 positive tumors who received a combination regimen with trastuzumab according to the approved recommendations; only three patients had received triplet regimens with platinum, fluoropyrimidine and anthracycline. No patient was previously exposed to taxanes, whereas seven patients were treated with paclitaxel and ramucirumab after failure of a previous second-line therapy with FOLFIRI. Several patients had poor prognostic characteristics: twenty-one patients (44.6%) experienced disease recurrence during adjuvant therapy (2) or had disease progression within 6 months from the start of first-line therapy (19); 20 patients (42,7 %) had peritoneal carcinosis and 12 patients (25,5%) had at least three metastatic sites, including brain metastases (2 cases); 1/3 of patients were underweight as expression of nutritional deficiency and low meal intake. After failure of therapy with paclitaxel and ramucirumab, thirteen patients received a subsequent line of therapy, mainly an irinotecan-based regimen (10 cases).

Table 1. Patients' characteristics

Age (range): median 56 years (32-78)	**Site of primary tumour**
<65 33 (70,2 %)	Gastric adenocarcinoma 34 (72,3 %)
≥65 14 (19,8 %)	GEJ adenocarcinoma 13 (27,7 %)
Sex	**ECOG performance status**
Male 29 (61,7 %) (median age 59 years; 44-76)	ECOG 0 29 (61,7 %)
Female 18 (38,3 %) (median age 50 years; 32-78)	ECOG 1 18 (38,3 %)
Histological subtype (Lauren classification)	**HER-2 status**
Intestinal/adenocarcinoma NAS 33 (70,2 %)	Positive 12 (25,5 %)
Diffuse 14 (19,8 %)	Negative 35 (74,5 %)
Number of metastatic sites	**Peritoneal metastases**
0-2 35 (74,5 %)	YES 20 (42,5 %)
≥3 12 (25,5 %)	NO 27 (57,5 %)
TTP on previous platinum-based therapy	**Previous platinum exposition**
<6 months 21 (44,6 %)	Oxaliplaltin 12 (25,5 %)
≥6 months 26 (55,4 %)	Cisplatin 35 (74,5 %)
Previous treatment with FOLFIRI	**Subsequent line with FOLFIRI**
YES 7 (14,9 %)	YES 10 (21,3 %)
NO 40 (85,1 %)	NO 37 (78,7 %)
Previous surgery for gastric cancer	**Nutritional status**
YES 25 (53,1 %)	Normal weight (BMI ≥ 15) 34 (72,4 %)
NO 22 (46,9 %)	Underweight (BMI <15) 13 (27,6 %)

2.2 Efficacy analysis

As of data cuto (March 31, 2018), after a median follow-up of 10.74 months, 31 patients have experienced disease progression, while 16 patients are still on treatment. Median PFS was 5.4 months (95% CI: 3.04 – 5.63) (fig. 1). Objective radiological response to treatment is reported in table 2. Among forty-one evaluable patients, we observed ten partial responses, including two complete responses according to mRECIST criteria, and fifteen stable disease, accounting for a disease control rate of 61%; three partial responses and one stable disease were achieved in patients who had previously received two lines of therapy. The median duration of response was 5.8 months (95% CI: 5.02 – 6.80).

Table 2. Best overall response

Response (41 patients)	N (%)
Complete response	0 (0%)
Partial response	10 (24.4%)
Stable disease	15 (36,6%)
Disease control rate (CR + PR + SD)	25 (61 %)
Progressive disease	16 (39%)

At the time of the analysis, 23 patients had died. Early deaths (within 30 days of last treatment) were observed in three patients and were related to clinical disease progression. The median OS was 8.3 months (95% CI: 6.2 – 11.0) (fig. 1).

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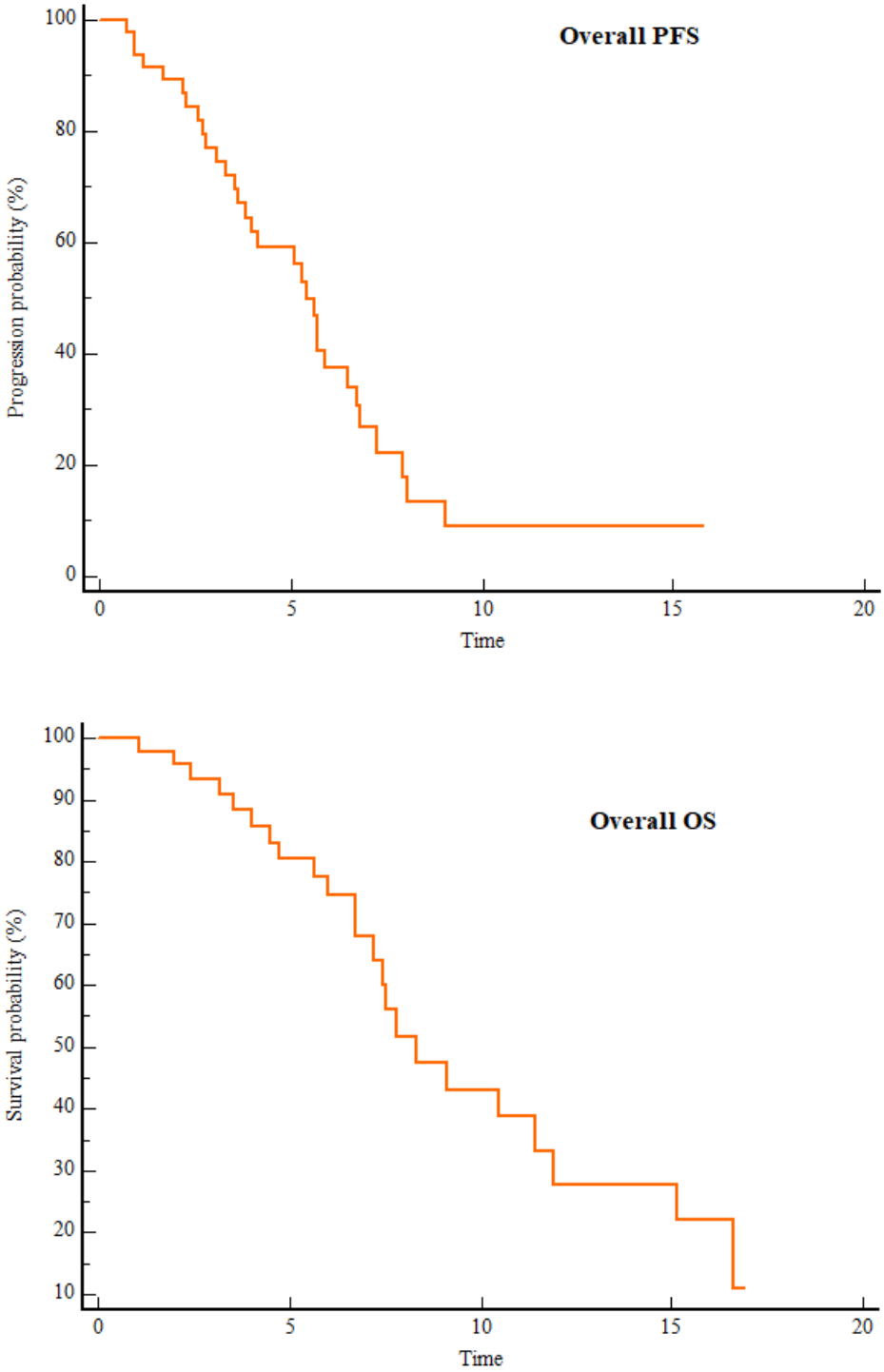

Figure 1. Kaplan-Maier curves for PFS and OS.

Results of the univariate analyses for clinical characteristics are summarized in table 3. Despite no statistically significant difference emerged, it is interesting to note that the better outcomes, including longer PFS (median PFS 6.8 months) and higher disease control rate (8 out of 9 evaluable patients, accounting for RR 44% and DCR 89%), have been recorded in HER-2 positive patients, that also resulted the subgroup with higher number of ongoing treatments (6/12, 50%) and the shortest median time of follow-up (8.64 months). Neither factors associated with previous treatments (TTP after first line, platinum compound used,

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exposure to irinotecan, gastrectomy) nor the presence of peritoneal metastases had a significant impact on survival outcomes.

Table 3. Subgroups analysis for PFS and OS

	PFS median HR (CI 95%)	**OS median HR (CI 95%)**
Age (< 65 vs ≥ 65)	5.27 mo. vs 7.23 mo. HR 0.57 (0.23 – 1.41) p = 0.2088	7.8 mo. vs 10.45 mo. HR 0.57 (0.19 – 1.69) p= 0.3192
Gender (Male vs Female)	5.7 mo. vs 3.83 mo. HR 1.14 (0.55 – 2.38) p = 0.7151	7.8 mo. vs 8.3 mo HR 1.00 (0.2 – 2. 36) p = 0.9958
Histology (diffuse vs intestinal/ADC NAS)	4.62 mo. vs 5.6 mo. HR 1.02 (0.50 - 2.10) p = 0.9377	7.8 mo. vs 8.3 mo. HR 0.91 (0.40 – 2.09) p = 0.8362
HER 2 status (positive vs negative)	6.8 mo. vs 5.27 mo. HR 0.51 (0.25 – 1.19) p = 0.1341	10.25 vs 7.8 mo. HR 0.65 (0.25 – 1.78) p = 0.4364
Site of primary tumor (EGJ vs stomach)	5.7 mo. vs 5.27 mo. HR 1.15 (0.51 – 2.59) p =0.7237	7.8 mo. vs. 11.4 mo. HR 1.93 (0.65 – 5.7) p = 0.2350
Previous gastrectomy (NO vs YES)	4.13 mo. vs 5.9 mo. HR 0.55 (0.27 – 1.11) p = 0.1013	6.73 mo. vs 11.40 mo. HR 0.50 (0.21 – 1.17) p = 0.1132
Metastatic sites (1-2 vs ≥ 3)	***5.7 mo. vs 2.77 mo. HR 0.42 (0.20 – 0.92) p = 0.0266***	***10.45 mo. vs 5.63 mo. HR 0.39 (0.10 – 0.83) p = 0.0212***
Peritoneal metastases (YES vs NO)	3.83 mo. vs 5.9 mo. HR 0.56 (0.27 – 1.15) p = 0.1184	7.5 mo. vs 10.45 mo. HR 2.39 (1.00 – 5.7) p = 0.0490
PS ECOG (0 vs 1)	5.7 mo. vs 3.97 mo. HR 0.60 (0.29 - 1.23) p = 0.1584	***11.4 mo. vs 6.0 mo. HR 0.29 (HR 0.08 – 0.56) P = 0.0016***
Nutritional status (BMI ≥ 15 vs BMI < 15)	***6.5 mo. vs 2.57 mo. HR 0.17 (0.07 – 0.41) p = 0.0001***	***10.45 mo. 4.73 mo. HR 0.29 (0.07 – 0.54) p = 0.0016***
PFS with first line CT (> 6 mo. vs < 6 mo.)	5.67 mo. vs. 3.46 mo.	11.4 mo. vs 6.7 mo.

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	HR 0.49 (0.21 – 0.97) p = 0.0431	HR 0.36 (0.14 – 0.79) p = 0.0126
Previous platinum-based CT (OXA vs CDDP)	3.63 mo. vs 5.9 mo. HR 0.36 (1.40 – 10.23) p = 0.0114	7.5 mo. vs 9.1 mo. HR 1.38 (0.54 – 3.82) p = 0.4586
Previous FOLFIRI treatment (NO vs YES)	5.27 mo. vs 7.9 mo. HR 0.51 (0.17 – 1.47) p = 0.2191	7.8 mo. vs 11.4 mo. HR 2.11 (0.59 – 5.54) p = 0.2904

In the multivariable stepwise Cox regression analysis only three factors resulted associated with poor prognosis: high number of metastatic sites (more than two), BMI < 15 and PS ECOG of 1 (table 4). Patients with BMI ≥15 experienced a longer PFS (6.5 months) and OS (10.45 months) than patients with BMI < 15 (2.57 months and 5.63 months, respectively); conversely, PS ECOG status showed a significant association only with OS. The survival curves of in relation to BMI are shown in the figure 2.

Table 4. Multivariable Cox regression analysis of PFS and OS for prognostic factors

	PFS		**OS**	
	HR (95%CI) for progression	**p value**	**HR (95% CI) for mortality**	**p value**
BMI < 15	HR 5.98 (2.52 - 14.17)	< 0.0001	5.38 (2.02 - 14.31)	< 0.0001
≥ 3 metastatic sites	HR 2.48 (1.15 – 5.3)	< 0.0001	HR 2.94 (1.09 – 7.95)	0.0277
PS ECOG 1	*HR 0.96*	*0.92*	HR 3.30 (1.27 – 8.57)	< 0.0001

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Figure 2a. Progression free survival in relation to BMI

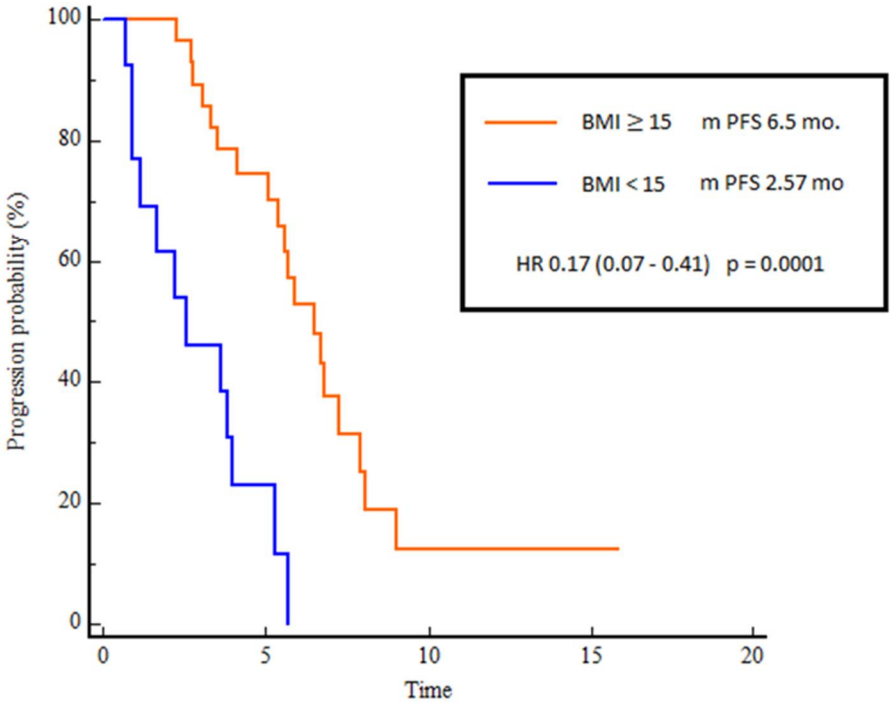
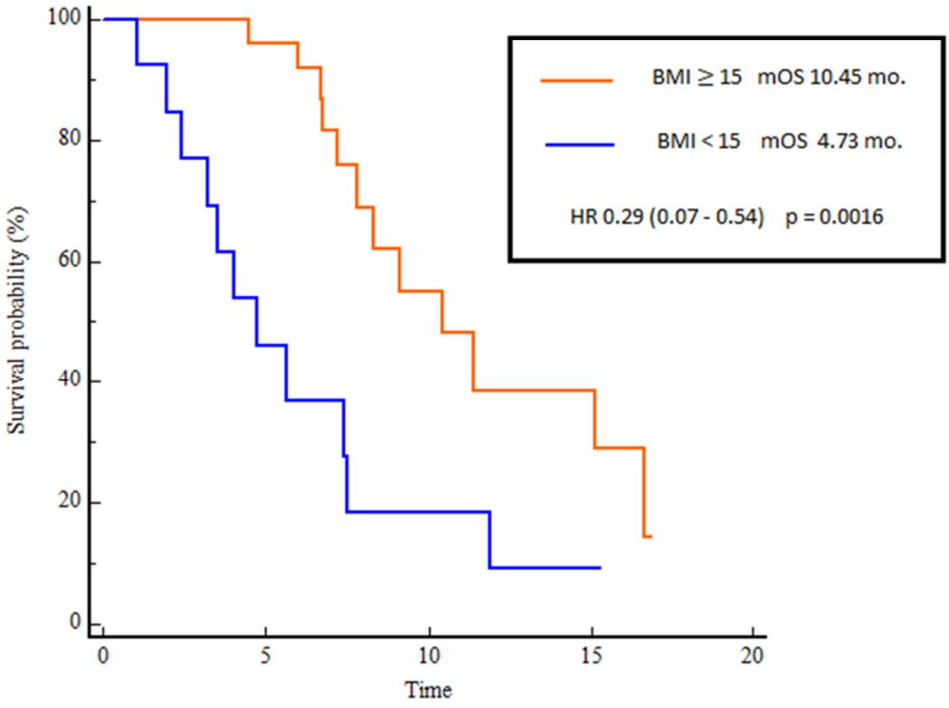


Figure 2b. Overall survival in relation to BMI



2.3 Dose administration and Safety analysis

Fifty hundred and eighty-one doses of the combination of paclitaxel and ramucirumab and ten infusions of ramucirumab alone due to taxane-related toxicity were administered. The median number of paclitaxel and ramucirumab cycles was 4.12 (range 1.0 to 15). Disease

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progression was the primary reason for treatment discontinuation. Ramucirumab-related toxicities were responsible for three treatment discontinuations: in one case the treatment was continued with paclitaxel alone for further 6 cycles, while in the other two cases the radiological assessment showed a disease progression, so paclitaxel was also discontinued at the same time. Details on toxicity profile are shown in table 5.

Peripheral neuropathy related to paclitaxel was the most common adverse event and, as expected, it was associated with cumulative dose; due to grade 3 neuropathy, two patients required dose reduction of paclitaxel (60 mg/mq) and three patients needed to discontinue the taxane administration maintaining the treatment with ramucirumab alone. Other grade 3 non-hematological toxicities were uncommon and included one case of stomatitis and one case of hypertransaminasemia that were both responsible for treatment delay.

The most common grade 3-4 hematological toxicity was neutropenia and it was the major cause of dose delay; however, no febrile neutropenia was observed and no patient required G-CFS support. Anemia was a common finding at the start of treatment and it was related to disease condition and previous chemotherapy treatments; two patients needed erythropoietin support but only one case of worsening to G3 toxicity (hemoglobin < 8.0 gr/dl) was observed requiring blood transfusion. One patient had G3 thrombocytopenia combined with G3 neutropenia.

Among adverse events of interest related to the anti-angiogenic activity of ramucirumab, the incidence of any grade hypertension and bleeding was low. We had only one case of bleeding of the primary tumor requiring endoscopic argon plasma coagulation and one case of gastric perforation occurring five days after the last dose of ramucirumab in a woman who had required an implementation of corticosteroids due to brain metastases progression. One male patient experienced partial loss of vision caused by micro-embolization of the optical nerve; the event cleared up spontaneously after few days but led to treatment discontinuation.

Table 5. Toxicity profile

Event	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Anemia	6	4	1	0
Thrombocytopenia	1	0	1	0
Neutropenia	4	5	4	1
Non hematological				
Peripheral neuropathy	10	6	2	0
Stomatitis	1	1	0	0
Hypertransaminasemia	0	0	1	0
Diarrhea	2	2	0	0
Asthenia	5	2	1	0
Special interest (anti VEGFR activity)				
Hypertension	5	0	1	0
Bleeding	4	0	1	0
Gastrointestinal perforation	0	0	0	1
Embolism	0	1	1	0

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3. Discussion

Despite the increasing number of available agents in oncology, the clinical management of patients with mGC/mGOJC is still disappointing and the prognosis remains poor [6]. After the results of RAINBOW trial, the combination of paclitaxel and ramucirumab has become the preferable therapy for patients who progress on platinum-based therapy. The aim of our analysis was to assess the activity and safety of this drug combination in our clinical daily practice. We are aware that the limited number of patients does not allow any definitive conclusion or generalization of the results; however, the validation of efficacy and safety outcomes in an unselected and heterogeneous patient population gives to this combination more sense and relevance in the real life practice.

Despite the likely underestimation of overall survival due to the short time of median follow-up and the number of patients still on treatment, the median PFS (5.4 months) seems longer than that reported in the RAINBOW trial and in several previous reports. Taking into consideration the poor survival generally observed in Western population, the PFS in our study not only confirms the results achieved in the RAINBOW trial, but also suggests that they are reproducible in a general population with unfavorable prognosis. The clinical value of the combination of RAM and PXT resulted also in a recently published phase II study with nab-paclitaxel instead of paclitaxel carried out in an Asian less intensively pre-treated population with mainly gastric cancer, in which ORR and mPFS were even more higher (table 6) [7-9].

Table 6. Comparison with RAINBOW trial (RAM + PXT arm) and other single arm studies

Outcomes	RAINBOW	Western pts	RAMoss	Bando et al	Present paper
Median OS (mo.)	9.6	8.6	8.3	n.r.	8.3 (*)
Median PFS (mo)	4.4	4.2	4.5	7.6	5.4
ORR (%)	28	26.8	20.3	54.8	24.4
DCR (%)	80	76.8	59.7	92.9	61
	(*) Median follow-up: 9.6 mo				

Subgroup analysis confirms the well-known positive prognostic factors affecting survival; however, the most relevant finding in our study is the strong association between PFS and BMI index. As a matter of fact, a better nutritional status implies a longer overall survival, but in our patients normal BMI was related not only to overall survival but also to PFS, an outcome that is primarily influenced by drug activity. The relevance of nutritional status as independent prognostic factor for PFS is confirmed by the lack of statistical relationship with performance status. Other reports have already focused the impact of malnutrition on chemotherapy dose intensity and toxicity incidence, but in our study no significant difference was observed in subgroup analysis [10, 11]. Therefore, we hypothesize a relationship between drug activity and nutritional status. One assumption may be that malnutrition could affect drug distribution and metabolism due to low levels of serum albumin and lower enzymatic activity. On the other hand, it is known that IgG monoclonal antibodies like ramucirumab are able to recall antibody-dependent cell-mediated cytotoxicity (ADCC) that might be impaired in malnourished patients [12].

Interestingly, the median duration of response is longer in our retrospective study than in the RAINBOW trial (5.4 months vs 4.4 months), despite the disease control rate is lower; this result may suggest that some patients obtain a greater benefit from the treatment. As previously underlined, our

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HER-2 positive patients achieved a longer duration of response, according to similar data recently published in an Italian-Canadian paper [13]. Although the cohort was very small (12 patients) for definitive conclusions and the huge number of ongoing treatments likely affected outcomes estimations, the Cox analysis showed a trend toward an association with a longer PFS (6.8 vs 5.27 months; HR 0.65, p = 0.1341.). These data suggest a possible relationship between HER-2 overexpression and downstream activation of the VEGF pathway within gastric tumor cells; an overlap of these pathways has been demonstrated in in-vitro models of HER-2 breast cancer [14-16].

We did not find that the presence of peritoneal metastases is a negative prognostic factor; since some patients experienced disease progression due only to the worsening of peritoneal involvement and ascites, we think that treatment of peritoneal disease by locoregional procedures (HIPEC, PIPAC) could be a useful option in the management of selected cases.

The combination of paclitaxel and ramucirumab showed a favorable safety profile even in this unselected and heavily pre-treated population of patients. Grade 3-4 AEs leading to dose reduction or withdrawal were relatively rare. Only two severe adverse events may be related to the class of anti-angiogenic agents, including one case of gastric perforation following the increase of corticosteroid medication due to brain metastases. Low incidence of these AEs is noteworthy particularly considering that half of patients do not have undergone gastric surgery.

4. Materials and Methods

We retrospectively collected clinical and radiological data of patients with metastatic gastric and gastro-oesophageal junction adenocarcinoma treated with paclitaxel and ramucirumab as second or third line therapy at Medical Oncology Department of "Policlinico Universitario A. Gemelli" in Rome. Medical records were reviewed in order to obtain information about demography, treatment, outcome and safety. CT scan were performed about every 12 weeks or less in cases in which there was evidence of clinical deterioration.

Between November 2015 and March 2018, 47 patients were treated with ramucirumab (8 mg/kg intravenously on days 1 and 15) plus paclitaxel (80 mg/m^2 intravenously on days 1, 8, and 15 of a 28-day cycle) for metastatic GOJC/GC after failure of previous platinum-based therapy. Drugs were mostly infused in outpatient department and the treatment was continued until disease progression or unacceptable toxicity. Prophylactic antiemetic therapy with steroids and 5-HT3 receptor antagonists was administered before each cycle according to routine clinical practice. Primary prophylaxis with C-CSF was not planned.

Disease responses were classified according to RECIST criteria (version 1.1). Overall survival was defined as the time interval from the start of therapy to the date of death or last follow-up visit. Progression-free survival was defined as the time interval from the first day of therapy to the date of clinical or radiological disease progression or death, whichever occurred first.

OS and PFS were estimated using the Kaplan-Meier method. Prognostic factors were analyzed using Cox proportional hazards regression models in 2 steps. Firstly, each potential prognostic factor was screened as indipendent covariate. Then, the final prognostic factors were identified based on a multivariable Cox model that was built using stepwise selection of covariates (entry significance level 0.05, exit significance level = > 0.1). All data were analyzed using statistical software SPSS 20 for Windows (IBM Corp., NY, USA). Toxicities were reported according to the CTCAE criteria version 4.0.

5. Conclusions

In conclusion, our study confirms the efficacy and safety of the combination of ramucirumab with paclitaxel also in real-life practice. These findings need further validation in a larger cohort of patients with a longer follow-up; we think that the significant impact of nutrition on survival deserves a particular attention especially if it would be related to drug activity rather than to patients' frailty. It implies that nutritional counselling should be part of clinical practice for patients with gastric cancer and that an accurate assessment of nutritional parameters, including also sarcopenia and lack of nutrients, would be necessary in planning future clinical studies. Finally, the possible

relationship of HER-2 expression to PFS raises the important question of identifying predictive biomarkers of response to ramucirumab, including HER-2 status and exposure to trastuzumab [17,18]. As result of expanding therapeutic options, our report underlines also the importance both of the oncologist experience and of the multidisciplinary approach in clinical decision-making process for patients with gastric cancer.

6. Compliance with ethical standards

Conflict of interest. No funding sources were used in the preparation of this manuscript and the authors declare that they have no conflicts of interest.

Author Contributions. First two authors contributed equally to this manuscript

Conceptualization, Antonia Strippoli and Alessandra Cassano; Data curation, Emanuele Vita, Antonia Strippoli, Vincenzo Di Noia, Carmela Di Dio, Valeria Zurlo, Michele Basso, Ettore D'Argento and Giovanni Schinzari; Formal analysis, Emanuele Vita and Vincenzo Di Noia; Investigation, Emanuele Vita, Antonia Strippoli, Vincenzo Di Noia, Carmela Di Dio, Valeria Zurlo, Michele Basso, Ettore D'Argento and Giovanni Schinzari; Methodology, Emanuele Vita and Vincenzo Di Noia; Project administration, Antonia Strippoli and Alessandra Cassano; Supervision, Michele Basso, Ettore D'Argento, Giovanni Schinzari, Carlo Barone and Alessandra Cassano; Validation, Carlo Barone and Alessandra Cassano; Writing – original draft, Emanuele Vita and Antonia Strippoli; Writing – review & editing, Emanuele Vita, Antonia Strippoli, Carlo Barone and Alessandra Cassano.

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