KSR Ltd

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

ERRATUM TO
Ramucirumab for treating advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy

Corrected pages from the ERG report are presented below.

treated with placebo (HR=0.776, 95% CI: 0.603 to 0.998). The relative gain in PFS was 0.8 months for patients treated with ramucirumab with a median PFS of 2.1 months (95% CI: 1.5 to 2.7) in the ramucirumab group and 1.3 months (95% CI: 1.3 to 1.4) in the placebo group (HR=0.483, 95% CI: 0.376 to 0.620).

Ramucirumab plus paclitaxel

Ramucirumab+paclitaxel was used in one trial, the RAINBOW trial, which compares ramucirumab+paclitaxel with paclitaxel. The trial shows favourable results for ramucirumab+paclitaxel in terms of overall survival (HR=0.807 (95% CI: 0.678 to 0.962)) and PFS (HR=0.635 (95% CI: 0.536 to 0.752)). This represents a 31% (2.27 months) longer median overall survival in the ramucirumab+paclitaxel arm (9.63 months (95% CI 8.5-10.8) versus 7.36 (95% CI 6.3-8.4) months in the placebo+paclitaxel arm). The relative gain in PFS was 1.5 months for patients treated with ramucirumab+paclitaxel with a median PFS of 4.4 months (95% CI: 4.2 to 5.3) in the ramucirumab+paclitaxel group and 2.9 months (95% CI: 2.8 to 3.0) in the placebo+paclitaxel group.

Using indirect comparisons and network meta-analyses, the CS presents results comparing ramucirumab+paclitaxel with other relevant comparators such as docetaxel and best supportive care. In response to the clarification questions from the ERG, the company also presented results for ramucirumab+paclitaxel compared with irinotecan and (m)FOLFIRI.

In terms of overall survival, ramucirumab+paclitaxel was found significantly better than BSC (HR=0.41; 95% CrI: 0.24 to 0.70), paclitaxel (HR=0.81; 95% CrI: 0.68 to 0.96) and irinotecan (HR=0.71; 95% CrI: 0.52 to 0.99). In terms of progression free survival, ramucirumab+paclitaxel was found significantly better than paclitaxel (HR=0.64; 95% CrI: 0.54 to 0.75) and irinotecan (HR=0.56; 95% CrI: 0.41 to 0.76). A comparison with BSC was not possible for PFS.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

Ramucirumab monotherapy

The main issue with the evidence for ramucirumab monotherapy (the REGARD trial) is that the REGARD trial (ramucirumab monotherapy) did not specify whether patients were suitable for treatment in combination with paclitaxel. Therefore, patients for whom treatment in combination with paclitaxel is appropriate will have been included in the REGARD trial. Given that eligibility criteria for RAINBOW and REGARD were almost the same and that all patients in the RAINBOW trial received paclitaxel, it is possible that all patients in the REGARD trial were eligible for paclitaxel. We did ask the company how many patients in each arm of the REGARD trial were not suitable for paclitaxel, but the company responded that it was not possible to estimate this.

The comparison of ramucirumab monotherapy versus BSC is sufficient and in line with the NICE final scope if it is accepted that 'not suitable for paclitaxel' is the same as 'not suitable for further cytotoxic chemotherapy'. If this is not accepted, comparisons with cytotoxic chemotherapy other than paclitaxel (docetaxel, irinotecan and FOLFIRI) are missing.

Table 4.7: Summary of methodology of the RAINBOW and REGARD trials

Trial title	RAINBOW	REGARD
Location	170 centres across 27 countries in North and South America, Europe, Asia, and Australia. (2.25% of patients were from the UK)	119 centres across 29 countries in North America, Central and South America, Europe, Asia, Australia, and Africa. (4.78% of patients were from the UK)
Design	Phase III, randomised, double-blind, placebo-controlled study of RAM +PAC versus PAC (1:1)	Phase III, randomised, double-blind, placebo-controlled study of RAM +BCS versus PBO+BSC (2:1)
Patient population	Patients with histologically or cytologically confirmed unresectable or metastatic gastric or GEJ carcinoma who had received at least 1 cycle of combination therapy with any platinum and any fluoropyrimidine as first-line treatment with/without anthracyclines	Patients with metastatic and locally advanced gastric cancer (including adenocarcinomas of the GEJ) and radiographic evidence of disease progression on prior first-line chemotherapeutic regimens.
Duration of study	2 years	2 years and 3 months
Method of randomisation	Eligible patients were randomised (1:1) using a centralised IVRS/IWRS system and were stratified by time to progression from the start of first-line chemotherapy (<6 months vs. ≥6 months), disease measurability (measurable vs. nonmeasurable disease) and geographic region. • Region 1 (Europe, Israel, US, and Australia) • Region 3 (Hong Kong, Japan, South Korea, Singapore, Taiwan) • Region 2: (Argentina, Brazil, Chile, and Mexico).	Eligible patients were randomised (2:1) using a centralised IVRS/IWRS system to ramucirumab + BSC or placebo + BSC treatment, respectively. Randomisation was stratified by weight loss (≥10% over the prior 3 months vs. <10% over the prior 3 months), geographic region (Region 1, 2 and 3) and location of the primary tumor (Gastric [including tumors of the gastric cardia that extend into the GEJ] vs. GEJ [including tumors of the distal esophagus that extend into the GEJ, and tumors involving the GEJ when precise identification of the organ of origin was not possible]).
Method of blinding (care provider, patient and outcome assessor)	Double-blinded: patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments for the duration of the study. Ramucirumab and placebo for infusion were identical in appearance and there were no anticipated or identified toxicity of ramucirumab that would potentially unblind investigators to treatment assignment	Double-blinded: patients, investigators, sponsor and all other personnel involved in the conduct of the study were blinded to individual treatment assignments for the duration of the study. Ramucirumab and placebo for injection were identical in appearance. The study drug (ramucirumab or placebo) was uniquely labelled, and assigned to a patient by using IVRS/IWRS. Unblinding of the study team did not occur until the reporting database was validated and locked for final statistical analysis on 26 September 2012.
Intervention(s) (n =) and comparator(s) (n =)	1) Ramucirumab 8 mg/kg plus paclitaxel 80 mg/m2 administered intravenously (IV). Paclitaxel was given on Days 1, 8, and 15 of a 28-day cycle, in combination with ramucirumab given on Days	1) BSC plus ramucirumab administered intravenously (IV) every 2 weeks at a dose of 8 mg/kg (n=238) 2) BSC plus an equivalent volume of placebo administered IV

Trial title	RAINBOW	REGARD
	1 and 15. (N=330) 2) Placebo plus paclitaxel 80 mg/m2 administered IV. Paclitaxel was given on Days 1, 8, and 15 of a 28-day cycle, in combination with an equivalent volume of ramucirumab placebo (placebo) given on Days 1 and 15. (N=335) Each treatment cycle was 28 days in length.	every 2 weeks (n=117) Each treatment cycle was two weeks in length
Primary outcomes	The primary outcome was overall survival (OS), defined as the time from the date of randomisation to the date of death from any cause. OS was censored on the last date the patient was known to be alive (on or before data cut-off date or lost to follow-up). Patient survival status was collected every 8 weeks after treatment discontinuation, until the data cut-off date.	The primary efficacy variable was overall survival (OS), defined as the time from randomisation to the date of death from any cause.
Secondary outcomes	Progression-Free Survival, Time to Progression, Objective response rate (ORR) defined as the number of randomised patients who achieved complete response (CR) or partial response (PR) divided by the ITT population. Quality of Life (QoL): Assessed using EORTC QLQ-C30 (version 3.0), and the European Quality of Life-5 Dimensions (EQ-5D). Time to deterioration (TTD) in EORTC QLQ-C30. Time to deterioration (TTD) in ECOG PS and Safety (NCI CTCAE, version 4.02)	Progression-Free Survival, Investigator-assessed Objective response rate (ORR), Duration of Response, QoL (EORTC QLQ-C30 (version 3.0)), Time to deterioration of ECOG PS and Safety (NCI CTCAE, version 4.02)
Other endpoints	Pharmacodynamics, immunogenicity and pharmacokinetic parameters	

Abbreviations: IDMC, Independent Data Monitoring Committee; ITT, intent-to-treat; IVRS, Interactive Voice Response System; IWRS, Interactive Web Response System; N/A, not applicable; PS, performance status. AE, Adverse Events; BSC, Best supportive care; CI, Confidence Interval; CR, Complete response; TTP, Time to disease progression; RECIST, Response Evaluation Criteria in Solid Tumours; RCT, Randomised Controlled Trial; RR, Relative Risk; PR, Partial response; OS, Overall survival; OR, Odds Ratio; ORR, Objective response rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EQ-5D, European Quality of Life-5 Dimensions; EORTC QLQ-C3,0 European Organization for Research and Treatment of Cancer QLQ-C30; TTD, Time to deterioration; HRQL, Health-related Quality of Life; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QOL, Quality of Life; DCR, Duration of Response.

Table 4.9: Reasons for treatment discontinuation

	RAINBOW		REGARD	
	Ramucirumab + Paclitaxel (N=330)	**Placebo + Paclitaxel (N=335)**	**Ramucirumab (N=238)**	**Placebo (N=117)**
Patients treated, n (%)	326 (98.8)	330 (98.5)	236 (99.2)	115 (98.3)
Never Treated	4 (1.2)	5 (1.5)	2 (0.8)	2 (1.7)
Treatment discontinued	313 (94.8)	323 (96.4)	222 (93.3)	114(97.4)
Treatment ongoing	13	7	14	1
Reasons for discontinuation, n (%)				
Progressive Disease	236 (71.5)	255 (76.1)	126(52.9)	73 (62.4)
Symptomatic deterioration			41 (17.2)	16 (13.7)
Death	12 (3.6)	13 (3.9)	20 (8.4)	13 (11.1)
AE	39 (11.8)	38 (11.3)	25 (10.5)	7 (6.0)
Withdrawal of consent	23 (7.0)	13 (3.9)	7 (2.9)	3 (3.6)
Other	3 (0.9)	3 (0.9)	3 (1.3)	2 (1.7)
Lost to follow-up	0	1 (0.3)	0	0

Source: CS, Figure 7, page 58 & Figure 17, page 91
Abbreviations: AE, adverse event; ITT, intent-to-treat; N, number of randomised patients; n, number of patients in category; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

ERG comment: Reasons for treatment discontinuation are well balanced between the two trial arms of the RAINBOW trial. A greater proportion of patients in the ramucirumab+ paclitaxel group withdrew consent to treatment than in the placebo+paclitaxel group. According to the investigators, the majority of the patients who withdrew consent experienced a Grade ≥ 3 adverse event or serious adverse event within 2 weeks before or after discontinuation of therapy.

In the REGARD trial, a greater proportion of patients in the ramucirumab group discontinued due to an adverse event.

Patient characteristics in two trials

The demographics, baseline disease characteristics and medical history of patients in both trials by treatment arm are presented in Table 4.10.

Table 4.10: Characteristics of participants in the trials by randomised group (ITT)

	RAINBOW		REGARD	
Baseline characteristic	**RAM+PAC (n=330)**	**PBO+PAC (n=335)**	**RAM (n=238)**	**PBO (n=117)**
Age (years) <65 ≥65 Median (range) Median (IQR)	 204 (62) 126 (38) 61 (25 – 83)	 212 (63) 123 (37) 61 (24 – 84)	 60 (52-67)	 60 (51-71)
Gender Male Female	229 (69)	243 (73)	169 (71) 69 (29)	79 (68) 38 (32)
Geographic Regions* 1. 2.	 198 (60) 23 (7)	 200 (60) 21 (6)	 165 (69) 55 (23)	 80 (68) 29 (25)

	RAINBOW		REGARD	
Baseline characteristic	**RAM+PAC (n=330)**	**PBO+PAC (n=335)**	**RAM (n=238)**	**PBO (n=117)**
Prior treatment lines received Neoadjuvant therapy Adjuvant therapy First-line therapy	 24 (7) 31 (9) 329 (100)	 15 (4) 32 (10) 335 (100)	 2 (1) 37 (15) 199 (84)	 0 14 (12) 103 (88)
First-line platinum/fluoropyrimidine Triplet: platinum/fluoropyrimidine with anthracycline Doublet: platinum/fluoropyrimidine without anthracycline	 76 (23) 253 (77)	 87 (26) 246 (73)	NR	NR
Previous anti-cancer treatment (by type of drug), n (%) Fluoropyrimidine plus platinum Fluoropyrimidine + other sys drug Fluoropyrimidine alone Platinum plus other systemic drug	NR	NR	200 (84) 13 (5) 16 (7) 9 (4)	88 (75) 17 (15) 7 (6) 5 (4)
Prior treatment with a regimen containing targeted agent (any targeted agent)	31 (9)	26 (8)	NR	NR

Source: CS, Table 16, Page 61
Data are number (%) unless otherwise indicated.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; PLAT, platinum; FLUO, fluoropyrimidine; GOJ, Gastro-oesophageal junction adenocarcinoma; IQR, interquartile range; RECIST, Response Evaluation Criteria in Solid Tumours. Data are number (%) unless otherwise indicated.
* REGARD: Region 1= North America, Europe, Australia, New Zealand, Israel, Region 2= South and Central America, India, South Africa, Middle East, Region 3=Asia.
RAINBOW: Region 1= Europe, Israel, US and Australia, Region 2=Argentina, Brazil, Chile and Mexico, Region 3= Hong Kong, Japan, South Korea, Singapore and Taiwan.

ERG comment: Overall, treatment arms were well balanced in the two trials. In the RAINBOW trial there was an imbalance with respect to the presence of ascites and ECOG Performance Status. In the REGARD trial there was an imbalance between the treatment arms with respect to histological subtype, percentage of peritoneal metastases and previous anticancer treatment.

Stratification by geographic region occurred at the time of randomization as Geographic region was considered to be an important potential confounder. The investigators state that region 1 was most similar to the UK, (although the criterion by which this was determined was not stated). Overall the treatment arms for Region 1 participants are reasonably balanced.

As most patients in both trials had gastric cancer (75 to 80%), the evidence from this study is more limited with respect to gastroesophageal cancer and as a greater proportion of the recruited patients were male (70%), the evidence is more limited for female participants.

4.2.1 Results of the RAINBOW trial

The final scope lists the following outcome measures: overall survival, progression-free survival, response rate, health-related quality of life and adverse events. These results will now be discussed. Results presented in the CS are based on the data cut-off point of 12 July 2013. Efficacy analyses were performed using the ITT population.

Overall Survival

The primary endpoint of the study was overall survival. At the analysis cut-off date, 256 death events had been observed (256 [77.6%] in the ramucirumab+paclitaxel group and 260 [77.6%] in the placebo+paclitaxel group). According to the investigators ramucirumab+paclitaxel reduced the relative risk of death from any cause in this population by 19% (HR = 0.807; 95% CI: 0.678, 0.962; p=0.0169) compared with placebo+paclitaxel. This represents a 31% (2. 27 months) longer median overall survival in the ramucirumab+paclitaxel arm (9.63 months (95% CI 8.5-10.8) versus 7.36 (95% CI 6.3-8.4) months in the placebo+paclitaxel arm). The 6- and 12-month survival rates were (ramucirumab+paclitaxel vs placebo+paclitaxel) 71.5% versus 56.9% and 40.1% versus 30.2%, respectively. The Kaplan Meier survival curves overlapped during the first month, but separated within two months of treatment commencement and remained separate beyond one year of treatment.

Table 4.11: Overall survival of patients in the RAINBOW trial (ITT)

Outcome	**Median (95% CI) months to outcome**	
	RAM + PAC (N=330)	**PBO + PAC (N=335)**
Number of deaths n%	256 (77.6)	260 (77.6)
Number censored	74 (22.4)	75 (22.4)
Median survival-months (95% CI)	9.63 (8.5, 10.8)	7.36 (6.3, 8.4)
HR (95% CI)	0.807 (0.678-0.962)	
P value	0.0169	

Source: CS, Table 17, Page 63
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; N, number of randomized patients; n, number of patients in category; RAM, ramucirumab; PAC, paclitaxel; PBO, placebo.
Note: Median and survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method.

The Kaplan Meier plot of overall survival (ITT population) is presented in Figure 4.2.

Progression-free survival

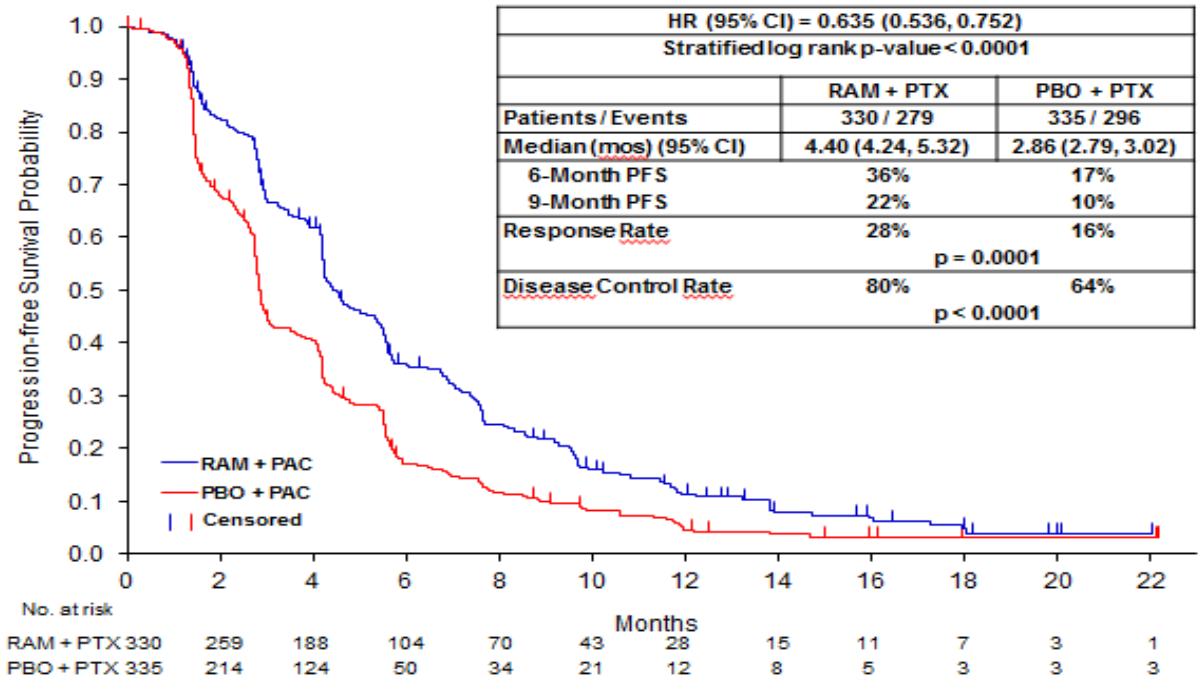
Treatment with ramucirumab+paclitaxel resulted in a 37% relative reduction in the risk of disease progression or death compared with placebo+paclitaxel and increased PFS by 1.5 months compared with the placebo plus paclitaxel arm (4.4 months versus 2.9 months. (See Table 4.12). The Kaplan–Meier plot for PFS (ITT) is presented in Figure 4.4.

Table 4.12: RAINBOW: Progression-free survival results (ITT population)

Outcome	Median (95% CI) months to outcome	
	RAM + PAC (N=330)	PBO +PAC (N=335)
Number of deaths or progression n%	279 (84.5)	296 (88.4)
Number censored	51(15.5)	39 (11.6)
Median PFS -months (95% CI)	4.40 (4.24, 5.32)	2.86 (2.79, 3.02)
HR (95% CI)	0.635 (0.536, 0.752)	
P value	< 0.0001	

Source: CS, Page 64, Table 18
Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; PFS = progression-free survival; PAC, paclitaxel; PBO, placebo; RAM, ramucirumab.
Note: Median and survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method.

Figure 4.4: RAINBOW: Kaplan-Meier plot of Progression-Free Survival (ITT population)



Source: Page 94, Table 11.5.2 RAINBOW clinical study report
Abbreviations: CI, confidence interval; HR, Hazard ratio; ITT, intent to treat; PBO, placebo; PFS, progression free survival; PTX, paclitaxel; RAM, ramucirumab.

Response rate

Response rates are reported below. Significant differences in favour of the ramucirumab+ paclitaxel group were observed for objective response rate (complete or partial response according to RECIST criteria).

Table 4.13: RAINBOW: Response to treatment results – ITT population

Best overall response	**RAM + PAC N = 330**	**PBO + PAC N = 335**
Patients with measurable disease at baseline	267 (81)	273 (81)
Patients with best overall response, n (%)	92 27.9%	54 16.1%
Complete response (CR)	2 (0.6)	1 (0.3)
Partial response (PR)	90 (27.3)	53 (15.8)
Stable disease (SD)	172 (52.1)	159 (47.5)
Progressive disease (PD)	43 (13.0)	83 (24.8)
Not evaluable (NE) /Not Done	23 (7.0)	39 (11.6)

Source: CS, Table 20, Page 65
Abbreviations: ITT, intent-to-treat; N, number of randomised patients; n, number of patients in category; PAC, paclitaxel; PBO, placebo; RAM, ramucirumab.

Health related quality of life

Health related quality of life in the RAINBOW trial was assessed using two validated instruments: the European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire, Core 30. Version 3.0 (EORTC-QLQ-C30) and EuroQol 5-dimension (EQ-5D).

Overall, the change in quality of life was similar in both treatments arms. There were no significant differences between treatment arms for both instruments, as can be seen in Tables 4.14 and 4.15.

Table 4.14: RAINBOW: EORTC QLQ-C30 - global health status results, ITT population

EORTC QLQ-C30, mean (SD)	**Ramucirumab+paclitaxel N=330**	**Placebo+paclitaxel N=335**
Baseline (N=322/326)	61.46 (21.952)	58.03 (22.031)
End of Treatment (N=211/204)	48.97 (22.979)	48.28 (23.897)
Change from Baseline (N=209/202)	-13.48 (23.238)	-12.13 (24.813)

Source: CSR RAINBOW, Table 14.2.36, page 516; Cut-off Date: 12 July 2013
Abbreviations: SD, standard deviation.
Based on a 100-point scale, with a higher score representing better quality of life

Table 4.15: RAINBOW: EQ-5D Results, ITT population

EQ-5D Index Score, mean (SD)	**Ramucirumab+paclitaxel N=330**	**Placebo+paclitaxel N=335**
Baseline (N=323/328)	0.741 (0.228)	0.732 (0.250)
End of Treatment (N=211/206)	0.581 (0.335)	0.570 (0.366)

Source: CS, Table 21, page
Abbreviations: SD, standard deviation.
Based on a –0.59 to 1 scale, with 1 representing perfect health. Calculated based on the UK population-based preference weights for EQ-5D. These are based on values elicited from a representative national sample using the time trade-off (TTO) method.

Adverse events

All adverse events data presented in the CS are from the RAINBOW and REGARD trials. Overall safety results for the RAINBOW trial are shown in Table 4.16. Similar numbers of patients had at least one serious adverse event (153 [47%] of 327 in the ramucirumab plus paclitaxel group versus 139 [42%] of 329 in the placebo plus paclitaxel group), or treatment-emergent adverse event leading to death (39 [12%] versus 51 [16%], respectively).

Progression-free survival

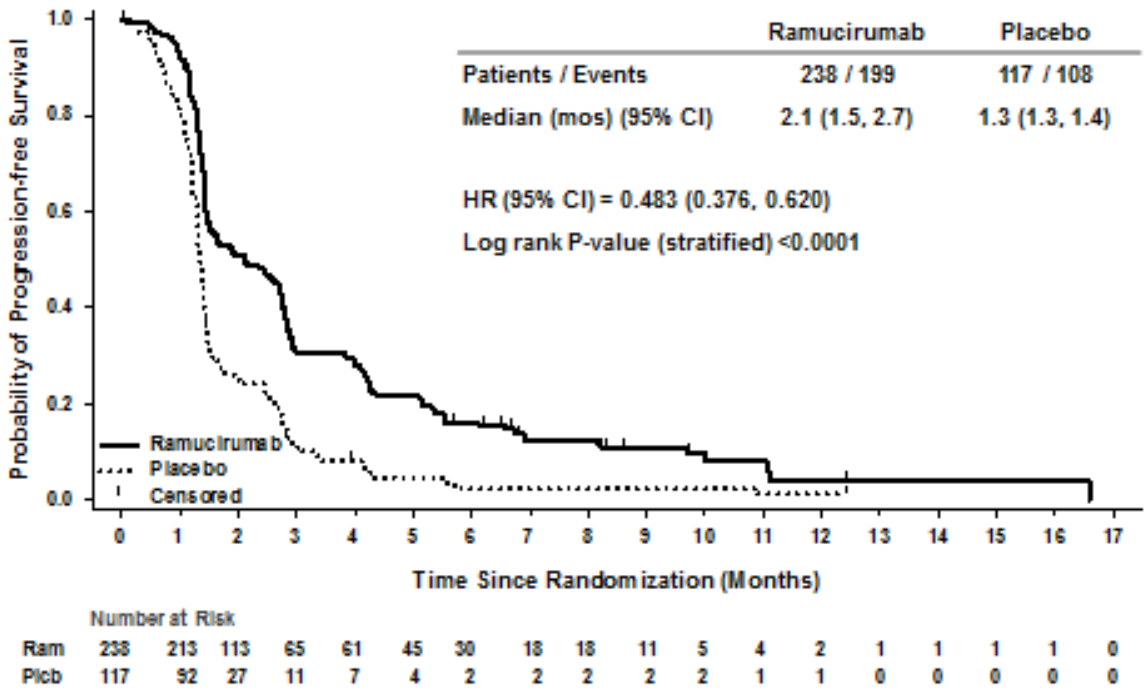
Treatment with RAM resulted in a 62% longer median time to disease progression in the ramucirumab arm (2.1 months versus 1.3 months) (See Table 4.20). The Kaplan–Meier plot for PFS is presented in Figure 4.7.

Table 4.20: REGARD: Progression-free survival results (ITT population)

Outcome	Median (95% CI) months to outcome	
	RAM (N=238)	PBO (N=117)
Number of deaths or progression n%	199 (83.6)	108 (92.3)
Number censored	39 (16.4)	9 (7.7)
Median PFS -months (95% CI)	2.1 (1.5, 2.7)	1.3 (1.3, 1.4)
HR (95% CI)	0.483 (0.376, 0.620)	
P value	p<0.0001	

Source: CS, Page 97, Table 36
Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; PFS = progression-free survival; PBO, placebo; RAM, ramucirumab.
Note: Median and survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method.

Figure 4.7: REGARD: Kaplan-Meier plot of Progression-Free Survival (ITT population)



Source: CS, Figure 19, Page 98
Abbreviations: mos = months.

Response rate

Response rates are reported in Table 4.21. There was no significant difference between groups for objective response rate (complete or partial response according to RECIST criteria).

Table 4.21: REGARD: Response to treatment results – ITT population

Best overall response	Ramucirumab (N=238)	Placebo (N=117)
Patients with measurable disease at baseline	218 (92)	106 (91)
Patients with best overall response, n (%)	8 (3.4)	3 (2.6)
Complete response (CR)	1 (0.4)	0 (0)
Partial response (PR)	7 (2.9)	3 (2.6)
Stable disease (SD)	108 (45.4)	24 (20.5)
Progressive disease (PD)	78 (32.8)	63 (53.8)
Not evaluable (NE) /Not Done	44 (18.5)	27 (23.1)

Source: CS, Table 37, Page 99
Abbreviations: ITT, intent-to-treat; N, number of randomized patients; n, number of patients in category; PBO, placebo; RAM, ramucirumab.

Health related quality of life

Health related quality of life in the REGARD trial was assessed using the European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire, Core 30. Version 3.0 (EORTC-QLQ-C30).

The number of completed QoL questionnaires decreased with time. At six weeks, only 114 (48%) patients in the ramucirumab arm versus 29 (25%) in the placebo arm provided QoL data, primarily due to disease progression and study discontinuation before the first scheduled post-baseline assessment, rather than non-compliance. At 18 weeks, only 38 (16%) patients in the ramucirumab arm versus five (4%) in the placebo arm provided QoL data

At six weeks, the proportion of patients with improved or stable QoL was higher for the ramucirumab arm (34.1%) than the placebo arm (13.7%); however, the difference was not statistically significant (p=0.23). Also at six weeks, there were higher proportions of stable or improved patients in the RAM arm for the physical functioning, fatigue and pain subscales.

Adverse events

Overall safety results for the REGARD trial are shown in Table 4.22. Similar percentages of patients had at least one serious adverse event (106 [45%] of 236 in the ramucirumab group *vs* 51 [44%] of 115 in the placebo group), or adverse event leading to death (22 [9%] versus 15 [13%], respectively).

Table 4.22: REGARD: Overall safety results, safety population

Safety outcome, n (%)	RAM N=236	PBO N=115
Number of patients with TEAEs	223 (94.5)	101 (87.8)
Number of patients with grade 3–4 TEAEs	134 (56.8)	67 (58.3)
Number of patients with treatment-emergent SAEs	106 (44.9)	51 (44.3)
Number of patients with TEAEs leading to treatment discontinuation	25 (10.5)	7 (6.0)
Deaths due to an AE	22 (9.3)	15 (13.0)

Source: Table 12.3, REGARD clinical study report
Abbreviations: TEAE, treatment-emergent adverse event; SAE serious adverse events
Patients may be counted in more than one category.

An indirect comparison with docetaxel, using the COUGAR-02 trial shows that the hazard ratio of overall survival of ramucirumab versus docetaxel is not significantly different, but actually favours docetaxel (HR=1.16 (95% CI: 0.77 to 1.73)).

Time to progression was not measured in the active symptom control group of the COUGAR-02 trial because the authors decided that the value of measuring time to progression in a population not receiving cancer treatment but with known progressive disease at study entry was questionable. Therefore, the authors felt that it was not appropriate to subject these patients to additional unnecessary investigations. This means PFS could not be assessed in the COUGAR-02 trial.

Ramucirumab plus paclitaxel

Ramucirumab+paclitaxel was used in one trial, the RAINBOW trial, which compares ramucirumab+paclitaxel with paclitaxel. The trial shows favourable results for ramucirumab+paclitaxel in terms of overall survival (HR=0.807 (95% CI: 0.678 to 0.962)) and PFS (HR=0.635 (95% CI: 0.536 to 0.752)). This represents a 31% (2. 27 months) longer median overall survival in the ramucirumab+paclitaxel arm (9.63 months (95% CI 8.5-10.8) versus 7.36 (95% CI 6.3-8.4) months in the placebo+paclitaxel arm). The relative gain in PFS was 1.5 months for patients treated with ramucirumab+paclitaxel with a median PFS of 4.4 months (95% CI: 4.2 to 5.3) in the ramucirumab+paclitaxel group and 2.9 months (95% CI: 2.8 to 3.0) in the placebo+paclitaxel group.

Using indirect comparisons and network meta-analyses, the CS presents results comparing ramucirumab+paclitaxel with other relevant comparators such as docetaxel and best supportive care. In response to the clarification questions from the ERG, the company also presented results for ramucirumab+paclitaxel compared with irinotecan and (m)FOLFIRI. However, all these analyses rely on using data from a trial in a completely Japanese population (Hironaka 2013).[29] As explained in the CS, “high rates of salvage therapy have been reported in previous Asian trials.[32] A higher rate of post discontinuation (PDT) third-line therapy was expected in Region 3 (parts of Asia, including Japan), potentially confounding the OS treatment effect of the ramucirumab+paclitaxel regimen due to differing rates of PDT.” In addition, the CS lists the following differences between Western and Asian countries:

Asian countries have a higher incidence and prevalence of Gastric cancer (GC) than Western nations.[33,34] The adoption of national screening programs in Asian countries has resulted in diagnosis in the early stages of the disease in up to 50-60% of cases, while in Western nations patients are typically diagnosed at an advanced stage of GC and therefore have a poorer prognosis.[35]

Differences also exist in GC histology (Western patients have a higher incidence of diffuse histology/proximal tumour types having a poorer prognosis than intestinal histology/distal tumour types seen in Asian patients).[4] The surgical treatment of early GCs with extensive lymph node dissection (D2 resection) occurs more frequently in Asian countries.[4,35] A higher proportion of patients receive second-line chemotherapy (and beyond) in Asia compared to US and Europe which extends survival in those patients.[4]

addressed in the clarification letter and according to the company this was not used in the model because these data were unavailable for BSC or DOC (and using BCO+PAC was considered inappropriate for these comparators). However, according to the ERG this data could have been used to validate the approach currently chosen in the model.

5.2.8 Resources and costs

5.2.8.1 Intervention and comparators' costs and resource use

Cost of the intervention and the comparators are comprised of the drug acquisition, drug administration costs and the cost of monitoring and the tests.

Drug acquisition costs depend on five main components:

- Cost of the drug(s)
- Average dose required
- Treatment duration
- Relative dose intensity
- Required pre-medication

Cost of the drug(s)

Cost of the generically available chemotherapies are taken from eMIT (CS Table 87), which includes the actual prices paid by hospitals over the last 12 months. The prices from eMIT are different from BNF prices (CS Table 88[53]), due to tendering of generic pharmaceuticals. eMIT prices were used in the base case analysis and BNF prices were used in the scenario analysis.

Drug dosing and regimen

Ramucirumab combination and monotherapy treatment regimens were from the SPC, which were the same as the relevant clinical trials.[54] For DOC, a dosage of 75 mg/m2 three-weekly was used from the clinical trials included in the NM[27, 28] and deemed appropriate conforming to English clinical practice by the authors. Dosing/ regimen info of RAM, PAC in RAM+PAC combination therapy, of RAM as a monotherapy, and of DOC as a monotherapy applied as second line treatment were given in Table 89 in the CS.

Patient weight/BSA

In order to calculate the required drug doses for each regimen, an estimate of body weight and body surface area (BSA) was needed.

For combination therapy, patient characteristics from the RAINBOW study were used for all comparators in the combination therapy. The base case analysis used the average of all patients (weight/ BSA) in the trial (i.e. 63.33 kg), and as a scenario analysis weight/BSA from the patient population in region 1 (i.e. 64.83) (CS Table 90).

For monotherapy, patient characteristics from the REGARD study were used. The base case analysis used the average of all patients (weight=65.19 kg, BSA=1.73m^2) in the trial, and as a scenario analysis weight/BSA from the patient population in region 1 (weight=68.15kg, BSA=1.78m^2, given in CS Table 91).

For each regimen, planned dosage was calculated by multiplying the dose by the mean weight or BSA per treatment cycle (CS Table 92).

Table 5.13: Base case: Combination therapy results

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£) vs BSC	Incremental LYs vs BSC	Incremental QALYs vs BSC	Incremental cost/LYs vs BSC	ICER (£) incremental (QALYs) vs BSC
BSC	£13,400	0.45	0.29	-	-	-	-	
DOC	£18,779	0.59	0.39	£5,378	0.14	0.10	£38,498	£53,830
RAM+PAC	£52,996	0.94	0.62	£39,595	0.48	0.33	£81,809	£118,209

The incremental effects for RAM+PAC compared to BSC were 0.48 LYs and 0.33 QALYs. Incremental costs were £39,595 corresponding to an ICER of £118,209.