NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

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

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness issues

- The company considers BSC to be the only relevant comparator for both combination and monotherapy. Consultee statements appear to conflict with this. Does the Committee consider that the other comparators listed in the scope are relevant for both combination and monotherapy?

- For the ramucirumab monotherapy population only – people in the REGARD trial may have been able to tolerate paclitaxel. Can the evidence presented be relied

upon to base a decision on the clinical effectiveness of ramucirumab for the licensed population (i.e. those for whom treatment in combination with paclitaxel is not appropriate')?

- How reliable are the results from the network meta-analysis (NMA)?
    - The NMA relies on 1 trial in an entirely Japanese population (Hironaka 2013), and 1 trial that was small and aborted early (Thuss-Patience 2011)
    - Should Roy et al (2013) be included in the network?

Cost effectiveness issues

- The ERG made 5 minor amendments to the model and implemented these in an exploratory base case. Does the Committee agree with these amendments?
    - Programming errors
    - Docetaxel treatment cost coding error
    - Double counting of hospitalisations due to adverse effects
    - Hospitalisation rate
    - Body surface area and weight based on region 1 rather than intention to treat population
- The ERG carried out an exploratory scenario analysis for the combination therapy in which EQ-5D utility values were taken from RAINBOW (the company base case used a utility value for the post progression health state from REGARD, taken 30 days after discontinuation)
- Is the Committee satisfied with the methods and assumptions used for modelling treatment duration:
    - The model estimated treatment duration using parametric curves, although PFS data in RAINBOW was about 96% complete – was it necessary to model treatment duration for PFS?

- Patients in the trial (and in the model) were assessed every 6 weeks. Progression was confirmed by radiological assessment. Does this reflect clinical practice?

End of life and innovation

- The company states that a minority of people in the trial received a third line post-discontinuation chemotherapy (although this was between 30% and 50%). Can ramucirumab be considered to be a treatment that is given at the end of life?
- Is ramucirumab innovative? It is the first licensed treatment for second line gastric cancer patients.

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal is: To appraise the clinical and cost effectiveness of ramucirumab within its marketing authorisation for advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	Adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy	• Ramucirumab in combination with paclitaxel: Adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy. • Ramucirumab monotherapy Adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy for whom further cytotoxic chemotherapy is not appropriate.	• Ramucirumab monotherapy The licence for ramucirumab monotherapy specifies 'for whom treatment in combination with paclitaxel is not appropriate'. Clinically speaking, this population can be more broadly characterised as patients for whom further cytotoxic chemotherapy is not appropriate.	• Ramucirumab monotherapy The REGARD trial inclusion criteria did not specify whether patients were suitable for treatment in combination with paclitaxel. Therefore, patients for whom treatment in combination with paclitaxel is appropriate may have been included in the REGARD trial.
Intervention	Ramucirumab alone or in combination with paclitaxel	As per scope	N/A	N/A
Comparators	Chemotherapy including but not limited to: • Docetaxel	Ramucirumab in combination with paclitaxel: • Best supportive care (using	• Ramucirumab in combination with paclitaxel: Company justified by referencing results of its	• Ramucirumab in combination with paclitaxel: Comparisons with irinotecan monotherapy and FOLFIRI are

	monotherapy • Irinotecan monotherapy • Irinotecan and fluorouracil-based therapy (FOLFIRI) • Paclitaxel monotherapy (only for people for whom treatment in combination with paclitaxel is appropriate) Best supportive care (including but not limited to antiemetics, blood transfusions, oesophageal stents, palliative radiotherapy and palliative surgery)	indirect comparison) • Docetaxel monotherapy (using indirect comparison) • Paclitaxel monotherapy (only for model validation) Ramucirumab monotherapy: • Best supportive care	survey of UK treatment patterns which stated that this indicated only 3% of all patients moving to second-line received paclitaxel so this was only included in the economic model to validate the clinical outputs. Irinotecan and FOLFIRI were not included in the economic analysis as 2% and fewer of all patients were reported to receive these treatments. • Ramucirumab monotherapy: The licence for ramucirumab specifies its use for patients in whom treatment with paclitaxel is not appropriate. In clinical practice patients who are 'not eligible for paclitaxel' can be more broadly characterised as 'not eligible for cytotoxic chemotherapy'. The standard of care for these patients is best supportive care only.	missing. It is particularly odd that the comparison with irinotecan monotherapy is missing, because a comparison of ramucirumab in combination with paclitaxel versus best supportive care or docetaxel is only possible in a network that includes irinotecan monotherapy. • Ramucirumab monotherapy: Comparator of best supportive care seems reasonable if the Committee accept reasoning that patients 'for whom treatment in combination with paclitaxel is not appropriate' are the same as patients 'for whom further cytotoxic chemotherapy is not appropriate'.
Outcomes		As per scope	N/A	N/A

2 The technology and the treatment pathway

The technology

2.1 Ramucirumab (Cyramza, Eli Lilly and Company) was approved by the European Commission on 19th December 2014 for the following indications:

- Ramucirumab in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy.
- Ramucirumab monotherapy is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate.

Ramucirumab is administered as an intravenous infusion over approximately 60 minutes. Ramucirumab is a human receptor-targeted monoclonal antibody that specifically binds VEGF Receptor 2. This interaction prevents VEGF Receptor 2 from binding with activating ligands (VEGF-A, VEGF-C, and VEGF-D). Upregulation of VEGF-A, VEGF-C, and VEGF-D ligands in gastric cancer are associated with poorer prognosis for patients with resected or metastatic disease.

2.2 The summary of product characteristics lists the following adverse reactions: fatigue/asthenia, neutropenia, leukopenia, diarrhoea, epistaxis, and hypertension. For full details of adverse reactions and contraindications, see the summary of product characteristics.

The disease and treatment pathway

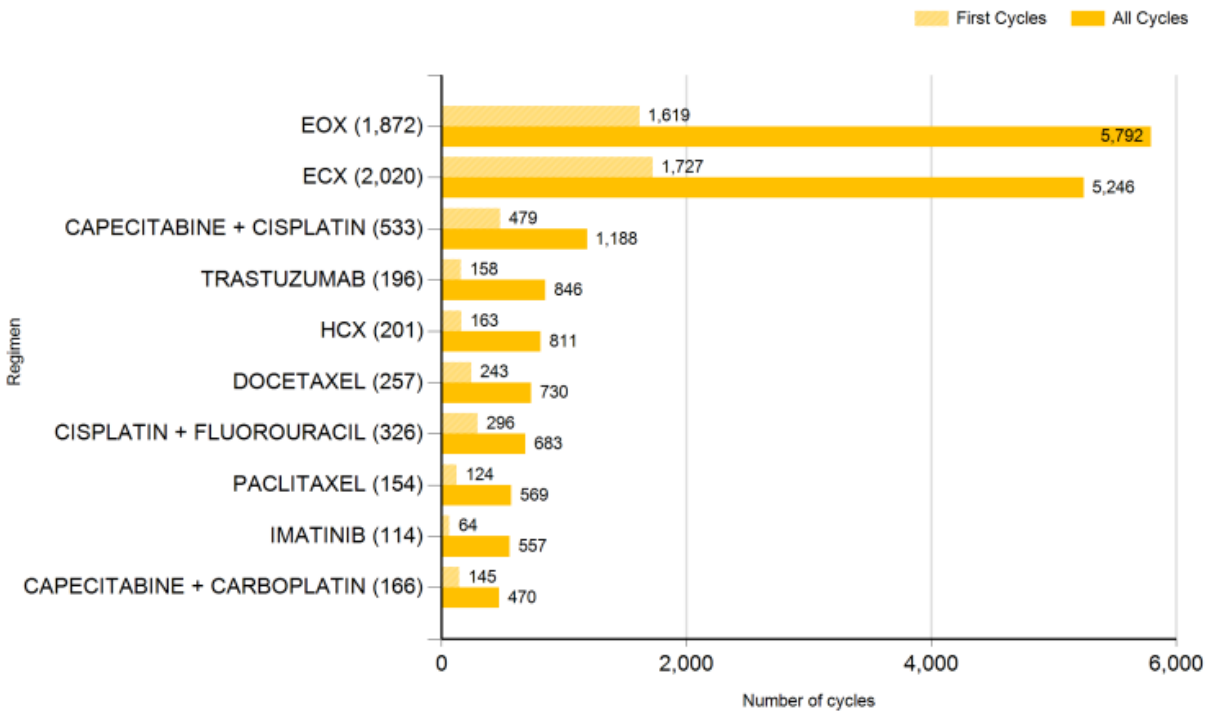
2.3 Gastric cancer is a malignant tumour arising from cells in the stomach. The most common type of gastric cancer is gastric or gastro-oesophageal

junction adenocarcinoma, which affects about 95% of people with the disease. In 2011, 5681 people in England were diagnosed with gastric cancer and there were 3921 deaths from gastric cancer in England. About 80% of people have metastatic disease at diagnosis.

2.4 The aim of treatment in advanced gastric or gastro-oesophageal junction adenocarcinoma (that is, locally advanced unresectable or metastatic disease) is to prevent progression, extend survival and relieve symptoms with minimal adverse effects. Current clinical practice for first-line therapy in the UK is usually a triple regimen that includes an anthracycline, a platinum agent, and a fluoropyrimidine. NICE TA191 'Capecitabine for the treatment of advanced gastric cancer' recommends the fluoropyramidine, capecitabine to be taken with platinum-containing drugs. For the sub-group of patients (approximately 20%) with HER2 amplification, NICE TA208 'Trastuzumab for the treatment of HER2-positive metastatic gastric cancer' recommends people receive trastuzumab in addition to platinum/fluoropyrimidine-based chemotherapy. It is of relevance to this appraisal to state the first line treatment options, since the marketing authorisation for ramucirumab is for patients who have received prior platinum therapy. For the full wording of the marketing authorisation see table 2 below.

2.5 There is no standard treatment for previously treated advanced disease: treatment options include chemotherapy, palliative radiotherapy and palliative surgery. The Systemic Anti-Cancer Therapy (SACT) dataset (accessed online at http://www.chemodataset.nhs.uk on 14 July 2015) provides the following information regarding the top regimens for treating upper gastrointestinal (oesophago-gastric) cancer from July 2013 to June 2014:

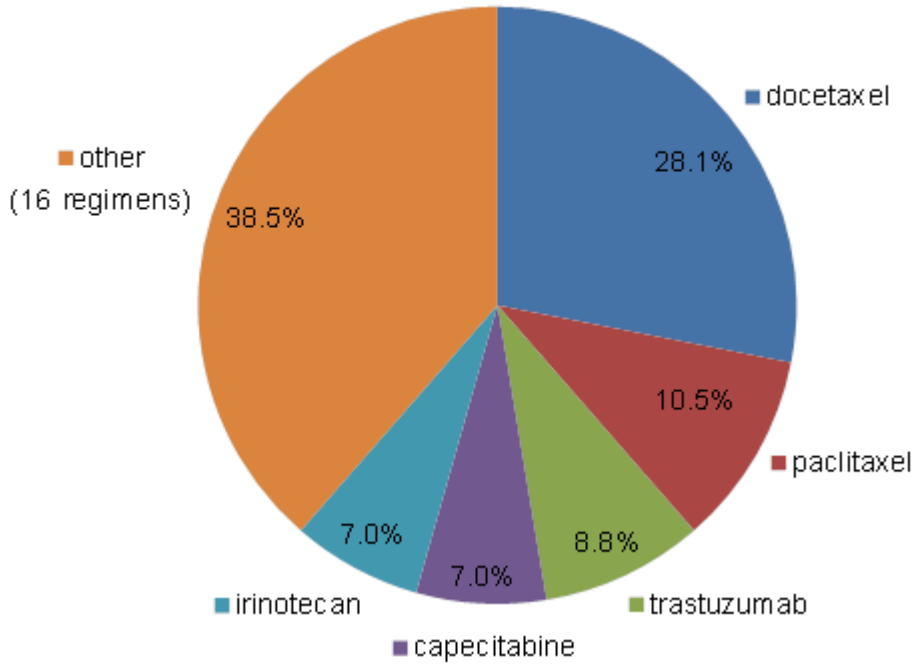
Figure 1 top regiments for upper gastrointestinal (oesophago-gastric) cancer



(EOX, Epirubicin, oxaliplatin and capecitabine; ECX, Epirubicin, cisplatin and capecitabine)

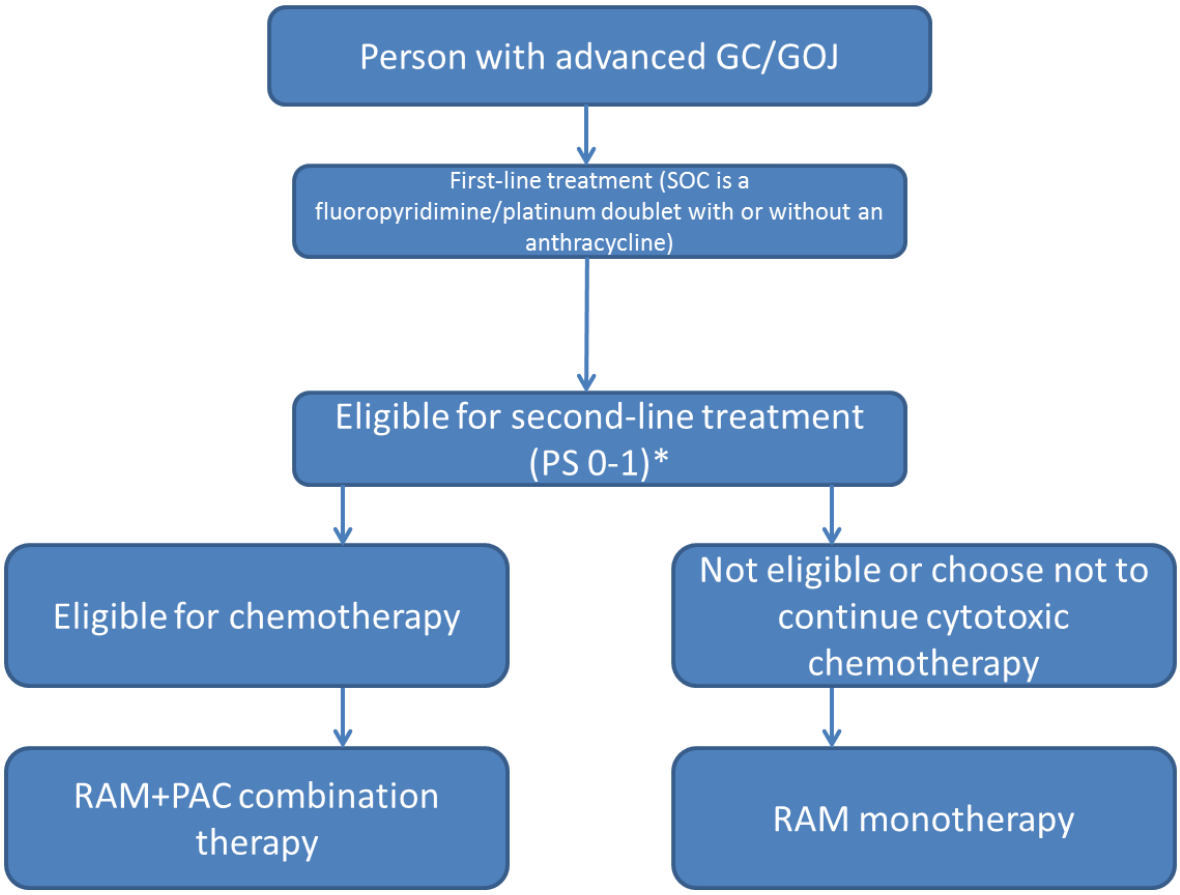
2.6 The company submission referenced a survey of UK treatment patterns which found best supportive care to be the most commonly used second-line option in UK clinical practice (71.5% of patients). The remaining 28.5% of patients receiving 'active' second-line treatment were treated with a total of 21 different regimens (see Figure 2). However, results from the company's survey of UK treatment patterns appears to contrast with statements from professional organisations that across the UK second-line taxane use with either docetaxel or paclitaxel is widespread (see section 3).

Figure 2 Chemotherapies used to treat previously treated gastric cancer in the UK; presented by the company, from a survey of UK treatment patterns (n=57). See page 145 of the company's submission.



2.7 The company's proposed place for ramucirumab in clinical practice is shown in Figure 3.

Figure 3 Proposed place of ramucirumab in treatment pathway



*Abbreviation: GC/GOJ, gastric cancer or gastro-oesophageal junction adenocarcinoma; PS = performance status; RAM+PAC, ramucirumab plus paclitaxel

Table 2 Technology

	Ramucirumab
Marketing authorisation	EU marketing authorisation received 19th December 2014 Ramucirumab in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy. Ramucirumab monotherapy is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate.
Administration method	Administered by IV infusion in a hospital outpatient care setting.
Dose and dosing frequency	The recommended dose of ramucirumab is 8 mg/kg both as combination therapy with paclitaxel and as monotherapy. Dosing frequency:

	• Ramucirumab + paclitaxel – Ramucirumab: Days 1 and 15 of a 28-day cycle, prior to paclitaxel infusion – Paclitaxel: Days 1, 8, and 15 of a 28-day cycle. • Ramucirumab as a single agent – Every 2 weeks Treatment is continued until disease progression or until unacceptable toxicity has occurred.
Average cost of a course of treatment:	• Ramucirumab + paclitaxel: £5031 per 28-day cycle. **Total treatment cost per patient = £31,041** • Ramucirumab: £3000 per 2-week cycle. **Total treatment cost per patient = £20,820** (Calculated using the weight/body surface area [from trial data] multiplied by required dose, relative dose intensity and number of administrations per treatment cycle. Number of cycles as per RAINBOW and REGARD trials; 6.17 and 6.94 respectively)
Acquisition cost (excl. VAT)	• 500mg = £2,500 (list price) • 100mg = £500 (list price)

Table 3 Chemotherapy costs (electronic Market Information Tool [eMIT], February 2014 except for ramucirumab)

Drug	Units (mg)	Vial size (mL)	Strength	Price
Ramucirumab (source: BNF)	500mg	50	10mg/mL	£2,500
	100mg	10	10mg/mL	£500
Paclitaxel (intravenous infusion)	30mg	5	6mg/mL	£3.65
	100mg	16.7	6mg/mL	£7.64
	150mg	25	6mg/mL	£11.58
	300mg	50	6mg/mL	£21.94
Docetaxel (intravenous infusion)	20mg	1	20mg/mL	£6.42
	80mg	4	20mg/mL	£21.23
	140mg	7	20mg/mL	£34.29
	160mg	16	10mg/mL	£47.30

Table 4 Best supportive care components and costing source

Best supportive carec category	Currency code	Currency description	Service description
Morphine	Oral drug costs		
Distress management	A06A1	Occupational Therapist, Adult, One to One (1 care contact)	-
Transfusions	SA13A	Procedures in outpatient,	Medical oncology

		Single Plasma Exchange, Leucophoresis or Red Cell Exchange, 19 years and over, Medical oncology	
Radiation therapy	SC47Z	Preparation for simple radiotherapy with imaging and simple calculation (outpatient)	Outpatient
	SC31Z	Deliver a fraction of adaptive Radiotherapy on a megavoltage machine (outpatient)	Outpatient

3 Comments from consultees

Statements indicate that:

- Current second line options are taxane (either paclitaxel or docetaxel)
- Clinicians do re-treat with a platinum therapy if the patient experienced a good first line response
- FOLFIRI (5-fluororacil and irinotecan) is also given, but it requires central venous device so is less favoured
- Ramucirumab combination treatment offers a survival advantage with modest additional side effects, and with no additional hospital attendances, but with increased chair, nurse, pharmacy time
- CT scanning occurred every 6 weeks in the trial but would be every 8 to 12 weeks in NHS
- "across the UK second-line taxane use with either docetaxel or paclitaxel is widespread"
- There is clinical equipoise between paclitaxel and docetaxel
- Irinotecan and the FOLFIRI regimen may be used in preference to a taxane for some people

3.1 Currently within the NHS, second-line taxane use with either docetaxel or paclitaxel is widespread (ranging from 30 to 50%) for patients of good performance status, which represents an evidence-based approach associated with an improvement in progression free survival and overall survival compared with best supportive care alone. Three weekly

docetaxel may be used, or weekly paclitaxel represents a well-tolerated alternative taxane utilised within the NHS. Consultees stated that if patients with relapsed gastro-oesophageal junctional tumours have received previous taxane therapy as part of a neo-adjuvant chemo-radiation approach or if patients have persistent peripheral neuropathy due to oxaliplatin use in the first-line, then irinotecan (with or without fluorouracil i.e. the FOLFIRI regimen) may be used in preference of a taxane in the second-line setting. Clinical experts stated that there is clinical equipoise between weekly paclitaxel and 3-weekly docetaxel and the choice depends on physician and patient preference. However, weekly paclitaxel is a well-tolerated regimen and is used in multiple tumour types (for example, breast and gynaecological cancers). If irinotecan is combined with fluorouracil (FOLFIRI regimen), a central access venous device is required which is usually not the case with docetaxel or weekly paclitaxel.

3.2 Consultees stated that for patients with a good progression-free interval of 3 to 6 months or more following first-line platinum therapy, there is the option to re-challenge with the same first-line regimen. Clinical experts stated nearly half of the initial responders will be re-challenged with a platinum combination, but the remaining half is poorly served as there is limited option in the form of different cytotoxic agents with poor efficacy. Clinical experts stated that treatment tolerance is an important consideration in this group of patients who can have multiple co-morbidities and are often of an older age.

3.3 Clinical experts stated that ramucirumab will need resourcing for clinic time, chemotherapy chair time and health-care facilities utilisation in order to deal with adverse effects of the treatment.

4 Clinical-effectiveness evidence

Overview of the clinical trials

RAINBOW (Ramucirumab combination therapy)

4.1 RAINBOW was a global, randomised, placebo-controlled, double-blind, phase 3 study in which ramucirumab plus paclitaxel was compared with placebo plus paclitaxel. The study involved adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma who had disease progression on or within 4 months after treatment with platinum-containing and fluoropyrimidine-containing chemotherapeutic regimens with or without an anthracycline.

4.2 The trial randomised 665 adults to receive either ramucirumab 8 mg/kg (n=330) or placebo (n=335) intravenously on days 1 and 15, plus paclitaxel 80 mg/m^2 intravenously on days 1, 8, and 15 of a 28-day cycle. Stratification was carried out according to geographic region (region 1 was Europe including Israel, United States, Australia; region 2 was Argentina, Brazil, Chile, Mexico; region 3 was Hong Kong, Japan, South Korea, Taiwan) , time to progression on first-line therapy, and disease measurability. The study was conducted across 170 centres in 27 countries in North and South America, Europe, Asia, and Australia.

4.3 People in the trial had metastatic or non-resectable locally advanced disease, an Eastern Cooperative oncology Group (ECOG) performance status score of 0 or 1, and adequate haematologic, hepatic, coagulation, and renal function. People with squamous cell or undifferentiated gastric cancer were excluded from the trial. People who had received any chemotherapy other than platinum and fluoropyrimidine with or without an anthracycline were also excluded from the trial. Prior treatment with trastuzumab (which has a marketing authorisation in combination with capecitabine or 5-fluorouracil and cisplatin for HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction, and which

has been recommended in NICE TA208 as a first line treatment) was permitted.

4.4 At baseline, most characteristics in RAINBOW were balanced between the treatment groups. These characteristics included age, sex, race, region, disease measurability, time to progression from start of first-line therapy, weight loss in the previous 3 months, and location and presence of the primary tumour. There was a difference between the treatment groups in ECOG performance status: 35% of people in the ramucirumab plus paclitaxel arm had an ECOG performance score of 0 compared with 43% in the placebo plus paclitaxel arm. A high proportion of people in RAINBOW were male (71%) and the majority were also of white ethnicity (61% white, 35% Asian, 4% black). The majority of people (79%) had gastric cancer and those remaining had gastro-oesophageal junction adenocarcinoma. Previous trastuzumab therapy was received by 20 people in the ramucirumab plus paclitaxel arm compared with 11 people in the placebo plus paclitaxel arm.

4.5 The primary endpoint of RAINBOW was overall survival. Primary and secondary endpoints were analysed using the intention to treat population (that is, the full population of 665 people who were randomised to the trial). At the date of data cut-off (12 July 2013), 256 (77.6%) people had died in the ramucirumab plus paclitaxel arm compared with 260 (77.6%) in the placebo plus paclitaxel arm. The data for those people who had not died (22.4%) were censored on the last date the person was known to be alive (on or before data cut-off date or lost to follow-up). Median overall survival was 9.63 months for ramucirumab plus paclitaxel and 7.36 months for placebo plus paclitaxel (2.27-month improvement in survival; hazard ratio: 0.81; 95% confidence intervals [CI]: 0.68, 0.96; p=0.0169). Results for overall survival and for progression-free survival for RAINBOW are presented in Table 5.

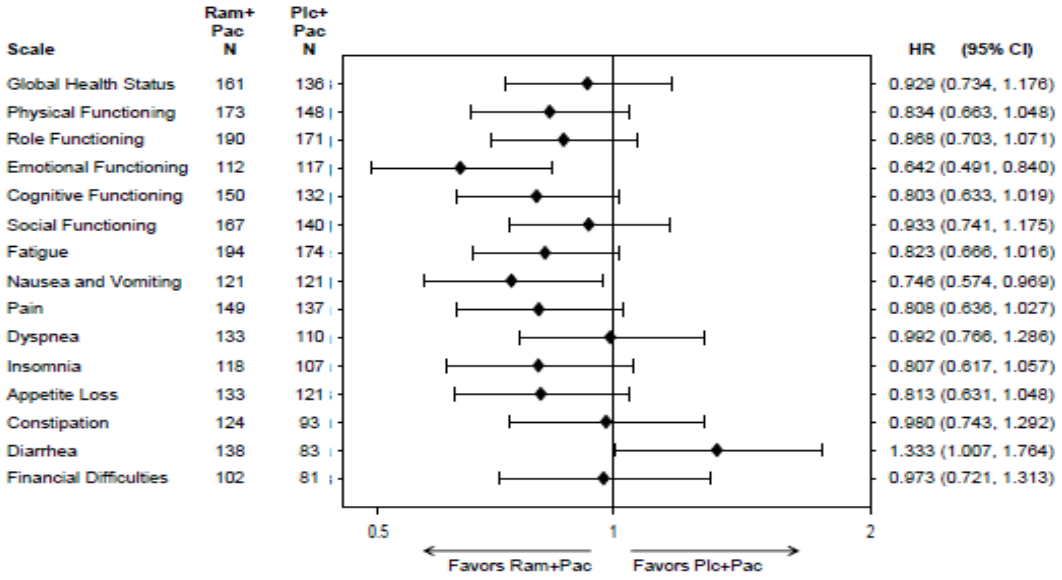
Table 5 RAINBOW: overall survival and progression-free survival results in the intention to treat population

Outcome	Ramucirumab plus paclitaxel	Placebo plus paclitaxel	Treatment difference
ITT Population	n=330	n=335	
Median OS, months (95% CI)	9.63 (8.5, 10.8)	7.36 (6.3, 8.4)	2.27
Log-rank p-value (2-sided)[a]	0.0169		
Hazard ratio (95% CI)[a]	0.807 (0.678, 0.962)		
Median PFS, months (95% CI)	4.40 (4.24, 5.32)	2.86 (2.79, 3.02)	1.54
Log-rank p-value (2-sided)[a]	<0.0001		
Hazard ratio (95% CI)[a]	0.635 (0.536, 0.752)		

Abbreviations: CI, confidence intervals; ITT, intention to treat; OS, overall survival; PFS, progression-free survival
[a] Stratified by randomisation strata (geographical region, time to progression from start of first-line therapy, and disease measurability)

4.6 Quality of life was assessed in RAINBOW using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (global health status, functioning and symptoms) instrument. Ramucirumab plus paclitaxel was associated with improved outcomes for 14 of the 15 symptom scales compared with placebo plus paclitaxel although statistical significance was only reached in 2 of the symptom scales (emotional function and nausea and vomiting; see Figure 4).

Figure 4 RAINBOW: Time to deterioration in EORTC QLQ-C30 Scales



4.7 In RAINBOW, a similar percentage of people in both study arms discontinued treatment due to adverse events (11.8% in the ramucirumab plus paclitaxel arm and 11.3% in the placebo plus paclitaxel arm). The most frequently reported treatment-emergent serious adverse event with a higher incidence in the ramucirumab plus paclitaxel arm (54.4%) than the placebo plus paclitaxel arm (31.0%) was neutropenia. The EPAR's conclusions regarding the clinical safety of ramucirumab are that it "is generally acceptable and in line with other agents targeting inhibition of the VEGF/VEGFR axis, with fatigue/asthenia, neutropenia, leukopenia, diarrhoea, epistaxis and hypertension being the most common adverse reactions observed in ramucirumab-treated patients".

ERG comments

4.8 The ERG stated that the RAINBOW trial is a good quality RCT including more than 300 patients in each treatment group in the trial. Uncertainty regarding long term follow up is likely to be small, since both overall survival and progression-free survival were mature. It also stated that the direction of the imbalances in baseline characteristics in the RAINBOW trial was in favour of a worse outcome for patients receiving ramucirumab plus paclitaxel.

Geographic region subgroup results

4.9 The company presented a pre-specified analysis according to geographic region for RAINBOW. The proportion of people in each geographic region was as follows:

- 60% from region 1 (Europe, Israel, Australia, USA)
- 7% from region 2 (Argentina, Brazil, Chile and Mexico)
- 33% from region 3 (Hong Kong, Japan, South Korea, Singapore, Taiwan)

The company stated that region 1 had characteristics most representative of patients in England. The company presented the outcomes for region 1 showing that in this subgroup median overall survival gain increased 45% to 2.66 months and progression-free survival increased by 50% (1.41 months) for ramucirumab plus paclitaxel compared with placebo plus paclitaxel (see Table 6). The company attributed the longer median survival times for both treatment arms in RAINBOW in the ITT population compared with region 1 to the higher rates of third line chemotherapy use after discontinuing treatment.

Table 6 RAINBOW: overall survival and progression-free survival results in the region 1 subgroup

Outcome	Ramucirumab plus paclitaxel	Ramucirumab plus placebo	Treatment difference
Region 1 subgroup	n=198	n=200	
Median OS, months (95% CI)	8.57 (7.43, 9.79)	5.91 (4.99, 7.06)	2.66
Log-rank p-value (2-sided)[a]	0.0050		
Hazard ratio (95% CI)[a]	0.726 (0.580, 0.909)		
Median PFS, months (95% CI)	4.24 (3.91, 5.32)	2.83 (2.56, 3.09)	1.41
Log-rank p-value (2-sided)[a]	<0.0001		
Hazard ratio (95% CI)[a]	0.631 (0.506, 0.786)		

Abbreviations: CI, confidence intervals; ITT, intention to treat; OS, overall survival; PFS, progression-free survival
[a] Stratified by randomisation strata (geographical region, time to progression from start of first-line therapy, and disease measurability)

ERG comments

4.10 The ERG stated that overall the treatment arms for region 1 participants were reasonably balanced, although it noted that it included very few UK patients.

REGARD (ramucirumab monotherapy)

4.11 REGARD was an international, randomised, double-blind, placebo-controlled, phase 3 trial in which ramucirumab plus best supportive care was compared with placebo plus best supportive care. The study involved adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma who had disease progression on or within 4 months after treatment with first-line platinum-containing or fluoropyrimidine-containing chemotherapy.

4.12 The trial randomised 355 adults in a 2:1 ratio to receive ramucirumab 8 mg/kg (n=236) or placebo (n=115) intravenously once every 2 weeks (in contrast to RAINBOW, in which treatment was given every 28 days). Treatment was given until evidence of progressive disease or unacceptable toxicity. Randomisation was stratified by geographic region, weight loss over the previous 3 months, and location of the primary tumour (gastric or gastro-oesophageal junction). The study was across 119 centres in 29 countries in North, Central, and South America, Europe, Asia, Australia and Africa.

4.13 People in the trial had metastatic disease or locally recurrent, unresectable disease, a life expectancy of 12 weeks or less, and an Eastern Cooperative oncology Group (ECOG) performance status score of 0 or 1.

4.14 The primary endpoint was overall survival. Efficacy analysis was by intention to treat. Results for overall survival and for progression-free survival for REGARD are presented in Table 7.

Table 7 REGARD: overall survival and progression-free survival results in the intention to treat population

Outcome	Ramucirumab plus best supportive care	Placebo plus best supportive care	Treatment difference
ITT population	n=238	n=117	
Median OS, months (95% CI)	5.2 (4.4, 5.7)	3.8 (2.8, 4.7)	1.4
Log-rank p-value (2-sided)[a]	0.0473		
Hazard ratio (95% CI)[a]	0.776 (0.603-0.998)		
Median PFS, months (95% CI)	2.1 (1.5, 2.7)	1.3 (1.3, 1.4)	0.8
Log-rank p-value (2-sided)[a]	<0.0001		
Hazard ratio (95% CI)[a]	0.483 (0.376, 0.620)		
Abbreviations: CI, confidence intervals; ITT, intention to treat; OS, overall survival; PFS, progression-free survival [a] Stratified by randomisation strata (weight loss over the prior 3 months, location of primary tumour, and geographical region)			

4.15 Health related quality of life in the REGARD trial was assessed using the EORTC-QLQ-C30 instrument. At 6 weeks, the proportion of patients with improved or stable quality of life was higher for the ramucirumab arm (34.1%) than the placebo arm (13.7%); however, the difference was not statistically significant (p=0.23).

4.16 Overall safety results for the REGARD trial showed similar numbers of people in each group had at least 1 serious adverse event: 45% in the ramucirumab group compared with 44% in the placebo group. There was a greater proportion of people who discontinued treatment in the ramucirumab group (11.3%) compared with the placebo group (6.1%).

4.17 A forest plot of overall survival for pre-specified subgroups showed that ramucirumab compared with placebo was less clinically effective in women, people who were not white or Asian, and people with an ECOG score of 0 (see figure 22, section 4.8, in the company submission).

ERG comments

4.18 The ERG stated that the main issue with the evidence for ramucirumab monotherapy was that the REGARD trial's inclusion criteria did not specify whether patients were suitable for treatment in combination with paclitaxel. Given that eligibility criteria for RAINBOW and REGARD were almost the same and that all patients in the RAINBOW trial received paclitaxel, the ERG stated it was possible that all patients in the REGARD trial were eligible for paclitaxel.

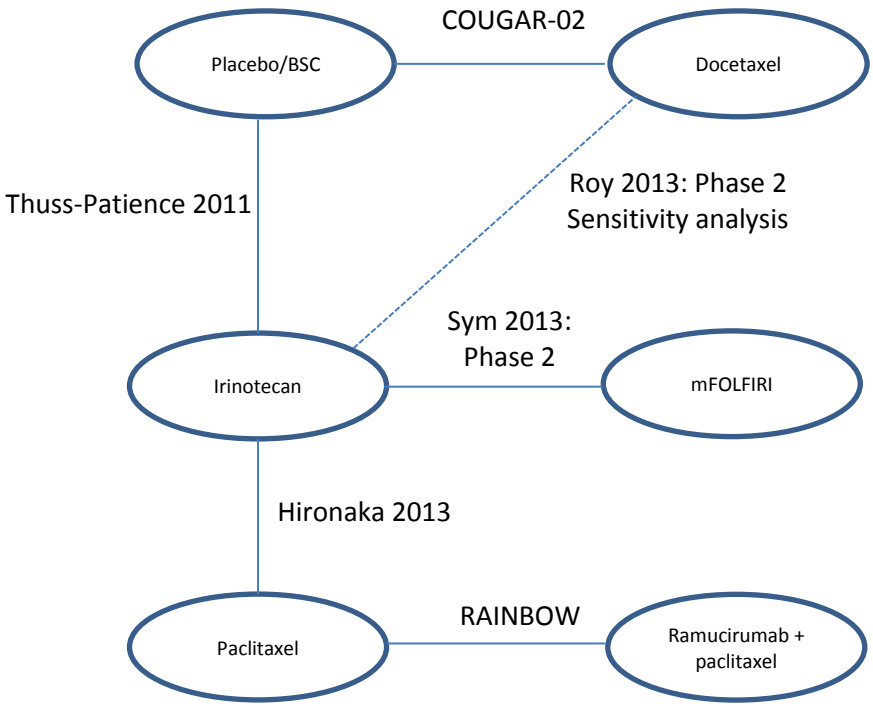
4.19 The ERG noted that in the REGARD trial there was an imbalance with respect to histological subtype, percentage of peritoneal metastases, number of metastatic sites and previous anticancer treatment. It commented that the majority of the imbalances in baseline characteristics in the REGARD trial favoured a worse outcome for patients in the placebo arm.

Network meta-analysis

4.20 The company conducted a network meta-analysis to compare ramucirumab plus paclitaxel with best supportive care and docetaxel. The company identified 23 trials for inclusion in the network, but only 5 trials were included in the analyses of overall survival in the original company submission. The meta-analysis incorporated evidence for ramucirumab plus paclitaxel (RAINBOW), docetaxel (COUGAR-02), irinotecan (Hironaka 2013, Roy 2013, Thuss Patience 2011), paclitaxel (RAINBOW, Hironaka 2013) and placebo/best supportive care (COUGAR-02, Thuss-Patience 2011). Roy 2013 was a non-randomised multinational study comparing second-line irinotecan with docetaxel. The company did not include the Roy (2013) study to estimate overall survival in the base case, although it did include this study in a sensitivity analysis. Although it was possible to include FOLFIRI in the network, this was not performed in the analysis until the clarification stage, at which point evidence was incorporated for FOLFIRI from the Sym 2011 trial, see Figure 5 for the revised network diagram submitted in response to clarification. (N.b.

FOLFIRI was originally developed using 180mg/m^2 bi-weekly, mFOLFIRI refers to the modified regimen of 150 mg/m^2).

Figure 5 Evidence network for Overall Survival (OS) supplied in response to clarification



4.21 Ramucirumab plus paclitaxel was associated with a statistically significant improved overall survival compared with best supportive care (hazard ratio: 0.34, 95% CI: 0.17, 0.71), paclitaxel (hazard ratio: 0.81, 95% CI: 0.68, 0.96), and irinotecan (hazard ratio: 0.72, 95% CI: 0.52, 0.99), and with a numerically (but not statistically significant) improved overall survival compared with docetaxel (hazard ratio: 0.51, 95% CI: 0.23, 1.13) and (m)FOLFIRI (hazard ratio: 0.86, 95% CI: 0.45, 1.65).

Table 8 Network meta-analysis: results for base-case overall survival. Comparisons of treatment A vs. treatment B, HR (95% credible interval), from company submission (appendix 2 of clarification response)

Treatment A	Treatment B				
	Placebo/BSC	Docetaxel	Paclitaxel	Irinotecan	mFOLFIRI
Docetaxel	*0.67*‡ *(0.49, 0.92)*				

Paclitaxel	*0.42 (0.21, 0.86)*	0.63 (0.29, 1.37)			
Irinotecan	*0.48*§ *(0.25, 0.92)*	0.72 (0.35, 1.48)	1.13 (0.86, 1.49)		
mFOLFIRI	*0.40 (0.17, 0.94)*	0.59 (0.24, 1.48)	0.93 (0.51, 1.70)	0.83 (0.47,1.45)	
Ramucirumab + paclitaxel	*0.34 (0.17, 0.71)*	0.51 (0.23, 1.13)	*0.81 (0.68, 0.96)*	*0.72 (0.52, 0.99)*	0.86 (0.45, 1.65)

BSC, best supportive care; CI, credible interval; HR, hazard ratio; OS, overall survival. mFOLFIRI, modified (i.e.150mg/m^2 instead of 180mg/m^2) folinic acid, fluorouracil and irinotecan
‡ Compared with a HR (95% CI) of 0.71 (0.56-0.90), p=0.004 reported in Kim 2013.
§ Compared with a HR (95% CI) of 0.55 (0.40-0.77), p=0.0004 reported in Kim 2013

ERG comments

4.22 The ERG considered that the results of the network meta-analysis should be interpreted with caution. Due to significant differences between western and Asian countries in the incidence of gastric cancer, histology, and screening and treatment approaches, the inclusion of at least 1 trial in a multinational or western population and 1 trial in an Asian population would lead to a high level of heterogeneity. In addition, the ERG were particularly concerned at the reliance of the network on a study which was carried out in an entirely Japanese population (Hironaka 2013); (all comparisons with ramucirumab plus paclitaxel used this link). The ERG stated that the network meta-analysis would have been more reliable if it had included results from Roy et al. 2013 because the Thuss-Patience study closed prematurely due to poor accrual, and as a result the study only included 40 patients meaning it was underpowered.

5 Cost-effectiveness evidence

Model details

5.1 The company submitted 2 separate 3-state partitioned survival models to assess the cost effectiveness of ramucirumab 1) as a monotherapy and 2) in combination with paclitaxel. The structures of both models were the same. The 3 states included pre-progression, post-progression and death,

with all patients entering in the pre-progression health state. The models used a cycle length of 1-week, and a half-cycle correction was applied to all calculations. The models were conducted over a lifetime horizon (equating to approximately 7 years). Both costs and benefits were discounted at a rate of 3.5%. In the post progression health state, the company stated that 'a minority' of patients received a third line treatment, (47.9%, 46%, 30.3% and 37.6% in the ramucirumab plus paclitaxel, paclitaxel alone, ramucirumab monotherapy and best supportive care plus placebo arms of the trials respectively). One-way sensitivity analyses were undertaken on utility values, survival analysis, unit costs, choice of third-line therapy, and various resource use assumptions. Probabilistic sensitivity analysis was also undertaken to explore parameter uncertainty in the model.

ERG comments

5.2 The ERG commented that the model structure is a common model structure for patients with cancer and was used for first-line gastric cancer (TA208). It was clearly described and straightforward. However, a single post-progression health state is a simplification of the treatment pathway, as some patients may receive a third line treatment.

Comparators

5.3 The primary comparator in the combination therapy model was best supportive care; docetaxel was also included in the model because the company stated that the COUGAR study was UK based and was important in shaping clinical practice. Paclitaxel was also included in the combination therapy model, although only as a means of validating clinical evidence. The company stated that although irinotecan and FOLFIRI were listed in the final scope as potential appropriate comparators, they were not included in the economic model because they were not (according to the company's survey of UK treatment patterns) in sufficient use in clinical practice.

5.4 The only comparator included in the monotherapy economic model was best supportive care, which the company justified by noting the licence for ramucirumab which specifies its use for patients in whom treatment with paclitaxel is not appropriate. The company argued that in clinical practice people who are not eligible for paclitaxel can be more broadly characterised as not eligible for cytotoxic chemotherapy.

ERG comments

5.5 For the combination therapy model, the ERG agreed with the company that best supportive care and docetaxel were relevant comparators for ramucirumab pus paclitaxel. However, the ERG did not agree with excluding comparators that were included in the final scope based on the 'established use' criteria (put forward by the company) for 3 reasons:

- Established NHS practice is already incorporated as criteria for defining the most appropriate scope
- The inclusion criterion used by the company of at least 10% is not a formal rule
- The proportion of treated patients is very low and therefore the proportion of patients receiving certain comparators will always be low when it is calculated over all patients that progressed after first-line therapy.

5.6 The ERG noted that according to the company's survey of real world treatment patterns paclitaxel was used for 3% of patients, but that this proportion would be 10.5% if the number of patients that received paclitaxel was divided by the total number of patients that received second-line therapy (instead of by all the patients that progressed after first-line therapy). The ERG commented that, compared with patients who receive best supportive care, the group of patients receiving a second-line treatment (who are in general in better health) will potentially be more likely to start treatment with ramucirumab plus paclitaxel. The ERG also considered it plausible that the proportion of patients receiving paclitaxel

may increase if ramucirumab plus paclitaxel receive were to receive positive guidance. The ERG also commented that the company's survey of real world treatment patterns was based on data provided from June to July 2013, and that since then, favourable results for paclitaxel from the COUGAR II study have been published which may have resulted in increased real-world use of paclitaxel. The ERG also stated that the use of irinotecan and FOLFIRI could increase as a result, and hence the inclusion of these treatments in the comparison could also be considered relevant.

5.7 Regarding ramucirumab monotherapy, the ERG stated that the comparison with best supportive care was sufficient and in line with the NICE final scope if it was accepted that 'not suitable for paclitaxel' is the same as 'not suitable for further cytotoxic chemotherapy'. If this was not accepted, the ERG stated comparisons with cytotoxic chemotherapy other than paclitaxel (docetaxel, irinotecan and FOLFIRI) were missing.

Transition probabilities

5.8 Transition probabilities between the health states were determined from parametric survival functions obtained from the RAINBOW and REGARD trial data for combination therapy and monotherapy, respectively. Time in the pre-progression state was estimated directly from the progression-free survival curves, and time in the post-progression state was estimated by the difference between the progression-free survival and the overall survival curves at each time point.

5.9 Transition probabilities for the comparators docetaxel and BSC were estimated using results from the network meta-analysis.

ERG comments

5.10 The ERG reported an error in the company's model for how the newly progressed patients were calculated which resulted in an overestimation of newly progressed patients. The ERG commented that the impact of this error on the ICER was minimal.

Treatment effectiveness and extrapolation

5.11 For the combination therapy model, the company modelled overall survival using Kaplan-Meier data until the end of the trial period and then extrapolated with an exponential distribution. The company stated that this represented the most conservative approach and utilised the trial data to the fullest extent. The overall survival data were relatively mature with survival in both arms of about 10% by the end of follow up. The company did not use the Kaplan Meier data from the trial for progression-free survival because the 6 weekly assessments caused a stepped curve so parametric curves were used to incorporate the interval censoring. The Weibull distribution was chosen and the company stated that this provided a more plausible fit to the trial data. Progression-free survival data were mature with less than 4% who had not progressed at the end of the trial in both arms. The hazard ratio estimates from the network meta-analysis for best supportive care and docetaxel compared with ramucirumab plus paclitaxel were applied to the baseline curves for ramucirumab plus paclitaxel.

5.12 In the monotherapy model, the company used the gamma distribution to model overall survival and the interval-censored lognormal distribution to model progression-free survival. Lognormal for progression-free survival was stated to be superior to other distributions because of the shorter tails of extrapolation, which was more conservative.

Table 9 Summary of company's approach to extrapolation of survival data for ramucirumab (combination and monotherapy)

	Parameter	Chosen approach in company base case	Company's justification	Explored in scenario analysis
Combination	Overall survival	Kaplan Meier (trial) data until last observed event, then exponential distribution (assuming no difference in hazard between intervention and control)	Most conservative approach	Log-logistic and Weibull

	Progression free survival	Weibull (n.b data was almost complete)	Proportional hazard assumption was valid	Log-Logistic
Monotherapy	Overall survival	Gamma	Although this was the 3rd best fit to the data, it was a more conservative approach	Log-normal
	Progression free survival	Log-normal	Cox-snell residual plots reaffirmed findings of AIC/BIC tests, i.e. log-log and log-normal provided best fit. Lognormal chosen as had shorter tails of extrapolation.	Not explored

ERG comments

5.13 The ERG stated that in general, the process for the extrapolation of survival curves was clear; however, the choice of the survival modelling did not follow the same procedure for all progression-free survival and overall survival curves in the combination therapy and monotherapy models. The ERG agreed that for the combination therapy model the Kaplan-Meier overall survival curve with exponential extrapolation was more plausible than other parametric functions. For modelling progression-free survival, the ERG stated while it understood the reasons for interval censoring adjustments, this approach appeared to slightly underestimate progression-free survival for the paclitaxel plus placebo arm to a greater extent that in the ramucirumab plus paclitaxel arm. The ERG also noted that the company had justified using the Weibull distribution because the proportional hazards assumption was held; however, it stated that there was evidence suggesting violation such as censoring in the tails, overlapping of Kaplan-Meier curves in the first month and interval censoring. The ERG also noted that the proportional hazards assumption was only assessed between the paclitaxel plus

placebo and ramucirumab plus paclitaxel arms; it was assumed to hold for the PFS curves of best supportive care and docetaxel. According to the ERG, choosing the Weibull distribution for progression-free survival over the log-logistic (with a better fit) for the sake of the proportional hazards assumption was unnecessary as well as conflicting with the approach taken for the modelling of overall survival curves.

5.14 For the monotherapy model, the ERG commented that it was not clear which approach had been followed in interval censoring adjustments. In addition, the ERG commented that considering Akaike Information Criteria/Bayesian Information Criteria fit and Cox-Snell residuals, the log-logistic distribution might have been a more appropriate choice for modelling progression-free survival, but that the log-normal and log-logistic parametric estimates were almost the same. Overall, the ERG concluded that the interval-censored log-normal distribution for progression-free survival modelling and the Gamma distribution for overall survival modelling were plausible.

5.15 For the indirect treatment comparison for overall survival, the ERG stated that the network meta-analysis would have been more reliable if it had included results from Roy et al. 2013 (see section 4.22). The ERG noted that this inclusion yielded more favourable results in terms of hazard ratios for the comparators of ramucirumab plus paclitaxel.

Utility values

5.16 Utility values for the pre-progression health state were taken from EQ-5D data from the RAINBOW trial which was used in both the combination therapy and monotherapy models, and the post-progression utility value was taken from the REGARD trial (see Table 10). The company stated that for the monotherapy model it used EQ-5D data from the RAINBOW trial because utility data in the REGARD trial was only collected with the EORTC QLQ C-30 instrument which would require mapping to the EQ-5D. In addition, the company stated that this would require data

imputation since there were insufficient post-baseline data available because of the rapid disease progression in both arms.

5.17 Baseline utility values were adjusted with utility decrements applied for treatment-related adverse events in both the combination therapy model and monotherapy model. The type of adverse events included in the models were based on those that were grade 3 and 4 and occurred in more than 5% of people for each relevant trial. The values of the utility decrements were taken from the literature. A utility increment was applied in the combination therapy model to the proportion of people who responded to ramucirumab plus paclitaxel in the RAINBOW trial (27.9%). The company assumed the response rate for docetaxel was the same as that observed for placebo plus paclitaxel in the RAINBOW trial (16.1%). No response rate was applied to best supportive care in the combination therapy model because the response rate observed in REGARD was very low (2.6%). In addition, no utility increments were applied to responders in the monotherapy model as a result of the low response rates observed in the REGARD trial.

Table 10 Utility values for the combination therapy and monotherapy model

Health state	**Mean**
Pre-progression baseline value (n = 646)	0.737
Adjustment for combination therapy	
Adjustment response rate RAM+PAC each cycle	+0.004
Decrement AEs RAM+PAC cycle 1 only	-0.004
Adjustment response rate DOC each cycle	+0.002
Decrement AEs DOC cyle 1 only	-0.005
Adjustment response rate BSC each cycle	+0.000
Decrement AEs BSC cycle 1 only	-0.002
Adjustment for monotherapy	
Decrement AEs RAM cycle 1 only	-0.001
Decrement AEs BSC cycle 1 only	-0.001
Post-progression utility value (n = 357)	0.587

AEs, adverse events; BSC, best supportive care; DOC, docetaxel; PAC, paclitaxel; RAM, ramucirumab

ERG comments

5.18 The ERG stated that while the company claimed there were insufficient data in the REGARD trial due to rapid disease progression, the lack of data was caused by both the rapid disease progression and the length of time between administering the questionnaires (every 6 weeks), meaning more people had progressed before the first post-baseline questionnaire in the REGARD trial. The ERG also commented that, although the company stated that mapping was second best to direct use of EQ-5D, the population from the REGARD trial might better reflect the patient population for monotherapy (although not suitable for chemotherapy was not an inclusion criteria in the REGARD trial).

Costs and resources

5.19 The costs of the intervention and comparators comprised the drug acquisition, administration and monitoring costs as well as the costs of tests. Drug acquisition costs depended on the cost of the drug, average dose required, treatment duration, relative dose intensity and required pre-medication. The cost of generically available chemotherapies were taken from eMIT, which uses the actual price paid by hospitals over the last 12 months. In order to calculate the required drug doses for each regimen, estimates of body weight and body surface area were taken from the baseline patient characteristics of the RAINBOW and REGARD studies for use in the combination therapy and monotherapy models, respectively. Treatment duration was estimated using parametric curves to determine the time on treatment from trial data. The trials confirmed progression by radiological assessment and patients in the trial (and therefore also in the model) were assessed every 6 weeks. Time on treatment for docetaxel was taken from the literature. Rates of the tests/monitoring were based on expert clinical input. A chart review of hospital medical records was used to identify the cost components of best supportive care.

5.20 Costs further consisted of follow-up costs, adverse event costs, hospitalisation costs, third-line therapy costs (including drug acquisition and administration cost and the cost of follow-up care) and terminal care costs. The company included hospitalisation costs taken from trial data as well as adverse events because it stated hospitalisation may occur as a result of other factors than just treatment related adverse events. Costs of adverse events were included in the models based on their incidence and impact. Inclusion in the model required a threshold for incidence of 5% or more of grade 3 or 4 adverse events, and a significant impact on cost and health-related quality of life were determinants in selecting the relevant adverse events.

ERG comments

5.21 The ERG stated that it would expect the average weight of UK patients to be higher than the RAINBOW baseline patient population (approximately one third of all patients were Asian). The ERG considered it more appropriate to use region 1 data for body surface area and body-weight since it is believed that region data better reflected the UK population.

5.22 The ERG commented that using an incidence based threshold criteria (5% in each relevant treatment arm) for the inclusion of adverse events resulted in a different selection of adverse events for best supportive care in the combination therapy and in the monotherapy models. According to the ERG this approach was inconsistent.

5.23 The ERG indicated a potential double counting of hospitalisation costs because HRGs referring to adverse events also take hospitalisations into account. In the response to the clarification letter, the company provided a scenario which reduced the rate of hospitalisations by an estimate of proportion of hospitalisations due to adverse events. The ERG used these adjusted hospitalisation rates in its exploratory analyses.

5.24 In addition, in the company submission it was mentioned that hospitalisation cost per day was calculated based on the weighted

average of different hospitalisation costs (with HRG codes). However, it was not clear to the ERG which weights were used and the original cost values of the HRG coded hospitalisations.

Company's base-case results and sensitivity analysis

Table 11 Time on treatment, mean overall survival and progression-free survival estimates from the models

Treatment	Time on treatment (months)	Estimated no. of cycles	Mean overall survival (months)	Mean progression free survival (months)
Ramucirumab plus paclitaxel	5.68	6.17	11.63	6.00
Paclitaxel	4.01	6.94	10.07	3.93
Docetaxel	2.19	3.07	7.33	3.53
BSC	1.85	n/a	5.60	1.85
Ramucirumab plus BSC	3.19	6.94	8.21	3.50
Placebo plus BSC	1.57	3.41	6.14	1.57

5.25 The base case ICERs (cost per QALY gained) for the combination therapy model was £118,209 per QALY gained for ramucirumab plus paclitaxel compared with best supportive care (see Table 12 for the full cost effectiveness results from the combination therapy model). The company estimated a probabilistic ICER from the combination therapy model of £116,820 per QALY gained for ramucirumab plus paclitaxel compared with best supportive care. The deterministic sensitivity analysis of the combination therapy model showed that the ICER was most sensitive to the source of drug prices (eMIT compared with BNF), length of hospitalisation stay, dose intensity and the body surface area/body weight source data (all trial patients versus region 1 trial patients).

Table 12 Company's base case deterministic cost effectiveness results compared with best supportive care for the combination therapy model

Technologies	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER (£)
Best supportive care	£13,400	0.29	-	-	
Docetaxel	£18,779	0.39	£5,378	0.10	£53,830
Ramucirumab plus paclitaxel	£52,996	0.62	£39,595	0.33	£118,209

5.26 The base case ICER for the monotherapy model was £188,640 per QALY gained for best supportive care compared with ramucirumab monotherapy (see Table 13 for the full cost effectiveness results from the monotherapy model). The probabilistic ICER from the monotherapy model was £189,232 per QALY gained for ramucirumab compared with best supportive care. The deterministic sensitivity analysis of the monotherapy model revealed that the ICER was most sensitive to the hospitalisation rates, length of hospitalisation, assumptions on wastage (vial wastage versus vial sharing) and extrapolation of post-progression survival.

Table 13 Company's base case deterministic cost effectiveness results for the monotherapy model

Technologies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Placebo plus best supportive care	£14,137	0.31	-	-	-
Ramucirumab plus best supportive care	£36,678	0.43	£22,542	0.12	£188,640

ERG comments

5.27 The ERG identified an error in the half cycle correction of the model submitted by the company. The impact of this correction on the ICER was negligible. The ERG also detected a technical error in the costs for

docetaxel (both in the second and third line). Furthermore, according to the ERG, the drug acquisition costs for ramucirumab plus paclitaxel were underestimated since these were derived based on the average weight of the patients in the RAINBOW trial (one third of patients in RAINBOW were Asian). The ERG identified double counting of hospitalisation costs because the hospitalisation obtained from the trial included hospitalisations due to adverse events. The ERG also considered it more appropriate to use region 1 data for length of hospitalisation stay stratification but in addition to treatment stratification.

Company scenario analyses

Subgroup

5.28 For the combination therapy model, the company performed a scenario analysis using the geographical subgroup, region 1 (North America, Europe, Australia and Israel). In this analysis, it adjusted overall survival, progression-free survival and time on treatment. The company used log-logistic and Weibull distributions. Costs per QALY for ramucirumab plus paclitaxel compared with best supportive care were £114,474 for the Weibull distribution and £95,618 for the log-logistic distribution.

ERG comments

5.29 The ERG considered it plausible to adjust the analysis for region 1, but it stated that this was more relevant for body surface area / body-weight and hospitalisations. Therefore, the ERG considered that the scenario that only adjusted for overall survival, progression-free survival and time on treatment was not appropriate as a new base case.

Modelling overall survival

5.30 For modelling overall survival, the company's base case for the combination therapy model used Kaplan-Meier data until the end of the trial period and then extrapolated with an exponential distribution. Independently fitted overall survival curves showed that the Weibull

distribution followed by the log-logistic distribution had the best fit to the observed trial data for ramucirumab plus paclitaxel. The log-logistic distribution was the best fit for the placebo plus paclitaxel trial data and the Weibull the second worst fitting distribution. The company explored alternative approaches to modelling overall survival as scenario analyses using the Weibull and log-logistic distributions. For ramucirumab plus paclitaxel compared with placebo plus paclitaxel, the Weibull distribution resulted in similar results to the base case analysis (ICER of £117,236 per QALY gained), while the log-logistic distribution reduced the ICER to £96,103 per QALY gained.

5.31 For the monotherapy model, the company modelled overall survival in the base case using the Gamma distribution. In a scenario analysis the company used the lognormal distribution (the distribution with a better fit using the goodness-of-fit diagnostic tests) which reduced the ICER to £174,485 per QALY gained.

ERG exploratory analyses

ERG base case

5.32 The ERG carried out an exploratory analysis (ERG base case) which included the following adjustments:

- Programming errors removed
- Programming errors relating to docetaxel price
- Hospitalisation stratification based on treatment and region
- Body surface area/weight based on region 1
- Double counting of hospitalisations due to adverse events corrected

5.33 The ERG analysis resulted in ICERs compared with best supportive care of £129,431 and £188,055 per QALY gained for the combination therapy and monotherapy models, respectively.

Table 14 ERG Exploratory base case for combination therapy compared with best supportive care

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Best supportive care	£6,695	0.29	-	-	
Docetaxel	£10,523	0.39	£3,828	0.10	£38,280
Ramucirumab plus paclitaxel	£50,050	0.62	£43,354	0.33	£129,431

Table 15 ERG exploratory base case for monotherapy compared with best supportive care

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Best supportive care	£6,853	0.31	-	-	
Ramucirumab	£29,325	0.43	£22,472	0.12	£188,055

Additional comparators

5.34 In additional exploratory analyses, the ERG included the comparators as defined in the final scope. The results of these exploratory analyses are presented in Table 16. The results are presented as pairwise ICERs compared with ramucirumab plus paclitaxel. The ERG commented that these analyses should be interpreted with caution because they relied on the network meta-analysis which was associated with significant uncertainty as a result of heterogeneity between the studies.

Table 16 Pairwise base case results with additional comparators compared with ramucirumab plus paclitaxel

Intervention	Comparator	Hazard ratio	Incr. QALY	Incr. Cost	ICER
Ramucirumab plus paclitaxel	Best supportive care	3.70	0.33	£39,584	£118,174
	Docetaxel	1.79	0.24	£34,153	£145,302
	Irinotecan	Not reported	0.15	£31,238	£213,015
	Paclitaxel	1.59	0.1	£26,790	£273,657
	FOLFIRI	Not reported	0.1	£28,166	£294,362

5.35 In addition, the ERG explored 3 different scenarios in the combination therapy model.

- First, the study of Roy et al. (2013) was included in the overall survival network meta-analysis which revealed the ICER was sensitive to its inclusion (increase of about £14,000 per QALY gained for ramucirumab plus paclitaxel compared with best supportive care).
- Second, an analysis was carried out in which the efficacy data was only based on direct evidence from the RAINBOW trial, (that is, not using the estimates of treatment effectiveness results obtained from the network meta-analysis). This showed that the ICER for ramucirumab plus paclitaxel compared with paclitaxel would be almost £400,000 per QALY gained.
- Third, the utility values from the RAINBOW trial were directly implemented. In the company's base case, the baseline mean EQ-5D index score for the entire RAINBOW intention to treat population was used with UK weights applied along with utility increments due to response and utility decrements due to adverse events. It was also assumed that the pre-progression state utility value remains constant, and the utility increments due to disease response last for the entire progression-free survival period. In the scenario analysis by the ERG, RAINBOW EQ-5D results for each trial arm (from table 21 of the company submission) were used for both the pre-progression and post-progression states. In this scenario analysis the amount of time each utility value is applied in the pre-progression state is taken into consideration. The impact of this scenario on the ICER was limited.

Table 17 Compilation of company and ERG analyses

	Comparator	Incr. QALY	Incr. Cost	ICER
Company base case	BSC**	0.33	£39,595	£118,209
	DOC**	0.23	£34,217	£148,769
Pairwise comparisons with all comparators in NICE scope – performed by ERG using company base case assumptions	BSC**	0.33	£39,584	£118,174
	DOC**	0.24	£34,153	£145,302
	IRI	0.15	£31,238	£213,015
	PAC	0.1	£26,790	£273,657
	FOLFIRI	0.1	£28,166	£294,362 *
ERG exploratory base case - • Remove/correct programming errors • hospitalisation stratification change • Use region 1 body surface area & weight • Correct double counting of adverse event hospitalisations	BSC	0.33	£43,354	£129,431
	DOC	0.23	£39,527	£168,164
ERG exploratory analysis including Roy et al.	BSC	0.30	£43,095	£143,577
ERG exploratory analysis using overall survival data from RAINBOW	PAC	0.09	£35,112	£392,108
ERG exploratory analysis using utility values directly from RAINBOW EQ-5D results	BSC	0.34	£43,354	£129,384

* ERG incremental analysis (using company base case assumptions) also results in this ICER
** Slight difference in costs/QALYs due to ERG correction of programming errors

Innovation

5.36 The company asks the Committee to consider ramucirumab to be innovative for the following reasons:

- The company states that ramucirumab (in combination with paclitaxel or as monotherapy) is the first licensed treatment for advanced gastric cancer or gastro-oesophageal junction adenocarcinoma in the second-line setting. This innovation has been recognised by the EMA in their granting of orphan designation, which is reserved for products that provide an effective treatment option where currently none exist, representing substantial clinical innovation.

- Gastric cancer or gastro-oesophageal junction adenocarcinoma is an orphan disease with very poor prognosis; as such even small absolute gains in survival outcomes can represent important relative increases in survival.

- Ramucirumab is the first biologic agent to have demonstrated efficacy in the second-line setting in 2 phase III trials, providing an alternative to cytotoxic chemotherapy.

6 End-of-life considerations

6.1 The ERG commented that it was very unlikely that the end of life criteria are fulfilled for ramucirumab monotherapy and the company made no claims that it should be considered as such.

6.2 For ramucirumab plus paclitaxel, the company claimed that the end of life criteria had been met: Table 18 summarises the considerations for each criterion.

Table 18 End-of-life considerations for ramucirumab plus paclitaxel therapy

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Patients in the placebo arm of the REGARD trial had a median overall survival of 3.8 months (95% CI: 2.8 to 4.7) and the Kaplan-Meier curve showed that only 2 out of 117 patients are still at risk after 18 months follow-up.
There is sufficient evidence to indicate that the treatment	The company presented additional survival in comparison with best supportive care (mean additional survival: 6.03

offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	months) and docetaxel (mean additional survival: 4.13 months). In the response to the clarification letter the company also presented additional survival in comparison with paclitaxel (mean additional survival: 1.44 months). The ERG presented additional survival of ramucirumab plus paclitaxel versus the other comparators in the scope: irinotecan (mean additional survival: 2.27 months) and (m)FOLFIRI (mean additional survival: 1.1 months). The ERG stated the comparison with paclitaxel is most reliable and should probably be used as the main comparator representing current NHS treatment.
The treatment is licensed or otherwise indicated for small patient populations	Approximately 657 patients diagnosed with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma living in the United Kingdom are estimated to be eligible for second-line treatment following the first-line chemotherapy (based on 2012 data).

7 Equality issues

7.1 None identified

8 Authors

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with input from the Lead Team (Claire McKenna, Gail Coster and Judith Wardle).

Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002829/WC500180726.pdf