NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Ramucirumab alone or with paclitaxel is not recommended within its marketing authorisation for advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy.

1.2 People whose treatment with ramucirumab was started within the NHS before this guidance was published should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Ramucirumab (Cyramza, Eli Lilly and Company) has a UK marketing authorisation 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'.

2.2 Ramucirumab is given as an intravenous infusion over about 60 minutes. Ramucirumab is a human receptor-targeted monoclonal antibody that specifically binds vascular endothelial growth factor (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 is associated with poorer prognosis for people with resected or metastatic disease.

2.3 The summary of product characteristics lists the following adverse reactions: fatigue or asthenia (weakness), neutropenia, leukopenia, diarrhoea, epistaxis (nosebleeds) and hypertension. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The acquisition cost of ramucirumab is £500 per 10-ml (100 mg) vial and £2500 per 50-ml (500 mg) vial (excluding VAT; British national formulary [BNF] edition 69). The recommended dose of ramucirumab with paclitaxel is 8 mg/kg on days 1 and 15 of a 28-day cycle and the recommended dose for ramucirumab monotherapy is 8 mg/kg every 2 weeks. So, assuming the company's estimated mean body weight of 63.33 kg, the drug cost for each treatment cycle is £6000 for combination therapy (2 × 50-ml vials and 2 × 10-ml vials per cycle), or

£3000 for monotherapy (1 × 50-ml vials and 1 × 10-ml vials per cycle). The company estimated that a person having treatment with ramucirumab combination therapy would have 6 cycles (rounded down from a mean of 6.17 cycles). It estimated a person having treatment with ramucirumab monotherapy would have an average of 7 cycles (rounded up from a mean of 6.94 cycles). So the average costs of a course of ramucirumab combination therapy and monotherapy are £36,000 and £21,000 per person respectively (excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.

3 The company's submission

The Appraisal Committee (section 6) considered evidence submitted by Eli Lilly and Company and a review of this submission by the Evidence Review Group (ERG; section 7). See the Committee papers for full details of the evidence.

Clinical effectiveness

RAINBOW (Ramucirumab combination therapy)

3.1 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, which started in 2010, recruited 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.

3.2 The trial randomised 665 adults to have 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, over a 28-day cycle. Randomisation was stratified according to geographic region (region 1 was Europe, Israel, USA and Australia; region 2 was Argentina, Brazil, Chile and Mexico; and region 3 was Hong Kong, Japan, South Korea, Singapore and Taiwan), time to progression from the start of first-line therapy, and disease measurability. The study was carried out in 170 centres in 27 countries in North and South America, Europe, Asia and Australia.

3.3 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 previously had 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 gastro–oesophageal junction, and which has been recommended in NICE's technology appraisal guidance on trastuzumab for the treatment of HER2-positive metastatic gastric cancer as a first-line treatment) was permitted.

3.4 At baseline, most characteristics were balanced between the treatment groups in RAINBOW. These characteristics included: age; sex; ethnic origin; geographic region; disease measurability; time to progression from the start of first-line therapy; weight loss in the preceding 3 months; and presence and location 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 most were white (61% white, 35% Asian, 4% black and other). Most people (79%) had gastric cancer and those remaining had gastro–oesophageal junction adenocarcinoma. Previous trastuzumab therapy was had by 20 people in the ramucirumab plus paclitaxel arm compared with 19 people in the placebo plus paclitaxel arm.

3.5 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 people who had not died (22.4%) were censored on the last date that the person was known to be alive (on or before the 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 [HR] 0.81; 95% confidence interval [CI] 0.68 to 0.96; p=0.0169). Median progression-free survival was 4.40 months for ramucirumab plus paclitaxel and 2.86 months for placebo plus paclitaxel (1.54-month improvement in progression-free survival; HR 0.64; 95% CI 0.54 to 0.75; p=0.0001).

3.6 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.

3.7 In RAINBOW, a similar percentage of people in both study arms stopped treatment because of 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 adverse event was neutropenia, which had a higher all-grade incidence in the ramucirumab plus paclitaxel arm (54.4%) than the placebo plus paclitaxel arm (31.0%).

Geographic region subgroup results

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

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

3.9 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 there was a 2.66-month greater median overall survival ($p=0.0050$), and 1.41-month greater median progression-free survival ($p<0.0001$) for ramucirumab plus paclitaxel compared with placebo plus paclitaxel. The median survival times for both treatment arms in the intention-to-treat population of RAINBOW were longer compared with those for region 1, which the company attributed to the higher rates of third- and fourth-line chemotherapy use among people in region 3 (Asia) after stopping treatment with ramucirumab.

REGARD (ramucirumab monotherapy)

3.10 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, which started in 2009, involved adults with advanced gastric cancer or gastro–oesophageal junction adenocarcinoma who had disease progression on or within 4 months after the last dose of treatment with first-line, platinum-containing or fluoropyrimidine-containing chemotherapy, or on or within 6 months after the last dose of adjuvant therapy.

3.11 The trial randomised 355 adults in a 2:1 ratio to have ramucirumab 8 mg/kg (n=238) or placebo (n=117) intravenously once every 2 weeks. Treatment was given until there was 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 done across 119 centres in 29 countries in North, Central and South America, Europe, Asia, Australia and Africa.

3.12 People in the trial had metastatic disease or locally recurrent, unresectable disease, a life expectancy of 12 weeks or more, and an ECOG performance status score of 0 or 1.

3.13 The primary endpoint was overall survival. Efficacy analysis was by intention to treat. Median overall survival was 5.2 months for ramucirumab plus best supportive care and 3.8 months for placebo plus best supportive care (1.4-month improvement in median survival; HR 0.78; 95% CI 0.60 to 1.0; p=0.047). Median progression-free survival was 2.1 months for ramucirumab plus best supportive care and 1.3 months for placebo plus best supportive care (0.8-month improvement in median progression-free survival; HR 0.48; 95% CI 0.38 to 0.62; p<0.0001).

3.14 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%); but the difference between those people for whom quality-of-life data were available was not statistically significant (p=0.23).

3.15 Overall safety results for the REGARD trial showed similar percentages 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 stopped treatment in the ramucirumab group (10.5%) compared with the placebo group (6.0%).

Network meta-analysis

3.16 The company carried out 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 et al. 2013; Roy et al. 2013; Thuss-Patience et al. 2011), paclitaxel (RAINBOW; Hironaka et al. 2013) and placebo or best supportive care (COUGAR-02; Thuss-Patience et al. 2011). Roy et al. (2013) was a non-randomised multinational study comparing second-line irinotecan with docetaxel. The company did not include the Roy et al. study to estimate overall survival in the base case, but it did include this study in a sensitivity analysis. It was not the company's preference to include FOLFIRI (a regimen made up of folinic acid, irinotecan and fluorouracil) in the network, but in the company's response to clarification it incorporated FOLFIRI using the trial by Sym et al. (2011).

3.17 Results from the indirect comparison suggested that ramucirumab plus paclitaxel was associated with a statistically significantly improved overall survival compared with best supportive care (HR 0.34; 95% CI 0.17 to 0.71), paclitaxel (HR 0.81; 95% CI 0.68 to 0.96) and irinotecan (HR 0.72; 95% CI 0.52 to 0.99), and with a numerically (but not statistically significant) improved overall survival compared with docetaxel (HR 0.51; 95% CI 0.23 to 1.13) and FOLFIRI (HR 0.86; 95% CI 0.45 to 1.65).

Cost effectiveness

3.18 The company submitted 2 separate 3-state partitioned survival models to assess the cost effectiveness of ramucirumab as monotherapy and 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. A lifetime horizon was used in both models (equating to about 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 had 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 used to explore the uncertainty around utility values, survival analysis, unit costs, choice of third-line therapy and various resource-use assumptions. Probabilistic sensitivity analysis was also used to explore parameter uncertainty in the model.

3.19 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, based on the results of its survey of UK treatment patterns, irinotecan and FOLFIRI were not used sufficiently in clinical practice to warrant their inclusion in the economic model.

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

3.21 Transition probabilities between the health states were determined from

parametric survival functions fitted to the data from the RAINBOW (combination therapy) and REGARD (monotherapy) trials. Time in the pre-progression state was estimated directly from the progression-free-survival curves, and time in the post-progression state was estimated from the difference between the progression-free-survival and the overall-survival curves at each time point. Transition probabilities for the comparators docetaxel and best supportive care were estimated using results from the network meta-analysis.

3.22 For the combination-therapy model, the company modelled overall survival using Kaplan–Meier data from the RAINBOW trial until the end of the trial period and then extrapolated with an exponential distribution from 22.14 months (the point at which the last event was seen in the placebo plus paclitaxel arm) to 53.5 months (the time point at which survival was 0.1% in the placebo plus paclitaxel arm when extrapolated using the Weibull distribution). The company stated that this represented the most conservative approach and used 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% whose disease 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.

3.23 In the monotherapy model, the company used the gamma distribution to model overall survival and the interval-censored log-normal distribution to model progression-free survival. Log-normal for progression-free survival was stated to be better than other distributions because of the shorter tails of extrapolation, which made it more conservative.

3.24 Utility values for the pre-progression and the post-progression health

states were taken from EQ-5D data from the RAINBOW trial. The company stated that for the monotherapy model it used EQ-5D data from the RAINBOW trial because utility data in the REGARD trial were only collected with the EORTC-QLQ-C-30 instrument, which would need to be mapped to the EQ-5D. In addition, the company stated that this would need data to be inputted, because there were insufficient post-baseline data available as a result of the rapid disease progression in both arms.

3.25 Baseline utility values were adjusted with utility decrements applied for treatment-related adverse events in both the combination-therapy model and monotherapy model. The types 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 whose disease responded to ramucirumab plus paclitaxel in the RAINBOW trial (27.9%). The company assumed that the response rate for docetaxel was the same as that seen 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 seen in REGARD was very low (2.6%). In addition, no utility increments were applied to people whose disease responded in the monotherapy model because of the low response rates seen in the REGARD trial.

3.26 The costs of the intervention and comparators included the drug acquisition, administration and monitoring costs as well as the costs of tests. Any leftover drug in opened vials was assumed to be discarded (no vial sharing). Drug acquisition costs depended on the cost of the drug, average dose needed, treatment duration, relative dose intensity and pre-medication needed. The costs of available generic chemotherapies were taken from the electronic market information tool (eMIT), which uses the actual price paid by hospitals over the last 12 months. The drug dosages for each regimen were based on estimates of body weight and body surface area, which 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 for the tests and monitoring were based on expert clinical input. The cost components of best supportive care were identified from a review of hospital medical records.

3.27 Costs further consisted of follow-up, adverse event, hospitalisation, third-line therapy (including drug acquisition, administration and follow-up care) and terminal care costs. The company included hospitalisation costs taken from trial data as well as adverse events, because it stated that people may be admitted to hospital because of factors other than treatment-related adverse events. Costs of adverse events were included in the models based on their incidence and impact. Grade 3 or 4 adverse events with an incidence of 5% or more and adverse events that had a significant impact on cost- and health-related quality of life were determinants for inclusion in the model.

3.28 The base-case incremental cost-effectiveness ratio (ICER) for the combination-therapy model was £118,209 per quality-adjusted life year (QALY) gained for ramucirumab plus paclitaxel compared with best supportive care. 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 hospital stay, dose intensity and the body surface area or body weight source data (all trial patients compared with region 1 trial patients).

3.29 The base-case ICER for the monotherapy model was £188,640 per QALY gained for best supportive care compared with ramucirumab monotherapy. 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 showed that the ICER was most sensitive to the hospital admission rates, length of hospital stay, assumptions on waste (vial waste compared with vial sharing) and extrapolation of

post-progression survival.

3.30 For the combination-therapy model, the company did a scenario analysis using the region 1 geographical subgroup (Europe, Israel, USA and Australia). 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.

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

3.32 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 log-normal 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 critique

3.33 The ERG stated that the RAINBOW trial was a good-quality randomised controlled trial including more than 300 patients in each treatment group, and uncertainty about long-term follow-up is likely to be small because 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 the comparator group (that is, paclitaxel alone). 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.

3.34 The ERG noted that in the REGARD trial there was an imbalance in histological subtype, percentage of peritoneal metastases, number of metastatic sites and previous anticancer treatment. It commented that most of the imbalances in baseline characteristics in the REGARD trial favoured the intervention group (that is, ramucirumab monotherapy). 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 had paclitaxel, the ERG stated it was possible that all patients in the REGARD trial could have been eligible for paclitaxel.

3.35 The ERG considered that the network meta-analysis results should be interpreted with caution. Because of significant differences in countries in Europe and North, Central and South America compared with Asian countries in the incidence of gastric cancer, histology, and screening and treatment approaches, the inclusion of at least 1 trial in an Asian population would lead to a high level of heterogeneity. In addition, the ERG was particularly concerned at the reliance of the network on a study that was carried out in an entirely Japanese population (Hironaka et al. 2013); all comparisons with ramucirumab plus paclitaxel used this link in the evidence network. The company included a study by Thuss-Patience et al. (2011), which included an irinotecan arm. The ERG noted that this study closed prematurely because of poor recruitment, and only included 40 patients meaning it was underpowered. The ERG stated that the network meta-analysis would have been more reliable if it had included results from Roy et al. (2013), which also included an irinotecan arm. The ERG noted that the inclusion of Roy et al. made the hazard ratios for the comparator treatments more favourable.

3.36 For the combination-therapy model, the ERG agreed with the company that best supportive care and docetaxel were relevant comparators for

ramucirumab plus paclitaxel. However, the ERG did not agree with the company's decision to exclude comparators, which were included in the final scope, based on the 'established use' criterion for 3 reasons:

- Established NHS practice is already incorporated as a criterion for defining the most appropriate scope.
- The inclusion criterion used by the company of at least 10% usage in the NHS is not a formal rule.
- The proportion of treated patients is very low and therefore the proportion of patients having certain comparators will always be low when calculated over all patients whose disease progressed after chemotherapy.

3.37 According to the company's survey of real-world treatment patterns, paclitaxel was used for 3% of patients, which included all people whose disease progressed after chemotherapy; the ERG noted that this proportion would be 10.5% if the number of people who had paclitaxel was divided by the total number of people who had second-line therapy. The ERG also considered it plausible that the proportion of people having paclitaxel may increase if NICE was to recommend ramucirumab plus paclitaxel for this indication in the NHS. The ERG also commented that the company's survey of real-world treatment patterns was based on data from June to July 2013, and that since then favourable results for docetaxel from the COUGAR II study have been published, which may have resulted in increased real-world use of taxanes in general (paclitaxel as well as docetaxel). The ERG stated that the use of irinotecan and FOLFIRI could also increase as a result, and so the inclusion of these treatments in the comparison could also be considered relevant.

3.38 In additional exploratory analyses, the ERG included the comparators defined in the final scope. These analyses were presented using the company's base-case assumptions (with the exception of correcting confirmed programming errors – see section 3.45). The results of these exploratory analyses are presented in table 1. The ERG commented that these analyses should be interpreted with caution because they relied on the network meta-analysis that was associated with significant uncertainty as a result of heterogeneity between the studies. For this

reason, the ERG presented results of the exploratory analyses as ICERs for ramucirumab plus paclitaxel compared with each treatment separately (pairwise), rather than in an incremental analysis.

Table 1 Pairwise base-case results for additional comparators compared with ramucirumab plus paclitaxel using the company's base-case assumptions*

Intervention	Comparator	Hazard ratio	Incremental QALY	Incremental 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

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

*Company's base-case assumptions were used except for a corrected programming error.

3.39 The ERG stated that comparing ramucirumab with best supportive care was sufficient. It noted the comparison was in line with the final scope of this guidance, if it is accepted that 'not suitable for paclitaxel' means the same as 'not suitable for further cytotoxic chemotherapy'. If this is not accepted, the ERG stated that comparisons with cytotoxic chemotherapy, other than paclitaxel (docetaxel, irinotecan and FOLFIRI), were missing.

3.40 The ERG stated that, in general, the process for the extrapolation of survival curves was clear; but 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 the most plausible approach because of the poor fit of parametric functions from independent modelling approaches. The ERG stated that, although it understood the reasons for interval-censoring adjustments in the modelling for progression-free survival, this approach appeared to slightly underestimate progression-free survival for the paclitaxel plus placebo arm to a greater extent than in the ramucirumab plus paclitaxel arm. The ERG also noted that the company had justified using the Weibull-distribution model because the proportional hazards assumption was held; but 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 progression-free-survival curves of best supportive care and docetaxel. According to the ERG, choosing the Weibull-distribution model 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 modelling overall-survival curves.

3.41 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.

3.42 The ERG stated that it would expect the average weight of UK patients to be higher than the RAINBOW baseline patient population (about 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 because it is believed that region 1 data better reflected the UK population. The ERG considered the company's scenario analysis in which it adjusted the analysis for region 1 was plausible, but it stated that this was more relevant for body surface area, body weight and hospitalisations. Therefore, the ERG considered that the company's scenario analysis, which only adjusted for overall survival, progression-free survival and time on treatment, was not appropriate as a new base case.

3.43 The ERG commented that using an incidence-based threshold criterion (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 monotherapy models. According to the ERG, this approach was inconsistent.

3.44 The ERG indicated a potential double counting of hospitalisation costs because Health Resource Groups' (HRGs) codes referring to adverse events also take hospitalisations into account. In the response to the clarification letter, the company provided a scenario that reduced the rate of hospitalisations by an estimate of the proportion of hospitalisations due to adverse events. The ERG used these adjusted hospitalisation rates in its exploratory analyses for its base case. The ERG found 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 found 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 because these were based on the average weight of the patients in the RAINBOW trial (one-third of patients in RAINBOW were Asian).

3.45 The ERG did an exploratory analysis and in its base case it included the following adjustments:

- removal of programming errors
- correction of programming errors relating to docetaxel price
- hospitalisation stratification based on treatment and region

- body surface area and weight based on region 1
- correction of double counting of hospitalisations due to adverse events.

3.46 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. For the combination therapy model, the ERG also applied these amendments to analyses in which the comparator was first, docetaxel, and second, paclitaxel. When the comparator treatment was docetaxel, the ICER increased to £168,164 per QALY gained. When the comparator treatment was paclitaxel, the ICER increased substantially to £359,794 per QALY gained. In both of these analyses, the increase in the ICER was largely due to removing the double counting of hospitalisations for adverse events and using body surface or weight based on region 1. However, the increase was much greater when the comparator was paclitaxel. This was because the impact on the costs of docetaxel when the body surface area was based on region 1 was much lower than for ramucirumab and paclitaxel.

3.47 In addition, the ERG explored 3 different scenarios in the combination-therapy model:

- The study of Roy et al. (2013) was included in the overall-survival network meta-analysis, which showed that the ICER was sensitive to its inclusion (increase of about £14,000 per QALY gained for ramucirumab plus paclitaxel compared with best supportive care).
- An analysis was carried out in which the efficacy data were only based on direct evidence from the RAINBOW trial (that is, not using the estimates of treatment effectiveness results from the network meta-analysis). This showed that the ICER for ramucirumab plus paclitaxel compared with paclitaxel increased from the ERG's base case of £359,794 per QALY gained to £392,108 per QALY gained.
- In addition to using the efficacy data, the utility values from the RAINBOW trial were also directly implemented. In this scenario analysis, the amount of time each utility value is applied in the pre-progression state was taken into consideration. This resulted in an ICER for ramucirumab plus paclitaxel compared with paclitaxel of £408,223 per QALY gained.

4 Committee discussion

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ramucirumab, having considered evidence on the nature of advanced gastric cancer or gastro–oesophageal junction adenocarcinoma and the value placed on the benefits of ramucirumab by people with the condition, those who represent them and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee considered the nature of gastric cancer and gastro–oesophageal junction adenocarcinoma. It acknowledged that the prognosis for people with this disease is very poor. In addition, it understood that gastric cancers have a major impact on the person's quality of life, as well as that of carers and other family members. The Committee heard from clinical experts that although there have been some advances in this disease area over the last 2 decades through the use of chemotherapies and a targeted agent (for people with HER2 amplification), there was still a need for new active agents, in particular, for those people whose disease had progressed after prior chemotherapy. The Committee concluded that the outlook for people with this disease was poor and that new active treatments offering improved outcomes were needed.

4.2 The Committee noted that the company submission had considered 2 populations, in line with the marketing authorisation for ramucirumab. Each population included people with advanced gastric cancer or gastro–oesophageal junction adenocarcinoma with disease progression. The Committee noted that for people in whom treatment in combination with paclitaxel is appropriate, progression must be after platinum **and** fluoropyrimidine chemotherapy, whereas for people in whom treatment in combination with paclitaxel is not appropriate, progression must be after platinum **or** fluoropyrimidine chemotherapy. The Committee heard from the clinical experts that about 50% of people have an initial active treatment, and that for these people, current clinical practice usually includes a triple regimen of an anthracycline (or trastuzumab for people with HER2 amplification), a platinum agent and a fluoropyrimidine. The Committee also heard that about 30% of people will have a second treatment after their disease progresses while on the first treatment, at

which point ramucirumab would be considered. The Committee concluded that the populations included in the company submission were appropriate and in line with current clinical practice.

4.3 The Committee considered the company's decision problem, and noted that it was in line with the NICE scope, with the exception of the choice of comparators. The Committee understood that the company had carried out a survey of UK treatment patterns, which found that best supportive care was the most commonly used option in UK clinical practice for people whose disease has progressed after chemotherapy, and therefore the company considered that best supportive care was the only relevant comparator for ramucirumab. However, the Committee noted comments from professional groups that active treatments, particularly the taxanes (docetaxel and paclitaxel), are routinely used throughout the UK, and that irinotecan and FOLFIRI are sometimes used, although to a much lesser extent. With regard to deciding between the taxanes, it heard from a clinical expert that for the population under consideration, paclitaxel is an established treatment option in the tertiary centre in which the expert works. Regarding docetaxel, the Committee heard from clinical experts that after the publication of the COUGAR-02 study results, there was a shift in clinical practice towards increased use of docetaxel but that this trend has not continued because of its toxicity profile. It also noted that the company had chosen paclitaxel as the comparator for its own trial. Finally, the Committee noted the clinical expert's statements, which reported 'there is clinical equipoise between weekly paclitaxel and three-weekly docetaxel and the choice depends on physician and patient preference'. The Committee understood that people who are considered fit for ramucirumab in combination with paclitaxel must by definition be able to tolerate paclitaxel monotherapy. Given this rationale in conjunction with the comments from clinical experts, the Committee was not persuaded that best supportive care was an appropriate comparator for the ramucirumab plus paclitaxel population. The Committee considered whether best supportive care was the only relevant comparator for ramucirumab monotherapy. It understood that the company considered that people for whom treatment in combination with paclitaxel is not appropriate could be more broadly characterised as not eligible for cytotoxic chemotherapy. It further understood that there are no alternative non-cytotoxic active

treatments for the disease. The Committee therefore agreed with the company that best supportive care would be the only option for the ramucirumab monotherapy population. The Committee concluded that for people for whom ramucirumab combination therapy is appropriate, paclitaxel and docetaxel were both relevant comparators and are in established use in clinical practice in England. Best supportive care was not considered an appropriate comparator for this population because people who are considered suitable for ramucirumab in combination with paclitaxel must be suitable for paclitaxel alone. FOLFIRI and irinotecan were not considered relevant comparators for this population because they are not in established use. The Committee further concluded that best supportive care was the only relevant comparator for ramucirumab monotherapy when treatment with cytotoxic chemotherapy is not appropriate.

Clinical effectiveness

4.4 The Committee discussed the nature and quality of evidence for the clinical effectiveness of ramucirumab in combination with paclitaxel (RAINBOW) and for ramucirumab monotherapy (REGARD). Regarding ramucirumab monotherapy, the Committee was aware that the trial population for REGARD was very similar to that of RAINBOW, and it heard from clinical experts that the only notable difference between the trials was the choice of comparator. It heard that REGARD started 1 year earlier (2009) than RAINBOW (2010) and that the difference in comparators reflected a change in clinical practice in that year. The Committee considered that there was some uncertainty in whether people in REGARD were eligible for paclitaxel. However, it was persuaded that overall the evidence was representative of the population included in the marketing authorisation for ramucirumab monotherapy. It also noted that there was no other evidence put forward for this population, and considered it likely that no further evidence for this population would become available in the future. Regarding the evidence for ramucirumab plus paclitaxel from the RAINBOW trial, the Committee was aware that the population in the study was in agreement with the marketing authorisation and that the Evidence Review Group (ERG) had considered the study to be a good-quality, international, randomised controlled trial with low levels of uncertainty because of the mature overall-survival and

progression-free-survival data. The Committee concluded that the REGARD trial was suitable evidence on which it could base a decision on the clinical efficacy of ramucirumab monotherapy. It further concluded that the evidence from the RAINBOW trial was also appropriate for basing a decision on the clinical efficacy of ramucirumab plus paclitaxel.

4.5 The Committee considered the relative clinical-effectiveness evidence for ramucirumab. It was aware of the overall-survival and progression-free-survival outcomes for ramucirumab plus paclitaxel compared with placebo plus paclitaxel (see section 3.5) and for ramucirumab plus placebo compared with placebo plus best supportive care (see section 3.13). Regarding the clinical safety of ramucirumab, the Committee was aware that neutropenia was the most frequently reported serious adverse event, with a higher incidence in people who had ramucirumab. The Committee noted that the European public assessment report (EPAR) on the clinical safety of ramucirumab concluded that it was generally acceptable and in line with other similar treatments, and the Committee therefore considered that overall it did not have any particular safety concerns. The Committee concluded that ramucirumab plus paclitaxel provided an extension to life of 2.3 median months in overall survival with similar toxicity to placebo plus paclitaxel. It further concluded that ramucirumab plus best supportive care provided a median extension to life of 1.4 months compared with placebo plus best supportive care, and that it also offers an active treatment option for people for whom cytotoxic chemotherapy is not considered appropriate.

4.6 The Committee discussed the network meta-analysis that had been carried out by the company. It noted that the mean additional survival gains using the results of the network meta-analysis for ramucirumab plus paclitaxel were 4.13 and 6.03 months compared with docetaxel and best supportive care respectively. The Committee questioned why these survival gains were substantially higher than the median overall-survival gains seen from the trial data. It considered comments from the ERG that the results of the network meta-analysis should be interpreted with caution because of the heterogeneity of the included studies. The network was weakened by 2 crucial links. First, the Committee was aware that the network of evidence relied on the Hironaka et al. (2013)

study that was in an entirely Japanese population where there is a national screening programme to diagnose the disease in the earlier stages. It also heard from the clinical experts that patients included in the Hironaka et al. study had much longer survival gains than are typically seen in UK clinical practice. The Committee noted comments from the company during consultation that there was no clear biological rationale for why the hazard ratio from the Hironaka et al. study (which relied on the relative rather than absolute treatment effect of paclitaxel compared with irinotecan) would be different in a western population. However, the Committee noted that no evidence had been presented to confirm that this would be the case, and so it was still of the opinion that there was significant uncertainty about using the results of this trial in the network meta-analysis. Second, the network also relied on the Thuss-Patience et al. (2011) study, which had few patients and was stopped early. The Committee noted comments from the company during consultation that the early termination of the trial was related to difficulties in recruitment, rather than efficacy, so the trial results should still be unbiased. However, the Committee, noting that the trial was based on a sample of only 40 randomised patients, considered the point estimates for the treatment effect to be associated with considerable uncertainty. The Committee discussed how network meta-analysis can be useful to strengthen the evidence base, but noted that in this case there were multiple single trials between ramucirumab and docetaxel, each associated with increased uncertainty, and with no link to ramucirumab other than the RAINBOW trial. The Committee was also mindful of clinical expert statements (see section 4.3) that the choice between paclitaxel and docetaxel depends on physician and patient preference. The Committee was aware that the guide to the methods of technology appraisal (section 5.2.12) states 'Data from head-to-head RCTs should be presented in the reference-case analysis'. The Committee therefore considered there to be no requirement to accept the results of the network meta-analysis, with its associated uncertainty, rather than directly relevant head-to-head data from a good-quality, international, randomised controlled trial with mature overall-survival and progression-free-survival data. The Committee concluded that for the basis of decision-making, the results of the network meta-analysis would not be used in preference to the RAINBOW trial data comparing ramucirumab plus paclitaxel with paclitaxel plus placebo.

Cost effectiveness

4.7 The Committee considered the company's economic models for ramucirumab combination therapy and monotherapy. It noted that the structures were identical, but that they included different populations according to the indications for combination therapy and monotherapy in the marketing authorisation. The Committee was aware that the structure of the models was commonly used for cancer cost-effectiveness analyses with pre-progression, post-progression and death states, and considered that this was appropriate. The Committee was further aware that the ERG had included the following adjustments to the model in its base case (see section 3.45):

- Corrected programming errors and errors relating to the price of docetaxel.
- Corrected the double counting of hospitalisations because Healthcare Resource Groups' (HRGs) codes referring to adverse events also take hospitalisations into account.
- Used region 1 data for stratifying length of hospitalisation stay and treatment stratification.

- Used body surface area and body weight based on region 1 data instead of the intention-to-treat population data.

  The Committee was aware that the company had confirmed the errors related to programming and the price of docetaxel at clarification stage, noting that the impact on the ICER was negligible. The Committee considered that the drug acquisition costs for ramucirumab and paclitaxel had been underestimated by the company because they were based on the average weight of all people in the RAINBOW trial, about one-third of whom were Asian. It therefore agreed with the adjustments carried out by the ERG to use region 1 data for body surface area and body weight. It also agreed with the ERG's adjustments to correct for double counting of hospitalisations, and to adjust length of hospitalisation stay for region 1. The Committee noted that the ERG's adjustments resulted in ICERs compared with best supportive care of £129,400 and £188,100 per QALY gained for the combination-therapy and monotherapy models respectively. The Committee concluded that the model submitted by the company was robust and suitable for the purposes of its decision-making and that the ERG's suggested amendments to the model were appropriate.

4.8 The Committee considered the use of health-state utility values in the model. Regarding the health-state utility value for the pre-progression health state, the Committee understood that the model used the baseline utility value adjusted for treatment response and adverse effects. It was aware that the company's approach assumed that this value remained constant throughout the time that a person is in the pre-progression health state. The Committee discussed the alternative approach suggested by the ERG in a scenario analysis, in which it used the RAINBOW trial data from different time points during the pre-progression period to avoid adjusting the trial data. The Committee expressed a preference for data that do not have to be manipulated and therefore agreed that the ERG's approach was reasonable. It noted that the impact of this scenario analysis was very small (decreasing the ERG's base-case ICER by less than £50 per QALY gained). The Committee concluded that, although it made only a minor difference to the ICER, it had a preference for using the ERG's approach to modelling pre-progression health-state utility and that this was incorporated into its consideration of the most plausible ICER.

4.9 The Committee considered the use of parametric curves for estimating

progression-free survival. It understood that the company had used this approach because the 6-weekly assessments caused a stepped curve, so parametric curves were used to incorporate interval censoring. It noted that this approach was inconsistent with the methods used for the combination-therapy model to estimate overall survival, in which the company had used Kaplan–Meier data from the trial. The Committee was aware that the company had carried out sensitivity analyses for the combination-therapy model using alternative parametric curves and that this had made little difference to the ICER. The Committee noted that the progression-free-survival data were mature and it considered that the company's approach to fitting parametric curves to estimate progression-free survival rather than using Kaplan–Meier data from the trial was not necessary. It concluded that although it has a preference for using direct trial data when they are available, this did not influence the cost-effectiveness analyses and therefore the company's approach to modelling progression-free survival was considered acceptable.

4.10 The Committee understood that treatment with ramucirumab is continued until disease progression and therefore the assumptions around frequency of assessment of disease progression were potential drivers of cost effectiveness. This was because the total acquisition costs of the technology were dependent on this assumption. It understood that people in the trial, and therefore in the model, were assessed for progression every 6 weeks. The Committee heard from the clinical experts that this reflected UK clinical practice. The Committee concluded that the assumption of 6-weekly assessments was therefore reasonable.

4.11 The Committee considered the most plausible ICER for the combination-therapy model. The Committee was mindful of its previous conclusions that paclitaxel and docetaxel are both appropriate comparators for ramucirumab combination therapy (see section 4.3), that the overall survival and progression-free survival results of the network meta-analysis should not be used in preference to the direct head-to-head data from the RAINBOW trial (see section 4.6), and its preferred approach to the utility values for the pre-progression health state (see section 4.8). On this basis, the Committee considered the most robust estimate was the ERG's exploratory analysis, which used

RAINBOW trial data for ramucirumab plus paclitaxel compared with placebo plus paclitaxel, and which used utility values from RAINBOW data over different time points during the pre-progression period. The Committee therefore concluded that the most plausible ICER for people with gastric cancer or gastro–oesophageal junction adenocarcinoma for whom treatment in combination with cytotoxic chemotherapy is appropriate was £408,200 per QALY gained (representing incremental costs of £35,100 and incremental QALYs of 0.09).

4.12 The Committee considered the most plausible ICER for the monotherapy model. The Committee was aware of its earlier conclusions during which it established that best supportive care was a valid comparator (see section 4.3), and in which it accepted the adjustments to the model made by the ERG (see section 4.7). The Committee therefore concluded that the most plausible ICER for people with gastric cancer or gastro–oesophageal junction adenocarcinoma for whom further cytotoxic chemotherapy is not appropriate was £188,100 per QALY gained (representing incremental costs of £22,500 and incremental QALYs of 0.12).

4.13 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for people with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.14 The Committee noted the views of the company that ramucirumab combination therapy fulfils all 3 end-of-life criteria when compared with best supportive care or docetaxel. It considered whether ramucirumab met the first criterion for an end-of-life treatment that patients have a short life expectancy, normally less than 24 months. It noted that patients in the placebo plus best supportive care arm of the REGARD trial had a median overall survival of 3.8 months, and patients in the placebo plus paclitaxel arm of the RAINBOW trial had a median overall survival of 7.4 months. The Committee therefore concluded that the life expectancy for people with advanced gastric cancer or gastro–oesophageal junction adenocarcinoma was less than 24 months.

4.15 The Committee considered whether ramucirumab offered an extension to life of at least 3 months. It was aware that the company had considered this criterion had been met using results of the network meta-analysis for overall survival gains compared with best supportive care (6.03 months), and compared with docetaxel (4.13 months). It was also aware that the company had stated during consultation that the overall-survival gains of all relevant comparators should be considered when determining if the end-of-life criteria have been met. The Committee considered the survival gains for all relevant comparators (see section 4.3 for the discussion of relevant comparators), but it was aware of its previous conclusions about the network meta-analysis, and considered that the overall-survival gain from the network meta-analysis for ramucirumab plus paclitaxel compared with docetaxel was not plausible, objective or robust. The Committee considered that the RAINBOW trial data for overall survival were mature, and therefore the modelled mean overall survival gain of 1.30 months compared with placebo plus paclitaxel using direct evidence from the RAINBOW trial was the most robust estimate available, and consequently the only estimate on which it could consider the criterion relating to extension to life of at least 3 months. The Committee therefore agreed that ramucirumab plus paclitaxel did not offer an extension to life of at least an additional 3 months. The Committee was aware that the company had only presented a case for ramucirumab combination therapy to fulfil the end-of-life criteria, and that the median survival gain of ramucirumab monotherapy was 1.4 months compared with placebo plus best supportive care from the REGARD trial. The Committee therefore

considered ramucirumab monotherapy did not offer an extension to life of at least an additional 3 months.

4.16 The Committee considered the total size of the population in the ramucirumab marketing authorisation for advanced gastric cancer or gastro–oesophageal junction adenocarcinoma for people who have already had platinum therapy. It noted that the company had estimated the size of this population in England as 657 people. It understood that the company had calculated this figure by using 2012 Office for National Statistics (ONS) data adjusted to 2015 (the effect of which was to reduce the figure by around 500 people) to give 8270 people with gastric cancer or gastro–oesophageal junction adenocarcinoma. The Committee heard from the ERG that since this appraisal started, 2013 ONS data have become available, and that these data showed the number of people with gastric cancer or gastro–oesophageal junction adenocarcinoma had not gone down, but had increased to 9198 people. The Committee therefore considered that any downward adjustment was not needed. The Committee agreed with the company, based on data from Cancer Research UK, that 80% of people with gastric cancer or gastro–oesophageal junction adenocarcinoma have metastatic or advanced disease. The Committee noted that the company then assumed 43% of people have oncology treatment (based on data from the 2013 National Oesophago-Gastric Cancer Audit), representing those who have palliative oncology treatment, with the remaining 57% having best supportive care, palliative surgery, and endoscopic or radiological palliation. Of this 43%, the company had then used a figure of 77% (also based on the audit data) to calculate the number of people who would have chemotherapy, with the remaining 23% having either radiotherapy or chemoradiotherapy. The Committee considered the audit data to be a reliable source. It noted that, in the final step of the company's population estimate, the company assumed 30% of people who have chemotherapy go on to have second-line chemotherapy. The Committee heard from the ERG that this was based on a survey of UK treatment patterns that the company had conducted 1 month before COUGAR II had been published, and that since then the positive results for docetaxel in the COUGAR II study may have led to increased use of chemotherapy in general. In the absence of other data, the Committee considered the value of 30% was reasonable, but believed there to be

some uncertainty because of changes to clinical practice since the results of COUGAR II were published. The Committee estimated that based on a population size of 9198 people with gastric cancer or gastro–oesophageal junction adenocarcinoma, and using all other company assumptions, the total population would be around 731 people. The Committee considered that the total population size for the ramucirumab marketing authorisation for advanced gastric cancer or gastro–oesophageal junction adenocarcinoma, for people who have already had platinum therapy, was likely to be greater than 731 people, but fewer than 1000 people. The Committee, noting that this range was considerably less than 7000, concluded that the small population size criterion was met.

4.17 The Committee concluded that the end-of-life considerations could not be applied for ramucirumab in combination with paclitaxel or as a monotherapy, because in both cases the extension-to-life criterion of at least an additional 3 months was not met.

4.18 The Committee discussed how innovative ramucirumab is in its potential to make a significant and substantial impact on health-related benefits. It noted that ramucirumab is the first biologic agent to have shown efficacy in people whose disease had progressed after chemotherapy, and that it provides an active treatment option for people for whom cytotoxic chemotherapy is not appropriate. Mindful of its conclusion in section 4.1 about the prognosis for people with this disease, the Committee also agreed that this is an area of high unmet medical need, with consequences not only for people but also carers and family members. However, the Committee concluded that all health-related benefits had been adequately captured by the QALYs in the model, and it agreed that ramucirumab did not offer a step change in the treatment of this disease.

4.19 The Committee concluded that ramucirumab in combination with paclitaxel for the treatment of adults with advanced gastric cancer or gastro–oesophageal junction adenocarcinoma, with disease progression after platinum and fluoropyrimidine chemotherapy, was not a cost-effective use of NHS resources at the usual range of ICERs (£20,000 to £30,000 per QALY). It further concluded that ramucirumab monotherapy for the treatment of adults with advanced gastric cancer or

gastro–oesophageal junction adenocarcinoma with disease progression after platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate was not a cost-effective use of NHS resources at the usual range of ICERs (£20,000 to £30,000 per QALY).

4.20 The Committee discussed whether there were any equality issues it should consider before making its recommendations. It noted the company submission and comments received during consultation had stated that the lack of an available licensed treatment after disease progression on chemotherapy can lead to inequalities in access in different parts of England. It considered this was an issue of geographical variation and it was not aware that the potential inequality in access applied to any protected groups covered by the equality legislation. It also considered that any NICE recommendation would be applied consistently across England, thereby reducing variation in practice. It concluded that there was no unfairness or unlawful discrimination, and as a result there were no equality issues, and it did not need to alter its recommendations in any way.

4.21 The Committee considered whether it should take into account the consequences of PPRS 2014, and in particular the PPRS payment mechanism, when appraising ramucirumab. The Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view on the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not applicable when considering the cost effectiveness of ramucirumab.

Summary of Appraisal Committee's key conclusions

TA378	Appraisal title: Ramucirumab for treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy	Section

Key conclusions	
Ramucirumab alone or with paclitaxel is not recommended within its marketing authorisation for advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy.	1.1
Based on the results of the RAINBOW trial, the Committee concluded that ramucirumab plus paclitaxel provided an extension to life of 2.3 median months in overall survival compared with paclitaxel plus best supportive care. Based on the results of the REGARD trial, ramucirumab plus best supportive care provided an extension to life of 1.4 median months in overall survival compared with placebo plus best supportive care.	4.5
The Committee considered the network meta-analysis was weakened by 2 crucial links; the Hironaka et al. (2013) trial and the Thuss-Patience et al. (2011) trial. It considered there to be significant uncertainty about using the results of these trials in the network meta-analysis. The Committee concluded that for the basis of decision-making, the overall survival and progression-free survival results of the network meta-analysis would not be used in preference to the RAINBOW trial data comparing ramucirumab plus paclitaxel with paclitaxel plus placebo.	4.6
The Committee considered the most robust estimate was the ERG's exploratory analysis, which used RAINBOW trial data for ramucirumab plus paclitaxel compared with placebo plus paclitaxel, and which used utility values from RAINBOW data over different time points during the pre-progression period. The Committee concluded that the most plausible incremental cost-effectiveness ratio (ICER) for ramucirumab plus paclitaxel compared with best supportive care plus paclitaxel for people in whom treatment in combination with cytotoxic chemotherapy is appropriate was £408,200 per quality-adjusted life year (QALY) gained.	4.11
The Committee concluded that the most plausible ICER for ramucirumab monotherapy compared with best supportive care for people in whom treatment in combination with cytotoxic chemotherapy is not appropriate was £188,100 per QALY gained.	4.12
The Committee concluded that the end-of-life considerations could not be applied for ramucirumab in combination with paclitaxel or as a monotherapy, because in both cases the extension-to-life criterion of at least an additional 3 months was not met.	4.17

The Committee concluded that ramucirumab, alone or in combination with paclitaxel, for adults with advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy was not a cost-effective use of NHS resources.		4.19
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee concluded that the outlook for people with this disease was poor and that new active treatments offering improved outcomes were needed.	4.1
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	Ramucirumab has shown efficacy in people whose disease had progressed after chemotherapy, and it provides an active treatment option for people for whom cytotoxic chemotherapy is not appropriate. The Committee also agreed that this is an area of high unmet medical need. However, the Committee concluded that all health-related benefits had been adequately captured by the QALYs in the model, and it agreed that ramucirumab did not offer a step change in the treatment of this disease.	4.18
What is the position of the treatment in the pathway of care for the condition?	The Committee heard from the clinical experts that about 50% of people have an initial active treatment, and that for these people, UK clinical practice usually includes a triple regimen of an anthracycline (or trastuzumab for people with HER2 amplification), a platinum agent and a fluoropyrimidine. The Committee also heard that about 30% of people will have a second treatment after their disease progresses while on the first treatment. Ramucirumab (in combination with paclitaxel, or as a monotherapy) would be considered as a potential second treatment option after disease progression, because the marketing authorisation is for adults with disease progression after prior platinum and/or fluoropyrimidine chemotherapy.	4.2

Adverse reactions	The Committee noted that the European public assessment report (EPAR) on the clinical safety of ramucirumab concluded that it was generally acceptable and in line with other similar treatments, and the Committee therefore considered that overall it did not have any particular safety concerns.	4.5
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee considered evidence from the 2 main randomised controlled trials for ramucirumab monotherapy compared with best supportive care (the REGARD trial) and for ramucirumab plus paclitaxel compared with paclitaxel plus best supportive care (the RAINBOW trial). The Committee was aware that the Evidence Review Group (ERG) had considered the RAINBOW study to be a good-quality, international, randomised controlled trial with low levels of uncertainty because of the mature overall-survival and progression-free-survival data.	4.4
Relevance to general clinical practice in the NHS	The Committee considered that there was some uncertainty in whether people in REGARD were eligible for paclitaxel. However, it was persuaded that overall the evidence was representative of the population included in the marketing authorisation for ramucirumab monotherapy. Regarding the evidence for ramucirumab plus paclitaxel from the RAINBOW trial, the Committee was aware that the population in the study was in agreement with the marketing authorisation and concluded that the overall survival evidence was also appropriate for basing a decision on the clinical efficacy of ramucirumab plus paclitaxel.	4.4

Uncertainties generated by the evidence	The Committee considered that there was some uncertainty in whether people in REGARD were eligible for paclitaxel. However, it was persuaded that overall the evidence was representative of the population included in the marketing authorisation for ramucirumab monotherapy. The Committee concluded that for the basis of decision-making, the results of the network meta-analysis would not be used in preference to the RAINBOW trial data comparing ramucirumab plus paclitaxel with paclitaxel plus placebo.	4.4 4.6
Estimate of the size of the clinical effectiveness including strength of supporting evidence	Based on the results of the RAINBOW trial, the Committee concluded that ramucirumab plus paclitaxel provided a median overall survival of 2.3 months compared with paclitaxel plus best supportive care. Based on the results of the REGARD trial, ramucirumab plus best supportive care provided a median overall survival of 1.4 months compared with placebo plus best supportive care.	4.5
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee considered the company's 2 economic models (which had identical structures but included different populations for ramucirumab monotherapy and combination therapy), and the critique of these by the ERG to inform its discussions.	4.7
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee considered the choice of the company to use parametric curves for estimating progression-free survival. It noted that this approach was inconsistent with the methods used for the combination-therapy model to estimate overall survival, in which the company had used Kaplan–Meier data from the trial. The Committee concluded that although it has a preference for using direct trial data when they are available, this issue did not influence the cost-effectiveness analyses.	4.9

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee understood that the company's model used utility-value data from the RAINBOW trial. The baseline utility value for the pre-progression health state was adjusted for treatment response and adverse effects, which remained constant throughout the time that a person was in the pre-progression health state. The Committee discussed the alternative approach suggested by the ERG, in which it used the RAINBOW trial data from different time points during the pre-progression period to avoid adjusting the trial data. The Committee expressed a preference for data that do not have to be manipulated and therefore agreed that the ERG's approach was reasonable.	4.8
Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that the most plausible ICER for ramucirumab plus paclitaxel compared with best supportive care plus paclitaxel for people in whom treatment in combination with cytotoxic chemotherapy is appropriate was £408,200 per QALY gained.	4.11
	The Committee concluded that the most plausible ICER for ramucirumab monotherapy compared with best supportive care for people in whom treatment in combination with cytotoxic chemotherapy is not appropriate was £188,100 per QALY gained.	4.12
Additional factors taken into account		
Patient access schemes (PPRS)	There is no patient access scheme.	-

End-of-life considerations	The Committee concluded that the end-of-life considerations could not be applied for ramucirumab in combination with paclitaxel or as a monotherapy, because in both cases the extension-to-life criterion of at least an additional 3 months was not met. The Committee considered that ramucirumab plus paclitaxel met the end-of-life criteria for a short life expectancy and a small patient population.	4.17 4.14 4.16
Equalities considerations and social value judgements	The Committee noted the company submission and comments received during consultation had stated that the lack of an available licensed treatment after disease progression on chemotherapy can lead to inequalities in access in different parts of England. The Committee concluded that there was no unfairness or unlawful discrimination, and as a result there were no equality issues, and it did not need to alter its recommendations in any way.	4.20

5 Review of guidance

5.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon
Chief Executive
January 2016

6 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne
Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Dr David Black
Medical Director, NHS South Yorkshire and Bassetlaw

Mr David Chandler
Lay Member

Gail Coster
Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome
Honorary Professor, Department of Primary Care and Population Health, University College London

Professor Rachel A Elliot
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Nigel Langford
Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

Dr Patrick McKiernan
Consultant Paediatrician, Birmingham Children's Hospital

Dr Andrea Manca
Health Economist and Senior Research Fellow, University of York

Dr Iain Miller
Founder and Chief Executive Officer, Health Strategies Group

Dr Paul Miller
Director, Payer Evidence, AstraZeneca UK Ltd

Professor Stephen O'Brien
Professor of Haematology, Newcastle University

Dr Anna O'Neill
Deputy Head of Nursing & Health Care School, Senior Clinical University Teacher, University of Glasgow

Dr Claire Rothery
Research Fellow in Health Economics, University of York

ProfessorPeter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Dr Paul Tappenden
Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Professor Robert Walton
Clinical Professor of Primary Medical Care, Barts and The London School of Medicine and Dentistry

Dr Judith Wardle
Lay Member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Chris Chesters
Technical Lead

Joanne Holden
Technical Adviser

Lori Farrar
Project Manager

7 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Reviews Ltd:

- Riemsma R, Al M, Büyükkaramikli N et al. Ramucirumab for treating advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy, July 2015

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to make written submissions. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company:

- Eli Lilly and Company

II. Professional/expert and patient/carer groups:

- Independent Cancer Patients' Voice
- Association of Cancer Physicians
- Cancer Research UK
- Oesophageal Patients Association
- Royal College of Nursing
- Royal College of Physicians
- Royal College of Radiologists

III. Other consultees:

- Department of Health
- NHS England
- NHS Greater Huddersfield Clinical Commissioning Group
- NHS Wigan Borough Clinical Commissioning Group
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Institute of Cancer Research
- National Cancer Research Institute
- Kleijnen Systematic Reviews Ltd
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Cancer

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on ramucirumab for treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma after chemotherapy by attending the initial Committee discussion and providing a written statement to the Committee. They were also invited to comment on the ACD.

- Dr Naureen Starling, Consultant Medical Oncologist, nominated by Royal College of Physicians – clinical expert
- Dr Wasat Mansoor, Consultant Medical Oncologist, nominated by Eli Lilly – clinical expert

E. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Eli Lilly and Company

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Accreditation