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RE: Lilly response to STA clarification questions: Ramucirumab for treating metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma after chemotherapy [ID741]

Dear Frances

Please find enclosed the clarification requested by the ERG and the NICE technical team in relation to the clinical and cost effectiveness data of ramicirumab.

Please contact me if you have any further queries, either by email or telephone (01256 775022).

Kind regards

[redacted]
[redacted] **Health Outcomes & HTA**

Section A: Clarification on effectiveness data

A1. ***Priority request:*** *Please provide the full clinical study reports for the RAINBOW and REGARD studies. We received clinical study reports for REGARD and RAINBOW, but these are short versions (each less than 200 pages).*

We have sent the clinical study reports (CSRs) for REGARD and RAINBOW - up to and including chapter 14 - to Lori Farrar (Committee C Project Manager) on an encrypted USB stick.

Due to the layout of chapter 14, patient level data has been included in that section. As we do not believe it appropriate to share potentially identifiable patient level data, the CSRs are both cropped from the beginning of the patient narratives and some data has been redacted.

Please note that between the date that the RAINBOW CSR was finalised and the ramucirumab STA submission, an inconsistency was identified due to a SAS programming error in the SDTM dataset for the EQ-5D domain. This error has been corrected and since it did not result in an invalid conclusion, it has been corrected without an amendment of the approved RAINBOW CSR. We have provided the corrected tables and figures on the encrypted USB stick. The following corrections should be considered when reviewing chapter 14 of the RAINBOW CSR:

Table/Figure in Rainbow CSR	To be replaced with table/figure in following file (sent on encrypted USB stick)
Table 14.2.43	tdimr
Figure 14.2.24	fdimr
Table 14.2.44	tinds
Figure 14.2.25	finds

The evidence dossier and economic model relating to ramucirumab submitted to NICE on 15 May 2015 utilises the correct EQ-5D values.

A2. *Please provide the number of UK patients for each arm in the two trials: RAINBOW and REGARD.*

Number of UK patients in RAINBOW (ITT population)[1] (Table 14.1.1. pg 172)

	Number of patients
Ramucirumab + Paclitaxel arm	6
Placebo + Paclitaxel arm	9
Total	15

Number of UK patients in REGARD (ITT population)[2] (Table 14.1. pg 129)

	Number of patients
Ramucirumab + BSC arm	13
Placebo + BSC arm	4

Total	17

A3. Please provide the number of participants from the subgroup 'Region 1' by individual country (separate for each European country, Israel, Australia, USA and New Zealand) and for each arm.

Number of participants in subgroup 'Region 1' in RAINBOW[1] (Table 14.1.1. pg 167)

	Paclitaxel plus Ramucirumab N=330	Paclitaxel plus Placebo N=335	Total N=665
Australia	18	23	41
Austria	4	2	6
Belgium	12	14	26
Bulgaria	7	5	12
Estonia	5	5	10
France	20	14	34
Germany	20	20	40
Great Britain	6	9	15
Hungary	20	9	29
Israel	15	15	30
Italy	13	15	28
Lithuania	6	6	12
Poland	15	18	33
Portugal	2	0	2
Romania	7	7	14
Russia	8	13	21
Spain	8	13	21
United States	12	12	24
Total in Region 1	**198**	**200**	**398**

Number of participants in subgroup 'Region 1' in REGARD[2] (Table 14.1. pg 127)

	Ramucirumab plus BSC N=238	Placebo plus BSC N=117	Total N=355
Australia	8	4	12
Bosnia and Herzegovina	1	3	4
Canada	8	2	10
Czech Republic	24	13	37
Spain	12	4	16
United Kingdom	13	4	17
Croatia	7	0	7
Italy	23	11	34
Malta	2	3	5
New Zealand	1	1	2
Poland	9	4	13
Romania	13	4	17
Russia	14	8	22
Turkey	5	1	6

United States	25	18	43
Total in Region 1	**165**	**80**	**245**

A4. Please indicate whether there were differences in overall dose modification between patients with gastric cancer and gastric oesophageal junction cancer.

Assessment of dose modification by pre-treatment factors was restricted to special subgroups (age, race, gender) and geographical region for regulatory purposes. We did not conduct an assessment by location of primary disease.

A5. Please indicate the number and proportion of patients recruited for each arm that received anthracycline in the two trials: RAINBOW and REGARD.

Patients receiving prior anthracycline and related substances in RAINBOW study[1] (Table 14.1.12 pg 234)

	Number of patients (%)
Ramucirumab + Paclitaxel arm (n=330)	82 (24.8)
Placebo + Paclitaxel arm (n=335)	96 (28.7)

Summary of prior anthracycline use in REGARD: (Lilly Data on File)

	Number of patients (%)
Ramucirumab + BSC arm (n=238)	72 (30.3)
Placebo + BSC arm (n=117)	28 (23.9)

A6. Neuropathy (peripheral sensory, neuropathy peripheral, polyneuropathy, peripheral motor neuropathy, neuralgia, hypoesthesia, paraesthesia) as an adverse event occurred at a higher rate in the intervention group compared to the comparator. Please indicate the proportion of neuropathy cases (adverse events) that were irreversible in both RAINBOW and REGARD, by treatment group.

An analysis of outcome of neuropathy was not performed for the following reasons:

1. <u>Neuropathy was not associated with ramucirumab but rather with paclitaxel.</u>

   Paclitaxel treatment is often associated with neuropathy[3], which appears dependent on schedule and on cumulative dose[4]. In REGARD, the incidence of neuropathy was comparable between the ramucirumab arm (any grade 4.2%, grade 3/4 0%) and the placebo arm (any grade 6.1%, grade 3/4 0.9%). In RAINBOW, the higher incidence of neuropathy in the ramucirumab plus paclitaxel arm was likely related to that, on average, patients in the ramucirumab plus paclitaxel arm remained on paclitaxel treatment for a longer duration and received a higher cumulative dose of paclitaxel. The median cumulative dose of paclitaxel was 813.0 mg/m^2 in the ramucirumab plus paclitaxel arm versus 714.0 mg/m^2 in the placebo plus paclitaxel arm. This was supported by an analysis of the incidence of neuropathy at 4-week intervals (0-4 weeks, 4-8 weeks, 8-12 weeks, etc.). This analysis showed that the incidence of neuropathy

was mostly comparable between the 2 arms, when compared across an individual 4-week-interval (that is, 0-4 weeks).

The incidence of paclitaxel-related grade 3/4 neuropathy found in RAINBOW is consistent with those previously reported in studies using the same dose and schedule of paclitaxel. In the RAINBOW study, grade 3/4 neuropathy (consolidated term) occurred with an incidence of 8.3% and 4.6% in the ramucirumab plus paclitaxel and placebo plus paclitaxel arms, respectively. The Phase 3 WJOG 4007 study that compared weekly paclitaxel and biweekly irinotecan in patients with advanced gastric cancer refractory to treatment with fluoropyrimidine plus platinum reported a similar incidence of grade 3/4 neuropathy for patients treated with weekly paclitaxel (7.4% ; sensory neuropathy only).[5]

2. <u>Due to incomplete follow-up of all neuropathy events, an analysis of outcome would not provide the information on whether these neuropathy events were reversible or not.</u>

According to the study protocol, adverse event (AE) monitoring was to occur on a continuous basis only for the duration that patients were on study therapy. The time from the first dose of study treatment until 30 days following the last dose of study treatment was considered the 'on study therapy' duration. Additionally, only serious adverse events and adverse events considered at least possibly-related to study therapy were followed until resolved, stabilised, returned to baseline, or deemed irreversible. In RAINBOW, the percentage of patients with study drug-related neuropathy was low (ramucirumab: 7.6%, placebo: 5.5%) compared with paclitaxel-related neuropathy (ramucirumab plus paclitaxel arm: 45.9%, placebo plus paclitaxel arm: 36.2%). Hence, most of these events were not followed up until resolution, and the outcome was reported as 'NOT RECOVERED/NOT RESOLVED' on the case report form.

A7. The population chosen for the monotherapy analysis is people for whom further cytotoxic chemotherapy is not appropriate. The marketing authorisation population for the monotherapy indication is those for whom treatment in combination with paclitaxel is not appropriate. However, the inclusion/exclusion criteria of the REGARD trial suggests that people who would be suitable for further cytotoxic chemotherapy or for whom treatment with paclitaxel is appropriate, would still have been eligible to join the trial. Please confirm if this was the case.

Yes, at the time of the REGARD trial design, there was no restriction to patients for whom further cytotoxic chemotherapy would not be appropriate. At the time the study was designed and initiated, there was no evidence that any therapy was superior to other agents/regimens and no agent had been demonstrated to improve survival over BSC.

Priority request: *Please provide numbers of patients in each arm and separate data of overall survival and progression-free survival from the REGARD trial for patients for whom treatment in combination with paclitaxel is not appropriate.*

It is not possible to estimate the number of patients in each arm of REGARD for whom treatment in combination with paclitaxel is not appropriate. Data from the trial were not collected to

systematically identify these patients, especially as the REGARD trial was initiated before the RAINBOW trial was designed to evaluated ramucirumab in combination with paclitaxel. More importantly, choice of whether the patient is appropriate for monotherapy or combination therapy is a matter of clinical judgment.

The licensing restriction of ramucirumab monotherapy to patients for whom treatment in combination with paclitaxel is not appropriate was the result of discussion with the Committee for Human Medicines Products and was based on a full consideration of the clinical trial evidence from REGARD and RAINBOW and clinical expert opinion regarding current treatment options available in second-line gastric and gastro-oesophageal junctional cancers (GC/GOJ).

A8. Please provide the number of responders of the EQ-5D index scores of Table 21 of the company submission.

RAINBOW: EQ-5D Results (ITT population)[1] (Lilly Data on File: tinds)

	RAM+PAC N=330	PBO+PAC N=335
EQ-5D Index Score, n		
Baseline	323	323
Cycle 2, Day 15	246	221
Cycle 4, Day 1	178	128
Cycle 5, Day 15	118	78
Cycle 7, Day 1	71	42
Cycle 8, Day 15	57	22
Cycle 10, Day 1	35	18
End of Treatment	206	206

*A9. **Priority request:** Please provide the additional mean survival of ramucirumab in combination with paclitaxel compared with all comparators in the NICE scope (similar to the comparisons provided in tables 51 [versus BSC] and 52 [versus docetaxel]).*

Given the prior lack of licensed treatments for second-line GC/GOJ, Lilly applied clear criteria to determine which treatments are currently used in clinical practice in the England and therefore which are appropriate comparators in this economic evaluation. These criteria were:

1) Inclusion in the final NICE scope
2) Used in >10% of the second-line patient population

Using real world data from UK clinical practice, FOLFIRI and irinotecan were shown to be used in only ≤2% of all patients who have progressed following first- line treatment and paclitaxel is

estimated to be used in 3% of all patients. Based on this evidence, FOLFIRI and irinotecan were not included in the cost-effectiveness model and incremental mean survival estimates are not available for these comparators.

The mean additional survival of ramucirumab in combination with paclitaxel compared with paclitaxel is presented below.

Mean additional survival of ramucirumab plus paclitaxel versus paclitaxel (Combination therapy economic model)

Intervention	Life years	Months
PAC	0.81	9.72
RAM+PAC	0.94	11.28
Incremental	0.12	1.44

NB: Numbers may not compute due to rounding

Network meta-analysis

A10. ***Priority request:*** *Please provide a full list of the 18 trials included and the corresponding 22 publications mentioned in Figure 24 (page 109 of the company submission). Please explain how this relates to Figure 25 (page 111 of the company submission) and Appendix 6. (Figure 25 includes 21 trials and Table 3 of Appendix 6 lists 18 trials, but does not include the RAINBOW trial, Qin 2014, Nishikawa 2014, Satah 2014 and Cohen 2014; Table 3 does include Kim 2011 and Kim 2012, but these are not in Figure 25.)*

Please provide data extraction tables (as in Appendix 6) for studies used in the network meta-analysis, such as RAINBOW.

References and/or PDFs for Sym 2013, Qin 2014, Nishikawa 2014, Satah 2014 and Cohen 2014 seem to be missing. Please provide these, and any other missing publications.

The numbers in the appendix do not seem to correspond with the references in the folder 'Appendices Refs'. Please provide all PDFs for the references in the appendices.

The network meta-analysis (NMA) literature search was updated in May 2014, but the PRISMA diagram for the search run in December 2013 was wrongly included in the submission (Figure 24 on page 109). 23 trials were included in the final potential NMA, which were presented in 30 publications. The updated PRISMA flow diagram, the network of randomised clinical trials identified and the full data extraction tables of all included studies can be found in Appendix 1. However, the actual analysis was limited to regimens that are cited in ESMO and NCCN guidelines.

The requested references for missing publications are as follow:

1. Sym SJ, Hong J, Park J, Cho EK, Lee JH, Park YH, et al. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. Cancer Chemotherapy & Pharmacology. 2013 Feb;71(2):481-8.

2. Qin S, Li J, Xu J, Xiong J, Wu C, Bai Y, et al. Phase III study of apatinib in advanced gastric cancer: A randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2014;32(5s):suppl; abstr 4003. http://hwmaint.meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/4003
3. Nishikawa K, Tanabe K, Fujii M, Kunisaki C, Tsuji A, Matsuhashi N, et al. A randomized phase III trial of second-line chemotherapy comparing CPT-11 alone versus S-1 plus CPT-11 combination therapy in advanced gastric cancer refractory to first-line therapy with S-1 (JACCRO GC-05). J Clin Oncol. 2014;32:Suppl 3; abstr 87.http://meetinglibrary.asco.org/content/122666-143
4. Satoh T, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study. J Clin Oncol. 2014 Jul 1;32(19):2039-49.
5. Cohen SJ, Feng Y, Catalano PJ, Mitchell EP, O'Dwyer PJ, Lubner SJ. E2208: Randomized phase II study of paclitaxel with or without the anti-IGF-IR antibody cixutumumab (IMC-A12) as second-line treatment for patients with metastatic esophageal or GE junction cancer. J Clin Oncol. 2014; 32(5s): suppl; abstr 4020. http://meetinglibrary.asco.org/content/131896-144

It should however be noted that *Qin 2014*, *Nishikawa 2014*, *Satoh 2014 and Cohen 2014* were not used in the analysis. References 1 and 4 are provided. References 2, 3 and 5 are available online.

The references used in the submission appendices have been provided. There are six additional references also provided: numbers 1 and 4 mentioned above and three newly referenced in this response (Scripture, 2006; Kim, 2013 and Iacovelli, 2014) and one in the WinBUGS code in the appendices (Fryback, 2001).

A11. Please clarify the meaning of the 'm' in mFOLFIRI on page 110 of the company submission, as leucovorin (folinic acid) is already in the FOLFIRI regimen.

mFOLFIRI refers to modified FOLFIRI. FOLFIRI was originally developed using irinotecan 180 mg/m^2 bi-weekly, but now more commonly the modified regimen of 150 mg/m^2 is used globally.

A12. Please explain why (m)FOLFIRI was not included in any of the evidence networks for combination therapy. According to Figure 25 this is possible using Sym 2013, but Sym 2013 is not included in Fig 26 (overall survival), Fig 27 (progression-free survival) or Fig 28 (adverse events).

FOLFIRI was not included in the evidence networks for combination therapy for this submission because its use in clinical practice in the UK does not justify its inclusion as a comparator in the cost-effectiveness model. The data were however identified in the search and are provided in Appendix 2.

A13. ***Priority request:*** *For table 44 (overall survival), table 46 (progression-free survival) and table 48 (adverse events), please add results for comparisons with irinotecan and FOLFIRI. These are relevant comparators as per the final scope issued by NICE and*

the data are available. Please do the same for the network meta-analyses analyses in Appendix 6.

Please see appendix 2.

A14. Please provide a full list of eligibility criteria for indirect comparisons. Table 42 lists some criteria, but according to Figure 24 (page 109 of the company submission), language and year of publication were also exclusion criteria.
Please explain why language and year of publication were exclusion criteria and please provide a list of references of records excluded because of language and year of publication.

Year of publication was not an exclusion criterion. Reporting it as such was an error. The updated PRISMA diagram does not include this criterion.

The restriction to English language studies only was for practical reasons and is commonly applied in searches. Search strategies were similar for two recently reported meta-analyses for previously treated GC/GOJ[6,7]. Iacovelli et al[7] explicitly restricted the search to English only. The list of studies excluded due to language is provided in Appendix 3.

The analysis was limited to interventions cited in ESMO and NCCN guidelines, but the search strategy eligibility included:

Study designs

Included:

- Clinical (human) Phase II or III RCTs
- Superiority or non-inferiority RCTs
- Blinded or open label RCTs

Population

Adult patients (≥18 years) who received prior chemotherapy (no restriction on line of therapy) for the following:

- Gastric cancer
- Gastro-esophageal junction (GEJ) cancer

Interventions and comparators

Eligible studies included at least one treatment arm examining one of the following therapies:

Chemotherapy

- Capecitabine
- Carboplatin
- Cisplatin
- Docetaxel
- Epirubicin
- Etoposide

- Irinotecan
- Mitomycin
- Oxaliplatin
- Paclitaxel
- CAPOX
- EOX
- FLOT
- FOLFIRI
- mFOLFIRI
- 5-FU
- S-1
- Tegafur

Targeted therapy

- Apatinib
- Bevacizumab
- Everolimus
- Lapatinib
- Ramucirumab
- Trastuzumab

Comparators to include any of the above interventions, placebo, BSC, or active symptom control (ASC).

Outcomes

Eligible studies reported at least one of the following outcomes listed below. The primary focus of the review was a measure of survival. However studies which report response rates only were flagged.

- Overall Survival (OS)
- Progression-free survival (PFS) with definition (N.B. RECIST 2009 guidelines change the definition of disease progression and therefore of PFS).
- 12-week PFS rate
- Time to progression (TTP) with definition
- Objective response rate (ORR) (complete response (CR), partial response (PR), overall response (=CR+PR)) as measured by WHO or RECIST or revised v1.1 RECIST guidelines
- Stable disease (SD)
- Clinical benefit or disease control rate (DCR) (=CR+PR+SD)
- Any of the above with respect to prognostic factor subgroups

A15. ***Priority request:*** *Please provide full Winbugs codes and the corresponding data used in all network meta-analyses.*

The WinBUGs code is provided in Appendix 4. Please note two additional comparators are included in the code but their results are not presented as they are not relevant to the decision problem.

Section B: Clarification on cost-effectiveness data

B1. ***Priority request:*** *Please provide the cost-effectiveness analyses (including all relevant input values and outcomes) for the additional comparators in the scope issued by NICE but not in the model: ramucirumab in combination with paclitaxel compared with irinotecan and compared with FOFIRI (in the same way as has been provided for the comparisons with docetaxel and BSC).*

Given the prior lack of licensed treatments for second-line gastric cancer Lilly applied clear criteria to determine which treatments are currently used in clinical practice in the England and therefore which are appropriate comparators in this economic evaluation. These criteria were:

- Inclusion in the final NICE scope
- Used in >10% of the second-line patient population

Using real world data from UK clinical practice FOLFIRI and irinotecan were shown to be used in only ≤2% of all patients who have progressed following first line treatment. Lilly therefore chose not to include FOLFIRI and irinotecan in the cost-effectiveness model given this evidence. Full cost-effectiveness analyses are therefore not available for these comparators.

B2. *Please clarify if the hazard ratio=1.00 arrow in figure 42, (page 160 of the company submission) between best supportive care and irinotecan should instead have been drawn between ramucirumab and irinotecan. In its current position the figure implies that the indirect comparison of best supportive care compared with ramucirumab is also 1, which is not in line with the hazard ratio observed in the REGARD trial.*

Yes we can confirm that this was an error. Thank you for bringing this to our attention.

B3. *Please provide a rationale for using adjusted baseline EQ-5D utility scores for clinically meaningful events (i.e., adverse events and tumour response) instead of using the treatment arm specific utility values (Table 21) derived at different time points (including response rate and adverse events).*

Treatment specific utility values derived at different time points were not used because this data was not available for the relevant comparators of interest, BSC and docetaxel. As both these comparators would be expected to have either a different response rate or different adverse event profiles, it would not be appropriate to use the ramucirumab plus paclitaxel or the placebo plus paclitaxel utility values during treatment for either BSC or docetaxel.

B4. *Please explain why studies which may have provided inputs for the cost estimates in the model were excluded from the literature search (Figure 29, page 136 of the company submission). Alternatively, please clarify if these 5 excluded studies were included in the literature search on page 185 of the company submission.*

The results of the literature search of economic models were reviewed for potential sources of cost and resource to use in the economic model. The studies (including the cost analyses) were

conducted in a number of different countries, all of which have different health care systems to the UK. Specifically two were from Brazil, two from Romania, two from China, one from South Korea, one from Mexico and two from the US. The only study identified which was concerning the provision of health care in the UK was an adaptation of the economic model from TA208. Given the difference in the provision of health care in these other countries versus England, it was decided that they were unlikely to contain information which would be directly applicable to English clinical practice.

However, the review of NICE appraisals had identified TA191 and TA208 as relating to first-line gastric cancer. These appraisals were reviewed for appropriate cost and resource data sources which were utilised where appropriate, as is outlined on page 185.

B5. Please provide a rationale to explain why the adverse events odds ratios from the indirect treatment comparison or network meta-analyses were not used in the model.

The network meta-analyses for adverse events did not provide data on all adverse events of interest (as specified in the inclusion criteria). A completed network was only available for grade 3 and 4 anaemia, neutropenia and febrile neutropenia for the relevant comparators. Therefore for consistency across the estimation of AEs it was decided to use the count data for all adverse events rather than using odd ratios for some and not for others.

B6. Please provide a sensitivity analysis in which patients remain on treatment whilst they are in the pre-progression health state (i.e. time on treatment = progression-free survival).

This has been added as a sensitivity analysis to both economic models.

B7. Please clarify whether data relating to the duration of hospitalisations due to adverse events were collected in the RAINBOW and REGARD trials.

Duration of hospitalisations due to adverse events in RAINBOW[1] (Table 14.3.81. pg 2861)

	Number of patients	
	RAM +PAC (N=327)	PBO+PAC (N=329)
Total Duration of hospitalization due to AEs (for patients who were hospitalized for AEs) (days)		
n	120	102
Mean (SD)	14.7 (14.09)	17.2 (20.81)
Median	10.0	11.0
Q1-Q3	5.0 - 19.0	7.0-19.0
Min-Max	1 - 74	0 – 146

REGARD (Source: Lilly Data on File)

	Number of patients	
	RAM (N=236)	PBO (N=115)

Total Duration of hospitalization due to AEs (for patients who were hospitalized for AEs) (days)		
n	80	44
Mean (SD)	13.36	10.55
Median	10.5	9
Q1-Q3	5-17.5	6-15.5
Min-Max	1-44	1-26

B8. In the model, treatment-specific hospitalisation probabilities have been estimated that are used in both the post-progression and progression-free health states. This means that the probability of hospitalisation in the post-progression health state after ramucirumab in combination with paclitaxel is different to the probability of hospitalisation after paclitaxel (or another comparator) as indicated in Table 108 of the company submission. However, it is also assumed that the treatment after progression in both arms do not differ much (the majority of patients receive palliative care and only a small proportion receive active 3rd line treatment). Please explore the effect of this assumption in sensitivity analysis, using an alternative scenario with the post progression rate equal for all treatments, based on the individual patient level data.

Individual patient level data is not available for hospitalisation in the post-progression health state as this data was only collected whilst patients were receiving study drug or placebo. To explore a sensitivity analysis where the rate of hospitalisation is set equal for all treatments in the post-progression health state, the lowest and highest rate observed in each trial (from the pre-progression health state) was applied in the model. The following rates are used based on the individual patient level data from the trials.

Probability of hospitalisation used in sensitivity analysis (Source: RAINBOW and REGARD safety data)

Economic model	Probability	
	Highest value	Lowest value
Combination therapy	0.055	0.034
Monotherapy	0.055	0.024

B9. Please clarify whether the Healthcare Resource Groups provided in table 115 of the company submission include hospitalisations for adverse events. If so, please clarify if hospitalisations are double counted in the model, as they are also estimated through the individual patient level data from the pivotal trials. According to the CSR of REGARD "The most common reason for hospitalization was AEs, accounting for 80 (33.9%) patients in the ramucirumab arm and 44 (38.3%) patients in the placebo arm".

The Health Resource Groups provided in table 115 were costed using the long and short stay episodes, which relates to admission to hospital for >1 day or ≤1 day respectively. The only

exception was neutropenia which used the day case value because no values were reported for long-stay and only 1 for short-stay.

To address the concern regarding the potential for double counting, a scenario has been added in the monotherapy model to reduce the rate of hospitalisations by the estimate proportion of hospitalisations due to adverse events. This relates to a reduction by 88% for ramucirumab and 95% for best supportive care in the monotherapy model. Similarly a scenario has been added for the combination therapy model to reduce the rate of hospitalisations by 68% for ramucirumab plus paclitaxel, 74% for docetaxel (or paclitaxel) and 95% for best supportive care.

B10. ***Priority request:*** *Please provide more details on the clinical expert consultation mentioned in Chapter 5 of the company submission (for example for follow-up costs on page 187). How many experts were consulted, what was their area of expertise, which questions were asked and if applicable, what was the range of their responses?*

At the latter stages of the development of the submission, three medical oncologists who specialise in gastric cancer were approached to review the submission and validate the relevant clinical assumptions relating to English practice. One based on [redacted], one in [redacted] and the third in [redacted]. They were chosen because of their involvement in clinical trials within the UK and experience in treating patients at large cancer centres in England.

A copy of the relevant questions is attached along with the range of responses provided in Appendix 5.

Supplementary clinical opinion was referenced in the appendices which relates to the following. At advisory boards in 2014 ten oncologists were requested to provide an overview of the resource associated with treating certain adverse events. The oncologists were chosen to participate in the ad board given their experience in treating gastric and oesophageal cancers. One ad board was set in Bristol and included clinicians from the South West and Wales, the other was in Scotland which may limit its applicability to English clinical practice. The responses however show broad consistent in their responses across the regions. These responses were used to sense-check the AE costs estimated using the NHS reference costs but did not contain enough detail to conduct a micro-costing exercise. A table of the responses is provided in Appendix 6.

B11. *Please explain if there is potential double counting by including both terminal costs separately and the admission days as obtained from the trial data during the post-progression phase.*

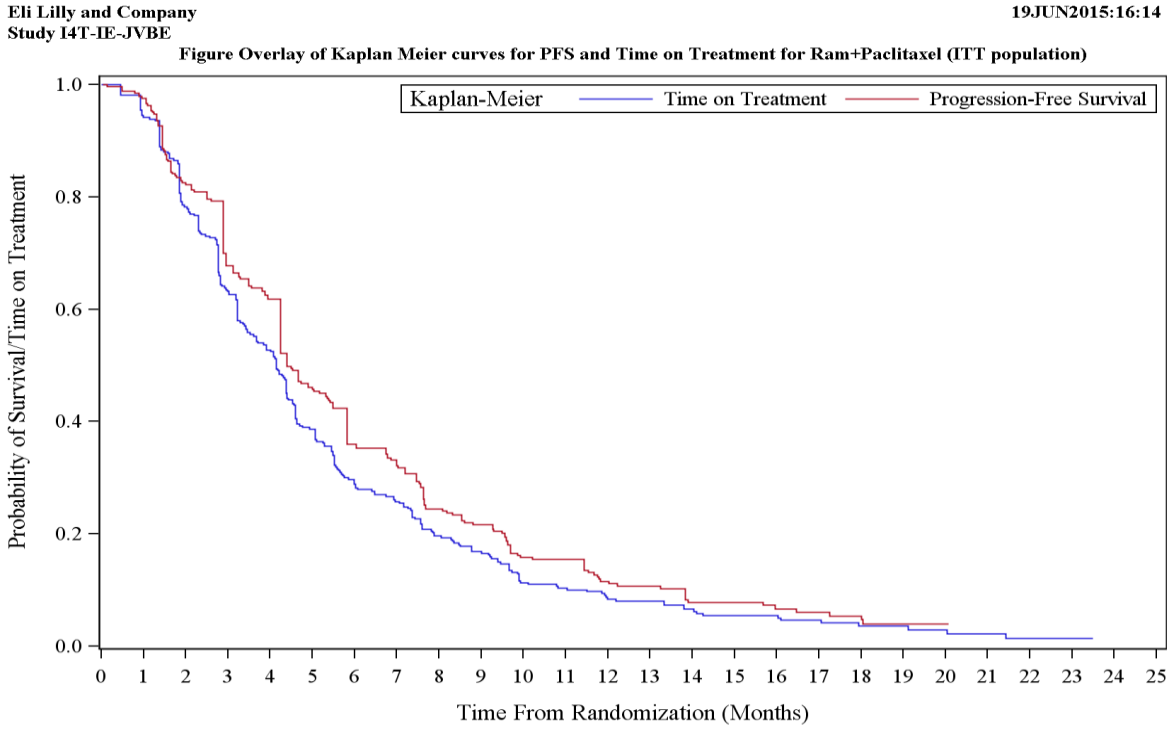
The value used to estimate terminal care is taken from the appraisals for gastric cancer (trastuzumab – TA208) and gastrointestinal stromal tumours (sunitinib – TA179), which are based on Coyle (1999). In the manufacturers original submission (TA 179) it is stated that this value is averaged over both hospice and hospital stays therefore there is some potential for double counting with hospitalisation in the post-progression health state. To explore this, a sensitivity analysis has been included which decreases the proportion of patients receiving terminal care by 50 percent and 100 percent to explore the potential impact of double counting.

B12. In the treatment pattern study, were the inclusion or exclusion criteria for selecting BSC components discussed with clinical experts? (Table 85 of the company submission).

Selection of BSC components to be assessed in the chart review was based on clinical expert input. These components were also similar to those therapies described in the REGARD and RAINBOW protocols as BSC interventions. As this chart review was also conducted in other countries, the criteria were not UK-specific.

B13. Please provide an overlay of Kaplan Meier curves for progression-free survival (figures 33 and 43) and time on treatment (figures 53 and 55), separately for the ramucirumab in combination with paclitaxel, placebo in combination with paclitaxel, and the ramucirumab in combination with best supportive care arms.

Overlay of Kaplan Meier curves for progression-free survival and time on treatment for ramucirumab plus paclitaxel



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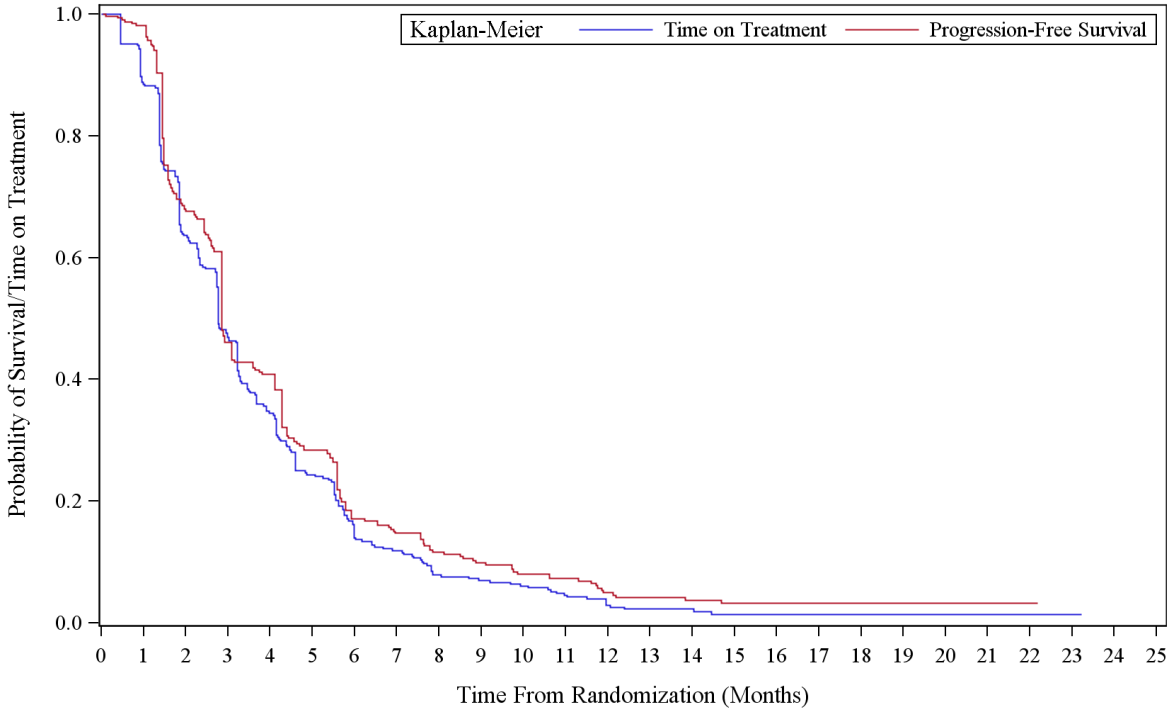
Overlay of Kaplan Meier curves for progression-free survival and time on treatment for paclitaxel

Eli Lilly and Company **19JUN2015:16:15**
Study I4T-IE-JVBE

Figure Overlay of Kaplan Meier curves for PFS and Time on Treatment for Paclitaxel (ITT population)



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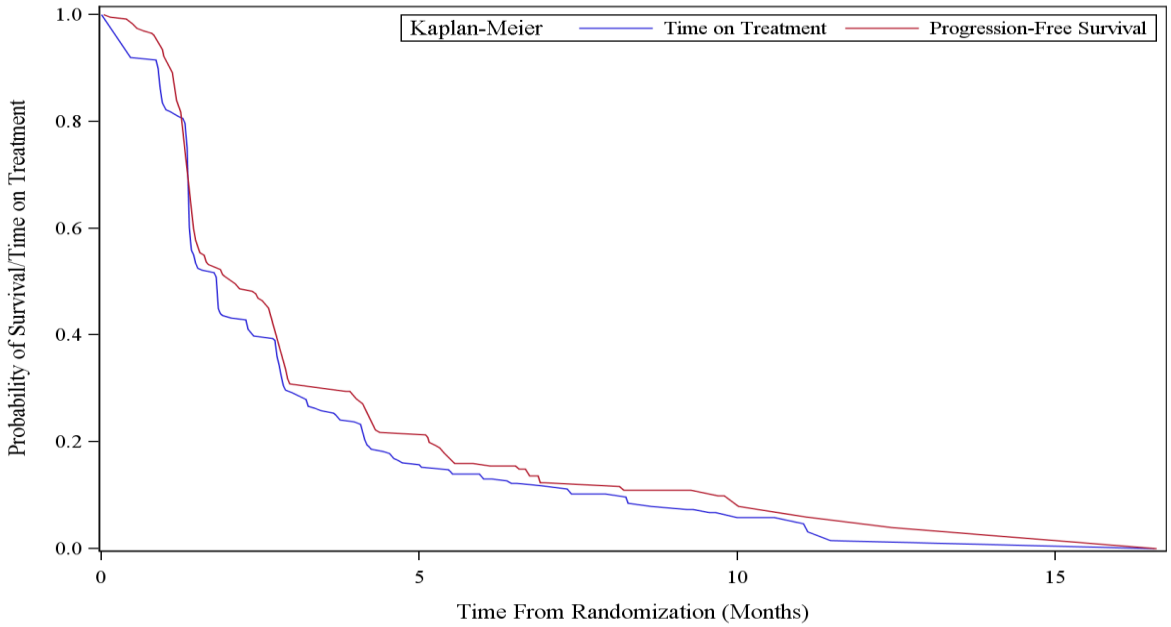
Overlay of Kaplan Meier curves for progression-free survival and time on treatment for ramucirumab plus BSC

Eli Lilly and Company **16JUN2015:17:06**
Study I4T-IE-JVBD

Figure 14.2.1.5.a3 Overlay of Kaplan Meier curves for PFS and Time on Treatment for Ram+BSC (ITT population)



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Output: lillyce\imclone\prd\imc1121b\gastric\cp120715\launch20120925\tfl

B14. Figure 55 shows clear steps in the Kaplan Meier curve, just as with the progression-free survival Kaplan Meier curve (figure 43). Please clarify if the fitted parametric curve in figure 55 was based on interval-censoring or not. If not, please provide justification.

The fitted parametric curve in figure 56 is not interval-censored. Interval censoring was not required for time on treatment because there was no risk that the event of interest (in this case treatment) occurs between the two specific intervals (in this case two scheduled administrations) but is unobserved. All actual administrations were recorded and are represented in the Kaplan Meier curves which are used to estimate the parametric curve.

B15. On page 240 of the company submission the results are presented for region adjusted overall survival, progression-free survival and time on treatment. Two incremental cost effectiveness ratios (ICERs) are presented, one for the log-logistic distribution and one for the Weibull distribution. Please clarify if these distributions were used for overall survival, progression-free survival and time on treatment.

The labelled distributions (log-logistic and Weibull distribution) refer only to the distribution used to estimate overall survival. Progression-free survival and time on treatment were estimated in the same way in both models, as they were for the ITT population. This is as follows;

- Progression-free survival was estimated using the Weibull distribution. The justification for this choice is outlined on pages 151-154.
- Time on treatment was estimated using the lognormal distribution. The justification for this choice is outlined on pages 194-196.

B16. Table 146 of the company submission shows that the median observed progression-free survival was 4.40, 95% confidence intervals (CI) of 4.24 and 5.32, and the median modelled progression-free survival was 4.14, which is outside the 95% CI of the randomised controlled trial. Please clarify why no further adjustments have been made to the model to reduce the difference between observed and modelled results.

Generating parametric predictions which aligned with the observed data, or making adjustments to improve fit to these data, were not objectives given the data are interval censored. The median progression-free survival estimated by the model is less than the median observed in the trial given the prior is generated by parametric models which account for this censoring.

B17. On page 242 of the company submission Table 147 presents results of the comparison of model results and clinical data for median overall survival. Please provide the same results for progression-free survival.

A comparison of the model results and clinical data for progression-free survival was not provided for the scenario analyses using the log-logistic and Weibull distribution. This is because these scenario analyses only changed the choice of approach and distribution for modelling overall survival. A table presenting the results of the comparison of model results and clinical data for progression-free survival is provided below for both scenario analyses.

Comparison of model results and clinical data for progression-free survival (Combination therapy model)

Outcome	Clinical trial results (CI)			Model results		
	RAM+PAC	PBO+PAC	Inc*	RAM+PAC	PBO+PAC	Inc*
Scenario Analysis 1 - Weibull distribution						
Median PFS	4.40 months (4.24 , 5.32)	2.86 months (2.79, 3.02)	1.54 months	4.14 months	2.53 months	1.61 months
Scenario Analysis 2 - Log-logistic distribution						
Median PFS	4.40 months (4.24 , 5.32)	2.86 months (2.79, 3.02)	1.54 months	4.14 months	2.53 months	1.61 months

B18. Please clarify if unit costs from previous years have been adjusted to 2015 prices.

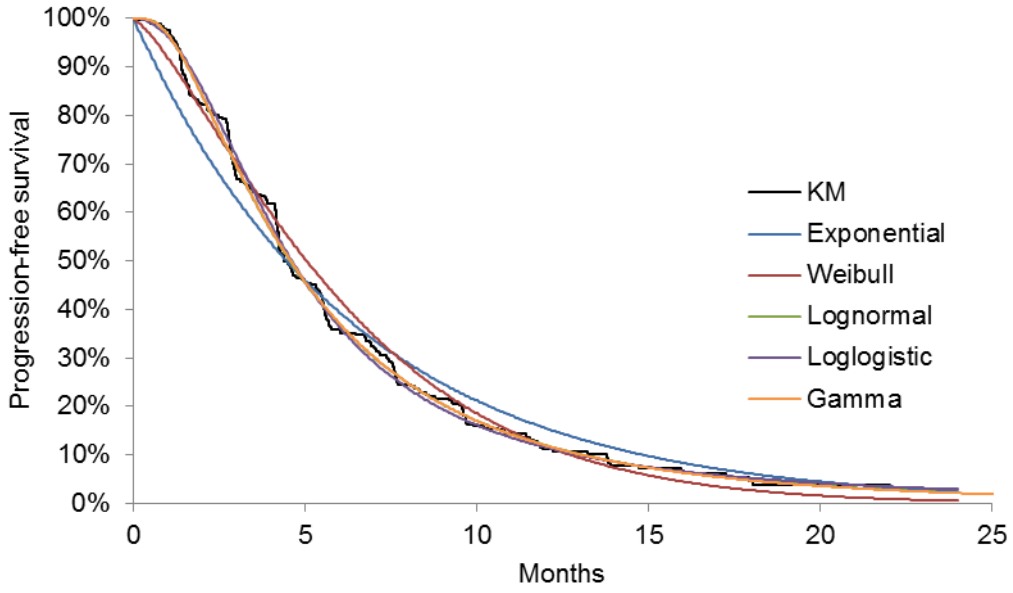
At the time of model development (2014) the costs from the most recent, published data was used for the following sources: BNF (March-September 2014), eMIT (published February 2014 representing the 12 month period to end December 2013) and NHS Reference costs (published December 2013 for 2012-13).

No attempt was made to uplift the data to 2015 as NHS reference costs in particular relate to a specific code which can change year on year. Other costs (i.e. the terminal care cost) were adjusted for inflation to 2014 if required.

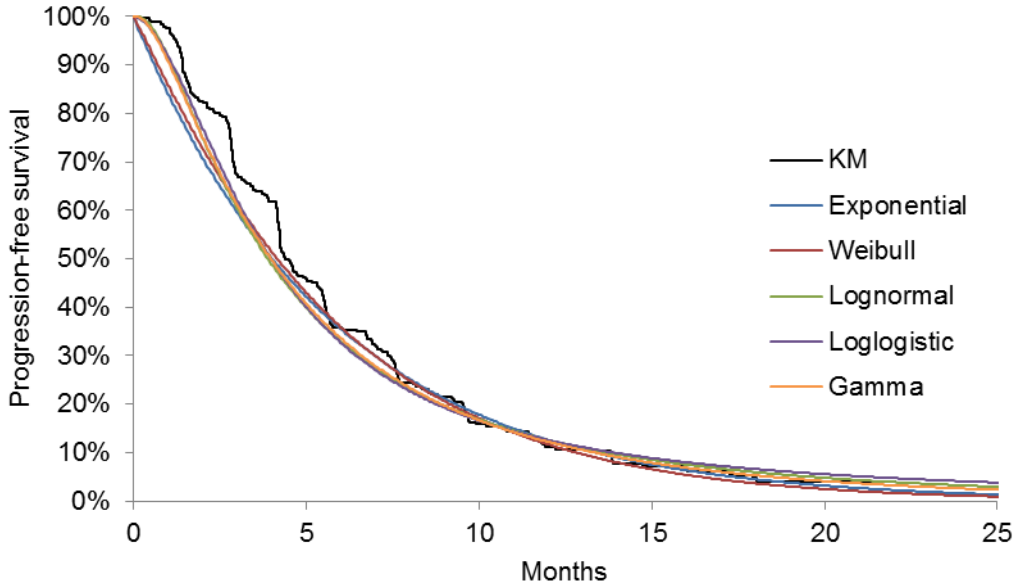
B19. Please provide similar progression-free survival Kaplan-Meier curves as presented in figures 6 and figure 7 on page 60 of Appendix 9 for the ramucirumab in combination with paclitaxel arm, and for each of these please also provide the Cox-Snell residual plots.

Please find below the progression-free survival Kaplan-Meier curves for RAM+PAC overlay onto both the non-interval censored and interval censored parametric curves.

Overlay of PFS Kaplan-Meier and parametric estimates for ramucirumab plus paclitaxel (RAINBOW)



Overlay of PFS Kaplan-Meier curves and interval censored parametric estimates for the ramucirumab plus paclitaxel (RAINBOW)



The Cox-Snell Residual plots for progression-free survival are provided for the progression-free survival distribution, unadjusted for interval censoring below. The Cox-Snell Residual plots adjusted for interval censoring were provided in Appendix 9 Figure 8.

Cox-Snell Residuals plots for PFS for combination therapy - unadjusted for interval censoring

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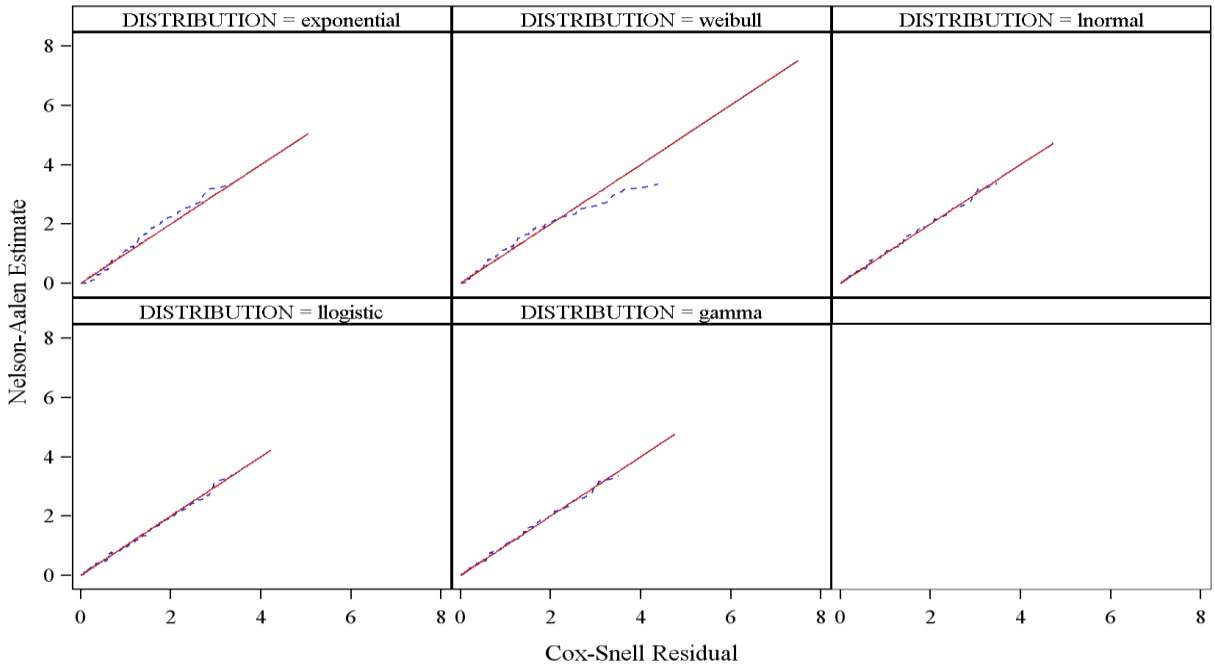
Study I4T-IE-JVBE

13JUN2014:15:36

Figure 14.2.1.5.a5 Goodness of Fit - PFS (ITT population)



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B20. *Appendix 9: Please clarify if the Cox-Snell residual plot in figure 8 (page 61) matches figure 6 or figure 7.*

Figure 8 corresponds to progression-free survival models adjusted for interval censoring therefore it matches figure 7.

B21. *Excel model: on the worksheet 'trace' a column 'progressing' is defined. The formula shows that the percentage of patients progressing in each cycle is estimated by the %PF in cycle t-1 minus %PF in cycle t. This seems to imply that all patients leaving the progression-free survival state go to post-progression survival, and that there are no deaths. This is not clear from figure 21 (page 140 of the company submission). Should the arrow between the pre-progression health state and the death state be deleted in figure 21?*

The column in the 'trace' sheet which is labelled 'progressing' does not determine state occupancy. This column is there simply to allow for the calculation of the costs associated with third line therapy and consultation visits. It is still possible for patients to transition from the pre-progression health state to the death state.

B22. *Excel model: on the worksheet 'trace', half cycle correction is applied for the one-off type cost component "Third-line" (Column AO), but not applied for other one-off type cost components: "Terminal" (Column AP) or "Consultation (PPS)" (Column AQ). Please can you explain if there is a rationale behind this?*

The model has been edited so that the half-cycle correct is added to these components.

B23. ***Priority request:*** *For ramucirumab in combination with paclitaxel compared with docetaxel, progression-free survival is informed by an assumed hazard ratio of 1,this is despite there being a hazard ratio from Roy 2013 estimated (as with overall survival) using methods of Parmar 1998 i.e. 1.26 (0.94,1.68). Please provide a justification for this and re-run the analysis using the estimated value?*

The primary reason for making this assumption was because there is no progression-free survival data for docetaxel (or irinotecan in the network) versus BSC. Given this constraint, to connect the network the assumption was made that both docetaxel and irinotecan would have similar efficacy to ramucirumab versus BSC (more detail regarding the rationale for this assumption was provided on page 159). Hence the assumed hazard ratio of1 between all three active comparators.

In addition, the Roy 2013 was not intended to compare the docetaxel and irinotecan arms. In fact, the study was not designed for any statistical comparisons among treatment arms. Also Kaplan Meier curves for progression-free survival show that the curves are very close together and only separate at the point where median progression-free survival is reached. Therefore the use of assumed hazard ratios based on trials intended to compare treatment arms was considered more appropriate.

A sensitivity analysis using the hazard ratio of 1.26 has been included in the model but this sensitivity analysis only provides results for ramucirumab plus paclitaxel versus docetaxel and paclitaxel.

B24. *On page 147 of the company submission, it is stated that: "The choice of dosing regimen for the economic model was based on the clinical trials of DOC included in the NMA [REFS 2, 110]. In these studies, DOC was administered at a dose of 75mg/m2 every 3 weeks. Treatment is assumed to be continued until disease progression, unacceptable toxicity or for a maximum of 6 cycles due to toxicity concerns as per the COUGAR II study [REF2]. This was a UK-only study and its dosing regimen for DOC was confirmed to be reflective of clinical practice in England."*

In the Excel model (combination therapy), in the base case (when Developer!G69=1), docetaxel is administered to all patients (progressed /non-progressed) for the first 9.2 weeks. Please explain the difference in the time on treatment modelling calculations for docetaxel treatment in the combination therapy Excel model compared to how it is reported in the company submission? Please also explain the scenarios in the Excel model (Sheet "Developer", Cell G69)?

The text on page 147 which is quoted relates to the choice of treatment regimen used for docetaxel in the submission. The time-on-treatment is estimated for docetaxel using the data from Ford (2012). The corresponding mean number of cycles received in Ford (2012) was 3.07. On looking into the time-on-treatment for DOC we noticed an error in the calculation for this arm only. It has minimal impact on the total costs for DOC which we have corrected in the model. We can confirm that DOC is only received in the pre-progression health state.

A scenario analysis was included which allows for 'treatment until progression'.

B25. On page 160, it is stated that: "The objective of assigning HR=1 for RAM, IRI and DOC was to constrain the hazards of progression to be equivalent, (i.e. no uncertainty) so standard errors of 0.01 were assigned."

In the Excel model (combination therapy), in the base case it seems that standard error=0 values are used (for best supportive care, please see sheet "HR", Cells V13 and W13) in contrast to standard error=0.01 (95% CrI 1.89, 7.14) that was mentioned in the sentence above in the company submission. Please explain this discrepancy.

Before submission of the final model to NICE the hazard ratios for the base case and scenario analyses seem to have been inverted. A base case using standard error = 0.01 should have been used as this was found to be the lowest value required to run the analysis in WinBUGs. This has been corrected in the model provided.

Furthermore, please confirm that the following assumptions in the options for sheet "User", Cell J29 are correct:

- *Base case standard error=0*
- *Scenario 1 standard error=0.287*
- *Scenario 2 standard error=0.01*

No this is an error. The assumptions should have been as follows. This has been amended in the model provided.

- Base case standard error=0.01
- Scenario 1 standard error=0.287
- Scenario 2 standard error=0

Also, in the company submission in table 65, the progression-free survival hazard ratio estimates (plus 95% CI) for paclitaxel cannot be found, even though they seem to be used in the Excel model on sheet HR, Cells U9, V9 and W9. Please document the progression-free survival hazard ratio estimates for paclitaxel.

The progression-free survival hazard ratio estimates for paclitaxel are not provided in the submission because paclitaxel is not believed to be an appropriate comparator in this decision problem. Paclitaxel was included in the economic model only for validation of the inclusion of the clinical trial data from RAINBOW. The progression-free survival hazard ratios are provided below.

Treatment	NMA using SE = 0.01 HR (95% CrI)	NMA using SE = 0.287 HR (95% CrI)	NMA using SE = 0 HR (95% CI)
RAM+PAC	-	-	-
PAC	1.56 (1.33, 1.85)	1.59 (1.33, 1.85)	1.59 (1.33, 1.85)

Section C: Literature searches

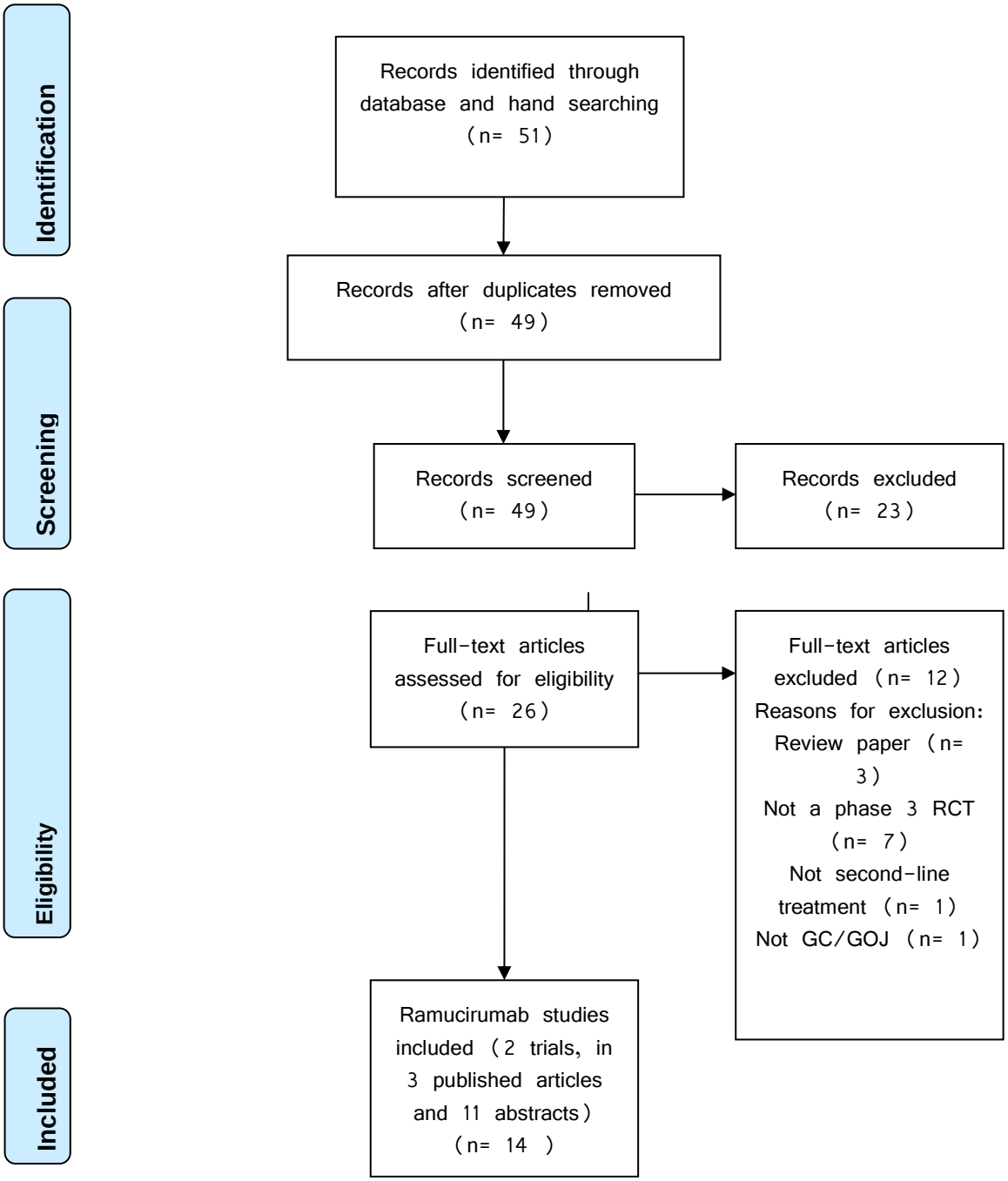
C1. Please clarify the date on which the clinical effectiveness searches took place. Section 4.1 states 2nd December 2014 but the search strategies provided in Appendix 2 indicate the searches may have taken place in February 2015.

The searches took place in February 2015.

C2. Please clarify the number of records identified through database searching. The results from the search strategy in Appendix 2 (45 records) do not match those detailed in the PRISMA flow diagram in figure 5, page 46 of the company submission (55 records).

This was a typing error. The PRISMA flow diagram on page 46 should specify that 51 records were identified through database (45) and hand (6) searches. Please find updated PRISMA flow diagram below.

Figure 1 **PRISMA flow diagram for systematic literature review of ramucirumab clinical studies**



C3. Please clarify the date span for the Embase search detailed in Table 26, page 73 of Appendix 10: it is given as 1980-2012 but searched on 25th September 2013.

Table 26 on page 73 of Appendix 10 should have read "Embase 1980 to Present. Date searched: 25th September 2013"

C4. Please clarify whether the date for the search for studies included in the evidence network is correct. Appendix 6 dates the search as December 2013, yet several papers were published in 2014 (for example, Qin 2014, Nishikawa 2014, Satah 2014 and Cohen 2014, Wilke 2014).

The wrong flow diagram was included in the submission (please see response to NMA questions). The NMA literature search was updated in May 2014 and the updated PRISMA flow diagram has been provided.

References

1. ImClone. Clinical Study Report of RAINBOW. A randomized, multicenter, double-blind, placebo-controlled phase 3 study of weekly paclitaxel with or without ramucirumab (IMC-1121B) drug product in patients with metastatic gastric adenocarcinoma, refractory to or progressive after first-line therapy with platinum and fluoropyridine. Confidential Lilly document. 2014
2. ImClone. Clinical Study Report for REGARD. A phase 3, randomized, double-blinded study of IMC-1121B and best supportive care (BSC) versus placebo and BSC in the treatment of metastatic gastric or gastroesophageal junction adenocarcinoma following disease progression on first-line platinum- or fluoropyrimidine-containing combination therapy. Confidential Lilly document. 2013.
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4. Scripture CD, Figg WD, Sparreboom A. Peripheral Neuropathy Induced by Paclitaxel: Recent Insights and Future Perspectives. Curr Neuropharmacol. 2006 April; 4(2): 165–172.
5. Hironaka S, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol 2013 Dec 10;31(35):4438-4444.
6. Kim HS, Kim HJ, Kim SY, Kim TY, Lee KW, Baek SK, et al. Second-line chemotherapy versus supportive cancer treatment in advanced gastric cancer: a meta-analysis. Ann Oncol. 2013 Nov;24(11):2850-4
7. Iacovelli R, Pietrantonio F, Farcomeni A, Maggi C, Palazzo A, Ricchini F, et al. Chemotherapy or Targeted Therapy as Second-Line Treatment of Advanced Gastric Cancer. A Systematic Review and Meta-Analysis of Published Studies. PlosOne. 9 (2014), p. e108940