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Single technology appraisal (STA)

Ramucirumab for treating metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma after chemotherapy

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Abbreviations used in this submission	
Admins	Administrations
AFT	Accelerated failure time
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike Information Criterion
ASC	Active symptom control
ASCO	American Society for Clinical Oncology
BIC	Bayesian Information Criterion
BSA	Body surface area
BSC	Best supportive care
BSG	British Society of Gastroenterology
CEA	Cost-effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CILL	Confidence interval, lower limit
CIUL	Confidence interval, upper limit
CR	Complete response
CRF	Case report form
CRD	Centre for reviews and dissemination
CSR	Clinical study report
CUA	Cost-utility analysis
DARE	Database of Abstracts of Reviews of Effects
DC101	Specific angiogenesis inhibitor
DCF	Docetaxel, cisplatin, and fluorouracil
DCR	Disease control rate
DOC	Docetaxel
DSU	Decision Support Unit
eCRF	Electronic case report form
ECF	Epirubicin, cisplatin, and fluorouracil
ECX	Epirubicin, cisplatin, and capecitabine

EDC	Electronic data capture
EMBASE	Excerpta Medica dataBASE
EOF	Epirubicin, oxaliplatin and fluorouracil
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ-C30	The European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire, Core 30
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5-dimension: Standardised instrument used as a measure of health outcomes
ESMO	European Society for Medical Oncology
FDA	US Food and Drug Administration
GC	Gastric cancer
GC/GOJ	Gastric cancer or gastro-oesophageal junction adenocarcinoma
GOJ	Gastro-oesophageal junction adenocarcinoma
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumour
HSCIC	Health and Social Care Information Centre
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQL	Health related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual-patient level data
IRI	Irinotecan
IRR	Infusion related reaction
ITT	Intention-to-treat
KM	Kaplan-Meier
LY	Life years
LYG	Life years gained
MCF	Mitomucin C, cisplatin, and fluorouracil
MEDLINE	Medical Literature Analysis and Retrieval System Online

MedRA	Medical Dictionary for Regulatory Activities
N	Number
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Care and Health Excellence
NMA	Network Meta-Analysis
OC	Oesophageal cancer
ORR	Objective response rate
OS	Overall survival
OVID	OVID provides access to online bibliographic databases and academic journals in the area of health sciences
PAC	Paclitaxel
PBO	Placebo
PBO+PAC	Placebo+paclitaxel
PD	Progressive disease
PDT	Post-discontinuation therapy
PFS	Progression-free survival
PH	Proportional Hazards
PR	Partial response (RECIST criteria)
PPS	Post-progression survival
PS	Performance status
QALY	Quality adjusted life year
QoL	Quality of Life
RAINBOW	Pivotal trial of ramucirumab in combination with paclitaxel in patients previously treated advanced gastric and gastro-oesophageal junctional adenocarcinoma
RAM	Ramucirumab monotherapy
RAM+PAC	Ramucirumab in combination with paclitaxel
RCT	Randomised controlled trial
REGARD	Pivotal trial of ramucirumab monotherapy in patients with previously treated advanced gastric and gastro-oesophageal junctional adenocarcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
SACT	Systemic Anti-Cancer Therapy Chemotherapy Dataset
SAS	Type of software used for the parametric survival analysis

SD	Stable disease
s.d.	Standard deviation
s.e.	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SR	Systematic review
SPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TTD	Time to deterioration
TTP	Time to progression
VEGF	Vascular endothelial growth factor (A, B, C, or D)
VTE	Venous thromboembolism
WGIC	World Congress on Gastrointestinal Cancer

For clarity when reading the submission document, ramucirumab has been written out in full when referring to ramucirumab as an agent. The abbreviation RAM has been used when referring to ramucirumab monotherapy and RAM+PAC has been used when referring to ramucirumab combination therapy.

1 Executive summary

Advanced gastric cancer and gastro-oesophageal junction adenocarcinomas (GC/GOJ) are aggressive, difficult to treat cancers which severely impact patients' quality of life (QoL). Everyday activities such as eating and swallowing are painful and challenging due to the high symptom burden (1). Prognosis for second-line patients is poor, with median overall survival (OS) for patients receiving best supportive care (BSC) ranging from 2.4 to 3.8 months in clinical trials (2-4). Aside from ramucirumab, there are no licensed second-line treatments for patients with advanced GC/GOJ. A chart review of UK clinical practice revealed low rates of active treatment and widespread variation in the second-line setting (5).

In two double-blind, phase 3, randomised controlled trials (RCTs) ramucirumab was demonstrated to be an effective treatment for patients with advanced GC/GOJ who have progressed after prior platinum and/or fluoropyrimidine chemotherapy (6,7). Ramucirumab extended median progression free survival (PFS) by more than 50% and OS by more than 30% in both trials, with a predictable and manageable side-effect profile. Data from the trials demonstrates that these efficacy gains were accompanied by a trend to improvement in QoL, while on ramucirumab.

Patients with advanced GC/GOJ have notable unmet need for cancer care. Ramucirumab provides a licensed, evidence-based second-line treatment option, for the first time.

Gastric cancer and gastro-oesophageal junction adenocarcinoma (GC/GOJ)

GC/GOJs are rare (designated orphan status by the European Medicines Agency (EMA)) and aggressive cancers. The annual incidence of GC/GOJ is low in the UK at less than 5 per 100,000 persons (8). In 2012, there were 5,637 new cases of GC and 3,085 new cases of GOJ cancer in England (9). Of patients diagnosed with GC, approximately 80% are diagnosed with advanced, metastatic GC (10). The prognosis in this group of patients is very poor with a five-year survival rate of approximately 5% (11). An estimated 657 patients diagnosed with advanced GC/GOJ would be eligible for second-line treatment following first-line chemotherapy.

As curative options do not exist for this group of patients, the aim of treatment in advanced GC/GOJ is to delay progression, extend survival and relieve symptoms with minimal adverse effects or detriment to quality of life.

Current treatment practice

Aside from ramucirumab, there are no licensed or established standard second-line treatments. In the absence of NICE clinical guidelines or national treatment algorithms, wide variations in clinical practice exist in the second-line setting. A chart review of UK clinical practice reported BSC to be the most commonly used second-line option (71.5% of patients) (5). The remaining 28.5% of patients receiving 'active' second-line treatment were treated with a total of 21 different regimens (5).

Patient-level decisions about receiving second-line treatment are likely to be multi-factorial, depending on individual and clinician preferences and first-line treatment experience. The lack of a licensed, available treatment option, no clear standard of care and inequality in access to off-licence treatments across the country, means that some patients fit enough (performance status 0-1) to be eligible for second-line chemotherapy are not always receiving it.

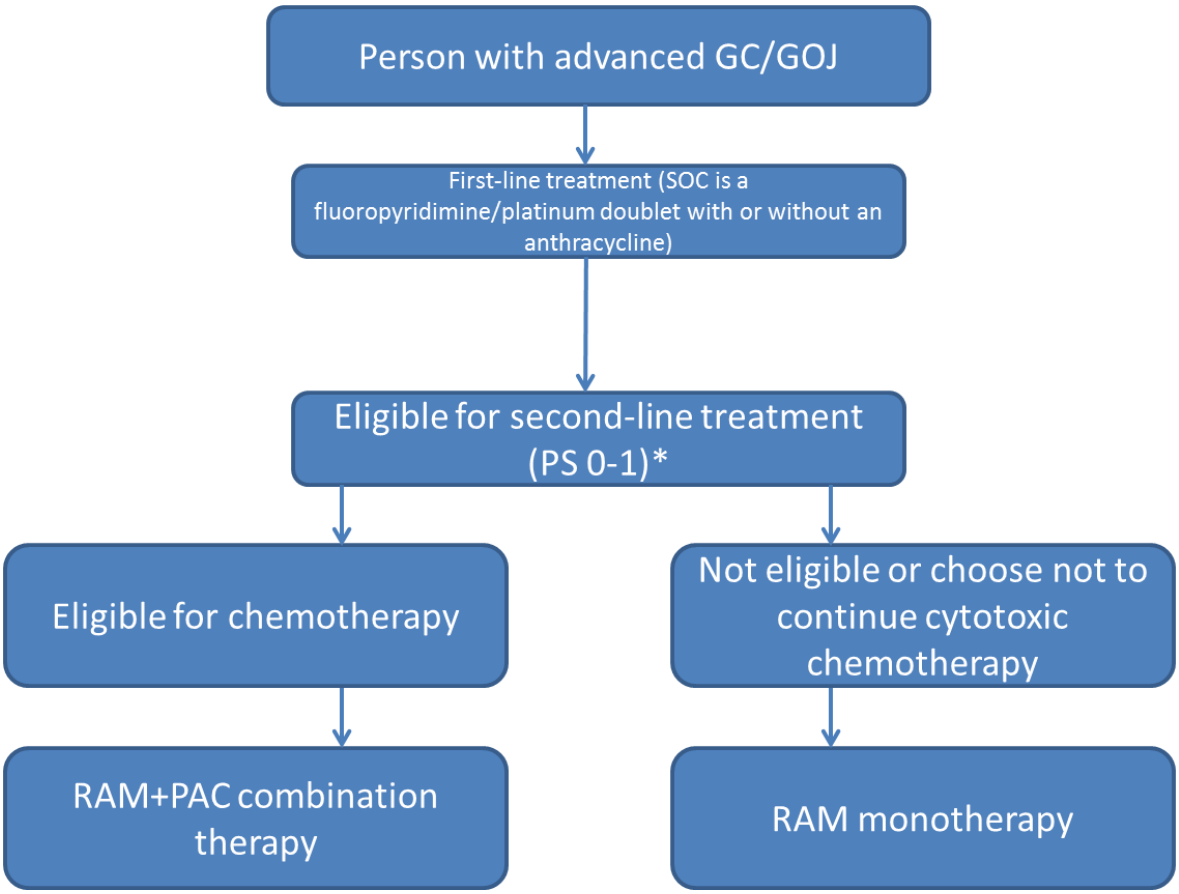
Additionally, some patients are unable to tolerate the toxicities associated with the chemotherapy treatments currently available. A significant unmet need for treatments that improve clinical outcomes with an acceptable tolerability profile, while maintaining QoL, exists.

Ramucirumab: anticipated place in clinical practice

Ramucirumab is a human receptor-targeted monoclonal antibody that specifically binds to vascular endothelial growth factor (VEGF) Receptor 2. Ramucirumab is an orphan drug (12) approved for use for the treatment of adult patients with advanced GC/GOJ with disease progression:

- in combination with paclitaxel (RAM+PAC) after prior platinum and fluoropyrimidine chemotherapy and
- as a monotherapy (RAM) after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate.

Figure 1 Anticipated ramucirumab position in treatment pathway



*Abbreviation: PS = performance status

Ramucirumab is the only licensed treatment in this setting providing patients and physicians with two, evidence-based, treatment options (Figure 1):

a) RAM+PAC combination therapy for patients who are willing and able to receive further cytotoxic chemotherapy and

b) RAM monotherapy for patients in whom further cytotoxic chemotherapy is not appropriate (e.g. due to lingering toxicities, patient choice or co-morbidities)

By providing a standard treatment pathway where none currently exists, ramucirumab represents the opportunity to allow equal access to a second-line treatment across England.

Clinical efficacy and safety

The clinical efficacy and safety of ramucirumab combination and monotherapy has been demonstrated in two double-blind, placebo-controlled, multi-centre phase III trials; RAINBOW and REGARD (6,7). These are the largest positive trials of second-line treatment for GC/GOJ to date, demonstrating statistically and clinically significant survival

benefits in terms of overall survival (OS) and PFS for patients treated with RAM or RAM+PAC.

As a combination therapy, RAM+PAC increased median OS by 30.8% (2.27 months) compared to placebo + paclitaxel (PBO+PAC). In the pre-specified patient subgroup with characteristics most representative of patients in England (Region 1: Europe, Israel, Australia, USA), median OS gain was greater at 45% (2.66 months) for RAM+PAC compared to PBO+PAC (Table 1). Relative PFS gains were even greater, RAM+PAC increased median PFS by 54% (1.54 months) in the ITT population and by 50% (1.41 months) in Region 1.

Table 1 RAINBOW: OS and PFS results in the ITT population and Region 1

Outcome	RAM+PAC	PBO+PAC	Treatment difference
ITT Population	**N=330**	**N=335**	
Median OS, months (95% CI)	9.63 (8.5, 10.8)	7.36 (6.3, 8.4)	2.27
Log-rank p-value (2-sided)[a]	0.0169		
Hazard ratio (95% CI)[a]	0.807 (0.678, 0.962)		
Median PFS, months (95% CI)	4.40 (4.24, 5.32)	2.86 (2.79, 3.02)	1.54
Log-rank p-value (2-sided)[a]	<0.0001		
Hazard ratio (95% CI)[a]	0.635 (0.536, 0.752)		
Region 1 subgroup	**N=198**	**N=200**	
Median OS, months (95% CI)	8.57 (7.43, 9.79)	5.91 (4.99, 7.06)	2.66
Log-rank p-value (2-sided)[a]	0.0050		
Hazard ratio (95% CI)[a]	0.726 (0.580, 0.909)		
Median PFS, months (95% CI)	4.24 (3.91, 5.32)	2.83 (2.56, 3.09)	1.41
Log-rank p-value (2-sided)[a]	<0.0001		
Hazard ratio (95% CI)[a]	0.631 (0.506, 0.786)		

a Stratified by randomisation strata (geographical region, time to progression from start of first-line therapy, and disease measurability)

In REGARD, RAM monotherapy was associated with a 36.8% (1.4 month) increase in median OS in comparison to PBO. The relative gain in PFS was 62% (0.8 months) for patients treated with RAM with a median PFS of 2.1 months. These results represent a clinically meaningful benefit for this patient group who have such a poor prognosis and short life expectancy (Table 2).

Table 2 REGARD: OS and PFS results in the ITT population

Outcome	RAM (N=238)	PBO (N=117)	Treatment difference
Median OS, months (95% CI)	5.2 (4.4, 5.7)	3.8 (2.8, 4.7)	1.4
Log-rank p-value (2-sided)[a]	0.0473		
Hazard ratio (95% CI)[a]	0.776 (0.603-0.998)		
Median PFS, months (95% CI)	2.1 (1.5, 2.7)	1.3 (1.3, 1.4)	0.8
Log-rank p-value (2-sided)[a]	<0.0001		
Hazard ratio (95% CI)[a]	0.483 (0.376, 0.620)		

[a] Stratified by randomisation strata (geographical region, time to progression from start of first-line therapy, and disease measurability)

Both trials demonstrated that ramucirumab is well tolerated and characterised by adverse events that were manageable. In RAINBOW, a similar percentage of patients in both study arms discontinued treatment due to AEs (11.8% RAM+PAC and 11.3% PBO+PAC). In REGARD these figures were 11.3% (RAM) and 6.1% (PBO).

It is essential that for patients receiving palliative chemotherapy, PFS and OS gains are not achieved at the expense of QoL. The importance of disease control and PFS in maintaining QoL has been highlighted in an independent systematic review (13). Both trials provide relevant and robust evidence that PFS gains were accompanied by maintained, and in some cases improved QoL outcomes for ramucirumab treated patients. In an analysis of time to deterioration of EORTC in RAINBOW, RAM+PAC treatment was favourable on 14 of the 15 symptom scales and statistically significantly improved emotional function and nausea and vomiting. In REGARD, at 6 weeks, the proportion of patients with improved or stable QoL was higher for the RAM arm (34.1%) than the PBO arm (13.7%).

A network meta-analysis (NMA) was conducted to allow for the clinical and economic comparison of RAM+PAC with the two most commonly used treatments in UK clinical practice; BSC and DOC. RAM+PAC was associated with a statistically significant lower hazard of death compared with BSC (HR: 0.34, 95% CI: 0.17, 0.71), and with a numerically lower hazard of death compared to docetaxel (HR: 0.51, 95% CI: 0.23, 1.13). In terms of PFS, there was also a numerically lower hazard of progression or death for RAM+PAC compared to docetaxel (HR: 0.70, 95% CI: 0.46, 1.07).

End of life criteria

RAM+PAC for the second-line treatment of adult patients with advanced GC/GOJ fulfils all three criteria specified in NICE's 'Supplementary Advice for Appraising life-extending,

end of life treatments. Therefore the supplementary advice should be applied to this appraisal:

- *The treatment is indicated for patients with a short life expectancy, normally less than 24 months:* Median OS for patients receiving BSC ranges from 2.4 to 3.8 months in clinical trials (2-4)
- 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:
    - RAM+PAC versus BSC; incremental modelled mean OS = 5.76 months
- *The treatment is licensed or otherwise indicated for small patient populations:* The patient population estimated to be eligible for treatment with previously treated, advanced gastric cancer is 657

Cost-effectiveness of ramucirumab

Model overview

Two separate economic models were developed to assess the cost-effectiveness of ramucirumab as 1) a monotherapy and 2) in combination with paclitaxel. The same structure was used for both economic models.

The model is a three-state partitioned survival model, commonly used for advanced, late-stage oncology (14,15). The states are pre-progression, post-progression and death, with all patients entering the model in the pre-progression state. In accordance with the NICE reference case an NHS and personal social services perspective was used and an annual discount rate of 3.5% and half-cycle correction were applied to costs and benefits. A lifetime time horizon was employed to capture all the costs and benefits relevant for patients receiving the intervention and comparators. A one-week cycle length was used in both models.

Combination therapy comparators

Other than ramucirumab there are no licensed second-line treatments in the UK.

A UK treatment pattern study reported that the majority of patients do not receive any active second-line therapy, even when eligible. The risk/benefit profile of existing off-licensed agents may inform patient/clinical treatment decisions, alongside other factors. Because 71.5% of patients are reported to receive BSC, this is the primary comparator for the cost-effectiveness analysis (CEA) of RAM+PAC.

Clear inclusion criteria were applied to establish which other proposed comparators could be considered standard clinical practice in England. None of the proposed comparators met the stated inclusion criteria of 10% use in all patients. Although DOC did not meet this criteria, it was included because advice from clinical experts confirmed its importance in shaping evolving clinical practice due to the COUGAR II study (2).

Monotherapy comparators

RAM monotherapy is licensed for patients for whom treatment in combination with PAC is not appropriate (16). Specifically, the EPAR states that monotherapy is a “therapeutic option in this second-line setting, when chemotherapy in combination with ramucirumab is not the preferred option” (17).

Based on clinical rationale, patients whom the EMA refer to for which chemotherapy in combination with ramucirumab is not the preferred option, are presumed to not be currently receiving active cytotoxic chemotherapy. The only appropriate comparator for this patient population is therefore BSC.

Model methodology

In order to estimate lifetime outcomes and costs from censored survival data an extensive survival analysis exercise was undertaken. As a result of this analysis, PFS for RAM+PAC is estimated using the Weibull distribution. OS is estimated for RAM+PAC using the Kaplan-Meier data from the RAINBOW trial and then extrapolated using the exponential distribution. The outputs of the NMA are applied to the RAM+PAC survival estimates to determine the relative efficacy of RAM+PAC versus BSC and DOC.

Similarly, in the monotherapy model, PFS is estimated using the lognormal distribution for RAM+BSC and PBO+BSC. OS is estimated using the Gamma distribution.

Combination therapy model results

The base case CEA of RAM+PAC versus BSC, the most commonly used treatment and primary comparator, shows an incremental cost effectiveness ratio (ICER) of £118,209 (Table 3). The NICE Methods Guide states that comparator selection should be based on the comparator’s cost-effectiveness as well as its licensing status and whether it is established NHS practice in England. It should be noted that the ICER for DOC versus BSC was over £50,000 which is above standard willingness to pay thresholds (Table 3). Given this, BSC was considered the only appropriate comparator and the results are presented only for RAM+PAC versus BSC.

Table 3 Ramucirumab in combination with paclitaxel: Incremental Cost Effectiveness Analysis versus BSC

Technology (and comparators)	Total cost	Total life years	Total QALY	Incremental costs versus BSC	Incremental life years versus BSC	Incremental QALY versus BSC	ICERs versus BSC
BSC	£13,400	0.45	0.29	-	-	-	-
DOC	£18,779	0.59	0.39	£5,378	0.14	0.10	£53,830
RAM+PAC	£52,996	0.94	0.62	£39,595	0.48	0.33	£118,209

NB: Numbers may not compute due to rounding

RAM+PAC increases mean estimated OS by 0.48 life years (LY) versus BSC which is an extension of almost 6 months (5.78 months). An additional 0.33 quality adjusted life years (QALYs) are gained from treatment with RAM+PAC versus BSC. It is associated with an increase in total costs of £39,595 versus BSC, the majority of which is associated with the acquisition and administration cost of ramucirumab.

The disaggregated results show that RAM+PAC increases mean PFS by over 4 months versus BSC.

Scenario analyses were conducted using alternative methodologies to estimate OS in the economic model. Using fully parametric OS curves, independently fitted to each treatment arm and utilising the log-logistic distribution, the ICER for RAM+PAC vs BSC is £96,103. The log-logistic was the best fitting distribution to the trial data across both arms in the parametric curve fitting exercise. Using independently fitted Weibull OS curves the ICER is £117,236 vs BSC.

Monotherapy model results

The ICER for RAM+BSC versus PBO+BSC is £188,640 per QALY gained. RAM+BSC increases mean OS by 1.92 months (0.16 LYs) and provides an additional 0.12 QALYs versus PBO+BSC (Table 4).

Table 4 Ramucirumab monotherapy: Incremental Cost Effectiveness Analysis

Technology and comparator	Total cost	Total LY	Total QALY	Incremental cost vs PBO+BSC	Incremental LY vs PBO+BSC	Incremental QALY vs PBO+BSC	ICERs versus PBO+BSC
PBO+BSC	£14,137	0.49	0.31	-	-	-	-
RAM+BSC	£36,678	0.66	0.43	£22,542	0.16	0.12	£188,640

NB: Numbers may not compute due to rounding

The disaggregated results show that mean estimated PFS is increased by 1.92 months (0.16 LYs) versus PBO+BSC, which is more than twice the PFS of patients currently receiving PBO+BSC who have 1.44 months (0.12 LYs) of PFS.

Interpretation

Extending the period of pre-progression for patients experiencing the high tumour burden associated with late-stage GC/GOJ is incredibly important. The link between efficacious treatments and the maintenance of HRQL for oesophago-gastric cancer patients has been highlighted in the literature (13) and the evidence from the trials involving ramucirumab supports this.

Advanced GC/GOJ is an aggressive cancer. Patients who have progressed on first-line chemotherapy have a mean estimated life expectancy of less than 6 months when treated with BSC only (0.45 LYs in the combination therapy model and 0.49 LYs in the monotherapy model). The increase in estimated overall survival with RAM+PAC is more than a doubling in mean OS versus BSC. An extension of almost 6 months of overall survival is a very significant improvement for a patient population with such a poor prognosis.

Additionally, treatment with RAM+BSC provides a further 1.92 months of PFS versus PBO+BSC. This is very clinically meaningful as patients receiving monotherapy are able to spend over twice as long in a progression free health state. Importantly, PFS translates to an OS benefit. RAM+BSC extends modelled OS by almost 2 months, this is an increase in OS of over 30% for this patient population.

Cost-effectiveness challenges

Patients with advanced GC/GOJ require considerable medical and palliative care to allow them to retain some QoL at the end of their life. The high cost of providing palliative care to these patients means that any extension in life will also be associated with a large increase in the resources required to treat the symptoms of GC/GOJ. The resulting cost-effectiveness case is therefore challenging to prove and even generic therapies have ICERs above the standard willingness to pay thresholds used by NICE. As a drug with orphan designation for a rare cancer, demonstrating the cost-effectiveness of ramucirumab is always going to be very difficult using standard cost-effectiveness methods (18). Given this, and the qualification of RAM+PAC as an end of life treatment, the use of flexible cost-effectiveness thresholds could be applied.

Conclusions

As the first licensed treatment option, ramucirumab - both as a combination therapy and monotherapy - represents a step change in the management of advanced GC/GOJ. This innovation has been recognised by the EMA in their granting of orphan designation to ramucirumab.

There is a clear unmet need in improving outcomes for GC/GOJ patients. The clinical gains with ramucirumab must be viewed in the context of this difficult-to-treat disease and not compared to the outcomes achieved in other cancers with a better prognosis (e.g. breast and prostate cancer).

If made available, ramucirumab could lead to the development of a standard pathway for the evaluation and treatment of patients who have progressed following first-line treatments. It would also help reduce inequality in access to active second-line treatment options. For patients for whom treatment in combination with chemotherapy is not appropriate, RAM monotherapy is the only treatment option which these patients could receive. By providing a treatment option for patients who currently have none, it is clear that ramucirumab is a step-change in clinical practice and addresses a high unmet need.

1.1 Statement of decision problem

The decision problem for this submission is specified in Table 5. Please refer to section 5.2 – Intervention technology and comparators of this submission for an explanation of the chosen comparators.

Table 5 The decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy	*Ramucirumab in combination with paclitaxel* Adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy. *Ramucirumab monotherapy* Adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy for whom further cytotoxic chemotherapy is not appropriate.	*Ramucirumab monotherapy* The licence wording for ramucirumab as a monotherapy specifies its use in patients 'for whom treatment in combination with paclitaxel is not appropriate'. Clinically speaking, this patient population can be more broadly characterised as patients for whom further cytotoxic chemotherapy is not appropriate.
Intervention	Ramucirumab alone or in combination with paclitaxel	As per scope	n/a
Comparator (s)	Chemotherapy including but not limited to: • Docetaxel monotherapy • Irinotecan monotherapy • Irinotecan and fluorouracil-based therapy (FOLFIRI) • Paclitaxel monotherapy (only for people for	Ramucirumab in combination with paclitaxel: • Best supportive care • Docetaxel monotherapy • Paclitaxel monotherapy (only for model validation) Ramucirumab monotherapy:	*Ramucirumab in combination with paclitaxel:* Prior to ramucirumab, there were no licensed treatments for advanced, previously treated GC/GOJ. The most commonly used treatment for patients who have progressed after first-line treatment with platinum and fluoropyrimidine containing treatment is BSC (71.5%) (5). The most commonly reported active treatment was docetaxel, but this was used in only 8% of patients who progressed after first-line therapy. The remaining patients actively treated received one of 20 different regimens. Only 3% of all patients received paclitaxel. This is only included in the economic model to validate the clinical

	whom treatment in combination with paclitaxel is appropriate) Best supportive care (including but not limited to antiemetics, blood transfusions, oesophageal stents, palliative radiotherapy and palliative surgery)	• Best supportive care	outputs. Irinotecan and FOLFIRI are not included in the economic analysis as 2% and fewer of all patients were reported to receive these treatments. *Ramucirumab monotherapy:* The licence for RAM specifies its use for patients in whom treatment with PAC is not appropriate. In clinical practice patients who are 'not eligible for paclitaxel' can be more broadly characterised as 'not eligible for cytotoxic chemotherapy'. The standard of care for these patients is BSC only.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment health-related quality of life	As per scope	n/a
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per scope	n/a

Subgroups to be considered			A scenario analysis was conducted for Region 1 (North America, Europe, Australia and Israel) due to previously identified differences in treatment patterns and survival outcomes between Asian and non-Asian countries (19-21). A subgroup analysis was not possible for the monotherapy model as the sample size in the clinical trial was too small.
Special considerations including issues related to equity or equality			Ramucirumab has been designated orphan status by the EMA. Orphan designation is reserved for treatments which provide an effective treatment option where currently none exist. Ramucirumab fulfils this criteria by being the only licensed treatment for previously treated advanced GC/GOJ, addressing a significant unmet need in this treatment setting. At present the only treatment options available to patients are off-licence chemotherapy regimens. These treatments are associated with notable toxicities and are therefore not suitable for all patients. For example, older patients are less likely to receive active treatment (22) , an inequality as there are currently no treatment options available to them. In the absence of any licensed treatment or any NICE clinical guidelines or national algorithms in this setting, trusts develop their own treatment protocols meaning access to treatment is contingent upon physician preference and upon any restrictions in place by the trust in which they practice. This leads to notable variation and inequity in provision of treatment for this disease across regions in England. This is clearly reflected in the wide variations in current clinical practice in GC/GOJ (5). As ramucirumab is the first licensed second-line therapy, it provides the opportunity for equal access to a second-line treatment and reduces the continued use of off-licence drugs, providing a standard treatment pathway where none presently exists.

1.2 Description of technology under assessment

Provide a description of the technology under assessment in the table below

Table 6 Technology under assessment

UK approved name and brand name	Approved name: Ramucirumab Brand name: Cyramza ®
Marketing authorisation status	EU marketing authorisation received 19th December 2014
Indications and any restriction(s) as described in the summary of product characteristics	Cyramza 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. Cyramza 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.
Method of administration and dosage	*Ramucirumab in combination with paclitaxel* Ramucirumab can be administered in a hospital outpatient care setting. The recommended dose of ramucirumab is 8mg/kg, on days 1 and 15 of a 28-day cycle, prior to paclitaxel infusion. The recommended dose of paclitaxel is 80 mg/m^2 administered on days 1, 8, and 15 of a 28-day cycle. *Ramucirumab as a single agent* The recommended dose of ramucirumab as a single agent is 8 mg/kg every 2 weeks. Method of administration: IV infusion

2 The technology

2.1 Description of the technology

Brand Name	Cyramza ®
Approved Name	Ramucirumab
Therapeutic Class	Angiogenesis inhibitor, human IgG1 monoclonal antibody

Overview of the mechanism of action

Ramucirumab is a human receptor-targeted monoclonal antibody that specifically binds VEGF Receptor 2. The binding of ramucirumab to VEGF Receptor 2 prevents its interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D) (23,24).

Studies have shown that upregulation of VEGF is associated with more aggressive disease and that upregulation of VEGF-A, VEGF-C, and VEGF-D ligands in GC are associated with poorer prognosis for patients with resected or metastatic disease, with worse disease-free survival and OS (25-27). Inhibition of VEGF Receptor 2 in GC xenografts with the administration of angiogenesis inhibitor DC101 has been associated with reduced tumour growth in animal models, providing a strong rationale for the use of ramucirumab in the treatment of GC/GOJ.

2.2 Marketing authorisation/CE marking

Approved indications

Ramucirumab (Cyramza) was approved by the European Commission on 19th December 2014 for the following indications:

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

Ramucirumab was made commercially available in the UK on 16th January 2015.

European public assessment report (EPAR)

The European Union Marketing Authorisation Application (EU MAA) submission for ramucirumab was based on a review of data from the combination trial RAINBOW (ramucirumab administered in combination with paclitaxel (PAC), hereafter referred to as RAM+PAC) and the monotherapy trial REGARD. The EPAR and summary of product characteristics (SPC) for ramucirumab in these particular therapeutic indications can be found in Appendix 1. The final EPAR was published on 22nd January 2015 (17).

According to the EPAR, for the RAM+PAC combination, the observed improvement in OS was considered to be clearly shown. In view of the reasonably well tolerated toxicity, the benefit/risk balance for the combination of RAM+PAC therapy was considered to be positive.

Similarly, the benefit/risk balance for monotherapy (RAM) was considered positive based on the improvement in overall survival (OS) and the very well tolerated safety. The Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits outweighed the risks and although the effect on median OS was smaller with RAM than with RAM+PAC, this was still a useful therapeutic option in the second-line setting, when chemotherapy in combination with ramucirumab is not the preferred option. The CHMP therefore restricted single agent treatment to patients for whom treatment with RAM+PAC is not appropriate (see SPC section 4.1).

Regulatory approval outside the UK

Ramucirumab was approved by the U.S. Food and Drug Administration (FDA) on 21st April 2014 as a single-agent treatment for patients with advanced or metastatic GC/GOJ with disease progression on or after prior fluorpyrimidine or platinum-containing chemotherapy.

- Ramucirumab was also approved by the U.S. FDA on 5th November 2014 in combination with PAC as a treatment for people with advanced or metastatic GC/GOJ whose cancer has progressed on or after prior fluoropyrimidine or platinum-containing chemotherapy
- Ramucriumab was approved by the U.S. FDA on 12th December 2014 in combination with docetaxel (DOC) as a treatment for people with metastatic NSCLC whose cancer has progressed on or after prior chemotherapy
- Ramucirumab was approved by the U.S. FDA on 24th April 2015 in combination with FOLFIRI, for the treatment of metastatic colorectal cancer with disease

progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine

- The Japan Ministry of Health, Labour and Welfare approved Cyramza as a treatment for patients with unresectable, advanced or recurrent GC on 26th March 2015
- The Korean Ministry of Health and Welfare approved Cyramza as a treatment for advanced GC on 15th April 2015

Other health technology assessment in the UK

Ramucirumab will be appraised by the Scottish Medicines Consortium (SMC). The estimated timeline for submission is later this year.

Ramucirumab will also be appraised by the National Centre for Pharmacoeconomics (NCPE) Ireland. The estimated timeline for submission is later this year.

2.3 Administration and costs

Ramucirumab in combination with paclitaxel

Ramucirumab can be administered in a hospital outpatient care setting. The recommended dose of RAM is 8 mg/kg, on days 1 and 15 of a 28-day cycle, prior to PAC infusion. The recommended dose of PAC is 80 mg/m^2 administered by intravenous infusion over approximately 60 minutes on days 1, 8 and 15 of a 28-day cycle. Prior to each PAC infusion, patients should have a full blood count and blood chemistry (performed to evaluate hepatic function).

It is recommended that treatment is continued until disease progression or until unacceptable toxicity has occurred.

Ramucirumab as a single agent

The recommended dose of RAM as a single agent is 8 mg/kg every 2 weeks.

It is recommended that treatment is continued until disease progression or until unacceptable toxicity has occurred.

Note on dosing cycles: a RAM+PAC dosing cycle is 28-days, to accommodate the paclitaxel dosing regimen, whereas the RAM monotherapy dosing cycle is 14 days. In both cases the RAM element of treatment is given every 14 days.

Table 7 Costs of technology being appraised

Pharmaceutical formulation	Concentrate for solution for infusion (sterile concentrate)
Acquisition cost (excluding VAT) *	500mg = £2,500 (list price) 100mg = £500 (list price)
Method of administration	IV infusion
Doses	The recommended dose of RAM is 8 mg/kg both as combination therapy with PAC and as monotherapy.
Dosing frequency	*RAM+PAC* RAM: Days 1 and 15 of a 28-day cycle, prior to PAC infusion PAC: Days 1, 8, and 15 of a 28-day cycle. *RAM as a single agent* Every 2 weeks
Average length of a course of treatment[1]	*RAM+PAC* 28 days *RAM as a single agent* 2 weeks
Average cost of a course of treatment	*RAM+PAC*: £5,031 *RAM*: £3,000
Anticipated average interval between courses of treatments	N/A – treatment as per dosing frequency until disease progression or unacceptable toxicity
Anticipated number of repeat courses of treatments	*RAM+PAC:* Mean estimated number of cycles = 6.17 (Source: combination therapy economic model) *RAM:* Mean estimated number of cycles = 6.94 (Source: monotherapy economic model)
Dose adjustments	*RAM+PAC*: Relative dose intensity (of RAM) = 96.70% (Source: RAINBOW trial) *RAM*: Relative dose intensity = 97.52% (Source: REGARD trial)
Anticipated care setting	Hospital

* indicate whether this acquisition cost is list price or includes an approved patient access scheme

[1] A course of treatment is assumed to be a cycle of treatment for ramucirumab

2.4 Changes in service provision and management

Additional tests and investigations required

The following tests and investigations are required during the course of treatment with ramucirumab:

Table 8 Tests and investigations required during treatment with ramucirumab

	Ramucirumab	Paclitaxel
Full blood count	✓	✓
Renal function test	✓	✓
Hepatic function test	✓	✓
Blood pressure	✓	
Urinalysis	✓	

Full blood counts, renal function tests, and hepatic function tests would be required for treatment with paclitaxel and are not specific to ramucirumab only.

Premedication

Premedication is recommended with a histamine H1 antagonist (for example diphenhydramine) prior to infusion of ramucirumab. If a patient experiences a Grade 1 or 2 infusion-related reaction (IRR; as per the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]), premedication must be given for all subsequent infusions. If a patient experiences a second Grade 1 or 2 IRR administer dexamethasone (or equivalent); then, for subsequent infusions, premedicate with the following or equivalent medicinal products: an intravenous histamine H1 antagonist (for example diphenhydramine hydrochloride), paracetamol and dexamethasone.

Impact on healthcare resource use and costs

The dosing schedule of RAM+PAC means administration is required 3 times per month; this is an increase in administrations compared to BSC (no active treatment) or an active therapy given at two or three weekly intervals.

This will only be an issue in centres where high volumes of GC/GOJ patients are treated. As GC/GOJ is such a rare cancer in the UK (and designated orphan status by

the EMA), it is unlikely to have a significant impact on the majority of hospitals in England. Furthermore, any innovation in treatment in this setting is likely to increase resource use as currently no licensed treatment is available on the NHS.

2.5 Innovation

Ramucirumab (in combination with PAC or as monotherapy) is the first licensed treatment for advanced GC/GOJ in the second-line setting. This innovation has been recognised by the EMA in their granting of orphan designation (12), which is reserved for products that provide an effective treatment option where currently none exist, representing substantial clinical innovation.

GC/GOJ is an orphan disease with very poor prognosis; as such even small *absolute* gains in OS outcomes can represent important *relative* increases in survival. Important advances can happen incrementally over time and over the course of a treatment pathway, transforming treatment for a condition (28). For example, a relative increase in OS of 45% in metastatic breast cancer would correspond to a substantial increase in median OS of 9.45 months (currently median OS is between 18 and 21 months (29)). However, because GC/GOJ has such a poor prognosis, an equivalent 45% increase in median OS, from a baseline of 2.4-3.8 months, would be an apparently more modest gain in median OS of 1.08-1.71months but would be just as clinically meaningful.

Previous anti-angiogenic molecules that have targeted different receptors within the VEGF pathway have failed to demonstrate a significant impact on GC/GOJ overall survival outcomes (30-32). Ramucirumab is the first biologic agent to have demonstrated efficacy in the second-line setting in two phase III trials, providing an alternative to cytotoxic chemotherapy.

The most widely used treatment option for patients who progress following first-line chemotherapy is BSC. Survival with BSC alone is approximately 3-4 months (33). A recent chart review suggests that a wide variety of single agents and combination therapies (up to 21 different regimens) are used in current clinical practice in this setting (5). This is supported by the latest systemic anti-cancer therapy chemotherapy (SACT) data which reports the use of over 152 different regimens for oesophago-gastric cancer treatment (34). As ramucirumab is the first licensed second-line therapy, it provides the opportunity to remove inequality in access to a second-line treatment by creating a new standard treatment pathway where none currently exists. The introduction of a standard care pathway would not only improve the treatment options available to patients, but it would also improve the monitoring and assessment of patients following first-line treatment.

Ramucirumab provides a licensed treatment option for this rare, aggressive, terminal disease, offering meaningful and significant benefit to patients and clinicians that cannot easily be quantified through QALYs. For example, the availability of ramucirumab monotherapy would mean there is an active treatment option for patients for whom cytotoxic chemotherapy is not appropriate, where currently there is no treatment option. This may allow them to maintain a good performance status (PS) and QoL and eligibility for further treatment – effectively providing a bridge to third-line therapy.

3 Health condition and position of the technology in the treatment pathway

Gastric cancer and gastro-oesophageal junction adenocarcinoma

GC is a significant health issue globally. It is the third most common cause of cancer related deaths in men and women worldwide (8). GC/GOJs are rare and aggressive types of cancer that significantly shorten life expectancy.

The term GC refers to cancers that originate in the lining of the stomach and the GOJ. Stomach cancer includes malignancies occurring in any part of the stomach, whereas, GOJ is defined as one that arises “within 5 cm proximal and distal of the anatomic cardia” (35).

Although over 90% of GC/GOJs are adenocarcinomas (36,37), the clinical presentation varies considerably. Cancers that arise in the body of the stomach are believed to be linked to a number of factors including: a diet high in smoked, salted, or pickled food, dried fish and meat, refined carbohydrates (38-41), *Helicobacter pylori* (H. pylori) infection of the inner lining of the stomach (42), family history of stomach cancer (43,44) and cigarette smoking (40,41). In Western populations, GC/GOJs more commonly present in the proximal stomach or gastro-oesophageal junction and the risk factors for these more proximal tumours include gastro-oesophageal reflux disease (GORD), Barrett’s oesophagus (45-47), a complication of gastro-oesophageal reflux disease (GORD), smoking, and obesity (47,48).

Diagnosed at an early stage (stage 0 to 2), there is a high chance of cure. In more advanced stages (stages 3 to 4), the chance of cure reduces dramatically. Unfortunately in Western populations, the majority of patients present with inoperable or advanced disease.

Prognosis

Diagnosis often occurs in the later stages of the disease as the signs and symptoms may not appear until the disease is advanced. Delay in diagnosis can be exacerbated by the fact symptoms may be non-specific and common to a range of non-malignant gastrointestinal symptoms. Symptoms of GC include indigestion, abdominal discomfort, loss of appetite, nausea, vomiting, anaemia, early satiety, anorexia, difficulty swallowing, weight loss and bleeding (49). Those which relate specifically to GOJ cancer include difficulty swallowing (dysphagia), painful swallowing (odynophagia), and

weight loss (50). Gastric and GOJ cancer have a very poor prognosis because of these vague symptoms and diagnosis late in the course of the disease (51,52).

In 2012, there were 5,637 new cases of GC and 3,085 cases of GOJ cancer in England (9) with 4,118 deaths from GC in England in 2013 (53). Of patients diagnosed with GC, approximately 80% are diagnosed with advanced, metastatic GC (54). For all patients diagnosed with GC between 2010-2011 in England and Wales, the predicted 5-year survival rate was 18.9% (54). This is below the 2000-2007 European mean 5-year age standardised relative survival rate for GC of 25.1% (55). For the approximately 80% of patients with advanced, metastatic disease at diagnosis the 5-year survival rate is much lower at around 5% (54).

For patients diagnosed early with localised, distal GC/GOJ adenocarcinoma, more than 50% can be cured (56). However, for the majority of patients who have unresectable, locally advanced or metastatic disease at diagnosis, curative options do not exist and palliative chemotherapy or BSC are the only options. The aim of BSC is to improve the QoL of patients by preventing and relieving suffering due to disease symptoms, and treating other physical, psycho-social and spiritual problems.

Burden of disease

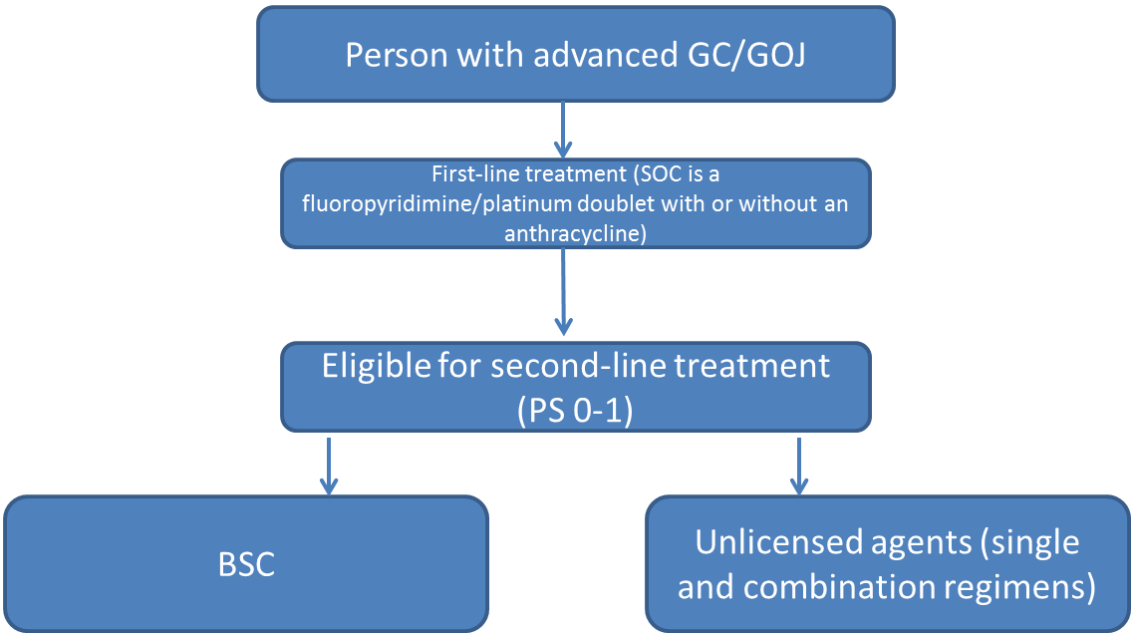
There is limited literature exploring the burden of advanced GC on patients, carers, and society. HRQL has been explored; however this evidence is limited to data collected during the course of clinical trials to examine the impact of treatment on HRQL. It is clear however that GC/GOJ has a substantial economic burden as age-specific incidence rates rise significantly from the ages of 60-64 (57) with a 1-year survival rate of 41.8% (57). In addition to this, age-specific mortality rates rise gradually in GC from the ages of 40-44, with the sharpest increases taking place from ages 65-69. This relates to a loss of approximately 25-30 (working) years in terms of productivity. A treatment option that can improve survival outcomes alongside maintaining QoL in this setting could reduce the economic burden of the disease.

Treatment pathway

For patients diagnosed with GC/GOJ in the early stages of the disease, or for those with localised disease, resection is the usual treatment with partial or total gastrectomy (58). However, only surgically fit patients are eligible for extensive resection. Unfortunately, patients are rarely diagnosed at stage 1 (1 in 100 cases) or stage 2 (6 in 100 cases) of the disease. Despite treatment with curative-intent resections in early stage disease, the majority of patients will relapse (59).

The aim of treatment for inoperable or advanced GC/GOJ is to slow progression, extend survival and relieve symptoms with minimal adverse effects without detriment to QoL. Most patients are treated with a fluoropyridimine/platinum doublet with or without an anthracycline as a first-line treatment (5). However, once patients progress, there is no universally accepted, standard treatment. The most widely reported treatment according to a recent chart review for patients who progress after first-line chemotherapy is BSC (5).

Figure 2 Current UK clinical practice for patients with GC/GOJ



Evidence supporting the use of different single and double-agent chemotherapy regimens for the second-line treatment of advanced GC/GOJ is sparse (2,4,60). A few relatively small open-label phase 3 studies comparing single-agent chemotherapy with BSC have demonstrated efficacy for single agent taxanes and irinotecan (IRI) after disease progression on prior chemotherapy leading to an increase in their use. Other treatment is based on phase 2 studies that have suggested activity with single-agent and combination regimens subsequent to progression on initial chemotherapy, including taxanes (PAC or DOC) and IRI (61-75).

The studies of ramucirumab presented in this submission are the largest positive phase 3 trials in advanced GC/GOJ by a significant margin and provide robust evidence for the efficacy of ramucirumab as a second-line treatment.

The proposed use of ramucirumab, in line with the licensed indication, is for treatment of adult patients with advanced GC/GOJ with disease progression after prior platinum

and/or fluoropyrimidine chemotherapy. Ramucirumab is the first licensed treatment in this setting and has demonstrated a survival benefit in two phase 3 trials.

Clinical Guidelines

British Society of Gastroenterology (BSG) - Guidelines for the Management of Oesophageal and Gastric Cancer (2011) (33)

First-line

For the first-line treatment of advanced GC/GOJ, the BSG recommend palliative combination chemotherapy with epirubicin, cisplatin and fluorouracil 5FU (ECF) as the preferred regimen (triplet regimens containing anthracyclines, cisplatin and 5FU (e.g., ECF) are superior for OS than doublet regimens containing either cisplatin/5FU or anthracyclines/5FU). Capecitabine can be substituted for 5FU, and oxaliplatin for cisplatin in ECF therefore EOX (epirubicin, oxaliplatin, capecitabine) or ECX (epirubicin, cisplatin, capecitabine) can also be used.

Second-line

For second-line treatment it is recommended that patients are enrolled into a RCT. Information on RAINBOW and REGARD was not available at the time of publication of the BSG guidelines and the guidelines have not been updated since.

ESMO – Gastric Cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up (2013) (76)

First-line

The ESMO guidelines recommend first-line palliative chemotherapy with combination regimens including a platinum agent and a fluoropyrimindine; ECF, ECX, EOF (epirubicin, oxaliplatin, fluorouracil), EOX can also be used. Alternatively, taxane-based regimens or IRI and 5FU can be used.

Second-line

For second-line treatment in patients with adequate performance status, DOC, PAC, or IRI may be used. Considerations should be given to clinical trials and in patients with disease progression after 3 months of first-line chemotherapy, re-challenge with the same drugs.

The ESMO guidelines also mention that ramucirumab has recently been shown to have single-agent activity in the second-line setting with improved OS. However, it should be noted that the full trial results of RAINBOW and REGARD were not available at the time of publication of the ESMO guidelines and the guidelines have not been updated since.

National Comprehensive Cancer Network (NCCN) – Clinical practice guidelines in oncology: Gastric cancer (2015) (77)

First-line

The NCCN guidelines recommend two-drug cytotoxic regimens because of their lower toxicity for the first-line treatment of patients with metastatic or locally advanced cancer. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation. Preferred first-line regimens include DCF (docetaxel, cisplatin, and fluorouracil), DCF modifications (substituting cisplatin with oxaliplatin or carboplatin), ECF (epirubicin, cisplatin, and fluorouracil), ECF modifications (substituting cisplatin with oxaliplatin or substituting fluorouracil with capecitabine), fluorouracil and IRI, and fluoropyridimine and cisplatin/oxaliplatin.

Second-line

The NCCN recommend that second-line therapy should be dependent on prior therapy and PS. Both RAM+PAC and RAM monotherapy are mentioned as preferred regimens in this setting (category 1).

Scottish Intercollegiate Guidelines Network (SIGN) – Management of oesophageal and gastric cancer (2006) (78)

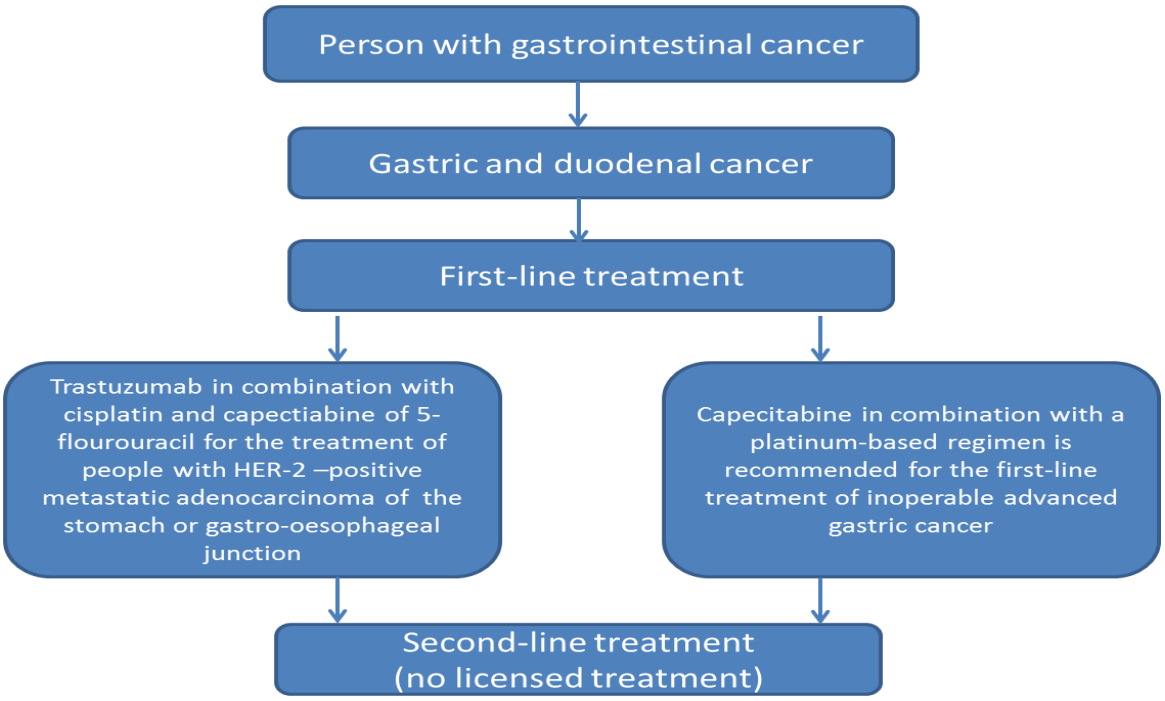
The SIGN guidelines recommend that in patients with locally advanced or metastatic cancer of the oesophagus or stomach with good PS, combination chemotherapy including cisplatin and infusional 5-FU (such as ECF or mitomycin C, cisplatin and fluorouracil (MCF)) should be considered as a palliative chemotherapy option.

At the time of publication (2006), the role of agents such as oxaliplatin, taxanes and IRI remained under investigation. In addition, the SIGN guidelines state that there is no established role for routine use of second-line chemotherapy.

National Institute for Health and Care Excellence (NICE)

Based on the licensed indication, ramucirumab would be expected to fit under the ‘gastric and duodenal cancer’ section of the gastrointestinal cancer pathway (pathway created November 2013 updated in Figure 3). Under this section currently there is only guidance for first-line treatment relating to Trastuzumab (TA208; guidance on static list published July 2010 titled ‘Trastuzumab for the treatment of HER2-positive metastatic gastric cancer) (15) and Capecitabine (TA191; guidance on static list published July 2010 titled ‘Capecitabine for the treatment of advanced gastric cancer’) (79) for the first-line treatment of GC and GOJ adenocarcinoma.

Figure 3 NICE Pathway: Gastrointestinal cancers (created November 2013)



Uncertainty/variation in clinical practice

There is currently no licensed second-line treatment available in England. As a result there is significant variation, uncertainty, and geographic inequality in clinical practice in the second-line setting.

In order to understand what is actually being used in clinical practice in England a chart review (5) found that only 28.5% of patients were receiving an active second-line therapy after their first-line treatment. Amongst those who received second-line treatment, a wide variety of regimens were being used including DOC (28%), PAC (10%), trastuzumab (9%), capecitabine (7%), IRI (7%), and 16 other regimens (monotherapy and combination therapy; 39%) (5).

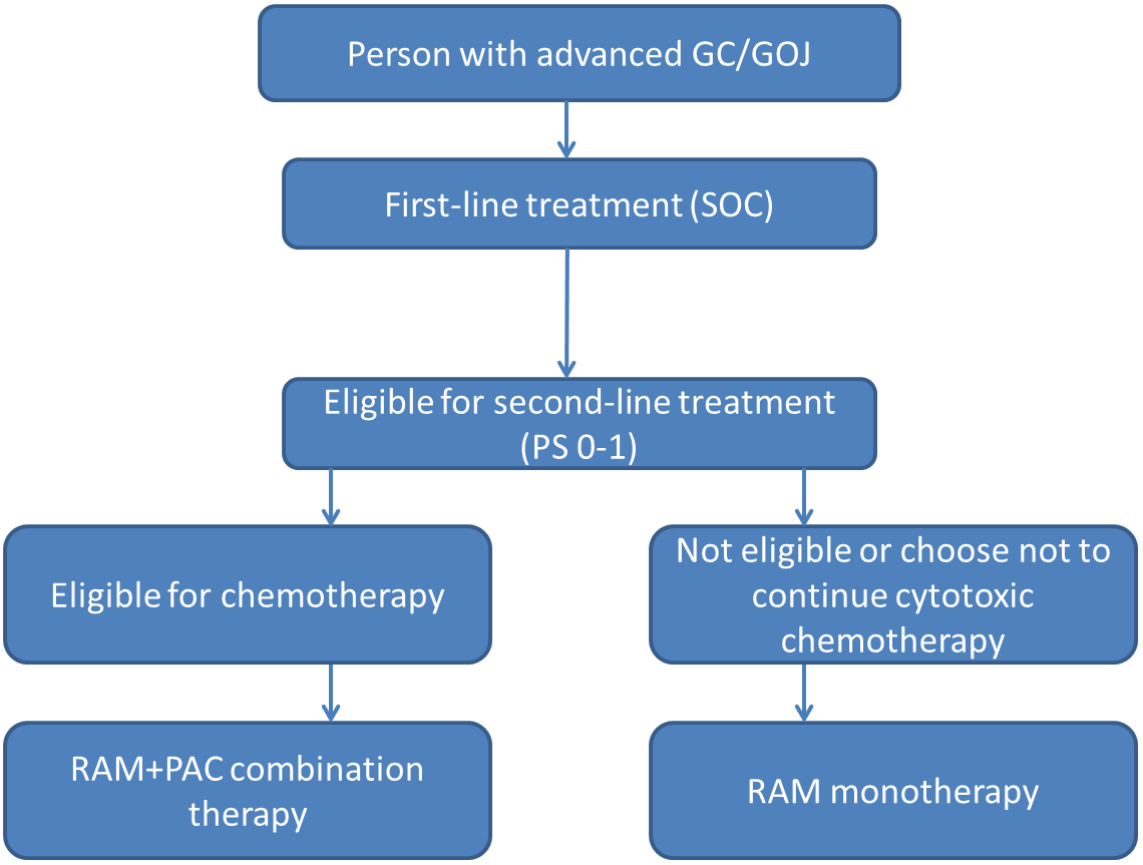
These data therefore suggest that the most widely used treatment for patients upon progression from first-line chemotherapy is BSC with 21 different regimens (monotherapy and combination therapy) used second-line. Survival with BSC alone is approximately 3-4 months (2,4,33).

Anticipated place of ramucirumab in clinical practice

The introduction of ramucirumab monotherapy or combination therapy as treatment options for patients eligible (PS 0/1) for second-line treatment would present a significant change in clinical practice and provide patients and clinicians with an evidence-based treatment choice. The most widely used treatment for patients with

GC/GOJ who have progressed following first-line treatment is BSC. Ramucirumab would provide two alternative treatment options, see 0.

Figure 4 The impact of ramucirumab combination and monotherapy on UK clinical practice



Patients with advanced GC/GOJ who progress following first-line treatment who are of good performance status (PS 0/1) and eligible for second-line treatment may or may not be suitable for chemotherapy. Cytotoxic chemotherapy may not be deemed appropriate for a range of reasons including:

- Lingering toxicities from first-line treatment (such as neuropathy and fatigue) making patients unsuitable for further cytotoxic chemotherapy
- Co-morbidities (such as obesity, heart disease, emphysema, and compromise of bowel function)
- Patient/clinician choice not to continue with chemotherapy
- Prior clinician or patient experience

For patients who are eligible for cytotoxic chemotherapy, RAM+PAC combination therapy provides a valuable treatment option which is shown to improve survival outcomes.

As a result of the introduction of ramucirumab monotherapy, clinicians now have a treatment option for a patient group with poor prognosis who are not suitable for cytotoxic chemotherapy, where currently no treatment option exists. The CHMP acknowledged the value of ramucirumab monotherapy even whilst recognising that the OS gain with monotherapy is less than the combination therapy. The CHMP outlined that this could still represent a useful therapeutic option in this second-line setting when chemotherapy in combination with ramucirumab is not the preferred option (17).

Equality

Ramucirumab is the first and only licensed treatment for previously treated advanced GC/GOJ patients, consequently fulfilling a significant unmet need for this orphan disease. Orphan status is reserved for treatments which provide an effective treatment option where currently none exist representing an inequality in treatment options in this disease area. At present the only treatment options available to patients are off-licence cytotoxic chemotherapy regimens. These treatments are associated with notable toxicities and are therefore not suitable for all patients. Older patients are more likely to fit into this category (22) meaning there are currently no treatment options available to them. This represents an inequality for older patients which has been well documented in the literature (22,80,81).

Ramucirumab monotherapy and combination therapy present treatment options that are suitable for use in elderly patients (refer to SPC section 4.2 and 5.2 in Appendix 1). In both RAINBOW and REGARD there was no indication that patients aged 65 years of age or older were at increased risk of AEs compared to patients younger than 65 years of age. The existence of a treatment option which is not a cytotoxic chemotherapy (i.e. a taxane) would allow equity in treatment options for all fit and willing patients.

The choice of a licensed treatment option in this setting also reduces the ethical dilemma for doctors who are currently limited to using unlicensed treatments in this setting. The General Medical Council (GMC) guidance indicates that clinicians should usually prescribe medicines in accordance with the terms of their licence, but that clinicians may prescribe off-licence medicines where there is no licensed medicine applicable to the particular patient (82).

The lack of an available licensed treatment can lead to inequalities in access across geographies. This is clearly reflected in the wide variations in current clinical practice in GC/GOJ (5). In the absence of any NICE clinical guidelines or national algorithms in this setting, each trust independently develops their own treatment protocols. The use of unlicensed treatment in clinical practice becomes contingent upon physician preferences and upon any restrictions in place by the trust in which they practise. There are likely to be differences in the acceptance of the use of unlicensed treatment in trusts leading to geographical inequalities. Ramucirumab is the first licensed second-line therapy. It presents an option for equal access to a second-line treatment in this setting, reducing the continued use of off-licence drugs and providing a standard treatment pathway where none currently exists.

The introduction of a standard care pathway would not only improve the treatment options available to patients, but it would also improve the monitoring and assessment of patients following first-line treatment. The existence of an effective, licensed treatment option would create an impetus for imaging and evaluation of patients to promptly identify those suitable for second-line treatment.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

A comprehensive review of the published literature was performed on 2nd December 2014 to identify RCTs of ramucirumab for the second-line treatment of adult patients with advanced GC/GOJs.

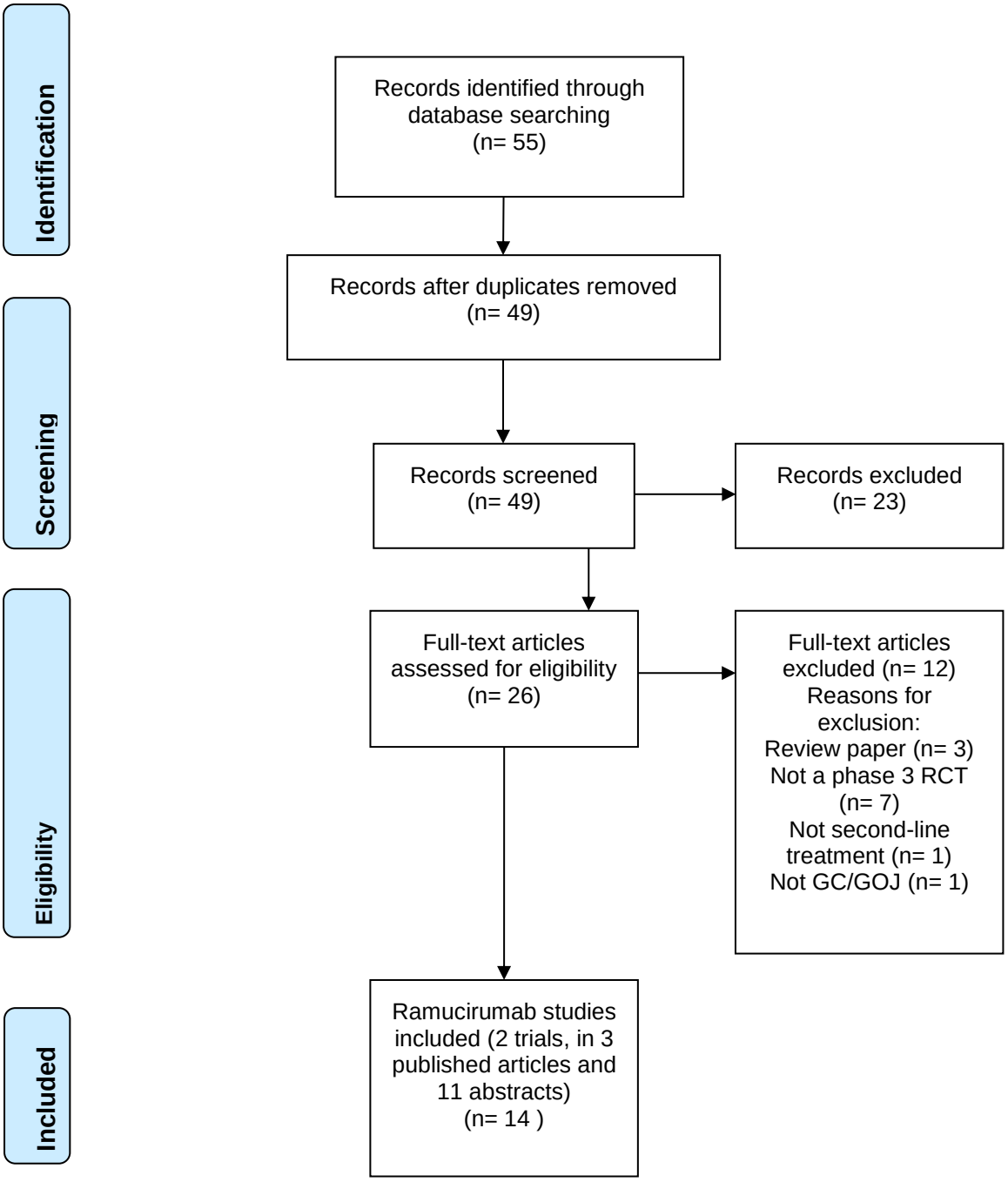
The literature search was conducted in Medline and Medline ® In-Process, Embase, and the Cochrane Library with no date restrictions applied. A protocol was prepared for the literature search detailing inclusion and exclusion criteria, search terms, and search dates. Details of the search strategy can be found in Appendix 2. Full references were also checked for any additional studies that may have provided useful and relevant clinical data. Additionally, the website of the American Society of Clinical Oncology (ASCO) was also searched electronically for relevant abstracts. The full eligibility criteria used in the search strategy are presented in Table 9.

Table 9 Eligibility criteria used in search strategy

	INCLUSION	EXCLUSION
Population	Adult patients with advanced GC/GOJ adenocarcinoma being treated with second-line treatment	Paediatric patients; Early stage GC/GOJ adenocarcinoma
Intervention	Ramucirumab (Cyramza) given as second-line treatment	Ramucirumab (Cyramza) given as first-line treatment or maintenance treatment
Comparator	No restrictions	
Outcomes	Trials with primary outcome measures of either PFS and OS	Trials with primary outcome measures other than OS or PFS
Setting/Study type	Randomised Controlled Trial (phase 3 or phase 4)	Non-randomised trials; phase 1/2 trials; review articles; notes or correspondence; editorials; conference proceedings
Language restrictions	English	

The search of the literature yielded 55 citations. De-duplication resulted in the removal of 6 citations. Following screening of the remaining 49 studies, 23 studies were excluded. Full texts of the remaining 26 studies were obtained. Following the application of exclusion criteria, two trials remained (RAINBOW and REGARD). The PRISMA flow diagram in Figure 5 details the number of papers included and excluded at each stage of the review.

Figure 5 **PRISMA flow diagram for systematic literature review of ramucirumab clinical studies**



The literature search identified 8 publications (1 published article, 7 conference abstracts) pertaining to RAINBOW (6), the phase 3 clinical trial of RAM+PAC in the second-line clinical setting. These publications are detailed below.

Table 10 RAINBOW publications

Primary study reference	Additional publications
Wilke H, Muro K, Van Cutsem E *et al*. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial. The Lancet Oncology. 2014;15 (11): 1224-1235. (6)	Al-Batran SE, Van Cutsem E, Oh SC et al. RAINBOW: A global, phase 3, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel with previously treated gastric or gastroesophageal junction (GEJ) adenocarcinoma: Quality-of-life (QoL) results). J Clin Oncol 2014; 32:5s (suppl; abstr 4058). (83)
	Al-Batran SE, Van Cutsem E, Kim TY et al. RAINBOW: A global, phase 3, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel with previously treated gastric or gastroesophageal junction (GEJ) adenocarcinoma – Patient reportedoutcomes and performance status.. ESMO World Congress on GO; 2014. (84)
	Hironaka S, Shimada Y, Sugimoto N, et al. RAINBOW: A global, phase 3, randomized, double-blind study of ramucirumab (RAM) plus paclitaxel (PTX) versus placebo (PL) plus PTX in the treatment of metastatic gastroesophageal junction and gastric adenocarcinoma (mGC) following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy-Efficacy analysis in Japanese and Western patients. J Clin Oncol 2014; 32:5s (suppl; abstr 4005). (85)
	Wilke H, Cunningham D, Ohtsu A, et al. A randomized, multicenter, double-blind, placebo (PBO)-controlled phase 3 study of paclitaxel (PTX) with or without ramucirumab (IMC-1121B; RAM) in patients (pts) with metastatic gastric adenocarcinoma, refractory to or progressive after first-line therapy with platinum (PLT) and fluoropyrimidine (FP). J Clin Oncol 2012;30. (86)
	Wilke H, Clingan P, Ananda S et al. RAINBOW: A global, phase 3, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of gastric cancer following disease progression: Western population subgroup. ESMO World Congress on GI, 2014. (87)
	Wilke H, Van Custem E,Cheul S, et al. RAINBOW: a global, phase 3, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastric adenocarcinoma following disease progression on first-line platinum-and fluoropyrimidine-containing combination therapy: results of a multiple Cox regression analysis adjusting for prognostic factors. J Clin Oncol 2014; 32:5s (suppl; abstr 4076). (88)

	Wilke H. RAINBOW: A global, phase 3, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum-and fluoropyrimidine-containing combination therapy rainbow IMCL CP12-0922 (I4T-IE-JVBE). ASCO Annual Meeting Proceedings; 2014. (89)

The literature search identified 6 publications (2 published articles, 4 conference abstract) pertaining to REGARD (7), the phase 3 clinical trial of RAM used as monotherapy in the second-line clinical setting. These publications are detailed below.

Table 11 REGARD Publications

Primary study reference	Additional publications
Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial. The Lancet 2014; 383 (9911): 31-39 (7)	Chau I, Passalacqua R, Zalcberg JR, et al. Tolerability and quality-of-life (QoL) results from the phase 3 REGARD study: Ramucirumab versus placebo in patients with previously treated gastric or gastroesophageal junction (GEJ) adenocarcinoma. European Cancer Congress, 2013. (90)
	Fuchs C, Tomášek J, Cho JY, et al. REGARD: A phase 3, randomized, double-blind trial of ramucirumab and best supportive care (BSC) versus placebo and BSC in the treatment of metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma following disease progression on first-line platinum-and/or fluoropyrimidine-containing combination therapy: Age subgroup analysis. J Clin Oncol 2014; 32:5s (suppl; abstr 4057). (91)
	Fuchs C, Tomasek, J, Cho JY, et al. REGARD: A phase III, randomized, double-blinded trial of ramucirumab and best supportive care (BSC) versus placebo and BSC in the treatment of metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma following disease progression on first-line platinum-and/or fluoropyrimidine-containing combination therapy. J Clin Oncol 2013; 31;4 (suppl; abstr LBA5). (92)
	Fuchs C, Tomasek, J, Cho JY, et al. REGARD: A phase III, randomized, double-blind trial of ramucirumab and best supportive care (BSC) versus placebo and BSC in the treatment of metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma following disease progression on first-line platinum-and/or fluoropyrimidine-containing combination therapy. American Association for Cancer Research Annual Meeting, 2013.(93)
	Liguigli W, Tomasello G, Toppo L., Ratti M., Passalacqua R. Ramucirumab for metastatic gastric or gastroesophageal junction cancer: Results and implications of the REGARD trial. Future Oncology

	2014; 10(9):1549-1557. (94)

4.2 List of relevant randomised controlled trials

This submission is based on clinical data from the two phase 3 RCTs; RAINBOW and REGARD (See Table 12). RAINBOW (6) was a phase 3, international, multicentre, randomised, placebo-controlled, double-blind trial investigating RAM+PAC versus PBO+PAC in the second-line clinical setting. REGARD (7) was an international, multicentre, randomised, placebo-controlled, double-blind phase 3 trial investigating RAM used as monotherapy in the second-line clinical setting versus PBO and best supportive care (BSC).

Table 12 List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
RAINBOW	RAM+PAC	PBO+PAC	Patients aged 18 years and older; having metastatic or non-resectable, locally advanced GC/GOJ; documented objective radiological or clinical disease progression during or within 4 months of the last dose of first-line platinum and fluoropyridimine doublet with or without anthracycline; an ECOG PS of 0 or 1; and measurable or non-measurable evaluable disease.	Wilke et al (2014) (6)
REGARD	RAM+BSC	PBO+BSC	Patients aged 18 years and older, had metastatic or unresectable, locally recurrent GC/GOJ; had experienced disease progression during or within 4 months after the last dose of first-line therapy for metastatic disease, or during or within 6 months after the last dose of adjuvant therapy; and had a ECOG PS of 0 or 1; and measurable or evaluable disease.	Fuchs et al (2014) (7)

Scientific background and study rationale for RAINBOW and REGARD

Clinical activity was seen early in the development of ramucirumab. A lack of licensed or effective treatment options in second-line GC/GOJ at the time of study design identified an area of significant unmet medical need. Treatment options that extend survival and maintain QoL without adding significant toxicity were required.

Given this and promising early phase clinical data for ramucirumab, a programme of evaluation of ramucirumab as a potential treatment for patients with advanced GC/GOJ was initiated. Two phase 3 trials were set up for patients whose disease had progressed after the initial treatment of metastatic GC/GOJ with chemotherapy: RAINBOW and REGARD.

RAINBOW was set up to compare the efficacy and safety of RAM+PAC with PBO+PAC and REGARD to compare the efficacy and safety of RAM as monotherapy with BSC.

The two trials represent two distinct treatment regimens for ramucirumab. Since MA this has led to two indications and patient populations for the use of ramucirumab in advanced GC/GOJ. Therefore, the two trials are reported separately in this section.

4.3 Summary of methodology of relevant randomised controlled trials

RAINBOW

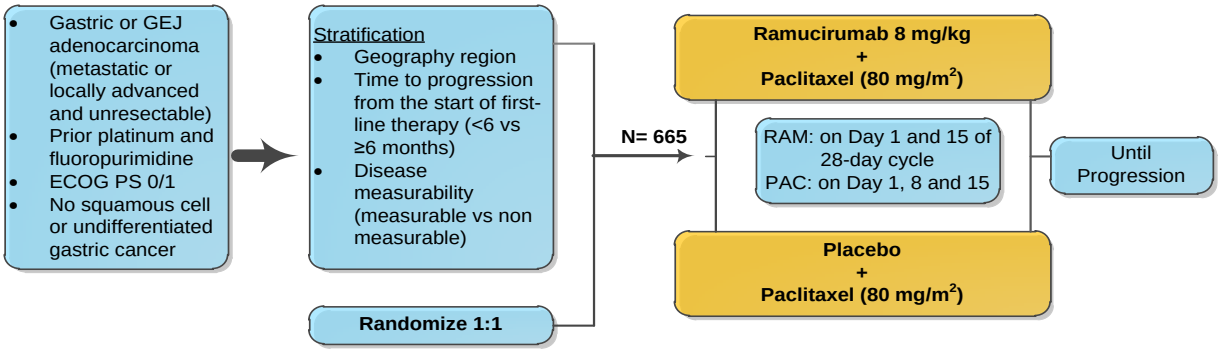
Methods

Trial design

RAINBOW was a global, randomised, placebo-controlled, double-blind, phase 3 study which compared RAM+PAC to PBO+PAC in 665 patients with advanced GC/GOJ who had disease progression after first-line therapy with platinum-containing and fluoropyrimidine-containing chemotherapeutic regimens with or without an anthracycline.

The study was completed after a sufficient number of events were observed for final analysis of the primary endpoint, 510 OS events (explained in further detail in section 4.4). Figure 6 presents a diagrammatic representation of the trial design.

Figure 6 RAINBOW: Trial Design



Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; GEJ = gastro-oesophageal

Selection of comparator

At the time of RAINBOW trial design, as well as there being no licensed treatment in this setting, wide disparities in global clinical practice existed. A number of Phase 2 studies had suggested activity associated with single-agent chemotherapy subsequent to progression on

initial chemotherapy, including taxanes (PAC or DOC), as well as with regimens using these agents in combination with other agents (61-75).

As there was no standard regimen globally for second-line treatment, paclitaxel was chosen as the comparator against RAM+PAC in RAINBOW. The primary reason for choosing PAC as the comparator was that in relation to all the agents that have demonstrated efficacy in this treatment setting, the safety analyses and dosing schedule of PAC have demonstrated advantages over other regimens lower frequency of grade 4 neutropenia and non-haematological toxicities (63,66,70,95-98)(99).

Objectives and outcomes

The primary objective of this study was to demonstrate efficacy in terms of increased OS in patients treated with RAM+PAC compared with patients treated with PBO+PAC, as second-line treatment of metastatic GC/GOJ after failure of any platinum and fluoropyrimidine doublet with or without anthracycline (epirubicin or doxorubicin). Key secondary outcomes included PFS, time to disease progression (TTP), objective response rate (ORR) and disease control rate (DCR), QoL, and safety outcomes. Further details regarding secondary outcomes, how they were measured, and a comparative summary of trial methodology in relation to REGARD can be seen in Table 28.

Participants

RAINBOW took place between December 2010 and July 2013 in 170 centres across 27 countries in North America, Europe, Israel, Australia, South and Central America, and Asia.

Study eligibility criteria are summarised in Table 13. A complete list of all inclusion and exclusion criteria is given in Appendix 3. Patients could be enrolled regardless of HER2 status.

Table 13 RAINBOW: Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• Histologically or cytologically confirmed gastric carcinoma, including gastric or GOJ adenocarcinoma • Metastatic disease or locally recurrent, unresectable disease • Disease progression during or ≤4 months after the last dose of first-line platinum/fluoropyrimidine doublet with or without anthracycline (epirubicin, doxorubicin) for unresectable or metastatic disease • Age ≥18 years and the Eastern Cooperative oncology Group (ECOG) performance status (PS) score of 0 or 1 • Adequate recovery from toxicities or effects of prior therapy • Adequate haematologic, hepatic, coagulation, and renal function	• Patients with squamous cell or undifferentiated gastric cancer. • Patients had undergone major surgery within 28-days prior to randomisation, or central venous access device placement within 7 days prior to randomisation • Patients received any chemotherapy other than platinum and fluoropyrimidine with or without anthracycline for advanced gastric or GOJ adenocarcinoma • History of GI perforation and/or fistulae within 6 months prior to randomisation. • Significant bleeding disorders, vasculitis, or had a significant bleeding episode from the GI tract within 3 months prior to study entry • History of deep vein thrombosis, pulmonary embolism, or any other significant thromboembolism during the 3 months prior to randomisation. • Symptomatic congestive heart failure • Uncontrolled arterial hypertension • Arterial thrombotic event (MI, transient ischemic attack, cerebrovascular accident, or unstable angina) within 6 months prior to randomisation • Serious or non-healing wound or peptic ulcer or bone fracture within 28-days prior to randomisation. • Current chronic platelet therapy, NSAIDs. • Pregnancy/breastfeeding

GI = gastrointestinal; MI = myocardial infarction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID = non-steroidal anti-inflammatory agent.

Interventions

- Intervention (n=330): RAM (8 mg/kg IV) plus PAC (80 mg/m^2 IV). PAC was given on days 1, 8, and 15 of a 28-day cycle, in combination with RAM given on days 1 and 15.
- Comparator (n=335): PBO+PAC (80 mg/m^2 IV). PAC was given on days 1, 8, and 15 of a 28-day cycle, in combination with an equivalent volume of PBO given on days 1 and 15.

Patients underwent radiographic assessment of disease status, evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, every 6 weeks for the first 6 months (±3 days) following the first dose of study therapy, and every 9 weeks (±3 days) thereafter. Treatment continued until there was evidence of progressive disease, unacceptable toxicity, withdrawal of consent, or until other withdrawal criteria were met.

Dose modifications and discontinuations

RAM (or PBO) dose could be reduced up to two times, first to 6 mg/kg and then to 5 mg/kg. Dose reductions were allowed in the occurrence of treatment-related, non-life threatening, reversible grade 3 clinical AEs and grade 4 fever or laboratory abnormalities that resolved to grade ≤ 1 or pre-treatment baseline within 1 treatment cycle. RAM (or PBO) was to be discontinued in case of related grade 4 toxicities other than fever or laboratory abnormalities.

No PAC dose reductions were allowed within a given cycle. In the event of treatment-related grade 4 haematological toxicity or grade 3 non-haematological toxicity (except for alopecia), PAC dose reductions by 10 mg/m^2 were to occur for the subsequent cycle. PAC was to be permanently discontinued if it was necessary to reduce the dose to less than 60 mg/m^2 or in the case of a PAC-related life-threatening event, regardless of grade.

Supportive care

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment was offered to all patients in this trial. Supportive care included, but was not limited to, anti-emetic agents, opiate and non-opiate analgesic agents, appetite stimulants, granulocyte-colony stimulating factors, erythroid growth factors, laxatives, and anti-depressants.

Prohibited therapies

Additional concurrent chemotherapy, radiation therapy (with curative intent), biologic response modifiers, or other investigational anti-cancer agents were not to be administered to patients during this study. Palliative radiation to symptomatic sites of disease was permitted during the study.

Restricted therapies

Anticoagulation therapy was permitted in the setting of venous thromboembolism occurring during the study.

Randomisation sequence generation

Patients were randomised 1:1 in a double-blind fashion to RAM+PAC and PBO+PAC using an Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS). Randomisation was stratified by:

- Geographic region - Due to differences in standard care, geographic region was considered an important prognostic factor (explained in further detail in the subgroup analyses section).

    - Region 1 - US, Europe, Australia, Israel
    - Region 2 - Argentina, Brazil, Chile, Mexico
    - Region 3 - Hong Kong, Japan, South Korea, Singapore, Taiwan
- TTP from the start of first-line chemotherapy (<6 months vs. >6 months) - TTP was considered an important prognostic factor due to evidence suggesting TTP greater than 6 months was potentially favourable to advanced GC patients likely to benefit from subsequent therapy(100)
- Disease measurability (measureable vs. non-measurable) - As objective response rate was a secondary endpoint, disease measurability was chosen to ensure balance between the treatment groups with respect to patients with measurable disease.

Allocation concealment, implementation and blinding

Patients, investigators, and all other personnel involved in the conduct of the study (including the pharmacists at the study sites) were blinded to individual treatment assignments for the duration of the study. The identity of the investigational product assigned was contained in the IVRS/IWRS.

Centres enrolled/registered patients into this study by accessing a call-in IVRS or IWRS. An IVRS/IWRS was used to randomly assign patients on a 1:1 basis to Arm A (RAM+PAC) or Arm B (PBO+PAC). RAM and PBO for infusion were identical in appearance in order to preserve blinding and uniquely labelled.

Unblinding did not occur at disease progression, there were no anticipated or identified toxicities of RAM that would potentially unblind investigators to treatment assignment, and unblinding of the study team did not occur until after the reporting database was validated and locked for final statistical analysis.

4.4 Statistical analysis and definition of study groups

Sample size

Primary and secondary efficacy endpoints were analysed using the ITT population (with allocation of patients to treatment arms “as randomised”). It was calculated that to achieve 90% power to detect an overall difference in survival between the two treatment groups, 663 patients would need to be randomly assigned. The ITT population (N = 665 patients) included 330 patients randomised to receive RAM+PAC and 335 patients randomised to receive PBO+PAC.

Statistical methods

The primary outcome for RAINBOW was OS, defined as the time from the date of randomisation to the date of death from any cause. OS was censored on the last date the patient was known to be alive (on or before data cut-off date or lost to follow-up). Patient survival status was collected every 8 weeks after treatment discontinuation, until the date of death or data cut-off date.

The primary analyses of OS used the ITT population which included all randomised patients. Unless otherwise specified, missing data were not imputed. OS was compared using a log-rank test stratified by randomisation strata (geographic region, time to progression on first-line therapy, and disease measurability) at a one-sided 0.025 (two-sided 0.05) level of significance. The HR and 95% CI were determined using a Cox regression model. Kaplan-Meier estimates including 95% CIs were presented for median OS, 6 month and 12 month OS rates for each treatment group. A restricted mean analysis was conducted for OS in order to estimate the difference in average OS between the treatment arms.

Sensitivity analyses performed to test the robustness of the primary OS result included an unstratified log-rank test, stratified analysis using case report forms (CRF) as the data source, a Cox regression analysis adjusting for potential prognostic factors, and a per protocol population analysis.

The key secondary outcomes and their statistical analyses are detailed in Table 31.

Primary hypothesis under investigation and power calculation

To achieve 90% power to detect an overall difference in survival between the two treatment groups, it was calculated that 510 deaths were needed, and 663 patients would be required to be randomly assigned to the two treatment groups.

Based on a uniform accrual rate of 30 patients per month and median OS time of 7 months in PBO+PAC group and 9.3 months in the RAM+PAC group, it was calculated that a total of 663 patients (and 510 OS events) would be accrued in approximately 32 months after first patient randomised (about 10 months after last patient randomised) based on a one-sided type I-error rate of 0.025 (or two-sided at 0.05) This consideration takes into account a dropout rate of approximately 5%.

A summary of the statistical analyses for RAINBOW can be found in Table 14.

Table 14 Summary of statistical analyses in RAINBOW

Trial acronym	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
RAINBOW	The primary objective of this study was to demonstrate efficacy in terms of prolonged survival time in patients treated with RAM+PAC compared with patients treated with PBO+PAC as second-line treatment of metastatic GC/GOJ after failure of any platinum and fluoropyrimidine doublet with or without anthracycline (epirubicin or doxorubicin).	OS was compared using a log-rank test stratified by randomisation strata at a one-sided 0.025 (two-sided 0.05) level of significance. The HR and 95% CI were determined using a Cox regression model. Kaplan-Meier estimates including 95% CIs were presented for median OS, 6 month and 12 month OS rates for each treatment group. A restricted mean analysis was conducted for OS in order to estimate the difference in average OS between the treatment arms. Sensitivity analyses performed to test the robustness of the primary OS result included an unstratified log-rank test, stratified analysis using CRF as the data source, a Cox regression analysis adjusting for potential prognostic factors, and a per protocol population analysis.	A total of 663 patients (and 510 OS events) would be accrued in approximately 32 months after first patient randomised (about 10 months after last patient randomised) based on the following assumptions: overall one-sided type I-error rate of 0.025 (or two-sided at 0.05) and study power of 90%; median OS of 7.0 months in the PBO arm and 9.33 months in the RAM arm; randomisation ratio of 1:1; one interim futility analysis at 25% of total number of OS events; and a dropout rate of 5%.	Patients who discontinued from all study therapy were to be followed for survival at regularly scheduled intervals (at least every 8 weeks [+ 0-7 days]) for as long as he or she remained alive (until study completion) and: • The reason(s) for discontinuation was to be documented in the patient's medical record and electronic case report form (eCRF) • An end-of-therapy evaluation was to be performed • Patients who discontinued for reasons other than progression of disease were to continue to receive radiographic assessment for tumour response every 6 weeks following the first dose of study therapy (± 3 days) for the first 6 months following the first dose, and every 9 weeks (± 3 days) thereafter, until there was radiographic documentation of PD • A follow-up evaluation was to be performed at least 30 days after the last dose of study therapy. The patient should have been followed for survival at regularly scheduled intervals (at least every 8 weeks [+ 0-7 days]) for as long as he or she remained alive.

Subgroup analyses

Subgroups included stratification and potential prognostic factors (Table 15). Of interest was an analysis to evaluate the treatment effect of ramucirumab between geographic regions. High rates of salvage therapy have been reported in previous Asian trials (3). A higher rate of post discontinuation (PDT) third-line therapy was expected in Region 3 (parts of Asia), potentially confounding the OS treatment effect of the RAM+PAC regimen due to differing rates of PDT. Stratified and unstratified analyses were performed. Forest plots of the estimated HRs with 95% CIs were generated.

Table 15 RAINBOW: Pre-specified subgroups

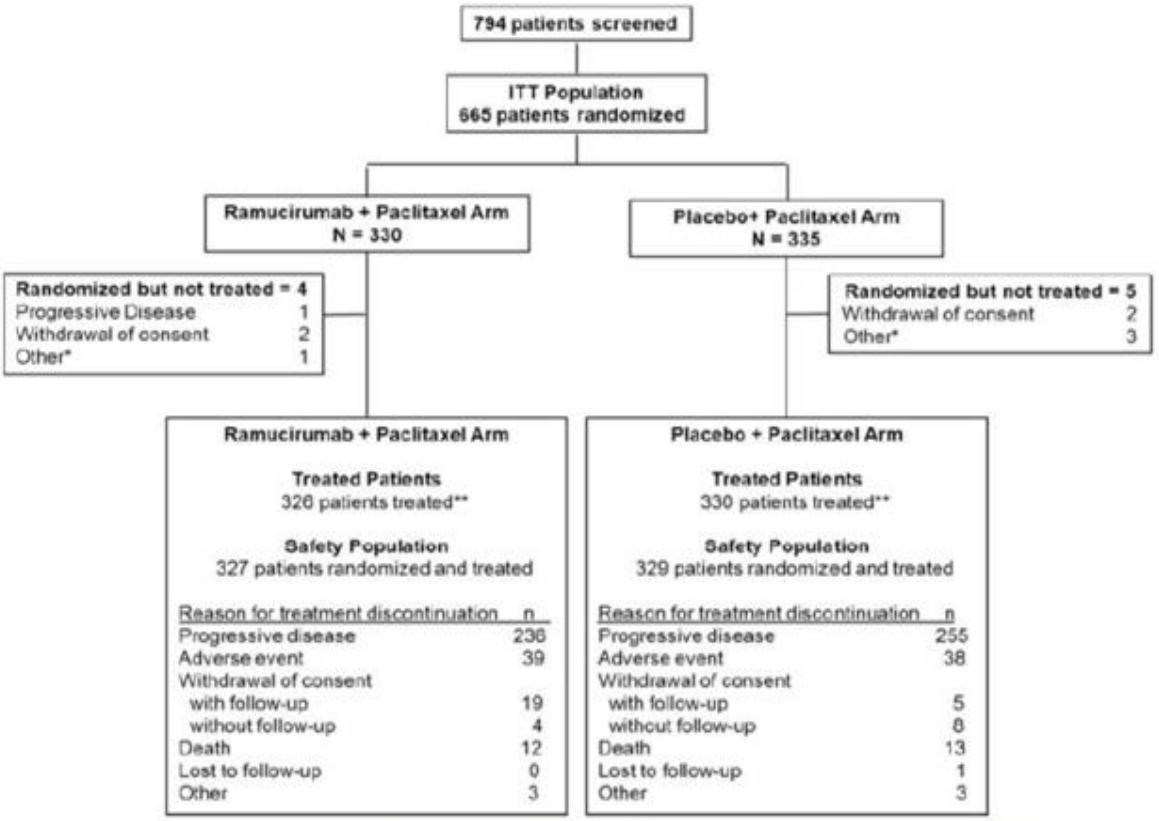
Stratification factors	Other factors
Geographical region • Region 1 – Europe, Israel, US and Australia • Region 2 – Argentina, Brazil, Chile and Mexico • Region 3 – Hong Kong, Japan, South Korea, Singapore and Taiwan TTP on first-line therapy • <6 months • ≥6 months Disease measurability • Measureable • Non-measureable	• Sex (males vs. females) • Age (<65 vs. ≥65 years) • Race (White vs. Asian vs. all others) • ECOG PS (0 vs. 1) • Weight loss (≥10% over the 3 months prior to study entry vs. <10%) • Primary tumour location (gastric vs. GOJ tumour) • Prior first-line chemotherapy (doublets, triplets) • Histologic subtype (Diffuse, Intestinal, mixed/unknown/missing) • Number of metastatic sites (≤2 vs. ≥3) • Peritoneal metastasis (yes vs. no) • Liver metastasis (yes vs. no) • Presence of ascites (yes vs. no) • Tumour differentiation (well, moderately, poorly, unknown) • Number of previous treatment lines (1 vs. >1 (including first-line, adjuvant and neoadjuvant)) • Prior gastrectomy (yes (full or partial) vs. no)

4.5 Participant flow in RAINBOW

RAINBOW randomised 665 patients; 330 patients to RAM+PAC and 335 patients to PBO+PAC. Four patients randomised to the RAM+PAC arm (1.2%) and 5 randomised to the PBO+PAC arm (1.5%) did not receive treatment, hence were not included in the safety population.

At data cut off (12 July 2013), 13 patients in the RAM+PAC arm and 7 patients in the PBO+PAC arm were receiving study treatment. The majority of patients discontinued treatment due to progressive disease (71.5% RAM+PAC and 76.1% PBO+PAC) and a similar percentage of patients in both study arms discontinued treatment due to AEs (11.8% RAM+PAC and 11.3% PBO+PAC). Detailed information can be found in Figure 7.

Figure 7 RAINBOW: Patient disposition



Abbreviations: ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category.
* Patients randomized but not treated for "other" reasons consisted of failure of inclusion/exclusion criteria (n=3) and 1 patient discontinued prior to administration of the first dose.
** Patient 137-0001 was randomized to the placebo plus paclitaxel arm; however, the patient received ramucirumab plus paclitaxel treatment. This patient is included in the placebo plus paclitaxel treatment arm for the ITT population, and is counted in the ramucirumab plus paclitaxel arm for the Safety population.
As of data cut-off date: 12 July 2013.

4.6 Quality assessment of the relevant randomised controlled trials

A quality assessment of both trials is provided after a discussion of REGARD.

4.7 Clinical effectiveness results: RAINBOW

- In total 665 patients were randomised; 330 patients to RAM+PAC and 335 patients to PBO+PAC
- Baseline patient demographics, disease and other characteristics were balanced between treatment arms
- The median age of participants was 61 years in both arms
- The majority of patients had measurable disease (81% in both arms) and a primary tumour present (63% in RAM+PAC compared to 62% in PBO+PAC)
- The majority of patients had received a doublet chemotherapy (RAM+PAC 77% and PBO+PAC 73%) as first-line treatment
- RAM+PAC significantly improved OS compared with PBO+PAC
- Median OS was 9.63 months (95% CI: 8.5, 10.8) in patients receiving RAM+PAC and 7.36 months (95% CI: 6.3, 8.4) in patients receiving PBO+PAC
- Rates of 12 month OS were 40% for patients treated with RAM+PAC versus 30% for patients treated with PBO+PAC
- Median PFS was 4.4 months (95% CI: 4.24, 5.32) in the RAM+PAC arm versus 2.9 months (95% CI: 2.79, 3.02) in PBO+PAC arm, reducing the risk of disease progression or death by 37% (HR=0.635; 95% CI 0.536, 0.752; P<0.0001)
- Median TTP was 5.5 months (95% CI: 4.50, 5.68) in patients treated with RAM+PAC versus 3.0 months (95% CI:2.86, 4.14) in patients treated with PBO+PAC
- More patients responded to treatment with RAM+PAC with a significantly greater ORR and DCR in patients treated with RAM+PAC (ORR: 27.9%; DCR: 80%) compared to PBO+PAC (ORR: 16.1%; 63.6%)
- More patients treated with RAM+PAC reported stable or improved QoL (as measured by EORTC QLQ-C30) compared to patients treated with PBO+PAC, and time to deterioration in QoL was longer in patients treated with RAM+PAC compared to PBO+PAC

Baseline patient demographic and clinical characteristics

Baseline patient demographics, disease and other characteristics (Table 16) were balanced between treatment arms in RAINBOW. The median age of participants was 61 years. In the UK, age specific incidence rates of GC rise significantly from age 60-64 (57), implying that the average age of the trial population was representative of GC patients in the UK. The majority of patients had measurable disease (81% in both), a primary tumour present (63% in RAM+PAC vs. 62% in PBO+PAC), and between 0 and 2 metastatic sites (63% in RAM+PAC vs. 69% in PBO+PAC).

All patients in the trial had received prior chemotherapy; the majority had received doublet chemotherapy (RAM+PAC 77% and PBO+PAC 73%) in the first-line setting. Less than 10% of patients in both arms had previously received a targeted therapy such as trastuzumab, cetuximab, panitumumab or lapatinib.

A large percentage of patients had adverse prognostic factors in both RAM+PAC and PBO+PAC arms such as poorly differentiated tumours (56% for both), disease progression less than 6 months from first-line therapy (76% for both), and at least 3 metastatic sites (37% and 31%).

Table 16 RAINBOW: Baseline patient characteristics

RAINBOW Baseline characteristics	RAM+PAC (n=330) n(%)	PBO+PAC (n=335) n(%)
Age (years)		
<65	204 (62)	212 (63)
≥65	126 (38)	123 (37)
Median (range)	61 (25 – 83)	61 (24 – 84)
Gender		
Male	229 (69)	243 (73)
Geographic Regions		
1. Europe, Israel, US and Australia	198 (60)	200 (60)
2. Argentina, Brazil, Chile and Mexico	23 (7)	21 (6)
3. Hong Kong, Japan, South Korea, Singapore and Taiwan	109 (33)	114 (34)
Race		
White	208 (63)	199 (59)
Asian	110 (33)	121 (36)
Black or other	12 (4)	15 (4)
ECOG performance status		
0 (fully active)	117 (35)	144 (43)
1 (restricted in physically strenuous activity)	213 (65)	191 (57)
Disease measurability		
Measurable	267 (81)	273 (81)
Non measurable	63 (19)	62 (19)
Time to progression from start of first-line therapy		
<6 months	250 (76)	256 (76)
≥6 months	80 (24)	79 (24)
Weight loss in the previous 3 months		
≥10%	53 (16)	47 (14)
<10%	277 (84)	286 (85)
Missing	0	2 (1)
Primary tumour present		
Yes	209 (63)	209 (62)
No	121 (37)	126 (38)
Location of primary tumour		
Gastric	264 (80)	264 (79)
GOJ	66 (20)	71 (21)
Histological subtype		
Intestinal	145 (44)	135 (40)
Diffuse type	115 (35)	133 (40)
Mixed	21 (6)	14 (4)
Unknown or not available	49 (15)	53 (16)
Tumour grade		
Well differentiated	28 (8)	22 (7)
Moderately differentiated	96 (29)	106 (32)

Poorly differentiated	186 (56)	186 (56)
Unknown/missing	20 (6)	21 (6)
Peritoneal metastasis	163 (49)	152 (45)
Number of metastatic site		
0 - 2	209 (63)	232 (69)
≥3	121 (37)	103 (31)
Presence of ascites		
Yes	130 (39)	107 (32)
No	200 (61)	228 (68)
Prior surgery for gastric cancer (Yes)	133 (40)	126 (38)
Total gastrectomy	52 (16)	65 (19)
Partial gastrectomy	80 (24)	59 (18)
Other	1 (<1)	2 (<1)
Prior treatment lines received		
Neoadjuvant therapy	24 (7)	15 (4)
Adjuvant therapy	31 (9)	32 (10)
First-line therapy	329 (100)	335 (100)
First-line platinum/fluoropyrimidine		
Triplet: platinum/fluoropyrimidine with anthracycline	76 (23)	87 (26)
Doublet: platinum/fluoropyrimidine without anthracycline	253 (77)	246 (73)
Prior treatment with a regimen containing targeted agent (any targeted agent)	31 (9)	26 (8)

Abbreviations: IQR= interquartile range; LN = lymph nodes; RECIST = Response Evaluation Criteria in Solid Tumours; Std Dev = standard deviation; TNM = tumour, lymph node, metastasis.
Data are number (%) unless otherwise indicated.

Primary endpoint: Overall Survival (OS)

The primary endpoint of RAINBOW was OS. Primary and secondary endpoints were analysed using the ITT population.

RAINBOW met its primary endpoint demonstrating a statistically significant and clinically meaningful improvement in OS for RAM+PAC compared to PBO+PAC (Table 17 and 0). At the date of data cut-off, 256 (77.6%) patients had died in the RAM+PAC arm versus 260 (77.6%) in the PBO+PAC arm.

Median OS was 9.63 months for RAM+PAC and 7.36 months for PBO+PAC. RAM+PAC prolonged median survival by 30.8% (2.27 months) and reduced the risk of death by 19% (HR = 0.807; 95% CI 0.678, 0.962; p=0.0169). Survival rates at 6 and 12 months were higher in the RAM+PAC group than in the PBO+PAC group at 71.5% and 40.1% versus 56.9% and 30.2%, respectively (Table 17, and 0 summarise these results).

The robustness of the primary OS analysis was demonstrated by the four sensitivity analyses, where HRs ranged from 0.745 to 0.822 and were similar to those of the primary analysis, all with p<0.05 (Appendix 4). The percentage of patients who received systemic

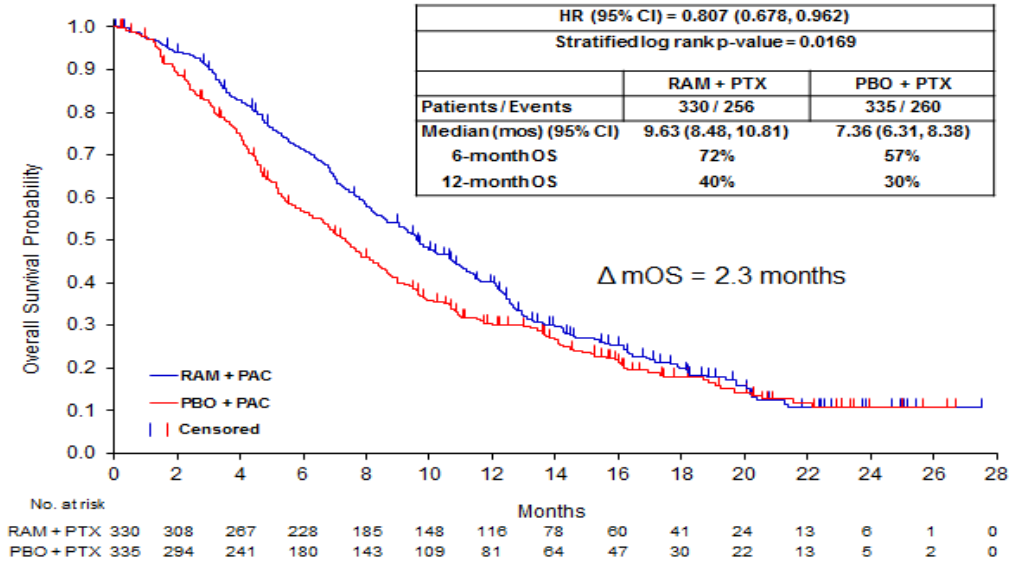
PDT and the types of PDT used were similar between treatment arms (discussed in further detail in conclusions). There were regional differences which are discussed in further detail in the subgroup analysis.

Table 17 RAINBOW: OS Results (ITT population)

Outcome	RAM+PAC (N=330)	PBO+PAC (N=335)	Treatment difference
Number of deaths, n (%)	256 (77.6)	260 (77.6)	
Number censored, n (%)	74 (22.4)	75 (22.4)	
Median survival, months (95% CI)	9.63 (8.5, 10.8)	7.36 (6.3, 8.4)	2.27
Log-rank p-value (2-sided)[a]	0.0169		
Hazard ratio (95% CI)[a]	0.807 (0.678, 0.962)		
Survival rate, % (95% CI)[b]			
6-month	71.53 (66.27, 76.12)	56.86 (51.27, 62.06)	14.67 (7.36, 21.98)
12-month	40.11 (34.65, 45.49)	30.16 (25.14, 35.33)	9.95 (2.48, 17.41)

[a] Stratified by randomisation strata (geographical region, time to progression from start of first-line therapy, and disease measurability).

Figure 8 RAINBOW: Kaplan-Meier plot of OS (ITT population)



Abbreviations: PAC = paclitaxel; PBO = placebo; PTX = paclitaxel; RAM = ramucirumab.

Secondary outcomes

Progression-free survival

Treatment with RAM+PAC significantly reduced the risk of disease progression or death. At the data cut-off date, 278 PFS events had occurred in the RAM+PAC arm versus 296 in the PBO+PAC arm. The median PFS time was 4.4 months in the RAM+PAC arm versus 2.9 months in PBO+PAC arm, reducing disease progression or death by 37% (HR=0.635; 95%

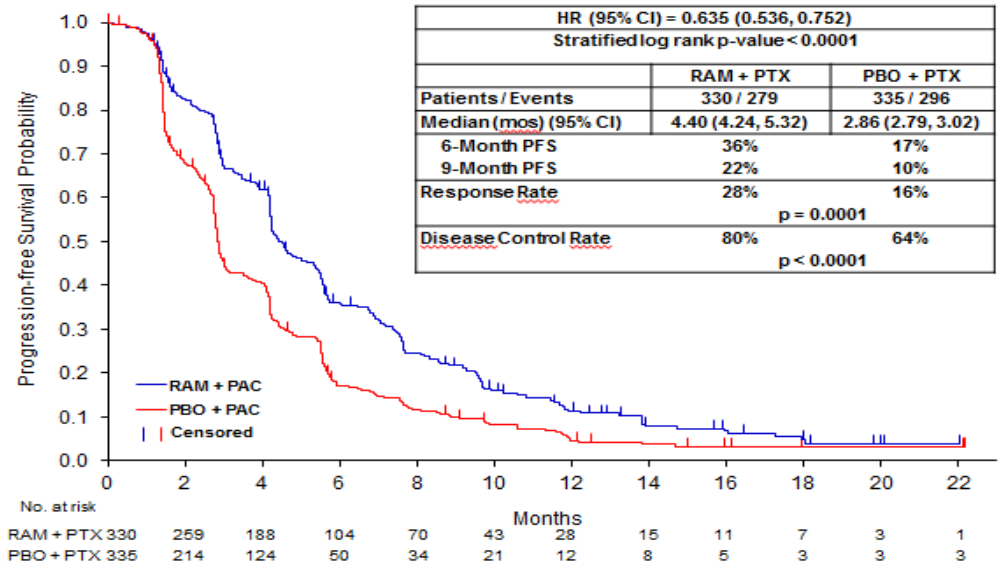
CI 0.536, 0.752; P<0.0001). At 12 months, the rate of PFS was 21.6% in the RAM+PAC arm versus 9.9% in PBO+PAC arm. Table 18 and 0 summarise these results.

Table 18 RAINBOW: PFS Results (ITT population)

Outcome	RAM+PAC (N=330)	PBO+PAC (N=335)	Treatment difference
Number of PFS events, n (%)	279 (84.5)	296 (88.4)	
Number censored, n (%)	51 (15.5)	39 (11.6)	
Median PFS, months (95% CI)	4.40 (4.24, 5.32)	2.86 (2.79, 3.02)	1.54
Log-rank p-value (2-sided)[a]	<0.0001		
Hazard ratio (95% CI)[a,b]	0.635 (0.536, 0.752)		
PFS rate, % (95% CI)[b]			
3 month	67.42 (61.94, 72.29)	45.50 (39.92, 50.91)	21.92 (14.36, 29.48)
6 month	35.94 (30.55, 41.34)	17.15 (13.15, 21.59)	18.79 (11.92, 25.66)
12 month	21.63 (17.12, 26.50)	9.92 (6.86, 13.64)	11.71 (5.90, 17.51)

Abbreviations: CI = confidence interval; ITT = intent-to-treat; [a] Stratified by randomisation strata (geographical region, time to progression from start of first-line therapy, and disease measurability)

Figure 9 RAINBOW: Kaplan-Meier plot of PFS (ITT population)



Abbreviations: PAC = paclitaxel; PBO = placebo; PTX = paclitaxel; RAM = ramucirumab.

Time to Progression (TTP)

The risk of disease progression was reduced by 40% (HR = 0.596, p<0.0001) in the RAM+PAC group versus the PBO+PAC group. The median TTP was 5.5 months in the RAM+PAC group versus 3.0 months in the PBO+PAC group Table 19.

Table 19 RAINBOW: Results of TTP (ITT population)

Outcome	RAM+PAC (N=330)	PBO+PAC (N=335)	Treatment difference
Number of PD events, n (%)	223 (67.6)	241 (71.9)	
Number censored, n (%)	107 (32.4)	94 (28.1)	
Median TTP, months (95% CI)	5.52 (4.50, 5.68)	3.02 (2.86, 4.14)	2.50
Log-rank p-value (2-sided)[a]	<0.0001		
Hazard ratio (95% CI)[a, b]	0.596 (0.494, 0.720)		

[a] Stratified by randomisation strata (geographical region, time to progression from start of first-line therapy, and disease measurability)

Objective Response Rate (ORR) and Disease Control Rate (DCR)

More patients responded to RAM+PAC treatment than PBO+PAC (ORR 27.9% versus 16.1%; odds ratio=2.14; 95% CI 1.45. 3.16; p=0.0001) (Table 20).

A greater rate of disease control was also observed with RAM+PAC over PBO+PAC (80.0% versus 63.6%; odds ratio=2.32; 95% CI 1.63, 3.31; p<0.0001) (Table 20).

Table 20 RAINBOW: ORR and DCR results (ITT population)

Outcome	RAM+PAC (N=330)	PBO+PAC (N=335)	p-value
	n (%)	n (%)	
Best overall response,			
Complete response (CR)	2 (0.6)	1 (0.3)	
Partial response (PR)	90 (27.3)	53 (15.8)	
Stable disease (SD)	172(52.1)	159 (47.5)	
Progressive disease	43 (13.0)	83 (24.8	
Not evaluable/No assessment	23 (7.0)	39 (11.6)	
Objective response rate (CR+PR)	92 (27.9)	54 (16.1)	
95% CI	23.3, 33.0	12.6, 20.4	
Odds ratio (95% CI)	2.14 (1.45, 3.16)		0.0001
Disease control rate (CR+PR+SD)	264 (80.90	213 (63.6)	
95% CI	75.4, 84.0	58.3, 68.6	
Odds ratio (95% CI)	2.32 (1.63, 3.31)		<0.0001

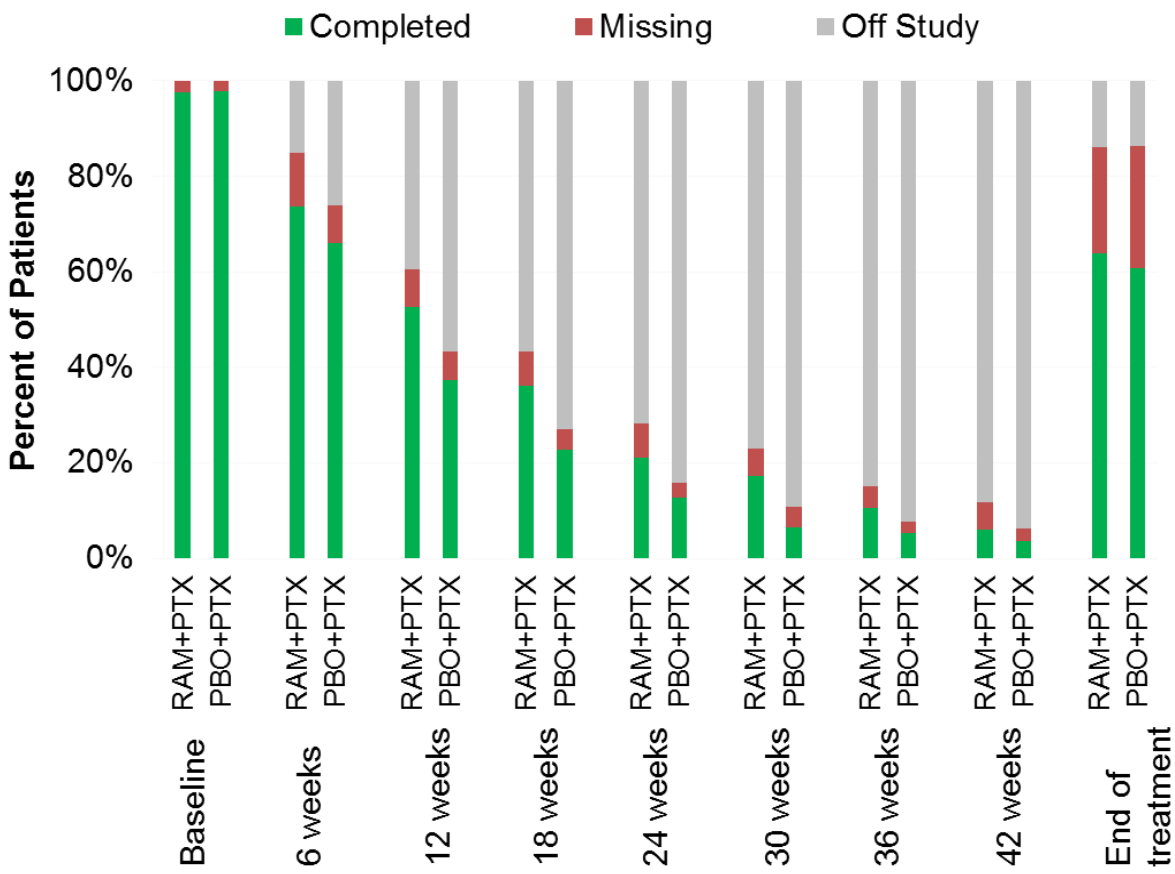
Quality of Life

- Overall, QoL was not negatively impacted for patients in the RAM+PAC arm compared to those in the PBO+PAC arm as measured by the EORTC QLQ-C30 and EQ-5D.
- More patients reported stable or improved QoL, and time to deterioration in QoL was longer in the RAM+PAC arm than in the PBO+PAC arm.
- As expected the number of completed assessments decreased over time as the number of patients discontinuing treatment increased, however this occurred more in the PBO+PAC arm.

EORTC QLQ-C30 Response

Compliance in completing the EORTC QLQ-C30 was high and the number of expected questionnaires to be completed at each scheduled assessment decreased over time as the number of patients discontinuing from therapy increased. In addition, as patients were still on treatment at the time of data lock, this also contributed to the higher rate of “missing” responses at the end of treatment time point for RAM+PAC. However, this was more marked in the PBO+PAC arm at all time-points following baseline (Figure 10).

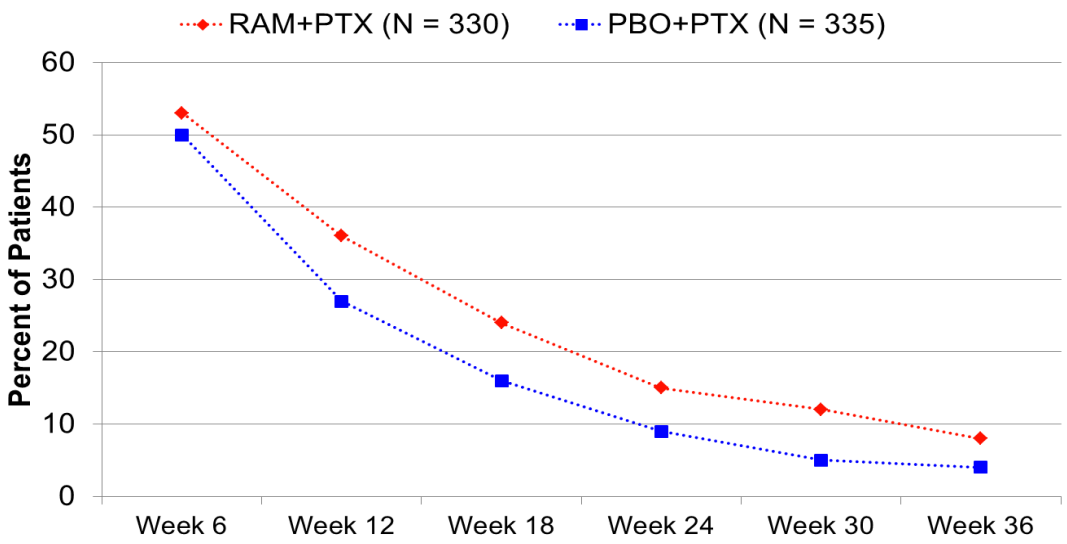
Figure 10 RAINBOW: EORTC QLQ-C30 completion rates for ITT population



Abbreviations: PBO = placebo; PTX= paclitaxel; RAM= ramucirumab

A greater percentage of patients in the RAM+PAC arm experienced stable or improved QoL parameters for a longer period of time, compared to patients treated with PBO+PAC (Figure 11). At all on-therapy assessment time points from six weeks onwards, for all QoL scales, a higher percentage of patients in the RAM+PAC arm were classified as improved or stable compared to the PBO+PAC arm. This suggests that the meaningful improvement in PFS were observed while maintaining or improving QoL.

Figure 11 Percentage of patients with improved or stable Global Health Status (ITT population) as measured by EORTC QLQ-C30

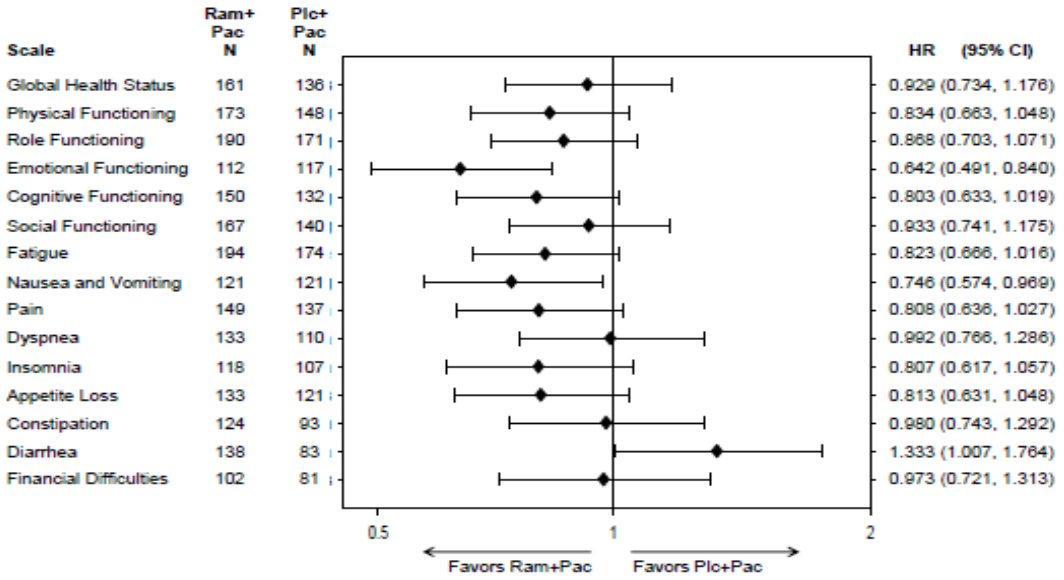


Abbreviations: PBO = placebo; PTX= paclitaxel; RAM= ramucirumab

Time to Deterioration in EORTC QLQ-C30

The efficacy benefits of RAM+PAC treatment were achieved without detriment to QoL. Figure 12 shows the time to deterioration in QoL as assessed by EORTC QLQ-C30. Except for diarrhoea, HRs for the other 14 scales favoured RAM+PAC compared to PBO+PAC (although not all significant). Of note, emotional functioning and nausea and vomiting were improved for patients treated with RAM+PAC compared PBO+PAC.

Figure 12 RAINBOW: Time to deterioration in EORTC QLQ-C30 Scales



Abbreviations: Pac = paclitaxel; Plc = placebo; Ram = ramucirumab.

EQ-5D

The results of the EQ-5D showed similar and small decreases from baseline in index scores while on study therapy in both treatment arms (Table 21).

Table 21 RAINBOW: EQ-5D Results

	RAM+PAC N=330	PBO+PAC N=335
Compliance, n (%)		
Patients completing baseline EQ-5D	323 (98)	328 (98)
Patients completing baseline plus post-baseline EQ-5D	287 (87)	274 (82)
Patients completing end of treatment EQ-5D	211 (64)	206 (61)
EQ-5D Index Score, mean (SD)		
Baseline	0.741 (0.228)	0.732 (0.250)
Cycle 2, Day 15	0.752 (0.226)	0.772 (0.227)
Cycle 4, Day 1	0.743 (0.212)	0.767 (0.230)
Cycle 5, Day 15	0.737 (0.241)	0.777 (0.189)
Cycle 7, Day 1	0.708 (0.277)	0.756 (0.246)
Cycle 8, Day 15	0.712 (0.241)	0.821 (0.135)
Cycle 10, Day 1	0.750 (0.236)	0.800 (0.191)
End of Treatment	0.581 (0.335)	0.570 (0.366)

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

Time to deterioration in ECOG PS

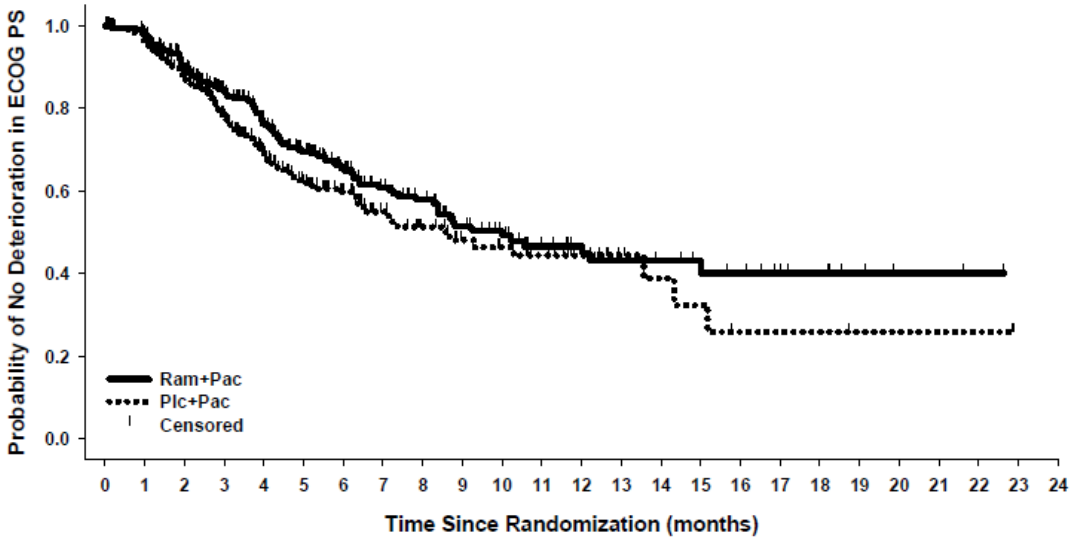
Treatment with RAM+PAC was associated with a delay in time to worsening performance status over PBO+PAC: 10.0 months versus 8.6 months; HR = 0.798; 95% CI 0.612, 1.040; p = 0.0941). Two thirds of the patients were censored in this analysis. Table 22 and Figure 13 show the results of the time to deterioration in ECOG PS analysis.

Table 22 RAINBOW: Time to deterioration in ECOG PS (ITT population)

	RAM+PAC N=330		PBO+PAC N=335	
	n	**Events**	**n**	**events**
Deterioration to ECOG PS ≥2	218	112	226	109
Median, months (95% CI)	10.0 (8.3, 15.0)		8.6 (6.3, 14.3)	
HR (95% CI)	0.798 (0.612, 1.040)			
Log Rank p value	0.0941			

Abbreviations: NA = not available.
Note: Median was estimated by the Kaplan-Meier method. Patients without post-baseline assessments were censored at the randomisation date. Hazard ratio and 95% CI were estimated using an unstratified Cox model

Figure 13 RAINBOW: Time to deterioration in ECOG PS ≥ 2 (ITT population)



Abbreviations: Pac = paclitaxel; Plc = placebo; Ram = ramucirumab.

4.8 Subgroup analysis: RAINBOW

- Patients in region 1 (US, Europe, Israel and Australia) of RAINBOW represent the patient group most similar to the English population
- Baseline patient characteristics were balanced across treatment groups including prognostic factors and similar to the ITT population
- Region 1 patients presented with a higher percentage of diffuse tumours and a higher percentage receiving first-line triplet chemotherapy than the ITT population
- RAM+PAC prolonged median survival by 2.7 months and reduced the risk of death by 27% (HR = 0.726; 95% CI 0.580, 0.909; p=0.005)
- RAM+PAC prolonged median PFS by 1.4 months and reduced the risk of progression or death by 39% (HR = 0.631; 95% CI 0.506, 0.786; p<0.0001)
- ORR and DCR was greater in the RAM+PAC arm (ORR: 26.8%; DCR: 76.8%) compared to the PBO+PAC arm (ORR: 13.0%; DCR: 56.5%)

The RAINBOW Region 1 population results have been presented because they can be generalised to the English population. Region 1 consisted of randomised patients from the US, Europe, Israel and Australia only. Regional differences exist between Western and Asian countries and are listed below:

- Asian countries have a higher incidence and prevalence of GC than Western nations (8,101).
- The adoption of national screening programs in Asian countries has resulted in diagnosis in the early stages of the disease in up to 50-60% of cases, while in Western nations patients are typically diagnosed at an advanced stage of GC and therefore have a poorer prognosis (102).
- Differences also exist in GC histology (Western patients have a higher incidence of diffuse histology/proximal tumour types having a poorer prognosis than intestinal histology/distal tumour types seen in Asian patients) (19).
- The surgical treatment of early GCs with extensive lymph node dissection (D2 resection) occurs more frequently in Asian countries (19,102).
- A higher proportion of patients receive second-line chemotherapy (and beyond) in Asia compared to US and Europe which extends survival in those patients (19).

RAINBOW Region 1 results

Region 1 consisted of randomised patients from Western countries including Europe, US, Australia and Israel. Nearly two thirds of the patients in RAINBOW were randomised to Region 1 (Table 23). Baseline patient and disease characteristics are presented in Table 24. Overall the baseline patient and disease characteristics are similar to the ITT population except for a higher percentage of patients with diffuse tumours and a higher percentage of patients receiving first-line triplet chemotherapy in Region 1 than the ITT population, consistent with regional differences described earlier. Similar to the ITT population, median patient age was 60 (RAM+PAC) and 61 years (PBO+PAC) which is representative of the age at which the incidence of GC increases in the UK (57). Due to region included as a stratification factor, baseline patient characteristics were balanced across treatment groups including prognostic factors.

Table 23 RAINBOW: Geographic Region Stratification

Stratification factor	RAM+PAC N=330	PBO+PAC N=335	Total N=665
Geographic regions, n (%)			
1. Europe, US, Australia, Israel,	198 (60)	200 (60)	398 (60)
2. Argentina, Brazil, Chile and Mexico	23 (7)	21 (6)	44 (7)
3. Hong Kong, Japan, South Korea, Singapore, Taiwan	109 (33)	114 (34)	223 (33)

Table 24 RAINBOW: Baseline Patient and Disease Characteristics (Region 1: Europe, US, Australia, Israel)

Characteristics	RAM+PAC (N=198)	PBO+PAC (N=200)
Age, median (range)	60.0 (25-83)	61.0 (24-84)
Male Gender, n (%)	140 (71)	147 (73)
Age Group, n (%)		
<65 years	123 (62)	126 (63)
≥65 years	75 (38)	74 (37)
Race, n (%)		
White	193 (97)	186 (93)
Asian	1 (<1)	7 (3)
Black	2 (1)	3 (1)
Other	2 (1)	2 (1)
ECOG PS, n (%)		
0	68 (34)	75 (37)
1	130 (66)	125 (63)
Measurable disease, n (%)		
Yes	164 (83)	168 (84)
No	34 (17)	31 (16)
Weight loss in previous 3 months, n (%)		
≥10%	30 (15)	29 (14)
<10%	168 (85)	169 (85)
Location of primary tumour, n (%)		
Gastric	139 (70)	137 (68)
GOJ	59 (30)	63 (32)
Histology, n (%)		
Intestinal	92 (46)	86 (43)
Diffuse	62 (31)	72 (36)
Mixed	13 (7)	7 (3)
Undetermined/not available	31 (16)	35 (18)
Number of metastatic sites, n (%)		
0 - 2	110 (56)	127 (64)
≥3	88 (44)	71 (36)
Previous type of anti-cancer treatment, n (%)		
First-line therapy	197 (100)	200 (100)
Adjuvant therapy only (no first-line therapy)	14 (7)	18 (9)
Neoadjuvant therapy only	21 (11)	15 (7)
Time to progression from start of prior therapy, n (%)		
<6 months	126 (64)	124 (62)
≥6 months	72 (36)	75 (38)
First-line platinum/fluoropyrimidine, n (%)	198 (100)	200 (100)
Triplet: PLAT/FLUO with anthracycline	68 (34)	80 (40)
Doublet: PLAT/FLUO without anthracycline	129 (65)	118 (59)
No PLAT/FLUO	1 (<1)	2 (1)

Abbreviations: PLAT = platinum; FLUO = fluoropyrimidine

Overall Survival

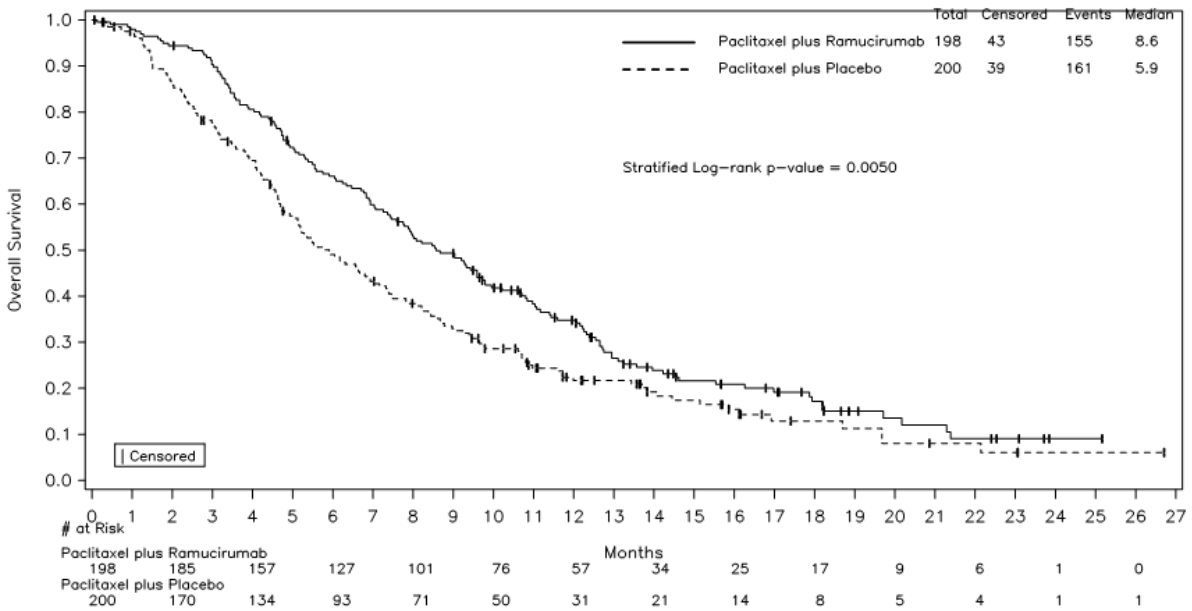
Median OS for Region 1 patients was 8.6 months for RAM+PAC and 5.9 months for PBO+PAC (Table 25 and Figure 14). RAM+PAC prolonged median survival by 45% (2.7 months) and reduced the risk of death by 27% (HR = 0.726; 95% CI 0.580, 0.909; p=0.005). Survival rates at 6 and 12 months were higher in the RAM+PAC group than in the PBO+PAC group.

Table 25 RAINBOW: OS Results (Region 1: Europe, US, Australia, Israel)

	RAM+PAC (N=198)	PBO+PAC (N=200)	Treatment difference
Number of deaths, n (%)	155 (78.3)	161 (80.5)	
Number censored, n (%)	43 (21.7)	39 (19.5)	
Median OS, months (95% CI)	8.57 (7.43, 9.79)	5.91 (4.99, 7.06)	2.66
Log-rank p-value (2-sided)[a]	0.0050		
Hazard ratio (95% CI)[a]	0.726 (0.580, 0.909)		
Survival rate, % (95% CI) 6 month 12 month	 66.04 (58.92, 72.23) 34.77 (27.99, 41.63)	 49.01 (41.78, 55.83) 21.70 (15.97, 28.01)	 17.04 (7.33, 26.74) 13.07 (3.91, 22.22)

[a] Stratified by randomisation strata (time to progression from start of first-line therapy, and disease measurability)

Figure 14 RAINBOW: Kaplan-Meier Plot of OS (Region 1: Europe, US, Australia, Israel)



Asian countries are known to use more aggressive treatment regimes, with higher rates of use of PDT (103) compared to Western countries. As expected, the rate of any systemic PDT was higher (almost double for third- and fourth-line chemotherapy) in Region 3 than

Region 1 (Table 26). Consequently the median survival times for both treatment arms in RAINBOW were longer in the ITT population than Region 1 (Table 26).

Table 26 RAINBOW: Regional PDT

Type of post-discontinuation therapy	Region 1		Region 3	
	RAM+PAC (N=198)	PBO+PAC (N=200)	RAM+PAC (N=109)	PBO+PAC (N=114)
Any systemic PDT, n (%)	76 (38.4)	72 (36.0)	75 (68.8)	75 (65.8)
By line of therapy, n (%)				
3rd line	74 (37.4)	69 (34.5)	72 (66.1)	74 (64.9)
≥4th line[a]	27 (13.6)	14 (7.0)	30 (27.5)	34 (29.8)

[a] All of these patients but one had 2 or more PDT lines (the one patient was from region 1).

The most frequently used PDT agent was IRI (28.8% of patients in the RAM+PAC arm, 24.0% of patients in the PBO+PAC arm), followed by fluorouracil (27.8% in RAM+PAC arm and 23.5% in PBO+PAC) in region 1. This differed slightly in region 3 where IRI was also the most frequently used PDT agent but at a much higher rate (56.0% the RAM+PAC arm, 54.4% of patients in the PBO+PAC arm), followed by fluorouracil (23.9% in RAM+PAC arm and 20.2% in PBO+PAC), docetaxel (18.3% in RAM+PAC arm and 14.0% in PBO+PAC), and cisplatin (15.6% in RAM+PAC arm and 16.7% in PBO+PAC).

Progression-free Survival

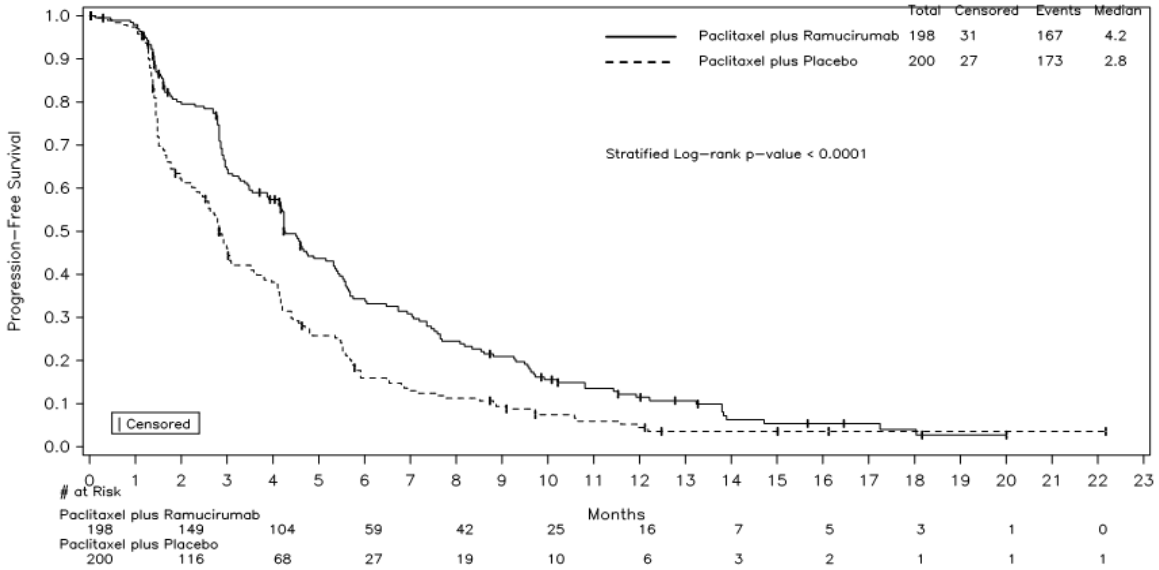
Median PFS for Region 1 patients was 4.2 months for RAM+PAC and 2.8 months for PBO+PAC (Table 27 and Figure 15). RAM+PAC prolonged median PFS by 1.4 months and reduced the risk of progression or death by 39% (HR = 0.631; 95% CI 0.506, 0.786; p<0.0001). PFS rates at 3, 6 and 12 months were higher in the RAM+PAC group than in the PBO+PAC group. These results are similar to those seen in the ITT population.

Table 27 RAINBOW: PFS Results (Region 1: Europe, US, Australia, Israel)

	RAM+PAC (N=198)	PBO+PAC (N=200)	Treatment difference
Number of events, n (%)	167 (84.3)	173 (86.5)	
Number censored, n (%)	31 (15.7)	27 (13.5)	
Median PFS, months (95% CI)	4.24 (3.91, 5.32)	2.83 (2.56, 3.09)	1.41
Log-rank p-value (2-sided)[a]	<0.0001		
Hazard ratio (95% CI)[a,]	0.631 (0.506, 0.786)		
Survival rate, % (95% CI)[b]			
3 month	64.40 (57.09, 70.79)	46.01 (38.72, 52.98)	18.40 (8.48, 28.31)
6 month	34.33 (27.45, 41.30)	15.96 (11.01, 21.73)	18.36 (9.55, 27.18)
12 month	20.93 (15.25, 27.23)	9.39 (5.62, 14.31)	11.54 (4.10, 18.98)

[a] Stratified by the randomisation strata (disease measurability, time to progression on first-line therapy. [b] 95% CIs for Difference were calculated using a normal approximation.

Figure 15 RAINBOW: Kaplan-Meier Plot of PFS (Region 1: Europe, US, Australia, Israel)



Objective Response Rate

For Region 1 patients, the ORR was greater in the RAM+PAC arm (26.8%) than in the PBO+PAC arm (13.0%) (Table 28). DCR was also greater in the RAM+PAC arm (76.8%) than in the PBO+PAC arm (56.5%). These results are similar to those seen in the ITT population.

Table 28 RAINBOW: ORR and DCR Results (Region 1: Europe, US, Australia, Israel)

	Region 1	
Outcome	**RAM+PAC (N=198)**	**PBO+PAC (N=200)**
Best overall response, n (%)		
Complete response	1 (0.5)	1 (0.5)
Partial response	52 (26.3)	25 (12.5)
Stable response	99 (50.0)	87 (43.5)
Progressive disease	32 (16.2)	57 (28.5)
Not evaluable/Not done	14 (7.1)	30 (15.0)
ORR, n (%)	53 (26.8)	26 (13.0)
p-value[a]	0.0004	
Odds Ratio (95% CI)	2.51 (1.49, 4.23)	
DCR, n (%)	152 (76.8)	113 (56.5)
p-value[a]	<0.0001	
Odds ratio (95% CI)	2.52 (1.64, 3.89)	

[a] From two-sided Cochran-Mantel-Haenszel test adjusted for randomisation strata (time to progression from start of first-line therapy, and disease measurability)

A summary of the rate of adverse events in Region 1 is presented in section 4.12.

Conclusions from RAINBOW

RAM+PAC significantly increased OS in patients with advanced GC/GOJ with significantly more patients responding to treatment with RAM+PAC (27.9%) than PBO+PAC (16.1%). A pre-planned subgroup analysis specifically considered patients from region 1 (Europe, Israel, Australia, USA) in RAINBOW; the patient population most relevant to this submission. In this region, further improvements in OS were observed in patients treated with RAM+PAC compared to PBO+PAC. RAM+PAC prolonged median survival by 45% (2.7 months).

An analysis of PDT revealed that the use of systemic PDT was similar between treatment arms in the ITT population. Therefore, it is unlikely that the use of PDT contributed to the survival benefit seen with RAM+PAC. Regional differences did exist however and the rate of any systemic PDT was higher (almost double for third- and fourth-line chemotherapy) in Region 3 than Region 1. This explains why the median survival times for both treatment arms in RAINBOW were longer in the ITT population than in Region 1.

Table 29 RAINBOW: Systemic PDT (ITT population)

Systemic PDT	RAM+PAC N=330 n (%)	PBO+PAC N=335 n (%)
Overall	158 (48)	154 (46)
Chemotherapy	158 (48)	152 (45)
Targeted agent[a]	24 (7)	23 (7)
Other	0	2 (0<1)

[a] Targeted agent includes targeted antibody and targeted small molecule.

Patients treated with RAM+PAC combination therapy also had a significantly longer PFS with a higher proportion of patients achieving disease control (80% of patients treated with RAM+PAC compared to 63% of patients treated with PBO+PAC). In region 1 specifically, RAM+PAC reduced the risk of disease progression or death by 39%.

It is important to note that the survival benefit observed in patients in RAINBOW was not at a detriment to QoL. QoL was not negatively impacted for patients treated with RAM+PAC combination therapy compared to those treated with PBO+PAC as measured by the EORTC QLQ-C30 and EQ-5D. At all on-therapy assessment time points from six weeks onwards, for all QoL scales of the EORTC QLQ-C30, a higher percentage of patients in the RAM+PAC arm were classified as improved or stable compared to the PBO+PAC arm. This suggestsa meaningful improvement in PFS while maintaining or improving QoL The time to deterioration in QoL was also longer in patients treated with RAM+PAC than in patients treated with PBO+PAC.

REGARD

Methods

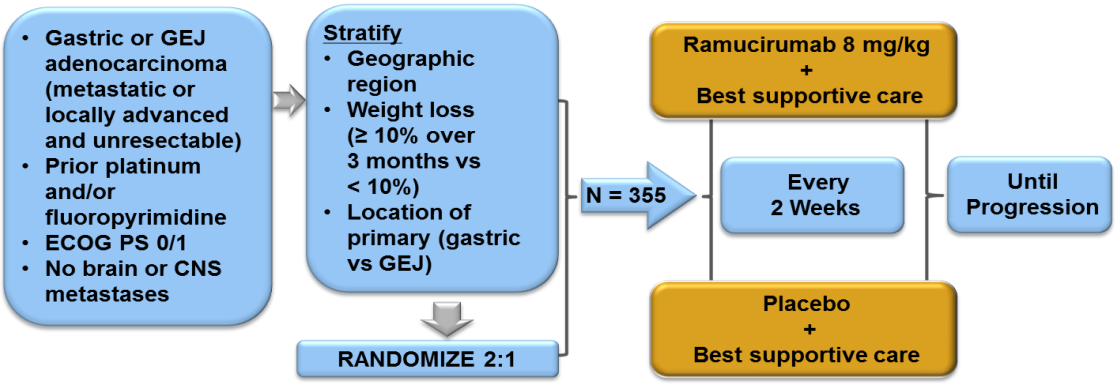
Trial design

REGARD was a global, randomised, placebo-controlled, double-blind, phase 3 trial that included 355 patients with advanced GC/GOJ, who had disease progression following treatment with platinum-containing or fluoropyrimidine-containing chemotherapeutic regimens.

Eligible patients, were randomly allocated in a 2:1 ratio to receive RAM (8 mg/kg) plus BSC or PBO+BSC, administered intravenously (IV) once every 2 weeks. This design differs from RAINBOW where patients were randomised 1:1 and cycle length was 28-days; however it is appropriate for monotherapy. As PAC was not used in REGARD the cycle length was determined by the frequency of administration of RAM only.

The study was completed after a sufficient number of events were observed for final analysis of the primary endpoint, 268 OS events (See statistical analyses and definition of study groups for further details). Figure 16 presents a diagrammatic representation of the trial design.

Figure 16 REGARD: Trial Design



Abbreviations: CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; GEJ = gastro-oesophageal

Selection of comparator

At the time of REGARD study design, there was no evidence that any therapy was superior to other agents/regimens and no agent had been demonstrated to improve survival over BSC. Given the lack of a regimen specifically approved in this setting and the lack of an established standard of care, single-agent ramucirumab (plus BSC) was selected for the investigational arm (104).

Objectives and outcomes

The primary objective of REGARD was to evaluate the OS of patients with metastatic or locally advanced, unresectable GC/GOJ following disease progression on first-line platinum- or fluoropyrimidine-containing combination chemotherapy who underwent treatment with RAM+BSC versus PBO+BSC. Key secondary objectives included evaluating the PFS, ORR, duration of response, QoL, safety and pharmacodynamics profiles, as well as assessing the immunogenicity of ramucirumab.

Participants

REGARD took place between 6 October 2009 and 26 January 2012, at 119 centres in 29 countries in North America, Central and South America, Europe, Asia, Australia, and Africa.

Study eligibility criteria are summarised in Table 30. A complete list of all inclusion and exclusion criteria is given in Appendix 3.

Table 30 REGARD: Eligibility criteria

Inclusion Criteria	Exclusion Criteria
• Histologically or cytologically confirmed gastric carcinoma, including gastric or GOJ adenocarcinoma • Metastatic disease or locally recurrent, unresectable disease • Measurable disease (defined as at least one unidimensionally-measurable target lesion according to RECIST) and/or evaluable disease. • The patient has experienced disease progression during or within 4 months after the last dose of first-line therapy for metastatic disease, or during or within 6 months after the last dose of adjuvant therapy • Age ≥18 years, life expectancy of ≥12 weeks, and ECOG PS score of 0 or 1 • Adequate recovery from toxicities or effects of prior therapy • Adequate haematologic, hepatic, coagulation, and renal function	• Documented or symptomatic brain or leptomeningeal metastases • Any grade 3/4 gastrointestinal bleeding within 3 months prior to randomisation • Any arterial thromboembolic event (myocardial infarction, transient ischemic attack, cerebrovascular accident, unstable angina, or other within 6 months prior to randomisation) • Ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, uncontrolled thrombotic or haemorrhagic disorder, any other serious uncontrolled medical disorder • Uncontrolled or poorly controlled hypertension • Serious or unhealing wound, ulcer, or bone fracture within 28-days prior to randomisation • Current chronic antiplatelet therapy, including aspirin, NSAIDs, dipyridamole or clopidogrel, or similar agents. Once daily use of aspirin was permitted. • Known allergy to any treatment component • Pregnancy/breastfeeding • Concurrent active malignancy other than adequately-treated non-melanomatous skin cancer, other non-invasive carcinoma, or *in situ* neoplasm

Interventions

- Intervention (n=238): RAM 8mg/kg IV over approximately 60 minutes administered every 2 weeks plus BSC.
- Comparator (n=117): equivalent volume of PBO IV over approximately 60 minutes administered every 2 weeks plus BSC.

Treatment was given within 7 days of randomisation and was administered in two-week cycles. RAM and PBO doses were administered over approximately 60 minutes. Timing of dose was allowed to be within 3 days of start or end of cycle.

All patients received 8 mg/kg of RAM once every 2 weeks. The initial dose was dependent upon the patient's baseline body weight, and was recalculated in the event of a 10% or more change in body weight. If non-life threatening reversible Grade 3 or 4 AEs occurred, two reductions in the dose were allowed (from 8 to 6 mg/kg, then from 6 to 5 mg/kg).(7).

Patients underwent radiographic assessment of disease status, evaluated according to RECIST version 1.0 (105) every 6 weeks. Treatment continued until there was evidence of progressive disease (PD), unacceptable toxicity, withdrawal of consent, or until other withdrawal criteria were met. ECOG PS was assessed at baseline, on the day of each treatment and 30 days after last dose of study drug.

Supportive care

All patients in the trial received BSC for disease-related symptoms and for treatment-associated toxicity. BSC included but was not limited to anti-emetic agents, opiate and non-opiate analgesic agents, appetite stimulants, granulocyte-colony stimulating factors, erythroid growth factors, laxatives, and anti-depressants.

Prohibited therapies

Additional concurrent chemotherapy, radiation therapy, biologic response modifiers, or other investigational anti-cancer agents were not to be administered to patients during this study. Palliative radiation to symptomatic sites of disease was not permitted during the study as this could have led to skewed interpretation of QoL scores.

Restricted therapies

Anticoagulation therapy was permitted in the setting of venous thromboembolism occurring during the study. Patients who began anticoagulation therapy on-study treatment were to receive low molecular weight heparin (not oral anticoagulation).

Randomisation sequence generation

Patients were randomised 2:1 via a centralised IVRS/IWRS to RAM+BSC and PBO+BSC, respectively. Similar to RAINBOW, potential prognostic factors were identified and randomisation was stratified by:

- Weight loss (≥10% vs. <10% of body weight in the previous 3 months)
- Geographic region:
  - Region 1 - North America, Europe, Australia, and New Zealand
  - Region 2 - South and Central America, India, South Africa, and Middle East
  - Region 3 - Asia
- Location of the primary tumour (gastric vs. GOJ)

Allocation concealment, implementation and blinding

Patients, investigators, and all other personnel involved in the conduct of the study (including the pharmacists at the study sites) were blinded to individual treatment assignments for the duration of the study.

Centres enrolled patients into the study using either an electronic data capture (EDC) system or by accessing a call-in IVRS or IWRS. An IVRS/IWRS was used to randomly assign patients on a 2:1 basis to RAM or PBO treatment, respectively. RAM and PBO for injection were identical in appearance in order to preserve blinding and uniquely labelled.

Unblinding did not occur at disease progression. Emergency unblinding was only allowed for medical reasons where the identity of the test drug was integral to the treatment of an adverse event. However, the occurrence of a serious adverse event should not routinely precipitate the immediate unblinding of an investigational product label.

4.4 Statistical analysis and definition of study groups

Sample size

Primary and secondary efficacy endpoints were analysed using the ITT population (with allocation of patients to treatment arms “as randomised”). It was calculated that to achieve 80% power to detect an overall difference in survival between the two treatment groups, 348 patients would need to be randomly assigned. The ITT population (N = 355) included 238 patients randomised to receive RAM+BSC and 117 patients randomised to receive PBO+BSC.

Statistical methods

The primary outcome of REGARD was OS, which was defined as the time from the date of randomisation to the date of death from any cause or censoring. Censoring occurred where patients were still alive at the time of data cut-off or were lost to follow-up.

OS was assessed in the ITT population. Survival curves for the two treatment arms were estimated by the Kaplan-Meier method (median, 95% CI). The primary efficacy analysis was a two-sided log-rank test stratified by randomisation strata (weight loss over the prior 3 months, location of primary tumour, and geographical region as per IVRS/IWRS strata). The HR was estimated with a stratified Cox proportional hazards model.

Sensitivity analyses performed to test the robustness of the primary OS result included a stratified log-rank test, stratified analysis using CRF as the data source, a Cox regression analysis adjusting for potential prognostic factors, and a per protocol population analysis.

Key secondary outcomes and their statistical analyses are detailed in Table 32.

Primary hypothesis under investigation and power calculation

To achieve 80% power to detect a hazard ratio of 0.69 for OS, with a one-sided type I error rate of 0.025 (two-sided at 0.05), it was estimated that 348 patients would need to be randomised with 268 deaths. This sample size was determined using group sequential analysis methods based on the assumption that a 45% improvement in median OS in the RAM arm versus the PBO arm was considered to be clinically relevant (7.25 versus 5 months, or HR = 0.69). This consideration took into account a dropout rate of approximately 10% (7).

Based on a 30-month accrual period and a varying accrual rate (1 patient a month for the first 4 months increasing to 21 patients a month from 21 months onwards), it was estimated that a 11-month follow up period would be needed to accumulate the required number of events, and the total duration of the study would be approximately 41 months.

At the time of study design, other RCTs with BSC comparator arms had made similar assumptions, but had not yet reported results (2-4).

A summary of the statistical analyses for REGARD can be found in Table 31.

Table 31 Summary of statistical analyses in REGARD

Trial acronym	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
REGARD	The primary objective of this study was to evaluate the overall survival (OS) of patients with metastatic or locally advanced, unresectable gastric cancer (including adenocarcinomas of the GOJ) following disease progression on first-line platinum- or fluoropyrimidine-containing combination chemotherapy who underwent treatment with RAM+BSC versus PBO+BSC.	OS was assessed in the ITT population. Survival curves for the two treatment arms were estimated by the Kaplan-Meier method (median, 95% CI). The primary efficacy analysis was a two-sided log-rank test stratified by randomisation strata (weight loss over the prior 3 months, location of primary tumour, and geographical region as per IVRS/IWRS strata). The HR was estimated with a stratified Cox proportional hazards model.	REGARD estimated 348 patients would need to be randomised with 268 deaths. This sample size was determined using group sequential analysis methods based on the assumptions: one-sided type I error rate of 0.025 (two-sided at 0.05) and study power 80%; a 45% improvement in median OS in the RAM arm versus the PBO arm was considered to be clinically relevant (7.25 versus 5 months, or HR = 0.69); randomisation ratio of 2; one interim futility analysis at 35%; a 30 month accrual period; and a dropout rate of 10%.	Following discontinuation of study therapy, all patients were to be followed every 2 months (as long as the patient was alive) until the required 268 OS events were reported. After sufficient (268) OS events were reported, individual patients who remained on study were to have at least 1 year of follow-up from their date of therapy discontinuation to obtain information regarding subsequent objective progressive disease (if discontinuation of therapy was not based on PD) and subsequent anti-cancer therapy.

Subgroup analyses

Pre-planned subgroup analyses were performed for the primary OS and secondary PFS efficacy endpoints using the same methods as in the primary analysis. Subgroups included stratification (detailed in randomisation sequence generation) and potential prognostic factors (such as age, gender, race, ethnicity, ECOG PS, weight loss, primary tumour location, prior first-line chemotherapy, histologic subtype, number of metastatic sites, peritoneal metastasis, liver metastasis, presence of ascites, tumour differentiation, number of previous treatment lines, prior gastrectomy).

Treatment effect was assessed in each subgroup by the HR, which was estimated using a stratified Cox proportional hazards model, according to the pre-defined randomisation strata. An unstratified analysis (Cox proportional hazards model) was performed due to the possibility of overstratification in this study. Note: the number of strata (n=12) were relatively high given the sample size of the trial; the median number of patients in each stratum was 13 (range 0-137); thus not all stratification factors were significant prognostic factors in this study.

A comparative summary of trial methodology for RAINBOW and REGARD can be seen in Table 32.

Table 32 Comparative summary of trial methodology

Trial no. (acronym)	RAINBOW	REGARD
Location	Global, multicentre study	Global, multicentre study
Trial design	Randomised, placebo-controlled, double-blind phase 3 trial.	Randomised, placebo-controlled, double-blind phase 3 trial.
Settings and locations where the data were collected	170 centres across 27 countries in North and South America, Europe, Asia, and Australia.	119 centres across 29 countries in North America, Central and South America, Europe, Asia, Australia, and Africa.
Duration of study	2 years	2 years, 3 months
Method of randomisation	Patients were randomly assigned in a 1:1 ratio via a centralised IVRS/IWRS to RAM+PAC or PBO+PAC. Randomisation was stratified by 3 factors: geographic region (region 1, 2, or 3)[2], time to progression from the start of first-line chemotherapy (<6 months vs. ≥6 months), and disease measurability (measurable vs. non-measurable disease)	Patients were randomised 2:1 via a centralised IVRS/IWRS to RAM+BSC or PBO+BSC, respectively. Randomisation was stratified by 3 factors: Geographic region (region 1, 2, or 3)[2], weight loss (≥10% vs.<10% of body weight in the previous 3 months), and location of the primary tumour (gastric vs. GOJ).
Method of blinding (care provider, patient and outcome assessor)	Patients, investigators, and all other personnel involved in the conduct of the study (including the pharmacists at the study sites) were blinded to individual treatment assignments for the duration of the study. RAM and PBO for infusion were identical in appearance in order to preserve blinding. The study drug (RAM or PBO) was uniquely labelled and assigned to a patient using IVRS/IWRS. Unblinding did not occur at disease progression, there were no anticipated or identified toxicity of RAM that would potentially unblind investigators to treatment assignment. Unblinding of the study team did not occur until after the reporting database was validated and locked for final statistical analysis. Emergency unblinding was only allowed for medical reasons where the identity of the test drug was integral to the treatment of an adverse event.	Patients, investigators, and all other personnel involved in the conduct of the study (including the pharmacists at the study sites) were blinded to individual treatment assignments for the duration of the study. RAM and PBO for injection were identical in appearance in order to preserve blinding. The study drug (RAM or PBO) was uniquely labelled, and assigned to a patient by using IVRS/IWRS. Unblinding did not occur at disease progression, there were no anticipated or identified toxicity of RAM that would potentially unblind investigators to treatment assignment. Unblinding of the study team did not occur until after the reporting database was validated and locked for final statistical analysis. Emergency unblinding was only allowed for medical reasons where the identity of the test drug was integral to the treatment of an adverse event.

[2]RAINBOW regions; Region 1: Europe, Israel, US and Australia; Region 2: Argentina, Brazil, Chile and Mexico; Region 3: Hong Kong, Japan, South Korea, Singapore and Taiwan. REGARD regions; Region 1: North America, Europe, Australia, and New Zealand; Region 2: South and Central America, India, Egypt, South Africa, Lebanon, Jordan, and Saudi Arabia; Region 3: Asia.

Intervention(s) and comparator(s)	Intervention (n=330): RAM (8 mg/kg IV) plus PAC (80 mg/m^2 IV). PAC was given on days 1, 8, and 15 of a 28-day cycle, in combination with RAM given on days 1 and 15. Comparator (n=335): PBO+PAC (80 mg/m^2 IV). PAC was given on days 1, 8, and 15 of a 28-day cycle, in combination with an equivalent volume of PBO given on days 1 and 15.	Intervention (n=238): RAM (8 mg/kg) plus BSC or PBO, administered intravenously (IV) once every 2 weeks. Comparator (n=117): PBO+ BSC, administered intravenously (IV) once every 2 weeks.
Permitted and disallowed concomitant medication	**Concomitant therapy:** Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment was offered to all patients in this trial. Supportive care included, but was not limited to, anti-emetic agents, opiate and non-opiate analgesic agents, appetite stimulants, granulocyte-colony stimulating factors, erythroid growth factors, laxatives, and ant-idepressants. **Prohibited therapies**: Additional concurrent chemotherapy, radiation therapy (with curative intent), biologic response modifiers, or other investigational anti-cancer agents were not to be administered to patients during this study. Palliative radiation to symptomatic sites of disease was permitted during the study. **Restricted therapies:** Anticoagulation therapy was permitted in the setting of venous thromboembolism occurring during the study.	**Concomitant therapy:** Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment was offered to all patients in this trial. Supportive care included, but was not limited to, anti-emetic agents, opiate and non-opiate analgesic agents, appetite stimulants, granulocyte-colony stimulating factors, erythroid growth factors, laxatives, and anti-depressants. **Prohibited therapies:** Additional concurrent chemotherapy, radiation therapy, biologic response modifiers, or other investigational anti-cancer agents were not to be administered to patients during this study. Palliative radiation to symptomatic sites of disease was not permitted during the study. **Restricted therapies:** Anticoagulation therapy was permitted in the setting of venous thromboembolism occurring during the study. Patients who began anticoagulation therapy on-study treatment were to receive low molecular weight heparin (not oral anticoagulation).

Primary outcomes (including scoring methods and timings of assessments)	The primary outcome for RAINBOW was overall survival (OS), defined as the time from the date of randomisation to the date of death from any cause. OS was censored on the last date the patient was known to be alive (on or before data cut-off date or lost to follow-up). Patient survival status was collected every 8 weeks after treatment discontinuation, until the data cut-off date. The primary analyses of OS used the ITT population which included all randomised patients. Unless otherwise specified, missing data were not imputed. OS was compared using a log-rank test stratified by randomisation strata at a one-sided 0.025 (two-sided 0.05) level of significance. The HR and 95% CI were determined using a Cox regression model. Kaplan-Meier estimates including 95% CIs were presented for median OS, 6 month and 12 month OS rates for each treatment group. A restricted mean analysis was conducted for OS in order to estimate the difference in average OS between the treatment arms. Sensitivity analyses performed to test the robustness of the primary OS result included an unstratified log-rank test, stratified analysis using case report forms (CRF) as the data source, a Cox regression analysis adjusting for potential prognostic factors, and a per protocol population analysis.	The primary outcome of REGARD was OS, which was defined as the time from the date of randomisation to the date of death from any cause or censoring. Censoring occurred where patients were still alive at the time of data cut-off or were lost to follow-up. OS was assessed in the ITT population. Survival curves for the two treatment arms were estimated by the Kaplan-Meier method (median, 95% CI). The primary efficacy analysis was a two-sided log-rank test stratified by randomisation strata (weight loss over the prior 3 months, location of primary tumour, and geographical region as per IVRS/IWRS strata). The HR was estimated with a stratified Cox proportional hazards model.
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	The key secondary outcomes and their statistical analyses are described below. Analyses were performed on the ITT population unless otherwise specified. Pharmacokinetic, pharmacodynamic and immunogenicity outcomes were evaluated in RAINBOW but are not relevant to this submission. A description of the QoL questionnaires is in Appendix 5. **Progression-free survival (PFS):** Time from the date of randomisation to the date of radiographic progression, or death due to any cause. Censoring occurred at the last adequate assessment or date of randomisation if no event had occurred. Assessment was through imaging studies which included, but was not limited to computer tomography (CT) scan of chest, abdomen and pelvis. Tumour response was assessed according to RECIST (version 1.1) at baseline and every 6 weeks for the first 6 months, and every 9 weeks thereafter.	The key secondary outcomes and their statistical analyses are described below. Analyses were performed on the ITT population unless otherwise specified. Pharmacokinetic, pharmacodynamic and immunogenicity outcomes were evaluated in REGARD but are not relevant to this submission. **Progression-free survival (PFS):** Time from the date of randomisation to the date of radiographic progression, or death due to any cause. Censoring occurred at the last adequate assessment, or date of randomisation if no event had occurred. Imaging studies included, but not limited to, CT scan of chest, abdomen and pelvis. Tumour response was assessed according to RECIST (version 1.0). Assessed at baseline and every 6 weeks thereafter.

	Time to disease progression (TTP): Time from date of randomisation until date of radiographic progression. Assessed at baseline and every 6 weeks for the first 6 months, and every 9 weeks thereafter. **Objective response rate (ORR) and Disease control rate (DCR):** ORR was the number of randomised patients who achieved complete response (CR) or partial response (PR) divided by the ITT population. Patients with no assessment included in denominator. CR was defined as the disappearance of all non-nodal target lesions, with the short axes of any target lymph nodes reduced to < 10 mm. PR was defined as at least a 30% decrease in the sum of the longest diameters of target lesions (including the short axes of any target lymph nodes), taking as reference the baseline sum diameter. DCR was CR, PR and stable disease (SD). SD was defined when there was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum diameter since the study started (this includes the baseline sum if that is the smallest on study). Also, any cases that do not qualify for either non-evaluable, PR, or PD. **Quality of Life (QoL):** Assessed using EORTC QLQ-C30 (version 3.0), and the European Quality of Life-5 Dimensions (EQ-5D) at baseline, every 6, weeks and at end of treatment. **Time to deterioration (TTD) in EORTC QLQ-C30:** TTD from baseline in each of the 15 scales of the EORTC QLQ-C30, assessed at baseline, every 6, weeks and at end of treatment. **Time to deterioration (TTD) in ECOG PS:** Time from randomisation to the first documentation of an ECOG performance status score of 2 or worse. Assessed at baseline, day 1 of every cycle, end-of-therapy and 30-day safety follow up. **Safety:** Adverse events and toxicity assessed in the safety population. Investigators assessed using NCI CTCAE, version 4.02. Assessed at every visit (at baseline, day 1, 8, 15, end-of therapy, 30-day safety follow-up, end-of-study and survival follow-up at least every 8 weeks).	**PFS 12-week rate:** The 12-week PFS was defined as the probability of being alive and progression-free 12 weeks after. Assessed at baseline and every 6 weeks thereafter. **ORR and DCR:** ORR was the number of randomised patients who achieved CR or PR) divided by the ITT population. Patients with no assessment included in denominator. DCR was the proportion of patients with CR, PR and SD. Please see details of RAINBOW for definition of CR, PR and SD. **QoL[b]:** Assessed using EORTC QLQ-C30 (version 3.0) at baseline, 6, 12, 18 weeks. **Time to deterioration of ECOG PS[a]:** Time from randomisation to the first documentation of an ECOG performance status score of 2 or worse. This was assessed prior to each cycle (every 2 weeks). **Safety:** Adverse events and toxicity assessed in the Safety population. Investigators assessed using NCI CTCAE, version 4.02 at every visit (at baseline, every two weeks, at the end-of-therapy, at the 30-day follow up and in the extension phase[c]).

Pre-planned subgroups	Subgroup analyses were pre-planned for the primary (OS) and secondary (PFS) efficacy endpoints, provided there were a sufficient number of events in the subgroup. Subgroups included the stratification factors and other factors (age, gender, race, ethnicity, ECOG PS, measurable disease vs. non-measurable disease, received prior therapy for metastatic disease, prior first-line chemotherapy, histologic subtype, number of metastatic sites, peritoneal metastasis, progression-free interval on prior first-line therapy for patients who has first-line therapy for metastatic disease only). Stratification factors: • Geographical regions (Region 1: North America/Europe/Australia/New Zealand; Region 2: South and Central America/India/South Africa/Jordan/Egypt/Saudi Arabia/Lebanon; Region 3: Asia). • Weight loss over the prior 3 months (>10% vs. <10%) • Location of primary tumour (Gastric vs. GOJ)	Subgroup analyses were pre-planned for the primary (OS) and secondary (PFS) efficacy endpoints. Subgroups included the stratification factors and other factors (age, gender, race, ethnicity, ECOG PS, weight loss, primary tumour location, prior first-line chemotherapy, histologic subtype, number of metastatic sites, peritoneal metastasis, liver metastasis, presence of ascites, tumour differentiation, number of previous treatment lines, prior gastrectomy). Stratification factors: • Geographical region (Region 1: Europe, Israel, US, and Australia; Region 2: Argentina, Brazil, Chile, and Mexico; Region 3: Hong Kong, Japan, South Korea, Singapore, and Taiwan. • Time to progression on first-line therapy (<6 months vs. ≥6 months) • Disease measurability (measurable vs. non-measurable disease).

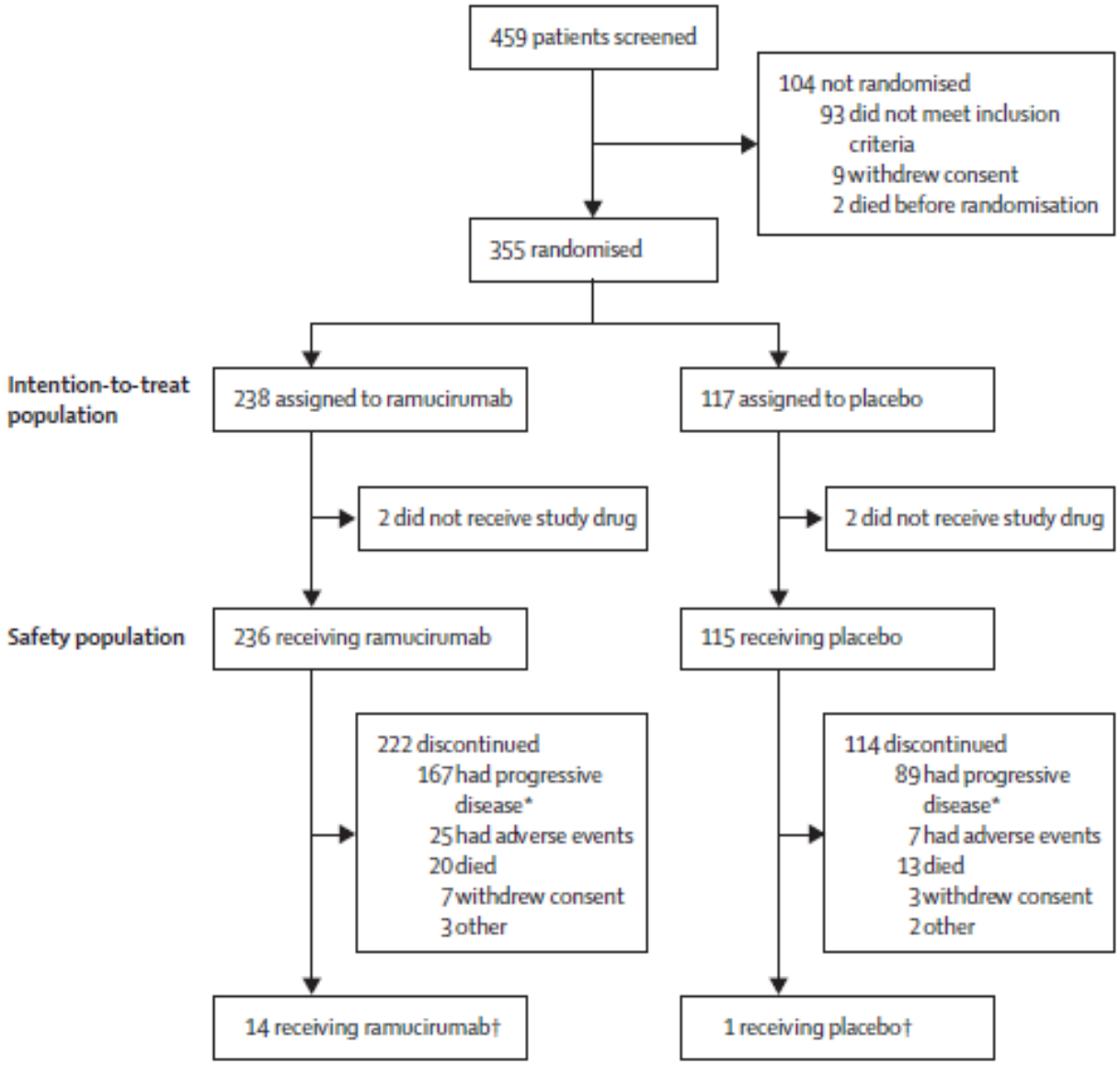
a Time to deterioration of ECOG PS was a post-hoc exploratory analysis
b Scores were categorised as “Not Deteriorated” (improved or stable) versus “Deteriorated”; patients with no data were not included in analyses. Secondarily, those with no data were classified with the “Deteriorated” group.
c Patients experiencing clinical benefit from the study drug after the targeted 268 OS events occurred could enter the extension phase until there was documented disease progression, intolerable toxicity, or withdrawal of consent.

4.5 Participant flow in REGARD

Figure 17 shows patient flow through REGARD. REGARD randomised 355 patients: 238 patients to RAM and 117 patients to PBO. As of the data cut-off date (25 July 2012) a total of 336 patients discontinued treatment (RAM n=222 (93%); PBO n=114 (97%)) leaving 14 patients receiving study treatment in the RAM arm versus one in the PBO arm. Two patients in each arm did not receive the assigned treatment and were not included in the safety population.

Disease progression was the most common reason for discontinuation followed by adverse events. In the RAM arm, 11.3% (25) of patients discontinued treatment due to AEs, 13 out of 25 discontinuations were considered by the investigator to be at least possibly related to study therapy. In the PBO arm, 6.1% (7) of patients discontinued treatment due to AEs, 2 out of 7 discontinuations were considered by the investigator to be at least possibly related to study therapy.

Figure 17 REGARD: Patient disposition



* assessed both radiographically and symptomatically
† As of data cut-off date of 25 July 2012

4.6 Quality assessment of relevant randomised controlled trials

Table 33 presents a quality assessment of RAINBOW and REGARD. Both trials were completed to the highest standard with adequate randomisation and blinding procedures.

Table 33 Quality assessment results for RAINBOW and REGARD

Trial number (acronym)	RAINBOW	REGARD
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and where appropriate methods used to account for missing data?	Yes, yes	Yes, yes
Adapted from Systematic review: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)		

4.7 Clinical effectiveness results: REGARD

- In total 355 patients were randomised: 238 patients to RAM and 117 patients to PBO
- Baseline patient demographics, disease and other characteristics were balanced between treatment arms
- The median age of participants was 60 years in both arms
- The majority of patients had measurable disease (92% RAM and 91% PBO) and a primary tumour present (73% in RAM and 74% in PBO)
- The majority of patients had received prior chemotherapy with both fluoropyrimidine and platinum (84% RAM and 75% PBO)
- RAM significantly improved OS compared with PBO
- Median OS was 5.2 months (IQR: 2.3-9.9) in patients receiving RAM and 3.8 months (IQR: 1.7-7.1) in patients receiving PBO
- Rates of 12 month OS were 17.6% for patients treated with RAM versus 11.8% for patients treated with PBO
- 44 (37.6%) patients treated with PBO received systemic PDT versus 72 (30.3%) of patients treated with RAM
- Median PFS was 2.1 months (95% CI: 1.5-2.7) in the RAM arm versus 1.3 months (95% CI: 1.3, 1.4) in PBO, reducing the risk of disease progression or death by 52% (HR=0.483; p<0.0001)
- More patients responded to treatment with RAM with a significantly greater (P<0.0001) DCR in patients treated with RAM (48.7%) compared to PBO (23.1%)
- The median duration of disease control was significantly higher for patients treated with RAM (4.2 months) compared to PBO (2.9 months)
- Although compliance in completing QoL questionnaires was high, the number of expected and completed QoL questionnaires decreased with time. At 6 weeks, only 48% of patients in the RAM arm versus 25% in the PBO arm provided QoL data
- More patients treated with RAM (34.1%) reported stable or improved QoL (as measured by EORTC QLQ-C30) compared to patients treated with PBO (13.7%) and time to deterioration in QoL was longer in patients treated with RAM (5.1 months) compared to PBO (2.4 months)

Baseline patient demographic and clinical characteristics

Baseline demographic and clinical characteristics were similar between treatment groups (Table 34). The majority of patients had measurable disease (92% RAM and 91% PBO), a primary tumour present (73% RAM and 74% PBO), between 0 and 2 metastatic sites (68% RAM and 61% PBO), and were free of disease progression for less than 6 months (65% RAM and 71% PBO). Most patients had received prior chemotherapy with both fluoropyrimidine and platinum (84% RAM and 75% PBO). Slightly fewer patients in the RAM arm (27%) had peritoneal metastases versus the PBO arm (38%). As histology may not be not routinely documented (see inclusion criteria), the large number of "unknown" type in this trial was not unexpected.

Table 34 REGARD: Baseline patient characteristics

REGARD Baseline Characteristics	**RAM (n=238) n (%)**	**PBO (n=117) n (%)**
Age (years) Median (IQR)	60 (52-67)	60 (51-71)
Gender, n (%)		
Male	169 (71)	79 (68)
Female	69 (29)	38 (32)
Geographic Regions, n (%)		
1. North America, Europe, Australia, New Zealand, Israel	165 (69)	80 (68)
2. South and Central America, India, South Africa, Middle East	55 (23)	29 (25)
3. Asia	18 (8)	8 (7)
Race, n (%)		
White	181 (76)	91 (78)
Asian	39 (16)	17 (15)
Black	4 (2)	2 (2)
Other	14 (6)	7 (6)
ECOG performance status, n (%)		
0 (fully active)	67 (28)	31 (26)
1 (restricted in physically strenuous activity)	171 (72)	85 (73)
2 (ambulatory but unable to carry out work)[a]	0	1 (1)
Measurable disease according to RECIST, n (%)		
Yes	218 (92)	106 (91)
No	20 (8)	11 (9)
Weight loss in the previous 3 months, n (%)		
≥10%	41 (17)	20 (17)
<10%	197 (83)	97 (83)
Primary tumour present, n (%)		
Yes	174 (73)	86 (74)
No	64 (27)	31 (26)

Location of primary tumour, n (%)		
Gastric	**178 (75)**	**87 (74)**
GOJ	**60 (25)**	**30 (26)**
Histological subtype, n (%)		
Intestinal	52 (22)	35 (30)
Diffuse	96 (40)	44 (38)
Undetermined/not available	90 (38)	38 (32)
Number of metastatic sites, n (%)		
0- 2	163 (68)	71 (61)
≥3	75 (32)	46 (39)
Peritoneal metastases, n (%)	64 (27)	45 (38)
Previous anti-cancer treatment (by type of therapy), n (%)		
First-line therapy	199 (84)	103 (88)
Adjuvant therapy only (no first-line therapy)	37 (15)	14 (12)
Neoadjuvant therapy only	2 (1)	0
Previous anti-cancer treatment (by type of drug), n (%)		
Fluoropyrimidine plus platinum	200 (84)	88 (75)
Fluoropyrimidine plus other systemic drug	13 (5)	17 (15)
Fluoropyrimidine alone	16 (7)	7 (6)
Platinum plus other systemic drug	9 (4)	5 (4)
Progression-free interval on prior therapy, n (%)		
<6 months	154 (65)	83 (71)
≥6 months	81 (34)	34 (29)
Missing	3 (1)	0
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee		

Abbreviations: IQR= interquartile range; LN = lymph nodes; RECIST = Response Evaluation Criteria in Solid Tumours; Std Dev = standard deviation; TNM = tumour, lymph node, metastasis.
Data are number (%) unless otherwise indicated.

Primary endpoint: Overall survival

The primary endpoint of REGARD was OS. Primary and secondary endpoints were analysed using the ITT population.

At the data cut-off date, 179 (75.2%) patients had died in the RAM arm and 99 (84.6%) in the PBO arm (Table 35 and Figure 18). Median OS was 5.2 months among patients treated with RAM and 3.8 months among those treated with PBO (HR=0.776; log-rank p=0.047 in stratified analysis), representing a 36.8% increase in median OS with RAM. Survival at 3, 6, and 12 months was higher in the RAM group compared to the PBO group. An analysis of PDT revealed that more patients in the PBO arm received systemic PDT than in the RAM arm (discussed in further detail in the conclusions).

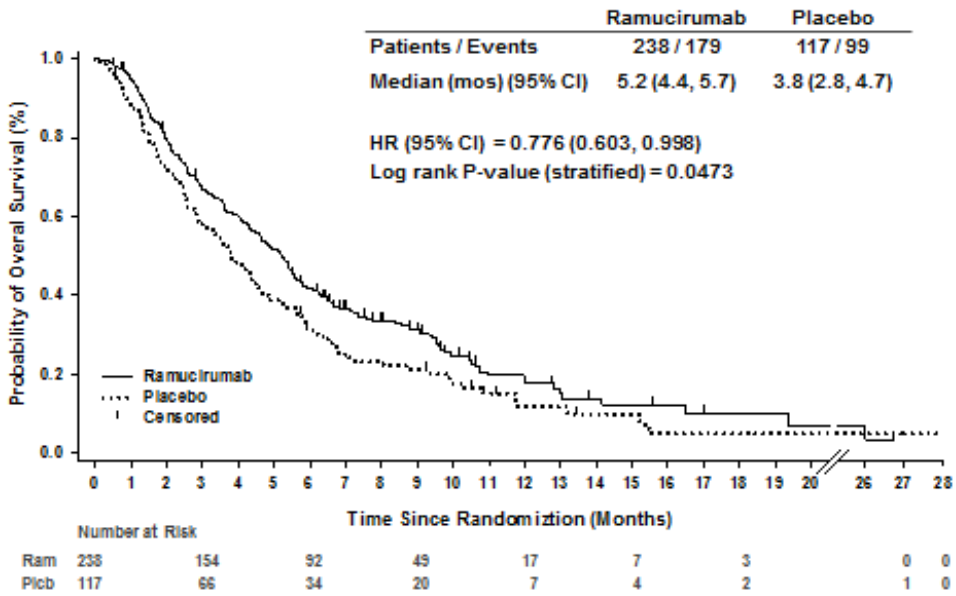
HRs estimated from the sensitivity analyses ranged from 0.737 to 0.776 and were similar to those of the base case analysis, all with p<0.05 (Appendix 4).

Table 35 REGARD: OS Results (ITT Population)

Outcome	RAM (N=238)	PBO (N=117)	Treatment difference
Number of deaths, n (%)	179 (75.2)	99 (84.6)	NA
Median survival, months (IQR)	5.2 (2.3-9.9)	3.8 (1.7-7.1)	1.4
Median survival, months (95% CI)	5.2 (4.4, 5.7)	3.8 (2.8, 4.7)	1.4
Log-rank p-value (2-sided)[a]	0.0473		
Hazard ratio (95% CI)[a]	0.776 (0.603, 0.998)		
Survival rate, %			
3-month	66.7	58.0	8.6
6-month	41.8	31.6	10.3
12-month	17.6	11.8	5.8

Abbreviations: IQR = interquartile range;
[a] Stratified by randomisation strata (weight loss over prior 3 months, location of primary tumour, geographical region)

Figure 18 REGARD: Kaplan-Meier Plot of OS (ITT Population)



Abbreviations:; mos = month; Plcb = placebo; Ram = ramucirumab.

Secondary Outcomes

PFS and 12-week PFS

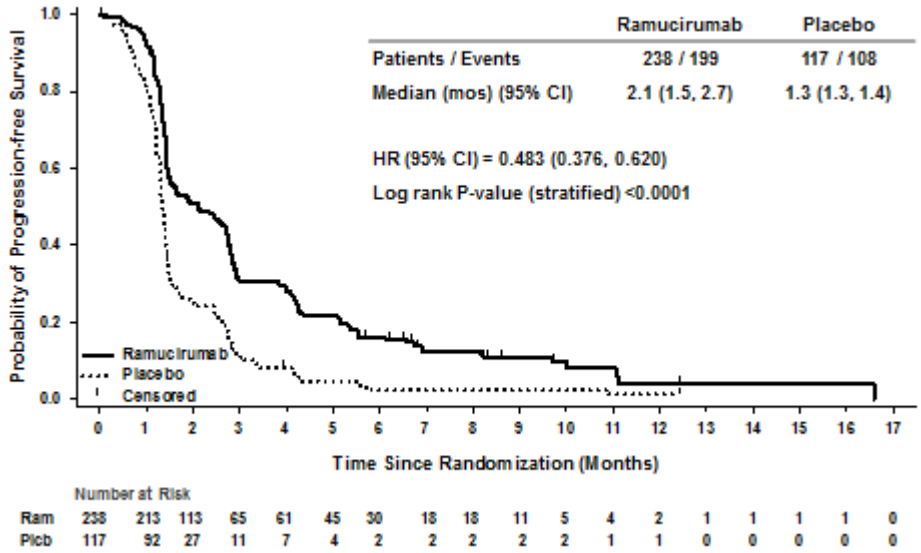
At the data cut-off date, 199 PFS events had occurred in the RAM arm and 108 in the PBO arm (Table 36 and Figure 19). The risk of disease progression or death was reduced by 52% with RAM treatment, compared to PBO (HR=0.483; p<0.0001). The median PFS time was 2.1 months in the RAM arm versus 1.3 months in PBO arm. At 12 weeks, the rate of PFS was 40.1% in the RAM arm versus 15.8% in PBO arm.

Table 36 REGARD: PFS Results (ITT Population)

Outcome	RAM (n=238)	PBO (n=117)	Treatment difference
Number of events, n (%)	199 (83.6)	108 (92.3)	
Number censored, n (%)	39 (16.4)	9 (7.7)	
Median PFS, months (95% CI)	2.1 (1.5, 2.7)	1.3 (1.3, 1.4)	0.8
Log-rank p-value, [a] (2-sided)	<0.0001		
Hazard ratio[a] (95% CI)	0.483 (0.376, 0.620)		
PFS rate, %			
12-week	40.1 -	15.8	24.2
p-value	p<0.0001		
6-month	16.0	2.3	13.7
p-value	p<0.0001		

[a] Stratified by randomisation strata (weight loss over prior 3 months, location of primary tumour, geographical region)

Figure 19 REGARD: Kaplan-Meier Plot of PFS (ITT Population)



Abbreviations: mos = month; Plcb = placebo; Ram = ramucirumab.

Objective Response Rate

The ORR was 3.4% in the RAM arm, compared with 2.6% in the PBO arm (Table 37). The DCR, which takes into account the rate of stabilised disease, was significantly higher (p<0.0001) in the RAM arm (48.7%) compared to the PBO arm (23.1%). Furthermore, the median duration of disease control was significantly higher in the RAM (4.2 months) compared to the PBO arm (2.9 months). The duration of response was not analysed because the number of patients with a complete or partial response was low.

Table 37 REGARD: ORR and DCR Results (ITT Population)

Outcome	RAM (N=238)		PBO (N=117)		p-value
	n (%)	95% CI	n (%)	95% CI	
Best overall response					
Complete response (CR)	1 (0.4)	0.0, 2.3	0 (0)	0.0, 3.1	
Partial response (PR)	7 (2.9)	1.2, 6.0	3 (2.6)	0.5, 7.3	
Stable disease (SD)	108 (45.4)	38.9, 51.9	24 (20.5)	13.6, 29.0	
Progressive disease	78 (32.8)	26.8, 39.1	63 (53.8)	44.4, 63.1	
Not evaluable/No assessment	44 (18.5)	13.8, 24.0	27 (23.1)	15.8, 31.8	
Objective response rate (CR+PR)	8 (3.4)	1.5, 6.5	3 (2.6)	0.5, 7.3	0.76
Disease control rate (CR+PR+SD)	116 (48.7)	42.2, 55.3	27 (23.1)	15.8, 31.8	<0.0001
Median duration of disease control, in months (IQR)	4.2 (2.8, 8.1)		2.9 (2.7, 4.3)		0.036

Abbreviations: IQR = interquartile range;
Response was assessed by RECIST (Response Evaluation Criteria in Solid Tumours), version 1

Quality of Life

Compliance was high in both arms throughout the trial. While on therapy, QLQ-C30 completion rates were >86% of all expected assessments during periods shown in Table 38. The number of expected and completed QoL questionnaires decreased with time. At 6 weeks, only 114 (48%) patients in the RAM arm versus 29 (25%) in the PBO arm provided QoL data, primarily due to disease progression and study discontinuation before the first scheduled post-baseline assessment, rather than non-compliance.

Table 38 REGARD: EORTC QLQ-C30 Compliance (ITT Population)

Time	RAM (N=238)		PBO (N=117)	
	Number Completed/Number Expected[a]	Compliance (%)	Number Completed/Number Expected[a]	Compliance (%)
Baseline	230/238	97	110/117	94
6 weeks	114/130	88	29/36	81
12 weeks	66/72	92	11/12	92
18 weeks	38/42	90	5/5	100

[a] The number of expected questionnaires decreased over time as the number of patients discontinuing therapy increased.

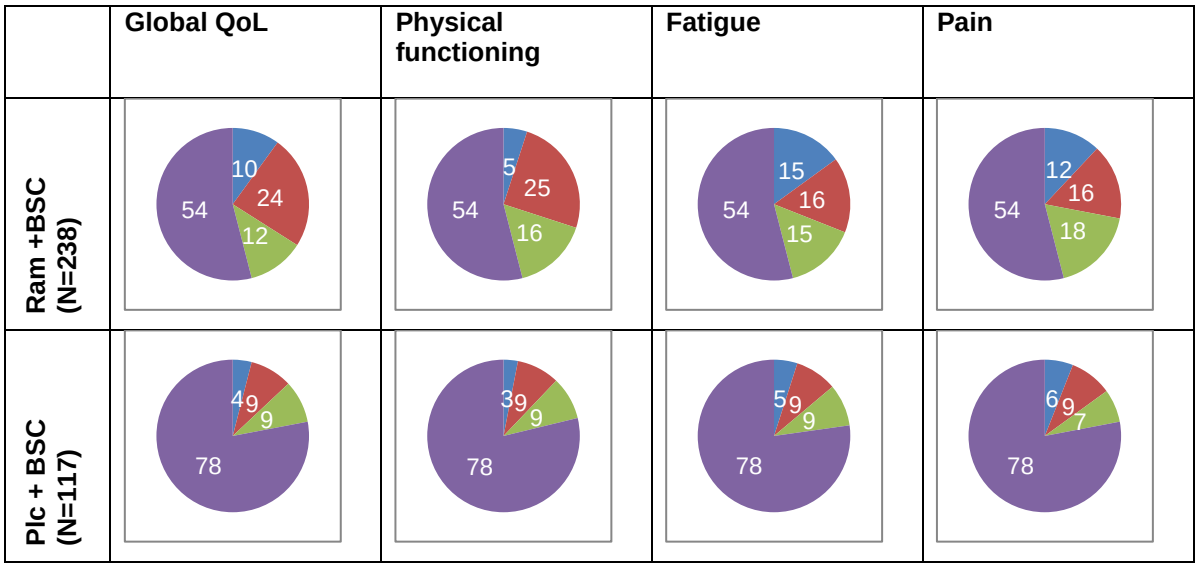
Changes in global QoL scores at 6, 12 and 18 weeks from baseline are shown in Table 39. At 6 weeks, the proportion of patients with improved or stable QoL was higher for the RAM arm (34.1%) than the PBO arm (13.7%); however, the difference was not statistically significant (p=0.23). Also at 6 weeks, there were higher proportions of patients in the RAM

arm for the physical functioning, fatigue and pain subscales. It should however be considered that in such a rapidly progressing disease, six weekly intervals may have been too short to sensitively capture the differences in QoL between treatment arms.

Table 39 REGARD: EORTC QLQ-C30 Global Health Status

Time of measurement	RAM (N=238) n (%)				PBO (N=117) n (%)			
	Improved	Stable	Deteriorated	Missing	Improved	Stable	Deteriorated	Missing
6 weeks	23 (9.7)	58 (24.4)	29 (12.2)	128 (53.8)	5 (4.3)	11 (9.4)	10 (8.5)	91 (77.8)
12 weeks	15 (6.3)	28 (11.8)	19 (8.0)	176 (73.9)	4 (3.4)	3 (2.6)	2 (1.7)	108 (92.3)
18 weeks	6 (2.5)	21 (8.8)	9 (3.8)	202 (84.9)	1 (0.9)	2 (1.7)	1 (0.9)	113 (96.6)

Figure 20 REGARD: QoL response rates for Week 6 on EORTC QLQ-C30 subscales



Legend: blue = improved; red = stable, green = worsened, purple = no data
Abbreviations: care; Plc = placebo; Ram = ramucirumab.

ECOG PS Deterioration

In a post-hoc analysis, median time to deterioration in ECOG PS ≥2 was 5.1 months (IQR 1.9-16.8) in the RAM arm and 2.4 months (1.3 to not reached) in the PBO arm.

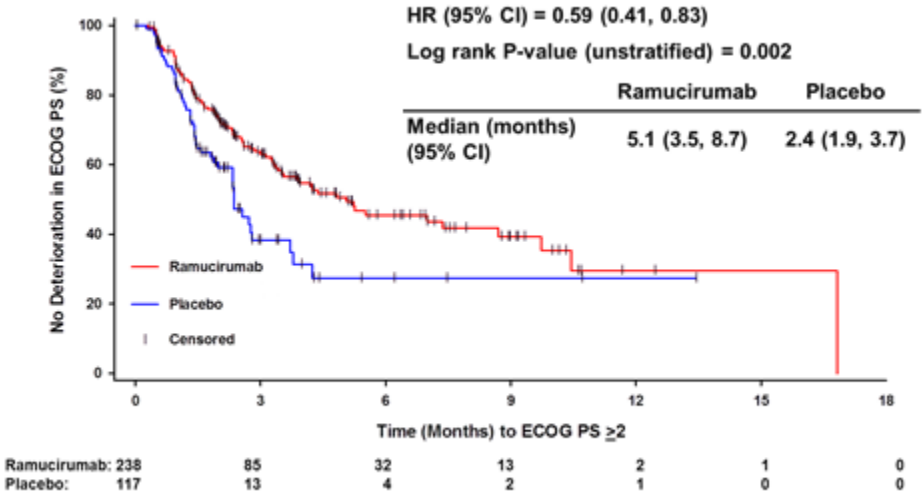
Patients assigned to RAM experienced a longer time to deterioration (5.1 months) than did patients assigned to PBO (2.4 months) (Table 40 and Figure 21). Patients without observed deterioration were censored at their last documented PS. Analyses using alternative definitions of ECOG PS deterioration also demonstrated a statistically significant benefit of RAM over PBO (unstratified HRs of 0.516 to 0.628, $p<0.05$).

Table 40 REGARD: Time to Deterioration in ECOG Performance Status ≥2 (ITT Population)

Outcome	RAM (N=238)	PBO (N=117)	Difference in medians	HR (95% CI)	p-value
Number of deterioration events, n (%)	94 (39.5)	51 (43.6)	NA	0.586 (0.414-0, 829)	0.0024
Median time to deterioration, in months (IQR)	5.1 (1.9-16.8)	2.4 (1.3 to not reached)	2.7		

Abbreviations:; NA = not applicable

Figure 21 REGARD: Kaplan-Meier Plot of Time to deterioration in ECOG PS ≥2 (ITT Population)

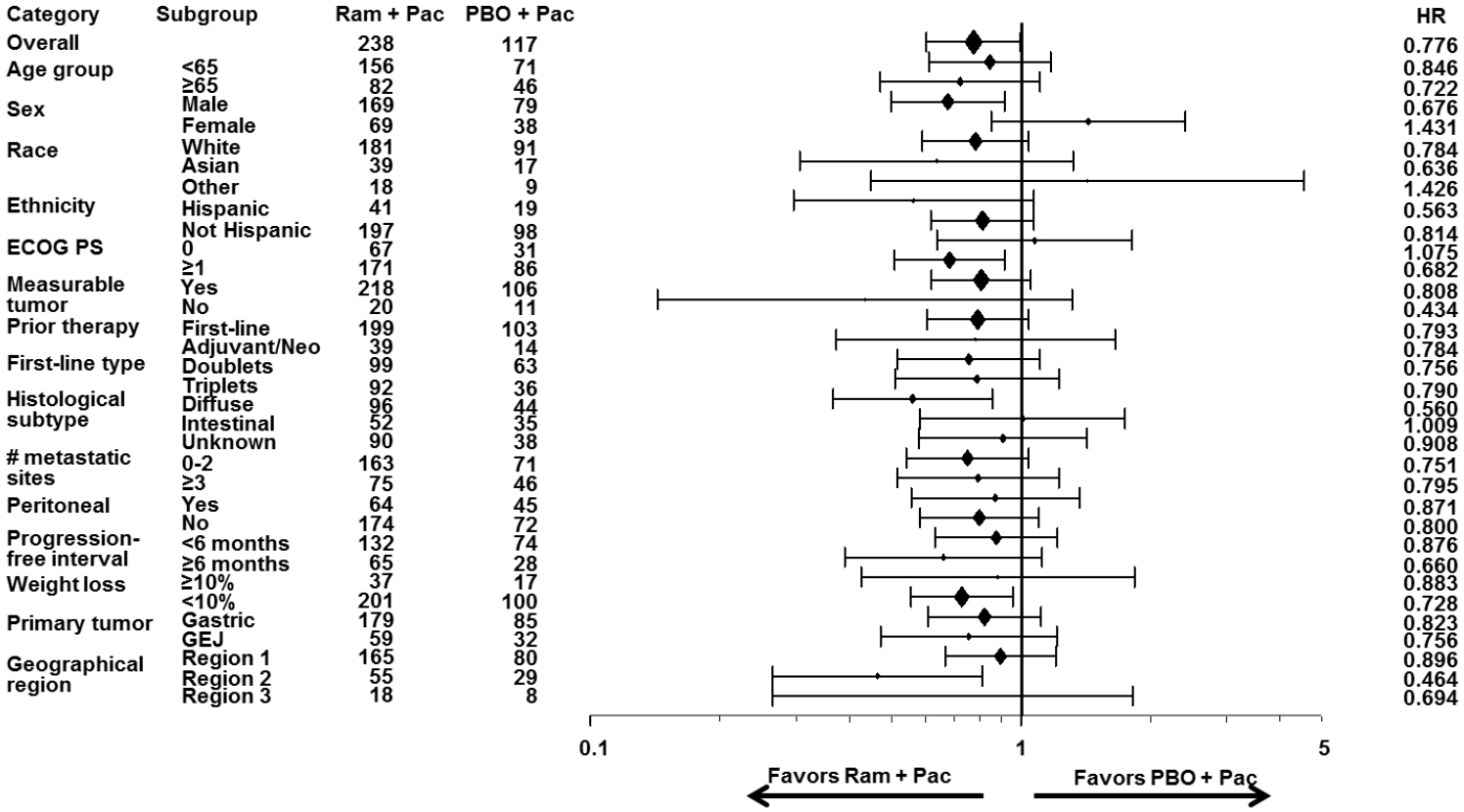


Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status

4.8 Subgroup analyses: REGARD

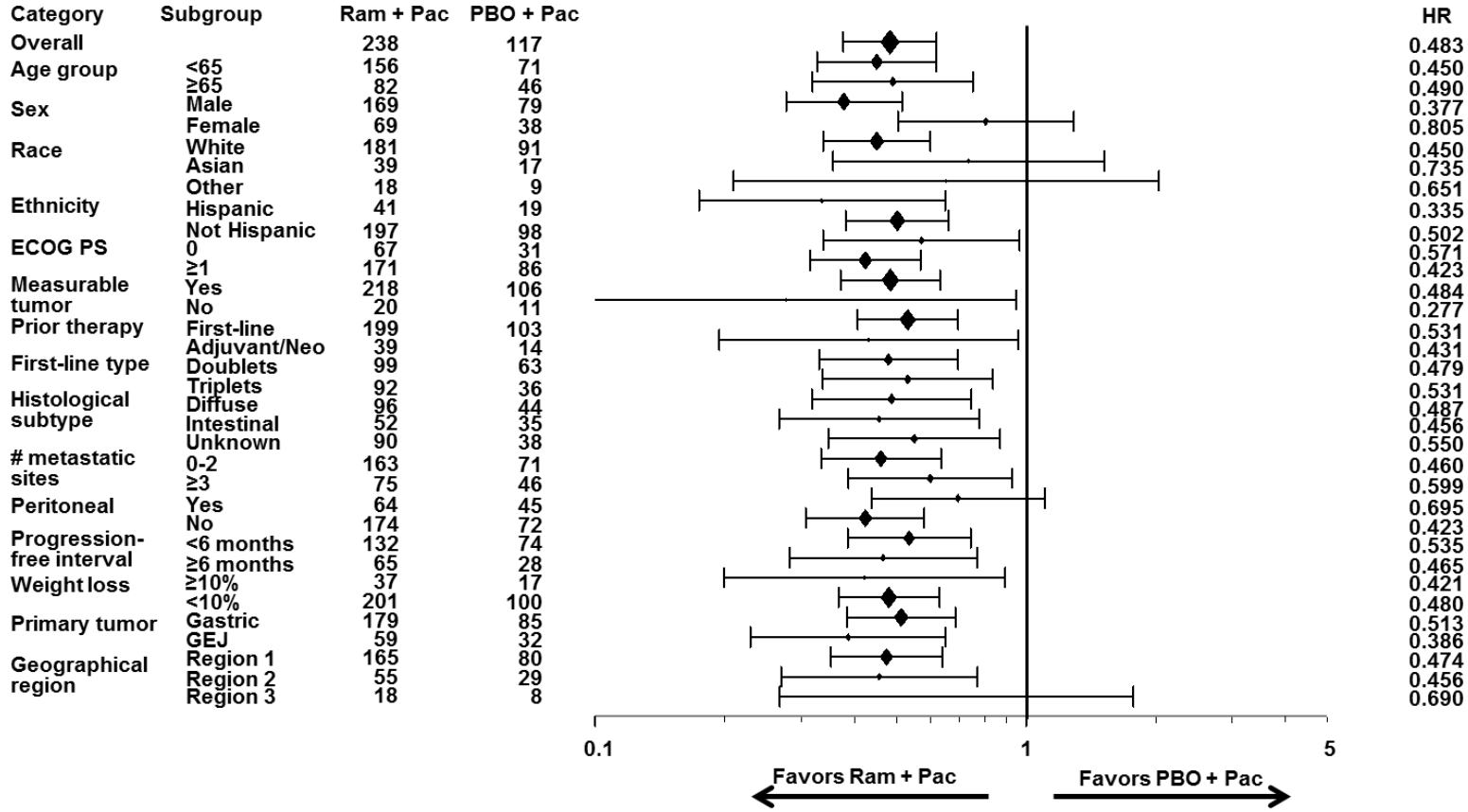
Subgroup analyses were pre-planned for the primary (OS) and secondary (PFS) efficacy endpoints. For OS and PFS, subgroup analyses (Figure 22 and Figure 23) revealed a consistent beneficial effect of RAM treatment across most subgroups. Only 2 subgroups (female gender and “other” race) did not show a benefit for RAM for OS. In both cases this is likely to result from insufficient power due to small subgroups and over stratification.

Figure 22 REGARD: Forest plot for subgroup analysis of OS (stratified; ITT population)



Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; GEJ = gastro-oesophageal junction; Ram = ramucirumab; Plcb =placebo
Notes: HRs are based on a stratified Cox proportional hazards model. The size of the diamonds is proportional to the size of the subgroup. Horizontal bars represent 95% CIs.

Figure 23 REGARD: Forest plot for subgroup analysis of PFS (stratified; ITT population)



Abbreviations:ECOG PS = Eastern Cooperative Oncology Group performance status; GEJ= gastro-oesophageal junction; Ram = ramucirumab; Plcb =placebo.
Notes: HRs are based on a stratified Cox proportional hazards model. The size of the diamonds is proportional to the size of the subgroup. Horizontal bars represent 95% CIs.

A detailed subgroup analysis by region for REGARD is not presented in this submission. In REGARD, the majority of patients were enrolled in Region 1 (n=245, 69.0%; the majority from the EU and North America), followed by Region 2 (n=84, 23.7%; most from Brazil and India). Only a few patients were enrolled in Region 3 (n=26, 7.3%; most from South Korea). Therefore, the analysis focused on differences between region 1 and region 2. The OS outcomes observed in REGARD were different across the 2 regions; in particular, there was a lower median survival observed in the PBO arm of Region 2 compared with Region 1 (2.6 months vs. 4.5 months, respectively), while median survival was similar between the RAM arms in these regions (5.1 months vs. 5.2 months, respectively).

As there was consistency of PFS (median and HR) between Regions 1 and 2, it was postulated that the differences in survival (median OS in the PBO arms and OS HR) between the 2 regions was driven by a post-discontinuation effect. Active treatment administered after study discontinuation can impact the absolute or relative treatment benefit in randomised trials that use OS as an endpoint (106). Therefore, the use of PDT was analysed by region in REGARD. The analysis revealed differences in the use of PDT between Regions 1 and 2 and in particular between the PBO arms of both regions. The PDT use in the PBO arm in Region 1 (45.0%) and Region 2 (17.2%) were different, with Region 1 being higher and Region 2 being lower than the trial as a whole (37.6%). Consistent with this, the median OS in the PBO arm was higher in Region 1 and lower in Region 2 than the trial as a whole. Thus, this differential use of PDT in the PBO arm between Regions 1 and 2 is thought to be the cause of differential OS effects between the 2 regions, when the PFS effects are similar. There were no relevant differences in terms of AEs between the regions.

Conclusions from REGARD

RAM as a single agent provided a significant increase in median OS (36.8%) in patients with advanced GC/GOJ that had progressed after first-line chemotherapy. This represents a clinically meaningful increase in OS in a patient population with an otherwise poor prognosis. An analysis of PDT revealed that more patients in the PBO arm received systemic PDT than in the RAM arm (Table 41). A total of 116 patients (30.3% for RAM vs. 37.6% for PBO) received systemic PDT (including surgery and radiotherapy) which could explain the survival difference observed between the two arms.

Table 41 REGARD: Systemic PDT (ITT population)

Systemic PDT	RAM N=238 n (%)	PBO N=117 n (%)
Overall	72 (30.3)	44 (37.6)
Chemotherapy	69 (29.0)	44 (37.6)
Biologic	6 (2.5)	1 (0.9)
Other	1 (0.4)	1 (0.9)

The most frequently used PDT agent was IRI (13.0% of patients in the RAM arm, 20.5% of patients in the PBO arm), followed by fluorouracil (9.2% in RAM arm and 10.3% in PBO) and carboplatin (7.1% in RAM arm and 6.8% in PBO).

In addition to this patients treated with RAM also had a significantly longer PFS with a higher proportion of patients achieving disease control (49% of patients treated with RAM compared to 23% of patients treated with PBO).

The survival benefit observed in patients in REGARD was not at a detriment to QoL. QoL was not negatively impacted for patients treated with RAM compared to those treated with PBO as measured by the EORTC QLQ-C30. The proportion of patients with improved or stable QoL was higher for the RAM arm compared to PBO at all time-points. In addition, the time to deterioration in QoL was longer in patients treated with RAM than in patients treated with PBO.

Overall, RAINBOW and REGARD are the largest phase 3 trials of the second-line treatment for patients with advanced GC/GOJ. Both trials present robust evidence of two treatment options that have demonstrated clinically meaningful survival benefits while maintaining QoL in a group of patients with an otherwise poor prognosis.

4.9 Meta-analysis

No head-to-head clinical trials were found that provided evidence of the efficacy and safety of RAM+PAC versus best supportive care or DOC in the second-line treatment of patients with advanced GC/GOJ. On this basis, no direct meta-analysis was performed. Instead the evidence networks were analysed via single pair-wise meta-analysis and/or a series of indirect treatment comparisons. Details of this analysis are provided in section 4.10.

4.10 Indirect and mixed treatment comparisons

A meta-analysis was performed to focus on the relative efficacy of RAM as a monotherapy or combination therapy in comparison with treatments of interest in adult patients who have received prior chemotherapy for GC/GOJ in terms of survival, tumour response and toxicity. In order to perform the meta-analysis, a systematic literature review (SR) was conducted to identify RCT evidence for the efficacy and safety of RAM+PAC and other treatments in the second-line treatment of adult patients with advanced GC/GOJ adenocarcinoma.

Search strategy

Studies were identified by searches of the following electronic databases (restricted to English language publications; accessed December 3rd 2013):

- MEDLINE (R) In-Process & Other Non-Indexed Citations
- Ovid MEDLINE (R) 1946 to present (via OVID)
- EMBASE, 1980 to present (via OVID)
- The Cochrane Library (via OVID), searching the following databases:
  - The Cochrane Central Register of Controlled Trials (CENTRAL)
  - The Cochrane Database of Systematic Reviews (Cochrane Reviews)
  - The Database of Abstracts of Reviews of Effects (DARE)
  - The Health Technology Assessment Database (HTA)

The search strings for the database searches are documented in Appendix 6. The following conference proceedings were also reviewed for eligible abstracts/posters (last two years availability):

- European Society for Medical Oncology (ESMO) - www.esmo.org/ (published in Annals of Oncology)
- American Society for Clinical Oncology (ASCO) - www.asco.org.

- World GI Cancer Congress

The eligibility criteria applied to select appropriate studies are detailed in Table 42.

Table 42 Eligibility criteria applied to studies

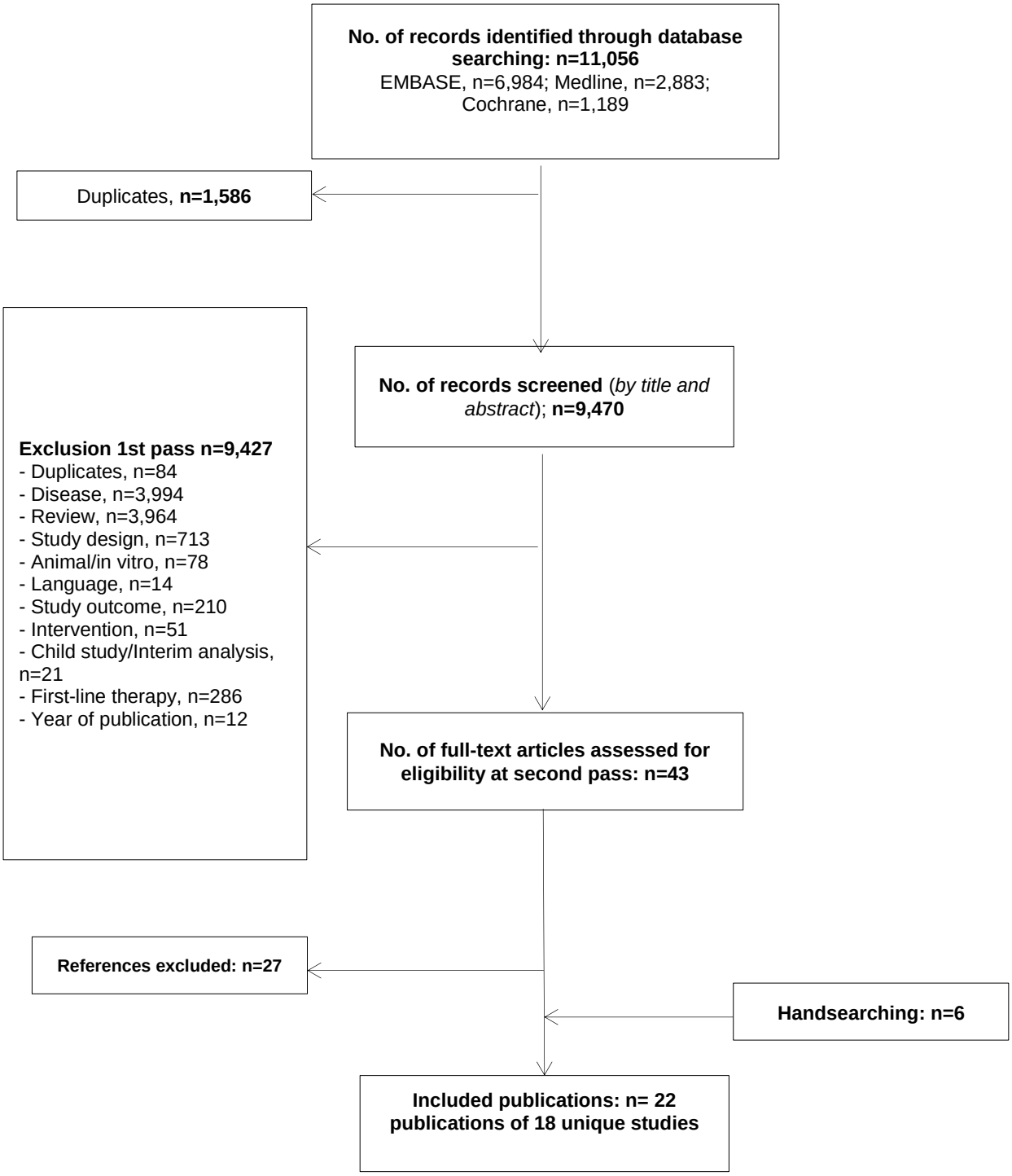
	Inclusion
Population	Adult patients (≥18 years) who received prior chemotherapy (no restriction on line of therapy) for the following: • Gastric cancer • Gastro-esophageal junction (GOJ) cancer
Intervention	Eligible studies included at least one treatment arm examining one of the following therapies: Chemotherapy • Capecitabine • Cisplatin • Docetaxel • Irinotecan • Paclitaxel • Oxaliplatin • CAPOX • EOX • FLOT • FOLFIRI • 5-FU • S-1 • Tegafur • Mitomycin • Etoposide • Epirubicin • Carboplatin Targeted therapy • Apatinib • Bevacizumab • Everolimus • Lapatinib • Ramucirumab • Trastuzumab
Comparator	Comparators to include any of the interventions, PBO, BSC, or active symptom control (ASC).

Outcomes	***Efficacy:*** • OS • PFS with definition (N.B. RECIST 2009 guidelines change the definition of disease progression and therefore of PFS). • 12-week PFS rate • TTP with definition • ORR, CR, PR, overall response (=CR+PR)) as measured by WHO or RECIST 2000 or revised v1.1 RECIST 2009 (107) guidelines • SD • Clinical benefit or DCR (=CR+PR+SD) • Any of the above with respect to prognostic factor subgroups *Safety/tolerability:* • Specified adverse drug reactions or serious adverse events including anaemia, diarrhoea, febrile neutropenia, hand-foot syndrome, infection, lethargy, leucopenia, neutropenia, nausea and vomiting, peripheral neuropathy, rash, stomatitis, thrombocytopenia classified as any of grade 1-4 (using any classification system) • Withdrawal from study (or postponement of treatment cycle) due to adverse events or due to serious adverse events. • Any cause discontinuation rates (from treatment/study)
Setting/Study type	• Clinical (human) Phase 2 or III RCTs • Superiority or non-inferiority RCTs • Blinded or open label RCTs

Study selection

The electronic database search identified 11,056 articles, of which 9,470 were screened (after removal of duplicates). In total, 43 were potentially relevant as judged by title, abstract, and keywords (Figure 24). Screening the full publications resulted in a further 27 exclusions. A total of six publications were identified from hand searching. This resulted in 22 publications reporting on 18 unique RCTs (details on these 18 RCTs can be found in Appendix 6).

Figure 24 Flowchart of inclusions/exclusions



Statistical analyses

The evidence networks were analysed via single pair-wise meta-analysis and/or a series of indirect comparisons. Subgroup analyses were also performed for the outcome of OS. Results from an NMA for the outcomes of OS and PFS are provided in Appendix 6.

Analyses of safety outcomes have also been performed. However the size of the evidence networks were limited for several of the AEs analysed due to inconsistent reporting of AEs across studies. Also, the precise definitions of safety outcomes across the study publications were rarely reported. In addition, recent review articles have highlighted that the reporting of AE data in oncology RCTs is both suboptimal and subject to considerable heterogeneity (108,109). Therefore the safety results from the current meta-analysis should be considered in the context of these limitations.

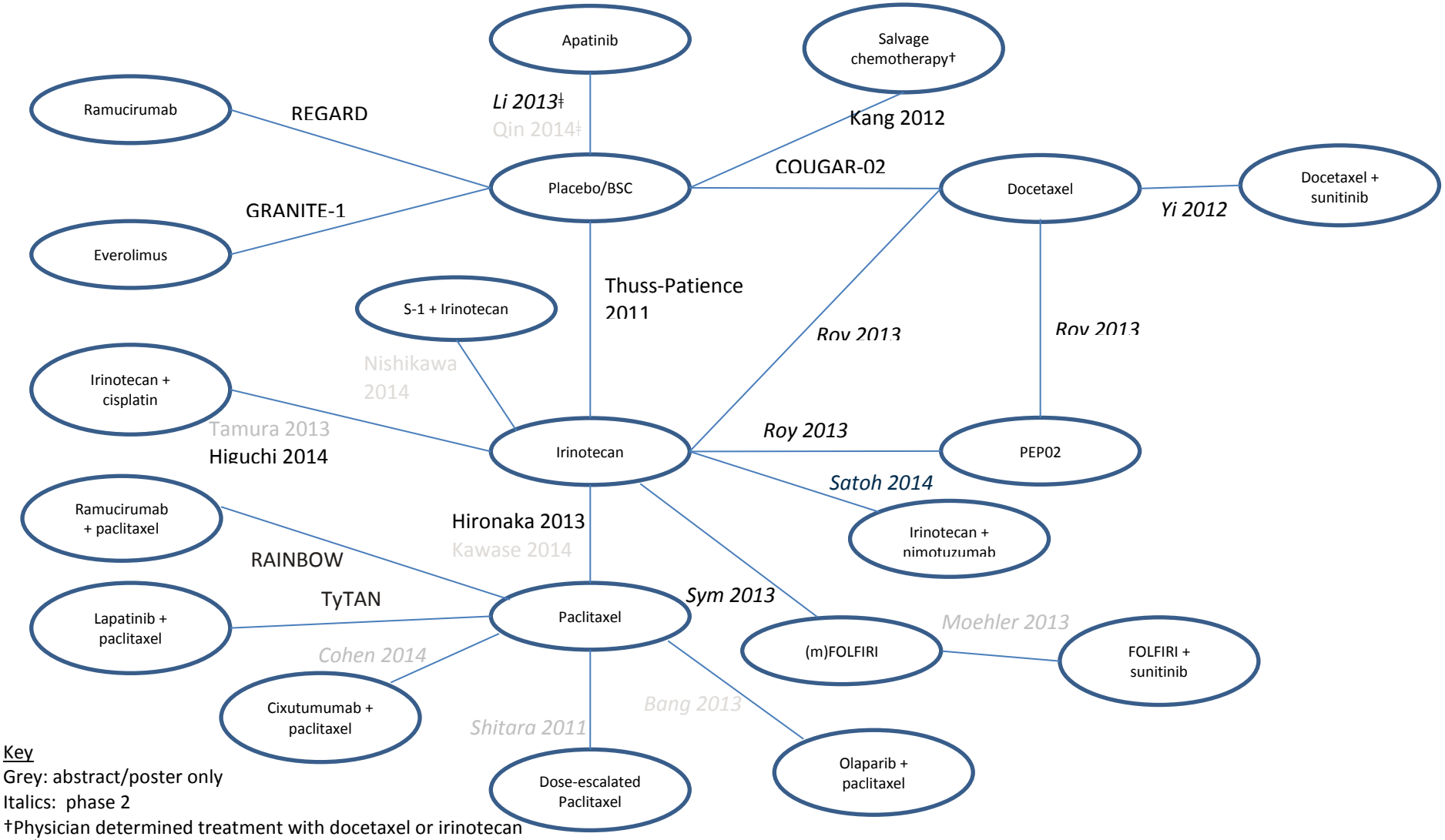
Evidence network for meta-analysis

The meta-analysis was restricted to treatments cited in guidelines or used in clinical practice, but only comparators of interest are reported here:

- Ramucirumab
- Ramucirumab + paclitaxel
- Paclitaxel
- Irinotecan
- Irinotecan + cisplatin
- Docetaxel
- mFOLFIRI (leucovorin, fluorouracil and irinotecan)

The best-case evidence scenario network for treatments of interest only is shown in Figure 25. Note that the phase 2, three-arm trial reported by Roy 2013 includes PEP02 (liposomal formulation of IRI) as a treatment arm but this treatment is not of interest for the current analysis (110).

Figure 25 Best-case evidence network of RCTs eligible for inclusion in the SR



Key
Grey: abstract/poster only
Italics: phase 2
†Physician determined treatment with docetaxel or irinotecan
‡3rd-line

Results

- RAM+PAC was associated with a statistically significant lower hazard of death compared with PBO/BSC
- There was no significant difference in the hazard of progression or death for RAM+PAC compared with DOC, however RAM+PAC was associated with a statistically significant lower hazard of progression or death compared with PAC
- There were no significant differences in withdrawals due to AEs for RAM+PAC compared with DOC and PAC

Overall survival

In the current analysis, OS has been analysed employing the simplifying assumptions of proportional hazards (PH). That is, it is assumed that the treatment effects are constant over time and the trial level reported HRs have been used in the analysis. The published data for OS and evidence network are presented in Table 43 and Figure 26. The direct and indirect comparisons are presented in 0. A base case NMA and further sensitivity analyses including data for Roy 2013 obtained by estimating the study level treatment effect from the Kaplan-Meier curve are provided in Appendix 6.

Table 43 Reported OS data. Primary outcome was OS unless otherwise stated

Study	Treatment arms	N	Unadjusted HR for death (95% CI)	Adjusted HR
COUGAR-02 (2)	DOC, 75 mg/m^2/3 weeks, up to 6 cycles + active symptom control until progression	84	0.67 (0.49, 0.92)	NR
	Active symptom control	84	control	control
RAINBOW (6)	RAM, 8 mg/kg/2 weeks, until progression + PAC 80 mg/m^2 3 times every 4 weeks	330	0.822 (0.691, 0.977)	0.807 (0.678, 0.962)
	PBO + PAC 80 mg/m^2 3 times every 4 weeks until progression	335	control	control
Hironaka 2013 (111)	IRI, 150 mg/m^2 2 times ever 4 weeks, until progression	111	1.13 (0.86, 1.49)	NR
	PAC, 80 mg/m^2 3 times every 4 weeks, until	108	control	control

Study	Treatment arms	N	Unadjusted HR for death (95% CI)	Adjusted HR
	progression			
Roy 2013 (110)	PEP02, 120 mg/m^2/3 weeks, until progression	44	0.96 (0.60, 1.53)§ [Primary outcome: ORR]	NR§
	IRI, 300 mg/m^2/3 weeks, until progression	44		
	DOC, 75 mg/m^2/3 weeks, until progression	44		
Thuss-Patience 2011 (4)	IRI (250-350 mg/m^2/3 weeks) + BSC, limit of 10 cycles	21	0.48 (0.25, 0.92)†	NR
	BSC	19	control	control

Abbreviations: NR= not reported;
†Univariate analyses were performed – time of progression after first-line treatment of less versus more than three months was a significant prognostic factor- this variable was equally distributed between the two treatment arms.
§OS reported as a figure only, no HR reported. Authors contacted to obtain HR, but no reply to date. Estimate of IRI. vs. DOC obtained from digitising Kaplan-Meier curve and using the methods of Parmar et al 1998 (112)

Figure 26 Evidence network for Overall Survival (OS)

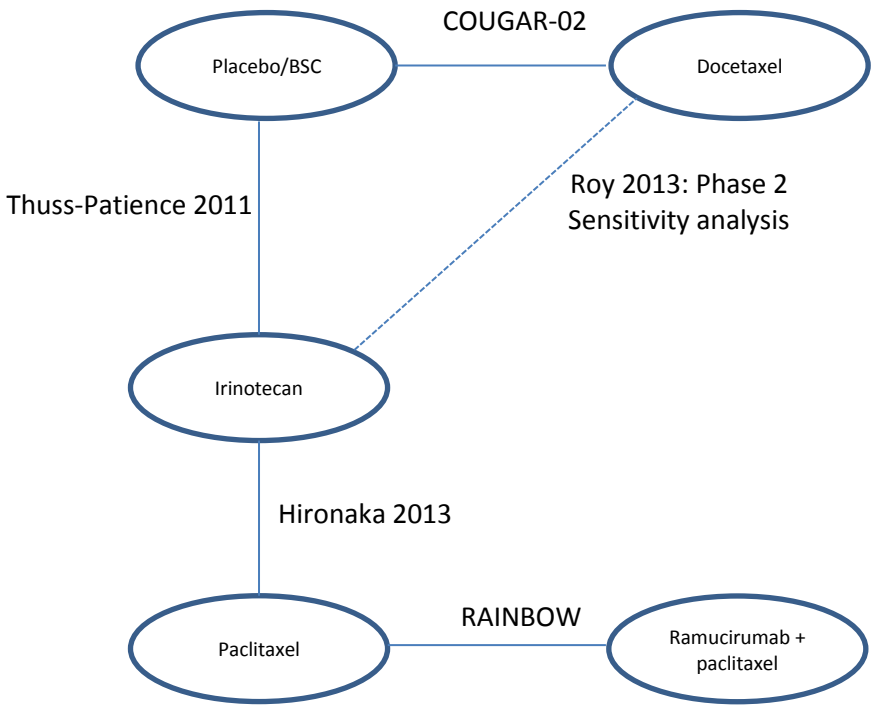


Table 44 Indirect comparison results for base case OS. Comparisons of treatment A vs. treatment B, HR (95% CI)

Treatment A	Treatment B		
	PBO/BSC	DOC	PAC
DOC	*0.67* *(0.49, 0.92)*		
PAC	*0.42* *(0.21, 0.86)*	0.63 (0.29, 1.37)	
RAM+PAC	*0.34* *(0.17, 0.71)*	0.51 (0.23, 1.13)	*0.81* *(0.68, 0.96)*

Abbreviations: CI= confidence interval; HR= hazard ratio
Statistically significant results are bold and italicised; grey cells represent direct evidence and white cells represent indirect comparisons.

Summary of OS

RAM combination therapy versus PBO/BSC

- RAM+PAC was associated with a statistically significant lower hazard of death compared with PBO/BSC.

RAM combination therapy versus comparators

- RAM+PAC was associated with a statistically significant lower hazard of death compared with PAC (refer to 0).
- There was a numerically lower hazard of death for RAM+PAC compared with DOC although this was not statistically significant.

The summary measures of effect from the pair-wise meta-analysis and indirect comparisons (HR [95% CI]) are consistent with those from the base case NMA (HR [95% CrI]) presented in Appendix 6.

Progression-free survival

The published data for PFS and evidence network are presented in PFS data Table 45 and Figure 27. The direct and indirect comparisons are presented in Table 46. Note that the Kaplan-Meier curve for PFS published in Roy 2013 was used to derive a HR using the method of Parmar (112) and allow for DOC to be included in the network as a comparator.

Table 45 PFS data

Study	Treatment arms	N	Unadjusted HR (95% CI)	Adjusted HR
COUGAR-02 (2)	DOC, 75 mg/m^2/3 weeks, up to 6 cycles + active symptom control until progression	84	NR	NR
	Active symptom control	84		
Hironaka 2013 (111)	IRI, 150 mg/m^2 2 times ever 4 weeks, until progression	108	1.14 (0.88,1.49)	NR
	PAC , 80 mg/m^2 3 times every 4 weeks, until progression	111	control	control
Roy 2013 (110)	IRI, 300 mg/m^2/3 weeks, until progression	44	1.26 (0.94,1.68)†	NR
	DOC, 75 mg/m^2/3 weeks, until progression	44		
	BSC	19		
RAINBOW (6)	RAM, 8 mg/kg/2 weeks, until progression + PAC 80 mg/m^2 3 times every 4 weeks	330	0.641 (0.544, 0.756)	0.635 (0.536, 0.752)
	PBO + PAC 80 mg/m^2 3 times every 4 weeks	NR	control	control

Abbreviations: CI= confidence interval; HR= hazard ratio; NR= not reported;
† PFS was obtained from digitisation of Kaplan-Meier curve in publication.
.

Figure 27 Evidence network for PFS

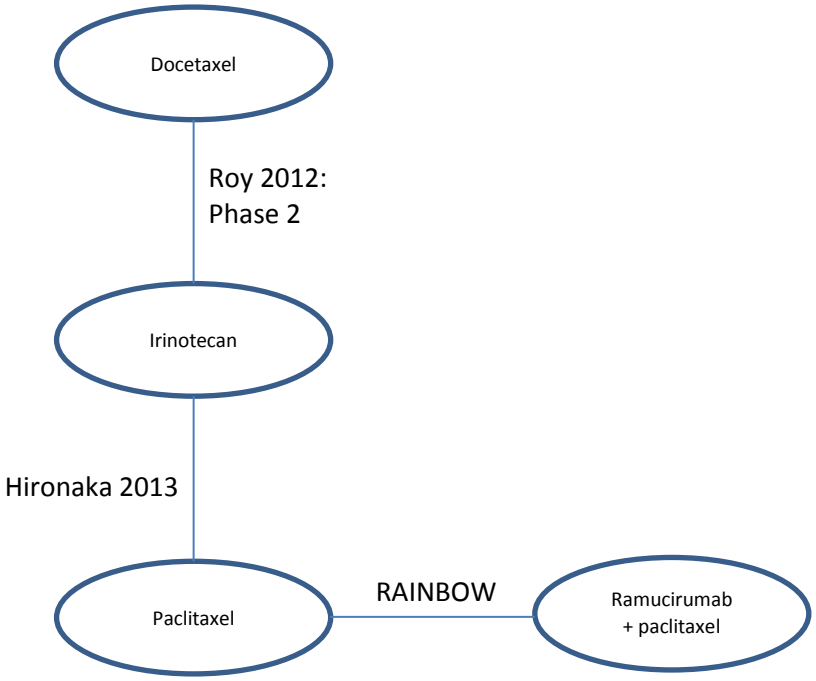


Table 46 Indirect comparisons for PFS. Comparisons of experimental (treatment A) vs. control arm (treatment B), HR (95% CI)

Treatment A	Treatment B	
	DOC	PAC
PAC	1.10 (0.75, 1.63)	
RAM+PAC	0.70 (0.46, 1.07)	*0.64* *(0.54, 0.75)*

Statistically significant results are bold and italicised; grey cells represent direct evidence and white cells represent indirect comparisons.

Summary of PFS

RAM combination therapy versus comparators

- There was no significant difference in the hazard of progression or death for RAM+PAC compared with DOC (refer to Table 46), however, the point estimate of the HR was less than 1.
- RAM+PAC was associated with statistically significant lower hazard of progression or death compared with PAC.

The summary measures of effect from the pair-wise meta-analysis and indirect comparisons (HR [95% CI]) are consistent with those from the base case NMA (HR [95% CrI]) presented in Appendix 6.

Treatment withdrawals due to AEs

The published data for treatment withdrawals due to AEs and evidence network are presented in Table 47 and Figure 28. The direct and indirect comparisons are presented in Table 48.

Table 47 Withdrawals due to AEs data

Study	Treatment arms	N	Discontinuation due to AE/unacceptable toxicity, n (%)	OR (95% CI)
COUGAR-02 (2)	DOC, 75 mg/m^2/3 weeks for up to 6 cycles + active symptom control until progression	84	20 (23.8)	53.81 (3.19, 906.64)
	Active symptom control	84	0† (0.0)	control
RAINBOW (6)	RAM, 8 mg/kg/2 weeks, until progression + PAC 80 mg/m^2 3 times every 4 weeks	330	39 (11.8)	1.05 (0.65, 1.68)
	PBO + PAC 80 mg/m^2 3 times every 4 weeks	335	38 (11.3)	control
Hironaka 2013 (111)	IRI, 150 mg/m^2 2 times ever 4 weeks, until progression	111	10 (9.0)	1.68 (0.59, 4.80)
	PAC , 80 mg/m^2 3 times every 4 weeks, until progression	108	6 (5.6)	control
Roy 2013 (110)	IRI, 300 mg/m^2/3 weeks, until progression	44	6‡ (13.6)	1.00 (0.30, 3.38)
	DOC, 75 mg/m^2/3 weeks, until progression	44	6‡ (13.6)	control

Abbreviations: NA= not applicable; NR= not reported; OR= odds ratio
†If there are no events in either the treatment or control arms, the application of a continuity correction has been applied. This approach adds 0.5 to each cell of the 2X2 table.

Figure 28 Evidence network for withdrawals due to adverse events (AEs)

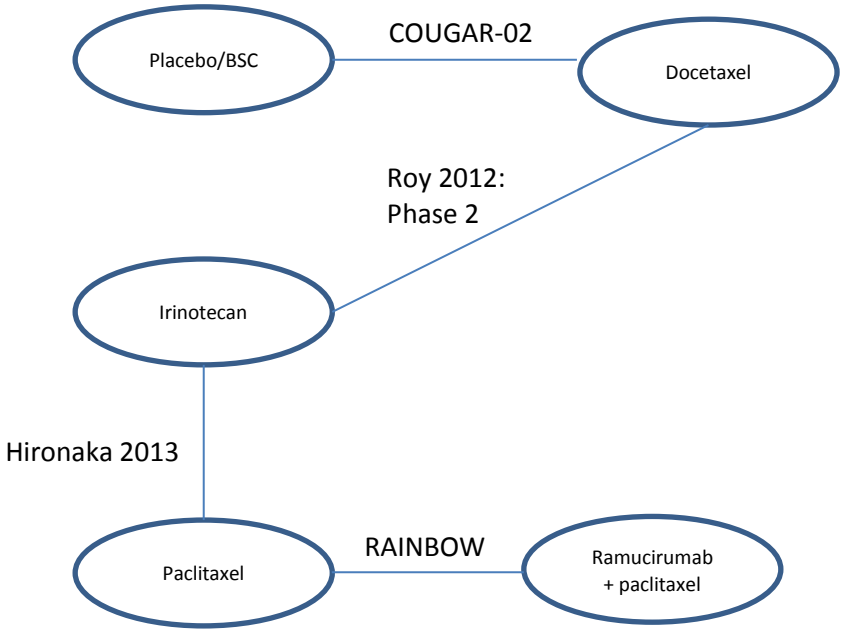


Table 48 Withdrawals due to AEs. Comparisons of experimental (treatment A) vs. control arm (treatment B), OR (95% CI)

Treatment A	Treatment B		
	PBO/BSC	DOC	PAC
DOC	*53.81* *(3.19, 906.64)*		
PAC	*31.97* *(1.24, 824.12)*	0.59 (0.12, 2.96)	
RAM+PAC	*33.49* *(1.26, 893.60)*	0.62 (0.12, 3.33)	1.05 (0.65, 1.68)

Abbreviations: AEs= adverse events; CI= confidence interval; OR= odds ratio
Statistically significant results are bold and italicised; grey cells represent direct evidence and white cells represent indirect comparisons.
† This estimate was obtained by fixed effect pair-wise meta-analysis.

Summary of withdrawals due to AEs

RAM combination therapy versus PBO/BSC

- RAM+PAC was associated with statistically significant higher odds of withdrawals due to AEs compared with PBO/BSC.

RAM combination therapy versus comparators

- There were no significant differences in withdrawals due to AEs for RAM+PAC compared with DOC and PAC

Additional analyses of outcomes such as the incidence of grade 3 or 4 anaemia, neutropenia, and febrile neutropenia can be found in Appendix 6.

Data considerations

Quality assessment

Although all studies were randomised and controlled, the absence of double-blinding in the majority of the included studies may be considered a limitation, leading to potential selection bias.

Size of the evidence networks

The size of the outcome specific evidence networks may be considered relatively small for meta-analysis methods (2-9 studies). The networks contained no closed loops and data from single studies were available for all but one of the direct comparisons within the networks. Consistency of the network could not be assessed because the networks contained no closed loops; that is, there was not direct and indirect evidence available for single comparisons. One of the studies included in the network enrolled a comparatively small number of patients: Thuss-Patience 2011 (n=40) (4). This compares with a minimum of 130 patients in the remaining studies included in the network. A discussion of Thuss-Patience 2011 (4) is presented further on in this section.

Heterogeneity

There were several sources of heterogeneity which were identified across the studies included in the analyses. Briefly these include:

- Site of primary disease (gastric or GOJ)
- Disease stage/PS
- Criteria/schedule used for tumour assessment
- Previous chemotherapy
- Treatment duration
- Patient cross-over
- Differential dosing of IRI across studies
- Lower dosing of DOC monotherapy in Asian studies compared with non-Asian studies
- Third-line chemotherapy administered post protocol
- Inconsistent reporting of safety outcomes across study publications

- The country where the study was conducted may be of importance as prognosis may vary across territories. For example, data show that tumour biology differs between white and Asian populations (20,113). In addition, diagnostic and treatment practices vary among East Asian countries and other regions of the world due to differences in incidence. Studies included in the network were conducted across the following territories:
  - Japan (n=1) (114)
  - Germany (n=1) (4)
  - UK (n=1) (2)
  - Multinational (n=3) (6,7,111). Percentage of patients enrolled from Asian countries:
    - Roy 2013, 46% (n=62: Taiwan and South Korea) (110)
    - RAINBOW, 34% (n=223: Hong Kong, Japan, South Korea, Singapore, Taiwan) (7).

The evidence networks were too small (single studies for most treatment comparisons within the networks) to explore potential sources of heterogeneity as listed above or to employ

meta-regression to explore the effects of various covariates. However where feasible, subgroup analyses were performed in an attempt to explore a variety of patient subgroups.

The results of the report must be interpreted in consideration of the potential sources of heterogeneity identified and in the context of the following assumptions which have been validated with clinical opinion (internal Lilly clinical expert):

1. There is no interaction between treatment effects and primary disease site (gastric vs. GOJ).
2. There is no interaction between treatment effects and PS.
3. There is no interaction between treatment effects and the number of prior chemotherapy regimens.
4. There is no interaction between treatment effects and treatment duration.
5. ASC, BSC and BSC + PBO are considered equivalent treatments.
6. The dosing regimens of individual treatments across studies are equivalent.
7. There is no interaction between (second-line) treatment effects and post-protocol treatment regimens (e.g. subsequent chemotherapy following disease progression).

Levels of uncertainty

The evidence networks were analysed via a single pair-wise meta-analysis and a series of indirect comparisons. Note that indirect comparison estimates will increase in uncertainty with each additional link in the evidence network. Therefore a number of the treatment comparisons were associated with large confidence intervals representing uncertainty in the point estimates. In addition, large confidence intervals may also be observed when information on the given comparator(s) is obtained from small single studies, and/or those with low event data.

Survival analysis

Proportional hazards (PH) assumption

Survival data were analysed using HRs. The calculation of HRs from patient data is usually based on the PH assumption. The PH assumption means that if two treatment groups are considered in the model, even though the individual treatment hazards may vary over time, the hazard of the event for one group at any time point is proportional to the hazard in the other group. Further, the survival curves fitted to each treatment group have a similar shape.

In the current analysis we have made simplifying assumptions whereby treatment effects are assumed to be constant over time.

Thuss-Patience 2011

Thuss-Patience 2011 (4) creates the linkage for one of the comparisons within the evidence network. In the case of OS, a low HR is reported (0.48 [0.25, 0.92]) indicating IRI is associated with lower hazard of death compared with BSC. The low HR for this study has an impact on the indirect comparisons of the network. The study reported the lowest median survival for a BSC/PBO arm in the network (2.4 months) allowing for a larger treatment effect of IRI. Potential explanations for the low HR for OS reported in this study may be related to the small study size (N=40; it is the smallest study within the evidence network) or to the open-label design. The study was also the earliest of all studies included in the network (recruitment started in 2002) which may have limited detection of imbalances in patient characteristics.

4.11 Non-randomised and non-controlled evidence

No non-RCT evidence has been presented in this submission.

4.12 Adverse reactions

It is expected that the majority of ramucirumab use in clinical practice in England will be in combination with PAC. The safety profile of ramucirumab was assessed in the PBO-controlled pivotal Phase 3 trials, RAINBOW and REGARD and is discussed below. The NMA presented earlier provides safety comparisons to DOC and BSC, the relevant comparators for England. Overall, RAM was well tolerated as a single agent, and with manageable toxicities when used in combination with PAC.

RAINBOW reported higher rates of overall treatment emergent adverse events (TEAEs) than REGARD which is to be expected when a chemotherapy regimen contains a cytotoxic agent. PAC is associated with haematologic toxicities (such as neutropenia, anaemia, thrombocytopenia and leukopenia), and neurotoxicity (mainly peripheral neuropathy) (115). These toxicities were reported in higher rates in RAINBOW than REGARD. In general, TEAEs were consistent with those expected from the individual agents and GC patients.

Due to the anti-angiogenic mechanism of action of ramucirumab, a number of AEs were considered to be of special interest (AESI) including hypertension, bleeding/haemorrhagic events, arterial and venous thromboembolic events, and GI perforation.

RAINBOW

- Rates of TEAEs were similar between treatment arms with 99% of patients treated with RAM+PAC experiencing a TEAE and 98% of patients treated with PBO+PAC
- Neuropathy was more common in patients treated with RAM+PAC compared to PBO+PAC and was associated with a higher cumulative PAC dose
- Neutropenia and leukopenia were the most frequently reported haematological toxicities in both arms and occurred more frequently in the RAM+PAC arm
- The incidence of febrile neutropenia was low and similar between patients treated with RAM+PAC (3%) and PBO+PAC (2%)
- Hypertension occurred more frequently in the RAM+PAC (25%) arm than in the PBO+PAC (6%) arm although it was managed adequately with standard anti-hypertensive medication
- The frequency of deaths was similar between arms (78% for both). However deaths while on treatment or within 30 days of last dose were lower in the RAM+PAC arm (11%) than in the PBO+PAC arm (16%)
- The safety profile of RAM+PAC in the Region 1 population was similar to that seen in the ITT population

The overall rates of TEAEs were similar between arms (RAM+PAC 99% and PBO+PAC 98%). Grade ≥3 TEAEs (82% and 63%) and TEAEs leading to discontinuation of study drug (31% and 24%) were reported more frequently in the RAM+PAC arm than PBO+PAC. PAC was discontinued because of ≥1 TEAE by 28% of patients in the RAM+PAC arm and 23% in the PBO+PAC arm, whilst RAM/PBO was discontinued by 21% of patients in the RAM+PAC arm and 21% in the PBO+PAC arm.

Non-haematological toxicities included fatigue/asthenia, decreased appetite, abdominal pain and diarrhoea - all of which are easily managed and usually reversible (Table 49). Neuropathy was more common in the RAM+PAC arm (any grade: 46%) over the PBO+PAC arm (any grade: 37%). An analysis of the incidence of neuropathy 4-week interval (0-4 weeks, 4-8 weeks, 8-12 weeks, etc.) was performed to explore this further. This analysis showed that the incidence of neuropathy was mostly comparable between the two arms, when compared across an individual 4-week-interval (that is, 0-4 weeks). Therefore the higher incidence of neuropathy in the RAM+PAC arm was likely related to the fact that, on

average, patients in the RAM+PAC arm remained on PAC treatment for a longer duration and received a higher cumulative dose of PAC compared to the PBO+PAC arm.

Neutropenia and leukopenia were the most frequently reported haematological toxicities in both arms and occurred more frequently in the RAM+PAC arm (Table 49). As treatment with PAC is often associated with neutropenia, the higher incidence in the RAM+PAC arm could be associated with a higher cumulative dose of PAC. However, the incidence of febrile neutropenia was low and similar in the groups (RAM+PAC 3%, PBO+PAC 2%).

Bleeding was the most frequent AESI and was reported more in the RAM+PAC arm (any grade: RAM+PAC 42%, PBO+PAC 18%) (Table 49). Epistaxis (nose bleed) was the underlying cause of 75% of these events while GI bleeding accounted for the other 25%. The incidence of grade ≥3 bleeding events was low. Additionally, proteinuria (17% and 6%) and hypertension (25% and 6%) occurred more frequently in the RAM+PAC arm than in the PBO+PAC arm. Hypertension was managed adequately with standard anti-hypertensive medication. There were no reports of grade ≥4 hypertension.

Hospitalisations due to an AE were slightly higher for the RAM+PAC arm (38%) than the PBO+PAC arm (32%). Anti-hypertensive medications were used more frequently in the RAM+PAC arm (55%) than PBO+PAC (38%). Transfusion rates were slightly less in RAM+PAC (18%) than PBO+PAC (20%).

Overall, the frequency of deaths was similar between arms (78% for both) however deaths while on treatment or within 30 days of last dose were lower in the RAM+PAC arm (11%) than in the PBO+PAC arm (16%). The subgroup analyses of AEs found no relevant differences between age groups (<65 years and ≥65 years) or between males and females.

Table 49 RAINBOW: Most Frequent MedDRA® TEAEs and AESI (Safety population)

Event	RAM+PAC N=327 n (%)				PBO+PAC N=329 n (%)			
Grades	**1-2**	**3**	**4**	**5**	**1-2**	**3**	**4**	**5**
Nonhaematological TEAE								
Fatigue[a]	147 (3945)	39 (12)	0	0	126 (38)	18 (5)	0	0
Neuropathy[a]	123 (38)	27 (8)	0	0	104 (32)	15 (5)	0	0
Decreased appetite	121 (37)	10 (3)	0	0	92 (28)	13 (4)	0	0
Epistaxis	100 (31)	0	0	0	23 (7)	0	0	0
Abdominal pain[a]	98 (30)	20 (6)	0	0	87 (26)	10 (3)	1 (<1)	0
Diarrhoea	94 (29)	12 (4)	0	0	71 (22)	4 (1)	1 (<1)	0
Hypertension	32 (10)	46 (14)	0	0	8 (2)	8 (2)	0	0
Haematological TEAE								
Neutropenia[a]	45 (14)	71 (22)	62 (19)	0	40 (12)	51 (16)	11 (3)	0
Anaemia[a]	84 (26)	30 (9)	0	0	85 (26)	31 (9)	3 (<1)	0
Leukopenia[a]	54 (17)	52 (16)	5 (2)	0	47 (14)	19 (6)	3 (<1)	0
Thrombocytopenia[a]	38 (12)	5 (2)	0	0	14 (4)	6 (2)	0	0
AESI								
Bleeding/haemorrhage[a]	123 (38)	12 (4)	1 (<1)	1 (<1)	51 (16)	4 (1)	2 (<1)	2 (<1)
GI haemorrhage	21 (6)	10 (3)	1 (<1)	1 (<1)	15 (5)	3 (<1)	1 (<1)	1 (<1)
Proteinuria	51 (16)	4 (1)	0	0	20 (6)	0	0	0
Liver failure/injury	39 (12)	12 (4)	3 (<1)	0	28 (9)	11 (3)	2 (<1)	0
Hypertension	34 (10)	48 (15)	0	0	10 (3)	9 (3)	0	0

[a] Consolidated adverse event category comprising synonymous MEdDRA® preferred terms.

RAINBOW Region 1 Safety Population

Overall the safety profile of RAM+PAC in the Region 1 population was similar to that seen in the ITT population. The rate of reported TEAEs was similar for both arms (RAM+PAC 99% and PBO+PAC 97%). Fatigue was the most common non-haematological toxicity and was reported more frequently in the RAM+PAC arm than PBO+PAC (any grade: 65% and 49%). Neuropathy was also reported more frequently in the RAM+PAC arm than PBO+PAC (any grade: 38% and 30%), although the rates overall were less than the ITT population. Haematological toxicities (neutropenia and leukopenia) were reported less frequently in the RAINBOW 1 population than the ITT population (TEAE table in Appendix 7).

For AESI, bleeding was more frequently reported in the RAM+PAC arm than PBO+PAC (any grade: 37% and 14%) and epitaxis accounted for the majority of events. Hypertension (any

grade: 29% and 14%) and proteinuria (12% and 6%) occurred more frequently in the RAM+PAC arm than PBO+PAC.(AESI table in Appendix 7).

REGARD

- The frequency of TEAEs were slightly higher in the RAM arm (94%) compared to PBO (88%), however rates of serious AEs were similar (57% and 58%) between the two treatment groups
- The frequency of death was lower in the RAM arm (75%) compared to PBO (85%) as well as deaths while on treatment or with 30 days of last dose
- Haematological toxicities, such as neutropenia, leukopenia and thrombocytopenia, were reported in <5% of patients in both arms
- Hypertension occurred more frequently in the RAM arm (16%) than in the PBO arm (8%) although it was managed adequately with standard anti-hypertensive medication
- The frequency of venous thromboembolism (VTE) events was lower in the RAM (4%) compared to PBO (7%)

Slightly more patients in the RAM arm experienced a TEAE over PBO (94% and 88%) however rates of serious and Grade ≥3 were similar (57% and 58%). Overall there were fewer deaths in the RAM arm than PBO (75% and 85%), as well as deaths while on treatment or within 30 days of last dose (20% in the RAM arm and 26% in PBO). Discontinuation of study drug due to TEAEs was 10.5% in the RAM arm and 6.0% in the PBO arm.

The most frequently reported TEAEs in REGARD were non-haematological. Fatigue was the most common and was reported at a slightly higher rate in PBO (any grade: RAM 36%, PBO 40%). RAM was not associated with increased rates of decreased appetite, vomiting and abdominal pain (Table 50).

Haematological toxicities, such as neutropenia, leukopenia and thrombocytopenia, were reported in <5% of patients in both arms in REGARD. Anaemia was reported at similar rates (any grade: 15% both arms).

Of the AESI, RAM was not associated with increased rates over PBO of any grade bleeding (13% and 11%), venous thromboembolism (4% and 7%), proteinuria (3% for both), GI perforation (<1% for both), fistula formation (<1% for both) or IRRs (<1% and 2%).

Hypertension (16% and 8%) and arterial thromboembolism (2% and 0) were more common in RAM than PBO.

Supportive care was similar between the RAM arm and PBO arm – hospitalisations due to an AE (34% and 38%), transfusions (11% and 9%) and anti-hypertensive use (43% and 40%).

The subgroup analyses of adverse events found no relevant differences between age groups (<65 years and ≥65 years), males and females, geographic region or race.

Table 50 REGARD: Frequently Reported TEAEs

Event	RAM (N=236) n (%)		PBO (N=115) n (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Non-haematological				
Fatigue*	84 (36)	15 (6)	46 (40)	11 (10)
Decreased appetite	57 (24)	8 (3)	26 (23)	4 (3)
Vomiting	47 (20)	6 (3)	29 (25)	5 (4)
Abdominal pain*	68 (29)	14 (6)	32 (28)	3 (3)
Haematological				
Anaemia	35 (15)	15 (6)	17 (15)	9 (8)
AESI				
Hypertension	38 (16)	18 (8)	9 (8)	3 (3)
Bleeding/haemorrhage[a]	30 (13)	8 (3)	13 (11)	3 (3)
Arterial thromboembolism	4 (2)	3 (1)	0	0
Venous thromboembolism	9 (4)	3 (1)	8 (7)	5 (4)
Proteinuria	7 (3)	1 (<1)	3 (3)	0
GI perforation	2 (<1)	2 (<1)	1 (<1)	1 (<1)

[a]Consolidated adverse event category comprising synonymous MEdDRA preferred terms.

4.13 Interpretation of clinical effectiveness and safety evidence

RAINBOW and REGARD trials

RAINBOW and REGARD were two double-blind, placebo-controlled, multi-centre phase 3 trials designed for unbiased assessment of the efficacy of ramucirumab. RAINBOW and REGARD are the largest trials of second-line treatment for GC/GOJ and contribute greatly to the limited but growing body of evidence of the potential survival benefits that second-line therapy can offer to patients with a rare cancer such as GC/GOJ. The trials jointly included a total of over 1000 patients, providing the most robust clinical evidence in this setting in comparison to existing data.

The aims of treatment in this aggressive cancer are to delay progression, prolong survival and control symptoms with minimal adverse effects and detriment in QoL. Both trials demonstrated that ramucirumab could help address these aims. RAINBOW and REGARD met their primary endpoints and demonstrated that RAM+PAC, or RAM as a single agent, confers a survival benefit with no detriment to QoL for patients with advanced GC/GOJ who have progressed following prior chemotherapy. This fulfils the aim of treatment in this palliative setting and is relevant to clinical practice in England.

Survival outcomes

Survival was evaluated in RAINBOW and REGARD using OS and PFS. As combination therapy, RAM+PAC increased median OS by 30.8% (2.3 months) in RAINBOW compared to PBO+PAC. When considering the patient group with characteristics most similar to and representative of patients in England (Region 1), the increase in median OS survival was even greater at 45% (2.7 months) with RAM+PAC compared to PBO+PAC.

Clinically relevant improvements in PFS were also observed with RAM+PAC, increasing median PFS by 54% (1.54 months) in the ITT population and by 50% (1.41 months) in Region 1. PFS gains were observed alongside an improvement or maintenance in QoL, demonstrating how meaningful these gains are in improving patient outcomes.

Additional comparisons were conducted through the NMA to allow for the clinical and economic comparison of RAM+PAC with the two most commonly used treatments in UK clinical practice; BSC and DOC. RAM+PAC was associated with a statistically significant lower hazard of death compared with BSC (HR: 0.34, 95% CI: 0.17, 0.71), and with a numerically lower hazard of death compared to docetaxel (HR: 0.51, 95% CI: 0.23, 1.13). In terms of PFS, there was also a numerically lower hazard of progression or death for RAM+PAC compared to docetaxel (HR: 0.70, 95% CI: 0.46, 1.07).

As a monotherapy, the survival benefit seen with RAM was also meaningful with a 36.8% (1.4 month) increase in median OS with RAM in comparison to PBO. The relative gain in PFS was 62% (0.8 months) for patients treated with RAM with a median PFS of 2.1 months.

In the real-world setting, these outcomes represent a meaningful and relevant clinical benefit to GC/GOJ patients who face a very poor prognosis with no previously licensed treatment options. Improving not only their overall survival but also their survival in a progression-free state is paramount to these patients that experience a disproportionally high tumour burden and loss of QoL. Both trials met their primary OS and secondary PFS/TTP endpoints resulting in significant reductions in the risk of death and disease progression. Furthermore, PFS gains were not achieved at the expense of QoL meaning patients are able to spend more time in a good state of health. The size of the OS benefit observed in each trial should be viewed in the context of the very limited current survival profile of these patients.

Adverse event outcomes

Currently few patients receive second-line chemotherapy in clinical practice, most likely because the risk/benefit profile of the unlicensed therapeutic options is not compelling enough to persuade patients to receive one (100,116). The safety of ramucirumab was evaluated for combination use with PAC in RAINBOW, and for monotherapy use in REGARD. Both trials demonstrated that ramucirumab was well tolerated by patients and the side effects were manageable and not treatment limiting.

The most frequent non-haematological TEAEs in both trials were fatigue/asthenia, decreased appetite, and diarrhoea, all of which are easily managed and usually reversible. PAC is associated with neuropathy and haematological toxicities e.g. neutropenia, leukopenia thus these occurred at higher rates in RAINBOW than REGARD. Ramucirumab was associated with higher rates of hypertension in both trials; however these were managed with standard anti-hypertensive medications. Bleeding occurred more frequently in the RAM+PAC arm in RAINBOW however the majority of events were epistaxis and the incidence of severe bleeding was low. Bleeding occurred at a similar rate for RAM and PBO in REGARD.

The frequency of deaths while on treatment or within 30 days of last dose were lower in the ramucirumab arm in both RAINBOW and REGARD. In RAINBOW, a similar percentage of patients in both study arms discontinued treatment due to AEs (11.8% RAM+PAC and 11.3% PBO+PAC). In REGARD these figures were 11.3% (RAM) and 6.1% (PBO). The NMA found no significant differences in withdrawals due to AEs for RAM+PAC compared with DOC. A comparison for RAM+PAC versus BSC was not feasible in the network.

QoL Outcomes

The assessment of QoL is challenging for patients with GC/GOJ due to the rapid progression and rare nature of the disease. QoL data for ramucirumab was evaluated using the EORTC QLQ-C30 and EQ-5D in RAINBOW and the EORTC QLQ-C30 in REGARD. The EORTC is a valid and reliable general cancer scale and has been used previously in advanced GC trials (117). Patient compliance with completing both questionnaires was high and over 80% at the early assessment times. Compliance in completing the questionnaires decreased throughout the course of the trials. This was to be expected as patients experience disease progression and discontinue study treatment. However, this decrease in compliance was more marked in the PBO+PAC or PBO arms compared to the RAM+PAC or RAM arms at all time-points following baseline.

A higher percentage of patients in the RAM+PAC arm, at all-time points from six weeks onwards, and on all QoL scales, were classified as improved or stable compared to the PBO+PAC arm in RAINBOW. In an analysis of time to deterioration of EORTC in RAINBOW, RAM+PAC was favoured on 14 of the 15 symptom scales including a statistically significant improvement in emotional functioning and nausea and vomiting. From this it is evident that QoL was improved or maintained alongside the observed extension in PFS. The results of the EQ-5D analysis showed similar index scores across the two arms with a small decrease from baseline while on treatment.

In REGARD, the proportion of patients with improved or stable QoL was higher for the RAM arm (34.1%) than the PBO arm (13.7%) at 6 weeks and 18 weeks (RAM: 11.8%; PBO: 2.6%). The improvement or maintenance in QoL demonstrated in both trials provides further evidence to support the benefits of ramucirumab in this patient group.

End of life criteria

Ramucirumab as a monotherapy fulfils two of the three criteria specified in NICE's 'Supplementary Advice for Appraising life-extending, end of life treatments' (criterion 1 and 3). RAM+PAC for the second-line treatment of adult patients with advanced GC/GOJ fulfils all three criteria specified in the supplementary advice from NICE. Please see below for a detailed explanation of how these criteria are met.

Criterion 1: The treatment is indicated for patients with a short life expectancy, normally less than 24 months

The prognosis for patients with advanced GC/GOJ who have progressed following first-line therapy is very poor. In the absence of both a licensed treatment (prior to ramucirumab) and a national algorithm in the second-line treatment setting, wide variations in clinical practice exist, with BSC being the most commonly used treatment. Median OS has ranged from 2.4 to 3.8 months for BSC in phase 3 clinical trials (2-4) indicating a life expectancy of less than 4 months in this population.

Criterion 2: 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 modelled OS shows that RAM+PAC increases mean OS by 5.76 months versus the most widely used treatment, BSC.

Table 51 Mean OS for RAM+PAC versus BSC (combination therapy economic model)

Intervention	Life years	Months
BSC	0.45	5.4
RAM+PAC	0.94	11.28
Incremental	0.48	5.76

Note: Numbers may not compute due to rounding.

For the minority of patients who receive an active treatment, DOC was the most commonly used at 8% (5). RAM+PAC increases OS by 4.13 months versus DOC.

Table 52 Mean OS for RAM+PAC versus DOC (combination therapy economic model)

Intervention	Life years	Months
DOC	0.59	7.08
RAM+PAC	0.94	11.28
Incremental	0.34	4.13

Note: Numbers may not compute due to rounding

RAM+PAC offers a clinically meaningful increase in patients' survival prognosis, increasing their overall survival by almost 6 months compared to the most commonly used NHS treatment.

For the monotherapy indication, RAM is shown to increase OS by 1.92 months versus the current NHS treatment for these patients, BSC.

Table 53 Mean OS for RAM versus BSC (monotherapy economic model)

Intervention	Life years	Months
BSC	0.49	5.88
RAM	0.66	7.92
Incremental	0.16	1.92

Note: Numbers may not compute due to rounding.

Criterion 3: The treatment is licensed or otherwise indicated for small patient populations

Ramucirumab has been designated orphan status by the EMA. The EMA states GC affects not more than 3 in 10,000 people in the European Union which is well below the ceiling for orphan designation of 5 in 10,000 (17) indicating that this treatment is licensed for small patient populations. An estimated 657 patients diagnosed with advanced GC/GOJ would be eligible for second-line treatment following first-line chemotherapy.

Table 54 Annual GC/GOJ patient numbers and second-line eligibility

Description	% patients	Number	References
Patients with gastro-oesophageal junction cancer (ICD 10 Code 15.2, 15.5*)	-	3413 (calculated)	ONS Cancer Registration statistics 2012 adjusted to 2015
Patients with stomach (gastric) cancer (ICD 10 Code 16*)	-	4857 (calculated)	ONS Cancer Registration statistics 2012 adjusted to 2015
Total patients with GC/GOJ	-	8270 (calculated))	ONS Cancer Registration statistics 2012 adjusted to 2015
Patients with advanced/metastatic disease	80% (reported)	6616 (calculated)	Cancer Research UK, 2014 (54)
Patients receiving oncology treatment	43% (reported)	2845 (calculated)	National Oesophago-Gastric Cancer Audit 2013
Patients receiving chemotherapy	77% (reported)	2191 (calculated)	National Oesophago-Gastric Cancer Audit 2013
Patients eligible for second-line chemotherapy	30%	657 (calculated)	Clinical expert opinion, validated by Chart Review

*source for ICD 10 Code was Report October 2009 Epidemiology OG Cancers (118); Number may not compute due to rounding

Table 55 End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS has ranged from 2.4 to 3.8 months for BSC in phase 3 clinical trials) (2-4).
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	RAM+PAC versus BSC; incremental mean OS = 5.76 months RAM+PAC versus DOC; incremental mean OS = 4.2 months
The treatment is licensed or otherwise indicated for small patient populations	The patient population estimated to be eligible for treatment with previously treated, advanced GC is 657.

Therefore, RAM+PAC combination therapy meets all three criteria specified by NICE for appraising life-extending, end of life treatments and should be considered within this context.

4.14 Ongoing studies

There are no additional studies involving ramucirumab in advanced, previously-treated GC/GOJ expected to report in the next 12 months.

5 Cost-effectiveness

Ramucirumab is indicated for the second-line treatment of advanced GC/GOJ both in combination with PAC and as a monotherapy. Two separate CEA were carried out to address the decision problem for this appraisal. Full details of how these analyses were conducted and the results are provided in this section.

5.1 Published cost-effectiveness studies

Identification of studies

A literature review was conducted to identify any existing economic analyses in this area in order to address the decision problem and inform the economic model structure. The scope of this review was to review all available published data on economic evaluations of second-line treatment for GC/GOJ. Specifically this was to identify any economic and pharmacoeconomic studies for ramucirumab or comparator technologies. This search strategy was also used to identify any relevant sources to inform the resource requirements of the economic model.

The following databases were searched up to March 2014:

- Embase
- Ovid MEDLINE
- NHS Economic Evaluation Database (EED)

The eligibility criteria used in the search strategy are presented in Table 56. Search terms are presented in Appendix 8.

Table 56 Eligibility criteria used in economic search strategy

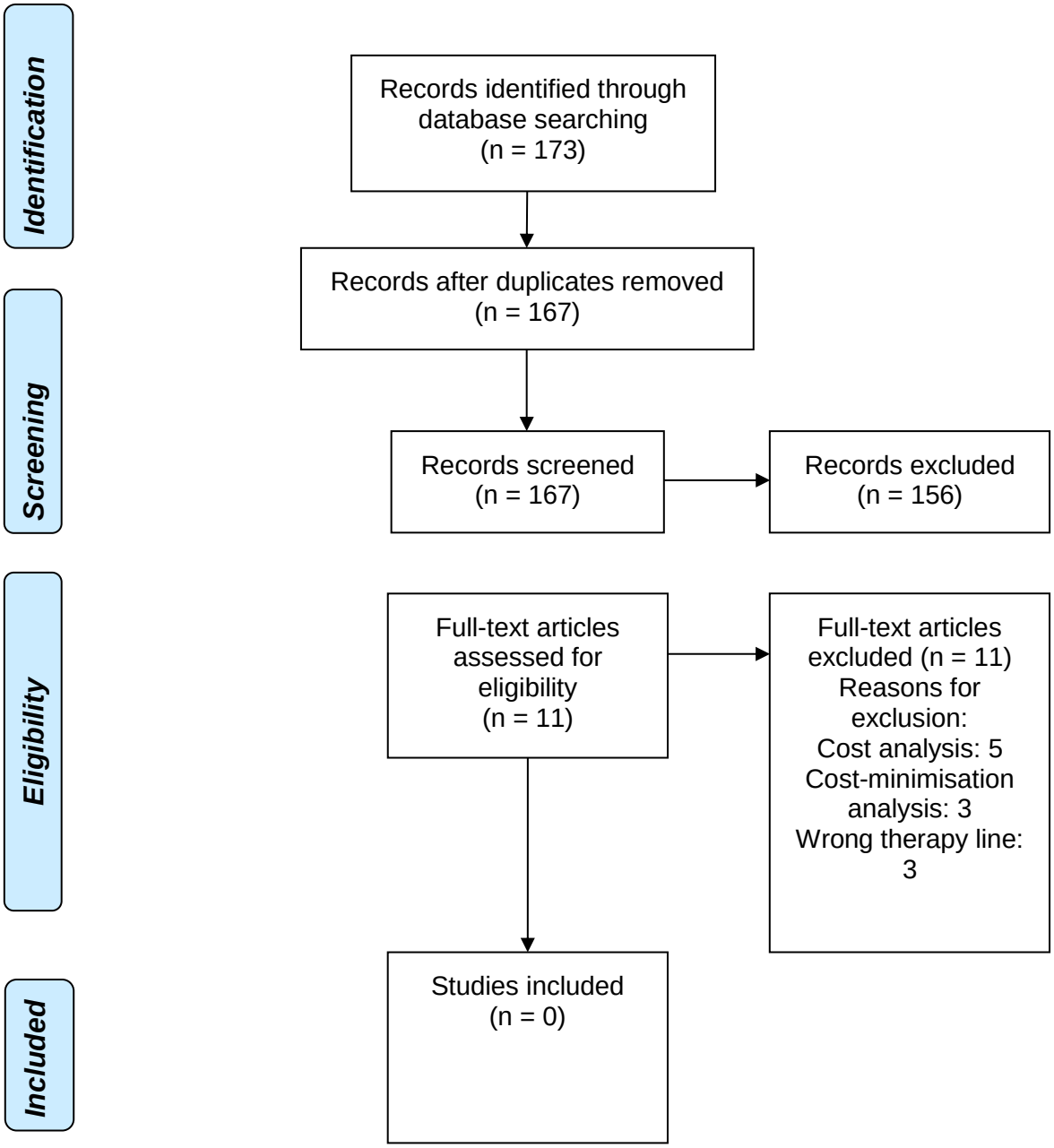
	INCLUSION	EXCLUSION
Population	Adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma being treated with second-line treatment	Paediatric patients; Early stage gastric cancer or gastro-oesophageal junction adenocarcinoma
Intervention	Any second-line treatment for gastric cancer or gastro-oesophageal junction adenocarcinoma: - Monotherapy - Combination therapy Other interventions that are considered standard care (e.g. BSC) in the patient population that will be relevant to the economic model	Patients receiving first-line treatment, treatment-naïve patients, or patients receiving third-line treatment or more
Comparator	No restrictions	
Outcomes	Economic models: - Cost-utility analyses - Cost-effectiveness analyses - Cost-benefit analyses	Cost-minimisation analyses
Study design	Economic models/Economic studies	Not an economic model
Language restrictions	English	

An additional targeted search of the NICE website and of the Centre for Reviews and Dissemination (CRD) database was conducted to identify any economic evaluations of GC/GOJ treatments. Again, the details of the search strategies can be found in Appendix 8.

Results

No economic analyses were found specific to the second-line setting. The PRISMA flow diagram in Figure 29 details the number of papers included and excluded at each stage of the review. There are no licensed therapies for previously-treated GC/GOJ other than ramucirumab (which received MA in December 2014). It is therefore unsurprising that there are no economic evaluations in the second-line setting on which to base these economic analyses. De-novo economic evaluations for ramucirumab in combination with PAC (hereafter 'RAM+PAC') and ramucirumab as a monotherapy (hereafter 'RAM') have been conducted.

Figure 29 PRISMA flow diagram for economic models in GC/GOJ



Two papers were identified in both searches (119,120), both of which explored a cost-utility analysis (CUA) of trastuzumab for the treatment of HER2-positive metastatic gastric cancer which was appraised by NICE (NICE Technology Appraisal [TA] 208) (15) (Table 57). The economic evaluation submitted to NICE for trastuzumab (15) was used to inform the approach to this evaluation where possible. The model developed for TA208 utilised a conventional partitioned survival (area under the curve) approach comprising three health states (pre-progression, post-progression, dead). A quality assessment of the economic model for trastuzumab can be found in Appendix 8.

Table 57 Published papers of the economic evaluation of trastuzumab used to inform the model structure

Author	Title	Journal	Further information
Shiroiwa 2011	Cost-effectiveness analysis of trastuzumab to treat HER2-positive advanced gastric cancer based on the randomised ToGA trial	British Journal of Cancer (2011) 105, 1273–1278	Adaptation of analysis presented for TA 208
Wu 2012	Costs of trastuzumab in combination with chemotherapy for HER2-positive advanced gastric or gastroesophageal junction cancer: an economic evaluation in the Chinese context	Clinical Therapeutics 2012; 34(2): 468-479	Adaptation of analysis presented for TA 208

5.2 De novo analysis

Patient population

The ramucirumab SPC (16) identifies two indications for ramucirumab for GC/GOJ: in combination with PAC and as a monotherapy. These two indications are informed by two pivotal, phase 3 trials (which have been described in detail in section 4) representing two different patient populations and will therefore be represented in two separate economic models. A simple overview of the two regimens of ramucirumab and the patient populations represented in the economic models is provided in Figure 30. Further detail is provided under the specific sections.

Figure 30 Overview of ramucirumab indications and economic models

Indication	Ramucirumab in combination with paclitaxel (RAM+PAC)	Ramucirumab monotherapy (RAM)
Economic model name	Combination therapy model	Monotherapy model
Dosing schedule	Ramucirumab 8mg/kg on day 1 & 15	Ramucirumab 8mg/kg every two weeks
	Paclitaxel 80mg/m^2 on day 1, 8 & 15 of a 28 day cycle	
Model patient population	Adult patients with metastatic or locally advanced GC/GOJ, of PS 0-1, who have experienced disease progression on/after first-line	
	Platinum- and fluoropyrimidine-containing therapy	Platinum- or fluoropyrimidine-containing therapy, for whom treatment in combination with paclitaxel is not appropriate
Ramucirumab clinical trial evidence	RAINBOW trial (Wilke, 2014)	REGARD trial (Fuchs, 2013)

Combination therapy patient population

The patient population included in the combination therapy economic model is in keeping with the licence for RAM+PAC: RAM+PAC is indicated for patients with metastatic or locally advanced GC/GOJ that experience disease progression after prior platinum and fluoropyrimidine chemotherapy.

The patient population in the economic evaluation is aligned with the patient population defined in the decision problem for this technology appraisal, and it is aligned with the RAINBOW trial. It is identical to the eligibility criteria for the RAINBOW trial. The primary analysis is presented for the ITT population from the RAINBOW trial with a scenario analysis for Region 1 (North America, Europe, Australia and Israel). This is due to previously identified differences in treatment patterns and patient prognosis between Asian and non-Asian countries (19,21).

Monotherapy patient population

The monotherapy model patient population comprises patients with metastatic or locally advanced GC/GOJ, who have experienced disease progression after prior platinum- or fluoropyrimidine chemotherapy[3]. The analysis is based on the ITT population of the REGARD trial.

The licensed indication for RAM specifies its use in patients for whom treatment in combination with PAC is not appropriate. As discussed under Section 3 (Ramucirumab in clinical practice) this population may be characterised as those patients who are experiencing lingering toxicities from first-line treatment, or do not wish to receive further cytotoxic chemotherapy for reasons of patient/physician preference.

The patient population in the REGARD trial deviates slightly from that the final licence wording as patients in the REGARD trial did not have to be unsuitable for treatment in combination with paclitaxel (or more broadly, cytotoxic chemotherapy) upon entry into the trial. In reality, when the REGARD trial was initiated, no therapeutic options had been shown to improve overall survival in this setting (104). As treatment practice has moved on and RAM+PAC has shown to be a compelling treatment option for patients for whom treatment in combination with PAC is appropriate, the EMA concluded that RAM is a useful monotherapy option in this second-line setting, when chemotherapy in combination with ramucirumab is not the preferred option (17).

The patient population in the monotherapy economic model is aligned with the licensed indication for RAM. The decision problem in the final scope specifies the population for the appraisal as simply ‘adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy’. The appraisal remit is to assess ramucirumab within its MA and therefore the patient population in the economic model is aligned with the decision problem.

Model structure

De novo model structure

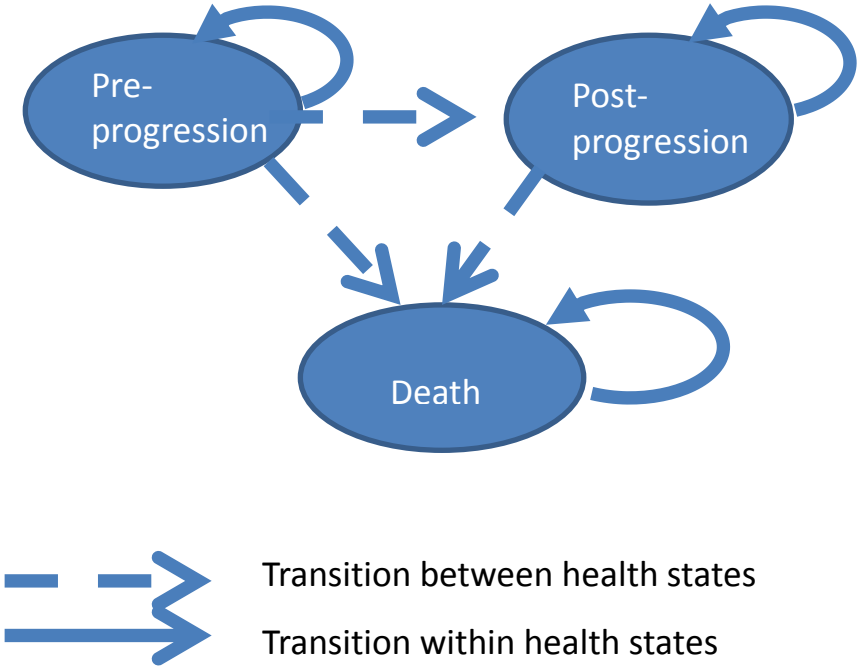
The same model structure was chosen for both the combination and monotherapy economic models. An overview of the economic model structure, its health states and how patients transition through the model is provided. Each of the health states are described in more detail, providing specific details of how the health states relate to English clinical practice and to the costs and utilities accrued by patients with advanced GC/GOJ.

A partitioned survival (area under the curve) model was chosen to conduct the economic evaluation of RAM+PAC and RAM. This methodology is analogous to a Markov transition model in that costs and benefits are estimated at fixed time points based on the proportion of the cohort in

[3] In the trial 84.0% of RAM patients and 75.2% of PBO patients received both fluoropyrimidine and platinum

each of the three health states at a given time. Patients move through the models based on transition probabilities which are estimated from the data provided by the pivotal clinical trials and by the indirect treatment comparison for the non-trial comparators.

Figure 31 Model schematic for monotherapy and combination therapy economic models



This is a common model structure employed for advanced, terminal cancer as it accurately captures the progression of patients from the initiation of treatment to death (Figure 31). It was used in previous appraisals for other tumour types (i.e. lung – NICE TA309 (14)) and first-line gastric cancer (TA208) (15).

Clinical pathway of care

The model was designed to represent the treatment pathway in England for patients with previously-treated advanced GC/GOJ as it is described in section 3.3. A brief outline of the overall treatment pathway and how it is implemented in the model is provided below.

First-line patient pathway

Patients with advanced GC/GOJ (i.e. unsuitable for curative treatment) may, if fit and willing, be offered chemotherapy to prolong survival and alleviate symptoms. As discussed in section 3.3, first-line treatment in England is most commonly characterised as a platinum/fluoropyrimidine base with an anthracycline (19). Patients in the RAINBOW and REGARD trials received first-line therapy as specified in the trial inclusion/exclusion criteria (fluoropyrimidine and platinum, fluoropyrimidine or platinum, respectively). First-line treatment is not included in the economic model as the decision problem relates only to the use of second-line therapies.

Many patients experience disease progression whilst on, or within months of completing their first-line treatment. If patients remain of a good PS, they may be a candidate for second-line treatment.

Second-line pathway

All patients enter the economic model at the point which represents the initiation of second-line treatment or BSC only. They enter in the pre-progression health state. Patients remain in this health state until they experience disease progression or death.

Patients who have progressed continue to receive supportive care for symptom alleviation in accordance with clinical practice. Third-line treatment with off-licence agents is included in the post-progression state for the minority of patients who receive it in UK clinical practice (12%) (121). Patients remain in this health state until death which is an absorbing health state. All patients receive terminal care before they pass into the death state.

Health States

The model is designed to capture all the relevant costs and benefits associated with the treatment strategies being evaluated. Costs and quality-adjusted life years QALYs are accrued by patients in the pre-progression and post-progression health states over time. A more detailed overview of the health states is provided below.

Pre-progression

All patients begin in the pre-progression health state. They either commence active treatment, or receive BSC only, depending on patient and physician choice. Patients remain in this health state whilst they have stable disease (SD) or partial response or complete response (PR/CR)[4]. They continue to receive active treatment until disease progression or treatment cessation for other reasons (for example adverse events).

[4] The radiological definition of SD, PR and CR is provided in detail in Table 32

Post-progression

After experiencing disease progression, patients move into the post-progression health state. In this health state they receive BSC, a small minority of patients receive a third-line treatment. Third-line therapy is included in the economic model only with respect to the cost of treatment, and all patients receive palliative care in the terminal setting. This is designed to represent what happens to patients once they have progressed, up until the point at which they pass into the death state.

The cost of terminal care is applied in the cycle prior to death, to reflect the increased resource burden associated with the final stages of the disease. Again this is consistent with the patient pathway.

Death

Death is the absorbing health state. Advanced GC/GOJ are very aggressive cancers and clinical trials for second-line GC/GOJ have reported a median OS of 4.0 to 5.3 months for chemotherapy and 2.4 to 3.8 months for BSC (2-4). The transition rates calculated from the OS Phase 3 trial data are believed to be representative of all-cause mortality for GC/GOJ patients, as the competing risk of a non-cancer death is assumed to be incredibly low in this patient group. Once patients have passed into the death state, no costs or benefits are applied. However, the model uses the time point at which death occurs to back calculate the costs associated with the terminal phase of the disease.

Cycle length & half cycle correction

The model utilises a weekly cycle length. Given the differing lengths of treatment regimens this was believed to be the appropriate length over which transitions are modelled and costs and benefits are accrued.

A half-cycle correction was applied to all calculations to reduce the potential for bias in the cost-effectiveness estimates, though this potential is believed to be very low given the weekly cycle length.

The features of the *de novo* analysis for the combination and monotherapy models are provided in Table 58.

Table 58 Features of the mono and combo therapy *de novo* analysis

Factor	Chosen values	Justification
Time horizon	Lifetime[5] *Equates to 7.23 years for both the combination and monotherapy model*	In an economic analysis of treatments for advanced oncology a lifetime horizon is required to capture all costs and benefits accruing to the intervention and comparators
Were health effects measured in QALYs; if not, what was used?	QALYs Life-years	NICE Reference Case (122)
Discount of 3.5% for utilities and costs	3.5% for costs and benefits	NICE Reference Case (122)
Perspective (NHS/PSS)	NHS/PSS	NICE Reference Case (122)

Abbreviations: NHS, national health service; PSS, personal social services

Intervention technology and comparators

In this section, the inclusion of the intervention technology – RAM+PAC and RAM - is described, including the use of treatment continuation rules. The rationale for the choice of comparators for the economic analyses is also outlined. As none of the comparators in the decision problem are licensed for second-line GC/GOJ, they cannot be implemented as per their MA. Instead the assumptions for their frequency and dosing are described and referenced to the appropriate supporting clinical trials.

Intervention – RAM+PAC

Ramucirumab should be administered on day 1 and 15 at 8mg/kg with PAC administered 80mg/m^2 on day 1, 8 and 15 of a 28-day cycle, as per the RAINBOW study. This is in keeping with the MA for RAM+PAC.

Intervention – RAM monotherapy

Ramucirumab is administered as a monotherapy every two weeks at 8mg/kg as per the REGARD study. This is in keeping with the MA for RAM as a monotherapy.

Treatment continuation rules

No treatment continuation rules are applied outside of the MA for ramucirumab. Ramucirumab is recommended to be continued until disease progression or until unacceptable toxicity has occurred (16).

[5] Corresponds to the point at which the per-cycle percentage change in the average cost-effectiveness ratio for all treatments has reached 0.01%

Comparators – RAM+PAC

The primary comparator for the economic analysis is:

- BSC

GC/GOJ is an orphan disease and there were no licensed therapies for second-line prior to the approval of ramucirumab in December 2014. The little published evidence available indicates the rates of second-line usage in the UK are low (19).

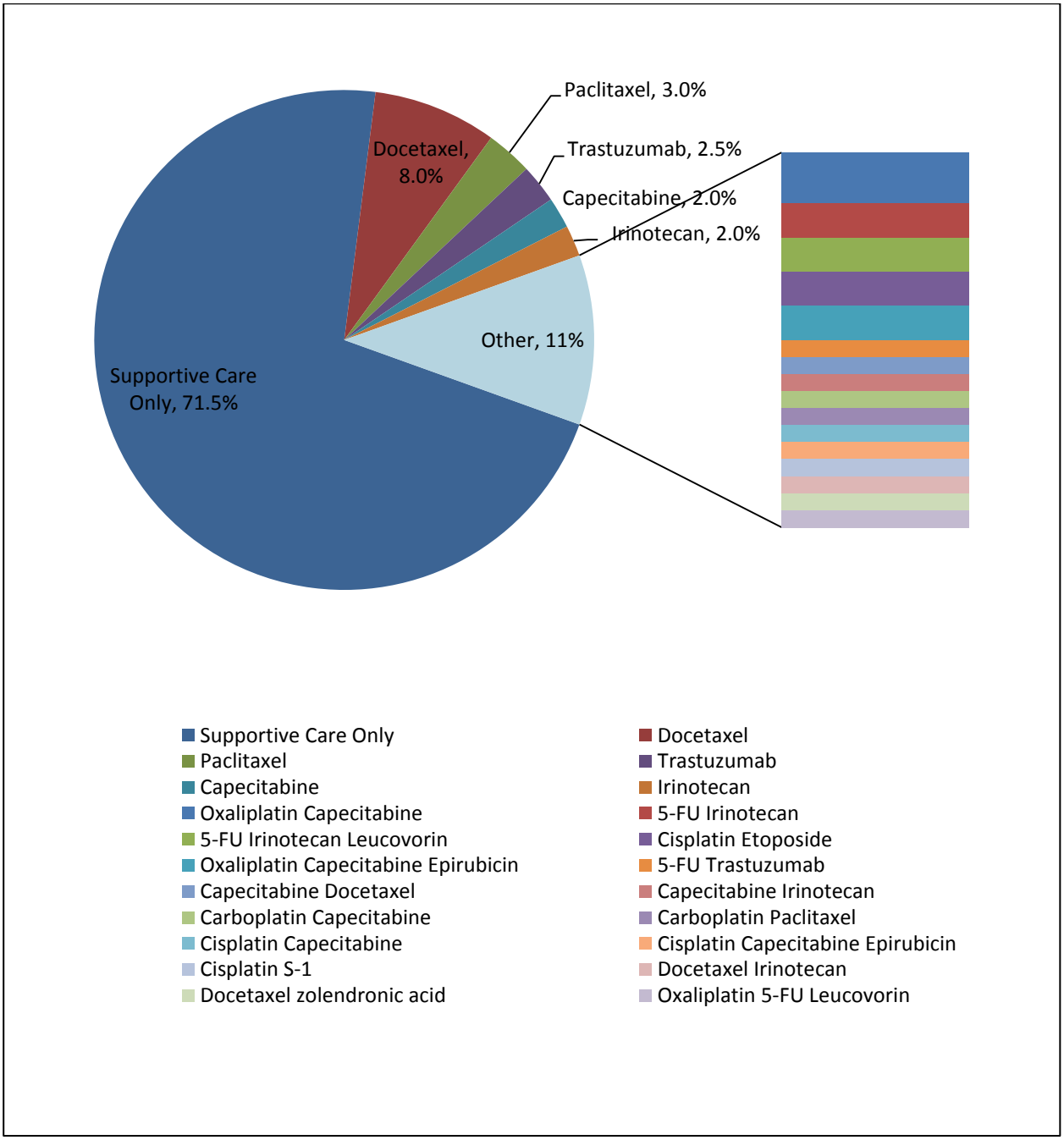
To understand the current treatment landscape better Lilly commissioned a chart review to explore real-world treatment patterns in previously-treated GC/GOJ. The study included sites across the UK though over 75% were in England. It is therefore broadly presumed to be representative of English clinical practice. The data were presented at the ASCO Gastrointestinal Cancer Symposium in 2015 (5). The chart review included 200 patients who had received a first-line chemotherapy treatment for advanced GC/GOJ. Only 28.5% of patients went on to receive an active second-line therapy after their first-line treatment. Of the 71.5% of patients who did not receive an active second-line therapy, 56% had an ECOG PS of 0 or 1 at discontinuation of first-line treatment. The chart review indicates that over 40% of all patients remain of good performance status at discontinuation of first-line treatment, but are currently not receiving active treatment (i.e. supportive care only). This confirmed that BSC is the most widely used treatment in current clinical practice and validates its inclusion as the primary comparator for the economic analysis.

Patient-level decisions about receiving second-line treatment are likely to be multi-factorial, depending on individual and clinician preferences and first-line treatment experience. The lack of a licensed, available treatment option, no clear standard of care and inequality in access to off-licence treatments, are likely to be the key reasons for eligible patients not receiving second-line treatment. The risk/benefit profile of the current treatments available may also inform current treatment decisions. RAM+PAC offers a clinically meaningful increase in survival prognosis compared to BSC and may be an appropriate treatment option for patients currently receiving BSC.

Additional comparators

The results in Figure 32 show wide variation in clinical practice with over 20 different single agent and combination regimens used in the second-line setting. Single agent DOC is the most commonly used treatment at 8%.

Figure 32 Second-line treatment practice in UK



Source: Liepa (5)

The NICE Methods Guides states specifically that the Appraisal Committee can consider as comparators technologies that do not have an MA (or CE mark for medical devices) for the indication defined in the scope when they are considered to be part of established clinical practice for the indication in the NHS (122). To this end, the inclusion criteria for additional comparators were:

- Treatment is outlined in the final scope
- Treatment is used routinely in the NHS in England (>10% usage)

These inclusion criteria have been employed in previous technology appraisals (15) and were verbally endorsed in the NICE/ABPI Masterclass “How to do a good NICE submission”. DOC is the only treatment which is used in anywhere near 10% of all patients. Despite it not meeting the inclusion criteria DOC was however included in the economic model for the following reason: COUGAR II (DOC versus active symptom control) (2) was a UK study and advice from clinical experts confirmed that it is important in shaping clinical practice moving forward.

PAC is included as a comparator only for validation of the clinical evidence in the economic model as it was the comparator in the RAINBOW trial. Evidence on treatment patterns in the UK indicate that PAC does not meet the standard inclusion criteria reasonably applied in determining established clinical practice in England.

IRI and FOLFIRI were listed in the final scope as potential appropriate comparators for RAM+PAC. They have not been included as comparators as their use is not sufficient to be considered established clinical practice in the NHS, as shown in Figure 32.

The definition for BSC, the primary comparator, is provided below. The dosing schedule for DOC is also shown.

Best Supportive Care

BSC definitions may differ slightly across clinical trial protocols but the universally accepted principle is that supportive care is provided to alleviate symptoms and maximise QoL for patients, without attempting to alter the natural history of the condition. It is therefore assumed not to have an impact on efficacy. The BSC-controlled trials included in the NMA (2,4) and the REGARD trial (7), where reported, provided similar definitions of BSC and therefore are assumed to be comparable and generalisable to English clinical practice. This comparability was validated by clinical expert opinion.

In the REGARD study patients received optimal supportive care measures, which may have included but were not limited to: antiemetic agents, opiate and non-opiate analgesic agents, appetite stimulants, and granulocyte-colony stimulating factors and erythroid growth factors. Other agents useful in controlling disease-related symptoms (for example, laxatives and antidepressants) were permitted unless specified as prohibited in the protocol.

In the COUGAR II study of DOC versus active symptom control (2), the protocol stated that active symptom control measures included any or all of the following: analgesics (including opioids), anti-emetics, steroids, palliative radiotherapy, and any other supportive measure deemed appropriate by the clinicians treating the patient.

To ensure that the inclusion of supportive care in the economic models is reflective of English clinical practice, the definition of BSC is based on the treatment pattern study (5). Specific details of what is included under BSC are outlined in Section 5.5 and Table 113.

Docetaxel

DOC is not licensed for second-line GC/GOJ. It is licensed for first-line gastric adenocarcinoma at a recommended dose of 75 mg/m^2 every 21 days in combination with cisplatin and 5-fluorouracil. (123).

The choice of dosing regimen for the economic model was based on the clinical trials of DOC included in the NMA (2,110). In these studies, DOC was administered at a dose of 75mg/m^2 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 (2). This was a UK-only study and its dosing regimen for DOC was confirmed to be reflective of clinical practice in England.

Paclitaxel

Given that PAC was the trial comparator for RAINBOW, but not widely used in clinical practice in England, it was included in the economic model for validation of the clinical evidence in the model only. The methods and results are therefore not reported for PAC in the following sections.

PAC is not licensed in advanced GC (except as RAM+PAC). It is licensed for breast cancer at a recommended dose of 260 mg/m2 every 3 weeks. It is also licensed for pancreatic adenocarcinoma in combination with gemcitabine at a recommended dose of 125 mg/m2 on days 1, 8 and 15 of each 28-day cycle (115).

An overview of the comparators and their dosing schedule is provided in Table 59.

Table 59 Comparators and Interventions for combination therapy

	Regimen	Dose	Source
Intervention	RAM	8mg/kg Day 1 & 14 of a 28-day cycle	Cyramza® SPC (16)
	PAC	80mg/m^2 Day 1, 8 & 15 of a 28-day cycle	
Comparators	BSC	No disease modifying treatment given	UK clinical practice (5)
	DOC	75mg/m^2 Day 1 of a 21-day cycle	Ford, 2014 (2)

Abbreviations: mg = milligrams; kg = kilograms

Comparators – RAM monotherapy

The licence for RAM specifies its use for patients in whom treatment in combination with *PAC is not appropriate*. The clinical rationale for this licensing restriction is based on the fact that the benefit of RAM+PAC is larger in terms of the size of the effect and therefore, for patients who can tolerate chemotherapy, RAM+PAC is the preferred treatment option. However, the benefit-risk balance for ramucirumab as a monotherapy was considered to be favourable, meaning it could still represent a useful therapeutic option for patients in the second-line setting when chemotherapy in combination with ramucirumab is not the preferred option (17).

Based on clinical rationale, patients whom the EMA refer to for which chemotherapy in combination with ramucirumab is not the preferred option are presumed to not currently be receiving active chemotherapy. The only appropriate comparator for this patient population is therefore BSC.

The final scope for this appraisal does not reflect this and only PAC is removed from the active comparator list for RAM as a monotherapy (i.e. DOC, IRI and FOLFIRI are still listed as comparators). However, in clinical practice, the licence for RAM is such that it is for use in a patient population who are currently receiving BSC, not a cytotoxic chemotherapy.

The definition of BSC is described above and its inclusion in the model is outlined in Section 5.5 and Table 113.

Table 60 Comparators and Interventions for monotherapy

	Regimen	Dose	Source
Intervention	RAM	8mg/kg Day 1 of a 14-day cycle	Cyramza® SPC (16)
Comparator	BSC	No disease modifying treatment given	UK clinical practice (5)

5.3 Clinical parameters and variables

The model partitions patients into the pre-progression, post-progression and death health states. The transitions between health states are determined by the clinical trial data and the outputs of the NMA (for the combination therapy model only). This section will discuss how these clinical parameters are applied to estimate the transition of patients through the model.

Methodology: parameter estimation and selection

To estimate the parameters which inform the transition of patients through the model a systematic approach to survival analysis was conducted for PFS and OS. This was conducted according to the principles outlined the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 (124). The following five parametric models were estimated and considered for goodness of fit to PFS and OS data from the RAINBOW and REGARD trials; exponential, Weibull, lognormal, log-logistic and Gamma. The Gompertz distribution is not supported by the PROC LIFEREG procedure in SAS, the software used for all the survival regression analyses described here. An attempt was made to use a macro to fit the Gompertz model but there were significant concerns regarding the validity of the outputs generated and so it was decided that this distribution should not be considered further.

A robust selection process was used to evaluate the internal and external validity of each function to the observed data. Both aspects are important to ensure that the parametric model not only provides a suitable fit to the observed data, but also provides long term predictions which are clinically plausible. The following methodology was applied in modelling PFS and OS.

1) Assess for the functional form of the underlying hazard, including if the proportional hazards (PH) assumption holds
2) Conduct goodness of fit tests and assess suitability of each parametric distribution
3) Select the most appropriate distribution

The specific methods used to assess each distribution are presented in Table 61.

Table 61 Methods for assessing the suitability of parametric survival models

Criteria	Method	Description
Observed trial period	AIC & BIC statistics	Assess the relative fit of parametric models whilst accounting for the number of parameters
	Cox-Snell residuals	Assess how closely a parametric function follows the Kaplan-Meier function
	Log-log hazard plot	Assess the behaviour of the hazard function over time and the plausibility of the proportional hazards assumption
	Visual inspection	Assess how closely a parametric function follows the Kaplan-Meier function and the clinical plausibility of the prediction in relation to other endpoints
Extrapolation period	Visual inspection	Assess how closely the tail of the parametric function fitted to the active treatment arm(s) concur with any available external longer term data or clinically expected outcomes

Abbreviations: AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion

Combination therapy model (RAM+PAC)

PFS and OS modelling summary

In the base case economic model PFS is estimated using the Weibull distribution. The log-logistic was shown to be the best fit using the goodness of fit statistics. However there was evidence that the PH assumption for PFS was still valid and so it was decided that a PH distribution would be more appropriate.

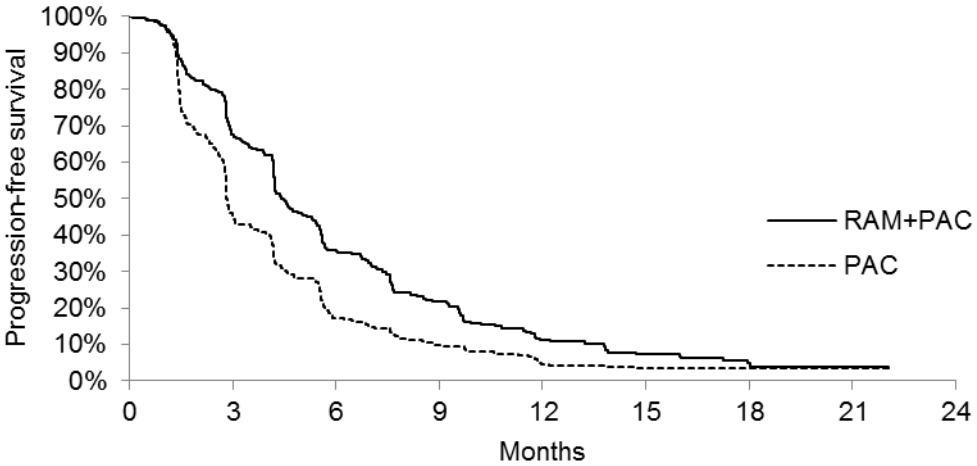
The Weibull was implemented as the base case and the log-logistic was used as a sensitivity analysis. The fully parametric curves are all estimated to adjust for the interval censoring which occurred in the trial.

OS was estimated using the Kaplan-Meier data from the trial and with an exponential distribution implemented from the last observed event in the PBO+PAC arm. This was chosen as the most conservative approach which provided a good fit to the observed trial data. Additional scenario analyses were conducted using the log-logistic and Weibull distribution independently fitted to each treatment arm.

Progression-free survival

The model uses investigator assessed PFS data from the RAINBOW trial whereby progression was confirmed by radiological assessment. The PFS Kaplan-Meier curves are presented in Figure 33.

Figure 33 PFS Kaplan-Meier plots from the RAINBOW



In the RAINBOW trial, PFS data were collected to a high level of maturity with only 3.9% and 3.3% of patients progression-free at the end of the trial in the RAM+PAC and PBO+PAC arms, respectively. However, patients were assessed every 6 weeks and as such this gives rise to a 'stepped' shape of the PFS curves, caused by this interval censoring. Due to this, PFS parametric curves, including those which incorporate the potential for interval censoring, were considered, rather than using the Kaplan-Meier data.

Assessment of underlying hazards

The log-log plots were used to examine the changing hazard over time and assess the assumption of PH (Figure 34). There was some evidence of a violation though this was not consistent in all plots. This is most likely due to the censoring in the tails and the overlapping of KM curves in the first month or so as patients were not assessed until the sixth week. The cumulative hazard plot for example does not show a violation in the assumption (Figure 35). The interval censoring in the PFS analysis also means plots may be limited as they do not reflect the 'true' observed event times and therefore may not fully capture the hazards in both arms. Given this, an assessment of proportional hazards using the observed data should be taken with caution and an assumption of PH is plausible.

Figure 34 Log-log hazard plot of PFS in RAM+PAC and PBO+PAC arm

Log Cumulative Hazard Function of Progression Free Survival over Log time 13:19 09SEP2014
Intent-to-Treat Population Page 1 of 1
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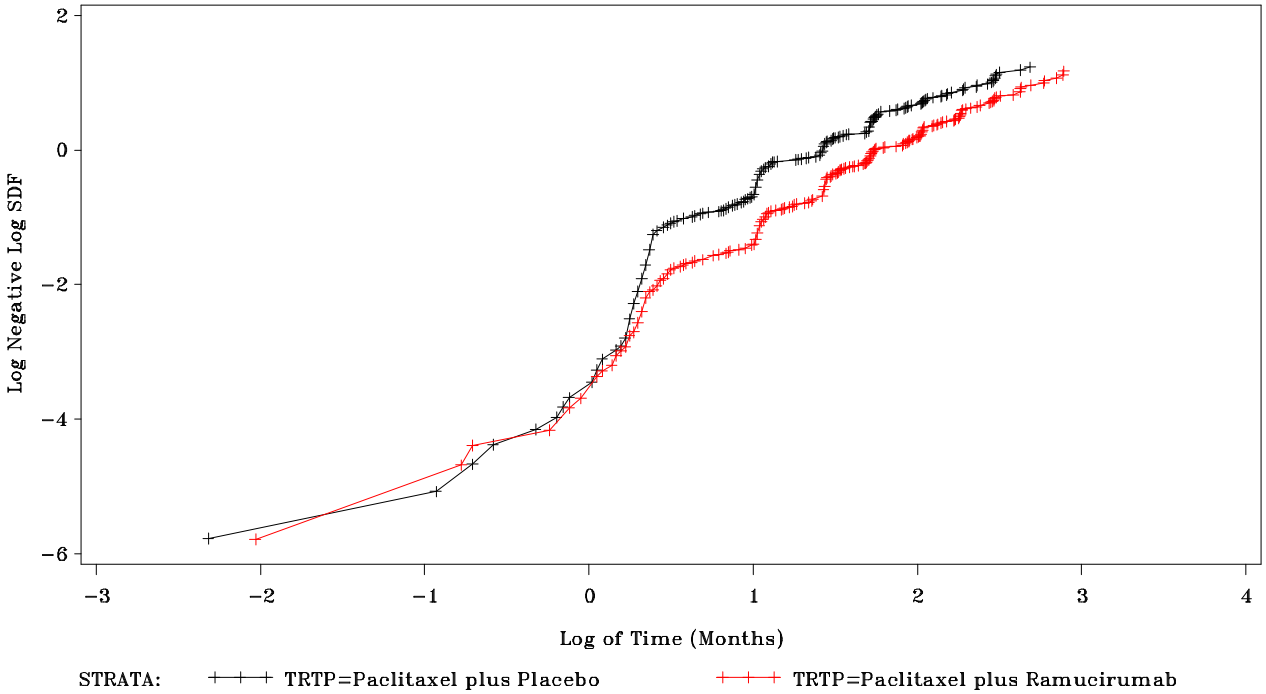

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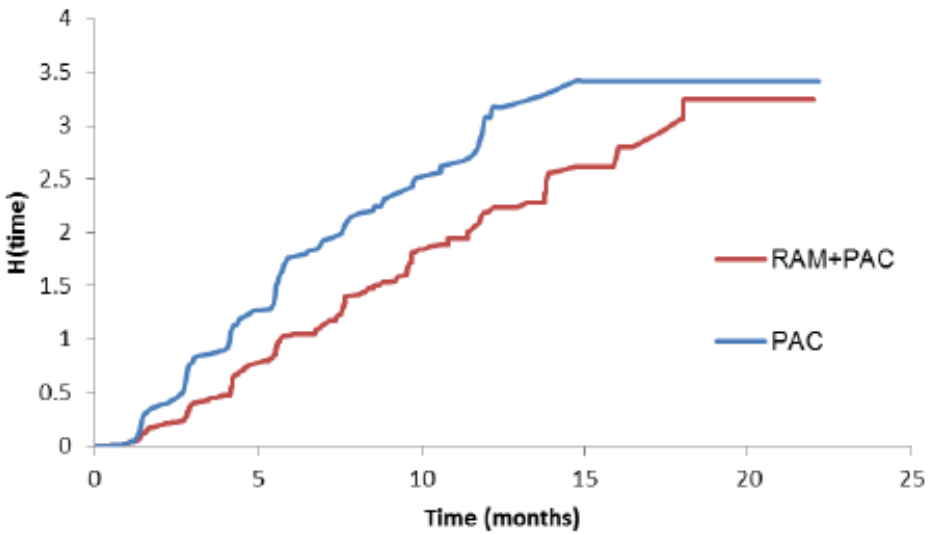
Data Location: H:\lillyce\prd\ly3009806\i4t_ie_jvbe\final_restricted\data\shared\adam\ADSL, ADTTE

Figure 35 Cumulative hazard plot for PFS in RAM+PAC and PBO+PAC arm



Goodness of fit

A comparison of the interval censored and non-interval censored parametric curves showed that the interval censored curves provided a much more plausible fit to the trial data (Appendix 9). Specifically, the curves generated by the interval censored analysis generally intersect the Kaplan-Meier curve at the lower points of the 'steps' in the Kaplan-Meier curve which result from the interval censoring and hence align with the 6-weekly assessments. This is both more clinically plausible and avoids underestimating the hazard associated with progression/death, which the unadjusted curves would. Based on this assessment, the parametric curves which did not account for interval censoring were not considered further.

Goodness of fit tests showed that the accelerated failure time (AFT) models (log-normal, log-logistic and the gamma distribution) provided the best fit to the PFS data from the RAINBOW trial.

Table 62 AIC and BIC statistics for PFS for combination therapy model

Model	N	LogL	DF	AIC	BIC	AIC ranking	BIC ranking
Exponential	665	-1181.50	2	2367.00	2376.00	5	4
Weibull	665	-1179.76	3	2365.51	2379.01	4	5
Lognormal	665	-1165.47	3	2336.95	2350.45	3	2
Log-logistic	665	-1161.50	3	2329.01	2342.51	1	1
Gamma	665	-1164.27	4	2336.54	2354.54	2	3

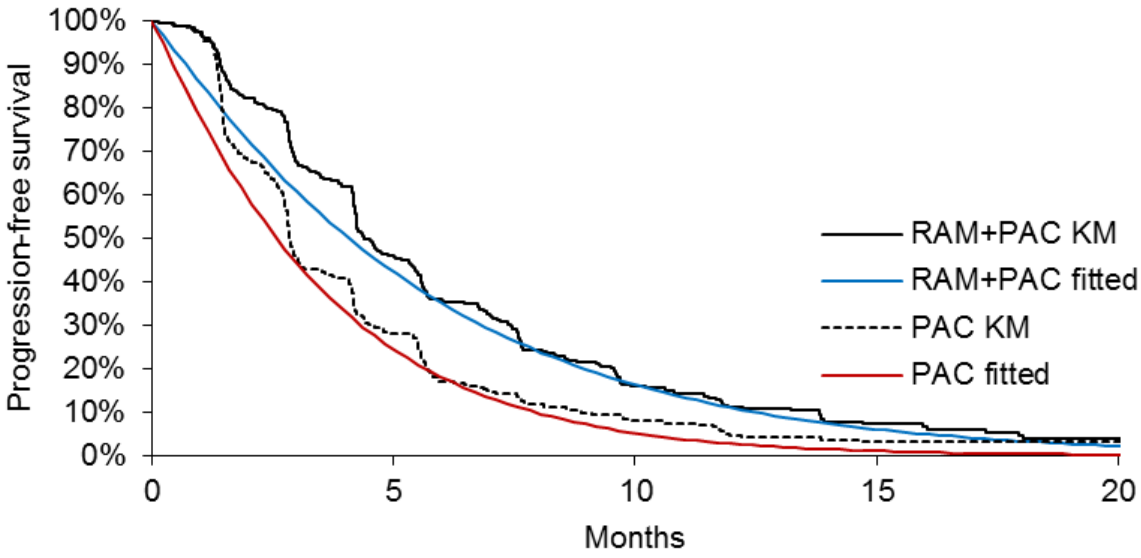
The Cox-Snell Residual plots (Appendix 9) for PFS from the combination therapy model indicate the log-logistic and lognormal models provide the best fit to the underlying hazard though the proportion hazards models did provide a reasonable fit also.

Choice of parametric distribution for PFS

In order to estimate PFS for BSC and DOC, an indirect treatment effect estimated in the NMA was applied to the RAM+PAC arm. Using this method a PH model (either exponential or Weibull) is preferred to make the indirect treatment comparison. The Weibull was selected – PH appears not to be violated for PFS, making it a plausible distribution to estimate PFS.

The Weibull is used for the base case analysis of PFS. The log-logistic was used in the sensitivity analysis as the best fitting of the AFT models.

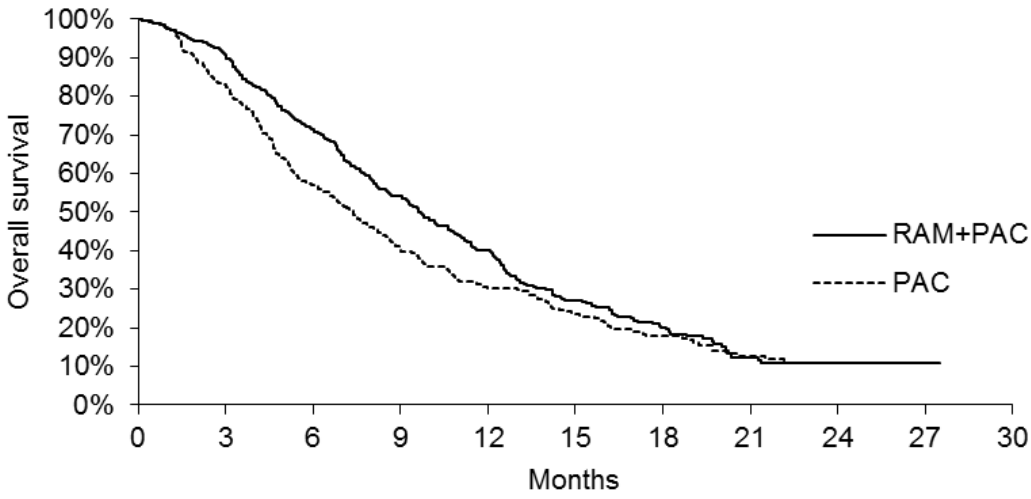
Figure 36 Base case PFS estimated using the Weibull distribution for combination therapy



Overall survival

The model uses OS data from the RAINBOW trial. The OS Kaplan-Meier curves for the ITT population are presented in Figure 37. The data were quite mature as survival in both arms was about 10% by the end of the follow up time.

Figure 37 Overall survival Kaplan-Meier plots for ITT population

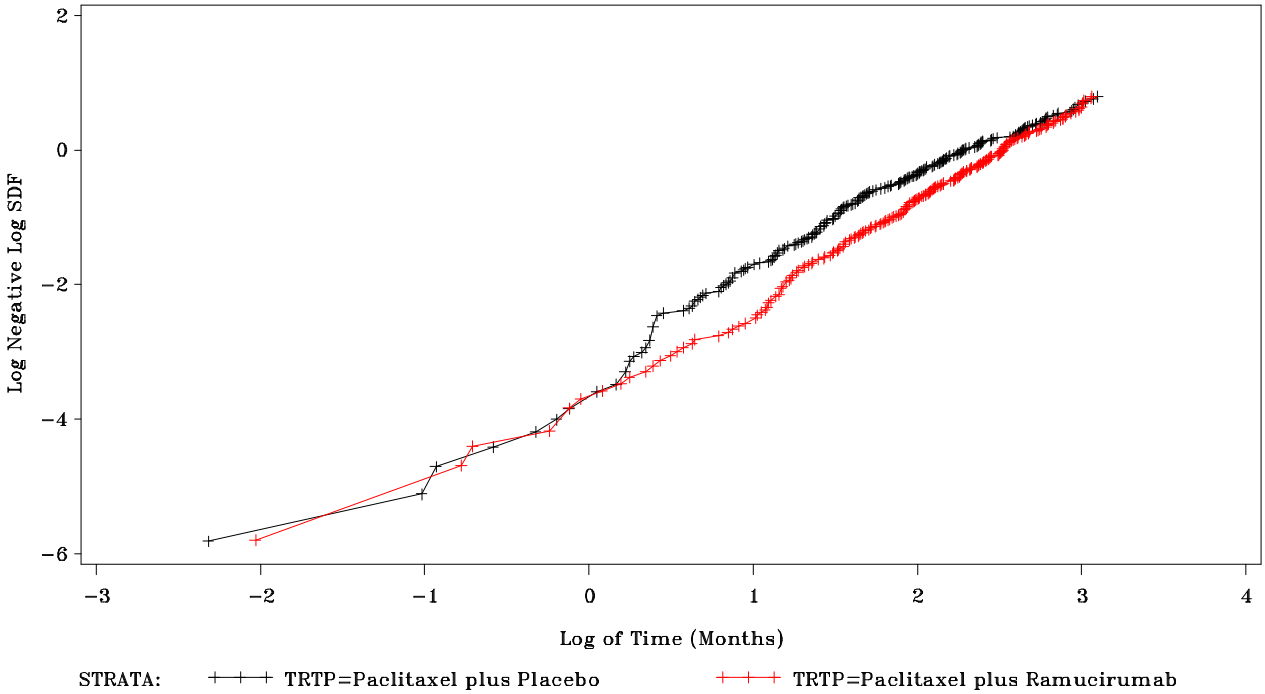


Assessment of hazards

The log-log hazard plots (Figure 38) show a change in the hazard rate over time for both the RAM+PAC and PBO+PAC arms. This visual change in the hazard indicates a potential violation of the PH assumption.

Figure 38 Log-log hazard plot of OS in RAM+PAC and PBO+PAC arm

Log Cumulative Hazard Function of Overall Survival over Log time 13:18 09SEP2014
Intent-to-Treat Population Page 1 of 1
I4T-IE-JVBE PDPM



Data cut-off date: Jul 12, 2013.
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Data Location: H:\lillyce\prd\ly3009806\i4t_ie_jvbe\final_restricted\data\shared\adam\ADSL, ADTTE

Goodness of fit

The standard approach of jointly fitting parametric distributions to the OS curves was attempted. When this was shown to be a poor fit to the trial data a number of other approaches were assessed. The aim was to find the best way to characterise the survival observed in the RAM+PAC and PBO+PAC arm over time.

Joint parametric modelling

Attempts were made to fit the parametric functions jointly to the OS data, with treatment as the covariate, as was done in the PFS analysis. The visual inspection showed that the PH models did not fit the data well (Appendix 9). The AFT models, which do not require an assumption of PH, were a better fit although they did show an over estimation of survival benefit in the RAM+PAC arm which might not be appropriate. Joint modelling of the parametric functions was therefore not considered further.

Independent parametric modelling

The parametric curves were fitted independently to each arm of the trial to characterise the trial data more accurately. This allows the parameter estimates for each model to differ between the arms, specifically allowing the shape parameters to differ independently. The potential danger with this methodology is that the functional form of the hazard can differ between the two arms which may not be clinically plausible for two arms of the same trial. To avoid this, the independent models fitted were chosen to have the same distribution for both arms, such that the survival functions would have a similar shape.

An assessment of the exponential, Weibull, log-logistic, lognormal and gamma distributions was made by independently fitting them to each treatment arm. The goodness of fit was explored using the AIC and BIC statistics alongside a visual inspection of the Cox-Snell residuals in Appendix 9.

Table 63 AIC and BIC statistics for OS using independent models for PBO+PAC

Model	N	LogL	DF	AIC	BIC	AIC ranking	BIC ranking
Exponential	333	-450.74	2	903.48	907.29	5	5
Weibull	333	-444.06	3	892.12	899.75	4	4
Lognormal	333	-438.06	3	880.13	887.76	3	2
Log-logistic	333	-436.20	3	876.40	884.02	1	1
Gamma	333	-436.58	4	879.17	890.61	2	3

Table 64 AIC and BIC statistics for OS using independent models for RAM+PAC

Model	N	LogL	DF	AIC	BIC	AIC ranking	BIC ranking
Exponential	330	-419.89	2	841.78	845.58	4	4
Weibull	330	-398.54	3	801.07	808.67	1	1
Lognormal	330	-408.03	3	820.05	827.65	3	3
Log-logistic	330	-399.63	3	803.25	810.85	2	2
Gamma	330	-436.58	4	879.17	890.61	5	5

The log-logistic was the best fitting distribution for the PBO+PAC arm and the second best fitting distribution for the RAM+PAC arm, where the Weibull was the best fitting (though the difference in AIC and BIC values was minor). This was supported by the visual inspection of the Cox-Snell residuals, although there is some evidence that the Kaplan-Meier curves deviated from the OS modelled by the log-logistic distribution at the end of the curves.

Kaplan-Meier data with extrapolation

An alternative survival modelling approach was explored to address the concerns with the estimates produced from the independent parametric modelling. The Kaplan-Meier trial data for the trial period were used and then extrapolated from the end of the trial until the point at which all patients are believed to have died. An exponential distribution was used which assumed no difference in the hazard between the RAM+PAC arm and the PBO+PAC arm.

The hazard was estimated using the time of extrapolation (referred to as [t_1]), survival at the time of extrapolation (s[t_1]) and the time point at which survival is 0.1% (i.e. close to zero, referred to as [t_2]) in the PBO+PAC arm. The exponential distribution function was then re-arranged to allow the hazard (λ) to be estimated[6].

The extrapolation was implemented from the point at which the last event was observed in the PBO+PAC arm (22.14 months) though it is possible in the model to adjust the time point at which this extrapolation begins. This is explored in the sensitivity analyses. The choice of t_2 was made based on the time point at which survival is 0.1% in the PBO+PAC arm when extrapolated using the Weibull distribution (53.5 months). An illustration of the modelling approach used to model the Kaplan-Meier data and the extrapolation is provided in Appendix 9.

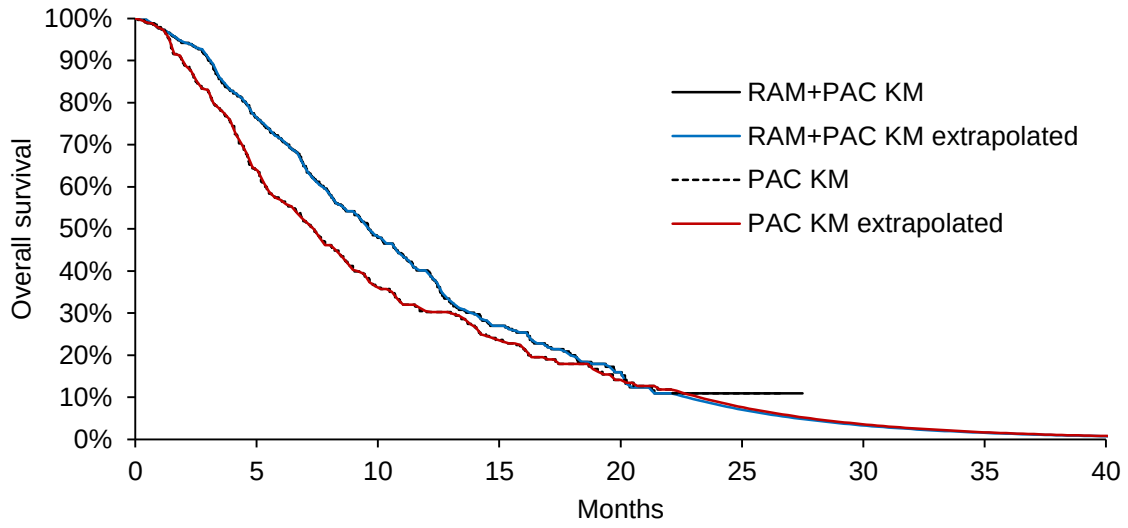
Choice of distribution for OS

All the approaches discussed above were assessed for their goodness of fit and the plausibility of the survival estimates generated for RAM+PAC. Based on the assessment of the results from the Kaplan-Meier methodology and the independent parametric modelling it was decided that the Kaplan-Meier methodology provided the most conservative approach to estimating OS and was therefore chosen as the base case. This approach uses the available RAINBOW trial data and completes the OS curves using the simplest distribution (the exponential) and assumes no difference in the hazard between the RAM+PAC and PBO+PAC arm.

The base case OS curves are presented below.

[6] $\lambda = -\ln(\frac{s(t_2)}{s(t_1)})/(t_2 - t_1)$

Figure 39 Base case OS for RAM+PAC and PBO+PAC using the Kaplan-Meier data with exponential extrapolation



There are however limitations with this approach, as with all modelling approaches. Concerns around the choice of the cut point and the impact on the results are explored in the sensitivity analyses.

Additionally, the independently modelled log-logistic and Weibull distributions were also implemented as scenario analyses. The log-logistic distribution was the best fitting across both curves and shown to be a good visual fit to the majority of the trial data, albeit a less good fit at the end of the curve where there is greater uncertainty.

Figure 40 Sensitivity analysis OS estimated using the log-logistic distribution for combination therapy

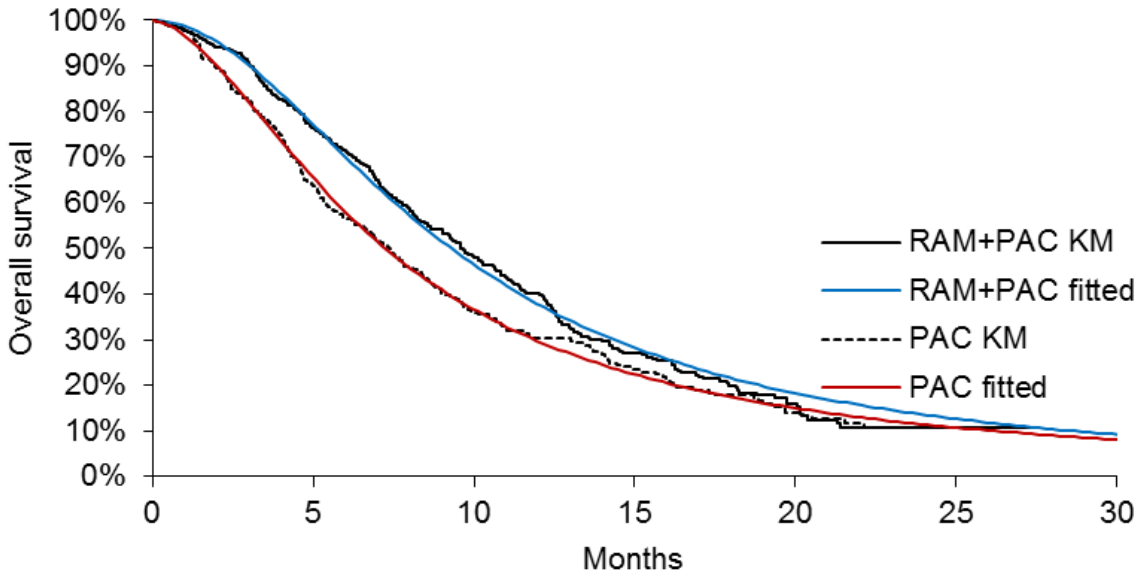
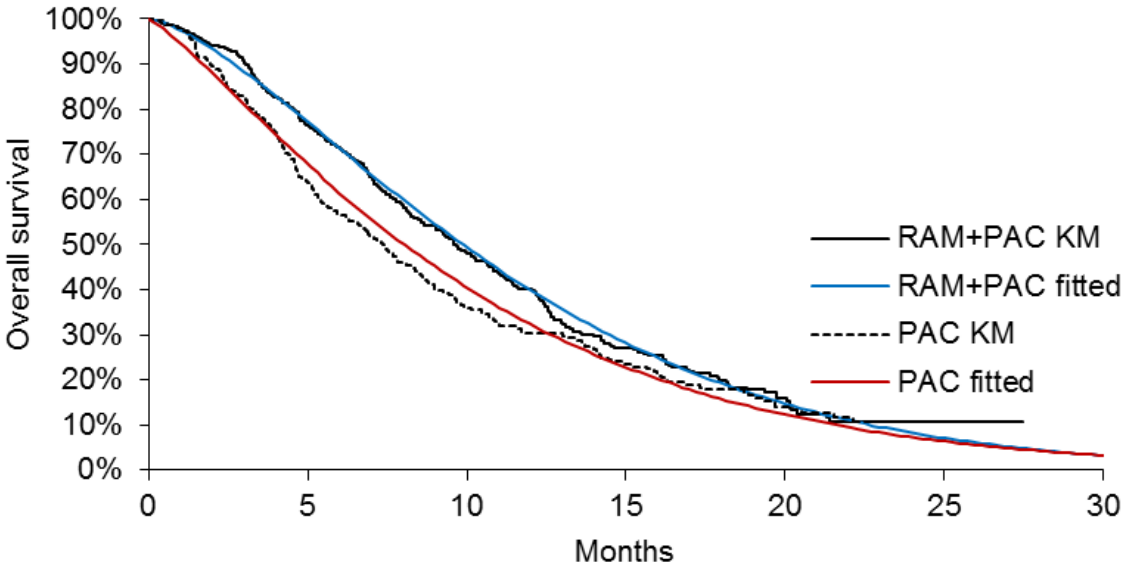


Figure 41 Sensitivity analysis OS estimated using the Weibull distribution for combination therapy



Application of treatment effect for indirect comparison

In order to conduct the comparison of RAM+PAC to BSC and DOC, the HR estimates from the NMA for BSC and DOC compared to RAM+PAC were applied to the baseline curves for RAM+PAC. This allows the relative treatment effect for OS and PFS of RAM+PAC versus the comparator to be estimated. An assumption of PH is made across the trials included in the evidence network to allow this methodology to be implemented. This approach was chosen in preference to exploring the non-proportional hazards methods proposed in the literature (125) which would introduce more uncertainty into the NMA and the economic model.

Indirect treatment comparison for progression-free survival

The evidence network for PFS was presented in Figure 27. A feasibility assessment identified the network of RCTs for PFS was disconnected. Specifically, Thuss-Patience (4), Roy (110) and Ford (2) did not report HRs for PFS for either comparator.

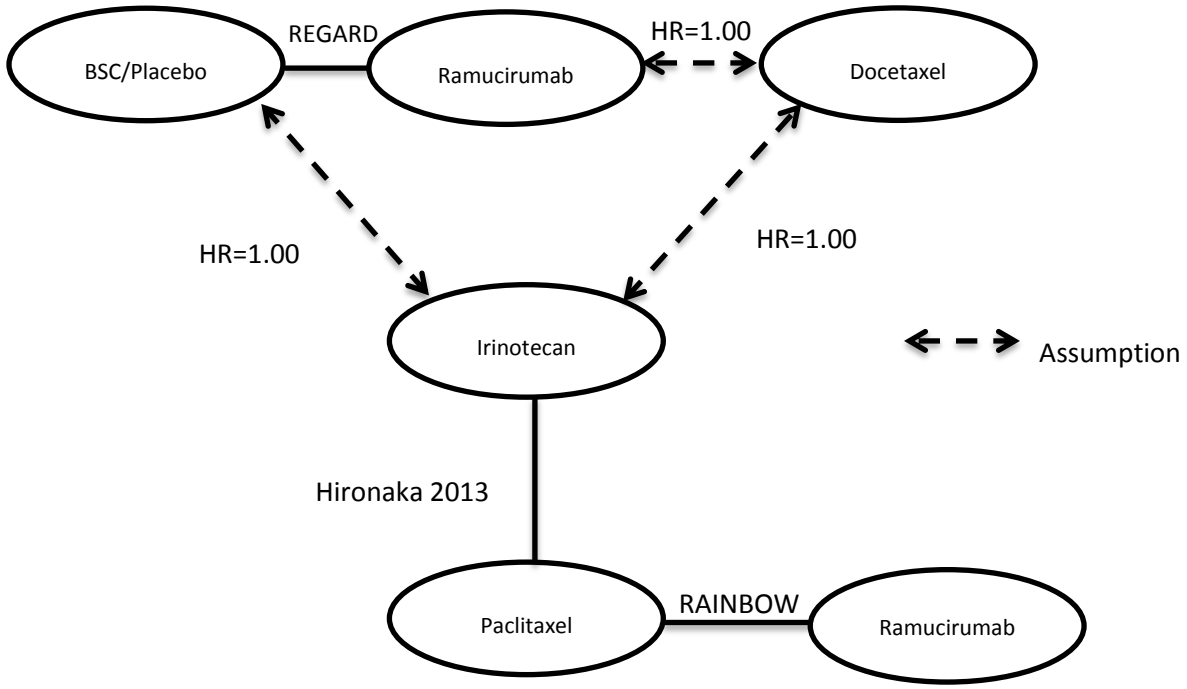
Therefore to connect the network to compare BSC and DOC to RAM+PAC the following assumptions were required. A naive comparison of the Kaplan-Meier estimates of PFS from Roy (110) and the REGARD trial (Figure 43) and the corresponding median PFS estimates (2.1 months (95% CI: 1.5, 2.7) with RAM; 2.6 months (95% CI: 1.5, 4.3) with IRI; 2.7 months (95% CI: 1.4, 5.5) with DOC) suggested that the hazards of progression for patients receiving IRI or DOC were very similar to that of RAM monotherapy. Within the first 3 months there was very little difference between the treatments. Beyond 3 months the Kaplan-Meier curves deviated, however estimates from this time point for IRI and DOC were uncertain due to small patient numbers which was

reflected in the confidence intervals around the median PFS estimates. Based on this comparison the following assumptions were made:

- HR for RAM vs. DOC = 1
- HR for RAM vs. IRI = 1
- HR for IRI vs. DOC = 1

The evidence network for PFS incorporating these assumptions is presented in Figure 42.

Figure 42 Evidence network for PFS (with assumptions)



To conduct the NMA it was necessary to assign a level of uncertainty to the PFS HRs assumed to be 1. 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. This was identified by an exploratory analysis of the lowest acceptable level of error required to run the analysis in WinBUGS. To explore the impact of this assumption of uncertainty the following additional analyses were conducted and included in the economic model:

- Assigned a standard error of 0.287 to all HRs assumed to be 1, conducted as an NMA. This standard error was obtained from a Cox analysis (126) of the Roy (110) Kaplan-Meier data which were digitised using a recently published algorithm (127). The accuracy of this estimate was limited by the poor quality of the Kaplan-Meier curves in the publication.
- Assigning a standard error of 0 (i.e. no uncertainty) to all HRs assumed to be 1, conducted as an indirect comparison based on the method proposed by Bucher and colleagues (128).

The estimates of the PFS HRs estimated from the NMA and indirect comparison are presented in Table 65. As expected, the point estimates were stable irrespective of the assumptions made about the uncertainty, while the uncertainty in the point estimates (credible intervals (CrI) for the NMA or confidence intervals (CI) for the indirect comparison) corresponded with the level of uncertainty assigned.

Table 65 HRs (95% CrIs or CIs) for PFS obtained from NMA and indirect comparison (vs. RAM+PAC)

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	-	-	-
BSC	3.7(1.89, 7.14)	3.7 (1.85, 7.14)	3.7 (2.5, 5,56)
DOC	1.79 (1.32, 2.44)	1.79 (0.76, 4.17)	1.79 (1.32, 2.44)

95% credible interval: 95% probability that true value lies within the interval
95% confidence interval: In the long run, if the analysis was repeated many times on the same population, there was a 95% probability that the true value lies within the interval

Indirect treatment comparison for overall survival

The evidence network for OS was presented in Figure 26. As all comparators relevant to the decision problem were connected in the network it was not necessary to make any assumptions.

The corresponding estimates of the OS HRs are presented in Table 66.

Table 66 HRs (95% CrIs) for OS obtained from NMA (vs. RAM+PAC)

Treatment	HR (95% CrI)
RAM+PAC	-
BSC	2.94 (1.41, 5.88)
DOC	1.96 (0.88, 4.35)

95% credible interval: 95% probability that true value lies within the interval

Monotherapy model (RAM+BSC)

PFS and OS modelling summary

PFS is estimated using the lognormal distribution. Although the log-logistic provided the best fit to the observed trial data the modelled estimates were believed to be more clinically plausible with the lognormal distribution. The log-logistic and Weibull distributions are included as sensitivity analyses. The parametric curves for PFS were all estimated to adjust for the interval censoring which occurred in the trial.

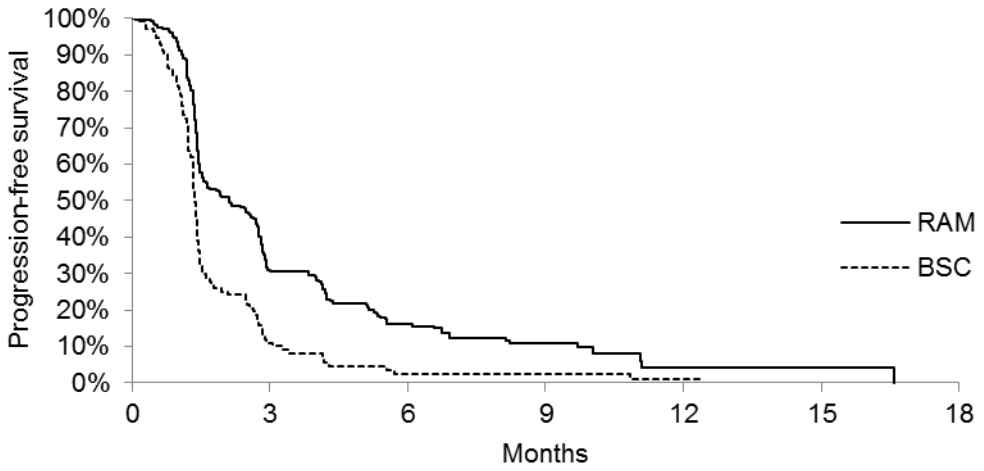
OS is modelled using the Gamma distribution which was the third best fit to the observed trial data. The Gamma was chosen because it provided a more conservative approach than the two better fitting distributions. A scenario analysis using the lognormal distribution as an alternative is

implemented. The lognormal was a better fit to the data but provided slightly longer tails in the extrapolated part of the OS curve and so was not chosen as the base case.

Progression-free survival

The model uses investigator assessed PFS data from the REGARD trial. The PFS Kaplan-Meier curves are presented in Figure 43.

Figure 43 PFS Kaplan-Meier plots from the REGARD



In the REGARD trial, PFS data were also collected to a high level of maturity with 0% and 1.1% of patients remaining progression-free at the end of the trial in the RAM+BSC and PBO+BSC arms, respectively. Again however, patients were assessed every 6 weeks leading to quite pronounced interval censoring. PFS parametric curves, including those which incorporate the potential for interval censoring, were therefore considered to avoid underestimating the hazard of progression/death.

Assessment of underlying hazards

The log-log hazard plot is provided to allow an assessment of the PH assumption (Figure 44). The plots show no clear violation of the PH assumption.

Figure 44 Log-log hazard plot of PFS in RAM+BSC and PBO+BSC arm

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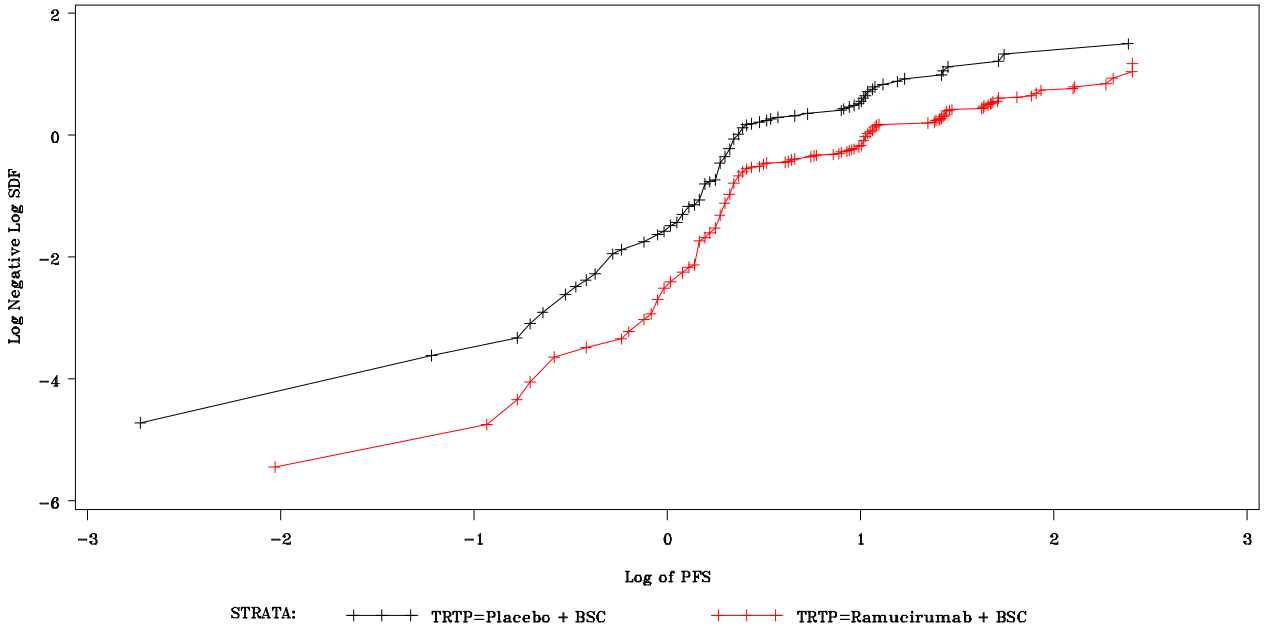
Figure 16.1.9.6.a1 Assessment of PFS Proportional Hazard Assumption: Log-Log Plot (ITT population)



Data cut-off date: July 25, 2012.
H:\lillyce\imclone\prd\imc1121b\gastric\cp120715\adhoc20120925_restricted\programs\f_logneglog_itt.sas

Goodness of fit

Again a visual comparison of the interval censored and non-interval censored parametric curves showed that the interval censored curves provided a much more clinically plausible fit to the trial data (Appendix 9) by accounting for the 6-weekly assessment period. Therefore the non-interval censored curves were not considered further.

Goodness of fit tests showed that the AFT models (log-logistic, lognormal and the gamma distribution) provided the best fit to the PFS data from the REGARD trial.

Table 67 AIC and BIC statistics for PFS for monotherapy model

Model	N	AIC	BIC	AIC ranking	BIC ranking
Exponential	355	946.99	954.74	5	5
Weibull	355	941.91	953.53	4	4
Lognormal	355	914.62	926.23	2	2
Log-logistic	355	913.99	925.61	1	1
Gamma	335	915.24	930.73	3	3

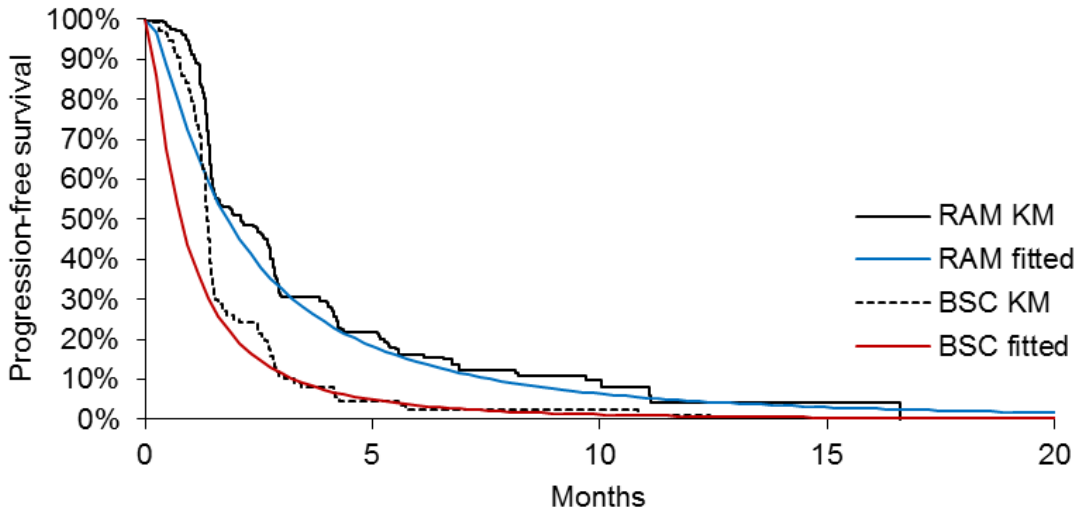
The Cox-Snell Residual plots for PFS (Appendix 9) for the monotherapy model indicate the log-logistic and Gamma models provide the best fit to the underlying hazard with their fit being marginally better than that of the lognormal model. In both cases, the exponential and Weibull proportional hazards models provided a poor fit.

Choice of parametric distribution for PFS

The lognormal was however chosen as the base case approach for modelling PFS. The lognormal distribution was preferred to the log-logistic and gamma distributions due to the shorter tail of the extrapolation (estimating 99% of patients to have progressed by 24.6, 30.6 and 35.1 months respectively) which is more conservative given the poor prognosis of GC/GOJ patients.

The log-logistic was included as a sensitivity analysis. The Weibull was also included as a sensitivity analysis as the PH assumption was shown not to be violated, though it did not provide a sufficiently good fit for use in the base case.

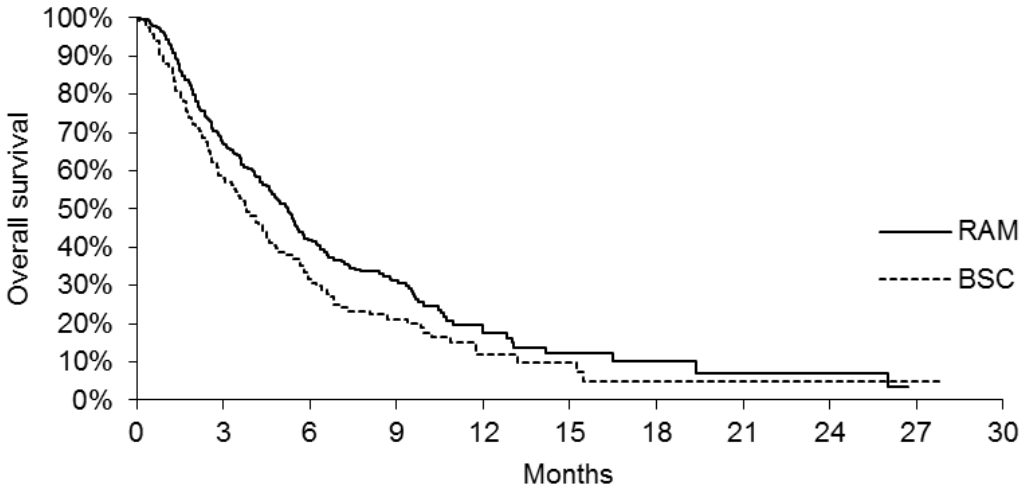
Figure 45 Base case PFS extrapolations using lognormal distribution for monotherapy



Overall survival

The model uses OS data from the REGARD trial. The OS Kaplan-Meier curves are presented in Figure 46.

Figure 46 Overall survival Kaplan-Meier plots from REGARD

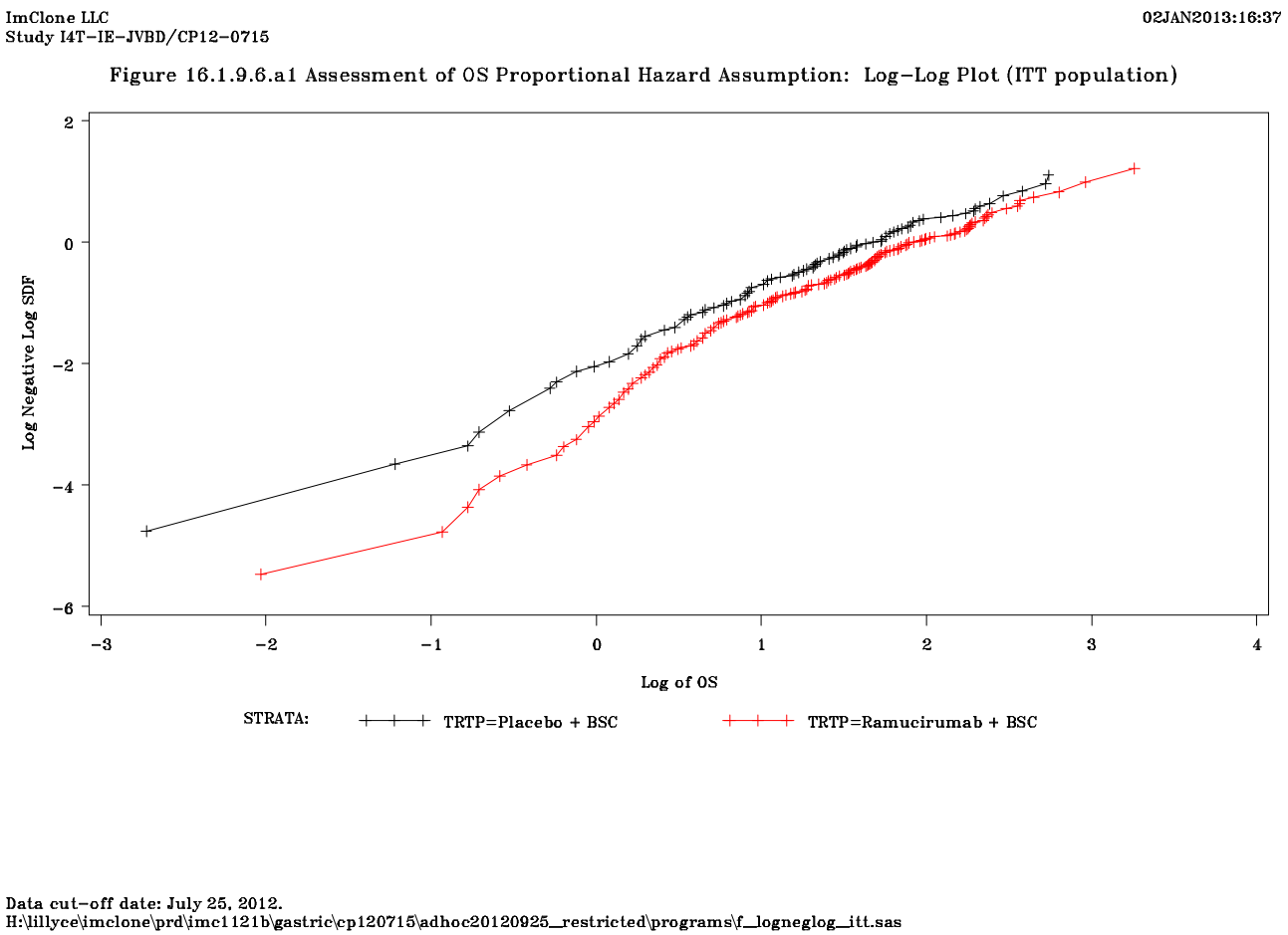


At the end of trial follow-up 5% and 3% of patients were still alive in the RAM+BSC and PBO+BSC arms, respectively.

Assessment of hazards

The log-log plot shows the hazard rate over time for both the RAM+BSC and PBO+BSC arms of the REGARD trial. Visual inspection shows no clear evidence of PH violation.

Figure 47 Log-log hazard plot of OS in RAM+BSC and PBO+BSC arm



Goodness of fit

The AIC and BIC values were lowest for the lognormal, log-logistic and gamma distributions indicating that they were the best fit to the trial data (Table 68). These results were supported by the Cox-Snell Residuals (Appendix 9) with some minor divergence at the end of the trial period.

Table 68 AIC and BIC statistics for OS for monotherapy model

Model	N	AIC	BIC	AIC ranking	BIC ranking
Exponential	355	987.05	994.79	5	5
Weibull	355	982.35	993.96	4	4
Lognormal	355	964.14	975.76	2	2
Log-logistic	355	963.82	975.44	1	1
Gamma	355	964.51	980.00	3	3

Choice of distribution for OS

The Gamma distribution was chosen as the base case for the modelling of OS in the monotherapy model. Combining the data from the AIC/BIC, Cox-Snell Residuals and visual fit it was chosen as the most conservative of the AFT models, all of which seemed to provide a reasonable fit. The

lognormal is also included as a sensitivity analysis which provides slightly longer long-term survival predictions.

Figure 48 Base case OS extrapolations for monotherapy model: gamma distribution

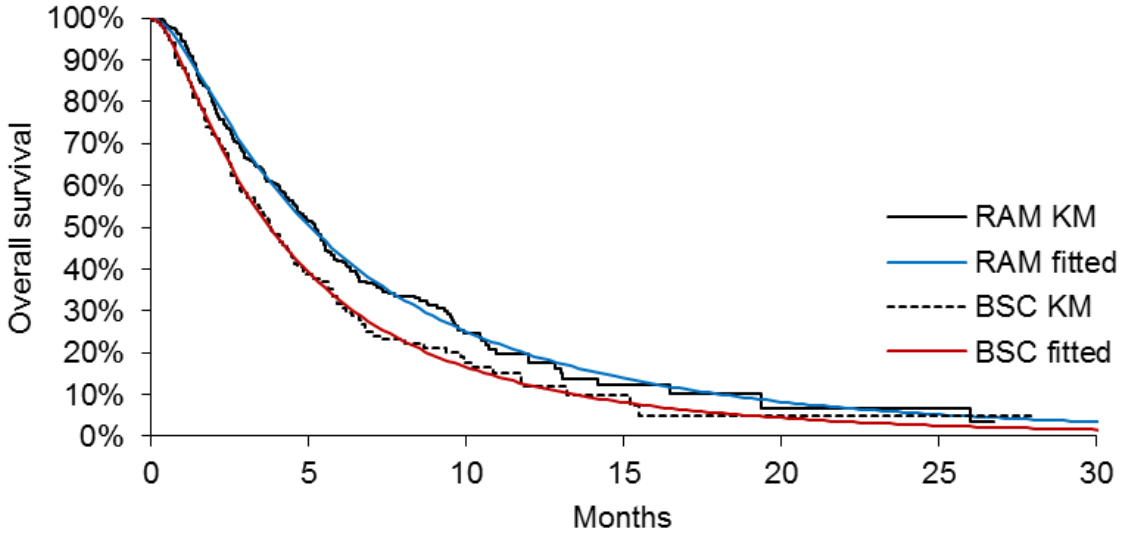
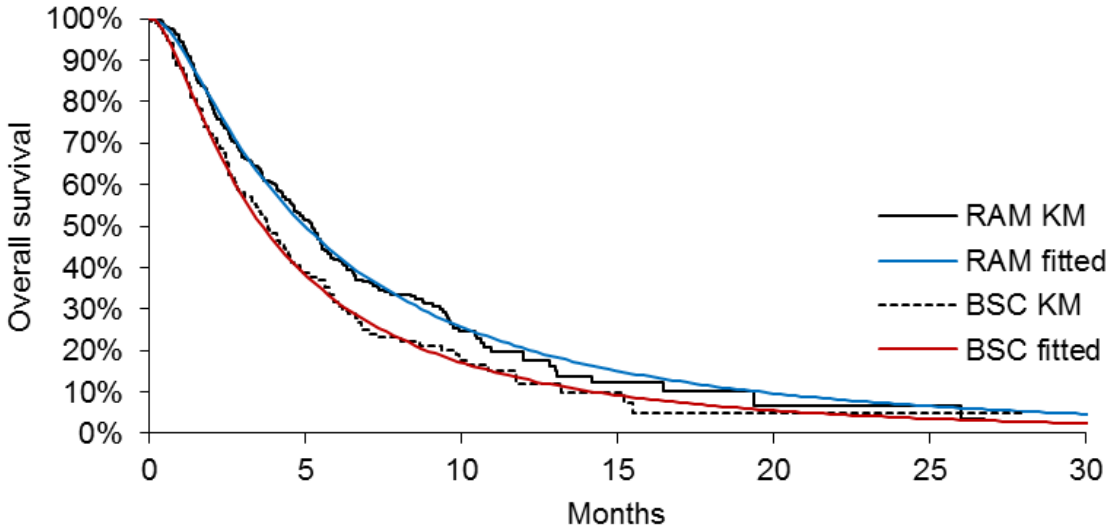


Figure 49 Sensitivity analysis OS extrapolation for monotherapy: lognormal distribution



Application of treatment effect for indirect comparison

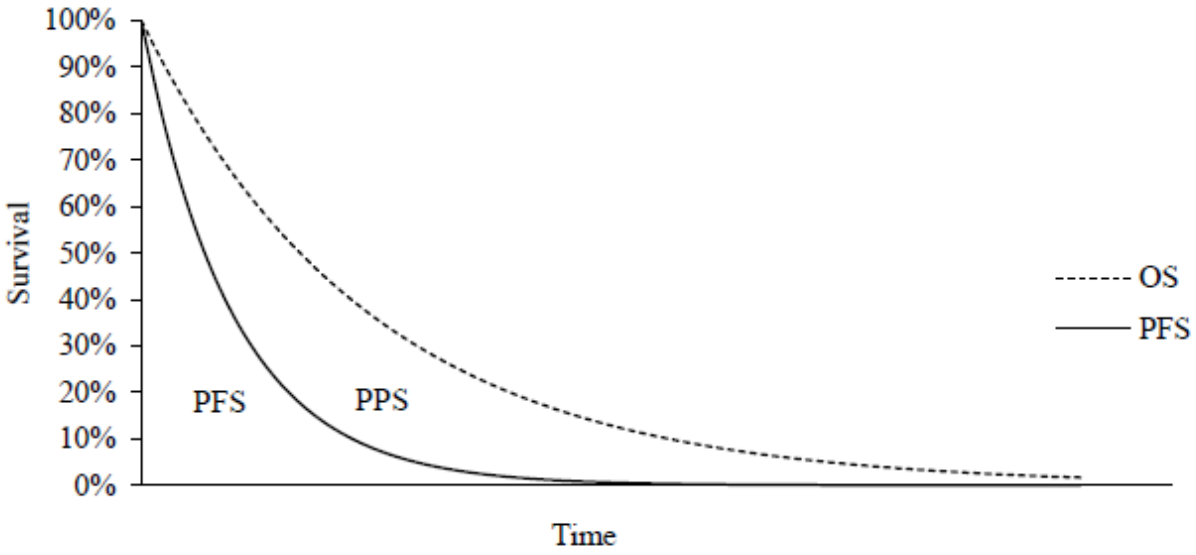
The only comparator which is relevant for RAM monotherapy is BSC which was the trial comparator in REGARD. Therefore, no indirect treatment comparison was required for the monotherapy model.

Transition probabilities in combination and monotherapy model

The transition between health states is estimated by parametric survival functions. These functions are used to estimate the proportion of the cohort remaining free of endpoints that defined the three health states - pre-progression, post-progression and death. Time in the 'pre-progression' state was estimated directly from the PFS curve. Time in the 'post-progression' state was estimated by the difference between the PFS and the OS curve at each time point.

PFS and OS curves were modelled independently (i.e. using different parametric functions), with no relationship linking them. Therefore care has been taken to ensure that the PFS curve does not lie above the OS curve, yielding negative patients in the 'post-progression' health state. In such cases the PFS curve was set equal to the OS curve to retain face validity.

Figure 50 Graphical representation of calculation of post-progression survival (not representative of trial data)



An indirect comparison was required for comparators not included in the trial. In this case the HR obtained from the NMA was applied to the modelled PFS and OS curves for RAM+PAC to estimate the relative treatment effect of RAM+PAC to the comparators. This determines the transition probabilities between health states for the non-trial comparators.

Together these parameters determine the rate at which patients progress and die and therefore the costs and benefits accruing to each intervention and comparator.

5.4 Measurement and valuation of health effects

Accurately capturing the impact of treatment and disease progression on HRQL is an essential part of evaluating the benefit of a new treatment. An overview of the experience of patients with advanced GC/GOJ is provided to appropriately frame the aspects of the disease and condition which most affect patients' HRQL. A systematic review of HRQL in this disease area was conducted to find suitable alternative utility values - the results of this review are presented and discussed.

The change in HRQL over time and across health states in the economic models is then discussed. An overview of the HRQL data collected in the clinical trials, RAINBOW and REGARD, are provided and their suitability for use in the economic model is discussed.

The utility values used to represent the health states are outlined and a cross-validation of the values with other similar patient populations is provided. Important HRQL events are applied in the model to appropriately reflect the experience of patients with GC/GOJ – the rationale for the inclusion of these and the chosen values are described. Finally, a summary of all the utility values chosen and used in the CEA is provided for the combination and monotherapy economic models.

HRQL and patient experience in advanced GC/GOJ

Patients with advanced GC/GOJ have a very limited survival prognosis and relief of symptomatic burden is a key component of HRQL (13). Treatments which reduce tumour burden should be seen as paramount in the context of this high symptom burden disease. Importantly also, any extension in OS should not be achieved at the expense of patients' HRQL in their remaining months.

A range of symptoms are associated with advanced GC/GOJ and significantly impact on patient's HRQL. Some of the mostly commonly reported symptoms are an inability to swallow (dysphagia), early satiety, weight loss, fatigue and breathlessness (1). Chemotherapy may improve these tumour-related symptoms, prolong symptom-free intervals, and consequently improve or maintain HRQL (13). The impact of GC/GOJ on a patient's ability to eat, especially after surgery, is an essential aspect of HRQL for patients and specialist nutritional support should also be offered to improve patient outcomes (129).

HRQL and chemotherapy

An independent systematic literature review has been published, aimed at evaluating the effects of chemotherapy on HRQL of patients with advanced, inoperable oesophago-gastric cancer (13). The review included the results of 19 clinical trials (11 Phase 2 trials, seven Phase 3 trials, and one of which the phase was not reported) published between January 1988 and June 2008. All trials

examined HRQL in patients with metastatic or locally advanced, inoperable oesophago-gastric cancer, and 17 of the 19 RCTs assessed HRQL with the EORTC QLQ-C30. The majority of trials reported that for patients who remained in the study, many had symptomatic relief across the treatment period, but that there was no change in global HRQL versus BSC following the administration of chemotherapy.

Interestingly the authors found that improvements in HRQL were correlated with improved efficacy endpoints, including OS and TTP, but were not linked to increased toxicity. They explained these findings as being due to the aggressive and rapidly progressing nature of oesophago-gastric cancer. Whereby, if chemotherapy fails, tumour-related symptoms such as gastrointestinal obstruction and deterioration in ECOG PS immediately impact on patients' HRQL.

Additionally, they found the studies available had used a variety of analytic methods, and varying time points to measure HRQL, making comparability and consistency across studies difficult (13). They conclude that there is a need for further studies which systematically include HRQL as a predefined study endpoint.

Given this, it is postulated that active treatment can reduce tumour burden and delay symptom progression and that this is better demonstrated by measures of disease symptoms than measures of global HRQL.

Health-related quality-of-life studies

A systematic review of HRQL studies was conducted for GC, GOJ or oesophageal cancer to determine whether there was a suitable source of utility data for the model. The following search criteria were employed.

Table 69 Study Inclusion Criteria

Population	**Adult patients with advanced GC, GOJ or oesophageal cancer**
Intervention	Any
Comparators	Any
Outcomes	Health state utility values (HSUVs), as estimated by: Short form (SF-36, SF-12, SF-6D) EQ-5D Health utilities index (HUI2 and HUI3) Mapping condition-specific measure algorithms into preference-based instruments, e.g. the EQ-5D
Study Design	Any

Full details of the search strings are documented in Appendix 10.

The review found nine studies which met the inclusion criteria and these were reviewed and are presented in Table 17. Of the studies identified which report utility values for patients with GC, GOJ or gastrointestinal (GI) cancer, three studies are consistent with the NICE reference case (130-132) i.e. health states were described using a validated generic questionnaire, and valued using appropriate societal preferences.

However, in these three studies, the patient populations were not relevant to the decision problem being addressed in this appraisal. One was from a different patient population to this appraisal (i.e. chemotherapy naïve patients) (131), the other enrolled patients with localised GC (130), and the third study reported utilities from a number of other cancer sites (colorectal, n=43; oesophageal, n=38; pancreatic, n=11, GC, n=38), making it was unclear whether the utilities reported would be applicable to a GC/GOJ population (132).

The full list of reasons of the unsuitability of the identified studies is outlined in Appendix 10. Given the appropriateness of the patient population to this decision problem and the fact that the EQ-5D meets the requirements of the NICE reference case, EQ-5D data from the RAINBOW trial is used to estimate health benefits in the combination and monotherapy economic model.

Figure 51 Systematic review flow diagram

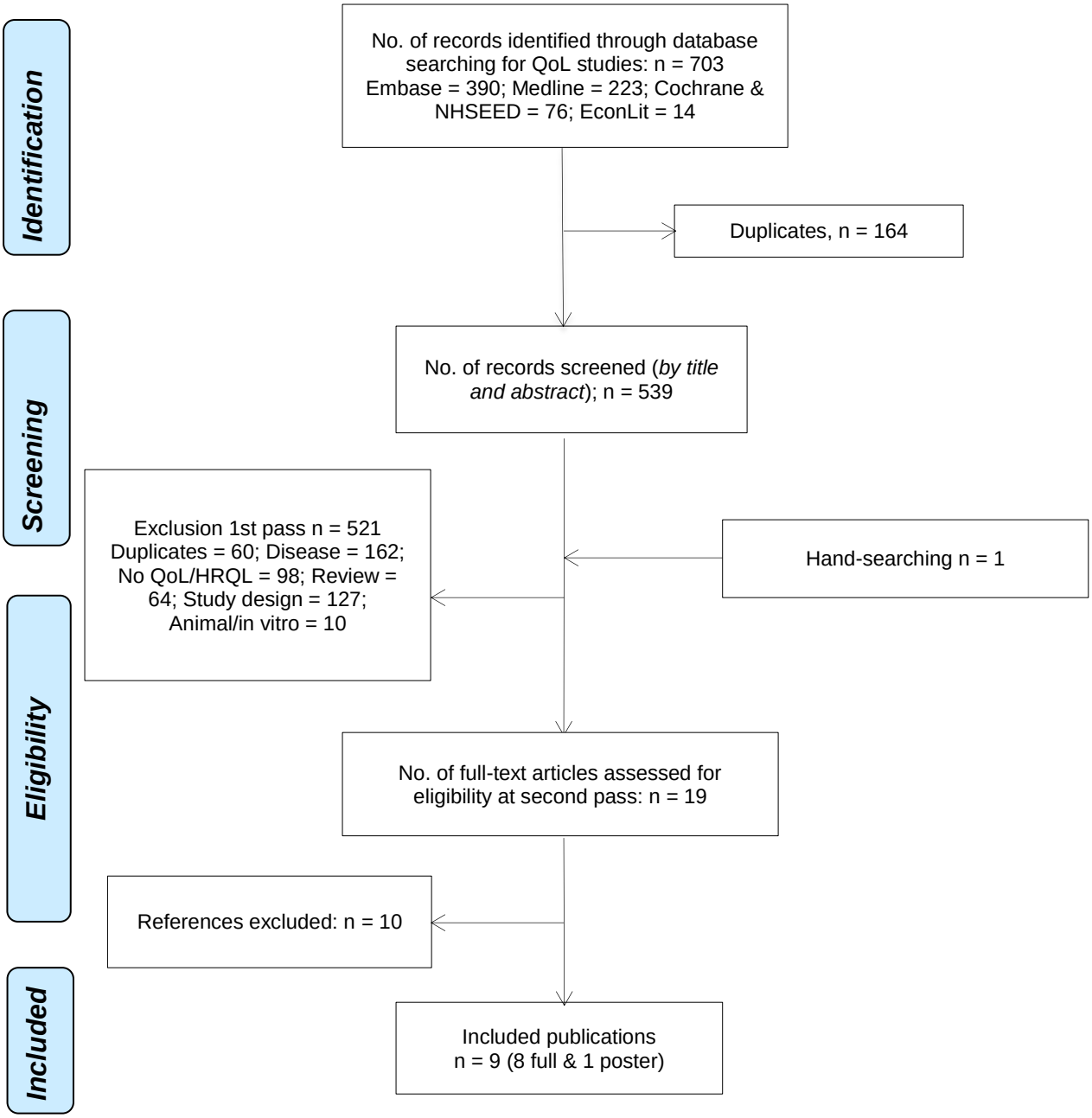


Table 70 HRQL studies identified in the systematic literature review

Study (country)	Cancer type	Population	Sample (N)	Health state	Instrument	Mean (median) HSUV, (s.d), or <CILL, CIUL> of HSUV
Aultman, 2010 (24 countries) (131)	GC	Patients with HER2+ locally advanced metastatic GC; primarily chemotherapy naïve at baseline ††	584	PFS post-chemotherapy	EQ-5D	0.73 (0.71, 0.75)
Kontodimopoulos 2009 (Greece) (130)	GC	Patients had previously attended two to four chemotherapy sessions (≥20 days previously), and had undergone surgery	48	Post-chemotherapy	EQ-5D	0.550 (0.307)
					SF-6D	0.606 (0.094)
					15D	0.685 (0.166)
Ajani 2007 (US) (133)	MP (GC, GOJ)	Gastric or oesophagogastric junction adenocarcinoma; measurable and/or assessable metastatic disease according to WHO criteria, or locally recurrent disease associated with one or more measurable lymph nodes	NR	Baseline, chemo naive	EQ-5D VAS	54.7 (22.5)
McNamee, 2004 (UK) (134)	OC	Recruited from a database of patients who had received curative treatment for oesophageal cancer (OC)	56	Health states post-curative treatment for OC	TTO	0.08-0.66, depending on health state
					SG	0.08-0.78, depending on health state

Wildi, 2004 (US) (135)	OC	• Patients with OC (n=50) • Pre-treated (n=13): palliative chemotherapy (n=6), noncurative surgery, (n=1), or both (n=6) • Treated after interview (n=37) • EUS and CT staged: localised (n=11), regional (n=24) or metastatic (n=12) cancer; non-detectable tumour after palliative care (n=3) • In situ (n=3), localised (n=11), regional (n=24), metastatic (n=12) • Dysphagia score‡‡: 0 (n=16), 1 (n=18), 2 (n=5), 3 (n=8), 4 (n=3)	50	Patient's own health status (localised to metastatic)	TTO	In situ: 0.99 (0) Localised: 0.80 (0.30) Regional: 0.54 (0.39) Metastatic: 0.52 (0.31)
				Societal perspective (localised to metastatic)		Localised: 0.77 (0.24) Regional: 0.46 (0.35) Metastatic: 0.15 (0.21)
				Patient's own health status (in situ to metastatic)	EQ-5D	In situ: 0.93 (0.12) Localised: 0.60 (0.29) Regional: 0.71 (0.21) Metastatic: 0.69 (0.35)
				Patient's own health status (dysphagia scores 0 to 4)	TTO	Dysphagia 0: 0.86 (0.23) Dysphagia 1: 0.62 (0.36) Dysphagia 2: 0.29 (0.25) Dysphagia 3: 0.51 (0.37) Dysphagia 4: 0.25 (0.17)
					EQ-5D	Dysphagia 0: 0.82 (0.17) Dysphagia 1: 0.67 (0.30) Dysphagia 2: 0.80 (0.19) Dysphagia 3: 0.60 (0.22) Dysphagia 4: 0.39 (0.27)

Curran, 009 (Not reported) (136)	MP (GC, GOJ)	Patients had histologically confirmed metastatic adenocarcinoma of the stomach or oesophagogastric junction, with measurable or evaluable metastatic disease, or locally recurrent disease	333	Post-baseline IF‡	EQ-5D	0.76 (0.23)
				Post-baseline CF§		0.66 (0.27)
McMillan, 1999 (Scotland, assumed) (137)	MP (GI)	Patients with histologically proven, locally advanced or metastatic gastrointenstinal cancer, with weight loss and receiving supportive care only, and had a life expectancy of at least 2 months and no moderate/severe dysphagia	73	Weight-losing patients	EQ-5D	Megestrol acetate/PBO group: [0.630; range -0.095-1.000] Megestrol acetate/ibuprofen group: [0.689; range -0.261-1.000]
O'Gorman, 1998 (Scotland, assumed) (132)	MP (GI)	Outpatients, advanced or metastatic gastrointestinal disease	119	Weight-stable patients	EQ-5D	[0.85]
				Weight-losing patients		[0.52]
Homs, 2004 (The Netherlands) (138)	MP (OC/GOJ)	Patients with inoperable OC or GOJ due to metastatic disease and/or a poor medical condition with progressive dysphagia	209	Inoperable OC/GEJ cancer with progressive dysphagia	EQ-5D	63

Abbreviations: CILL = confidence interval lower limit; CIUL = confidence interval upper limit; HSUV = health-state utility value; OC = oesophageal cancer; MP = mixed population; N = number of patients; s.d. = standard deviation; SG = standard gamble; TTO = time trade-off. †See source publication for further details; ‡Irinotecan followed by FA, followed by 5-FU; §Cisplatin followed by 5-FU; ¶EQ-5D index score (100=best); ††Additional data on patient characteristics reported in publication by Bang 2013 {Bang, 2010 #23}; ‡‡Dysphagia score (0=best)

HRQL over time and in the economic model

There is limited published information on the changing course of HRQL for patients with advanced GC, or even the impact of treatment on HRQL. Given the relatively limited progress made in treating this condition this is unsurprising. This makes it difficult to assess the impact on a patient's HRQL as the condition progresses, although the systematic review by Al-Batran (2010) (13) found strong evidence of HRQL deterioration as soon as patients progressed on chemotherapy.

Pre-progression health state

Within the economic model HRQL is assumed to be constant in the pre-progression health state. HRQL is also adjusted in the presence of important treatment-related AEs and tumour response (PR/CR) to more accurately reflect the patient experience. AEs and tumour response are believed to be clinically meaningful events which would have an impact on patient HRQL, but which are not already captured in the health state utility values used.

Post-progression health state

Disease progression is generally associated with a notable decline in patient HRQL (13). There is however limited HRQL data collected for patients who have experienced disease progression given the ethical difficulties associated with assessing HRQL in patients who are receiving end-of-life care. Given the lack of further data in the post-progression health state, no attempt has been made to model HRQL across time or with respect to proximity to death. Again this approach is the same across both models.

Health-related quality-of-life data from clinical trials

The full explanation of the method of elicitation, valuation and time points when measurements were made and the results of the HRQL collected in the RAINBOW and REGARD trial is provided in Section 4.7. An overview is provided below.

RAINBOW

The RAINBOW trial included two measures of HRQL as secondary endpoints; the EQ-5D and the EORTC QLQ C-30 (Version 3).

EQ-5D

EQ-5D data were collected at baseline, then every six weeks and at the end of treatment. Compliance was high in both arms of the trial at baseline and follow-up visits though it decreased as patients stopped treatment in the PBO+PAC and RAM+PAC arms. In the RAINBOW trial over 60% of patients in both arms completed the 30-day post discontinuation EQ-5D questionnaire.

Table 71 RAINBOW: EQ-5D Results

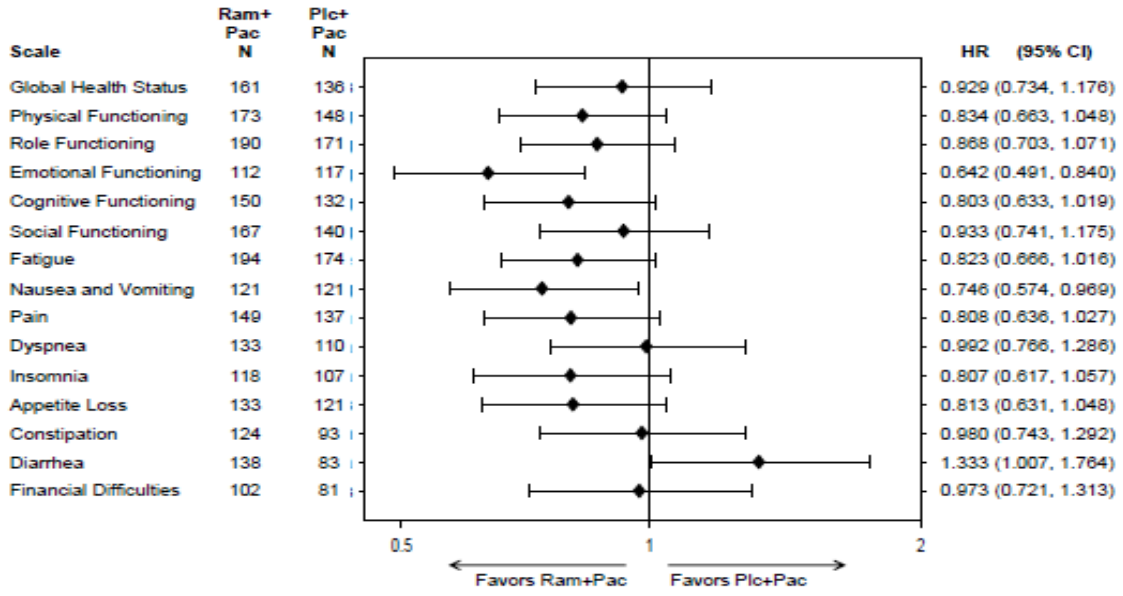
	RAM+PAC N=330	PBO+PAC N=335
Compliance, n (%)		
Patients completing baseline EQ-5D	323 (98)	328 (98)
Patients completing baseline plus post-baseline EQ-5D	287 (87)	274 (82)
Patients completing end of treatment (30-day post-continuation) EQ-5D	211 (64)	206 (61)

Source: Wilke (6)

EORTC-QLQ-C30

The RAINBOW trial also collected HRQL data using the cancer-specific measure, the EORTC QLQ C-30 (Version 3). Data were collected at baseline, then every six weeks and at the end of treatment (30 days post-discontinuation visit). A trend was shown toward improvement for RAM+PAC compared to PBO+PAC in all fifteen components except diarrhoea and a statistically significant improvement in emotional function and nausea and vomiting.

Figure 52 Time to deterioration in EORTC QLQ-C30 Scales



Source: ASCO presentation (83), RAINBOW CSR (99)
Abbreviations: N = number of events; Plc = placebo

REGARD

In the REGARD trial HRQL data was collected using the EORTC QLQ-C30 (Version 3). The questionnaires were administered at baseline and prior to infusion at Cycles 4, 7 and 10. Again completion rates of questionnaires were good amongst those who were progression-free but rapid disease progression meant that over half of all patients completed only the baseline questionnaire.

Table 72 REGARD: EORTC QLQ-C30 Compliance (ITT Population)

Time	RAM (N=238)		PBO (N=117)	
	Number Completed/Number Expected[a]	Compliance (%)	Number Completed/Number Expected[a]	Compliance (%)
Baseline	230/238	97	110/117	94
6 weeks	114/130	88	29/36	81
12 weeks	66/72	92	11/12	92
18 weeks	38/42	90	5/5	100

Source: Chau (90)
[a] The number of expected questionnaires decreased over time as the number of patients discontinuing therapy increased.

The use of the REGARD EORTC data would have required a mapping algorithm to be applied to the data to convert it into EQ-5D values. Mapping is always second best to the direct use of EQ-5D and may lead to increased uncertainty (139). Importantly, there were insufficient post-baseline EORTC data available due to the rapid disease progression of

patients in both arms. Estimating this data would require data imputation which would have created even more uncertainty. For these reasons EQ-5D data collected in the RAINBOW trial was used in both the monotherapy and combination therapy models.

The EORTC QLQ-C30 baseline data was compared across the RAINBOW and REGARD trials using the Wilcoxon-Mann-Whiney test to assess if patient baseline HRQL was different across the trials. The reported values were shown to be the same across 13 of the 15 components. The evidence is presented in Appendix 10.

Mapping

No mapping exercise has been conducted.

Health-related quality-of-life data used in cost-effectiveness analysis

Pre and post-progression utility values

The pre-progression health state utility value was calculated using the baseline mean EQ-5D index score for the entire RAINBOW ITT population (i.e. across both arms) and applying UK weights (140). These estimates are summarised in Table 73.

The utility estimated at baseline was used to estimate the health state utility value for pre-progression.

The post-progression health state utility value was estimated using the mean EQ-5D index score at the end of treatment for all patients who discontinued due to progressive disease (measured at the 30-day post-discontinuation visit).

Table 73 Utility values for combination and monotherapy models

Health state	N	Mean	s.d	s.e
Pre-progression	646	0.737	0.239	0.009
Post-progression	357	0.587	0.346	0.018

Abbreviations: s.d./s.e. = standard deviation/standard error
SE calculated from s.d. and N across both trial arms in each health state

Key differences with literature search

The only study identified which provided utility estimates using a validated generic utility instrument and reported directly by patients and/or carers was the utility publication from the ToGA trial of trastuzumab for the first-line treatment of HER2+ gastric cancer (131). This utility value was used in the NICE technology appraisal of trastuzumab for advanced, HER2+ GC patients (15). The utility values used are provided in Table 74 and compared for validation purposes only. They are shown to be consistent across both pre and post-progression values with those used in the combination and monotherapy models.

Table 74 HRQL from Combination/Monotherapy model and TA208

Economic model for trastuzumab for advanced HER2+ GC			
Health state	**Mean**	**(s.d) or {CILL,CIUL}**	**Reference**
Progression-free	0.7292 at baseline Increasing by 0.000142 daily during PFS	{0.71,0.75}	TA 208 2010
Progressive disease	0.577	(0.3)	TA179 2009, TA208 2010
Economic models for ramucirumab for previously treated advanced GC/GOJ			
Health state	**Mean**	**(s.d) or {CILL,CIUL}**	**Reference**
Pre-progression	0.737	(0.239)	RAINBOW trial
Post-progression	0.587	(0.346)	RAINBOW trial

HRQL Events Applied in the Model

Disease Response

As discussed above, GC/GOJ can have a severe effect on patient HRQL due to symptom burden. The use of chemotherapy may improve HRQL by offering symptom relief and improving gastrointestinal obstruction (13).

Given this clinical rationale, the impact of disease response on patient HRQL in the RAINBOW trial was explored. Of note, the rates of PR/CR seen in the REGARD trial were low and given the absence of EQ-5D data in REGARD, the evidence for the impact of response on HRQL in the monotherapy economic was deemed to be too uncertain to justify its inclusion. Therefore use of a response utility was restricted to the combination therapy model.

The response utility was calculated by looking at the change in utility for all patients who experienced a response in the trial. The change from baseline utility was measured at Cycle 2. This was used because clinically speaking, responding patients would be expected to show the response within the first two cycles. This time period was validated by clinical

experts as plausible. This increment was then applied to the proportion of patients who experienced PR/CR in the RAM+PAC. The response is assumed to last for the whole PFS period and the utility value is applied to the first model cycle for simplicity. As no data were available for DOC, it was assumed that the proportion of patients responding and the utility increment would be the same as for PBO+PAC, to avoid biasing against DOC. No response utility was applied to the BSC arm in the combination therapy model as the rate observed in clinical trials was very low.

Table 75 Disease response rates and utility values by interventions

Intervention	% of CR/PR assumed in model	Standard error* (s.e)	Utility Increment (s.e) †	Source
RAM+PAC	27.9%	2.79%*	0.014 (0.019)	RAINBOW IPD
DOC	16.1%	1.62%*	0.014 (0.019)	RAINBOW IPD
BSC	-	-	-	-
RAM	-	-	-	-

*Assumption that s.e. was equal to 10% of the mean proportion. †Calculated from s.d. for patients across both trial arms (s.d.=0.214, N=130)

Adverse reactions

Adverse events may occur as a result of the underlying condition and subsequent tumour burden, or they may be due to the use of active treatments. To fully incorporate the potential impact of treatment or disease related AEs on HRQL, utility decrements are applied for each AE meeting the model inclusion criteria. The inclusion criteria were informed by TA208 (15).

- In the monotherapy model AEs were included if they occurred in >5% of patients, in either arm of the REGARD trial.
- In the combination therapy model AEs were included if they occurred in >5% of patients in either arm of the RAINBOW trial, or in > 5% of patients in the BSC and DOC arms of the relevant clinical trials (2,7,92).

An additive approach to applying AE disutilities was adopted. The expected total QALY decrement associated with each AE was calculated by multiplying the utility decrement of an individual event by the duration of the event and the proportion of patients experiencing the event (Equation 1). This decrement then applied to the first cycle of the model for simplicity.

Equation 1: QALY decrement calculation

QALY loss = % patients experiencing AE x AE utility decrement x AE duration in years

Adverse event utility decrements

The literature reviews for economic evaluations and utility studies were reviewed to identify potential sources of disutility values and event durations for each of the AEs identified as potentially important. None of the identified utility studies contained individual AE utility decrements. The only CEA identified in the economic evaluation literature review (15) did not contain any information on the AE disutilities or duration of events. To identify alternative sources a targeted review was conducted of NICE appraisals of therapies for solid tumours and other cancers. One recent single technology appraisal of pixantrone for the treatment of adults with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma (NICE TA306 (141)) included utility data from a number of studies reporting HRQL data for solid tumour patients. These studies have been sourced and the utility values have been taken directly from them. In the case where a disutility cannot be sourced from the literature for an AE, assumptions were made. The full list of AEs, the disutility applied, its source and any assumption made are presented in Table 76.

Table 76 AE utility decrements

Adverse event	Utility decrement	s.e.*	Source
Abdominal pain	-0.069	0.007	Assumption: same as pain
Anaemia	-0.115	0.012	Swinburn 2010 (142)
Anorexia	-0.153	0.015	Assumption: maximum disutility of all other G3-4 AEs
Fatigue	-0.119	0.012	Lloyd 2006 (143)
Febrile neutropenia	-0.150	0.015	Lloyd 2006 (143)
Hypertension	-0.153	0.015	Swinburn 2010 (142)
Infection	-0.090	0.015	Assumption: same as neutropenia (Nafees 2008 (144))
Neutropenia	-0.090	0.015	Nafees 2008 (144)
Pain	-0.069	0.007	Doyle 2008 (145)

*s.e. has been set to 10% of mean value to enable calculation of probabilistic value where not reported

Adverse event duration

The duration of each AE was estimated using the same source as was used for the AE disutility values – TA306 for pixantrone. The manfucturer's submission reported data from the PIX301 trial for the duration of each of the AEs which have been included in this

economic model. These AE durations were used in the ramucirumab combination and monotherapy economic models in the absence of any other data source. They were validated by clinical experts who agreed they appeared appropriate for GC/GOJ, though the duration of infection might be overestimated. The potential impact of this is explored in the results section. The data are reported in Table 77 in days and have been converted into years within the model to allow the QALY decrement to be calculated as shown in Equation 1.

Table 77 AE durations

Adverse event	Days	Source
Abdominal pain	17.0	TA306 MS
Anaemia	16.1	TA306 MS
Anorexia	35.0	TA306 MS
Fatigue	31.5	TA306 MS
Febrile neutropenia	7.1	TA306 MS
Hypertension	8.0	Assumption: same as hypotension (TA306 MS)
Infection	15.1	Assumption: same as neutropenia (TA306 MS)
Neutropenia	15.1	TA306 MS
Pain	17.0	Assumption: same as abdominal pain (TA306 MS)

Abbreviation: MS, manufacturer's submission

Summary of quality-of-life values for cost-effectiveness analysis

To summarise, the baseline utility value for all patients in the RAINBOW trial (Table 73) was used as the pre-progression utility value for all patients in the combination and monotherapy models. Events which affect HRQL, such as AEs, or experiencing a disease response, are subtracted or added to this value as appropriate. All utility increments or decrements are added in the first cycle of the pre-progression health state for simplicity.

After passing into the post-progression health state all patients receive a utility value of 0.587 (Table 73) for the duration that they are in post-progression survival (PPS). This is the mean value from the 30-day post-treatment discontinuation visit for patients who discontinued due to progressive disease in the RAINBOW trial.

A utility value of zero is applied in the death state.

Table 78 Summary of quality-of-life values for cost-effectiveness analysis: combination therapy model

Health state	Utility value	s.d./s.e.	Reference in submission	Rationale
Pre-progression	0.737	0.009	Table 73	RAINBOW trial IPD
Post-progression	0.587	0.018	Table 73	RAINBOW trial IPD
Increment/decrement	**Utility value**	**s.d./s.e.**	**Reference in submission**	**Rationale**
Disease response	0.014	0.019	Table 75	RAINBOW trial IPD
Abdominal pain	-0.069	0.007	Table 76	See Table 76
Anaemia	-0.115	0.012	Table 76	Table 76
Anorexia	-0.153	0.015	Table 76	Table 76
Fatigue	-0.119	0.012	Table 76	Table 76
Febrile neutropenia	-0.150	0.015	Table 76	Table 76
Hypertension	-0.153	0.015	Table 76	Table 76
Infection	-0.090	0.015	Table 76	Table 76
Neutropenia	-0.090	0.015	Table 76	Table 76
Pain	-0.069	0.007	Table 76	Table 76

Table 79 Summary of quality-of-life values for cost-effectiveness analysis: monotherapy model

Health state	Utility value	s.d./s.e.	Reference in submission	Rationale
Pre-progression	0.737	0.009	Table 73	RAINBOW trial IPD
Post-progression	0.587	0.018	Table 73	RAINBOW trial IPD
Increment/decrement	**Utility value**	**s.d./s.e.**	**Reference in submission**	**Rationale**
Abdominal pain	-0.069	0.007	Table 76	Table 76
Anaemia	-0.115	0.012	Table 76	Table 76
Hypertension	-0.153	0.015	Table 76	Table 76

5.5 Cost and healthcare resource use identification, measurement and valuation

This section reports the resource utilisation and unit costs used in the CEA of RAM+PAC and RAM.

Resource identification, measurement and valuation studies

Literature Search

The literature searches of economic models were reviewed to identify appropriate potential resource use and cost data sources for these economic models.

The only UK studies involving resource use and cost data were relating to the NICE appraisals for trastuzumab (TA208) (15) and capecitabine (TA191) (79). These studies highlighted the following cost data sources which have been utilised in this submission;

- NHS Reference costs for drug administration, follow-up and support care, adverse events;
- Coyle, 1999 (145) for terminal care costs
- British National Formulary (BNF) for drug costs

Other cost sources have been applied as appropriate. Resource use values have been identified from appropriate GC/GOJ specific sources and clinical opinion.

NHS References Costs

Unit costs were used for the most recent period reported at the time of model development. For the NHS reference costs these were the costs for 2012/13 which were published in December 2013 by the Health and Social Care Information Centre (HSCIC) (146).

The resources required are based on clinical practice and evidence from the clinical trials. Resources are costed using the Health Resource Groups (HRGs) where available. Table 80 summarises the resource components which have been included in both economic models and their primary source. A full explanation of each resource component is provided in the accompanying text.

Table 80 Summary of resource components included

Resource	Component	Source
Drug costs	Acquisition costs	eMIT/BNF
	Delivery costs	NHS HRGs
	Pre-medication costs	BNF
Follow-up costs	Monitoring	NHS HRGs
	Tests	NHS HRGs
Adverse events	Grade 3-4 AEs	NHS HRGs
Hospitalisation	Hospitalisation costs	NHS HRGs
Terminal care	Terminal care cost	TA208
Best supportive care	BSC components	NHS HRGs
		BNF

Abbreviation: eMIT= electronic market information tool

Chemotherapy procurement and delivery costs

Unbundled HRGs are available for chemotherapy procurement but were not available for ramucirumab at the time of model development, and are not appropriate in estimating the drug cost.

A bottom up approach is instead used for calculating chemotherapy acquisition costs. This is done using estimates of the required dose and drug costs from eMIT for the generically available chemotherapies and from the BNF for ramucirumab.

Delivery codes are available for each chemotherapy attendance which reflects the complexity of the treatment administration and resources required. The delivery HRGs can be generated for day cases, outpatients and regular attenders (147).

Chemotherapy delivery codes

Chemotherapy delivery codes were available for the 2013/14 (published February 2013) at the time of model development. The codes relevant to and used in this appraisal are provided in Table 81.

Table 81 Chemotherapy delivery codes (Department of Health 2013/14)

Code	Description
SB11Z	Deliver exclusively oral chemotherapy
SB12Z	Deliver simple parenteral chemotherapy at first attendance
SB13Z	Deliver more complex parenteral chemotherapy at first attendance
SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance
SB15Z	Deliver subsequent elements of a chemotherapy cycle

Source: Department of Health (147)

Follow-up costs

The follow-up costs capture resources such as procedures, tests and monitoring which are used in both the pre- and post-progression health states. The list was primarily informed by the supportive care elements identified in TA208 (15) and was adapted for the second-line setting based on clinical expert opinion. Patients on active treatment will have complete blood count, renal function tests and hepatic function tests. Monitoring of patients, both whilst on and off treatment, is based on clinical practice.

The following costs are included in the economic model:

1. Monitoring - consultant visits, CT scans
2. Tests – full blood count, renal function test, hepatic function test

Ramucirumab always requires blood pressure monitoring and urinalysis (i.e. a dipstick test). These are bench side tests and therefore they are assumed to occur during the consultation visit and be included in that cost.

Monitoring HRGs

The relevant codes for monitoring treatment are consultant-led follow-up attendance and CT scans. HRG codes for CT scans vary depending on the number of areas to be scanned and the inclusion or exclusion of contrast. A clinical expert advised on the selection of relevant codes for CT scans for monitoring patients with NSCLC in a previous technology appraisal (TA309) (14) which was used in these economic models.

Table 82 HRGs for monitoring

Code	Description	Category
370	Medical Oncology	Consultant Led
RA12Z	Computerised Tomography Scan, two areas with contrast	Diagnostic Imaging
RA13Z	Computerised Tomography Scan, three areas with contrast	Diagnostic Imaging

Source: HSCIC (146)

HRGs for Tests

Complete blood counts, hepatic and renal function tests are assumed to be administered at the start of each treatment cycle. This is to assess patients' eligibility for continued treatment. Routine testing is assumed not to continue once treatment has ceased.

Table 83 HRGs for tests

Code	Description	Category
DAPS05	Haemotology	Directly Accessed Pathology Services
WA20Z	Examination, Follow-up or Special Screening	Directly Accessed Diagnostic Services
WA20Z	Examination, Follow-up or Special Screening	Directly Accessed Diagnostic Services

Source: HSCIC (146)

Adverse events

The full list of HRG codes used for the costing of AEs has been provided under section 5.5.7; *adverse reaction unit costs and resource use.*

Hospitalisation

The rate of hospitalisations was collected in the RAINBOW and REGARD trials and included in the economic models. Hospitalisation was costed using the HRG codes for non-elective inpatients stays (long-stay, ie >1 day) for 'Malignant Gastrointestinal Tract Disorders, with multiple Interventions' with various complication and comorbidity scores. These were combined by calculating a weighted average (weight by their frequency) to reflect the potential variation in the resource requirements associated with hospitalisation.

Table 84 HRG codes used for hospitalisation costs; non-elective inpatient (long stay), medical oncology (code 370)

Currency Code	Currency Description
FZ92A	Malignant Gastrointestinal Tract Disorders, with Multiple Interventions, with CC Score 7+
FZ92B	Malignant Gastrointestinal Tract Disorders, with Multiple Interventions, with CC Score 3-6
FZ92C	Malignant Gastrointestinal Tract Disorders, with Multiple Interventions, with CC Score 0-2
FZ92D	Malignant Gastrointestinal Tract Disorders, with Single Intervention, with CC Score 6+
FZ92E	Malignant Gastrointestinal Tract Disorders, with Single Intervention, with CC Score 3-5
FZ92F	Malignant Gastrointestinal Tract Disorders, with Single Intervention, with CC Score 0-2
FZ92G	Malignant Gastrointestinal Tract Disorders, without Interventions, with CC Score 9+
FZ92H	Malignant Gastrointestinal Tract Disorders, without Interventions, with CC Score 5-8
FZ92J	Malignant Gastrointestinal Tract Disorders, without Interventions, with CC Score 3-4
FZ92K	Malignant Gastrointestinal Tract Disorders, without Interventions, with CC Score 0-2

Source: HSCIC (146)

Terminal Care

No suitable HRGs for terminal care exist. For consistency, these resources have been costed using the same approach as previous appraisals (TA208) (15). Terminal care costs were applied as a one-off cost in the final cycle prior to death for simplicity and to reflect that there is an increased resource burden at the end of a patient's life.

Best supportive care

There is a lack of existing literature or data concerning the treatment of GC/GOJ patients in the second-line setting. To fill this gap Lilly conducted a treatment pattern study of patients who received a platinum plus fluoropyrimidine in the first-line setting in the UK. The study was a chart review of hospital medical records which assessed the supportive care received by all patients (n=200), disaggregated by whether they received a second-line therapy (n=57) or supportive care only (n=143) (5).

Specific BSC components were identified for inclusion if they were received by at least 10% of patients receiving supportive care alone or receiving active treatment. The list was then refined based on expected resource impact and the possibility of double counting with the treatment of AEs. The BSC components recevied in >10% patients are outlined in Table 85 along with the rationale for their inclusion or exclusion.

Table 85 BSC elements identified in chart review and included in model

BSC Category	Resources	Additionally treated (N=57)		BSC only (N=143)		Included	Comment/resource for exclusion
		n	%	N	%		
Pain control	Opiate analgesics	24	42.1%	90	62.9%	Yes	Morphine most commonly used opiate analgesic in REGARD/RAINBOW CSRs
	Other analgesics	8	14.0%	42	29.4%	No	Cost impact of other analgesics (e.g. NSAIDs) judged to be low relative to opiates
Distress management	Not specified	6	10.5%	21	16.9%	Yes	Cognitive behavioural therapy used as a proxy
Antiemetics	Not specified	12	21.1%	52	36.4%	No	Not a cost driver
Antibiotics	Not specified	4	7.0%	17	11.9%	No	Not a cost driver and assumed to be captured in infection and febrile neutropenia AEs
Transfusions	Red blood cell transfusion	5	8.8%	34	23.8%	Yes	May be included under blood loss and anemia AEs but included as likely to be a cost driver
Admitted to hospice for palliation	Not specified	26	45.6%	37	25.9%	No	Assumed to be captured in terminal care
Radiation therapy	Not specified	8	14.0%	17	11.9%	Yes	May be included under blood loss AE but included as likely to be a cost driver
Nutritional support	Oral dietary supplements	17	29.8%	34	23.8%	No	Not a cost driver and assumed to be captured under anorexia AEs

Abbreviations: NSAIDs = non-steroidal anti-inflammatory drugs

The supportive care components were costed using the relevant HRG codes where possible or an alternative data source where not (Table 86).

Table 86 BSC components and costing source

BSC Category	Currency code	Currency description	Service description	Data sheet
Morphine	Oral drug costs	N/A – drug cost used (BNF)		
Distress management	A06A1	Occupational Therapist, Adult, One to One (1 care contact)	-	CHSAHP - Community Health Services - Allied Health Professionals
Transfusions	SA13A	Procedures in outpatient, Single Plasma Exchange, Leucophoresis or Red Cell Exchange, 19 years and over, Medical oncology	Medical oncology	OPROC – outpatient procedures
Radiation therapy	SC47Z	Preparation for simple radiotherapy with imaging and simple calculation (outpatient)	Outpatient	RAD- radiotherapy
	SC31Z	Deliver a fraction of adaptive Radiotherapy on a megavoltage machine (outpatient)	Outpatient	RAD- radiotherapy

Source: HSCIC (146)

Intervention and comparators' costs and resource use

The cost of ramucirumab and the comparators are comprised of the drug acquisition cost, drug administration cost and the cost of monitoring and tests.

Drug acquisition cost

The drug acquisition cost depends on five main components; the cost of the drug, the average dose required, treatment duration, relative dose intensity (RDI) and any pre-medication required.

Drugs costs

The cost of the generically available chemotherapies has been taken from eMIT. The data from eMIT is the actual price paid by hospitals over the previous twelve month period. There can often be marked differences compared to the BNF due to tendering for generic pharmaceuticals.

Table 87 Chemotherapy costs (eMIT, February 2014 except for ramucirumab)

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

Source: Commercial Medicines Unit (CMU) (148)

The BNF prices are included as a sensitivity analysis.

Table 88 Chemotherapy costs for sensitivity analysis (British National Formulary, 67 March-Sept 2014)

Drug	Units (mg)	Vial size (mL)	Strength	Price
RAM	500mg	50	10mg/mL	£2,500
	100mg	10	10mg/mL	£500
PAC	30mg	5	6mg/mL	£66.85
	100mg	16.7	6mg/mL	£200.35
	150mg	25	6mg/mL	£300.52
	300mg	50	6mg/mL	£601.03
DOC	20mg	2	10mg/mL	£138.33
	80mg	8	10mg/mL	£454.53
	160mg	16	10mg/mL	£1,069.50
	20mg	10	20mg/mL	£160.00
	80mg	4	20mgmL	£530.00
	140mg	7	20mg/mL	£900.00

Source: Medicines Complete (149)

Drug dosing and regimen

The ramucirumab combination and monotherapy treatment regimens were taken from the SPC which is aligned with the relevant clinical trials (16). The dosage used for DOC is taken from the clinical trials included in the NMA (2,110). A regimen of 75mg/m^2 three-weekly is in keeping with English clinical practice.

Table 89 Second-line treatment regimens

Treatment	Drug	Dose	Mode of admin	Treatment admins per cycle	Treatment cycle length (days)	Source
RAM+PAC	RAM	8mg/kg	IV	2	28	Cyramza® SPC (16)
	PAC	80mg/m^2	IV	3	28	Cyramza® SPC (16)
RAM	RAM	8mg/kg	IV	1	14	Cyramza® SPC (16)
DOC	DOC	75mg/m^2	IV	1	21	Ford, 2014 (2)

Abbreviations: admins = administrations

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

Patient weight/BSA: Combination therapy model

For consistency, the patient characteristics from the RAINBOW study were used for all comparators in the combination therapy model. The base case analysis uses the mean body weight (kg) and BSA (m^2) from all patients in the trial. A sensitivity analyses was conducted using the patient population from Region 1.

Table 90 Combination model patient characteristics

Parameter	All patients (base case)	
	Mean	s.e.
BSA (m^2)	1.71	0.01
Body weight (kg)	63.33	0.58

Source: RAINBOW CSR
Abbreviations: kg = kilograms; m=meters

Patient weight/BSA: Monotherapy model

Similarly, the patient characteristics from the REGARD trials are used. A sensitivity analysis was conducted using the patient population in Region 1.

Table 91 Monotherapy model patient characteristics

Parameter	All patients (base case)	
	Mean	s.e.
BSA (m^2)	1.73	0.01
Body weight (kg)	65.19	0.82

Source: REGARD CSR

For each regimen, the required dose is calculated by multiplying the dose by the mean weight or BSA to calculate the planned dosage per treatment cycle (Table 92). For example, in the combination model the DOC 75mg/m^2 regimen reported in COUGAR II (2) results in a dose of 128.25mg for a patient with mean BSA of 1.71 m^2 administered once every 21-day cycle. The planned dosage per treatment cycle is therefore 128.25mg.

Table 92 Dosage planned per treatment

Treatment	Drug	Dose	Mg required	Administration per treatment cycle
RAM+PAC	RAM	8mg/kg	506.64	2
	PAC	80mg/m^2	136.8	3
RAM	RAM	8mg/kg	521.52	1
DOC	DOC	75mg/m^2	128.25	1

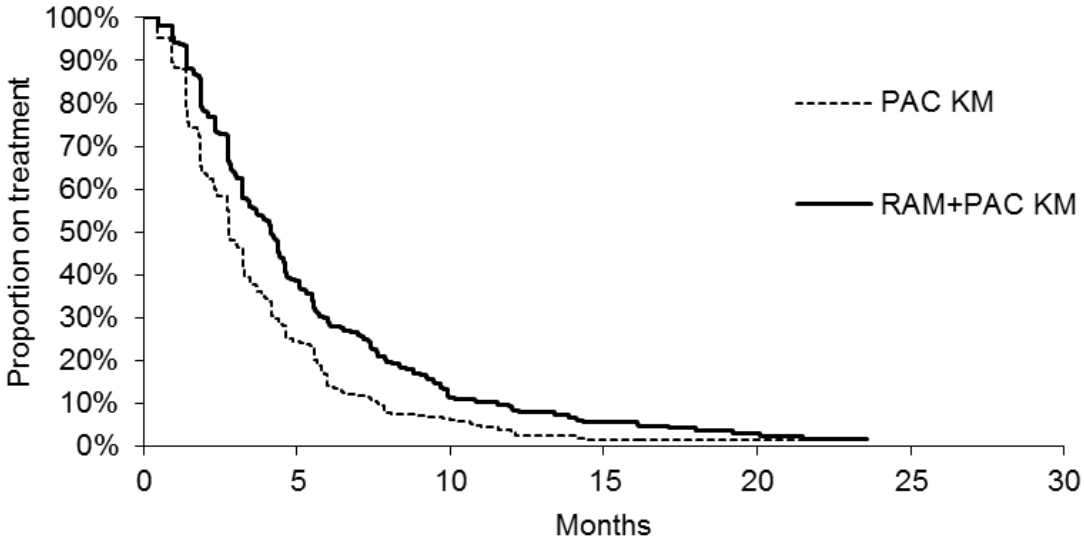
Treatment duration

Treatment duration was estimated using parametric curves to determine the time on treatment from the Kaplan-Meier data. The methodology used to select the most appropriate choice of distribution is the same as outlined in Section 5.3 for PFS and OS. The five parametric distributions were estimated and assessed for goodness of fit compared to the Kaplan-Meier data.

Combination therapy

The Kaplan-Meier plots for time on treatment are provided in Figure 53.

Figure 53 Time on treatment Kaplan-Meier plots for RAM+PAC and PBO+PAC

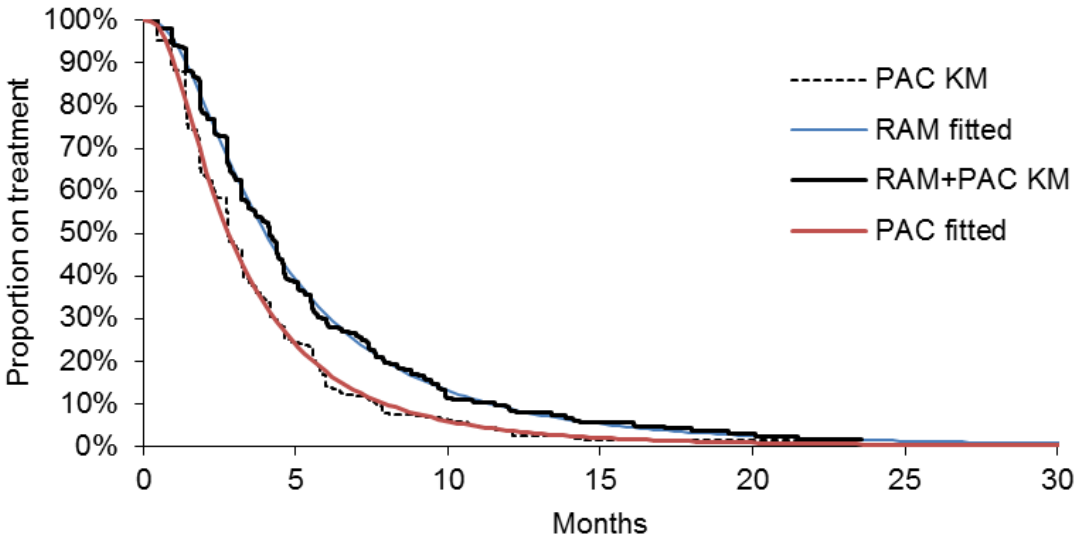


The lognormal was the best fitting distribution using the AIC/BIC (Table 93) and the Cox-Snell residuals (Appendix 11). It was therefore selected as the base case distribution for modelling RAM+PAC time-on-treatment. The log-logistic distribution is included as a sensitivity analysis as the second best fitting distribution.

Table 93 AIC and BIC statistics for time-on-treatment: combination therapy

Model	N	LogL	DF	AIC	BIC	AIC ranking	BIC ranking
Exponential	665	-873.49	2	1750.98	1759.95	5	5
Weibull	665	-839.91	3	1685.82	1699.28	4	4
Lognormal	665	-797.99	3	1601.98	1615.44	1	1
Log-logistic	665	-800.72	3	1607.45	1620.90	3	2
Gamma	665	-797.96	4	1603.91	1621.86	2	3

Figure 54 Kaplan-Meier and lognormal estimates of time-on-treatment for RAM+PAC

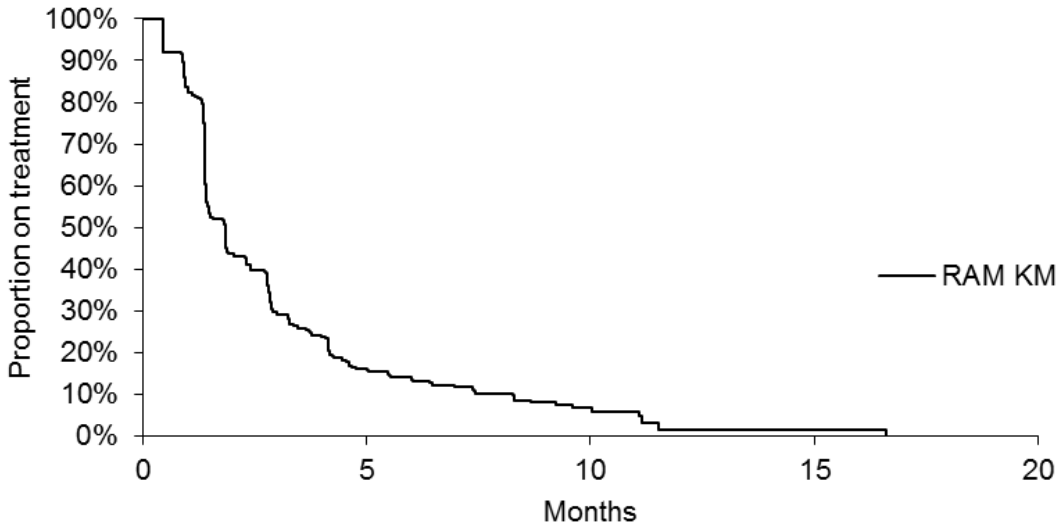


The time on treatment for DOC was calculated as follows; Ford (2) reports the proportion of patients completing different numbers of cycles of DOC in the COUGAR-02 study in which the maximum was six cycles. Given this constraint on the maximum cycles administered, DOC treatment costs were calculated based on the mean cycles received, calculated as 3.07 cycles using these data.

Monotherapy

The Kaplan-Meier plots for time on treatment are provided in Figure 55.

Figure 55 Time on treatment Kaplan-Meier plots for RAM+BSC

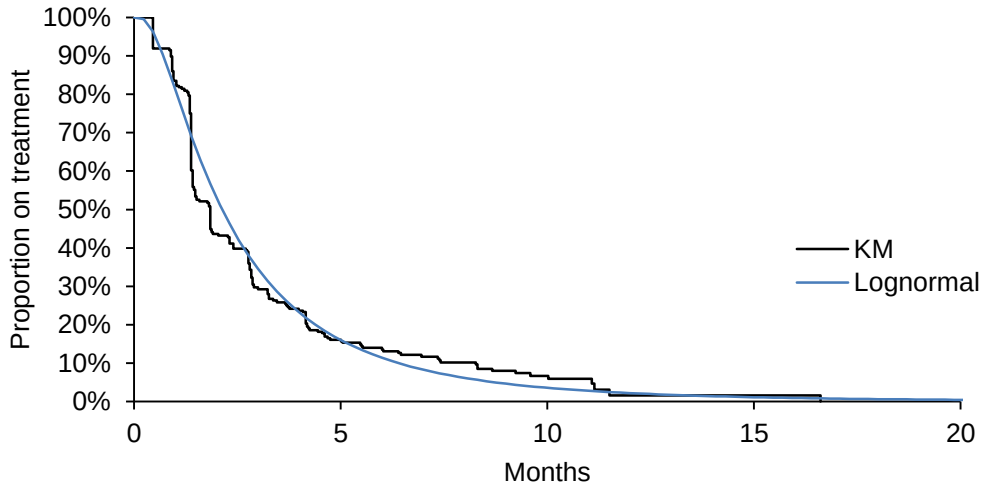


The criteria indicate that the Gamma distribution provides the best fit, with the lognormal and log-logistic distributions providing a marginally poorer fit (Table 94). Additionally, the Cox-Snell Residual plots (Appendix 11) indicate the lognormal distribution provides the best fit to the underlying hazard. The Gamma distribution however provides a significantly longer extrapolation relative to the lognormal and log-logistic distributions, predicting 99% of patients to have discontinued treatment by 113.3 weeks. Given that all patients had experienced disease progression (and therefore discontinued treatment) in REGARD by 71.9 weeks, this was not considered to be a plausible fit even when allowing for uncertainty in the KM estimate. The lognormal was therefore used which estimated 99% of patients to have discontinued treatment by week 68. The log-logistic has been included also as a sensitivity analysis.

Table 94 AIC and BIC statistics for time-on-treatment: monotherapy

Model	N	AIC	BIC	AIC ranking	BIC ranking
Exponential	236	663.00	666.46	5	5
Weibull	236	656.89	663.81	4	4
Lognormal	2236	601.66	608.58	2	2
Log-logistic	236	602.98	609.91	3	3
Gamma	236	593.35	603.74	1	1

Figure 56 Base case distribution for time on treatment in monotherapy model: lognormal



The time on treatment for all comparators is summarised below.

Table 95 Time on treatment for each comparator

Model	Intervention/ Comparator	Time on treatment (mean in months)	Estimated number of treatment cycles*	Mean trial number of treatment cycles
Combination therapy	RAM+PAC	5.69	6.17	5.70
	DOC	2.22	3.07	3.07
	BSC	2.04	N/A	N/A
Monotherapy	RAM+BSC	3.19	6.94	6.10
	PBO+BSC	1.57	3.41	3.9

*note treatment cycles have different lengths for RAM+PAC, DOC and RAM

Relative Dose Intensity

With systemic anti-cancer therapies, the actual dose delivered may differ from the planned dose per treatment cycle. To reflect the ratio of actual to scheduled drug delivery, RDI adjustments are applied to the planned dose per cycle. As patients are more likely to miss or postpone doses or experience dose reductions than to receive additional doses per cycle the assumption was made, in the model, that the RDI is bounded between 0% and 100%. RDI was applied in the base case analysis, and switching off the RDI adjustment is explored as a sensitivity analysis.

The mean RDI estimates for each comparator are presented in Table 96. These estimates were sourced from the single clinical trials for RAM and RAM+PAC. For DOC, the RDI was taken from the Kang study (3) which utilises a lower dose at

60mg/m^2 every three weeks and is not included in the NMA because patients were not randomly assigned to treatment. However, this RDI value was used because the reported median dose intensity in COUGAR II (2) was 46%. That value of 46% was based on the ratio of actual dose received per week to the expected dose averaged over the number of cycles administered, up to a maximum of 6 cycles. The method was notably different to the calculation of RDI for RAM+PAC and so the median RDI from Kang (3) was considered more appropriate. The RDI for ramucirumab both as a monotherapy and in combination with PAC was high, very close to 100 percent, demonstrating that it is a well-tolerated treatment.

Table 96 Relative dose intensity for second-line treatments

Drug	Drug	Mean RDI	s.e.	Source
RAM+PAC	RAM	96.70%	0.44%*	RAINBOW CSR (99)
	PAC	83.60%	0.82%*	RAINBOW CSR (99)
RAM	RAM	97.52%	0.52%**	REGARD CSR (104)
DOC	DOC	95.00%†	1.00%‡	Kang 2012 (3)

*s.e. calculated from s.d. of 8.0 (RAM) and 14.8 (PAC), n=327 for RAM+PAC arm (RAINBOW) and s.d. of 12.0, N=329 for PBO+PAC arm (RAINBOW);
**s.e. calculated from s.d. of 7.95, N=236 for RAM (REGARD) and s.d. of 12.0
†Median RDI values reported in Kang 2012; ‡ s.e. assumed to enable calculation of probabilistic values

Drug acquisition costs per patient were then calculated by determining the number of vials needed to provide the required dose and costed based on the unit price.

Drug wastage

The base case assumption is that there is vial wastage from opened vials and any leftover drug is discarded and not used for another patient. Given this is an orphan condition; the majority of hospitals are unlikely to be treating multiple GC/GOJ patients at any given time making vial sharing unfeasible. In specialist centres which treat a high volume of GC/GOJ patients, there may be some possibility of scheduling patients to allow for vial sharing. An assumption of no vial wastage is included therefore as a sensitivity analysis.

Table 97 Per treatment cycle cost

Treatment	Drug	Dose required per treatment cycle*	Cost per treatment cycle**
RAM+PAC	RAM	972.84mg	£5030.56
	PAC	342.69mg	
DOC	DOC	121.70mg	£34.29
RAM	RAM	508.59mg	£3000

*Equal to weight/BSA multiplied by required dose, RDI and number of administrations per treatment cycle
**Note these treatments have varying cycle lengths

Pre-medication

Pre-medication was included as per the SPC for ramucirumab (16), which references the SPC for PAC (115) for PAC-specific pre-meds. DOC is not licensed for advanced, previously treated GC or GOJ so the pre-medication instructions for DOC from its first-line GC indication were used (Table 98). Pre-medications are costed using the BNF (Table 99) and the cost per cycle is detailed in Table 100.

Table 98 Second-line treatment premedication requirements

Drug	Pre-medication	Dosing	Regimen	Source
RAM	Diphenhydramine hydrochloride**	50mg IV	Pre-administration*	Cyramza SPC (16)
PAC	Diphenhydramine hydrochloride**	50mg IV	Pre-administration*	Paclitaxel SPC (115)
	Dexamethasone	20mg PO	12-6 hours prior	
	Ranitidine	300mg IV	Pre-administration*	
DOC	Dexamethasone	16mg (i.e 8mg b.i.d)	3 days	Docetaxel SPC (123)

*pre-administration is noted as the administration regimen whereby no specific timing is described and therefore assumed to be just prior to the administration of therapy
** or an equivalent antihistamine e.g. chlorphenamine 10 mg IV

Table 99 Premedication drug cost (BNF March-September 2014)

Premedication	Cost	Mg per vial/tablet	Vial size/tabs per pack
Dexamethasone	£12.05	2mg	100
Ranitidine	£0.54	25mg/mL	2-mL
Chlorphenamine	£2.80	10mg/mL	1-mL

Source: Medicines Complete (149)

Table 100 Premedication costs per treatment cycle

Regimen	Premedication	Cost per admin	Admins per treatment cycle	Total cost per treatment cycle**	Treatment cycle length
RAM+PAC	Dexamethasone	£4.02	3	£30.16	28 days
	Ranitidine	£3.24	3		
	Chlorphenamine*	£2.80	3		
RAM	Chlorphenamine	£2.80	1	£2.80	14 days
DOC	Dexamethasone	£12.05	1	£12.06	21 days

*patients receiving RAM+PAC are assumed to require premedication with only one dose of antihistamine per administration of both drugs
**includes wastage

Drug administration cost

As discussed, drug administration was costed according to the appropriate HRG code for chemotherapy delivery, taken from the DH Chemotherapy Regimen List 2013-14 V3 (147). The codes used for each regimen and the associated cost are provided in Table 101. Ramucirumab is yet not included on the chemotherapy regimen list so the delivery code as a monotherapy is estimated to be SB12Z - deliver a simple parenteral chemotherapy. The delivery code for combination therapy is estimated using SB14Z - deliver complex chemotherapy, including prolonged infusional treatment, at first attendance – for the first administration in a cycle and SB15Z – deliver subsequent elements of a chemotherapy cycle – for the subsequent administrations in a cycle. The daycase costs are used as the base case and the outpatient costs are used as a sensitivity analysis.

Table 101 Delivery HRGs for each treatment

Code	Regimen	Daycase Cost	Outpatient Cost
SB12Z	RAM	£214	£155
	DOC	£214	£155
SB14Z	RAM+PAC (Day 1)	£330	£287
SB15Z	RAM+PAC (Day 8 & 15)	£302	£255

Source: HSCIC (146), department of health (147) and estimated

Follow-up care

The follow-up costs capture resources such as tests and clinical monitoring which are used in both the pre- and post-progression health states depending on whether patients are on- (Table 102) or off- (Table 103) active treatment. The rates and frequencies applied were based on expert clinical input.

Consultant visits & CT Scans

In the combination therapy economic model, consultant visits whilst on active treatment were assumed to occur every four weeks. In clinical practice consultation visits are expected every treatment cycle but for simplicity in the economic model they were applied every four weeks. As RAM+PAC is administered every four weeks this is aligned. The cost of consultation visits for DOC are slightly underestimated as the treatment cycle length is three weeks. Upon disease progression patients are then assumed to have consultant visits every twelve weeks based on clinical practice.

Patients receiving BSC only have consultation visits every twelve weeks in the pre-progression and post-progression health states.

CT scanning is assumed to occur every twelve weeks whilst patients are on treatment based on expert clinical input. This is also in keeping with previous technology appraisals of treatments for advanced, late-stage cancer (14). Once patients have progressed CT scanning is assumed not to continue, again in line with clinical practice.

Patients who are receiving BSC do not receive any CT scans.

Full blood count

A full blood count is presumed to be conducted prior to every cycle of treatment in order to ensure patients eligibility for continued treatment.

Hepatic and renal function tests

Similarly, all patients on active treatment are assumed to be assessed using renal and hepatic function tests at the beginning of each treatment cycle.

Once patients have stopped treatment routine testing is ceased in-line with clinical practice.

Patients who receive third-line treatment are assumed to receive consultant visits, CT scanning and tests at the rates assumed for patients on active second-line therapy.

Table 102 Rate and frequencies of follow-up care components on treatment

Follow-up care component	On treatment			
	Mean proportion of patients	Frequency	Weeky frequency in model	Source
CT scan	100%	Every 12 weeks	0.08 per week	Expert opinion
Full blood count	100%	Every treatment cycle	1.00 per treatment cycle	Expert opinion
Renal function test	100%	Every treatment cycle	1.00 per cycle	Expert opinion
Hepatic function test	100%	Every treatment cycle	1.00 per cycle	Expert opinion
Consultation visit	100%	Every 4 weeks	0.25 per week	Expert opinion

Table 103 Rate and frequencies of follow-up care components off treatment

Follow-up care component	Off treatment			
	Mean proportion of patients	Frequency	Weeky frequency in model	Source
CT scan	100%	N/A	N/A	Expert opinion
Consultation visit	100%	Every 12 weeks	0.08 per week	Expert opinion

Unit costs for the different components of follow-up care are provided in Table 104.

Table 104 Overview of follow-up care component costs

Follow-up care component	Costs	Cost year	Source
CT Scan	£133	2012-13	NHS References costs
Full blood count	£3	2012-13	NHS References costs
Hepatic function tests	£28	2012-13	NHS Reference costs
Renal function test	£28	2012-13	NHS References costs
Consultation vistion (on-treatment)	£139	2012-13	NHS References costs
Consultation visit (off-treatment)	£139	2012-13	NHS References costs

Source: HSCIC (146)

The weekly cost for each treatment is broken down by drug cost, pre-mediation, administration, consultation visits and tests required during active treatment. Only consultant visits are applied for patients receiving BSC only. In clinical practice patients receiving no active therapy may be referred to palliative care or discharged to the community and therefore not receive active follow-up with an oncologist. However, as a proportion of these patients are assumed to receive third-line

treatment in both models, continued follow-up is maintained at a frequency of 12 weeks, just as it is for all patients once they have stopped active treatment.

Table 105 Unit costs associated with the technology in the economic model (per week)

	RAM+PAC	DOC	RAM	BSC
Drug cost	£1,257.64	£14.15	£1,500	N/A
Pre-med cost	£15.94	£4.02	£1.40	N/A
Administration cost	£233.50	£71.33	£107	N/A
Consultation	£34.81	£34.81	£34.81	£11.14
Follow-up (tests and CT scan)	£25.82	£30.74	£39.68	N/A
Total	£1,567.71	£155.05	£1,682.89	£11.14

Health-state unit costs and resource use

Table 106 provides a summary of the health states and all the associated costs.

Table 106 Summary table of unit costs associated with the health states

Health state	Item	Value	Ref in submission
Pre-progression			
Drug cost	Ramucirumab	£5/mg	Table 87
	Docetaxel	£0.24/mg	
	Paclitaxel	£0.07/mg	
Drug administration	SB12Z	£214 per admin	Table 101
	SB14Z	£330 per admin	
	SB15Z	£302 per admin	
Pre-medication	Dexamethasone	£0.12 per tablet	Table 99
	Ranitidine	£0.01/mg	
	Chlorphenamine	£0.28/mg	
Monitoring and tests	Consultation visit	£139 per visit	Table 104
	CT scan	£133 per visit	
	Hepatic function tests	£28 per test	
	Renal function tests	£28 per test	
	Blood tests	£3 per test	
Adverse events	Abdominal pain	£722 per episode	Table 115, Table 116
	Anaemia	£1,211 per episode	
	Fatigue	£562 per episode	
	Anorexia	£399 per episode	
	Febrile neutropenia	£3,019 per episode	
	Hypertension	£1,199 per episode	
	Infection	£2,160 per episode	
	Neutropenia	£364 per episode	
	Pain	£722 per episode	
BSC	Morphine	£0.95 per day	Table 114
	Distress management	£76.10 per session	
	Blood transfusion	£290.03 per admin	
	Radiotherapy	£430.00 per fraction	
Hospitalisation	Per day cost	£526.05 per day	Table 111
Post-progression			
Third-line therapy	Docetaxel	£0.24/mg	See Appendix 11
	Paclitaxel	£0.07/mg	
	Capecitabine	£2.15 per tablet	
	5-FU	£0.70/g	
Third-line drug administration	SB12Z	£214 per admin	Table 101
	SB14Z	£330 per admin	
	SB15Z	£302 per admin	
Hospitalisation	Per day cost	£526.05 per day	Table 111
Terminal care	Terminal care cost	£4,467.60	Table 112

Hospitalisation

Patients with advanced GC/GOJ can experience quite significant tumour burden and disease related symptoms. Hospitalisation may occur for a number of reasons due to disease related or treatment specific side effects. Hospitalisation costs are therefore included as well as AEs because hospitalisation occurs for reasons other than treatment-related AEs (such as pneumonia, ascites, plural effusion, etc.). The hospitalisation data from the trials was incorporated and costed using NHS reference costs.

As discussed previously, active treatment is associated with symptom reduction and improved disease-specific QoL (13). The hospitalisation data from the RAINBOW and REGARD trials provide further evidence of the reduced symptom burden for patients receiving ramucirumab, either as a combination or a monotherapy.

Combination therapy model

In the RAINBOW trial, hospitalisation data were collected for the safety population (patients receiving a study drug). These data were used to inform the following parameters for the economic model:

- Length of stay
- Rate of hospitalisations

The length of stay by treatment arm is presented in Table 107.

Table 107 Length of stay: combination therapy model

Treatment	Mean days	s.d	Source
RAM+PAC	14.60	1.20	RAINBOW safety population
PBO+PAC	18.20	1.68	RAINBOW safety population

The observed data was used to inform the mean rate of hospitalisations in the combination therapy model. Attempts were made to fit a Poisson and negative binomial model to the data but results from the Chi-squared goodness of fit tests indicated that they were a poor fit to the data. They have been included in the economic model to estimate the rate of hospitalisation as sensitivity analyses.

Due to lack of data collected for patients post-progression, the rate of hospitalisation was assumed to be constant in the post-progression period. An alternative assumption of increased hospitalisation due to disease progression is explored in the sensitivity analysis by applying a relative risk of 2 and 3 to hospitalisation in the post-

progression health state. This assumption was validated by clinical expert opinion who expected hospitalisation to either stay the same (with fewer treatment complications balanced with greater symptom burden) or double.

The data from the REGARD trial (discussed below) was used for the BSC comparison. The data for PAC will be used for the DOC comparator given the lack of published hospitalisation specific data available for DOC.

Table 108 Hospitalisation probabilities: combination therapy model

Cohort	Probabilities per week		Source
	PFS	PPS	
RAM+PAC	0.024	0.024	RAINBOW
DOC*	0.036	0.036	RAINBOW
BSC	0.055	0.055	REGARD

* assumed to be the same as PAC due to lack of alternative data

Monotherapy model

In the REGARD trial, data on the length of stay and rate of hospitalisation were also collected for the safety population. These data were used to inform the length of stay and hospitalisation parameters in the monotherapy model.

Table 109 Length of stay: REGARD

Treatment	Mean days	s.d	Source
RAM	13.40	10.68	REGARD safety population
BSC	10.40	6.79	REGARD safety population

Similar to the combination therapy model, the observed data were used to inform the mean rate of hospitalisations in the monotherapy model.

Poisson and negative binomial regression models were also fitted to the pre-progression data though the Chi-squared goodness-of-fit test indicated the Poisson model did not provide a good fit of the data. The negative binomial seemed to provide a reasonable fit though the observed data was used in the base case for consistency with the combination therapy. Both models are also implemented in the sensitivity analyses.

Again the same probability of hospitalisation is applied in the post-progression period which is explored in the sensitivity analysis.

Table 110 Hospitalisation probabilities: monotherapy model

Cohort	Probabilities per week		Source
	PFS	PPS	
RAM	0.034	0.034	REGARD
BSC	0.055	0.055	REGARD

The model combines the rate of hospitalisations with the length of stay and per day unit cost data. This average cost per inpatient day provided for the UK was £526.05 with a standard error of £242.68. This is the average weight by activity of the non-elective inpatients stays for 'Malignant Gastrointestinal Tract Disorders, with multiple Interventions' with various complication and comorbidity scores (Table 84).

Table 111 Hospitalisation cost per day (NHS Reference Costs)

	Cost per day	s.e
Hospitalisation cost (weighted by complication and comorbidity score)	526.05	242.68

Source: HSCIC (146)

Terminal care cost

All patients are assumed to receive terminal care as a one-off cost prior to death. The cost for terminal care was taken from TA208 for trastuzumab (15) where an 'end of life' cost of £4,000 (2010 values) was applied. The end of life value was sourced from a then recent appraisal of sunitinib for the treatment of GIST (150). The cost is intended to reflect the intensive palliative and hospice related care which is necessary at the end of life. The cost used in the appraisals TA179 and TA208 was based on an estimate from the literature (145) which represents the average cost of hospital and hospice stays. It was inflated to 2014 values for the purpose of these economic analyses.

Table 112 Terminal care costs

Cost	s.e.	Year	Source
£4,467.60	£1,833.88	2014	TA 208 (15)

Best supportive care

As discussed already, a chart review of UK treatment patterns was used to inform the components and rates of supportive care received by all patients with advanced GC/GOJ (5). Clinical expert opinion has been used to inform the frequency with which some components of BSC are administered. Table 113 provides an overview of the components, and rates, taken from the chart review, and the frequencies used.

The rates of BSC components varied between the additionally treated and supportive care only patients in the chart review. The rates from the additionally treated patients were applied for those receiving an active comparator, and the rates for supportive care only for those receiving BSC.

Post-progression, all patients receive BSC and a small minority receive third-line treatment. The same rates used in the pre-progression state were applied there.

Table 113 BSC components: frequency and proportion of administrations

Component	Frequency/dose of administration	Proportion of patients receiving		Source
		Additionally treated	Supportive care only	
Morphine	Daily, 40mg	As 42.1%	62.9%	BNF 67 2014
Cognitive behavioural therapy	6 contacts, weekly	10.5%	16.9%	NHS Choices
Blood transfusions	1 transfusion per month	8.8%	23.8%	Assumption
Radiotherapy	1 fraction of radiotherapy per month	14.0%	11.9%	Assumption

The BNF guidance on prescribing morphine in palliative care indicates that "Recommended starting doses vary but, generally, a starting dose between 20–30 mg daily is safe for opioid-naïve patients and 40–60 mg daily for patients being switched from a regular weak opioid" (151). The model applied a 40mg dose as the midpoint between the minimum and maximum recommended doses.

The NHS choices website recommends between 5 and 20 sessions of cognitive behavioural therapy (CBT)(152). Six weekly sessions is used as an estimate, given the terminal nature of the condition.

As a simplifying assumption, for patients receiving blood transfusions and radiotherapy, one administration per month is assumed.

A summary of the BSC frequency per week and cost per administration is provided in Table 114.

Table 114 BSC rates implemented in model

Component	Frequency/week	Cost per episode/administration
Morphine	7.00	£0.95
Cognitive behavioural therapy	1*	£76.10
Blood transfusions	0.23	£290.03
Radiotherapy	0.23	£430.00

*applied as a total of 6 weekly CBT sessions

A scenario whereby all patients (actively treated or BSC only) received the same rate for each BSC component is tested in the sensitivity analysis.

Adverse reaction unit costs and resource use

The cost of treating AEs was included in the economic models to capture their impact. AEs were included primarily based on their incidence compared to specific thresholds (described below). AEs which met these criteria were then reviewed in terms of their expected impact on cost and HRQL. Those deemed to have an insignificant impact on costs and HRQL (based on the required treatment protocol and symptoms) were excluded. This process is described in Appendix 11.

Combination therapy economic model

AE counts were sourced directly from the RAINBOW clinical study report (CSR) for RAM+PAC, from the REGARD CSR for BSC and for the COUGAR II study for DOC. Grade 3-4 AEs were included if they occurred in more than 5% of patients on any treatment. An attempt to estimate the AEs using the NMA was made but data was not available for all adverse events of relevance (see Appendix 6). Therefore the rates observed in the trials have been used.

Monotherapy economic model

AE counts for the REGARD model were sourced directly from the CSR for RAM and BSC. Grade 3-4 AEs occurring in > 5% of patients, in the RAM arm, were included in the economic model.

Adverse event HRGs

The NHS reference costs were considered the most appropriate source for costing adverse events as they allow maximum relevance to clinical practice in England. This is in keeping with TA208 which used HRGs where they were available.

Table 115 and Table 116 shows the AE costs included in the economic model. A full explanation of the HRG codes chosen and the rationale is provided in Appendix 11.

Table 115 Adverse event costs used in the combination model

Grade	Adverse Event	Cost	HRG Code
3-4	Abdominal pain	£722	PA29Z
	Anaemia	£1,211	SA04G-L
	Anorexia	£399	PA28A-B
	Fatigue	£562	FZ92K
	Febrile neutropenia	£3,019	PA45Z
	Hypertension	£1,199	EB04Z
	Infection	£2,160	FZ36M-Q
	Neutropenia	£364	WA02W
	Pain	£722	PA29Z

Source: HSCIC (146)

Table 116 Adverse event costs used in the combination model

Grade	Adverse Event	Cost	HRG Code
3-4	Abdominal pain	£722	PA29Z
	Anaemia	£1,211	SA04G-L
	Hypertension	£1,199	EB04Z

Source: HSCIC (146)

Rates

AE counts were entered into the model for all comparators and converted to a rate. If an AE count was not reported in the full publication of a comparator, the assumption was made that this AE was not observed (rather than not recorded) and a count of zero was applied with a small increment (0.01) added to enable the calculation of probabilistic event rates.

The AEs in the REGARD and RAINBOW trials are described in detail in section 4.12. A summary of the rates included in the combination (Table 117) and monotherapy (Table 118) economic model are provided below for ease of reference.

Table 117 Grade 3-4 adverse event rates used in combination model

Adverse event	RAM+PAC	BSC	DOC
Abdominal pain	5.50%	2.61%%	0.01%*
Anaemia	9.17%	7.83%	6.17%
Anorexia	3.06%	3.48%	6.06%
Fatigue	7.03%	8.70%	0.01%*
Febrile neutropenia	1.22%	0.01*%	7.41%
Hypertension	14.07%	2.61%	0.01%*
Infection	0.01%*	0.01%	14.81%
Neutropenia	40.67%	0.01%*	14.81%
Pain	0.92%	0.01%*	1.11%
Source	RAINBOW CSR (99)	REGARD CSR (104)	Ford, 2014 (2)

*Increment added to allow calculation of probabilistic sensitivity analysis

Table 118 Adverse event rates used in monotherapy model

Grade	Adverse Event	RAM (n=236)	BSC (n=115)
3-4	Abdominal pain	5.08%	2.61%
	Anaemia	6.36%	7.83%
	Hypertension	7.20%	2.61%
	Source	REGARD CSR (104)	REGARD CSR (104)

Miscellaneous unit costs and resource use

Third-line treatment

All patients are assumed to continue to receive BSC upon disease progression, and a proportion of patients go on to receive third-line chemotherapy. Third-line therapies are included only with respect to the drug acquisition and administration cost, and the cost of follow-up care. For simplicity the total cost of receiving third-line therapy is applied to the first cycle following progression. The rates of post-discontinuation chemotherapy in the RAINBOW and REGARD trial are provided below. This included third and further lines of therapies. The rate used in the model is taken from market research (12%) (121).

Table 119 Post-discontinuation in RAINBOW and REGARD

Component	RAINBOW		REGARD	
	RAM+PAC	PBO+PAC	RAM+BSC	PBO+BSC
Post-discontinuation rate	47.9%	46.0%	30.3%	37.6%
Rate used in the model	12%		12%	

Source: RAINBOW and REGARD CSRs

Patients who are eligible for RAM monotherapy are not appropriate for treatment in combination with PAC, in accordance with the MA for ramucirumab (16). These patients may have lingering toxicities from first-line treatment (such as neuropathy, fatigue), or perhaps do not want further cytotoxic therapy. The likelihood of these patients being eligible for treatment with an active chemotherapy in the third-line setting is unknown. After consultation with clinical experts it was still unclear whether RAM monotherapy may allow patients to remain of good PS whilst their toxicities resolve, acting almost as a bridge to third-line therapies. As the base case, patients receiving RAM and BSC only (in either model) were assumed to be able to receive active third-line treatment (at the rate of 12%). Sensitivity analyses are conducted where the third-line treatment rate in the monotherapy model is assumed to be zero, and where it is the rate observed in the REGARD clinical trial. These two sensitivity analyses are also implemented in the combination therapy model (using the RAINBOW observed trial rate).

There are no licensed treatments in the third-line setting for the treatment of advanced GC/GOJ and no published evidence on its usage. Market research data was used to estimate third-line treatment patterns (121). The results showed that third-line treatment is also very heterogeneous with no clear standard therapy. Treatments were included if they were used to treat >10% of patients. This included PAC (19%) and DOC (15%). Capecitabine (10%) and 5FU (5-flurouracil) (10%) were included as otherwise patients receiving a taxane in the second-line setting (RAM+PAC or DOC) would not have a third-line treatment option without rechallenge (i.e treatment with the same type of drug after progressing on it). The assumption of no-rechallenge was made based on clinical practice. These treatments and their proportions were then scaled up to make 100 percent across the four treatments or two treatments for patients who received RAM+PAC or DOC second-line.

Table 120 Distribution of third-line regimens combination model

Second-line regimen	Third-line regimen	Market research share	Proportion of patients in model
RAM + PAC	Capecitabine	10%	50%
	5FU	10%	50%
DOC	Capecitabine	10%	50%
	5FU	10%	50%
BSC	Capecitabine	10%	18.5%
	DOC	15%	27.8%
	PAC	19%	35.2%
	5FU	10%	18.5%

Table 121 Distribution of third-line regimens in monotherapy model

Second-line regimen	Third-line regimen	Market research share	Proportion of patients in model
RAM	Capecitabine	10%	18.5%
	DOC	15%	27.8%
	PAC	19%	35.2%
	5FU	10%	18.5%
BSC	Capecitabine	10%	18.5%
	DOC	15%	27.8%
	PAC	19%	35.2%
	5FU	10%	18.5%

The cost of third-line treatment was estimated in the same way as second-line treatment. Information regarding drug regimens, RDI and mean patient body weight and BSA data were used to determine the required dosage per third-line treatment cycle. Treatment duration was based on an assumption in the absence of alternative available data. The drug acquisition costs and administration costs were estimated from the same sources as for second-line regimens. The full details are provided in Appendix 11.

5.6 Summary of base case de novo analysis inputs and assumptions

Summary of base case de novo analysis inputs

Table 122 Summary of main variables applied in the combination therapy economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Progression free survival	6.00 months (Figure 36)	NR (Weibull)	Clinical parameters and variable
Overall survival	11.63 months (Figure 39)	NR (KM + exponential)	Clinical parameters and variable
Time on treatment	5.68 months (Figure 54)	NR (lognormal)	Treatment duration
Hospitalisation	0.024 per week (Table 108)	NR (multivariate normal)	Hospitalisation
Utility: pre-progression	0.737 (Table 73)	0.009* (Beta)	HRQL data used in CEA
Utility: post-progression	0.587 (Table 73	0.018* (Beta)	HRQL data used in CEA

*s.e.

Table 123 Summary of main variables applied in the monotherapy economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Progression free survival	3.50 months (Figure 45)	NR (lognormal)	Clinical parameters and variable
Overall survival	8.21 months (Figure 48)	NR (Gamma)	Clinical parameters and variable
Time on treatment	3.19 months (Figure 56)	NR (lognormal)	Treatment duration
Hospitalisation	0.034 per week (Table 110	NR (multivariate normal)	Hospitalisation
Utility: pre-progression	0.737 (Table 73	0.009* (Beta)	HRQL data used in CEA
Utility: post-progression	0.587 (Table 73	0.018* (Beta)	HRQL data used in CEA

*s.e.

Base case assumptions

Proportional hazards assumption

To allow the estimation of the treatment effect of RAM+PAC versus BSC and DOC it was necessary to estimate the relative efficacy of RAM+PAC through an NMA. An assumption of PH was made to allow this analysis to be conducted. This assumption was made in favour of alternative methods (i.e. fractionated polynomials) which do not require the PH assumption and would introduce considerable additional uncertainty into the economic model.

Third-line

Post discontinuation therapy is included in the economic model only with respect to the cost associated with treatment as the rates seen in both trials were similar across arms.

The rates of post discontinuation therapy across the ramucirumab trials were between 30 to 50 percent. However, evidence from clinical practice indicates that the rate in England is much lower – an estimate of 12% was used in the model (121). The impact of the rate of third-line therapies is tested in the economic model by including the observed rates from both trials and also a rate of 0 percent.

There is no third-line clinical trial evidence upon which to base the duration of third-line treatment. Therefore, an assumption is needed regarding how long patients receive third-line therapies for. The model assumes patients receive third-line receive treatment for 50% of the time they are in the post-progression health state. This assumption is also tested in the sensitivity analyses with alternative values (25% and 75%).

Hospitalisation

The RAINBOW and REGARD trials collected information on the rate and length of hospitalisation during the period in which the study drugs (RAM+PAC and PBO+PAC; RAM and PBO respectively) were being administered.

The RAINBOW trial showed a statistically different rate of hospitalisation for patients receiving RAM+PAC compared to the PBO+PAC patients (p=0.018). Patients receiving RAM+PAC had lower rates of hospitalisation, which is believed to be due to be improvements in symptom control and reduced tumour burden. A reduction in the rate of hospitalisation was observed in the REGARD trial though this was not

statistically significant (p=0.0736). The differential rate observed in each trial is included in the respective economic models as it is supported by the data and clinical rationale. This assumption is explored in the deterministic sensitivity analysis (DSA) which applies the same rate across both treatments and explores the use of statistical methods to estimate hospitalisation rates.

Additionally, hospitalisation data were not collected in either trial once patients had discontinued study drug. In the absence of alternative data the rate of hospitalisation is assumed to be same in the post-progression health state. Alternative values for the relative risk of post-progression hospitalisation are included at a rate of 2 and 3 times the pre-progression rate. Terminal care costs are included separately, to capture the increased resource burden associated with providing terminal care.

Utility

The model assumes that the use of the EQ-5D data from the combination therapy model is appropriate for both the combination and monotherapy model. No alternative HRQL values appropriate to the patient population in decision problem were identified in the literature search. This method is also preferred to mapping the data from the EORTC-QLQ-C30 to the EQ-5D given the low amount of post-baseline EORTC data collected in the REGARD trial. The appropriateness of using the baseline and post-discontinuation EQ-5D values from RAINBOW is supported by a comparison of the EORTC-QLQ-C30 data at baseline across the REGARD and RAINBOW trial (Appendix 10) which showed the baseline values were similar across the two trials.

The model assumes patients have the same HRQL value for the entire time that they are in the post-progression health state. This is in line with the only other HTA appraisal in this disease area.

5.7 Base case results

Base case incremental cost-effectiveness analysis results

Combination therapy

The total costs, LYs and QALYs for the new intervention, RAM+PAC, and the comparator treatments, BSC and DOC, are presented in Table 124. The corresponding incremental values and the ICER are also presented versus the most widely used treatment currently, BSC. DOC is shown to have an ICER versus BSC of above £50,000 per QALY. Given that DOC treatment is not licensed in this indication and does not appear to be cost-effective at standard willingness to pay thresholds it is not discussed further. This view is supported by the NICE Methods Guide (122) which states that in selecting the most appropriate comparator the committee will include the comparator's cost-effectiveness as well as whether it is established NHS practice in England and licensing status.

Table 124 Base case: Combination therapy results

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

Note: Numbers may not compute due to rounding

The results therefore focus on the incremental cost-effectiveness of RAM+PAC versus the most common treatment in second-line GC/GOJ, BSC.

Versus BSC, RAM+PAC provides a meaningful increase in modelled overall survival for patients with this difficult to treat disease. With the current standard of care, BSC, mean estimated OS is 5.40 months (0.45 LYs) whilst treatment with RAM+PAC offers patients an additional 5.76 months (0.48 LYs) of estimated survival, increasing total life expectancy to 11.28 months (0.94 LYs) from the start of treatment with RAM+PAC. This is an increase of over 100 percent compared to BSC only.

There are also an additional 0.33 QALYs gained from treatment with RAM+PAC. This corresponds with an ICER of £118,209.

Monotherapy

The total costs, LYs and QALYs estimated from the model for RAM+BSC and PBO+BSC are presented in Table 125. The incremental results and ICER for RAM+BSC versus PBO+BSC are also presented. The ICER for RAM+BSC versus PBO+BSC is £188,640 per QALY gained with an addition of 0.12 QALYs.

Table 125 Base case: Monotherapy results

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	Incremental cost/LYs	ICER (£) incremental (QALYs)
PBO+BSC	£14,137	0.49	0.31	-	-	-	-	-
RAM+BSC	£36,678	0.66	0.43	£22,542	0.16	0.12	£137,723	£188,640

Note: Numbers may not compute due to rounding

RAM+BSC offers an additional 1.92 months (0.16 LYs) of estimated OS for patients compared to PBO+BSC only. Overall life expectancy is increased from 5.88 months (0.49 LYs) to 7.92 months (0.66 LYs), an increase of over 30 percent compared to PBO+BSC.

Clinical validation

Combination therapy

A comparison of the outputs of the economic model to the clinical data from the RAINBOW trial is provided in Table 126. The model estimated median and mean values for RAM+PAC are shown to be a reasonable representation of the clinical trial data.

Table 126 Summary of model results compared with clinical data: Combination therapy

Outcome	Clinical trial results (CI)			Model results		
	RAM+PAC	BSC	Incremental	RAM+PAC	BSC	Incremental
Median OS	9.63 months (8.5, 10.8)	N/A	N/A	9.43 months	4.60 months	4.83 months
Median PFS	4.40 months (4.24, 5.32)	N/A	N/A	4.14 months	1.15 months	2.99 months
Mean OS	11.13 months (10.30, 11.96) (restricted mean)	N/A	N/A	11.63 months	5.60 months	6.03 months
Mean PFS	6.20 months (5.62, 6.78) (restricted mean)	N/A	N/A	6.00 months	1.85 months	4.15 months

Abbreviations: N/A = not applicable

The mean reported health benefits from the combination therapy model for RAM+PAC and BSC are presented in Table 127. The LYs and QALYs gained according to health state are detailed. With BSC, patients spend the majority of their overall survival in the post-progression health state where quality of life is lower and their symptoms worse. Treatment with RAM+PAC allows patients to spend a greater proportion of their remaining life progression-free, and with a better HRQL.

Table 127 Results by technology/health state: Combination therapy model

Technology	Outcome	LYs	% of overall LYs	QALYs	% of overall QALYs
BSC	Progression-free survival	0.14	32%	0.10	36%
	Progressed disease	0.31	68%	0.18	64%
	Overall survival	0.45	100%	0.29	100%
RAM+PAC	Progression-free survival	0.48	52%	0.35	57%
	Progressed disease	0.45	48%	0.27	43%
	Overall survival	0.94	100%	0.62	100%

Note: Numbers may not compute due to rounding

Monotherapy

The same validation exercise is undertaken for the clinical results from the monotherapy model and compared with the results from the REGARD trial (Table 128). The results are shown to be a good fit to the observed trial data. The comparison of the median PFS data shows an underestimation of the median PFS for both the RAM+BSC and PBO+BSC arms from the model. However the incremental result is very similar to the trial with a difference of only 0.12 months.

Table 128 Summary of model results compared with clinical data: Monotherapy

Outcome	Clinical trial results (CI)			Model results		
	RAM+BSC	PBO+BSC	Inc	RAM+BSC	PBO+BSC	Inc
Median OS	5.2 months (2.3, 9.9)	3.8 months (1.7, 7.1)	1.4 months	5.06 months	3.68 months	1.38 months
Median PFS	2.1 months (1.5, 2.7)	1.3 months (1.34, 1.4)	0.8 months	1.61 months	0.69 months	0.92 months

Abbreviations: inc = incremental

The results for median OS estimated by the model slightly underestimate the median OS in the RAM+BSC and PBO+BSC arms but the incremental difference is minimal, with the model underestimating incremental median OS by 0.02 months.

Additionally, the mean reported health benefits by health state show that patients receiving RAM+BSC spend a greater proportion of their remaining life expectancy in the pre-progression state where HRQL is better compared to patients receiving PBO+BSC.

Table 129 Results by technology/health state: Monotherapy model

Technology	Outcome	LYs	% of overall LY	QALY	% of overall QALYs
PBO+BSC	Progression-free survival	0.12	24%	0.09	29%
	Progressed disease	0.37	76%	0.22	71%
	Overall survival	0.49	100%	0.31	100%
RAM+BSC	Progression-free survival	0.28	42%	0.20	48%
	Progressed disease	0.38	58%	0.22	52%
	Overall survival	0.66	100%	0.43	100%

Note: Numbers may not compute due to rounding

Markov trace

A visual overview of the Markov trace is provided for each comparator for the proportion of the cohort in each health state over time (PFS, PPS and death), up to 99.9% of patients are dead.

Combination therapy

Figure 57 Markov trace for proportion of cohort in health states: RAM+PAC

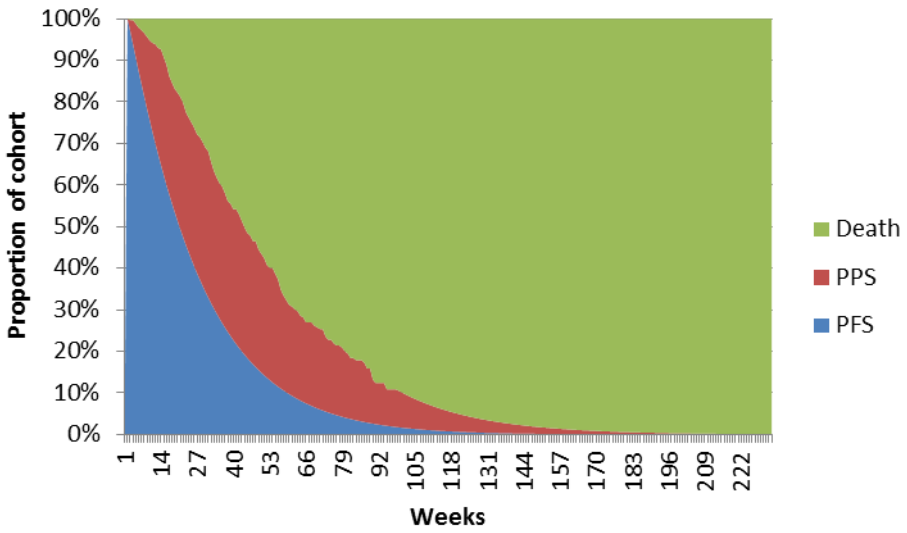
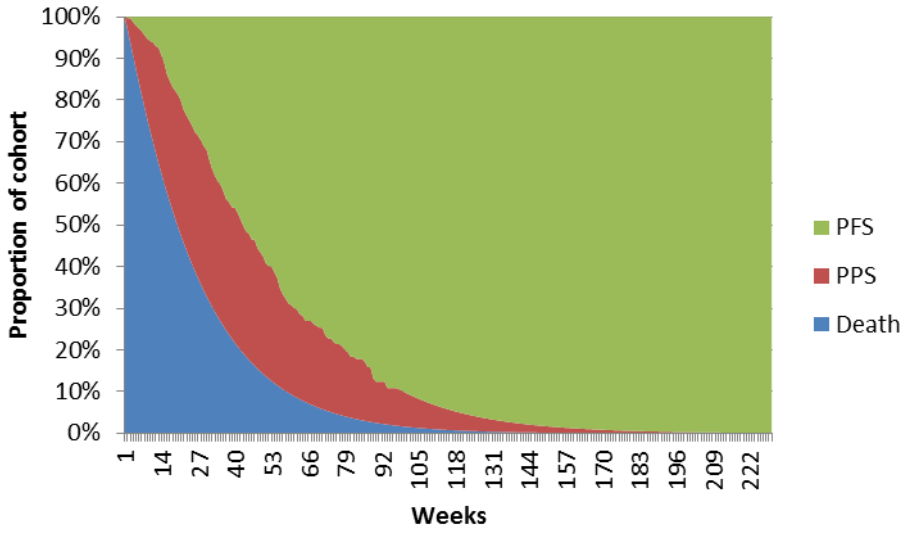


Figure 58 Markov trace for proportion of cohort in health states: BSC (combination therapy model)



Monotherapy

Figure 59 Markov trace for proportion of cohort in health states: RAM+BSC

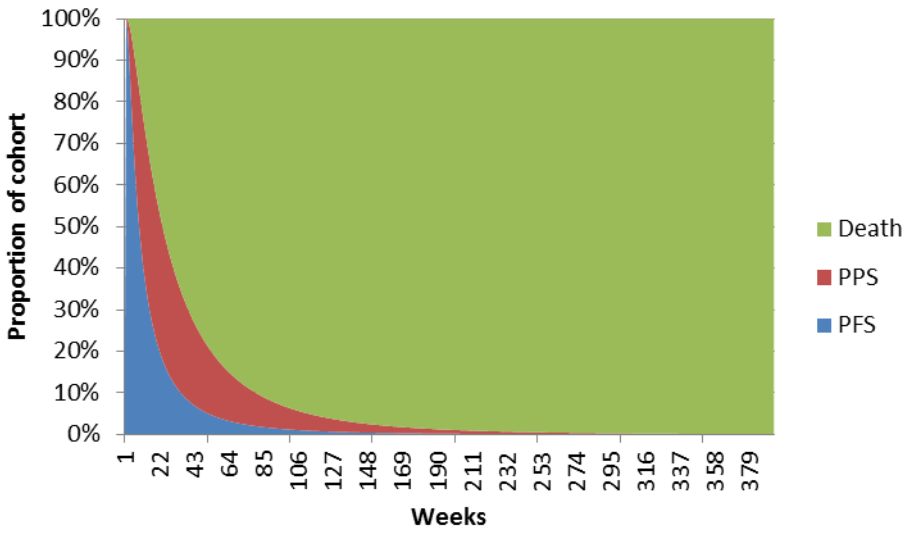
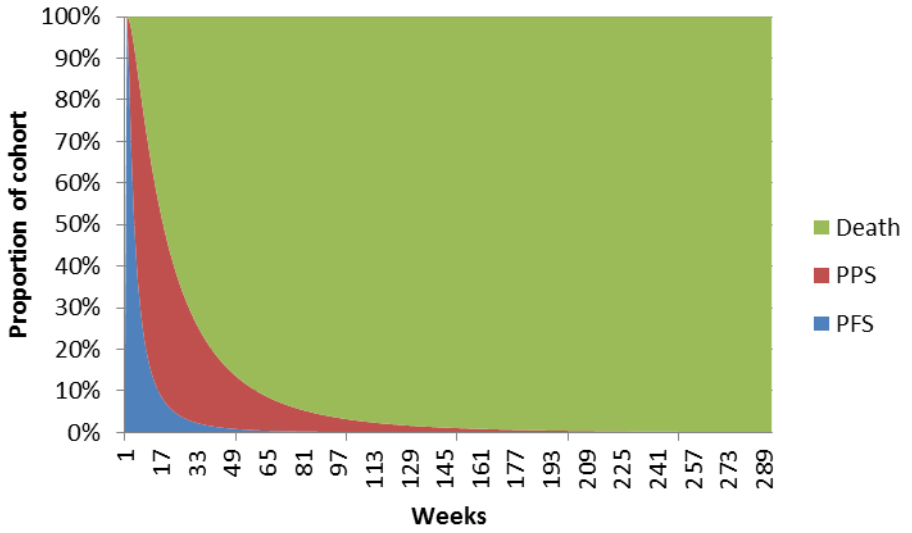


Figure 60 Markov trace for proportion of cohort in health states: PBO+BSC



Disaggregated results of the base case incremental cost-effectiveness analysis

The disaggregated results of the incremental cost-effectiveness analysis from the combination and monotherapy model are provided. This allows the incremental QALYs and costs gained to be attributed to the pre- and post-progression health states, and the incremental cost drivers to be identified.

Combination therapy

Disaggregated QALYs: Combination therapy

The disaggregated QALYs demonstrate that the majority of the QALYs accrued from treatment with RAM+PAC are accrued in the pre-progression health state.

Table 130 Summary of QALYs gained by health state: Combination therapy model

Health state	QALYs RAM+PAC	QALYs BSC	Increment	% absolute increment
Pre-progression	0.35	0.10	0.25	75%
Post-progression	0.27	0.18	0.08	25%
Total	**0.62**	**0.29**	**0.33**	**100%**

Note: Numbers may not compute due to rounding

The importance of disease control (i.e. stable disease or partial/complete disease response) in maintaining HRQL has been highlighted in an independent systematic review (13). The value of an additional 4.08 months (0.34 LYs) gained in the pre-progression health state should be seen within this context (Table 131).

Table 131 Summary of LYs gained by health state: Combination therapy

Health state	LYs RAM+PAC	LYs BSC	Increment	% absolute increment
Pre-progression	0.48	0.14	0.34	70%
Post-progression	0.45	0.31	0.14	30%
Total	**0.94**	**0.45**	**0.48**	**100%**

Note: Numbers may not compute due to rounding

Disaggregated costs: combination therapy

The disaggregated costs by categories of resource use demonstrate clearly the majority of incremental costs are associated with the cost of administration and acquisition of ramucirumab.

Importantly also, treatment with RAM+PAC increases the life expectancy of patients with a resource-intensive disease. There is an increase in the total cost of hospitalisation and supportive care due to the extension of life expectancy, compared to BSC, even though the cost per week is lower with RAM+PAC.

Table 132 Summary of predicted resource use by category of cost: Combination therapy model

Item	Cost RAM+PAC	Cost BSC	Increment	% absolute increment
Therapy cost	£30,186	£0	£30,186	76.2%
Administration costs	£5,571	£0	£5,571	14.1%
Adverse event cost	£617	£197	£420	1.1%
Follow up care costs	£2,100	£660	£1,439	3.6%
Hospitalisation	£8,865	£7,158	£1,707	4.3%
BSC	£1,148	£827	£322	0.8%
Third-line	£184	£159	£24	0.1%
Terminal care costs	£4,325	£4,400	-£74	-0.2%
Total	**£52,996**	**£13,400**	**£39,595**	**100%**

Note: Numbers may not compute due to rounding. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 133 Costs estimated by health state: Combination therapy model*

Health state	Cost RAM+PAC	Cost BSC	Increment	% absolute increment
Pre-progression	£42,928	£4,476	£38,452	97%
Post-progression	£10,068	£8,925	£1,144	3%
Total	**£52,996**	**£13,400**	**£39,595**	**100%**

Note: Numbers may not compute due to rounding. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.
*based on simplifying assumptions

Monotherapy

Disaggregated QALYs: Monotherapy model

The results for the disaggregated LYs and QALYs calculated in the model show that almost all of the survival benefit of RAM occurs in the pre-progression health state.

Table 134 Summary of LY gains by health state: Monotherapy model

Health state	LY RAM+BSC	LY PBO+BSC	Increment	% absolute increment
Pre-progression	0.28	0.12	0.16	96%
Post-progression	0.38	0.37	0.01	4%
Total	**0.66**	**0.49**	**0.16**	**100%**

Note: Numbers may not compute due to rounding

Table 135 Summary of QALY gain by health state: Monotherapy model

Health state	QALY RAM+BSC	QALY PBO+BSC	Increment	% absolute increment
Pre-progression	0.20	0.09	0.12	97%
Post-progression	0.22	0.22	0.00	3%
Total	**0.43**	**0.31**	**0.12**	**100%**

Note: Numbers may not compute due to rounding

The disaggregated costs show that the majority of the incremental costs associated with RAM are due to the administration and acquisition of ramucirumab.

Table 136 Summary of predicted resource use by category of cost: Monotherapy model

Item	Cost RAM+BSC	Cost PBO+BSC	Increment	% absolute increment
Therapy cost	£19,879	£0	£19,879	88.2%
Administration costs	£1,417	£0	£1,417	6.3%
Adverse event cost	£200	£135	£65	0.3%
Follow up care costs	£1,555	£703	£852	3.8%
Hospitalisation	£8,223	£7,787	£436	1.9%
BSC	£816	£889	-£73	-0.3%
Third-line	£225	£231	-£6	0.0%
Terminal care costs	£4,365	£4,392	-£28	-0.1%
Total	**£36,678**	**£14,137**	**£22,542**	**100.0%**

Note: Numbers may not compute due to rounding. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 137 Costs estimated by health state: Monotherapy*

Health state	Cost RAM+BSC	Cost PBO+BSC	Increment	% absolute increment
Pre-progression	£27,103	£4,720	£22,383	99%
Post-progression	£9,576	£9,417	£158	1%
Total	**£36,678**	**£14,137**	**£22,542**	**100%**

Note: Numbers may not compute due to rounding. Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee
*based on simplifying assumptions

5.8 Sensitivity analyses

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was undertaken to capture the uncertainty in the estimation of input variables. Distributions were assigned to the input parameters and randomly sampled using 10,000 Monte Carlo simulations.

Probabilistic estimate of KM data

A summary of the choice of distributions for each parameter is included below. The choice of distribution was based on the features of the parameter in question to allow for the accurate representation of the associated uncertainty.

For a number of parameters standard errors were not available. In these instances the s.e. was calculated to be 10% of the mean value to allow them to be estimated probabilistically.

Table 138 Summary of PSA distributions used for parameters

Parameter	Distribution	Rationale
Discount rates	N/A	Not subject to sampling uncertainty, explored in the deterministic sensitivity analysis
Regression parameters*	Multivariate normal	To capture correlation between normally distribution regression parameters
KM data for OS**	Normal	To capture uncertainty in the KM trial data
Drug costs	N/A	Not subject to sampling uncertainty
Other unit costs	Gamma	Constrained to interval of 0 and positive infinity
Resource use rates	Gamma	Constrained to interval of 0 and positive infinity
Resource use probabilities	Beta	Constrained to interval of 0 and 1
Health state utilities	Beta	Both the 'pre-progression' and 'post-progression' health states are sufficiently far from death hence constrained on interval 0 and 1
Adverse event utility decrement	Gamma	Constrained to interval of 0 and positive infinity
Response utility increment and proportion of overall response rate**	Beta	Constrained to interval of 0 and 1

*PFS, OS with parametric distributions, time on treatment and hospitalisation rates
**For combination therapy only

Combination therapy results

The results of the PSA are presented in Table 139. They are also presented in graphical form on a cost-effectiveness plane and as cost-effectiveness acceptability curves (CEACs).

Table 139 Cost-effectiveness results of probability sensitivity analysis: Combination therapy

Technologies	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	Incremental cost/LYG	ICER (£) incremental (QALYs)
BSC	£13,787	0.47	0.30	-	-	-	-	-
RAM+PAC	£53,444	0.96	0.64	£39,657	0.49	0.34	£80,858	£116,820

Figure 61 Cost –effectiveness plane for combination therapy (QALYs)

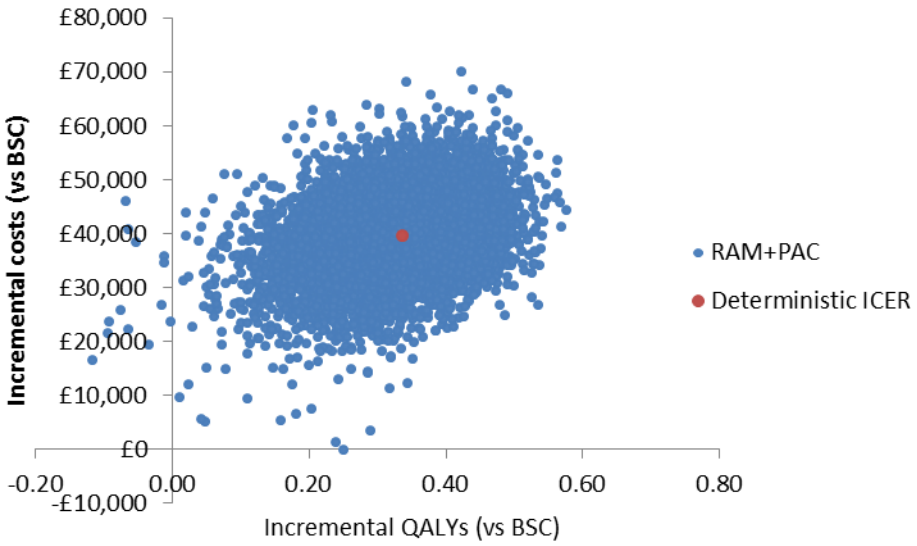
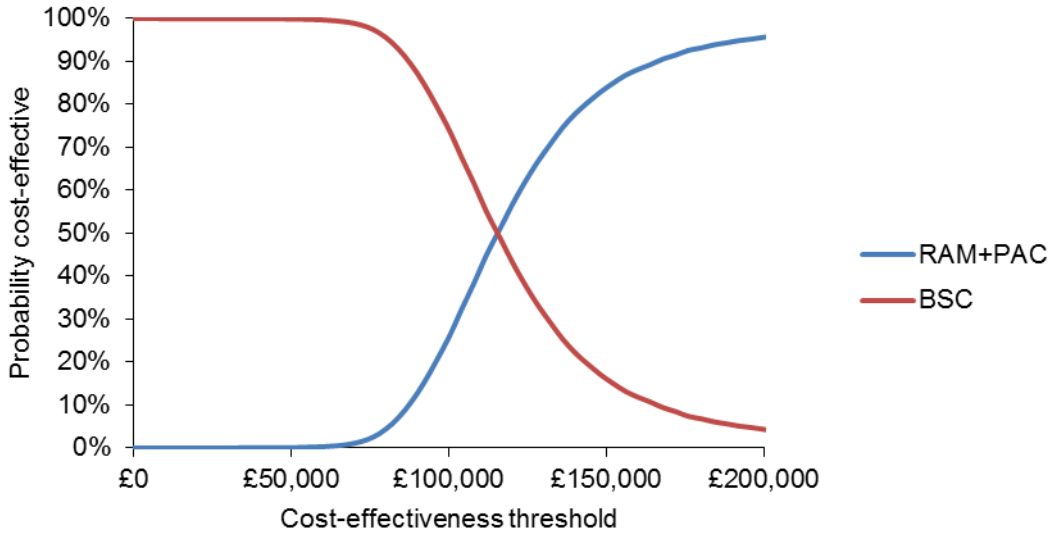


Figure 62 Cost-effectiveness acceptability curve for combination therapy



Monotherapy results

The results of the PSA are presented in Table 140. They are also presented in graphical form on a cost-effectiveness plane and as a CEAC.

Table 140 Cost-effectiveness results of probability sensitivity analysis: Monotherapy

Technologies	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	Incremental cost/LYG	ICER (£) incremental (QALYs)
PBO+BSC	£14,149	0.50	0.31	-	-	-	-	-
RAM	£36,376	0.66	0.43	£22,227	0.16	0.12	£138,573	£189,232

Figure 63 Cost-effectiveness plane for monotherapy (QALYs)

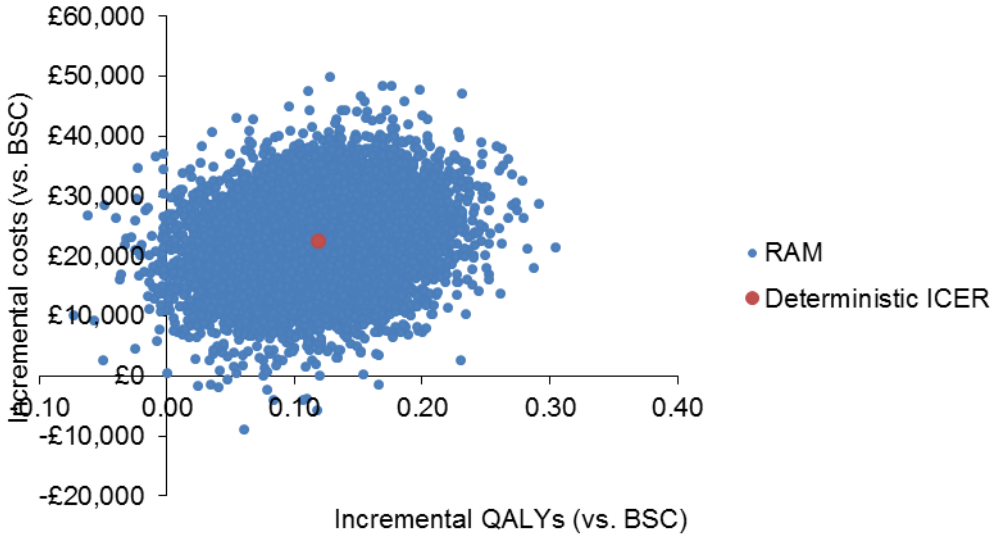
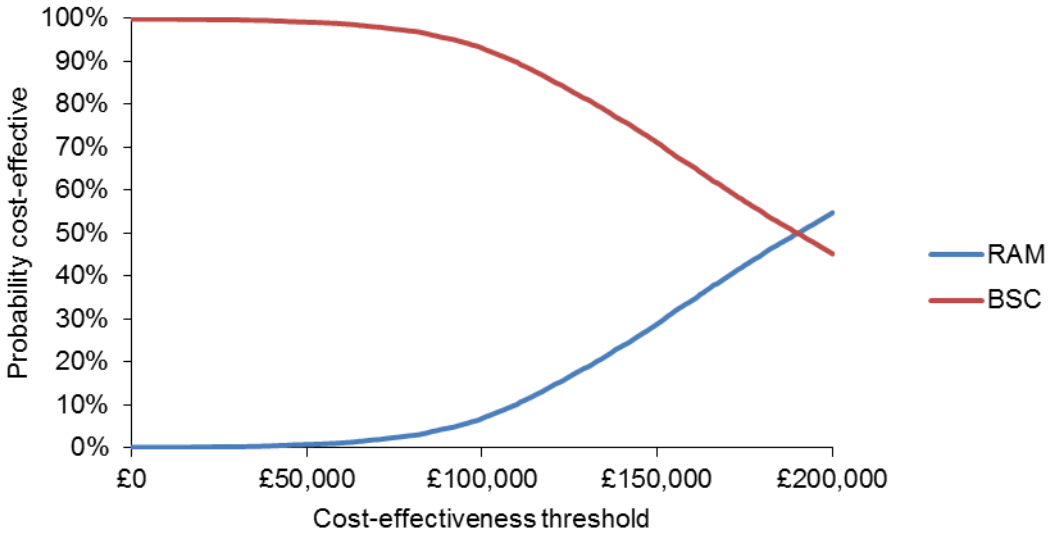


Figure 64 Cost-effectiveness acceptability curve for monotherapy



Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was conducted to test the assumptions included in both economic models. The DSA attempts to explore the uncertainty around the base case assumptions described in section 5.6, where possible. Specifically, an exploration of the inclusion of third-line therapy and hospitalisation costs was conducted by using alternative assumptions. DSA was also conducted for a range of structural aspects and cost inputs as outlined below. The following sensitivity analyses were conducted and are presented in Table 141 and Table 142.

Second-line drug costs

- Changing the body weight and BSA
- Assuming no wastage (i.e. vial sharing)
- Relative dose intensity on/off
- Alternative distribution to estimate time on treatment
- Apply BNF prices for drug costs
- Day case versus outpatient delivery codes

Utility

- Assume no utility increment associated with response (combination therapy only)

Resource use - hospitalisation

- Use statistical models to estimate probability of hospitalisation
- Apply no differential rate by treatment arm
- Length of stay estimated using data from trial for all patients; by region; by treatment and region

Resource use - BSC & AEs

- Same BSC rates applied across all arms
- AE costs scaled down by 50%
- AE length decreased for infection to 10 days

Efficacy

- Use alternative distribution for estimating PFS

Combination therapy only

- Implement extrapolation from t_1+2 months
- Implement extrapolation from t_1-2 months
- Implement extrapolation from last event in RAM+PAC arm

Discount rate

- 1.5% for costs and benefits

Third-line therapy costs

- Assume 0% of patients receive third-line therapy in both arms
- Assume third-line rate observed in clinical trials
- Assume proportion of post-progression spent on treatment = 25%
- Assume proportion of post-progression spent on treatment = 75%

Combination therapy

Table 141 Results of deterministic sensitivity analysis

	Base case value	Deterministic sensitivity analysis value	ICER
Base case			**£118,209**
Costs			
Drug cost	eMIT prices	BNF	£131,537
Drug administration	Day case setting	Outpatient setting	£115,781
Hospitalisation rate	Observed, adjusted for treatment	Negative binomial, adjusted for treatment	£119,127
	Observed, adjusted for treatment	Poisson, adjusted for treatment	£113,191
	Observed, adjusted for treatment	Observed, unadjusted	£123,858
Length of hospitalisation stay stratified by	Treatment	Region 1	£109,434
	Treatment	All patients	£109,143
	Treatment	Region 1 and treatment	£116,420
Hospitalisation rate post-progression	Relative risk of post-progression hospitalisation = 1	Relative risk of post-progression hospitalisation = 2	£116,944
	Relative risk of post-progression survival = 1	Relative risk of post-progression survival = 3	£116,146
Wastage	Vial wastage	Vial sharing	£116,167
Relative dose intensity	On	Off	£127,186
Time on treatment	Lognormal distribution	Log-logistic distribution	£120,360
Third-line therapy	12% in each arm	0% in each arm	£118,097
	12% in each arm	Trial rate (47% in both arms)	£118,495
Proportion of time in post-progression spent on treatment	Proportion = 50%	Proportion = 25%	£118,035
	Proportion = 50%	Proportion = 75%	£118,383
AEs costs	100%	Scaled down by 50%	£117,581
	Infection length = 15.1 days	Infection length = 10 days	£118,209
BSC resource rates	Differential rates across active treatments and BSC	Equal rates	£119,455
BSA and body-weight data source	All patients	Region 1	£127,128
Efficacy			
Progression-free survival	Unadjusted, Weibull	Unadjusted, log-normal	£117,588
	Unadjusted, Weibull	Unadjusted, log-logistic	£117,040

	Base case value	Deterministic sensitivity analysis value	ICER
Overall survival	Kaplan-Meier extrapolated from T1= last event in PAC arm	Kaplan-Meier extrapolated from t_1= last event in PAC arm + 2 months (t_1=24.12)	£115,886
	Kaplan-Meier extrapolated from T1= last event in PAC arm	Kaplan-Meier extrapolated from t_1= last event in PAC arm - 2 months ($t_{1=}$20.14)	£117,304
	Kaplan-Meier extrapolated from T1= last event in PAC arm	Kaplan-Meier extrapolated from t_1= last event in RAM+PAC arm (t_1=21.39)	£119,198
Other			
Discount rate (costs and health)	3.5%	1.5%	£117,253
Utility	Response utility applied	No response utility applied	£118,878

Monotherapy

Table 142 Results of deterministic sensitivity analysis

	Base case value	Deterministic sensitivity analysis value	ICER
Base case			**£188,640**
Costs			
Drug administration	Day case setting	Outpatient setting	£185,379
Hospitalisation rate	Observed, adjusted	Negative binomial, adjusted	£192,735
	Observed, adjusted	Poisson, adjusted	£188,705
	Observed, adjusted	Observed, unadjusted	£217,891
Length of hospitalisation stay stratified by	Treatment	Region 1	£171,426
	Treatment	All patients	£170,974
	Treatment	Region 1 and treatment	£173,706
Hospitalisation rate post-progression	Relative risk of post-progression hospitalisation = 1	Relative risk of post-progression hospitalisation = 2	£180,476
	Relative risk of post-progression hospitalisation = 1	Relative risk of post-progression survival = 3	£173,582
Proportion of time in post-progression spent on treatment	Proportion = 50%	Proportion = 25%	£188,644
Proportion of time in post-progression spent on treatment	Proportion = 50%	Proportion = 75%	£188,637
Wastage	Vial wastage	Vial sharing	£163,319
Relative dose intensity	On	Off	£188,640
Time on treatment	Lognormal	Log-logistic	£189,358
Third-line therapy	5% in each arm	RAM = 30.3% BSC = 37.6%	£187,043
	5% in each arm	0% in each arm	£188,690
Drug cost source	eMIT	BNF	£188,600
AEs costs	100%	Scaled down by 50%	£188,369
BSC resource rates	Differential rates across arms	Equal rates	£191,347
BSA and body-weight data source	All patients	Region 1 patients	£188,640
Efficacy			
Progression-free survival	Lognormal	Log-logistic	£188,926
	Lognormal	Weibull	£197,904
Overall survival	Gamma	Lognormal	£174,485
Other			
Discount rate (costs and benefit)	3.5%	1.5%	£185,708

Scenario analysis

The choice of survival modelling used in economic models can have a significant impact on the cost-effectiveness results, especially for OS modelling. A thorough survival modelling exercise was conducted to explore the most appropriate way to characterise the PFS and OS curves in the model so they accurately represent the trial data. However, there is always uncertainty regarding the most optimal technique which should be explored using alternative distributions. As mentioned in Section 5.3, alternative approaches are explored in these scenario analyses.

For the modelling of OS in the combination therapy model, a range of different approaches were explored to best characterise the RAM+PAC OS curve. The base case using the Kaplan-Meier data and extrapolating with an exponential distribution from the end of the trial period was chosen as the base case as it represented the most conservative approach and utilises the trial data to the fullest extent possible. However, the methodology is not without its potential limitations and for this reason alternative approaches were also explored.

Alternative source for OS modelling for combination therapy model: independently fitted log-logistic and Weibull distribution

An alternative approach of using fully parametric survival curves, independently fitted to each arm, was explored and implemented in the economic model. This avoids needing to implement a ‘cut-point’ to start the extrapolation and uses all the trial data to determine the appropriate shape of the curve in the unobserved period.

The independently fitted survival curves showed that the log-logistic and the Weibull were the best fit to the observed trial data for RAM+PAC (AIC: 803.25 vs 801.07; BIC: 810.85 vs 808.67 in favour of the Weibull). The log-logistic was the best fit to the PBO+PAC and the Weibull was the second worst fitting distribution (4th out of 5).

The results for the independently modelled log-logistic and Weibull distribution are presented in Table 143. The use of the log-logistic distribution reduces the ICER to £96,103 versus BSC. The use of the Weibull distribution results in an ICER of £117,236 which is similar to the base case.

Table 143 Combination therapy model results with independently modelled log: logistic and Weibull distribution

	Weibull distribution		Log-logistic distribution	
	RAM+PAC	**BSC**	**RAM+PAC**	**BSC**
Total costs (£)	£52,999	£13,361	£55,107	£13,419
Total LYs	0.94	0.45	1.11	0.45
Total QALYs	0.62	0.28	0.72	0.29
Incremental costs (£)	£39,638	-	£41,687	-
Incremental LYs	0.49	-	0.65	-
Incremental QALYs	0.34	-	0.43	-
Incremental cost/LYG	£81,002	-	£63,904	-
ICER (£) (QALYs)	**£117,236**	-	**£96,103**	-

Note: Numbers may not compute due to rounding

The full results and incremental analysis from the combination therapy model using the log-logistic and Weibull distribution are provided in Appendix 12.

Alternative source for OS modelling for monotherapy model: lognormal distribution

In the monotherapy model, all three AFT models were shown to be a good fit using the AIC/BIC criteria and the Cox-Snell residuals. The Gamma distribution was shown to be the most conservative of these approaches with the shortest overall length of the extrapolation. The lack of long-term registry data or more mature trial data makes it difficult to assess the appropriateness of long-term extrapolations for the RAM arm of the trial. Given this, the most conservative approach was chosen as the base case.

An alternative analysis using the lognormal distribution was conducted to assess the impact on the cost-effectiveness of using an alternative distribution which was shown to be a better fit using the goodness-of-fit diagnostic tests. The ICER decreases down to £174,485.

Table 144 Monotherapy therapy results with lognormal distribution

Technologies	Total costs (£)	Total LY	Total QALYs	Incremental costs (£)	Incremental LY	Incremental QALYs	Incremental cost/LYG	ICER (£) incremental (QALYs)
PBO+BSC	£14,645	0.52	0.32	-	-	-	-	-
RAM	£37,373	0.70	0.45	£22,728	0.18	0.13	£124,874	£174,485

Note: Numbers may not compute due to rounding

Summary of sensitivity analyses results

The sensitivity analyses and scenario analyses explore the drivers of the incremental cost-effectiveness results and identify any areas of uncertainty associated with the modelling.

Combination therapy

The acquisition cost of ramucirumab is a significant proportion of the overall cost. Changing parameters which affect the total amount of ramucirumab required per patient are therefore important cost-effectiveness drivers. Specifically, the application of RDI and the use of the Region 1 body weight/BSA lead to an increase in the ICER by around £10,000 due to higher incremental costs.

Hospitalisation costs are also a significant proportion of the total costs associated with each treatment option. Changing the individual parameters chosen in the base case has some impact on the ICER. The base case calculates length of stay based on the observed length of stay in each arm of the trial. The sensitivity analyses shows that using the length of stay for all patients in the trial combined, or for patients in region 1 only, leads to a decrease in the ICER to around £109,000 in each case. Alternatively by applying the same rate of hospitalisation across both arms, rather than the observed trial difference, the ICER increases to around £124,000.

The scenario analyses explore the impact of alternative modelling approaches for OS. The use of the independently fitted log-logistic curves is shown to decrease the ICER to £96,103. The use of the independently fitted Weibull however gives a similar result to the base case modelling approach at £117,236.

Monotherapy

In the monotherapy model the choice of hospitalisation rate is an important factor in the cost-effectiveness results. Application of the same rate of hospitalisation across arms increases the ICER by almost £30,000 but using the region 1, region 1 and treatment adjusted patient populations as well as a pooled population (all patients) to

estimate length of stay decreases the ICER by almost £20,000. The removal of drug wastage reduces the ICER down to £163,319.

The choice of survival modelling also impacts on the ICER. Using the Weibull distribution to estimate PFS leads to an increase in the ICER by almost £10,000, but is shown in section 5.3 to be a poor fit to the data. The use of the lognormal distribution for OS decreases the ICER to £174,485 which is shown to be a good fit to the trial data, but a less conservative OS modelling approach than the Gamma.

Summary on the stability of the results

Across both models the results are shown to be very stable with respect to most inputs except for the choice of OS modelling, the factors which determine the total amount of drug which is required per patient (RDI, wastage, weight) and the choice of the rate and length of stay parameters used to model hospitalisation costs. The exploration of the impact of the changes in these inputs should however allow for greater certainty in the choice of the most appropriate and plausible ICER.

5.9 Subgroup analysis

A scenario analysis using a geographic subgroup was conducted to validate the results of the ITT analysis in the combination therapy model. Regional differences associated with the treatment of GC/GOJ patients were identified prior to the commencement of the RAINBOW trial and have been investigated before (19).

Only PFS, OS and time on treatment were adjusted for region by including it as a covariate in the economic model. The results reported related to the subgroup which included English patients, referred to as region 1: North America, Europe, Australia and Israel.

Scenario analysis results: region adjusted OS, PFS and time on treatment

The results for region 1 are presented for RAM+PAC versus BSC. The incremental analysis shows that the cost per QALY for RAM+PAC versus BSC is £95,618 using the log-logistic distribution and £114,474 using the Weibull distribution.

Table 145 Regional scenario analysis results

	Weibull distribution		Log-logistic distribution	
	RAM+PAC	**BSC**	**RAM+PAC**	**BSC**
Total costs (£)	£48,943	£12,211	£50,724	£12,205
Total LY	0.86	0.39	0.99	0.39
Total QALYs	0.57	0.25	0.65	0.25
Incremental costs (£)	£36,731	-	£38,519	-
Incremental LY	0.46	-	0.60	-
Incremental QALYs	0.32	-	0.40	-
Incremental cost/LYG	£79,048	-	£63,740	-
ICER (£) (QALYs)	**£114,474**	-	**£95,618**	-

Note: Numbers may not compute due to rounding

5.10 Validation

Validation of de novo cost-effectiveness analysis

Validation of combination therapy model

The validation of the economic model was done by the inclusion of the trial comparator, PBO+PAC, as a comparator in the economic model. The clinical results from the model are presented for RAM+PAC and PBO+PAC in this section and validated against the trial results to demonstrate the appropriate implementation of clinical evidence in the model.

Clinical outcomes from the model

The clinical outcomes from the economic model are compared to the clinical outcomes from the RAINBOW trial in Table 146. As discussed in section 5.3, the choice of survival modelling for the base case was the use of the Kaplan-Meier trial data and then the extrapolation with the exponential distribution from the end of the trial period. The model results very closely match the clinical trial results with respect to the median PFS and OS predicts for both the RAM+PAC and PBO+PAC arms indicating that the modelling approach was reasonable.

Table 146 Summary of model results compared with clinical data RAINBOW, ITT with Kaplan-Meier extrapolation

Outcome	Clinical trial results (CI)			Model results		
	RAM+PAC	PBO+PAC	Incremental	RAM+PAC	PBO+PAC	Incremental
Median OS	9.63 months (8.5, 10.8)	7.36 months (6.3, 8.4)	2.27 months	9.43 months	7.13 months	2.3 months
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

Additional analysis was done using fully parametric survival curves and is presented as scenario analysis. The model outputs using the Weibull and log-logistic distribution for RAM+PAC and PBO+PAC are presented in Table 147 to provide further evidence to fully assess the most appropriate choice of survival modelling.

The Weibull distribution is shown to underestimate the incremental median OS benefit of RAM+PAC because it over-estimates the survival benefit associated with the control arm. As discussed in Section 5.3 the Weibull was not a good fit to the PBO+PAC arm but a good fit to the RAM+PAC arm.

Table 147 Summary of model results compared with clinical data: Combination therapy (Weibull and log-logistic extrapolation)

Outcome	Clinical trial results (CI)			Model results		
	RAM+PAC	PBO+PAC	Inc*	RAM+PAC	PBO+PAC	Inc*
Weibull distribution						
Median OS	9.63 months (8.5, 10.8)	7.36 months (6.3, 8.4)	2.27 months	9.66 months	7.82 months	1.84 months
Log-logistic distribution						
Median OS	9.63 months (8.5, 10.8)	7.36 months (6.3, 8.4)	2.27 months	9.20 months	7.13 months	2.07 months

The log-logistic was shown in the goodness of fit tests to be a better fit overall to both arms of the trial and this is reflected in the model results above. There remains a slight underestimation of the median OS benefit in the RAM+PAC arm and as a result the incremental median OS benefit is lower than the benefit observed in the trial.

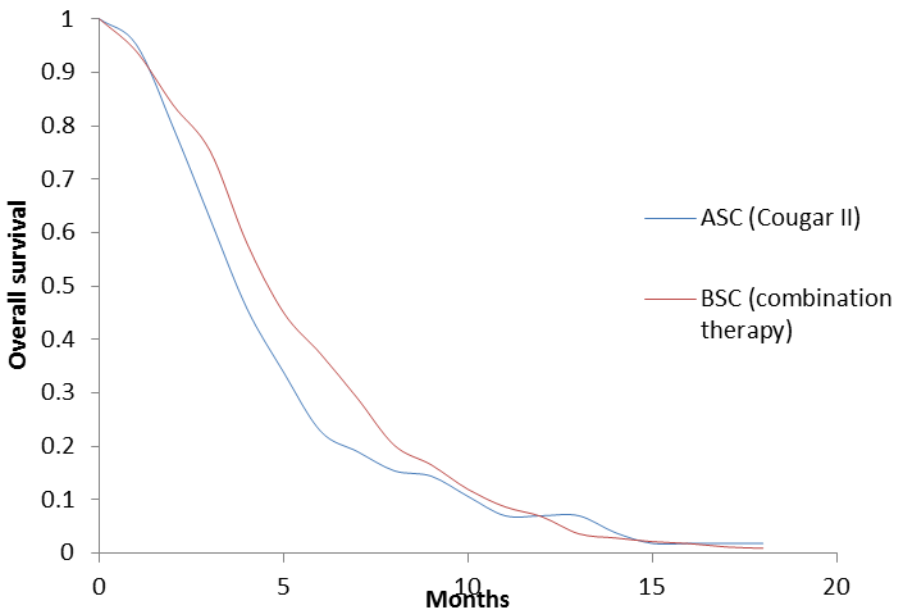
In conclusion, the analyses shown in tables 146-147 demonstrate that the incorporation of the PFS and OS data from the RAINBOW trial into the economic model is done in a way which is reflective of the clinical trial results. More importantly, it is incorporated in a way which does not over-estimate the benefit associated with treatment with RAM+PAC.

Validation of BSC estimates

The BSC results from the combination therapy model are calculated by an indirect comparison of RAM+PAC to BSC through an appropriate evidence network which yields a hazard ratio. As discussed under section 5.3, this is then applied to the survival curve for RAM+PAC to calculate the survival curve for BSC.

To assess that the estimates generated by the model are reliable and generalisable to English clinical practice they are plotted against the digitized OS curve from the COUGAR II trial, a UK-based trial. Whilst these two OS curves are not directly comparable - one is modelled, the other is from a clinical trial - it helps to illustrate that the modelled OS is plausible and does not underestimate the performance of BSC in UK clinical practice.

Figure 65 Modelled OS from combination therapy economic model and ASC arm from COUGAR II



Source: Digitised Kaplan-Meier curves from active symptom control arm of COUGAR II (2)
Combination therapy economic model BSC estimated OS curve

Technical validation of the model

The model was built by an external consultancy and adapted for the UK under the direction of Lilly. Upon development of the global economic model it was validated by an external consultant who did a comprehensive cell-by-cell review of the formulae. All subsequent adaptations for the UK were cross checked by two members of the team at the consultancy.

Validation of monotherapy model

The cost-effectiveness analysis of RAM as a monotherapy did not require an indirect comparison to any non-trial comparators as the only appropriate comparator for this regimen is BSC. Validation of the clinical outputs of the monotherapy model is addressed in section 5.7 in Table 128 where the model results and clinical trial results are compared.

Technical validation of the model

The monotherapy model was validation using the same methodology as the combination therapy model and a cell-by-cell review was conducted by the same external consultant.

5.11 Interpretation and conclusions of economic evidence

Combination therapy

Advanced GC/GOJ is an aggressive, difficult to treat condition which severely impacts on patients' QoL, making everyday activities such as eating and swallowing painful and challenging.

GC/GOJ is also associated with a burden on the health system as patients require a high degree of medical and palliative care to allow them to retain some HRQL at the end of their life. As a result even off-licence generic therapies with a minimal drug acquisition cost (i.e. only around £100) are shown to be not cost-effective compared to BSC (Table 124). Additional evidence discussed previously also showed that BSC is overwhelmingly the most commonly used treatment option for patients.

RAM+PAC increases estimated PFS by over 4 months (0.34 LYs). The extension of the time period in which patients are progression-free is incredibly important to patients with late stage GC/GOJ as tumour growth is associated with an increasingly high tumour burden. The link between efficacious treatments and the maintenance of QoL for oesophago-gastric cancer patients has been highlighted in the literature (13). This is clearly demonstrated in the EORTC results for patients in the progression-free period where RAM+PAC is shown to have a clear trend in the improvement of almost all HRQL aspects. Patients receiving RAM+PAC also experienced a statistically significant improvement in emotional function and nausea and vomiting.

Advanced GC/GOJ is a very aggressive cancer and patients who have progressed on first-line chemotherapy have a modelled life expectancy of less than 6 months when treated with BSC only. Mean estimated OS is shown to increase by almost an additional 6 months with treatment with RAM+PAC, a very significant improvement for a patient population with such a poor prognosis.

Monotherapy

RAM as a monotherapy provides a non-cytotoxic treatment option for patients who are PS 0-1 following disease progression but for whom treatment in combination with paclitaxel is not appropriate. For these patients, RAM will be the only treatment option suitable for them, addressing a high unmet need.

RAM doubles estimated PFS for patients, again allowing patients to spend a longer period of time without tumour growth and with better symptom control. This benefit in PFS translates directly into an extension of OS by over 30% (~2 months).

Importantly, as an orphan disease with a very poor prognosis, even this modest *absolute* gain in OS represents an important *relative* increase in survival. Such incremental innovation over time can lead to important advances in the treatment pathway (28).

For patients who remain fit for further treatment following first-line chemotherapy, RAM offers a meaningful increase in life expectancy for those patients who are not suitable for treatment with ramucirumab in combination with PAC.

Cost-effectiveness challenges

Orphan drugs

The incidence of gastric and gastro-oesophageal cancers is low in the UK and Europe at less than 3 in 10,000. As the first approved second-line treatment for this life-threatening condition, ramucirumab was granted orphan designation (12). The difficulty in proving the cost-effectiveness case of orphan drugs using standard methods of health technology assessment (HTA) is well documented in the literature (18). The reality is that orphan drugs do not usually prove to be cost-effective and this, coupled with their high cost, means that funding and patient access may be limited.

The current NICE technology appraisal process does not formally recognise the challenges associated with achieving reimbursement for orphan drugs, although other European countries have specific provisions to allow them to assess orphan drugs within this context (Scottish Medicines Consortium) (153) and based on their expected budget impact (HAS (France), German (IQWIG)) (154).

Ramucirumab does not meet the current cost-effectiveness threshold required by NICE for the approval of a new technology, despite being a clinically effective treatment, with significant survival benefits, and the first approved treatment option for this poor prognosis disease.

End of life criteria

As discussed under section 4.13, ramucirumab as a combination therapy qualifies for the End of Life criteria which allows for further discretion in the application of cost-effectiveness thresholds by NICE appraisal committees.

The current life expectancy for patients is well below the normal threshold of 24 months. Patients in the UK trial COUGAR II (2) had a median life expectancy of only

3.6 months on active symptom control. The mean OS for RAM+PAC versus the most commonly used treatment in the NHS (BSC) is 5.76 months. GC/GOJ is also a rare cancer - the total estimated patient population in England according to the licence for ramucirumab is 657.

A summary of the End of Life criteria and relevant data available for RAM+PAC is provided in Table 148.

Table 148 End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS has ranged from 2.4 to 3.8 months for BSC in phase 3 clinical trials) (2-4).
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	RAM+PAC versus BSC; incremental mean OS = 5.76 months
The treatment is licensed or otherwise indicated for small patient populations	The patient population estimated to be eligible for treatment with previously treated, advanced gastric cancer is 1173.

The importance of and potential for improvement in GC/GOJ outcomes with the introduction of ramucirumab into English clinical practice should be considered when assessing the cost-effectiveness of ramucirumab. The application of flexible cost-effectiveness thresholds should be done with this, and the orphan designation of this medicine, in mind.

6 Assessment of factors relevant to the NHS and other parties

6.1 Estimated patient numbers

The total patient numbers for GC/GOJ are taken directly from the 2012 Office of National statistics (ONS) Cancer registration statistics for England. There is a clear downward trend in the incidence of GC and an increase in oesophageal cancer (Appendix 13). The 2012 values have been adjusted to reflect the changing incidence observed in the ONS statistics to calculate the 2015 estimated incidence in England.

Additional supplementary information on the proportion of patients treated is taken from Cancer Research UK (54) and the Oesophago-Gastric Cancer Audit conducted by the Royal College of Surgeons (RCS) in partnership with the HSCIC and other professional bodies (155). The audit was conducted in England and Wales and identified all cases of GC and GOJ which were diagnosed in a twelve month period between April 2011 and March 2012.

Table 149 Annual GC/GOJ patient numbers and second-line eligibility

Description	% patients	Number	References
Patients with gastro-oesophageal junction cancer (ICD 10 Code 15.2, 15.5*)	-	3,413 (calculated)	ONS Cancer Registration statistics 2012 adjusted to 2015
Patients with stomach (gastric) cancer (ICD 10 Code 16*)	-	4,857 (calculated)	ONS Cancer Registration statistics 2012 adjusted to 2015
Total patients with GC/GOJ	-	8,270 (calculated)	ONS Cancer Registration statistics 2012 adjusted to 2015
Patients with advanced/metastatic disease	80% (reported)	6,616 (calculated)	Cancer Research UK, 2014 (54)
Patients receiving oncology treatment	43% (reported)	2,845 (calculated)	National Oesophago-Gastric Cancer Audit 2013
Patients receiving chemotherapy	77% (reported)	2,191 (calculated)	National Oesophago-Gastric Cancer Audit 2013
Patients eligible for second-line chemotherapy	30%	657 (calculated)	Clinical expert opinion, validated by Chart Review

*source for ICD 10 Codes was Report October 2009 Epidemiology OG Cancers (118); Number may not compute due to rounding

The eligible second-line patient population over the next five years is calculated using the estimated incidence data from the ONS with a twelve-year prior time-trend applied.

Table 150 Eligible second-line patient population over time

ICD 10 Code	2015	2016	2017	2018	2019
Total patients with GC/GOJ	8,270	8,048	7,854	7,739	7,753
Patients eligible for second-line chemotherapy (calculated)	657	640	624	615	616

6.2 Potential use of Ramucirumab and budget impact

Share of market data

Share of market (SoM) data has been estimated by Lilly based on expected uptake across the lifecycle of the product.

Table 151 RAM estimated market share

	2015	2016	2017	2018	2019
Share of market	10%	40%	65%	65%	65%

Source: internal estimate

Ramucirumab is the first licensed therapy for the treatment of second-line advanced GC/GOJ. It offers a treatment option for patients in combination with paclitaxel (RAM+PAC) and as a treatment option for patients when treatment in combination with PAC is not appropriate (RAM).

Clinical experts were consulted to estimate the proportion of patients for whom cytotoxic chemotherapy is likely to be not appropriate (20% for the monotherapy patient population) and those who are suitable (80% for the combination therapy patient population).

Table 152 Patients eligible for combination therapy and monotherapy

	Patients suitable for further cytotoxic chemotherapy	Patients not suitable for further cytotoxic chemotherapy
Proportion	80%	20%

Source: expert clinical opinion

Ramucirumab combination therapy

Patient numbers

The total estimated patients who will receive RAM+PAC are calculated by applying the proportion eligible for further cytotoxic chemotherapy and the share of market estimation.

Table 153 Total estimated patients receiving RAM+PAC

Patient numbers	2015	2016	2017	2018	2019
Patients eligible for second-line chemotherapy	657	640	624	615	616
Patients eligible for further cytotoxic chemotherapy (80%)	526	512	499	492	493
Estimated patients numbers receiving RAM+PA (SoM applied)	53	205	325	320	320

Per patient cost

As a simplification, all patients are assumed to receive BSC (as the most common second-line treatment). Therefore no potential cost offset is implemented for patients receiving current treatments. The cost per patient is estimated from the combination therapy economic model taking the drug acquisition and administration cost.

Table 154 Per patient cost of treatment with RAM+PAC

	RAM +PAC
Drug cost	£30,186
Drug cost offset	-
Administration cost	£5,571
Administration cost offset	-
Total cost per patient	£35,757

Source: combination therapy economic model

Budget impact

The estimated cost per year of RAM+PAC is shown to be £1,879,848 in 2015 and increasing to £11,455,140 in 2019 for all patients.

Table 155 Budget impact of RAM+PAC

	2015	2016	2017	2018	2019
Estimated budget impact of RAM+PAC	£1,879,848	£7,317,542	£11,604,369	£11,434,455	£11,455,140

Ramucirumab monotherapy

As discussed, RAM as a monotherapy now offers a treatment option for patients who are currently unsuitable for treatment in combination with chemotherapy.

Patient numbers

Based on clinical opinion the estimated proportion of RAM monotherapy patients is 20% of all second-line eligible patients. The estimated five-year numbers based on market uptake are presented in Table 156.

Table 156 Estimated monotherapy patient numbers

Patient numbers	2015	2016	2017	2018	2019
Patients eligible for second-line chemotherapy	657	640	624	615	616
Patients not eligible for further cytotoxic chemotherapy (20%)	131	128	125	123	123
Estimated patients numbers receiving RAM (SoM applied)	13	51	81	80	80

Per patient cost

The cost per patient is estimated using data from the monotherapy therapy economic model for the acquisition and administration cost. There are no cost offsets as patients currently have no treatment options.

Table 157 Per patient cost of treatment with RAM

	2015
Drug cost	£19,879
Administration cost	£1,417
Total cost per patient	£21,295

Source: monotherapy economic model

Budget impact

The total budget impact of RAM as a monotherapy treatment option for suitable patients is estimated to be £279,894 in 2015 increasing to £1,705,574 in 2019.

Table 158 Budget impact of RAM

	2015	2016	2017	2018	2019
Estimated budget impact of RAM	£279,894	£1,089,520	£1,727,793	£1,702,494	£1,705,574

Total annual budget impact

The total budget impact expected from the introduction and availability of ramucirumab for patients in the NHS, both as a combination and monotherapy treatment option is £2,159,742 in 2015 increasing to £13,160,714 in 2019.

Table 159 Total ramucirumab budget impact

	2015	2016	2017	2018	2019
Total budget impact of ramucirumab	£2,159,742	£8,407,063	£13,332,162	£13,136,949	£13,160,714

GC/GOJ is an orphan disease and ramucirumab is the first licensed treatment in the second-line setting. As such providing at treatment option for patients who currently have none is likely to be associated with a budget impact. The total estimated budget impact is however quite small due to the rare nature of the disease. This should be considered in the decision making process for the introduction of ramucirumab for previously treated, advanced GC/GOJ in England.

As a sensitivity analysis an assessment of budget impact has been conducted using a 50%/50% split between patients receiving ramucirumab as a combination and monotherapy. The resulting 5-year budget impact is below.

Table 160 Budget impact with 50/50 combination/monotherapy split

	2015	2016	2017	2018	2019
Total budget impact of ramucirumab	£1,874,639	£7,297,265	£11,572,213	£11,402,770	£11,423,398

Opportunity for cost savings and limitations of the budget impact analysis

There are no expected overall cost savings.

7 References

(1) Cancer Research UK. Stomach Cancer Symptoms. 2014; Available at: http://www.cancerresearchuk.org/about-cancer/type/stomach-cancer/about/stomach-cancer-symptoms. Accessed 03/10, 2015.

(2) Ford HER, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): An open-label, phase 3 randomised controlled trial. The Lancet Oncology 2014 January 2014;15(1):78-86.

(3) Kang JH, Lee SI, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 2012;30:1513-1518.

(4) Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer - A randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 2011 October 2011;47(15):2306-2314.

(5) Real world treatment patterns of previously treated advanced gastric and gastroesophageal junction adenocarcinoma (GC) in the United Kingdom (UK). American Society for Clinical Oncology 2015 Gastrointestinal Cancers Symposium; 2015. http://meetinglibrary.asco.org/content/104536?media=vm&poster=1

(6) Wilke H, Muro K, Van Cutsem E, Oh S, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial The Lancet Oncology 2014;15(11):1224 <last_page> 1235.

(7) Fuchs CS, Tomasek J, Yong C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31-39.

(8) International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012: Stomach Cancer.

2015; Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed 01/23, 2014.

(9) Office for National Statistics. Cancer Registration Statistics, England, 2012. 2014.

(10) Cancer Research UK. Stomach Cancer Incidence Statistics. Available at: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/stomach/incidence/. Accessed 08/10, 2014.

(11) Cancer Research UK. Stomach cancer mortality statistics. 2014; Available at: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/stomach/mortality/#By. Accessed December, 2014.

(12) European Medicines Agency. Public summary of opinion on orphan designation: Ramucirumab for the treatment of gastric cancer. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2012/07/WC500130310.pdf. Accessed 09/03, 2014.

(13) Al-Batran S, Ajani JA. Impact of chemotherapy on quality of life in patients with metastatic esophagogastric cancer. Cancer 2010;116(11):2511-2518.

(14) National Institute for Health and Care Excellence. Pemetrexed maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer (TA309). 2014; Available at: http://www.nice.org.uk/guidance/ta309. Accessed 03/07, 2015.

(15) National Institute for Health and Care Excellence. Trastuzumab of the treatment of HER2-positive metastatic gastric cancer (TA208). 2010; Available at: http://www.nice.org.uk/guidance/ta208. Accessed 03/07, 2015.

(16) Eli Lilly and Company Ltd. Summary of Product Characteristics: Cyramza 10 mg/ml concentrate for solution for infusion. 19th Jan 2015; Available at: http://www.medicines.org.uk/emc/medicine/29765. Accessed 7th March, 2015.

(17) European Medicines Agency. CHMP Assessment Report: Cyramza. 2015;EMEA/H/C/002829/0000. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002829/WC500180726.pdf

(18) Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. Assessing the economic challenges posed by orphan drugs. Int J Technol Assess Health Care 2007;23(01):36-42.

(19) Kim R, Tan A, Choi M, El-Rayes BF. Geographic differences in approach to advanced gastric cancer: Is there a standard approach? Crit Rev Oncol Hematol 2013;88(2):416-426.

(20) Kim J, Sun CL, Mailey B, Prendergast C, Artinyan A, Bhatia S, et al. Race and ethnicity correlate with survival in patients with gastric adenocarcinoma. Ann Oncol 2010 Jan;21(1):152-160.

(21) Ohtsu A, Yoshida S, Saijo N. Disparities in gastric cancer chemotherapy between the East and West. J Clin Oncol 2006 May 10;24(14):2188-2196.

(22) NHS England. Are older people receiving cancer drugs? An analysis of patterns in cancer drug delivery according to the age of patient. 2013; Available at: http://www.england.nhs.uk/wp-content/uploads/2013/12/old-people-rec-cancer-drugs.pdf. Accessed 09/22, 2014.

(23) Lu D, Shen J, Vil MD, Zhang H, Jimenez X, Bohlen P, et al. Tailoring in vitro selection for a picomolar affinity human antibody directed against vascular endothelial growth factor receptor 2 for enhanced neutralizing activity. J Biol Chem 2003 Oct 31;278(44):43496-43507.

(24) Zhu Z, Hattori K, Zhang H, Jimenez X, Ludwig D, Dias S, et al. Inhibition of human leukemia in an animal model with human antibodies directed against vascular endothelial growth factor receptor 2. Correlation between antibody affinity and biological activity. Leukemia 2003;17(3):604-611.

(25) Xie L, Zhai T, Yang L, Yang E, Zhang X, Chen J, et al. Lymphangiogenesis and Prognostic Significance of Vascular Endothelial Growth Factor C in Gastro-oesophageal Junction Adenocarcinoma. Int J Exp Pathol 2013;94(1):39-46.

(26) Roy H, Bhardwaj S, Ylä-Herttuala S. Biology of vascular endothelial growth factors. FEBS Lett 2006;580(12):2879-2887.

(27) Oh SY, Kwon HC, Kim SH, Lee S, Lee JH, Graves CA, et al. Prognostic significance of serum levels of vascular endothelial growth factor and insulin-like growth factor-1 in advanced gastric cancer patients treated with FOLFOX chemotherapy. Chemotherapy 2012;58(6):426-434.

(28) International Federation of Pharmaceutical Manufacturers & Associations. Incremental innovation: Adapting to patient needs. 2013. http://www.ifpma.org/fileadmin/content/Publication/2013/IFPMA_Incremental_Innovation_Feb_2013_Low-Res.pdf

(29) Chia SK, Speers CH, D'yachkova Y, Kang A, Malfair-Taylor S, Barnett J, et al. The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer Cancer 2007;110(5):973 <last_page> 979.

(30) Bang YJ, Kang YK, Kang WK, Boku N, Chung HC, Chen JS, et al. Phase II study of sunitinib as second-line treatment for advanced gastric cancer Invest New Drugs 2011 Dec;29(6):1449-1458.

(31) Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advancedgastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 2011;29(30):3968-3976.

(32) Rosa G, Marta M, Carles P, Jesus G, Bernardo Q, Esther C, et al. Phase II study of oxaliplatin and sorafenib in advanced gastric cancer after failure of cisplatin-fluoropyrimidine-based (PF) treatment. 2012 2012;2015(4/28/2015). http://meetinglibrary.asco.org/content/71002?media=vm&poster=1

(33) Allum WH, Blazeby JM, Griffin M, Cunningham D, Jankoowski JA, Wong R. Guidelines for the management of oesohogeal and gastric cancer. Gut 2011;60:1449-1472.

(34) National Cancer Intelligence Network, Public Health England. Systemic anti-cancer therapy Chemotherapy dataset: Top regimens by diagnostic group between July 2013 and June 2014. 2014:1-1-75.

(35) Siewert J, Stein H. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg 1998;85(11):1457-1459.

(36) Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: Understanding the rising incidence of this disease. Semin Radiat Oncol 2013;23:3-9.

(37) Cancer Research UK. Types of Stomach Cacner. 2014; Available at: http://www.cancerresearchuk.org/about-cancer/type/stomach-cancer/about/types-of-stomach-cancer. Accessed December, 2014.

(38) Bertuccio P, Rosato V, Andreano A, Ferraroni M, Decarli A, Edefonti V, et al. Dietary patterns and gastric cancer risk: a systematic review and meta-analysis. Ann Oncol 2013 Jun;24(6):1450-1458.

(39) Campbell PT, Sloan M, Kreiger N. Dietary patterns and risk of incident gastric adenocarcinoma. Am J Epidemiol 2008 Feb 1;167(3):295-304.

(40) Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev 2014 May;23(5):700-713.

(41) Ladeiras-Lopes R, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I, Santos-Pereira R, et al. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. Cancer causes & control 2008;19(7):689-701.

(42) Compare D, Rocco A, Nardone G. Risk factors in gastric cancer. Eur Rev Med Pharmacol Sci 2010;14(4):302-308.

(43) Bernini M, Barbi S, Roviello F, Scarpa A, Moore P, Pedrazzani C, et al. Family history of gastric cancer: a correlation between epidemiologic findings and clinical data. Gastric Cancer 2006;9(1):9-13.

(44) Zanghieri G, Gregorio CD, Sacchetti C, Fante R, Sassatelli R, Cannizzo G, et al. Familial occurrence of gastric cancer in the 2-year experience of a population-based registry. Cancer 1990;66(9):2047-2051.

(45) Bhat S, Coleman HG, Yousef F, Johnston BT, McManus DT, Gavin AT, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J Natl Cancer Inst 2011 Jul 6;103(13):1049-1057.

(46) Hvid-Jensen F, Pedersen L, Drewes AM, Sørensen HT, Funch-Jensen P. Incidence of adenocarcinoma among patients with Barrett's esophagus. N Engl J Med 2011;365(15):1375-1383.

(47) Cook MB, Corley DA, Murray LJ, Liao LM, Kamangar F, Ye W, et al. Gastroesophageal Reflux in Relation to Adenocarcinomas of the Esophagus: A Pooled Analysis from the Barrett’s and Esophageal Adenocarcinoma Consortium (BEACON). PloS one 2014;9(7):e103508.

(48) Rubenstein J, Taylor J. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. Aliment Pharmacol Ther 2010;32(10):1222-1227.

(49) Bowles MJ, Benjamin IS. ABC of the upper gastrointestinal tract: Cancer of the stomach and pancreas. BMJ 2001 Dec 15;323(7326):1413-1416.

(50) Ferri FF. Esophageal Tumors. Ferri's Clinical Advisor 2013: 5 books in 1: Elsevier Health Sciences; 2012. p. 389-391.

(51) American Cancer Society. Stomach Cancer. Available at: http://www.cancer.org/acs/groups/cid/documents/webcontent/003141-pdf.pdf. Accessed 09/03, 2014.

(52) Yada T, Yokoi C, Uemura N. The current state of diagnosis and treatment for early gastric cancer. Diagnostic and therapeutic endoscopy 2013;2013.

(53) Office for National Statistics. Mortality Statistics: Deaths Registered in England and Wales (Series DR), 2013. 2014. http://www.ons.gov.uk/ons/rel/vsob1/mortality-statistics--deaths-registered-in-england-and-wales--series-dr-/index.html

(54) Cancer Research UK. Stomach cancer statistics and outlook. 2014; Available at: http://www.cancerresearchuk.org/about-cancer/type/stomach-cancer/treatment/statistics-and-outlook-for-stomach-cancer. Accessed 04/13, 2015.

(55) De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. The lancet oncology 2014;15(1):23-34.

(56) National Cancer Institute. Gastric Cancer Treatment (PDQ®). 2015; Available at: http://www.cancer.gov/cancertopics/pdq/treatment/gastric/HealthProfessional/page1. Accessed 3/19/2015, 2015.

(57) Cancer Research UK. Stomach cancer incidence statistics by age : Cancer Research UK. 2014; Available at: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/stomach/incidence/#age. Accessed 3/20/2015, 2015.

(58) Müller J, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. Br J Surg 1990;77(8):845-857.

(59) Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345(10):725-730.

(60) Ohtsu A, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, et al. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. J Clin Oncol 2013 Nov 1;31(31):3935-3943.

(61) Giuliani F, Gebbia V, De Vita F, Maiello E, Di Bisceglie M, Catalano G, et al. Docetaxel as salvage therapy in advanced gastric cancer: A phase II study of the Gruppo Oncologico Italia Meridionale (GOIM). Anticancer Research 2003;23(1):4219-4222.

(62) Giuliani F, Molica S, Maiello E, Battaglia C, Gebbia V, Di Bisceglie M, et al. Irinotecan (CPT-11) and mitomycin-C (MMC) as second-line therapy in advanced gastric cancer: a phase II study of the Gruppo Oncologico dell' Italia Meridionale (prot. 2106). Am J Clin Oncol 2005;28(6):581-585.

(63) Hironaka S, Zenda S, Boku N, Fukutomi A, Yoshino T, Onozawa Y. Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer 2006;9(1):14-18.

(64) Assersohn L, Brown G, Cunningham D, Ward C, Oates J, Waters JS, et al. Phase II study of irinotecan and 5-fluorouracil/leucovorin in patients with primary refractory or relapsed advanced oesophageal and gastric carcinoma. Ann Oncol 2004;15(1):64-69.

(65) Barone C, Basso M, Schinzari G, Pozzo C, Trigila N, D'Argento E, et al. Docetaxel and oxaliplatin combination in second-line treatment of patients with advanced gastric cancer. Gastric Cancer 2007;10(2):104-111.

(66) Cascinu S, Graziano F, Cardarelli N, Marcellini M, Giordani P, Menichetti ET, et al. Phase II study of paclitaxel in pretreated advanced gastric cancer. Anticancer Drugs 1998;9(4):307-310.

(67) Chun JH, Kim HK, Lee JS, Choi JY, Lee HG, Yoon SM, et al. Weekly irinotecan in patients with metastatic gastric cancer failing cisplatin-based chemotherapy. Jpn J Clin Oncol 2004;34(1):8-13.

(68) Jo JC, Lee JL, Ryu MH, Sym SJ, Lee SS, Chang HM, et al. Docetaxel monotherapy as a second-line treatment after failure of fluoropyrimidine and platinum in advanced gastric cancer: experience of 154 patients with prognostic factor analysis. Jpn J Clin Oncol 2007;37(12):936-941.

(69) Kim ST, Kang WK, Kang JH, Park KW, Lee J, Lee SH, et al. Salvage chemotherapy with irinotecan, 5-fluorouracil and leucovorin for taxane- and cisplatin-refractory, metastatic gastric cancer. Br J Cancer 2005;92(10):1850-1854.

(70) Kodera Y, Ito S, Mochizuki Y, Fujitake S, Koshikawa K, Kanyama Y, et al. A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric Cancer (CCOG0302 study). Anticancer Res 2007;27(4C):2667-2671.

(71) Lee KW, Kim JH, Yun T, Song EK, Na II, Shin H, et al. Phase II study of low-dose paclitaxel and cisplatin as a second-line therapy after 5-fluorouracil/platinum chemotherapy in gastric cancer. J Korean Med Sci 2007;22(Suppl):S115-S121.

(72) Lee JL, Ryu MH, Chang HM, Kim TW, Yook JH, Oh ST, et al. A phase II study of docetaxel as salvage chemotherapy in advanced gastric cancer after failure of fluoropyrimidine and platinum combination chemotherapy. Cancer Chemother Pharmacol 2008;61(4):631-637.

(73) Polyzos A, Tsavaris N, Kosmas C, Polyzos K, Giannopoulos A, Felekouras E, et al. Subsets of patients with advanced gastric cancer responding to second-line chemotherapy with docetaxel-cisplatin. Anticancer Res 2006;26(5B):3749-3753.

(74) Wesolowski R, Lee C, Kim R. Is there a role for second-line chemotherapy in advanced gastric cancer? Lancet Oncol 2009;10(9):903-912.

(75) Zhong H, Zhang Y, Ma S, Ying JE, Yang Y, Yong D, et al. Docetaxel plus oxaliplatin (DOCOX) as a second-line treatment after failure of fluoropyrimidine and platinum in Chinese patients with advanced gastric cancer. Anticancer Drugs 2008;19(10):1013-1018.

(76) Waddell T, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(Suppl 6):vi57-63.

(77) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer. 2015;2.2015.

(78) Alderson D. Scottish Intercollegiate Guidelines Network (SIGN) 87—the management of oesophageal and gastric cancer. Clin Oncol 2008;20(7):530-531.

(79) National Institute for Health and Care Excellence. Capecitabine for the Treatment of Advanced Gastric Cancer (TA 191). 2010; Available at: https://www.nice.org.uk/guidance/ta191. Accessed 09/22, 2014.

(80) Coleman M, Rachet B, Woods L, Mitry E, Riga M, Cooper N, et al. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. Br J Cancer 2004;90(7):1367-1373.

(81) Rachet B, Woods L, Mitry E, Riga M, Cooper N, Quinn M, et al. Cancer survival in England and Wales at the end of the 20th century. Br J Cancer 2008;99:S2-S10.

(82) General Medical Council. Good practice in prescribing and managing medicines and devices. 2013. http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp

(83) RAINBOW: a global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel patients with previously treated gastric or gastroesophageal junction (GEJ) adenocarcinoma - Quality-of-life (QoL) results. ASCO Annual Meeting Proceedings; 2014. http://meetinglibrary.asco.org/content/129972-144

(84) RAINBOW: A global, phase 3, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel with previously treated gastric of gastroesophageal junction (GEJ) adenocarcinoma - Patient Reported Outcomes and Performance status. ESMO World Congress on GI; 27 June 2014; ; 2014. http://oncologypro.esmo.org/Meeting-Resources/World-GI-2014/RAINBOW-global-phase-3-randomized-double-blind-study-of-ramucirumab-plus-paclitaxel-vs-placebo-plus-paclitaxel-patients-with-previously-treated-gastric-or-gastroesophageal-junction-adenocarcinoma-patient-reported-outcomes-and-performance-status

(85) RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab (RAM) plus paclitaxel (PTX) versus placebo (PL) plus PTX in the treatment of metastatic gastroesophageal junction and gastric adenocarcinoma (mGC) following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy-Efficacy analysis in Japanese and Western patients. . Journal of Clinical Oncology. Conference 2014 Annual Meeting od the American Society of Clinical Oncology; 2014. http://meetinglibrary.asco.org/content/132412-144

(86) Wilke H, Cunningham D, Ohtsu A, Nuber U, Bruns R, Schmitt-Bormann B. A randomized, multicenter, double-blind, placebo (PBO)-controlled phase III study of paclitaxel (PTX) with or without ramucirumab (IMC-1121B; RAM) in patients (pts) with metastatic gastric adenocarcinoma, refractory to or progressive after first-line therapy with platinum (PLT) and fluoropyrimidine (FP). J Clin Oncol 2012;30. http://meetinglibrary.asco.org/content/93982-114

(87) RAINBOW: A global, phase 3, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of gastric cancer following disease progression: Western population subgroup. ESMO World Congress on GI; 26 June

2014; ; 2014. http://oncologypro.esmo.org/Meeting-Resources/World-GI-2014/RAINBOW-a-global-phase-3-double-blind-study-of-ramucirumab-plus-paclitaxel-versus-placebo-plus-paclitaxel-in-the-treatment-of-gastric-cancer-following-disease-progression-Western-population-subgroup

(88) RAINBOW: a global, phase 3, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastric adenocarcinoma following disease progression on first-line platinum-and fluoropyrimidine-containing combination therapy: results of a multiple Cox regression analysis adjusting for prognostic factors. ASCO Annual Meeting Proceedings; 2014. http://meetinglibrary.asco.org/content/132453-144

(89) RAINBOW: A global, phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal junction (GEJ) and gastric adenocarcinoma following disease progression on first-line platinum-and fluoropyrimidine-containing combination therapy rainbow IMCL CP12-0922 (I4T-IE-JVBE). ASCO Annual Meeting Proceedings; 2014. http://meetinglibrary.asco.org/content/90231

(90) Chau I, Passalacqua R, Zalcberg JR, et al. Tolerability and Quality-of-life (QoL) results from the phase 3 REGARD study: Ramucirumab versus placebo in patients with previously treated gastric or gastroesophageal junction (GEJ) adenocarcinoma. ESMO 2013.

(91) REGARD: A phase 3, randomized, double-blind trial of ramucirumab (RAM) and best supportive care (BSC) versus placebo (PL) and BSC in the treatment of metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma following disease progression (PD) on first-line platinum- and/or fluoropyrimidine-containing combination therapy: Age subgroup analysis. American Society of Clinical Oncology; May 30 - Jun 3, 2014; ; 2014. http://meetinglibrary.asco.org/content/129855-144

(92) Fuchs CS, Tomasek J, Cho JY, Dumitru F, Passalacqua R, Goswami C, et al. REGARD: A phase III, randomized, double-blinded trial of ramucirumab and best supportive care (BSC) versus placebo and BSC in the treatment of metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma following disease progression on first-line platinum- and/or fluoropyrimidine-containing combination therapy. J Clin Oncol 2013;31(Suppl 4; abstr LBA5). http://meetinglibrary.asco.org/content/106221-133

(93) REGARD: A phase III, randomized, double-blind trial of ramucirumab and best supportive care (BSC) versus placebo and BSC in the treatment of metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma following disease progression on first-line platinum- and/or fluoropyrimidine-containing combination therapy. American Association for Cancer Research Annual Meeting 2013; 07 April 2013; ; 2013. http://meetinglibrary.asco.org/content/106221-133

(94) Liguigli W, Tomasello G, Toppo L, Ratti M, Passalacqua R. Ramucirumab for metastatic gastric or gastroesophageal junction cancer: results and implications of the REGARD trial. Future Oncology 2014;10(9):1549-1557.

(95) Matsuda G, Kunisaki C, Makino H, et al. Phase II study of weekly paclitaxel as a second-line treatment for S-1-refractory advanced gastric cancer. Anticancer Res 2009;29(7):2863-2867.

(96) Ohtsu A, Boku N, Tamura F, et al. An early phase II study of a 3-hour infusion of paclitaxel for advanced gastric cancer. Am J Clin Oncol 1998;21(4):416-419.

(97) Yamada Y, Shirao K, Ohtsu A, et al. Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. Ann Oncol 2001;12(8):1133-1137.

(98) Yamaguchi K, Tada M, Horikoshi N, et al. Phase II study of paclitaxel with 3-h infusion in patients with advanced gastric cancer. Gastric Cancer 2002;5(2):90-95.

(99) 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.

(100) Kanagavel D, Pokataev IA, Fedyanin MY, et al. A prognostic model in patients treated for metastatic gastric cancer with second-line chemotherapy. Ann Oncol 2010;21(9):1779-1785.

(101) Leung WK, Wu MS, Kakugawa Y, et al. Screening for gastric cancer in Asia: current evidence and practice. Lancet Oncology 2008;9:279-287.

(102) Han HS, Lauwers GY. Connection - Her 2 in Gastric Carcinoma. Dako. Available at: http://www.dako.com/28830_14dec10_connection_15_her2_in_gastric_cancer.pdf. Accessed 10/13, 2013.

(103) Sasako M, Inoue M, Lin J-, Khor C, Yang H-, Ohtsu A. Gastric Cancer Working Group Report Jpn J Clin Oncol 2010; 2010;40(Supplement 1):i28 <last_page> i37.

(104) 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.

(105) Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205-216.

(106) Korn, E.L., Freidlin, B., Abrams, J.S. Overall Survival As the Outcome for Randomized Clinical Trials With Effective Subsequent Therapies J Clin Oncol 2011;29(17):2439-2442.

(107) Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-247.

(108) Peron J, Maillet D, Gan HK, Chen EX, You B. Adherence to CONSORT adverse event reporting guidelines in randomized clinical trials evaluating systemic cancer therapy: a systematic review. J Clin Oncol 2013 Nov 1;31(31):3957-3963.

(109) Sivendran S, Latif A, McBride RB, Stensland KD, Wisnivesky J, Haines L, et al. Adverse event reporting in cancer clinical trial publications. J Clin Oncol 2014 Jan 10;32(2):83-89.

(110) Roy AC, Park SR, Cunningham D, Kang YK, Chao Y, Chen LT, et al. A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma. Ann Oncol 2013 Jun;24(6):1567-1573.

(111) 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.

(112) Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998 Dec 30;17(24):2815-2834.

(113) Al-Refaie WB, Tseng JF, Gay G, Patel-Parekh L, Mansfield PF, Pisters PW, et al. The impact of ethnicity on the presentation and prognosis of patients with gastric adenocarcinoma. Cancer 2008;113(3):461-469.

(114) Tamura S, Nishikawa K, et al. Randomized phase III trial of irinotecan plus cisplatin versus irinotecan in patients with metastatic gastric cancer resistant to S-1 monotherapy: Survival analysis. . European Cancer Congress 2013;Abstract 2599.

(115) Hospira UK Ltd. Summary of Product Characteristics: Paclitaxel 6mg/ml concentrate for solution for infusion. 2014; Available at: https://www.medicines.org.uk/emc/medicine/15842#. Accessed 10/20, 2014.

(116) Park S. Second-line chemotherapy for patients with oesphogastric adenocarcinoma. Lancet Oncol 2014;15(1):8-10.

(117) Xu J, Evans TJ, Coon C, Copley-Merriman K, Su Y. Measuring patient-reported outcomes in advanced gastric cancer. Ecancermedicalscience 2013;7:351.

(118) National Cancer Intelligence Network. Report October 2009 Epidemiology OG Cancers .

(119) Shiroiwa T, Fukuda T, Shimozuma K. Cost-effectiveness analysis of trastuzumab to treat HER2-positive advanced gastric cancer based on the randomised ToGA trial. Br J Cancer 2011 25 Oct 2011;105(9):1273-1278.

(120) Wu B, Ye M, Chen H, Shen JF. Costs of Trastuzumab in Combination With Chemotherapy for HER2-Positive Advanced Gastric or Gastroesophageal Junction Cancer: An Economic Evaluation in the Chinese Context. Clin Ther 2012 February 2012;34(2):468-479.

(121) Eli Lilly and Company Ltd. Market Research Data. Company Confidential. 2014.

(122) National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. 2013.

(123) Accord Healthcare Limited. Summary of Product Characteristics: Docetaxel 160 mg/8 ml concentrate for solution for infusion. 2014; Available at: http://www.medicines.org.uk/emc/medicine/26771. Accessed 03/09, 2015.

(124) Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. Sheffield: Report by the Decision Support Unit 2011.

(125) Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol 2011 May 6;11:61-2288-11-61.

(126) Collett D.
Modelling Survival Data in Medical Research. London: Chapman & Hall; 1994.

(127) Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012 Feb 1;12:9-2288-12-9.

(128) Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50(6):683-691.

(129) Scottish Intercollegiate Guidelines Network. 87 - Management of oesophageal and gastric cancer. A national clinical guideline. 2006;2006.
http://www.sign.ac.uk/guidelines/fulltext/87/index.html

(130) Kontodimopoulos N, Aletras VH, Paliouras D, Niakas D. Mapping the Cancer-Specific EORTC QLQ-C30 to the Preference-Based EQ-5D, SF-6D, and 15D Instruments. Value in Health 2009;12(8):1151-1157.

(131) Aultman R, Urspruch A. PCN116 ANALYSIS OF THE EQ-5D QUESTIONNAIRE FOR PATIENTS WITH ADVANCED HER2-POSITIVE GASTRIC CANCER (HER2 AGC) BASED ON THE TRASTUZUMAB FOR GASTRIC CANCER (TOGA) STUDY. Value in Health 2010;13(7):A273.

(132) O'Gorman P, McMillan DC, McArdle CS. Impact of weight loss, appetite, and the inflammatory response on quality of life in gastrointestinal cancer patients. 1998.

(133) Ajani JA, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Quality of life with docetaxel plus cisplatin and fluorouracil compared with cisplatin and fluorouracil from a phase III trial for advanced gastric or gastroesophageal adenocarcinoma: the V-325 Study Group. J Clin Oncol 2007 Aug 1;25(22):3210-3216.

(134) McNamee P, Glendinning S, Shenfine J, Steen N, Griffin SM, Bond J. Chained time trade-off and standard gamble methods. The European Journal of Health Economics, formerly: HEPAC 2004;5(1):81-86.

(135) Wildi SM, Cox MH, Clark LL, Turner R, Hawes RH, Hoffman BJ, et al. Assessment of health state utilities and quality of life in patients with malignant esophageal dysphagia. Am J Gastroenterol 2004;99(6):1044-1049.

(136) Curran D, Pozzo C, Zaluski J, Dank M, Barone C, Valvere V, et al. Quality of life of palliative chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction treated with irinotecan combined with 5-fluorouracil and folinic acid: results of a randomised phase III trial. Quality of life research 2009;18(7):853-861.

(137) McMillan DC, Wigmore SJ, Fearon KC, O'Gorman P, Wright CE, McArdle CS. A prospective randomized study of megestrol acetate and ibuprofen in gastrointestinal cancer patients with weight loss. Br J Cancer 1999 Feb;79(3-4):495-500.

(138) Homs MY, Essink-Bot M, Borsboom GJ, Steyerberg EW, Siersema PD, Dutch SIREC Study Group. Quality of life after palliative treatment for oesophageal carcinoma–a prospective comparison between stent placement and single dose brachytherapy. Eur J Cancer 2004;40(12):1862-1871.

(139) Longworth L, Rowen D. NICE DSU technical support document 10: the use of mapping methods to estimate health state utility values. London: NICE 2011.

(140) Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35(11):1095-1108.

(141) National Institute for Health and Care Excellence. Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. 2014; Available at: http://www.nice.org.uk/guidance/ta306. Accessed 03/10, 2015.

(142) Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. Current Medical Research & Opinion 2010;26(5):1091-1096.

(143) Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer 2006;95(6):683-690.

(144) Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes 2008;6(84):84.

(145) Coyle D, Small N, Ashworth A, Hennessy S, Jenkins-Clarke S, Mannion R, et al. Costs of palliative care in the community, in hospitals and in hospices in the UK. Crit Rev Oncol 1999;32(2):71-85.

(146) Health and Social Care Information Centre. NHS Reference costs 2012/13. 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/261154/nhs_reference_costs_2012-13_acc.pdf

(147) Department of Health Payment by Results team. Payment by Results Guidance for 2013/14. 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/214902/PbR-Guidance-2013-14.pdf

(148) Commercial Medicines Unit. Drugs and pharmaceutrical electronic Market Information(eMIT). 2014; Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Accessed 04/23, 2015.

(149) Medicines Complete. British National Formulary. 2015; Available at: https://www.medicinescomplete.com/mc/bnf/current/. Accessed 04/24, 2015.

(150) National Institute for Health and Care Excellence. Sunitinib for the treatment of gastrointestinal stromal tumours (TA179). 2009; Available at: http://www.nice.org.uk/guidance/ta179. Accessed 03/07, 2015.

(151) British Medical Association. British National Formulary 67. 67th ed.: BNF Publications Management; 2014.

(152) NHS Choices. Cognitive behavioural therapy. 2014; Available at: http://www.nhs.uk/conditions/Cognitive-behavioural-therapy/Pages/Introduction.aspx. Accessed 05/05, 2015.

(153) Scottish Medicines Consortium. PACE (Patient and Clinician Engagement) Overview Document. 2014; Available at: http://www.scottishmedicines.org.uk/files/new_medicines_review/PACE_Overview_Document_May_2014.pdf. Accessed 05/06, 2015.

(154) Tordrup D, Tzouma V, Kanavos P. Orphan drug considerations in Health Technology Assessment in eight European countries. Rare Diseases and Orphan Drugs: An International Journal of Public Health 2014;1(3):86-97.

(155) The Royal College of Surgeons of England. National Oesophago-Gastric Cancer Audit 2013. Available at: http://www.rcseng.ac.uk/media/docs/press_releases/national-oesophago-gastric-cancer-audit-2013. Accessed 10/10, 2014.