Horizon Scanning in Oncology

Ramucirumab in combination with paclitaxel as second-line treatment for adult patients with advanced gastric or gastro-oesophageal junction carcinoma

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DISCLAIMER

This report is based on an assessment of the European HTA network EUnetHTA with the title “Ramucirumab in combination with paclitaxel as second-line treatment for adult patients with advanced gastric or gastro-oesophageal junction carcinoma” published in March 2015. This short report was compiled by mainly using the information provided in the EUnetHTA assessment directly. Context-specific information for Austria on e.g. costs and epidemiologic data was incorporated whenever possible and further information on the included phase III study was added.

Project team

Project Coordination:	National Health Care Institute (The Netherlands)
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Internal review:	The internal review of the original assessment was performed by the Slovak Ministry of Health (Slovakia), the Finnish Medicines Agency (Finland), GYMESZI (Hungary), A.Gemelli Teaching Hospital (Italy) and Haute Autorité de Santé (France).

Adaptation of original report:

Dr. med. Anna Nachtnebel, MSc was responsible for adapting the EUnetHTA Pilot WP5-SA4 for the Ludwig Boltzmann Institute for Health Technology Assessment.

The internal review of this short report was conducted by Dr. med. Eleen Rothschedl.

The original report is available at:

http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/WP5-SA-4_RAMUCIRUMAB%20for%20the%20treatment%20of%20gastric%20cancer.pdf

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1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

Table 1: Research questions

Element ID	Research question
B0001	What is ramucirumab and the comparators?
B0002	What is the claimed benefit of ramucirumab in relation to the comparators?
A0020	For which indications has ramucirumab received marketing authorisation?
A0021	What is the reimbursement status of ramucirumab?
A0002	What is the precise definition of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma and which diagnosis is given according to ICD-10?
A0004	What is the natural course of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma?
A0005	What are the symptoms and the burden of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma for the patient?
A0006	What is the burden of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma for society?
A0025	How is advanced gastric cancer or gastro-oesophageal junction adenocarcinoma currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
D0001	What is the effect on overall mortality of ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?
D0005	How does ramucirumab in combination with paclitaxel affect symptoms and findings (severity, frequency) of patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma compared to other treatments in second-line therapy?
D0006	How does ramucirumab in combination with paclitaxel affect progression-free survival (PFS) of patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma compared to other treatments in second-line therapy?
D0016	How does ramucirumab in combination with paclitaxel affect performance status, such as ECOG score, compared to other treatments in second-line therapy?
D0012	What is the effect on health-related quality of life for ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?
D0013	What is the effect on disease-specific quality of life for ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?
C0008	How safe is the technology in relation to (the) comparator(s)? **C0008a** – What is the frequency of all adverse events with ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy? **C0008b** – What is the frequency of discontinuation of treatment due to adverse events with ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy? **C0008c** – What is the frequency of and what are the serious adverse events (SAEs) with ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy? **C0008d** – What is the frequency of serious adverse events (SAEs) leading to death with ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy? **C0008e** – What are the most frequent adverse events with ramucirumab in combination with paclitaxel compared to other treatments in second-line therapy?
C0005	What are the susceptible patient groups that are more likely to be harmed with ramucirumab treatment in combination with paclitaxel?

2 Drug description

Generic/Brand name/ATC code:

Ramucirumab/Cyramza®/LO1XC

Developer/Company:

Eli Lilly

Description of the technology:

B0001: drug description

Ramucirumab is a human immunoglobulin G1 (IgG1) monoclonal antibody produced in murine (NS0) cells by recombinant DNA technology. Vascular endothelial growth factor (VEGF) receptor 2 is the key mediator of VEGF induced angiogenesis. Ramucirumab, is a human receptor-targeted antibody that specifically binds VEGF receptor 2 (VEGFR-2; the extracellular domain) and blocks binding of VEGF-A, VEGF-C, and VEGF-D, preventing the interaction of VEGF R2 with activating ligands (VEGF-A, VEGF-C, and VEGF-D). As a result, ramucirumab inhibits ligand-stimulated activation of VEGF R2 and its downstream signalling components, including p44/p42 mitogen-activated protein kinases, neutralising ligand-induced proliferation and migration of human endothelial cells [2, 3].

recommended dosages

The recommended dose of ramucirumab is 8 mg/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 by intravenous infusion over approximately 60 minutes on days 1, 8 and 15 of a 28 day cycle. The recommended treatment duration is until disease progression or until unacceptable toxicity has occurred. Prior to infusion of ramucirumab, a histamine H1 antagonist (e.g. diphenhydramine) should be administered.

B0002: claimed benefit of ramucirumab in relation to the comparators

Rational multi-target approaches to angiogenesis are needed to overcome resistance mechanisms. Inhibition of VEGFR-2 (or VEGF-A) may have some impact on these elements given pathway crosstalk, but is likely insufficient to prevent all escape mechanisms from occurring. Despite these potential mechanisms of resistance, ramucirumab may have distinct mechanistic advantages compared to other anti-angiogenic modalities. Although a number of tyrosine kinase inhibitors are being used, their biochemical promiscuity and potential for off-target toxicities present potential limitations in cancer therapy.

Ramucirumab offers a novel mechanism for anti-angiogenic therapy with the potential for both high affinity and high specificity blockade of VEGFR-2. Because ramucirumab binds to VEGFR-2 specifically and with high affinity, it may offer a rational modulation advantage. In contrast to other agents directed against the VEGFR-2/VEGF axis, ramucirumab binds a specific epitope on the extracellular domain of VEGFR-2, thereby blocking all VEGF ligands from binding to this therapeutically validated target.

Moreover, in contrast to bevacizumab, which binds to VEGF-A only, ramucirumab blocks all known VEGFs from binding to VEGFR-2. The combined effects of high specificity and more complete target inhibition could lead to a more complete blockade of angiogenesis [15].

3 Indication

A0007: target population

Ramucirumab in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction (GEJ) adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy. According to treatment guidelines, only patients who have a good performance status at the time of progression after first-line treatment are considered to be candidates for second-line therapy (see Scope) [4].

4 Current regulatory status

A0020: approval status

In Europe, ramucirumab received orphan drug status in 2012 and market authorization by the EMA in December 2014 [5]:

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

In the US, the FDA granted market authorization for ramucirumab [6]

- as a single agent or in combination with paclitaxel, for treatment of advanced gastric or gastro-esophageal junction adenocarcinoma, with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy in April 2014.
- in combination with docetaxel, for treatment of metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on FDA – approved therapy for these aberrations prior to receiving Cyramza® in December 2014.
- 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 in April 2015.

5 Burden of disease

A0002: definition of disease

Gastric cancers include malignancies that arise from the lining of the stomach and the GEJ [7, 8]. Whereas stomach cancers occur in any part of the stomach, GEJ cancers occur "within 5 cm proximal and distal of the anatomic cardia" [9]. The vast majority of gastric cancers are adenocarcinomas histopathological (about 90%), and in a minority of cases include lymphomas, gastrointestinal stromal tumours, or carcinoid tumours [7].

Lauren classification

The commonly used Lauren classification of gastric adenocarcinoma defines 2 subtypes, diffuse and intestinal, based on location and histopathological features [10, 11]. Diffuse cancers develop in the stomach wall and mucosa, usually in the distal part of the stomach and often in younger patients; they commonly metastasise to the peritoneum, and have a poor prognosis. Intestinal-type adenocarcinomas are characterised by gland formation, and are microscopically similar to colonic mucosa and commonly affect older patients. Gland formation includes a range from well to poorly differentiated carcinomas, which grow by expansion, and not by infiltration [11, 12].

risk factors

Dietary (nitroso compounds, high salt diet with low vegetables) and lifestyle risk factors (smoking and alcohol consumption) account for one-third to one-half of all gastric cancers. An important risk factor is H. pylori infection, especially certain genotypes (vacAs1-, vacAm1-, and cagA-positive). The risk is increased in hosts who possess specific types of cytokine polymorphisms (IL-1B-511*T/*T or IL-1B-511*T/*C). Gastric ulcers, adenomatous polyps, and intestinal metaplasia have been associated with an increased risk of gastric cancer [13].

A0005: symptoms and burden

The symptoms and burden of advanced gastric cancer for the patient commonly include fatigue, nausea, vomiting, anorexia, abdominal pain, diarrhoea or constipation, melaena, haematemesis, weight loss, and anaemia [14-18] .

A0004: natural course

In Western countries, 80% to 90% of patients with gastric cancer (in more than 90% adenocarcinomas) are either diagnosed at an advanced stage, when the tumour is inoperable and/or metastatic, or develop recurrence within 5 years after initial surgery [19]. Patients who present with advanced gastric cancer at diagnosis have a poor prognosis and expected survival times of less than a year. They typically have lymph node metastases and surgery is not considered curative (but palliative if performed) [12, 19, 20]. The results of the EUROCARE-5 study showed that for patients diagnosed in 2000-2007 the European mean 5-year age-standardised relative survival for stomach cancer was 25.1% (95%CI 24.8% to 25.4%), the second lowest rate (after lung cancer) among all the common cancer sites studied [21]. The 5-year relative and period survival by stage was different for localised gastric cancer and that with distant metastases, namely 28.8% versus 4.2% [22].

A0006: burden for society

According to the EUCAN [23, 24] database, in 2012 the estimates of age-standardised (European) incidence rates (per 100,000) of gastric cancer (ICD C16) in men was 13.9 in Austria, the overall EU (27) rate being 15.2. The age-standardised incidence rates of gastric cancer in 2012 in women was 7.3 in Austria, the overall EU (27) rate being 7.1. [23, 24].

poor prognosis

In 2008, stomach cancer caused an estimated total loss of 378, 103, 197 and 108 disability-adjusted life years (DALYs) per age- adjusted 100,000 population in men in the Europe East, North, South and West WHO regions, respec-

tively. For women the corresponding estimated losses were 185, 60, 107 and 63 DALYs per age-adjusted 100,000 population [25].

A0023: target population

Based on the estimated prevalence in the European countries of interest in the calendar year of 2011 the prevalence of gastric cancer, including GEJ cancer, was estimated to range from 2.8 to 3.6 per 10,000 in the EU community. Based on an updated literature review conducted in October 2014 and indirect methods (estimation of gastric cancer prevalence as a function of incidence and mean duration of disease) the population prevalence of gastric cancer (which includes GEJ cancer, as per ICD codes) in the European countries of interest (EU-28, plus Norway and Iceland) in the calendar year of 2014, was estimated to range from 2.80 to 4.24 per 10,000 in the EU community. This is below the threshold of 5 per 10,000 required by the European Commission for an orphan drug designation [26].

6 Current treatment

A0025: current management guidelines

Most patients with advanced-stage disease will need palliative chemotherapy but not all patients receive first-line therapy; primarily because they are not considered fit enough to receive chemotherapy. According to the most current ESMO-ESSO-ESTRO clinical practice guidelines [4] first-line palliative chemotherapy combination regimens based upon a platinum-fluoropyrimidine doublet are generally used. Other doublet and triplet combinations are also sometimes used, including addition of an anthracycline (epirubicin) or a taxane (docetaxel). However, almost all patients with metastatic gastric cancer develop progressive disease after first-line therapy.

With the availability of several active chemotherapy drugs, patients who retain a good performance status after the initial treatment remain good candidates for additional therapy [27]. Relatively few patients in Western countries (approximately 15% to 50% of patients receiving first-line treatment) receive second-line treatment [28-30].

no standard second-line treatment for patients with advanced gastric/GEJ adenocarcinoma after disease progression despite prior chemotherapy

In the EU there is currently no standard second-line treatment for patients with advanced gastric or GEJ adenocarcinoma following progression despite prior chemotherapy. According to the above mentioned ESMO-ESSO-ESTRO guidelines, in patients of adequate performance status, second-line chemotherapy is associated with proven improvements in overall survival (OS) and quality of life (QoL) compared with best supportive care (BSC), with treatment options including irinotecan, docetaxel, or paclitaxel (Level of evidence I, Grade of recommendation A) [4].

None of the 3 above-mentioned drugs is approved for second-line treatment but all are used off-label for patients with advanced disease whose cancer has progressed despite prior first-line chemotherapy. They are the most common agents recommended in treatment guidelines and the only agents listed in the most recent European ESMO-ESSO-ESTRO guidelines as second-line therapies, except when patients have a progression-free interval of >3 months after first-line therapy when patients could be re-challenged with first-line therapy [4]. According to the manufacturers' file data paclitaxel and docetaxel are used in between 16% and 46%, irinotecan in be-

tween 17% and 41% and BSC in between 15% and 37% of patients as a second line treatment [26].

Evidence supports the use of paclitaxel, in combination therapy, as reasonable medical therapy at some point in the management of advanced gastric carcinoma. Paclitaxel monotherapy has demonstrated only minimal activity against gastric cancer. Paclitaxel plus radiation has shown some activity against gastric cancer [26, 31-35].

In second-line clinical trials the following chemotherapy regimens have been used: irinotecan plus cisplatin or fluoropyrimidines; single-agent irinotecan; single-agent docetaxel; docetaxel plus oxaliplatin (expert opinion indicates that docetaxel is used more commonly with cisplatin or 5-fluorouracil [5-FU]); paclitaxel single-agent or plus platinum agents; and FOLFOX (folinic acid, 5-FU, oxaliplatin) [36].

ramucirumab already included in NCCN clinical practice guideline for gastric cancer

Ramucirumab alone or in combination with paclitaxel is currently the only approved treatment option for patients with advanced disease whose cancer has progressed despite prior fluoropyrimidine and platinum chemotherapy, and for whom there are currently no standard therapies available. It is therefore already included in The National Comprehensive Cancer Network (NCCN) clinical practice guideline for gastric cancer [37].

further treatment options

Further treatment options include: palliative radiotherapy; endoscopic methods for relieving dysphagia such as oesophageal intubation, oesophageal dilatation, brachytherapy and stents; laser therapy and stents; and palliative surgery – to bypass obstruction in patients with distal stomach cancers that are obstructing the passage of food out of the stomach [36].

7 Evidence

systematic search in 5 databases

3 sources of information, submitted by the marketing authorisation holder (MAH), were mainly used: the submission dossier, the draft and published European public assessment report (EPAR) for ramucirumab and a meta-analysis report. The MAH performed a systematic literature search as a part of their submission dossier. They used a combination of subject terms and text words to define the population and all interventions and controls relevant for this assessment, and searched in several relevant databases. The search strategy was adapted to each database. When necessary, additional non-systematic searches were performed.

The study types included in the clinical effectiveness and safety domains were limited to randomised controlled trials. The Cochrane risk of bias tool was used to assess the internal validity (see Risk of bias) and external validity was formally assessed only for direct evidence for the major outcomes. The evidence was assessed as part of assessing the overall documentation for each outcome using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) (see Evidence profile).

The systematic search was undertaken initial in December 2013 and updated on 28 May 2014. For this report, a further update was conducted on 21 August 2015. The search included subject headings and text words for the disease and the possible treatment, and run in:

- Ovid MEDLINE(R) <1946 to August Week 2 2015>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <August 20, 2015>, Ovid MEDLINE(R) Daily Update <August 20, 2015>, Ovid OLDMEDLINE(R) <1946 to 1965>
- EMBASE (via Elsevier)
- The Cochrane Central Register of Controlled Trials (via The Cochrane Library)
- Cochrane Database of Systematic Reviews (via The Cochrane Library)
- Database of Abstracts of Reviews of Effects (via CRD, The Cochrane Library)
- Health Technology Assessment Database (via CRD, The Cochrane Library)
- NHS Economic Evaluation Database (via CRD, The Cochrane Library).

included: 1 study for direct evidence

The initial search identified 11,056 records via databases but only 43 remained after exclusion of duplicates and of studies that did not meet eligibility criteria (based on title/abstract); additional publications were identified from conference abstracts and hand-searching. Finally 30 publications for 23 unique studies were identified but after limiting the focus to the intervention the included studies were reduced to only one study for direct evidence [38]. The update from August 2015 yielded 61 further references, but none met the inclusion criteria. Thus, only 1 phase III study was included.

7.1 Efficacy and safety – Phase III studies

Table 2: Summary of efficacy

Study title		
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 [38, 39]		
Study identifier	NCT01170663, I4T-IE-JVBE, (IMCL CP12-0922)	
Design	Phase 3, randomized, multicentre, placebo-controlled, double-blind study	
	Duration of main phase	Until PD, unacceptable toxicity, withdrawal of consent, or until other withdrawal criteria were met.
Hypothesis	Superiority	
Funding	Eli Lilly and Company	
Treatment groups	Ramucirumab + paclitaxel (n=330)	Ramucirumab 8mg/kg on days 1 and 15 + paclitaxel 80mg/m^2 on days 1, 8 and 15 intravenous over app 60 minutes administered on a 28-day cycle
	Placebo + paclitaxel (n=335)	Placebo + paclitaxel 80mg/m^2 intravenous over approx. 60 minutes administered on a 28-day cycle.

Endpoints and definitions	Overall survival (primary outcome)	OS	Interval between date of randomization and the date of death from any cause.		
	Progression-free survival	PFS	Time from the date of randomization until the date of objectively determined PD (RECIST 1.0) or death due to any cause, whichever was first.		
	Overall response rate	ORR	Proportion of patients achieving a best overall response of PR or CR.		
	Patient-reported outcomes	-	Assessed using EORTC QLQ-C30 and EQ-5D-3L		
	Safety	-	-		
Database lock	31 December 2012				
Results and analysis					
Analysis description	Primary analysis ITT (cut-off date at 12 July 2013) (all randomized patients): 665				
Analysis population	Inclusion	✿ ≥ 18 years ✿ Metastatic or non-resectable, locally advanced gastric or gastro-oesophageal junction adenocarcinoma; ✿ Documented objective radiological or clinical disease progression during or within 4 months of the last dose of first-line platinum and fluoropyrimidine doublet with or without anthracycline; ✿ ECOG performance status score of 0 or 1; ✿ Measureable or non-measurable evaluable disease (defined with RECIST, version 1.1			
	Exclusion	✿ Squamous or undifferentiated gastric cancer; gastrointestinal perforation, fistulae, or any arterial thromboembolic event within 6 months ✿ Any significant gastrointestinal bleeding or any significant venous thromboembolism within 3 months before randomisation; ✿ Poorly controlled hypertension			
	Characteristics		Ramucirumab + paclitaxel	Placebo + paclitaxel	
		Age, years Median (range) < 65, % > 65, %	 61 (25-83) 62 38	 61 (24-84) 63 37	
		Sex, % Male	 69	 73	
		Ethnic origin (self-reported), % White Asian Black or other	 63 33 4	 59 36 4	
		ECOG PS 0 1	 35 65	 43 57	
		Site of primary tumor, % Gastric Gastro- oesophageal junction adenocarcinoma	 80 20	 79 21	
		Disease, % Measurable Non-measurable	 81 19	 81 19	
		Time to progressive disease on first-line therapy, % < 6 months ≥ 6 months	 76 24	 76 24	
		Disease progression during first-line therapy, %	69	65	

Analysis population *(continuation)*	Characteristics *(continuation)*	Tumor grade, %		
		Well differentiated	8	7
		Moderately differentiated	29	32
		Poorly differentiated	56	56
		Unknown or missing	6	6
		Histological subtype, % (Lauren classification)		
		Intestinal	44	40
		Diffuse	35	40
		Mixed	6	4
		Unknown or not available	15	16
		Primary tumor present, %	63	62
		Number of metastatic Sites, %		
		0-2	63	69
		≥ 3	37	31
		Peritoneal metastases, %	49	45
		Presence of ascites, %		
		Yes	39	32
		No	61	68
		Weight loss (past 3 months)		
		< 10%	84	85
		≥ 10%	16	14
		Previous treatment, %		
		Triplet: platinum and fluoropyrimidine withanthracycline	23	26
		Doublet: platinum and fluoropyrimidine	77	73
		HER2, EGFR, or other	9	8
		Previous surgery for gastric cancer, %		
		Yes	40	38
		Total gastrectomy	16	19
		Partial gastrectomy	24	18
		Other	<1	<1

Descriptive statistics and estimated variability	Treatment group	*Ramucirumab + paclitaxel*	*Placebo + paclitaxel*
	Number of subjects	N = 330	N = 335
	Median OS, months 95%CI for median	9.6 8.5 - 10.8	7.4 6.3 - 8.4
	Median PFS, months 95%CI for median	4.4 4.2 - 5.3	2.9 2.8 - 3.0
	ORR, % 95%CI	27.9 23.3 - 33.0	16.1 12.6 - 20.4
	Best overall response, % Complete response Partial response Stable disease Progressive disease Not evaluable or not assessed	 <1 27 52 13 7	 <1 16 47 25 12
	EQ-5D, mean (SD) Baseline index score End-of-treatment index score	 0·75 (0·22) 0·61 (0·32)	 0·75 (0·24) 0·60 (0·35)

Effect estimate per comparison	*Comparison groups*		*Ramucirumab vs. Placebo*
	OS	HR (stratified)	0.807
		95%CI	0.678-0.962
		P value	0.0169
	PFS	HR (stratified)	0.635
		95%CI	0.536-0.752
		P value	<0.0001
	ORR	Odds ratio	2.140
		95%CI	1.449, 3.160
		P value	0.0001

Abbreviations: CI = confidence interval, CR = complete response, ECOG = Eastern Cooperative Oncology Group, EGFR = epidermal growth factor receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, ITT = intention-to-treat, ORR = overall response rate, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors

Table 3: Treatment-emergent AEs occurring in at least 10% of patients on ramucirumab plus paclitaxel, irrespective of causality

Adverse events (according to NCI-CTCAE; version 4.02)	**Ramucirumab + paclitaxel (n= 327)**				**Placebo + paclitaxel (n= 329)**			
	Grade 1-2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)	Grade 1-2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Any patients with a treatment-emergent AE	57 (17)	155 (47)	73 (22)	39 (12)	116 (35)	128 (39)	27 (8)	51 (16)
Non-haematological AEs								
Fatigue	147 (45)	39 (12)	0	0	126 (38)	18 (5)	0	0
Neuropathy	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
Abdominal pain	98 (30)	20 (6)	0	0	87 (26)	10 (3)	1 (<1)	0
Nausea	109 (33)	5 (2)	1 (<1)	0	100 (30)	8 (2)	0	0
Alopecia	107 (33)	0	0	0	126 (38)	1 (<1)	0	0
Diarrhoea	94 (29)	12 (4)	0	0	71 (22)	4 (1)	1 (<1)	0
Epistaxis	100 (31)	0	0	0	23 (7)	0	0	0
Vomiting	78 (24)	9 (3)	1 (<1)	0	56 (17)	12 (4)	0	0
Peripheral oedema	77 (24)	5 (2)	0	0	43 (13)	2 (<1)	0	0
Hypertension	32 (10)	46 (14)	0	0	8 (2)	8 (2)	0	0
Constipation	70 (21)	0	0	0	69 (21)	2 (<1)	0	0
Stomatitis	62 (19)	2 (<1)	0	0	22 (7)	2 (<1)	0	0
Pyrexia	56 (17)	3 (<1)	0	0	36 (11)	1 (<1)	0	0
Proteinuria	50 (15)	4 (1)	0	0	20 (6)	0	0	0
Malignant neoplasm progression	5 (2)	16 (5)	4 (1)	27 (8)	1 (<1)	24 (7)	1 (<1)	34 (10)
Weight decreased	39 (12)	6 (2)	0	0	45 (14)	4 (1)	0	0
Dyspnoea	34 (10)	8 (2)	0	0	29 (9)	2 (<1)	0	0
Rash	42 (13)	0	0	0	31 (9)	0	0	0
Cough	40 (12)	0	0	0	25 (8)	0	0	0
Back pain	35 (11)	4 (1)	0	0	35 (11)	5 (2)	0	0
Hypoalbuminaemia	32 (10)	4 (1)	0	0	13 (4)	2 (<1)	0	1 (<1)
Myalgia	34 (10)	0	0	0	32 (10)	1 (<1)	0	0
Ascites	21 (6)	11 (3)	1 (<1)	0	14 (4)	13 (4)	0	0
Headache	32 (10)	0	0	0	21 (6)	1 (<1)	0	0

Adverse events (according to NCI-CTCAE; version 4.02)	Ramucirumab + paclitaxel (n= 327)				Placebo + paclitaxel (n= 329)			
	Grade 1-2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)	Grade 1-2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Haematological AEs								
Neutropenia	45 (14)	71 (22)	62 (19)	0	40 (12)	51 (16)	11 (3)	0
Anaemia	84 (26)	30 (9)	0	0	85 (26)	31 (9)	3 (<1)	0
Leucopenia	54 (17)	52 (16)	5 (2)	0	47 (14)	19 (6)	3 (<1)	0
Thrombocytopenia	38 (12)	5 (2)	0	0	14 (4)	6 (2)	0	0

Abbreviations: AE = adverse event, NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

RAINBOW: a global, multicentre, randomised, double-blind phase III trial

The RAINBOW [38] study is a global, multicentre, randomised, double-blind phase 3 study comparing the efficacy and safety of ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with metastatic gastric cancer or GEJ adenocarcinoma whose disease progressed while on or within 4 months after the last dose of standard first-line platinum- and fluoropyrimidine-based combination chemotherapy. All 665 patients were randomised in a ratio of 1:1 to receive either ramucirumab plus paclitaxel or placebo plus paclitaxel. The primary endpoint in RAINBOW was OS, and the secondary endpoints included PFS, overall response rate (ORR), and QoL. Median duration of treatment with ramucirumab was 18 weeks (approximately 4 to 5 cycles) in the ramucirumab and paclitaxel group and 12 weeks in the placebo and paclitaxel group. Tumour assessments were made every 6 weeks.

7.1.1 Effectiveness

D0001: overall mortality

Ramucirumab plus paclitaxel reduced the risk of death from any cause by 19% (HR= 0.81; 95%CI: 0.68 to 0.96; p=0.0169) compared with placebo plus paclitaxel. The study demonstrated a statistically significant improvement in OS, with an improvement in median survival of 2.27 months among patients treated with ramucirumab plus paclitaxel compared with those in the placebo plus paclitaxel group. Median OS was 9.63 (95%CI 8.6 to 10.8) months among patients treated with ramucirumab plus paclitaxel compared with 7.36 (95%CI 6.3 to 8.4) months among those treated with placebo and paclitaxel (31% increase in survival time) [38].

D0006: progression-free survival

Treatment with ramucirumab plus paclitaxel significantly reduced the risk of disease progression or death (HR=0.64; 95%CI: 0.54-0.75; p<0.0001); the median progression-free survival (PFS) was 1.5 months longer in the ramucirumab plus paclitaxel group compared with the placebo plus paclitaxel group. Median PFS in the ramucirumab plus paclitaxel group was 4.4 (95%CI 4.2 to 5.3) months vs. 2.9 (95%CI 2.8 to 3.0) months in the placebo plus paclitaxel group.

D0005: symptoms and findings

Information provided by the MAH [40] showed that a slightly greater proportion of patients in the ramucirumab plus paclitaxel group compared with the placebo plus paclitaxel group experienced stability or improvement in symptoms such as fatigue (45% vs. 42%) and pain (56% vs. 49%). Slightly more patients reported better or stable physical functioning in the ramucirumab plus paclitaxel group compared with the placebo plus paclitaxel group (56% vs. 47%). The results presented were collected after 6 weeks of treatment and are based on data collected from 75% of patients in the ra-

mucirumab plus paclitaxel group and only 66% of patients in the placebo plus paclitaxel group.

The results for overall response rate (ORR) are driven by the difference in partial responses (28% in the ramucirumab plus paclitaxel group compared with 16% in the paclitaxel plus placebo group). Complete response was achieved only in less than 1% of patients in both groups (0.6% vs 0.3%).

D0016: performance status

Activities of daily living were not assessed in the RAINBOW trial. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) was used as an approximation. The time to deterioration in ECOG PS assessed the risk of functional status worsening to the extent that patients were no longer able to work and may have been confined to bed for at least part of the day. Treatment with ramucirumab plus paclitaxel was associated with a delay in the time to worsening of functional status, as measured with the ECOG PS compared with treatment with placebo plus paclitaxel. The median time to deterioration, that is to ECOG PS=2 or higher was 10.0 months (95%CI 8.3 to 15.0) in the ramucirumab plus paclitaxel group versus 8.6 months (95%CI 6.3 to 14.3) in the placebo plus paclitaxel group. The difference between the medians was 1.4 months (HR=0.798 (95%CI 0.612 to 1.040), p=0.094). The results are based on less than 50% of the patients from the RAINBOW study.

D0012: effect on health-related quality of life

Quality of life assessments were performed using the European Organisation for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ-C30) and the EuroQol five-dimensions, three-level scale (EQ-5D-3L).

The EQ-5D quality of life questionnaire is a generic scale for assessing quality of life and incorporates five functional scales: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The RAINBOW study presents limited EQ-5D-3L results [38], restricted to the data for baseline and for the end of treatment. The scale is from -0.59 to 1 with 1 representing perfect health [38].The EQ-5D-3L index scores were similar at baseline and at end of treatment. For the ramucirumab plus paclitaxel group mean at baseline and end of treatment were (0.75 (SD 0.22) and 0.61 (SD 0.32) and for the placebo plus paclitaxel group 0.75 (SD 0.24) and 0.60 (SD 0.35).

D0013: disease-specific quality of life

The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health related QoL of cancer patients participating in international clinical trials. The QLQ-C30 incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease.

Patients in RAINBOW completed the EORTC QLQ-C30 (v3) at baseline, every 6 weeks from start to discontinuation. Time to deterioration (TtD) was defined as time from randomization to first worsening of ≥10 points (on 100-point scale). In addition, scores were classified as improved or worsened if changed by ≥10 points relative to baseline, otherwise classified as stable.

Based on results published as abstract and on information provided by the MAH, more patients in the ramucirumab plus paclitaxel group reported improved or stable EORTC QLQ-C30 global health status compared with the placebo plus paclitaxel group at each visit during the treatment, mostly due to stabile status. By the end of treatment however a higher proportion of pa-

tients in the placebo plus paclitaxel group had a stable or improved global health status (RR= 0.92 [95%CI 0.74 to 1.15]) [39, 41].

7.1.2 Safety

C0008a: frequency of all AEs

In the RAINBOW trial most patients experienced adverse events (AEs), but there is no indication for a different frequency of AEs in patients treated with ramucirumab plus paclitaxel compared with placebo plus paclitaxel treatment, RR 1.01 (95%CI 0.99 to 1.03). Concerning AEs of grade 3 or higher, the RR is 1.30 (95%CI 1.18 to 1.44), which is a statistically significant difference in favour of the control group.

C0008b: frequency of discontinuation of treatment due to AEs

The frequency of patients that discontinued treatment because of AEs was similar between patients treated with ramucirumab plus paclitaxel and placebo plus paclitaxel. Calculations based on the ITT population give an RR of 1.04 (95%CI 0.68 to 1.59).

C0008c: frequency and description of SAEs

Treatment-emergent serious adverse events (SAEs) were reported for the time that patients were on the study drug and for 30 days after treatment. The time could be extended to include any time past treatment as long as the SAE was considered possibly, probably, or definitely related to study treatment by the investigator. The proportion of patients who experienced any SAE was similar among patients treated with ramucirumab plus paclitaxel and those treated with placebo plus paclitaxel. Based on the frequencies of SAE submitted by the MAH, an RR of 1.11 (95%CI 0.93 to 1.31) was calculated. Calculations based on selecting SAEs of grade 3 or above gave a similar result, RR 1.15 (95%CI 0.95 to 1.38).

The following SAEs occurred in 2% or more of patients receiving ramucirumab plus paclitaxel and are listed in order of decreasing frequency: malignant neoplasm progression, neutropenia, abdominal pain, febrile neutropenia, general physical health deterioration, anaemia, pyrexia and vomiting. The control calculation of risk ratio and 95%CI for the top 2 events at any grade gave an RR 0.89 (95%CI 0.60-1.33) for malignant neoplasm progression and RR 4.02 (95%CI 1.15-14.13) for neutropenia (statistically significant in favour of the control group).

C0008d: frequency of SAEs leading to death

The number of deaths due to an AE was similar in patients treated with ramucirumab plus paclitaxel and those treated with placebo plus paclitaxel, 13/327 (4%) vs. 15/329 (4.6%); RR 0.87 (95%CI 0.42 - 1.80) [26, 41]. This includes deaths due to AEs that occurred during treatment or up to 30 days after the last dose of study drugs. The numbers of patients with an AE leading to death are also reported to be 39/327 vs. 51/329, giving an RR of 0.77 (95%CI 0.52-1.13) [26, 38]. Further, the numbers of deaths with a causal relationship to any study drug are reported as 6/327 vs. 5/329 patients for the ramucirumab plus paclitaxel and placebo plus paclitaxel groups, respectively [33, 38].

C0008e: most frequent AEs compared to other second-line treatments

The following AEs occurred in 10% or more of the patients in the ramucirumab plus paclitaxel group, and based on the safety population (listed in order of decreasing frequency): fatigue, neutropenia, neuropathy, decreased appetite, abdominal pain, nausea, anaemia, leukopenia, alopecia, diarrhoea, epistaxis, vomiting, oedema peripheral, hypertension, constipation, asthenia, stomatitis, pyrexia, proteinuria, malignant neoplasm progression, peripheral neuropathy, weight decrease, thrombocytopenia, dyspnoea, cough, back pain, rash, hypoalbuminaemia, myalgia and ascites [26, 38].

C0005: susceptible patient groups

The draft EPAR stated that no studies were conducted in special populations [3]. The submission dossier does comment on whether there is a need to optimise the use of the technology, or monitor the use of the technology to minimise the potential risks to safety. Labelling for ramucirumab will include the following warnings and precautions; arterial thromboembolism, hypertension, infusion related reactions, gastrointestinal perforation, severe bleeding, impaired wound healing, and hepatic impairment and severe gastrointestinal haemorrhage. If patients are predisposed towards any of these events, they may be more likely to be harmed. Wound healing and changes in the blood and lymphatic systems may be of importance if emergency operations are necessary. As far as possible, this will be handled by the warning statements and the fact that the drug can be prescribed only by doctors experienced in oncology [2].

In addition, the draft EPAR states that data on VEGF over-expression was not collected during the RAINBOW trial [3]. Based on data from the REGARD trial of ramucirumab monotherapy it appeared that those with higher VEGFR-2 neoplastic vessel staining may have better OS and/or PFS. However, this was mainly due to differences in the placebo group, so it may be a prognostic factor [3].

The draft EPAR also comments on the issue that with both treatment alternatives in the RAINBOW study, patients with a previous history of hypertension had an increased incidence of grade 3 or higher hypertension, older patients had an increased incidence of grade 3 or higher neutropenia, and Asian patients had an increased incidence of grade 3 or higher neutropenia and leukopenia. In view of these findings it is not possible to attribute the increased risk to ramucirumab, but these risk factors are still issues that could be considered when selecting treatment for individuals.

8 Estimated costs

A0021: reimbursement status, monthly costs of € 7,562

In Austria, one 50ml vial Cyramza® containing 500 mg ramucirumab costs € 3,131 and one vial containing 100 mg costs € 651 [42]. Assuming an average body weight of 70kg, 560 mg are needed. Thus 1 vial each would be needed, resulting in costs of € 3,781 per day and in monthly costs of € 7,562 when ramucirumab is administered every two weeks.

9 Ongoing research

ongoing trials

No planned or ongoing RCT of ramucirumab in combination with paclitaxel was identified. One ongoing phase III study (the REGARD trial) for stomach cancer was found, investigating ramucirumab monotherapy for the sec-

ond-line therapy of adenocarcinomas of the stomach or GEJ (NCT00917384: estimated study completion date: June 2015).

5 planned, ongoing or unpublished studies using ramucirumab in patients with gastric cancer and/or GEJ adenocarcinoma were also found: 4 were non-randomised open- label studies and in the EPAR a study called "I4T-MC-JVDD: Safety and Effectiveness of Ramucirumab in Patients with Advanced Gastric Cancer in the European Union and North America: A Prospective Observational Registry" is mentioned. The final study report is estimated for completion in Q4 2021 [41].

Ramucirumab is also under investigation in phase III trials for other types of cancer such as non-small cell lung cancer, hepatocellular carcinoma and breast cancer.

10 Commentary

direct evidence: 1 randomised controlled trial (RAINBOW)

Particularly in Western countries, where up to 90% of patients with gastric or GEJ adenocarcinoma are diagnosed at an advanced stage, the prognosis remains poor despite some progress in the treatment of gastric cancer. Currently in the EU there is no standard second-line treatment for patients with advanced gastric or GEJ adenocarcinoma following progression after first-line chemotherapy and ramucirumab alone or in combination with paclitaxel is the only approved treatment option for these patients.

The direct evidence for ramucirumab plus paclitaxel is based on one randomised controlled trial with a low risk of bias (RAINBOW study [38]). Even though other drugs currently available (docetaxel, irinotecan, paclitaxel) are used as off-label second-line therapy, paclitaxel seems an appropriate choice for the control group of the RAINBOW trial since paclitaxel had been shown to have similar activity to other single-agent (including docetaxel and irinotecan) or combination chemotherapy regimens in off-label use in second-line treatment of advanced gastric cancer.

RAINBOW is the largest clinical trial of second-line therapy in this patient population to date. The demographic, disease, and other baseline characteristics (ECOG PS; age; previous treatment) reflect a typical clinical trial population of advanced gastric cancer patients and are largely representative of the target patient population.

improvements in OS, PFS and maintenance of QoL

The primary endpoint of improved OS was met in addition to improvements in PFS, while maintaining QoL. The robustness of the OS and PFS results was supported by sensitivity analyses. However, defining the size of clinically meaningful outcomes is challenging. There are no published recommendations for what effect size on OS or PFS is acceptable as clinically meaningful for this particular patient population, even though the topic has been discussed for example by the American Society of Oncology (ASCO). The difference of approximately 2 months in median OS achieved in RAINBOW seems a good result in this poor-prognosis population since patients whose disease progresses after first-line treatment can expect median survival under 6 months. Results in secondary endpoints such as PFS and objective re-

to define the size of clinically meaningful outcomes is challenging

sponse rate supported the observed improvement in OS. QoL was maintained for a longer duration in the ramucirumab plus paclitaxel arm with more patients reporting stable or improved QoL. However, differences in quality of life between the treatment groups were small and may indicate that ramucirumab plus paclitaxel does not impose an extra burden on the patients compared with paclitaxel treatment.

nearly all patients in both treatment arms experienced AEs

Nearly all patients with ramucirumab plus paclitaxel with placebo plus paclitaxel experienced an AE. There were no statistically significant differences between the treatments. However, limiting the AEs to those of grade 3 adding ramucirumab increased the risk from 626 per 1,000 treated to 814 (95%CI 739 to 902), which some may find clinically important. We did not find differences between the groups in withdrawal due to AEs, frequency of SAEs or AEs leading to death. The evidence suggests that the addition of ramucirumab to paclitaxel did not add to the burden of treatment in an unmanageable way. Finally, caution is needed, because the results are based on only one study.

low risk of bias

The study itself, RAINBOW [38], has a low risk of bias and high internal validity (see Risk of bias), but its external validity is more uncertain. In addition, for some outcomes there are few events, resulting in wide confidence intervals. The quality of the evidence is considered moderate according to GRADE because it was limited to only one clinical study (details of individual GRADE assessments are shown in the Evidence profile).

quality of evidence: moderate

second-line gastric population is a selected population direct comparisons and large observational studies and data are needed

There is no direct head-to-head evidence to position ramucirumab plus paclitaxel compared with the other treatment alternatives used in second-line treatment of advanced gastric cancer or GEJ adenocarcinoma - except for paclitaxel alone. Direct comparisons and large observational studies and data are thus needed to facilitate more robust conclusions. Upcoming evidence from registries will provide results that should help to clarify these issues. The RAINBOW study included patients with ECOG PS 0 and 1. For patient with performance status worse than 1, efficacy data are not available.

In the absence of clear signals against the generalizability of results, the CHMP concluded against a restriction of the indication to patients with good performance status. Use in a substantially larger patient population, and perhaps in a more heterogeneous patient group with more comorbidities could lead to the discovery of additional AEs or changes in the expected frequencies. Ramucirumab has a risk management plan, a pharmacovigilance plan and a risk minimisation plan. This includes a large observational study to collect systematically additional data from real-life use.

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Appendix

Scope

Table 4: Inclusion criteria

Description	Project Scope
Population	Adults with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy and with good performance status (Eastern Cooperative Oncology Group [ECOG] score of 0 or 1). International Classification of diseases (ICD)-10 code: C 16; C16.0 MeSH-terms: stomach neoplasms; esophageal neoplasms or non-MeSH term gastro oesophageal junction adenocarcinoma
Intervention	Ramucirumab in combination with paclitaxel (as second- line therapy). Ramucirumab is not yet mapped as a MeSH term. Alternative MeSH terms: antineoplastic agents; antibodies; submapped to: antibodies, monoclonal; or non-MeSH term ramucirumab
Comparison	✲ Docetaxel monotherapy ✲ Paclitaxel monotherapy ✲ Irinotecan monotherapy ✲ Best supportive care At present there are no other technologies (pharmaceuticals) than ramucirumab with marketing authorisation for the intended patient population. The off-label comparators were chosen based on information in published guidelines [ESMO-ESSO-ESTRO, 2013; EUnetHTA, 2013] MeSH terms: antineoplastic agents; taxoids; paclitaxel; antineoplastic agents, phytogenic; or non-MeSH term docetaxel; irinotecan; best supportive care.
Outcomes	Efficacy ✲ Overall survival (OS); ✲ Progression-free survival (PFS); ✲ Objective response rate (ORR); ✲ Health-related quality of life (HRQoL); Safety ✲ Adverse events (AEs) of treatment (Any AEs, serious AE [SAE], discontinuation due to AE, AE of special interest, most frequent, death as SAE) ✲ Rationale for choosing the outcomes: commonly used outcomes in cancer studies and outcomes important for relative effectiveness assessment; based on recommendations from the EUnetHTA methods guideline on clinical and surrogate endpoints and safety.

Risk of bias

Table 5: Risk of bias – study level

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Medicinal personnel and other staff			
RAINBOW (I4T-IE-JVBE/IMCL CP12- 0922)	Yes	Yes	Yes	Yes	Yes	Yes	Low

Table 6: Risk of bias – outcome level

Outcome Trial	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects according to risk of bias	Risk of bias – outcome level
Overall survival (OS)					
RAINBOW	Low	Low	Low	Low	Low
Progression free survival (PFS)					
RAINBOW	Low	Low	Low	Low	Low
Objective response rate (ORR)					
RAINBOW	Low	Low	Low	Low	Low
Health-related quality of life (HRQoL)					
RAINBOW	Low	Low	Low	Low	Low
Adverse events					
RAINBOW	Low	Low[0]	Low	Low	Low
comments: 0: Adverse events was reported for the safety population (all patients that received at least one dose of any study drug) instead of all randomised patients					

Evidence profile

The external validity was assessed using GRADE
(Grading of Recommendations, Assessment, Development and Evaluation, www.gradeworkinggroup.org) only for the following outcomes:

OS, PFS, QoL of direct evidence. The GRADE method involves an evaluation of factors influencing our confidence in the reported estimates. It includes an evaluation of study type, study quality (risk of bias), consistency of results between trials, directness (how similar the population, intervention, and outcomes are among the trials and the objectives of this report), precision of the estimates and publication bias. GRADE may also take into account whether there are strong associations between the intervention and the outcome such as a very large effect, whether there are dose-response associations or whether all confounding variables would have reduced the effect. Results are as far as possible presented as absolute and relative terms. Finally, the overall quality, or confidence in the estimate, was categorised as high, moderate, low or very low.

The categories should be interpreted as follows:

- **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect
- **Moderate quality:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- **Low quality:** Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
- **Very low quality:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

Table 7: GRADE evidence profile for direct evidence and effectiveness outcomes

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ramucirumab + paclitaxel**	**placebo + paclitaxel**	**Relative (95%CI)**	**Absolute (95%CI)**	
Mortality											
1	randomised trials	not serious	serious[1]	not serious	not serious	none	256/330 (77.6%)	260/335 (77.6%)	**HR 0.807** (0.678 to 0.962)	75 fewer per 1000 (from 13 fewer to 139 fewer)	⊕⊕⊕◯ MODERATE
Patients with progression											
1	randomised trials	not serious	serious[1]	not serious	not serious	none	279/330 (84.5%)	296/335 (88.4%)	**HR 0.635** (0.536 to 0.752)	139 fewer per 1000 (from 82 fewer to 199 fewer)	⊕⊕⊕◯ MODERATE
Median survival											
1	randomised trials	not serious	serious[1]	not serious	not serious	none	330	335	-	median **9.63 higher** (8.48 higher to 10.81 higher)	⊕⊕⊕◯ MODERATE
Objective response rate (ORR) (assessed with: complete or partial response)											
1	randomised trials	not serious	serious[1]	not serious	not serious	none	92/330 (27.9%)	54/335 (16.1%)	**OR 2.14** (1.45 to 3.16)	130 more per 1000 (from 57 more to 217 more)	⊕⊕⊕◯ MODERATE
Quality of Life (end of treatment) (assessed with: EORTC QLQ-C30)											
1	randomised trials	not serious	serious[1]	not serious	not serious	none	101/330 (30.6%)	111/335 (33.1%)	**RR 0.92** (0.74 to 1.15)	27 fewer per 1000 (from 50 more to 86 fewer)	⊕⊕⊕◯ MODERATE
Quality of Life (18 weeks) (assessed with: EORTC QLQ-C30)											
1	randomised trials	not serious	serious[1]	not serious	not serious	none	80/330 (24.2%)	52/335 (15.5%)	**RR 1.56** (1.14 to 2.14)	87 more per 1000 (from 22 more to 177 more)	⊕⊕⊕◯ MODERATE

Question: Ramucirumab+paclitaxel compared to placebo + paclitaxel for patients with gastric cancer or gastro-oesophageal junction adenocarcinoma

Settings: after treatment with chemotherapy

MD – mean difference, RR – relative risk

[1] Single study, thus results not confirmed/shown consistently across different studies

Table 8: GRADE evidence profile for direct evidence and safety outcomes

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ramucirumab + paclitaxel**	**placebo + paclitaxel**	**Relative (95%CI)**	**Absolute (95%CI)**	
Patients with one or more adverse events vs placebo+paclitaxel											
1	randomised trials	not serious	serious[1]	not serious	not serious	none	324/327 (99.1%)	322/329 (97.9%)	**RR 1.01** (0.99 to 1.03)	10 more per 1000 (from 10 fewer to 29 more)	⊕⊕⊕○ MODERATE
Patients with AE of grade 3 or higher											
1	randomised trials	not serious	serious[1]	not serious	not serious	none	267/327 (81.7%)	206/329 (62.6%)	**RR 1.3** (1.18 to 1.44)	188 more per 1000 (from 113 more to 276 more)	⊕⊕⊕○ MODERATE
Patients who discontinued treatment due to adverse events											
1	randomised trials	not serious	serious[1]	not serious	serious[2]	none	38/335 (11.3%)	39/330 (11.8%)	**RR 1.04** (0.68 to 1.59)	5 more per 1000 (from 38 fewer to 70 more)	⊕⊕○○ LOW
Patients with serious adverse event (Treatment-emergent SAE)											
1	randomised trials	not serious	serious[1]	not serious	serious[2]	none	153/327 (46.8%)	139/329 (42.2%)	**RR 1.11** (0.93 to 1.31)	46 more per 1000 (from 30 fewer to 131 more)	⊕⊕○○ LOW
Deaths due to an AE											
1	randomised trials	not serious	serious[1]	not serious	serious[2]	none	13/327 (4.0%)	15/329 (4.6%)	**RR 0.87** (0.42 to 1.8)	6 fewer per 1000 (from 26 fewer to 36 more)	⊕⊕○○ LOW

Question: Ramucirumab+paclitaxel compared to placebo + paclitaxel for patients with gastric cancer or gastro-oesophageal junction adenocarcinoma

Settings: after treatment with chemotherapy

MD – mean difference, RR – relative risk

[1] Single study, thus results not confirmed/shown consistently across different studies

[2] Confidence interval include both no difference and clear harm or benefit