17 December 2015
EMA/CHMP/69143/2016
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: CYRAMZA

International non-proprietary name: RAMUCIRUMAB

Procedure No. EMEA/H/C/002829/II/0004

Marketing authorisation holder (MAH): Eli Lilly Nederland B.V.

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

5-FU	5-fluorouracil
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ATE	arterial thromboembolic events
AUC	area under curve
BSC	best supportive care
CHF	congestive heart failure
CI	confidence interval
CL	clearance
Cmax	maximum concentration
CNS	central nervous system
CR	complete response
CRC	colorectal carcinoma
CRF	clinical report form; also called case report form
DCR	disease control rate
DDI	drug-drug interaction
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
E-R	exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
FOLFIRI	folinic acid, 5-FU, and irinotecan
FOLFOX	folinic acid, 5-FU, and oxaliplatin
GEJ	gastro-esophageal junction
GI	gastrointestinal
GM-CSF	granulocyte macrophage colony-stimulating factor
HR	hazard ratio
IDMC	independent data monitoring committee
IND	investigational new drug (application)
IRR	infusion-related reaction
ITT	intent-to-treat
I.V.	intravenous(ly)
IVRS	interactive voice response system
KRAS	Kirsten RAS
LCSS	Lung Cancer Symptom Scale
MAA	Marketing Authorization Application
mAb	monoclonal antibody
mBC	metastatic breast cancer
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
NCCN	National Comprehensive Cancer Network
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI	package insert
PK	pharmacokinetic(s)
PopPK	population pharmacokinetics
PR	partial response

PS	performance status
PT	(MedDRA) preferred term
QoL	quality of life
ROW	rest of world
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	stable disease
SN	sequence number
SOC	(MedDRA) system organ class
SPC	Summary of Product Characteristics
TE	treatment emergent
TEAE	treatment-emergent adverse event
TE-SAE	treatment-emergent serious adverse event
TKI	tyrosine kinase inhibitor
TTD	time to deterioration
US	United States
V2	peripheral volume of distribution
Vss	volume of distribution at steady state
VEGF	vascular endothelial growth factor
VTE	venous thromboembolic event
WBC	white blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 27 February 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include a new indication for Cyramza, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), for the treatment of adult patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct minor editorial mistakes.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

CYRAMZA was designated as an orphan medicinal product EU/03/12/1004 on 4 July 2012. CYRAMZA was designated as an orphan medicinal product in the following indication: Treatment of gastric cancer

The new indication, which is the subject of this application, does not fall within any orphan condition. According to Article 7 of Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products, it is not possible to combine an orphan indication and a non orphan indication in the same marketing authorisation. Consequently, the MAH has requested the withdrawal of the orphan designation from the Community Register of Orphan Medicinal Products.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The applicant received Protocol assistance from the CHMP on 20 November 2014. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Kolbeinn Gudmundsson

Timetable	Actual dates
Submission date	27 February 2015
Start of procedure:	28 March 2015
Rapporteur's preliminary assessment report circulated on:	26 May 2015
CoRapporteur's preliminary assessment report circulated on:	26 May 2015
PRAC Rapporteur's preliminary assessment report circulated on:	26 May 2015
PRAC RMP advice and assessment overview adopted by PRAC:	11 June 2015
Joint Rapporteurs' updated assessment report circulated on:	18 June 2015
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 June 2015
MAH's responses submitted to the CHMP on:	23 July 2015
Joint Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	1 September 2015
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	21 August 2015
PRAC RMP advice and assessment overview adopted by PRAC:	10 September 2015
Joint Rapporteurs' updated assessment report on the MAH's responses circulated on:	18 September 2015
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	24 September 2015
MAH's responses submitted to the CHMP on:	16 October 2015
Joint Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	23 November 2015
Joint Rapporteurs' updated assessment report on the MAH's responses circulated on:	10 December 2015
CHMP Opinion:	17 December 2015

2. Scientific discussion

2.1. Introduction

About the disease

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide (Globocan 2012). In Europe, CRC is the most frequently diagnosed cancer and the second leading cause of cancer death. The stage of disease at the time of diagnosis represents the most relevant prognostic factor. Five-year survival rates range from 93% for stage I disease to less than 10% for stage IV (Ferlay J et al.).

Surgery, followed by adjuvant chemotherapy in certain cases, represents the standard therapeutic approach for patients with loco-regional disease. However, approximately 25% of patients present with metastases at initial diagnosis and almost 50% of patients with CRC will develop metastases, contributing to the high mortality rates reported for CRC. The CRC-related 5-year survival rate approaches 60% (Van Cutsem et al.)

For most patients with metastatic CRC (mCRC), treatment is palliative rather than curative. The goals of systemic treatment in these patients are to prolong survival and to maintain quality of life for as long as possible.

The backbone of first-line palliative chemotherapy alone, as well in combination with targeted agents, consists of a fluoropyrimidine (FP) [intravenous (i.v.) 5-fluorouracil (5-FU) or the oral FP capecitabine] in various combinations and schedules. These consist essentially in combination chemotherapy with 5-FU/LV/oxaliplatin (FOLFOX) or 5-FU/LV/irinotecan (FOLFIRI).

The combination of capecitabine plus oxaliplatin (CAPOX) and the combination of capecitabine plus irinotecan (CAPIRI) are alternatives. Fluoropyrimidine based regimens are given as first or second line therapy (ESMO guideline). Second-line chemotherapy is expected to be offered to patients with good performance status and adequate organ function.

Monoclonal antibodies (bevacizumab) or proteins (aflibercept) against vascular endothelial growth factor (VEGF) and against the epidermal growth factor receptor (EGFR) in combination with chemotherapy can be considered in patients with mCRC, since they have been shown to improve the outcome of mCRC (see EPAR Avastin and EPAR Zaltrap, respectively). Bevacizumab is indicated in combination with fluoropyrimidine-based chemotherapy for treatment of adult patients with metastatic carcinoma of the colon or rectum.

Zaltrap is indicated in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy in adults with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen. The efficacy and safety of Zaltrap were evaluated in a randomised, double-blind, placebo-controlled study in patients with metastatic colorectal cancer who had previously been treated with an oxaliplatin-based treatment with or without prior bevacizumab. The difference in median OS was 1.44 months in favour of the aflibercept arm, 13.50 months (95.34% CI:12.517 to 14.949) in the aflibercept arm compared to 12.06 months (11.072 to 13.109) in the placebo arm (see Zaltrap SmPC).

In patients with RAS wild-type mCRC, the anti- EGFR monoclonal antibodies cetuximab or panitumumab can also be administered as monotherapy or in combination with FP-based regimens (see EPAR Erbitux and EPAR Vectibix).

Regorafenib, an orally available multikinase inhibitor is also available in EU for the for the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy (see EPAR Stivarga).

About the product

Ramucirumab is a human receptor-targeted monoclonal antibody that specifically binds VEGF Receptor 2, which is the primary receptor of transmitting VEGF signals downstream in endothelial cells. The binding of ramucirumab to VEGF Receptor 2 prevents interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D). As a result, ramucirumab inhibits activation of VEGF Receptor 2 and thereby the VEGFR-2 signalling pathway. The VEGFR-2 signalling pathway is crucial for angiogenesis by bringing about the effects of VEGFs including vasodilatation, endothelial cell migration and proliferation.

Ramucirumab was firstly approved in EU on 19 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 (see section 5.1).

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 (see section 5.1).

The recommended dose of ramucirumab for the already approved indication in gastric cancer is 8 mg/kg every 2 weeks as monotherapy or in combination with paclitaxel.

For the use of Cyramza in combination with paclitaxel, the approved dosing is 8 mg/kg on day 1 and 15 of a 28 days cycle indications, prior to paclitaxel infusion. As single agent the recommended dose of ramucirumab is 8 mg/kg every 2 weeks. Treatment should be continued until disease progression or until unacceptable toxicity has occurred.

The MAH applied to extend the indication as follows: “Cyramza, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine”.

The recommended dose of ramucirumab in patients with mCRC is 8 mg/kg on day 1 of a 14 day cycle prior to FOLFIRI administration. Prior to chemotherapy, patients should have a complete blood count. Criteria to be met prior to FOLFIRI are provided in the SmPC section 4.2 (Table 2).

The MAH received Scientific Advice from the CHMP on 20 May 2010 (EMEA/H/SA/1505/2/2010/II). The Scientific Advice pertained to clinical aspects of the dossier. In particular, the CHMP discussed the inclusion criteria and agreed that there was no scientific rationale for limiting the study to patients with KRAS mutated disease. The use of FOLFIRI as background chemotherapy was considered acceptable. The CHMP agreed that due to the relatively short prognosis for patients progressing after 1st line treatment (1 year) the overall survival was the most direct measure of clinical benefit and the appropriate endpoint. Since extensive immunogenicity testing was planned in 7 Phase II studies and 2 Phase III studies in other indications, it was considered acceptable that for this study in MCRC patients routinely immunogenicity testing was not incorporated.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. No animal studies have been performed to test ramucirumab for potential of carcinogenicity or genotoxicity (see SmPC section 5.3 and EPAR). Carcinogenicity and genotoxicity are safety concerns included in the RMP under missing information (see RMP).

2.2.1. Ecotoxicity / environmental risk assessment

No ERA was submitted.

2.2.2. Discussion on non-clinical aspects

Antibodies, as other peptides and proteins, are exempted from environmental risk assessment (ERA) based on the EMA 2006 Guideline on Environmental Risk Assessment (EMEA/CHMP/SWP/4447/00).

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1. Overview of trial design in RAISE (pivotal study) and additional studies

Study	Indication	Phase	Treatment Arms	Ramucirumab Dose Regimens	ITT Population (Ram vs. comparator)	Variables Evaluated
Pivotal Study						
RAISE; I4T-MC-JVBB (JVBB; IMCL CP12-0920)	mCRC 2nd Line	3	Ram + FOLFIRI vs. Placebo + FOLFIRI	8 mg/kg every 2 wks	1072 (536 vs 536)	**Primary:** OS **Secondary:** PFS, ORR, patient-reported outcomes, safety profile, immunogenicity, serum levels of ramucirumab **Other:** Association between biomarkers and clinical outcome
Additional Studies						
I4T-IE-JVBY (JVBY; IMCL CP12-1029)	mCRC 2nd Line	1b	Ram + FOLFIRI	8 mg/kg every 2 wks	6 (safety population) (6 vs 0)	**Primary:** Safety and tolerability **Secondary:** PK, immunogenicity, antitumor activity, effect of ramucirumab on pharmcodynamic biomarkers
I4T-IE-JVCB (JVCB; IMCL CP12-1033)	Solid Tumors (DDI)	2	Cycle 1: FOLFIRI Cycle 2+: Ram + FOLFIRI	8 mg/kg every 2 wks	29[a] (25)	**Primary:** Effect of ramucirumab on PK of irinotecan and its metabolite SN-38 when coadministered with folinic acid and 5-fluorouracil **Secondary:** Safety profile, immunogenicity, and PK **Exploratory:** Relationship between genetic assays and outcomes
I4T-IE-JVBH (JVBH; IMCL CP12-0709)	mCRC 1st Line	2	Ram + FOLFOX-6	8 mg/kg every 2 wks	48 (48 vs 0)	**Primary:** PFS **Secondary:** ORR, OS, duration of response, safety profile, PK profile, and immunogenicity of ramucirumab
I4Y-IE-JCDB (JCDB; IMCL CP20-0801)	mCRC 2nd Line	2	Ram + FOLFOX-6 vs. icrucumab + FOLFOX-6 vs. FOLFOX-6	8 mg/kg every 2 wks	158 (52 vs 52 vs 54) mITT 153 (52 vs 52 vs 49)	**Primary:** PFS **Secondary:** ORR, OS, duration of response, safety profile, immunogenicity of ramucirumab, and PK profile of ramucirumab and icrucumab
REACH ; I4T-IE-JVBF (JVBF ; IMCL CP12-0919)	HCC 2nd Line	3	Ram + BSC Placebo + BSC	8 mg/kg every 2 wks	Child-Pugh A: 565 (283 vs 282) Child-Pugh B: 79 (41 vs 38)	**Primary:** OS **Secondary:** PFS, ORR, time to radiographic progression, patient-reported outcomes, safety profile, immunogenicity, and serum levels of ramucirumab

Abbreviations: BSC = best supportive care; DDI = drug-drug interaction; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; FOLFOX-6 = folinic acid, 5-fluorouracil, and oxaliplatin); HCC = hepatocellular carcinoma; ITT = intent-to-treat; mCRC = metastatic colorectal carcinoma; mITT = modified intent-to treat; N = number of patients in the safety population; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; Ram = ramucirumab; wks = weeks.

a For Study JVCB, 29 patients were treated and 25 patients completed both Cycle 1 and Cycle 2. Cycle 2 included the ramucirumab treatment.

2.3.2. Pharmacokinetics

The clinical pharmacology package comprised ramucirumab PK data from 4 new studies (RAISE, REACH, JVCB, and JCDB). Data from the previously submitted Study JVBY, a Phase 1b trial in which Japanese patients with metastatic colorectal cancer whose disease had progressed during or following first-line combination therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine received ramucirumab in combination with FOLFIRI, were also presented. In addition, an updated PopPK analysis integrating the data from RAISE was provided (RAISE PopPK).

Table 2. New Clinical Studies Providing PK Data Supporting the Ramucirumab Metastatic CRC Submission

Study Code (location in CTD)	Population	Study Characteristics [Primary Objective]	Dose Regimen of Ramucirumab, Route of Administration and Formulation	Description of PK Data [N_{PK}]
RAISE I4T-MC-JVBB (CP12-0920)	Metastatic colorectal cancer	Phase 3, placebo-controlled randomized, double-blind study of ramucirumab in combination with FOLFIRI [efficacy]	8 mg/kg, Q2W, I.V. Process C0	Sparse [512]
REACH I4T-MC-JVBF (CP12-0919)	Hepatocellular carcinoma	Phase 3, placebo-controlled randomized, double-blind study of ramucirumab monotherapy [efficacy]	8 mg/kg, Q2W, I.V. Process C0	Sparse [315]
I4T-IE-JVCB (CP12-1033)	Solid tumors	Phase 2, open-label, single-arm study ramucirumab in combination with FOLFIRI [PK, drug-drug interaction]	8 mg/kg, Q2W, I.V. Process C0	Intensive [25]
I4Y-IE-JCDB (CP20-0801)	Metastatic colorectal cancer	Phase 2, open-label, randomized study of modified FOLFOX-6 alone or in combination with either ramucirumab or LY3012212 [efficacy]	8 mg/kg, Q2W, I.V. Process C0	Sparse [10]

Note: Study I4T-IE-JVBH (JVBH; IMCL-CP12-0709), and I4T-IE-JVBY (JVBY; IMCL-CP12-1029), supporting the use of ramucirumab in combination with FOLFIRI for the treatment of second-second-line metastatic CRC, have been provided in a prior gastric cancer submission(s).

Abbreviations: CRC = colorectal carcinoma; FOLFIRI = treatment regimen consisting of irinotecan 180 mg/m^2, folinic acid 400 mg/m^2, and 5-fluorouracil as 400 mg/m^2 bolus, then 2400 mg/m^2 continuous infusion on Days 1 and 2; FOLFOX-6 (modified) = treatment regimen consisting of oxaliplatin 85 mg/m^2 as I.V. infusion over 2 h, folinic acid 400 mg/m^2 as I.V. infusion over 2 h, and 5-fluorouracil 400 mg/m^2 as I.V. bolus over 2-4 min, then 2400 mg/m^2 as I.V. infusion over 46 h; I.V. = intravenous; N_{PK} = number of patients with PK data; PK = pharmacokinetics; Q2W = every 2 weeks.

PopPK analysis

In the updated PopPK analysis for RAISE (RAISE PopPK), ramucirumab PK data from RAISE (Study JVBB) and supporting studies were integrated with the data previously analysed in REVEL (REVEL PopPK) and RAINBOW (RAINBOW PopPK). The final dataset for the RAISE PopPK included 11 studies (RAISE, REACH, REVEL [JVBA], REGARD [JVBD], JVBJ, JVBW, JVBX, JVBY, JVCA, JVCC, and RAINBOW [JVBE]). The final analysis included 6427 evaluable ramucirumab concentrations obtained from 1639 patients.

The PK of ramucirumab was described by a linear two-compartment model with zero-order input and first-order elimination. None of the covariates investigated including age (range 19-87), gender (male N=1125, female=587), race (white N=1125, Asian N=433), cancer type (gastric, NSCLC, mCRC, HCC), hepatic function, renal function (including 6 subjects with severe renal impairment), and body weight (range 30-139 kg) were found to satisfy the predefined criteria (reduction in the objective function value [MOF] of at least 10.828 points ($p>0.001$) and reduction in inter-patient variability [IIV] of at least 5%). Therefore, the final model contained no covariates (see Table below).

Table 3: Pharmacokinetic Parameters in Final Population Model for ramucirumab

Parameter Description	Population Estimate (%SEE)	Inter-Patient Variability (%SEE)
Clearance Parameter for CL (L/hr)	0.0148 (1.52)	34.7% (5.45)
Central Volume of Distribution Parameter for V_1 (L)	3.28 (0.948)	26.8% (7.64)
Inter-compartmental Clearance Parameter for Q (L/hr)	0.00977 (11.8)	81.2% (22.3)
Peripheral Volume of Distribution Parameter for V_2 (L)	2.07 (4.98)	54.7% (20.0)
Inter-Patient Variability Correlation Coefficient (CL and V_1)		0.727 (7.33)
Residual Error Additive (µg/mL) Proportional		4.84 (9.03) 22.4% (5.28)

Abbreviation: SEE = standard error of the estimate.

PopPK estimated mean volume of distribution at steady state (Vss) was 5.4 L (CV=15%).

Ramucirumab PopPK estimated clearance was 0.015 L/hour (CV=30%) and elimination half-life ($t_{1/2}$) longer, i.e., 14 days (CV=20%).

Dose proportionality and time dependencies

In phase 3 study RAISE, samples for determination of serum ramucirumab concentrations were scheduled prior to infusion (trough or C_{min}) at Doses 1, 3, and 5 and optionally at Doses 9, 13, and 17. Additional optional samples were scheduled at 1 hour following the end of infusion (approximate Cmax) for Doses 3, 5, 9, 13, and 17. PK analyses derived from descriptive statistics following ramucirumab administrations are shown in the table below.

Table 4. Summary of Ramucirumab Trough Concentrations for Patients With Metastatic Colorectal Carcinoma Following Administration of 8 mg/kg of Ramucirumab Every 2 Weeks as an I.V. Infusion over approximately 1 Hour Plus FOLFIRI in RAISE

8 mg/kg Ramucirumab Every 2 Weeks + FOLFIRI					
Trough Serum Concentrations (µg/mL)					
Dose Number	3	5	9	13	17
n_{PK}	248[a]	154[a]	27	11	5
Min	7.65	14.50	24.85	40.90	34.50
Max	118.75	204.50	199.00	145.00	107.25
Median	48.50	67.00	82.75	71.25	75.25
Geo Mean	46.3	65.1	77.9	75.9	72.0
Geo CV%	45	43	51	43	49
Arith Mean	50.3	70.4	86.5	81.9	77.8
Arith SD	19.7	27.4	39.3	34.2	30.5
Arith CV%	39	39	45	42	39

Special populations

Hepatic impairment

Effect of hepatic function on the pharmacokinetics of ramucirumab was investigated in the REACH study in patients with HCC. REACH was a global, randomized, placebo-controlled, double-blind, multicenter Phase 3 study that compared ramucirumab with placebo in patients with HCC who had disease progression during or following first-line therapy with sorafenib or who were intolerant to sorafenib.

Samples for determination of ramucirumab serum concentrations were scheduled prior to infusion (trough or C_{min}) and 1 hour following the end of infusion (approximate C_{max}) for Doses 1, 4, and 7, with an additional sample scheduled at the 30-day follow-up visit. In the ramucirumab treatment arm (317 patients treated), PK data were available for 315 patients throughout the study. PK data were available for 276 patients in the Child-Pugh A Group and 39 patients in the Child-Pugh B Group.

The geometric mean trough concentrations prior to Dose 4 and Dose 7 (minimal concentrations following Dose 3 and Dose 6) for patients with baseline Child-Pugh Class A were 42.5 µg/mL and 55.5 µg/mL, respectively and for patients with baseline Child-Pugh Class B 45.4 µg/mL and 53.3 µg/mL, respectively.

Table 5. Summary of Ramucirumab Trough and 1-Hour Post End-of-Infusion Concentrations for Patients with HCC Following Administration of 8 mg/kg of Ramucirumab as an I.V. Infusion over Approximately 1 hour on Day 1 of a 14-Day Cycle – Patients with Child Pugh Scores A or B

Trough Serum Concentrations (μg/mL)				
	Prior to Dose 4		Prior to Dose 7	
	CP-A[a]	CP-B[a]	CP-A[a]	CP-B[a]
n_{PK}	155[b]	17	89	9
Min	7.0	12.6	9.2	18.0
Max	121.0	163.5	173.0	113.5
Geo Mean	42.5	45.4	55.5	53.3
Geo CV%	60.9	71.6	63.5	67.2

1-Hour Post End-of-Infusion Serum Concentrations (μg/mL)						
	Following Dose 1		Following Dose 4		Following Dose 7	
	CP-A[a]	CP-B[a]	CP-A[a]	CP-B[a]	CP-A[a]	CP-B[a]
n_{PK}	247	37	140	17	81	8
Min	36.5	51.0	50.0	104.5	17.2	132.0
Max	390.0	265.5	418.0	332.5	427.0	377.5
Geo Mean	149.6	135.6	189.5	201.0	184.4	214.5
Geo CV%	36.9	38.8	39.1	29.2	56.3	35.6

Abbreviations: CP = Child-Pugh Class; CV = coefficient of variation; Geo = geometric; HCC = hepatocellular carcinoma; I.V. = intravenous; Max = maximum; Min = minimum; n_{PK} = number of pharmacokinetic observations included in calculation.

[a] Patients with Child Pugh Scores A or B.

[b] Excludes 2 concentrations reported below the limit of quantitation.

Pharmacokinetic interaction studies

In Study JVCB potential interaction between ramucirumab and FOLFIRI was investigated; intensive PK sampling was performed.

Study JVCB was designed to assess the effect of concomitant ramucirumab on the pharmacokinetics of irinotecan and its metabolite SN-38 when coadministered with folinic acid and 5-FU in patients with advanced malignant solid tumours resistant to standard therapy or for whom no standard therapy is available. The PK of 5-FU was not assessed owing to its very short half-life (approximately 11-15 minutes) when administered intravenously. Irinotecan, as part of the FOLFIRI regimen and without ramucirumab, was administered in Cycle 1; in Cycle 2, ramucirumab was administered prior to the administration of FOLFIRI, with a 60-minute observation period in between ramucirumab and FOLFIRI. Blood samples for the assessment of irinotecan and SN-38 PK were collected at 0, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 22, 25, 28, 31, 34, 48, 72, 96, and 168 hours after the start of the infusion in Cycle 1 (FOLFIRI alone) and Cycle 2 (FOLFIRI plus ramucirumab). Blood samples for the assessment of ramucirumab PK were collected at -2, -1, -.5, 0, 2, 3, 4, 5, 8, 10, 25, 48, 72, 96, 168, 264, and 336 hours (this timing is relative to the start of the irinotecan infusion which occurs at t=0, after a 1-hour ramucirumab infusion and subsequent 1 hour observation period) in Cycle 2.

Table 6 displays the results of the statistical analysis evaluating the effect of concomitant ramucirumab on PK of irinotecan and SN-38. Dose-normalized AUC (0-inf) and C_{max} of irinotecan and SN-38 in Cycle 2 when administered with ramucirumab were similar to those when FOLFIRI was administered alone in Cycle 1. For PK of irinotecan, the ratios of geometric LS means and 90% CI are 0.93 (90% CI: 0.83, 1.05) for AUC(0-inf), and 1.04 (90% CI: 0.97, 1.12) for Cmax. For PK of SN-38, the ratios of geometric LS means and 90% CI are 0.95 (90% CI: 0.88, 1.04) for AUC(0-inf) and 0.97 (90% CI:

0.85, 1.12) for Cmax. These results support the conclusion that coadministration of FOLFIRI with ramucirumab is unlikely to have an effect on the PK of irinotecan and SN-38.

Table 6. Statistical Analysis of Dose-Normalized PK Parameters for Irinotecan and SN-38 in Study JVCB (DDI Population)

	FOLFIRI (Cycle 1)		RAM+FOLFIRI (Cycle 2)		Ratio of Geometric Least Squares Means
Parameter	N	Geometric Least Squares Means (90% CI)	N	Geometric Least Squares Means (90% CI)	RAM+ FOLFIRI / FOLFIRI
Irinotecan					
$AUC_{(0-\infty)}$ (ng*h/mL/mg)	25	22.12 (19.72, 24.82)	25	20.56 (18.33, 23.06)	0.93 (0.83, 1.05)
C_{max} (ng/mL/mg)	23	3.18 (2.91, 3.48)	23	3.31 (3.02, 3.62)	1.04 (0.97, 1.12)
SN-38					
$AUC_{(0-\infty)}$ (ng*h/mL/mg)	25	0.81 (0.70, 0.93)	24	0.77 (0.67, 0.89)	0.95 (0.88, 1.04)
C_{max} (ng/mL/mg)	23	0.05 (0.04, 0.06)	23	0.05 (0.04, 0.06)	0.97 (0.85, 1.12)

The drug interaction population is defined as patients who completed the assigned mandatory treatment started on Cycle 1, Day 1 and Cycle 2, Day 1.

Abbreviations: $AUC_{(0-\infty)}$ = area under the concentration versus time curve from zero to infinity (it is adjusted by dividing the actual dose); CI = confidence interval; C_{max} = maximum observed drug concentration (it is adjusted by dividing the actual dose in plasma); N = number of patients included in the analysis.

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To assess whether coadministration of FOLFIRI had any effect on ramucirumab PK, pharmacokinetics of ramucirumab in combination with FOLFIRI study JVCB were compared with pharmacokinetics of ramucirumab monotherapy from study JVCA. Results are shown in Table **7**. Ramucirumab exposure appears to be comparable regardless of concomitant FOLFIRI based on this cross study comparison in patients with solid tumours. These results show that coadministration of FOLFIRI is unlikely to have any effect on ramucirumab PK.

Table 7. Effect of FOLFIRI on pharmacokinetics of ramucirumab – across study comparison. Ramucirumab Pharmacokinetic Parameters Following Single-Dose Administration of 8 mg/kg in Study JVBC (in Combination with FOLFIRI) and Study JVCA Part B (Monotherapy)

Parameter	Geometric Mean (Geometric CV%) n_{PK}	
	JVCB	JVCA (Part B)
Dose	8 mg/kg	8 mg/kg
N	25	16
C_{max} (µg/mL)	201.6 (31) 25	205.71 (14) 16
$AUC_{(0-\infty)}$[a] (µg*day/mL)	1180 (35) 18	1340 (29) 15
$t_{1/2}$[a,b] (day)	6.00 (4.17-8.83) 18	6.54 (3.25-10.0) 15
CL (L/h)	0.0226 (29) 18	0.018 (27) 15
V_{ss} (L)	4.50 (25) 18	3.95 (23) 15

Abbreviations: $AUC_{(0-\infty)}$ = area under the concentration versus time curve from time zero extrapolated to infinity; C_{max} = maximum observed drug concentration; CL = total body clearance of drug calculated after intravenous administration; CV% = percentage coefficient of variation; N = number of subjects who had data for calculation of at least 1 PK parameter; NCA = noncompartmental analysis; n_{PK} = number of pharmacokinetic observations included in calculation; PK = pharmacokinetic; $t_{1/2}$ = apparent elimination half-life; V_{ss} = volume of distribution at steady state following intravenous administration.

a Reported values for $t_{1/2}$ and $AUC_{(0-\infty)}$ were derived from summary data reported in hr or µg*hr/mL and converted to day or µg*day/mL by dividing by 24.

b Geometric mean (minimum - maximum) reported for $t_{1/2}$.

2.3.3. Pharmacodynamics

No new data were submitted.

2.3.4. PK/PD Modelling

Exposure-response analysis

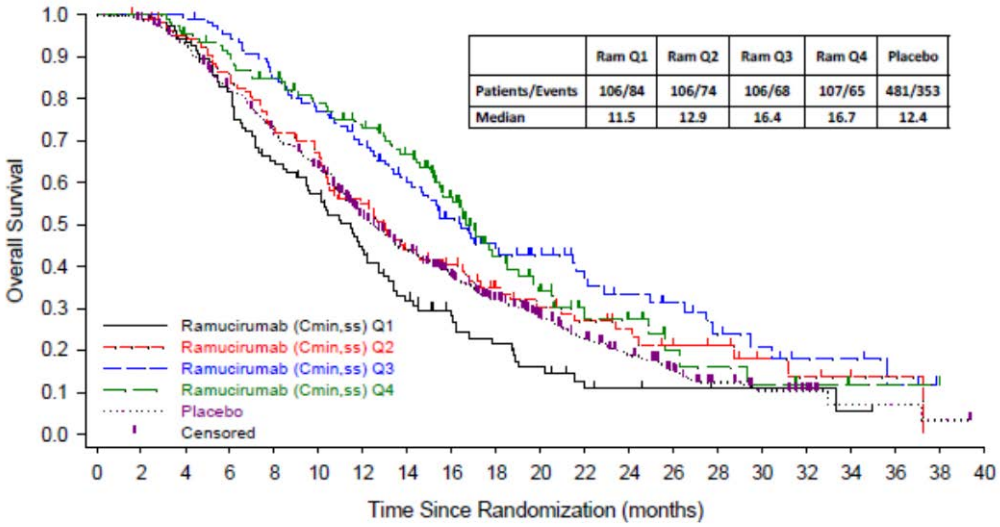
Exposure-response (E-R) analyses based on RAISE were performed to characterize the relationship between ramucirumab exposure and selected measures of efficacy and safety in RAISE.

- Efficacy

Exposure-response analyses indicated that efficacy of ramucirumab was correlated with ramucirumab exposure. Better efficacy, as measured by OS and PFS, was associated with increasing ramucirumab exposure over the ranges of exposures achieved by a dose of 8 mg/kg ramucirumab (see Figure 1). From the lowest to the highest ramucirumab exposure, median OS increased from 11.5 to 16.7 months. Median OS in the placebo plus FOLFIRI arm was 12.4 months. Median progression free

survival increased from 5.4, to 8.5 months. Median PFS in the placebo plus docetaxel arm was 5.2 months.

$C_{min,ss}$: Overall Survival



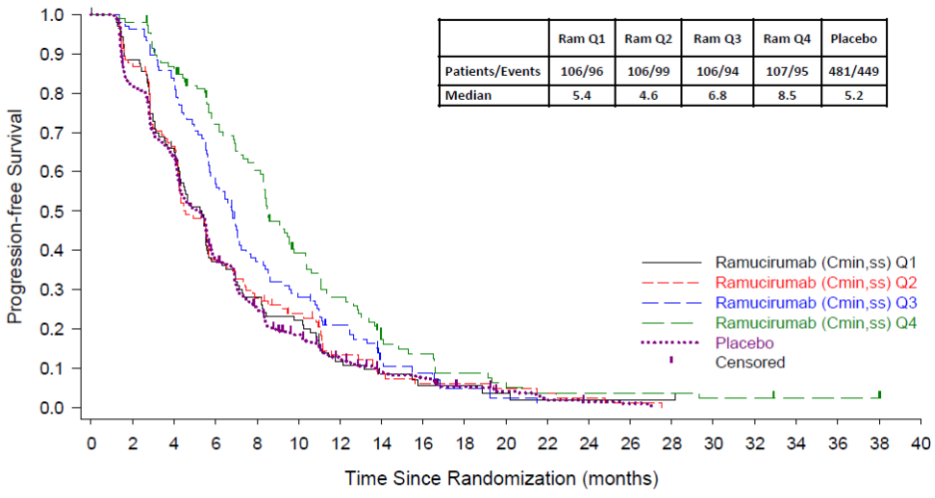
	Ram Q1	Ram Q2	Ram Q3	Ram Q4	Placebo
Patients/Events	106/84	106/74	106/68	107/65	481/353
Median	11.5	12.9	16.4	16.7	12.4

Number at Risk

Ram Q1	106	106	100	84	66	57	42	29	21	16	11	7	5	4	3	2	2	1	0	0	0
Ram Q2	106	104	98	88	75	68	52	37	32	24	19	16	13	9	8	4	3	2	1	0	0
Ram Q3	106	106	105	100	89	80	70	56	44	33	27	20	17	14	9	7	4	4	2	0	0
Ram Q4	107	107	101	95	88	80	72	63	46	27	19	10	9	5	4	3	2	1	1	1	0
Plc	481	475	442	386	333	292	223	181	141	106	77	57	43	29	17	10	7	2	2	1	0

Abbreviations: $C_{min,ss}$ = minimum concentration at steady-state; Plc = placebo; Q = quartile; Ram = ramucirumab.

$C_{min,ss}$: Progression-Free Survival



	Ram Q1	Ram Q2	Ram Q3	Ram Q4	Placebo
Patients/Events	106/96	106/99	106/94	107/95	481/449
Median	5.4	4.6	6.8	8.5	5.2

Number at Risk

Ram Q1	106	91	66	37	28	22	11	6	4	3	2	1	1	1	1	0	0	0	0	0	0
Ram Q2	106	91	69	39	29	22	11	7	5	5	4	3	2	1	0	0	0	0	0	0	0
Ram Q3	106	102	86	59	37	28	18	7	5	2	1	0	0	0	0	0	0	0	0	0	0
Ram Q4	107	105	92	73	61	38	27	14	11	7	5	3	3	3	3	2	2	1	1	1	0
Plc	481	392	305	176	116	80	50	32	26	17	11	6	3	2	0	0	0	0	0	0	0

Abbreviations: $C_{min,ss}$ = minimum concentration at steady-state; Plc = placebo; Q = quartile; Ram = ramucirumab.

Figure1. Kaplan–Meier plots of overall survival and progression free survival by Ramucirumab Cmin,ss quartiles for RAISE. (Ramucirumab Cmin,ss concentrations: Q1=6-<50 µg/ml, Q2=50-<63 µg/ml, Q3=63-<81 µg/ml, Q4=81-229 µg/ml)

To adjust for potential impact of imbalance in baseline characteristics or important factors (including time to progression after beginning first-line therapy, Kirsten rat sarcoma (KRAS) tumor mutation status, Eastern Cooperative Oncology Group performance status, number of metastatic sites, liver-only metastasis, carcinoembryonic antigen, sex, and combined prior bevacizumab use) that could be prognostic between the treatment arms within each exposure group, matched case-control analysis and univariate - multivariate Cox regression analyses were performed to evaluate the exposure efficacy relationship for efficacy endpoints OS and PFS. Cox regression analysis (Table 8) showed a statistically significant positive association between OS or PFS and $C_{min,ss}$ in the univariate analysis. This relationship remained statistically significant after adjusting for prognostic factors found to be significantly associated with OS or PFS in RAISE.

Table 8. Analysis of $C_{min,ss}$ and OS and PFS for mCRC Patients in study RAISE included in the Exposure-Efficacy Analysis

Efficacy parameter	Hazard Ratio[a] (95% CI)	p-Value (Wald's)
Overall survival (N = 425/291 events)		
Univariate analysis	0.600 (0.490, 0.734)	<0.0001
Multivariate analysis adjusting for significant factors[b]	0.605 (0.494, 0.741)	<0.0001
Progression free survival (N = 425/384 events)		
Univariate analysis	0.670 (0.564, 0.797)	<0.0001
Multivariate analysis adjusting for significant factors[c]	0.681 (0.569, 0.814)	<0.0001

Abbreviations: CI = confidence interval; $C_{min,ss}$ = minimum concentration at steady-state; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; KRAS = Kirstin rat sarcoma; N = number of patients; OS = overall survival; PFS = progression-free survival.

a With log2-transformed exposure measure, reported HR measures the change in the hazards of death when the value of $C_{min,ss}$ is doubled.

b Adjusted for time to progression after beginning first-line therapy, KRAS status, ECOG performance status, number of metastatic sites, liver only metastasis, and carcinoembryonic antigen.

c Adjusted for ECOG performance status, number of metastatic sites, liver only metastasis, carcinoembryonic antigen, and prior bevacizumab use (a composite group of the 3 individual bevacizumab factors was created and analyzed as a separate subgroup, described further in RAISE CSR, Section 9.7.1.2).

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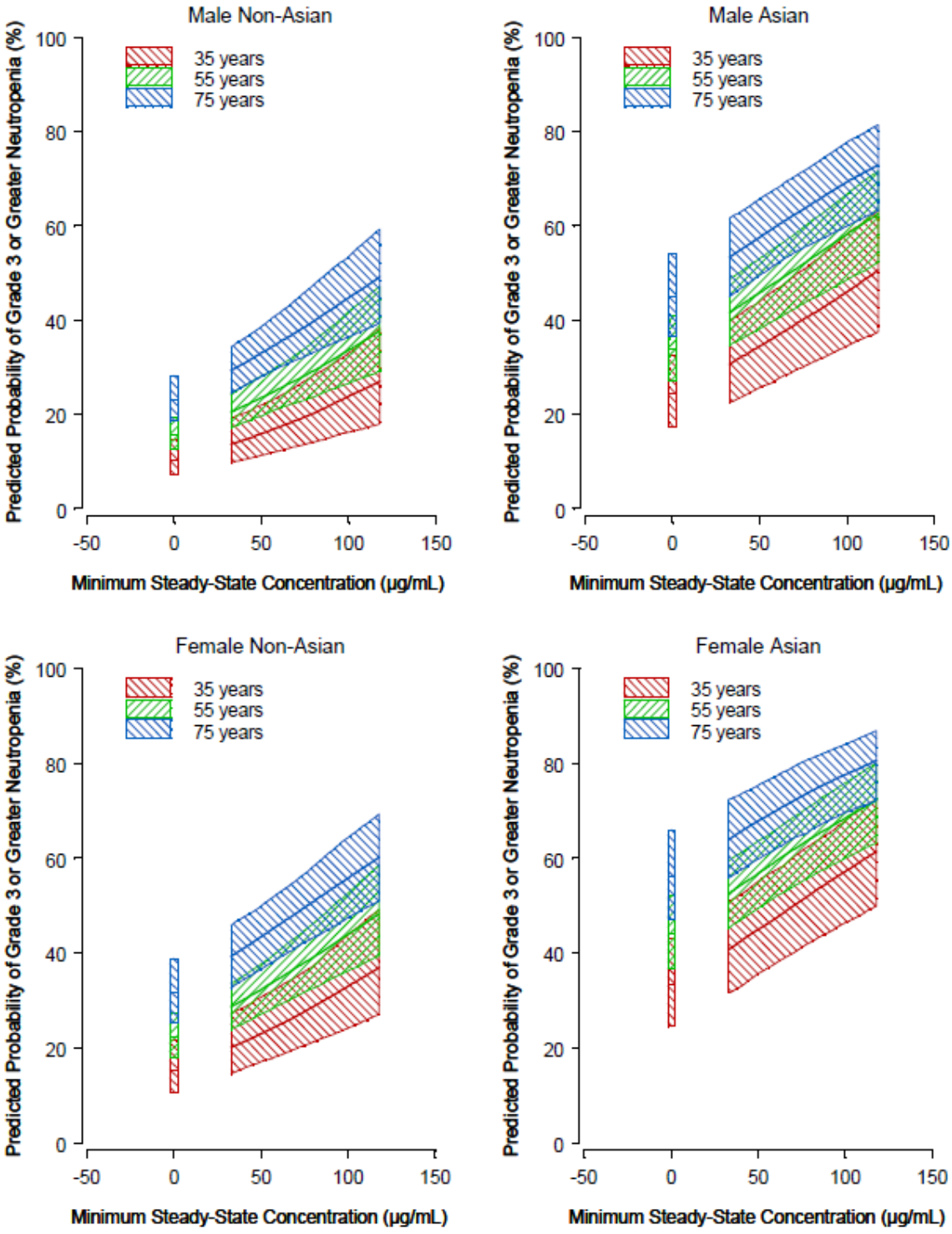
– *Safety*

The E-R analysis for safety, evaluated Grade ≥3 neutropenia (consolidated term), hypertension, fatigue (consolidated term), and diarrhoea. There was no relationship between ramucirumab exposure and the risk of Grade ≥3 hypertension, Grade 3 fatigue, or Grade ≥3 diarrhea but the risk of Grade ≥3 neutropenia was increased with increasing ramucirumab exposure. Additional covariate analyses found age at study entry, sex, and Asian race to be significant predictors for risk of neutropenia in metastatic CRC patients. The model-predicted risk of neutropenia (Grade ≥3) for 5th to 95th percentile range of $C_{min,ss}$ in RAISE is shown below in Figure 2 for male and female, Asian and non-Asian patients of representative ages. The likelihood of experiencing Grade 3 or greater neutropenia increased with age. The shape and trend of the curves for neutropenia between male and female patients of both Asian and non-Asian race were similar, with female Asian patients in both the placebo plus FOLFIRI

arm and ramucirumab plus FOLFIRI arm exhibiting the greatest risks of Grade ≥3 neutropenia. The higher risk of neutropenia observed in Asian patients relative to non-Asian patients is independent of treatment arm.



Solid lines represent population prediction for probability of neutropenia incidence. Shaded regions represent 95% confidence intervals. Predictions at minimum concentration of zero represent predicted incidence for placebo plus FOLFIRI. The concentrations shown comprise the 5th to 95th percentile range of predicted concentrations from the RAISE study population.

Figure 2. Predicted incidence of Grade 3 or greater neutropenia versus minimum ramucirumab concentration at steady-state in mCRC patients (study RAISE).

Figure 3 shows that patients with higher ramucirumab exposure had higher incidences of dose modifications (dose delays, dose reductions, and dose omissions) of components of FOLFIRI as compared to patients with lower exposure. Higher incidence of 5-FU dose discontinuation was observed in patients with higher ramucirumab exposure. No apparent relationship was observed between ramucirumab exposure and dose discontinuation of irinotecan and folinic acid.

Patients with higher ramucirumab exposure appeared to have higher incidence of ramucirumab dose delay as compared to patients with lower exposure. No apparent relationship was observed between ramucirumab exposure and dose reduction, dose omission, or dose discontinuation of ramucirumab.

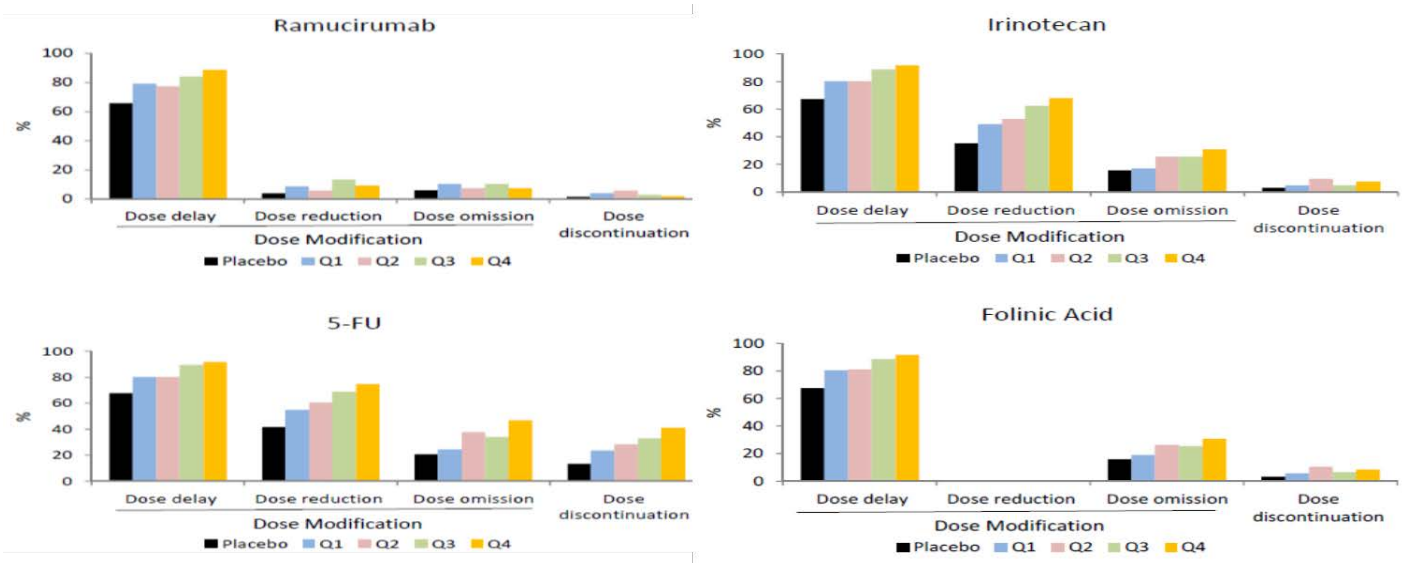


Figure 3. Summary of dose modification (dose delay, dose reduction, and dose omission) and dose discontinuation for ramucirumab, 5-FU, irinotecan, and folinic acid) in RAISE Exposure-Safety Analysis Population.
Per protocol, no dose reductions in folinic acid were allowed. Abbreviations: 5-FU = 5-fluorouracil; Q = quartile (Q1=6-<50 µg/ml, Q2=50-<63 µg/ml, Q3=63-<81 µg/ml, Q4=81-229 µg/ml)

2.3.5. Discussion on clinical pharmacology

The pharmacokinetics of irinotecan and its active metabolite, SN-38, were not affected when co-administered with ramucirumab (see SmPC section 4.5).

No dose finding study for the combination of ramucirumab in combination with FOLFIRI was conducted. The same dose 8 mg/kg and frequency of ramucirumab every two weeks as for the approved indication of metastatic gastric cancer has been selected. In the dose finding studies for ramucirumab monotherapy no clear dose effect relation was apparent and no MTD was established for the every other week or every three week dose administration up to 20 mg/kg. It should be noted that for gastric cancer the CHMP had a concern that the 8 mg/kg may not be the optimal dose, and a post-approval dose optimisation study is to be conducted (see Study 14T-MC-JVDB in Annex II). Based on popPK analysis, pharmacokinetics of ramucirumab appeared similar in patients with CRC as with other cancer types. Non-compartmental analysis of a PK rich single dose study of ramucirumab exposure with FOLFIRI suggested a time-dependency in pharmacokinetics of ramucirumab. Based on available data, the contribution of target mediated clearance at the dose of 8 and 10 mg/kg ramucirumab seems to be limited. Results from study JVCZ (ramucirumab 8 mg/kg + docetaxel vs ramucirumab 12 mg/kg

+ docetaxel), a 2-arm study that will compare safety and PK of the currently approved dose and regimen of ramucirumab (8 mg/kg every 2 weeks) plus paclitaxel with another, higher dose of ramucirumab (12 mg/kg every 2 weeks) plus paclitaxel, may provide further information on the dose dependency of the target mediated clearance. The MAH is recommended to submit the results of this study as soon as available (REC).

Results from univariate and multivariate analysis of OS and PFS with ramucirumab exposure in RAISE suggest that with the 8 mg/kg ramucirumab dosing, higher ramucirumab exposure is associated with improved efficacy. The relationship between exposure and efficacy remained after adjusting for the baseline prognostic factors.

In RAISE the incidences of grade ≥3 neutropenia were increased in the ramucirumab with FOLFIRI arm compared to the placebo with FOLFIRI arm and incidence of grade ≥3 neutropenia was correlated with ramucirumab exposure. More patients with high ramucirumab exposure discontinued treatment with 5-FU but continued with irinotecan and ramucirumab treatment. Patients in the ramucirumab arm experienced a worse quality of life (see also clinical safety).

Higher doses of ramucirumab may be more efficacious but ramucirumab seems to increase FOLFIRI related toxicity in RAISE (see clinical safety), therefore higher dosing of ramucirumab when given in combination FOLFIRI appears not justified. Since analyses suggest the exposure response relationship is very similar across indications, results from Study 14T-MC-JVDB (see Annex II condition) may provide a better insight about the optimal dose regimen in patients with mCRC.

Ramucirumab exposure was higher in patients with higher bodyweight. However, no increase in incidences of Grade ≥ 3 AEs or dose modifications were observed in patients in the highest baseline body weight quartile group. Based on these data, no dose modification is necessary for patients weighing >85 kg. There are no safety and efficacy data in patients > 139 kg.

PopPK analyses did not identify any specific patient groups that were associated with low or high ramucirumab exposure, thus no dose recommendations can be made for certain subpopulations. However, the ramucirumab-OS Kaplan-Meier curve indicated that subjects with low ramucirumab exposure had worse OS compared to FOLFIRI treatment, suggesting an imbalance in baseline characteristics/prognostic factors in the low ramucirumab exposure group. Nevertheless, tumour related factors such as lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), Eastern Cooperative Oncology Group performance status (ECOG PS), number of metastatic sites, and VEGF Receptor 2 expression level in tumour tissues had no significant effect on pharmacokinetics of ramucirumab in popPK analysis. Patients with low CEA levels (≤10 ng/ml) appeared to derive more OS benefit of ramucirumab treatment HR 0.679 (0.498, 0.924) than patients with higher baseline CEA levels (>10 ng/ml) OS HR 0.903 (0.764, 1.068). However, the treatment effect on PFS was similar across the different baseline CEA quartile groups. Therefore, CEA baseline levels are not considered useful as a marker for treatment effect of ramucirumab.

Based available data, no specific dose recommendations are considered necessary in the elderly and the general recommendations in SmPC section 4.2 and 4.5 are considered to also apply to the mCRC population.

Only 6 patients with severe renal impairment were included in the popPK analysis. This is not sufficient for dose recommendations. Patients with severe renal impairment have often more co-morbidities / other medications and may have a different safety profile. Only limited efficacy and safety experience is available in patients with severe renal impairment (see SmPC sections 4.2, 4.4 and 5.2).

The PK of ramucirumab was similar between Child-Pugh Class A and Class B patients. Therefore, no dose adjustments are required in patients with mild or moderate hepatic impairment (see SmPC section 4.2). There are no data in patients with severe hepatic impairment (see sections 4.2, 4.4 and 5.2).

The safety and efficacy of Cyramza in children and adolescents (<18 years) has not been established. No data are available. There is no relevant use of ramucirumab in the paediatric population for the indications of adenocarcinoma of the colon and rectum (see SmPC section 4.2).

2.3.6. Conclusions on clinical pharmacology

Exposure of ramucirumab in mCRC is consistent with the exposure in patients with gastric cancer or non-small cell lung cancer. Exposure effect relationships revealed that both efficacy (OS and PFS) and safety (grade 3 neutropenia) were related to ramucirumab exposure but patients treated with ramucirumab in combination with FOLFIRI experienced a worse quality of life than treatment with FOLFIRI alone (see discussion on clinical efficacy and clinical safety).

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response study was submitted (see discussion on clinical pharmacology).

2.4.2. Main study

Study RAISE

RAISE was a global, randomized, placebo-controlled, double-blind, multicenter Phase 3 study that evaluated the efficacy of ramucirumab versus placebo, each in combination with FOLFIRI, in patients with mCRC whose disease had progressed during or after first-line combination therapy of bevacizumab, oxaliplatin, and a fluoropyrimidine.

Methods

Study participants

Main in- and exclusion criteria:

Patients were eligible for the study if they met any of the following criteria:

1. The patient had histologically or cytologically confirmed CRC, excluding primary tumours of appendiceal origin. Patients were eligible to enrol irrespective of KRAS mutation status.
2. The patient had confirmed metastatic CRC (Stage IV).
3. The KRAS mutation status (wild-type versus mutant) of the patient was known prior to randomization.
4. The patient had received 1st line combination therapy of bevacizumab, oxaliplatin, and a fluoropyrimidine for metastatic disease and:
    a. experienced radiographic disease progression during 1st line therapy, or

b. experienced radiographic disease progression ≤6 months after the last dose

c. of 1st line therapy, or

d. discontinued part or all of first-line therapy due to toxicity and experienced radiographic disease progression ≤6 months after the last dose of first-line therapy.

Note that a patient was required to have received a minimum of 2 doses of bevacizumab as part of a 1st line regimen containing chemotherapy. In addition, a patient must have received at least 1 cycle of 1st line therapy that included bevacizumab, oxaliplatin, and a fluoropyrimidine in the same cycle.

Note that a patient must not have received more than 2 different fluoropyrimidines as part of a 1st line regimen; disease progression was not an acceptable reason for discontinuing one fluoropyrimidine and starting a second fluoropyrimidine.

5. The patient had metastatic disease that was not amenable to potentially curative resection in the opinion of the investigator.
6. The patient had received no more than 2 prior systemic chemotherapy regimens in any setting (only 1 prior regimen for metastatic disease was permitted). For patients with rectal cancer, sequential neo-adjuvant and adjuvant therapy was counted as a single systemic regimen. Note that rechallenge with oxaliplatin was permitted and was considered part of the 1st line regimen for metastatic disease. Both the initial oxaliplatin treatment and the subsequent rechallenge were considered as 1 regimen.
7. The patient had measurable or nonmeasurable disease based on the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v. 1.1).

Patients were excluded from the study if they met any of the following criteria:

1. The patient had received bevacizumab ≤28 days prior to randomization.
2. The patient had received chemotherapy ≤21 days prior to randomization.
3. The patient had received wide-field (full-dose pelvic) radiotherapy ≤28 days prior to randomization or had received any radiotherapy ≤14 days prior to randomization.
4. The patient had received any investigational therapy for a non-oncology clinical indication ≤28 days prior to randomization.
5. The patient had received any previous systemic therapy, other than a combination of bevacizumab, oxaliplatin, and a fluoropyrimidine, for first-line treatment of mCRC.
6. The patient had a history of uncontrolled hereditary or acquired bleeding or thrombotic disorders.
7. The patient had an uncontrolled intercurrent illness, including, but not limited to uncontrolled hypertension, symptomatic congestive heart failure (CHF), unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, psychiatric illness/social situations, or any other serious uncontrolled medical disorders in the opinion of the investigator.
8. The patient had experienced any arterial thrombotic or arterial thromboembolic events, including, but not limited to myocardial infarction, transient ischemic attack, or cerebrovascular accident, ≤12 months prior to randomization.

9. The patient has a history of inflammatory bowel disease or Crohn's disease requiring medical intervention (immunomodulatory or immunosuppressive medications or surgery) ≤12 months prior to randomization.
10. The patient has an acute or subacute bowel obstruction or history of chronic diarrhoea which was considered clinically significant in the opinion of the investigator.
11. The patient had experienced a Grade 3 or higher bleeding event ≤3 months prior to randomization.
12. The patient had either peptic ulcer disease associated with a bleeding event, or known active diverticulitis.
13. The patient experienced any of the following during first-line therapy with a bevacizumab-containing regimen: an arterial thrombotic/thromboembolic event, Grade 4 hypertension, Grade 3 proteinuria, a Grade 3-4 bleeding event or bowel perforation.

Treatments

Patients were randomized (1:1) to receive either ramucirumab (8 mg/kg q 2) plus FOLFIRI (Irinotecan: 180 mg/m^2 D1 q cycle; followed by folinic acid 400 mg/m^2 D1 q cycle; 5-FU 400 mg/m^2 bolus [over 2-4 minutes] followed by 5-FU 2400 mg/m^2 48-hour infusion) on D1 and 2 of q 2-week cycle weeks) or placebo plus FOLFIRI.

- Ramucirumab (8 mg/kg) or placebo (equivalent volume), administered as an 60-min intravenous [I.V.] infusion on Day 1 of each cycle followed by a 1- hour observation period (cycle 1 and 2) followed by the FOLFIRI regimen.
- FOLFIRI
    - Irinotecan: 180 mg/m^2 administered IV over 90 (±10) minutes, 1 hour after the end of the infusion of ramucirumab/placebo (or immediately after the infusion of ramucirumab/placebo if no observation period is required) on Day 1 of each cycle; followed by Folinic acid: 400 mg/m2 administered IV over 120 (±10) minutes on Day 1 of each cycle (alternatively, FA could be administered [via separate infusion lines] concurrently with IRI); followed by
    - 5-Fluorouracil (5-FU): 400 mg/m^2 bolus over 2 to 4 minutes administered IV immediately following completion of the FA infusion on Day 1 of each cycle (infusions of up to 15 minutes in duration were permitted at the discretion of the investigator in order to comply with institutional guidelines); followed by
    - 5-FU: 2400 mg/m^2 administered IV over 46 to 48 hours (continuously) on Days 1 and 2 of each cycle.

Patients who discontinued one or more components of treatment because of an adverse event were permitted to continue therapy with the other treatment component(s) until disease progression or unacceptable toxicity.

Objectives

The primary objective of RAISE was to show superiority of ramucirumab plus FOLFIRI in terms of OS by comparing ramucirumab plus FOLFIRI with placebo plus FOLFIRI in patients with mCRC progressing after prior 1st line 5FU, oxaliplatin and bevacizumab containing combination treatment.

Secondary objectives were to compare ramucirumab plus FOLFIRI treatment with placebo plus FOLFIRI treatment for: progression-free survival (PFS), objective response rate (ORR), patient-reported

outcome (PRO) measures (using European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 and EuroQol EQ-5D), safety profile, assessment of anti-ramucirumab antibodies (immunogenicity), assessment of serum levels of ramucirumab.

Outcomes/endpoints

Primary endpoint

- Overall survival, defined as the time from the date of randomization until the date of death from any cause. If the patient was alive at the end of the follow-up period (or was lost to follow-up), OS data were censored for analysis on the last date the patient was known to be alive.

Secondary endpoints

- PFS, defined as the time from the date of randomization until the date of objectively determined progressive disease (according to RECIST v. 1.1, as assessed by the investigator) or death due to any cause, whichever was first. Patients who died without a reported prior progression were considered to have progressed on the day of their death. Patients who did not progress or were lost to follow-up were censored at the day of their last radiographic tumor assessment.
- ORR was equal to the proportion of patients achieving a best overall response of partial or complete response (PR + CR). Response assessments were undertaken every 6 weeks (±3 days) through Week 36, then every 12 weeks (±3 days) thereafter, as calculated from the first dose of study therapy. Patients were evaluated for response according to RECIST, v 1.1 guidelines (Eisenhauer et al. 2009).
- PRO measures (using European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 and EuroQol EQ-5D).
- Safety profile
- Assessment of anti-ramucirumab antibodies (immunogenicity)
- Assessment of serum levels of ramucirumab

Exploratory endpoints

- Assessment of the association between biomarkers and clinical outcome. The biomarker plan for RAISE included investigation of those markers deemed most likely to show a relationship with ramucirumab activity (e.g. VEGF 2 receptor expression, blood vessel density, circulating factors related to VEGF mediated signalling etc), and the markers analysed were prioritized by availability of samples and assays.

Sample size

Sample size was calculated using group sequential analysis methodology based on the following assumptions: the 1-sided overall significance level is 0.025 (2-sided 0.05); Power 85%; The median overall survival is 10 months in the control arm (based on review of literature (Tourigand 2004, Malbro 2006, Bidard 2009)) and 12.5 months in the active treatment arm; hazard ratio, experimental/control=0.8; The randomization ratio is 1:1; 2 interim futility analyses with beta spending will be based on Pocock (1977); The accrual rate per month would be 5 (Months 1-2), 10 (Month 3), 20 (Month 4), 30 (Month 5), 40 (Month 6+); Overall discontinuation rates are assumed to be 5% in both active treatment as well as the control arm.

Seven hundred and fifty six (756) OS events (deaths) were needed for the final analysis. To allow for censoring due to data cut-off and drop-outs, a total of 1050 patients will be randomized.

Based on actual accrual during the first 10 months of the study, sample size may be increased to observe the required number of events within the estimated study duration of approximately 40 months. Increasing sample size based on the accrual in the first 10 months does not affect type I error as 1) it is not evaluating the effect size and 2) it is not the number of patients but the number of deaths that counts for the hypothesis test and the latter is kept the same.

Randomisation

Randomization (on a 1:1 basis) was conducted. Randomisation was stratified by geographic region, tumour KRAS status (mutant or wild type), and time to disease progression (TTP) after commencing first line treatment (<6 months versus ≥ 6 months).

Blinding (masking)

This was a double-blind study.

Statistical methods

Primary analysis: OS was analysed in the ITT population, consisting of all randomized patients, using the p-value from a log-rank test stratified by geographic region (North America vs. Europe vs. all other regions), KRAS status (mutant vs. wild-type), and time to disease progression after beginning first-line treatment (<6 months vs. ≥6 months).

Survival curves and hazard ratio were estimated using the Kaplan-Meier methodology and stratified Cox regression model, respectively.

OS will not be censored in cases where study treatment results in tumour regression allowing for potentially curative surgical resection and/or radiofrequency ablation.

Supportive analysis: restricted mean difference in OS between the treatment groups and its 95% CI, with the area under the Kaplan-Meier survival curve calculated up to the minimum across treatment arms of the maximum observed (i.e., event or censored) time.

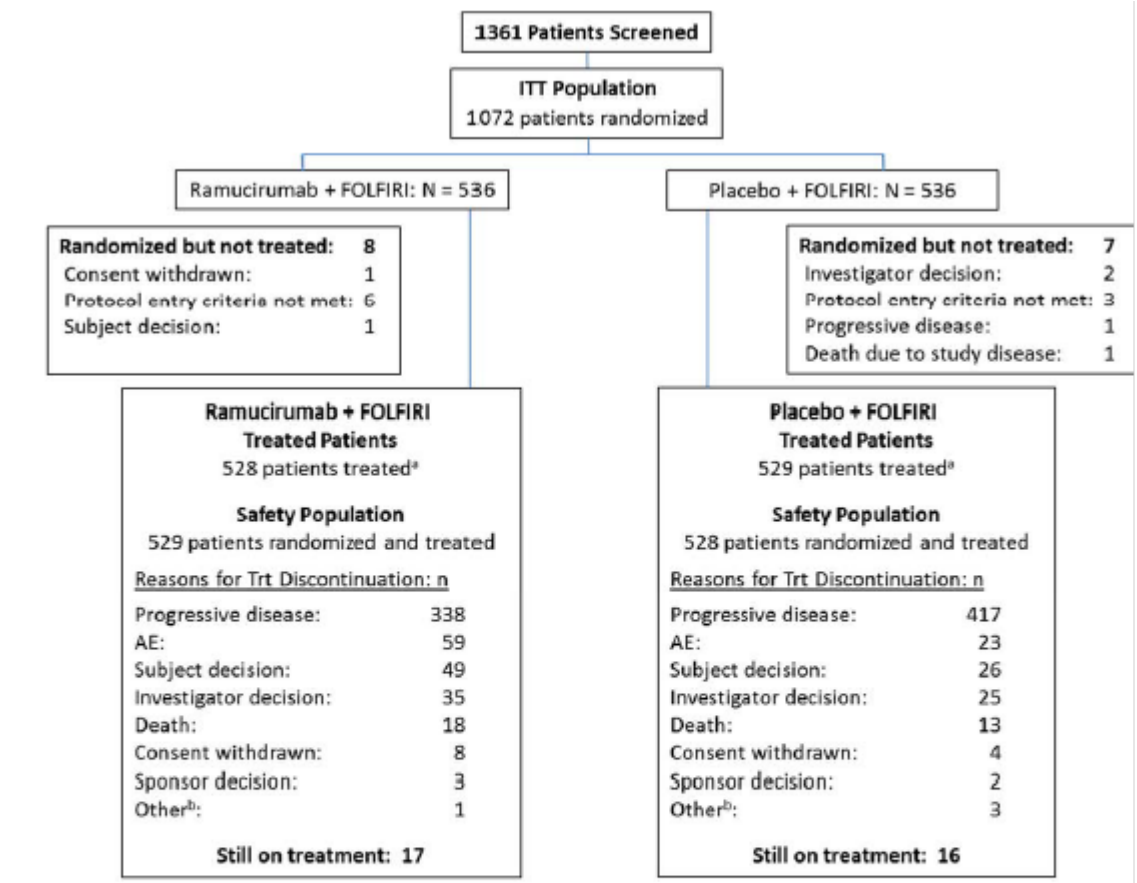
Interim analyses and DMC: There will be 2 interim futility analyses. The first one, based on PFS, will be performed when 122 PFS events are observed among approximately 250 patients. The second one, based on OS, will be performed when 30% (227) of the OS events are observed. Although no stopping for efficacy will be allowed, formally alpha=0.00001 (one-sided) will be spend at the futility analysis of OS, so that the final OS analysis will be at one-sided significance level 0.02499.

An independent DMC with statistician other than the trial statistician will perform these interim analyses and additional analysis for safety. Efficacy data provided only consists of Kaplan-Meier curves and hazard ratios (PFS, OS), and estimated difference with 95%-CI (ORR, DCR).

The comparison of PFS using the same method as that for the primary analysis of OS was considered confirmatory only in case of significant results for OS analysis (that is, as a gatekept analysis so as not to inflate the type I error rate). The comparison of ORR was also considered confirmatory only in case of significant results for OS and PFS analysis.

Results

Participant flow



Abbreviations: AE = adverse event; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; ITT = intent-to-treat; N = total population size; n = number of patients; Trt = treatment.

a One patient randomized to the placebo plus FOLFIRI arm received ramucirumab as the first dose. This patient is included in the placebo plus FOLFIRI arm for the ITT population, and is counted in the ramucirumab plus FOLFIRI arm for the Safety population.

b 'Other' includes protocol entry criterion not met and protocol deviation.

Figure 4. Participant flow

A total of 1072 patients were randomized, and the safety population consisted of 529 patients in the ramucirumab plus FOLFIRI arm and 528 patients in the placebo plus FOLFIRI arm (1057 patients overall).

Table 9. Reasons for Treatment Discontinuation (End of Treatment), Intent-to-Treat Population

Parameters	Ramucirumab + FOLFIRI N = 536 n (%)	Placebo + FOLFIRI N = 536 n (%)	Total N = 1072 n (%)
Randomized and not treated	8 (1.5)	7 (1.3)	15 (1.4)
Treated	528 (98.5)	529 (98.7)	1057 (98.6)
On-treatment[a]	17 (3.2)	16 (3.0)	33 (3.1)
Off-treatment	511 (95.3)	513 (95.7)	1024 (95.5)
Reasons for Treatment Discontinuation			
Progressive disease	338 (63.1)	417 (77.8)	755 (70.4)
Adverse event[b]	59 (11.0)	23 (4.3)	82 (7.6)
Subject decision	49 (9.1)	26 (4.9)	75 (7.0)
Death	18 (3.4)	13 (2.4)	31 (2.9)
Investigator decision	35 (6.5)	25 (4.7)	60 (5.6)
Consent Withdrawn	8 (1.5)	4 (0.7)	12 (1.1)
Other[c]	1 (0.2)	3 (0.6)	4 (0.4)
Sponsor decision	3 (0.6)	2 (0.4)	5 (0.5)

Abbreviations: AE = adverse event; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; N = total population size; n = number of patients; TEAE = treatment-emergent adverse event.

a As of data cut-off date of 17 July 2014.

b Discontinuation of study treatment (whole regimen or the last component of the regimen) due to AE. Note that Table JVBB.12.3.4 summarizes patients with TEAEs that led to discontinuation of any study drug (any component of the regimen).

c 'Other' includes protocol entry criterion not met and protocol deviation.

Recruitment

Enrolment started on 13 December 2010 and the last patient was randomized on 23 August, 2013, who completed study treatment on 14 June, 2014. The data cut-off date was 17 July 2014. Follow-up for survival was scheduled for up to 24 months from randomization.

Conduct of the study

The database was locked on 22 August 2014. The original protocol was issued on 22 July 2010. The protocol was amended 5 times (before first patient in trial: 05 August 2010; 07 October 2010; during recruitment: 31 May 2011; 25 September 2012; three months before the last patient completed study treatment: 26 March 2014).

Patients were enrolled under all Protocol Versions: (a) to (e). Only the main changes are described.

- Protocol Amendment (a) (05 August 2010)

Sponsor of the study was changed; References to the investigator's brochure (IB) were clarified by specifying the ramucirumab IB.

- Protocol Amendment (b) (07 October 2010)

As originally written, the protocol mandated that blood chemistries be determined by a central laboratory. The protocol was revised to permit the use of local chemistry laboratories to make on-study dosing decisions; The use of NCI-CTCAE v. 4.02 was revised to NCI-CTCAE v. 4.0; Consistent with RECIST 1.1, two sections of the protocol were updated to reflect that radiographic confirmation of complete response and partial response with repeat confirmatory radiographic imaging was not required.

- Protocol Amendment (c) (31 May 2011)

Section 5 was changed to include additional nonclinical data that provided proof-of-concept for the conduct of study I4T-MC-JVBB; Inclusion Criterion [4] was changed to permit use of up to 2 fluoropyrimidines as part of the first-line treatment for metastatic disease; Provisions for windows around study treatment infusion times and to allow dose capping; according to a maximum patient body surface area were added to Section 9.1; ; Section 9.5.1 was changed to clarify the dose modifications of investigational drug in response to Grade 3 and Grade 4 AEs; update the definition of febrile neutropenia in order to make it consistent with the latest version of the NCI-CTCAE; The baseline radiographic disease assessment was changed from within 14 days to within 21 days of randomization; The storage time for plasma and whole blood samples was changed; The pre-specified subgroup analysis of route of administration of fluoropyrimidine during first-line treatment was removed in accordance with revisions to inclusion criterion 4; Attachment 3 (Clinical Laboratory Tests) was revised to permit collection of an automated white blood cell differential.

- Protocol Amendment (d) (25 September 2012)

Based on the independent DMC recommendations from the ramucirumab CP12-0919 study, information on liver injury/liver failure was added; a ramucirumab discontinuation criterion and an exclusion criterion were included; Information concerning congestive heart failure, surgery and wound healing, and reversible posterior leukoencephalopathy syndrome were added due to emerging data during the development of ramucirumab; The thyroid-stimulating hormone test was added to collect information on thyroid function during ramucirumab treatment.

- Protocol Amendment (e) (26 March 2014)

The biomarker and analysis endpoints were moved from “Secondary Objectives,” and listed separately in “Other Objectives”. Gatekeeping was added in the Statistical Methods section for OS, PFS, and ORR. The type I error control was extended from OS to OS, PFS, ORR (three months before the last patient had the last dose).

Baseline data

Table 10. Distribution of stratification factors at randomization, ITT population RAISE.

Factor	Ramucirumab + FOLFIRI N = 536 n (%)[a]	Placebo + FOLFIRI N = 536 n (%)[a]	Total N = 1072 n (%)[a]
Geographic region[b,c]			
Europe[d]	235 (43.8)	235 (43.8)	470 (43.8)
North America[e]	143 (26.7)	143 (26.7)	286 (26.7)
Other regions[f]	158 (29.5)	158 (29.5)	316 (29.5)
***KRAS* status**[b]			
Mutant	269 (50.2)	261 (48.7)	530 (49.4)
Wild-type	267 (49.8)	275 (51.3)	542 (50.6)
Time to disease progression after beginning first-line therapy[b]			
<6 months	125 (23.3)	129 (24.1)	254 (23.7)
≥6 months	411 (76.7)	407 (75.9)	818 (76.3)

Abbreviations: CRF = case report form; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; ITT = intent-to-treat; IVRS = interactive voice response system; *KRAS* = Kirsten Ras; N = total population size; n = number of patients in given category.

a Percentages are based on the total population size (N).

b Based on CRF data if present, or IVRS value if CRF data were missing for the parameter.

c Hungary is included in 'Other Regions'. Forty-seven patients (4.4%), 2.0% in ramucirumab plus FOLFIRI arm and 2.1% in the placebo plus FOLFIRI arm, were randomized from Hungary.

d Included Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Portugal, Romania, Spain, and Sweden.

e Included Puerto Rico and United States.

f Included Argentina, Australia, Brazil, Hungary, India, Israel, Japan, Korea, and Taiwan.

Table 11. Patient Demographic Characteristics at Baseline ITT Population RAISE

Parameter	Ramucirumab + FOLFIRI N = 536	Placebo + FOLFIRI N = 536	Total N = 1072
Sex, n (%)[a]			
Female	247 (46.1)	210 (39.2)	457 (42.6)
Male	289 (53.9)	326 (60.8)	615 (57.4)
Age, years			
Median age (range)	62.0 (21, 83)	62.0 (33, 87)	62.0 (21, 87)
Age group, n (%)[a]			
Age <65 years	324 (60.4)	321 (59.9)	645 (60.2)
Age ≥65 years	212 (39.6)	215 (40.1)	427 (39.8)
Age 65 - <75	160 (29.9)	173 (32.3)	333 (31.1)
Age 75 - <85	52 (9.7)	40 (7.5)	92 (8.6)
Age ≥85	0	2 (0.4)	2 (0.2)
Race, n (%)[a]			
White	405 (75.6)	410 (76.5)	815 (76.0)
Asian	111 (20.7)	103 (19.2)	214 (20.0)
Black	14 (2.6)	16 (3.0)	30 (2.8)
Other	4 (0.7)	2 (0.4)	6 (0.6)
Missing	2 (0.4)	5 (0.9)	7 (0.7)

Abbreviations: FOLFIRI = irinotecan, folinic acid and 5-fluorouracil; ITT = intent-to-treat; N = total population size; n = number of patients in given category.

a Percentages are based on the total population size (N).

Table 12. Summary of Baseline Disease Characteristics, ITT Population RAISE

Parameter	Ramucirumab + FOLFIRI N = 536	Placebo + FOLFIRI N = 536	Total N = 1072
ECOG PS, n (%)			
0	263 (49.1)	259 (48.3)	522 (48.7)
1	268 (50.0)	273 (50.9)	541 (50.5)
2	1 (0.2)	1 (0.2)	2 (0.2)
3	0	1 (0.2)	1 (0.1)
Missing	4 (0.7)	2 (0.4)	6 (0.6)
***KRAS* status at study entry, n (%)**			
Mutant	269 (50.2)	261 (48.7)	530 (49.4)
Wild-type	267 (49.8)	275 (51.3)	542 (50.6)
Liver only Metastasis, n (%)			
No	444 (82.8)	441 (82.3)	885 (82.6)
Yes	92 (17.2)	95 (17.7)	187 (17.4)
Site of Primary Tumor, n (%)			
Colon	358 (66.8)	358 (66.8)	716 (66.8)
Rectal	174 (32.5)	171 (31.9)	345 (32.2)
Colorectal	4 (0.7)	7 (1.3)	11 (1.0)
Carcinoembryonic Antigen, n (%)			
<200 µg/L	389 (72.6)	393 (73.3)	782 (72.9)
≥200 µg/L	108 (20.1)	107 (20.0)	215 (20.1)
Missing	39 (7.3)	36 (6.7)	75 (7.0)
Metastatic sites, n (%)			
1	171 (31.9)	157 (29.3)	328 (30.6)
2	205 (38.2)	194 (36.2)	399 (37.2)
≥3	157 (29.3)	182 (34.0)	339 (31.6)
Missing	3 (0.6)	3 (0.3)	6 (0.6)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; ITT = intent-to-treat; *KRAS* = Kirsten Ras; N = total population size; n = number of patients in given category.

Prior therapies

The use of prior therapies was similar between treatment arms (Table below).

Table 13. Prior Therapies, ITT Population RAISE

Parameter	Ramucirumab + FOLFIRI N = 536 n (%)	Placebo + FOLFIRI N = 536 n (%)	Total N = 1072 n (%)
Prior therapies	533 (99.4)	535 (99.8)	1068 (99.6)
Surgery	402 (75.0)	411 (76.7)	813 (75.8)
Radiotherapy	82 (15.3)	82 (15.3)	164 (15.3)
Systemic Therapy	533 (99.4)	534 (99.6)	1067 (99.5)
Type of prior systemic therapy	533 (99.4)	534 (99.6)	1067 (99.5)
Bevacizumab	533 (99.4)	532 (99.3)	1065 (99.3)*
Fluoropyrimidine	532 (99.3)	533 (99.4)	1065 (99.3)*
5-FU	377 (70.3)	390 (72.8)	767 (71.5)
Capecitabine	206 (38.4)	201 (37.5)	407 (38.0)
Gimeracil	1 (0.2)	0	1 (<0.1)
Oteracil potassium	1 (0.2)	0	1 (<0.1)
TS-1	7 (1.3)	7 (1.3)	14 (1.3)
Tegafur	11 (2.1)	14 (2.6)	25 (2.3)
Oxaliplatin	530 (98.9)	533 (99.4)	1063 (99.2)*

Abbreviations: 5-FU – 5-fluorouracil; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; ITT = intent-to-treat; N = total population size; n = number of patients.

* Six patients did not have prior therapy with at least one of bevacizumab, oxaliplatin, and/or a fluoropyrimidine.

Numbers analysed

The RAISE study randomised 1072 patients, 1057 of which received study treatment. Fifteen (15) patients did not receive the assigned treatment for various reasons, which are listed in Figure 4.

Outcomes and estimation

Primary endpoint - Overall Survival

At the time of the data cut-off, a total of 769 death events (71.7%) had occurred, 372 in the ramucirumab+FOLFIRI arm and 397 in the placebo+FOLFIRI arm (Table below). Ramucirumab in combination with FOLFIRI reduced the risk of death in this population by 15.6% (HR = 0.844; 95% confidence interval [CI]: 0.730, 0.976; p=0.0219; (two-sided 0.04998)) (Figure 5), resulting in a 1.6-month longer median survival (13.3 months vs. 11.7 months).

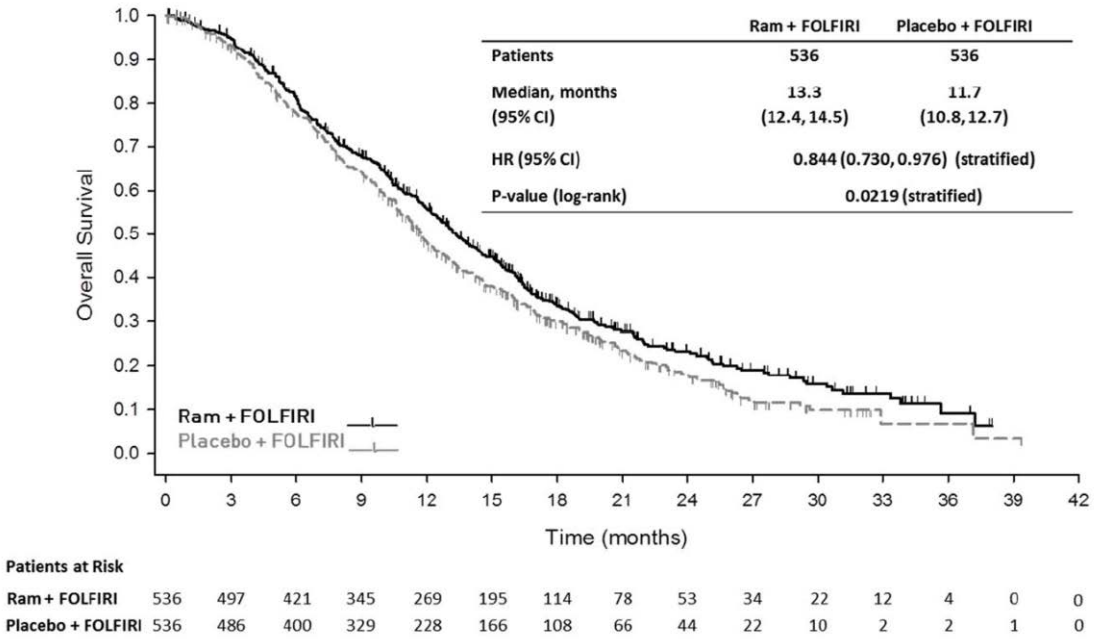
Table 14. Summary of Overall Survival Time ITT Population RAISE

	Ramucirumab + FOLFIRI N = 536	**Placebo + FOLFIRI N = 536**
Number of Deaths, n (%)	372 (69.4)	397 (74.1)
Number censored, n (%)	164 (30.6)	139 (25.9)
Median Survival – months (95% CI)	**13.3 (12.4, 14.5)**	**11.7 (10.8, 12.7)**
Log-rank p-value Stratified	0.0219	
Hazard ratio (95% CI) Stratified	0.844 (0.730, 0.976)	

Abbreviations: CI = confidence interval; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; ITT = intent-to-treat; N = total population size; n = number of patients.

Note: Overall survival is the duration from randomization to death. For patients who are alive, overall survival is censored at the last contact.

Figure 5. Kaplan-Meier graph of overall survival time by treatment group, ITT population, RAISE



Sensitivity analysis

Table 15: Sensitivity Analyses of Overall Survival Time ITT Population, RAISE

Overall Survival	HR (95% CI)	Log-rank p-value
Primary Analysis		
Stratified by CRF (N=1072)	0.844 (0.730, 0.976)	0.0219
SAP-specified		
Stratified by IVRS (N=1072)	0.846 (0.732, 0.977)	0.0233
Multivariate Cox Regression[a] (N=989)	0.844 (0.728, 0.978)	0.0245[b]
Unstratified (N=1072)	0.854 (0.741, 0.984)	0.0291[c]
Per Protocol Population (N=1006)	0.850 (0.732, 0.986)	0.0324

Abbreviations: CEA = carcinoembryonic antigen; CI = confidence interval; CRF = case report form; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; ITT = intent-to-treat; IVRS = interactive voice response system; *KRAS* = Kirsten Ras; N = total population size; PD = progressive disease; SAP = statistical analysis plan.

Note: Overall survival is the duration from randomization to death. For patients who were alive at time of database lock, overall survival was censored at the last contact.

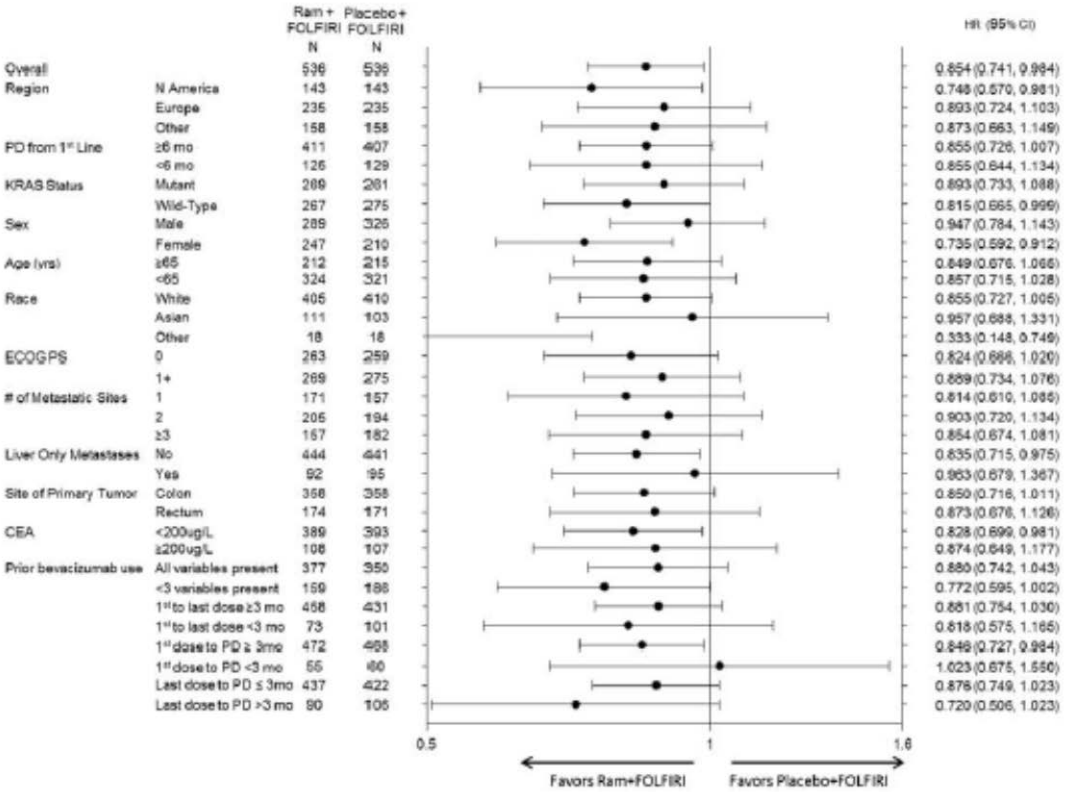
a Cox proportional hazard model: stepwise selection of significant prognostic factors:
Significant Factors: time to PD after beginning first-line therapy, ECOG PS, tumor *KRAS* mutation status, number of metastatic sites, liver-only metastases, and CEA.
Variables included in model selection: geography, time to PD after beginning first-line therapy (<6 months, ≥6 months), tumor *KRAS* status (mutant, wild-type), sex, age (using <65 and ≥65 years), race (White, Asian, Other), ECOG PS (0, 1+), number of metastatic sites (1, 2, ≥3), liver-only metastases, site of primary tumor, CEA, and prior bevacizumab use (composite only, which includes the combination of all 3 variables [time from first bevacizumab dose to last bevacizumab dose ≥3 months; time from first bevacizumab dose to progression ≥3 months; and time from last bevacizumab dose to progression ≤3 months]).

b Wald's p-value.

c Unstratified log-rank p-value.

Subgroup analyses

Figure 6. Forest plot for subgroup analysis of overall survival (unstratified analysis), ITT population



Abbreviations: CEA = carcinoembryonic antigen; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; HR = hazard ratio; ITT = intent-to-treat; N = total population size; PD = progressive disease, Ram = ramucirumab.

Note: For the characteristics of prior bevacizumab use, "All variables present" includes the combination of all 3 variables (time from first bevacizumab dose to last bevacizumab dose ≥3 months; time from first bevacizumab dose to progression ≥3 months; and time from last bevacizumab dose to progression ≤3 months). "<3 variables present" includes at least 1 of these variables present (time from first bevacizumab dose to last bevacizumab dose <3 months; or time from first bevacizumab dose to progression <3 months; or time from last bevacizumab dose to progression >3 months).

Note: The HR and lower CI are not depicted in the Forest plot for the Race/Other subgroup. The HR (95% CI) is 0.333 (0.148, 0.749).

Post-study therapies

Table 16. Summary of Post-discontinuation Anticancer Therapy ITT Population RAISE

Postdiscontinuation Anticancer Therapy[a]	Ramucirumab + FOLFIRI N = 536 n (%)[b]	Placebo + FOLFIRI N = 536 n (%)[b]	Total N = 1072 n (%)[b]
Patients with at least 1 PDT	306 (57.1)	318 (59.3)	624 (58.2)
Systemic therapy	290 (54.1)	300 (56.0)	590 (55.0)
Radiotherapy	40 (7.5)	49 (9.1)	89 (8.3)
Surgery	24 (4.5)	29 (5.4)	53 (4.9)
Systemic Therapies (≥1.5%)			
Systemic anti-cancer therapy	290 (54.1)	300 (56.0)	590 (55.0)
Biologic agents	214 (39.9)	223 (41.6)	437 (40.8)
Anti-EGFR antibody	137 (25.6)	153 (28.5)	290 (27.1)
Anti-angiogenic agents	68 (12.7)	70 (13.1)	138 (12.9)
Tyrosine kinase inhibitor[c]	57 (10.6)	58 (10.8)	115 (10.7)
Chemotherapy	231 (43.1)	248 (46.3)	479 (44.7)
Anti-folate	6 (1.1)	12 (2.2)	18 (1.7)
Fluoropyrimidines	179 (33.4)	182 (34.0)	361 (33.7)
Platinum	48 (9.0)	58 (10.8)	106 (9.9)
Topoisomerase I inhibitor	164 (30.6)	154 (28.7)	318 (29.7)
Other	9 (1.7)	21 (3.9)	30 (2.8)
Other Investigational agents	17 (3.2)	24 (4.5)	41 (3.8)
Other Systemic Therapy Drugs[d]	117 (21.8)	96 (17.9)	213 (19.9)
Adjunctive Therapy	116 (21.6)	94 (17.5)	210 (19.6)

Abbreviations: EGFR = epidermal growth factor receptor; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; ITT = intent-to-treat; N = total population size; n = number of patients in given category; PDT = postdiscontinuation anticancer therapy.

a Patients may have received more than 1 treatment.

b Percentages are based on the total population size (N).

c One patient on the ramucirumab plus FOLFIRI arm received dovitinib. All other patients on both treatment arms received regorafenib.

d One patient in the ramucirumab plus FOLFIRI arm and 2 patients in the placebo plus FOLFIRI arm received supportive care; all other patients received leucovorin.

OS results stratified by presence of neutropenia

Figure 7. KM plot of OS in patients treated with ramucirumab plus FOLFIRI who did and did not experience neutropenia

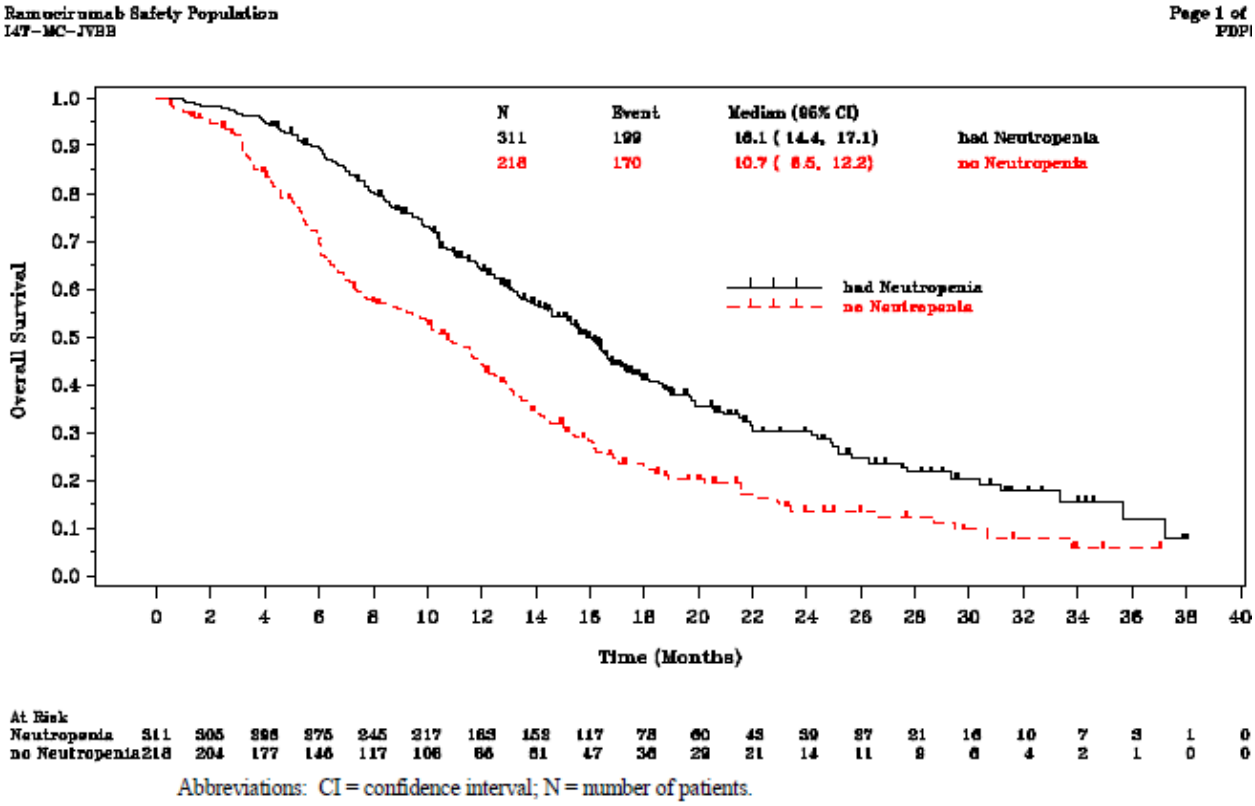
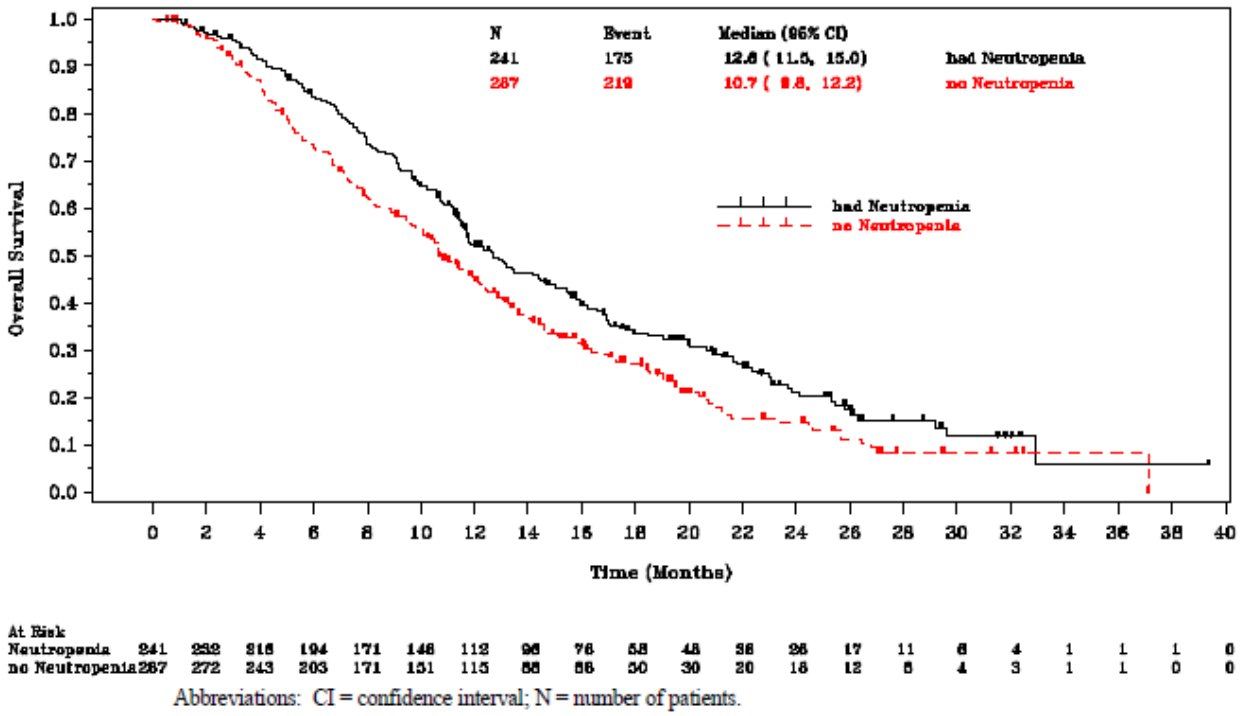
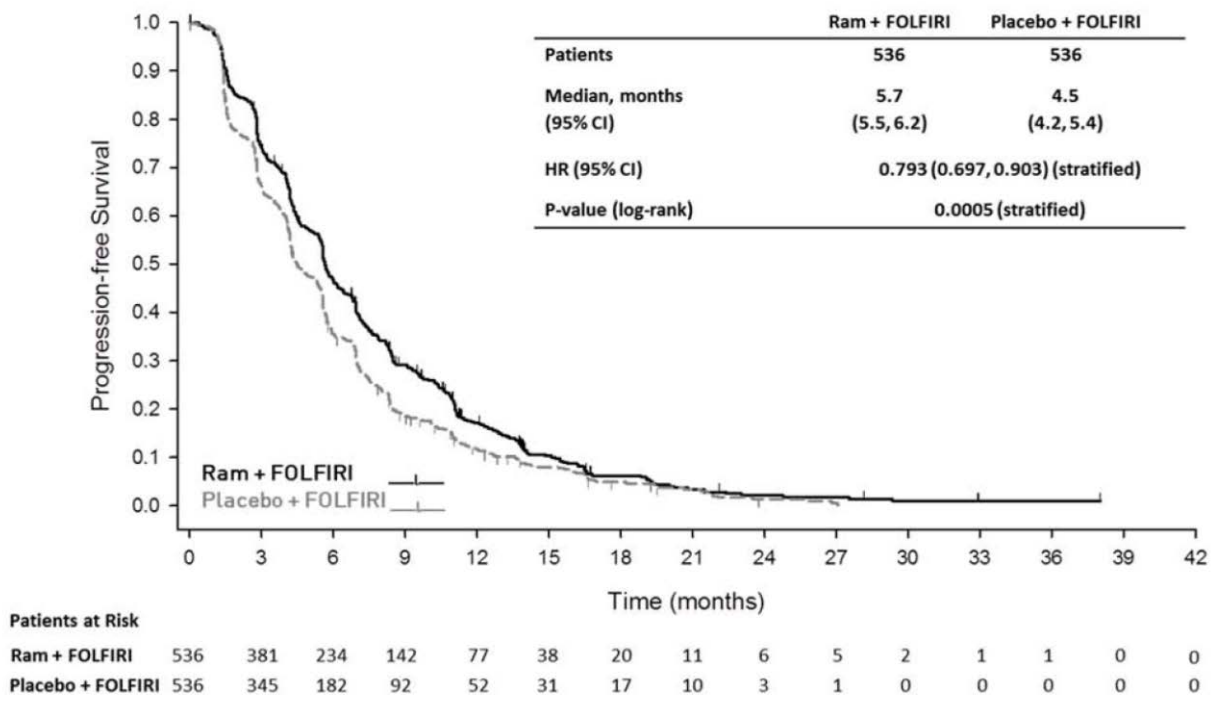


Figure 8 KM plot of OS in patients who did and did not experience neutropenia, placebo-treated patients, RAISE.



Secondary endpoint - Progression Free Survival (PFS)

Figure 9. Kaplan-Meier graph of progression-free survival time by treatment group, ITT population, RAISE.



Abbreviations: CI = confidence interval; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; HR = hazard ratio; ITT = intent-to-treat; Ram = ramucirumab.

Table 17. Sensitivity Analysis of Progression-Free Survival Intent-to-Treat Population.

Sensitivity Analyses	HR (95% CI)[a]	p-Value[b]
Main Analysis		
Stratified, N=1072	0.793 (0.697, 0.903)	0.0005
Sensitivity Analyses		
Unstratified (N=1072)	0.797 (0.702, 0.904)	0.0004[c]
Progressed at date of earlier of 2 visits if documented progression between visits and censored at date of later of 2 visits if censored between visits (N=1072)	0.800 (0.703, 0.910)	0.0007
Censored at date of new anticancer therapy (N=1072)	0.772 (0.675, 0.882)	0.0001
Censored at date of last adequate radiological assessment before missed assessments or date of randomization if no other tumor assessment in between if death or documented progression was reported after ≥2 missed assessments (N=1072)	0.750 (0.653, 0.861)	<.0001
Worst Case: Progressed at date of next scheduled radiological assessment at or after becoming lost to follow-up without documented progression (N=1072)	0.803 (0.706, 0.912)	0.0007
Worst Comparison: Progressed for treatment arm or censored for the control arm at date of next scheduled radiological assessment before lost to follow-up if lost to follow-up without documented progression (N=1072)	0.821 (0.722, 0.933)	0.0025
Per protocol population (N=1006)	0.800 (0.701, 0.914)	0.0010
Primary PFS using IVRS strata (N=1072)	0.791 (0.696, 0.900)	0.0004
Multivariate cox regression[d] (N=989)	0.769 (0.674, 0.878)	<0.0001[e]

Abbreviations: CEA = carcinoembryonic antigen; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; IVRS = interactive voice response system; N = number of patients; PD = progressive disease; PFS = progression-free survival.

a Ramucirumab + FOLFIRI versus placebo + FOLFIRI.

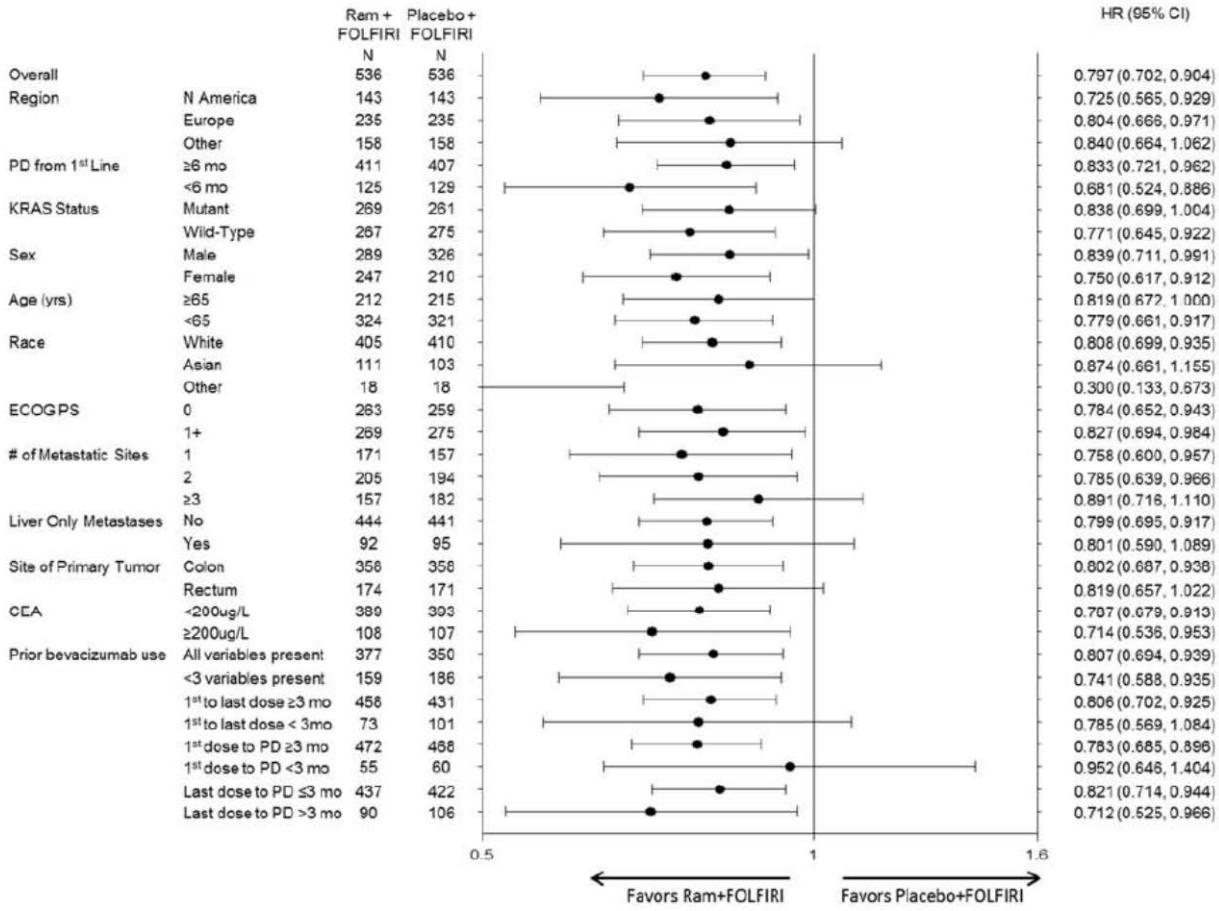
b p-Value based on stratified log-rank test, unless otherwise noted.

c Unstratified log-rank p-value.

d Cox proportional hazard model: stepwise selection of significant prognostic factors:
Significant Factors: ECOG PS, number of metastatic sites, liver-only metastases, CEA, characteristics of prior bevacizumab use (composite only).
Variables included in model selection: geography, time to PD after beginning first-line therapy, tumor *KRAS* mutation status (mutant, wild-type), sex, age (using <65 and ≥65 years), race (White, Asian, Other), ECOG PS (0, 1+), number of metastatic sites (1, 2, ≥3), liver-only metastases, site of primary tumor, CEA, prior bevacizumab use (composite only), these factors are defined in the SAP (provided in an appendix to this report [Documentation of Statistical Methods]) and Section 9.7.1.2.

e Wald's p-value.

Figure 10. Forest plot for subgroup analysis of progression-free survival (unstratified analysis), ITT population, RAISE.



Abbreviations: CEA = carcinoembryonic antigen; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; HR = hazard ratio; ITT = intent-to-treat; KRAS = Kirsten Ras; N = total population size; N America = North America; PD = progressive disease, Ram = ramucirumab.

Note: The subgroup of ECOG 1+ includes 541 patients with ECOG PS 1, and 3 patients with ECOG PS >1 (see Table 2.7.3.5).

Note: For the characteristics of prior bevacizumab use, "All variables present" consolidates all 3 variables (time from first bevacizumab dose to last bevacizumab dose ≥3 months; time from first bevacizumab dose to progression ≥3 months; and time from last bevacizumab dose to progression ≤3 months).

"<3 variables present" includes at least 1 of these variables present (time from first bevacizumab dose to last bevacizumab dose <3 months; or time from first bevacizumab dose to progression <3 months; or time from last bevacizumab dose to progression >3 months).

Note: The HR and lower CI are not depicted in the Forest plot for the Race/Other subgroup. The HR (95% CI) is 0.300 (0.133, 0.673).

Secondary endpoint: Objective Response Rate (ORR) and Disease Control Rate (DCR)

Table 18. Summary of Best Overall Tumor Response and Disease Control Rate, ITT Population RAISE.

	Ramucirumab + FOLFIRI N = 536 n (%)	Placebo + FOLFIRI N = 536 n (%)	p-Value[b]
Best overall response[a]			
Complete response (CR)	0	2 (0.4)	
Partial response (PR)	72 (13.4)	65 (12.1)	
Stable disease (SD)	325 (60.6)	302 (56.3)	
Progressive disease (PD)	87 (16.2)	134 (25.0)	
Unknown	2 (0.4)	2 (0.4)	
Not done	50 (9.3)	31 (5.8)	
Objective response (CR+PR) rate	13.4%	12.5%	.6336
95% CI[c] for response rate	(10.7, 16.6)	(9.8, 15.6)	
Disease control (CR+PR+SD) rate	74.1%	68.8%	.0587
95% CI[c] disease control rate	(70.1, 77.7)	(64.7, 72.7)	

Abbreviations: CI = confidence interval; CR = complete response; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; ITT = intent-to-treat; N = total population size; n = number of patients; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors; SD = stable disease.

a Response criteria used was RECIST v 1.1.

b The p-value is based on the Cochran-Mantel-Haenszel test adjusting for the stratification variables.

c Confidence intervals are based on the exact method.

Patient-Reported Outcomes

Overall, the score for global health decreased from 67.6 at baseline to 57.3 at the summary visit for patients in the ramucirumab +FOLFIRI arm and from 67.5 to 58.7 in the placebo+FOLFIRI arm. The Summary Visit was ≤7 days after the documentation of PD, cessation of treatment due to toxicity, withdrawal of consent, or other treatment discontinuation criteria were met.

Table 19: Summary of EORTC QLQ-C30 Scale Score by cycle, Global health status/QoL, ITT population

			Ramucirumab (N=536)		Placebo (N=536)	
Parameter	Cycle		At Cycle	Change from Baseline	At Cycle	Change from Baseline
Global health status/QoL	Baseline	n	522		517	
		Mean	67.6		67.5	
		SD	21.26		21.53	
		Median	66.7		66.7	
		Minimum	0		0	
		Maximum	100		100	

Global health status/QoL	Maximum Imp.	n	497	491	500	486
		Mean	71.9	4.0	74.6	6.6
		SD	19.95	20.61	19.52	18.84
		Median	75.0	0.0	83.3	0.0
		Minimum	0	-67	0	-100
		Maximum	100	83	100	100
		Stable		242 (45.1%)		255 (47.6%)
		Improved		148 (27.6%)		170 (31.7%)
		Deteriorated		101 (18.8%)		61 (11.4%)
		Missing		45 (8.4%)		50 (9.3%)
		p-value*a				0.012
	3	n	386	383	408	402
		Mean	62.3	-7.1	67.8	-0.9
		SD	21.14	20.71	20.56	17.99
		Median	66.7	-8.3	66.7	0.0
		Minimum	0	-75	0	-50
		Maximum	100	75	100	92
		Stable		184 (34.3%)		235 (43.8%)
		Improved		52 (9.7%)		78 (14.6%)
		Deteriorated		147 (27.4%)		89 (16.6%)
		Missing		153 (28.5%)		134 (25.0%)
		p-value*a				<0.001
Global health status/QoL	5	n	306	304	310	303
		Mean	65.1	-4.6	68.0	-2.1
		SD	20.11	21.37	19.35	20.52
		Median	66.7	0.0	66.7	0.0
		Minimum	0	-67	0	-67
		Maximum	100	67	100	100
		Stable		147 (27.4%)		166 (31.0%)
		Improved		53 (9.9%)		59 (11.0%)
		Deteriorated		104 (19.4%)		78 (14.6%)
		Missing		232 (43.3%)		233 (43.5%)
		p-value*a				0.119
	7	n	272	271	261	256
		Mean	65.8	-2.4	69.0	-1.7
		SD	19.44	21.78	18.47	17.20
		Median	66.7	0.0	66.7	0.0
		Minimum	0	-67	17	-58
		Maximum	100	75	100	67
		Stable		128 (23.9%)		147 (27.4%)
		Improved		60 (11.2%)		49 (9.1%)
		Deteriorated		83 (15.5%)		60 (11.2%)
		Missing		265 (49.4%)		280 (52.2%)
		p-value*a				0.610
Global health status/QoL	9	n	226	224	222	216
		Mean	66.5	-2.9	67.3	-3.8
		SD	19.57	20.87	22.16	20.03
		Median	66.7	0.0	66.7	0.0
		Minimum	0	-67	0	-83
		Maximum	100	67	100	67
		Stable		104 (19.4%)		112 (20.9%)
		Improved		48 (9.0%)		39 (7.3%)
		Deteriorated		72 (13.4%)		65 (12.1%)
		Missing		312 (58.2%)		320 (59.7%)
		p-value*a				0.946
	11	n	180	179	172	166
		Mean	66.6	-2.1	67.9	-3.5
		SD	20.63	22.20	20.43	19.03
		Median	66.7	0.0	66.7	0.0
		Minimum	0	-67	0	-67
		Maximum	100	83	100	50
		Stable		81 (15.1%)		91 (17.0%)
		Improved		41 (7.6%)		28 (5.2%)
		Deteriorated		57 (10.6%)		47 (8.8%)
		Missing		357 (66.6%)		370 (69.0%)
		p-value*a				0.826

Abbreviation: Imp. = improvement from baseline; N = total population size; n = number of patients; SD = standard deviation.
Note: Percentages are based on the total population size (N).
Note: Improved = decrease of >= 10 points for the symptom scales or increase of >= 10 points for the functional scales and the global health status/QoL scale; Stable = no change or increase/decrease < 10 points; Deteriorated = increase of >= 10 points for the symptom scales or decrease of >=10 points for the functional scales and the global health status/QoL scale.

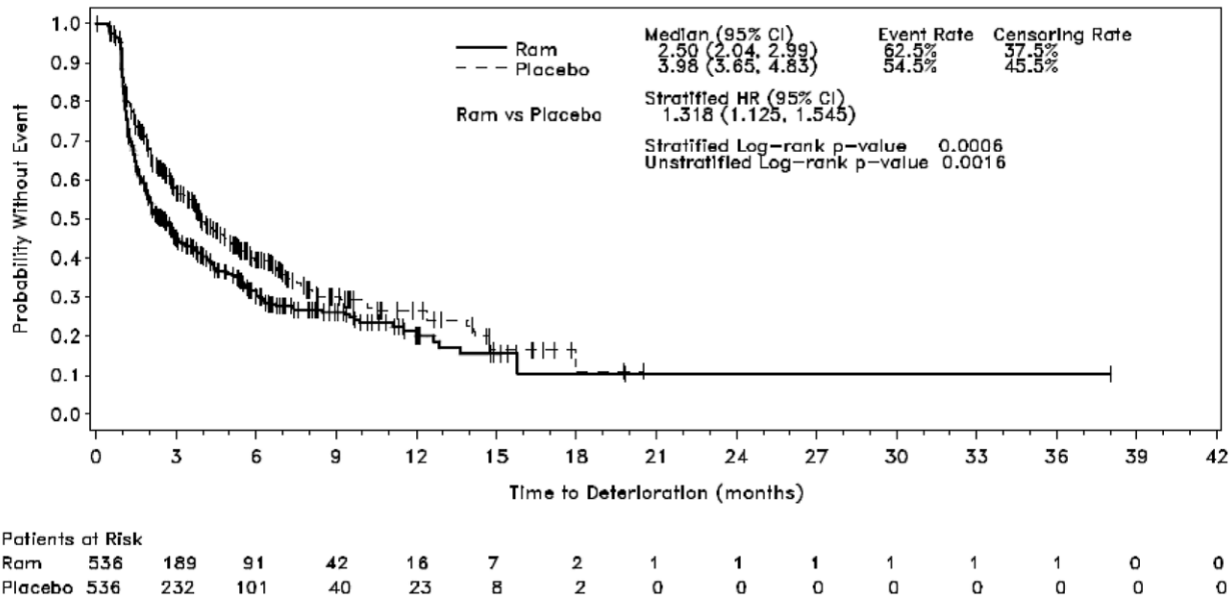
Time to Deterioration in EORTC QLQ-C30

Hazard ratios for the pre specified time to deterioration (defined as>10 points change from baseline) were >1 for most of the QLQ-C30 scales, indicating a shorter time to deterioration for patients in the ramucirumab plus FOLFIRI arm (for 7 of the 15 scales, the 95% CIs did not include 1 (global) health

status/QoL, physical functioning, role functioning, emotional functioning, fatigue, appetite loss, and constipation) and were statistically significantly different.

The time to deterioration regarding global health was 1.5 months shorter for the ramucirumab+FOLFIRI arm (2.50 vs. 3.98 months; Figure 11). As observed in the response analysis described above, after the first 2 post baseline assessments, the percentage of patients with reported stable or improved scores were similar between arms, suggesting that the initial decrease in QoL in the ramucirumab plus FOLFIRI treatment arm was transient. Therefore, a post-hoc alternate definition of deterioration in QoL was explored, as “time to sustained deterioration”. Median time to sustained deterioration was similar between arms (7.69 (6.31- 8.61 versus 7.52 (6.51, 8.15) months. There was a statistically significant difference for only 3 scales: emotional functioning, fatigue, and appetite loss.

Figure 11. Kaplan Meier of time to deterioration (>10 points change from baseline) in EORTC QLQ-C30 (global health status/QOL).



Abbreviations: CI = confidence interval; HR = hazard ratio; NE = not estimable.

EQ5D

Baseline scores for the index and visual analog scale were similar between treatment arms. On-therapy scores were relatively unchanged except for greater decreases at the first protocol-scheduled assessment for patients in the ramucirumab plus FOLFIRI arm, which returned to baseline at the next assessment.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 20: Summary of Efficacy for trial RAISE

Title: A Randomized, Double-Blind, Multicenter Phase 3 Study of Irinotecan, Folinic Acid, and 5-Fluorouracil (FOLFIRI) Plus Ramucirumab or Placebo in Patients With Metastatic Colorectal Carcinoma Progressive During or Following First-Line Combination Therapy With Bevacizumab, Oxaliplatin, and a Fluoropyrimidine			
Study identifier	14T-MC-JVBB, IMCL CP12-0920, RAISE study		
Design	Randomized, placebo-controlled, double-blind, multicenter		
	Duration of main phase:		until disease progression, the development of unacceptable toxicity, noncompliance or withdrawal of consent by the patient, or investigator decision
Hypothesis	Superiority		
Treatments groups	Ramucirumab+FOLFIRI		Ramucirumab (8 mg/kg) as an intravenous (IV) infusion over approximately 60 minutes on Day 1 of each cycle; then a 1-hour observation period following the initial and second infusions of ramucirumab followed by the FOLFIRI regimen N=536
	Placebo+FOLFIRI		Placebo (a volume equivalent to that of ramucirumab) then a 1-hour observation period following the initial and second infusions of placebo followed by the FOLFIRI regimen N=536
Endpoints and definitions	Primary endpoint	Overall Survival (OS)	Time from the date of randomization until the date of death from any cause.
	Secondary	Progression Free Survival (PFS)	Time from the date of randomization until the date of objectively determined progressive disease (according to RECIST v. 1.1, as assessed by the investigator) or death due to any cause,
	Secondary	Overall Response Rate (ORR)	Proportion of patients achieving a best overall response of partial or complete response (PR + CR).
	Secondary	Patient reported outcomes: EORTC QLQ-C30 Global Health Status	Time (months) to deterioration (>10 points from baseline) in global health status
Database lock	17 July, 2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Ramucirumab+ FOLFIRI	Placebo+FOLFIRI
	Number of subject	536	536

	OS (median (months))	13.3	11.7
	Confidence interval	(12.4, 14.5)	(10.8, 12.7)
	PFS (median (months))	5.7	4.5
	Confidence interval	(CI 5.5-6.2)	(4.2-5.4)
	ORR Confidence interval	13.4% (10.7%-19.6%)	12.5% (9.8%-15.6%)
	EORTC QLQ-C30 Global Health Status (median (months)) Confidence interval	2.50 (2.04, 2.99)	3.98 (3.65, 4.83)
Effect estimate per comparison	Primary endpoint: OS	HR	0.844
		Confidence interval	(0.730-0.976)
		P-value	0.0219
	Secondary endpoint: PFS	HR	HR 0.793
		Confidence interval	(0.697-0.903)
		P-value	P=0.0005
	Secondary endpoint: ORR	P-value	0.6336
	Secondary endpoint: EORTC QLQ-C30 Global Health Status	HR	1.318
		Confidence interval	CI 1.125-1545
		P-value	p= 0.0006

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The evidence of efficacy of ramucirumab in patients with mCRC is based on the results of one pivotal study, the RAISE study. According to EMA guidelines, the exceptional event of authorising based on one single pivotal study is acceptable (CPMP/EWP/2330/99), but the study has to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency.

RAISE was a global, randomized, placebo-controlled, double-blind, multicenter Phase 3 study that evaluated the efficacy of ramucirumab versus placebo, each in combination with FOLFIRI, in 1072 patients with mCRC whose disease had progressed during or after first-line combination therapy of bevacizumab, oxaliplatin, and a fluoropyrimidine.

The choice of control (placebo+FOLFIRI) is considered appropriate, since an irinotecan-based regimen can be considered at the time of start of the RAISE study to reflect the clinical practice as a second line treatment after an oxaliplatin-based regimen for patients with mCRC, whose disease progressed after combination treatment with bevacizumab, oxaliplatin and a fluoropyrimidine. Because the patients studied in RAISE were still eligible for treatment with fluoropyrimidine-based chemotherapy along with anti-VEGF therapy, these patients are not candidates for treatment with regorafenib. For patients with KRAS wild-type tumour, these patients will need to be treated with an anti-EGFR inhibitor, such as cetuximab, before they meet the eligibility for regorafenib.

Overall, the statistical methods were considered standard for time to event endpoints and acceptable. With regards to protocol amendments, the first two protocol amendment (a and b) were before entry of the first patient in the trial and are therefore considered not to have affected the conduct or analysis of the trial. Amendment c (31 March 2011) included the change of inclusion criterion 4 to permit use of up to 2 fluoropyrimidines as part of first line treatment for metastatic disease. Since the number of lines of first line treatment potentially impacts survival for patients with mCRC, this modification may have influenced the outcome. Other protocol amendments were not considered to affect the conduct or outcome of the study. Since all of the changes conducted regarding important endpoints were before database lock and unblinding, hence without knowledge of the data, this is considered acceptable. Nevertheless, extending type I error control from OS to OS, PFS, ORR (hierarchical testing) so late in the trial is noteworthy.

OS was the primary endpoint of the study, which is considered appropriate. Secondary endpoints were PFS (according to investigator), ORR and patient-reported quality-of-life outcomes and also considered acceptable.

Overall, 43.8% of patients were randomized in Europe, 26.7% in North America, and 29.5% in other regions. The majority of patients (76.3%) had disease progression ≥6 months after beginning first-line therapy. The stratification factors were evenly distributed between both arms.

Demographic and baseline characteristics and prior treatment appeared largely comparable between the two study arms, except for sex (more females [46.1% vs. 39.2%] in the ramucirumab+FOLFIRI arm), the number of patients with ≥3 metastases (lower [29.3% vs. 34.0%] in the ramucirumab+FOLFIRI arm) and for age (more patients [9.7% vs. 7.9%] in the ramucirumab+FOLFIRI arm were 75 years of age or older).

Patients with ECOG score ≥2 were excluded from the pivotal study, therefore the safety and efficacy of Cyramza in this patient population is unknown (see Section 5.1).

No information was provided about the number of first line treatments received as a repeat treatment after lasting response to initial palliative treatment. The number of treatment cycles was not recorded but only the duration of first line treatment. The median duration of treatment to 1st line therapy appeared balanced between the two study arms (254 days in the Cyramza containing arm versus 241 days in the population in the control arm of RAISE). However, the median duration of 1st line treatment in RAISE was almost double as could be expected based on the standard first line treatment, showing that the patients tested must have had generally relatively non-aggressive disease. The difference between the median duration of disease (as defined by the interval between the moment of initial diagnosis and randomisation) in the two arms in RAISE was 1.32 months in favour of ramucirumab (median duration of disease: 14.3 versus 13.0 months; mean duration 20.4 versus 19.4 months, for ramucirumab versus placebo group, respectively). However, sensitivity analyses adjusting for baseline prognostic factors did not reveal major differences in the treatment effect associated with ramucirumab.

Efficacy data and additional analyses

Ramucirumab in combination with FOLFIRI reduced the risk of death in this population by 15.6% (HR = 0.844; 95% confidence interval [CI]: 0.730, 0.976; p=0.0219), resulting in a 1.6-month longer median survival (13.3 months vs. 11.7 months).

Pre-specified analyses for OS and PFS by stratification factors were performed. The HR of OS was 0.82 (95% CI: 0.67 to 1.0) in patients with a KRAS wild type tumour, and 0.89 (95% CI: 0.73 to 1.09) in patients with a KRAS mutant tumour. For patients with TTP ≥ 6 months after commencing first-line treatment the HR of OS was 0.86 (95% CI: 0.73 to 1.01), and 0.86 (95% CI: 0.64 to 1.13) in patients with TTP < 6 months after commencing first-line treatment.

Pre-specified subgroup analyses for both PFS and OS according to age (<65 and ≥65 years), gender, race, ECOG PS (0 or ≥ 1), number of organs involved, liver metastases only, site of primary tumour (colon or rectum), carcinoembryonic antigen levels (<200µg/mL, ≥200µg/mL), all showed a treatment effect favouring Cyramza plus FOLFIRI treatment over placebo plus FOLFIRI.

In 32 of the 33 pre-specified sub-group analyses for OS, the HR was < 1.0. The one sub-group with HR > 1 was for patients with disease progression from start of first-line bevacizumab treatment of < 3 months (HR 1.02 [95% CI: 0.68 to 1.55]). This one sub-group is a group which can be considered to have aggressive disease that is relatively refractory to first-line treatment (see SmPC section 5.1).

In addition, subgroup results showed that the estimate of treatment effect favours the ramucirumab plus FOLFIRI arm, although the effect for patients recruited in Europe (the largest region in the RAISE study) was not statistically significant (HR 0.893; CI 0.724-1.103). A causal and clear link between lack of efficacy with any of the subgroups assessed is difficult to establish, apart from early treatment in aggressive disease.

Furthermore, the relevance of KRAS mutation status remains uncertain as differences in outcome were reported (2.5 and 1.4 months for KRAS wt and mutant), respectively.

High VEGF and/or VEGFR expression have been associated with poor prognosis in a variety of cancers. However, VEGF and VEGFR expression in RAISE have not been reported.

A causal link between lack of efficacy with any of the subgroups assessed is difficult to establish. This raises the question whether benefit can be increased by further selection of the patients, in particular on the basis of biomarkers. Therefore, in order to investigate the potential correlation between biomarker measures (VEGF-C. VEGF-D, sVEGFR1, sVEGFR2 and sVEGFR3 from plasma, VEGFR2 IHC, additional KRAS, NRAS and BRAF mutations) and efficacy outcome (PFS, OS), the MAH will submit the results of a biomarker assay from the RAISE translational research population (see Annex II condition). In view of the uncertainty to address, the conduct of this study is considered a post authorisation efficacy study (PAES) in accordance with the following criteria from the Commission Delegated Regulation (EU) No. 357/2014 “c) uncertainties with respect to the efficacy of a medicinal product in certain sub-populations that could not be resolved prior to marketing authorisation and require further clinical evidence.”

Overall, the observed OS gain is modest but could be considered of potential clinical relevance.

More than half of the patients (55.0%) received at least 1 additional systemic anticancer therapy after discontinuation from study therapy (54.1% in the ramucirumab plus FOLFIRI arm and 56.0% in the placebo plus FOLFIRI arm). Since the use of Post discontinuation anticancer treatments were balanced and the usage of specific anticancer treatments was similar between treatment arms, the use of post-

discontinuation anticancer therapy is unlikely to have had an important effect on the OS benefit observed in favour of the ramucirumab+FOLFIRI arm.

Since a high proportion of patients (21.7%) in the ramucirumab+FOLFIRI arm suffered from neutropenia and half of these patients discontinued treatment (FOLFIRI mostly), the MAH was requested to provide OS results stratified by the presence of neutropenia. In both treatment arms, patients who experienced neutropenia had a longer median OS compared to patients who did not experience neutropenia. The median OS in patients with any-grade neutropenia was greater in the ramucirumab (16.1 months) than in the placebo arm (12.6 months). Median OS in patients who did not experience neutropenia was 10.7 months in both arms (see SmPC section 5.1).

Treatment results for PFS were consistent with the OS results. Treatment with ramucirumab plus FOLFIRI resulted in a statistically significant improvement in PFS (HR = 0.793; 95% CI: 0.697, 0.903; p=0.0005), corresponding 1.2 months increase in median PFS (Median PFS 5.7 vs. 4.5 months). No difference between arms was observed for ORR or disease control rate.

The statistical significance, magnitude of treatment effect, and robustness of the main PFS analysis results were supported by pre-specified sensitivity analyses.

The results of subgroup analyses of PFS consistently favour the ramucirumab+FOLFIRI arm. This was also observed for patients with time from bevacizumab first dose to disease progression <3 months, although the effect size suggested a small benefit (HR 0.952 (CI 0.646-1.404). Also, in contrast to the subgroup result for OS, a significant effect on PFS was also observed for patients recruited in Europe (HR 0.804; CI 0.666-0.971).

No difference in the ORR was observed between the two treatment arms.

Regarding quality of life, a shorter time to deterioration of 1.5 months in global health was observed for patients in the ramucirumab plus FOLFIRI arm as assed by the EORTC QLC-30. This observation was confirmed by EQ5D assessments.

2.4.4. Conclusions on the clinical efficacy

The OS results showed a statistically significant improvement in OS for the ramucirumab + FOLFIRI arm resulting in a 1.6-month longer median survival (13.3 months vs. 11.7 months). The OS benefit was supported by modest but statistically significant improvement in median PFS by 1.2 months.

A causal link between lack of efficacy with any of the subgroups assessed is difficult to establish. This raises the question whether benefit can be increased by further selection of the patients, in particular on the basis of biomarkers.

Due to the above uncertainties with respect to the efficacy of Cyramza in certain sub-populations, the CHMP considers that following measures necessary to address issues related to efficacy:

Post authorisation efficacy study (PAES): In order to investigate the potential correlation between biomarker measures (VEGF-C. VEGF-D, sVEGFR1, sVEGFR2 and sVEGFR3 from plasma, VEGFR2 IHC, additional KRAS, NRAS and BRAF mutations) and efficacy outcome (PFS, OS), the MAH should submit the results of a biomarker assay from the RAISE translational research population.

- Correlation with VEGF-C. VEGF-D, sVEGFR1, sVEGFR2 and sVEGFR3 from plasma, VEGFR2 IHC will be submitted by 30 June 2016

- Correlation with additional KRAS, NRAS and BRAF mutations will be submitted by 30 September 2016

2.5. Clinical safety

Introduction

In the second line treatment of advanced gastric carcinoma or gastro-oesophageal junction adenocarcinoma, the overall safety profile of ramucirumab (Cyramza) monotherapy was more or less consistent across studies and in line with other agents targeting inhibition of the VEGF/VEGFR axis, Hypertension, proteinuria, gastrointestinal symptoms being most prominent, whereas haematological toxicities were limited. In combination with paclitaxel, a higher incidence of fatigue, leukopenia, neutropenia, neuropathy, abdominal pain, diarrhoea, peripheral oedema, hypertension, epistaxis and stomatitis were observed. AE grade ≥3 events, occurring in at least 10% of patients and at a higher rate in the ramucirumab plus paclitaxel arm were leukopenia, neutropenia, hypertension and fatigue in the ramucirumab plus paclitaxel arm as compared to paclitaxel.

Patient exposure

Table 21. Completed Studies Included in the Summary of Clinical Safety

Study[a]	Tumor Type	Phase	Treatment Arms	Ramucirumab Dose Regimen	Safety Population Ram-treated Patients (vs. Comparator)
Pivotal Study					
RAISE; I4T-MC-JVBB (JVBB; IMCL CP12-0920)	mCRC 2nd-line	3	Ram + FOLFIRI vs. Placebo + FOLFIRI	8 mg/kg every 2 wks	529 (vs. 528)
Additional New Studies Included in this SCS					
I4T-IE-JVCB (JVCB; IMCL CP12-1033)	Solid Tumors (DDI)	2	Cycle 1: FOLFIRI Cycle 2+: Ram + FOLFIRI	8 mg/kg every 2 wks	25[b]
I4Y-IE-JCDB[c] (JCDB; IMCL CP20-0801)	mCRC 2nd-line	2	Ram + mFOLFOX-6 mFOLFOX-6	8 mg/kg every 2 wks	52 (vs. 49)
REACH; I4T-IE-JVBF[d] (JVBF; IMCL CP12-0919)	HCC 2nd-line	3	Ram + BSC Placebo + BSC	8 mg/kg every 2 wks	Safety population: 277 (vs. 276) CP-B Safety population: 40 (vs. 37)
Previously Submitted Studies Included in this SCS (will not be resubmitted)					
I4T-IE-JVBY (JVBY; IMCL CP12-1029)	mCRC 2nd-line	1b	Ram + FOLFIRI	8 mg/kg every 2 wks	6
I4T-IE-JVBH (JVBH; IMCL CP12-0709)	mCRC 1st-Line	2	Ram + mFOLFOX-6	8 mg/kg every 2 wks	48

Abbreviations: BSC = best supportive care; CP-B = Child-Pugh Class B; DDI = drug-drug interaction; HCC = hepatocellular carcinoma; IMCL = ImClone; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; mCRC = metastatic colorectal carcinoma; mFOLFOX-6 = modified FOLFOX-6 (folinic acid, 5-fluorouracil, oxaliplatin); N = number of patients in the safety population; Ram = ramucirumab; SCS = summary of clinical safety; wk = week.

[a] Primary analysis database lock on or before 22 August 2014.

[b] The safety population comprised all patients who received *either* ramucirumab or FOLFIRI; however, ramucirumab was not started until Cycle 2. Of the 29 patients who received study treatment, 4 patients discontinued before Cycle 2; thus, 25 patients received ramucirumab.

[c] Only ramucirumab plus mFOLFOX-6 or mFOLFOX-6 only arms included.

[d] The evaluation of safety was conducted primarily in the population of patients with Child-Pugh Class A score, defined as the Safety population. Exploratory safety analyses were conducted in the CP-B Safety population. Further details regarding study design for REACH are provided in Section 2.7.4.0.2.5.1.

Overall, 660 patients with mCRC were exposed to ramucirumab in company-sponsored trials at a dose of 8 mg/kg every 2 wks, 529 of which participated in the pivotal RAISE study (Table 21), in which treatment with ramucirumab was combined with FOLFIRI. In addition to a number of small phase 2 trials including patients with metastatic colorectal cancer, the Applicant included patients with hepatocellular carcinoma participating in a phase 3 trial in the safety database. Previously conducted studies, including the pivotal studies conducted in patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma and in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), were not included in the safety database for unknown reasons.

Of 1072 patients randomized to treatment in RAISE, 1057 (98.6%) received at least 1 dose of any study therapy (529 of 536 patients randomized to receive ramucirumab plus FOLFIRI and 528 of 536

randomized to receive placebo plus FOLFIRI). Fifteen randomized patients (1.4%) did not receive any treatment (8 [1.5%] patients in the ramucirumab plus FOLFIRI arm and 7 [1.3%] patients in the placebo plus FOLFIRI arm, for reasons listed in Figure 4). Thus, the safety population consisted of 529 patients in the ramucirumab plus FOLFIRI arm and 528 patients in the placebo plus FOLFIRI arm. The median duration of treatment (all components of study treatment) received was similar between treatment arms (20.4 weeks for the ramucirumab plus FOLFIRI arm with a median of 9.0 infusions received vs. 18.3 weeks for the placebo plus FOLFIRI arm with a median of 8.0 infusions received (Table 22).

Table 22. Extent of Exposure (Ramucirumab or Placebo), RAISE

Parameter	Ramucirumab + FOLFIRI N = 529	Placebo + FOLFIRI N = 528
Duration of Treatment (weeks)		
Mean (SD)	25.9 (21.9)	23.0 (19.1)
Median	20.4	18.3
Range	2-167	2-112
Infusions Received		
Mean (SD)	11.1 (9.7)	10.4 (8.7)
Median	9.0	8.0
Range	1-69	1-48
	Ramucirumab	**Placebo**
Duration of Treatment (weeks)		
Mean (SD)	24.9 (21.7)	22.4 (19.1)
Median	19.0	18.0
Range	2-167	2-112
Infusions Received		
Mean (SD)	10.7 (9.5)	10.2 (8.7)
Median	8.0	8.0
Range	1-68	1-48
Cumulative Dose (mg/kg)[a]		
Mean (SD)	84.51 (75.24)	80.73 (68.7)
Median	65.18	64.0
Range	3.8-514.7	7.9-384.7
Dose Intensity (weekly) (mg/kg/week)[b]		
Mean (SD)	3.4 (0.55)	3.7 (0.41)
Median	3.5	3.8
Range	1.5-4.3	1.4-4.3
Relative Dose Intensity (%)		
Mean (SD)	86.0 (13.65)	91.2 (10.14)
Median	88.2	93.8
Range	37.3-108.3	35.6-107.2

Abbreviations: FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; N = total population size; SD = standard deviation.

a Placebo was administered at a volume equivalent to a dose of 8 mg/kg on Day 1 of every 2-week cycle.

b Weekly Dose Intensity is calculated as cumulative dose/component-specific duration of treatment in weeks, where component-specific duration = (date of last dose prior to discontinuing the component - date of first dose of the component + 14)/7.

Note: Dose intensity and cumulative dose calculations for ramucirumab are based on mg/kg/week dosing guidelines. Dose intensity and cumulative dose calculations for placebo are based on the volume of placebo administered.

As of the data cutoff date (17 July 2014), 33 patients (17 patients [3.2%] in the ramucirumab plus FOLFIRI arm and 16 patients [3.0%] in the placebo plus FOLFIRI arm) were receiving study treatment. The majority of patients discontinued treatment due to disease progression (63.1% in the ramucirumab plus FOLFIRI arm; 77.8% in the placebo plus FOLFIRI arm). The percentage of patients who discontinued treatment (any study drug) due to AEs was 29.1% for the ramucirumab plus FOLFIRI arm and 13.3% for the placebo plus FOLFIRI arm.

Adverse events

Table 23. Summary of Treatment-Emergent Adverse Events, RAISE

Adverse Event[a]	Ramucirumab + FOLFIRI N = 529 n (%)	Placebo + FOLFIRI N = 528 n (%)
Patients with ≥1 TEAE	522 (98.7)	519 (98.3)
Patients with ≥1 TE-SAE	189 (35.7)	164 (31.1)
Patients with ≥1 TEAE Grade ≥3	418 (79.0)	329 (62.3)
Patients with ≥1 TEAE leading to discontinuation of any study drug[b]	154 (29.1)	70 (13.3)
Ramucirumab/Placebo discontinuation	19 (3.6)	7 (1.3)
FOLFIRI discontinuation	142 (26.8)	66 (12.5)
Patients with a TEAE leading to death[c]	21 (4.0)	19 (3.6)
Patients with TEAEs with outcome of death up to 30 days after last dose of study drug	14 (2.6)	18 (3.4)

Abbreviations: AE = adverse event; CSR = Clinical Study Report; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; N = total population size; n = number of patients; TEAE = treatment-emergent adverse event; TE-SAE = treatment-emergent serious adverse event.

a Patients may be counted in more than one category.

b Any study drug = ramucirumab/placebo or any component of FOLFIRI.

c Includes deaths that occurred up to 30 days after the last dose of study drug.

Table 24. Treatment-Emergent Adverse Events Occurring in ≥10% of Patients in the Ramucirumab plus FOLFIRI Arm, by MedDRA Preferred Term - Any Grade and Grade ≥3, RAISE.

	Regardless of Causality			
	Ramucirumab + FOLFIRI N = 529 n (%)		Placebo + FOLFIRI N = 528 n (%)	
Preferred Term	Any Grade	≥ Grade 3	Any Grade	≥ Grade 3
Patients with ≥1 TEAE	**522 (98.7)**	**418 (79.0)**	**519 (98.3)**	**329 (62.3)**
Diarrhoea	316 (59.7)	57 (10.8)	271 (51.3)	51 (9.7)
Nausea	262 (49.5)	13 (2.5)	271 (51.3)	14 (2.7)
Fatigue	247 (46.7)	42 (7.9)	219 (41.5)	27 (5.1)
Decreased appetite	198 (37.4)	13 (2.5)	144 (27.3)	10 (1.9)
Neutropenia	188 (35.5)	115 (21.7)	131 (24.8)	59 (11.2)
Epistaxis	177 (33.5)	0 (0.0)	79 (15.0)	0 (0.0)
Stomatitis	163 (30.8)	20 (3.8)	110 (20.8)	12 (2.3)
Alopecia	155 (29.3)	0 (0.0)	165 (31.3)	0 (0.0)
Vomiting	154 (29.1)	15 (2.8)	144 (27.3)	13 (2.5)
Constipation	151 (28.5)	5 (0.9)	120 (22.7)	8 (1.5)
Neutrophil count decreased	137 (25.9)	92 (17.4)	115 (21.8)	64 (12.1)
Hypertension	136 (25.7)	57 (10.8)	45 (8.5)	15 (2.8)
Abdominal pain	118 (22.3)	16 (3.0)	112 (21.2)	18 (3.4)
Oedema peripheral	108 (20.4)	1 (0.2)	48 (9.1)	0 (0.0)
Mucosal inflammation	92 (17.4)	14 (2.6)	52 (9.8)	9 (1.7)
Proteinuria	89 (16.8)	15 (2.8)	24 (4.5)	1 (0.2)
Anaemia	84 (15.9)	8 (1.5)	109 (20.6)	18 (3.4)
Pyrexia	80 (15.1)	2 (0.4)	56 (10.6)	1 (0.2)
Headache	78 (14.7)	3 (0.6)	41 (7.8)	0 (0.0)
Platelet count decreased	78 (14.7)	10 (1.9)	35 (6.6)	2 (0.4)
Asthenia	77 (14.6)	20 (3.8)	63 (11.9)	14 (2.7)
Thrombocytopenia	77 (14.6)	7 (1.3)	39 (7.4)	2 (0.4)
Weight decreased	69 (13.0)	2 (0.4)	40 (7.6)	0 (0.0)
Palmar-plantar-erythrodysaesthesia syndrome	68 (12.9)	6 (1.1)	29 (5.5)	2 (0.4)
Cough	66 (12.5)	0 (0.0)	42 (8.0)	2 (0.4)
Dyspnoea	53 (10.0)	4 (0.8)	48 (9.1)	6 (1.1)

Abbreviations: FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; MedDRA = Medical Dictionary for Regulatory Activities; N = total population; n = number of patients in category; TEAE = treatment-emergent adverse event.
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Table 25. Differences in treatment-Emergent Adverse Events Occurring in ≥10% of Patients in the Ramucirumab plus FOLFIRI Arm, by MedDRA Preferred Term - Any Grade and Grade ≥3, RAISE.

TEAE	Difference in % incidence any grade AE between ramucirumab/ FOLFIRI arm and placebo/ FOLFIRI arm*	Difference in % incidence ≥grade 3 AE between ramucirumab/ FOLFIRI arm and placebo/ FOLFIRI arm*
epistaxis	+19 (33.5/15.0)	= (0/0)
hypertension	+17 (25.7/8.5)	+8 (10.8/2.8)
proteinuria	+12 (16.8/4.5)	+3 (2.8/0.2)
Oedema peripheral	+11 (20.4/9.1)	= (0.2/0.0)
stomatitis	+10 (30.8/20.8)	+2 (3.8/2.3)
Decreased appetite	+10 (37.4/27.3)	+1 (2.5/1.9)
neutropenia	+10 (35.5/24.8)	+11 (21.7/11.2)
thrombocytopenia	+8 (14.6/7.4)	+1 (1.3/0.4)
diarrhoea	+8 (59.7/51.3)	+1 (10.8/9.7)
Platelet count decreased	+8 (14.7/6.6)	+2 (1.9/0.4)
Palmar-plantar-erythrodysesthesia (PPE)	+7 (12.9/5.5)	+1 (1.1/0.4)
headache	+7 (14.7/7.8)	= (0.4/0.2)
Mucosal inflammation	+7 (17.4/9.8)	-1 (2.6/1.7)
constipation	+6 (28.5/22.7)	-1 (0.9/1.5)
Weight decreased	+5 13.0/7.6)	= (0.4/0.0)

fatigue	+5 (46.7/41.5)	+3 (7.9/5.1)
cough	+5 12.5/8.0	= (0.0/0.4)
Neutrophil count decreased	+4 (25.9/21.8)	+5 (17.4/12.1)
pyrexia	+4 (15.1/10.6)	= (0.4/0.2)
pyrexia	+4 (15.1/10.6)	= (0.4/0.2)
Alopecia	+2 (29.3/31.3)	= (0/0)
vomiting	+2 (29.1/27.3)	= (2.8/2.5)
Abdominal pain	+1 (22.3/21.2)	= (3.0/3.4)
asthenia	+3 (14.6/11.9)	+1 (3.8/2.7)
nausea	-2 (49.5/51.3)	= (2.5/2.7)
anaemia	-5 (15.9/20.6)	-1 (1.5/3.4)
dyspnoea	-8 (1.0/9.1)	= (0.8/1.1)

* more in ramucirumab/FOLFIRI arm; - more in placebo/FOLFIRI arm; = no difference

Adverse events of special interest

The AESIs are potentially associated with other agents that inhibit VEFG- or VEGF Receptor 2-mediated angiogenesis, or that were observed in preclinical or earlier clinical studies of ramucirumab. The following AEs are considered to be AESIs for ramucirumab: IRRs, hypertension, proteinuria, ATEs, VTEs, bleeding/hemorrhagic events, GI perforation, CHF, wound healing complications, fistula, liver failure/liver injury, and reversible posterior leukoencephalopathy syndrome (RPLS).

Hypertension

Both any grade (25.7% vs. 8.5%) and ≥grade 3 hypertension (10.8% vs. 2.8%) occurred more frequently in the ramucirumab+FOLFIRI arm, whereas 62.2% of patients in the ramucirumab+FOLFIRI arm and 54.2% in the placebo+FOLFIRI arm received concomitant treatment with antihypertensives. A total of 22 patients (4.2%) in the ramucirumab+FOLFIRI arm had dose modifications or discontinuations, compared to 1 (0.2% in the placebo arm.

Proteinuria

Treatment-emergent adverse events of proteinuria occurred at a higher incidence in the ramucirumab plus FOLFIRI arm than in the placebo plus FOLFIRI arm (17.0% vs. 4.5%, respectively). The incidence of Grade 3 proteinuria was higher in the ramucirumab plus FOLFIRI arm than the placebo plus FOLFIRI arm (2.8% vs. 0.2%, respectively). Nephrotic syndrome was reported in 3 patients (2 patients with Grade 3 proteinuria and 1 patient with Grade 4 proteinuria [reported as an SAE]), all in the ramucirumab plus FOLFIRI arm.

Nineteen patients (3.6%) in the ramucirumab plus FOLFIRI arm had dose modifications or discontinuations of any study drug due to proteinuria, compared to 6 patients (1.1%) in the placebo plus FOLFIRI arm. Of these, 8 patients (1.5%) in the ramucirumab plus FOLFIRI arm and 2 patients (0.4%) in the placebo plus FOLFIRI arm discontinued any study drug due to a TEAE of proteinuria.

Independent of treatment arm, a higher incidence of any-grade proteinuria was observed in Asian patients than in White patients. The incidence of any grade proteinuria in Asian patients was 38.2% in the ramucirumab plus FOLFIRI arm versus 10.7% in the placebo plus FOLFIRI arm. The incidence of any grade proteinuria in White patients was 11.3% in the ramucirumab plus FOLFIRI arm versus 2.7% in the placebo plus FOLFIRI arm. This higher incidence of proteinuria in Asian patients compared to White patients was primarily due to Grade 1 and Grade 2 events. The incidence of Grade 3 proteinuria was lower in both groups (6.4% vs. 0 for Asian patients and 2.0% vs. 0.2% for White patients for ramucirumab plus FOLFIRI vs. placebo plus FOLFIRI treatment arms, respectively). Of note, there

were 3 events of nephrotic syndrome reported in Asian patients, of which 1 event was reported as Grade 4 (although not defined in CTCAE V4.0), in the ramucirumab plus FOLFIRI arm. There were no events of nephrotic syndrome reported in White patients in the ramucirumab plus FOLFIRI arm.

Neutropenia/Febrile Neutropenia and Infection

Neutropenia was among the most frequently reported AEs in both treatment arms, with a higher any-grade incidence observed in the ramucirumab plus FOLFIRI arm (311 patients [58.8%] vs. 241 patients [45.6%], respectively). The majority of neutropenia TEAEs, regardless of treatment arm, were Grade 3 or Grade 4 events. The incidence of Grade 3 neutropenia was higher in the ramucirumab plus FOLFIRI arm than in the placebo plus FOLFIRI arm (28.2% vs. 14.6%, respectively). The incidence of Grade 4 was similar between the ramucirumab plus FOLFIRI arm and the placebo plus FOLFIRI arm (10.2% vs. 8.7%, respectively). There were no Grade 5 events. Treatment-emergent adverse events under the SOC of infections and infestations, any grade, were reported for 37.4% of patients in the ramucirumab plus FOLFIRI arm and 29.2% of patients in the placebo plus FOLFIRI arm. The incidences of Grade ≥3 infection events were 8.3% in the ramucirumab plus FOLFIRI arm and 7.4% in the placebo plus FOLFIRI arm. The percentage of patients with a hospitalization due to febrile neutropenia was also low in both treatment arms (2.3% in the ramucirumab plus FOLFIRI arm vs. 1.5% in the placebo plus FOLFIRI arm), suggesting that the clinical impact on safety as result of the increased rate of neutropenia in the ramucirumab plus FOLFIRI arm was limited. However, the proportion of patients discontinuing any study drug due to neutrophil count decreased or neutropenia was higher in the ramucirumab+FOLFIRI arm (7.0% vs. 3.4% and 5.5% vs. 1.9%, respectively).

Thrombocytopenia

The incidence of thrombocytopenia was higher in the ramucirumab+FOLFIRI arm (28.4% vs. 13.6%), although the incidence of grade≥3 thrombocytopenia was rather low (3.0% vs. 0.8%). More dose adjustments and discontinuations occurred in the ramucirumab+FOLFIRI arm. The frequency of patients experiencing any drug dose adjustment was 8.5% in the ramucirumab group vs. 3.2% in the placebo group (regardless of causality).

Infusion related reactions (IRR)

Any-grade IRR was reported for 31 (5.9%) patients in the ramucirumab plus FOLFIRI arm and 16 (3.0%) patients in the placebo plus FOLFIRI arm. Four patients (0.8%) experienced Grade 3 events in the ramucirumab plus FOLFIRI arm and 2 patients (0.4%) experienced Grade 3 IRR in the placebo plus FOLFIRI arm. There were no patients with Grade 4 or Grade 5 IRRs in either treatment arm.

Bleeding/Haemorrhage Events

In RAISE, a higher percentage of patients experienced bleeding events (any grade) in the ramucirumab plus FOLFIRI arm than the placebo plus FOLFIRI arm (43.9% vs. 22.7%, respectively). The incidence of Grade 3 or higher bleeding events was low in both treatment arms (2.5% vs. 1.7%). The majority of bleeding events in the ramucirumab plus FOLFIRI arm and the placebo plus FOLFIRI arm were epistaxis (33.5% and 15.0%, respectively). There were no Grade ≥3 epistaxis events in either arm.

A higher incidence of any grade GI haemorrhage events occurred in the ramucirumab plus FOLFIRI arm than the placebo plus FOLFIRI arm (12.3% vs. 6.8%, respectively). The incidence of severe (Grade ≥3) GI haemorrhage events was low in both treatment arms (1.9% in the ramucirumab plus FOLFIRI arm and 1.1% in the placebo plus FOLFIRI arm). Fourteen patients (2.6%) in the

ramucirumab plus FOLFIRI arm and 6 patients (1.1%) in the placebo plus FOLFIRI arm had dose modifications or discontinuations (referred to as dose adjustments in the table) of any drug due to any bleeding/ hemorrhage events.

Table 26. Gastrointestinal Haemorrhage Events, Safety Population, RAISE study

	Ramucirumab + FOLFIRI N = 529 n (%)				Placebo + FOLFIRI N = 528 n (%)			
Pooled AE Term Preferred Term	Any Grade	Gr 3	Gr 4	Gr 5	Any Grade	Gr 3	Gr 4	Gr 5
GI haemorrhage events	65 (12.3)	6 (1.1)	1 (0.2)	3 (0.6)	36 (6.8)	3 (0.6)	2 (0.4)	1 (0.2)
Anal haemorrhage	11 (2.1)	1 (0.2)	0	0	3 (0.6)	0	0	0
Anal ulcer haemorrhage	1 (0.2)	0	0	0	0	0	0	0
Diarrhea haemorrhagic	1 (0.2)	0	0	0	1 (0.2)	0	0	0
Gastric haemorrhage	2 (0.4)	0	0	1 (0.2)	1 (0.2)	0	0	0
GI haemorrhage	1 (0.2)	0	0	0	0	0	0	0
Haematemesis	4 (0.8)	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0	0
Haematochezia	3 (0.6)	0	0	0	5 (0.9)	0	0	0
Haemorrhoidal haemorrhage	11 (2.1)	1 (0.2)	0	0	3 (0.6)	1 (0.2)	0	0
Intestinal haemorrhage	0	0	0	0	1 (0.2)	0	1 (0.2)	0
Large intestinal haemorrhage	6 (1.1)	0	0	1 (0.2)	3 (0.6)	0	0	1 (0.2)
Lower GI haemorrhage	2 (0.4)	1 (0.2)	0	0	4 (0.8)	2 (0.4)	0	0
Melaena	2 (0.4)	0	0	0	0	0	0	0
Oesophageal varices haemorrhage	1 (0.2)	1 (0.2)	0	0	0	0	0	0
Rectal haemorrhage	21 (4.0)	0	0	0	15 (2.8)	0	1 (0.2)	0
Small intestine haemorrhage	2 (0.4)	1 (0.2)	0	0	0	0	0	0
Ulcer haemorrhage	1 (0.2)	1 (0.2)	0	0	1 (0.2)	0	0	0

Abbreviations: AE = adverse event; FOLFIRI = irinotecan, folinic acid and 5-fluorouracil; GI = gastrointestinal; Gr = grade; MedDRA = Medical Dictionary for Regulatory Activities; N = total population; n = number of patients in category.
MedDRA Version 17.0.

The overall incidence of GI perforation in the study was low in both treatment arms (. Grade 3 or higher GI perforation events were identified in both treatment arms (see Table 27).

Table 27. Gastrointestinal Perforations, study RAISE

Pooled AE Term Preferred Term	Ramucirumab + FOLFIRI N = 529 n (%)				Placebo + FOLFIRI N = 528 n (%)			
	Any Gr.	Gr. 3	Gr.4	Gr. 5	Any Gr.	Gr. 3	Gr. 4	Gr. 5
Gastrointestinal Perforation	**9 (1.7)**	**2 (0.4)**	**3 (0.6)**	**4 (0.8)**	**3 (0.6)**	**2 (0.4)**	**1 (0.2)**	**0**
GI perforation	1 (0.2)	0	1 (0.2)	0	0	0	0	0
Intestinal perforation	3 (0.6)	1 (0.2)	0	2 (0.4)	0	0	0	0
Large Intestine perforation	4 (0.8)	1 (0.2)	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)	0	0
Rectal perforation	0	0	0	0	1 (0.2)	1 (0.2)	0	0
Small Intestine perforation	1 (0.2)	0	0	1 (0.2)	1 (0.2)	0	1 (0.2)	0

Abbreviations: AE = adverse event; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; GI = gastrointestinal; Gr. = grade; MedDRA = Medical Dictionary for Regulatory Activities; N = total population; n = number of patients in category.
MedDRA Version 17.0.

In the Phase 2 combination studies, low-grade epistaxis and other bleeding events were observed in Study JVCB and in Study JVBH. One patient in Study JVBH had a Grade 3 bleeding/haemorrhage event. In Study JCDB, 24 of 52 patients in the ramucirumab plus mFOLFOX-6 arm had Grade 1-2 events and 1 patient had Grade 3 bleeding/haemorrhage events. In the mFOLFOX-6 only arm, 9 patients had bleeding/haemorrhage events (all Grade 1-2 events). No patients in any of the Phase 2 combination studies had Grade 4 or Grade 5 bleeding/haemorrhage events. In the Phase 2 combination studies, only in study JCDB, one patient in the mFOLFOX-6 only arm had a Grade 1-2 GI perforation.

In REACH, any grade bleeding events were observed at a higher incidence in the ramucirumab arm than the placebo arm; however, the incidence of Grade ≥3 events was similar between treatment arms. The most frequently reported bleeding event in the ramucirumab arm was epistaxis, and its incidence was higher than in the placebo arm. No Grade ≥3 epistaxis events occurred in either treatment arm. In patients with chronic liver disease, there is a potential increased risk of GI haemorrhage. The ramucirumab and placebo arms were similar in the incidence of GI haemorrhage events of any grade or Grade ≥3. In the ramucirumab arm, 1 patient had a Grade 4 bleeding event (GI haemorrhage) and 1 patient had a Grade 5 bleeding event (oesophageal varices haemorrhage). In the placebo arm, 1 patient had a Grade 5 bleeding event (oesophageal varices haemorrhage). No events of GI perforation were observed.

Liver failure/liver injury

In RAISE, the overall incidence of any-grade liver-related events (laboratory and clinical) was similar between treatment arms (11.5% vs. 9.5%). The incidence of Grade ≥3 liver failure/liver injury, including clinical and laboratory events, was higher in the ramucirumab+FOLFIRI arm (4.9% vs. 3.9%). In the Phase 2 combination studies, 2 of 25 patients in Study JVCB had liver failure/liver injury events (both reported as Grade 1-2). In Study JVBH, 6 of 48 patients in the ramucirumab plus mFOLFOX-6 arm had liver failure/liver injury events. Two patients had Grade 3 events and 1 patient had a Grade 4 liver failure/liver injury event (gamma-glutamyltransferase increased). In Study JCDB, 7 of 52 patients in the ramucirumab plus mFOLFOX-6 arm had Grade 1-2 events and 1 patient had a Grade 3 liver failure/liver injury event (aspartate aminotransferase increased; blood bilirubin increased). In the mFOLFOX-6 only arm, 5 patients had Grade 1-2 events and 2 patients had a Grade 3 liver failure/liver injury event (AST increased; blood bilirubin increased). In REACH, the incidence of any-grade clinical and laboratory liver failure/liver injury events was higher in the ramucirumab arm

than in the placebo arm; however, when adjusted for duration of exposure to study treatment, there was no difference between treatment arms. There was no difference in the incidence of Grade 3-4 liver failure/injury in the ramucirumab arm compared with the placebo arm. Five of 140 patients in the ramucirumab arm and 3 of 103 patients in the placebo arm had a Grade 5 liver failure/injury event.

Fistula

In RAISE, the overall incidence of fistula was low in both treatment arms (0.8% vs. 0.4%) and there were no Grade ≥3 events reported in either treatment arm. No events of fistula were observed in the Phase 2 studies (Studies JVCB, JVBH, and JCDB) or in the Phase 3 study (REACH).

Wound Healing Complications

In RAISE, the overall incidence of wound healing complications was low in both treatment arms (1.3% vs. 0.2%). All but one wound healing complication event (Grade 3 wound dehiscence in the ramucirumab plus FOLFIRI arm) were Grade 1-2. In the Phase 2 combination studies, no events of wound healing were observed in Studies JVCB and JCDB. In Study JVBH, 1 patient treated with ramucirumab plus mFOLFOX-6 arm had Grade 1-2 impaired healing.

Adverse drug reactions

Table 28. ADRs reported in ≥ 5 % of ramucirumab treated patients in RAISE

System organ class	Frequency	ADR	Cyramza plus FOLFIRI (N=529)		Placebo plus FOLFIRI (N=528)	
			All grades toxicity (%)	Grade ≥3 toxicity (%)	All grades toxicity (%)	Grade ≥3 toxicity (%)
Blood and lymphatic system disorders	Very common	Neutropenia	58.8	38.4	45.6.	23.3
	Very common	Thrombocytopenia	28.4	3.0	13.6	0.8
Metabolism and nutrition disorders	Common	Hypoalbuminaemia	5.9	1.1	1.9	0.0
Vascular disorder	Very common	Hypertension	26.1	11.2	8.5	2.8
Respiratory, thoracic, and mediastinal disorders	Very common	Epistaxis	33.5	0.0	15.0	0.0
Gastrointestinal disorders	Very common	Gastrointestinal haemorrhage events	12.3	1.9	6.8	1.1
	Very common	Stomatitis	30.8	3.8	20.8	2.3

Renal and urinary disorders	Very common	Proteinuria[a]	17.0	3.0	4.5	0.2
Skin and subcutaneous tissue disorders	Very common	Palmar-plantar erthyrodysaesthesia syndrome	12.9	1.1	5.5	0.4
General disorders and administration site disorders	Very common	Peripheral oedema	20.4	0.2	9.1	0.0

[a] Includes cases of nephrotic syndrome.

Serious adverse event/deaths/other significant events

Similar percentages of patients in the ramucirumab plus FOLFIRI arm and the placebo plus FOLFIRI arm, respectively, had any-grade TE-SAEs (35.7% vs. 31.1%) and Grade ≥3 TE-SAEs (30.6% vs. 26.7%). The most frequently reported TE-SAEs in the ramucirumab plus FOLFIRI arm compared to the placebo plus FOLFIRI arm, respectively, were diarrhea (3.6% vs. 3.2%), intestinal obstruction (3.0% vs. 2.5%), and febrile neutropenia (2.8% vs. 1.5%) (Table 28a).

Overall, deaths that occurred while on treatment and up to 30 days after the last dose of study treatment occurred at similar frequency in both treatment arms (4.3% in the ramucirumab plus FOLFIRI arm vs. 5.5% in the placebo plus FOLFIRI arm). The incidence of deaths due to AE was low and similar in the ramucirumab plus FOLFIRI arm and the placebo plus FOLFIRI arm (2.5% vs. 3.4%, respectively). The most common causes of Grade 5 (fatal) TEAEs by SOC were GI disorders (10 in the ramucirumab+F and 4 in the placebo+F group), infections and infestations (4 and 3), and cardiac disorders (1 and 6).

Table 28. Serious Adverse Events Occurring in ≥1% of Patients in the Ramucirumab plus FOLFIRI Arm, by MedDRA Preferred Term, study RAISE

	Regardless of Causality			
	Ramucirumab + FOLFIRI N = 529 n (%)		Placebo + FOLFIRI N = 528 n (%)	
Preferred Term	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Patients with any TE-SAE	189 (35.7)	162 (30.6)	164 (31.1)	141 (26.7)
Diarrhoea	19 (3.6)	16 (3.0)	17 (3.2)	15 (2.8)
Intestinal obstruction	16 (3.0)	14 (2.6)	13 (2.5)	12 (2.3)
Febrile neutropenia	15 (2.8)	15 (2.8)	8 (1.5)	8 (1.5)
Vomiting	12 (2.3)	9 (1.7)	6 (1.1)	5 (0.9)
Pulmonary embolism	10 (1.9)	9 (1.7)	6 (1.1)	6 (1.1)
Abdominal pain	9 (1.7)	6 (1.1)	14 (2.7)	10 (1.9)
Fatigue	8 (1.5)	7 (1.3)	7 (1.3)	6 (1.1)
Neutropenia	8 (1.5)	8 (1.5)	2 (0.4)	2 (0.4)
Decreased appetite	7 (1.3)	6 (1.1)	3 (0.6)	3 (0.6)
Nausea	6 (1.1)	5 (0.9)	5 (0.9)	4 (0.8)
Pneumonia	6 (1.1)	6 (1.1)	6 (1.1)	3 (0.6)

Abbreviations: FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; MedDRA = Medical Dictionary for Regulatory Activities; N = total population; n = number of patients in category; TE-SAE = treatment-emergent serious adverse event.

MedDRA Version 17.0.

Note: Consolidated terms are italicized.

Table 29. Summary of Deaths, RAISE.

	Ramucirumab + FOLFIRI N = 529 n (%)	Placebo + FOLFIRI N = 528 n (%)
All Deaths	369 (69.8)	394 (74.6)
Disease Progression	342 (64.7)	369 (69.9)
Adverse Event[a]	27 (5.1)	25 (4.7)
Deaths Up to 30 Days after Last Dose of Study Drug	23 (4.3)	29 (5.5)
Disease Progression	10 (1.9)	11 (2.1)
Adverse Event	13 (2.5)[b]	18 (3.4)

Abbreviations: AE = adverse event; CRF = case report form; FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; N = total population; n = number of patients in category.

a Derived from the death CRF page and hence includes both treatment-emergent and non-treatment-emergent adverse events.

b One patient in the ramucirumab plus FOLFIRI arm developed thrombotic microangiopathy and intestinal obstruction, and the outcome of these 2 events was death on the AE CRF page. However, 'study disease' was reported as the cause of death on the Death CRF page; thus, this patient was not included in this death table. As a result, N=13 under 'Deaths Up to 30 Days after Last Dose of Study Drug' due to AE compared to N=14 under "Deaths Up to 30 Days after Last Dose of Study Drug" due to AE in the AE summary table (Table 2.7.4A.7).

Laboratory findings

Analysis of the laboratory shift tables indicated that decreases in the neutrophil and platelet counts, and increases in AST, ALT, and bilirubin were observed, consistent with the incidence of neutropenia, thrombocytopenia, and abnormal laboratory terms for the AESI Liver Failure/Liver Injury in the study.

Safety in special populations

Age

A similar proportion of patients with >= 1 TEAE was observed between patients <65 years and patients ≥65 years of age, but more patients ≥65 years had >=grade 3 TEAE (83.7% vs. 68.4%) compared to patients <65 years (75.9% vs. 58.2%).

Adverse events in Asian patients

A higher frequency of ≥grade 3 AEs was observed in Asian compared to white patients (88.2% vs. 76.8%); Most notable were hypertension and neutropenia and proteinuria. The overall incidence of hypertension in Asian patients was higher (39.1%) compared to White patients (22.5%) but similar in the placebo plus FOLFIRI arm (Asian [10.7%] vs. White [8.0%] patients. Independent of treatment arm, a higher incidence of any grade neutropenia (consolidated term) was observed in Asian patients. The incidence of neutropenia any grade in Asian patients in the ramucirumab plus FOLFIRI arm vs. placebo plus FOLFIRI arm was 80.0% vs. 59.2%, respectively. The incidence and magnitude of difference of Grade 3 neutropenia was also higher in Asian (46.4%vs. 26.2%) patients as compared to White (24.0% vs. 11.9%) patients. A higher rate of discontinuations of treatment was also observed in Asian patients (45.5% vs. 21.4%) compared to white patients (25.3% vs. 11.7%). Patients who had a known history or clinical evidence of Gilbert's Syndrome, or was known to have any of the following genotypes: UGT1A1*6/*6, nUGT1A1*28/*28, or UGT1A1*6/*28, known to be related to toxicity for irinotecan in Asian patients, were not eligible for participation in the RAISE study.

Table 30. Summary of Treatment-Emergent Adverse Events in Patients by Race (White, Asian, and Other Patients) RAISE

	White		Asian		Other	
	Ramucirumab + FOLFIRI N = 400 n (%)	Placebo + FOLFIRI N = 402 n (%)	Ramucirumab + FOLFIRI N = 110 n (%)	Placebo + FOLFIRI N = 103 n (%)	Ramucirumab + FOLFIRI N = 17 n (%)	Placebo + FOLFIRI N = 18 n (%)
Patients with ≥1 TEAE	394 (98.5)	393 (97.8)	110 (100.0)	103 (100.0)	16 (94.1)	18 (100.0)
Patients with ≥1 TEAE Grade ≥3	307 (76.8)	246 (61.2)	97 (88.2)	72 (69.9)	12 (70.6)	9 (50.0)
Patients with ≥1 TE-SAE	146 (36.5)	128 (31.8)	37 (33.6)	27 (26.2)	5 (29.4)	7 (38.9)
Patients with TEAEs leading to any study drug dose adjustment[a]	297 (74.3)	250 (62.2)	98 (89.1)	76 (73.8)	12 (70.6)	9 (50.0)
Investigational drug dose adjustment[a]	245 (61.3)	201 (50.0)	86 (78.2)	54 (52.4)	12 (70.6)	8 (44.4)
Chemotherapy dose adjustment[a]	295 (73.8)	242 (60.2)	97 (88.2)	76 (73.8)	11 (64.7)	9 (50.0)
Patients with TEAEs leading to any study drug discontinuation	101 (25.3)	47 (11.7)	50 (45.5)	22 (21.4)	1 (5.9)	1 (5.6)
Investigational drug discontinuation	14 (3.5)	6 (1.5)	5 (4.5)	1 (1.0)	0	0
Chemotherapy discontinuation	92 (23.0)	44 (10.9)	47 (42.7)	21 (20.4)	1 (5.9)	1 (5.6)
Patients with a TEAE with outcome of death	16 (4.0)	16 (4.0)	4 (3.6)	2 (1.9)	0	0
Patients with a TEAE leading to death up to 30 days after last dose of study drug	13 (3.3)	15 (3.7)	1 (0.9)	2 (1.9)	0	0

Abbreviations: FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; N = total population; n = number of patients in category; TEAE = treatment-emergent adverse event; TE-SAE = treatment-emergent serious adverse event.

[a] Includes dose delays, reductions, omissions, and discontinuations.

Table 31. Efficacy subgroup results by race.

	Overall Survival			Progression-Free Survival		
	HR	Log-rank p-value	Interaction p-value	HR	Log-rank p-value	Interacti p-value
White (n=815)	0.855	0.0569	0.0755	0.808	0.0043	0.0128
Asian (n=214)	0.957	0.7938		0.874	0.3454	
Other (n=36)	0.333	0.0056		0.300	0.0022	

Abbreviations: HR = hazard ratio; n = number of patients.

Discontinuation due to adverse events

As noted above, the percentage of patients who experienced at least 1 TEAE leading to discontinuation of any study drug was higher in the ramucirumab + FOLFIRI arm, although FOLFIRI was usually discontinued and ramucirumab rarely (Table 23).

Table 32. Adverse Events Leading to Discontinuations of Study Therapy Occurring in ≥1% of Patients in the Ramucirumab plus FOLFIRI arm RAISE

	Ramucirumab + FOLFIRI N = 529 n (%)	Placebo + FOLFIRI N = 528 n (%)
Patients with any TEAE leading to discontinuation of:		
Any study drug	154 (29.1)	70 (13.3)
Ramucirumab/placebo	19 (3.6)	7 (1.3)
FOLFIRI	142 (26.8)	66 (12.5)
TEAEs leading to any study drug discontinuation		
Neutropenia	66 (12.5)	28 (5.3)
Thrombocytopenia	22 (4.2)	4 (0.8)
Diarrhoea	12 (2.3)	7 (1.3)
Stomatitis	12 (2.3)	6 (1.1)
Mucosal inflammation	10 (1.9)	3 (0.6)
Proteinuria	8 (1.5)	2 (0.4)
TEAEs leading to ramucirumab/placebo discontinuation		
Proteinuria	8 (1.5)	1 (0.2)
TEAEs leading to FOLFIRI discontinuation		
Neutropenia	66 (12.5)	28 (5.3)
Thrombocytopenia	22 (4.2)	4 (0.8)
Diarrhoea	12 (2.3)	7 (1.3)
Stomatitis	12 (2.3)	6 (1.1)
Mucosal inflammation	10 (1.9)	3 (0.6)

Abbreviations: FOLFIRI = irinotecan, folinic acid, and 5-fluorouracil; MedDRA = Medical Dictionary for Regulatory Activities; N = total population; n = number of patients in category; TEAE = treatment-emergent adverse event.
MedDRA Version 17.0.
Note: Consolidated terms are italicized.

2.5.1. Discussion on clinical safety

The presented safety database included few small phase 2 studies in patients with mCRC and the pivotal RAISE study. It should be noted that almost all patients in the pivotal study received another VEGF inhibitor in the 1st line (bevacizumab) that has led to a pre-selection of patients favouring the safety of ramucirumab. This reflects the applied indication (see SmPC section 4.1).

In the RAISE study, the median duration of treatment (all components of study treatment) received was 20.4 weeks for the ramucirumab plus FOLFIRI arm and 18.3 weeks for the placebo+FOLFIRI arm.

Treatment with ramucirumab+ FOLFIRI resulted in a similar frequency of patients with ≥1 TEAE. However, a higher frequency of Grade ≥3 TEAEs was observed (79.0% vs. 62.3%, respectively). Also, the percentage of patients who experienced at least 1 TEAE leading to discontinuation of any study drug was higher in the ram+FOLFIRI arm (29.1% vs. 13.3%), although FOLFIRI was usually discontinued and ramucirumab rarely.

Overall, the most common adverse reactions observed in ramucirumab-treated patients were diarrhoea (59.7%), nausea (49.5%), fatigue (46.7%), decreased appetite (37.4%), neutropenia (35.5%), epistaxis (33.5%) and stomatitis (30.8%). The most common ≥grade 3 AEs were neutropenia (21.7%), neutrophil count decreased (17.4%), diarrhoea (10.8%) and hypertension (10.8%).

The most notable adverse events occurring at a higher frequency compared to the placebo+FOLFIRI arm were epistaxis (+19%), hypertension (+17%), proteinuria (+12%), peripheral oedema (+11%), stomatitis (+10%), decreased appetite (+10%). Neutropenia (+10%) and hypertension (+8%) were the most notable ≥grade 3 AEs occurring with a higher frequency in the ramucirumab+FOLFIRI arm.

This toxicity profile is comparable with that observed in the pivotal study supporting marketing authorization of Cyramza for advanced gastric cancer in combination with paclitaxel, although the difference in discontinuations due to adverse events was smaller (31.2% vs. 24.3%) and in the pivotal study submitted to obtain marketing authorization for non-small cell lung cancer in combination with docetaxel (9.3% vs. 5.2%). An AE with a substantially higher frequency (+7%), not previously reported with ramucirumab use was Palmar-plantar-erythrodysesthesia (PPE).

It is noted that a substantially more favourable toxicity profile was observed when ramucirumab was used as monotherapy in the REGARD trial, where the frequency of neutropenia amounted to only 3.8%.

The incidence of serious related AEs, such as gastrointestinal bleeding events (12.3% vs. 6.8% for any grade; 1.9% vs. 1.2% for ≥grade 3), GI perforations (9 [1.7%] vs. 3 [0.6%] ≥grade 3 AE, of which 4 [0.8%] vs. 0 were grade 5 events) and fistula (4 [0.8%] vs 2 [0.4%] for any grade and no ≥grade 3 AE observed), was also increased in the ramucirumab+ FOLFIRI arm. The incidence of Grade 3 neutropenia was higher in the ramucirumab plus FOLFIRI arm than in the placebo plus FOLFIRI arm (28.2% vs. 14.6%, respectively) and a higher frequency of treatment-emergent adverse events under the SOC of infections and infestations, any grade, were reported in the ramucirumab plus FOLFIRI arm (37.4% vs. 29.2%), although the percentage of patients with a hospitalization due to febrile neutropenia was low in both treatment arms (2.3% vs. 1.5%). Nonetheless, the proportion of patients discontinuing any study drug due to neutropenia was higher in the ramucirumab+FOLFIRI arm (12.5% vs. 5.3%).

Ramucirumab is an antiangiogenic therapy and may increase the risk of gastrointestinal perforations. Cases of gastrointestinal perforation have been reported in patients treated with ramucirumab in study RAISE including four lethal perforations. Severe gastrointestinal haemorrhage, including fatal events, were also reported in patients with mCRC treated with ramucirumab in combination with FOLFIRI. These events are adequately covered in the current SmPC of Cyramza (see sections 4.2, 4.4 and 4.8).

Stomatitis was reported in 30.8% in the ramucirumab arm versus 20.8% in the placebo arm. The SmPC has been revised to reflect that an increased incidence of stomatitis was reported in patients receiving ramucirumab in combination with chemotherapy as compared to patients treated with placebo plus chemotherapy. Symptomatic treatment should be instituted promptly if stomatitis occurs (see SmPC section 4.4).

The proportion of patients discontinuing treatment due to any AE was also substantially higher in the ramucirumab+FOLFIRI arm (29.1% vs. 13.3%), suggesting limited tolerability of the study treatment, although FOLFIRI was generally discontinued rather than ramucirumab. Although the toxicity of the combination may be managed by adapting the dose and content of the FOLFIRI treatment or even discontinuation, there is an increase in drop-outs in the ramucirumab arm. Posology adjustments for ramucirumab are already included in section 4.2 of the SmPC. In addition, dose reductions for individual components of FOLFIRI may be made for specific toxicities. Dose modifications of each component of FOLFIRI should be made independently and are provided in Table 4 of the SmPC. Table 5 of the SmPC provides details of dose delays or dose reductions of components of FOLFIRI at the next cycle based on maximum grade of specific adverse events (see SmPC section 4.2, Table 4 and Table

5). Furthermore, prior to chemotherapy, patients should have a complete blood count. Criteria to be met prior to FOLFIRI are provided in section 4.2 of the SmPC.

Asian patients suffered from a higher frequency of adverse events and also a higher frequency of discontinuations from treatment due to AE. Although higher incidence of hypertension, neutropenia, and proteinuria was observed in Asian patients, the majority of the events were manageable and did not lead to any significant clinical consequences.

There appears to be a relationship between safety and exposure (see discussion on clinical pharmacology).

2.5.2. Conclusions on clinical safety

Overall, the observed safety profile is in line with that previously observed when ramucirumab was used in combination with paclitaxel in gastric cancer. The occurrence of adverse events related to inhibition of the VEGFR axis was increased, with hypertension being the most notable adverse event. The ramucirumab+FOLFIRI combination also resulted in a higher proportion of ≥grade 3 AE and in AEs resulting in discontinuation of treatment, suggesting that ramucirumab amplifies the toxicity induced by FOLFIRI.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP).

The PRAC considered that the RMP version 6.0 (dated 26 February 2015) is acceptable, with minor revisions required at the time of submitting the next PSUR (submission due in December 2015), as detailed in the PRAC endorsed PRAC Rapporteur updated assessment report dated 11 June 2015.

The CHMP endorsed this advice.

The MAH provided feedback in relation to the changes in the RMP requested by PRAC and CHMP.

The PRAC considered that the MAH's proposed updates to the RMP version 6.0, to be implemented in the next PSUR (submission due in December 2015), are acceptable. The PRAC endorsed PRAC Rapporteur assessment report dated 10 September 2015 is attached. However, the RMP required updating on time for this CHMP opinion in relation to the post-authorisation efficacy development plan.

The CHMP endorsed the RMP version 6.1 with the following content:

Safety concerns

Important Identified Risks	• Arterial thromboembolic events[a] • Hypertension[a] • Infusion-related reaction[a] • Proteinuria[a]

	• Gastrointestinal perforation[a] • Bleeding/Haemorrhagic events[a] • Impaired wound healing[b] • Neutropenia • Fistula formation[b] • Liver failure / liver injury[b] • Congestive heart failure[c]
Important Potential Risks	• Reversible Posterior Leukoencephalopathy Syndrome[b] • Anaemia • Abdominal pain • Reproductive and developmental toxicity[b] • Venous thromboembolic events[b]
Missing Information	• Carcinogenicity[d] • Genotoxicity[d]

Abbreviation:

a Categorised as important identified risk in Core RMP

b Categorised as important potential risk in Core RMP

c Categorised as important identified risk when used in combination with mitoxantrone or following prior anthracycline therapy in Core RMP

d Categorised as missing information in Core RMP

Pharmacovigilance plan

Table of ongoing and planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
PASS/Registry: **I4T-MC-JVDD:** Safety and effectiveness of ramucirumab in patients with advanced gastric cancer in the European Union (EU) and North America: a prospective observational registry **Category 3**	**Primary objective**: To evaluate the safety profile of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer under real-world disease conditions in the EU and North America	Potential safety signals in special populations, such as elderly, patients with cardiac comorbidities, hepatic impairment and renal impairment	Planned	Final study report estimated for completion: Q4 2021

	Secondary objective: To evaluate the effectiveness of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer under real-world disease conditions in the EU and North America			

The PRAC also considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Arterial Thromboembolic Events	Proposed text in SmPC	None proposed
Hypertension	Proposed text in SmPC	None proposed
Infusion-Related Reactions	Proposed text in SmPC	None proposed
Proteinuria	Proposed text in SmPC	None proposed
Gastrointestinal perforation	Proposed text in SmPC	None proposed
Bleeding/Haemorrhagic events	Proposed text in SmPC	None proposed
Impaired wound healing	Proposed text in SmPC	None proposed
Neutropenia	Proposed text in SmPC	None proposed
Fistula formation	Proposed text in SmPC	None proposed
Liver failure/liver injury	Proposed text in SmPC	None proposed
Congestive heart failure	Not applicable	None proposed
Important Potential Risks		
Reversible Posterior Leukoencephalopathy Syndrome	Not applicable	None proposed
Anaemia	Proposed text in SmPC	None proposed
Abdominal pain	Proposed text in SmPC	None proposed
Reproductive and developmental toxicity	Proposed text in SmPC	None proposed
Venous Thromboembolic Events	Not applicable	None proposed
Missing Information		
Carcinogenicity, genotoxicity	Proposed text in SmPC	None proposed

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning with regard to stomatitis has been added to the product information. The Package Leaflet has been updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to correct minor editorial mistakes.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The evidence of efficacy of ramucirumab in patients with mCRC is based on the results of one pivotal study, the RAISE study. The proposed ramucirumab dose regimen is 8 mg/kg i.v. every 2 weeks. RAISE was a global, randomized, placebo-controlled, double-blind, multicenter, Phase 3 study that evaluated the efficacy of ramucirumab versus placebo, each in combination with FOLFIRI, in 1072 patients with mCRC whose disease had progressed during or after first-line combination therapy of bevacizumab, oxaliplatin, and a fluoropyrimidine.

The OS results, based on 769 events (71.7%), showed a statistically significant improvement in OS for the ramucirumab + FOLFIRI arm (HR = 0.844; 95% confidence interval [CI]: 0.730, 0.976; p=0.0219), resulting in a 1.6-month longer median survival (13.3 months vs. 11.7 months). The OS benefit is supported by modest but statistically significant improvement in median PFS by 1.2 months (from 4.5 to 5.7 months median; HR = 0.793; 95% CI: 0.697, 0.903; p=0.0005).

Numerically the OS was improved by 1.4 and 2.5 months (1.6 in the ITT pop) and the PFS was improved by 1 and 1.3 months (1.2 in the ITT pop), in KRASmut and KRASwt population, respectively. Differences between KRAS wt and mutant may also be clinically relevant.

Uncertainty in the knowledge about the beneficial effects

No dose finding study for the combination of ramucirumab in combination with FOLFIRI was conducted. The same dose (8 mg/kg) and frequency of ramucirumab (q2w) as for the treatment of metastatic gastric cancer was applied. Exposure-effect relationships revealed that both efficacy (OS and PFS) and safety (grade 3 neutropenia) were related to ramucirumab exposure. PopPK analyses did not identify any specific patient groups that were associated with low or high ramucirumab exposure. However, data suggested an imbalance in baseline characteristics/prognostic factors in the low ramucirumab exposure group. When taking into account the substantially improved efficacy (PFS and OS) related to the occurrence of AE, in particular neutropenia, appropriate dose finding may be even more important as this phenomenon may be exposure related. At the time of initial marketing authorisation it was agreed that an alternative dosing regimen may be explored for ramucirumab in second line gastric adenocarcinoma (study 14T-MC-JVDB) as reflected in Annex II. Since analyses suggest the exposure

response relationship is very similar across indications, results from Study 14T-MC-JVDB may provide useful information to further explore the optimal dose regimen in patients with mCRC.

Although clinically relevant, the benefit is limited. Assessment of benefit shows variability in response as is seen more often in these patients. No benefit of ramucirumab was shown in patients that showed PD within 3 months of onset of bevacizumab containing 1st line treatment (see SmPC section 5.1).

The possible impact of biomarkers (e.g. VEGF-C, VEGF-D, soluble VEGFR1, sVEGFR2 and sVEGFR3, tissue expression of VEGFR1 and VEGFR2) is difficult to determine because data appear not available from all patients included in study RAISE. A more complete analysis is anticipated in 2016 (see Annex II condition).

Although the downstream signalling pathway of VEGFR2 seems intertwined with those related to EGFR the consequences of mutations in genes defining the latter may also influence the inhibition of VEGFR2 (Pyne & Pyne, Nature Reviews Cancer 10, 489-503 (2010)). The OS benefit in the RAISE study was observed without complete knowledge of RAS mutation status (including NRAS), making it difficult to generalize the study results to patients seen in current practice at this time. RAISE was performed prior to the knowledge on the influence of the NRAS mutation status on the biology of mCRC. More extensive analyses on biomarkers are anticipated in 3Q 2016 (see Annex II condition).

No information was provided about the number of first line treatments received as a repeat treatment after lasting response to initial palliative treatment. A difference between the median duration of disease (defined by the interval between the moment of initial diagnosis and randomisation in RAISE) in the two arms in RAISE was 1.32 months in favour of ramucirumab. Therefore, the distribution of patients considered suffering from relatively more aggressive disease over the two study arms might have favoured the ramucirumab containing arm of RAISE (see SmPC section 5.1).

Risks

Unfavourable effects

Overall, the safety profile of ramucirumab (Cyramza) was consistent across studies and in line with the already known toxicity for Cyramza known from registration studies REGARD and RAINBOW for the indication gastric cancer. However, combined with FOLFIRI, Cyramza was less tolerated by patients, as observed in almost one third of patients (29.1% vs. 13.3% in the placebo+FOLFIRI arm) discontinuing study treatment due to adverse events (in 27% of patients this referred to discontinuation of FOLFIRI).

In mCRC patients treated with ramucirumab plus FOLFIRI, the most frequent (≥1%) ADR that led to the discontinuation of ramucirumab was proteinuria (1.5%). The most frequent (≥1%) ADRs leading to discontinuation of one or more components of FOLFIRI were: neutropenia (12.5%), thrombocytopenia (4.2%), diarrhoea (2.3%) and stomatitis (2.3%). The most frequent component of FOLFIRI to be discontinued was the 5 FU bolus (see SmPC section 4.8). Cases of gastrointestinal perforation have been reported in patients treated with ramucirumab in study RAISE (see SmPC section 4.4).

An increase in the incidence of palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome), not previously reported with ramucirumab use, was observed in the RAISE study (see SmPC section 4.8).

The other adverse events occurring at a substantially higher percentage in the ramucirumab+FOLFIRI arm such as epistaxis, hypertension, proteinuria, peripheral oedema, stomatitis, decreased appetite and neutropenia were also observed when ramucirumab was combined with paclitaxel.

The incidence of neutropenia was particularly higher in the ramucirumab arm (28.2% vs. 14.6% for grade 3 and 10.2% vs. 8.7% for grade 4 AEs). Neutropenia rarely resulted in febrile neutropenia

necessitating hospitalisation (2.3% vs. 1.5%) and no deaths due to neutropenia were observed. However, the frequency of discontinuation of treatment due to neutropenia was high (12.5% compared to 5.3% in the placebo arm).

Regarding quality of life, a 1.5 months shorter time to deterioration (defined as >10 points change from baseline on a scale from 0-100) in global health was observed for patients in the ramucirumab plus FOLFIRI arm as assessed by the EORTC QLC-30, which was confirmed by EQ5D results.

Uncertainty in the knowledge about the unfavourable effects

There is no new uncertainty to reflect regarding the unfavourable effects of ramucirumab.

Effects Table

Table 33. Effects Table for Cyramza plus FOLFIRI for the 2nd line treatment of metastatic colorectal cancer (data cut-off: 17 July, 2014)

Effect	Short Description	Unit	Cyramza + FOLFIRI	Placebo + FOLFIRI	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	Overall survival: Median time from randomisation to death of any cause	Months	13.3 (12.4, 14.5)	11.7 (10.8, 12.7)	HR of 0.844 (CI 0.730-0.976); p=0.0219; Time since diagnosis and number of lines of first line treatment unclear; no significant effect in Europe	See 'clinical efficacy' section
PFS	Progression free survival (investigator assessment): Median time from randomization to progression or death	Months	5.7 (5.5, 6.2)	4.5 (4.2, 5.4)	HR of 0.793 (CI 0.697-0.903) P=0.0005	See 'clinical efficacy' section
ORR	Objective response rate (ORR): equal to the proportion of patients achieving a best overall response of partial or complete response (PR + CR)	%	13.4 (10.7-19.6)	12.5 (9.8-15.6)	P=0.6336	See 'clinical efficacy' section
Unfavourable Effects						
EORTC QLQ-C30	Time to deterioration in global health	Months	2.50 (2.04-2.99)	3.98 (3.65-4.83)	P=0.0006; HR 1.318; CI 1.125-1.545	

Effect	Short Description	Unit	Cyramza + FOLFIRI	Placebo + FOLFIRI	Uncertainties / Strength of evidence	References
≥1 TAE ≥ grade 3	Patients who experienced ≥ 1 grade 3 TAE	%	79.0	62.3		
Neutropenia	Incidence of ≥grade 3 events	%	21.7	11.2		
Hypertension	Incidence of ≥grade 3 events	%	10.8	2.8		
Diarrhoea	Incidence of ≥grade 3 events	%	10.8	9.7		

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Although the benefit in terms of OS and PFS improvement is limited and there was a lack of supportive improvement in ORR, it is considered clinically relevant in this patient population with progressive metastatic CRC (mCRC) after 1st line of palliative treatment.

Side effects of ramucirimab are related to its mechanism of action. Tolerability appears to be a problem for ramucirumab, in particular concerning haematological and gastrointestinal toxicities, when given in combination with FOLFIRI. Well known side effects of FOLFIRI, such as neutropenia and infections were enhanced by the combination with ramucirumab. This may partially explain the observed decrease in quality of life.

The toxicity of the combination was manageable mainly by adapting the dose and content of the FOLFIRI treatment or even discontinuation.

Benefit-risk balance

Since the benefit is statistically significant although modest and toxicity limited when the right precautions are taken, the benefit/risk balance of Cyramza, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), for the treatment of adult patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine, is considered positive.

Nevertheless, the question whether the benefit/risk could be enhanced by further patient selection, in particular on the basis of biomarkers remains unresolved. The apparent difference, albeit small, in magnitude of benefit in KRASmut and KRASwt and data external to the registration study justify further studies, including the possible influence of NRAS and BRAF mutation status.

Discussion on the Benefit-Risk Balance

For all patients with progressive metastatic CRC (mCRC) after 1st line of palliative treatment, further systemic treatment is palliative rather than curative. The goals of systemic treatment in these patients are to prolong survival while maintaining quality of life, by reducing disease related symptoms and limit treatment related toxicity, for as long as possible. Therefore, overall survival is considered the most important endpoint.

It is noted that the patient population recruited in the pivotal study was highly selected regarding performance status, lack of co-morbidities and risk for toxicities from anti VEGF targeting agents (e.g. no disturbances in coagulation function or with a recent history of bleeding events). This has been adequately reflected in the SmPC (see SmPC section 5.1).

Efficacy may depend on KRAS mutations in exons currently known to harbour mutations. Information on the actual mutation status and related efficacy of ramucirumab in mCRC is lacking. Similarly, the impact of currently recognized importance of mutations in NRAS (overall, mutations within the RAS genome) as well as in BRAF in CRC on the efficacy of ramucirumab is yet unclear. KRAS, BRAF, and NRAS mutations are considered mutually exclusive. The MAH committed to retrospectively analyse samples from patients with KRAS wild-type tumours for additional KRAS mutations and NRAS and BRAF mutations and evaluate the efficacy of ramucirumab in this population (see Annex II condition).

High VEGF and/or VEGFR expression have been associated with poor prognosis in a variety of cancers. VEGF and VEGFR expression in RAISE have not been reported sufficiently yet but will be evaluated retrospectively together with the other potential biomarkers. The MAH committed to submit biomarker analysis of the entire RAISE population by the end of 2016.

Regarding the issue of the relationship between exposure and the benefit/risk of ramucirumab, it should be considered that this issue was also raised in relation to the currently approved indication of gastric carcinoma, where a similar dose was used, resulting in a requirement of an additional dose-response study after registration (see Study 14T-MC-JVDB in Annex II). These results might provide valuable exploratory information for the mCRC indication. Depending on the outcome of this study further data might be requested to the applicant.

Due to the above uncertainties with respect to the efficacy of Cyramza in certain sub-populations, the CHMP considers the following measures necessary to address issues related to efficacy (see Annex II condition):

In order to investigate the potential correlation between biomarker measures (VEGF-C. VEGF-D, sVEGFR1, sVEGFR2 and sVEGFR3 from plasma, VEGFR2 IHC, additional KRAS, NRAS and BRAF mutations) and efficacy outcome (PFS, OS), the MAH should submit the results of a biomarker assay from the RAISE translational research population.

- Correlation with VEGF-C. VEGF-D, sVEGFR1, sVEGFR2 and sVEGFR3 from plasma, VEGFR2 IHC will be submitted by 30 June 2016

- Correlation with additional KRAS, NRAS and BRAF mutations will be submitted by 30 September 2016.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include a new indication for Cyramza, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), for the treatment of adult patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, Annex II has been updated to include an obligation for the MAH to conduct a Post Authorisation Efficacy Study (PAES). In addition, the Marketing authorisation holder (MAH) took the opportunity to correct minor editorial mistakes and to align Annex II to the QRD version 9.1.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP)(final version 6.1).

This CHMP recommendation is subject to the following amended condition:

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

This CHMP recommendation is also subject to the following new condition:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to investigate the potential correlation between biomarker measures (VEGF-C. VEGF-D, sVEGFR1, sVEGFR2 and sVEGFR3 from plasma, VEGFR2 IHC, additional KRAS, NRAS and BRAF mutations) and efficacy outcome (PFS, OS), the MAH should submit the results of a biomarker assay from the RAISE translational research population. - Correlation with VEGF-C. VEGF-D, sVEGFR1, sVEGFR2 and sVEGFR3 from plasma, VEGFR2 IHC will be submitted by - Correlation with additional KRAS, NRAS and BRAF mutations will be submitted by	 30 June 2016 30 September 2016

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include a new indication for Cyramza, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), for the treatment of adult patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, Annex II has been updated to include an obligation for the MAH to conduct a Post Authorisation Efficacy Study (PAES). In addition, the Marketing authorisation holder (MAH) took the opportunity to correct minor editorial mistakes and to align Annex II to the QRD version 9.1.

Summary

Please refer to the published Assessment Report Cyramza H-2829-II-04-AR.