12 December 2019
EMA/CHMP/647625/2019
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Cyramza

International non-proprietary name: ramucirumab

Procedure No. EMEA/H/C/002829/II/0033

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

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List of abbreviations

AC	assessment committee
ADA	anti-drug antibodies
ADR	adverse drug reactions
AESIs	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATEs	arterial thromboembolic events
BRIC	blinded independent review committee
CHF	congestive heart failure
CI	confidence interval
CL	Clearance
Cmax	maximum concentration
Cmin	minimum concentration
CNS	central nervous system
DDI	drug-drug interaction
DLT	dose-limiting toxicity
EC	European Commission
ECOG PS	Eastern Cooperative Oncology Group Performance status
EGFR	epidermal growth factor receptor
EQ-5D-5L	EuroQol- 5-dimension, 5-level questionnaire
ER	exposure-response
ESMO	European Society for Medical Oncology
FFPE	formalin-fixed paraffin embedded
GI	gastrointestinal
HCC	hepatocellular carcinoma
HR	hazard ratio
HSR	Hypersensitivity reactions
ILD	interstitial lung disease
IRR	infusion-related reaction
ITT	intention to treat
IV	intravenous
KM	Kaplan-Meier
LRTI	lower respiratory tract infection
MAD	multiple dose ascending
MedDRA	standardized Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
NCA	Non-compartmental methods of analysis
NSAID	nonsteroidal anti-inflammatory agents
NSCLC	non-small cell lung cancer
OS	overall survival
PFS	progression free survival
PFS2	progression free survival 2
PK	pharmacokinetic
PopPK	population pharmacokinetics

PT	preferred term
Q2W	every 2 weeks
QoL	quality of life
RPLS	reversible posterior leukoencephalopathy syndrome
SMQs	standardized Medical Dictionary for Regulatory Activities queries
SOC	system organ class
T1/2	half life
TEAEs	treatment-emergent adverse events
TKIs	tyrosine kinase inhibitors
TtD	time to deterioration
VEGF	binds vascular endothelial growth factor
Vss	volume of distribution at steady state
VTEs	thromboembolic events

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 June 2019 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 for Cyramza to include in combination with erlotinib, the first-line treatment of adult patients with metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations; 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 accordingly. The RMP version 9 has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMEA-002074-PIP01-16 on the granting of a product-specific 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.

Scientific advice

The MAH received Scientific Advice from the CHMP on 18 December 2014 (EMEA/H/SA/1505/7/2014/II). 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: Paula Boudewina van Hennik Co-Rapporteur: Kolbeinn Gudmundsson

Timetable	Actual dates
Submission date	27 June 2019
Start of procedure:	20 July 2019
CHMP Rapporteur Assessment Report	13 September 2019
CHMP Co-Rapporteur Assessment Report	13 September 2019
PRAC Rapporteur Assessment Report	20 September 2019
PRAC members comments	25 September 2019
Updated PRAC Rapporteur Assessment Report	26 September 2019
PRAC Outcome	3 October 2019
CHMP members comments	7 October 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 October 2019
Request for supplementary information (RSI)	17 October 2019
PRAC Rapporteur Assessment Report	18 November 2019
CHMP Rapporteur Assessment Report	27 November 2019
PRAC Outcome	28 November 2019
CHMP members comments	02 December 2019
Updated CHMP Rapporteur Assessment Report	05 December 2019
Opinion	12 December 2019

2. Scientific discussion

2.1. Introduction

Problem statement

Worldwide, lung cancer represents 11.6% (2.1 million) of the total cancer cases in 2018 (Bray et al. 2018). Lung cancer is the leading cause of cancer death, with an estimated 1.8 million deaths (18.4% of the total) in 2018. Around 80-90% of the patients with lung cancer have non-small cell lung cancer (Planchard et al. Ann of Oncol. 2018). The majority of patients with non-small cell lung cancer (NSCLC) present with locally advanced or metastatic disease and for these patients the prognosis is poor, with overall 5-year survival rates of 5% (Surveillance, Epidemiology, and End Result Program [SEER]). The symptomatic burden is high, with patients experiencing debilitating symptoms such as fatigue, loss of appetite, shortness of breath, cough, pain, and blood in sputum (Iyer et al. 2014).

The EGFR pathway is an important signalling pathway that regulates tumourigenesis and cell survival and is frequently overexpressed in the development and progression of NSCLC. Activating mutations in EGFR are present in a distinct subset of patients with NSCLC and have biological, clinical, and therapeutic implications. Epidermal growth factor receptor mutations are found in about 10% to 20% of Caucasian patients with lung adenocarcinomas and up to 40% to 60% in Asian patients (Midha et al. 2015; Hsu et al. 2018). Patients who are Asian, female, non-smokers, or have NSCLC of adenocarcinoma histology are more likely to harbour an EGFR mutation (Zhang et al. 2016). The median age of these patients at diagnosis is 67 years (Sandelin et al. 2015; Inoue et al. 2016). Approximately 25% to 40% of patients with EGFR-mutated NSCLC present with central nervous system (CNS) metastases (Chooback et al. 2017; Preusser et al. 2018).

The majority of EGFR mutations (90%) are due to deletions within exon 19 or a leucine-858-to arginine substitution mutation in exon 21 (L858R) (Murray et al. 2008). Both mutations result in activation of the tyrosine kinase domain. The presence of these activating EGFR mutations in advanced NSCLC is associated with sensitivity to the small molecule EGFR tyrosine kinase inhibitors (TKIs), however the degree of benefit may differ based on the type of mutation, with the benefit of EGFR TKIs being larger in exon19 deletion mutations (Sheng et al. 2016). With currently available EGFR TKIs, prognosis is improving, but remains poor as most patients eventually develop treatment resistance and will eventually experience disease progression on EGFR TKI therapy. The 5-year survival rate was 14.6% in EGFR-mutated NSLC patients treated with erlotinib or gefitinib (Lin et al. 2016). There thus remains a need for new treatment options to improve the outcome of these patients.

Current treatment option

According to the ESMO guideline for metastatic non-small cell lung cancer, first-line treatment options for patients with EGFR-positive NSCLC are: gefitinib, erlotinib ± bevacizumab, afatinib, dacomitinib, osimertinib or gefitinib + carboplatin + pemetrexed. Of these, gefitinib, erlotinib ± bevacizumab, afatinib, dacomitinib, osimertinib are approved by EC as first-line therapy.

Second-line treatment consists of osimertinib in case of a T790M mutation and platinum-based chemotherapy or carboplatin/paclitaxel/bevacizumab/atezolizumab in T790M negative patients. Subsequent treatment for patients who become progressive on osimertinib consist also of platinum-based chemotherapy or carboplatin/paclitaxel/bevacizumab/atezolizumab.

About the product

Ramucirumab is a human receptor-targeted antibody that specifically binds vascular endothelial growth factor (VEGF) receptor 2 and blocks binding of its activating ligands VEGF-A, VEGF-C, and VEGF-D. VEGF Receptor 2 is the key mediator of VEGF induced angiogenesis. As a result, ramucirumab inhibits ligand stimulated activation of VEGF Receptor 2 and its downstream signalling components, including p44/p42 mitogen-activated protein kinases, neutralising ligand-induced proliferation and migration of human endothelial cells (Cyramza : EPAR - Product Information).

In the EU, Cyramza is approved for the second-line treatment of advanced gastric cancer or gastro-oesophageal junction adenocarcinoma (as monotherapy or in combination with chemotherapy), locally advanced or metastatic non-small cell lung cancer (NSCLC) (in combination with chemotherapy), and metastatic colorectal cancer (in combination with chemotherapy). Marketing authorisation of Cyramza as second-line treatment of patients with hepatocellular carcinoma who have serum alpha fetoprotein of ≥ 400 ng/ml is pending European Commission (EC) decision (EMA/CHMP/360998/2019).

The MAH applied for the following indication which was considered acceptable by CHMP:

Cyramza in combination with erlotinib is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations.

The recommended dose of ramucirumab in combination with erlotinib is 10 mg/kg every two weeks.

EGFR mutation status should be determined prior to initiation of treatment with ramucirumab and erlotinib using a validated test method. See erlotinib prescribing information for the posology and method of administration of erlotinib (see section 4.2 of the SmPC).

Scientific advice

On 17 October 2014 the applicant Eli Lilly requested scientific advice for their product ramucirumab (Procedure No.: EMEA/H/SA/1505/7/2014/II). The CHMP accepted PFS as primary endpoint, but recommended that progression free survival 2 (PFS2) data will be collected for additional support of the benefit-risk assessment. Erlotinib as background therapy and placebo as comparator were accepted. It was

recommended that within patient changes in blood pressure during the first treatment cycle are reported for control and experimental arms, i.e. not only as percentage of patients with hypertension, and that these data are discussed from an unblinding perspective.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Ramucirumab is a protein, which is expected to be metabolised in the body and biodegrade in the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), ramucirumab is exempt from the submission of Environmental Risk Assessment studies as the product and excipients do not expect to pose a significant risk to the environment.

2.2.2. Discussion and conclusion on non-clinical aspects

The applicant did not submit studies for the ERA. According to the guideline, in the case of products containing proteins as active pharmaceutical ingredient(s), a justification for the lack of ERA studies is acceptable.

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. Tabular overview of clinical studies

Study ID/Participating Countries	Study Title	Treatment Arms	Dose Regimen	N (ITT Population) (Ram + Erlotinib vs. Placebo + Erlotinib)	Objectives
RELAY; I4T-MC-JVCY **Participating Countries** Part A: Japan, Spain Part B: Canada, France, Germany, Hong Kong, Italy, Japan, South Korea, Romania, Spain, Taiwan, Turkey, UK, and US	A Multicenter, Randomized, Double-Blind Study of Erlotinib in Combination with Ramucirumab or Placebo in Previously Untreated Patients with *EGFR* Mutation-Positive Metastatic Non-Small Cell Lung Cancer	Part A (Phase 1b)[a]: Ram + Erlotinib Part B (Phase 3): Ram + Erlotinib vs. Placebo + Erlotinib	**Ramucirumab:** 10 mg/kg on D1 every 2 weeks **Erlotinib:** 150 mg/day	Part B (Phase 3) 449 (Ram + Erlotinib: 224, Placebo + Erlotinib: 225)	**Part A:** Safety and tolerability of ramucirumab + erlotinib **Part B:** Primary: PFS Secondary: OS, ORR, DCR, DoR, PROs, safety and toxicity, PK and immunogenicity of ramucirumab, DDI substudy to assess the PK of erlotinib without ramucirumab Exploratory: PFS2, association between biomarkers and clinical outcome, TtD in ECOG PS, time to diagnosis of CNS metastases, PFS2 and OS for patients who receive osimertinib after disease progression vs. those who do not.

2.3.2. Pharmacokinetics

The clinical pharmacology package includes ramucirumab pharmacokinetic (PK) and immunogenicity data from the target population, drug-drug interaction (DDI), and exposure-response (ER) analyses. These analyses were based on data obtained in the RELAY study.

RELAY was a phase 1b/3 study in patients with metastatic NSCLC with activating EGFR mutations (exon 19 deletions or exon 21 [L858R] substitution mutations) who were being treated for their disease for the first time. Patients with a known T790M mutation were excluded from study participation.

Patients received ramucirumab or placebo Q2W until disease progression, the development of unacceptable toxicity, noncompliance or withdrawal of consent by the patient, or investigator decision.

Part A (phase 1b)

The primary objective of part A was to assess the safety and tolerability of ramucirumab (10 mg/kg Q2W) when administered in combination with erlotinib (150 mg/day) as therapy in previously untreated patients with metastatic NSCLC with activating EGFR mutations.

Part B (phase 3)

The primary objective of part B was to compare PFS for ramucirumab administered in combination with erlotinib versus placebo in combination with erlotinib in previously untreated patients with metastatic NSCLC with activating EGFR mutations.

- Ramucirumab (10 mg/kg) or an indistinguishable placebo intravenous infusion was administered over approximately 1 hour on Day 1 of each cycle (14 days [±3 days]).
- Erlotinib (150 mg) was taken orally once daily. On Day 1 of each cycle, patients received erlotinib after completion of ramucirumab infusion (after the observation period, post-ramucirumab or placebo infusion).

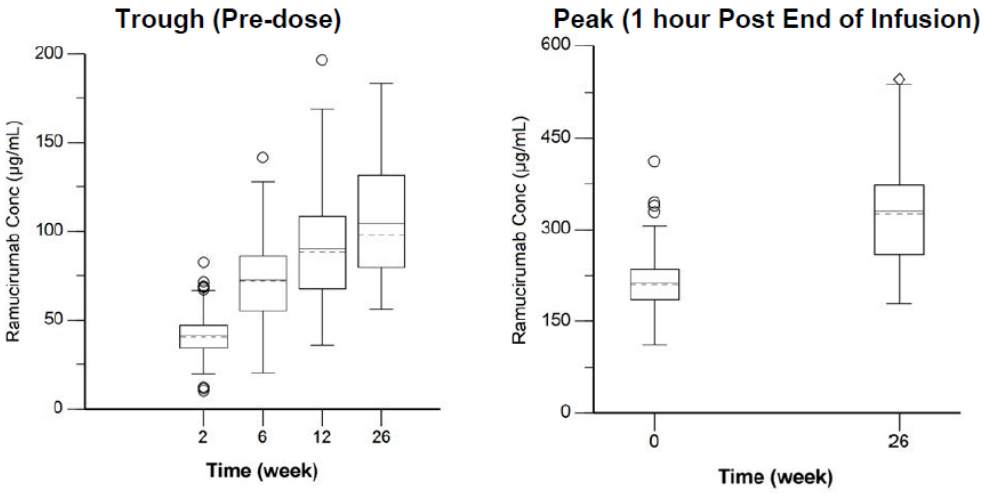
In part B, patients were randomised evenly between the 2 treatment arms using the following stratification factors:

- EGFR mutation (exon 19 deletion versus exon 21 [L858R] substitution mutation)
- gender (male versus female)
- region (East Asia versus other)
- EGFR testing method (Therascreen® [Qiagen] and Cobas® [Roche] versus other polymerase chain reaction (PCR) and sequencing-based methods)

Blood samples for the determination of serum concentrations of ramucirumab were collected from patients in part B. No ramucirumab PK data were collected in part A. Samples were collected prior to infusion (trough concentration or minimum concentration [Cmin]) for Cycles 1, 2, 4, 7, and 14 (Weeks 0, 2, 6, 12, and 26) and approximately 1 hour following the end of infusion (approximate peak or maximum concentration [Cmax]) for Cycles 1 and 14 (Weeks 0 and 26). The PK data from 215 patients receiving ramucirumab plus erlotinib in RELAY part B were included in the descriptive PK summary.

Ramucirumab concentrations were measured in serum samples using a validated enzyme-linked immunosorbent assay. The bioanalytical method was developed and validated at Intertek Pharmaceutical Services (San Diego, CA, USA) and Charles River Laboratories (Senneville, Quebec, Canada) as provided in previous submissions (hepatocellular carcinoma and advanced gastric cancer). The bioanalytical methods performed at Intertek and Charles River Laboratories were cross-validated and shown to perform comparably.

Ramucirumab serum trough and approximate peak concentration (1 hour post end of infusion) data following administration of 10 mg/kg ramucirumab Q2W in combination with erlotinib are summarized in **Error! Reference source not found.** and **Error! Reference source not found.**.



Abbreviations: Conc = concentration; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; Q2W = every 2 weeks.
Outline of box shows the 25th and 75th percentiles with inside lines being the arithmetic mean (solid) and median (dashed). Whiskers show lowest and highest values within 1.5 times the difference between the 1st and 3rd quartiles. Individual observations outside the whiskers are shown with open circles.

Figure 1: Summary of ramucirumab trough (left) and peak (right) concentrations for previously untreated patients with metastatic NSCLC with activating EGFR mutations following administration of 10 mg/kg of ramucirumab Q2W as an IV infusion over approximately 1 hour in combination with erlotinib (RELAY Study).

Table 2: Summary of ramucirumab trough and peak concentrations for previously untreated patients with metastatic NSCLC with activating EGFR mutations following administration of 10 mg/kg of ramucirumab Q2W as an IV Infusion over approximately 1 hour in combination with erlotinib (RELAY Study)

	Time (W)	0	2	6	12	26
Regimen	Dose Number	1	2	4	7	14
Trough (Predose) Ramucirumab Concentrations (µg/mL)						
10 mg/kg Q2W	n_{PK}	--	185	145	110	59
	Geo Mean	--	39.6	68.5	85.7	99.4
	Geo %CV	--	32	37	32	31
	Min	--	10.3	20.3	36.0	56.4
	Max	--	82.5	142	197	184
Peak Ramucirumab Concentrations (µg/mL)						
10 mg/kg Q2W	n_{PK}	194	--	--	--	53
	Geo Mean	210	--	--	--	319
	Geo %CV	19	--	--	--	26
	Min	111	--	--	--	180
	Max	412	--	--	--	547

Abbreviations: CV = coefficient of variation; EGFR = epidermal growth factor receptor; Geo = geometric; IV = intravenous; Max = maximum; Min = minimum; nPK = number of pharmacokinetic observations included in calculation; NSCLC = non-small cell lung cancer; Q2W = every 2 weeks; W = week.

Administration of ramucirumab to NSCLC patients in the RELAY study using the 10 mg/kg Q2W posology yielded a C_{min} of 68.5 µg/ml (range of 20.3-142 µg/ml) and 85.7 µg/ml (range of 36.0 -197 µg/ml) prior to administration of the fourth and seventh dose, respectively. This exposure is somewhat higher than that obtained following administration of 10 mg/kg Q3W, as is used for the treatment of NSCLC patients with ramucirumab and docetaxel (with geometric means of ramucirumab C_{min} of 28.3 µg/ml (range of 2.5-108 µg/ml) and 38.4 µg/ml (range of 3.1-128 µg/ml) prior to administration of the third and fifth dose).

Further, dose-normalised ramucirumab peak concentrations obtained with ramucirumab given as 10 mg/kg Q2W in the RELAY study were comparable with those obtained at a 8 mg/kg Q2W dose given in other clinical studies with ramucirumab (Table 3), indicating a relatively modest increased absolute peak exposure in the RELAY study. The comparable PK of ramucirumab in the RELAY study in combination with erlotinib as compared to the other clinical studies where ramucirumab was given as singe agent indicates that co-administration of erlotinib is unlikely to affect ramucirumab PK.

Table 3: Summary of dose-normalized ramucirumab trough and 1-hour post end-of-infusion concentrations (approximate peak) following ramucirumab administered as an IV infusion over approximately 1 hour Q2W

Dose-Normalized Ramucirumab Trough Serum Concentrations [(μg/mL)/(mg/kg)]					
Dose	**Prior to Dose 4 (Week 6)**				
	REACH-2	**REACH[a]**	**REGARD**	**RAINBOW**	**RELAY**
n_{PK}	120	155[b]	53	203[c]	145
Geo Mean	5.51	5.31	6.19	5.63	6.85
Dose	**Prior to Dose 7 (Week 12)**				
	REACH-2	**REACH[a]**	**REGARD**	**RAINBOW**	**RELAY**
n_{PK}	69	89	34	142	110
Geo Mean	7.53	6.94	9.30	7.85	8.57

Dose-Normalized Ramucirumab Peak (1-Hour Post End-of-infusion) Serum Concentrations [(μg/mL)/(mg/kg)]					
Dose	**Following Dose 1 (Week 0)**				
	REACH-2	**REACH[a]**	**REGARD**	**RAINBOW**	**RELAY**
n_{PK}	165	247	N/C	259	194
Geo Mean	19.5	18.7	N/C	18.3	21.0

Abbreviations: Geo = geometric; IV = intravenous; N/C = not collected; n_{PK} = number of pharmacokinetic observations included in calculation; Q2W = every 2 weeks.

[a] Data from patients with a Child-Pugh Class A Score.

[b] Two trough concentrations that were reported below the limit of quantitation were treated as missing for the concentration summaries.

[c] Four trough concentrations that were reported below the quantitation limit were treated as missing for the concentration summaries.

Sources: REACH-2 Clinical Study Report, Table JVDE.11.16; REACH Clinical Study Report, Table JVBF.11.5.11; REGARD Clinical Study Report, Table 11.14; RAINBOW Clinical Study Report, Table JVBE.11.5.11; RELAY Clinical Study Report, Table JVCY.11.16.

Population pharmacokinetics in first-line treatment of patients with metastatic NSCLC with activating EGFR mutations

Sparse ramucirumab PK data collected in the RELAY study were pooled together with the most recently submitted REACH-2 (hepatocellular carcinoma) pooled population pharmacokinetics (PopPK) dataset (containing PK data from previously conducted 17 Phase 2 and Phase 3 studies) for an updated PopPK analysis.

The ramucirumab concentration-time data were well described by a previously developed (REACH-2 PopPK report) two-compartment structural model parameterized in terms of CL, V1, V2, and Q with time-varying CL. The time-varying CL was incorporated into the model using a sigmoid function parameterized in terms of CL, T_{max}, T50, and a sigmoid shape parameter. The effect of body weight was included on CL and V1 and exponential inter-patient variability terms were included for CL, V1, and V2. An additive inter-patient variability term was included on T_{max}, with covariance between CL and V1, and CL and T_{max}. Residual variability was accounted for by an additive/proportional error structure.

The new patient population (first-line treatment of patients with metastatic NSCLC with activating EGFR mutations) made up about 8% of the RELAY pooled PopPK dataset. In addition, the majority of RELAY patients were Asian (77%), with the Asian patients in the RELAY study comprising more than 20% of the Asian population in the RELAY pooled PopPK analysis dataset. Distribution of other patient factors and lab values were similar between the RELAY and REACH-2 (hepatocellular carcinoma (HCC)) pooled populations. Therefore, only race and patient population were included into the covariate assessment in the PopPK analysis. Adding RELAY data into the REACH-2 (HCC) pooled dataset is unlikely to affect previous conclusions on other covariates.

In this updated PopPK analysis, patient population and race were not found to satisfy the predefined inclusion criteria. Therefore, the final model is same as the previous REACH-2 PopPK analysis.

A summary of the post hoc estimates of PK parameter (clearance (CL), volume of distribution at steady state (Vss)), and half-life ($t_{1/2}$)) at steady state is presented in Table 4. As shown in this table, the results in RELAY study were similar to those previously reported in the REACH-2 pooled PopPK analysis and the RELAY pooled PopPK analysis.

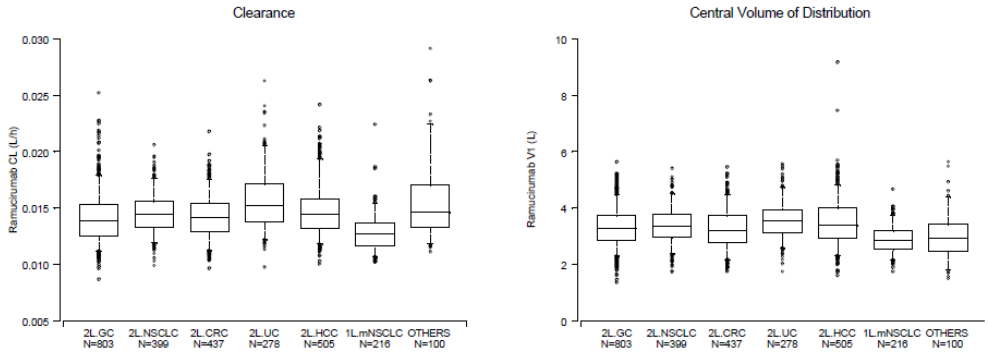
Table 4: Post hoc estimates of pharmacokinetic parameters for ramucirumab (steady state)

	RELAY Only Geometric Mean (%CV)	RELAY Pooled PopPK Dataset Geometric Mean (%CV)	REACH-2 Pooled PopPK Dataset Geometric Mean (%CV)
Clearance; CL (L/h)	0.0113 (22.1)	0.0133 (30.0)	0.0136 (30.4)
Volume of Distribution at Steady State; V_{ss} (L)	4.03 (15.1)	4.48 (19.7)	4.57 (19.6)
Terminal Half-Life; $t_{1/2}$ (days)	10.7 (20.7)	10.1 (27.2)	10.1 (27.7)
N	216	2738	2522

Abbreviations: CV = coefficient of variation; N= number of patients; PopPK = population pharmacokinetics; $t_{1/2}$ = apparent terminal elimination half-life.

Predicted estimates of ramucirumab PK parameters derived from this pooled analysis (RELAY + REACH-2 PopPK dataset) are summarized in **Figure 2** for different patient populations and in **Figure 3** for patients with different races. The PK parameters are generally comparable among different patient populations and races, consistent with the findings from the covariate assessment.

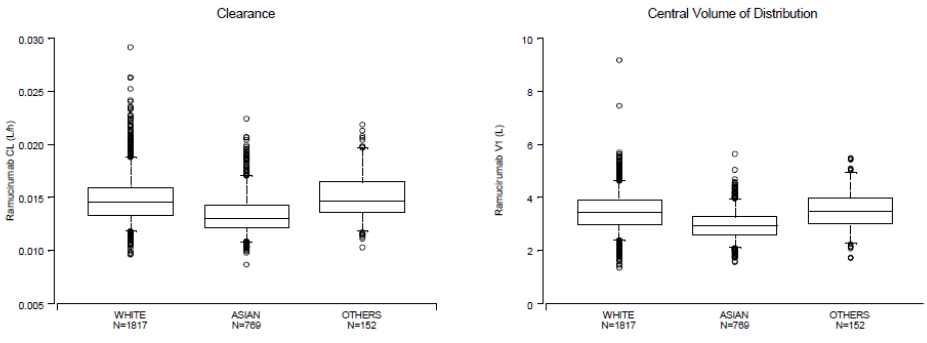
(A) **(B)**



Abbreviations: 1L = the first line treatment; 2L = the second line treatment; CRC = colorectal cancer; EGFR = epidermal growth factor receptor; GC= gastric cancer; HCC = hepatocellular carcinoma; NSCLC = non-small cell lung cancer; mNSCLC = metastatic NSCLC with activating *EGFR* mutations; UC = urothelial cancer.

Figure 2. Distribution of ramucirumab (A) clearance (CL) and (B) central volume of distribution (V1) in different patient populations.

(A) **(B)**



Abbreviation: N = number of patients.

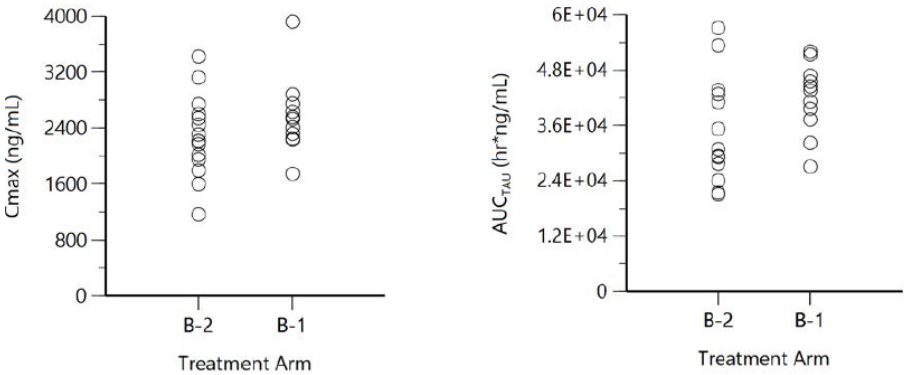
Figure 3. Distribution of ramucirumab (A) clearance (CL) and (B) central volume of distribution (V1) in different races.

Pharmacokinetic interaction studies

To support the registration of ramucirumab in combination with erlotinib as 1L treatment for patients with metastatic NSCLC with activating EGFR mutations, a DDI substudy was conducted in RELAY part B to assess the effect of concomitant ramucirumab on the PK of erlotinib.

Serial blood samples for determination of erlotinib concentration in plasma were collected in a subset of patients in RELAY part B on Day 1 of Cycle 2 and at 24 hours (Day 2 Cycle 2) following their erlotinib dose on Day 1 of Cycle 2. Non-compartmental methods of analysis (NCA) were performed on concentration-time data from 11 patients in the ramucirumab plus erlotinib arm and 15 patients in the placebo plus erlotinib arm.

Distribution of erlotinib exposure parameters in plasma were generally similar between 2 arms (Figure 4). Table 5 shows the results of the statistical analysis to assess the effect of co-administration of ramucirumab on PK of erlotinib. The ratios of geometric LS means and 90% CIs at 1.23 (90% CI; 1.02, 1.50) for AUC_{TAU} and 1.14 (90% CI; 0.97, 1.34) for C_{max}, indicated that co-administration with ramucirumab is unlikely to affect erlotinib PK. The erlotinib exposure levels observed in ramucirumab plus erlotinib or placebo plus erlotinib arms are generally consistent with data published in the literature (Hidalgo and Bloedow 2003; Lu et al. 2006; Gray et al. 2014).



Abbreviations: AUC_{TAU} = area under the concentration-time curve over the dosing interval; C_{max} = maximum serum concentration; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer.
Arm B-1: Erlotinib + Ramucirumab
Arm B-2: Erlotinib + Placebo

Figure 4: Erlotinib noncompartmental pharmacokinetic parameters (C_{max} and AUC_{TAU}, Day 1 of Cycle 2) for metastatic NSCLC patients with EGFR activating mutations following administration of erlotinib (150 mg, once daily) with ramucirumab (10 mg/kg) (n=11) or placebo (n=15).

Table 5: Primary statistical analysis of DDI assessment (DDI population)

Parameter	Erlotinib + Ramucirumab		Erlotinib + Placebo*		Ratio of geometric least squares means (90% CI)
	N	Geometric least squares means (90% CI)	N	Geometric least squares means (90% CI)	Erlotinib + Ramucirumab: Erlotinib + Placebo
AUC_{TAU} (hr*ng/mL)	11	41237.24 (35759.06, 47554.66)	13	33437.78 (29328.82, 38122.41)	1.23 (1.02, 1.50)
C_{max} (ng/mL)	11	2516.17 (2222.08, 2849.18)	15	2213.59 (1990.08, 2462.19)	1.14 (0.97, 1.34)

Abbreviations: AUC = area under the concentration-time curve; AUC_{TAU} = AUC over the dosing interval (TAU is 24 hr); CI = confidence interval; C_{max} = maximum observed drug concentration; DDI = drug-drug interaction; hr = hour; N = number of patients included in the analysis; PK = pharmacokinetic.
Model: Log(PK) = Actual Treatment Arm + Random Error. * - reference level.

2.3.3. PK/PD and exposure-response analyses

Exposure-response (ER) analyses were performed to characterize the relationship between ramucirumab exposure and selected measures of efficacy and safety in first-line treatment of patients with metastatic NSCLC with activating EGFR mutations.

Exposure-Efficacy Analysis

The relationship between ramucirumab exposure and PFS was evaluated using Kaplan-Meier (KM) methods, Cox models, and case-matched control analysis for RELAY part B ITT population (n=216 ramucirumab plus erlotinib arm, n=225 placebo plus erlotinib arm). Model-predicted $C_{min,1}$ was selected for exposure-efficacy analysis.

For the purpose of comparison of the ramucirumab treatment arm with the placebo treatment arm, patients who had non-missing ramucirumab concentration data were grouped into 4 quartiles ($C_{min,1}$: <25%, 25% to <50%, 50% to <75%, and ≥75%). Efficacy was compared between the ramucirumab treatment arm and placebo treatment arm for each of the 4 groups.

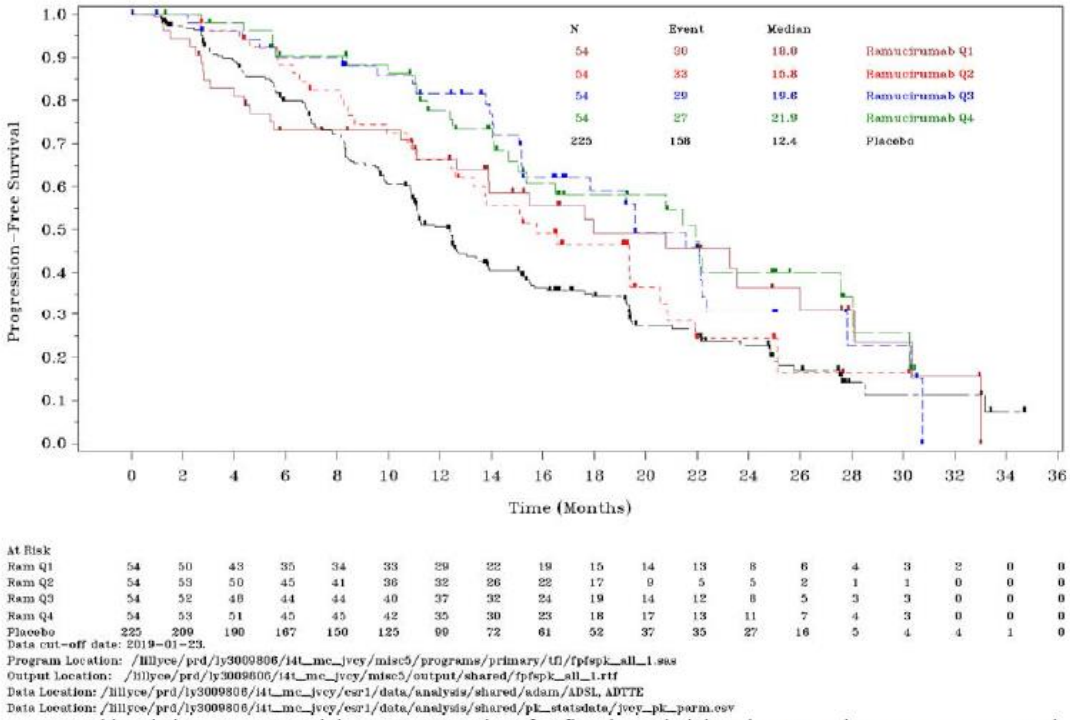
Of note, imbalanced baseline factors were observed among different quartile groups. A couple of factors potentially associated with poorer prognosis, including Eastern Cooperative Oncology Group Performance status (ECOG PS) (1) and number of metastatic sites (≥3), were somewhat more frequent in lower exposure groups. In addition, mean values of tumour burden appeared to be greater in lower exposure groups.

Exposure as a Continuous Covariate

Univariate analysis was performed to evaluate the exposure-efficacy relationship for PFS. Results are shown in Table 6 for the predicted $C_{min,1}$. This approach did not adjust the imbalanced prognostic factors associated with PFS among the quartiles and placebo group.

The KM plots of PFS by $C_{min,1}$ quartiles for RELAY Part B intention to treat (ITT) population are presented in Figure 5. Apparent separation was observed between placebo plus erlotinib arm and each ramucirumab plus erlotinib quartile. The median PFS was 18.0, 15.8, 19.6, and 21.9 months for Q1, Q2, Q3, and Q4 groups, respectively; the median PFS in the placebo treatment arm was 12.4 months. The median PFS values from all exposure quartiles were longer than that of placebo plus erlotinib arm, but no clear exposure-response relationship was observed within the exposure range following 10 mg/kg Q2W in the study.

Result from the univariate analysis showed that the association between PFS and $C_{min,1}$ was not statistically significant (p=0.3309) (Table 6).



Abbreviations: $C_{min,1}$ = minimum concentration after first dose administration; ITT = intent-to-treat; N = number of patients; PK = pharmacokinetics; Q = quartile; Ram = ramucirumab.

Figure 5: Kaplan-Meier plot of progression-free survival by predicted Cmin,1 quartiles for the RELAY part B ITT population.

Table 6: Analysis of predicted $C_{min,1}$ and progression-free survival (RELAY part b ITT population)

Efficacy Parameter Progression-Free Survival	Hazard Ratio[a] (95% CI)	p-Value (Wald's)
RELAY Part B ITT Population (N = 216/119 events)		
Univariate analysis	0.841 (0.594, 1.192)	0.3309
Multivariate analysis adjusting for significant factors[b]	0.824 (0.572, 1.186)	0.2971

Abbreviations: CI = confidence interval; $C_{min,1}$ = minimum concentration after first dose administration; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR = hazard ratio; ITT = intent-to-treat; N = number of patients; PK = pharmacokinetic.

a Log-2 transformation was applied before fitting the model; hence the HR should be interpreted as the change in hazard when the PK parameter doubles its value.

b Adjusted for ECOG PS (0 versus 1).

Multivariate Cox Regression Analysis

A multivariate Cox regression analysis was conducted to account for the significant prognostic factor associated with PFS (ECOG PS). The comparisons between the placebo and ramucirumab quartile groups are shown in (Table 7). After adjusting for the baseline factor that was significantly associated with PFS, a strong treatment effect on PFS was observed for all exposure groups with hazard ratio (HR) ranging from 0.504 to 0.769 among different exposure quartile groups. No apparent exposure-response trending was observed. After adjusting for this baseline prognostic factor, the association between PFS and $C_{min,1}$ remained statistically insignificant (p=0.2971) (Table 6).

Table 7: Multivariate cox regression analysis of progression-free survival by Cmin,1 quartiles

Efficacy Parameter Progression-Free Survival	Placebo N[a]	Ramucirumab N[a]	Hazard Ratio (95% CI)
RELAY Part B ITT Population[b]			
Q1 vs Placebo	225	54	0.671 (0.452, 0.994)
Q2 vs Placebo	225	54	0.769 (0.528, 1.120)
Q3 vs Placebo	225	54	0.566 (0.381, 0.843)
Q4 vs Placebo	225	54	0.504 (0.334, 0.759)

Abbreviations: CI = confidence interval; $C_{min,1}$ = minimum concentration after first dose administration; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ITT = intent-to-treat; N = number of patients contributing to analysis; Q = quartile.

[a] Patients with missing baseline covariate factors were omitted from analysis.

[b] Adjusted for ECOG PS (0 versus 1)

Note:
Q1 = ramucirumab-treated patients with $C_{min,1}$ <25%;
Q2 = ramucirumab-treated patients with $C_{min,1}$ 25% – <50%;
Q3 = ramucirumab-treated patients with $C_{min,1}$ 50% – <75%;
Q4 = ramucirumab-treated patients with $C_{min,1}$ ≥75%.

As another way to adjust for a potential impact of imbalance in baseline characteristics and of imbalance important prognostic factors between the treatments within each exposure group, case-matched control analyses for PFS were explored to evaluate the exposure-PFS relationship. There were 2 matching factors to be adjusted for PFS in the RELAY Part B ITT population: age group (<65 years versus ≥65 years) and ECOG PS (0 versus 1). Age was imbalanced, and ECOG PS (0 versus 1) was prognostic. Based on the Mahalanobis metric matching, 54 patients from the placebo treatment arm were selected to match 1:1 with each of the 4 case groups, respectively.

To compare the 2 treatment arms in each of the 4 matched case-control groups, KM curves for PFS in each quartile group were compared and a clear separation of the PFS curves was observed in all quartile groups. Furthermore, Cox regression models, including the interaction term of treatment by case-control group, were fitted in the pooled data of all pairs of case-control patients (Table 8). A strong treatment effect was found for all quartiles although the HRs of the Q3 and Q4 groups were numerically lower than those of the Q1 and Q2 groups. The trending is similar to that observed in Table 7.

Table 8: Cox regression of progression-free survival for matched case-control groups after Mahalanobis Distance Matching for the RELAY part b ITT population

Matched Case-Control Group $C_{min,1}$ Quartiles	Placebo (Control) N/Events	Ramucirumab (Case) N/Events	Hazard Ratio (95% CI)
Q1	54/33	54/30	0.740 (0.446, 1.229)
Q2	54/35	54/33	0.818 (0.508, 1.317)
Q3	54/35	54/29	0.555 (0.338, 0.912)
Q4	54/35	54/27	0.523 (0.316, 0.866)

Abbreviations: CI = confidence interval; $C_{min,1}$ = minimum concentration after first dose administration; ITT = intent-to-treat; N = number of patients; Q = quartile.

Overall, the exposure-efficacy analyses identified no statistical relationship between ramucirumab exposure ($C_{min,1}$) and PFS. A strong treatment effect on PFS was observed over the entire range of exposures achieved by a dosage of 10 mg/kg given Q2W in the ITT population.

Exposure-Safety Analysis

Data from a total of 216 patients from the ramucirumab plus erlotinib arm and 225 patients from the placebo plus erlotinib arm were included in the exposure-safety analysis. The exposure-safety analysis evaluated 6 safety endpoints in the safety population, namely the 3 most common grade ≥3 treatment-emergent adverse events (TEAEs) occurring in at least 5% of patients in the ramucirumab plus erlotinib arm with a difference in incidence from the placebo plus erlotinib treatment arm of at least 2-percentage points and 3 adverse events of special interest (AESIs), as follows:

- Grade ≥3 TEAEs: (hypertension (preferred term [PT]), diarrhoea, dermatitis acneiform)
- AESIs: (hypertension [any grade], proteinuria [any grade and grade ≥3], and liver failure/liver injury [alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased (any grade)]).

Two exposure parameters, $C_{min,1}$ and $C_{min,ss}$ were used for exposure-safety relationship assessment and the findings were generally consistent. Only results based on $C_{min,ss}$ are presented in this report.

The observed incidence of the selected safety endpoints by exposure quartiles was first summarized descriptively. Additional ordered categorical analysis was conducted only if a trend was observed in graphical examinations.

Grade ≥3 Treatment Emergent Adverse Events (TEAEs)

The incidence of the selected grade ≥3 TEAEs, including hypertension, diarrhoea, and dermatitis acneiform by $C_{min,ss}$ quartile is shown in Figure 6. Although the observed incidences of each ramucirumab plus erlotinib $C_{min,ss}$ quartile were greater than that of the placebo plus erlotinib arm for all 3 selected grade ≥3 TEAEs, no trend of increasing incidences with increasing exposure was observed. Therefore, no additional ordered categorical analysis was conducted.

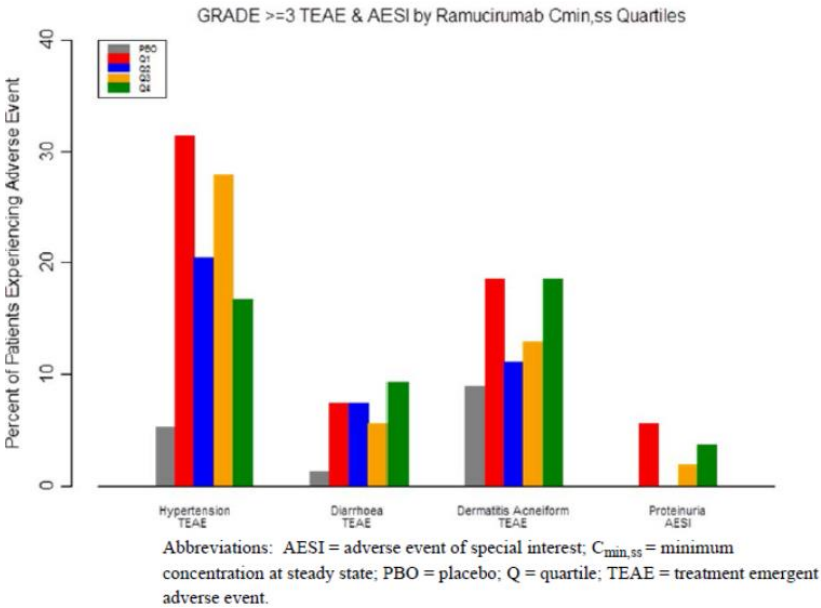
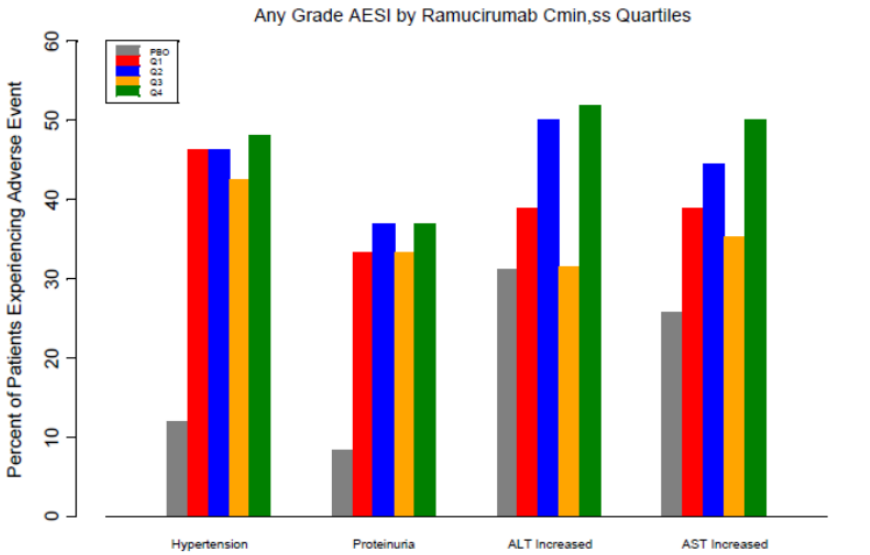


Figure 6: Observed incidence of the selected Grade ≥3 TEAE and AESI by quartile of ramucirumab $C_{min,ss}$ in the RELAY part B safety population.

Adverse Events of Special Interest (AESI)

A summary of incidence of the selected AESI by $C_{min,ss}$ quartile is shown in Figure 6 (grade ≥3 proteinuria), and in Figure 7 (any grade hypertension, proteinuria, and liver failure/liver injury).

The observed incidences of each ramucirumab plus erlotinib $C_{min,ss}$ quartile were generally greater than that of the placebo plus erlotinib arm for all of the selected AESIs (any grade and grade ≥3). For the AESIs of any grade ALT or AST increased, a trend towards highest incidence of any grade ALT or AST increased was observed in the highest ramucirumab exposure group (Figure 7). No association between increased ramucirumab concentration exposure and incidence was observed for any grade hypertension (Figure 7) and proteinuria (any grade [Figure 7] and grade ≥3 [Figure 6]). Therefore, additional ordered categorical analysis was only conducted for any grade ALT and AST increased.



Abbreviations: AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; $C_{min,ss}$ = minimum concentration at steady state; PBO = placebo; Q = quartile.

Figure 7: Observed incidence of the selected any grade AESI by quartile of ramucirumab Cmin,ss in the RELAY part B safety population.

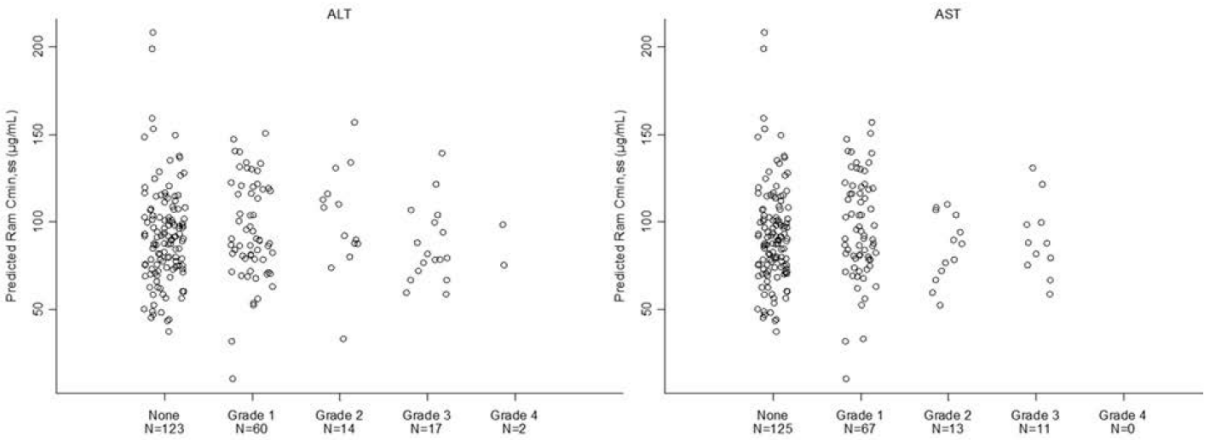
Ordered Categorical Model for ALT and AST Increased

A summary of the numbers of patients with each grade of AST or ALT increased grouped by treatment arms is presented in Table 9. Grade 1 incidence appeared to be the primary contribution to the difference observed between ramucirumab plus erlotinib and placebo plus erlotinib for any grade ALT or AST increased. Comparable incidences were observed between the 2 treatment arms for all other grades of ALT or AST increased except for grade 2 AST increased. The observed incidence of grade 2 AST increased was numerically higher in the ramucirumab plus erlotinib arm (6.0%) relative to that in the placebo plus erlotinib arm (2.2%). Figure 8 shows ramucirumab exposure distribution for each grade of ALT or AST increased. The results suggest that the severity of AST or ALT increased was unlikely related to ramucirumab exposure.

Table 9: Observed incidence of each grade 'ALT increased' and each grade 'AST increased' by treatment arm in the RELAY part B safety population

AE Grade	ALT Increased		AST Increased	
	Placebo + Erlotinib n (%)	Ramucirumab + Erlotinib n (%)	Placebo + Erlotinib n (%)	Ramucirumab + Erlotinib n (%)
None	155 (68.9)	123 (56.9)	167 (74.2)	125 (57.9)
Grade 1	33 (14.7)	60 (27.8)	43 (19.1)	67 (31.0)
Grade 2	20 (8.9)	14 (6.5)	5 (2.2)	13 (6.0)
Grade 3	14 (6.2)	17 (7.9)	9 (4.0)	11 (5.1)
Grade 4	3 (1.3)	2 (0.9)	1 (0.4)	0 (0)
Number of Patients (N)	225	216	225	216

Abbreviations: % = percentage of patients experiencing adverse event grade; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; N = number of patients; n = number of patients experiencing a particular grade of adverse event.



Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; $C_{min,ss}$ = minimum concentration at steady state; N = number of patients; Ram = ramucirumab.

Figure 8: Distribution of predicted ramucirumab $C_{min,ss}$ by grade of ALT and AST increased for patients in ramucirumab plus erlotinib arm in the RELAY Part B safety population.

Overall, exposure-safety analyses showed no clear relationship between ramucirumab exposure and the incidence of selected safety endpoints, including the most common grade ≥3 TEAEs (hypertension, diarrhoea, and dermatitis acneiform) and AESIs (any grade hypertension, any grade and grade ≥3 proteinuria, liver failure/liver injury [any grade ALT or AST increased]), over the range of exposures achieved by a dosage of 10 mg/kg given intravenously Q2W.

Exposure-Dose Adjustment analysis

The RELAY protocol (provided specific instructions for dose adjustments (dose delays [ramucirumab or placebo only], dose reductions and dose omissions) of ramucirumab/placebo and of erlotinib due to AEs.

Dose adjustments of each treatment (ramucirumab and erlotinib or placebo and erlotinib) were summarized by ramucirumab $C_{min,ss}$ and $C_{min,1}$ quartiles for the exposure-safety analysis population. The results were generally consistent between these 2 exposure parameters.

The summary results by ramucirumab and erlotinib $C_{min,ss}$ (for all causes) are presented in Figure 9. Analogous results were obtained for analysis by ramucirumab and erlotinib $C_{min,ss}$ (cause due to AEs) analysis by ramucirumab $C_{min,\ 1}$.

Ramucirumab

No apparent relationship was observed between ramucirumab exposure and dose adjustments (dose delay, dose reduction, dose omission) of ramucirumab (Figure 9, panel A). However, the percentage of patients with dose adjustments of ramucirumab in all 4 ramucirumab plus erlotinib quartiles was generally higher in the ramucirumab plus erlotinib arm as compared with the placebo plus erlotinib arm.

Erlotinib

No apparent relationship was observed between ramucirumab exposure and dose adjustments (dose reduction and dose omission) of erlotinib (Figure 9, panel B). The percentage of patients with dose adjustments of erlotinib was generally similar among the placebo plus erlotinib arm and all 4 ramucirumab plus erlotinib quartiles.

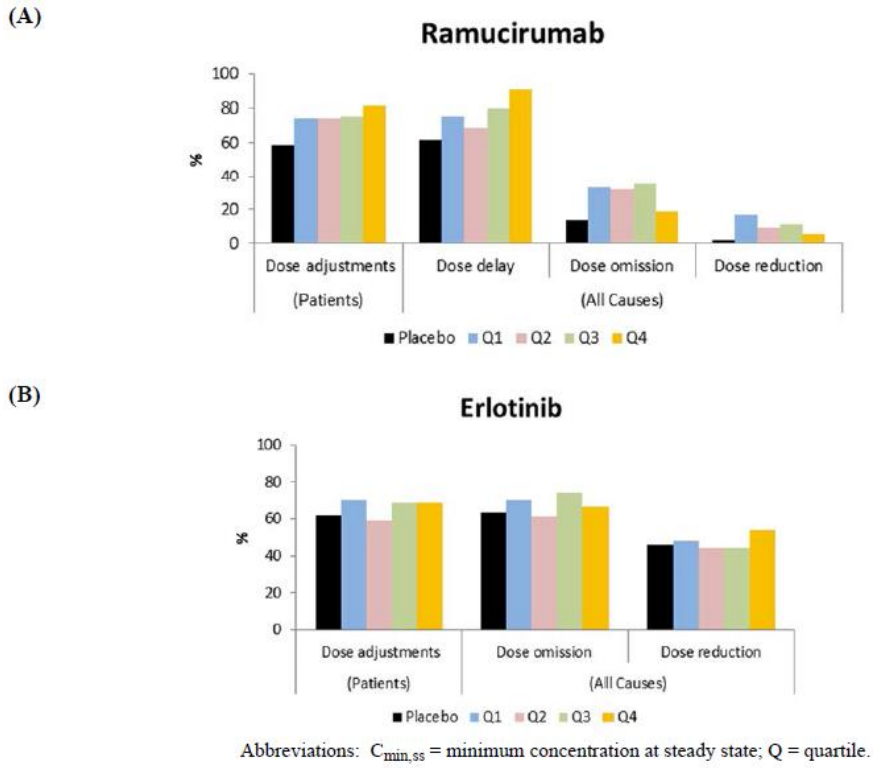


Figure 9: Summary of dose adjustments of (A) ramucirumab or placebo and (B) erlotinib by $C_{min,ss}$ quartiles in the RELAY Part B safety population due to all causes.

Overall, increasing ramucirumab exposure did not appear to be associated with an increased percentage of dose adjustments for ramucirumab or erlotinib over the range of exposures achieved by a dosage of 10 mg/kg given intravenously Q2W.

Immunogenicity

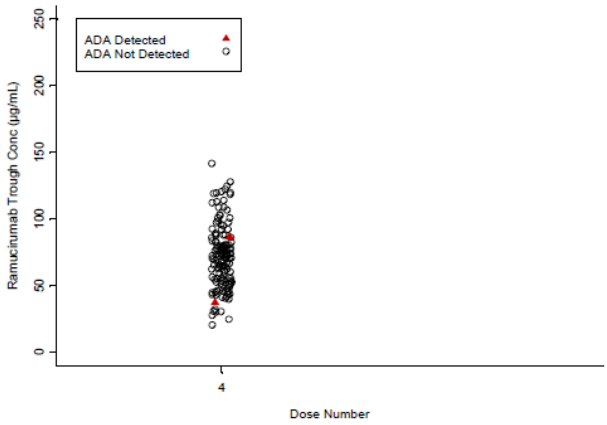
The incidence of ramucirumab immunogenicity was analysed in the RELAY study. This assessment was conducted in the safety population of RELAY, which consisted of all patients who received at least 1 dose of ramucirumab or placebo.

The immunogenicity of ramucirumab in RELAY in first-line metastatic NSCLC patients with activating EGFR mutations was low. Of the 416 evaluable patients, 6 were treatment–emergent ADA positive (1 patient in the ramucirumab plus erlotinib arm and 5 patients in the placebo plus erlotinib arm), and 410 patients were treatment–emergent ADA-negative.

One patient (0.5%) in the ramucirumab plus erlotinib arm and 5 patients (2.4%) in the placebo plus erlotinib arm developed ADA, which is consistent with results obtained in prior indications. No neutralizing antibodies were detected in any of the 6 patients who were treatment–emergent ADA positive in either treatment arm.

Effect of Immunogenicity on PK

As indicated in Figure 10, ramucirumab trough concentrations for the 2 Cycle 4 trough samples in which ADAs were detected were within the range of ramucirumab concentrations for samples, which did not have ADA detected. However, the limited number of time-matched ramucirumab trough samples precluded definitive conclusions regarding the effect of immunogenicity on ramucirumab PK



Abbreviations: ADA = anti-drug antibodies; Conc = concentration

Figure 10: Individual ramucirumab trough concentrations at Cycle 4 (Dose 4).

Effect of Immunogenicity on Safety

The AE profile in patients who tested positive for ramucirumab ADA either at baseline or post baseline (that is, treatment-emergent ADA positive) was consistent with that observed in the overall safety population. Specifically, any association between the presence of baseline ADA or post-baseline treatment-emergent ADA and the occurrence of infusion-related reactions, including anaphylactic reactions was evaluated. Infusion-related reactions were identified based on timing of events relative to study drug administration. Immediate hypersensitivity reactions (HSRs), defined as hypersensitivity events occurring on the day of drug administration, are considered more specific to identify infusion-related reactions. There were no reports of infusion-related reactions in treatment-emergent ADA-positive patients in either treatment arm. Overall, 14 treatment-emergent ADA-negative patients (7 patients in each treatment arm) reported an infusion-related reaction. The frequency of infusion-related reactions was low, and no difference was observed in the incidence of IRRs between treatment-emergent ADA-positive patients (0.0%) and treatment-emergent ADA-negative patients (3.4%). The evaluation of the data did not support that infusion-related reactions were mediated by treatment-emergent ADAs.

Overall immunogenicity incidence in RELAY submission combined with the REACH-2 submission

The overall immunogenicity incidence, including 25 studies across different indications, was previously reported in the REACH-2 submission. This cumulative summary from the REACH-2 submission has been updated to include data from the RELAY submission (Table 10).

The updated incidence of treatment-emergent ADA for all ramucirumab treated-patients and placebo-treated patients was 2.9% and 2.1%, respectively. Addition of results from RELAY had no effect on the immunogenicity conclusions of the overall ramucirumab program.

Table 10: Immunogenicity incidence for ramucirumab and placebo treated patients from the RELAY study and the cumulative REACH-2 submission

Submission	Patients Treated	Patients Analyzed Baseline			Patients Analyzed Postbaseline			
		Patients Analyzed[a]	ADA+ n (%)	NAb+ n[b]	Patients Analyzed[a]	ADA+ n (%)	Treatment-emergent ADA (%)	NAb+ n[b]
Ramucirumab treated patients								
RELAY	221	206	14 (6.8)	0	206	3 (1.5)	1 (0.5)	0
Reported in REACH-2 submission (25 Studies; see Table APP.2.7.2.13)	3653	2317	113 (4.9)	1	3059	158 (5.2)	94 (3.1)	14
Total (%):	**3874**	**2523**	**127 (5.0)**	**1**	**3265**	**161 (4.9)**	**95 (2.9)**	**14**
Placebo treated patients								
RELAY	225	210	18 (8.6)	0	210	20 (9.5)	5 (2.4)	0
Reported in REACH-2 submission (25 Studies; see Table APP.2.7.2.14)	2343	1811	102 (5.6)	1	1924	137 (7.1)	40 (2.1)	4
Total (%):	**2568**	**2021**	**120 (5.9)**	**1**	**2134**	**157 (7.4)**	**45 (2.1)**	**4**

Abbreviations: ADA = antidrug antibodies; ADA+ = ADA positive; n = number of patients; NAb = neutralizing antibodies; NAb+ = NAb positive.

2.3.4. Discussion on clinical pharmacology

The clinical pharmacology package of this type II variation includes ramucirumab PK and immunogenicity data from the target population, drug-drug interactions, and exposure-response analyses. These analyses were based on data obtained in the RELAY study.

Ramucirumab PK

Administration of ramucirumab to NSCLC patients in the RELAY study using the 10 mg/kg Q2W posology yielded a C_{min} of 68.5 µg/ml (range of 20.3-142 µg/ml) and 85.7 µg/ml (range of 36.0 -197 µg/ml) prior to administration of the fourth and seventh two-weekly dose, respectively. This exposure is somewhat higher than that obtained following administration of ramucirumab 10 mg/kg Q3W, as was used for the treatment of NSCLC patients with ramucirumab and docetaxel in the REVEL study (with geometric means of ramucirumab C_{min} of 28.3 µg/ml (range of 2.5-108 µg/ml) and 38.4 µg/ml (range of 3.1-128 µg/ml) prior to administration of the third and fifth dose). This higher C_{min} in the RELAY study is in line with the shorter dosing interval in the RELAY study as compared to the REVEL study, i.e., 10 mg/kg *Q2W* and *Q3W*, respectively.

Further, dose-normalised ramucirumab peak concentrations obtained with ramucirumab given as 10 mg/kg Q2W in the RELAY study were comparable with those obtained at an 8 mg/kg Q2W dose given in other clinical studies with ramucirumab, indicating a relatively modest increased absolute ramucirumab peak exposure in the RELAY study.

Sparse ramucirumab PK data collected in the RELAY study were analysed also using a previously developed PopPK model. The PK of ramucirumab in the RELAY study were reasonably well described by the previously established 2-compartment model with time-varying clearance. In the RELAY patient population, geometric mean (coefficient of variation) steady state ramucirumab PopPK model-derived estimates were as follows:

- clearance, 0.0113 L/hour (22.1%);
- volume of distribution at steady state (Vss), 4.03 L (15.1%);
- apparent terminal elimination half-life (t1/2), 10.7 days (20.7%).

These ramucirumab PK properties in first-line treatment of patients with metastatic NSCLC with activating EGFR mutations were found to be similar to other patient populations with different tumour types and different lines of therapy, as well as among different races.

Drug-drug interactions

The comparable PK of ramucirumab in the RELAY study in combination with erlotinib as compared to the other clinical studies in which ramucirumab was given as singe agent indicates that co-administration of erlotinib is unlikely to affect ramucirumab PK.

A DDI substudy was conducted in the RELAY study to assess the effect of concomitant ramucirumab on the PK of erlotinib. Based on non-compartmental methods of analysis on concentration-time data from 11 patients in the ramucirumab plus erlotinib arm and 15 patients in the placebo plus erlotinib arm, it was concluded that distribution of erlotinib exposure parameters in plasma were generally similar between the ramucirumab plus erlotinib and placebo plus erlotinib arms. The ratios of geometric LS means and 90% CIs at 1.23 (90% CI; 1.02, 1.50) for AUC_{TAU} and 1.14 (90% CI; 0.97, 1.34) for C_{max}, indicated that co-administration with ramucirumab is unlikely to affect erlotinib PK.

Exposure-response analyses

ER analyses were performed to characterize the relationship between ramucirumab exposure and selected measures of efficacy and safety in first-line treatment of patients with metastatic NSCLC with activating EGFR mutations.

For efficacy, the ER analysis encompassed PFS. The exposure-efficacy analysis identified no statistically significant relationship between ramucirumab exposure ($C_{min,1}$) and PFS. A strong treatment effect on PFS was observed over the entire range of exposures achieved by a dosage of 10 mg/kg given Q2W in the ITT population. The lack of a statistically significant relationship between ramucirumab $C_{min,1}$ and PFS is different from the findings from other ramucirumab Phase 3 studies in the second-line setting. A potential explanation may be the somewhat more intense dosing regimen that was applied in the RELAY study as compared to other studies.

The ER analyses for safety evaluated 6 safety endpoints in the safety population, namely the 3 most common grade ≥3 TEAEs occurring in at least 5% of patients in the ramucirumab plus erlotinib arm and 3 AESIs, i.e., hypertension, proteinuria and liver failure/liver injury. The exposure-safety analyses showed no relationship between ramucirumab exposure and the incidence of selected safety endpoints over the range of exposures achieved by a dosage of 10 mg/kg given intravenously Q2W. Finally, increasing ramucirumab exposure did not appear to be associated with an increased percentage of dose adjustments for ramucirumab or erlotinib over the range of exposures achieved by a dosage of 10 mg/kg given intravenously Q2W.

The incidence of treatment-emergent anti-drug antibody in the RELAY study was low and consistent with the known immunogenicity profile of ramucirumab and with the overall ramucirumab-treated population: 1 patient (0.5%) in the ramucirumab plus erlotinib arm and 5 patients (2.4%) in the placebo plus erlotinib arm. None of the 6 patients who were treatment-emergent ADA positive in either treatment arm had neutralizing antibodies. There was no observed link for ramucirumab between immunogenicity and safety for patients in RELAY, including occurrence of infusion-related reactions.

Due to the low rate of ADA formation, no definitive conclusions could be drawn on the potential effect of ADA on PK, though an effect seems unlikely, and no analysis of the effect of immunogenicity on efficacy was conducted.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology package supporting this type II variation, including ramucirumab and erlotinib PK and immunogenicity data from the target NSCLC population, drug-drug interactions, and exposure-response analyses, is sufficient in support of the application.

2.4. Clinical efficacy

The applicant submitted a single pivotal clinical trial (I4T-MC-JVCY) to support this extension of indication for Cyramza. Study I4T-MC-JVCY (RELAY) was a global, multicentre, randomised, placebo-controlled, double-blind, phase 1b/3 study to evaluate the safety and efficacy of ramucirumab in combination with erlotinib for the first-line treatment of patients with metastatic NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.

The applicant sought scientific advice in 2014 (EMEA/H/SA/1505/7/2014/II) on key study design elements for study RELAY. The applicant asked whether the CHMP agreed with PFS as primary endpoint and erlotinib as backbone therapy.

2.4.1. Dose response study

The selection of the ramucirumab 10 mg/kg Q2W dosing regimen in the RELAY study was based on an integrated assessment of the following previously available clinical data:

- *clinical safety data in early multiple dose ascending (MAD) studies, I4T-IE-JVBM (JVBM) and I4T-IE-JVBN (JVBN).* Weekly doses of ramucirumab ranging from 2 to 16 mg/kg were evaluated in the phase 1 Study JVBM. The MTD for weekly dosing was identified as 13 mg/kg every week. Further, every-2-week (6 to 10 mg/kg) and every-3-week (15 to 20 mg/kg) dose regimens were evaluated in an additional dose-ranging study (Study JVBN). All dose regimens in Study JVBN were well tolerated and no MTD was identified in this study.
- *clinical efficacy and safety data in REVEL, a randomized, placebo-controlled, double blind, multicentre phase 3 study of patients with stage IV NSCLC who had disease progression during or after 1 prior first-line platinum-based therapy for metastatic disease*. In this REVEL study, the ramucirumab dose of 10 mg/kg given every 3 weeks in combination with docetaxel, demonstrated statistically significant benefit in overall survival (OS) and a favourable benefit-risk profile in patients with NSCLC.
- *ER findings from prior randomised, second-line phase 3 ramucirumab studies in gastric or GEJ adenocarcinoma (REGARD and RAINBOW) and REVEL*. Exposure-efficacy response analyses performed on data obtained from these second-line phase 3 studies suggested that an increase in exposure may be associated with improvement in efficacy in terms of both OS and PFS.

At the time of RELAY study design, the applicant considered that the totality of clinical data indicated that there may be an opportunity to further enhance efficacy of ramucirumab while maintaining an acceptable safety profile by choosing a dosing regimen which produces higher ramucirumab exposure than the approved dosing regimen in second line NSCLC, 10 mg/kg every 3 weeks. Based on PK simulation, a dose regimen of 10 mg/kg on Day 1 Q2W was selected for Study JVCY for the following reasons:

- Using the same 10 mg/kg dose level as REVEL, the C_{max} level should not be significantly increased and, therefore, it may help mitigate any potential C_{max} related safety risk. The more frequent interval should produce higher overall exposure which may help maximize efficacy of ramucirumab.
- It is expected that ramucirumab-related AEs in the NSCLC indication may not be significantly increased using the selected ramucirumab dose of 10 mg/kg Q2W, since the selected dose for the RELAY Study is still approximately 60% lower than the maximum tolerated weekly dose identified in the phase 1 dose-escalation study, Study JVBM (13 mg/kg weekly).

The actual safety and tolerability of the chosen ramucirumab dose (10 mg/kg Q2W) in combination with erlotinib (150 mg/day) was initially investigated in part A of study RELAY, prior to start of the phase 3 part B of this study.

RELAY (I4T-MC-JVCY) – part A (phase 1b, safety lead-in portion of the study)

Part A of the RELAY study was a single-arm, open-label, phase 1b study to confirm the safety and tolerability of ramucirumab, at the recommended phase 3 (part B) dose (10 mg/kg Q2W), in combination with erlotinib (150 mg/day).

Methods

The planned target enrolment of part A was 12 patients (6 patients from Japan and 6 patients from North America and Europe).

Study participants

Refer to part B of the RELAY study.

Objectives

Primary objective:

The primary objective of part A was to assess the safety and tolerability of ramucirumab (10 mg/kg every 2 weeks [Q2W]) when administered in combination with erlotinib (150 mg/day) as therapy in previously untreated patients with EGFR mutation-positive metastatic NSCLC.

Treatments

Patients received the following:

- Ramucirumab (10 mg/kg) intravenous (IV) infusion over approximately 1 hour on day 1 of each cycle (14 days [±3 days]) followed by a 1-hour observation period. If there was no evidence of an infusion-related reaction (IRR) after the initial and second infusions of ramucirumab, no observation period was required for subsequent treatment cycles (in the event an IRR occurred thereafter, then the 1-hour observation should have been reinstituted).

- Erlotinib (150 mg) orally once daily. On day 1 of each cycle, patients received erlotinib after completion of ramucirumab infusion (after the observation period, post-ramucirumab infusion).

Dose-limiting toxicities

The dose-limiting toxicity (DLT) assessment period was through two 2-week treatment cycles, cycles 1 and 2 (totalling approximately 4 weeks).

DLT definitions included:

- Grade 4 anaemia
- Grade ≥3 thrombocytopenia
- Grade ≥3 febrile neutropenia
- Grade 4 neutropenia lasting >7 days
- Elevated urine protein of ≥3 g/24 hour
- Grade 4 or refractory hypertension
- Grade ≥3 non-hematologic toxicity excluding electrolyte abnormality or grade 3 skin rash

A patient in part A who either completed cycle 2 or discontinued from study treatment or study participation before completing 2 cycles due to a DLT was considered DLT-evaluable.

A DLT-non-evaluable patient was considered one who experienced disease progression, was noncompliant, or discontinued for reasons other than AEs within the first 2 cycles of treatment. Any patient who discontinued from the study before completing safety monitoring for the DLT assessment period for any other reason than DLT was considered non-evaluable for DLT assessment. Additional patients were enrolled as replacements for non-evaluable patients.

Safety data throughout part A were evaluated by an assessment committee (AC).

Upon review of safety data, the AC recommendation may have recommended one of the following:

- to start enrollment in part B with the starting dose of 10 mg/kg Q2W
- to enroll 3 additional patients at 10 mg/kg Q2W and reassess the dose tolerability once these additional 3 patients complete the DLT Assessment Period
- to start enrollment in part B with the starting dose of 8 mg/kg Q2W
- to stop the study

Statistical and analytical plans

Analysis populations

The safety population consists of all patients enrolled in part A and received at least 1 dose of any study treatment. The DLT-evaluable population consists of patients who either completed first 2 cycles of treatment (approximately 28 days +3 days) or discontinued from study treatment or study participations before completing first 2 cycles due to a DLT.

Safety

DLT assessment was performed in the DLT-evaluable population for the AEs reported during the DLT assessment period. The number of patients who experienced any DLT was presented based on the DLT-evaluable population.

All other safety analyses were performed using the part A safety population. The safety data collected in part A were not combined with the safety data collected in part B.

Sample size

At least 12 previously untreated patients with metastatic NSCLC with EGFR activating mutations were planned to be enrolled. Patients were enrolled across 2 countries (6 patients from Japan; 6 patients from Europe [Spain]). Since only 2 dose levels were considered, a modified 3+3 design was used for each cohort in Part A.

The recommended dose of ramucirumab for Part B was decided based on the following rules:

- If the proportion of patients experiencing DLT was <33% (0 or 1 patient with any DLTs) for DLT-eligible patients from each of the cohorts during the first 2 cycles, the ramucirumab starting dose in Part B would be 10 mg/kg Q2W.
- If the proportion of patients experiencing DLTs was ≥33% (2 or more patients with any DLTs) for DLT-eligible patients from any of the cohorts during the first 2 cycles, the ramucirumab starting dose in Part B would depend on AC recommendation.

Results

The part A safety population included 14 treated patients: 7 patients in Japan and 7 patients in Spain. Two patients in the safety population discontinued from ramucirumab and/or erlotinib before completion of cycle 2 because of non-DLT AEs, and therefore the DLT-evaluable population for the DLT assessment included 12 patients (6 patients in Japan and 6 patients in Spain).

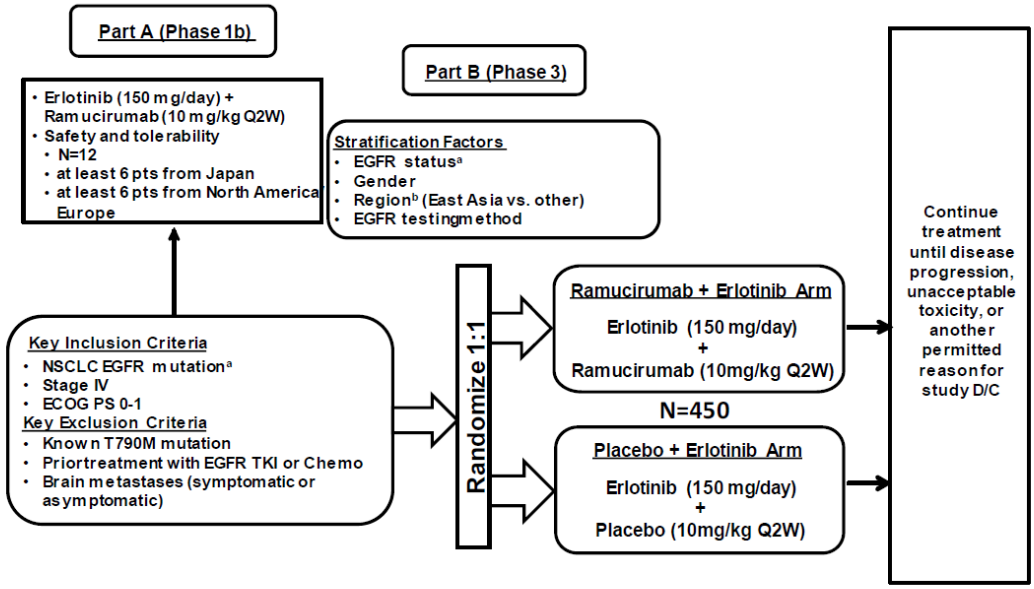
In the DLT-evaluable population, 1 patient experienced a DLT of grade 3 increased alanine aminotransferase (ALT) in cycle 2. This event was assessed as related to study treatment and led to discontinuation from the study and the event resolved.
Following DLT review in part A (on 16 December 2015), the AC recommended to initiate the randomised phase 3 portion of the study (part B) with ramucirumab at 10 mg/kg Q2W in combination with erlotinib 150 mg/daily.

2.4.2. Main study

RELAY (I4T-MC-JVCY) – part B

Part B of the RELAY study was a randomised, double-blind, phase 3 study that compared the efficacy and safety of treatment with ramucirumab plus erlotinib versus placebo plus erlotinib.

Figure 11 presents the study design of part A (phase 1b) and part B (phase 3).



Abbreviations: D/C = discontinuation; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; N = number of patients; NSCLC = non-small cell lung cancer; pts = patients; Q2W = every other week; TKI = tyrosine kinase inhibitor.

[a] Defined as exon 19 deletion or exon 21 (L858R) substitution mutation.

[b] East Asia includes: South Korea, Hong Kong, Japan, and Taiwan; Other includes: Canada, France, Germany, Italy, Romania, Spain, Turkey, United States, and United Kingdom.

Figure 11: Study design of part A and part B of RELAY.

Methods

Study participants

Key inclusion criteria:

- The patient had cytologically or histologically confirmed diagnosis of stage IV NSCLC.
    - Patients with recurrent metastatic disease were permitted to enter the study as long as the adjuvant or neo-adjuvant therapy was completed at least 12 months prior to the development of metastatic disease. However, prior adjuvant or neo-adjuvant therapy was not required.
- The patient was eligible for first-line treatment with erlotinib based on previously documented evidence of tumour that has EGFR exon 19 deletion or exon 21 (L858R) substitution mutation.
- The patient consented to submit an archived formalin-fixed paraffin embedded (FFPE) stage IV NSCLC tissue sample for assessment of biomarkers unless restricted per local regulations. For patients who did not submit stage IV disease tissue samples, a plasma sample for disease characterization was required unless restricted by local regulations. Once consented, availability of an adequate tumour tissue sample or any necessary plasma sample was required for study eligibility.

  Note: This tissue sample collection was not mandatory for patients enrolled in part A.
- The patient had at least one or more measurable lesions attributed to NSCLC at the time of study entry, documented by CT scan or MRI, as defined by RECIST v1.1.
- The patient had an ECOG PS of 0 or 1 and adequate organ function.

- The patient was at least 18 years of age or of an acceptable age according to local regulations and agreed to local requirements regarding methods and duration of contraception.

Key exclusion criteria:

- The patient had known T790M EGFR mutation.
- The patient had known leptomeningeal carcinomatosis, uncontrolled/unstable spinal cord compression, or CNS metastases.
- The patient had any evidence of clinically active interstitial lung disease (ILD).
- The patient had any prior anticancer therapy for stage IIIB/IV NSCLC, including prior TKI therapy for any stage.
- The patient had radiologically documented evidence of major blood vessel invasion or encasement by cancer.
- The patient had radiographic evidence of intratumour cavitation, regardless of tumour histology.
- The patient had pre-existing idiopathic pulmonary fibrosis; or has or had any disease of acute lung injury, idiopathic pulmonary fibrosis, disease of radiation pneumonia, or drug-induced pneumonia.
- The patient had a history of gross haemoptysis within 2 months prior to enrolment.
- The patient was receiving chronic therapy with nonsteroidal anti-inflammatory agents (NSAIDs) or other antiplatelet agents within 7 days prior to first dose of study treatment. Aspirin use at doses up to 325 mg/day was permitted.
- The patient had significant bleeding disorders, vasculitis, or experienced grade 3/4 gastrointestinal (GI) bleeding within 3 months prior to enrolment.
- The patient has experienced any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to enrollment.
- The patient had hepatic impairment (such as severe liver cirrhosis Child-Pugh B [or worse], cirrhosis with a history of hepatic encephalopathy, clinically meaningful ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis, or patients with a history of hepatorenal syndrome).
- The patient had uncontrolled hypertension, defined as systolic blood pressure >150 mmHg or diastolic blood pressure >90 mmHg, despite standard medical management.

Treatments

Patients received the following:

- Ramucirumab (10 mg/kg) or placebo (indistinguishable and equivalent volume to ramucirumab) IV infusion over approximately 1 hour on day 1 of each cycle (14 days [±3 days]). If there was no evidence of an IRR after the initial and second infusions of ramucirumab or placebo, no observation period was required for subsequent treatment cycles (in the event an IRR occurred thereafter, then the 1-hour observation should have been reinstituted).

- Erlotinib (150 mg) orally once daily. On day 1 of each cycle, patients received erlotinib after completion of ramucirumab infusion (after the observation period, post-ramucirumab infusion).

Premedication with a histamine H1 antagonist (for example, 50 mg of [IV] diphenhydramine or equivalent, unless otherwise restricted by local requirements) was required 30 to 60 minutes prior to infusion of

ramucirumab or placebo. Additional premedication may have been provided at investigator discretion. Premedication must have been provided in the setting of a prior grade 1 or 2 IRR.

Objectives

Primary objective:

The primary objective was to compare the progression free survival (PFS) of ramucirumab administered in combination with erlotinib versus placebo in combination with erlotinib in previously untreated patients with EGFR mutation-positive metastatic NSCLC.

Secondary objectives:

The secondary objectives were to compare ramucirumab administered in combination with erlotinib versus placebo administered in combination with erlotinib for:

- safety and toxicity profile
- overall survival (OS)
- objective response rate (ORR) (complete response [CR] + partial response [PR])
- disease control rate (DCR) (CR + PR + stable disease [SD])
- duration of response (DoR)
- pharmacokinetics (PK) and immunogenicity of ramucirumab
- patient-reported outcomes (using Lung Cancer Symptom Scale [LCSS] and EuroQol 5-dimension, 5-level questionnaire [EQ-5D-5L])
- drug-drug interaction (DDI) sub-study at selected sites in approximately 15 patients per arm to assess the PK of erlotinib with and without ramucirumab.

Exploratory objectives:

The exploratory objectives of part B were as follows:

- comparison of progression-free survival 2 (PFS2) between treatment arms
- association between biomarkers and clinical outcome
- time to deterioration (TtD) in Eastern Cooperative Oncology Group (ECOG)
- performance status (PS)
- time to diagnosis of CNS metastases
- PFS2 and OS analyses for patients who received osimertinib after disease progression versus those who did not time to response (CR or PR) for responders.

Outcomes/endpoints

Primary efficacy endpoint:

The primary endpoint was investigator-assessed PFS, defined as the time from the date of randomisation until the date of radiographic documentation of progression (as defined by RECIST v1.1) or the date of death due to any cause, whichever was earlier. **Table 11** lists rules for determining date of progression or censor for PFS. Censoring was taken in the following order:

- If a patient did not have a baseline disease assessment, then the PFS time was censored at the randomisation date, regardless of whether or not objective PD or death had been observed for the patient; otherwise,
- If a patient was not known to have died or have investigator-assessed PD as of the data-inclusion cut-off date for the analysis, the PFS time was censored at the date of last post-baseline adequate radiological tumour assessment, or at the date of randomisation if the patient did not have any post-baseline adequate radiological assessment.

Table 11: Rules for determining date of progression or censor for progression-free survival

Rule	Situation	Date of Progression or Censor	Outcome
1	No baseline tumor assessments	Date of Randomization	Censored
2	No postbaseline assessments and no death	Date of Randomization	Censored
3	No documented progression and no death (with a postbaseline tumor assessment)	Date of last adequate tumor assessment	Censored
4	Patient lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last adequate tumor assessment	Censored
5	Documented progression	Date of documented progression If a tumor assessment was done on multiple days, use the earliest date for that visit.	Progressed
6	Death without documented progression	Date of death	Progressed
7	Documented progression or death after missing ≥2 consecutive postbaseline tumor assessments	Date of last adequate tumor assessment before missed assessments or date of randomization, whichever is later	Censored
8	New anticancer treatment started and no tumor progression or death within 14 days	Date of adequate tumor assessment prior to start of new anticancer treatment +14 days or date of randomization, whichever is later	Censored

Note: PFS and associated outcome is determined by the earliest of the dates above, if more than 1 situation applies.

Secondary efficacy endpoints:

Secondary efficacy endpoints included OS, ORR, DCR, and DoR. Assessment for response, according to RECIST. The secondary endpoints are shown in **Table 12**.

Table 12: Secondary efficacy endpoints

Secondary Endpoint	Definition
Overall survival (OS)	Time from the date of randomization to the date of death from any cause. For each patient who was not known to have died as of the data-inclusion cutoff date for a particular analysis, OS was censored for that analysis at the date of last contact prior to the data-inclusion cutoff date (contacts considered in the determination of last contact date include AE date, lesion assessment date, visit date, and last known alive date).
Objective response rate (ORR)	Proportion of randomized patients achieving a best overall response of partial response (PR) or complete response (CR) per RECIST v1.1. Patients who did not have any postbaseline tumor response assessments for any reason were considered non-responders and were included in the denominator when calculating the response rate. Note. Tumor assessments performed after initiation of new anticancer treatment (systemic therapy) were excluded from evaluating the best overall response
Disease Control Rate (DCR)	Proportion of randomized patients achieving a best overall response of CR, PR, or stable disease (SD) per RECIST v1.1. Patients who did not have any postbaseline tumor response assessments for any reason were considered non-responders and were included in the denominator when calculating the response rate. Note. Best overall response was the best response recorded from the start of treatment until disease progression, in the order of CR, PR, and SD. Refer to Attachment 7 of the protocol, provided in an appendix to this report (Protocol and Addenda), for definitions of CR, PR, and SD.
Duration of Response (DoR)	From the date of first documented CR or PR (responder) to the date of objective progression or the date of death due to any cause, whichever was earlier. If a responder was not known to have died or have objective progression, then the patient was censored at the date of last evaluable tumor assessment.
Patient Reported Outcomes	
Average Symptom Burden Index (ASBI)	Calculated as the mean of the 6 symptom items of the LCSS. The ASBI was not computed for a patient if he/she had one or more missing values for the 9 items.
EQ-5D-5L index score	Calculated as recommended by EuroQol. Index score and VAS were calculated for each assessment period as per current recommendations (van Hout et al. 2012). The index score was calculated from a set of item weights to derive a score of 0 to 1, with 1 representing the best health status. United Kingdom (UK) weights were applied for the base case. The index score was computed for a patient if he/she had one or more missing values for the 5 items.

Change from baseline for each LCSS or EQ-5D item at any post-baseline visit was calculated by subtracting baseline assessment result from the current assessment result.

- LCSS total score was calculated as the mean of the 9 LCSS items. The LCSS total score was not computed for a patient if he/she had one or more missing values for the 9 LCSS items.

- Maximum change for each LCSS item was defined as the largest decrease from baseline, which was the smallest (that is, most negative or smallest positive) non-missing value among all change from baseline values. Note: negative values of change from baseline (that is, decreases in the LCSS score towards the lower end of the symptom scale) indicate improvement in symptoms. For a patient and given LCSS item, if all change values are positive, the smallest positive change will be the maximum change; if at least one change value is negative, the most negative value will be the maximum change.

- Time to deterioration (TtD) for each of the 9 LCSS items, Average Symptom Burden Index (ASBI), and the LCSS total score was defined as the time from the date of randomisation until the date of the first ≥15-mm increase from baseline (de Marinis et al. 2008). Alternative definitions of minimally important differences may have been explored as needed. Patients without deterioration were censored on the date of the patient's last post-baseline LCSS assessment for this item or randomisation date, whichever was last.

Exploratory efficacy endpoints:

Exploratory endpoints are shown in **Table 13**.

Table 13: Exploratory efficacy endpoints

Exploratory Endpoint	Definition/Assessment
Progression-free survival 2 (PFS2)	Time from randomization to second objective disease progression, or death from any cause, whichever occurred first. Patients alive and for whom a second objective disease progression had not been observed should have been censored at the last time known to be alive and without second objective disease progression.
Time to response	Time from randomization to response (CR or PR) for those patients that responded only.
Translational research	Association between biomarkers and clinical outcome (please see below for details on biomarker variables)
Time to deterioration (TtD) in ECOG PS	Time from the date of randomization to the first date observing a change (that is, deterioration) in ECOG PS to ≥2. Variations of the definition were: 1) a change to ≥3, 2) a change of ≥2 levels from baseline, and 3) a change of ≤1 level from baseline.
Time to diagnosis of CNS metastases	Time from randomization to CNS (brain or meninges or spinal cord) metastases.
Time to discontinuation of TKI (post-hoc endpoint)	Time from randomization to the end date of any EGFR-TKI, or death without interruption by any non-EGFR-TKI therapy (that is, includes study treatment and any sequential EGFR-TKI treatment).

Sample size

The sample size was determined based on the following assumptions:

- the randomisation ratio is 1:1 (ramucirumab:placebo)
- a nominal alpha <0.00001 was spent in order to maintain type-I error for 1 interim futility analysis when at least 114 PFS events
- assuming a HR of 0.71 and at least 270 PFS events (40% censoring), provides at least 80% statistical power to detect superiority of the ramucirumab plus erlotinib arm over the placebo plus erlotinib arm with a 1-sided log-rank test and a type-I error of 0.02499.

Randomisation

Approximately 450 patients were planned to be randomised (1:1) between the 2 treatment arms. Randomisation was stratified by the following factors:

- Gender (male or female)
- Region (East Asia or other)
    - East Asia included: South Korea, Hong Kong, Japan, and Taiwan
    - Other included: Canada, France, Germany, Italy, Romania, Spain, Turkey, United States, and United Kingdom
- EGFR mutation type (exon 19 deletion or exon 21 [L858R] substitution mutation)
- EGFR testing method (Therascreen® and Cobas® or other polymerase chain reaction [PCR] and sequencing-based methods).

The chosen stratification factors were identified as variables with potential influence on the primary objective of PFS. Patients with EGFR mutations benefit from targeted therapy whether they have an exon 19 deletion or exon 21 substitution mutation; however, the degree of benefit may differ based on the type of mutation (Seto et al. 2014). Gender is linked with prognosis; therefore, this was included as a stratification factor (Ou et al. 2009; Siddiqui et al. 2010). Region was included as a stratification factor due to the potential regional heterogeneity of standards of care. EGFR testing methods are considered a necessary stratification factor given that heterogeneity in testing methods might increase the enrolment of

patients with false positive EGFR mutations. Note that local EGFR testing results were used for enrolment into the study; central tissue testing was performed to corroborate activating mutation status.

Blinding (masking)

Part B of the RELAY study was double-blinded. For part B patients, investigators and all other personnel involved in the conduct of the study were blinded to individual treatment assessments for the duration of the study. Upon the observance of approximately 270 PFS events, a database cut-off was planned and the database was to be locked for the primary PFS analysis, results of which are summarized and discussed in this CSR. The database lock date for primary PFS analysis occurred on 14 February 2019 with 280 PFS events.

Statistical methods

Censoring rules PFS

Refer to Table 11 for the rules for determining date of progression or censor for progression-free survival.

ORR/DCR handling missing data

Patients who do not have any post-baseline tumour response assessments for any reason are considered non-responders and are included in the denominator when calculating the response rate. Tumour assessments performed after initiation of new anticancer treatment (systemic therapy) will be excluded from evaluating the best overall response and DCR.

Efficacy

PFS, PFS2, and interim OS was based on a stratified (using interactive web-response system [IWRS] factors) log-rank test and was performed on the ITT population. Additionally, the KM method was used to estimate parameters (medians and quartiles) by treatment arm. The HR and its 2-sided 95% confidence interval (CI) were estimated using a stratified Cox regression model. Restricted mean difference in PFS between the treatment arms and its 95% CI will be reported, while the restriction time is defined by the latest time where the standard error of the PFS estimates are ≤ 0.075 months. Several sensitivity analyses were performed on PFS and OS including one that does not censor for 2 or more visits and does not censor for new anti-cancer treatment, i.e. the EMA-preferred PFS analysis.

Objective response (CR + PR) rate and disease control (CR + PR + SD) rate were provided with exact 95%-CI per arm and compared using Cochran-Mantel-Haenszel test for the stratification variables.

Duration of response and time to diagnosis of CNS metastases were compared between both treatment arms using unstratified log-rank test and KM estimates.

Health Outcomes

TtD was calculated for each of the 9 LCSS items, ASBI, and LCSS total score. The KM method was used to estimate parameters for time-to-event analyses on each treatment arm. Hazard ratios for treatment effect and their 2-tailed 95% CIs were estimated using the Cox PH model stratified identically to the stratified log-rank tests. Mean change from baseline was estimated for the EQ-5D-5L index score and the VAS using longitudinal mixed-model repeated measures (MMRM) regression models. Additional analyses may investigate for example pattern mixture models in case of missing data.

Safety

Safety analyses were performed on all randomised patients who received at least 1 dose of study treatment. An overview of AEs was produced that included TEAEs, treatment-emergent SAEs, and AEs leading to death or discontinuation of study treatment. Drug exposure and the following safety-related outcomes were also

analysed: AESIs, dose adjustments, laboratory results, vital signs, electrocardiograms, and hospitalizations. Treatment-emergent adverse events were summarized by MedDRA Version 21.1 by system organ class (SOC) and PT (any grade and grade ≥3) and by maximum CTCAE grade 1-5. The incidence and percentage of patients with at least 1 occurrence of a PT were included by the most severe NCI-CTCAE v4.0 grade. Causality (relationship to study drug) as assessed by the investigator was summarized. Laboratory results were graded according to NCI-CTCAE v4.0, when applicable. Additionally, AE summaries were presented for selected subgroups including age, sex, and race.

Exploratory Biomarker Research

Liquid biopsy EGFR T790M analyses were conducted in patients who had disease progression by data cut-off and had post-progression next-generation sequencing results from the 30-day follow-up. The observed T790M mutation rates and the associated 95% CI were reported for each treatment group. The statistical significance of the difference in the T790M mutation rate between treatment groups was assessed using Fisher's exact test.

Multiplicity

Interim OS was only to be tested if PFS is statistically significant (hierarchical testing). Type I error control over the interim and final OS analysis at 2.5% one-sided was to be achieved via Haybittle Peto type spending function (i.e., 0.0001 at the interim analysis). Apart from the above efficacy interim analysis, one safety interim and one futility interim analyses are planned. The safety interim analysis will be performed after the first 50 treated patients completed 3 cycles or discontinued from all study therapies due to any reason prior to 3 cycles. A non-binding futility and safety interim analysis will be performed after approximately 107 investigator-assessed PFS events were observed. As guidance, an IDMC may recommend stopping the trial for futility if the p-value of the stratified log-rank test for PFS is >0.39 (this corresponds to approximately a HR >0.95 under a Cox PH model).

Results

Participant flow

The participant flow is seen in **Figure 12**.

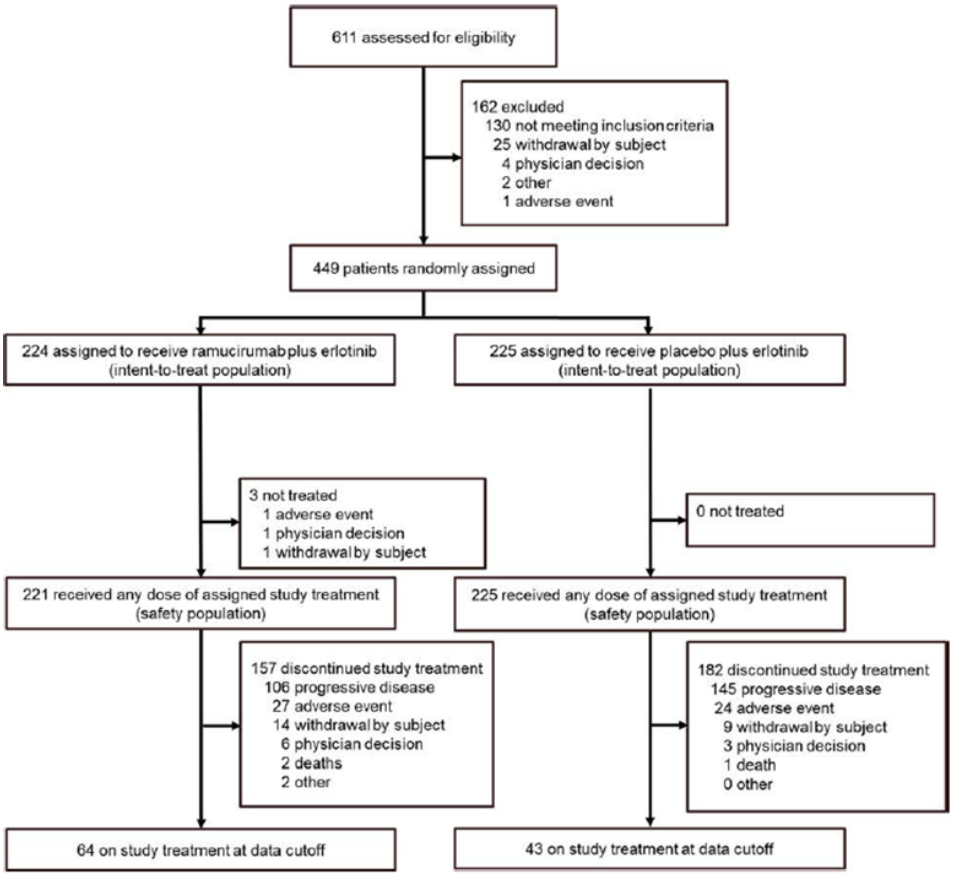


Figure 12: Participant flow

Recruitment

Part B was conducted at 106 study sites, of which 100 sites randomised patients across 13 countries (Canada, Germany, Spain, France, United Kingdom, Greece, Hong Kong, Italy, Japan, Korea, Romania, Turkey, Taiwan, United States). Date first patient randomised was 28 January 2016 and date last patient randomised was 1 February 2018.

As of the data cut-off date for the primary PFS analysis (23 January 2019) the median time of follow-up was 20.7 months (range, 0.1-35.4).

Conduct of the study

Protocol deviations:

Table 14 summarizes important protocol deviations. The number of patients who had at least one important protocol deviation was similar between treatment arms (22.3% in the ramucirumab plus erlotinib arm vs. 17.8% in the placebo plus erlotinib arm).

The most common protocol deviations were due to:

- use of prohibited concomitant medications (4.9% in the ramucirumab plus erlotinib arm and 2.2% in the placebo plus erlotinib arm).
- incorrect stratification of patients (4.5% in the ramucirumab plus erlotinib arm and 4.0% in the placebo plus erlotinib arm); 16 patients out of 19 were misstratified for the EGFR testing method,

- failure to suspend or dose reduce next study drug dose that could have significantly compromised patient safety (2.7% in the ramucirumab plus erlotinib arm and 2.2% in the placebo plus erlotinib arm), and
- patients who remained on study and on study therapy after PD (1.3 % in the ramucirumab plus erlotinib arm and 2.7% in the placebo plus erlotinib arm).

These protocol deviations were not likely to have affected the analyses or conclusions presented in this report.

Table 14: Summary of important protocol deviations ITT population

Deviation Category Deviation Subcategory	Ramucirumab + Erlotinib N=224 n (%)	Placebo + Erlotinib N=225 n (%)
Patients with at least 1 important deviation	**50 (22.3)**	**40 (17.8)**
Eligibility	**12 (5.4)**	**10 (4.4)**
Exclusion 15	0	1 (0.4)
Exclusion 35	1 (0.4)	2 (0.9)
Inclusion 10c	4 (1.8)	1 (0.4)
Inclusion 10d	0	1 (0.4)
Inclusion 4	2 (0.9)	0
Inclusion 5	0	3 (1.3)
Inclusion 6	2 (0.9)	1 (0.4)
Other inclusion/exclusion criteria	4 (1.8)	1 (0.4)
Erlotinib	**3 (1.3)**	**1 (0.4)**
Significantly noncompliant[a]	3 (1.3)	1 (0.4)
Investigational Product[b]	**20 (8.9)**	**15 (6.7)**
Failure to suspend or dose reduce next dose as specified in the protocol	5 (2.2)	1 (0.4)
Infusion rate more than 25 mg per min	1 (0.4)	1 (0.4)
Patient is stratified incorrectly[c]	10 (4.5)	9 (4.0)
Patient unblinded not for emergency	1 (0.4)	1 (0.4)
Received incorrect study medication	1 (0.4)	1 (0.4)
Significant premedication errors	2 (0.9)	2 (0.9)
Study Procedures	**17 (7.6)**	**13 (5.8)**
Baseline tumor assessment performed but more than 28 days prior to enrollment	1 (0.4)	1 (0.4)
Patient met discontinuation criteria but continue receiving all study treatments: Continue on therapy after PD	3 (1.3)	6 (2.7)
Patient met discontinuation criteria for erlotinib but continue receiving erlotinib	2 (0.9)	1 (0.4)
Patient met discontinuation criteria for ramucirumab /placebo but continue ramucirumab or placebo	2 (0.9)	1 (0.4)
Use of prohibited concomitant medications	11 (4.9)	5 (2.2)
Study drugs	**6 (2.7)**	**5 (2.2)**
Failure to suspend or dose reduce next dose for events that could have significantly compromised patient safety	6 (2.7)	5 (2.2)

Abbreviations: EGFR = epidermal growth factor receptor; ITT = intent-to-treat; N = number of patients; n = number of patients in specified category.

[a] In 1 patient erlotinib dose reduction from 100 mg to 50 mg daily was not followed. One patient was hospitalized and fell into coma and erlotinib was not administered. Non-compliance in 2 patients was confirmed as data entry issues.

[b] Ramucirumab

[c] Sixteen patients out of 19 were misstratified for the *EGFR* testing method (9 patients in the ramucirumab arm and 7 patients in the placebo plus erlotinib).

Source: b_s_tpd.rtf.

Protocol amendments:

The original protocol was approved on 11 December 2014 and amended 6 times. According to the applicant, no changes to the protocol were made based on knowledge of unblinded data.

The important changes and rationale for the changes made to this protocol were as follows:

- Revised the statistical assumptions for both the ramucirumab plus erlotinib and placebo plus erlotinib arms in part B based on emerging data from recent first-line erlotinib studies in EGFR mutation-positive NSCLC (Soria et al. 2018), meta-analysis of individual patient data from 6 randomised

controlled trials (Lee et al. 2017), and real-world evidence (Okamoto et al. 2018). The data showed that the placebo plus erlotinib arm may perform better than the initially assumed median PFS of 9.5 months. As a result, the median PFS assumption for the placebo plus erlotinib arm was increased to 11 months. As reported by Reck et al. (2018), data from the small, single-arm, open-label, phase 1b part (part A) of this study showed a median PFS of 17.1 months. Consequently, the median PFS assumption for the ramucirumab plus erlotinib arm was increased from approximately 13 months to 15.5 months. Under the assumption of exponential PFS, this translated to an HR of 0.71, and therefore the HR was reduced to reflect the revised statistical assumptions from 0.72 to 0.71.

- Removed the efficacy interim PFS analysis that was to occur at 224 PFS events due to regulatory feedback.
- The previous number of events planned for primary analysis was 320. Under the revised assumption of an HR equal to 0.71 and no interim analyses, 270 events are sufficient to ensure at least 80% power to show superiority of the ramucirumab plus erlotinib arm over the placebo plus erlotinib arm with a 1-sided type 1 error rate of 0.02499.

An interim futility analysis was conducted at 114 investigator-assessed PFS events (data cut-off date 16 October 2017), and the IDMC recommended the trial continue without modification. A nominal 1-sided alpha <0.00001 was spent in order to maintain type-I error.

Changes in the statistical analysis plan made after the first patient (31 May 2018 and 13-Dec-2018) was included but before the primary PFS analysis were:

Primary analysis:

- reduction of number of event from 320 to 270, which was based on external studies.
- Removal of PFS interim analysis (planned at 224 events)
- Updated rules for determining date of progression or censor
- Clarification that stratification factors will be drawn from the interactive web response system

PFS2 and OS analyses for patients who received osimertinib after disease progression vs those do not, and sensitivity analyses for PFS. Added a sensitivity analysis for primary PFS without censoring for either missed visits or new anticancer therapy.

Furthermore added were:

- additional analyses (additional age groups including the 75 age subgroup, liver-metastases subgroup, time-to-brain metastases, exposure, summary of TEAEs by narrow scope standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) and preferred term (PT)), updates (selected concomitant medications), clarification of wording ('protocol deviation' instead of 'protocol violation'), definitions (dose modification, immunogenicity-related variables and a sensitivity analysis of ORR/DCR/DOR based on independent assessment.
- Part C is an open-label, 2-period, single-arm, *exploratory* cohort that was added to the main protocol (I4T-MCJVCY [JVCY]) and is only applicable to sites in the East Asian region, including Japan (see protocol addendum 9.2, approved on 23 May 2018): objectives, analysis populations, analysis plan, interim analyses were added. No results from part C were included in the CSR.

Baseline data

Generally, the patient demographics and baseline disease characteristics of patients in the ITT population were balanced between treatment arms (**Table 15**). As is typical of randomised trials, small differences were observed between arms in terms of some baseline characteristics.

The median age was 65 years (range, 27 to 86 years) in the ramucirumab plus erlotinib arm and 64 years (range, 23 to 89 years) in the placebo plus erlotinib arm. Most patients in both treatment arms were female (62.9% vs. 63.1%), approximately 75% were Asian (76.8% vs. 77.3%), approximately 60% were never-smokers (59.8% vs. 61.8%), and all had an ECOG PS of 0 or 1.

Table 15: Summary of patient demographics and baseline characteristics based on CRF ITT population

Parameter	Ramucirumab + Erlotinib N=224	Placebo + Erlotinib N=225	Total N=449
Sex, n (%)			
Male	83 (37.1)	83 (36.9)	166 (37.0)
Female	141 (62.9)	142 (63.1)	283 (63.0)
Age, years			
Median age (range)	65.0 (27-86)	64.0 (23-89)	65.0 (23-89)
<65, n (%)	102 (45.5)	114 (50.7)	216 (48.1)
≥65, n (%)	122 (54.5)	111 (49.3)	233 (51.9)
<70, n (%)	160 (71.4)	166 (73.8)	326 (72.6)
≥70, n (%)	64 (28.6)	59 (26.2)	123 (27.4)
<75, n (%)	195 (87.1)	196 (87.1)	391 (87.1)
≥75, n (%)	29 (12.9)	29 (12.9)	58 (12.9)
65 to <75, n (%)	93 (41.5)	82 (36.4)	175 (39.0)
75 to <85, n (%)	28 (12.5)	28 (12.4)	56 (12.5)
≥85, n (%)	1 (0.4)	1 (0.4)	2 (0.4)
Race, n (%)			
Asian	172 (76.8)	174 (77.3)	346 (77.1)
White	52 (23.2)	48 (21.3)	100 (22.3)
Other[a]	0	2 (0.9)	2 (0.4)
Missing[b]	0	1 (0.4)	1 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	13 (5.8)	10 (4.4)	23 (5.1)
Non Hispanic or Latino	150 (67.0)	160 (71.1)	310 (69.0)
Not Reported	61 (27.2)	55 (24.4)	116 (25.8)
Geographic Region[c], n (%)			
East Asia	166 (74.1)	170 (75.6)	336 (74.8)
Other	58 (25.9)	55 (24.4)	113 (25.2)
Smoking History, n (%)			
Ever[d]	64 (28.6)	73 (32.4)	137 (30.5)
Never[d]	134 (59.8)	139 (61.8)	273 (60.8)
Unknown[e]	26 (11.6)	13 (5.8)	39 (8.7)
ECOG PS, n (%)			
0	116 (51.8)	119 (52.9)	235 (52.3)
1	108 (48.2)	106 (47.1)	214 (47.7)
Disease Stage at Diagnosis[f]			
Metastatic disease	195 (87.1)	189 (84.0)	384 (85.5)
Other	29 (12.9)	36 (16.0)	65 (14.5)
Pathological Diagnosis at Study Entry			
Adenocarcinoma of lung	215 (96.0)	218 (96.9)	433 (96.4)
Non-small cell lung cancer NOS	9 (4.0)	7 (3.1)	16 (3.6)
Measurable Disease, n (%)	223 (99.6)	225 (100.0)	448 (99.8)
Primary Tumor Present, n (%)	205 (91.5)	205 (91.1)	410 (91.3)
***EGFR* Mutation Type, n (%)**			
Exon 19 deletion	123 (54.9)	120 (53.3)	243 (54.1)
Exon 21 L858R	99 (44.2)	105 (46.7)	204 (45.4)
Other[g]	1 (0.4)	0	1 (0.2)
Missing[h]	1 (0.4)	0	1 (0.2)
***EGFR* Testing Method, n(%)**			
therascreen® and *cobas*®	96 (42.9)	101 (44.9)	197 (43.9)
Other (PCR and Sequencing-based)	127 (56.7)	124 (55.1)	251 (55.9)
Missing[i]	1 (0.4)	0	1 (0.2)

Abbreviations: CRF = case report form; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; IWRS = interactive web response system; NOS = not otherwise specified; N = number of patients; n = number of patients in the specified category; NSCLC = non-small cell lung cancer; PCR = polymerase chain reaction; PS = performance status.

a Includes American Indian or Alaskan Native or Black or African American.

b Patient was enrolled from France where collection of race requires patient's consent.

c East Asia includes South Korea, Hong Kong, Japan, and Taiwan, and Other includes Canada, France, Germany, Italy, Romania, Spain, Turkey, United States, and United Kingdom.

d The definition of 'ever smoker' includes those who smoked ≥100 cigarettes, cigars, or pipe-fulls in his/her lifetime and the definition of 'never smoker' is one who smoked <100 cigarettes, cigars, or pipe-fulls in his/her lifetime.

e Includes patients with unknown or missing smoking history.

f All patients were required to have Stage IV NSCLC at study entry. Patients with recurrent metastatic disease were permitted as long as the adjuvant or neo-adjuvant therapy was completed at least 12 months prior to development of metastatic disease. Prior adjuvant or neo-adjuvant therapy was not required.

g Patient was enrolled with an exon 21 mutation other than L858R and was reported as an important protocol deviation. Patient continued to receive study treatment due to continued treatment benefit and was subsequently discontinued from study prior to Cycle 30.

h Patient did not have documented evidence of exon 21 (L858R) substitution mutation at enrollment and was reported as an important protocol deviation. Patient was subsequently discontinued from study prior to Cycle 3.

i Testing method for 1 patient was missing on the CRF. Patient was stratified by Other PCR and Sequencing-based Method in IWRS.

Data cutoff date: 23 January 2019

Sources: b_s_dem_itt_total.rtf (Table JVCY.14.18), b_s_dischar_itt_total.rtf (Table JVCY.14.19).

Numbers analysed

The ITT population, defined in Table 16, included 449 randomised patients, including 224 randomised to the ramucirumab plus erlotinib arm and 225 randomised to the placebo plus erlotinib arm.

Primary and secondary efficacy analyses were performed on the ITT population (with allocation of patients to treatment arms considered as "randomised"). Selected efficacy parameters were analysed using the PP population.

Table 16 defines the PP population, which consisted of 437 patients in the ITT population (216 patients in the ramucirumab plus erlotinib arm and 221 patients in the placebo plus erlotinib arm). These patients did not have pre-specified criteria violations as defined in Table 16.

The safety population included 446 patients: 221 patients in the ramucirumab plus erlotinib arm and 225 patients in the placebo plus erlotinib arm.

Table 16: RELAY analysis populations

Population	Definition
Part A	
Safety Population	All patients enrolled in Part A and received at least 1 dose of any study treatment.
DLT-Evaluable Population	Patients who either completed first 2 cycles of treatment (approximately 28 days + 3 days) or discontinued from study treatment or study participation before completing first 2 cycles due to a DLT. Refer to Section 9.4.5.1 for detailed DLT definitions.
Part B	
ITT Population	All patients who were randomized to study treatment during Part B. Patients were grouped according to randomized treatment.
PP Population	All patients who were randomized and treated and did not have any major protocol deviations that could affect the efficacy conclusions of the study. Patients who met any of the following criteria were excluded from the PP population: • did not provide their written informed consent in the study per IC [1] • were not aged ≥18 years, ≥20 years in Japan and Taiwan at the time of study entry per IC [2] • were not eligible for first-line treatment with erlotinib per IC [4] • were not able to swallow tablets per IC [7] • had superior vena cava syndrome per EC [18] • had radiologically documented evidence of major blood vessel invasion or encasement by cancer per EC [26] • were inappropriately unblinded • were screen failures and randomized in error • received concurrent chemotherapy, biological response modifiers, other investigational agents, and radiation therapy during study treatment • received incorrect study dose at least 25% of the time
Safety Population	All randomized patients that received at least 1 dose of any study treatment in Part B. Patients were grouped according to treatment received in Cycle 1.

Abbreviations: DLT = dose-limiting toxicity; EC = exclusion criterion; IC = inclusion criterion; ITT = intent-to-treat; PP = per-protocol.

Outcomes and estimation

Primary endpoint: Progression-free survival

RELAY met its primary endpoint by demonstrating a statistically significant improvement in PFS for patients who received ramucirumab plus erlotinib compared with placebo plus erlotinib. Table 17 summarizes PFS data and Figure 13 displays the Kaplan-Meier plot of PFS for the ITT population.

Table 17: Summary of investigator-assessed progression-free survival ITT population according to primary definition (not EMA preferred analysis)

Statistic	Ramucirumab + Erlotinib N=224	Placebo + Erlotinib N=225
Number of Events, n (%)	122 (54.5)	158 (70.2)
Number of Patients Censored, n (%)	102 (45.5)	67 (29.8)
Median PFS, months (95% CI)	19.35 (15.38-21.55)	12.39 (10.97-13.50)
HR (95% CI) stratified[a]	0.591 (0.461-0.760)	
Log-rank p-value (2-sided) stratified[a, b]	<0.0001	
PFS Rate, % (95% CI)[c]		
6-month	84.3 (78.7-88.6)	79.9 (73.9-84.7)
12-month	71.9 (65.1-77.6)	50.7 (43.7-57.3)
18-month	52.4 (44.8-59.5)	34.5 (27.9-41.3)
24-month	32.4 (24.5-40.5)	22.9 (16.8-29.7)
30-month	21.7 (13.4-31.3)	11.3 (5.4-19.6)

Abbreviations: BIRC = Blinded Independent Radiological Review Committee; CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in specified category; PFS = progression-free survival.

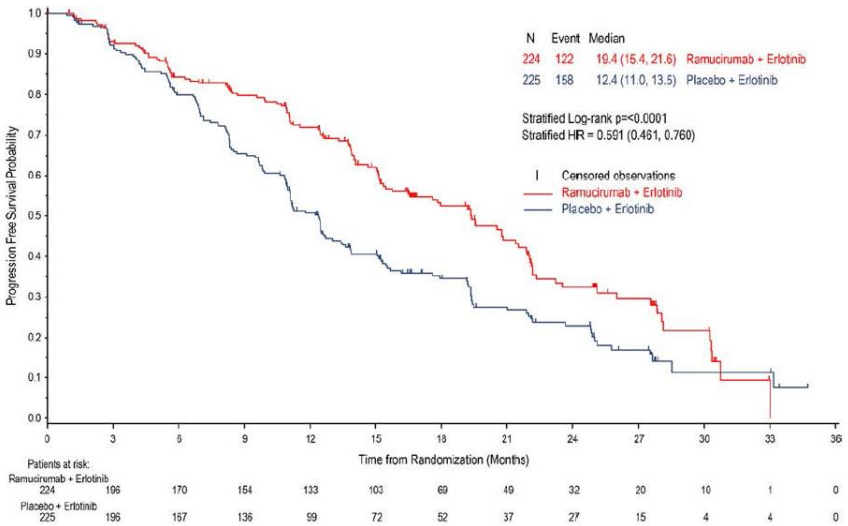
a Stratified by the randomization strata (*EGFR* mutation type, gender, region, and *EGFR* testing method).

b Treatment Effect/Difference/p-values are computed based on comparator Placebo+Erlotinib.

c 95% CIs and 2-sided p-values for the difference between rates were calculated based on normal approximation.

Data cutoff date: 23 January 2019

Sources: b_pfs_inv_iwrs_o_tte_summ_pfs_3_p1123191_t1123247.rtf (Table JVCY.14.22).



Abbreviations: HR = hazard ratio; ITT = intent-to-treat; N = number of patients.
Data cutoff date: 23 January 2019
Source: b_km_pfs.png.

Figure 13: Kaplan Meier plot of investigator-assessed progression-free survival, ITT population.

Secondary endpoints: overall survival

The OS results are immature with 79 deaths and a censoring rate of more than 80% (data maturity, 17.6%). However, no detrimental effect on OS has been observed with ramucirumab plus erlotinib as shown by the stratified HR (95% CI) of 0.832 (0.532, 1.303). Table 18 summarizes interim OS data and Figure 14 displays the KM plot of OS for the ITT population.

Table 18. Summary of interim overall survival ITT population

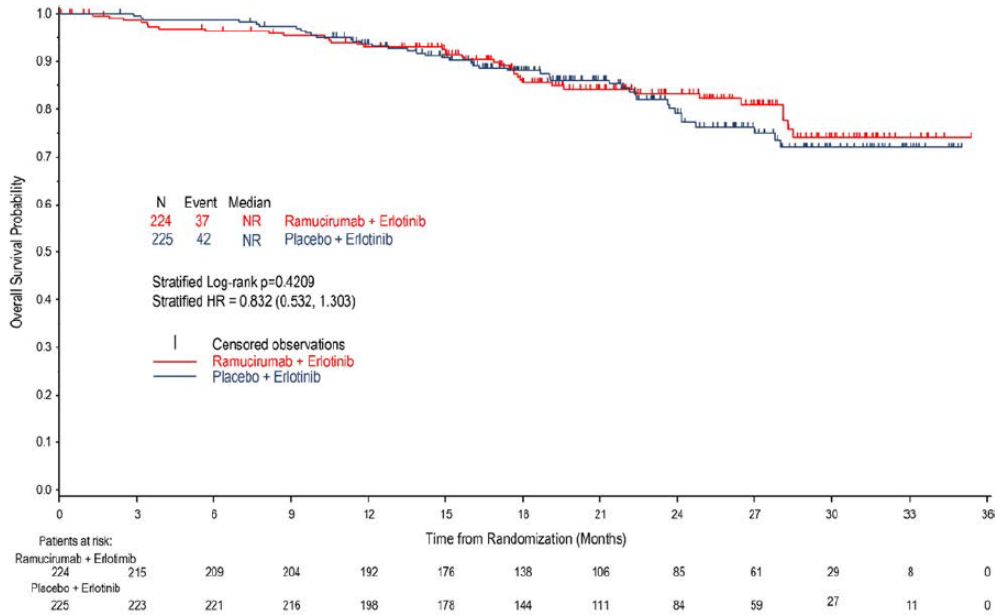
Statistic	Ramucirumab + Erlotinib N=224	Placebo + Erlotinib N=225
Number of Events, n (%)	37 (16.5)	42 (18.7)
Number of Patients Censored, n (%)	187 (83.5)	183 (81.3)
Median OS, months (95% CI)	NR	
HR (95% CI) stratified[a]	0.832 (0.532-1.303)	
Log-rank p-value (2-sided) stratified[a]	0.4209	

Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; ITT = intent-to-treat; N = number of patients; n = number of patients in specified category; NR = not reached; OS = overall survival.

a Stratified by the randomization strata (*EGFR* mutation type, gender, region, and *EGFR* testing method).

Data cutoff date: 23 January 2019

Sources: b_o_tte_summ_os_3_p1123191_t1123213.rtf (Table JVCY.14.37).



Abbreviations: HR = hazard ratio; ITT = intent-to treat; NR = not reached.

Data cutoff date: 23 January 2019

Source: b_os_inv_o_tte_figure_kmplot_2_p1123191_t1123234.rtf (Vector: b_km_os.png)

Figure 14. Kaplan-Meier plot of interim overall survival, ITT population

Secondary endpoints: Objective Response Rate, Disease Control Rate and Duration of Response

Table 19 presents a summary of ORR and DCR for the ITT population. Both ORR (CR + PR) and DCR (CR + PR + SD) were similar between treatment arms (76.3% vs. 74.7% and 95.1% vs. 95.6%, respectively).

Independently-assessed ORR and DCR were 68.7% and 96.3% in the ramucirumab plus erlotinib arm and 61.9% and 95.5% in the placebo plus erlotinib arm, respectively.

Table 19. Objective Response Rate and Disease Control Rate ITT Population

Parameter	Ramucirumab + Erlotinib N=224	Placebo + Erlotinib N=225
Best overall response		
Complete response (CR), n (%)	3 (1.3)	2 (0.9)
Partial response (PR), n (%)	168 (75.0)	166 (73.8)
Stable disease (SD), n (%)	42 (18.8)	47 (20.9)
Progressive disease (PD), n (%)	3 (1.3)	6 (2.7)
Non-evaluable, n (%)	8 (3.6)	4 (1.8)
ORR (CR+PR)		
Objective Response Rate (ORR), % (95% CI)[a]	76.3 (70.8-81.9)	74.7 (69.0-80.3)
p-value[b]	0.7413	
DCR (CP+PR+SD)		
Disease Control Rate (DCR), % (95% CI)[a]	95.1 (92.3-97.9)	95.6 (92.9-98.2)
p-value[b]	1.0000	

Abbreviations: CI = confidence interval; DCR = disease control rate (CR+PR+SD); EGFR = epidermal growth factor receptor; IWRS = interactive web response system; N = number of randomized patients; n = number of patients in specified category; ORR = objective response rate (CR+PR).

[a] 95% CIs are calculated based on normal approximation.

[b] p-value is calculated by Exact Cochran-Mantel-Haenszel test stratified by the randomization strata Region (IWRS), Gender (IWRS), EGFR Mutation (IWRS), EGFR Testing Method (IWRS).

Data cutoff date: 23 January 2019

Sources: b_inv_o_rs_best_resp_sum_mult_4_p1123191_t1123207.rtf (Table JVCY.14.44).

The median DoR was longer in the ramucirumab plus erlotinib arm than in the placebo plus erlotinib arm (18.0 months [95% CI: 13.9-19.8] vs. 11.1 months [95% CI: 9.7-12.3]; p=0.0003).

The independently-reviewed DoR was 13.73 months in the ramucirumab plus erlotinib arm and 8.38 months in the placebo plus erlotinib arm.

Secondary endpoints: Time to Objective Response (CR+PR):

There was no difference of median time to an objective response between treatment arms; the median time to objective response was 1.4 months (range: 0.9 to 21.9 months) in both treatment arms.

Secondary endpoints: Patient-Reported Outcomes:

Overall patient compliance for completion across all time points was high for both measures, with rates of 95.7% in the ramucirumab plus erlotinib arm and 96.7% in the placebo plus erlotinib arm for the LCSS and 96.1% in the ramucirumab plus erlotinib arm and 96.6% in the placebo plus erlotinib arm for the EuroQol-5-dimension, 5-level questionnaire (EQ-5D-5L).

At baseline, compliance for LCSS completion was 96.4% and 96.9% for the ramucirumab plus erlotinib and placebo plus erlotinib arms, respectively, and EQ-5D-5L completion was 97.3% in both treatment arms.

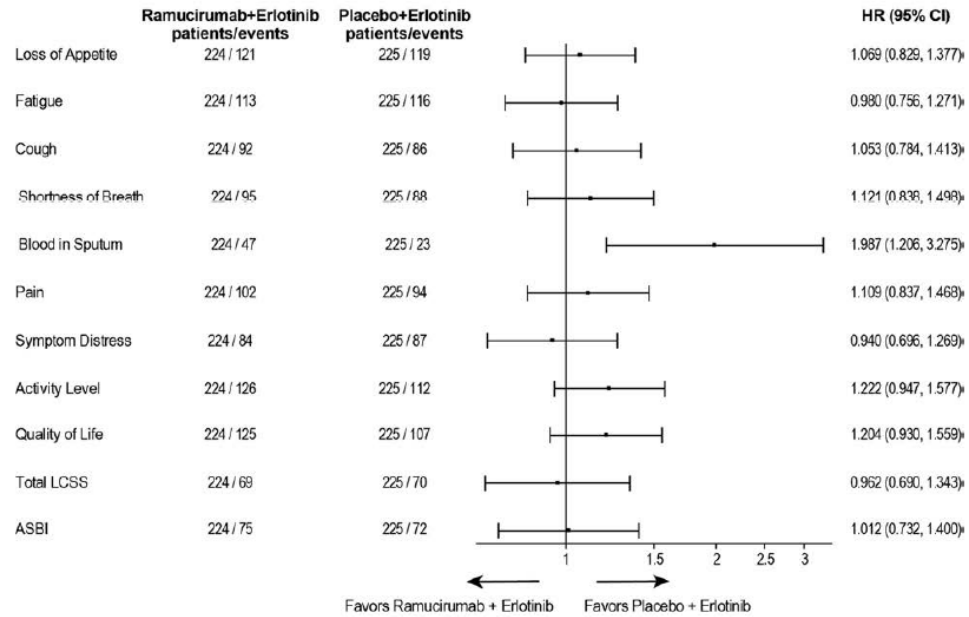
At the 30-day safety follow-up visit, compliance for the LCSS was 74.4% in the ramucirumab plus erlotinib arm and 79.1% in the placebo plus erlotinib arm, and compliance for the EQ-5D-5L was 74.4% in the ramucirumab plus erlotinib arm and 79.7% in the placebo plus erlotinib arm.

The number of expected questionnaires to be completed at each scheduled assessment decreased over time as the number of patients discontinuing from therapy increased.

LCSS Results

Individual LCSS item scores indicated no differences in time to deterioration (TtD) by treatment arm with 95% CIs including 1 for all scores except hemoptysis (blood in sputum) (HR = 1.987 [95% CI: 1.206-3.275]) (**Figure 15**).

Time to deterioration in the LCSS total score (HR = 0.962 [95% CI: 0.690-1.343]) and the ASBI did not differ between treatment arms (HR = 1.012 [95% CI: 0.732-1.400])



Abbreviations: ASBI = Average Symptom Burden Index; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat, LCSS = Lung Cancer Symptom Score.
Data cutoff date: 23 January 2019
Source: b_f_forest_ttlcss.png

Figure 15. Forest plot for time to deterioration for Lung Cancer Symptom Scale, ITT population

EQ-5D-5L Results

Mean scores for the index and VAS were generally similar between treatment arms and within arms over time, with the exception of apparent lower scores in both arms at the 30-day short-term follow-up assessment, which is not unexpected given that patients had progressed at that time. Minimal changes from baseline were observed in the scores at the subsequent study visits. Analysis of changes from baseline in the index score and VAS revealed no overall differences in health status between treatment arms.

Exploratory endpoints: Progression-free survival 2

Table 20 summarizes the pre-specified, exploratory post-progression endpoint of PFS2. PFS2 encompasses PFS on both the initial treatment and subsequent treatment and measures continued impact through second progression.

As of the data cut-off date (censoring rate 68.8%),

- 118 patients and 157 patients in the ramucirumab plus erlotinib and placebo plus erlotinib arms, respectively, had disease progression. Of these patients, 61 patients (51.7%) and 79 patients (50.3%) had second progression events or died.

- Median PFS2 was not reached in either arm. The KM curves separate, favouring the ramucirumab plus erlotinib arm, with benefit maintained throughout the duration of follow-up (**Figure 16**).

Table 20. Summary of progression-free survival 2 ITT Population

Parameter	Ramucirumab + Erlotinib N=224	Placebo + Erlotinib N=225
Number of Events, n (%)	61 (27.2)	79 (35.1)
Death, n (%)	30 (13.4)	27 (12.0)
PD after additional systemic anticancer therapy, n (%)	31 (13.8)	52 (23.1)
Number of Patients Censored, n (%)	163 (72.8)	146 (64.9)
Median PFS, months (95% CI)	NR	NR
HR (95% CI) stratified[a]	0.690 (0.490, 0.972)	
Log-rank p-value (2-sided) stratified[a,b]	p=0.0325	
PFS Rate, % (95% CI)[c]		
6-month	95.9 (92.2-97.8)	97.3 (94.1-98.8)
12-month	90.7 (86.0-93.9)	86.0 (80.7-89.9)
18-month	78.6 (72.1-83.8)	70.6 (63.9-76.4)
24-month	68.5 (60.5-75.3)	61.2 (53.4-68.1)
30-month	59.1 (48.8-68.1)	53.0 (43.6-61.6)

Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; ITT = intent-to-treat; N = number of patients; n = number of patients in specified category; NR = not reached; OS = overall survival; PD = partial disease; PFS = progression-free survival.

Note: PFS rates along with 95% CIs were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.

a Stratified by the randomization strata (IWRS) (*EGFR* mutation type, gender, region, and *EGFR* testing method).

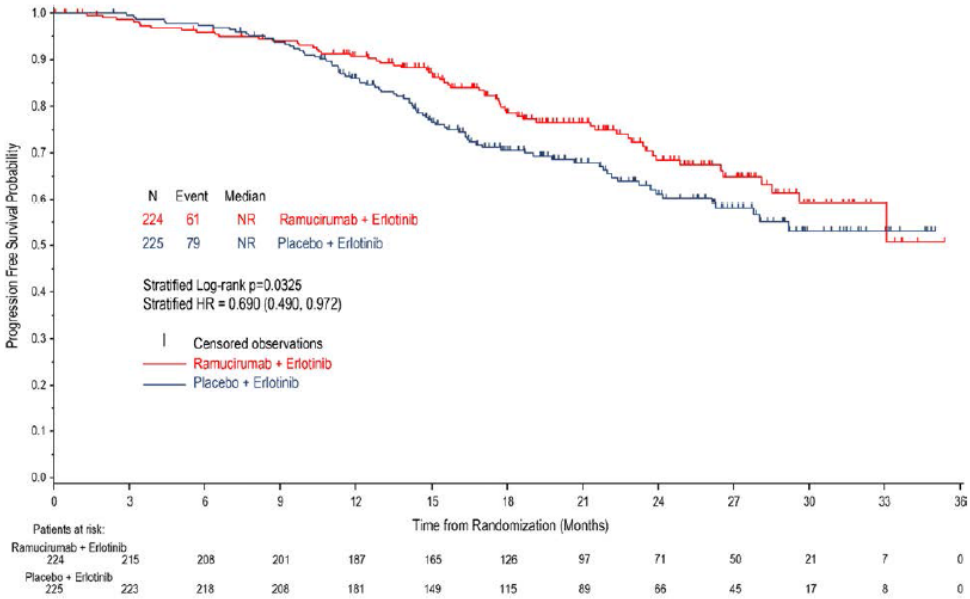
b p-values are computed based on comparator Placebo+Erlotinib.

c 95% CIs are calculated based on normal approximation.

d p-value is calculated by Exact Cochran-Mantel-Haenszel test stratified by the randomization strata.

Data cutoff date: 23 January 2019

Source: b_pfs2_o_tte_summ_pfs_3_p1123191_t1124187.rtf (Table JVCY.14.60).



Abbreviations: HR = hazard ratio; ITT = intent-to-treat; NR = not reached; PFS2 = progression-free survival 2.

Data cutoff date: 23 January 2019

Source: b_pfs2_o_tte_figure_kmplot_2_p1123191_t1124151.rtf (vector: b_km_pfs2.rtf)

Figure 16. Kaplan-Meier curve of investigator-assessed PFS2, ITT population

Exploratory endpoints: updated analysis for progression-free survival 2 (data cut-off date [25 September 2019]).

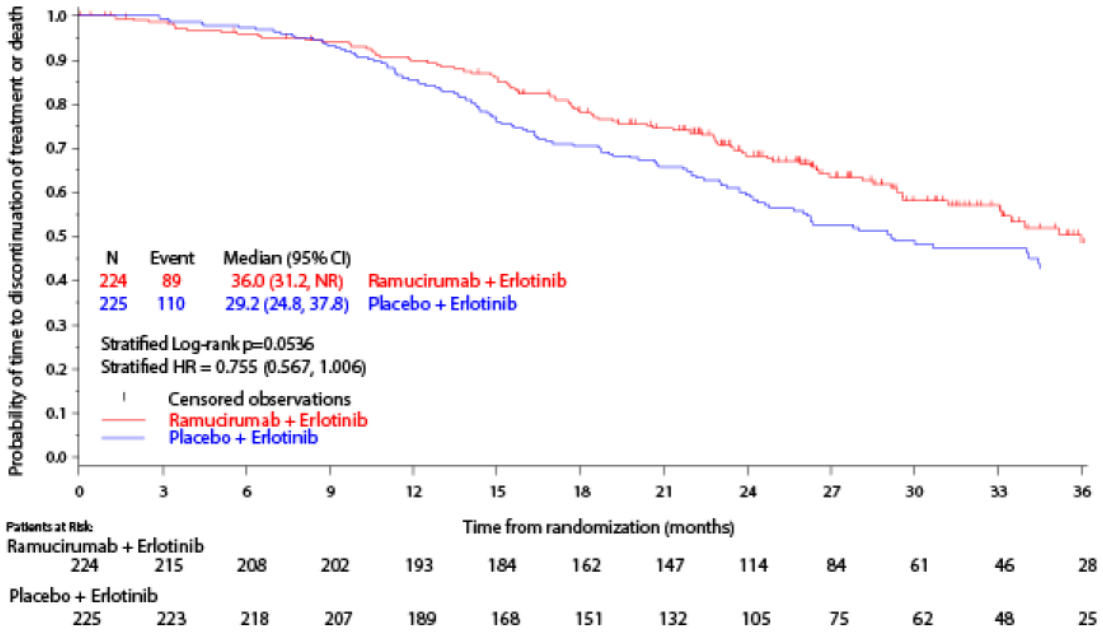
Table 21 and Figure 17 summarise updated PFS2 results. As of the data cut-off date of 25 September 2019:

- 199 PFS2 events have been observed (censoring rate, 55.7%). 89 of 224 patients (39.7%) in the ramucirumab plus erlotinib arm and 110 of 225 patients (48.9%) in the placebo plus erlotinib arm had second progression events or died.

Table 21. Summary of Progression-Free Survival 2 – Updated Analysis ITT Population

	Ramucirumab + Erlotinib N = 224	Placebo + Erlotinib N = 225
Number of events, n (%)	89 (39.7)	110 (48.9)
Number of patients censored, n (%)	135 (60.3)	115 (51.1)
Median PFS2, months (95% CI)	35.98 (31.21, NR)	29.17 (24.77, 37.82)
HR (95% CI) stratified[a]	0.755 (0.567, 1.006)	
Log-rank p-value (2-sided) stratified[a,b]	0.0536	

Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; ITT = intent-to-treat; IWRS = interactive web response system; N = number of patients; n = number of patients in specified category; NR = not reached; PFS2 = progression-free survival 2.
Data cutoff date: 25 September 2019.
a Stratified by the randomisation strata (IWRS), EGFR mutation type, gender, region, and EGFR testing method.
b p-value is computed based on comparator placebo plus erlotinib.



Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; N = number of patients; NR = not reached.
Data cutoff date: 25 September 2019.

Figure 17. Kaplan-Meier curves of progression-free survival 2 – updated analysis, ITT population

Ancillary analyses

PFS sensitivity analyses

Table 22 summarizes the results of sensitivity analyses for the primary PFS analysis. Statistical significance, magnitude of treatment effect, and robustness of the main PFS analysis were all supported by the sensitivity analyses, as demonstrated by consistent HRs ranging between 0.580 and 0.671.

A pre-specified blinded independent review of radiographic scans was conducted by the BIRC with respect to PFS assessment. Of the 449 randomised patients, 440 patients (217 in the ramucirumab plus erlotinib arm and 223 in the placebo plus erlotinib arm) were assessed. Per definition the patient were reviewed if baseline and at least one post-baseline tumour assessment scan were available. Based on the BIRC assessment, the ramucirumab plus erlotinib arm experienced improved PFS, with a stratified HR of 0.671 (95% CI: 0.518-0.869) similar to the investigator-assessed primary analysis (overlapping 95% CI) supporting the robustness of the investigator-based statistical results and conclusions with respect to PFS. The median BIRC-assessed PFS was 16.5 months versus 11.1 months. The KM plot for the BIRC assessment is presented in Figure 18.

The concordance rates were 80.6% in the ramucirumab plus erlotinib arm and 76.7% in the placebo plus erlotinib arm. Agreement between Investigator and BICR PFS is shown in Table 23.

The analysis without censoring for missing 2 or more tumour assessments prior to PD/Death or receiving anticancer therapy is shown in **Table 24**.

Table 22: Sensitivity analyses for the primary investigator-assessed progression-free survival analysis ITT population

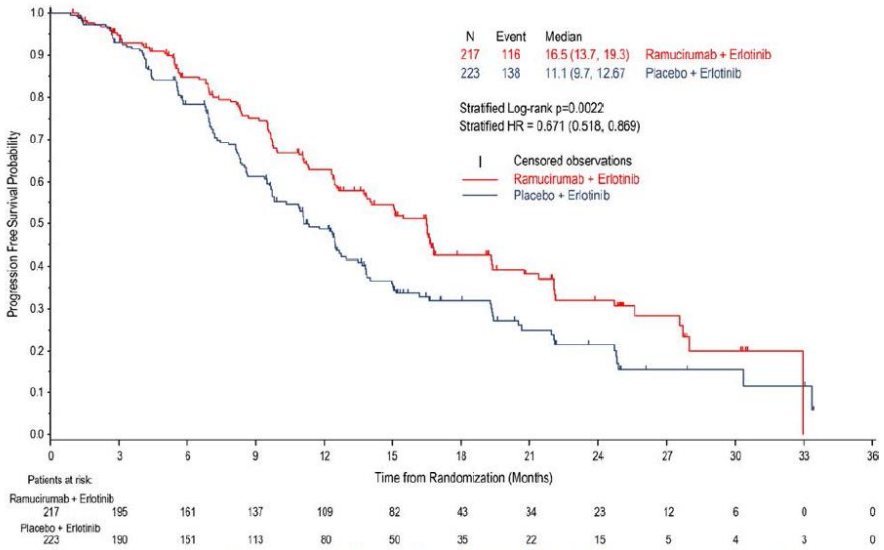
Analysis	Hazard Ratio (95% CI)
Primary PFS Analysis	
IWRS strata – 280 events	0.591 (0.461-0.760)
BIRC-assessment of PFS (stratified ITT population reviewed)	0.671 (0.518-0.869)
Per-protocol population analysis (stratified)	0.580 (0.450-0.747)
Using CRF strata[a]	0.607 (0.474-0.779)
Unstratified analysis	0.640 (0.505-0.812)
Treating lost to follow-up as progression (stratified)	0.591 (0.461-0.760)
Counting clinical and radiological progression as progression (stratified)	0.593 (0.462-0.761)
Ignoring missing tumor assessments (stratified)	0.597 (0.465-0.766)
Ignoring new anticancer treatment (stratified)	0.609 (0.478-0.776)
Ignoring anticancer therapy and missing tumor assessment (stratified)	0.615 (0.483-0.782)
Multivariate Cox regression analysis (adjusted for ECOG PS)	0.632 (0.498-0.802)

Abbreviations: BIRC = Blinded Independent Radiological Review Committee; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; ITT = intent-to-treat; IWRS = interactive web response system; PFS = progression-free survival; PS = performance status.

[a] Stratified by gender, geographic region, *EGFR* mutation type, and *EGFR* testing method.

Data cutoff date: 23 January 2019

Sources: Table JVCY.14.26, Table JVCY.14.27, Table JVCY.14.28, Table JVCY.14.29, Table JVCY.14.30, Table JVCY.14.31, Table JVCY.14.32, Table JVCY.14.33, Table JVCY.14.34, Table JVCY.14.35.



Abbreviations: BIRC = Blinded Independent Radiological Review Committee; HR = hazard ratio; ITT = intent-to-treat; N = number of patients
Data cutoff date: 23 January 2019
Source: b_pfs_ir_o_tte_figure_kmplot_2_p1123191_t1124143.rtf (Vector: b_km_pfs_ind.png)

Figure 18: Kaplan Meier plot of BIRC-assessment of progression-free survival, ITT population.

Table 23: Concordance between BIRC and INV PD assessments

	Assessment by the ICR						
	Ramucirumab+Erlotinib (N=217)			Placebo+Erlotinib (N=223)			Total (N=440)
Assenssment by the investigator	Progression	No progression	Missing*	Progression	No progression	Missing*	
Progression	104 (47.9)	21 (9.7)	0	130 (58.3)	36 (16.1)	0	
No progression	21 (9.7)	71 (32.7)	0	16 (7.2)	41 (18.4)	0	
Concordance rate ***	175(80.6)			171(76.7)			346(78.6)
Overall discordance rate ***	42(19.4)			52(23.3)			94(21.4)
Early discrepancy rate^	0.21			0.28			

Cutoff Date: 2019-01-23.
Abbreviations: ICR = Independent Central Review; INV = investigator; N = number of subjects in Intent-to-Treat Population.
* This represents cases where scans are not assessed by the ICR.
** This represents cases where scans are not assessed by the investigator.
*** included only cases with non-missing assessments by both ICR and INV.
^ Proportion of all INV PDs where INV declared PDs earlier than ICR (including the cases where only INV declared a PD).
^^ Proportion of all discrepancies (PD/no PD and timing of PDs) where investigator declared PDs later than ICR (including the case where only ICR declared a PD).
Concordance rate was calculated as the proportion of patients with concordant assessments (Progression or No progression).

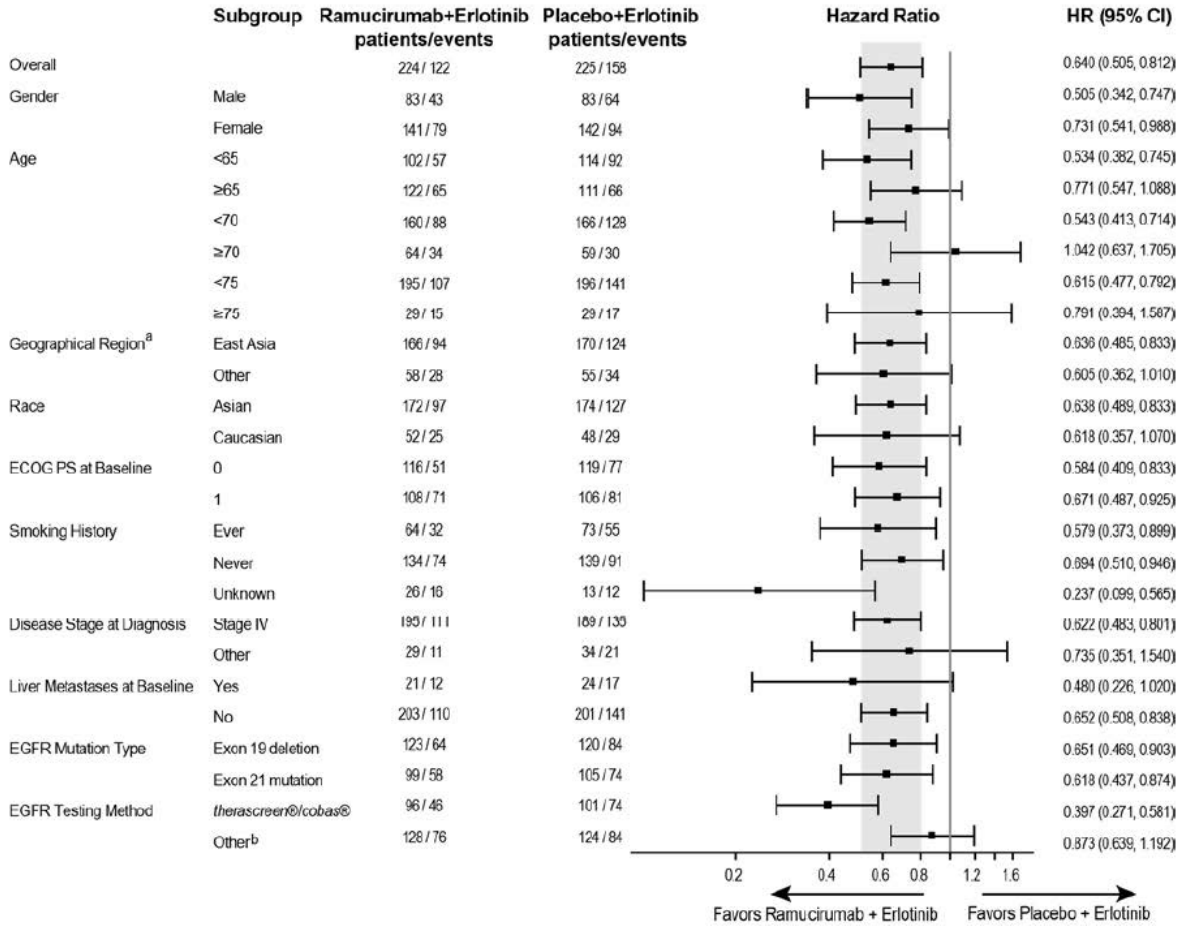
Table 24: PFS by investigator without censoring for missing 2 or more tumour assessments prior to PD/Death or receiving anticancer therapy

	Ramucirumab+ Erlotinib (N=224)	Placebo+ Erlotinib (N=225)	Treatment Effect/Difference / p-value*f
Number of Events, n (%)	133 (59.4)	170 (75.6)	
Death without PD, n (%)	7 (3.1)	3 (1.3)	
PD, n (%)	126 (56.3)	167 (74.2)	
Number of Patients Censored, n (%)	91 (40.6)	55 (24.4)	
No Post-Baseline Tumor Assessment, n (%)	5 (2.2)	0	
No documented PD with regular assessment, n (%)	81 (36.2)	53 (23.6)	
Summarization without Follow-up, n (%)	4 (1.8)	1 (0.4)	
Withdrawal by Subject, n (%)	1 (0.4)	1 (0.4)	
Minimum *a, month	0.03+	0.89	
25th percentile (95% CI)	10.94(8.28, 12.58)	7.00(5.78, 8.35)	
Median (95% CI)	19.35(15.38, 20.83)	12.39(10.97, 13.40)	6.97
75th percentile (95% CI)	28.06(23.26, 30.36)	22.01(19.25, 25.10)	
Maximum	33.02	34.73+	
Restricted Mean (95% CI) with restriction time = 33.02 month *b	18.47(17.05, 19.89)	14.85(13.51, 16.20)	3.62(1.66, 5.58) p = 0.0003*e
p-value (2-sided) - Log Rank Unstratified			p = 0.0003

Abbreviations: CI = Confidence Interval; N = total number of subjects in the population within the treatment group; n = number of patients; NC = not calculable; PD = progressive disease.
Note: Quartiles and PFS Survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.
*a - For minimum and maximum, + indicates a censored observation;
*b - Restriction time is defined by the latest time where the standard error of the survival estimates are <=0.075.
*c - Stratified by region(iwrs), gender(iwrs), egfr mutation(iwrs), egfr testing method(iwrs)
*d - 95% CIs and 2-sided p-values for the Difference between rates were calculated based on normal approximation.
*e - 2-sided p-value based on normal approximation
*f - Treatment Effect/Difference/p-values are computed based on comparator Placebo+Erlotinib
Cutoff Date: 2019-01-23

A number of pre-specified subgroup analyses of PFS were performed in order to further evaluate the treatment effect. A PFS treatment benefit for the ramucirumab plus erlotinib arm was consistently observed across all pre-specified patient subgroups (including regions, gender, smoking status and EGFR mutation type), except for patients ≥70 years of age. All other age subgroups, including ≥65, <75, and ≥75 years of age, favoured the ramucirumab plus erlotinib arm.

Figure 19 displays the Forest plot for PFS in the ITT population for all pre-specified subgroups.



Abbreviations: CI = confidence interval; CRF = case report form; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; HR = hazard ratio; ITT = intent-to-treat; IWRS = interactive web-response system; N = number of patients; n = number of patients in the specified category; PCR = polymerase chain reaction; PS = performance status.

[a] East Asia includes South Korea, Hong Kong, Japan, and Taiwan, and Other includes Canada, France, Germany, Italy, Romania, Spain, Turkey, United States, and United Kingdom

[b] Testing method for 1 patient was missing on the CRF. Patient was stratified by Other PCR and Sequencing-based Method in IWRS.

Data cutoff date: 23 January 2019

Source: b_f_forest_fpfsunstra (R_docs_race).png

Figure 19: Forest plot for unstratified subgroup analysis of investigator assessed progression-free survival, ITT population.

Local EGFR Testing Method

For the subgroups of patients by local EGFR testing method used for enrolment, a larger treatment effect was observed in patients whose tumours were tested by the EGFR testing method of Therascreen®/Cobas® test (HR = 0.397) compared with an Other test (HR = 0.873). The treatment-by-testing method interaction p-value was 0.0028.

Pre-planned central testing was conducted during the study using the Therascreen® EGFR tissue assay on submitted archival tissue samples and did not inform patient eligibility and study enrolment.

- Among the 316 patients (70% of the ITT population) with results obtained from the central Therascreen® testing, 305 patients (96%) had an EGFR activating mutation detected, corroborating the local EGFR testing results used for enrolment. It is expected that the lack of a positive EGFR

central test result in the 11 patients is likely due to tissue heterogeneity and the different tissue sections used for central versus local testing.

- Summarized by local testing method, activating EGFR mutations were detected centrally in 95% of tested patients who had been tested locally with a Therascreen®/Cobas® test, and in 97% of tested patients who had been tested locally with an Other test.

The similar EGFR activating mutation positivity rates found by central testing between the 2 local testing method subgroups, indicates that the difference in HRs observed between patients tested locally with Therascreen®/Cobas® vs. Other tests was not due to false positives from local assay variability.

Additionally, when the 11 patients were removed for whom an EGFR activating mutation could not be detected in the samples submitted and tested centrally, the HR was essentially the same as that within the full set of centrally tested patients.

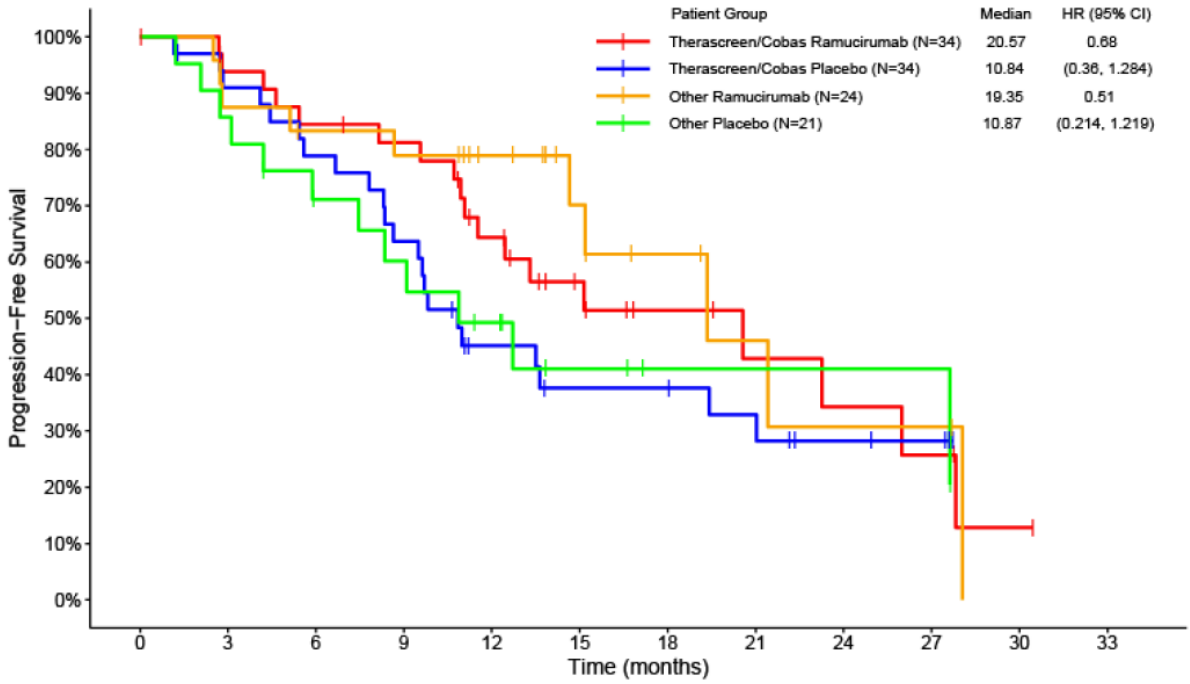
Further analyses of baseline characteristics and other factors did not identify an explanation for the PFS results for each testing method subgroup.

When evaluating within geographical regions (Table 21), the differential HR by testing method was only observed in patients from East Asia (Japan, Taiwan, South Korea, Hong Kong). This relationship did not appear to exist in patients from the EU and North America, in whom similar PFS HRs were observed with patients tested either with the local *therascreen*/*cobas* EGFR testing method or other test. This is further supported by Figure 20 which provides the corresponding PFS curve by testing method for EU and North America.

Table 25. Treatment hazard ratios by EGFR local testing method and geography

	N	EU and North America	N	East Asia
PFS HR by subgroups	**113**	**HR (95% CI)**	**336**	**HR (95% CI)**
Local therascreen cobas	68	0.68 (0.36, 1.28)	129	0.26 (0.16, 0.43)
Local Other test	45	0.51 (0.21, 1.21)	207	0.95 (0.68, 1.33)
Interaction p-value		0.5802		0.0001

Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; N = number of patients; PFS = progression-free survival.



Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; N = number of patients.
Note: The small vertical lines represent censored observations.

Figure 20. Kaplan-Meier curves of progression-free survival by local EGFR testing method, EU and North America population.

Analyses of post-discontinuation Anticancer Therapy:

The types of first subsequent therapy received were generally similar between treatment arms. Of those that received first subsequent therapy, approximately 24% of patients received chemotherapy and 73% received an EGFR TKI. The most common first subsequent EGFR TKI therapies received were erlotinib and osimertinib (Table 26).

Table 26. Summary of first subsequent therapies ITT population (N=449) who received first subsequent therapy

PDT	Ramucirumab + Erlotinib N=224 n (%)	Placebo + Erlotinib N=225 n (%)
Patients that did not receive study treatment n/n (%)	2[a]/224 (0.9)	0
Patients still on study treatment n/n (%)	64/224 (28.6)	43/225 (19.1)
Patients with no postdiscontinuation therapy n/n (%)	36/224 (16.1)	25/225 (11.1)
Patients that died on study n/n (%)	2/224 (0.9)	1/225 (0.4)
First subsequent line of therapy n/N (%)	**120[a]/224 (53.6)**	**156/225 (69.3)**
Chemotherapy n/n (%)	**27/120 (22.5)**	**40/156 (25.6)**
Platinum based chemotherapy n/n (%)	26/120 (21.7)	34/156 (21.8)
Non-platinum-based chemotherapy n/n (%)	1/120 (0.8)	6/156 (3.8)
EGFR TKI n/n (%)	**89/120 (74.2)**	**113/156 (72.4)**
First Generation		
Erlotinib n/n (%)	61/120 (50.8)	55/156 (35.3)
Gefitinib n/n (%)	8/120 (6.7)	9/156 (5.8)

Second Generation		
Afatinib n/n (%)	1/120 (0.8)	12/156 (7.7)
Third Generation		
Osimertinib n/n (%)	18/120 (15.0)	35/156 (22.4)
Lazertinib n/n (%)	1/120 (0.8)	0
Nazartinib (EGF816) n/n (%)	0	2/156 (1.3)
Immunotherapy n/n (%)	**4/120 (3.3)**	**3/156 (1.9)**

Abbreviations: c-met = tyrosine-protein kinase met; EGFR = epidermal growth factor receptor; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in specified category; PDT = postdiscontinuation anticancer therapy; RECIST = Response Evaluation Criteria in Solid Tumors; TKI = tyrosine kinase inhibitor.

[a] One patient that received first subsequent therapy did not receive study treatment.

Data cutoff date: 23 January 2019

Source: b_s_pdt_1stline (Table JVCY.14.40).

The most common second subsequent therapy in the ramucirumab plus erlotinib arm were EGFR TKIs (54.0%) with osimertinib (41.3%) as the most common (Table 27). The most common second subsequent therapy in the placebo plus erlotinib arm was chemotherapy (56.6%) with platinum-based chemotherapy (38.2%) in particular.

Table 27. Summary of second subsequent therapy ITT population (N=449) who received second subsequent therapy

PDT	Ramucirumab + Erlotinib N=224 n (%)	Placebo + Erlotinib N=225 n (%)
Patients that received a subsequent 2nd Line therapy	**63 (28.1)**	**76 (33.8)**
Chemotherapy[b] n/n (%)	**27/63 (42.9)**	**43/76 (56.6)**
Platinum based chemotherapy n/n (%)	17/63 (27.0)	29/76 (38.2)
Non-platinum-based chemotherapy n/n (%)	10/63 (15.9)	14/76 (18.4)
EGFR TKI n/n (%)	**34/63 (54.0)**	**24/76 (31.6)**
First Generation		
Erlotinib n/n (%)	0	2/76 (2.6)
Gefitinib n/n (%)	2/63 (3.2)	2/76 (2.6)
Second Generation		
Afatinib n/n (%)	5/63 (7.9)	1/76 (1.3)
Third Generation		
Osimertinib n/n (%)[a]	26/63 (41.3)	19/76 (25.0)
Lazertinib n/n (%)	1/63 (1.6)	0
Immunotherapy n/n (%)	**2/63 (3.2)**	**5/76 (6.6)**
c-met inhibitor n/n (%)	**0**	**1/76 (1.3)**

Summary of Second Subsequent Therapy
ITT Population (N=449) Who Received Second Subsequent Therapy

Abbreviations: c-met = tyrosine-protein kinase met; EGFR = epidermal growth factor receptor; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in specified category; PDT = postdiscontinuation anticancer therapy; TKI = tyrosine kinase inhibitor.

[a] One patient in the placebo plus erlotinib arm received a combination of afatinib plus osimertinib as second subsequent therapy and is counted in the osimertinib row.

[b] Two patients, 1 in the ramucirumab-erlotinib group and 1 in the placebo group received chemotherapy with osimertinib.

Approximately half of the patients in both groups who continued erlotinib had their second progression while still on erlotinib.

Data cutoff date: 23 January 2019

Source: b_s_pdt_2ndline.rtf (Table JVCY.14.41).

Translational Research Analyses - EGFR T790M point mutation

Among patients who had progressed by data cutoff, valid Guardant360 NGS results from central testing of liquid biopsies are available from 244 (89%) patients at baseline and from 190 (69%) patients at 30-day follow-up (Table 28).

Table 28: Patients with NGS results from baseline or 30-Day follow-up among patients whose tumours have progressed

	Ramucirumab + Erlotinib ITT N=224	Placebo + Erlotinib ITT N=225	Total ITT N=449
Patients with disease progression by data cutoff n	118	157	275[a]
Patients with disease progression by data cutoff who had valid NGS results from baseline n (% among patients with disease progression)	108 (92%)	136 (87%)	244 (89%)
Patients with disease progression by data cutoff who had valid post-progression NGS results from 30-day follow-up n (% among patients with disease progression)	74 (63%)	116 (74%)	190 (69%)

Abbreviations: ITT = intent-to-treat population; N = number of patients; n = number of patients in specified group; NGS = next-generation sequencing; PD = progressive disease; PFS = progression-free survival.

a Excludes 5 patients that died without PD who contributed to the total 280 PFS events.

Table 29 shows rates of post-progression T790M from 30-day follow-up samples by treatment arm. Given that different criteria are applied in the literature to define the population for this type of analysis, two approaches are presented.

The first analysis in the table includes the population of patients who had central liquid biopsy NGS results showing that no T790M was detected at baseline. Patients who had NGS results at 30-day follow-up, but no NGS results available at baseline were excluded from the population.

This analysis shows that the confirmed treatment-emergent T790M rates are similar between treatment arms (25% ramucirumab plus erlotinib, 30% placebo plus erlotinib, p=0.492).

Many tumours do not shed circulating tumour DNA into the blood, and the quantity of circulating tumour DNA appears to be related to the tumour burden. Therefore, the second analysis in Table 29 includes only those patients for whom an activating EGFR mutation (exon 19 deletion or L8585R) was detected in the 30-day follow-up sample, thereby indicating that the patient's tumour was shedding DNA and suggesting that the liquid biopsy is also likely to detect T790M if it is present in the tumour. This analysis also found similar T790M rates between treatment arms (43% ramucirumab plus erlotinib, 47% placebo plus erlotinib, p=0.849).

Table 29: Post-progression EGFR T790M rates from the 30-Day follow-up liquid biopsy sample analysed by two population definitions for sensitivity

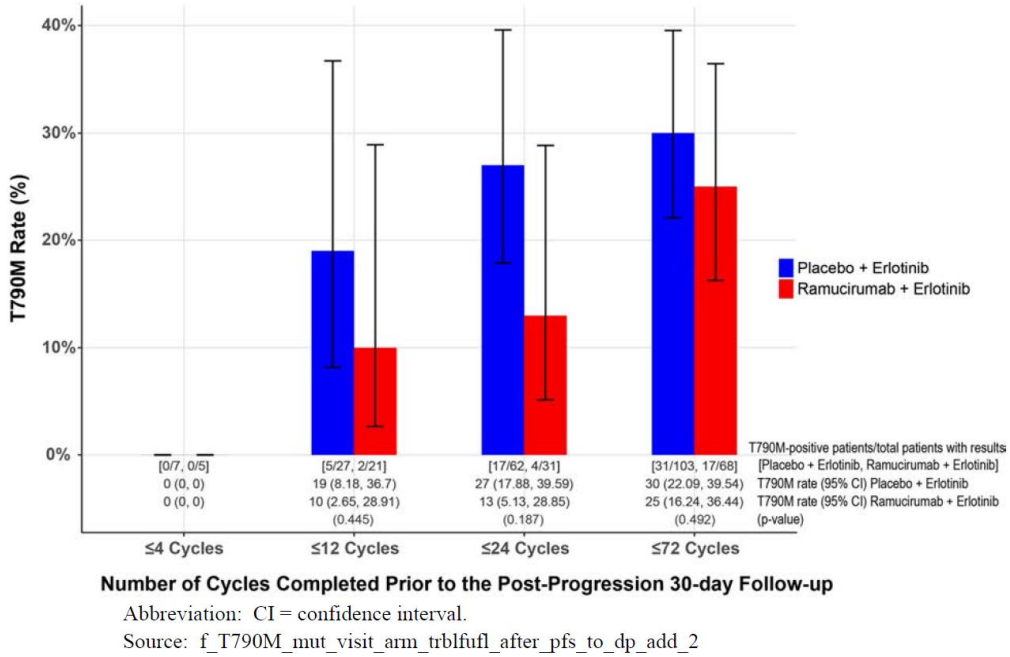
	Ramucirumab + Erlotinib	Placebo + Erlotinib
Number of patients with baseline NGS results in which T790M was not detected and with post-progression 30 day follow-up NGS results available[a]	**68**	**103**
Patients with T790M detected in 30-day follow-up sample n	17	31
Post-progression T790M positivity rate (%) (95% CI)	25 (16.24-36.44)	30 (22.09-39.54)
p-value	0.492	
Number of patients with post-progression 30-day follow-up NGS results in which *EGFR* activating mutation was detected[b]	**44**	**75**
Patients with T790M detected in 30-day follow-up sample n	19	35
Post-progression T790M positivity rate (%) (95% CI)	43 (29.68-57.78)	47 (35.82-57.84)
p-value	0.849	

Abbreviations: CI = confidence interval; EGFR= epidermal growth factor receptor; N = number of patients; n = number of patients in specified group; NGS = next-generation sequencing.

a There were 19 patients with post-progression 30 day follow-up NGS results who did not have corresponding baseline NGS results (compare Table JVCY.11.19).

b There were 71 patients with post-progression 30 day follow-up NGS results in which EGFR activating mutations could not be detected (compare Table JVCY.11.19).

The relationship between number of treatment cycles received and *EGFR* T790M emergence based on the currently available data is shown in Figure 21. Cumulative T790M rates for patients who had progressed by Cycles 12, 24, and 72 were 10%, 13%, and 25% for the ramucirumab plus erlotinib arm and 19%, 27%, and 30% for the placebo plus erlotinib arm. The cumulative incidence of T790M rates suggests that combination of ramucirumab with erlotinib may delay the emergence of this resistance mechanism, but did not change the post-progression T790M rate. Note that these patients constitute the set of patients who had progressed by the time of data cut-off, and therefore include many of the patients with the shorter progression times on the trial.



Abbreviation: CI = confidence interval.

Source: f_T790M_mut_visit_arm_trblfufl_after_pfs_to_dp_add_2

Figure 21: Post-progression T790M rate at the 30-day follow-up visit, distributed by number of treatment cycles received.

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 30: Summary of Efficacy for trial RELAY

Title: A multicentre, randomised, double-blind study of erlotinib in combination with ramucirumab or placebo in previously untreated patients with EGFR mutation-positive metastatic non-small cell lung cancer		
Study identifier	I4T-MC-JVCY (RELAY)	
Design	A multicentre, randomised, double-blind study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	First patient randomised:28-01-2016 Cut-off for primary PFS analysis: 23-01-2019 not applicable not applicable
Hypothesis	Superiority	
Treatments groups	Ramucirumab plus erlotinib	Ramucirumab (10 mg/kg) intravenously every two weeks + erlotinib (150 mg) orally once daily N= 221
	Placebo plus erlotinib	Placebo (indistinguishable and equivalent volume to ramucirumab) intravenously every two weeks + erlotinib (150 mg) orally once daily N= 225

Endpoints and definitions	Primary endpoint	Progression -free survival (PFS)	Time from the date of randomisation until the date of radiographic documentation of progression (as defined by RECIST v1.1) or the date of death due to any cause, whichever was earlier.
	Secondary endpoint	Overall survival (OS)	Time from the date of randomisation to the date of death from any cause.
	Secondary endpoint	Objective response rate (ORR)	Proportion of randomised patients achieving a best overall response of partial response (PR) or complete response (CR) per RECIST v1.1.
	Secondary endpoint	Disease control rate (DCR)	Proportion of randomised patients achieving a best overall response of CR, PR, or stable disease (SD) per RECIST v1.1.
	Secondary endpoint	Duration of response (DoR)	From the date of first documented CR or PR (responder) to the date of objective progression or the date of death due to any cause, whichever was earlier.
Database lock	14-02-2019		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Data cut-off date: 23-01-2019		
Descriptive statistics and estimate variability	Treatment group	Ramucirumab + erlotinib	Placebo + erlotinib
	Number of subject	224	225
	PFS, median	19.35	12.39
	95% CI	15.38-21.55	10.97-13.50
	OS, median	NR	NR
	95% CI	NR - NR	NR - NR
	ORR, percentage	76.3	74.7
	95% CI	70.8-81.9	69.0-80.3
	DCR, percentage	95.1	95.6
	95% CI	92.3-97.9	92.9-98.2
	DoR, median	18.0 months	11.1 months
	95% CI	13.9-19.8	9.7-12.3
Effect estimate per comparison	Primary endpoint (PFS)	Comparison groups	ramucirumab + erlotinib vs placebo + erlotinib
		HR	0.591
		95% CI	0.461-0.760
		P-value	<0.0001
	Secondary endpoint (OS)	Comparison groups	ramucirumab + erlotinib vs placebo + erlotinib
		HR	0.832
		95% CI	0.532-1.303
		p-value	0.4209
	Secondary endpoint (ORR)	Comparison groups	ramucirumab + erlotinib vs placebo + erlotinib
		P-value	0.7413
	Secondary endpoint (DCR)	Comparison groups	ramucirumab + erlotinib vs placebo + erlotinib
		P-value	1.0000
	Secondary endpoint (DoR)	Comparison groups	ramucirumab + erlotinib vs placebo + erlotinib
		P-value	0.0003

2.4.3. Discussion on clinical efficacy

Efficacy of ramucirumab plus erlotinib is based on a single pivotal trial (RELAY).

Design and conduct of clinical studies

The pivotal trial supporting this extension of indication is RELAY, a global, multicentre, randomised, placebo-controlled, double-blind, phase 1b/3 study. The double-blind design is considered adequate to investigate whether the addition of ramucirumab to erlotinib improves efficacy. The applicant mentions that there was no anticipated or identified toxicity of ramucirumab that would potentially unblind investigators to treatment assignment. This is not fully agreed, as it is possible that common adverse events specific to ramucirumab (e.g. hypertension, epistaxis) could have unblinded investigators. Even so, this is not apparent from other results, including BIRC-assessed PFS, which support the primary analysis. Patients were randomised 1:1 between the 2 treatment arms and 4 stratification factors were used. The study design is in accordance with scientific advice sought in 2014 on key study design elements for study RELAY (EMEA/H/SA/1505/7/2014/II).

Patients were selected based on 'classical' activating mutations (exon 19 and L858R), which occur in 90% of the patients with an EGFR mutation (Gazdar. Oncogene. 2019). This is similar to other procedures of EGFR-tyrosine kinase inhibitors (TKIs), like for instance Vizimpro (EMEA/H/C/004779/0000) or Tagrisso (EMEA/H/C/004124/II/0019). Nevertheless, EGFR TKIs have a broader indication, namely ''EGFR activating mutations'' (refer to Tarceva [erlotinib] SmPC). The reason for this is that efficacy of the EGFR-TKIs is extrapolated to patients with tumours bearing other (less common) mutations (EMEA/H/C/004779/0000). Both erlotinib and ramucirumab (in combination with docetaxel), as well as erlotinib plus bevacizumab and other EFGR-TKIs, are approved for the treatment of patients with locally advanced and metastatic NSCLC. In the RELAY study, only patients with metastatic NSCLC were allowed to enrol in the study; this is reflected in the proposed indication. Next, only patients with an ECOG performance status of 0-1 were included in the study. Real world data show that patients with an ECOG performance status of ≥1 can still be treated with an EGFR inhibitor (Schuette et al. Cancer Epidemiol Biomarkers. 2015, Li et al. PLoS one. 2019), but patients with ECOG score ≥2 were excluded from the pivotal studies of ramucirumab in all indications. Section 5.1 of the SmPC adequately reflects that studied patients had an ECOG performance status of 0-1. Also, patients with EGFR-positive NSCLC may have CNS metastases. It is appropriately mentioned in section 5.1 of the SmPC that patients with CNS metastases were excluded in RELAY. Lastly, the exclusion of patients with a T790M mutation is understandable, as resistance to some EGFR inhibitors (e.g. erlotinib) is caused by this mutation (Saito et al. The Lancet. 2019). Overall, the key inclusion and exclusion criteria of the RELAY study were acceptable.

Current treatment guidelines recommend the use of EGFR-TKIs as first-line treatment of patients with advanced EGFR mutation-positive NSCLC (Planchard et al. Ann of Oncol. 2018). The ESMO guideline for metastatic NSCLC does not define which of the currently approved EGFR-TKIs is the preferred first-line treatment option. At the time the RELAY study was initiated, erlotinib, gefitinib and afatinib were the only approved treatment options for EGFR mutation-positive NSCLC. Scientific advice was sought in 2014 and the CHMP agreed upon the choice of comparator for study RELAY (EMEA/H/SA/1505/7/2014/II), i.e. erlotinib (in combination with placebo).

The selection of the ramucirumab 10 mg/kg Q2W dosing regimen in the RELAY study was based on an integrated assessment of previously available clinical data. The applicant considered that the totality of clinical data indicated that there may an opportunity to further enhance efficacy of ramucirumab while maintaining an acceptable safety profile. Using the same 10 mg/kg dose as used in study REVEL the C_{max} level should not be significantly increased (mitigate potential C_{max}-related toxicity), but the more frequent dosing interval (every 2 weeks instead of every 3 weeks) should produce higher overall exposure (potentially enhancing efficacy). Also, study I4T-MC-JVCY (RELAY) included a phase 1b safety lead-in (part

A) to determine the tolerability of ramucirumab 10 mg/kg Q2W. One patient experienced a grade 3 increased alanine aminotransferase in the DLT-evaluable population (*n*=12). Based on these findings, the assessment committee recommended initiation of part B (phase 3) of study RELAY with the ramucirumab dose and schedule of 10 mg/kg Q2W in combination with erlotinib 150 mg once daily, which is understood and agreed.

PFS as primary endpoint is in accordance with scientific advice (EMEA/H/SA/1505/7/2014/II). The CHMP agreed with PFS as primary endpoint, given the expected long post-progression survival. The CHMP recommended that PFS2 should also be measured (PFS2 was included as an exploratory endpoint in the RELAY study). PFS is not an uncommon primary endpoint in studies investigating EGFR-TKIs in EGFR-positive NSCLC. For example, the pivotal trial supporting marketing authorisation of bevacizumab plus erlotinib as first-line treatment of patients with EGFR mutation-positive NSCLC had PFS as primary endpoint (EMEA/H/C/000582/II/0086). The primary definition of PFS (censoring for missed visits and start new anti-cancer therapy) is not the one recommended by EMA (EMA/CHMP/27994/2008/Rev.1), but the EMA recommended analysis is included as one of the sensitivity analysis. Secondary endpoints include overall survival, tumour response rate, which are relevant secondary endpoints.

In general, protocol deviations were unlikely to have had an impact on the efficacy analyses. Remarkably, the percentage of patients receiving prohibited concomitant medication was twice as high in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm. Of the prohibited concomitant medications, proton-pump inhibitors (PPIs) were most frequently administered. The use of proton-pomp inhibitors could potentially influence the efficacy of erlotinib (drugs affecting gastric pH decrease erlotinib plasma concentrations). Upon request for supplementary information the applicant informed that any concomitant PPI use was captured as a protocol deviation (35 patients in the ramucirumab plus erlotinib arm and 28 patients in the placebo plus erlotinib arm), and if continued for 14 days or longer it was defined as an important protocol deviation. Of the 16 patients summarised with important deviations due to use of prohibited concomitant medications, 10 patients in the ramucirumab plus erlotinib arm and 2 patients in the placebo plus erlotinib arm were treated with PPIs for 14 days or longer. The use of PPI was similar between both treatment arms (although more patients were treated with PPIs for 14 days or longer in the ramucirumab plus erlotinib arm), and hence it is unlikely that efficacy results were impacted by concomitant PPI use. **.**However, relatively few patients received prohibited concomitant medications and given that more patients in the ramucirumab plus erlotinib arm received prohibited medications, this would not be in favour of this treatment arm. Important changes to the protocol were made during the sixth amendment (amendment f), which included a revision of the sample size (see discussion in the next paragraph - statistical assumptions). The reason for this amendment was emerging data from first-line use of erlotinib and published data from the phase 1b of study RELAY (Reck et al. Clinical Lung Cancer. 2018) indicating that the assumed median PFS for both erlotinib (monotherapy) and ramucirumab plus erlotinib was likely underestimated.

Several protocol amendments were made. Addition of PFS2 as an explorative endpoint (amendment a) and measures to secure independent central review of tumour scans and prevent statistical bias due to informative censoring (amendment b) are considered adequate. Update of the guidance regarding prohibited and restricted concomitant CYP3A4 inducers or inhibitors (amendment d) to allow use of moderate CYP3A4 inducers (with any appropriate dose adjustments per the erlotinib package insert) is also considered adequate.

Changes in the primary analysis included removal of PFS interim analysis, which is agreed as such analyses are discouraged (EMA/CHMP/27994/2008/Rev.1). Also, rules for determining date of progression or censoring were updated, and the number of events was reduced from 320 to 270. Given the double blind design, it is considered unlikely that these decisions were informed by results from part b of study RELAY. Moreover, as for the updating of PFS censoring rules, there is consensus about which censoring rules to apply (EMA/CHMP/27994/2008/Rev.1). For the sample size revision, external data and data from the phase

1b part of study RELAY indicated that the assumed median PFS for both arms was likely underestimated. Given all these considerations, type I error is unlikely to be affected by the changes in the primary analysis. An interim futility analysis was conducted at 114 investigator-assessed PFS events (data cut-off date 16 October 2017) with a nominal 1-sided alpha <0.00001 spent in order to maintain type-I error and the IDMC recommending the trial continue without modification. For a futility aim, spending type I error had not been needed per se, but it is unlikely to have affected main conclusions from the trial. The statistical methods are considered otherwise standard and adequate.

Demographic and other baseline characteristics were balanced between treatment arms. Most patients in both treatment arms were female (62.9% vs. 63.1%), approximately 75% were Asian (76.8% vs. 77.3%), approximately 60% were never-smokers (59.8% vs. 61.8%). This is not surprising, since these patients are more likely to have an EGFR mutation (Zhang et al. Oncotarget. 2016).

Efficacy data and additional analyses

The primary endpoint of the study was met. Treatment with ramucirumab in combination with erlotinib resulted in a statistically significant improvement in PFS compared to placebo in combination with erlotinib (stratified HR = 0.591 [95% CI: 0.461-0.760]; p<0.0001). A gain of 7 months in median PFS was obtained with the addition of ramucirumab to erlotinib (19.4 months vs 12.4 months). The Kaplan-Meier curves separated at approximately 3 months and remained separated during the following months. The primary PFS analysis was supported by the sensitivity analyses. The EMA recommended PFS analysis (i.e. investigator assessed, not censoring for new anti-cancer therapy or missed visits) was in favour of ramucirumab with erlotinib (stratified HR=0.609 [95%-CI: 0.478, 0.776], median 19.35 vs 12.39 months). Moreover, possibly informative censoring reasons (no follow-up or withdrawal consent: 2.2 vs 0.8%) occurred little. Therefore, the results from the EMA preferred analysis (investigator-assessed PFS) seems quite robust against informative censoring. Agreement between blinded independent review committee (BIRC) and investigator-assessed PFS was similar between arms (80.6% [ramucirumab plus erlotinib arm] and 76.7% [placebo plus erlotinib arm]) in the applicant's primary analysis, but the nature of disagreement seems different between experimental and control arm. In the control arm, investigators but not BICR observed progression twice as much compared to the opposite (16.1% vs 7.2%), while in the experimental arm this occurred equally frequent (9.7%). The applicant mentions that this was likely due to random chance. This can be agreed, as importantly, both the primary PFS analysis and the BIRC-assessment of PFS show a consistent treatment effect in favour of the ramucirumab plus erlotinib arm..

Subgroup analyses show that all subgroups favoured the ramucirumab plus erlotinib arm, except for patients ≥70 years of age. The applicant explains that this is driven by a small number of patients between the age of 70 and 75 and was likely due to chance. Another observation from the subgroup analyses was that a larger treatment effect was found in the subgroup Therascreen®Cobas® compared to the subgroup others. This is a remarkable finding, and could not be explained by the applicant. Results of central EGFR testing (to confirm results by local testing) were available for 70% of the ITT population. Of the 30% (133 patients) without central tissue EGFR results, the majority (n=110) did not submit samples of sufficient quantity and/or quality. For the remaining patients, there were other reasons for the absence of central tissue EGFR results, such as patients that did not sign the optional tumour tissue consent in countries were mandatory tumour collections is not allowed. The available data showed that central EGFR testing confirmed the results of local testing. Even so, the applicant had conducted additional analysis, and an apparent difference by EGFR testing method appeared to be present in the geographic region of East Asia. The Applicant could not identify any explanation for this observation. Consistent HRs by testing method were observed for the EU and North America (0.68 [95% CI: 0.36, 1.28) vs 0.51 [95% CI: 0.21, 1.21]), which reassures that the overall results are representative for the EU/North America region. There were mostly Asian patients enrolled in Relay. However, the point estimate for the PFS hazard ratios indicate no difference in treatment effect between race (Asian vs Caucasian). This is in line with the previously agreed

notion that there are no relevant differences in EGFR activating mutations (exon 19 deletions and L858R) in tumours of Asian and Caucasian NSCLC patients (EMEA/H/C/000582/II/0086).

It is mentioned in the guideline on the evaluation of anticancer medicinal products in man that, if PFS is the primary endpoint, overall survival as secondary endpoint should ensure that there is no relevant impact on survival (EMA/CHMP/205/95 Rev.5). The interim analysis OS did not show a detrimental effect on OS (KM curves currently overlap; HR=0.832 [95% CI: 0.532, 1.303]). This finding is in line with the expectations of combining an angiogenesis inhibitor with an EGFR-TKI, as similar was seen for bevacizumab plus erlotinib in previously untreated EGFR-positive NSCLC (EMEA/H/C/000582/II/0086). However, at the data cut-off date, only 79 events occurred and OS data was not mature (data maturity, 17.6%). It is anticipated that the pre-specified final OS analysis will likely be conducted end of Q2 2023. The applicant is recommended to submit the results, once available.

ORR and DCR were similar between arms, but treatment with ramucirumab plus erlotinib result in a longer median duration of response compared to placebo plus erlotinib (extending the time-to-progression), supporting the primary endpoint. Thus, combining a VEFGR inhibitor with an EGFR inhibitor results in a longer duration of response, delaying progression. There are some discrepancies between the investigator-assessed and BIRC-assessed ORR, especially in the percentage of patients having a complete response (1.3% vs 7.4 % for ramucirumab plus erlotinib arm and 0.9% vs 4.9% in the placebo plus erlotinib arm, respectively). Despite these discrepancies, the BIRC numerically favoured the ramucirumab plus erlotinib arm.

Quality of life (QoL) was measured with two patient-reported outcome measures in the RELAY study. Unfortunately, an a priori specification of the expected effect (e.g., improvement, maintenance) was not included in the protocol, and it is not clear whether the applicant expected an improvement in QoL or no deterioration in QoL. QoL analyses did not show any difference between treatment arms, except for haemoptysis. Of interest is the time to deterioration for blood in sputum or haemoptysis. Especially taken into account the careful selection of patients in regard of risk for haemorrhagic complications of the disease or treatment and that haemoptysis did not seem to be a disease symptom of concern at baseline (**OC**). The applicant mentions that patient-reported symptoms, symptom burden, and overall quality of life (QoL) data indicated no significant detriment from the addition of ramucirumab to erlotinib. However, it is questioned whether these patient-reported outcome measures are sensitive enough to determine whether the addition of ramucirumab to erlotinib does not have a detrimental impact on quality of life. The LCSS focusses on the effect of treatment on symptom control, and how this effects quality of life and activity status (Hollen *et al.* Eur J Cancer. 1993) and the EQ-5D values health (in mobility, self- care, usual activities, pain/discomfort, and anxiety/depression) (Herdman et al. Qual Life Res. 2011). The influence of the additional toxicity caused by the addition of ramucirumab to erlotinib (treatment-related symptoms) on the QoL is not directly evaluated with these instruments, nor the influence of additional clinical visits necessary for ramucirumab administration. The latter would also be difficult to assess, as the RELAY study was placebo-controlled and both arms were administered ramucirumab or placebo (hence had additional clinical visits). Overall, the interpretability of the QoL results and therefore their clinical relevance is unclear. Besides, in the case it is expected that a drug improves PFS, a delay time to deterioration is expected (improvement in time to deterioration), as progression might worsen lung cancer symptoms. This means that no improvement with this instrument is not necessarily considered a favourable effect.

The tumour resistance profile can be affected by therapy, and might be of relevance for the activity of next-line therapies (guideline on the evaluation of anticancer medicinal products in man). Progression-free survival 2 was an exploratory endpoint of the RELAY study. The initial and updated PFS2 analyses (8 months follow-up) favoured the ramucirumab plus erlotinib arm, indicating that there is no negative impact on next line treatment by ramucirumab. The post-progression survival of patients with EGFR-positive NSCLC is long, and it is reassuring that the treatment benefit seems to be maintained after second progression, based on these preliminary results.

Based on Guardant NGS data, the rates of treatment-emergent *EGFR* T790M were similar between treatment arms, suggesting that subsequent treatment with agents targeting this *EGFR* mutation will remain viable options in the next line of disease care.

Limited data were available (limited number of events) for the remaining exploratory endpoints (time to deterioration in ECOG PS, time to diagnosis of CNS metastases), and no conclusion could be made at this moment.

2.4.4. Conclusions on the clinical efficacy

Treatment with ramucirumab in combination with erlotinib resulted in a significant improvement in PFS compared to placebo in combination with erlotinib. Median DoR and PFS2 favoured the ramucirumab plus erlotinib arm, supporting the primary endpoint. Overall survival data (data maturity, 17.6%) suggest no detrimental effect on OS and final overall survival data should be submitted to the agency for conformation of the preliminary results.

2.5. Clinical safety

Introduction

The safety of ramucirumab plus erlotinib was based on a global, multicentre, phase 1b/3 study (RELAY). The safety lead-in (part A) of study RELAY was to determine the safety and tolerability of ramucirumab 10 mg/kg Q2W plus erlotinib 150 mg QD. One dose limiting toxicity (grade 3 increased alanine aminotransferase [ALT]) was observed in part A and the randomised phase 3 portion of the study (part B) with ramucirumab at 10 mg/kg Q2W in combination with erlotinib (150 mg QD) was initiated. Given that only a few patients were treated in part A of study RELAY (n=14), the most relevant safety results are those observed in part B. Especially as this part of the study enables to identify the added toxicity of ramucirumab in addition to erlotinib due to the placebo-controlled design of this part of the study. Therefore, the safety section will only focus on part B of study RELAY.

Patient exposure

A summary of drug exposure for ramucirumab or placebo is given in Table 31. The RELAY safety population consisted of 221 patients who received at least 1 dose of study therapy in the ramucirumab plus erlotinib arm and 225 patients in the placebo plus erlotinib arm. In the ramucirumab plus erlotinib arm, the median duration of therapy was 11.0 months for ramucirumab and 14.1 months for erlotinib. In the placebo plus erlotinib arm, the median duration of treatment was 9.7 months for placebo and 11.2 months for erlotinib. The median relative dose intensity was similar between arms.

Table 31. Extent of exposure safety population

	Ramucirumab + Erlotinib N=221	Placebo + Erlotinib N=225
Ramucirumab or Placebo[a]		
Number of patients who received ramucirumab or placebo[a]	221	225
Duration of therapy (months)		
Median (Range)	11.04 (0.46-33.81)	9.66 (0.46-35.42)
Infusions received per patient		
Median (Range)	21.00 (1.00-69.00)	19.00 (1.00-74.00)
Relative Dose Intensity (%)[b]		
Median (Range)	94.48 (42.86-112.09)	97.67 (54.21-106.71)
Erlotinib		
Number of patients who received erlotinib[a]	221	225
Duration of therapy (months)		
Median (Range)	14.13 (0.03-33.84)	11.20 (0.36-35.45)
Weeks on treatment per patient[c]		
Median (Range)	60.00 (0-138.00)	47.00 (1.00-152.00)
Relative dose intensity (%)[b]		
Median (Range)	92.26 (30.16-100.00)	96.27 (27.88-100.00)

[a]Number of patients who received at least one dose of study drug ramucirumab placebo or erlotinib, either partial or complete.
[b]Relative dose intensity (%) is calculated as (actual amount of drug taken / amount of drug planned per protocol) * 100.
[c] Patient is considered to have received a week of therapy after receiving at least 7 doses of erlotinib, either partial or complete.

Dose Adjustments

The number of patients with a dose adjustment of ramucirumab or placebo included dose delays, dose reductions, or dose omissions is depicted in Table 32. Dose adjustments of erlotinib included dose reductions or dose omissions. Dose delays for erlotinib were not captured on the eCRF. Overall, a higher percentage of patients experienced ramucirumab dose adjustments compared with placebo. A higher percentage of patients in the ramucirumab plus erlotinib arm compared with the placebo plus erlotinib arm had erlotinib dose adjustments (dose reductions and dose omissions). A higher number of patients receiving ramucirumab experienced dose adjustments (76 vs 59.1%), dose reduction (10.4 vs 1.8%), dose delay (66,5 vs 53,8%) and dose omissions (28,1 vs 12.4%). Overall the most dose adjustments were due to AEs (TEAEs discussed below).

The proportion of patients experiencing dose adjustment for ramucirumab or placebo between age group < 65 years of age was 79.4 vs 54.4% and ≥65-year-old 73.1 vs 64.0%. These were most common due to proteinuria, hypertension, cytopenia, increased ALAT or increased bilirubin. In the subgroup of patients < 70 years of age dose adjustment for ramucirumab or placebo were 79.6 vs 56% compared to patients ≥ 70-year old 67.2 vs 67.8%.

Dose adjustments for ramucirumab were also more common in male compared to female patients, respectively 79.3 vs 55.4% and 74.1 vs 61.3%. The differences were smaller in case of geographic region and race.

Table 32. Summary of dose adjustments safety population

	Ramucirumab + Erlotinib N=221 n (%)		Placebo + Erlotinib N=225 n (%)	
	Ramucirumab	Erlotinib	Placebo	Erlotinib
Patients with at Least One Dose Adjustment	**168 (76.0)**	**143 (64.7)**	**133 (59.1)**	**134 (59.6)**
Patients with a Dose Reduction	**23 (10.4)**	**99 (44.8)**	**4 (1.8)**	**96 (42.7)**
1 dose reduction	14 (6.3)	64 (29.0)	3 (1.3)	71 (31.6)
2 dose reductions	7 (3.2)	31 (14.0)	1 (0.4)	22 (9.8)
≥3 dose reductions	2 (0.9)	4 (1.8)	0	3 (1.3)
Reasons leading to dose reductions				
AEs	23 (10.4)	96 (43.4)	4 (1.8)	93 (41.3)
Others	0	10 (4.5)	0	10 (4.4)
Patients with a Dose Delay	**147 (66.5)**	**NA**	**121 (53.8)**	**NA**
1 dose delay	50 (22.6)	NA	50 (22.2)	NA
2 dose delays	33 (14.9)	NA	31 (13.8)	NA
≥3 dose delays	64 (29.0)	NA	40 (17.8)	NA
Reasons leading to dose delays				
AEs	140 (63.3)	NA	102 (45.3)	NA
Scheduling conflict	32 (14.5)	NA	37 (16.4)	NA
Patients with a Dose Omission	**62 (28.1)**	**119 (53.8)**	**28 (12.4)**	**118 (52.4)**
1 dose omission	50 (22.6)	51 (23.1)	18 (8.0)	54 (24.0)
2 dose omissions	8 (3.6)	24 (10.9)	3 (1.3)	29 (12.9)
≥3 dose omissions	4 (1.8)	44 (19.9)	7 (3.1)	35 (15.6)
Reasons leading to dose omission				
AEs	48 (21.7)	116 (52.5)	20 (8.9)	113 (50.2)
Others	17 (7.7)	34 (15.4)	11 (4.9)	30 (13.3)

Abbreviations: AE = adverse events; CRF = case report form; N = number of patients; n = number of patients in the specified category; NA = not available (dose delays were not captured for erlotinib).
Data cutoff date: 23 January 2019.
Dose reductions of ramucirumab or placebo were defined as total number of reduction steps considering the intended dose level before each infusion (as entered in the CRF).
Dose reductions of erlotinib were defined as total number of reduction steps considering the intended dose level.
Dose delays of ramucirumab or placebo were defined total number of treatments reported as delayed in CRF that were administered >3 days but ≤11 days beyond a scheduled infusion where treatment was not given.
Dose delays of erlotinib were not captured on the CRF.
Dose omissions of ramucirumab or placebo were defined as total number of treatments reported as omitted or delayed in CRF that were administered >11 days beyond a scheduled infusion where treatment was not given.
Dose omissions of erlotinib were defined as total number of doses withheld in CRF as one per omission interval.
Source: b_o_ex_adjustment_summary_3_p1123191_t1123225 (Table JVCY.14.98).

Adverse events

An overview of the observed adverse events frequencies in the different adverse events categories is shown in Table 33.

All patients in both arms reported at least 1 TEAE. The incidence of grade ≥3 TEAEs was higher in the ramucirumab plus erlotinib arm than the placebo plus erlotinib arm (71.9% vs. 53.8%). The incidence of any-grade SAEs was higher in the ramucirumab plus erlotinib arm than the placebo plus erlotinib arm (29.4% vs. 20.9%).

Table 33. Overview of Adverse Events Safety Population

Adverse Event Category[a]	Ramucirumab + Erlotinib N=221 n (%)	Placebo + Erlotinib N=225 n (%)
Patients with ≥1 TEAE	221 (100.0)	225 (100.0)
Related to study treatment[b]	217 (98.2)	220 (97.8)
Patients with ≥1 TEAE CTCAE Grade ≥3	159 (71.9)	121 (53.8)
Related to study treatment[b]	130 (58.8)	94 (41.8)
Patients with ≥1 SAE	65 (29.4)	47 (20.9)
Related to study treatment[b]	34 (15.4)	26 (11.6)
Patients who discontinued all study treatment due to AE	29 (13.1)	24 (10.7)
Related to study treatment[b]	23 (10.4)	24 (10.7)
Patients who discontinued all study treatment due to SAE	10 (4.5)	9 (4.0)
Related to study treatment[b]	6 (2.7)	9 (4.0)
Patients who died due to AE on study treatment	2 (0.9)	0
Related to study treatment[b]	1 (0.5)	0
Patients who died due to AE within 30 days of discontinuation from study treatment[c]	4 (1.8)	0
Related to study treatment[b]	0	0

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients; n = number of patients in the specified category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Patients may be counted in more than 1 category.

[b] Includes events that were considered related to study treatment as judged by the investigator.

[c] Deaths are also included as serious adverse events and discontinuations due to adverse events.

Data cutoff date: 23 January 2019

Note: The incidence of AEs leading to discontinuation of study treatment refers to patients who are discontinued from the study (that is, all study drugs) due to an AE.

Note: All SAEs were treatment emergent.

Source: b_o_ae_overview_p620806_t620827.rtf.

Treatment-emergent adverse events (TEAEs)

All patients reported at least one TEAE. Of the common TEAEs reported in ≥20% of patients in the ramucirumab plus erlotinib arm and occurring at a 5-percentage point or higher incidence than in the placebo plus erlotinib arm, the majority of the differences in incidence rates were observed in low-grade events (grades 1 and 2), with the exception of hypertension, for which the difference in incidence between arms was driven equally by low-grade and grade ≥3 events. In addition to hypertension, the other specific grade ≥3 TEAEs in ≥5% of patients in the ramucirumab plus erlotinib arm and with a 2-percentage point or higher incidence than in the placebo plus erlotinib arm were dermatitis acneiform and diarrhoea.

Table 34summarizes the any-grade TEAEs occurring in ≥10% of patients in the ramucirumab plus erlotinib arm with any higher incidence in the ramucirumab plus erlotinib arm compared with the placebo plus erlotinib arm.

The most common any-grade TEAEs, with at least a 20% incidence in the ramucirumab plus erlotinib arm, and observed at a higher incidence (at least a 5-percentage point difference) in the ramucirumab plus erlotinib arm compared with the placebo plus erlotinib arm, respectively, were:

- hypertension (45.2% vs. 12.0%)
- ALT increased (42.5% vs. 31.1%)
- AST increased (41.6% vs. 25.8%)
- stomatitis (41.6% vs. 36.4%)
- alopecia (33.9% vs. 19.6%)
- proteinuria (33.9 vs. 8.4%)
- epistaxis (33.5% vs. 12.0%)
- nausea (25.8% vs. 19.6%)
- peripheral oedema (22.6% vs. 4.4%)
- cough (21.7% vs. 15.6%), and
- pyrexia (21.3% vs. 12.4%)

Of the any-grade TEAEs occurring with ≥20% incidence in the ramucirumab plus erlotinib arm, hypertension, proteinuria, epistaxis, and peripheral oedema were observed with at least twice the incidence than in the placebo plus erlotinib arm. The overall incidence of TEAEs leading to the discontinuation of all study treatment was similar in the ramucirumab plus erlotinib arm (12.7%) and the placebo plus erlotinib arm (10.7%). A higher percentage of patients discontinued ramucirumab alone due to TEAEs than placebo alone (73 patients [33.0%] vs. 34 patients [15.1%], respectively). The most common TEAEs (occurring in at least 5 patients in the ramucirumab plus erlotinib arm) reported in patients who discontinued ramucirumab or placebo alone and continued treatment with erlotinib, in the ramucirumab plus erlotinib arm versus placebo plus erlotinib arm, respectively, were:

- proteinuria (19 patients [8.6%] vs. 0%)
- hyperbilirubinemia (13 patients [5.9%] vs. 15 patients [6.7%])
- platelet count decreased (7 patients [3.2%] vs. 1 patient [0.4%])
- neutropenia (6 patients [2.7%] vs. 2 patients [0.9%])

Table 34. Treatment-emergent adverse events (any grade) occurring in ≥10% of patients in the ramucirumab plus erlotinib arm by MedDRA preferred term by decreasing frequency safety population

	Ramucirumab + Erlotinib N=221 n (%)		Placebo + Erlotinib N=225 n (%)	
MedDRA Preferred Term	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with any TEAE	221 (100.0)	159 (71.9)	225 (100.0)	121 (53.8)
Diarrhoea	155 (70.1)	16 (7.2)	160 (71.1)	3 (1.3)
Dermatitis acneiform	149 (67.4)	33 (14.9)	153 (68.0)	20 (8.9)
Paronychia	118 (53.4)	9 (4.1)	114 (50.7)	7 (3.1)
Hypertension	100 (45.2)	52 (23.5)	27 (12.0)	12 (5.3)
Alanine aminotransferase increased	94 (42.5)	19 (8.6)	70 (31.1)	17 (7.6)
Stomatitis	92 (41.6)	4 (1.8)	82 (36.4)	3 (1.3)
Aspartate aminotransferase increased	92 (41.6)	11 (5.0)	58 (25.8)	10 (4.4)
Dry skin	83 (37.6)	1 (0.5)	91 (40.4)	5 (2.2)
Alopecia	75 (33.9)	NA	44 (19.6)	NA
Proteinuria	75 (33.9)	6 (2.7)	19 (8.4)	0
Epistaxis	74 (33.5)	0	27 (12.0)	0
Blood bilirubin increased	68 (30.8)	3 (1.4)	70 (31.1)	2 (0.9)
Decreased appetite	57 (25.8)	6 (2.7)	47 (20.9)	4 (1.8)
Nausea	57 (25.8)	2 (0.9)	44 (19.6)	2 (0.9)
Pruritis	51 (23.1)	2 (0.9)	66 (29.3)	2 (0.9)
Oedema peripheral	50 (22.6)	2 (0.9)	10 (4.4)	0
Cough	48 (21.7)	1 (0.5)	35 (15.6)	0
Pyrexia	47 (21.3)	0	28 (12.4)	1 (0.4)
Constipation	43 (19.5)	0	32 (14.2)	0
Rash	39 (17.6)	2 (0.9)	54 (24.0)	5 (2.2)
Dysgeusia	39 (17.6)	NA	32 (14.2)	NA
Upper respiratory tract infection	38 (17.2)	0	34 (15.1)	0
Malaise	34 (15.4)	2 (0.9)	20 (8.9)	1 (0.4)
Headache	33 (14.9)	2 (0.9)	16 (7.1)	0
Insomnia	32 (14.5)	0	29 (12.9)	0
Platelet count decreased	31 (14.0)	3 (1.4)	6 (2.7)	0
Weight decreased	28 (12.7)	2 (0.9)	29 (12.9)	1 (0.4)
Vomiting	27 (12.2)	2 (0.9)	25 (11.1)	1 (0.4)
Fatigue	26 (11.8)	3 (1.4)	27 (12.0)	0
Neutrophil count decreased	25 (11.3)	6 (2.7)	16 (7.1)	2 (0.9)
Back pain	24 (10.9)	0	18 (8.0)	2 (0.9)
Blood alkaline phosphatase increased	23 (10.4)	1 (0.5)	20 (8.9)	3 (1.3)
Dry eye	22 (10.0)	0	23 (10.2)	0
Nasopharyngitis	22 (10.0)	0	18 (8.0)	0
Anaemia	22 (10.0)	4 (1.8)	10 (4.4)	1 (0.4)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities (Version 21.1); N = number of patients; n = number of patients in the specified category; NA = not applicable (Grade ≥3 alopecia and dysgeusia does not exist in CTCAE); TEAE = treatment-emergent adverse event.

Grade ≥3 TEAEs

A higher percentage of patients in the ramucirumab plus erlotinib arm (71.9%) reported grade ≥3 TEAEs compared with the placebo plus erlotinib arm (53.8%). The difference between the 2 treatment arms was predominantly due to the higher rate of grade 3 events in the ramucirumab plus erlotinib arm than the placebo plus erlotinib arm (64.3% vs. 49.3%, respectively). Grade 3 hypertension, reported in 23.5% of patients, made the largest single contribution by PT to grade≥3 TEAEs in the ramucirumab plus erlotinib arm. Grade ≥3 TEAEs occurring in ≥5% of patients in the ramucirumab plus erlotinib arm and at a higher incidence (at least a 2-percentage point difference) than in the placebo plus erlotinib arm were:

- hypertension (only grade 3 events) (23.5% vs. 5.3%)

- dermatitis acneiform (only grade 3) (14.9% vs. 8.9%)

- diarrhoea (only grade 3 events) (7.2% vs. 1.3%)

The incidence of grade 4 TEAEs was similar between treatment arms (ramucirumab plus erlotinib arm: 11 patients [5.0%]; placebo plus erlotinib arm: 9 patients [4.0%]). The most commonly-reported grade 4 TEAEs were ALT increased (2 [0.9%] vs. 3 [1.3%]) and hepatic function abnormal (2 [0.9%] vs. 2 [0.9%]).

Adverse events of interest

Adverse Events of Interest for Erlotinib

This section details selective adverse events of interest for erlotinib, including interstitial lung disease (ILD), skin reactions, diarrhoea, and nail disorders for which it was clinically relevant to assess any potential additional toxicity in the context of ramucirumab used in combination with erlotinib. These events were chosen for evaluation based upon medical judgment on the clinical relevance in the target population and/or potential overlapping toxicities between ramucirumab and erlotinib.

The Adverse Events of Interest for erlotinib were ILD, skin reactions, diarrhoea, and nail disorders for which it was clinically relevant to assess any potential additional toxicity in the context of ramucirumab used in combination with erlotinib.

Interstitial lung disease (ILD)

Any-grade ILD was reported in 4 patients (1.8%) in the ramucirumab plus erlotinib arm and 7 patients (3.1%) in the placebo plus erlotinib arm. Grade ≥3 ILD occurred in 1 patient (0.5%) in the ramucirumab plus erlotinib arm and 3 patients (1.3%) in placebo plus erlotinib arm. There were no grade 4 events in either treatment arm. One patient (0.4%) in the placebo plus erlotinib arm experienced a grade 5 (fatal) ILD event which occurred 30 days after discontinuation of study treatment and was assessed by the investigator as related to study treatment. Three patients (1.3%) discontinued all study treatment due to ILD in the placebo plus erlotinib arm. One patient in each treatment arm discontinued erlotinib alone due to ILD while continuing ramucirumab alone. No patients discontinued ramucirumab or placebo alone due to ILD while continuing erlotinib.

Skin Reactions

To evaluate the potential impact of ramucirumab on skin toxicity (including *rash*) associated with erlotinib, relevant TEAEs from the SOC Skin and Subcutaneous Tissue Disorders were chosen to create the composite term "skin reactions". Except for the higher incidence of grade ≥3 dermatitis acneiform (14.9%) in the ramucirumab plus erlotinib arm compared with the placebo plus erlotinib arm (8.9%), no other relevant differences in skin-related TEAEs were identified between treatment arms. In the race subgroups, for ramucirumab-treated patients, a higher incidence of any-grade and grade ≥3 dermatitis acneiform was observed in Asian patients compared to non-Asian patients (any grade: 77.6% vs. 33.3%, respectively; grade ≥3: 18.2% vs. 3.9% [all grade 3 events], respectively).

Diarrhoea

The incidence of diarrhoea of any grade was similar in the ramucirumab plus erlotinib arm (70.1%) and the placebo plus erlotinib arm (71.1%), with the majority of events being grade 1 in severity in both treatment arms (48.4% vs. 52.9%, respectively). The incidence of grade ≥3 diarrhoea was higher in the ramucirumab plus erlotinib arm than the placebo plus erlotinib arm (7.2% vs. 1.3%, respectively; all grade 3 events). No grade 4 or 5 events occurred in either treatment arm. The use of antidiarrheal medications as supportive treatment was similar in the ramucirumab plus erlotinib arm and the placebo plus erlotinib arm (58.8% vs. 56.0%, respectively).

Nail Disorders

To fully evaluate the potential impact of ramucirumab on nail toxicity (including paronychia) associated with erlotinib, relevant TEAEs from the SOC Skin and Subcutaneous Tissue Disorders were chosen to create the composite term "nail disorders". The incidence of any-grade and grade ≥3 nail disorders (including paronychia) was similar in the ramucirumab plus erlotinib arm (any grade: 56.6%; grade ≥3: 4.1%) and the placebo plus erlotinib arm (any-grade: 55.6%; grade ≥3: 3.1%).

Adverse Events of Special Interest for ramucirumab

The following AEs are considered to be AESIs for ramucirumab: IRRs, hypertension, proteinuria, arterial thromboembolic events (ATEs), venous thromboembolic events (VTEs), bleeding/haemorrhagic events, GI perforation, congestive heart failure (CHF), wound healing complications, fistula, liver failure/liver injury, and reversible posterior leukoencephalopathy syndrome (RPLS). No RPLS events were observed in this study. The AESI are shown in Table 35.

Table 35. Adverse Events of Special Interest for ramucirumab

AESI term	**Ramucirumab + erlotinib N = 221 n (%)**				**Placebo + erlotinib N = 225 n (%)**			
	Any Grade		**Grade ≥3**		**Any Grade**		**Grade ≥3**	
Patients with any treatment emergent AESI	176	(79.6)	63	(28.5)	88	(39.1)	20	(8.9)
Bleeding / haemorrhage events	121	(54.8)	4	(1.8)	59	(26.2)	4	(1.8)
Hypertension	100	(45.2)	52	(23.5)	27	(12.0)	12	(5.3)
Infusion related reaction (PT)	3	(1.4)	0	(0.0)	2	(0.9)	0	0
Proteinuria	76	(34.4)	6	(2.7)	19	(8.4)	0	(0.0)
Liver failure/liver injury	140	(63.3)	31	(14)	120	(53.3)	28	(12.4)
Venous thromboembolic events	7	(3.2)	3	(1.4)	9	(4.0)	5	(2.2)
Congestive heart failure	4	(1.8)	2	(0.9)	1	(0.4)	0	(0.0)
Healing complication	2	(0.9)	0	(0.0)	1	(0.4)	0	(0.0)
Arterial thromboembolic events	2	(0.9)	1	(0.5)	0	0.0)	0	(0.0)
Fistula	2	(0.9)	1	(0.5)	0	(0.0)	0	(0.0)
Gastrointestinal perforation	1	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)

Abbreviations: n = number of subjects; AESI = Treatment Emergent Adverse Events of Special Interest; PT = Preferred Term.

Infusion-Related Reactions, including Hypersensitivity and Anaphylactic Reactions

Immediate hypersensitivity reactions utilized the following SMQs and PT search criteria to collect relevant events: Anaphylactic reaction SMQ, Hypersensitivity SMQ, Angioedema SMQ, PT IRR, PT Cytokine release syndrome. The incidence of any-grade IRRs was low and similar in both treatment arms (ramucirumab plus erlotinib arm: 2.7%; placebo plus erlotinib arm: 1.8%). No Grade ≥3 IRR occurred during the study.

Hypertension

The incidence of any-grade and grade ≥3 hypertension was higher in the ramucirumab plus erlotinib arm compared with the placebo plus erlotinib arm (any grade: 45.2% vs. 12.0%; grade ≥3: 23.5% vs. 5.3%, respectively). No grade 4 or 5 hypertension events occurred in either treatment arm. Of any-grade hypertension events, 56.4% had recovered or were resolving at the data cut-off date. There was no association between hypertension and negative clinical outcomes in terms of cardiovascular or cerebrovascular complications. Twelve patients (12%) had ramucirumab dose delays due to hypertension, the majority (8 patients) of whom had only 1 dose delay. There were no dose reductions and 1 patient (1.0%) had a dose omission of ramucirumab due to hypertension. No patients discontinued all study treatment due to hypertension. One patient in each treatment arm discontinued ramucirumab or placebo alone due to hypertension. The most commonly used antihypertensive agents in both treatment arms were calcium channel antagonists and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), followed by diuretics:

- ramucirumab plus erlotinib arm: calcium channel antagonists (49.8%); ACEIs or ARBs (48.9%); and diuretics (22.2%).
- placebo plus erlotinib arm: calcium channel antagonists (24.9%); ACEIs/ARBs (26.7%); and diuretics (7.1%)

Proteinuria

A higher incidence of any-grade proteinuria was observed in the ramucirumab plus erlotinib arm (34.4%) than in the placebo plus erlotinib arm (8.4%). Most proteinuria events were low grade in severity (grade 2 in ramucirumab plus erlotinib arm and grade 1 in the placebo plus erlotinib arm). Grade ≥3 proteinuria was reported in 6 patients (2.7%) (all grade 3 events) and only in the ramucirumab plus erlotinib arm. No patients experienced nephrotic syndrome. There was 1 SAE of grade 3 proteinuria in the ramucirumab plus erlotinib arm. Proteinuria was the most common TEAE leading to dose adjustments of ramucirumab occurring in 27 patients (12.2%) (dose reduction: 8.1%; dose delay: 7.2%; and dose omission: 6.8%). There were no dose adjustments of placebo or erlotinib due to proteinuria. Of the 76 patients in the ramucirumab plus erlotinib arm who experienced one or more treatment-emergent proteinuria events, the majority (48 patients [63.2%]) experienced 1 event, and 47 patients (61.8%) experienced no dose adjustments of ramucirumab or all study treatment discontinuation due to proteinuria. The majority of proteinuria events (77.3%) had recovered by the data cut-off. Additional analyses showed that the occurrence of treatment-emergent proteinuria was associated with AESI hypertension. There was no association between proteinuria and renal failure. In the ramucirumab plus erlotinib arm, 2 patients (0.9%) discontinued all study treatment due to grade 2 proteinuria. No patients discontinued all study treatment due to proteinuria in the placebo plus erlotinib arm. In the ramucirumab plus erlotinib arm, 19 patients (8.6%), including all patients with grade 3 proteinuria (urine protein ≥3.5 g/24 hours), discontinued ramucirumab alone due to proteinuria and continued erlotinib therapy. No patients discontinued placebo or erlotinib alone due to proteinuria.

Thromboembolic Events

Arterial Thromboembolic Events (ATE)

The incidence of any grade ATEs was 0.9% in the ramucirumab plus erlotinib arm. No ATE occurred in the placebo plus erlotinib arm. One grade 3 myocardial infarction was reported in the ramucirumab plus erlotinib.

Venous Thromboembolic Events (VTE)

Any grade VTE were observed in 7 patients (3.2%) in the ramucirumab plus erlotinib arm compared to 9 patients (4.0%) in the placebo plus erlotinib arm and grade ≥3 occurred in 3 patients (1.4%) vs. 5 patients (2.2%), respectively. No Grade 4 or 5 events were observed.

Bleeding/Haemorrhagic Events

A higher incidence of any-grade bleeding/haemorrhage events was observed in the ramucirumab plus erlotinib arm compared with the placebo plus erlotinib arm (54.8% vs. 26.2%, respectively). The overall difference between arms was primarily driven by low-grade (grade 1-2) events of epistaxis. No difference was observed in the incidence of grade ≥3 bleeding events between treatment arms (1.8% in both arms).

The incidence of grade 1-2 gingival bleeding was higher in the ramucirumab plus erlotinib arm compared with the placebo plus erlotinib arm (8.6% vs. 1.3%). No grade ≥3 gingival bleeding occurred in either arm.

A higher incidence of any-grade pulmonary haemorrhage was observed in the ramucirumab plus erlotinib arm compared with the placebo plus erlotinib arm (15 patients [6.8%] vs. 4 patients [1.8%], respectively). The difference in incidence was primarily driven by grade 1 haemoptysis in 10 patients (4.5%). The incidence of grade ≥3 pulmonary haemorrhage was low and similar between treatment arms (0.5% vs. 0.4%). One treatment-related grade 5 event of haemothorax occurred in the ramucirumab plus erlotinib arm which was assessed by the investigator as related to study treatment.

A higher incidence of any-grade GI haemorrhage was observed in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm (23 patients [10.4%] vs. 6 patients [2.7%], respectively). The difference in incidence was driven by low grade (grade 1 and 2) events. The incidence of grade ≥3 GI haemorrhage was low and similar between treatment arms (1.4% vs. 0.4%). One treatment-related grade 4 small intestinal haemorrhage occurred in the ramucirumab plus erlotinib arm. There were no grade 5 events in either treatment arm. Dose adjustments of ramucirumab or placebo due to bleeding or haemorrhage were reported in 11 patients (5.0%) versus 4 patients (1.8%), respectively.

The rate of discontinuation of all study treatment due to bleeding/haemorrhage events was low and similar between treatment arms. Bleeding/haemorrhage was associated with anaemia in the ramucirumab plus erlotinib arm. Transfusion support (including packed red blood cells and platelets) was provided to 8 patients (3.6%) in the ramucirumab plus erlotinib arm versus none in the placebo plus erlotinib arm.

Gastrointestinal Perforation

One patient (0.5%) in the ramucirumab plus erlotinib arm reported a grade 2 GI perforation event (PT appendicitis perforated), which was assessed by the investigator as related to study treatment.

Congestive Heart Failure

Per protocol, ramucirumab was to be discontinued for grade 3 or grade 4 events consistent with congestive heart failure (CHF). Congestive heart failure was reported in 4 patients (1.8%) in the ramucirumab plus erlotinib arm compared to 1 patient (0.4%) in the placebo plus erlotinib arm. Two patients (0.9%) in the ramucirumab plus erlotinib arm experienced grade 3 CHF events (PTs cardiac failure and cardiac failure congestive) leading to discontinuation of ramucirumab treatment, and risk factors for acute coronary syndrome and cardiac failure was identified in 1 of these patients.

Wound Healing Complications

The overall incidences of wound healing complications were similar and low in both treatment arms. Two patients (0.9%) experienced grade 1 wound complication (PT) in the ramucirumab plus erlotinib arm and 1 patient (0.4%) in the placebo plus erlotinib arm experienced grade 1 impaired healing (PT). No patients experienced grade ≥3 wound healing complications.

Fistula

One (0.5%) grade 1 oral cavity fistula and one (0.5%) grade 3 tracheoesophageal fistula were reported in the ramucirumab arm plus erlotinib. No events of fistula occurred in the placebo plus erlotinib arm. There were no SAEs and neither TEAEs was assessed by the investigator as related to study treatment.

Liver Failure/Liver Injury

Treatment-emergent AEs of liver failure/liver injury including both clinical and laboratory terms were identified based on the Standardized MedDRA Query for hepatic disorder. The incidence of any-grade liver failure/liver injury events, including clinical and laboratory events, was higher in the ramucirumab plus erlotinib arm than in the placebo plus erlotinib arm (63.3% vs. 53.3%, respectively). The difference between treatment arms was due to the higher incidence of laboratory-related TEAEs in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm (61.5% vs. 49.3%, respectively), primarily driven by grade 1 and 2 events of ALT and AST increased. The incidence of grade ≥3 liver failure/liver injury events, including ALT and AST increased, was similar between the ramucirumab plus erlotinib arm (14.0%) and the placebo plus erlotinib arm (12.4%). The incidence of clinical TEAEs of liver failure/liver injury events was similar in the ramucirumab plus erlotinib arm and the placebo plus erlotinib arm (any grade: 4% vs. 5.3%; grade ≥3: 3.2% vs. 3.1%, respectively).

Reversible posterior leukoencephalopathy syndrome

No reversible posterior leukoencephalopathy syndrome events were observed in this study.

Neutropenia and infections

In addition to the above presented AESIs, given the known risk of neutropenia associated with ramucirumab, it was relevant to assess the impact of neutropenia in terms of negative clinical outcomes, namely serious infection secondary to neutropenia. Evaluation of infection in the context of combination therapy with ramucirumab plus erlotinib is of clinical interest given the documented risk of infections associated with erlotinib alone. The incidence of neutropenia (consolidated term) was similar in the ramucirumab plus erlotinib arm and the placebo plus erlotinib arm.

Neutropenia

The incidence of any-grade and grade ≥3 neutropenia was similar in the ramucirumab plus erlotinib arm and the placebo plus erlotinib arm (any-grade: 12.7% vs. 8.0%; grade ≥3: 2.7% vs. 1.3%, respectively. One patient (0.5%) in the ramucirumab plus erlotinib arm had a grade 4 neutropenia. No patient in the placebo plus erlotinib arm experienced grade 4 neutropenia. One patient (0.5%) experienced grade 3 febrile neutropenia (non-serious event) in the ramucirumab plus erlotinib arm. There were no reports of SAEs of neutropenia in either treatment arm. No association was observed between treatment-emergent neutropenia or febrile neutropenia and the occurrence of treatment-emergent infection events.

Infections

The incidence of any-grade TEAEs coded to the SOC Infections and Infestations was similar in the ramucirumab plus erlotinib and placebo plus erlotinib arm (80.5% vs.76.0%, respectively). The majority of events in both arms were low-grade infections (grade 1: 14.9% and grade 2: 48.4% in the ramucirumab plus erlotinib arm; grade 1: 18.7% and grade 2: 50.7% in the placebo plus erlotinib arm). The incidence of grade ≥3 infections in the Infections and Infestations SOC was higher in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm (17.2% vs. 6.7%, respectively). Grade 4 and grade 5 infection TEAEs were reported only in the ramucirumab plus erlotinib arm. In the ramucirumab plus erlotinib arm, 38 patients experienced grade ≥3 infections. Of these 38 patients, 27 patients (71.1%) experienced 1 event, with 10 patients (26.3%) and 1 patient (2.6%) experiencing 2 events and 3 or more events, respectively. Of the 38 patients experienced grade ≥3 infections, 19 patients (50%) had no treatment changes (including dose adjustments of study drug or all treatment discontinuation) due to infection. Dose adjustments of study drug due to grade ≥3 infections were mainly erlotinib dose omissions in 13 patients (34.2%) and reductions in 8 patients (21.1%). Dose delays of ramucirumab were reported in 9 patients (23.7%). There were no dose reductions or dose omissions of ramucirumab. Dose adjustments due to grade ≥3 infections were mainly erlotinib dose omissions in 9 patients (60.0%). The majority of patients (11 patients [73.3%]) required treatment with at least 3 systemic antimicrobial agents. The majority of severe

infections occurred in the absence of concurrent neutropenia in both treatment arms (36 of 39 events [92.3%] in the ramucirumab plus erlotinib arm; and all 15 events in the placebo arm).

Lower Respiratory Tract Infections

In order to fully evaluate pulmonary infections in the NSCLC population, relevant TEAEs from the clinical database were chosen to create the composite term of lower respiratory tract infection (LRTI). The incidence of any-grade LRTI was similar between the ramucirumab plus erlotinib arm and the placebo plus erlotinib arm (14 patients [6.3%] vs. 13 patients [5.8%], respectively). The incidence of grade ≥3 LRTIs was higher (at least 2% difference) in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm: 9 patients (4.1%) (including two grade 5 events of pneumonia and one event of pneumonia bacterial) versus 2 patients (0.9%), respectively.

Pneumonia was the only grade ≥3 LRTI event reported with a higher (at least 2% difference) incidence in the ramucirumab plus erlotinib arm than the placebo plus erlotinib arm (6 patients [2.7%] vs. 0%). One of the LRTIs reported in the ramucirumab plus erlotinib arm (pneumonia bacterial) occurred with concurrent neutropenia. There was no association between LRTI and neutropenia in either treatment arm.

Adverse drug reactions

Table 36: ADRs reported in patients treated with ramucirumab in combination with chemotherapy or erlotinib in phase 3 clinical trials (RAINBOW, REVEL, RAISE and RELAY)

System Organ Class (MedDRA)	Very Common	Common
Infections and infestations	Infections (45.7%)[j,k]	Sepsis (1.3%)[a,b]
Blood and lymphatic system disorders	Neutropenia (50.6%)[a] Leukopenia (19.3%)[a,c] Thrombocytopenia (18.4%)[a] Anaemia (20.7%)[j]	Febrile neutropenia (7.6%)[d]
Metabolism and nutrition disorders		Hypoalbuminaemia (6.3%)[a] Hyponatraemia (3.5%)[a]
Nervous system disorders	Headache (12.3%)[j]	
Vascular disorders	Hypertension (22.8%)[a,e]	
Respiratory, thoracic, and mediastinal disorders	Epistaxis (27.4%)	Pulmonary haemorrhage (4.2%)[j,l]
Gastrointestinal disorders	Stomatitis (27.3%) Diarrhoea (45.5%)	Gastrointestinal haemorrhage events (8.1%)[a,f] Gastrointestinal perforation (1.2%)[a] Gingival bleeding (2.9%)[j]
Skin and subcutaneous tissue disorders	Alopecia (29.3%)[j]	Palmar-plantar erthyrodysaesthesia syndrome (5.6%)[g]
Renal and urinary disorders	Proteinuria (14.2%)[a,h]	
General disorders and administration site disorders	Fatigue (51.4%)[a,I] Mucosal inflammation (12.7%)[d] Peripheral oedema (20.1%)	

[a] Terms represent a group of events that describe a medical concept rather than a single event or preferred term.
[b] Based on study RAINBOW (ramucirumab plus paclitaxel).
[c] Based on study RAINBOW (ramucirumab plus paclitaxel). Includes: leukopenia and white blood cell count decreased.
[d] Based on study REVEL (ramucirumab plus docetaxel).
[e] Includes: blood pressure increased, hypertension, and hypertensive cardiomyopathy.
[f] Based on study RAINBOW (ramucirumab plus paclitaxel) and study RAISE (ramucirumab plus FOLFIRI). Includes: anal haemorrhage, diarrhoea haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, haematemesis, haematochezia, haemorrhoidal haemorrhage, Mallory-Weiss syndrome, melaena, oesophageal haemorrhage, rectal haemorrhage, and upper gastrointestinal haemorrhage.
[g] Based on study RAISE (ramucirumab plus FOLFIRI).
[h] Includes cases of nephrotic syndrome.

[I] Based on study RAINBOW (ramucirumab plus paclitaxel) and study REVEL (ramucirumab plus docetaxel). Includes: fatigue and asthenia.
[J] Based on study RELAY (ramucirumab plus erlotinib).
[K] Infections includes all preferred terms that are part of the System Organ Class Infections and infestations. Most common (≥1%) Grade ≥3 infections include pneumonia, cellulitis, paronychia, skin infection, and urinary tract infection.
[L] Includes haemoptysis, laryngeal haemorrhage, haemothorax (a fatal event occurred) and pulmonary haemorrhage.

Serious adverse event/deaths/other significant events

Serious adverse events

Table 37 provides an overview of SAEs occurring in at least 2 patients in the ramucirumab plus erlotinib arm by MedDRA preferred term. A higher percentage of patients in the ramucirumab plus erlotinib arm than in the placebo plus erlotinib arm reported any-grade SAEs (29.4% vs. 20.9%) and grade ≥3 SAEs (22.6% vs. 15.6%).

Table 37: SAEs occurring in at least 2 patients in the ramucirumab plus erlotinib arm by MedDRA preferred term by decreasing frequency safety population

	Ramucirumab + Erlotinib N = 221 n (%)		Placebo + Erlotinib N = 225 n (%)	
MedDRA Preferred Term	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with at least 1 SAE	**65 (29.4)**	**50 (22.6)**	**47 (20.9)**	**35 (15.6)**
Pneumonia	7 (3.2)	6 (2.7)	1 (0.4)	0
Cellulitis	4 (1.8)	3 (1.4)	0	0
Pneumothorax	4 (1.8)	1 (0.5)	3 (1.3)	2 (0.9)
Decreased appetite	3 (1.4)	2 (0.9)	0	0
Diarrhoea	3 (1.4)	3 (1.4)	1 (0.4)	1 (0.4)
Hepatic function abnormal	3 (1.4)	3 (1.4)	2 (0.9)	2 (0.9)
Pyrexia	3 (1.4)	0	4 (1.8)	0
Alanine aminotransferase increased	2 (0.9)	2 (0.9)	1 (0.4)	1 (0.4)
Dyspnoea	2 (0.9)	0	1 (0.4)	1 (0.4)
Hypertension	2 (0.9)	2 (0.9)	0	0
Hypotension	2 (0.9)	2 (0.9)	0	0
Pulmonary embolism	2 (0.9)	2 (0.9)	2 (0.9)	2 (0.9)
Skin infection	2 (0.9)	2 (0.9)	0	0
Small intestinal haemorrhage	2 (0.9)	2 (0.9)	0	0
Urinary tract infection	2 (0.9)	2 (0.9)	0	0
Vomiting	2 (0.9)	1 (0.5)	1 (0.4)	1 (0.4)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the safety population; n = number of patients in specified category; SAE = serious adverse event.
MedDRA Version 21.1.
Data cutoff date: 23 January 2019
Source: b_s_tsaept_345.rtf (Table JVCY.14.196).

Deaths

The incidence of death was higher in the ramucirumab plus erlotinib arm than in the placebo plus erlotinib arm. Eight (3.6%) patients died while on study therapy or within 30 days of discontinuation of study treatment in the ramucirumab plus erlotinib arm.

AEs were the primary cause of death for 6 patients (encephalitis influenza, haemothorax, lymphoma, pneumonia, pneumonia bacterial, and renal failure). Three deaths were attributed to infection events, none of which were assessed as treatment-related. Two (0.9%) patients died while on study therapy or within 30 days of discontinuation of study treatment in the placebo plus erlotinib arm. Both deaths were due to study disease (**Table 38**). One treatment-related grade 5 event of haemothorax occurred in the ramucirumab plus erlotinib arm which was assessed by the investigator as related to study treatment.

The grade 5 TEAE of haemothorax that began on study Day 74 and ended on study Day 76. The patient was hospitalized on study Day 58 (14 days after the last dose of ramucirumab) with worsening dyspnoea and confusion, and diagnosed on CT thorax with a tracheoesophageal fistula associated with a right lower lobe abscess and pleural empyema. The patient was treated with thoracic drainage and intravenous

antibiotics. Following initial clinical improvement, the patient's condition deteriorated approximately 14 days later due to pleural haemorrhage and the patient died. The investigator assessed the event of pleural haemorrhage as related to ramucirumab and not related to erlotinib.

Table 38. Summary of deaths safety population

	Ramucirumab + Erlotinib N=221 n (%)	Placebo + Erlotinib N=224 n (%)
All Deaths	**37 (16.7)**	**42 (18.7)**
Deaths on Therapy	**2 (0.9)**	**1 (0.4)**
Due to AEs	2 (0.9)	0
Due to AEs related to study treatment	1 (0.4)	0
Due to study disease	0	1 (0.4)
Deaths within 30 Days of Treatment Discontinuation	**6 (2.7)**	**1 (0.4)**
Due to AEs	4 (1.8)	0
Due to study disease	2 (0.9)	1 (0.4)
Deaths on Therapy or within 30 Days of Treatment Discontinuation	**8 (3.6)**	**2 (0.9)**
Due to AEs	6 (2.7)	0
Due to AEs related to study treatment	1 (0.5)	0
Due to study disease	2 (0.9)	2 (0.9)
Deaths after 30 Days of Treatment Discontinuation	**29 (13.1)**	**40 (17.8)**
Due to AEs	0	1 (0.4)
Due to AEs related to study treatment	0	1 (0.4)
Due to study disease	29 (13.1)	39 (17.3)

Abbreviations: AE = adverse event; N = number of patients; n = number of patients in the specified category.
Data cutoff date: 23 January 2019
Source: b_o_ds_death_by_reason_5_p1123191_t1123216.

Laboratory findings

The assessments of analyses for haematology and serum chemistry laboratory toxicity shifts from baseline to worst grade post baseline were consistent with the AE data described earlier in the sections adverse events and adverse events of special interest. Findings from analysis of laboratory shift tables for serum chemistry and haematology were consistent with the analyses of TEAE data and the trends identified in TEAEs of anaemia, neutropenia, thrombocytopenia, and abnormal laboratory events for the AESI liver failure/liver injury as described in adverse event section. Regarding immunological events, the rates of treatment-emergent (TE) ADAs were low in both study arms. No patients developed neutralizing antibodies against ramucirumab.

Safety in special populations

Additional analyses summarising TEAEs by subgroups, including age, gender, race, and geographic region are provided in Table 39. The incidence of ≥3 grade was slightly higher in patients ≥65 years. The Asian population was overrepresented in the study.

Table 39. Subgroup analysis of Treatment-Emergent Adverse Events pooled safety population

AE Category [a]	ramucirumab plus erlotinib			placebo plus erlotinib		
	N	Any Grade n (%)	Grade ≥3 n (%)	N	Any Grade n (%)	Grade ≥3 n (%)
Age, years						
<65	102	102 (100.0)	69 (67.6)	114	114 (100.0)	54 (47.4)

≥65	119	119 (100.0)	90 (75.6)	111	111 (100.0)	67 (60.4)
Gender						
Male	82	82 (100.0)	56 (68.3)	83	83 (100.0)	43 (51.8)
Female	139	139 (100.0)	103 (74.1)	142	142 (100.0)	78 (54.9)
Race[b]						
Asian	170	170 (100.0)	121 (71.2)	174	174 (100.0)	87 (50.0)
Other	51	51 (100.0)	38 (74.5)	51	51 (100.0)	34 (66.7)

Abbreviations: AE = adverse event; N = number of treated patients in the safety population; n = number of patients in specified category

[a] Patients may be counted in more than 1 category.

Safety related to drug-drug interactions and other interactions

A drug-drug interaction (DDI) sub study was conducted in 11 patients to support this submission of ramucirumab in combination with erlotinib. The pharmacokinetics of erlotinib were not affected when co-administered with ramucirumab.

Discontinuation due to adverse events

The overall incidence of TEAEs leading to the discontinuation of all study treatment was similar in the ramucirumab plus erlotinib arm (12.7%) and the placebo plus erlotinib arm (10.7%).

A higher percentage of patients discontinued ramucirumab alone due to TEAEs than placebo alone (73 patients [33.0%] vs. 34 patients [15.1%], respectively). The incidence of TEAEs leading to discontinuation of erlotinib alone due to TEAEs was low and similar between treatment arms (ramucirumab plus erlotinib arm: 3 patients [1.4%]; placebo plus erlotinib arm: 2 patients [0.9%]).

Post marketing experience

Ramucirumab (8 mg/kg, intravenously Q2W) was first authorised on 21 April 2014 in the US for use as a single agent for the treatment of patients with advanced or metastatic, gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy. The European Commission granted a marketing authorisation in December 2014 for ramucirumab for the treatment of patients with advanced or metastatic, gastric or GEJ adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy in combination with paclitaxel and as monotherapy for adult patients for whom treatment in combination with paclitaxel is not appropriate.

Ramucirumab, as a single agent or in combination with different chemotherapy regimens, has been approved in second-line gastric or GEJ adenocarcinoma, NSCLC, and CRC.

The latest periodic safety update report (PSUR)/periodic benefit risk evaluation report (PBRER) from ramucirumab was completed in accordance with the International Conference on Harmonisation (ICH) E2C (R2) format and summarised safety and other pertinent data arising from worldwide sources that were received for the reporting period 22 April 2018 and 21 April 2019. Cumulatively, as of 21 April 2019, 10,491 patients have been enrolled into the ramucirumab clinical program, of which approximately 6426 patients have received ramucirumab. Cumulatively, as of 30 April 2019, an estimated 110,101 patients have received ramucirumab worldwide. The PSUR/PBRER review confirmed and supported the previously established favourable benefit-risk profile for ramucirumab in the currently approved indications.

No off-label use events have been reported for the use of ramucirumab for the treatment of metastatic NSCLC with activating EGFR mutations.

2.5.1. Discussion on clinical safety

Ramucirumab is currently approved in combination with docetaxel in NSCLC. Erlotinib is currently approved in NSCLC with EGFR activating mutations either as monotherapy or in combination with bevacizumab. Both drugs have a known safety profile.

Regarding **patient exposure**, the median duration of ramucirumab treatment was longer than that of placebo (11.04 vs 9.66 months); and similarly, the duration of erlotinib treatment was longer in the ramucirumab plus erlotinib arm than in the placebo plus erlotinib arm (14.13 vs 11.20 months). The median relative dose intensities of each study drug were consistent with the targeted dose and similar in both treatment arms.

Any-grade TEAEs leading to ramucirumab or placebo **dose adjustments** occurring at a higher incidence (≥ 5% difference) in the ramucirumab plus erlotinib arm compared with the placebo plus erlotinib arm, respectively, were proteinuria and platelet count decreased. Proteinuria was the only grade≥3 TEAE leading to ramucirumab or placebo dose adjustments with a higher incidence (≥ 2% difference) in the ramucirumab plus erlotinib arm than the placebo plus erlotinib arm. The difference in dose adjustments for ramucirumab versus placebo was completely based on the higher proportion of patients <70-year old needing dose adjustments.

The **adverse event** profile of ramucirumab or erlotinib as monotherapy is different. Therefore, the combination treatment is expected to result in an overall higher incidence of AE. Common TEAEs observed at a higher incidence in the ramucirumab plus erlotinib arm than in the placebo plus erlotinib arm, respectively, were adverse events known to be associated with ramucirumab, including bleeding/haemorrhage events, hypertension, proteinuria, thrombocytopenia, and neutropenia. Additionally, ramucirumab increased the incidence and/or severity of specific known toxicities of erlotinib, including hepatic laboratory events (ALT and AST increased), alopecia, dermatitis acneiform, and diarrhoea.

Grade 3 events occurring ≥5% and at a higher incidence (at least a 2-percentage point difference) were hypertension, dermatitis acneiform and diarrhoea. The higher incidence of dermatitis acneiform in the ramucirumab plus erlotinib arm was not expected, as it is a specific AE of erlotinib. Further evaluation revealed that there is currently insufficient evidence to support a causal association between ramucirumab and dermatitis acneiform due to the lack of biological plausibility, no increase in rates of other skin toxicities in ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm in RELAY and the absence of a consistent trend towards an increased incidence of any-grade or grade ≥3 rash in the ramucirumab arm versus the placebo/comparator arm in previously completed phase 3 studies. Therefore, based on the totality of the data, it is agreed with the MAH that dermatitis acneiform is not considered to be an ADR for ramucirumab in combination with erlotinib for the treatment of patients with metastatic NSCLC with activating EGFR mutations. A higher percentage of patients in the ramucirumab plus erlotinib arm than in the placebo plus erlotinib arm had an any-grade **serious adverse event** and grade ≥3 SAE. Hospitalizations due to AEs were higher in the ramucirumab plus erlotinib arm than in the placebo plus erlotinib arm.

The incidence of infections was high in both treatment groups. The majority of the infections were low-grade infections. The incidence of grade ≥3 infections in the infections and infestations SOC was higher in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm., i.e. 38 patients [17.2%] vs. 15 patients [6.7%], respectively. These infections were not associated with concurrent neutropenia. A difference of +1.3% percentage point in the incidence of grade ≥3 infections was seen in the REVEL study of ramucirumab and docetaxel versus docetaxel and placebo in NSCLC (EMA/CHMP/69093/2016). Infections of grade ≥3 occurred in 4% in the erlotinib group and in 2% in the placebo group in the erlotinib monotherapy versus placebo in the BR.21 phase III trial of erlotinib in NCSLC. Based on the notable imbalance in the incidence of grade ≥3 infections between the experimental and control arms in RELAY, the clinical significance of such events, the recognised association between other VEGF pathway inhibitors and

infections, it is agreed that the totality of the data provides a reasonable suspicion of the causal association between ramucirumab and the development of infections. Infections is therefore included as an ADR for ramucirumab in combination with erlotinib in Section 4.8 of the SmPC.

The incidence of any-grade and grade ≥3 hypertension was higher in the ramucirumab plus erlotinib arm compared with the placebo plus erlotinib arm. Hypertension was manageable with medication and dose delays. Of any-grade hypertension events, 56.4% had recovered or were resolving at the data cut-off date. No association was found between hypertension and negative clinical outcomes in terms of cardiovascular or cerebrovascular complications.

Hypertension, mucocutaneous bleeding, thromboembolic events, and proteinuria are known on target adverse events of VEGFR-inhibitors. A higher incidence of any-grade bleeding/haemorrhage events was observed in the ramucirumab plus erlotinib arm compared with the placebo plus erlotinib arm. The overall difference between arms was driven by low-grade events of epistaxis. No difference was observed in the incidence of grade ≥3 bleeding events between treatment arms. The incidence of grade ≥3 pulmonary haemorrhage was low and similar between treatment arms. One treatment-related grade 5 event of haemothorax occurred in the ramucirumab plus erlotinib arm which was assessed by the investigator as related to study treatment. A higher incidence of any-grade GI haemorrhage was observed in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib. The difference in incidence was driven by low grade events. The incidence of grade ≥3 GI haemorrhage was low and similar between treatment arms.

Most proteinuria events were low grade in severity. The majority of proteinuria events had recovered by the data cut-off. Additional analyses showed that the occurrence of treatment-emergent proteinuria was associated with AESI hypertension.

The **adverse drug reactions** proposed by the applicant to be included in the SmPC include infections and alopecia. Hair growth stimulated by VEGF may be related to improved follicular vascularisation or a direct effect on hair follicle DPCs via VEGF Receptor 2 expressed on DPCs. Due to the synergistic effect of VEGF and EGFR on normal hair development, combined inhibition of both the VEGF and EGFR pathways might be expected to increase the risk of alopecia in patients receiving both ramucirumab and erlotinib compared to erlotinib alone. This may in part explain the higher incidence of alopecia in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm in RELAY. The incidence of **death** was higher in the ramucirumab plus erlotinib arm than in the placebo plus erlotinib arm. Eight (3.6%) patients died while on study therapy or within 30 days of discontinuation of study treatment in the ramucirumab plus erlotinib arm. Three deaths were attributed to infection events, none of which were assessed as treatment-related. As mentioned above, one treatment-related grade 5 event of haemothorax occurred in the ramucirumab plus erlotinib arm which was assessed by the investigator as related to study treatment.

Regarding **laboratory findings,** the assessments of analyses for haematology and serum chemistry laboratory toxicity shifts from baseline to worst grade post-baseline were consistent with the available AE data.

Regarding the **safety in special populations**, the AE profile within gender subgroups between treatment arms was consistent with that observed in the overall safety population (gender subgroups male n=165 and female n=281). Independent of treatment arm, a higher proportion (≥ 5% difference) of female patients compared to male patients experienced grade ≥3 laboratory hepatic events, primarily driven by grade 3 ALT and AST increased. The AE profile within race subgroups between treatment arms was consistent with the overall safety profile in the safety population. Independent of treatment arm, the incidence of grade ≥3 TEAEs and SAEs was higher (at least a 5%) in patients ≥65 years than <65 years. There was a trend towards higher incidences of specific TEAEs and AESIs in patients ≥65 years compared to patients <65 years, however, most differences in the incidences were observed in low-grade (grade 1-2) events, except for hypertension. This is somewhat contra dictionary to the observed higher incidence of

dose adjustments due to AEs for the younger patient population receiving ramucirumab compared to placebo. In patients ≥70 years, the incidences of grade ≥3 TEAEs and SAEs were higher (at least a 5-percentage point difference) in the ramucirumab plus placebo arm compared to the placebo plus erlotinib arm (grade ≥3 TEAEs: 81.3% vs. 55.9%; any-grade SAEs: 40.6% vs. 27.1%, respectively). The difference in incidence of grade ≥3 TEAEs and SAEs between patients <70 years of age and patients ≥70 years of age is adequately reflected in section 4.4 of the SmPC.). Regarding **immunological events**, the rates of treatment-emergent ADAs were low in both study arms. No patients developed neutralizing antibodies against ramucirumab.

The overall incidence of TEAEs leading to the **discontinuation** of all study treatment was similar in the ramucirumab plus erlotinib arm (12.7%) and the placebo plus erlotinib arm (10.7%). A higher percentage of patients discontinued ramucirumab alone due to TEAEs than placebo alone (73 patients [33.0%] vs. 34 patients [15.1%], respectively).

2.5.2. Conclusions on clinical safety

Both ramucirumab and erlotinib have already approved indications in NSCLC and their safety profile is known. Overall, the AEs were in line with those expected for both study treatments. The additional toxicity due to the addition of ramucirumab to erlotinib was considered manageable. Unexpectedly, a higher incidence of grade ≥3 infections was observed in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm, and it should be further discussed whether there is a relationship between ramucirumab and infections. Additionally, a higher incidence of grade ≥3 dermatitis acneiform (an erlotinib-specific adverse drug reaction) was observed in the ramucirumab plus erlotinib arm, which warrants further discussion. One death due to haemothorax was considered related to study treatment occurring approximately 6 days after thoracic drainage for a pleural empyema.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The CHMP endorsed the Risk Management Plan version 9.2 with the following content:

Safety concerns

Table 40. Summary of the safety concerns

Summary of safety concerns	
Important identified risks	Arterial thromboembolic events Gastrointestinal perforation Serious haemorrhagic events Liver failure/liver injury (including hepatic encephalopathy in patients with HCC)
Important potential risks	Serious infection secondary to neutropenia Posterior reversible encephalopathy syndrome Severe clinical outcomes of venous thromboembolic events Reproductive and developmental toxicity
Missing information	Not applicable

Pharmacovigilance plan

Table 41. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
I4T-MC-JVDD: Safety and Effectiveness of Ramucirumab in Patients with Advanced Gastric Cancer in the European Union and North America: A Prospective Observational Registry Ongoing	**Primary objective**: To describe 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 **Secondary objectives:** To describe 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. To describe the safety profile in the following subgroups: • Elderly patients • Patients with cardiac comorbidities • Patients with hepatic impairment • Patients with renal impairment	Potential safety signals in special populations, such as elderly, patients with cardiac comorbidities, hepatic impairment and renal impairment	Protocol submitted[a]	12 December 2014
			First patient enrolled	9 December 2015
			Last patient enrolled	Estimated Q4 2020
			Final study report	Estimated Q4 2021

a Date of protocol submission to PRAC

Risk minimisation measures

Table 42. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Arterial thromboembolic events	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8 PL Sections 2, 3, and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Thromboembolism follow-up form Additional pharmacovigilance activities: None
Gastrointestinal perforation	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8 PL Sections 2, 3, and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Gastrointestinal perforation and/or fistula follow-up form Additional pharmacovigilance activities: None
Serious haemorrhagic events	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, and 4.8 PL Sections 2, 3, and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • General bleeding follow-up form Additional pharmacovigilance activities: None
Liver failure/ liver injury (including hepatic encephalopathy in patients with HCC)	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 4.8, and 5.2 PL Sections 2, 3, and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Hepatic disorders follow-up form Additional pharmacovigilance activities: None
Important Potential Risks		
Serious infection secondary to neutropenia	Routine risk minimisation measures: SmPC Sections 4.2, 4.8, and 5.2 PL Sections 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Posterior reversible encephalopathy syndrome	Routine risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Posterior reversible encephalopathy syndrome follow-up form Additional pharmacovigilance activities: None
Severe clinical outcomes of venous thromboembolic events	Routine risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Thromboembolism follow-up form Additional pharmacovigilance activities: None
Reproductive and developmental toxicity	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3 PL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Pregnancy outcome maternal form. Additional pharmacovigilance activities: None
Missing Information		
None	Not applicable	Not applicable

The CHMP, having considered the data submitted in the application was of the opinion that the risk management plan is acceptable.

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 higher incidence of grade ⩾3 adverse events and all grade serious adverse events in patients aged 70 years and older, has been added to the product information. The Package Leaflet has been updated accordingly.

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 MAH and has been found acceptable for the following reasons:

The proposed text modifications to the package leaflet resulting from the addition of this new indication are minor and do not include text that is significantly different from that already user tested. Overall, the structure and design of the revised Cyramza Package Leaflet has not changed due to the new information and the revisions do not significantly affect the overall readability.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed new therapeutic indication for Cyramza in this procedure is: ''Cyramza in combination with erlotinib is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations.''

3.1.2. Available therapies and unmet medical need

According to the ESMO guideline for metastatic NSCLC, first-line treatment options for patients with metastatic NSCLC harbouring an EGFR-activating (sensitising) mutation are: gefitinib, erlotinib ± bevacizumab, afatinib, dacomitinib, osimertinib or gefitinib + carboplatin + pemetrexed (Planchard et al. Ann of Oncol. 2018). The latter (gefitinib + carboplatin + pemetrexed) is not authorised in the EU.

With currently available EGFR TKIs, prognosis is improving, but remains poor as most patients eventually develop treatment resistance and will eventually experience disease progression on EGFR TKI therapy.

Expanding the selection of first-line options available for the treatment of metastatic *EGFR*-mutated NSCLC would enhance the strategic possibilities of oncologists on how to use the available agents to provide the best chance of long-term PFS, potentially prolonging time on targeted therapy and postpone cytotoxic chemotherapy.

3.1.3. Main clinical studies

The Applicant submitted a single pivotal clinical trial to support the extension of indication for Cyramza. Study JVCY (RELAY) was a multicentre, randomised, double-blind, phase 3 study that compared the efficacy and safety of treatment with erlotinib (150 mg daily) and ramucirumab (10 mg/kg every 2 weeks) versus erlotinib (150 mg daily) and placebo (10 mg/kg every 2 weeks) in previously untreated patients with metastatic NSCLC with epidermal growth factor receptor (EGFR) activating mutations. The ITT population consisted of 449 patients, 224 in the ramucirumab plus erlotinib arm and 225 in the placebo plus erlotinib arm. The primary endpoint of RELAY was PFS. Secondary endpoints were OS, ORR, DCR, DoR, PROs, safety and toxicity, PK and immunogenicity of ramucirumab, DDI substudy to assess the PK of erlotinib without ramucirumab.

3.2. Favourable effects

A statistically significant improvement in PFS (primary endpoint) was observed for patients who received ramucirumab plus erlotinib compared to placebo plus erlotinib (stratified HR = 0.591 [95% CI: 0.461-0.760]; p<0.0001). Median PFS was 19.4 months (95% CI: 15.4-21.6) in the ramucirumab plus erlotinib arm compared with 12.4 months (95% CI: 11.0-13.5) in the placebo plus erlotinib arm, representing a 7-month gain in median PFS. The primary analysis was supported by various sensitivity analyses (HRs ranging between 0.580 and 0.671). A PFS treatment benefit for the ramucirumab plus erlotinib arm was observed across all pre-specified patient subgroups. No detrimental effect on OS (secondary endpoint) has been observed with ramucirumab plus erlotinib as shown by the stratified HR of 0.832 (95% CI: 0.532-1.303; median OS was not reached in either arm).

In spite of similar ORR (76.3% vs 74.7%) and DCR (95.1% vs 95.6%) between arms, the median DoR (secondary endpoint) was longer in the ramucirumab plus erlotinib arm than in the placebo plus erlotinib arm (18.0 months [95% CI: 13.9-19.8] vs 11.1 months [95% CI: 9.7-12.3]).

The updated HR for PFS2 (exploratory endpoint) remained in favour of the ramucirumab plus erlotinib arm compared to placebo plus erlotinib arm (HR = 0.755 [95% CI: 0.567, 1.006]). Median PFS2 was 35.98 months (95% CI: 31.21, NR) for the ramucirumab plus erlotinib arm and 29.17 months (95% CI: 24.77, 37.82) for the placebo plus erlotinib arm.

3.3. Uncertainties and limitations about favourable effects

The OS results were immature with 79 deaths and a censoring rate of more than 80% (data maturity, 17.6%). However the PFS2 data are reassuring regarding the impact on post-progression treatment. In addition, the MAH is recommended to submit the final OS analysis by end of Q2 2023

3.4. Unfavourable effects

The safety analysis of ramucirumab in combination with erlotinib in patients with EGFR mutated NSCLC focussed on differences of the observed AEs of the combination arm compared with the erlotinib-placebo arm.

The most common any-grade TEAEs, with at least a 20% incidence in the ramucirumab plus erlotinib arm, and observed at a higher incidence (at least a 5-percentage point difference) in the ramucirumab plus erlotinib arm compared with the placebo plus erlotinib arm, respectively, were: hypertension (45.2% vs. 12.0%), ALT increased (42.5% vs. 31.1%), AST increased (41.6% vs. 25.8%), stomatitis (41.6% vs. 36.4%), alopecia (33.9% vs. 19.6%), proteinuria (33.9 vs. 8.4%), epistaxis (33.5% vs. 12.0%), nausea (25.8% vs. 19.6%), peripheral oedema (22.6% vs. 4.4%), cough (21.7% vs. 15.6%), and pyrexia (21.3% vs. 12.4%).

A higher percentage of patients in the ramucirumab plus erlotinib arm (71.9%) reported grade ≥3 TEAEs compared with the placebo plus erlotinib arm (53.8%). Grade ≥3 TEAEs occurring in ≥5% of patients in the ramucirumab plus erlotinib arm and at a higher incidence (at least a 2-percentage point difference) than in the placebo plus erlotinib arm were: hypertension (23.5% vs. 5.3%), dermatitis acneiform (14.9% vs. 8.9%) and diarrhoea (7.2% vs. 1.3%).

A higher percentage of patients in the ramucirumab plus erlotinib arm compared to the placebo plus erlotinib arm experienced grade ≥3 infections (38 patients [17.2%] vs. 15 patients [6.7%], respectively). There is a reasonable suspicion of a causal association between ramucirumab and the development of infections.

A higher percentage of patients in the ramucirumab plus erlotinib arm than in the placebo plus erlotinib arm reported any-grade SAEs (29.4% vs. 20.9%).

In patients ≥70 years, the incidences of grade ≥3 TEAEs and SAEs were higher (at least a 5-percentage point difference) in the ramucirumab plus placebo arm compared to the placebo plus erlotinib arm (grade ≥3 TEAEs: 81.3% vs. 55.9%; any-grade SAEs: 40.6% vs. 27.1%, respectively). This is adequately reflected in section 4.4 of the SmPC.

AEs leading to death while on study therapy or within 30 days of discontinuation of study treatment were reported only in the ramucirumab plus erlotinib arm in 6 patients (2.7%), of which 1 death was related to study treatment. In the placebo plus erlotinib arm, there were no deaths reported due to AEs during study treatment or within 30 days of treatment discontinuation.

The overall incidence of TEAEs leading to the discontinuation of all study treatment was 12.7% in the

ramucirumab plus erlotinib arm and 10.7% the placebo plus erlotinib arm. A higher percentage of patients discontinued ramucirumab alone due to TEAEs than placebo alone (73 patients [33.0%] vs. 34 patients [15.1%], respectively).

3.5. Uncertainties and limitations about unfavourable effects

The unfavourable effects are sufficiently characterised and routine pharmacovigilance activities are considered appropriate.

3.6. Effects Table

Table 43. Effects Table for Cyramza in combination with erlotinib as first-line treatment of adult patients with metastatic non-small cell lung cancer with activating epidermal growth factor mutations (data cut-off date: 23-01-2019)

Effect	Short description	Unit	Ramucirumab + erlotinib	Placebo + erlotinib	Uncertainties / Strength of evidence
Favourable Effects					
PFS	Time from the date of randomisation until the date of radiographic documentation of progression	Months	19.4	12.4	Stratified HR = 0.591 [95% CI: 0.461-0.760]; p<0.0001
OS	Time from the date of randomisation to the date of death from any cause.	Months	NR	NR	Stratified HR (95% CI) of 0.832 (0.532, 1.303) At the data cut-off date, OS data was not mature (data maturity, 17.6%)
ORR	Proportion of randomised patients achieving a best overall response of partial response (PR) or complete response (CR) per RECIST v1.1.	%	76	75	p=0.7413
DoR	From the date of first documented CR or PR (responder) to the date of objective progression or the date of death due to any cause, whichever was earlier.	Months	18.0	11.1	Unstratified HR (95% CI) = 0.619 (0.477-0.805)
PFS2	Time from randomisation to second objective disease progression, or death from any cause, whichever occurred first.	Months	NR	NR	Stratified HR = 0.755 (95% CI: 0.567, 1.006) At the data cut-off date, PFS2 data was not mature (data maturity, 44.3%)
Unfavourable Effects					
TEAEs	Patients with ≥1 TEAE	n (%)	221 (100)	225 (100)	
Grade ≥3 TEAEs	Patients with ≥1 TEAE CTCAE Grade ≥3	n (%)	157 (71.9)	121 (53.8)	
SAEs	Patients with ≥1 SAE	n (%)	65 (29.4)	47 (20.9)	
Discontinuations	Patients who discontinued all study treatment due to AE	n (%)	28 (12.7)	24 (10.7)	

Effect	Short description	Unit	Ramucirumab + erlotinib	Placebo + erlotinib	Uncertainties / Strength of evidence
	Patients who discontinued ramucirumab alone due to TEAEs than placebo alone	n (%)	73 (33.0)	34 (15.1)	
Hypertension	Any Grade	n (%)	100 (45.2)	27 (12.0)	
	Grade ≥3	n (%)	52 (23.5)	12 (5.3)	
Proteinuria	Any Grade	n (%)	75 (33.9)	19 (8.4)	
	Grade ≥3	n (%)	6 (2.7)	0 (0)	
Infections	Any Grade	n (%)	178 (80.5)	171 (76.0)	
	Grade ≥3	n (%)	38 (17.2)	15 (6.7)	
Bleeding/ haemorrhagic events	Any Grade	n (%)	121 (54.8)	59 (26.2)	
	Grade ≥3	n (%)	4 (1.8)	4 (1.8)	

Abbreviations: AE = serious adverse event; CTCAE = Common Terminology for Adverse Events; NR= not reached; SAE = serious adverse event; TEAE = treatment-emergent adverse event;

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Treatment with ramucirumab plus erlotinib resulted in a statistically significant PFS improvement compared to placebo plus erlotinib. In this setting (previously untreated patients with EGFR-positive NSCLC), significantly prolonging progression is considered clinical relevant, as discussed in other procedures of EGFR-TKIs. Sensitivity analyses support the primary results and key subgroups favoured ramucirumab plus erlotinib. Median DoR and PFS2 favoured the ramucirumab plus erlotinib arm, supporting the primary endpoint. Moreover, although data were immature, no detrimental effect on overall survival was observed with the addition of ramucirumab to erlotinib. The applicant commits to submit the results to the EMA once available.

A higher percentage of grade ≥3 TEAEs were reported in the ramucirumab plus erlotinib arm, but in general these events were manageable with dose adjustments/discontinuations or medication. Given the similar discontinuation rate for all study treatment (13.1% versus 10.7%), the addition of ramucirumab did not result in more frequent discontinuations of erlotinib.

3.7.2. Balance of benefits and risks

The PFS improvement observed with ramucirumab plus erlotinib is considered clinically meaningful, the current OS data and PFS2 data do not show a detrimental effect. The additional toxicity of ramucirumab to erlotinib is manageable.

In conclusion, the benefit-risk balance for ramucirumab in combination with erlotinib as first-line treatment of adult patients with metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations is positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Cyramza is positive.

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 and IIIB

Extension of indication for Cyramza to include in combination with erlotinib, the first-line treatment of adult patients with metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations; 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 accordingly. The RMP version 9.1 has also been agreed.

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular, the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to the Scientific Discussion Cyramza-H-C-2829-II-0033

Attachments

1. EN PI (changes highlighted) as adopted by the CHMP on 12 December 2019.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 27 December 2019. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/documents/regulatory-procedural-guideline/principles-be-applied-deletion-commercially-confidential-information-disclosure-emea-documents_en.pdf.

2. The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.

4. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, or prior to the next regulatory activity, whichever is first. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.