28 April 2016
EMA/CHMP/510480/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Avastin

International non-proprietary name: bevacizumab

Procedure No. EMEA/H/C/000582/II/0086

Marketing authorisation holder (MAH): Roche Registration Limited

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ADR: Adverse drug reaction

AE: Adverse event

AESI: Adverse event of special interest

ASCO: American Society of Clinical Oncology

AT: Avastin (bevacizumab) + Tarceva (erlotinib)

Bv: Bevacizumab

CAP: College of American Pathologists

CG: Cisplatin + gemcitabine

CL: Clearance

CP: Carboplatin + paclitaxel

CRC: Colorectal cancer

CSR: Clinical study report

CT: Chemotherapy

DCR: Disease control rate

DoR: Duration of response

ECOG-PS: Eastern Cooperative Oncology Group-Performance Status

EGF: Epidermal growth factor

EGFR: Epidermal growth factor receptor

EGFRmut+: EGFR mutation-positive

EGFRwt: EGFR wild-type

ESMO: European Society for Medical Oncology

FACT-L: Functional Assessment of Cancer Therapy-Lung

GCP: Good Clinical Practice

GLP: Good Laboratory Practice

HR: Hazard ratio

HRPC: Hormone refractory prostate cancer

HRQoL: Health-Related Quality of Life

IBD: International birth date

IRC: Independent Review Committee

KM: Kaplan-Meier

LNA: Locked nucleic acid

mBC: Metastatic breast cancer

mRCC: Metastatic renal cell carcinoma

MTD: Maximum tolerated dose

NSCLC: Non-small cell lung cancer

ORR: Objective response rate

OS: Overall survival

PBRER: Periodic Benefit-Risk Evaluation Report

PCR: Polymerase chain reaction

PD: Progressive disease

PFS: Progression-free survival

PK: Pharmacokinetics

PK-DDI: Pharmacokinetics-drug-drug interaction

PNA: Peptide nucleic acid

PopPK: Population pharmacokinetics

PSUR: Periodic Safety Update Report

SAE: Serious adverse event

SCE: Summary of Clinical Efficacy

SCP: Summary of Clinical Pharmacology

SCS: Summary of Clinical Safety

TKI: Tyrosine kinase inhibitor

TTP: Time to progression

VEGF: Vascular endothelial growth factor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Limited submitted to the European Medicines Agency on 6 July 2015 an application for a variation.

The following variation was requested:

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

Extension of indication to include the combination of bevacizumab with erlotinib for the first line treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) activating mutations. As a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and RMP (v.23.0) are updated in accordance.

The requested variation proposed amendments to the Summary of Product Characteristics, 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) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Bjorg Bolstad

Timetable	Actual dates
Rapporteur's preliminary assessment report circulated on:	17 September 2015

Timetable	Actual dates
CoRapporteur's preliminary assessment report circulated on:	17 September 2015
PRAC RMP advice and assessment overview adopted by PRAC	08 October 2015
Joint Rapporteur's updated assessment report circulated on:	16 October 2016
Request for supplementary information and extension of timetable adopted by the CHMP on:	22 October 2015
MAH's responses submitted to the CHMP on:	28 January 2016
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	01 March 2016
PRAC RMP advice and assessment overview adopted by PRAC:	17 March 2016
Updated Rapporteur's assessment report circulated on:	31 March 2016
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	01 April 2016
MAH's responses submitted to the CHMP on:	05 April 2016
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	12 April 2016
Updated Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	21 April 2016
Opinion:	28 April 2016

2. Scientific discussion

2.1. Introduction

Lung cancer has been among the most common cancers in the world for several decades. The 2012 worldwide estimates of cancer incidence and mortality by GLOBOCAN, indicate a total of 1.8 million new lung cancer cases and 1.6 million lung cancer related deaths, accounting for 13.0% of all cancer cases (except non-melanoma skin cancers) and 19.4% of all cancer deaths (except non-melanoma skin cancers). Furthermore, lung cancer incidence rates were two-fold higher in males compared to females (1,241,601 and 583,100, respectively). In 2013, the estimated number of lung cancer related deaths is 159,480 in the United States (Siegel et al 2013) and 269,610 in the European Union (Malvezzi et al 2013).

The two most prevalent sub-types of lung cancer are small cell lung cancer and non-small cell lung cancer (NSCLC). Approximately 85% of all lung cancers are NSCLC, which is frequently further subdivided into non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types) and squamous cell (epidermoid) carcinoma accounting for approximately 15% to 25% of all NSCLC (~230,000 to 380,000 cases) (Brambilla et al, WHO 2014 and Schrump et al, Principles and Practice of Oncology 2011).

Adenocarcinoma (40% of lung cancers) is the most common type of lung cancer, and is also the most frequently occurring in non-smokers as reported in United States (US) data (American Cancer Society 2013).

NSCLC is associated with high mortality rates as >70% of the patients are diagnosed with locally advanced or metastatic disease (Molina et al 2008) [stages III and IV according to the American joint committee on cancer staging (AJCC)].

In NSCLC, the first oncogenic driver mutations that were amenable to anti-cancer treatment were 'activating' mutations of the epidermal growth factor receptor (EGFR) (Lynch et al. 2004; Paez et al. 2004). The incidence of activating EGFR mutated NSCLC is approximately 40% in East Asian populations and approximately 10% in Western populations (Mansuet-Lupo et al. 2014).

According to the European Society for Medical Oncology (ESMO) guidelines, first-line treatment with a tyrosine kinase inhibitor (TKI), erlotinib, gefitinib, or afatinib, should be prescribed to patients with tumours bearing an activating (sensitising) mutation.

About the product

Avastin contains bevacizumab, a recombinant humanised monoclonal antibody which bind to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt 1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

Avastin was initially authorised in the EU on 12 January 2005 for the treatment of metastatic carcinoma of the colon or rectum in combination with fluoropyrimidine-based chemotherapy. It is currently approved in combination with other medicines to treat metastatic carcinoma of the colon or rectum (mCRC), metastatic breast cancer (mBC), Non-small cell lung cancer (NSCLC), advanced and/or metastatic renal cell cancer (mRCC), epithelial ovarian, fallopian tube, primary peritoneal cancer and metastatic carcinoma of the cervix (see SmPC section 4.1 for full detailed indications).

As part of the present variation, the applicant applied for the following indication:

Bevacizumab, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

Bevacizumab is a protein, which is expected to biodegrade in the environment and not to be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 corr 2[1]*), the ERA of bevacizumab may consist of a justification for not submitting any ERA studies as proteins are not expected to pose a significant risk to the environment.

In the current application IMS Health marketing data for Europe for the period 2004-2014 was used to refine the predicted environmental concentration in surface water (PECsw) for Tarceva. In terms of absolute values, the average European PECsw for Tarceva had the highest value at 0.00212 µg/l in 2010 and the highest maximum single-country PECsw is 0.00451 µg/l (Luxembourg). Thus, all use-based surface water PECs for Tarceva during the past decade, are well below the action limit of 0.01 µg/l. These PECs were derived without factoring in human metabolism or sewage works removal.

Based on the ERA submitted by the Applicant in 2010, erlotinib is not readily or inherently biodegradable. Further, in sediment/water systems it is only removed through formation of NERs (Non-Extractable Bound Residues), and not through biodegradation. Adsorption during sewage treatment is not sufficiently high to make a significant transfer to the soil compartment likely through land-spreading of surplus sludge.

Erlotinib showed limited chronic toxicity to the surface water model organisms algae, daphnia and fish, with the lowest NOEC (No Observed Effect Concentration) of these three organism groups being 0.52 mg/l for fish; hence, the surface water PNEC (Predicted No Effect Concentration) is 52 µg/l. Similarly, erlotinib was not highly toxic to sediment-dwelling midge larvae, oligochaetes or nematodes, with the lowest organic carbon corrected chronic sediment NOEC of 250 mg/kg. Lastly, erlotinib was not toxic to activated sludge micro-organisms with a NOEC of 1000 mg/l nominal concentration.

Erlotinib is not considered to be a persistent, bioaccumulative and toxic (PBT) substance as it does not fulfil the Bioaccumulation criterion (BCF <2000). It is, however, persistent due to its non inherent biodegradability and a whole system DT_{50} of 86 days. Erlotinb is also toxic according to the CMR classification as it causes mammalian embryolethality, however it is not toxic based on chronic aquatic ecotoxicity.

No new environmental fate and effect studies have been submitted for Tarceva in the current application.

2.2.2. Discussion and conclusion on non-clinical aspects

According to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 corr 2^1*), in the case of products containing proteins as active pharmaceutical ingredient(s), an ERA justifying the lack of ERA studies may be submitted. As bevacizumab is a protein (monoclonal antibody) the lack of ERA studies is acceptable.

The PECsw value for elotinib was below the action limit of 0.01 µg/l and thus a Phase II ERA was not required. The Applicant has nevertheless submitted chronic toxicity tests with algae (OECD 201), daphnia (OECD 211) and fish (OECD 210). All risk PEC/PNEC characterisation ratios are well below 1. Therefore, no significant risks to the environmental compartments of concern (sewage treatment plants, surface water, groundwater and sediment) have been identified. In addition, erlotinib is not considered a PBT substance.

With regard to erlotinib, the applied indication does not represent an expansion of the patient population in comparison to the already approved indication for erlotinib. The use of erlotinib is therefore not expected to increase significantly.

In conclusion the use of bevacizumab in combination with erlotinib, in this extension of indication of Avastin, is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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

Study Data Cut-off Date	Study Design, Country	Patient Characteristics	Total No of Patients Enrolled	No of Patients with EGFR Activating Mutations[a]	Treatment Arms
Studies Conducted in the 1st-line Setting					
Pivotal Study JO25567 30 June 2013	Phase II, R, OL, MC Japan	Patients (aged ≥ 20 years) without prior chemotherapy for locally advanced (stage IIIB), metastatic (stage IV) or recurrent non-squamous NSCLC with activating EGFRmut+ tumors (exon 19 deletion or exon 21 L858R mutation), without confirmed exon 20 T790M mutation and ECOG PS 0 or 1.	77[b] 77	77[b] 77	Bv 15 mg/kg q3w IV + Erl 150 mg/day orally Erl 150 mg/day orally
Supportive Study BO20571 9 September 2011	Phase II, R, OL, MC Global	Patients (aged ≥ 18 years) without prior systemic chemotherapy for locally advanced inoperable (stage IIIB with supraclavicular lymph node metastases or malignant pleural or pericardial effusion), metastatic (stage IV) or recurrent non-squamous NSCLC, ECOG PS 0 or 1, not selected on basis of EGFR mutation status.	63 61	13 11	Bv 15 mg/kg q3w IV + Erl 150 mg/day orally Bv 15 mg/kg q3w IV + CP or CG
Supportive Study SAKK 19/05 20 April 2010 [Zappa 2012]	Phase II, single-arm, MC Switzerland	Patients (aged ≥ 18 years) without prior systemic chemotherapy for histologically or cytologically confirmed de novo diagnosed or recurrent non-squamous NSCLC stage IIIB/IV, WHO PS 0-1, not selected on basis of EGFR mutation status.	101	12	Bv 15 mg/kg q3w IV + Erl 150 mg/day orally
Supportive Study AVF3671g 19 June 2009	Phase IIIb, R, DB, PC, MC Global	Patients (aged ≥ 18 years) without prior systemic treatment for histologically or cytologically confirmed NSCLC non-squamous NSCLC, stage IIIB/IV, ECOG PS 0 or 1 not selected on basis of EGFR mutation status.	1145	27 25	Bv 15 mg/kg q3w IV + Erl 150 mg/day orally Bv 15 mg/kg q3w IV + PL
Studies Conducted in the 2nd-line Setting					
Supportive Study OSI3364g 15 July 2008	Phase III, R, DB, PC, MC Global	Patients (aged ≥ 18 years) with recurrent or refractory NSCLC following standard first-line chemotherapy or chemo-radiotherapy, ECOG PS ≤ 2. Not selected on basis of EGFR mutation status.	319 317	12 13	Bv 15 mg/kg q3w IV + Erl 150 mg/day orally Erl 150 mg/day orally +PL
Supportive study OSI2950g 28 April 2006	Phase II, R, MC US	Patients (aged ≥ 18 years) with recurrent and unresectable non-squamous NSCLC (with progression after one line of platinum-based chemotherapy or previous adjuvant chemotherapy). ECOG PS ≤ 2.	42 40 40	0 0 1	Chemotherapy + PL Chemotherapy + Bv 15 mg/kg q3w IV Bv 15 mg/kg q3w IV + Erl 150 mg/day orally

[a] Number of patients with exon 19 deletion or exon 21 L858R mutations only
[b] 75 patients were treated
Bv bevacizumab; CP carboplatin/paclitaxel; CG cisplatin/gemcitabine; DB double-blind; ECOG PS Eastern Cooperative Oncology Group Performance Status; EGFRmut+ EGFR activating mutation-positive; Erl erlotinib; IV intravenous; MC multi-centered; NSCLC non-small cell lung cancer; OL open-label; PC placebo-controlled; PL placebo; q3w every three weeks; R randomized; WHO PS World Health Organization Performance Status.

2.3.2. Pharmacokinetics

No specific pharmacokinetics (PK) studies were conducted to support this application.

The MAH submitted a list of all available studies providing PK and PK-drug drug interaction for bevacizumab however three studies pertinent to the current application are summarised below.

- Study JO19907: Phase II study of first-line carboplatin-paclitaxel (CP) with or without bevacizumab in Japanese patients with advanced non-squamous NSCLC (Niho et al 2012).

After stratification for disease stage, performance status, and gender, patients were randomized in a 2:1 ratio to receive either 3-weekly (q3w) cycles of 15 mg/kg intravenous (IV) bevacizumab with 200 mg/m^2 paclitaxel and area under the curve (AUC) + 6 mg/mL/min (AUC6) carboplatin (bevacizumab + CP) or CP alone.

The study was conducted in two steps. Step 1 was performed to evaluate the tolerability of bevacizumab + CP in Japanese patients. In Step 2, eligible patients were randomly assigned to the two treatment arms. Serum samples for bevacizumab concentrations were collected at different time points from patients in the bevacizumab + CP treatment arms.

PK parameters for bevacizumab were assessed in 51 Japanese patients with non-squamous NSCLC who received bevacizumab + CP. PK analyses showed that bevacizumab had a mean CL of 2.92 ± 0.56 mL/day/kg, a mean half-life of 11.3 ± 2.1 days, mean V1 of 46.51 ± 6.79 mL/kg, a mean AUC_{inf} of 5,314 ± 1,013 µg • day/mL and a mean residence time (MRT) of 16.3 ± 3.0 days.

- Study NCT00043823 (OSI2486S): Phase I/II study evaluating bevacizumab in combination with erlotinib for patients with recurrent NSCLC (Herbst et al. 2005)

This was a single-arm trial carried out at two centres in the United States that investigated the efficacy, pharmacokinetics, and safety of combining bevacizumab (7.5 or 15 mg/kg q3w) with erlotinib (100 or 150 mg orally [po] daily [qd]) in patients with non-squamous NSCLC (Stage IIIB/IV) who were previously treated with ≥ 1 chemotherapy regimen. Patients were not selected on the basis of EGFR mutation status.

In Phase I of the study, 3 patients were treated in each of the first two cohorts (Cohort 1, 7.5 mg/kg bevacizumab q3w with 100 mg erlotinib po qd; Cohort 2, 15 mg/kg bevacizumab q3w with 100 mg erlotinib po qd); 6 patients were treated in Cohort 3 (15 mg/kg bevacizumab q3w with 150 mg erlotinib po qd). In the absence of dose-limiting toxicities, Phase II of the study was expanded to include an additional 28 patients in Cohort 3, ensuring that 34 patients were treated at the protocol-defined Phase II dose established in Phase I (15 mg/kg bevacizumab q3w and 150 mg/day erlotinib). Plasma samples for erlotinib concentrations and serum samples for bevacizumab concentrations were collected at different time points.

C_{max} was achieved approximately 4 hours after oral administration of both 100 and 150 mg daily erlotinib. C_{max} and AUC_{0-24} increased with dose. The AUC_{0-24} for 150 mg daily erlotinib was 26% higher than for the 100 mg dose. Plasma clearance values were comparable for 100 and 150 mg/d erlotinib (173 ± 200 L/d vs 184 ± 130 L/d); elimination half-life ($t_{½}$) values were 1.25 and 0.92 days, respectively. Minimum steady-state concentration ($C_{ss\ min}$) measured from days 8 to 147 was also similar for each dose.

For Bevacizumab, the mean terminal half-life ($t_{½}$) was 22.1 ± 14 days; the AUC_{0-N} was 5.0 ± 2.0 day • µg/mL. The clearance (CL), volume of distribution of the central compartment (Vc), and steady state volume of distribution (V_{ss}) were 3.2 ± 1.0 mL/kg/d, 36.8 ± 7.9 mL/kg, and 77.4 ± 25 mL/kg, respectively. The C_{max} was 396 ± 76 µg/mL which increased to 517 ± 82 µg/mL on day 64 after

multiple dosing.

Study OSI3364G (BETALUNG): Phase III, study evaluating the efficacy of bevacizumab in combination with erlotinib compared with erlotinib alone for treatment of advanced NSCLC after failure of standard first-line chemotherapy

This was a multicentre, placebo-controlled, double-blind, randomized Phase III study. Patients with advanced NSCLC who had experienced clinical or radiographic progression during or after standard first-line chemotherapy or chemoradiotherapy were randomized to receive 150 mg/day erlotinib po plus placebo, or 150 mg/day erlotinib + 15 mg/kg bevacizumab q3w, until disease progression or unmanageable toxicity. Plasma samples for erlotinib concentrations and serum samples for bevacizumab concentrations were collected at different time points.

The PK substudy did not meet its prespecified patient enrolment goal of at least 17 PK-evaluable patients in each treatment group. Although 17 patients in each arm were enrolled into the PK substudy, only 12 patients in the erlotinib + placebo group and 10 patients in the erlotinib + bevacizumab groups were evaluable for PK.

The average (CV%) peak concentration of erlotinib in the presence and absence of bevacizumab was 1491 ng/mL (53%) and 1890 ng/mL (45%), respectively. The average T_{max} was 5.2 and 3.5 hours and the average AUC was 23.4 and 31.5 hr • µg/mL in the presence and absence of bevacizumab, respectively. Overall, erlotinib in combination with bevacizumab had a lower C_{max}, a later T_{max}, and a lower overall exposure compared with erlotinib with placebo.

Trough concentrations (C_{trough}) for bevacizumab were similar to the observed C_{trough} values measured in previous bevacizumab PK studies that used the same dosing regimen (e.g., Study AVF0757g), and were also similar to C_{trough} values predicted using simulations from population PK modeling (Lu et al. 2008).

2.3.3. Discussion on clinical pharmacology

The PK of Bv have been extensively characterized in multiple clinical studies with doses from 1 to 20 mg/kg administered at a frequency ranging from weekly to q3w in patients with various tumour types including NSCLC.

There are no mechanistic reasons that suggest EGFR mutation status would affect the PK of Bv, and so no studies have been performed to address this. Because the clearance mechanism of Bv is not considered to be associated with the EGFR mutation status of patients' tumours, the PK of Bv in patients with activating EGFRmut+ NSCLC is expected to be consistent with the PK described by PopPK modelling.

These findings support the Bv dosing strategy proposed for patients with activating EGFRmut+ NSCLC, in which Bv is administered based on body weight-adjusted dose (15 mg/kg) q3w.

The PK of Erl has also been extensively characterized and thus not further addressed in this document.

Exploration of Influence of Racial/Ethnic Factors

Data from two studies in Caucasians and Japanese patients; JO19907 and JO16564 (Yamamoto et al. 2008), support the similarity in exposure for both Bv and Erl across racial/ethnic groups. Overall findings from Study JO19907 suggested that the PK of Bv in Japanese patients appeared similar to that reported in predominantly Caucasian patients treated with Bv + CP in Study AVF0757g (see EPAR for variation EMEA/H/C/582/II/09). Study JO16564 characterized the PK of Erl in Japanese patients and the results demonstrated that the Erl PK profile in Japanese patients to be similar to that observed in

Caucasian patients.

So far there has not been any indication of a treatment difference as function of ethnicity. With regard to erlotinib, the activating mutation is the main determinant of treatment effect regardless of ethnic origin. Studies OPTIMAL, EURTAC and ENSURE clearly demonstrate this (see Tarceva EPAR). Thus, based on current knowledge, it is expected that the effect of Erl+Bv observed in the Japanese population in study JO25567 could be extrapolated to a European population.

Population PK Analyses for Bevacizumab and Erlotinib

The PK of Bv has been characterized previously in patients with solid tumours (i.e., colorectal cancer [CRC], hormone refractory prostate cancer [HRPC], metastatic breast cancer [mBC], or NSCLC) from eight clinical trials in which Bv was administered either as a single agent or in combination with various chemotherapies. These data comprise the "Reference PopPK Model" provide a reference model for additional popPK analyses of data from other patient populations across various tumour types.

Although race was evaluated in the Reference PopPK Analysis, patient numbers were too low across the race categories to conclude whether a significant difference in Bv exposure was observed. An external analysis compared the results of Study JO19907 against the Reference PopPK Model, and confirmed that the PK of Bv from Japanese patients with NSCLC in Study JO19907 was similar to the predominantly Caucasian patients included in this model. This result is consistent with published results of PK analyses for therapeutic monoclonal antibodies that support that race (Japanese and others) is not a covariate associated with PK when body weight is taken into account.

Exploration of Bevacizumab-Erlotinib Pharmacokinetic Interaction

The PK of the combination of Bv and Erl was studied in a Phase I/II trial in patients with NSCLC (Study NCT00043823/OSI2486s). The results from this study showed that combining Bv (15 mg/kg q3w) and Erl (150mg/day) was well tolerated and active in NSCLC. These results, together with the results from Study OSI3364g, a phase III study where a PK sub-part of the study showed no clinically significant difference in the PK parameters of Erl or its metabolite OSI-420 in the presence or absence of Bv, were used to support the dose justification of Bv and Erl in Study JO25567.

Bv and Erl do not share clearance pathways. Thus, it is not expected that Bv would have any direct effect on exposure of Erl or its metabolites, and similarly, Erl would not be expected to alter Bv exposure. Erl is metabolized primarily via the CYP3A4 pathway and to a lesser extent by CYP1A2, and the pulmonary isoform CYP1A1. Agents known to inhibit or induce CYP3A4 and CYP1A2 function may alter the PK of Erl. However, the metabolism of Bv is primarily via proteolytic catabolism throughout the body and not via cytochrome P450 (CYP450) pathways. Therefore, Bv would not be expected to alter Erl disposition. Furthermore, Bv is not a cytokine modulator; therefore, it is not expected that any indirect or direct effect of Bv on CYP-450 enzyme levels would lead to alterations of the exposure of Erl or its metabolites. In addition, there is no known mechanism that would suggest that the mutated EGF receptor would affect the clearance of Bv.

2.3.4. Conclusions on clinical pharmacology

Based on the data submitted, it is expected that the effect of Erl+Bv observed in the Japanese population in study JO25567 could be extrapolated to a European population. The Population PK model for Erl indicates no clinical significant relationship between predicted apparent clearance and ethnicity and the PK-DDI data available for Bv given in combination with Erl do not suggest a potential for a PK-DDI between Bv and Erl.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No formal dose ranging studies were performed in patients with activating EGFRmut+ NSCLC.

2.4.2. Main study

Study JO25567: Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations: an open-label, randomised, multicentre, phase 2 study

Methods

Study participants

Key inclusion criteria

1) Histologically or cytologically (excluding sputum cytology) confirmed diagnosis of non-small cell lung cancer other than squamous cell carcinoma. (Mixed tumours will be categorized by the predominant cell type, unless small cell elements are present, in which case the patient will not be eligible for study participation.)

2) Exon 19 deletion or L858R mutation of exon 21 is evident in high-sensitivity EGFR gene mutation testing by means of polymerase chain reaction (PCR) using tumour tissue or cells.

3) Stage IIIB (not amenable for curable radiotherapy), IV or post-operative recurrence NSCLC. (Clinical stage is to be classified according to the 7th edition of the General Rule for Clinical and Pathological Record of Lung Cancer 22).)

4) Has not undergone chemotherapy. Patients who have history of pleurodesis with antineoplastic agents (excluding immunotherapy (BRM) such as Picibanil) are not eligible. In case patients who have history of neo-adjuvant chemotherapy or post-operative adjuvant chemotherapy are acceptable if at least 6 months have passed since the final administration date.

5) Patients who have history of radiotherapy are acceptable if they meet all of the following criteria.

a) No history of irradiation to pulmonary tumour lesions.

b) In case of palliative irradiation on thoracic bone lesions, at least 12 weeks must have passed since the date of the last radiation as of registration.

c) In case of irradiation on any area other than the chest, at least 2 weeks must have passed since the date of the last radiation as of registration.

6) As of registration, at least the following period has passed since the final date of the prior therapy.

a) Surgery (including exploratory / examination thoracotomy): 4 weeks or longer

b) Pleural cavity drainage: 2 weeks or longer

c) Pleurodesis without use of anti-neoplastic agents (BRM such as Picibanil): 2 weeks or longer

d) Biopsy accompanied by incision (including thoracoscopy): 2 weeks or longer

e) Procedure for trauma (excluding patients with unhealed wounds): 2 weeks or longer

f) Blood transfusion or hematopoietic factor products: 2 weeks or longer

g) Aspiration biopsy cytology: 1 week or longer

h) Other investigational drugs: 4 weeks or longer

7) Has one or more measurable lesions based on the criteria in Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1. However, the irradiated lesion cannot be considered measurable lesions.

Key exclusion criteria.

1) T790M mutation of exon 20 has been confirmed in high-sensitivity EGFR gene mutation testing by means of PCR using tumour tissue or cells.

2) Presence of brain metastasis.

3) Co-existence of malignancies at less than 5 years in disease-free period since its healing (acceptable regardless of disease-free period if judged that intra-epithelial cancer or intramucosal cancer can be cured by local treatment).

4) History or presence of haemoptysis or bloody sputum listed below (haemorrhage from the respiratory apparatus 2.5cc or more is assumed to be haemoptysis)

a) Bloody sputum that appears repeatedly (for more than 1 week), or a medical history of the same

b) Has a history of continuous administration of oral anastaltic, or has bloody sputum that requires continuous administration

c) Has a history of administration of intravenous injectable anastaltic, or has bloody sputum that requires administration

5) Presence of haemorrhagic tendency (coagulation disorder, etc.)

6) Tumour invading or abutting major blood vessels is clearly detected on the image.

7) Cavitation of pulmonary tumour lesion is apparently detected on the image.

8) Presence of poorly controlled pleural effusion, ascites or pericardial fluid.

9) Co-existence of superior vena cava syndrome.

10) Co-existence of spinal cord compression syndrome.

11) Co-existence of symptomatic cerebrovascular disorder, or its history within 1 year before registration.

12) Presence of clinically significant cardiac disorder (uncontrollable hypertension (blood pressure: >150/100 mmHg), unstable angina, congestive heart failure, severe arrhythmia requiring medication or history of myocardial infarction within 12 months before registration, etc.

13) Clearly has intestinal diverticulum

14) Co-existence of history of gastro-intestinal perforation within 1 year before registration

EGFR mutation testing

EGFR status was determined prior to study screening at each medicinal institution, using cells derived from paraffin embedded sections, pleural fluid, bronchial lavage or transbronchial brushing followed by analysis using polymerase chain reaction (PCR). The assay methods used and EGFR mutation status of patients were recorded at inclusion into the study. For patients enrolled in Study JO25567, EGFR testing was performed at three major reference laboratories that are certified by an international standard for clinical testing laboratories (ISO 15189) and maintain qualification by The College of

American Pathologists, and in addition conduct testing according to Japanese Good Laboratory Practice and Good Clinical Practice.

Treatments

Erlotinib 150 mg tablet was to be taken once daily before breakfast with 1 glass (approximately 200 mL) of water, every day.

Bevacizumab: 15 mg/kg intravenous drip infusion was performed on Day 1 of each cycle (1 cycle is assumed to be 21 days). When administering, the preceding cycle period must have ended (administration on the 22 to 25 day counting from the preceding administration day, excluding cases in which administration was delayed due to an adverse event).

Objectives

Primary Objective

To compare the progression-free survival (PFS) of erlotinib plus bevacizumab combination therapy (Erl+Bv group) with Erlotinib monotherapy (Erl group) based on blinded review by an IRC, to minimize any potential bias in the assessment of the primary endpoint.

Secondary Objectives

To compare the Erl+Bv group and Erl group with respect to each of the following items: Overall survival (OS), tumour response (response rate, disease control rate, and duration of response), improvement of symptoms and QOL based on Functional Assessment of Cancer Therapy for patients with Lung cancer (FACT-L), safety profile.

Exploratory Objectives

Measurement of serum angiogenic factor, ligands, etc., measurement of gene polymorphism, measurement of plasma VEGF, gene expression analysis using tumour tissue, measurement of protein, and measurement of proteomics.

Outcomes/endpoints

Primary endpoint

Progression free survival (PFS) defined as the period from registration in the study until the date of confirmation of progressive disease (PD) or the date of death from any cause, whichever occurs first.

Secondary endpoints

- Overall survival (OS) defined as the period from registration in the study until death irrespective of the cause

- Response rate defined as the percentage of patients whose best overall response is complete response (CR) or partial response (PR).

- Disease control rate defined as the percentage of patients whose best overall response is CR, PR or stable disease (SD), according to RECIST

- Duration of response (DOR) defined as the period from first report of response (CR or PR, whichever status was recorded first) until PD was confirmed or death (whichever occurs first).

- Quality of life (QoL) was evaluated using FACT-L including 5 low-order scales: 1. Feeling of physical health, 2. Feeling of social health, 3. Feeling of mental health, 4. Feeling of functional health, and 5. Lung cancer-related items.

Sample size

From past findings on patients with NSCLC who are positive for EGFR gene mutation, the median PFS of Erlotinib used alone was set at 13 months. Out of consideration for the anticipated additional effect of bevacizumab, HR was set at 0.7, and when supposing a one-sided significance level of 20% and a power of 80%, the required number of PFS events is 89. When setting the registration period at 12.5 months and the study period at 28 months, and taking into consideration the number of discontinued / dropout patients, the number of patients required to accumulate 89 events is 150 patients in the 2 groups (75 patients in each group).

In order to increase the precision of the estimated value, even if 89 events are observed in the early stages, observation will be continued during the 28-month study period, and even more events are to be accumulated. In addition, if the target number of events is not reached within the study period, the study period (follow-up period) will be extended until at least 89 events are observed.

Randomisation

Eligible subjects were randomly assigned to the Erl+Bv group or Erl group at a ratio of 1:1 using the dynamic allocation method, based on the stratification factors shown below.

Stratification factors:

1) Gender: Female vs. male

2) Clinical stage: IIIB vs. IV vs. post-operative recurrence

3) Smoking status: Non or Former light smoker vs. Other

4) EGFR gene mutation type: Exon19del vs. L858R

Blinding (masking)

Study JO25567 was an open-label study.

Statistical methods

The FAS was the main analysis set for the analysis of efficacy. In addition, as reference, efficacy was analysed using the per protocol set (PPS) as well.

The Kaplan-Meier method was used to estimate the survival function, the median PFS and the 95% confidence interval of the same was calculated, and the 2 groups were compared using the log-rank test. The confidence interval was calculated based on the Greenwood method.

In addition, the hazard ratio of PFS in the Erl+Bv group compared to that of the Erl group was shown using a proportional hazard model.

The estimate and the 95% confidence interval were calculated for response rate and disease control rate. The Clopper-Pearson method was used to calculate the confidence interval.

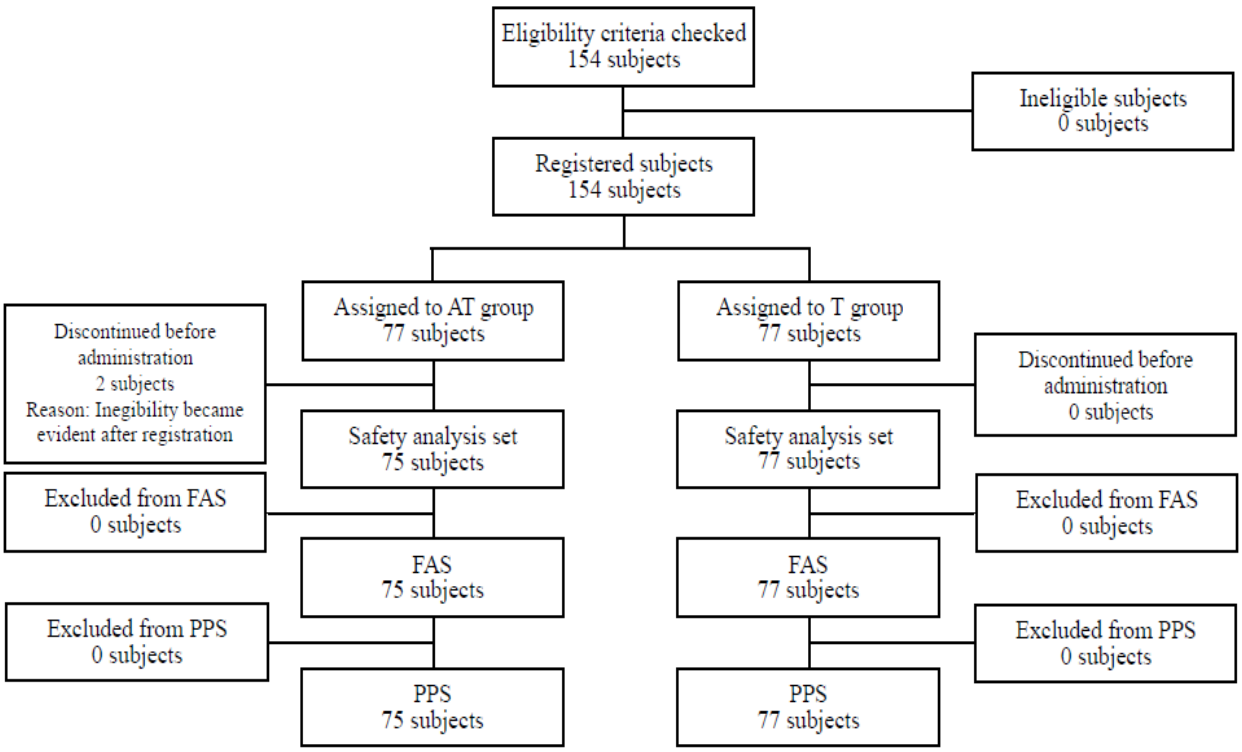
Overall survival and duration of response was analysed similarly to PFS.

QOL Evaluation was carried out in accordance with the FACT-L scoring manual. With respect to the total score and each subscale score, the statistics at each time point were calculated, and the changes over time were summarized. Similar summarization was carried out regarding changes in scores from baseline.

In the safety analysis population, the incidence of adverse events / adverse drug reactions and the 95% confidence interval were estimated.

Results

Participant flow



Recruitment

Date of informed consent of first subject: February 15, 2011. Interim cut-off date: June 30, 2013. Date of final tests (observations) of the final subject: March 4, 2014.

Conduct of the study

Amendments

The clinical trial protocol was revised 12 times after the start of the clinical trial. No changes were made concerning the analysis method, however it was decided that observation will be continued during the 28-month study period even if 89 events are observed in the early stages, and more events were accumulated.

Protocol deviations

Table 1: Protocol deviations (FAS) - Study JO25567

Classification of deviation	Number of subjects with deviation (number of incidents)		
	AT group N=75	T group N=77	Overall N=154
a: Subject violated in inclusion or exclusion criteria	0 (0)	0 (0)	0 (0)
b: Subject continued treatment despite meeting discontinuation criteria Subject did not conduct treatment delay, withholding, dose reduction or discontinuation despite meeting treatment delay, withholding, dose reduction or discontinuation criteria. Subject conducted treatment delay, withholding, dose reduction or discontinuation despite not meeting treatment delay, withholding, dose reduction or discontinuation criteria.	17 (22)	3 (3)	20 (25)
c: Deviation related to the dosage of investigational drug. Deviation related to the dosage of investigational drug.	34 (158)	16 (42)	50 (200)
d: Deviation related to concomitant therapy.	0 (0)	0 (0)	0 (0)
e: Deviation related to vital signs and PS. Deviation related to laboratory parameters. Deviation related to electrocardiogram and chest X-ray. Deviation related to lesion evaluation. Deviation related to QOL evaluation. Deviation related to biomarker.	28 (53)	29 (58)	57 (111)
f: Deviation related to delay in reporting serious adverse event. Deviation related to investigational drug management. Deviation related to subject information. Deviation related to study procedure.	10 (11)	5 (5)	15 (16)
Total	56 (244)	39 (108)	95 (352)

*): Details of deviations reported on or after the interim data cutoff date (June 30, 2013) are summarized in the appendix "Table 16.1.13-2: JO25567 deviation list contact table (as of data cutoff on March 31, 2014)."

Baseline data

Table 2: Demographic and other baseline characteristics (FAS) - Study JO25567

		AT	T	All
Age	20-29	0(0.0)	0(0.0)	0(0.0)
	30-39	2(2.7)	4(5.2)	6(3.9)
	40-49	4(5.3)	6(7.8)	10(6.6)
	50-59	13(17.3)	8(10.4)	21(13.8)
	60-69	22(29.3)	26(33.8)	48(31.6)
	70-79	29(38.7)	28(36.4)	57(37.5)
	>=80	5(6.7)	5(6.5)	10(6.6)
	<=69	41(54.7)	44(57.1)	85(55.9)
	>=70	34(45.3)	33(42.9)	67(44.1)
	<=74	63(84.0)	62(80.5)	125(82.2)
	>=75	12(16.0)	15(19.5)	27(17.8)
	Mean	65.8	65.1	65.5
	SD	10.6	12.0	11.3
	Min	38	36	36
	Median	67.0	67.0	67.0
	Max	83	84	84
Gender	Male	30(40.0)	26(33.8)	56(36.8)
	Female	45(60.0)	51(66.2)	96(63.2)
Smoking status	Non smoker(Lifetime amount of smoking of less than 100 pieces)	42(56.0)	45(58.4)	87(57.2)
	Former light smoker(More than 15 years after non smoking and less than 10 packs a year)	9(12.0)	6(7.8)	15(9.9)
	Other(Other than Non or Former light smoker)	24(32.0)	26(33.8)	50(32.9)
Brinkman index	<500	55(73.3)	58(75.3)	113(74.3)
	>=500,<1000	13(17.3)	12(15.6)	25(16.4)
	>=1000,<2000	6(8.0)	7(9.1)	13(8.6)
	>=2000	1(1.3)	0(0.0)	1(0.7)
	Mean	295.6	240.4	267.7
	SD	534.4	397.9	469.4
	Min	0	0	0
	Median	0.0	0.0	0.0
	Max	3000	1600	3000
Height(cm)	Mean	158.6	158.1	158.4
	SD	9.9	10.0	9.9
	Min	137	132	132
	Median	157.0	156.0	157.0
	Max	179	185	185
Body weight at screening(kg)	<50kg	28(37.3)	23(29.9)	51(33.6)
	>=50kg,<60kg	23(30.7)	33(42.9)	56(36.8)
	>=60kg,<70kg	15(20.0)	14(18.2)	29(19.1)
	>=70kg	9(12.0)	7(9.1)	16(10.5)
	Mean	55.09	55.27	55.18
	SD	11.27	9.39	10.33
	Min	29.3	35.3	29.3
	Median	54.40	53.50	54.10
	Max	82.9	79.7	82.9
BMI	Mean	21.75	22.05	21.90
	SD	3.21	2.74	2.97
	Min	13.2	14.3	13.2
	Median	21.70	22.00	21.85
	Max	29.4	29.0	29.4
Previous disaeses	Yes	20(26.7)	26(33.8)	46(30.3)
	No	55(73.3)	51(66.2)	106(69.7)
Concomitant/ Concurrent diseases	Yes	72(96.0)	69(89.6)	141(92.8)
	No	3(4.0)	8(10.4)	11(7.2)
ECOG PS at screening	0	43(57.3)	41(53.2)	84(55.3)
	1	32(42.7)	36(46.8)	68(44.7)
Chest X-ray at screening	Normal	74(98.7)	77(100.0)	151(99.3)
	Abnormal	0(0.0)	0(0.0)	0(0.0)
Electrocardiogram at screening	Normal	74(98.7)	75(97.4)	149(98.0)
	Abnormal	1(1.3)	2(2.6)	3(2.0)
Head CT/MRI at screening	Normal	75(100.0)	76(98.7)	151(99.3)
	Abnormal	0(0.0)	1(1.3)	1(0.7)

Number of subject(%)

Table 3: Baseline disease characteristics (FAS) - Study JO25567

		AT	T	All
Period from the initial date of diagnosis to the first day of administration (days)	n	75	77	152
	Mean	193.4	233.5	213.7
	SD	383.1	449.0	416.9
	Min	14	11	11
	Median	36.0	36.0	36.0
	Max	1687	1901	1901
Histopathological classification	Adenocarcinoma	74(98.7)	76(98.7)	150(98.7)
	Large cell carcinoma	0(0.0)	1(1.3)	1(0.7)
	Other	1(1.3)	0(0.0)	1(0.7)
Clinical stage at screening	IIIB	1(1.3)	0(0.0)	1(0.7)
	IV	60(80.0)	62(80.5)	122(80.3)
	Postoperative recurrence	14(18.7)	15(19.5)	29(19.1)
Period from the date of diagnosis of recurrence to the first day of administration (days)	n	14	15	29
	Mean	116.4	196.6	157.9
	SD	73.8	295.8	218.9
	Min	30	24	24
	Median	99.0	59.0	64.0
	Max	225	980	980
The presence or absence of the primary tumor at screening	Yes	60(80.0)	60(77.9)	120(78.9)
	No	15(20.0)	17(22.1)	32(21.1)

Number of subject(%)

Table 4: EGFR gene mutations (FAS) - Study JO25567

			AT N=75	T N=77	All N=152
Type of specimen and measurement methods		Type of specimen			
		Paraffin section	43(57.3)	48(62.3)	91(59.9)
		Pleural effusion	12(16.0)	10(13.0)	22(14.5)
		Bronchial washing fluid	11(14.7)	8(10.4)	19(12.5)
		Transbronchial brushing cells	7(9.3)	8(10.4)	15(9.9)
		Other	2(2.7)	3(3.9)	5(3.3)
		Measurement methods			
		PNA LNA PCR-Clamp method	28(37.3)	24(31.2)	52(34.2)
		PCR-Invader method	25(33.3)	29(37.7)	54(35.5)
		Cycleave method	13(17.3)	16(20.8)	29(19.1)
		Other	9(12.0)	8(10.4)	17(11.2)
EGFR gene mutation test	Exon19 deletion	Positive	40(53.3)	40(51.9)	80(52.6)
		Negative	35(46.7)	37(48.1)	72(47.4)
		Unclear	0(0.0)	0(0.0)	0(0.0)
	Exon21 L858R	Positive	35(46.7)	37(48.1)	72(47.4)
		Negative	40(53.3)	40(51.9)	80(52.6)
		Unclear	0(0.0)	0(0.0)	0(0.0)
	Exon18 G719X	Positive	0(0.0)	1(1.3)	1(0.7)
		Negative	68(90.7)	74(96.1)	142(93.4)
		Unclear	7(9.3)	2(2.6)	9(5.9)
	Exon20 S768I	Positive	0(0.0)	0(0.0)	0(0.0)
		Negative	59(78.7)	62(80.5)	121(79.6)
		Unclear	16(21.3)	15(19.5)	31(20.4)
	Exon20 T790M	Positive	0(0.0)	0(0.0)	0(0.0)
		Negative	68(90.7)	75(97.4)	143(94.1)
		Unclear	7(9.3)	2(2.6)	9(5.9)
	Exon21 L861Q	Positive	0(0.0)	0(0.0)	0(0.0)
		Negative	68(90.7)	75(97.4)	143(94.1)
		Unclear	7(9.3)	2(2.6)	9(5.9)
	Other	Positive	0(0.0)	0(0.0)	0(0.0)
EGFR gene mutation status		1. DOUBLE MUT.(T790M is N/A)	0(0.0)	0(0.0)	0(0.0)
		2. EX.19 DEL.(T790M is N/A)	3(4.0)	1(1.3)	4(2.6)
		3. L858R(T790M is N/A)	4(5.3)	1(1.3)	5(3.3)
		4. DOUBLE MUT.	0(0.0)	0(0.0)	0(0.0)
		5. EX.19 DEL.	37(49.3)	39(50.6)	76(50.0)
		6. L858R	31(41.3)	36(46.8)	67(44.1)

Number of subject(%)

Table 5: Prior-treatment for NSCLC (FAS) - Study JO25567

		AT N=75	T N=77	All N=152
Surgical procedure	Yes	15(20.0)	17(22.1)	32(21.1)
	No	60(80.0)	60(77.9)	120(78.9)
Period from the date of surgery to the first dose (days)	n	15	17	32
	Mean	710.4	893.6	807.8
	SD	367.4	555.4	478.3
	Min	227	68	68
	Median	722.0	663.0	692.5
	Max	1664	1901	1901
Radiation therapy	Yes	3(4.0)	2(2.6)	5(3.3)
	No	72(96.0)	75(97.4)	147(96.7)
Period from the last irradiation date to the first dose (days)	n	3	2	5
	Mean	282.3	20.5	177.6
	SD	441.4	3.5	343.5
	Min	25	18	18
	Median	30.0	20.5	25.0
	Max	792	23	792
Pre or postoperative chemotherapy	Yes	7(9.3)	5(6.5)	12(7.9)
	No	68(90.7)	72(93.5)	140(92.1)
Period from the last day of administration of adjuvant chemotherapy to the first dose (days)	n	7	5	12
	Mean	614.7	876.4	723.8
	SD	211.3	494.0	362.3
	Min	363	343	343
	Median	636.0	1031.0	658.5
	Max	899	1337	1337
Thoracic drainage	Yes	8(10.7)	12(15.6)	20(13.2)
	No	67(89.3)	65(84.4)	132(86.8)
Period from the drainage removal date to the first dose (days)	n	8	12	20
	Mean	27.3	23.8	25.2
	SD	11.5	6.1	8.6
	Min	17	16	16
	Median	23.5	22.0	22.0
	Max	48	32	48
Pleurodesis	Yes	6(8.0)	8(10.4)	14(9.2)
	No	69(92.0)	69(89.6)	138(90.8)
Period from the last day of administration of pleurodesis until the first dose (days)	n	6	8	14
	Mean	59.3	25.5	40.0
	SD	89.1	6.5	58.1
	Min	20	20	20
	Median	22.5	23.5	23.5
	Max	241	37	241

Number of subject(%)

The most common later lines of therapy were other EGFR TKI's, pemetrexed, docetaxel, carboplatin, cisplatin and bevacizumab. It is noted that bevacizumab was used more commonly by patients in the Erl arm than the Erl+Bv arm. More than three quarters of patients received second-line therapy in both treatment arms. Third-line of treatment was received by 63.6% and 56.0% of patients in the Erl arm and Erl+Bv arm, respectively. Fourth and later lines of treatment were used by more patients in the Erl arm (53.2%; n=41) compared to the Erl+Bv arm (37.3%, n=28).

Numbers analysed

Of 154 randomized patients, 2 patients (Erl+Bv group) were discontinued before the start of administration due to pulmonary artery thrombosis and increased pleural effusion, so the number of patients who were administered the investigational drug at least once (safety analysis population) was 152 patients (Erl+Bv group: 75 patients, Erl group: 77 patients).

Table 6: Analysis Data Set (All Randomized Population) - Study JO25567

	AT N=77	T N=77	All N=154
Safety analysis population	75(97.4)	77(100.0)	152(98.7)
Full Analysis Set(FAS)	75(97.4)	77(100.0)	152(98.7)
Per Protocol Set(PPS)	75(97.4)	77(100.0)	152(98.7)

Number of subject(%)

In addition, a breakdown of the reasons for discontinuation of Erlotinib and bevacizumab as of the interim cut-off date (June 30, 2013) was reported.

Outcomes and estimation

Primary endpoint – PFS:

Table 7: PFS outcome (FAS/Committee evaluation) - Study JO25567

	AT	T
Analyzed number of subject	75(100.0%)	77(100.0%)
Number of subject with event	46(61.3%)	57(74.0%)
Number of subject with event-free	29(38.7%)	20(26.0%)
Time to event (months)		
Median of Kaplan-Meier estimate	16.0	9.7
95% confidence interval	[13.9;18.1]	[5.7;11.1]
25 percentile, 75 percentile	11.1;26.1	4.2;19.3
Range	2.9 - 26.1	0.7 - 25.9
P-value (Log-rank test)	0.0015	
Hazard ratio	0.54	
95% confidence interval	[0.36;0.79]	
1 year event-free rate		
Patients remaining at risk	49	24
Event-free rate	0.73	0.38
95% confidence interval	[0.61;0.82]	[0.26;0.49]

Number of subject(%)

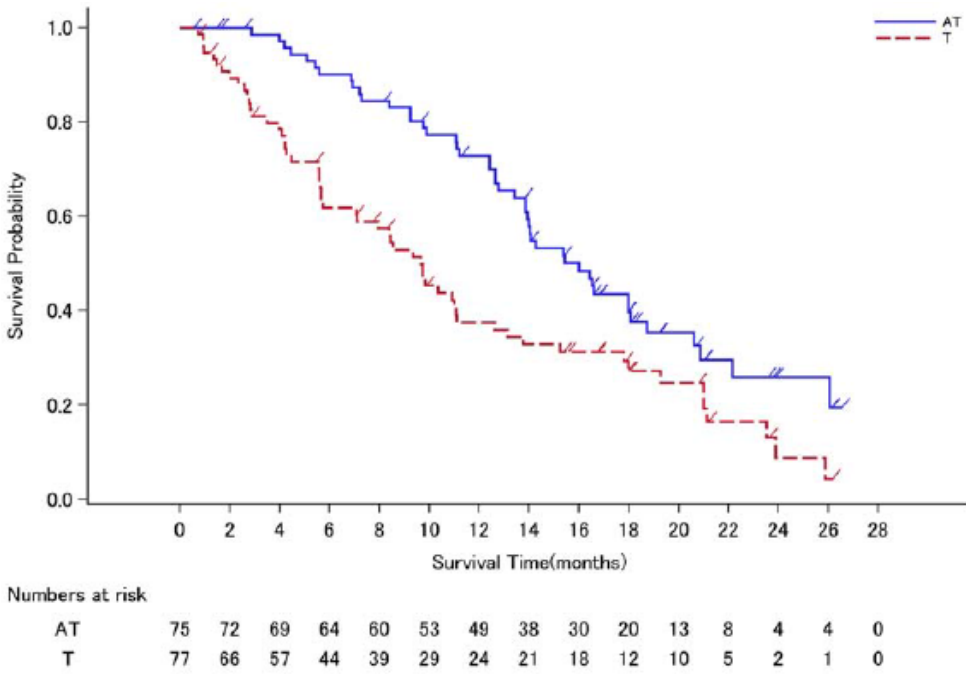


Figure 1: Kaplan-Maier curve for PFS (FAS/Committee evaluation) - Study JO25567

Table 8: Censoring of PFS events (FAS/Committee evaluation) - Study JO25567

	Erl (N=77)	Erl+Bv (N=75)
Total number of patients censored	20	29
No further CT assessment due to PD by Investigators	8 (40.0%)	4 (13.8%)
Withdrawal from assessment after treatment discontinuation	3 (15.0%)	6 (20.7%)
Ongoing on study	9 (45.0%)	19 (65.5%)

Data Cutoff: 30JUN2013.

CT= computed tomography; PD= progressive disease

Updated PFS analysis based on a data cut-off date of 31 March 2014 is presented below

Table 9: PFS updated analysis (FAS/investigator assessment) - Study JO25567

	AT N=75	T N=77
Analyzed number of subject	75(100.0%)	77(100.0%)
Number of subject with event	48(64.0%)	62(80.5%)
Number of subject with event-free	27(36.0%)	15(19.5%)
Time to event (months)		
Median of Kaplan-Meier estimate	16.4	9.8
95% confidence interval	[14.0;19.2]	[7.8;12.3]
25 percentile, 75 percentile	11.3;34.8	5.5;18.0
Range	2.9 - 34.8	1.1 - 26.3
P-value (Log-rank test)	0.0005	
Hazard ratio	0.52	
95% confidence interval	[0.35;0.76]	
1 year event-free rate		
Patients remaining at risk	50	28
Event-free rate	0.72	0.40
95% confidence interval	[0.60;0.81]	[0.29;0.51]

Number of subject(%)

Secondary endpoint

Overall survival:

OS analyses were performed at 4 clinical cut-off dates (30 June 2013, 31 March 2014, 7 November 2014 and 28 October 2015). At the time of the cut-off for the primary analysis of PFS (30 June 2013), 31 deaths had occurred (13 in the Erl+Bv arm, 18 in the Erl arm) representing 20% of the FAS population.

Table 10: Overall survival data – FAS (data cut-off: 30 June 2013) - Study JO25567

	AT	T
Analyzed number of subject	75(100.0%)	77(100.0%)
Number of subject with event	13(17.3%)	18(23.4%)
Number of subject with event-free	62(82.7%)	59(76.6%)
Time to event (months)		
Median of Kaplan-Meier estimate	-	-
95% confidence interval	[26.4;-]	-
25 percentile, 75 percentile	26.4;-	21.8;-
Range	9.9 - 26.4	1.3 - 21.8
P-value (Log-rank test)	0.4234	
Hazard ratio	0.75	
95% confidence interval	[0.37;1.53]	
1-year survival rate		
Patients remaining at risk	71	71
Survival rate	0.97	0.92
95% confidence interval	[0.90;0.99]	[0.83;0.96]
2-year survival rate		
Patients remaining at risk	19	23
Survival rate	0.80	0.74
95% confidence interval	[0.67;0.88]	[0.62;0.83]

Number of subject(%)

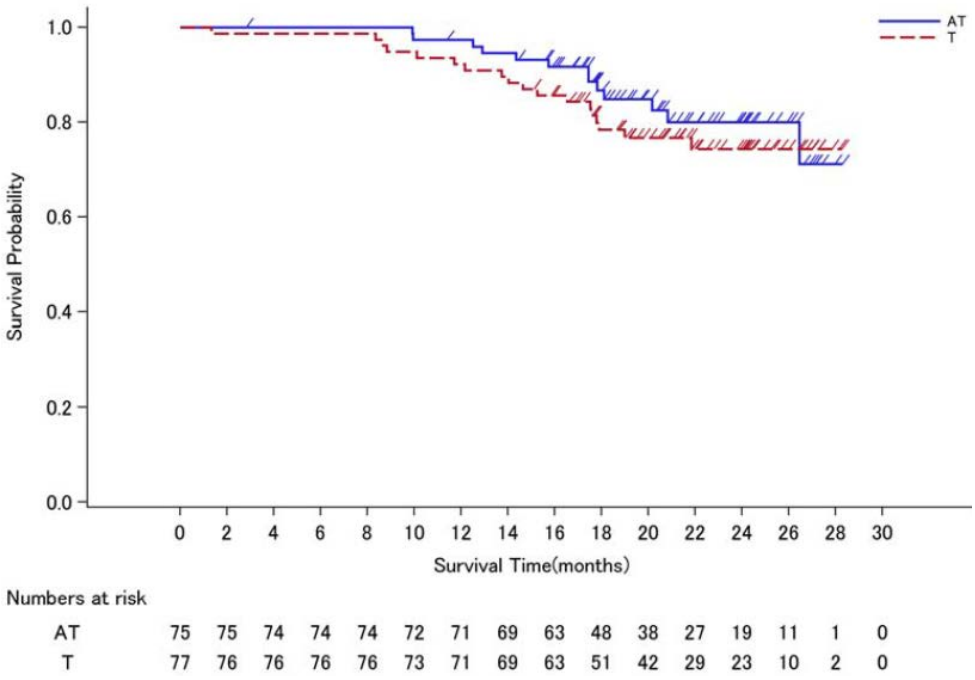


Figure 2: Kaplan-Maier curve for OS – FAS (data cut-off: 30 June 2013) - Study JO25567

Table 11: Overall survival data – FAS (data cut-off: 7 November 2014) - Study JO25567

	Erl N=77	Erl+Bv N=75
Patients analyzed	77 (100.0%)	75 (100.0%)
With events	27 (35.1%)	27 (36.0%)
Without events	50 (64.9%)	48 (64.0%)
Time to event (months)		
Kaplan-Meier estimated Median	-	-
95% confidence interval	[36.2;-]	[34.2;-]
25 percentile / 75 percentile	21.8;-	26.4;-
Range	1.3 - 36.2	9.9 - 36.2
p value（Log-rank test）	0.8926	
HR [95% confidence interval]	1.04 [0.61;1.77]	

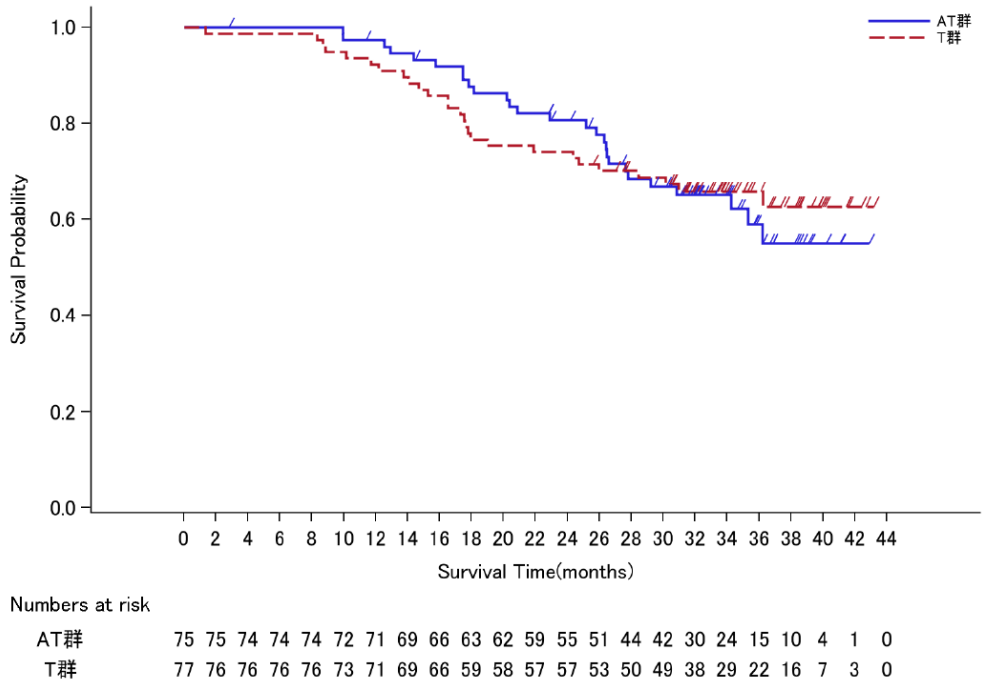


Figure 3: Kaplan-Maier curve for OS – FAS (data cut-off: 7 November 2014) - Study JO25567

At the request of CHMP further updated OS data were provided, at the cut-off of 28 October 2015.

Table 12: Overall survival data – FAS (data cut-off: 28 October 2015) - Study JO25567

	Erl N=77	Erl+Bv N=75
Number of subjects with events	37 (48.1%)	32 (42.7%)
Number of subjects without events	40 (51.9%)	43 (57.3%)
Time to event (months)		
Median OS (KM-estimated)	48.5	48.4
95% CI	[40.2; -]	[35.3; -]
Range	1.3 – 50.3	9.9 – 48.4
p-value (log-rank test)	0.6838	
Hazard ratio [95% CI]	0.91 [0.56; 1.46]	
2-year survival rate (KM-estimated)	0.74	0.81
3-year survival rate (KM-estimated)	0.64	0.62
4-year survival rate (KM-estimated)	0.52	0.53

KM=Kaplan-Meier

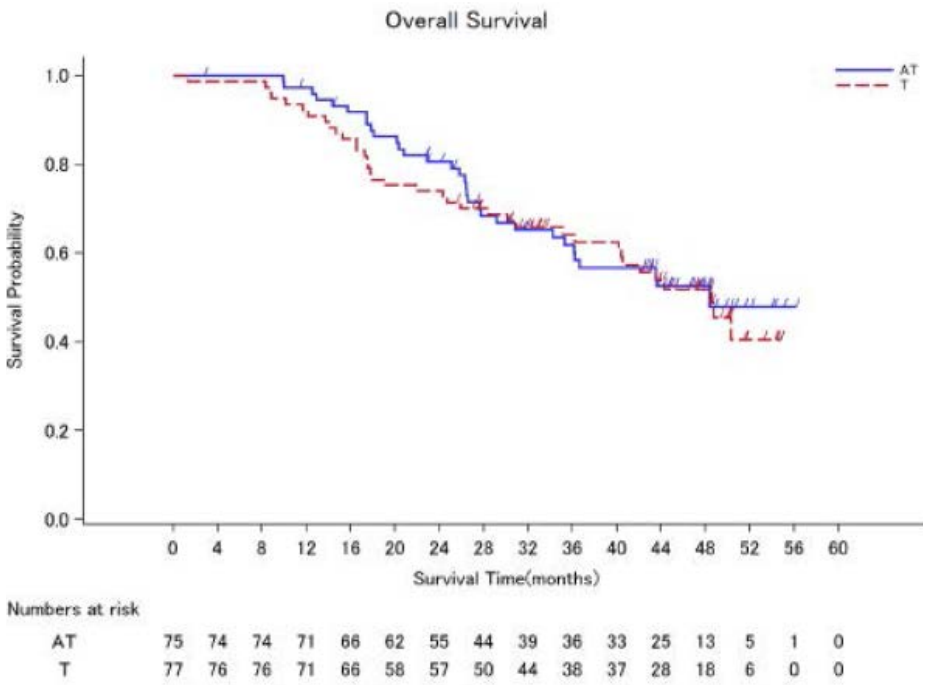


Figure 4: Kaplan-Maier curve for OS – FAS (data cut-off: 28 October 2015) - Study JO25567

Response rate:

Table 13: Response rate and best overall response (FAS/Committee evaluation) - Study JO25567

	AT	T
Analyzed number of subject	75(100.0%)	77(100.0%)
Number of responders	52(69.3%)	49(63.6%)
Number of non-responders	23(30.7%)	28(36.4%)
95% confidence interval of response	[57.6;79.5]	[51.9;74.3]
P-value (Fisher's exact test)	0.4951	
CR （Complete Response）	3(4.0%)	1(1.3%)
Rate of 95% confidence interval	[0.8;11.2]	[0.0;7.0]
PR （Partial Response）	49(65.3%)	48(62.3%)
Rate of 95% confidence interval	[53.5;76.0]	[50.6;73.1]
SD （Stable Disease）	22(29.3%)	19(24.7%)
Rate of 95% confidence interval	[19.4;41.0]	[15.6;35.8]
PD （Progressive Disease）	0(0.0%)	6(7.8%)
Rate of 95% confidence interval	[0.0;4.8]	[2.9;16.2]
NE （Not Evaluable）	1(1.3%)	3(3.9%)
Rate of 95% confidence interval	[0.0;7.2]	[0.8;11.0]

Number of subject(%)

Disease control rate:

Table 14: Disease control rate (FAS/Committee evaluation) - Study JO25567

	AT	T
Analyzed number of subject	75(100.0%)	77(100.0%)
Number of subject disease controlled	74(98.7%)	68(88.3%)
Number of subject disease uncontrolled	1(1.3%)	9(11.7%)
95% confidence interval of disease control rate	[92.8;100.0]	[79.0;94.5]
P-value (Fisher's exact test)	0.0177	

Number of subject(%)

Duration of response:

Table 15: Duration of response (FAS/Committee evaluation) - Study JO25567

	AT	T
Analyzed number of subject (Responders)	52(100.0%)	49(100.0%)
Number of subject with event	34(65.4%)	37(75.5%)
Number of subject with event-free	18(34.6%)	12(24.5%)
Time to event (months)		
Median of Kaplan-Meier estimate	13.3	9.3
95% confidence interval	[11.6;16.5]	[6.9;13.8]
25 percentile, 75 percentile	9.0;23.3	4.9;16.9
Range	3.7 - 23.3	2.1 - 24.4
P-value (Log-rank test)	0.1118	
Hazard ratio	0.68	
95% confidence interval	[0.43;1.10]	

Number of subject(%)

QoL:

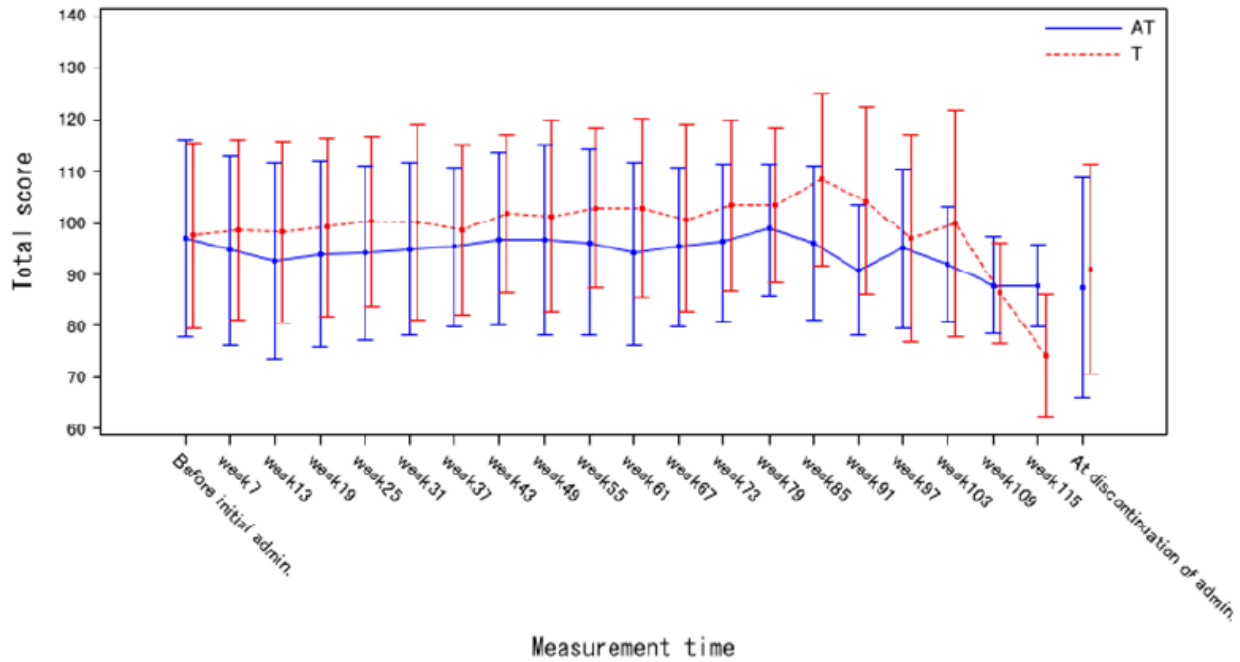


Figure 5: FACT-L Score Transition Diagram (FAS) - Study JO25567

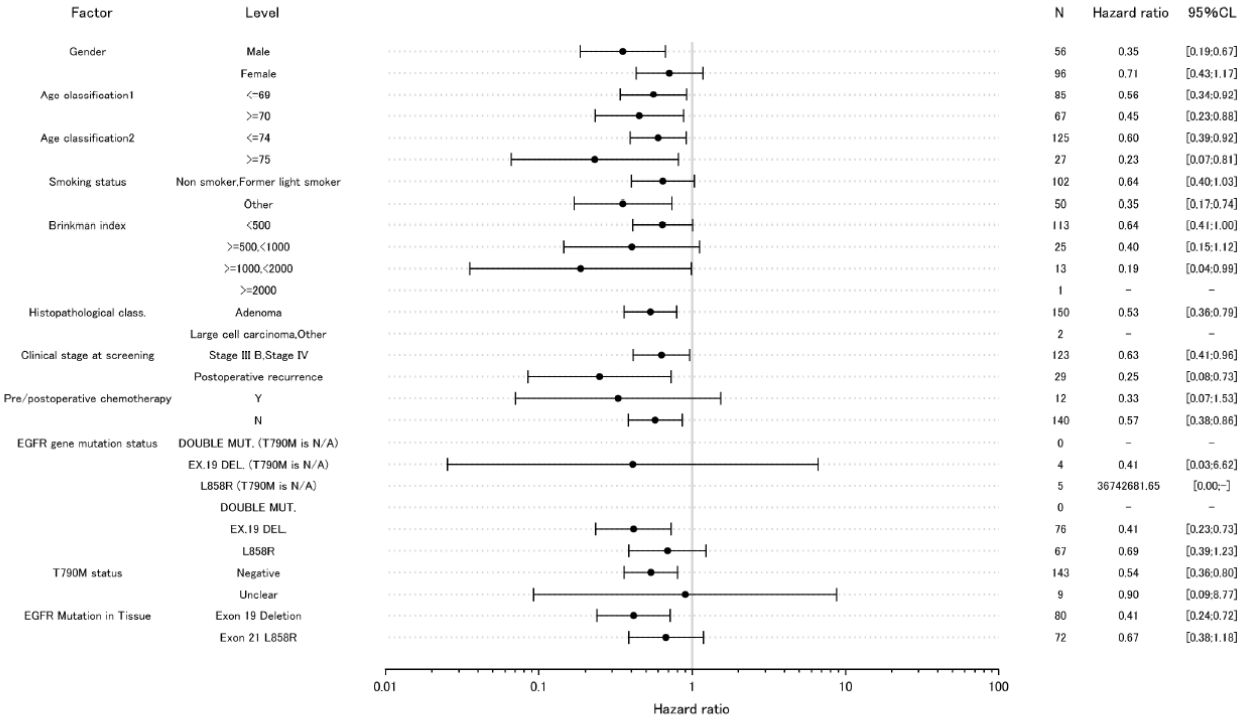
Evaluation was carried out in accordance with the FACT-L scoring manual. No clinically significant difference was seen between the 2 groups in terms of the total score, Trial Outcome Index (TOI) score, or each subscale score during the administration period.

Ancillary analyses

Subgroup analysis

Table 16: Subpopulation analysis of PFS (FAS/Committee evaluation) - Study JO25567

	AT				T				Hazard ratio	95% confidence interval of hazard ratio
	Number of subject	Number of subject with event	Median of survival time estimate		Number of subject	Number of subject with event	Median of survival time estimate			
			Median (month)	95% confidence interval			Median (month)	95% confidence interval		
Gender										
male	30	18	18.0	[14.0;26.1]	26	22	9.7	[5.7;11.1]	0.35	[0.19;0.67]
female	45	28	15.4	[11.1;20.6]	51	35	9.7	[5.6;15.2]	0.71	[0.43;1.17]
Age classification1										
<=69	41	32	14.1	[12.4;18.0]	44	33	8.5	[5.7;10.9]	0.56	[0.34;0.92]
>=70	34	14	22.1	[12.8;-]	33	24	11.1	[5.6;21.0]	0.45	[0.23;0.88]
Age classification2										
<=74	63	43	15.4	[13.4;18.0]	62	44	9.7	[5.7;11.1]	0.60	[0.39;0.92]
>=75	12	3	-	[5.4;-]	15	13	9.7	[2.8;21.0]	0.23	[0.07;0.81]
Smoking status										
Non smoker, Former light smoker	51	34	14.0	[11.1;18.0]	51	36	8.5	[5.6;13.1]	0.64	[0.40;1.03]
Other	24	12	18.7	[14.0;-]	26	21	10.3	[7.1;17.8]	0.35	[0.17;0.74]
Brinkman index										
<500	55	37	15.4	[12.4;18.0]	58	41	8.5	[5.7;13.1]	0.64	[0.41;1.00]
>=500,<1000	13	6	-	[13.4;-]	12	10	12.6	[0.9;21.0]	0.40	[0.15;1.12]
>=1000,<2000	6	3	26.1	[12.4;26.1]	7	6	5.6	[1.0;11.0]	0.19	[0.04;0.99]
>=2000	1	0	-	-	0	-	-	-	-	-
Histopathological classification										
Adenocarcinoma	74	45	16.0	[13.9;18.7]	76	56	9.7	[5.7;11.1]	0.53	[0.36;0.79]
Large cell carcinoma or other	1	1	5.6	-	1	1	7.1	-	-	-
Clinical stage at screening										
IIIB, IV	61	41	14.0	[12.4;18.0]	62	46	9.7	[5.7;11.1]	0.63	[0.41;0.96]
Postoperative recurrence	14	5	20.6	[14.3;-]	15	11	13.8	[2.7;17.8]	0.25	[0.08;0.73]
Pre or postoperative chemotherapy										
Yes	7	3	20.6	[13.9;-]	5	4	15.2	[2.7;21.0]	0.33	[0.07;1.53]
No	68	43	14.3	[12.8;18.0]	72	53	9.7	[5.7;11.1]	0.57	[0.38;0.86]
EGFR gene mutation status										
DOUBLE MUT. (T790M is N/A)	0	-	-	-	0	-	-	-	-	-
EX.19 DEL. (T790M is N/A)	3	2	18.1	[6.9;18.1]	1	1	8.0	-	0.41	[0.03;6.62]
L858R (T790M is N/A)	4	2	-	[2.9;-]	1	0	-	-	36742681.65	[0.00;-]
DOUBLE MUT.	0	-	-	-	0	-	-	-	-	-
EX.19 DEL.	37	21	16.5	[13.9;-]	39	29	10.3	[8.4;13.1]	0.41	[0.23;0.73]
L858R	31	21	13.7	[11.2;20.9]	36	27	5.7	[4.2;15.2]	0.69	[0.39;1.23]
T790M status										
None	68	42	15.4	[13.4;18.7]	75	56	9.7	[5.7;11.1]	0.54	[0.36;0.80]
Unclear	7	4	18.1	[2.9;-]	2	1	-	[8.0;-]	0.90	[0.09;8.77]
EGFR Mutation in Tissue										
Exon 19 Deletion	40	23	18.0	[14.1;20.6]	40	30	10.3	[8.0;13.1]	0.41	[0.24;0.72]
Exon 21 L858R	35	23	13.9	[11.2;20.9]	37	27	7.1	[4.3;15.2]	0.67	[0.38;1.18]



Bv bevacizumab; Erl erlotinib

Figure 6: IRC-assessed PFS in subgroups (FAS) - Study JO25567

Efficacy depending on rash

Table 17: PFS of each of peak of severity of rash (more than grade 2 and other) (FAS/Committee evaluation) - Study JO25567

	More than Grade 2		Other	
	AT	T	AT	T
Analyzed number of subject	53(100.0%)	50(100.0%)	22(100.0%)	27(100.0%)
Number of subject with event	33(62.3%)	35(70.0%)	13(59.1%)	22(81.5%)
Number of subject with event-free	20(37.7%)	15(30.0%)	9(40.9%)	5(18.5%)
Time to event (months)				
Median of Kaplan-Meier estimate	16.0	11.1	14.1	5.7
95% confidence interval	[13.9;20.6]	[8.0;18.0]	[9.8;-]	[2.9;9.3]
25 percentile, 75 percentile	11.2;26.1	5.6;21.1	10.4;-	2.9;9.7
Range	2.9 - 26.1	0.7 - 25.9	4.2 - 18.0	1.3 - 19.3
Hazard ratio	0.66		0.33	
95% confidence interval	[0.41;1.07]		[0.16;0.66]	
1 year event-free rate				
Patients remaining at risk	36	20	13	4
Event-free rate	0.74	0.48	0.70	0.17
95% confidence interval	[0.60;0.84]	[0.33;0.62]	[0.45;0.85]	[0.05;0.34]

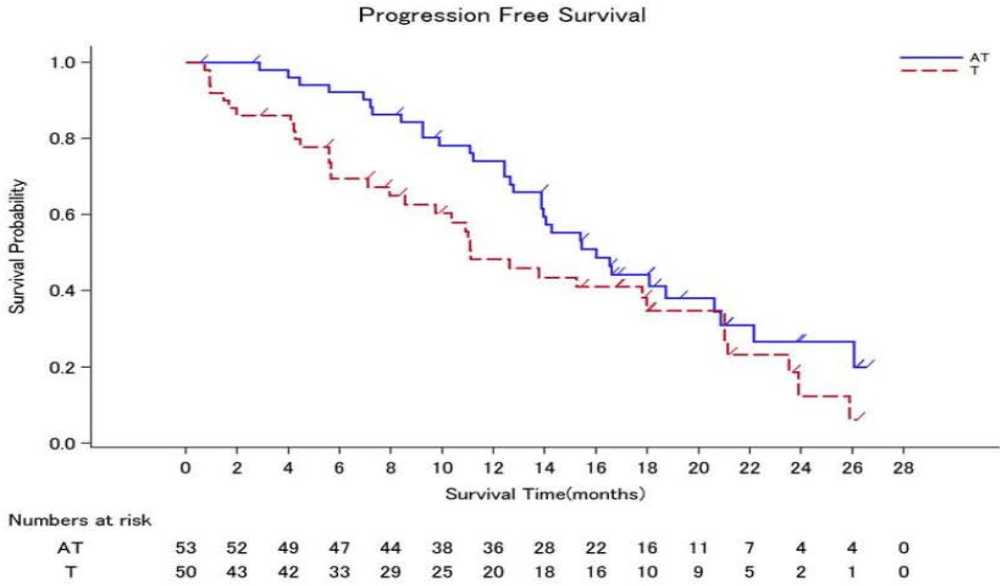
Number of subject(%)

Table 18: Response rate of each of peak severity of rash (more than grade 2 and other) (FAS/Committee evaluation) - Study JO25567

	More than Grade 2		Other	
	AT	T	AT	T
Analyzed number of subject	53(100.0%)	50(100.0%)	22(100.0%)	27(100.0%)
Number of responders	41(77.4%)	34(68.0%)	11(50.0%)	15(55.6%)
Number of non-responders	12(22.6%)	16(32.0%)	11(50.0%)	12(44.4%)
95% confidence interval of response rate	[63.8;87.7]	[53.3;80.5]	[28.2;71.8]	[35.3;74.5]
P-value (Fisher's exact test)	0.3761		0.7777	
CR (Complete Response)	3(5.7%)	1(2.0%)	0(0.0%)	0(0.0%)
Rate of 95% confidence interval	[1.2;15.7]	[0.1;10.6]	[0.0;15.4]	[0.0;12.8]
PR (Partial Response)	38(71.7%)	33(66.0%)	11(50.0%)	15(55.6%)
Rate of 95% confidence interval	[57.7;83.2]	[51.2;78.8]	[28.2;71.8]	[35.3;74.5]
SD (Stable Disease)	11(20.8%)	10(20.0%)	11(50.0%)	9(33.3%)
Rate of 95% confidence interval	[10.8;34.1]	[10.0;33.7]	[28.2;71.8]	[16.5;54.0]
PD (Progressive Disease)	0(0.0%)	6(12.0%)	0(0.0%)	0(0.0%)
Rate of 95% confidence interval	[0.0;6.7]	[4.5;24.3]	[0.0;15.4]	[0.0;12.8]
NE (Not Evaluable)	1(1.9%)	0(0.0%)	0(0.0%)	3(11.1%)
Rate of 95% confidence interval	[0.0;10.1]	[0.0;7.1]	[0.0;15.4]	[2.4;29.2]

Number of subject(%)

Grade 2 or higher



Other

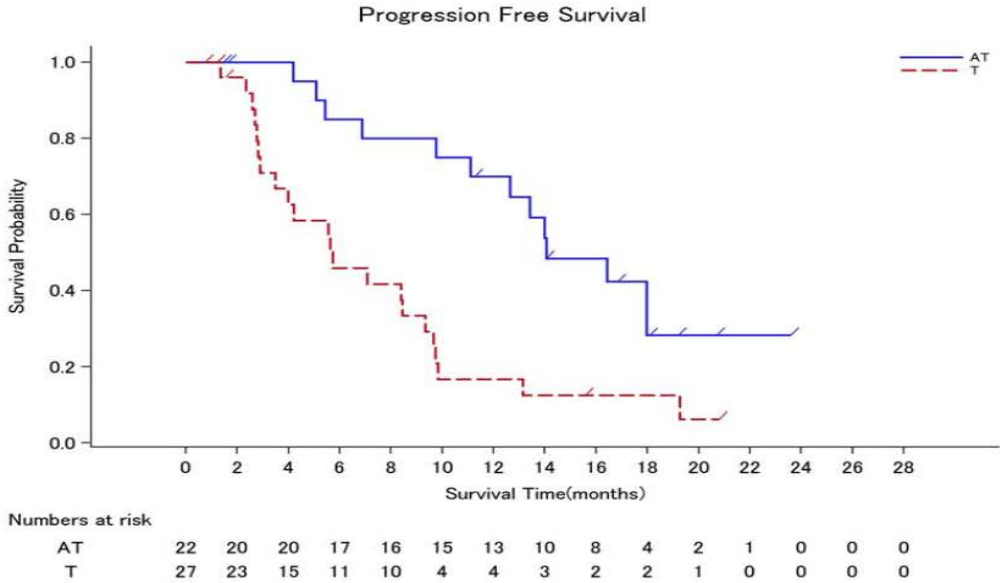


Figure 7: PFS of each of peak severity of rash (more than grade 2 and other) (FAS/Committee evaluation) - Study JO25567

Summary of main study

The following table summarises the efficacy results from the main study 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 19: Summary of Efficacy for trial JO25567

Title: Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations : an open-label, randomised, multicentre, phase 2 study	
Study identifier	JO25567
Design	Open-label, multi-center, randomized, comparative study

	Duration of main phase:		February 15, 2011 to March 4, 2014
Hypothesis	Superiority		
Treatments groups	AT (Erl+Bv)		Bv 15 mg/kg q3w IV + Erl 150 mg/day, n = 75 patients
	T (Erl)		Erl 150 mg/day, n= 77 patients.
Endpoints and definitions	Primary endpoint	PFS by IRC	Progression-free survival by blinded review by IRC.
	Secondary endpoint	OS	Overall Survival
	Secondary endpoint	Tumour response	Response rate, disease control rate and duration of response
	Secondary endpoint	QoL	Improvement of symptoms and QOL based on FACT-L questionnaire
Database lock	30 June 2013		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	AT (Erl+Bv)	T (Erl)
	Number of subject	N = 75	N = 77
	PFS (median in months)	16	9.7
	95% CI	13.9, 18.1	5.7, 11.1
	OS (median in months)	Data not mature	Data not mature
	Response rate (number of subjects (%))	52 (69.3%)	49 (63.6%)
	Disease control rate (number of subjects (%))	74 (98.7%)	68 (88.3%)
	Duration of response (median in months, 95%CI)	13.3 (11.6, 16.5)	9.3 (6.9, 13.8)
Effect estimate per comparison	Primary endpoint – PFS	Comparison groups	AT (Erl+Bv) vs. T (Erl)
		Hazard ratio	0.54
		95%CI	0.36, 0.79
		P-value	0.0015
	Secondary endpoint – OS (data not mature)	Comparison groups	AT (Erl+Bv) vs. T (Erl)
		Hazard ratio	0.75
		95%CI	0.37, 1.53
		P-value	0.4234
	Secondary endpoint – Response rate	Comparison groups	AT (Erl+Bv) vs. T (Erl)
		Fischer's exact test	p-value = 0.4951
	Secondary endpoint – Disease control rate	Comparison groups	AT (Erl+Bv) vs. T (Erl)
		Fischer's exact test	p-value = 0.0177
	Secondary endpoint – Duration of response	Comparison groups	AT (Erl+Bv) vs. T (Erl)
		Hazard ratio	0.68
		95%CI	0.43, 1.10
		p-value	0.1118

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive study(ies)

- Study OSI3364g: A Phase III, multicenter, placebo-controlled, double-blind, randomized clinical trial to evaluate the efficacy of bevacizumab in combination with erlotinib compared with erlotinib alone for treatment of advanced NSCLC after failure of standard first-line chemotherapy.

Patients with advanced NSCLC who had experienced clinical or radiographic progression during or after standard first-line chemotherapy or chemo-radiotherapy were randomized to receive either Erl (150 mg daily orally) plus placebo or Erl (150 mg daily orally) plus Bv (15 mg/kg IV q3w), until disease progression or unmanageable toxicity. All patients were followed for survival until death, loss to follow-up, or study termination.

The primary objective of the study was to evaluate the efficacy of Erl+Bv relative to Erl monotherapy, as measured by OS. Secondary objectives were PFS, ORR, duration of response, safety and pharmacokinetics (PK). The possible relationship between exploratory biomarkers including EGFR mutations and efficacy outcomes was also investigated.

A total of 636 (317 in the Erl+Pl arm, 319 in the Erl+Bv arm) patients were enrolled into this study. In the subgroup of 25 patients with activating EGFRmut+ tumours (13 in the Erl+Pl arm, 12 in the Erl+Bv arm), some differences were apparent between the two arms; a lower proportion of females, ECOG PS 0 and 'never smokers' and the higher proportion of patients ≥ 65 years in the Erl+Pl arm; see Section 3.1 for details. Overall, 64% of patients were Caucasian.

The results of the primary analysis showed a similar OS in both treatment arms (stratified HR 0.970; 95% CI 0.80, 1.18; p = 0.7583). The median OS was 9.2 months (95% CI 7.85, 11.60) in the Erl+Pl arm vs 9.3 months (95% CI 7.39, 11.47) in the Erl+Bv arm. One year survival rates were also similar in the two arms (42.1% in the Erl+Bv arm vs 40.7% in the Erl+Pl arm).

With respect to PFS, the risk of disease progression or death was reduced by 38% in the Erl+Bv arm compared to the Erl+Pl arm (stratified HR 0.62; 95% CI 0.52, 0.75; log-rank p-value = <0.0001). The median PFS was 1.7 months Erl+Pl vs 3.4 months Erl+Bv. The ORR was 12.6% with Erl+Bv compared with 6.2% for Erl+Pl. For patients with an objective response, the median duration of response was 9.7 months in the Erl+Bv arm vs 8.4 months in the Erl+Pl arm.

In the activating EGFRmut+ subgroup of 25 patients (13 Erl+Pl vs 12 Erl+Bv), the observed unstratified HR for OS was 0.47 (95% CI 0.11, 2.00); the KM estimated median OS was 20.2 months in the Erl+Pl arm and not reached in the Erl+Bv arm. Compared with Erl+Pl, treatment with Erl+Bv resulted in a 39% reduction in the risk of disease progression or death (unstratified HR: 0.61; 95%CI 0.21, 1.78), which is consistent with the HR observed in the ITT population. The median PFS was 11.0 months in Erl+Pl arm vs 17.1 months in Erl+Bv arm.

Study BO20571: A Phase II study of erlotinib in combination with bevacizumab versus chemotherapy plus bevacizumab in first-line advanced NSCLC patients

This was an open-label, multicentre, randomized, 2-arm study in patients with advanced non-squamous NSCLC without prior systemic chemotherapy for stage IIIB/IV or recurrent disease.

Patients were randomized on a 1:1 basis to either Erl+Bv or chemotherapy + Bv (CT+Bv) using the following stratification factors: region (Western Europe vs Eastern Europe vs other region), smoking status (current smoker vs past smoker vs never smoked), gender and tumour histology (adenocarcinoma vs other histology). In the Erl+Bv arm, Erl was given orally at a dose of 150 mg daily and Bv at 15 mg/kg IV q3w until disease progression. Patients in the CT+Bv arm received four to six cycles of a standard platinum-containing regimen (gemcitabine/cisplatin or carboplatin/paclitaxel) plus Bv (15 mg/kg q3w IV).

The primary efficacy parameter was PFS (RECIST version 1.0) with tumour assessments scheduled every 6 weeks for the first 8 cycles and then every 12 weeks thereafter.

This study was terminated prematurely as results from the first interim analysis (data cut-off 17 September 2008) indicated inferior PFS for patients in the Erl+Bv arm compared with the CT+Bv arm (HR 2.17; 95% 0.88; 5.34) which was confirmed in an updated interim analysis (data cut-off 6 January 2009; HR 2.05; 95% CI [1.11; 3.77]). The duration of follow-up was extended in order to observe more events, specifically for the subgroup of patients with EGFRmut+ tumours for whom a longer duration of OS was expected. The efficacy results presented for patients with activating EGFRmut+ tumours are based on the final analysis.

A total of 124 (61 CT+Bv vs 63 Erl+Bv) patients were enrolled into this study. The EGFRmut+ subgroup comprised 24 patients (11 CT+Bv vs 13 Erl+Bv). The median age was 58 years in the CT+Bv arm and 60 years in the Erl+Bv arm. In the overall activating EGFRmut+ population, the majority (83%) was Asian, men and women were equally distributed and all patients had good performance status at baseline (ECOG PS 0 or 1). Adenocarcinoma (88%) was the predominant histologic type reported. Overall, the study arms were generally well balanced except that the Erl+Bv arm had more past/current smokers than the CT+Bv arm (46% vs 27%, respectively).

At the final analysis, 73% (8/11) of patients in the CT+Bv arm vs 69% (9/13) in the Erl+Bv arm had experienced a PFS event. Relative to the CT+Bv arm, the risk of disease progression or death was reduced by 60% in the Erl+Bv arm (HR 0.40, 95%CI 0.13-1.19]). The KM-estimated median was 11.0 in the CT+Bv arm and 16.4 months in the Erl+Bv arm.

Study SAKK 19/05: Bevacizumab and erlotinib as first-line therapy in advanced non-squamous non-small-cell lung cancer (stage IIIB/IV) followed by platinum-based chemotherapy at disease progression: A multicenter phase II trial.

Knowledge of EGFR status was not required at study entry. Patients were scheduled to receive erlotinib (150 mg po daily) plus bevacizumab (15 mg/kg q3w IV) until disease progression or unacceptable toxicity. Upon disease progression, patients received 6 cycles of a standard platinum-containing regimen (gemcitabine [1250 mg/m2]/cisplatin [80 mg/m^2] or gemcitabine [1250 mg/m^2]/carboplatin [AUC 5]).

The primary endpoint for the study was IRC assessed disease stabilization rate (DSR; defined as CR, PR or SD) after 12 weeks of Erl+Bv treatment according to RECIST version 1.0. Secondary endpoints included DSR at 6 and 18 weeks, objective response, best ORR, AE, time to progression, time to treatment failure and QoL. Overall survival was assessed for both treatment phases.

QoL was assessed using the Lung Cancer Symptom Scale (LCSS), with the addition of one global indicator to assess patients' estimation of overall treatment burden.

Of the 101 evaluable patients, 12 (12%) had activating EGFR mutation tumours (exon 19 deletion or exon 21 L858R). In the overall evaluable population of 101 patients, the majority had stage IV disease (86%) with adenocarcinoma being the most common cancer histologic type (89%). The median age of patients was 65 years (range 32-80 years) and most of the patients were former/current smokers (67%). The gender distribution was balanced (52.5% women vs 47.5% men) and all patients had good functional status at baseline (ECOG PS 0 [52.5%] or 1 [47.5%]).

In the 12 patients with activating EGFR mutation tumours, the DSR at 12 weeks was 83.3% (10/12). Of the 10 patients with at least SD at 12 weeks, one patient had CR, five patients had a PR and four patients had SD. The median TTP was 11.1 months (95% CI 1.3 – 15.4 months) and the median OS was not reached. One-year and 2-year OS rates were 83% and 71%, respectively.

2.4.3. Discussion on clinical efficacy

No dose response study was conducted to support this extension of indication which is considered acceptable as there is no rationale for a change in dose based on EGFR mutation status. The tolerability of concomitant use of erlotinib 150 mg/day and bevacizumab 15 mg/kg/3 weeks was confirmed in previous studies (NCT00043823 and OSI2950g).

Design and conduct of clinical studies

Overall, the inclusion and exclusion criteria of the pivotal study are considered adequate. The inclusion criteria clearly define the patient population. Patients with T790M mutation of exon 20 were excluded. Furthermore, it seems that patients with symptomatic as well as asymptomatic progression were eligible. However, no patients with ECOG PS of 2 or higher were included in the pivotal study. This is reflected in the SmPC, Section 5.1. The posology as proposed for the study is considered tolerable and in line with current practice.

The objectives are considered clinically relevant. The primary endpoint was PFS by IRC, which is acceptable in a first-line setting. Secondary endpoints included OS, tumour response and QoL.

The sample size, with >70 patients in each group, is acceptable. The level of power (80%) is considered low, but acceptable and in accordance with the ICH guideline E9. However, the level of significance (one-sided alfa=20%) may be considered low, but not unusual in phase II studies. The risk of a false-positive result is considerably higher compared to standard alfa = 5% in phase III studies.

The MAH has used dynamic allocation, which is less preferred as discussed in the CHMP guideline on adjustment for baseline covariates (EMA/295050/2013). Nevertheless, it is considered reasonable for this specific study in order to avoid small strata. It seems unlikely that a selection bias could have had any impact on the patient allocation. This is supported by the fact that the deterministic part of the algorithm was never used, and it seems also unlikely that the individual sites would have had knowledge about all other sites in order to predict the next patient's allocation. The stratification factors are few and reasonable.

During the conduct of the study the protocol was amended 12 times. None of these are considered critical.

The majority of the patients are female, and the median age is 67 years in both groups. The mean Brinkman index is higher in the Erl + Bv group, meaning that these patients had a higher consumption of cigarettes but the groups seem to be well-balanced with regard to smoking status (non-smoker, former, other).

There is a difference in terms of initial date of diagnosis to the first day of administration, and also with regard to the period from the date of diagnosis of recurrence to the first day of administration. Patients in the Erl group seem to have a longer period from diagnosis to treatment. However, sensitivity analyses show that these differences did not have any major effect on the primary endpoint.

The included patients were solely Japanese. This may raise some concerns regarding the validity and generalizability of the results to a Western population. However, there is robust scientific evidence to support the claim that EGFR activating mutations (exon 19 deletions and L858R) in tumours of Asian and Caucasian NSCLC patients are sufficiently similar to justify extrapolation of the results from the Japanese study JO25567 to Caucasians. The effect of bevacizumab in different ethnic groups has been investigated in several clinical trials. So far there has not been any indication of a treatment difference depending on ethnicity. Studies OPTIMAL, EURTAC and ENSURE have previously demonstrated that the

EGFR mutations is the main driver of treatment effect, thus, allowing an extrapolation between Japanese (Asians) and Caucasians patients.

Distribution of exon 19 deletion and exon 21 L858R seems to be well balanced between treatment arms, and a sensitivity analysis excluding these patients from the PFS analysis, indicate that the HR and the 95%CI remain unchanged. Thus, these patients do not seem have any impact on the overall PFS estimate.

The currently validated testing to identify patients, for whom first-line treatment with erlotinib is considered appropriate, is based on polymerase chain reaction (PCR) detection of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. In this context, the cobas EGFR Mutation Test, based on PCR analysis of DNA extracted from patient tumour tissue, has been validated through CE-marking in the EU. This test is also approved by the FDA. The results from the concordance study WO29921 confirmed that there is concordance between the three main assay types (PNA-LNA PCR-Clamp, PCR Invader, and Cycleave) used in study JO25567 and the cobas test.

Efficacy data and additional analyses

Study JO25567 met its primary endpoint. The primary endpoint, PFS by IRC, shows a clear difference in favour of the Erl+Bv group. The median PFS is 16.0 months vs. 9.7 months. The HR is 0.54 (95%CI: 0.36; 0.79). The difference is both statistically and clinically significant. Treatment with Erl+Bv provides a longer period without progression, thus, prolonging the time to second-line therapy. However, having in mind that the population represents the same population as one would expect in a clinical setting and in a phase III study with the same primary endpoint, there is a reasonable biological rationale for observing the difference in PFS. The p-value for the HR is highly statistically significant.

PFS by exon 21 L858R mutation and exon 19 deletion are in line with the overall estimate. However, the difference in PFS in patients with exon 21 L858R is not statistically significant. This is mainly due to small numbers.

The subgroup analysis shows that the point estimate for all the different subgroups is below 1, and thus in line with the overall estimate. However, due to small number of patients in some subgroups, wide confidence intervals are observed, but no firm conclusion can be drawn with regard to these subgroups.

Looking at PFS by mutation status, patients with exon 19 deletion seems to have a greater effect of Erl+Bv. There has been some discussion in the scientific community whether the efficacy of EGFR-TKIs differs between exon 19 deletion and exon 21 L858R mutation. There seems to be some evidence/indications that exon 19 deletion might the associated with longer PFS (Jackman et al. (2006), Riely et al. (2006), Sun et al. (2011)).

It is well-known that skin rash due treatment with erlotinib is associated with good response. It may be somewhat problematic to interpret the data since both groups are treated with erlotinib. With regard to PFS the addition of Bv to Erl does not have any major detrimental effect on the good response associated with skin rash. There seems to be an advantage of adding Bv to Erl with regard to response rates. Patients with Grade > 2 rash seems to have higher response rates and much higher disease control. The addition of Bv to Erl does not seem to have a detrimental effect on the good response associated with skin rash in patients treated with Erl. In the primary endpoint PFS by IRC, patients were censored due to unconfirmed PD, withdrawal or continuation at data cut-off, and there are no apparent differences between treatment arms. Furthermore, the PFS by investigator supports PFS by IRC. Thus, the censoring of patients in the two treatment groups do not seem to have any major impact on the overall results, and do not seem to be biased.

With regard to the secondary endpoints, there seems to be no difference in OS between the two groups. The OS data is still considered immature at present due to the limited number of deaths. At the cut-off date of 7 November 2014 there were 27 deaths in each arm (36.0% of the patients in the Erl + Bv arm vs. 35.1% in the Erl arm). HR was 1.04 (95% CI 0.61; 1.77). Based on the further updated OS data (cut-off 28 October 2015) there seems to be no detrimental effect of bevacizumab on OS. However, data are still not mature. In addition, the multitude of additional lines of treatment and anti-cancer agents used (e.g. patients in the Erl-arm could also receive Bv) makes the interpretation of the OS data even more uncertain.

However, the MAH should submit mature OS data from Study JO25567 by June 2018, as an imposed post authorisation efficacy study to the marketing authorization as the initial efficacy assessment is based on surrogate endpoints. In addition, the MAH should discuss any further outcome data on the combination of bevacizumab + erlotinib in this indication (e.g. data from the ongoing ACCRU study, NCT number NCT01532089) (see Annex II).

A slight difference in favour of the Erl+Bv group with regard to overall response is observed, but the actual difference in number of patients is very small. Although one would expect a significant increase in response rate by the addition of bevacizumab to erlotinib, this was not observed. However, the response rate in both groups is considered high (64% in erl vs. 69% in Erl+Bv). But more importantly the duration of response was 13.3 months in Erl+Bv group compared to 9.3 months in erl group. This difference is considered clinically relevant and correlates very well with PFS data. Thus, it seems that the effect of erlotinib is maintained for a longer time with the addition of bevacizumab, and this is of clinical importance in a disease with a very aggressive course. The observed difference in PFS is clinically highly relevant, the point estimate is robust, and the study has met its primary endpoint. The observed median PFS in the Erl group is in line with previous findings.

With regard to QoL, there seems to be no clinically significant difference between the two groups. Thus, apparently the addition of Bv to Erl do not seem to have a detrimental effect on the QoL. However, since study JO25567 is an open-label study, the reliability of these data is questionable.

Three supportive studies are presented; OSI3364g, BO20571 and SAKK 19/05. The SAKK 19/05 study is not randomized. Only OSI3364g is a phase III double-blinded study. All studies were in first-line except for OSI3364g, which was in second-line setting. None of the supportive studies conducted a prospective EGFR mutation testing. Gender and smoking status were the only common stratification factors in the randomized studies. With regard to PFS, the observed results support the findings in study JO25567. However, a direct comparison is not possible, due to several differences between the studies. Nonetheless, it is encouraging to see supportive evidence from these studies.

2.4.4. Conclusions on the clinical efficacy

Study JO25567 met its primary endpoint. The primary endpoint, PFS by IRC, shows a clear difference in favour of the Erl+Bv group. The difference is both statistically and clinically significant. Treatment with Erl+Bv provides a considerable longer period without progression, thus, prolonging the time to second-line therapy. There seems to be no detrimental effect of bevacizumab + erlotinib on OS, however, data are not mature yet. In addition, the multitude of additional lines of treatment and anti-cancer agents used (e.g. patients in the Erl-arm could also receive Bv) makes the interpretation of the OS data even more uncertain.

The CHMP considers the following measure necessary to address issues related to efficacy:

Post authorisation efficacy study (PAES): In order to address the uncertainty regarding the survival advantage of bevacizumab in combination with erlotinib compared to erlotinib alone in the first-line

treatment of patients with non-squamous NSCLC harbouring EGFR activating mutations, the MAH should submit mature overall survival data for study JO25567 (due date: Q2 2018)

In addition, the MAH should discuss any further outcome data on the combination of bevacizumab + erlotinib in this indication (e.g. data from the ongoing ACCRU study, NCT number NCT01532089) (due date: Q4 2018).

2.5. Clinical safety

Introduction

Because of differences in trial designs (including studies with different comparator regimens compared with Study JO25567) and in order to be able to assess safety in patients of different ethnicity/race, it was not considered clinically meaningful to provide pooled integrated displays of the safety data from the pivotal Study JO25567 compared with the key supporting studies BO20571, AVF3671g, and OSI3364g. However, where feasible and appropriate, side-by-side displays of safety data from the different studies are presented for ease of comparison and identification of common characteristics of the safety profile across studies that employed a combination arm of bevacizumab and erlotinib.

Pivotal dataset from Study JO25567 is based on the clinical data cutoff date of 31 March 2014, which is an update from the cutoff date of 30 June 2013 of the primary CSR to provide an additional 9 months of safety follow-up.

Patient exposure

Table 20: Overview of bevacizumab exposure

			GLOBAL STUDIES – Patients not selected on basis of EGFR mutation status					
	Pivotal Study JO25567		BO20571 – 1st-line		AVF3671g – maintenance after 1st-line CT + Bv		OSI3364g – 2nd-line	
	Erl (n = 77)	Erl + Bv (n = 75)	CT + Bv (n = 61)	Erl + Bv (n = 63)	Pl + Bv (n = 378)	Erl + Bv (n = 382)	Erl + Pl (n = 313)	Erl + Bv (n = 313)
Median cumulative dose (mg)	NA	13410	7635	6750	3765	4731	NA	3960
Range	NA	737-46184	870-43850	960-57675	4-42140	705-44400	NA	690-65520
Median duration of exposure (days)	NA	325.0	NR	NR	64.0	72.0	NA	NR
Range	NA	1-1053	NR	NR	1-645	1-631	NA	NR
Median number of cycles/infusions received	NA	16.0	8.0	6.0	4.0	4.0	NA	4.0
Range	NA	1-50	1-36	1-45	1-30	1-30	NA	1-47
Median relative dose intensity [a] (%)	NA	93.7	NR	NR	NR	NR	NA	NR
Range	NA	68.9-99.7	NR	NR	NR	NR	NA	NR

Bv = bevacizumab; CT = chemotherapy; EGFR = epidermal growth factor receptor; Erl = erlotinib; mg = milligrams; NA = not applicable; NR = not reported; PD = disease progression.

[a] Defined as actual total dose received for the total treatment duration / planned total dose to be administered for the total treatment duration (Expressed as a percent).

[b] In Study OSI3364g, 44.9% of patients had received prior radiotherapy.

Table 21: Overview of erlotinib exposure

	Pivotal Study JO25567		GLOBAL STUDIES – Patients not selected on basis of EGFR mutation status					
			BO20571 – 1st-line		AVF3671g – maintenance after 1st-line CT + Bv		OSI3364g – 2nd-line	
	Erl (n = 77)	Erl + Bv (n = 75)	CT + Bv (n = 61)	Erl + Bv (n = 63)	Pl + Bv (n = 378)	Erl + Bv (n = 382)	Erl + Pl (n = 313)	Erl + Bv (n = 313)
Median cumulative dose (mg)	29750	51750	NA	19800	NA	10825	6600	11700
Range	2700-138450	2700-158700	NA	1650-104100	NA	114-91200	150-123000	900-134350
Median duration of exposure (days)	254.0	431.0	NA	NR	NA	85.0	48.5	84.0
Range	18-1075	21-1065	NA	NR	NA	1-649	1-835	1-1007
Median relative dose intensity [a] (%)	98.0	95.3	NA	150 [b]	NA	NR	NR	NR
Range	33.3-100	34.0-100	NA	32-150 [b]	NA	NR	NR	NR
Median period of withholding erlotinib (days)	8.0	19.0	NA	NR	NA	NR	NR	NR
Range	0-64	0-88	NA	NR	NA	NR	NR	NR
No. (%) patients dose reduced to 100 mg erlotinib	34 (44.2)	35 (46.7)	NA	18 (29)	NA	95 (25.7) [c]	25 (8.0)	49 (15.7)
No. (%) patients dose reduced to 50 mg erlotinib	9 (11.7)	17 (22.7)	NA	2 (3)	NA	see above	7 (2.2)	17 (5.4)

Bv = bevacizumab; CT = chemotherapy; Erl = erlotinib; EGFR = epidermal growth factor receptor; mg = milligrams; NA = not applicable; NR = not reported; PD = disease progression.

[a] Defined as actual total dose received for the total treatment duration / planned total dose to be administered for the total treatment duration. (Expressed as a percent).

[b] Statistics referring to patient's individual mean doses.

[c] Reported as any reduction- not provided by dose-level reductions.

The median duration of erlotinib exposure in the Erl+Bv arm is 431 days in study JO25567. A similar number of patients in both groups had a dose reduction to 100 mg erlotinib. The exposure to Erl+Bv may be considered adequate to allow evaluation of the safety profile. Few patient continued treatment beyond 18-20 months. Otherwise, a comparable number of patients are exposed to study treatment throughout the study duration.

Adverse events

The observed safety profile in studies supporting this application is described in the table below.

Table 22: Overview of key adverse event data across studies (safety analysis population)

	Pivotal Study JO25567		GLOBAL STUDIES – Patients not selected on basis of EGFR mutation status					
			BO20571 – 1st-line		AVF3671g – maintenance after 1st-line CT + Bv		OSI3364g – 2nd-line	
Number (%) Patients	Erl (n = 77)	Erl + Bv (n = 75)	CT + Bv (n = 60)	Erl + Bv (n = 63)	Pl + Bv (n = 378)	Erl + Bv (n = 382)	Erl + Pl (n = 313)	Erl + Bv (n = 313)
All Grade AE	77 (100)	75 (100)	59 (98)	60 (95)	349 (92)	373 (98)	309 (99)	312 (100)
Grade ≥ 3 AE	41 (53)	68 (91)	38 (63)	34 (54)	145 (38)	207 (54)	165 (53)	208 (67)
SAE	19 (25)	19 (25)	22 (37)	17 (27)	75 (20)	107 (28)	114 (36)	130 (42)
AE leading to discontinuation [a]	14 (18)	34 (45)	7 (12)	5 (8)	NR	NR	NR	NR
AE leading to Bv/Pl discontinuation	—	32 (43)	NR	NR	62 (16)	74 (19)	42 (13)	75 (24)
AE leading to Erl/Pl discontinuation	14 (18)	13 (17)	NR	NR	53 (14)	77 (20)	37 (12)	56 (18)
Deaths								
All causes	25 (33)	27 (36)	28 (46)	33 (52)	180 (48)	173 (45)	207 (66)	202 (65)
Non-PD/other	2 (3)	1 (1)	3 (5)	3 (5)	3 (1)	7 (2)	22(7)	19(6)
Any AE	1 (1)	0 (0)	2 (3)	2 (3)	18 (5)	17 (4)	14 (5)	20 (6)

Grade ≥ 3 AESIs for Bv/Pl *								
Hypertension	9 (11.7)	46 (61.3)	2 (3.3)	2 (3.2)	25 (7)	29 (8)	4 (1)	15 (5)
Proteinuria	0 (0)	6 (8.0)	3 (5.0)	5 (7.9)	12 (3)	13 (3)	0 (0)	4 (1)
VTE	2 (2.6)	1 (1.3)	5 (8.3)	4 (6.3)	7 (2)	6 (2)	16 (5)	16 (5)
ATE	1 (1.3)	2 (2.7)	2 (3.3)	1 (1.6)	6 (2)	11 (3)	1 (<1)	12 (4)
Bleeding/Hemorrhage	0 (0)	2 (2.7)	2 (3.3)	2 (3.2)	8 (2)	11 (3)	7 (2)	10 (3)
Neutropenia	1 (1.3)	0 (0)	16 (26.2)	0 (0)	4 (1)	3 (1)	NR	NR
CHF	0 (0)	0 (0)	2 (3.3)	1 (1.6)	1 (<1)	4 (1)	2 (1)	3 (1)
GI Perforation	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	3 (1)	2 (1)	3 (1)
Wound healing complication	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	2 (1)	0 (0)	0 (0)
PRES or RPLS	0 (0)	0 (0)	1 (1.7)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)
Grade ≥ 3 AESIs for Erl/Pl *	16 (20.8)	19 (25.3)	NR	NR	NR	NR	NR	NR
Rash	15 (19.5)	18 (24.0)	NA	14 (22)	2 (1)	32 (8)	10 (3)	30(10)
Diarrhea	1 (1.3)	2 (2.7)	NA	1 (1.6)	7 (2)	40 (11)	31 (10)	26 (8)
Interstitial lung disease	1 (1.3)	0 (0)	NA	0 (0)	0 (0)	3 (1)	2 (1)	2 (1)

AESI = adverse event of special interest, Bv = bevacizumab, CT = platinum-based chemotherapy, Erl = erlotinib, NR = not reported, Pl = placebo.

Includes AEs starting during or up to 28 days after stopping treatment (for all studies),and AESIs starting any time during or up to 6 months after stopping treatment (other than in study JO25567).

Multiple occurrences of the same AE in one individual counted only once.

* Based on groups of preferred terms for the AESI.

AE leading to discontinuation[a]: Discontinuation of at least one component of trial treatment (in Study JO25567).

Common AEs

Table 23: Overview across studies of All-grade adverse events occurring with a ≥10% higher incidence in the Erl+Bv arm than in Erl Arm (safety analysis population) - JO25567

			GLOBAL STUDIES – Patients not selected on basis of EGFR mutation status					
	Pivotal Study JO25567		BO20571 – 1st-line		AVF3671g – maintenance after 1st-line CT + Bv		OSI3364g – 2nd-line	
Number (%) Patients	Erl (n = 77)	Erl + Bv (n = 75)	CT + Bv (n = 60)	Erl + Bv (n = 63)	Pl + Bv (n = 378)	Erl + Bv (n = 382)	Erl + Pl (n = 313)	Erl + Bv (n = 313)
Paronychia	50 (64.9)	59 (78.7)	1 (1.7)	8 (12.7)	2 (0.5)	18 (4.7)	4 (1.3)	11 (3.5)
Hypertension	11 (14.3)	58 (77.3)	14 (23.3)	19 (30.2)	96 (25.4)	106 (27.7)	27 (8.6)	79 (25.2)
Dry skin	45 (58.4)	56 (74.7)	1 (1.7)	8 (12.7)	29 (7.7)	56 (14.7)	59 (18.8)	63 (20.1)
Proteinuria	2 (2.6)	35 (46.7)	9 (15.0)	12 (19.0)	29 (7.7)	41 (10.7)	8 (2.6)	18 (5.8)
Epistaxis	7 (9.1)	35 (46.7)	22 (36.7)	9 (14.3)	35 (9.3)	54 (14.1)	31 (9.9)	63 (20.1)
Weight decreased	19 (24.7)	33 (44.0)	4 (6.7)	4 (6.3)	24 (6.3)	49 (12.8)	41 (13.1)	65 (20.8)

Multiple occurrences of the same AE in one individual counted only once. AE = adverse event, Bv = bevacizumab, CT = platinum-based chemotherapy, Erl = erlotinib, PD = progressive disease, Pl = placebo.

Includes AEs starting during or up to 28 days after stopping treatment (for all studies),and AESIs starting any time during or up to 6 months after stopping treatment (other than in study JO25567).

Grade ≥ 3 AEs

There is a considerable difference in the overall number of patients experiencing a Grade ≥ 3 AEs; 68 (90.7%) in the Erl+Bv group vs. 41 (53.2%) in the Erl group in Study JO25567. There are slightly more infections in the Erl+Bv group, but no clear pattern is observed. There are considerable more patients experiencing hypertension in the Erl+Bv group, which is expected. As it will be discussed later, there are very few discontinuations due to hypertension. Dermatitis acneiform is more commonly seen in the Erl+Bv group. There are slightly more hepatobiliary disorders in the Erl group. An updated analysis with clinical cutoff of date of 31 March 2014 did not show any relevant changes or differences.

An overview of Grade ≥3 AEs with a ≥2% higher incidence in the Erl+Bv group than in the Erl group showed an excess of AEs in the Erl+Bv arm, primarily driven by a large difference in hypertension. Only one Grade 5 AE occurred (drowning), and it was observed in the Erl group. Seven Grade 4 AEs were observed in the Erl group compared to 1 in the Erl+Bv group. The incidence of Grade 3 AEs is

higher in the Erl+Bv group, and seems to be explained by the higher exposure to bevacizumab.

Table 24: Overview of Grade ≥ 3 adverse events in study JO25567

NCICTC-Adverse Event Grade	Erl (N = 77) No. (%)[a]	Erl + Bv (N = 75) No. (%)[a]
Grade ≥ 3	41 (53.2)	68 (90.7)
Grade 3	33 (42.9)	67 (89.3)
Grade 4	7 (9.1)	1 (1.3)
Grade 5	1 (1.3)	0

Bv = bevacizumab; Erl = erlotinib.
[a]:Number of patients with at least one adverse event.
Note: Multiple occurrences of the same adverse event in one individual are counted once at the highest grade for that patient.**Error! Reference source not found.**

Adverse Events of Special Interest (AESIs)

Table 25: Incidence of all grade adverse events of special interest for bevacizumab or erlotinib in studies JO25567, BO20571, AVF3671g and OSI3364g (safety analysis population)

			GLOBAL STUDIES – Patients not selected on basis of EGFR mutation status					
	Pivotal Study JO25567		BO20571 – 1st-line		AVF3671g – maintenance after 1st-line CT+Bv		OSI3364g – 2nd-line	
Number (%) Patients	Erl (n = 77)	Erl + Bv (n = 75)	CT + Bv (n = 60)	Erl + Bv (n = 63)	Pl + Bv (n = 378)	Erl + Bv (n = 382)	Erl + Pl (n = 313)	Erl + Bv (n = 313)
All Grade AESIs for Bv [a]								
Bleeding/Hemorrhage	22 (28.6)	54 (72.0)	26 (43.3)	14 (22.2)	66 (17.5)	81 (21.2)	71 (22.7)	112 (35.8)
Pulmonary hemorrhage/hemoptysis	1 (1.3)	7 (9.3)	4 (6.7)	2 (3.2)	19 (5.0)	18 (4.7)	18 (5.8)	26 (8.3)
Hypertension	11 (14.3)	59 (78.7)	14 (23.3)	19 (30.2)	96 (25.4)	106 (27.7)	29 (9.3)	82 (26.2)
Proteinuria	3 (3.9)	41 (54.7)	9 (15.0)	12 (19.0)	31 (8.2)	43 (11.3)	8 (2.6)	21 (6.7)
ATE	1 (1.3)	2 (2.7)	2 (3.3)	3 (4.8)	6 (1.6)	14 (3.7)	2 (0.6)	12 (3.8)
VTE	2 (2.6)	1 (1.3)	6 (10.0)	4 (6.3)	9 (2.4)	7 (1.8)	20 (6.4)	16 (5.1)
Wound healing complication	1 (1.3)	0 (0)	1 (1.7)	0 (0)	5 (1.3)	8 (2.1)	1 (0.3)	4 (1.3)
Cardiac disorders/cardiovascular	2 (2.6)	0 (0)	NR	NR	35 (9.3)	36 (9.4)	27 (8.6)	29 (9.3)
Neutropenia	2 (2.6)	0 (0)	21 (34.4)	0 (0)	7 (1.9)	12 (3.1)	2 (0.6)	5 (1.6)
Peripheral sensory neuropathy	3 (3.9)	6 (8.0)	3 (4.9)	0 (0)	9 (2.4)	20 (5.2)	7 (2.2)	6 (1.9)
Anaphylaxis and hypersensitivity	1 (1.3)	1 (1.3)	1 (1.6)	0 (0)	1 (0.3)	3 (0.8)	6 (1.9)	3 (1.0)
CHF	0 (0)	1 (1.3)	2 (3.3)	1 (1.6)	2 (0.5)	5 (1.3)	5 (1.6)	4 (1.3)
PRES/RPLS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.5)	0 (0)	2 (0.6)
GI perforation	0 (0)	0 (0)	1 (1.7)	1 (1.6)	0 (0)	7 (1.8)	2 (0.6)	3 (1.0)
All Grade AESIs for Erl [a]								
Rash	77 (100)	74 (98.7)	9 (15.0)	40 (63.5)	94 (24.9)	252 (66.0)	250 (79.9)	269 (85.9)
Diarrhea	61 (79.2)	61 (81.3)	15 (25.0)	27 (42.9)	82 (21.7)	206 (53.9)	182 (58.1)	213 (68.1)
Interstitial lung disease	3 (3.9)	2 (2.7)	0 (0)	0 (0)	1 (0.3)	5 (1.3)	6 (1.9)	6 (1.9)

AESI = adverse event of special interest, Bv = bevacizumab, CHF = congestive heart failure, CT = platinum-based chemotherapy, Erl = erlotinib, GI = gastrointestinal; Pl = placebo, PRES = posterior reversible encephalopathy syndrome, RPLS = reversible posterior leukoencephalopathy syndrome.
[a] Based on groups of preferred terms for the AESI.

AESI collected in JO25567 (cutoff: June 30, 2013)

• Erlotinib : Rash, ILD (interstitial lung disease), haemorrhagic events, paronychia, diarrhoea

• Bevacizumab : Haemorrhagic event, haemoptysis, hypertension, proteinuria

Adverse events of interest (Rash)

RASH occurred in a total of 85 events in 74 out of 75 subjects in the Erl + Bv group and in a total of 86 events in 77 out of 77 subjects in the Erl group. Adverse drug reactions to erlotinib occurred in 74

subjects (98.7%) in the Erl+Bv group and 76 subjects (98.7%) in the Erl group, and adverse drug reactions to bevacizumab occurred in 56 subjects (74.7%) in the Erl + Bv group. Rash of Grade ≥ 3 was seen in 18 subjects (24%) in the Erl+Bv group and 15 subjects (19.5%) in the Erl group. Rash categorized as a serious adverse event occurred in 1 subject (1.3%) in the Erl+Bv group, and was not seen in the Erl group. Rash that resulted in treatment discontinuation of erlotinib occurred in 2 subjects (2.7%) in the Erl+Bv group, and that resulted in treatment discontinuation of bevacizumab occurred in 1 subjects (1.3%) in the Erl+Bv group.

Adverse events of interest (ILD)

ILD occurred in a total of 2 events in 2 out of 75 subjects in the ErlL+Bv group and in a total of 3 events in 3 out of 77 subjects in the Erl group. Adverse drug reactions to erlotinib occurred in 2 subjects (2.7%) in the Erl+Bv group and 3 subjects (3.9%) in the Erl group, and adverse drug reactions to bevacizumab occurred in 1 subject (1.3%) in the Erl+Bv group. ILD of Grade ≥3 occurred in 1 subject (1.3%) in the Erl group, and was not seen in the Erl+Bv group. ILD categorized as a serious adverse event occurred in 2 subjects (2.7%) in the Erl+Bv group and 3 subjects (3.9%) in the Erl group. ILD that resulted in treatment discontinuation of erlotinib occurred in 2 subjects (2.7%) in the Erl+Bv group and 3 subjects (3.9%) in the Erl group, and that resulted in treatment discontinuation of bevacizumab occurred in 1 subject (1.3%) in the Erl+Bv group.

Adverse events of interest (haemorrhagic events)

Haemorrhagic event occurred in a total of 74 events in 54 out of 75 subjects in the Erl+Bv group and in a total of 25 events in 22 out of 77 subjects in the Erl group. Adverse drug reactions to erlotinib occurred in 39 subjects (52.0%) in the Erl+Bv group and 20 subjects (26.0%) in the Erl group, and adverse drug reactions to bevacizumab occurred in 49 subjects (65.3%) in the Erl+Bv group. Haemorrhagic event of more than Grade 3 occurred in 2 subjects (2.7%) in the Erl+Bv group, and was not seen in the Erl group. Haemorrhagic event categorized as a serious adverse event occurred in 2 subjects (2.7%) in the Erl+Bv group, and was not seen in the Erl group. No subjects were seen for whom administration of Erlotinib was discontinued due to haemorrhagic events, but the number of subjects for whom administration of bevacizumab was discontinued in the Erl+Bv group was 9 subjects (12.0%).

Adverse events of interest (paronychia)

Paronychia occurred in a total of 57 events in 59 out of 75 subjects in the Erl+Bv group and in a total of 50 events in 50 out of 77 subjects in the Erl group. Adverse drug reactions to erlotinib occurred in 57 subjects (76.0%) in the Erl+Bv group and 50 subjects (64.9%) in the Erl group, and adverse drug reactions to bevacizumab occurred in 38 subjects (50.7%) in the Erl+Bv group. Paronychia of more than Grade 3 was seen in 2 subjects (2.7%) in the Erl+Bv group and 3 subjects (3.9%) in the Erl group. Paronychia categorized as a serious adverse event was not seen. No subjects were seen for whom administration of erlotinib or bevacizumab was discontinued due to paronychia.

Adverse events of interest (diarrhoea)

Diarrhoea occurred in a total of 61 events in 61 out of 75 subjects in the Erl+Bv group and in a total of 60 events in 61 out of 77 subjects in the Erl group. Adverse drug reactions to erlotinib occurred in 59 subjects (78.7%) in the Erl+Bv group and 60 subjects (77.9%) in the Erl group, and adverse drug reactions to bevacizumab occurred in 46 subjects (61.3%) in the Erl+Bv group. Diarrhoea of Grade ≥3 was seen in 1 subject (1.3%) in the Erl+Bv group and 1 subjects (1.3%) in the Erl group. Diarrhoea categorized as a serious adverse event was not seen. No subjects were seen for whom administration of erlotinib or bevacizumab was discontinued.

Adverse events of interest (haemoptysis)

Haemoptysis occurred in a total of 7 events in 7 out of 75 subjects in the Erl+Bv group and in a total of 1 event in 1 out of 77 subjects in the Erl group. Adverse drug reactions to erlotinib occurred in 3 subjects (4.0%) in the Erl+Bv group and 0 subjects (0.0%) in the Erl group, and adverse drug reactions to bevacizumab occurred in 5 subjects (6.7%) in the Erl+Bv group. Haemoptysis of Grade ≥3 was not seen. Haemoptysis categorized as a serious adverse event was not seen. No subjects were seen for whom administration of erlotinib or bevacizumab was discontinued due to haemoptysis.

Adverse events of interest (hypertension)

Hypertension occurred in a total of 57 events in 57 out of 75 subjects in the Erl+Bv group and in a total of 10 events in 10 out of 77 subjects in the Erl group. Adverse drug reactions to rrlotinib occurred in 38 subjects (50.7%) in the Erl+Bv group and 10 subjects (13.0%) in the Erl group, and adverse drug reactions to bevacizumab occurred in 57 subjects (76.0%) in the Erl+Bv group. Hypertension of Grade ≥3 was seen in 45 subjects (60.0%) in the Erl+Bv group and 8 subjects (10.4%) in the Erl group. Hypertension categorized as a serious adverse event was not seen. No subjects were seen for whom administration of erlotinib was discontinued due to hypertension, but the number of subjects for whom administration of bevacizumab was discontinued in the Erl+Bv group was 2 subjects (2.7%).

Adverse events of interest (proteinuria)

Proteinuria occurred in a total of 39 events in 39 out of 75 subjects in the Erl+Bv group and in a total of 3 events in 3 out of 77 subjects in the Erl group. Adverse drug reactions to erlotinib occurred in 21 subjects (28.0%) in the Erl+Bv group and 2 subjects (2.6%) in the Erl group, and adverse drug reactions to bevacizumab occurred in 38 subjects (50.7%) in the Erl+Bv group. Proteinuria of Grade ≥3 occurred in 6 subjects (8.0%) in the Erl+Bv group, and was not seen in the Erl group. Proteinuria categorized as a serious adverse event was not seen. No subjects were seen for whom administration of erlotinib was discontinued due to proteinuria, but the number of subjects for whom administration of bevacizumab was discontinued in the Erl+Bv group was 11 subjects (14.7%).

Serious adverse event / deaths / other significant events

Deaths

In Study JO25567, the only AE leading to death seen during the clinical trial was one patient (1.3%) in the Erl arm who died due to drowning during the clinical trial period. No patient in the Erl+Bv group died due to an AE. The patient in the Erl group was a 67 year-old female and the drowning event occurred on Day 40 since start of erlotinib administration. Although unknown whether the death was an accident or suicide, the investigator assessed that the causal relationship with erlotinib was “unlikely related.”

The primary cause of PD-related deaths was not recorded. With regard to non-PD related deaths, there were only 3 cases: in the Erl+Bv group one patient died of pneumocystis pneumonia, in the Erl group one patient died due to drowning and one patient died due to thrombosis.

Serious Adverse Events (SAEs)

The overall incidence of SAEs was 25.3% vs. 24.7%, in Erl+Bv group and Erl group respectively. There is a tendency to more infections in the Erl+Bv arm, but no apparent pattern could be observed. One case of cancer (pancreatic cancer) was observed in the Erl+Bv group. On the other hand two cases of neoplasms (lipoma and nasal cavity cancer) were observed in the Erl group. No conclusions can be drawn based on these few cases. Eight cases of hepatobiliary disorders were observed in the Erl group compared to 0 in the Erl+Bv group. 5 out of 8 were classified as “hepatic function abnormal”.

Laboratory findings

Table 26: Summary of Newly Occurring Grade 3 and 4 Laboratory Test Values during Treatment (Safety Population)

	Erl (n = 77)		Erl + Bv (n = 75)	
Number (%) Patients	Grade 3	Grade 4	Grade 3	Grade 4
Hematology				
Low Hemoglobin	2 (2.6)	0	1 (1.3)	0
Low White blood cell (WBC)	0	0	0	0
Low Platelets	0	0	0	0
Differentials				
Low Neutrophils	2 (2.6)	0	0	0
Low Lymphocytes	4 (5.2)	1 (1.3)	2 (2.7)	0
Coagulation				
High PT, normalized ratio	1 (1.3)	0	0	0
High APTT (Ac. Part. Thrombopl.)	0	0	0	0
Liver Function				
High Alkaline Phosphatase	6 (7.8)	0	0	0
High ALAT (SGPT)	6 (7.8)	7 (9.1)	3 (4.0)	1 (1.3)
High ASAT (SGOT)	9 (11.2)	1 (1.3)	2 (2.7)	0
High Total Bilirubin	2 (2.6)	0	0	0
High Gamma Glutamyltransferase	5 (6.5)	1 (1.3)	3 (4.0)	0
Miscellaneous				
High Total Cholesterol	0	0	1 (1.3)	0
Renal Function				
High Serum Creatinine	0	0	0	0
Protein				
Low Albumin	1 (1.3)	0	1 (1.3)	0
Electrolytes				
Low Potassium	1 (1.3)	0	4 (5.3)	0
Low Sodium	0	1 (1.3)	0	0
Low Phosphate	0	0	4 (5.3)	0
Low Calcium	0	0	0	0
Urinalysis				
Urine Protein	0	0	0	0
Uric Acid	0	0	0	0

ALAT (SGPT) = alanine aminotransferase; APTT = activated partial thromboplastin time; ASAT (SGOT) = aspartate aminotransferase; Bv = bevacizumab; Erl = erlotinib; PT = prothrombin time; WBC = white blood cell.

Vital signs, physical findings and other observations related to safety

Blood pressure

In Study JO25567, hypertension (including increase in blood pressure) as an AE was seen in 59 patients (78.7%) in the Erl + Bv arm and 11 patients (14.3%) in the Erl arm. Throughout the clinical trial period, diastolic blood pressure tended to be somewhat higher in the Erl + Bv arm, but with systolic blood pressure, no marked changes in median values were seen in either arm at any point during the clinical trial period.

Body weight

Decrease in body weight as an AE was seen in 33 patients (44.0%) in the Erl + Bv arm and 19 patients (24.7%) in the Erl arm. No marked changes were seen in either arm at any point during the clinical trial period.

Other vital signs

No marked changes were seen in either arm at any point during the clinical trial period with respect to any of the other vital signs.

Other studies

In Study BO20571, vital signs (weight, diastolic blood pressure, systolic blood pressure and pulse rate) were summarized for the overall safety analysis population (absolute values and changes from baseline) and these data did not raise any safety concerns.

In Study AVF3671g, clinically significant abnormalities for vital signs, physical findings, and other observations related to safety were reported as AEs and summarized as the appropriate AE category.

In Study OSI3364g, vital signs were taken at baseline and every 3 weeks during infusion. Each of the groups showed a slight increase from baseline in mean diastolic and systolic blood pressures. The mean diastolic blood pressure among Erl + Bv patients was approximately 1−3 mmHg higher than that among Erl + Pl patients, and the mean systolic blood pressure among Erl + Bv patients was approximately 5−10 mmHg higher than that among Erl + Pl patients. These observations were consistent with the AE reporting of blood pressure increased under the MedDRA system organ class term of Investigation) in 6 patients (1.9%) in the Erl + Bv arm versus in 1 patient (0.3%) in Erl + Pl arm and of hypertension in 79 patients (25.2%) in the Erl + Bv arm versus in 27 patients (8.6%) in the Erl + Pl arm.

Safety in special populations

Male patients have a higher incidence of AEs than females, however, no differences in the AE pattern is observed between males and females. With regard to “age”, there seems to be higher incidence of SAE in elderly (>75 years) in the Erl+Bv group. This difference was not observed in the Erl group. However, the number of patients over 75 years is low in both groups.

With regard to ECOG, patients with PS 0 experienced more Grade>=3 AEs in Erl+Bv group, while patients with ECOG PS 1 experienced more Grade ≥3 AEs in the Erl group. The main drivers are hypertension and proteinuria. Both AEs are known AESIs related to the use of bevacizumab.

With regard to AE profile as function of smoking, no clinically relevant differences could be observed.

Safety related to drug-drug interactions and other interactions

Overall, the pharmacokinetics drug-drug interaction (PK-DDI) data available to date for bevacizumab given in combination with erlotinib (described below) do not suggest a potential for a PK-DDI between bevacizumab and erlotinib. Therefore, safety concerns are not expected from pharmacokinetic interaction between bevacizumab and erlotinib.

Discontinuation due to adverse events

In Study JO25567, discontinuation of one component of study treatment did not necessitate discontinuation of both drugs. The higher proportion of patients with AEs leading to discontinuation of study treatment in the Erl+Bv arm (Erl: 18.2% vs. Erl+Bv: 45.3%) was primarily driven by proteinuria and hemorrhagic events (epistaxis and haemorrhoidal haemorrhage).

There were no new safety findings, but a considerable number of patients in the Erl+Bv withdrew from Bv because of AEs. However, patients in the Erl+Bv arm received a median of 15.5 cycles of bevacizumab, which is considered a relatively high exposure. Having this in mind, the observed difference in withdrawal rate must somewhat be expected.

In the Erl+Bv group there was 34 AEs that led to the discontinuation of bevacizumab. Twenty-one of the 34 AEs are resolved or resolving. The unresolved events were related to proteinuria.

There are more AEs leading to discontinuation in patients older than 65 years. However, there is no difference in AE pattern between age groups.

There seems to be more AEs in elderly patients, but the AEs pattern is comparable between different age groups.

Adverse Events that Led to Dose Modification or Interruption

A total of 27 patients (36.0%) in the Erl+Bv group experienced an AE leading to withholding of bevacizumab. The AEs were both AESIs related to bevacizumab and erlotinib. A similar number of patients in both groups experienced an AE that led to erlotinib dose reduction. Slightly more patients (44(57.1%) vs. 51(68%)) in the Erl+Bv group experienced an AE that led to withholding of erlotinib.

Overall, there are more dose modifications and interruptions in the Erl+Bv group. However, this may also be expected when combining these two treatments.

The main reasons for dose interruption in the Erl+Bv group were hypertension, proteinuria, rash, dermatitis, haemoptysis, periodontal disease and paronychia. None of the events of proteinuria resolved and only 80% of the events of hypertension resolved. The majority of the rest of AEs resolved.

The most common AEs leading to erlotinib dose modification or interruption were skin and nail disorders. These AEs were most likely to stay unresolved with sequalae. However, these AEs can be treated in the clinical setting and often patients continue treatment.

Post marketing experience

Bevacizumab in combination with intravenous 5-fluorouracil–based chemotherapy for the first-line treatment of patients with metastatic carcinoma of the colon or rectum was approved in the United States on 26 February 2004 and in the EU on 12 January 2005. The total number of patients exposed to bevacizumab in the postmarketing setting, across indications, from the International Birth Date (IBD) up to 25 February 2015 is estimated to be approximately 2,048,911 patients.

2.5.1. Discussion on clinical safety

Duration of safety follow-up in the pivotal and supporting studies was until resolution or up to 28-30 days after the last dose of study treatment. The duration of safety follow-up is considered acceptable.

All the common AEs are well-known and clinically manageable. Exposure adjusted incidence of dermatitis and paronychia show that in the case of paronychia it seems that the addition of Bv to Erl leads to an increased incidence. The Applicant has reflected this in the SmPC.

The overall number of patients with Grade ≥3 **AEs** is higher in the Erl+Bv group. There are slightly more infections in the Erl+Bv group, but no clear pattern is observed. There are considerable more patients experiencing hypertension in the Erl+Bv group, which is expected, however, there are very few discontinuations due to hypertension. Other common AEs are paronychia and dermatitis acneiform, which mostly are associated with erlotinib, but seems to occur more frequently in the Erl+Bv group. Hypertension, proteinuria, epistaxis and decreased weight, which are mainly associated with bevacizumab, are also seen frequently in the Erl+Bv group.

The incidence of all grade **AESI** for Bv and Erl show some clear differences. There are considerably more bleedings, hypertension and proteinuria in the Erl+Bv group. With regard to AESI related to Erl there are no major differences between the two groups. Thus, the main differences are driven by AESI related to bevacizumab. Both erlotinib and bevacizumab are associated with GI perforation. However, the combination of these two products do not seem to increase the number of GI perforation.

Most Grade ≥3 AESI are related to hypertension, proteinuria and rash. No events of GI perforation, PRLS, wound healing complications and CHF are observed. Very few events of ATE and VTE are observed.

Rash is a well-known AESI that is associated with good response to erlotinib. No major differences were seen in the overall number of AEs, SAEs and in treatment discontinuation. The addition of bevacizumab to erlotinib does not seem to have a detrimental effect with regard to this prognostic AESI.

The addition of erlotinib to bevacizumab seems to lead to an increased number of haemorrhagic events. However, most of the bleeding events were Grade 1-2 epistaxis, and in most cases the event was manageable and did not lead to discontinuation of bev. Only two Grade 3 AEs haemorrhagic events were observed in the Erl+Bv group. The bleeding events did not have any major clinical implications. In addition, this fact should be seen in light of the higher exposure to study treatments in the Erl+Bv group.

Concerning hypertension, only 2 events led to treatment discontinuation, which reflects the fact that this event is clinically manageable. The majority of the hypertension AEs had a peak severity of Grade ≥3. The Applicant has revised the SmPC to reflect the findings in study JO25567. Patients with prior hypertension are at increased risk of developing proteinuria. Eleven (11) patients discontinued treatment and 6 patients experienced a peak severity of Grade ≥ 3 proteinuria. With regard to AESI related to Erl there are no major differences between the two groups. Thus, the main differences are driven by AESIs related to bevacizumab. No events of GI perforation, PRLS, wound healing complications and CHF are observed. Very few events of ATE and VTE are observed. This is reassuring. No AESIs led to death.

The majority of **deaths** across all studies were due to disease progression. In the pivotal Study JO25567: No patients died in the Erl + Bv arm due to an AE. The only AE leading to death seen during this clinical trial was one patient (1.3%) in the Erl arm who died due to drowning during the clinical trial period.

The incidence of **SAEs** was similar between the Erl + Bv and Erl treatment arms (Erl: 24.7% vs. Erl + Bv: 25.3%) in Study JO25567.

Male patients seem to have more AEs, but the AE profile is comparable between genders. There are too few patients over 75 years to draw any conclusion. A divergent picture is observed with regard to ECOG score between the two groups, but the main drivers are hypertension and proteinuria, which are known AESIs related to bevacizumab.

Overall, the AEs leading to dose modification or interruption are well-known AESIs related to Bv or Erl. The unresolved AEs are well-known and well-characterised, and reflected in the SmPC. These AEs are often clinically manageable.

There were no new safety findings, but a considerable number of patients in the Erl+Bv withdrew from Bv because of AEs. However, patients in the Erl+Bv arm received a median of 15.5 cycles of bevacizumab, which is considered a relatively high exposure. Having this in mind, the observed difference in withdrawal rate must somewhat be expected. In the Erl+Bv group there was 34 AEs that led to the discontinuation of bevacizumab. Twenty-one of the 34 AEs are resolved or resolving. The unresolved events were related to proteinuria.

Overall, males seem to have more AEs, but the AE profile is comparable between genders. There are too few patients over 75 years to draw any conclusion. A divergent picture is observed with regard to

ECOG score between the two groups, but the main drivers are hypertension and proteinuria, which are known AESIs related to bevacizumab.

2.5.2. Conclusions on clinical safety

There were no new safety findings, but the incidence rate for some of these AEs and the discontinuation rate was higher in the combination group. The reason(s) for this high incidence rate is most likely due to longer exposure to study treatments in the Erl+Bv group. No imbalance in deaths was observed in the pivotal study, in the Erl+Bv arm vs Erl arm. The safety findings are in general clinically manageable and do not give rise to any major concern.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 23.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and/or CHMP.

The CHMP endorsed the Risk Management Plan version 26.0 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Summary of safety concerns	
Important identified risks	Bleeding / hemorrhage Pulmonary hemorrhage Proteinuria Arterial thromboembolic events (ATE) Hypertension Congestive heart failure Wound healing complications Gastrointestinal perforations Posterior reversible encephalopathy syndrome (PRES) Neutropenia Venous thromboembolic events (VTE) Fistula (other than gastrointestinal) Thrombotic microangiopathy Pulmonary hypertension Ovarian failure Hypersensitivity reactions / infusion reactions Gall bladder perforation Peripheral sensory neuropathy Cardiac disorders (excluding CHF and ATE) Osteonecrosis of the jaw Necrotizing fasciitis Adverse events following off-label intravitreal use Embryo-fetal development disturbance

Summary of safety concerns	
	Osteonecrosis in children
Important potential risks	-
Missing information	Safety profile of the different treatment combinations in patients with non-squamous NSCLC Long-term effects of bevacizumab when used in the pediatric population Safety and efficacy in patients with renal impairment Safety and efficacy in patients with hepatic impairment Use in lactating women

Pharmacovigilance plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
Biomarker investigation 1	Identification and selection of a more targeted population of patients most likely to benefit from the combination of Avastin and paclitaxel in the treatment of first-line metastatic breast cancer.	None	Ongoing	Annually
BO20924 (BERNIE) 3	Assess safety and efficacy in pediatric patients	~~Physeal dysplasia~~ Long-term effects of bevacizumab when used in the pediatric population.	On-going	Q1 2017
Obtain long term follow up information from studies in the pediatric population after patients complete their 5.5 years of follow up in study BO20924 3	Assess safety in pediatric patients	Long-term effects of bevacizumab when used in the pediatric population.	Planned	Protocol submission Q4 2017

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Safety concern	Risk minimization measures	Additional risk minimization measures
Bleeding/ Hemorrhage	EU SPC section 4.4: Patients treated with Avastin have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Avastin should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during Avastin therapy (NCI-CTCAE v.3) (see section 4.8). Patients with untreated CNS metastases were routinely excluded from clinical trials with Avastin, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patients has not been prospectively evaluated in randomised clinical trials (see section 4.8). Patients should be monitored for signs and symptoms of CNS bleeding, and Avastin treatment discontinued in cases of intracranial bleeding. There is no information on the safety profile of Avastin in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting Avastin treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with a full dose of warfarin and Avastin concomitantly (NCI-CTCAE v.3). Labelled in section 4.8 of the EU SPC	None proposed
Pulmonary hemorrhage	EU SPC section 4.4: Patients with non-small cell lung cancer treated with Avastin may be at risk of serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/ haemoptysis (> 2.5 ml of red blood) should not be treated with Avastin.	None proposed
Proteinuria	EU SPC section 4.4: Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with Avastin. There is evidence suggesting that all Grade (US National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-	None proposed

Safety concern	Risk minimization measures	Additional risk minimization measures
	CTCAE (version 3.0)]) proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with Avastin. Therapy should be permanently discontinued in patients who develop ~~Grade 4 proteinuria~~ (nephrotic syndrome~~)~~ (NCI-CTCAE v.3). Labelled in section 4.8 of the EU SPC.	
Arterial thromboembolic events	EU SPC section 4.4: In clinical trials, the incidence of arterial thromboembolic reactions including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) was higher in patients receiving Avastin in combination with chemotherapy compared to those who received chemotherapy alone. Patients receiving Avastin plus chemotherapy, with a history of arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic reactionsduring therapy. Caution should be taken when treating these patients with Avastin. Therapy should be permanently discontinued in patients who develop arterial thromboembolic reactions. Labelled in section 4.8 of the EU SPC.	None proposed
Hypertension	EU SPC section 4.4: An increased incidence of hypertension was observed in Avastin-treated patients. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre existing hypertension should be adequately controlled before starting Avastin treatment. There is no information on the effect of Avastin in patients with uncontrolled hypertension at the time of initiating therapy. Monitoring of blood pressure is generally recommended during therapy. In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. Avastin should be permanently discontinued if medically	None proposed

Safety concern	Risk minimization measures	Additional risk minimization measures
	significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy. Labelled in section 4.8 of the EU SPC.	
Congestive heart failure	EU SPC section 4.4: Reactions consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with Avastin. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present. In patients in AVF3694g who received treatment with anthracyclines and who had not received anthracyclines before, no increased incidence of all Grade CHF was observed in the anthracycline + bevacizumab group compared to the treatment with anthracyclines only. CHF Grade 3 or higher reactions were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with results in patients in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment (NCI-CTCAE v.3). Labelled in section 4.8 of the EU SPC.	None proposed
Wound healing complications	EU SPC section 4.4: Avastin may adversely affect the wound healing process. Serious wound healing complications, including anastomotic complications, with a fatal outcome have been reported. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery. Labelled in section 4.8 of the EU SPC. ~~In addition, definition in glioblastoma study~~	None proposed

Safety concern	Risk minimization measures	Additional risk minimization measures
	~~protocols of in- and exclusion criteria (e.g. time between surgical procedures or traumatic injury and initiation of bevacizumab therapy), and not permitted concomitant treatment (e.g. craniotomy, intratumoral interstitial therapy, radiosurgery).~~	
Gastrointestinal perforations	EU SPC section 4.4: *Gastrointestinal perforations and Fistulae (see section 4.8)* Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with Avastin. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Prior radiation is a risk factor for GI perforation in patients treated for persistent, recurrent or metastatic cervical cancer with Avastin and all patients with GI perforation had a history of prior radiation. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation. *GI-vaginal Fistulae in study GOG-0240* Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin are at increased risk of fistulae between the vagina and any part of the GI tract (Gastrointestinal-vaginal fistulae). Prior radiation is a major risk factor for the development of GI-vaginal fistulae and all patients with GI-vaginal fistulae had a history of prior radiation. Recurrence of cancer within the field of prior radiation is an additional important risk factor for the development of GI-vaginal fistulae. Labelled in section 4.8 of the EU SPC Description of selected serious adverse reactions *Gastrointestinal (GI) perforations and Fistulae* (see section 4.4) Avastin has been associated with serious cases of gastrointestinal perforation. Gastrointestinal perforations have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer or non-squamous non-small cell lung cancer, up to 2.0% in patients with metastatic renal cell cancer or in patients with ovarian cancer receiving front-line treatment, and up	None proposed

Safety concern	Risk minimization measures	Additional risk minimization measures
	to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), GI perforations (all grade) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation The occurrence of these events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumour necrosis, diverticulitis, or chemotherapy-associated colitis. Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforations, which represents between 0.2%-1% of all Avastin treated patients. In Avastin clinical trials, gastrointestinal fistulae (all grade) have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer, but were also reported less commonly in patients with other types of cancer. *GI-vaginal Fistulae in study GOG-0240* In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of GI-vaginal fistulae was 8.3% in Avastin treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. The frequency of GI-vaginal fistulae in the group treated with Avastin + chemotherapy was higher in patients with recurrence within the field of prior radiation (16.7%) compared with patients with recurrence outside the field of prior radiation (3.6%). The corresponding frequencies in the control group receiving chemotherapy alone were 1.1% vs. 0.8%, respectively. Patients who develop GI-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies.	
Posterior Reversible Encephalopathy Syndrome(PRES)	EU SPC section 4.4: There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with PRES, a rare neurologic disorder, which can present with the following signs and symptoms among	None proposed

Safety concern	Risk minimization measures	Additional risk minimization measures
	others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of Avastin. The safety of reinitiating Avastin therapy in patients previously experiencing PRES is not known. Labelled in section 4.8 of the EU SPC.	
Neutropenia	EU SPC section 4.4: Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus Avastin in comparison to chemotherapy alone. This has mainly been seen in combination with platinum- or taxane-based therapies in the treatment of NSCLC, mBC, and in combination with paclitaxel and topotecan in persistent, recurrent, or metastatic cervical cancer.. Labelled in sections 4.5 and 4.8 of the EU SPC.	None proposed
Venous thromboembolic events	EU SPC section 4.4: Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under Avastin treatment. Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin in combination with paclitaxel and cisplatin ~~with Avastin~~ may be at increased risk of venous thromboembolic events. Avastin should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism (NCI-CTCAE v.3). Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored (NCI-CTCAE v.3). Labelled in section 4.8 of the EU SPC. Grade 3-5 (NCI-CTCAE v.3) venous thromboembolic reactions have been reported in up to 7.8% of patients treated with chemotherapy plus bevacizumab compared with up to 4.9% in patients treated with chemotherapy alone (across indications, excluding persistent, recurrent, or metastatic cervical cancer). From a clinical trial in patients with persistent,	None proposed

Safety concern	Risk minimization measures	Additional risk minimization measures
	recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 venous thromboembolic events have been reported in up to 15.6% of patients treated with Avastin in combination with paclitaxel and cisplatin compared with up to 7.0% ~~in~~ of patients treated with paclitaxel and cisplatin.	
Fistula (other than gastrointestinal)	EU SPC section 4.4: *Non-GI Fistulae (see section 4.8)* Patients may be at increased risk for the development of fistulae when treated with Avastin. Permanently discontinue Avastin in patients with tracheoesophageal (TE) fistula or any Grade 4 fistula [US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v.3)]. Limited information is available on the continued use of Avastin in patients with other fistulae. In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of Avastin should be considered. EU SPC Section 4.8 *Non-GI Fistulae (see section 4.4)* Avastin use has been associated with serious cases of fistulae including reactions resulting in death. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (GOG-240), 1.8% of Avastin treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae. Uncommon (≥ 0.1% to < 1%) reports of fistulae that involve areas of the body other than the gastrointestinal tract (e.g. bronchopleural and biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience. Reactions were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of Avastin, with most reactions occurring within the first 6 months of therapy.	None proposed
Thrombotic microangiopathy	Labelled in section 4.8 of the EU SPC.	None proposed
Pulmonary hypertension	Labelled in section 4.8 of the EU SPC.	None proposed
Ovarian failure	Section 4.4 of the EU SPC states: Avastin may	None proposed

Safety concern	Risk minimization measures	Additional risk minimization measures
	impair female fertility (see sections 4.6 and 4.8). Therefore fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with Avastin. Section 4.6 of the EU SPC states: Avastin may impair female fertility (see sections 4.6 and 4.8). Therefore fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with Avastin. Labelled in section 4.8 of the EU SPC.	
Hypersensitivity reactions and Infusion Reactions	EU SPC section 4.4: Patients may be at risk of developing infusion/hypersensitivity reactions. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanised monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted. Labelled in section 4.8 of the EU SPC.	None proposed
Gall Bladder perforations	EU SPC section 4.4: *Gastrointestinal (GI) perforations and Fistulae (see section 4.8)* Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with Avastin. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Prior radiation is a risk factor for GI perforation in patients treated for persistent, recurrent or metastatic cervical cancer with Avastin and all patients with GI perforation had a history of prior radiation. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation. Labelled in section 4.8 of the EU SPC.	None proposed
Peripheral sensory neuropathy	Labelled in section 4.8 of the EU SPC. Some of the adverse reactions are reactions commonly seen with chemotherapy; however, Avastin may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysaesthesia syndrome with pegylated	None proposed

Safety concern	Risk minimization measures	Additional risk minimization measures
	liposomal doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, ~~and~~ nail disorders or alopecia with paclitaxel, and paronychia with erlotinib.	
Cardiac disorders (excl. CHF and ATE)	Supraventricular tachycardia is labelled in section 4.8 of the EU SPC.	None proposed
Osteonecrosis of the Jaw	EU SPC section 4.4 Cases of ONJ have been reported in cancer patients treated with Avastin, the majority of whom had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when Avastin and intravenous bisphosphonates are administered simultaneously or sequentially. Invasive dental procedures are also an identified risk factor. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with Avastin. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible. Labelled in section 4.8 of the EU SPC.	None proposed
Necrotizing fasciitis	EU SPC section 4.4 *Wound healing complications* Avastin may adversely affect the wound healing process. Serious wound healing complications, including anastomotic complications, with a fatal outcome have been reported. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery. Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with Avastin. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Avastin therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated. Labelled in section 4.8 of the EU SPC.	None proposed
Adverse events following off-label intravitreal use of bevacizumab	EU SPC section 4.4 *Intravitreal use* Avastin is not formulated for intravitreal use.	None proposed

Safety concern	Risk minimization measures	Additional risk minimization measures
	Eye disorders Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of Avastin compounded from vials approved for intravenous administration in cancer patients. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness. Systemic effects following intravitreal use A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse reactions including non-ocular haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors.	
Embryo-fetal development disturbance	Text in SPC Section 4.6 Fertility, pregnancy and lactation *Women of childbearing potential* Women of childbearing potential have to use effective contraception during (and up to 6 months after) treatment. *Pregnancy* There are no clinical trial data on the use of Avastin in pregnant women. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). IgGs are known to cross the placenta, and Avastin is anticipated to inhibit angiogenesis in the foetus, and thus is suspected to cause serious birth defects when administered during pregnancy. In the postmarketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.8). Avastin is contraindicated in pregnancy. Section 4.8 of the EU SPC: Foetal abnormalities are labeled as an adverse reaction observed in the postmarketing setting. Labelled in section 5.3 of the EU SPC.	None proposed

Safety concern	Risk minimization measures	Additional risk minimization measures
Ostenecrosis in Children	EU SPC.Section 4.8 *Pediatric Population* The safety of Avastin in children and adolescents has not been established. Avastin is not approved for use in patients under the age of 18 years. In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years treated with Avastin.	None Proposed
Safety profile of the different treatment combinations in patients with non-squamous NSCLC	EU SPC text not applicable.	None proposed
Long-term use in pediatric patients	EU SPC section 4.2: The safety and efficacy of bevacizumab in children and adolescents have not been established. Avastin is not approved for use in patients under the age of 18 years. There is no relevant use of bevacizumab in the paediatric population in the granted indications. Currently available data are described in sections 4.8, 5.1, 5.2 and 5.3 but no recommendation on a posology can be made. Avastin should not be used in children aged 3 years to less than 18 years with recurrent or progressive high-grade glioma because of efficacy concerns (see section 5.1 for results of paediatric trials).	None proposed
Patients with renal impairment	EU SPC section 4.2: safety and efficacy have not been studied in patients with renal impairment. Section 5.2: No trials have been conducted to investigate the pharmacokinetics of bevacizumab in renally impaired patients since the kidneys are not a major organ for bevacizumab metabolism or excretion.	None proposed
Patients with hepatic impairment	EU SPC section 4.2: safety and efficacy have not been studied in patients with hepatic impairment. Section 5.2: No trials have been conducted to investigate the pharmacokinetics of bevacizumab in patients with hepatic impairment since the liver is not a major organ for bevacizumab metabolism or excretion.	None proposed
Use in Lactating Women	Pregnancy is listed as a contraindication in section 4.3 of the EU SPC SPC section 4.6 Fertility, pregnancy and	None proposed

Safety concern	Risk minimization measures	Additional risk minimization measures
	lactation *Breast-feeding* It is not known whether bevacizumab is excreted in human milk. As maternal IgG is excreted in milk and bevacizumab could harm infant growth and development (see section 5.3), women must discontinue breast-feeding during therapy and not breast-feed for at least six months following the last dose of Avastin.	

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Furthermore, the PI is brought in line with the latest QRD template version 10.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable as the changes are limited and considered to have no impact on the legibility of the package leaflet.

3. Benefit-Risk Balance

Benefits

Beneficial effects
Study JO25567 showed a clinically and statistically significant difference in favour of Erl+Bv in the treatment of non-squamous NSCLC in terms of PFS. Treatment with Erl+Bv provides a considerably longer period without progression (median PFS 16.0 months for Erl+Bv versus 9.7 months for Erl).

Uncertainty in the knowledge about the beneficial effects
Based on the updated OS (cut-off 28 October 2015) there seems to be no detrimental effect of Bv on OS. However, due to the multitude of additional lines of treatment and anti-cancer agents used, the OS data is difficult to interpret. In addition, the data are still not mature at this time point, and thus the Applicant is asked to provide mature OS post-approval (see Annex II condition).

Risks

Unfavourable effects
The overall number of patients with Grade ≥3 AEs is higher in the Erl+Bv group (41(53%) vs. 68 (91%)). There are considerably more patients experiencing hypertension in the Erl+Bv group, which is expected, however, there are very few discontinuations due to hypertension. Other common AEs are paronychia and dermatitis acneiform, which are mainly associated with erlotinib, but seem to occur more frequently in the Erl+Bv group. Hypertension, proteinuria, epistaxis and decreased weight, which are mainly associated with bevacizumab, are also seen frequently in the Erl+Bv group.

The addition of erlotinib to bevacizumab seems to lead to an increased number of haemorrhagic events (mostly epistaxis). Eight cases of hepatobiliary disorders were observed in the Erl group compared to 0 in the Erl+Bv group. 5 out of 8 were classified as “hepatic function abnormal”.

Finally, discontinuations due to adverse events are considerably more often observed in the Erl+Bv group. More than one third of the withdrawals in the Erl+Bv group are due to proteinuria and haemorrhage. There are also more dose modifications and interruptions in the Erl+Bv group.

Uncertainty in the knowledge about the unfavourable effects

None

Effects Table

Table 27: Effects Table for Avastin in combination with erlotinib, for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous NSCLC with EGFR activating mutations (data cut-off: 30 June 2013)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence
Favourable Effects					
PFS	Progression-free survival	Median in months	16 (13.9, 18.1)	9.7 (5.7, 11.1)	HR=0.54 (95%CI: 0.36, 0.79), p=0.0015
OS*	Overall survival	Median in months	48.5 (40.2, -)	48.4 (35.3, -)	HR=0.91 (95% CI: 0.56; 1.46), p=0.6838
Unfavourable Effects					
Grade≥3 AEs		N (%)	68 (90.7%)	41 (53%)	
Hypertension		N (%)	59 (78.7%)	11 (14.3%)	
Proteinuria		N (%)	41 (54.7%)	3 (2.9%)	
Bleeding/ haemorrhage		N (%)	54 (72%)	22 (28.6%)	
Discontinuations		N (%)	34 (45.3%)	14 (18.2%)	

*KM estimated at the 28 Oct 2015 data cut-off

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Patients with EGFR-mutated non-squamous NSCLC are often faced with rapid progression and death. The use of TKI targeted at EGFR activating mutations has prolonged PFS and OS. The addition of bevacizumab to erlotinib in the first-line setting seems to prolong PFS even more. Thus, the time to second-line therapy is extended considerably. This is considered of clinical relevance.

The combination of erlotinib and bevacizumab leads to more AEs, discontinuations and dose modifications of treatment. However, the toxicity was generally manageable with dose modification or interruptions. No patient in the Erl+Bv group died due to a treatment-related AE.

Benefit-risk balance

Overall, the benefit-risk balance of bevacizumab in combination with erlotinib in the treatment of EGFR-mutated non-squamous NSCLC patients is considered positive due to the clinically relevant PFS gain, which outweighs the toxicity.

Discussion on the Benefit-Risk Balance

Study JO25567 met its primary endpoint. The primary endpoint, PFS by IRC, shows a clear difference in favour of the Erl+Bv group. The difference is both statistically and clinically significant. Treatment

with Erl+Bv provides a longer period without progression, thus, prolonging the time to second-line therapy. The p-value for the HR is highly statistically significant.

PFS by exon 21 L858R mutation and exon 19 deletion are in line with the overall estimate.

The subgroup analysis of PFS shows that the point estimate for all the different subgroups is below 1. Looking at PFS by mutation status, patients with exon 19 deletion seems to have a greater effect of Erl+Bv. There has been some discussion in the scientific community whether the efficacy of EGFR-TKIs differs between exon 19 deletion and exon 21 L858R mutation. There seems to be some evidence that exon 19 deletion might the associated with longer PFS.

With regard to the secondary endpoints, there is no difference in OS between the two groups. The OS data is considered immature at present due to insufficient follow-up. A slight difference in favour of the Erl+Bv group with regard to overall response is observed, but the actual difference in number of patients is very small. The MAH will provide mature OS data from study JO25567 (see Annex II condition).

Although response rate was quite similar between treatment arms (64% in Erl vs. 69% in Erl+Bv) the duration of response was 13.3 months in Erl+Bv group compared to 9.3 months in Erl group. This difference is considered clinically relevant and correlates very well with PFS data. Thus, it seems that the effect of erlotinib is maintained for a longer time with the addition of bevacizumab, and this is of clinical importance in a disease with a very aggressive course. The observed difference in PFS is clinically relevant, the point estimate is robust, and the study has met its primary endpoint. The observed median PFS in the Erl group is in line with previous findings.

There were no new safety findings, but the incidence rate for some of these AEs and the discontinuation rate was higher in the combination group. The reason(s) for this high incidence rate is most likely due to longer exposure to study treatments in the Erl+Bv group. No imbalance in deaths was observed in the pivotal study, in the Erl+Bvarm vs Erl arm. The safety findings are in general clinically manageable and do not raise major concern.

The CHMP considers the following measures necessary to address issues related to efficacy:

The MAH should submit mature overall survival data for study JO25567 and discuss any further outcome data on the combination of bevacizumab + erlotinib in NSCLC patients with EGFR activating mutations (e.g. data from the ongoing ACCRU study, NCT number NCT01532089) by December 2018.

4. Recommendations

Outcome

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

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

Extension of indication to include the combination of bevacizumab with erlotinib for the first line

treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) activating mutations. As a consequence, sections 4.1, 4.2, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and RMP (v.26) are updated in accordance.

Furthermore, the PI is brought in line with the latest QRD template version 10.

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

This CHMP recommendation is subject to the following amended conditions:

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

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

Description	Due date
The MAH shall investigate suitable biomarkers (including VEGF-A) to allow identification and selection of a more targeted population of patients most likely to benefit from the combination of Avastin and paclitaxel in the treatment of first-line metastatic breast cancer. A report on the research programme should be submitted within 3 months of the Commission Decision. Progress reports should be submitted	On a yearly basis
Post authorisation efficacy study (PAES): In order to address the uncertainty regarding the survival advantage of bevacizumab in combination with erlotinib compared to erlotinib alone in the first-line treatment of patients with non-squamous NSCLC harbouring EGFR activating mutations, the MAH should submit mature overall survival data for study JO25567. In addition, the MAH should discuss any further outcome data on the combination of	June 2018

bevacizumab + erlotinib in this indication (e.g. data from the ongoing ACCRU study, NCT number NCT01532089)	December 2018