17 December 2015
EMA/CHMP/15391/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Portrazza

International non-proprietary name: necitumumab

Procedure No. EMEA/H/C/003886/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event(s) of special interest
ALK	Anaplastic lymphoma kinase
ATE	Arterial thromboembolic events
CI	Confidence interval
CL	Clearance
Cmax	Maximum concentration
CPP	Critical process parameter
CR	Complete response
Ctx	Chemotherapy
CV	Coefficient of variation
DCR	Disease control rate
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
EC50	Half-maximal response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor-1
ELISA	Enzyme-linked immunosorbent assay
Emax	Maximum efficacy
GC	Gemcitabine and cisplatin
GC+N	Gemcitabine and cisplatin plus necitumumab
GLP	Good Laboratory Practice
HR	Hazard ratio
HSR	Hypersensitivity reaction
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IgG1	Immunoglobulin G, subclass 1
ILD	Interstitial lung disease

IRR	Infusion-related reaction
ITT	Intent-to-treat
I.V.	Intravenous
kDa	Kilodalton(s)
LCSS	Lung Cancer Symptom Scale
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
nab	Albumin-bound
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PC	Pemetrexed and cisplatin
PC+N	Pemetrexed and cisplatin plus necitumumab
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PopPK	Population pharmacokinetics
PP	Per protocol
PR	Partial response
PS	Performance status
PT	Preferred Term
SAE	Serious adverse event
SOC	System Organ Class
TEAE	Treatment-emergent adverse event(s)
TGI	Tumour growth inhibition
TKI	Tyrosine-kinase inhibitors
TMDD	Target-mediated drug disposition
TTF	Time to treatment failure
VAS	Visual Analogue Scale
VEGF	Vascular endothelial growth factor

VTE	Venous thromboembolic events

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 1 December 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Portrazza, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: Portrazza in combination with gemcitabine and cisplatin chemotherapy is indicated for first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that necitumumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance necitumumab contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 September 2009 and 13 December 2012. The Scientific Advice pertained to quality and non-clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 1 December 2014.
- The procedure started on 24 December 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 March 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 March 2015.
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 10 April 2015.
- During the meeting on 23 April 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 August 2015.
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 10 September 2015
- During the CHMP meeting on 24 September 2015, the CHMP agreed on a List of Outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 October 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 31 August 2015.
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 6 November 2015
- During the CHMP meeting on 16-19 November 2015, Outstanding Issues were addressed by the applicant during an oral explanation before the CHMP. The CHMP agreed to a 2nd List of Outstanding Issues to be addressed in writing by the applicant
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 24 November 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 3 December 2015.
- During the meeting on 17 December 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Portrazza.

2. Scientific discussion

2.1. Introduction

Lung cancer is the most common cancer in the world (Ferlay et al. 2013). 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). In the EU, lung cancer is ranked as the fourth most frequent cancer; approximately 313,000 new cases were diagnosed in 2012 (Ferlay et al. 2013). 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 E et al 2014; Schrump DS et al. 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).

Non-small cell lung cancer 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)].

Tobacco use is the most important risk factor for lung cancer, with up to 80% of lung cancer patients reporting a history of tobacco use. Approximately 10% to 30% of non-squamous NSCLC occurs in patients with a never smoker history and a strong correlation with the presence of an activating epidermal growth factor receptor (EGFR) mutation or gene translocation. Squamous NSCLC almost universally occur in patients with a history of tobacco use and only rarely are tumours found which contain an EGFR activating mutation (Cancer Genome Atlas Research Network. 2012).

In addition to the high mortality associated with NSCLC, a high proportion of patients experience severe morbidity as a result of local and metastatic spread of disease. Common morbidities include generalized weakness and fatigue, cough, and dyspnoea. Local spread of tumour can result in obstructive pneumonia, lobar collapse, haemoptysis, pain from chest wall and rib invasion, and pleural effusions, while distant spread to bone, brain, liver, and adrenals can lead to pain, neurologic sequelae, and laboratory abnormalities. Generalized effects of metastatic disease also include cachexia, thrombotic and embolic events, paraneoplastic conditions, and infections.

Historically, patients with locally advanced or metastatic NSCLC have been treated with standard chemotherapy and/or radiation, and while these treatments may provide modest survival benefits, they are rarely curative.

Non-squamous NSCLC patients with advanced or metastatic disease treated with current standard treatment options have a median survival time in the range of 11 to 13.6 months.

However, for squamous NSCLC patients with advanced or metastatic disease, median survival is in the range of 9.5 to 10.8 months (Manegold et al. 2008; Scagliotti et al. 2008; Reck et al. 2009; Scagliotti et al. 2009; Sandler et al. 2010; Patel et al. 2012; Socinski et al. 2012, 2013).

In patients with advanced squamous NSCLC, platinum-based doublets remain the recommended first-line therapy. Despite new treatments for NSCLC in the last 15 years, most of the available agents do not benefit patients with squamous NSCLC, because they are not efficacious for this subtype (bevacizumab [BEV], pemetrexed [PEM]) or since activity is limited to tumours with specific mutations and gene alterations that are rarely found in squamous NSCLC tumours (erlotinib, gefitinib, afatanib, crizotinib). Recently, nivolumab has been approved in locally advanced or metastatic squamous NSCLC after prior chemotherapy (see EPAR Opdivo).

About the product

Necitumumab is a recombinant human IgG1 monoclonal antibody that binds with high affinity and specificity to the human epidermal growth factor receptor 1 (EGFR) and blocks the ligand binding site, blocking activation by all known ligands and inhibiting relevant biological consequences in vitro. Activation of EGFR has been correlated with malignant progression, induction of angiogenesis and inhibition of apoptosis or cell death. In addition, necitumumab induces EGFR internalization and degradation in vitro. In vivo studies in cell line derived xenograft models of human cancer, including non-small cell lung carcinoma, demonstrate that necitumumab has antitumor activity both in monotherapy and in combination with gemcitabine and cisplatin.

The applicant applied for the following indication:

Portrazza in combination with gemcitabine and cisplatin chemotherapy is indicated for first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer.

The final approved indication was:

Portrazza in combination with gemcitabine and cisplatin chemotherapy is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) expressing squamous non-small cell lung cancer who have not received prior chemotherapy for this condition.

Necitumumab therapy must be administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy.

Appropriate medical resources for the treatment of severe infusion reactions should be available during necitumumab infusions. Availability of resuscitation equipment must be ensured.

Portrazza is administered in addition to gemcitabine and cisplatin-based chemotherapy for up to 6 cycles of treatment followed by Portrazza as a single agent in patients whose disease has not progressed, until disease progression or unacceptable toxicity.

The recommended dose of Portrazza is 800 mg (flat dose) administered as an intravenous infusion over 60 minutes on Days 1 and 8 of each 3 week cycle via an infusion pump. If a decreased infusion rate is indicated, the infusion duration should not exceed 2 hours. Portrazza must not be administered as an intravenous bolus or push. There have been no studies performed with other routes of administration.

Patients should be monitored during infusion for signs of infusion-related reactions.

In patients who have experienced a previous Grade 1/2 hypersensitivity or infusion related reaction to necitumumab, premedication with a corticosteroid and an antipyretic in addition to an antihistamine is recommended.

Prior to each necitumumab infusion, premedication for possible skin reactions must be considered.

Posology adjustments

Recommendations for the management of infusion-related and skin reactions are provided in tables 1 and 2.

Hypersensitivity/Infusion-Related Reactions

Table 1 – Management recommendations for hypersensitivity/infusion-related reactions

Toxicity grade[a]	**Management recommendations (any occurrence)**
Grade 1	• Decrease infusion rate by 50 % for the duration of infusion.[b] • Monitor patient for worsening of condition. • For subsequent infusions, please see premedication section.
Grade 2	• Stop the infusion; when the reaction has resolved to Grade ≤ 1, resume infusion at a 50 % decreased infusion rate.[b] • Monitor patient for worsening of condition. • For subsequent infusions, please see premedication section.
Grade 3-4	• Immediately and permanently discontinue treatment with necitumumab.

[a] Grade per NCI-CTCAE, Version 3.0
[b] Once the infusion rate has been reduced for a Grade 1 or 2 hypersensitivity/infusion-related reaction, it is recommended that the lower infusion rate be utilized for all subsequent infusions. The infusion duration should not exceed 2 hours.

Skin Reactions

Table 2– Management recommendations for skin reactions

Toxicity grade[a]	**Management recommendations (any occurrence)**
Grades 1 and 2	• No dose adjustment necessary
Grade 3	• Temporarily withhold, for a maximum of 6 weeks following Day 1 of the most recent treatment cycle, until symptoms resolve to Grade ≤ 2. Permanently discontinue if symptoms do not resolve to Grade ≤ 2 after holding for 2 consecutive cycles (6 weeks) • Following improvement to Grade ≤ 2, resume at reduced dose of 400 mg. If symptoms worsen at 400 mg, permanently discontinue. • If symptoms do not worsen at 400 mg for at least 1 treatment cycle, the dose may be increased to 600 mg If symptoms worsen at 600 mg, temporarily withhold, for a maximum of 6 weeks following Day 1 of the most recent treatment cycle, until symptoms resolve to Grade ≤ 2. Following improvement to Grade ≤ 2, resume at reduced dose of 400 mg. • If symptoms do not worsen at 600 mg for another treatment cycle, the dose may be further increased to 800 mg. • Permanently discontinue if patients experience Grade 3 skin induration/fibrosis.
Grade 4	• Immediately and permanently discontinue treatment with necitumumab.

[a] Grade per NCI-CTCAE, Version 3.0

2.2. Quality aspects

2.2.1. Introduction

Necitumumab is a recombinant human monoclonal antibody of the immunoglobulin G subclass 1 (IgG1) that specifically binds to the extracellular domain III of the human epidermal growth factor receptor (EGFR).

Necitumumab, concentrate for solution for infusion, 16 mg/mL, is a sterile solution intended for single use. Necitumumab finished product is formulated in an aqueous buffered solution at pH 6.0, containing 10 mM sodium citrate, 40 mM sodium chloride, 133 mM glycine, 50 mM mannitol, and 0.01% w/v polysorbate 80 and is supplied as a 800 mg/50 mL presentation.

The finished product is diluted in 0.9% sodium chloride solution (normal saline) prior to administration.

2.2.2. Active Substance

General information

Necitumumab is a recombinant human DNA-derived monoclonal antibody of the IgG1κ subclass composed of two heavy chain (γ1-chain) molecules consisting of 451 amino acid residues each and 2 light chain (κ-chain) molecules consisting of 214 amino acid residues each. A schematic of the overall structure of necitumumab is shown in Figure 1. The disulfide bonds are shown in black, between the cysteine residues, the heavy chains are shown in red, and the light chains are shown in blue. The necitumumab molecular mass, determined by mass spectrometry, of the light chain and the heavy chain are 23.2 kilodaltons (kDa) and 50.7 kDa, respectively, resulting in a relative molecular mass for the necitumumab monoclonal antibody of 147.8 kDa.

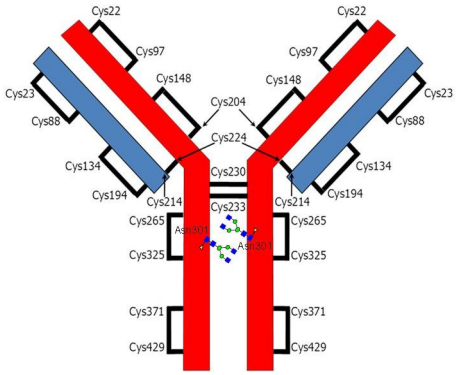


Figure 1. Schematic of Necitumumab

Necitumumab active substance is formulated in a citrate-buffered solution containing 10 mM sodium citrate, 40 mM sodium chloride, 133 mM glycine, 50 mM mannitol, and 0.01% (w/v) polysorbate 80; pH 6.0.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

Sufficiently detailed information on the manufacturing, storage and control facilities for necitumumab active substance has been provided.

The upstream manufacture of each batch of necitumumab begins with the thawing of a single vial of the Working Cell Bank (WCB), derived from the Master Cell Bank (MCB), that is serially scaled-up in flasks and bioreactors. The contents of the final scale-up bioreactor are used to inoculate the production bioreactor. The culture is harvested, clarified, and then transferred for further downstream processing.

The downstream manufacture of necitumumab consists of a series of chromatography, viral inactivation and nanofiltration and tangential flow filtration steps. Finally, the purified necitumumab (bulk active substance) is dispensed into single use, gamma-irradiated bags, and stored at 2 - 8°C.

During the downstream process, robust viral inactivation is achieved by the viral inactivation unit operations while robust physical removal of potential viral particles is attained by the chromatography and nanofiltration unit operations. The final tangential flow filtration unit operation ensures necitumumab is at the correct concentration and buffer composition prior to the bulk fill operation.

The necitumumab active substance manufacturing process has been adequately described with set limits for the process parameters, well-motivated and supported by appropriate data.

Control of materials

Origin, source, and history of the cell line development

Necitumumab is expressed from a NS0 (mouse) cell line. The description of the gene constructs and transfection of NS0 cells has been adequately detailed. Data is shown in support of correct sequence and integration of the gene construct.

A thorough description of the cell bank system has been provided, demonstrating stability of the construct and suitability of the Master Cell Bank (MCB) and Working Cell Bank (WCB) to be used for production. The monitoring and storage of cell banks are well motivated with supporting data for the set limits of cell density and temperature.

The stability of the MCB and WCB will be monitored and the stability analysis evaluated and documented.

The protocol for the preparation of a replacement WCB is adequately described with justified controls for its capacity to express the active substance.

The data from the analysis of cells of *in vitro* cell age limit are in support of a stable construct and expression of an active substance with a similar oligosaccharide pattern as for substance produced from either process C (used in the pivotal study) or process D at commercial scale. No extraneous agents could be detected.

Other raw materials are described and appropriate information on the control of raw materials have been submitted.

Control of critical steps and intermediates

The process controls applied to critical steps and intermediates during the manufacture of necitumumab include critical process parameters, critical in-process controls, and in-process specifications. The control strategy for the necitumumab active substance manufacturing process was developed in accordance with the principles of quality risk management. A risk assessment was performed to identify process parameters with the potential for having an effect on active substance critical quality attributes. The tests and limits for the critical process parameters (CPPs) and critical in-process controls (CIPCs) have been described for each step and supported by appropriate data.

The necitumumab active substance manufacturing process does not generate process intermediates for long-term storage. However, process intermediate solutions that are produced during the manufacturing process may be held at the temperature and for the time period defined in the dossier. The different hold times and conditions for process intermediates at different stages of the manufacturing process are well supported by data and deemed acceptable.

Process validation

Process validation of the necitumumab active substance manufacturing process was performed at the commercial manufacturing site to demonstrate that the commercial-scale manufacturing process performs consistently and is capable of meeting pre-determined acceptance criteria. Comprehensive process validation studies were conducted. All the tested batches fulfilled the acceptance criteria and showed good reproducibility.

The development and scale up of the manufacturing process for necitumumab has followed a traditional approach. The Applicant described adequately the procedure for the risk assessment and defines how the impact scores are set.

Holding times and storage of buffers as well as shipping have been adequately justified. The claims were considered acceptable.

The process was evaluated for its ability to remove impurities from the process stream. The qualification is deemed acceptable.

The Applicant has thoroughly described the process validation studies to justify the ranges for critical and non-critical parameters applied in the process.

Manufacturing process development

Four manufacturing processes for necitumumab have been developed: Process A, Process B, Process C, and Process D.

Active substance from process C was used in the pivotal study and process D substance is used in commercial batches. Biochemical analyses were conducted to demonstrate the analytical comparability of all investigational active substance and finished product materials with regard to their manufacturing processes. The changes introduced with Process D mainly relate to more optimal process control and improvement of viral clearance.

The comparability studies have been adequately described and in essence the substance from process C and D are comparable.

Characterisation

The necitumumab active substance has been thoroughly characterized using state-of-the-art methods. The characterization supports the selected analytical methods for the control of active substance. The characterization data confirms that the intended purity and activity of necitumumab is consistently achieved by the chosen manufacturing process.

N-linked oligosaccharide profiling was performed to determine the relative abundance of the N-linked oligosaccharides present in necitumumab. The results showed that the oligosaccharide structures are complex bi-antennary structures differing in the degree of galactosylation and sialylation. Small amounts of α-Gal and sialic acids are detected. These forms are common for the NS0 cell line.

The product-related impurities in necitumumab were characterized in detail using orthogonal methods that are stability indicating based on the ability to detect increases in impurity levels over time.

The primary mode of action for necitumumab is the inhibition of cell proliferation through blocking of the EGF receptor and it is the only mechanism of action that is supported by clinical data. Still, necitumumab was shown to bind to different Fc receptors and was able to mediate ADCC activity *in vitro*.

Necitumumab was shown to block binding of EGF required for cell growth and therefore inhibits the proliferation of cells expressing EGFR (potency assay). Receptor binding studies support the structure and function relationship of necitumumab. The potency assay is deemed suitable for its purpose. The characterization supports the selected methods used for process controls and release specifications.

Specification

The specification for necitumumab was established based on the quality of the product used in toxicological and clinical testing, the stability of necitumumab, process variability and the variability of the analytical methods used to analyse the active substance. The selected attributes tested were acceptable. The general test procedures for visual appearance, colour, clarity, osmolality, pH, endotoxin and bioburden are compliant with the Ph. Eur. and the USP.

Stability

Stability studies were carried out on three registration batches of necitumumab manufactured according to Process D through 24 months at 2 - 8°C. All results remained within the proposed acceptance criteria through the 24 month time point. No trend towards increasing impurity levels was seen over time at the recommended storage temperature up to 24 months. Studies were also conducted under accelerated (23 - 27°C) and stressed conditions (38 - 42°C).

Supporting stability studies were conducted with batches of necitumumab manufactured for use in clinical trials according to three earlier development processes (Processes A, B and C). The proposed stability acceptance criteria for necitumumab was established based on the historical experience gained from active substance derived from multiple manufacturing processes.

In general, necitumumab undergoes both physical and chemical degradation pathways similarly to other IgG1 antibodies. None of the stress conditions affected necitumumab binding affinity to its ligand EGFR, nor its potency as an inhibitor of EGF-mediated cell growth, indicating the stability of the molecule's biological properties.

On the basis of data from registration batches, commercial batches and supporting stability data, and the comparability established between them, the proposed shelf life of 24 months for necitumumab active substance under the recommended storage conditions of 2°C to 8°C is considered acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The proposed commercial Necitumumab finished product, 800 mg/50 mL, is supplied as a sterile solution in 50 mL Type I glass vials, intended for single use. The formulation contains the active pharmaceutical substance, necitumumab, in a matrix consisting of the inactive excipients sodium citrate, citric acid, glycine, mannitol, sodium chloride, polysorbate 80, and water for injections. For administration, the 50 mL (800 mg) solution is removed from the finished product vial and diluted in 0.9% sodium chloride solution in an infusion container prior to administration by intravenous infusion. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product

formulation. Portrazza infusions should not be administered or mixed with glucose solutions.

Pharmaceutical development

Formulation development has been extensive and was based on screening studies using design of experiment (DoE) approach, and included optimization for administration by IV infusion and for stability. The finished product and the formulation development have been described in sufficient detail.

Manufacture of the product and process controls

The finished product manufacturing process is a platform process that has been used throughout development, which involves dilution of active substance with a formulation buffer identical to the active substance formulation, sterile filtration and aseptic filling into an appropriate container closure.

The finished product manufacturing process consists of dilution of the bulk active substance in buffer that contains sodium citrate, sodium chloride, glycine, mannitol, and polysorbate 80. The finished product solution is sterile filtered and aseptically filled into Type I glass vials (800 mg/50 mL), stoppered with sterile stoppers, and crimp sealed. The filled vials are 100% visually inspected. Once vials are labelled and placed in secondary packaging, identity is confirmed via physicochemical analysis.

Operating ranges for process parameters and acceptance criteria for controls are provided for parameters/controls that have been determined to be critical to ensuring that the Critical Quality Attributes (CQA) are met. This determination of criticality was based on the risk analysis and experimental work described. Ranges are also provided for a subset of the non-critical process parameters and controls. The critical process controls are sufficiently described. The process control parameters and results presented are found acceptable.

The manufacturing process is well described and documented. Media fills are used to validate the aseptic filling process and results from simulations showed no contaminated vials. Bacterial retention testing of the sterilizing filters was performed using a scaled-down model of the finished product filtration process. The validation parameters challenge data are presented. The approach taken by the Applicant is deemed acceptable.

The routine manufacturing is a continuous process without isolated intermediates or extended hold times. Specified hold times were not used for the process steps, instead extended processing time limits were applied. The results from extended processing time during development and process validation pass the acceptance criteria for the process validation.

The process validation was performed using 3 batches of commercial process covering the proposed process scale. The results demonstrate that the manufacturing process is capable of providing a finished product of consistent quality.

Product specification

The finished product specification was based on the quality of necitumumab used in toxicological and clinical testing, the stability of finished product, process variability and the variability of the analytical methods used to analyse the finished product.

The proposed specification for the necitumumab finished product was developed as part of an integrated approach to the control strategy. This approach incorporates product and process understanding to establish a commercial analytical testing strategy that assures control of the finished product CQAs at release and throughout the proposed shelf-life of the finished product.

For those quality attributes for which routine testing is justified, the proposed acceptance criteria for Necitumumab finished product were established based upon the quality of necitumumab used in clinical studies, the classification of the quality attribute as critical, manufacturing experience, analytical variability, the stability of the finished product, and regulatory guidance. Since the quality of the finished product is largely determined by the quality of the active substance, the proposed acceptance criteria for the active substance were also considered in the determination of appropriate acceptance criteria for finished product. All non-compendial methods used in the release of active substance have been satisfactorily validated.

The proposed attributes to be tested for the necitumumab finished product are considered adequate.

However, initially the approach used to set the finished product acceptance criteria was not considered acceptable. A CQA is by default an attribute that may impact safety and/or efficacy if outside the limits. For this reason it is expected that the levels for CQA´s need to be in line with what has been qualified in clinical studies or clinically qualified by other means. The Applicant has revised the specifications taking into account the levels used in the clinical trials and the justification provided that the claimed acceptance criteria can be considered to be safe and efficacious is considered acceptable since the limits are within the same range as the clinical experience and the difference is not of a magnitude that may have a meaningful impact.

Stability of the product

The studies were performed according to the current ICH guidelines. Primary stability data for 24 months at 2°C to 8°C, accelerated conditions (23 - 27°C) and stressed (38 - 42°C) storage conditions were provided. The results demonstrate that the proposed formulation provides a good stability for the finished product with minor changes over the storage time therefore the proposed shelf life of 24 months at the recommended storage condition of 2°C to 8°C is considered acceptable.

Adventitious agents

The approach to ensuring the quality and safety of the necitumumab finished product is consistent and compliant with the current applicable guidelines.

The adventitious agent safety strategy consists of the following measures:

1. Control of sourcing, maintenance of documentation (e.g. certifications), and testing of raw materials used in cell-line generation and cell culture process with respect to adventitious agents

2. Testing of the Master Cell Bank (MCB), Working Cell Bank (WCB), and unprocessed bulk harvest (UBH) for adventitious agents (bacteria, fungi, mycoplasma, and viruses). Testing of cells beyond the limit of in vitro cell age to ensure that no new viruses are induced or introduced by the cell culture process conditions

3. Viral clearance by spike-recovery studies using four model viruses to demonstrate that the downstream purification process can effectively clear viruses exhibiting a broad range of biochemical and biophysical properties.

Animal-sourced materials were used in the generation of the cell line utilized for the production of necitumumab. The relevant information and TSE Certificates of Suitability from EDQM have been provided.

The testing programme of cell banks and all unprocessed bulk harvest batches for virus contamination is considered adequate and in compliance with ICH Q5A. Extensive testing of the cell banks and unprocessed bulk has been performed. This includes testing of cells beyond the limit of *in vitro* cell age. No other viruses than endogenous retroviruses have been found from this routine testing.

Viral removal/inactivation capacity by the necitumumab manufacturing process was evaluated in scale down models. All process steps evaluated in the viral spiking studies were appropriately scaled down from the commercial purification process. The virus validation studies are deemed well performed with adequate design of interference and cytotoxicity studies.

The overall viral clearance capacity is satisfactory and demonstrates the efficacy of the necitumumab manufacturing process to remove/inactivate possible viral contaminants. The approach used to assess residual retroviral risk can be considered appropriate. The validation data presented is considered acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The Applicant has presented a thoroughly documented dossier with well justified methods for the control and release of active substance and finished product.

The manufacturing processes divided into the different unit operations are adequately described with appropriate limits for the process parameters, well justified and supported by appropriate data.

The acceptance criteria proposed in the testing of the active substance and the finished product has been justified based on experience from clinical trials. In most cases the limits are not exactly covered by clinical experience but the small deviation is not considered to have a significant impact on safety and efficacy.

The stability results indicate that the active substance and finished product are sufficiently stable and justify the proposed shelf life in the proposed container.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The active substance and the finished product have been appropriately characterised and satisfactory documentation has been provided. The description of the manufacturing process and the manufacturing development is well performed and has resulted in a product with unusual stability with low levels of impurities. The manufacturing process has been validated. The in-process controls are adequate. The results indicate that the manufacturing process is capable of producing the active substance and finished product of intended quality in a reproducible manner.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Portrazza is approvable from the quality point of view.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended an additional point for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

***In vitro* studies**

X-ray crystal structure studies of the Fab fragment of necitumumab (Fab11F8) indicate that the antibody interacts with Domain III of EGFR. Cetuximab and necitumumab have remarkably similar epitopes, but binding of the two antibodies to the receptor occurs through a completely different set of interactions.

Key *in vitro* pharmacodynamics data to characterize the interaction of necitumumab with EGF receptor, related receptors, and with EGFR ligands are summarized in the following table:

Table 3: Summary of in vitro data on the interaction of necitumumab with EGFR, related receptors, and EGFR ligands

Type of Study	Assay	Test System	End Point	Report No.
Cell-free Binding/ Blocking Studies	Necitumumab binding to human EGFR ECD	SPR	Kd = 0.32 nM	IMC11F8-01
	Necitumumab binding to human EGFR ECD	ELISA	EC50 = 0.007 - 0.08 nM	IMC11F8-01 08-13-2013 2013-9-10
	Inhibition of 125I-EGF binding to EGFR-expressing A431 tumor cells by necitumumab	Cell-based	IC50 = 1 - 2 nM	IMC11F8-01
	Species cross-reactivity of necitumumab	ELISA	Necitumumab binds with high affinity (EC50 = 0.006 nM) to human and monkey EGFR and low affinity (EC50 = 2 nM) to rabbit EGFR Necitumumab does not bind to mouse and rat EGFR	2013-9-10
	Necitumumab cross-reactivity with other ErbB family members	ELISA	No binding to ErbB2, ErbB3, or ErbB4	08-13-2013
Cell-based Functional Studies	Inhibition of ligand-induced EGFR tyrosine phosphorylation by necitumumab	Cell-based	Necitumumab inhibits EGFR activation induced by all known EGFR ligands with IC50 < 0.70 nM	2014-03-05
	Inhibition of DiFi and NCI-H508 tumor cell viability by necitumumab	Cell-based	IC50 = 0.04 - 1 nM	IMC11F8-01 2014-03-06

Comparative *in vitro* studies – necitumumab and cetuximab

The binding kinetics of the clone C11F8 Fab and the antibody IMC-11F8 (necitumumab) were compared to the binding kinetics of C225 Fab and the antibody IMC-C225 (cetuximab) using surface plasmon resonance (SPR).

Table 4

Antibody	Form	k_{on} (10^5 $M^{-1}s^{-1}$)	k_{off} (10^{-4} s^{-1})	K_d (nM)
IMC-11F8	Fab	22.9 ± 9.9	36.7 ± 8.5	1.78 ± 0.51
	IgG	20.8 ± 7.7	6.5 ± 2.2	0.32 ± 0.05
Cetuximab	Fab	23.1 ± 4.8	11.7 ± 3.4	0.53 ± 0.17
	IgG	18.2 ± 6.4	6.0 ± 1.1	0.38 ± 0.18

The dose dependence of the binding of the two full-length anti-EGFR antibodies necitumumab and cetuximab (IgG1) to the extracellular domain of the EGFR (A) and the ability of necitumumab to block EGF binding to the EGFR on the surface of A431 tumour cells (B) are shown in Figure 6.

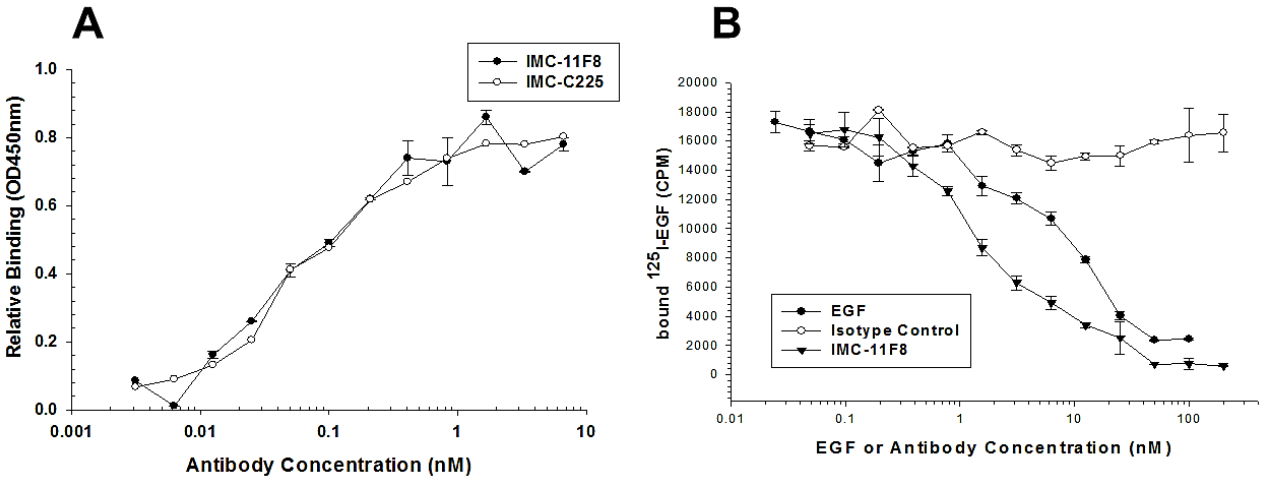


Figure 2: Necitumumab binding to human EGF receptor (A) and inhibition of EGF binding to cell surface EGFR in A431 cells by necitumumab (B).

Effect on EGFR-mediated signal transduction and tumour cell viability

Given that EGFR can be activated by 7 ligands (TGF-alpha, EGF, HB-EGF, betacellulin, amphiregulin, epiregulin, and epigen), the objective of these studies was (1) to evaluate the effect of necitumumab on EGFR tyrosine phosphorylation induced by various EGFR ligands and (2) to assess the effect of necitumumab on downstream signaling events and viability of EGFR-dependent cancer cells.

In LK-2 cells overexpressing EGFR, necitumumab potently inhibited EGFR tyrosine phosphorylation induced by the aforementioned ligands in a concentration-dependent manner with IC50 values less than 0.74 nM. The antibody also dose dependently inhibited EGFR and Erk1/2 phosphorylation in A431 cells with IC_{50} values at approximately 0.8 nM. Both necitumumab and cetuximab significantly reduced tumor cell viability with comparable IC_{50} values at approximately 0.030 - 0.040 nM and 1.0 nM in NCI-H508 and DiFi cells, respectively.

Effect on EGFR internalization and degradation

HeLa cells stably overexpressing a C-terminal fusion of EGFR to GFP (green fluorescent protein) designated as HeLa-EGFR-GFP cells were incubated with control IgG, necitumumab, or a noninternalizing benchmark comparator anti-EGFR antibody (panitumumab). As demonstrated by flow cytometry and confocal microscopy, treatment with necitumumab for 24 - 48 hours resulted in the reduction of total EGFR levels by approximately

40%. Necitumumab also time dependently increased EGFR delivery to the lysomal compartment suggesting lysosome-mediated EGFR degradation.

Antibody-dependent cytotoxicity induced by necitumumab

The Fc region of human IgG1 antibodies interacts with Fc-gamma receptors (FcγR) expressed on various immune cells including natural killer (NK) cells. Such an interaction may result in the immune effector functions that can contribute to the antitumor activity of the antibodies.

Binding of necitumumab to FcγRIII (CD16a) in a cell-free system was measured by SPR using a BIAcore instrument. Necitumumab binding to CD16a in a cell-based format was evaluated by flow cytometry using Jurkat (acute lymphoblastic T cell leukaemia) cells. The ability of necitumumab to simultaneously bind to EGFR and CD16a was examined by a bridging assay. The antibody was allowed to bind to the EGFR on the surface of HCC-827 lung adenocarcinoma cells, followed by the incubation with exogenously added CD16a. Binding of CD16a to the EGFR-necitumumab complexes on the surface of target cells was assessed by flow cytometry using fluorescently labelled anti-CD16a. HCC-827 cells were also used as target cells in reporter gene and PBMC assays to evaluate ADCC activity in response to necitumumab treatment.

As observed from the binding sensograms for necitumumab, there was an increase in binding response over time, indicating that the antibody effectively binds purified CD16a *in vitro*. Necitumumab was also capable of binding to the surface of Jurkat cells expressing CD16a. In the bridging EGFR-CD16a assay, a positive shift was observed for HCC-827 cells incubated with necitumumab, CD16a and PE-conjugated anti-CD16a. There was no shift for samples lacking necitumumab suggesting that the association of CD16a with HCC-827 cells is necitumumab-mediated. Finally, necitumumab displayed ADCC activity against HCC-827 cells in both gene reporter assay and peripheral blood mononucleated cells (PBMC) assay.

***In vivo* studies**

Initial *in vivo* proof of concept studies – monotherapy in xenograft tumour models

The objective of the initial proof-of-concept studies with necitumumab was to evaluate the antitumor efficacy of the antibody in A431 and BxPC-3 xenograft models of squamous cell carcinoma of the skin and pancreatic carcinoma, respectively. The antitumor activity of necitumumab was also investigated in GEO and HT-29 xenograft models of colorectal carcinoma. In addition to antitumor activity, plasma concentrations of the antibody associated with an efficacious dose were determined.

As shown in the Figure 7 and 8, necitumumab significantly inhibited tumour growth at all dose levels in A431, BxPC-3, and GEO xenograft models ($p<.05$), and this antitumour effect was comparable to that of cetuximab. Necitumumab monotherapy failed to inhibit tumour growth in HT-29 xenograft model of colon cancer known to harbour mutation in BRAF gene.

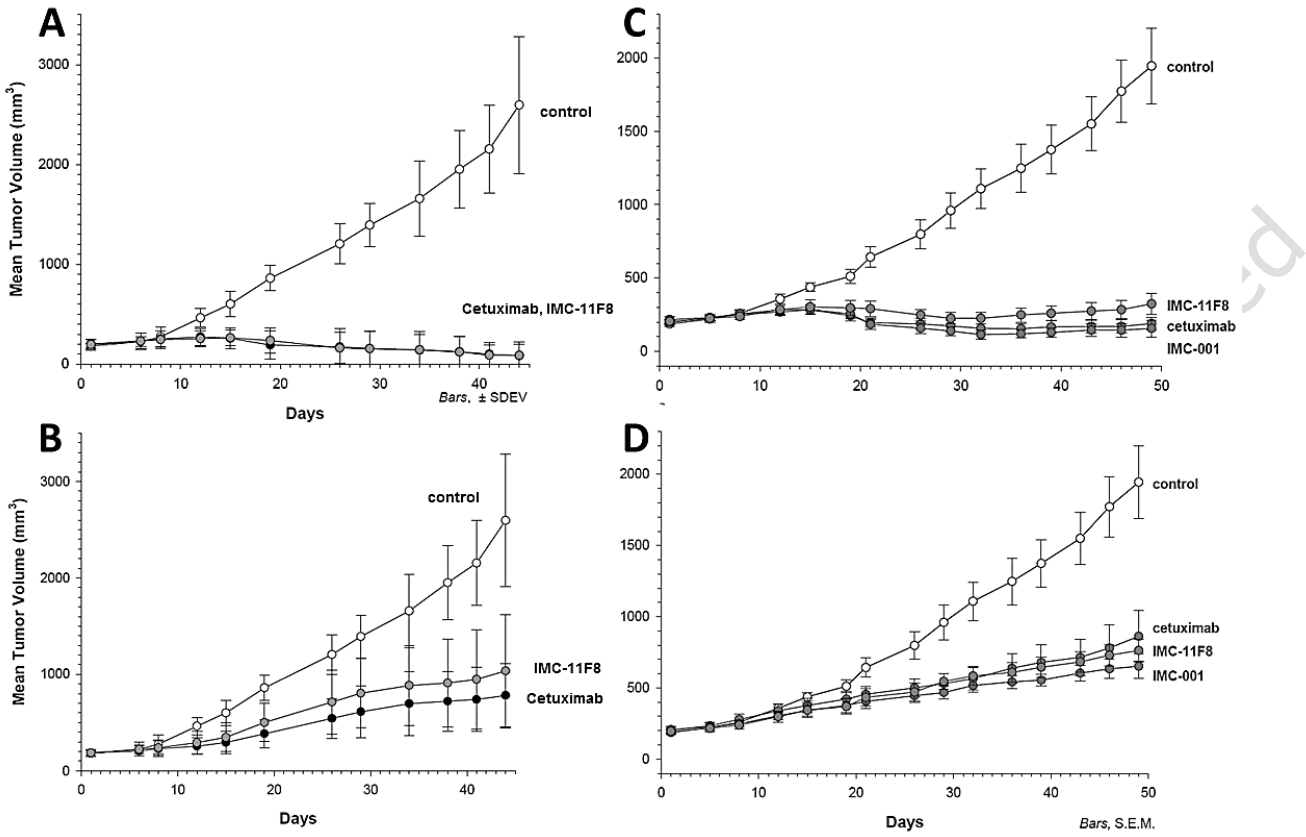


Figure 3: Antitumor effect of necitumumab (IMC-11F8) monotherapy in A431 (A, B) and BxPC-3 (C,D) xenograft tumor models dosed at 1 (A, C) and 0.3 (B, D) mg/animal.

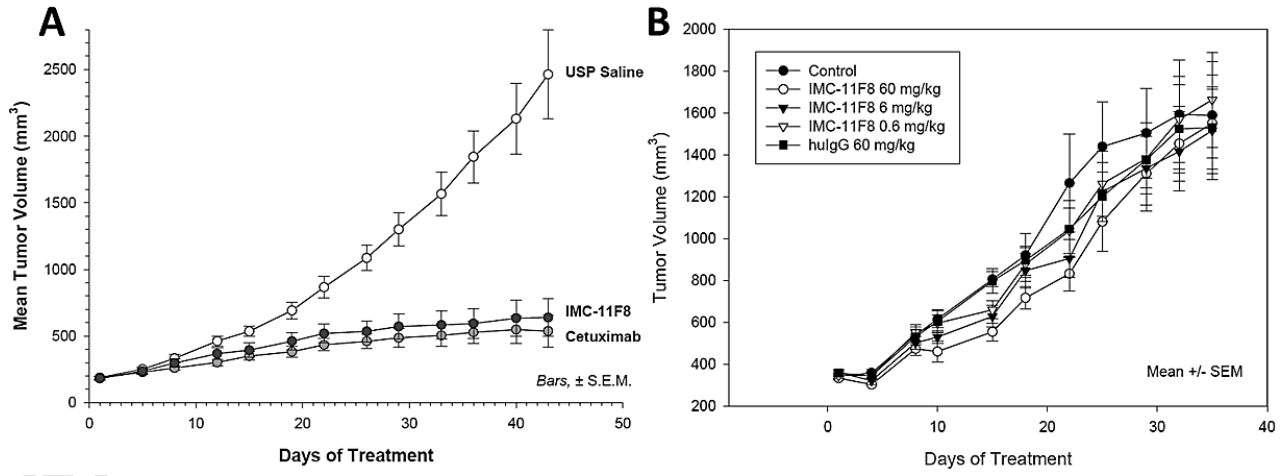


Figure 4: Antitumor effect of necitumumab (IMC-11F8) monotherapy in GEO (A) and HT-29 (B) xenograft tumour models

The results of the pharmacokinetic analysis in BxPC-3 model revealed that greater than 50% tumour growth inhibition occurred when the trough plasma antibody concentration was maintained above 40 μg/mL corresponding with an average plasma antibody concentration of 60 μg/mL.

Table 5:

IMC-11F8 dose (mg/kg)	Interdose average plasma concentration (µg/mL)	Half-life (days)	Maximum plasma concentration (µg/mL)	T_{max} (hours after dosing)	Trough concentration (µg/mL)	%T/C
6	59.9	4.5	115	3	40	44
20	542.4	4.4	510	3	100	35
60	1161.4	3.1	1440	24	465	30

%T/C : the ratio of the relative tumor volumes at the end of the treatment or observation period in the experimental treatment (T) group versus the control (C) group.

A summary of necitumumab monotherapy in xenograft models of squamous cell carcinoma of the skin, pancreatic and colon carcinoma is shown in the following table:

Table 6

Report Number	Model	n	Treatment	Treatment Duration	Necitumumab Lot Number	%T/C	p
1221-02	A431 (Squamous Cell Carcinoma of the Skin)	8	cetuximab (0.3 mg/dose, ip, 2x/week)	43 days	NA	30	<.005b
			cetuximab (1 mg/dose, ip, 2x/week)			3	<.005b
			C11F8a (0.3 mg/dose, ip, 2x/week)			40	<.005a
			C11F8a (1 mg/dose, ip, 2x/week)			3	<.005a
1300-02	BxPC-3 (Pancreatic Carcinoma)	8	A12 (1 mg/dose, ip, 2x/week	49 days	NA	25	<.002c
			cetuximab (0.3 mg/dose, ip, 2x/week)			24	NA
			cetuximab (1 mg/dose, ip, 2x/week)			9	.0031c
			IMC-11F8 (0.3 mg/dose , ip, 2x/week)			38	NA
			IMC-11F8 (1 mg/dose, ip, 2x/week)			15	.07c
2201-03Ad	BxPC-3 (Pancreatic Carcinoma)	10	IMC-11F8 (6 mg/kg, ip, 2x/week) (Loading Dose 16.6 mg/kg)	33 days	NA	44	<.0001b
			IMC-11F8 (20 mg/kg, ip, 2x/week) (Loading Dose 55 mg/kg)			35	<.0001b
			IMC-11F8 (60 mg/kg, ip, 2x/week) (Loading Dose 166.2 mg/kg)			30	<.0001b
2219-03	HT-29 (Colorectal Carcinoma)	12	IMC-11F8 (0.6 mg/kg, ip, 2x/week) (Loading Dose 1.5 mg/kg)	35 days	NA	NA	NA
			IMC-11F8 (6 mg/kg, ip, 2x/week) (Loading Dose 15 mg/kg)			NA	NA
			IMC-11F8 (60 mg/kg, ip, 2x/week) (Loading Dose 150 mg/kg)			NA	NA
3708-06	GEO (Colorectal Carcinoma)	10	cetuximab (1 mg/dose, ip, 3x/week)	42 days	1278-155	22	<.0001b
			IMC-11F8 (1 mg/dose, ip, 3x/week)			27	<.0001b

Monotherapy studies in xenograft Non-Small Cell Lung Cancer models

The objective of these studies was to evaluate the antitumor activity of necitumumab in NCI-H292, NCI-H441, NCI-H1975, and HCC-827 xenograft models of NSCLC which harbour wild-type EGFR gene (NCI-H292 and NCI-H441 cells) or activating EGFR mutations (NCI-H1975 and HCC-827 cells). *In vivo* experiments were also carried out with stably transduced variants of NCI-H441 cells overexpressing wild-type (WT) or mutant form

(exon 19 deletion; Δ746-750) of EGFR. In addition to antitumor activity, plasma concentrations of the antibody associated with an efficacious dose were determined in HCC-827 xenograft model.

Necitumumab significantly inhibited tumour growth ($p<.05$) at all dose levels in NCI-H292, NCI-H1975, and HCC-827 models irrespective of EGFR status. In HCC-827 model, the antitumor effect of necitumumab was comparable to that of cetuximab and panitumumab. Necitumumab did not inhibit *in vivo* growth of parental NCI-H441 cells. Overexpression of WT or mutant form of the EGFR in NCI-H441 tumor cells rendered sensitivity to the antibody (%T/C values 48% and 34%, respectively); however, this effect did not reach statistical significance in NCI-H441 model overexpressing WT EGFR.

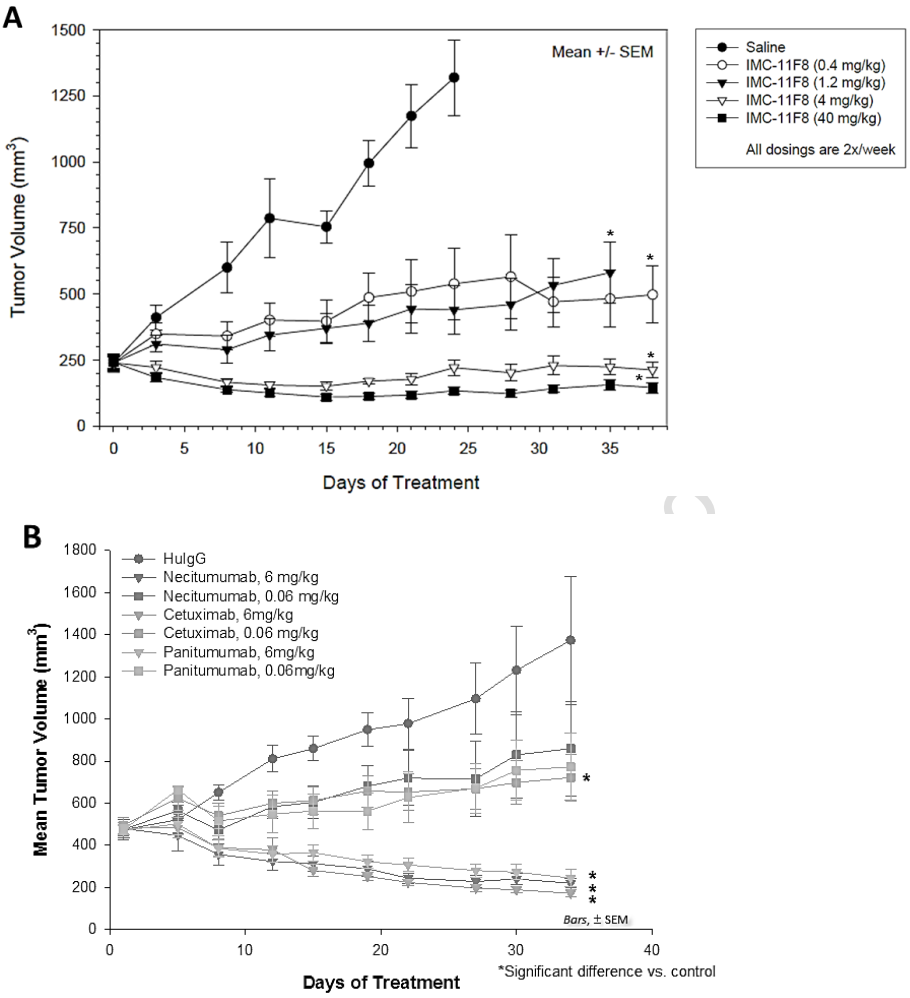


Figure 5: Antitumor effect of necitumumab (IMC-11F8) monotherapy in NCI-H292 (A) and HCC-827 (B) models of non-small cell lung cancer.

A summary of necitumumab monotherapy in xenograft models of non-small cell lung cancer is shown in the following table:

Table 7

Report Number	Model/EGFR Status	n	Treatment	Treatment Duration	Necitumumab Lot Number	%T/C	Regression %	p
3732-06	NCI-H1975 (EGFR-L858R/T790M)	8	IMC-11F8 (0.4 mg/kg, ip, 2x/week)	26 days	1275.155	29		.02[a]
			IMC-11F8 (1.2 mg/kg, ip, 2x/week)			38		.002[a]
			IMC-11F8 (4 mg/kg, ip, 2x/week)			13		.0003[a]
			IMC-11F8 (40 mg/kg, ip, 2/week)			15		.0002[a]
3733-06	NCI-H292 (WT EGFR)	10	IMC-11F8 (0.4 mg/kg, ip, 2x/week)	24 days	1275.155	41		.0002[a]
			IMC-11F8 (1.2 mg/kg, ip, 2x/week)			33		<.0001[a]
			IMC-11F8 (4 mg/kg, ip, 2x/week)			17		<.0001[a]
			IMC-11F8 (40 mg/kg, ip, 2x/week)			10		<.0001[a]
4983-10	HCC827 (EGFRΔ746-750)	10	IMC-11F8 (6 mg/kg, ip, 2x/week)	34 days	08T00297		54	.0002[a]
			IMC-11F8 (0.6 mg/kg, ip, 2x/week)				23	.001[a]
			IMC-11F8 (0.06 mg/kg, ip, 2x/week)			43		.34[a]
			cetuximab (6 mg/kg, ip, 2x/week)				64	<.0001[a]
			cetuximab (0.6 mg/kg, ip, 2x/week)				14	.002[a]
			cetuximab (0.06 mg/kg, ip, 2x/week)			23		.04[a]
			panitumumab (6 mg/kg, ip, 2x/week)				48	.0003[a]
			panitumumab (0.6 mg/kg, ip, 2x/week)			4		.005[a]
			panitumumab (0.06 mg/kg, ip, 2x/week)			34		.06[a]
5227-11	NCI-H441 (over expressing WT EGFR)	12	IMC-11F8 (60 mg/kg, ip, 2x/week)	53 days	08T00296	48		.1011[a]
5229-11	NCI-H441 (over expressing EGFRΔ746-750)	12	IMC-11F8 (60 mg/kg, ip, 2x/week)	50 days	NA	34		.0104 [a]
5249-11	NCI-H441 (WT EGFR)	12	IMC-11F8 (60 mg/kg, ip, 2x/week)	47 days	08T00296	92		.8683 [a]

Combination studies

Clinical antitumor activity of necitumumab has been evaluated in combination with various platinum doublets in frontline treatment of patients with metastatic NSCLC. To support clinical development of necitumumab in the intended tumour indication, the experimental studies described below evaluated the antitumor activity of necitumumab in combination with gemcitabine and cisplatin, paclitaxel and cisplatin, and/or pemetrexed and cisplatin, the most common platinum doublets used in first-line treatment of patients with metastatic NSCLC.

Athymic mice were subjected to subcutaneous inoculation of the following NSCLC cell lines: A549, EKVX, HCC-827, HOP-62, HOP-92, NCI-H226, NCI-H292, NCI-H358, NCI-H441, NCI-H520, NCI-H647, NCI-H1299, NCI-H1650, NCI-H1975, NCI-H2170, and NCI-H2405. When xenograft tumours reached an appropriate size for testing (ranging from 155 to 450 mm^3), mice were randomized by tumour size in treatment groups and dosed saline and/or human IgG, necitumumab, chemotherapy doublets (gemcitabine and cisplatin, paclitaxel and cisplatin, and/or pemetrexed and cisplatin), or a combination of necitumumab with respective chemotherapy doublet. Necitumumab was dosed at 60 mg/kg given intraperitoneally twice a week in combination studies.

Combination benefit was observed when necitumumab was dosed with the gemcitabine/cisplatin doublet as compared to the chemotherapy doublet alone ($p<.05$) in 9 out of 16 NSCLC xenograft models including 3 out of 4 models of squamous and adenosquamous carcinoma of the lung (NCI-H2170, NCI-H226, NCI-H647) and 6 out of 12 models of non-squamous NSCLC (A549, NCI-H1650, EKVX, HCC-827, HOP-62, NCI-H1975). Figures 10, 11 and 12 illustrate the antitumor activity of necitumumab in combination with gemcitabine and cisplatin and paclitaxel and cisplatin in A549 (WT EGFR) and NCI-H1650 (mutant EGFR with exon 19 deletion; Δ746-750) models of lung adenocarcinoma and NCI-H2170 and NCI-H226 models of squamous cell carcinoma of the lung.

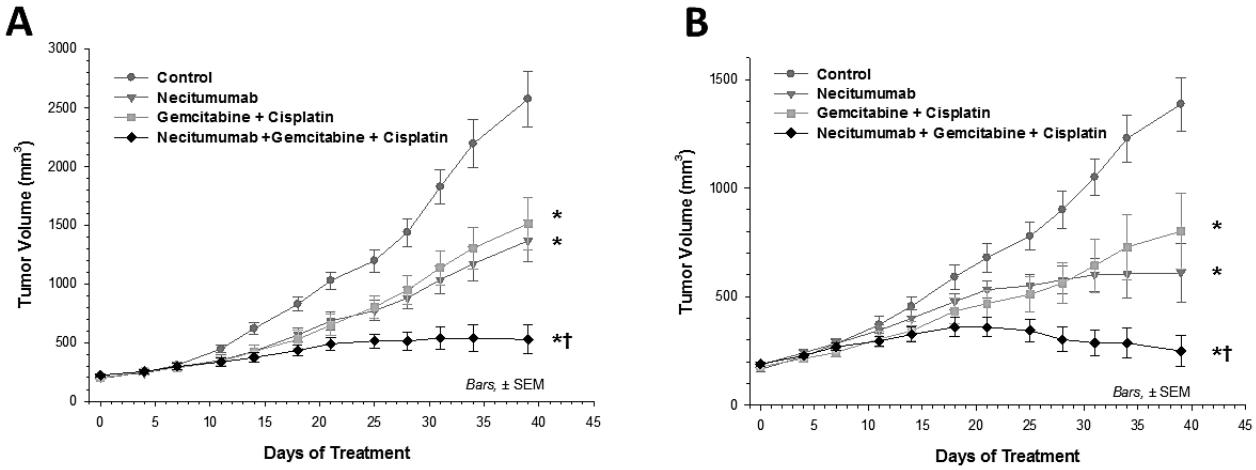


Figure 6: **Antitumor effect of necitumumab in combination with gemcitabine and cisplatin in A549 (A) and NCI-H1650 (B) models of non-small cell lung cancer.**

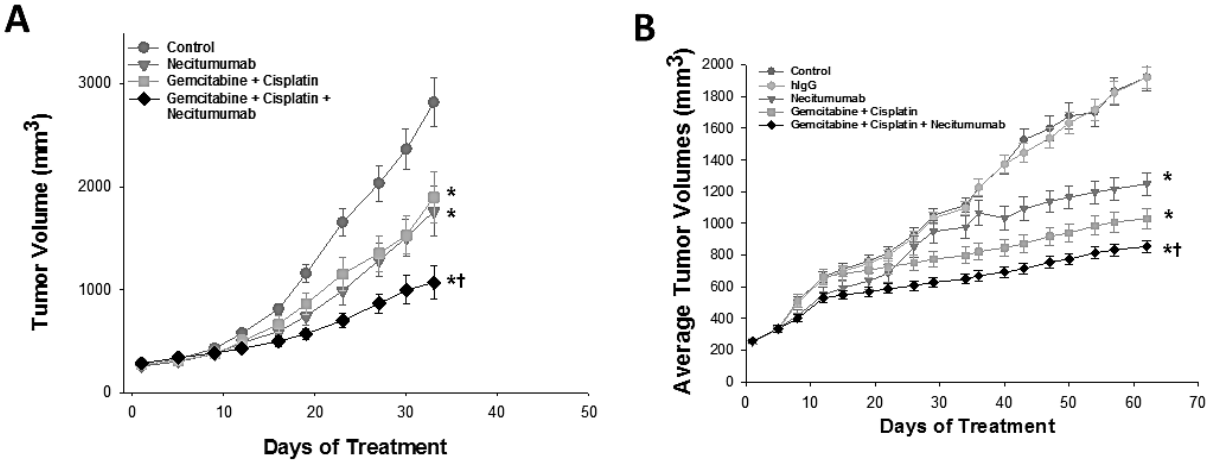


Figure 7: Antitumor effect of necitumumab in combination with gemcitabine and cisplatin in NCI-H2170 (A) and NCI-H226 (B) models of squamous cell carcinoma of the lung.

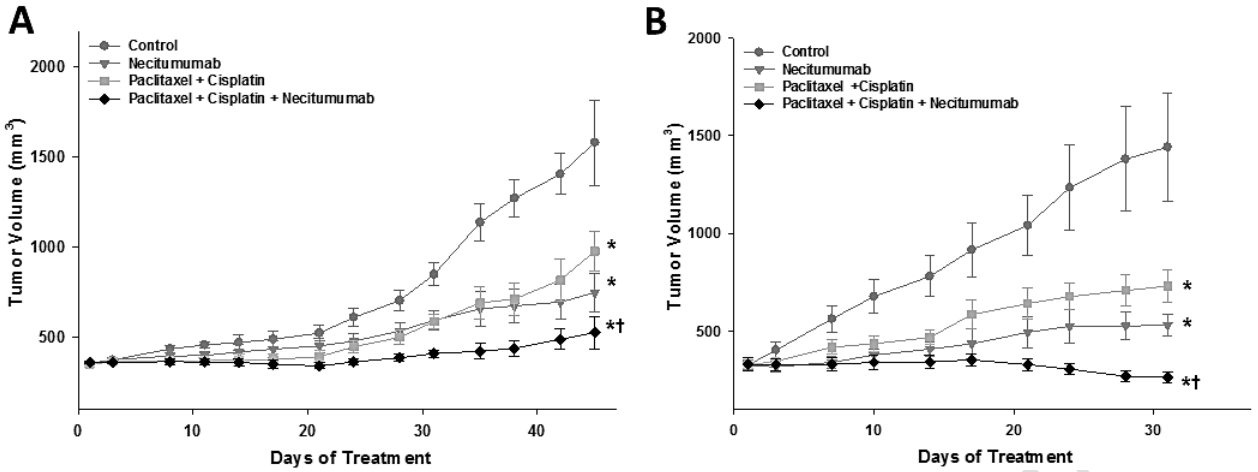


Figure 8: Antitumor effect of necitumumab in combination with paclitaxel and cisplatin in A549 (A) and NCI-H1650 (B) models of non-small cell lung cancer.

In a mechanistic substudy, tumour samples were collected on Day 9, 24 hours after the second dose of chemotherapy. After formalin fixation and paraffin embedding, specimens were subjected to immunohistological analysis of endothelial (Meca-32), proliferation (Ki-67 and phospho-histone H3, pHH3), and proapoptotic (ApopTag) markers. When compared to chemotherapy alone, treatment with necitumumab in combination with gemcitabine and cisplatin resulted in significantly reduced number of Meca-32 and Ki-67-positive tumours and increased number of ApopTag-positive cells in the A549 model. Similar changes, although not statistically significant, were observed in the NCI-H1650 model.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies of necitumumab have been submitted.

Safety pharmacology programme

No dedicated safety pharmacology studies were provided. The safety pharmacology endpoints were evaluated in the 26-week repeat-dose toxicology study (i.v).

In the 26-week study (Report SNBL-023-07), monkeys were administered weekly by i.v. infusion up to 60 mg/kg. In these animals:

- No findings on electrocardiogram (ECG) and measurements of heart rate, blood pressure and respiratory rate were observed during acclimation and on Days 2, 84, 86, 175, 177, and 237.
- No findings on physical examination.
- No specific examination or data collection was performed on the central nervous system (CNS), but no effects were noted on this system during physical examinations.

Pharmacodynamic drug interactions

Combination studies in xenograft tumour models are presented in the section on Primary pharmacodynamics.

2.3.3. Pharmacokinetics

Methods of analysis

Concentrations of necitumumab in mouse plasma were measured using a non-validated sandwich ELISA for quantifying total human IgG.

Two different methodologies were used to measure necitumumab concentrations in monkey serum during development. Serum concentrations of necitumumab were measured in a pilot single-dose monkey study (Report SSR07006) using a nonvalidated Biacore method. In the 5-week toxicity study in monkeys (Report SSR04010), a validated Biacore method was used to measure serum concentrations of necitumumab. In both the necitumumab lot comparability study (Report 7573-110) and the 26-week toxicity study in monkeys (Report SNBL.023.07), a validated ELISA was used to measure serum concentrations of necitumumab.

Two methods were developed to detect the presence of anti-drug antibodies (ADA) against necitumumab in the serum of monkeys treated with necitumumab in nonclinical toxicology studies. A double antigen radiometric assay specific for necitumumab was developed and validated and used to support the immunogenicity evaluation of serum samples from the 5-week monkey toxicology study (Report CR0878). Serum samples from the 26-week monkey toxicology study (Report SNBL.023.07) and monkey PK comparability study (Report 7573-110) were assessed for immunogenicity using an electrochemiluminescence (ECL) assay that was developed and validated.

Absorption

The pharmacokinetics of necitumumab was characterized after single and multiple doses in mice and single doses in monkeys. The multiple-dose PK study was conducted in Nude mice to determine plasma concentrations of necitumumab that were associated with antitumor effects. A study was conducted in monkeys to compare the single dose pharmacokinetics of 2 different lots from 2 different manufacturing processes, Process B and Process C, of necitumumab. Single dose and multiple dose toxicokinetics of necitumumab were characterized in monkeys as part of the 5-week and 26-week repeat dose toxicity studies.

The key nonclinical pharmacokinetic findings were as follows:

- The half-life of necitumumab in mice following a single intravenous (iv) or intraperitoneal (ip) dose was approximately 4.8 days, which supported a twice weekly dosing strategy to evaluate necitumumab activity in xenograft models.
- Systemic exposure to necitumumab increased with increasing dose in mice and monkeys, but the increases were greater than dose proportional.
- In monkeys, dose-dependent changes in clearance and half-life resulted in a greater than dose-proportional increase in exposure following intravenous administration. Accumulation was observed over 26-weeks of once a week dosing in monkeys.
- The steady-state volume of distribution was approximately equal to the vascular space.
- There were no apparent sex-related differences in necitumumab serum concentrations or resulting TK parameters in cynomolgus monkeys.
- In monkeys, no pharmacokinetic difference was observed between two lots of necitumumab that were manufactured by two different processes.
- Attempts to evaluate the formation of ADA were confounded by high circulating concentrations of necitumumab. However, monkeys were exposed to necitumumab throughout the toxicity evaluations and exposure did not decrease upon repeated dosing.

Table 8: Mean serum pharmacokinetics of necitumumab in cynomolgus monkeys following as single 20.5 mg/kg intreavenous dose.

	T_{max} (hr)	C_{max} (µg/mL)	$t_{1/2}$ (hr)	$AUC_{0\text{-last}}$ (µg·hr/mL)	$AUC_{0\text{-}\infty}$ (µg·hr/mL)	Cl (mL/hr/kg)	Vss (mL/kg)
Mean	0.722	1216	116	115694	115942	0.179	32.8
SD	0.411	387	13.0	14101	14241	0.022	1.9

Distribution

Tissue distribution studies have not been submitted with necitumumab, since it is a monoclonal antibody and is expected to be largely confined to the vascular space (ICHS6R1). This is supported by the relatively low volume of distribution determined in cynomolgus monkeys that suggests that necitumumab is not extensively distributed outside of the vasculature.

Metabolism

Metabolism studies have not been submitted with necitumumab. The catabolism of antibodies by mammalian systems is largely understood, and formal studies of the metabolic degradation of these molecules are not warranted (ICHS6R1).

Excretion

Necitumumab is an antibody and is presumably degraded into component amino acids by general catabolism pathways. Therefore non-clinical elimination studies were not provided (ICHS6R1).

Pharmacokinetic drug interactions

No non-clinical pharmacokinetic drug interaction studies were provided with necitumumab.

2.3.4. Toxicology

The toxicology program for necitumumab is summarised in the table below.

Table 9: Toxicology programme for necitumumab

Study Type and Duration (Report Number)	Route of Administration	Species	Test Article / Lot
Repeated Dose Studies			
5 Weeks with 6-week Recovery (CR0878)	Intravenous	Cynomolgus monkey	necitumumab / 1278-69
26 Weeks with 8-week Recovery (SNBL.023.07)	Intravenous	Cynomolgus monkey	necitumumab / 2158-30
Other Toxicity Studies			
Tissue Cross-reactivity (IM993)	Not Applicable (in vitro)	Tissues from human and cynomolgus monkey	necitumumab / 082803
Human, Monkey and Rat IHC (0409, non-GLP)	Not Applicable (in vitro)	Skin from human, cynomolgus monkey and rat	necitumumab / 082803

Single dose toxicity

No single-dose toxicity studies were performed.

Repeat dose toxicity

5-Week Repeat-Dose Study in Monkeys with a 6-Week Recovery Phase (Report CR0878)

Necitumumab (referred to as IMC-11F8 in the study report) was administered to male and female cynomolgus (3/sex/dose + 3 males/dose for recovery) on Days 1, 15, 22, and 29 by iv infusion at dose levels of 0, 4, 12, and 40 mg/kg as a solution in phosphate-buffered saline.

There was no mortality noted during the study period. There were no test-article-related effects on clinical signs, body weights, body weight gain, food consumption, haematology parameters, clinical chemistry parameters, coagulation parameters, or urinalysis parameters. No test-article-related changes were observed by gross pathologic or histopathologic examination.

Although not statistically significant, the absolute and relative weights of the submandibular glands in 40 mg/kg male and female animals were increased at terminal sacrifice. Relative submandibular organ weights were approximately 30% to 40% greater than those of control animals. In addition, absolute and relative weights of the submandibular glands showed apparent increases in 4 and 12 mg/kg females. Histopathological examination of the submandibular glands did not reveal any abnormalities that would explain the increased weight; thus, these weight changes were not considered adverse by the study pathologist.

Toxicokinetic analysis demonstrated that monkeys at all dose levels were exposed to necitumumab for the entire duration of the study. Blood samples for immunogenicity analyses were collected pre-dose prior to the first and last dose, prior to necropsy, and on the final day of the in-life study (Day 70) for the 9 recovery animals. The presence of an anti-IMC-11F8 immune response was assessed using a double-antigen radiometric assay. There were no apparent alterations in necitumumab exposure to suggest that neutralizing anti-drug antibodies affected the outcome of this study; however, the neutralization potential of the ADA-response was not assessed directly.

26-Week Repeat-Dose Study in Monkeys with an 8-week Recovery Phase (Report SNBL.023.07)

Necitumumab (referred to as IMC-11F8 in the study report) was administered once weekly for 26 weeks by a 10-minute iv infusion to male and female cynomolgus monkeys (3/sex/dose + 2/sex/dose for recovery at dose levels of 0, 6, 19, and 60 mg/kg.

Clinical observations included a dose-dependent time of onset and severity of skin effects (rash and/or erythema, scaling). In the terminal necropsy animals, a test-article-related constellation of skin lesions, collectively referred to as hyperplastic dermatitis, was observed both grossly and microscopically in the skin of the abdomen, inguinal area, mouth, nose, ears, and/or legs in all test-article-treated groups. Hyperplastic dermatitis was characterized by epidermal hyperplasia, hyperkeratosis, and lymphocytic interface inflammation. Histopathologic changes were not observed in any other tissues besides skin. Secondary responses to the epithelial conditions were noted and included hunched appearance and minimal alterations in platelet counts and globulin and albumin concentrations. Clinical observations and changes in clinical pathology resolved in all animals during the recovery period. Dermal observations and gross and microscopic findings were completely resolved at the end of the 8-week recovery period in animals dosed with 6 mg/kg; however, recovery varied in the animals dosed with 19 or 60 mg/kg. The incidence and severity of erythema, dry skin, skin coloration changes, skin condition scores, and hyperplastic dermatitis was decreased, but not completely resolved, at the end of the recovery period.

While 2 animals were found dead or euthanized during the study, neither death was attributed to test article by the study pathologist. There were no treatment-related effects on body weight, food consumption, ophthalmoscopy, heart rate, blood pressure, respiratory rate, electrocardiograms (ECGs), coagulation, urinalysis, or organ weight at any dose level.

A no-observed-adverse-effect level (NOAEL) was not established in the 26-week toxicity study due to adverse skin effects at all dose levels.

Genotoxicity

No genotoxicity studies have been submitted.

Carcinogenicity

No carcinogenicity studies have been submitted.

Reproduction Toxicity

No reproductive and developmental toxicity studies have been submitted.

Toxicokinetic data

Toxicokinetic analyses showed that monkeys at all dose levels in the repeat-dose studies were exposed to necitumumab for most or all of the duration of these studies. In the 5-week study, exposure at the NOAEL dose level (40 mg/kg) was approximately the same as the median exposure expected at the maximum clinical dose level, while exposure at the maximum tolerated dose (MTD) dose level (60 mg/kg) in the 26-week study was approximately 2-fold higher than expected clinical exposure (see table below). Human exposure in the table is total exposure over a 3-week period while animal exposure was measured over a period of no more than 2 weeks (5-week study) or 1 week (26-week study). Thus, the exposure multiples in the table are considered a conservative estimate (i.e. they would likely be higher if exposure over the same length of time were compared).

Table 10Toxicokinetic analyses with necitumumab

	Exposure (AUC, µg·hr/mL)	Exposure Multiple[a]
Human Dose		
800 mg, Day 1 and Day 8, Q3W	112000[b] (0-3weeks)	
Monkey Dose		
5-week repeat-dose NOAEL[c] 40 mg/kg Q7D	103552[e](0-last)	0.92
26-week repeat-dose MTD[d] 60 mg/kg Q7D	233431[f](0-last)	2.1

Abbreviations: AUC = area under the exposure curve, hr= hour, MTD = maximum tolerated dose, NOAEL = no-observed-adverse-effect level.
a Exposure Multiple is the is the exposure in animals at the specified dose divided by the exposure in humans.
b Predicted median (95% CI) AUC over the 3-week cycle during the sixth cycle of 800-mg, iv dosing on Days 1 and 8 (range: 59900 – 201000 µg·hr/mL). Data simulated from the population pharmacokinetic model (I4X-IE-JFCC Population PKPD Report).
c The NOAEL was determined in a 5-week repeat dose toxicity study with a 6-week recovery period (Report CR0878). Necitumumab was administered once weekly at dose levels up to 40 mg/kg.
d The MTD was determined in a 26-week repeat dose toxicity study with an 8-week recovery period (Report SNBL.023.07). Necitumumab was administered once weekly at dose levels up to 60 mg/kg.
e Average of male and female exposure after a single dose.
f Average of male and female exposure after 26-weeks of once weekly dosing.

Local Tolerance

Local tolerance was investigated in the 5-week and 26-week repeat-dose toxicity evaluations in cynomolgus monkeys by clinical observations, and as part of the histopathological evaluations. Intravenous administration of necitumumab was well-tolerated and no treatment-related adverse reactions at the injection site were observed in either study.

Other toxicity studies

Tissue Cross Reactivity

The purpose of this study (Report IM993) was to measure the binding of necitumumab to normal human and monkey tissues. Binding of FITC-labeled necitumumab to 38 tissues in human (n = 3) and monkey (n = 2) was measured. FITC-labeled human IgG was used as a negative control. The positive control tissue was human placental trophoblast epithelium while human placental fibroblasts were used as a negative control tissue.

In most tissues, binding was consistent in both human and monkey tissue, sometimes with minor differences in localization within the organ. There was no unexpected tissue cross-reactivity based on literature and the biology of EGFR (see report for literature references). Overall, the similarities in tissue cross reactivity between cynomolgus monkey and human indicate that monkey is an appropriate species for toxicity testing of necitumumab.

Human, Monkey and Rat Skin IHC (Report 0409)

In non-GLP Report 0409, the binding of FITC-labeled necitumumab (refered to as 11F8 in the study report) was measured in human skin (n = 1), monkey skin (n = 2), and rat skin (n = 2). Rabbit polyclonal anti-human EGFR antibody (NeoMarkers) was used as a positive control. Human IgG was used as a negative control for experiments with necitumumab and rabbit IgG was the negative control for experiments with the polyclonal anti-human EGFR antibody.

In both human and monkey skin, necitumumab bound to the cell membrane of basal cells. The positive control (rabbit polyclonal anti-human EGFR antibody) bound to the cell membrane and cytoplasm of basal cells, while

the negative control rabbit IgG showed weak background binding. There was no specific binding of necitumumab nor the rabbit polyclonal anti-human EGFR antibody to rat skin.

2.3.5. Ecotoxicity/environmental risk assessment

Necitumumab is a protein, which is expected to biodegrade in the environment and not 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), necitumumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

The pharmacology of necitumumab has been adequately addressed. It is to note that in several cases, necitumumab has been compared *in vitro* and *in vivo* with another anti-EGFR IgG1, cetuximab (Erbitux). In all cases the biological activity was very similar.

A large number of NSCLC cell lines were used in xenograft models to assess the antitumor activity of: 1) necitumumab alone; 2) necitumumab in combination with chemotherapy; 3) chemotherapy alone. The Applicant identified EGFR expression as well as KRAS mutations as the most important determinants over NRAS and BRAF for necitumumab antitumoral effect when added to other chemotherapy agents.

The repeat-dose toxicology studies were performed in accordance with Good Laboratory Practice (GLP) regulations with the following main exceptions: Toxicokinetics and immunogenicity analyses. Lack of GLP status for the TK part is a deficiency that may impact on the conclusions drawn from the toxicity study. However, in this case the exposure values are not considered critical for the safety evaluation. Pharmacological effects, expressed as skin toxicity, were seen at all doses in the 26-week study and it is considered that the toxicological profile of necitumumab has been adequately established.

Dose dependent reversible skin toxicity was observed in the 26 week monkey study. The skin effects were consistent with the known class effects of EGFR inhibitors. Skin effects are expected based on the pharmacology of necitumumab and such effects are observed in humans (see clinical safety).

Studies to assess the genotoxicity of necitumumab have not been conducted, which is consistent with ICH Guidances S6 (ICH 2011) and S9 (ICH 2009).

Specific animal studies to test necitumumab for carcinogenic potential, mutagenic potential, or potential to impair fertility have not been performed. Carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer (ICH S9 [ICH 2009]) and there is no cause for concern (ICH S1A) based on the structure or mechanism of action of necitumumab. General toxicology studies on the effect on reproductive organs have been used as the basis of the assessment of impairment of fertility. The risk of fertility impairment is unknown. However, no adverse effects on male or female reproductive organs were observed in monkeys treated for 26 weeks with necitumumab.

Stand-alone developmental and reproductive toxicity (DART) studies of necitumumab have not been conducted based on scientific, regulatory, clinical, and animal use considerations. Based on animal models, epidermal growth factor receptor (EGFR) is involved in prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. Based on the ICH topic S9 guideline

on Nonclinical evaluation of for anticancer pharmaceuticals (EMEA/CHMP/ICH/646107/2008) the CHMP agreed that additional DART studies are not necessary.

Embryofoetal toxicity studies have been performed with two monoclonal antibodies acting on EGFR, cetuximab and panitumumab. In both cases there was maternal as well as embryofoetal toxicity. The embryofoetal toxicity manifested as an increased rate of abortions, but there were no other embryofoetal effects. Based on the available information on target biology and other EGFR inhibitors, necitumumab may cause foetal harm or developmental anomalies. Human IgG1 is also known to cross the placenta; therefore, necitumumab has the potential to be transmitted from the mother to the developing foetus (see sections 4.6 and 5.3 of the SmPC).

2.3.7. Conclusion on the non-clinical aspects

In conclusion, the non-clinical studies (pharmacology, pharmacokinetics and toxicology), submitted for the marketing authorisation application for necitumumab, were considered adequate and acceptable for the assessment of non-clinical aspects. The lack of carcinogenicity, mutagenicity, reproductive and developmental toxicity studies were well justified.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 11: Studies with Data Derived from the Biacore Bioanalytical Assay

Study Code Title	Design	Treatment (Infusion Duration or Rate) [Cycle length]	Necitumumab PK Timepoints (h post end of infusion)	N (M:F) N_{PK}
I4X-IE-JFCE [IMCL CP11-0401] Phase I Study of the Fully Human Anti-Epidermal Growth Factor Receptor (EGFR) Monoclonal Antibody IMC-11F8 in Patients With Solid Tumours Who Have Failed Standard Therapy	Phase 1, single-agent, dose-escalation study	Necitumumab 100, 200, 400, 600, 800, or 1000 mg (<25 mg/min) PK Sampling Period: single dose [2W] Arm A: necitumumab QW [6W] Arm B: necitumumab Q2W [6W]	PK Sampling Period: P, E, 0.5, 1, 2, 4, 8, 24, 48, 96, 168, 264, and 336 h C1, last infusion[a]: P, E, 0.5, 1, 2, 4, 8, 24, 48, 96, 168 h C2+, last infusion[a]: P and 1 h End of therapy Follow-up	N = 60 (35:25) N_{PK} = 59
I4X-IE-JFCD [CP11-0602] Open-Label, Multicenter, Phase 2 Study Evaluating the Efficacy and Safety of IMC-11F8 in Combination with 5-FU/FA and Oxaliplatin (Modified FOLFOX-6) in Patients with Treatment-Naïve, Locally Advanced or Metastatic Colorectal Cancer	Phase 2, single-arm study	Necitumumab 800 mg (>50 min) Q2W mFOLFOX-6 Q2W: Oxaliplatin 85 mg/m^2 (2 h) Folinic acid 400 mg/m^2 (2 h) 5-FU 400 mg/m^2 (2-4 min bolus) 5-FU 2400 mg/m^2 (46 h continuous, immediately following bolus) [2W]	C1, D1: P, E, 1, 2, 4, 24, 72, 96, 144, 168, and 236 h C2-C6, D1: P and 1 h End of therapy Follow-up	N = 44 (25:19) N_{PK}= 42

Abbreviations: 5-FU = 5-fluorouracil; E = end of infusion; FA = folinic acid; C = cycle; D = day; N = number of patients enrolled; N_{PK} = number of patients evaluable for PK noncompartmental analysis; P = pre-infusion; PK = pharmacokinetics; Q = every; W = week.

a For Arm A, the last infusion of each cycle was scheduled for Week 6; for Arm B, the last infusion of each cycle was scheduled for Week 5.

Table 12: Studies with Pharmacokinetic Data Derived from the ELISA Bioanalytical Assay

Study Code	Design	Treatment (Infusion Duration or Rate) [Cycle length]	Necitumumab PK Timepoints (h post end of infusion)	N (M:F) N_{PK}
Studies with a Full PK Profile				
I4X-IE-JFCA [IMCL CP11-0907] A Phase 1 Study of IMC-11F8 in Patients with Advanced Solid Tumours	Phase 1, single-agent, dose-escalation study in Japanese patients	Cohort 1: Necitumumab 600 mg (≤25 mg/min), D1 D8 Q3W Cohort 2: Necitumumab 800 mg (≤25 mg/min), Q2W Cohort 3: Necitumumab 800 mg (≤25 mg/min), D1 D8 Q3W [6W]	**Cohorts 1 and 3:** C1, D1 (I1): P, E, 0.5, 1, 2, 6, 24, 96 h C1, D8 (I2) and D22 (I3): P, 1 h C1, D29 (I4): P, E, 0.5, 1, 2, 4, 8, 24, 48, 96, 168, 264 h C2+, D1 D8: P, 1 h 30d follow up **Cohort 2:** C1, D1 (I1) and D29 (I3): P, E, 0.5, 1, 2, 4, 8, 24, 48, 96, 168, 264 h C1, D15 (I2): P, 1h C2+, D1, D15, and D29: P, 1h	N = 15 (7:8) N_{PK} = 15
I4X-IE-JFCJ [IMCL CP11-1115] An Open-Label, Non-controlled, Non-randomized Sequential Design, Drug-Interaction Study of Necitumumab (IMC-11F8) in Combination with Gemcitabine-Cisplatin in Patients with	Open-label, single-arm study (Phase 2)[a]	3-week PK run in period: Gemcitabine 1250 mg/m^2 (30 min), D1 Cisplatin 75 mg/m^2 (2 h), D1 Necitumumab 800 mg (50 min), D3 Cycles 1-6: Necitumumab 800 mg (50 min), D1 D8 Q3W Gemcitabine 1250	**Necitumumab:** PK run in period, D3: P, E, 0.5, 1, 3, 6.7, 24, 72, 168 h C1, D1[a]: P, E, 0.5, 1, 3, 6.7, 24, 72, 168 h C2-C6, D1: P, 1 h **Gemcitabine[a]:** PK run in period, D1: P, E, 0.5, 1, 2.5, 3.5, 6.2, 24 h C1, D1: P, E, 0.5, 1, 2.5, 4.2, 6.2, 24 h **Cisplatin[a]:**	N = 35 (14:21) N_{PK} = 35

Study Code	Design	Treatment (Infusion Duration or Rate) [Cycle length]	Necitumumab PK Timepoints (h post end of infusion)	N (M:F) N_{PK}
Advanced Solid Cancers		mg/m^2 (30 min), D1 D8 Q3W Cisplatin 75 mg/m^2 (2 h), D1 Q3W [3W]	PK run in period, D1: P, E, 2 min, 0.25, 1, 1.7, 3.7 h C1, D1: P, E, 2 min, 0.25, 1, 1.7, 3.7 h	
I4X-IE-JFCI [IMCL CP11-1114][a] A Study to Determine Whether Necitumumab (IMC-11F8) Monotherapy Affects the Corrected QT (QTc) Interval in Patients With Advanced Solid Tumours	Multicenter, open-label, single-arm monotherapy study (Phase 2)	Necitumumab 800 mg (50 min) QW [6W]	C1, D1 and D36: P, E, 1, 2, 4, 24, 48, 72 h C1, D8, D15, D22, and D29: P, E, 1, 2, 4 h C2-C4 D1: P, E	ongoing[b]
Studies with Trough Concentrations				
I4X-IE-JFCC [IMCL CP11-0806] SQUIRE A Randomized, Multicenter, Open-Label, Phase 3 Study of Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab (IMC-11F8) Versus Gemcitabine-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients With Stage IV Squamous NSCLC	Phase 3, randomized, open-label study	Arm A: Necitumumab 800 mg (≥50 min), D1 D8 Q3W Gemcitabine 1250 mg/m^2 (30 min), D1 D8 Q3W Cisplatin 75 mg/m^2 (2 h), D1 Q3W Arm B: Gemcitabine 1250 mg/m^2 (30 min), D1 D8 Q3W Cisplatin 75 mg/m^2 (2 h), D1 Q3W [3W]	**Arm A** C1-C6, D1: P 30-day follow-up	N = 1093 (908:185) N_{PK} = 470
I4X-IE-JFCB [IMCL CP11-0805] INSPIRE A Randomized, Multicenter, Open-Label Phase 3 Study of Pemetrexed-Cisplatin Chemotherapy Plus Necitumumab (IMC-11F8) Versus Pemetrexed-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients With Stage IV Nonsquamous NSCLC	Phase 3, randomized, open-label study	Arm A: Necitumumab 800 mg (≥50 min), D1 D8 Q3W Pemetrexed 500 mg/m^2 (10 min) D1 Q3W Cisplatin 75 mg/m^2 (2h) D1 Q3W Arm B: Pemetrexed 500 mg/m^2 (10 min) D1 Q3W Cisplatin 75 mg/m^2 (2h) D1 Q3W [3W]	**Arm A** C1-C6, D1: P 30-day follow-up	N = 633 (424:209) N_{PK} = 247

Abbreviations: C = Cycle; D = Day; DP = drug product; DS = drug substance; E = end of infusion; ELISA = enzyme-linked immunosorbent assay; I = Infusion; IND = Investigational New Drug application; N = number of patients enrolled; N_{PK} = number of patients included in the PopPK analysis (note: this number may differ from the numbers for the noncompartmental analysis); P = pre-infusion; PK = pharmacokinetics; PopPK = population PK; Q = every; W = week.

a Study JFCJ had 2 cohorts: Cohort 1 received DP using DS manufactured using Process C while Cohort 2 received DP using DS manufactured using Process D. Necitumumab PK sampling for Cohort 2 on Day 1 of Cycle 1 was scheduled for pre-infusion, 1 and 168 hours post end of infusion. PK sampling for gemcitabine and cisplatin was not done for Cohort 2.

b For Study JFCI, data presented in this summary are based upon an interim analysis.

2.4.2. Pharmacokinetics

PK data is available from 7 clinical studies, 5 with rich sampling and 2 with trough concentrations only (SQUIRE, INSPIRE). During the development of necitumumab, 2 bioanalytical methods were used; initially a Biacore assay and later an ELISA method. In a cross-comparison between the two methods, they produced discrepant results, and only data from the ELISA method were considered reliable and were used in the population PK model.

A population PK analysis was performed using pooled data from the 5 studies applying the ELISA bioassay (see table 16)

Table 13: Studies included in the popPK analysis

Study Code	$n_{Patients}$	Cancer Indication
I4X-IE-JFCA	15	Advanced Solid Tumors
I4X-IE-JFCB	247	Non-Squamous Non-Small Cell Lung Cancer
I4X-IE-JFCC	470	Squamous Non-Small Cell Lung Cancer
I4X-IE-JFCI	40	Advanced Solid Tumors
I4X-IE-JFCJ	35	Advanced Solid Tumors

The pharmacokinetics of necitumumab was best described by a target mediated drug disposition model (TMDD) model.

Absorption

Necitumumab is dosed via the IV route and therefore is completely bioavailable. There have been no studies performed with other routes of administration.

Bioequivalence

The parallel-group pharmacokinetic study JFCJ was performed in patients with mixed solid tumours to study the PK of necitumumab process C (used in the pivotal study) compared with process D (marketing formulation), using the same dosing as in the pivotal trial.

Table 14: Mean Necitumumab Pharmacokinetic Parameters following a 50 Minute Infusion of a Dose of Process C or Process D Necitumumab 800 mg on Day 3 of Run-in Period in Cohort 1 and Cohort 2

Parameter	Necitumumab (Day 3, Run-in, Cohort 1) N=18	Necitumumab (Day 3, Run-in, Cohort 2) N=17
C_{max} (µg/mL)	277 (22)	300[e] (36)
t_{max}[a] (h)	1.54 (0.83-7.50)	1.33[e] (0.80-7.85)
$t_{1/2}$[b] (h)	117[c] (70.1-185)	128[f] (74.3-201)
$AUC_{(0-\infty)}$ (µg *h/mL)	33800[c] (33)	35500[f] (35)
$AUC_{(0-8)}$ (µg *h/mL	1790 (18)	1810[g] (27)
$AUC_{(0-24)}$ (µg *h/mL	5270 (21)	4950[g] (26)
$AUC_{(0-168)}$ (µg *h/mL)	21900 (24)	21600[h] (30)
$AUC_{(0-450)}$ (µg *h/mL)	31300[d] (28)	32000[f] (33)
CL (L/h)	0.0237[c] (33)	0.0225[f] (35)
V_{ss} (L)	3.79[c] (22)	4.05[f] (35)
V_z (L)	4.00[c] (23)	4.17[f] (38)

Abbreviations: $AUC_{(0-\infty)}$ = area under the plasma concentration versus time curve from time zero extrapolated to infinity; C_{max} = maximum plasma drug concentration; CL = Clearance; N = number of subjects who had data for calculation of at least 1 pharmacokinetic parameter; $t_{1/2}$ = terminal half-life; t_{max} = time of maximum plasma drug concentration; V_{ss} = volume of distribution at steady state following intravenous administration; Vz = volume of distribution in the terminal phase.

[a] Median (range).

[b] Geometric mean (range).

[c] n=14, for 4 patients Kel dependent parameters were not calculated because not enough concentration data was available in terminal phase.

[d] n=15

[e] One patient had their C_{max} sample collected (or t_{max}) before the end of infusion .

[f] n=14, not enough data-points were available for calculation of parameter for 3 patients

[g] n=16, not enough data-points were available for calculation of parameter for 1 patient.

[h] n=15, not enough data-points were available for calculation of parameter for 2 patients.

Distribution

Distribution of necitumumab follows a biphasic decline. According to the population PK (PopPK) analysis, the mean volume of distribution at steady state (Vss) for necitumumab was 6.97 L (CV 31 %).

Table 15: Summary of predicted cycle 6 PK parameters for patients receiving 800 mg necitumumab as 1-h IV infusion on Days 1 and 8 of a 3-week cycle

	AUC(0-21d)[a] (µg·h/mL)	C_{max}[b] (µg/mL)	$C_{ss,ave}$[c] (µg/mL)	CL_{tot}[d] (L/h)	V_{ss}[e] (L)
Geometric Mean	111,000	508	221	0.0141	6.97
Geometric CV%	38	32	38	39	31
Median	112,000	509	223	0.0140	6.89
5th Percentile	59,900	302	119	0.00761	4.34
95th Percentile	201,000	843	399	0.0267	11.7

Note: Data simulated using the final PK model for the 807 patients in the PopPK dataset with 13 replicates (>10,000 patients). 800-mg necitumumab doses (1-h IV infusion) administered on Day 1 and Day 8 of each 3-week cycle.

[a] AUC is the total AUC in cycle 6 over the 3-week cycle.

[b] C_{max} is the maximum of the reported simulated concentrations for the Cycle 6, Day 8 profile.

[c] $C_{ss,ave}$ is the average steady-state concentration over the dosing interval: AUC(0-21d)/21d.

[d] Total clearance (CL_{tot}) is the sum of linear and nonlinear clearances: $CL_{tot} = CL + V_{max}/(C+K_m)$ with C being Cycle 6 $C_{ss,ave}$.

[e] Volume at steady state (V_{ss}) is the sum of central (V_1) and peripheral (V_2) volumes of distribution.

Elimination

No studies on the metabolism of necitumumab have been performed in humans, since necitumumab is a therapeutic protein and it is likely cleared mainly via the normal catabolic degradation to small peptides and individual amino acids.

Necitumumab exhibits concentration-dependent clearance. Mean total systemic clearance (CL_{tot}) at steady state following 800 mg on Day 1 and Day 8 of a 21 day cycle was 0.014 l/hr (CV 39 %). This corresponds to a half-life of approximately 14 days. The predicted time to reach steady state was approximately 70 days.

Dose proportionality and time dependencies

Study JFCA was a phase I study conducted in 15 Japanese patients with advanced solid tumours, where necitumumab (600 or 800 mg) was administered on days 1 and 8 every 2 or 3 weeks. Intensive PK sampling was performed after dose 1 and 3 or 4. Geometric mean AUC(0-168) for the 600-mg cohort was 72% of that for the two 800-mg cohorts. Accumulation index was estimated to 1.64 for cohort 2 with dosing Q2W at week 5 (dose 3).

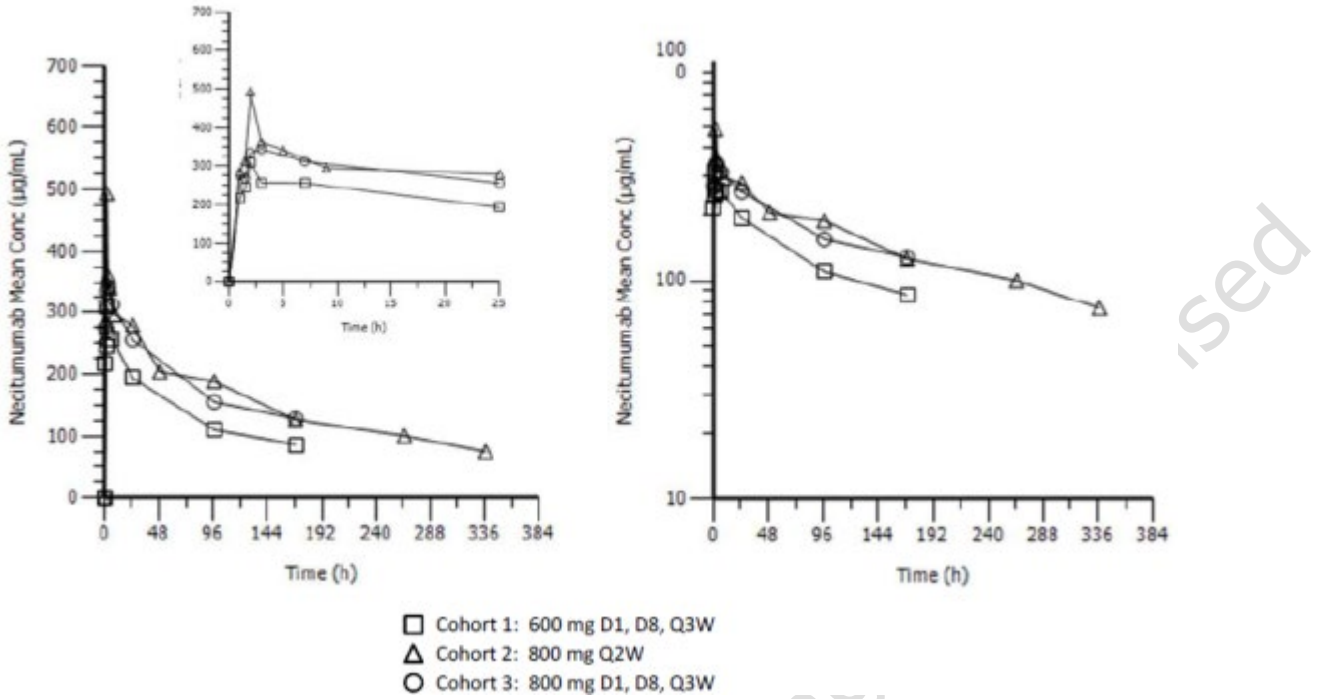


Figure 9: Mean necitumumab serum concentration-time profiles following the third (Cohort 2) or fourth (Cohorts 1 and 3) dose of necitumumab administered I.V. infusion in study JFCA.

A larger number of dose levels was investigated in study JFCE (for further details on the design of the study see section 2.5.1). In this study, an earlier necitumumab formulation was used (formulation A). Full PK sampling was performed, but bioanalysis was performed with the Biacore bioanalytical assay.

Table 16: Mean pharmacokinetic parameters of necitumumab in study JFCE arm B after the first dose.

Dose	n	Cmin (337 h) ug/ml	Cmax ug/ml	Cl ml/h	t1/2 h	AUC0-inf ugxh/ml
100 mg	3	2	38	58.89	60	1 707
200 mg	4	-	75	46.75	60	5 077
400 mg	3	10	179	24.67	84	16 972
600 mg	5	91	584	17.40	98	60 766
800 mg	9	49	505	14.53	121	58 071
1000 mg	9	75	724	11.78	137	95 434

Exploratory simulation on JFCE PK data, that was not submitted by the Applicant, was conducted in order to predict trough levels of necitumumab following dose of 600 mg and 800 mg on Day 1 and Day 2 of a 3-week cycle. The results suggested that only the dose of 800 mg would maintain serum concentration trough levels above 40 µg/mL.

In the pivotal phase III study JFCC (SQUIRE), necitumumab serum concentration-time data were available for 477 patients receiving 800 mg of necitumumab on Days 1 and 8 of a 3-week cycle. Mean pre-dose concentrations are summarised below.

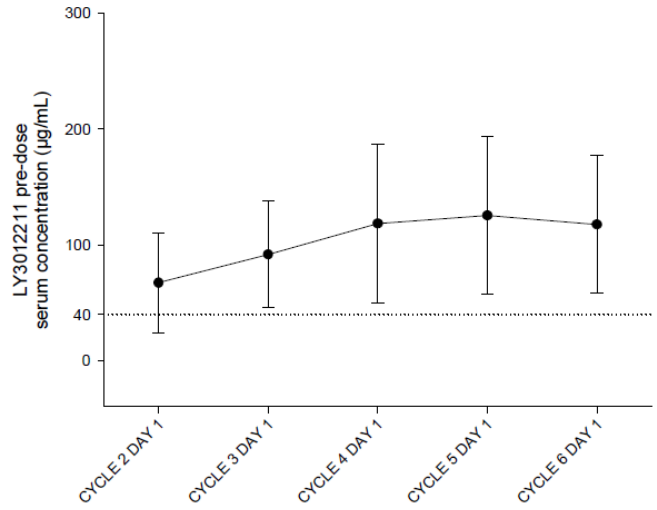


Figure 10: Mean necitumumab predose concentration data following doses of 800 mg administered on Day 1 of a 3-week cycle as an intravenous infusion over approximately 1 hour – Study JFCC

After five cycles of treatment in combination with gemcitabine and cisplatin, the geometric mean of necitumumab in serum from patients with squamous NSCLC, C_{min} was 98.5 µg/mL (Coefficient of Variation 80 %).

Special populations

Impaired renal function

No formal studies have been conducted to evaluate the effect of renal impairment on the PK of necitumumab. Calculated Cl_{crea} was tested as a covariate on Cl in the popPK model (range 36-250 ml/min), but was not found to be relevant.

Impaired hepatic function

No formal studies have been conducted to evaluate the effect of hepatic impairment on the PK of necitumumab. AST (range 5-216), ALT (range 1-387) and bilirubin (range 0.3-31) were tested as covariates on Cl and V in the popPK model, but were not found to be relevant.

Gender

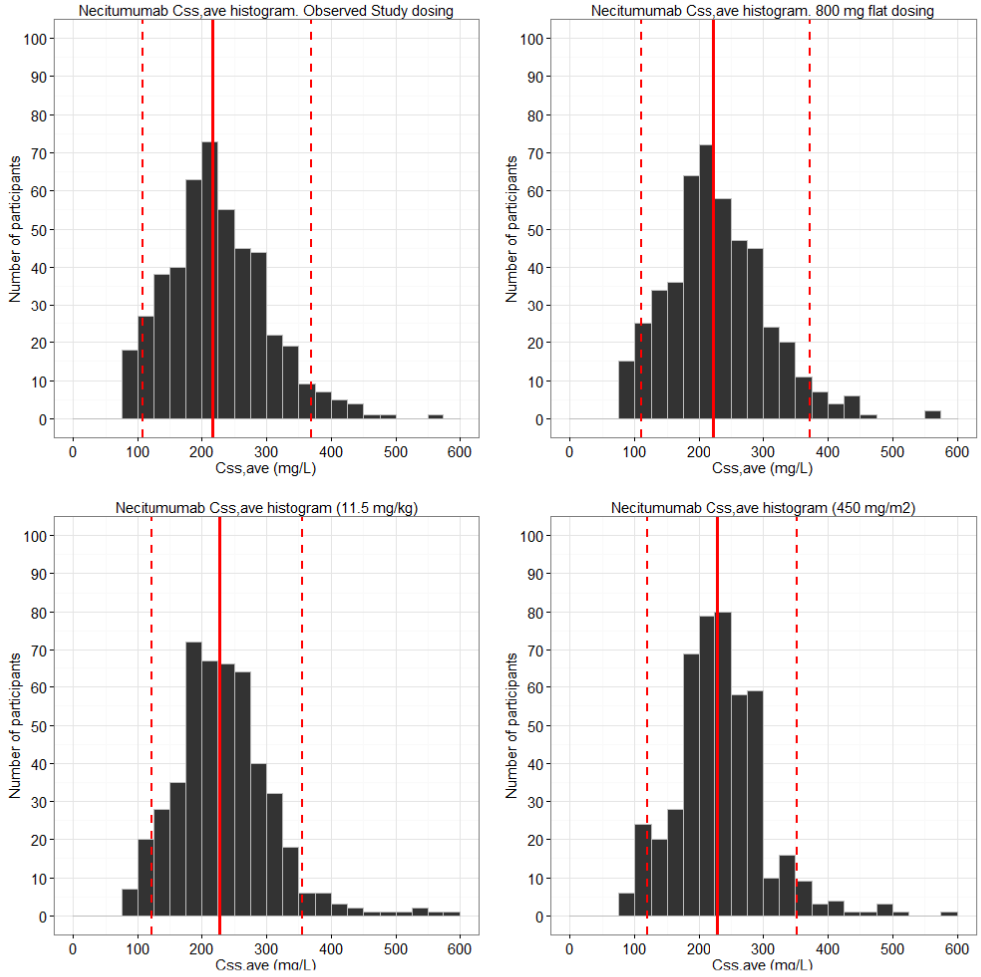
Gender was tested as a covariate on Cl in the popPK model (25% females, 75% males), but was not found to be relevant.

Race

Race was tested as a covariate on Cl in the popPK model (85% white, 7% asian, 2% black), but was not found to be relevant.

Weight

Weight was found to be a covariate in the popPK analysis, with higher V and Cl with increasing weight. The influence of body weight on steady state was however moderate (typical CL_{tot} ranged from 77% to 131% and typical Vss from 84% to 120% of median at 5th and 95th weight percentile. When simulating alternative body size adjusted dosings, no substantial decrease in variability in exposure was evident.



Observed SQUIRE dosing data included for reference. Solid red line represents median, dotted lines the 90% prediction interval.
Abbreviations: BSA = body surface area; $C_{ss,ave}$ = average concentration at steady state.

Figure 11: Predicted Css,ave necitumumab concentrations based on a flat 800 mg, weight-based (11.5 mg/kg) and BSA-based (450 mg/m²) dose regimen administered on Days 1 and 8 of a 3-week regimen.

Elderly

The population PK evaluation included PK data from 807 patients across 5 studies. Age ranged from 19 to 84 years with a median age of 62 years. The table below shows the number (%) of patients by age category for each study.

Table 17

	Age up to 64 N (%)	Age 65-74 N (%)	Age 75-84 N (%)	Age 85+ N (%)
JFCB (N =247)	163 (66.0)	76 (30.8)	8 (3.2)	0
JFCC (N =470)	287 (61.1)	161 (34.3)	22 (4.7)	0
JFCA (N =15)	9 (60.0)	5 (33.3)	1 (6.7)	0
JFCI (N =40)	24 (60.0)	13 (32.5)	3 (7.5)	0
JFCJ (N =35)	26 (74.3)	6 (17.1)	3 (8.6)	0
Total (N =807)	509 (63.1)	261 (32.3)	37 (4.6)	0

Age was tested as a covariate on Cl in the popPK model (range 19-84 years), but was not found to be relevant.

Children

There is no data in children, and use in children is not recommended.

Anti-drug antibody positivity

The impact of ADA on necitumumab PK across studies was assessed in the Population PK and exposure-response report. Patients with at least one post-treatment ADA positive sample show a tendency to higher estimated necitumumab clearance, while patients who express ADA positivity only at baseline (prior to treatment) show little difference to patients with no ADA positive samples.

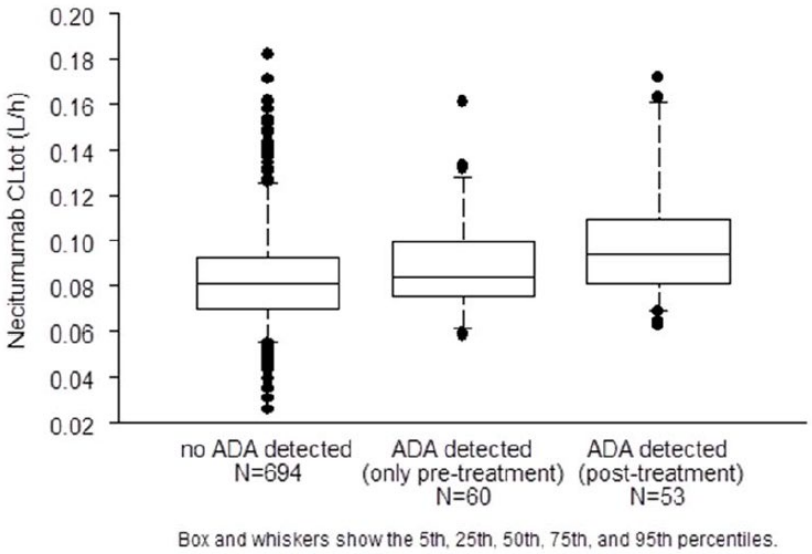


Figure 12: Estimated necitumumab clearance stratified by occurrence of ADA for patients included in the population PK analysis.

Classification of ADA into neutralising and non-neutralising was also performed for the PK-immunogenicity analysis.

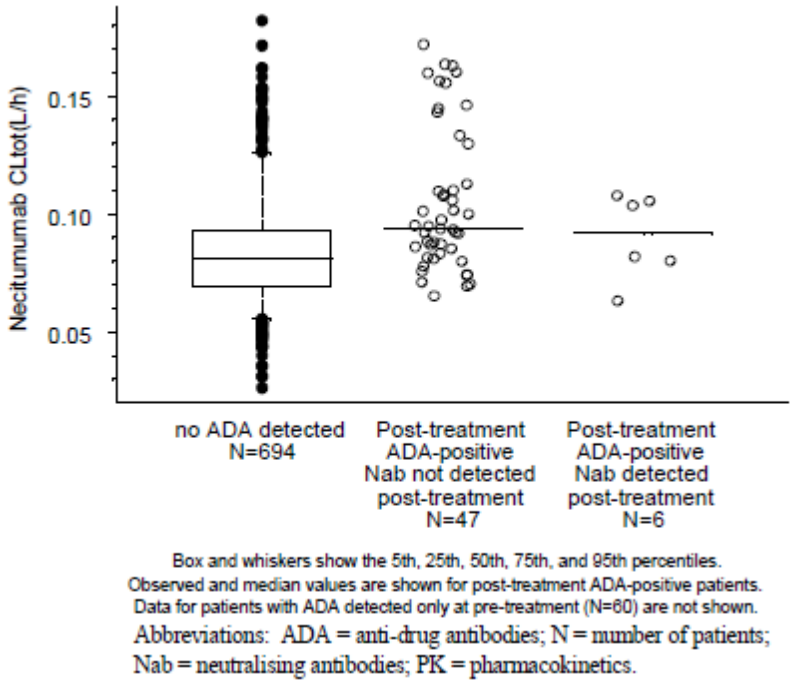


Figure 13: Estimated necitumumab clearance stratified by occurrence of neutralising ADA for patients included in the population PK analysis.

Pharmacokinetic interaction studies

No *in vitro* interaction data is available.

In the pharmacokinetic study JFCJ, performed in patients with mixed solid tumours, potential interactions between gemcitabin/cisplatin and necitumumab were studied. In a PK run-in period, gemcitabine 1250 mg/m^2 iv and cisplatin 75 mg/m^2 iv were given on day 1 and necitumumab was given iv on day 3. In a combination period 3 weeks thereafter, the dosing was as in the proposed labelling, with all 3 drugs administered on day 1. Intensive sampling for pharmacokinetic assessment was performed.

Gemcitabine

Mean plasma concentration-time profiles of gemcitabine 1250 mg/m^2 iv with (day 1 cycle 1) and without (day 1 on PK run-in period) co-administration of necitumumab is shown in Figure 18. A tendency to higher exposure was seen in the combination period. C_{max} was on average higher in Cycle 1 than in PK run-in period (mean ratio 1.66, 90% CI 1.18-2.32), and the same tendency was seen for AUC_{inf} (mean ratio 1.18; 90% CI 0.96-1.46). When looking at the individual values, it was evident that two individuals were responsible for a large part of the increase in C_{max} (Figure 18).

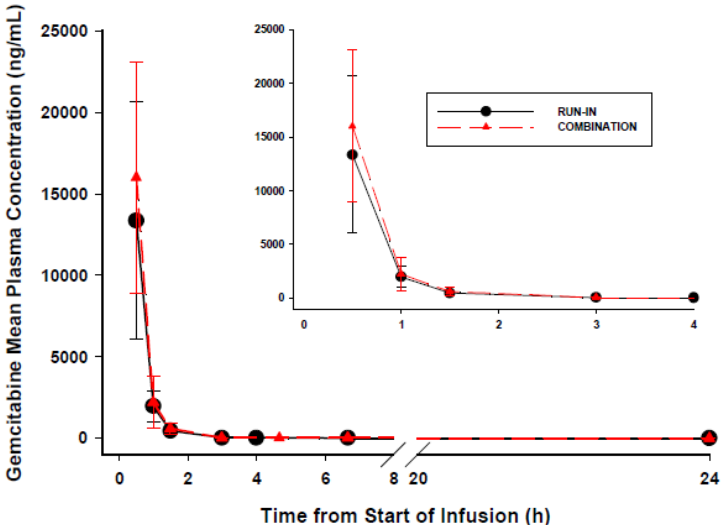


Figure 14. Arithmetic mean (±SD) plasma concentration-time profiles of gemcitabine following 1250 mg/m² gemcitabine administration as a 30-minute infusion on Day 1 of PK Run-in period (N=18) and on Day 1 Cycle 1 of the Combination period (N=12) following necitumumab infusion.

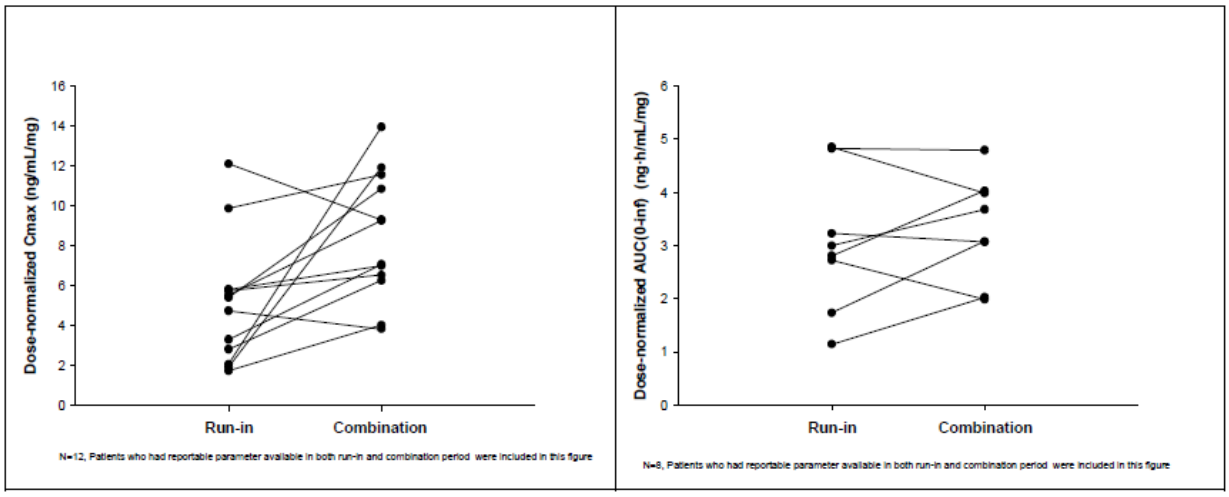


Figure 15: Gemcitabine individual dose-normalized Cmax and AUC(0-inf) following 1250 mg/m² gemcitabine administration as a 30-minute infusion on Day 1 of PK Run-in period (left panel) and on Day 1 Cycle 1 of the Combination period (right panel) following necitumumab infusion.

Cisplatin

Cisplatin 75 mg/m² was administered I.V. over 120 minutes on Day 1 of the PK run-in period and on Day 1 of Cycle 1 following necitumumab and gemcitabine infusions in the combination treatment period. Also for cisplatin, AUC and C_{max} appeared somewhat higher when combined with necitumumab. Geometric mean ratio of AUC0-5h was 1.11 (90% CI 1.06-1.15) and for C_{max} 1.18 (1.11-1.25). The increase was small but observed for most patients.

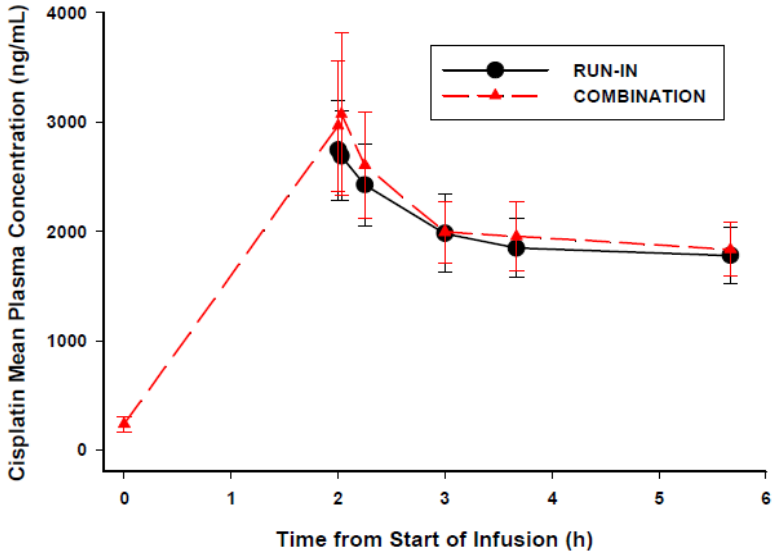


Figure 16: Arithmetic mean (±SD) plasma concentration-time profiles of cisplatin following 75 mg/m² cisplatin administration as a 120-minute infusion on Day 1 of PK Run-in period (N = 18) and on Day 1 Cycle 1 of the Combination period (N = 12) following necitumumab infusion.

Necitumumab PK was measured following administration of 800 mg administered I.V. over 50 minutes on Day 3 of the PK run-in period and on Day 1 of Cycle 1 prior to administration of gemcitabine and cisplatin infusions on the same day in the combination treatment period. There was a tendency to higher C_{max} in the combination period (mean ratio 1.22; 90% CI 1.11-1.34), whereas the difference in AUC was minor (mean ratio 1.08; 90% CI 0.99-1.18).

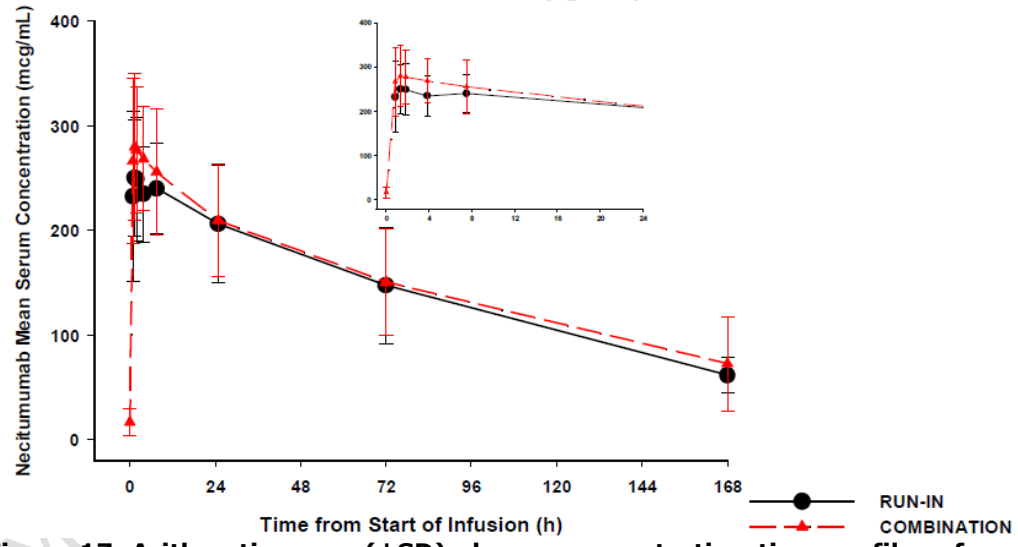


Figure 17: Arithmetic mean (±SD) plasma concentration-time profiles of necitumumab following 800 mg necitumumab administration as a 50-minute infusion on Day 3 of PK Run-in period (N=18) and on Day 1 Cycle 1 of the Combination treatment period (N=12).

Similar concentration-time curves were observed for all three drugs irrespectively of giving them separately or together. Somewhat higher C_{max} was however observed for all three agents (mean ratio gemcitabine 1.66, cisplatin 1.18 and necitumumab 1.22) in the combination period whereas the difference in AUC was minor.

No other formal interaction studies with necitumumab have been performed in humans.

Pharmacokinetics using human biomaterials

The applicant did not submit PK using biomaterials studies

2.4.3. Pharmacodynamics

Mechanism of action

Necitumumab (IMC-11F8; LY3012211) is a recombinant human mAb of the IgG1 class, which targets the EGFR.

Expression of EGFR has been correlated with malignant progression, induction of angiogenesis, and inhibition of apoptosis. It has furthermore been associated with chemoresistance and radioresistance. Inhibition of the EGFR pathway in cells can result in disruption of cell cycle progression and mitosis, decrease angiogenesis, and induce apoptosis. Many common human tumours express EGFR, including lung cancers (Salomon et al. 1995). The EGFR is detectable in tumour specimens in approximately 85% to 90% of patients with metastatic NSCLC (Fontanini et al. 1995; Pirker et al. 2009).

Necitumumab demonstrated a high affinity to EGFRs; binding of necitumumab to EGFRs resulted in blocking of ligand-induced receptor phosphorylation and downstream signalling. *In vitro* studies also demonstrated that necitumumab inhibits EGFR-dependent tumour cell proliferation.

Primary and Secondary pharmacology

As illustrated in the figure below, there was evidence of a correlation between necitumumab exposure and survival in the Phase III study, JFCC (SQUIRE). Exposure-efficacy as well as exposure-safety analyses were performed based on data from this study. In separate models, necitumumab $C_{ss,ave}$ was a significant predictor of both the shrink rate of the tumour ($\Delta OFV = -16$, $p<0.001$) and the hazard for OS ($\Delta OFV = -13$, $p<0.0025$). The OFVs are relative to the base model with ECOG status as a covariate.

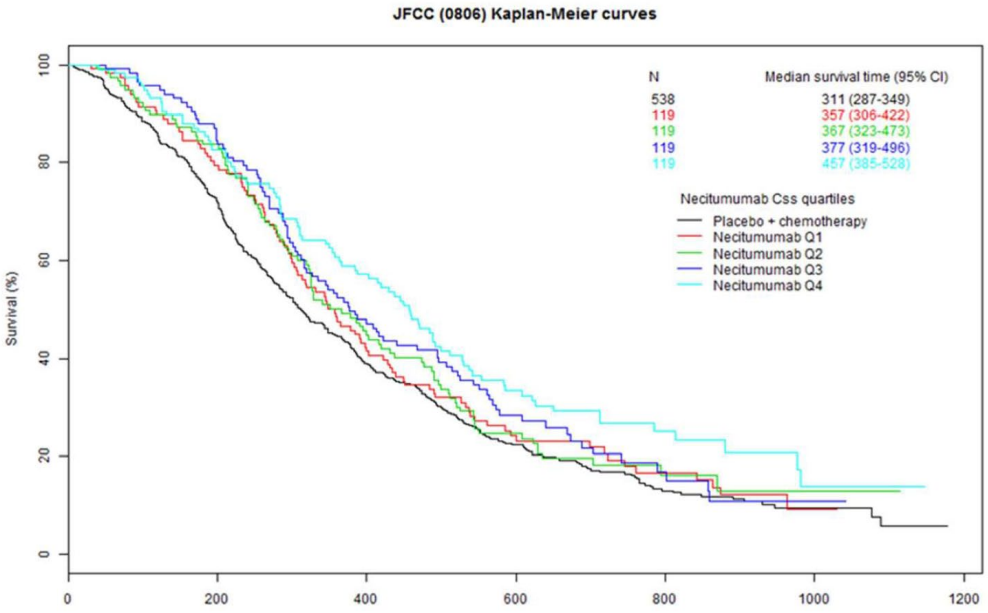
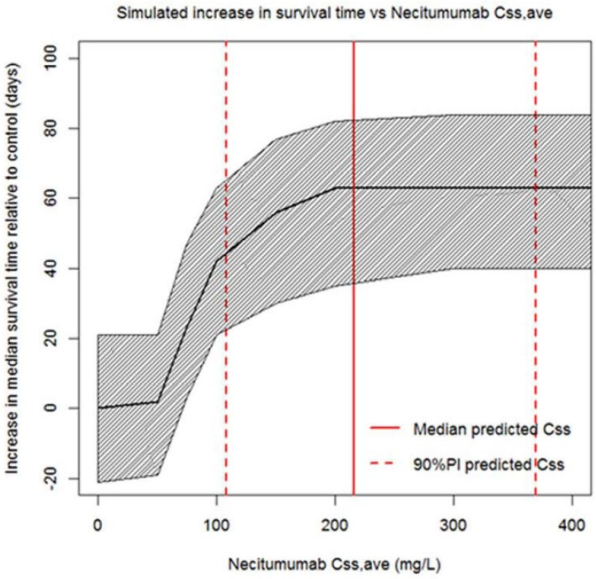


Figure 18: Kaplan-Meier curve of the observed survival in SQUIRE stratified by necitumumab exposure quartiles.

Using the final model, simulations of survival time using various values of necitumumab $C_{ss,ave}$ result in the exposure-response curve shown below.



The shaded area is the 95% confidence interval of the increase in median survival time relative to control. The vertical lines (median and 90% prediction interval) show the predicted range of $C_{ss,ave}$ for patients in the JFCC study.

Figure 19: Necitumumab exposure-response curve for overall survival based on final model.

The figure illustrates the model outcome; that the population median predicted necitumumab $C_{ss,ave}$ of 216 g/mL results in an increase in survival time of about 60 days relative to control, with an effective EC50 of

82µg/mL and an E_{max} of 63 days. Patients in the 5th percentile would experience an increase in survival time of over 40 days, whilst those in the 95th percentile would have in increase of over 60 days.

Exposure response correlations for the risk of AEs thrombocytopenia, rash and hypomagnesaemia could not be established from the available clinical data.

QT evaluation

The effect on QT by necitumumab was investigated in the JFCI study; a Phase II, open-label, non-randomized study conducted in patients with solid tumours. The primary objective of this study was to determine if necitumumab affects the QT/corrected QT (QTc) interval. Patients were administered necitumumab 800 mg once-weekly in 6 week long cycles. Time-matched replicate electrocardiograms and PK samples were collected from patients receiving 800 mg necitumumab once weekly.

The concentration-response plots for data collected in Study JFCI confirm a slight positive slope; however, at twice the Cmax (737.84 ng/mL), the upper bounds of the 90% two-sided CI do not exceed 10 msec for either the QTc-evaluable or QTc-complete population (Table not shown).

One out of 41 patients of QTc-complete population undergoing QT analysis discontinued the study treatment due to QTc prolongation. In the evaluable population, sixteen patients (21.3%) had increases >30 ms in QTcF interval compared with the time matched baseline QTcF interval. One patient had an increase >30 ms at Cycle 2, Week 1 (pre-infusion); all other increases >30 ms occurred in Cycle 1. Therefore, an increase of the QTc interval >30 msec was observed. No cases with QTcF interval >500 ms confirmed by central review or increase of >60 ms were observed.

2.4.4. Discussion on clinical pharmacology

Subcutaneous necitumumab exhibits non-linear pharmacokinetics which is expected for an antibody with target mediated clearance. No time-dependency is expected, and the proposed dosing (with dosing on day 1 and 8 every 3 weeks) results in approximately 2-fold accumulation and a time to steady state of around 70 days, which is in line with the reported half-life.

Population pharmacokinetic analysis suggested age, gender, and race had no effect on the pharmacokinetics of necitumumab, while CL and volume of distribution had a less than proportional positive correlation with body weight. Although modeling results suggest that the disposition of necitumumab was statistically dependent on body weight, simulations indicated that weight-based dosing would not significantly decrease PK variability. No dose adjustment is necessary for these sub-populations.

Based on the results of the popPK analysis, there was no impact of age, renal function as assessed by creatinine clearance [CrCl] on necitumumab exposure. No dose adjustments are required in patients with mild or moderate renal impairment. There are no data regarding necitumumab administration in patients with severe renal impairment. No dose reductions are recommended. Hepatic status (as assessed by alanine aminotransferase, aspartate transaminase and total bilirubin) had no significant effect on the pharmacokinetics of necitumumab. There are no data regarding necitumumab administration in patients with moderate or severe hepatic impairment. No dose reductions are recommended.

Overall, there was a low incidence of both treatment emergent anti-drug antibodies and neutralizing antibodies among necitumumab treated patients, and no correlation with safety outcomes in these patients (see sections 4.2 and 5.2 of the SmPC).

In the dose escalation study I4X-IE-JFCE (IMCL CP11-0401), PK data showed that necitumumab C_{min} reached at 200 mg dose was lower than 40 µg/mL, the level associated with anti-tumoral activity in tumour xenograft models (MEC) throughout the first cycle, and that only at doses higher than 400 mg, necitumumab C_{min} was above the MEC since the first infusion of cycle 1. A flat dose of 800 mg administered every 2 weeks was suggested to be a suitable regimen for further development and PK, non-clinical and limited clinical data appear to support this recommendation (see also section 2.5.1, Dose response study) .

No pharmacokinetic interactions through metabolic enzymes or transporters are expected for an EGFR-antibody. No *in vitro* studies have been performed, which is acceptable. No clinically relevant drug-drug interactions were observed between Portrazza and gemcitabine/cisplatin. The PK of gemcitabine/cisplatin were not affected when co-administered with necitumumab and the PK of necitumumab were not affected when co-administered with gemcitabine/cisplatin (see section 4.5 of the SmPC).

Furthermore, no interaction is expected from a mechanistic point of view, and the efficacy and safety of the combination has been studied in phase III. No further data is required.

The effect on QT by necitumumab was investigated in the JFCI study. The primary objective of this study was to determine if necitumumab affects the QT/corrected QT (QTc) interval. Based on available data from this study the lack of Portrazza effect on QTc cannot be concluded in particular considering the number of sudden unexplained death reported overall in necitumumab clinical trials (see clinical safety).

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetic data submitted for necitumumab sufficiently supports the approval in the final indication. Relevant information is included in the SmPC.

2.5. Clinical efficacy

2.5.1. Dose response study

The recommended dose and schedule of necitumumab is based on safety and PK data from 2 Phase 1 studies in heavily pre-treated patients with advanced solid tumours (14X-IE-JFCE and 14X-IE-JFCA).

I4X-IE-JFCE (IMCL CP11-0401) study – A Phase I study of the fully human anti- EGFR monoclonal antibody IMC-11F8 in patients with solid tumours who have failed standard therapy.

Methods

It is a single agent, dose-escalation study in which necitumumab was administered at doses of 100, 200, 400, 600, 800 or 1000 mg once per week in Arm A and every 2 weeks in Arm B. During the PK sampling period, PK blood samples were collected prior to the initial infusion of necitumumab, immediately after the infusion, and at 0.5, 1, 2, 4, 8, and 24 hours after the completion of the first infusion. Additional PK samples were drawn 48 hours, 96 hours, 168 hours, 264 hours, and 336 hours after the completion of the first infusion of the PK sampling period. A final PK evaluation was performed 45 days after the last dose of necitumumab.

The study population included patients ≥ 18 years of age with histologically confirmed solid tumours and ECOG PS of 0 to 2, life expectancy > 3 months, adequate hepatic, hematologic, and renal function.

A treatment cycle was defined as 6 weeks, with necitumumab (IMC-11F8) treatment every week in Arm A, and every other week in Arm B. Patients in both arms underwent an initial infusion of IMC-11F8 followed by a 2-week PK sampling period prior to the first cycle only. Patients were to undergo treatment until disease progression or until other criteria for study withdrawal were met.

The target dose for IMC-11F8 is hypothesized to be one that maintains IMC-11F8 trough plasma concentrations in excess of 40 µg/mL. Non-clinical PK/pharmacodynamic results have shown that the efficacy of IMC-11F8 (plasma $t_{1/2}$ = 4 to 5 days) in a murine BxPC-3 xenograft model was evident *in vivo* at trough concentrations of 40 µg/mL, indicating an approximate target plasma concentration for the clinic.

For both arms, PK data were used in an attempt to identify a target dose based on achieving a sustained serum trough level of IMC-11F8 of approximately 40 µg/mL and clearance indicating target saturation.

Results

A total of 60 patients completed all screening evaluations and were enrolled into this study at one of the two participating investigational centres. Of these 60 patients, 29 patients were enrolled in Arm A (Necitumumab once per week) and 31 patients were enrolled into Arm B (Necitumumab every 2 weeks).

All 60 patients were analysed for safety and 60 patients were included in the analysis of pharmacokinetic variables. A total of 36 patients were included in the analysis of antibodies against IMC-11F8 and 47 patients were evaluable for response.

Table 18: Pre-treatment Patient Characteristics

	Arm A N = 29	Arm B N = 31
Age (years)		
Mean	59.3	58.6
Median	60.0	59.0
Range	39 - 76	37 - 71
Sex		
Female	11 (37.9%)	14 (45.2%)
Male	18 (62.1%)	17 (54.8%)
Race		
Black	0 (0.0%)	1 (3.2%)
White	29 (100%)	30 (96.8%)
ECOG PS		
0	9 (31.0%)	8 (25.8%)
1	19 (65.5%)	19 (61.3%)
2	1 (3.4%)	4 (12.9%)
Prior Disease-Related Therapy		
Chemotherapy	25 (86.2%)	29 (93.5%)
Hormonal Therapy	3 (10.3%)	2 (6.5%)
Immunotherapy	5 (17.2%)	2 (6.5%)
Radiotherapy	11 (37.9%)	13 (41.9%)
Investigational Agent	5 (17.2%)	12 (38.7%)
Surgery	28 (96.6%)	28 (90.3%)
Tumor Type		
Colorectal	8 (27.6%)	14 (45.2%)
Esophageal	1 (3.4%)	2 (6.5%)
Ovarian	1 (3.4%)	1 (3.2%)
NSCLC	1 (3.4%)	3 (9.7%)
Pancreatic	3 (10.3%)	1 (3.2%)
Prostate	3 (10.3%)	2 (6.5%)
Renal	5 (17.2%)	3 (9.7%)
Stomach	1 (3.4%)	1 (3.2%)
Esophageal and Stomach	0 (0.0%)	1 (3.2%)
Other	6 (20.7%)	3 (9.7%)
Duration of Disease (months)		
Mean	25.9	25.5
Median	21.7	23.6
Range	3.4 - 83.4	1.0 - 84.5

Table 19: By-cohort enrolment of IMCL CP11-0401

Treatment Cohort	Number of Completed Patients[a]	IMC-11F8 Dose Level (mg)	Schedule
		Arm A[b]	
1	3	100	Once a week for 6 weeks
2	3	200	Once a week for 6 weeks
3	3	400	Once a week for 6 weeks
4	3	600	Once a week for 6 weeks
5	3-6[c]	800	Once a week for 6 weeks
6	3-6[c]	1000	Once a week for 6 weeks
		Arm B[b]	
1	3	100	Once every other week for 6 weeks
2	3	200	Once every other week for 6 weeks
3	3	400	Once every other week for 6 weeks
4	3	600	Once every other week for 6 weeks
5	3-6[c]	800	Once every other week for 6 weeks
6	3-6[c]	1000	Once every other week for 6 weeks

[a] Three additional patients were to be evaluated at any dose level where a DLT occurs.

[b] Prior to the initial 6-week cycle of therapy, patients in both Arms A and B (at each dose level) received one IMC-11F8 infusion at their assigned cohort dose level, followed by a 2-week pharmacokinetic sampling period.

[c] Up to six patients were to be enrolled in the final two cohorts of Arms A and B if no DLTs were observed during the first treatment cycle in any dose cohort.

DLT and MTD

Two out of nine patients receiving IMC-11F8 at a dose of 1000 mg every 2 weeks (Arm B) experienced DLTs (one patient with Grade 3 headache and a second patient with Grade 3 headache, nausea, and vomiting) following the first infusion of IMC-11F8. The MTD for every other week administration of IMC-11F8 was therefore set at 800 mg. No MTD was reached for weekly administration in this study.

Tumour activity

Twenty-three of 29 patients in Arm A and 24 of 31 patients in Arm B were evaluable for response i.e. completed at least one cycle of therapy and had post-baseline radiological assessments available.

CR: No patients experienced a complete response.

PR: Two patients (melanoma, colorectal cancer) experienced a partial response (response durations of 15.6 months and 5.6 months respectively).

BOR: Eight patients in Arm A and eight patients in Arm B experienced a best overall response of stable disease, including 8 of 22 patients with colorectal cancer.

DCR: Disease control (CR+PR+SD) was attained in 31% of patients treated with IMC-11F8 once weekly and 29% of patients treated with IMC-11F8 once every 2 weeks. A total of 17 patients were progression free for > 3 months; four patients had a PFS ≥ 9 months, including one patient who remained alive and progression-free for 18.9 months.

Immunogenicity

In Arm A, 29 patients have been tested for the development of anti-IMC-11F8 antibodies. Of these 29, there were 16 patients that had evaluable samples. None of these 16 patients exhibited anti-IMC-11F8 antibodies. In addition, there were two patients with no baseline sample but multiple post-baseline samples tested. Both

patients were negative for anti-IMC-11F8 antibodies. Similarly, in Arm B, 31 patients have been tested for the development of anti-IMC-11F8 antibodies. Of these 31, there were 20 patients that had evaluable samples as defined above. None of these 20 patients exhibited anti-IMC-11F8 antibodies.

In order to further investigate the optimal dose, a second Phase I study (JFCA) was conducted in Japanese patients with solids tumour in which doses of 600 mg and 800 mg (D1 D8 Q3W or D1 Q2W) were administered. In this study both 600 mg and 800 mg (D1 and D8) doses, every 3 weeks, reached through plasma concentration above the MEC, however no patient showed complete or partial responses.

On the basis of DLT data and on overall PK results, the dose of 800 mg was selected to be tested in the pivotal trial. In the pivotal trial SQUIRE, blood sampling revealed that necitumumab pre-dose concentrations on Day 1 in Cycles 2 through 6 were above the target concentration of 40 µg/mL.

14X-IE-JFCA (IMCL CP11-0907) study - A Phase 1 Study of IMC-11F8 in Patients with Advanced Solid Tumors.

Phase 1 study (I4X-IE-JFCA) conducted in 15 Japanese patients in which necitumumab was administered either in a 3-week or in a 2-week cycle. In these patients necitumumab at a dose of 800 mg on Days 1 and 8 of a 3-week cycle showed serum trough concentrations (Cmin) above 40 µg/mL throughout the study. DLTs were not observed during the first 6-week cycle for either the 800 mg on Days 1 and 8 every-3-week regimen or for the 800 mg every-2-week regimen. In this study, no patients experienced an objective response (CR or PR), and a total of 10 patients (66.7%) reported a best overall response of SD, including 9 of 12 patients (75.0%) treated at 800 mg (in Cohorts 2 and 3).

Based on these data, the recommended dose of necitumumab for Phase 2 and 3 studies is the same for Western and Japanese patients.

2.5.2. Main studies

Pivotal study I4X-IE-JFCC (SQUIRE): A Randomised, Multicentre, Open-Label Phase III Study of Gemcitabine-Cisplatin Chemotherapy plus Necitumumab (IMC-11F8) versus Gemcitabine-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients with Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)

Methods

Study Participants

Key inclusion criteria

- Histologically or cytologically confirmed squamous NSCLC, with measurable or non-measurable disease at the time of study entry (per Response Evaluation Criteria in Solid Tumours, Version 1.0).

- Stage IV disease (per the AJCC Staging Manual, Seventh Edition) at the time of study entry.

- Age ≥ 18 years.

- ECOG PS score of 0-2.

- Adequate hepatic, renal, and hematologic function, specifically:

- Total bilirubin ≤ 1.5 x the upper limit of normal (ULN), and aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 5.0 x the ULN in the presence of liver metastases or ≤ 2.5 x the ULN in the absence of liver metastases.
- Serum creatinine ≤ 1.2 x the ULN or calculated creatinine clearance > 50 mL/minute.
- White blood cell count ≥ 3000/µL, absolute neutrophil cell count (ANC) ≥ 1500/µL, hemoglobin ≥ 9.5 g/dL, and platelets ≥ 100,000/µL.

- Archived tumour tissue available for biomarker analysis.

Key exclusion criteria

- Non-squamous NSCLC (adenocarcinoma/large cell or other)

- Prior anticancer therapy with monoclonal antibodies, signal transduction inhibitors, or any therapies targeting the EGFR, vascular endothelial growth factor (VEGF), or VEGF receptor.

- Previous chemotherapy for advanced NSCLC (patients who have received adjuvant chemotherapy were eligible if the last administration of the prior adjuvant regimen occurred at least 1 year prior to randomization).

- Major surgery or any investigational therapy in the 4 weeks prior to randomization

- Chest irradiation within 12 weeks prior to randomization (except palliative irradiation of bone lesions, which was allowed)

- Brain metastases that were symptomatic or required ongoing treatment with steroids or anticonvulsants

- Current clinically relevant coronary artery disease or uncontrolled congestive heart failure, myocardial infarction within 6 months prior to randomization, ongoing or active infection (requiring antibiotics), history of significant neurological or psychiatric

Treatments

Patients in the GC+N Arm received:

- Necitumumab: 800 mg (absolute dose, intravenous [I.V.]) on Days 1 and 8 of each 3 week cycle
- Gemcitabine: 1250 mg/m^2 (I.V.) on Days 1 and 8 of each 3-week cycle (maximum of 6 cycles)
- Cisplatin: 75 mg/m^2 (I.V.) on Day 1 of each 3-week cycle (maximum of 6 cycles)

There was no routine premedication for necitumumab mandated by the study protocol. Pre-emptive treatment for skin reaction was not permitted prior to the beginning of the second treatment cycle.

Patients in the GC Arm received gemcitabine and cisplatin only, at the doses and schedules described above.

Patients in both treatment arms received G+C for a maximum of six cycles. In the GC+N arm, following these six cycles, patients without disease progression continued to receive necitumumab alone until there was radiographic documentation of PD, un-acceptable toxicity, protocol non-compliance, or withdrawal of consent. Patients in the control arm received G+C for a maximum of six cycles with no additional systemic anticancer therapy permitted, until documentation of PD (end of study).

Objectives

Primary Objective

To evaluate the overall survival (OS) in patients with Stage IV squamous NSCLC (per the American Joint Committee on Cancer [AJCC] Staging Manual, Seventh Edition [AJCC7]) treated with necitumumab plus gemcitabine and cisplatin chemotherapy (GC+N Arm) versus gemcitabine and cisplatin chemotherapy alone (GC Arm) in the first-line metastatic setting.

Secondary Objectives

- To evaluate progression-free survival (PFS), objective response rate (ORR) and time to treatment failure (TTF) in each arm;

- To evaluate the safety profile of necitumumab in combination with gemcitabine and cisplatin chemotherapy;

- To evaluate the pharmacokinetics (PK) and immunogenicity of necitumumab (GC+N Arm only);

- To evaluate Health Status.

Exploratory Objectives

Exploratory objectives were to further evaluate the relationships between biomarkers (related to the EGFR-pathway and the mechanism of action of necitumumab) and efficacy and safety outcomes, as follows:

- Tumour Tissue: Biomarkers that may have included, but were not limited to, EGFR protein expression (as measured by immunohistochemistry [IHC]), human epidermal growth factor receptor-2 (HER2) and HER3 protein expression (measured by IHC), and EGFR gene copy number (measured by fluorescence in situ hybridization [FISH]).

- Whole Blood: Biomarkers that may have included, but were not limited to, FCγR single nucleotide polymorphisms (by polymerase chain reaction [PCR]-based method).

- Plasma Proteomics: Various circulating factors that may have included, but were not limited to, epiregulin, amphiregulin, and transforming growth factor-α (TGFα).

Further biomarkers related to NSCLC aetiology may also have been evaluated on tumour tissue of patients who provided an additional consent.

Outcomes/endpoints

Primary efficacy endpoint:

Overall survival (OS) defined as the time from the date of randomization to the date of death from any cause.

Secondary efficacy endpoints:

Secondary efficacy endpoints included PFS, TTF, and ORR including disease control rate (DCR).

- Progression-Free Survival (PFS) defined as the time from randomisation until the first radiographic documentation of objective progression as defined by RECIST 1.0, or death from any cause.

- TTF defined as the time from randomisation to the first observation of progressive disease, death due to any cause, early discontinuation of treatment or initiation of new anticancer therapies.

- ORR is equal to the proportion of patients achieving a best overall response of confirmed partial or complete response (PR + CR), according to RECIST (Version 1.0) from the start of the treatment until disease progression/recurrence.

- DCR is equal to the proportion of patients achieving a best overall response of CR, PR, or stable disease (PR+CR+SD), according to RECIST 1.0. Radiographic evaluations were to be repeated every 6 weeks (± 3 days) following the first dose of study therapy until radiographic documentation of progressive disease.

- Safety: treatment-emergent adverse events (TEAEs) were defined as events that met either of the following criteria:

- Onset date occurred any time during or after the administration of the first dose of study treatment or up to 30 days after the last dose of study treatment (or up to any time if serious and related to study treatment); or
- The event occurred prior to the date of first dose and worsened while on therapy or up to 30 days after the last dose of study treatment (or up to any time if serious and related to study treatment).

Drug Concentration Measurements:

In the GC+N Arm only, blood samples for serum PK analysis were to be drawn at baseline (prior to the first [Cycle 1] infusion of necitumumab), and prior to the first necitumumab infusion (Day 1) in Cycles 2 through 6. PK parameters to be reported included, but were not limited to, trough (Cmin) concentrations of necitumumab.

Immunogenicity Measurements

Immunogenicity was to be assessed using serum drawn prior to the necitumumab infusion on Day 1 of Cycles 1, 3, and 5 (GC+N Arm only). An additional sample was to be collected at the 30-day safety follow-up visit. Immunogenicity samples were also to be obtained in the setting of a hypersensitivity or infusion-related reaction, as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.

Health Status Assessments

Patient Health Status was to be assessed using:

- the Patient Lung Cancer Symptom Scale (LCSS), a self-reported disease- and site specific instrument consisting of nine items including six major lung cancer symptoms and three global measures of symptom distress, activity, and quality of life (Hollen et al. 1994);

- The EQ-5D, a nonspecific and standardized instrument for use as a measure of self-reported health status (EuroQoL 1990) designed to be used in conjunction with other patient-reported measures (Nord et al. 1991).

Health status assessments were to be performed pretreatment (within 14 days of randomization), prior to the first infusion of Cycles 1-6, and every 6 weeks (± 3 days) thereafter until PD. Both instruments were to be administered together and in sequence order (the Patient LCSS first, directly followed by the EQ-5D instrument).

Sample size

A sample size of 1080 patients was based upon the assumption of a 27-month accrual period, a follow-up of 19 months after the last patient was enrolled and 1:1 randomization to treatment and control arms, respectively. A dropout rate of 5% was considered. This sample size will allow detection of an improvement in median OS from

11 months for gemcitabine-cisplatin alone to 13.75 months for IMC-11F8 plus gemcitabine-cisplatin (HR = 0.80), with a two-tailed log-rank test at the 0.05 significance level and a power of 90%. Final analysis was to be performed when at least 844 OS events (deaths) are observed.

Randomisation

Patients were randomized (ratio 1:1) to each of the two treatment arm by an Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS), according to a stratified, permuted block randomization plan. Randomization was stratified by ECOG PS (0-1 vs. 2) and geographic region (North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia).

Blinding (masking)

Not applicable as the study was open-label.

Statistical methods

Primary efficacy analyses were performed on ITT population.

The primary endpoint OS was estimated using the Kaplan-Meier method, and compared between the treatment groups using the log-rank test, stratified by ECOG PS and geographic region. The overall significance level was set at 0.05. The HR and its 95% confidence limit was estimated from a stratified proportional hazard model (Cox model). An unstratified log-rank test was also performed.

In the event that a statistically significant result was observed for the primary analysis of primary endpoint (OS), the secondary endpoints PFS and ORR were tested. Hochberg's method was used to adjust for multiplicity testing for the secondary endpoints. If the least significant p-value from PFS and ORR analyses was smaller than 0.05, both null hypotheses were rejected to claim significance for both endpoints PFS and ORR. Otherwise, if the most significant p-value was smaller than 0.025, the null hypothesis was rejected for this endpoint and the result was considered statistically significant.

PFS was compared using a stratified log-rank test (an additional unstratified log-rank test was also performed). The estimation of survival curves for the two treatment groups were generated using Kaplan-Meier methodology. A stratified Cox regression model to compare the treatments was performed to generate the HR. A sensitivity analysis was performed using alternative censoring roles for the ITT population.

TTF was compared across treatment groups using the same methodology as for PFS.

The ORR and DCR in each treatment group were compared using the Cochran-Mantel-Haenszel (CMH) test adjusting for the stratification variables.

Subgroup analysis was performed for OS, PFS and ORR, by assigned treatment arm, provided that there was a sufficient number of events in the subgroup. Each analysis used the similar methodology as for the primary analysis. Subgroup analysis was unstratified. A forest plot of the estimated HRs with 95% CIs was provided.

Health Status (LCSS and EQ-5D) data were separately summarized by treatment and time points using descriptive statistics and graphic displays.

Regarding LCSS, for each of the 12 variables based on the 9 item of patient scale, all patients with a baseline value and at least one post-baseline value were included in the analyses. Treatment hazard ratio for TTD was estimated using Cox proportional hazards models with assigned treatment arm as the only cofactor. For checking the robustness and sensitivity of the Cox model results, log-rank and Wilcoxon statistics were calculated as additional comparisons between treatment arms. The proportions of patients who had sustained

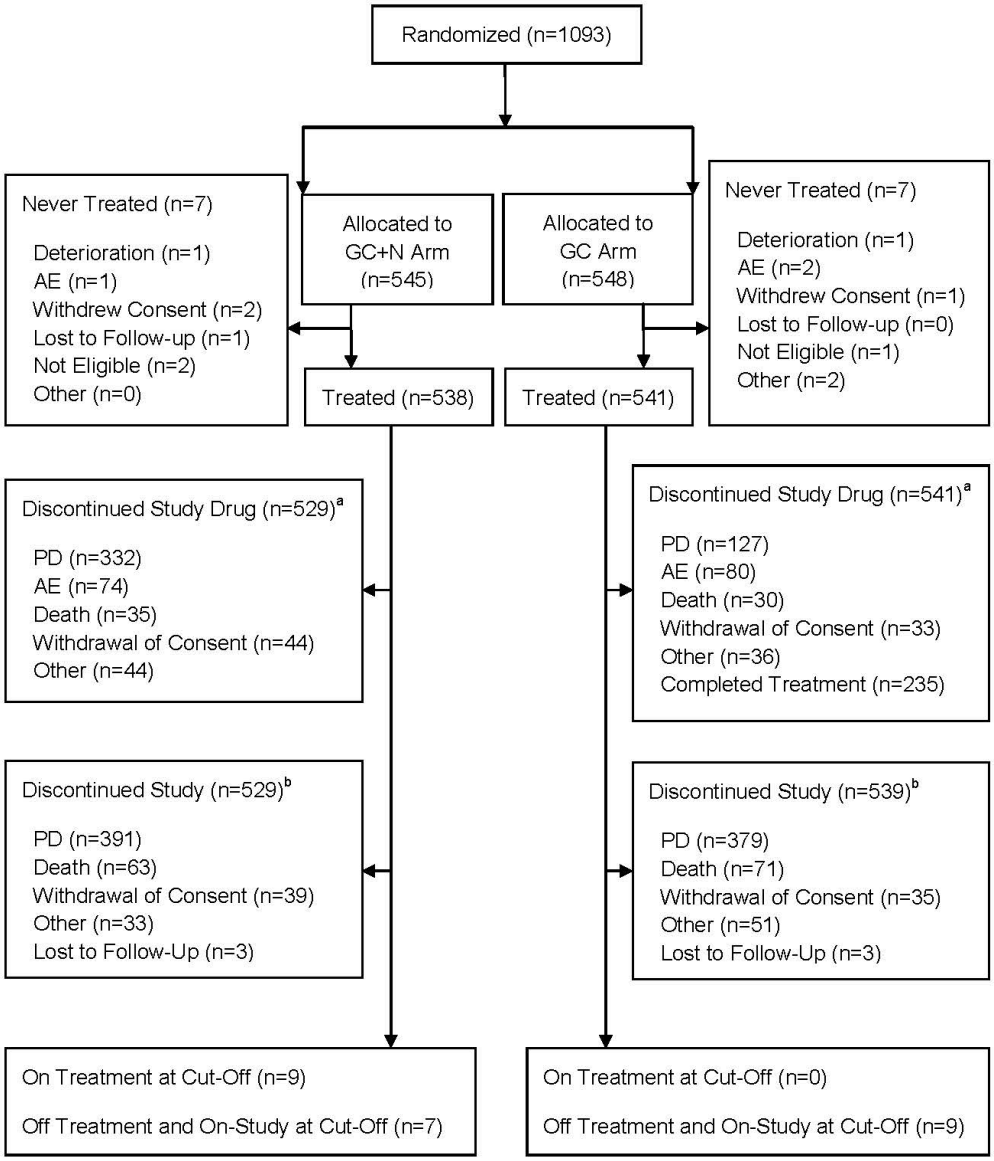
improvement, deteriorated, and were stable will be summarized and compared between study treatment arms using Fisher's exact test.

For EQ-5D, the frequency and percentage of patient's responses have been graphically presented (i.e., stacked bar charts over time) for each of the 5 dimensions by treatment arm and at each assessment time. The index score and the VAS have been presented using summary statistics (i.e., change from baseline), but also using box plots over time.

To evaluate its predictive role, the EGFR protein expression has been assessed by IHC assay in archived tumour tissue, using the commercially available Dako EGFR PharmaDx kit. A Cox regression analysis was performed for time-to-event endpoints, and logistic regression was performed for binary outcomes. Pre-specified subgroup analyses were performed, which assessed the treatment effect within each EGFR-defined subgroup. Additionally, interactions were tested using models in which biomarker, treatment and treatment-by-biomarker interaction were included as explanatory variables. The main effect model (without an interaction term) was also explored. Hazard ratio estimates from a Cox regression model were calculated.

Results

Participant flow



Abbreviations: AE = adverse event; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; n = number of patients; PD = progressive disease.
a Differences between arms in terms of patients discontinuing treatment due to PD and withdrawal of consent are attributable to the study design (i.e., patients in the GC+N Arm were planned to receive 6 cycles of chemotherapy plus necitumumab followed by necitumumab monotherapy until PD or other withdrawal criteria were met, while patients in the GC Arm were planned to receive a maximum of 6 cycles of chemotherapy and then followed for disease progression).
b Discontinuation of all assessments following PD or for other reasons.

Recruitment

From January 2010 to February 2012, a total of 1093 patients have been randomized at a total of 184 sites across 26 countries with the main contributing countries Russia, Poland, Germany, Hungary, Romania, Brazil and France. The first patient randomised was on 7 January 2010 and the data cut-off date was on 17 June 2013.

Conduct of the study

The original protocol, issued on 23 July 2009, was amended 6 times. Important changes from each protocol revision are summarised in the table below:

Table 20

Protocol Version	Version Date	Summary of main changes
2	20 Apr 2010	At the request of FDA for the parallel ongoing study CP11-0805/JFCB, references to "Stage IIIb or Stage IV" NSCLC were changed throughout to "Stage IV". The American Joint Committee on Cancer (AJCC) Staging Manual Version 7 became effective on 1 January 2010. The Version 2.0 protocol was updated to reference Version 7. Per this revision, those patients which would have been classified as "Stage IIIb with cytologically confirmed malignant pleural effusion" according to the sixth edition, and the previous protocol, were now included under the definition of "Stage IV". Guidelines for the radiographic evaluation of disease were revised, based on advice from the Steering Committee.
2.1	12 May 2010	Correction of the EUDRACT number on the cover of the protocol
3	09 June 2011	Increase of study power from 85% to 90%, thereby reducing the Type II-error from 15% to 10%. The sample size was then increased from 947 to1080. The protocol-defined HR and the level of significance remained the same. Important safety information regarding thromboembolic events from the INSPIRE study was added to the study protocol.
4	11 Oct 2011	Only administrative changes.
5	28 Mar 2013	Description of the immunogenicity results assessment using redeveloped validated immunogenicity assay. Definition of biomarker analyses as exploratory objectives.
6	14 May 2013	Correction of typographical error in the study synopsis.

Baseline data

Table 21: Patient Demographic Characteristics at Baseline as Reported on the Case Report Form (ITT Population) – SQUIRE study

Characteristic	GC+N N = 545 n (%)	GC N = 548 n (%)	Total N = 1093 n (%)
Age (years)			
Median	62.0	62.0	62.0
Range	32 – 84	32 - 86	32 - 86
Age Group, n (%)			
<65 years	332 (60.9)	340 (62.0)	672 (61.5)
≥65 years	213 (39.1)	208 (38.0)	421 (38.5)
<70 years	437 (80.2)	451 (82.3)	888 (81.2)
≥70 years	108 (19.8)	97 (17.7)	205 (18.8)
Sex, n (%)			
Male	450 (82.6)	458 (83.6)	908 (83.1)
Female	95 (17.4)	90 (16.4)	185 (16.9)
ECOG PS at baseline, n (%)			
0	164 (30.1)	180 (32.8)	344 (31.5)
1	332 (60.9)	320 (58.4)	652 (59.7)
2	49 (9.0)	47 (8.6)[a]	96 (8.8)[a]
Race, n (%)			
White	457 (83.9)	456 (83.2)	913 (83.5)
Asian	43 (7.9)	42 (7.7)	85 (7.8)
Black or African American	5 (0.9)	6 (1.1)	11 (1.0)
All Others[b]	40 (7.3)	44 (8.0)	84 (7.7)
Smoking History			
Ex-Light Smoker	18 (3.3)	26 (4.7)	44 (4.0)
Non-Smoker	26 (4.8)	27 (4.9)	53 (4.8)
Smoker	500 (91.7)	495 (90.3)	995 (91.0)
Missing	1 (0.2)	0	1 (0.1)
Geographic Region			
North America, Europe, Australia	472 (86.6)	475 (86.7)	947 (86.6)
South America, South Africa, India	30 (5.5)	32 (5.8)	62 (5.7)
Eastern Asia	43 (7.9)	41 (7.5)	84 (7.7)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category.

a One patient with ECOG PS = 3 at baseline was randomized to the GC Arm; this patient did not receive treatment.

b Including eCRF categories "American Indian or Alaska Native," "Native Hawaiian or Other Pacific Islander," "Multiple Race," and "Other."

Source: Section 14.1, Table JFCC.14.9.

Table 22: Summary of Baseline Disease Characteristics (ITT Population) – SQUIRE study

	GC+N N = 545	GC N = 548	Total N = 1093
Duration of Disease (months)[a]			
Mean (SD)	3.78 (10.738)	3.43 (10.033)	3.61 (10.388)
Median	0.72	0.72	0.72
Range	0.0 – 107.3	0.0 – 105.5	0.0 – 107.3
Disease Stage at Study Entry[b], n (%)			
IIIB without malignant pleural effusion (AJCC 6)	1 (0.2)	1 (0.2)	2 (0.2)
IV[c]	543 (99.6)	546 (99.6)	1089 (99.6)
Missing	1 (0.2)	1 (0.2)	2 (0.2)
Disease Histology, n (%)			
Squamous	543 (99.6)	545 (99.5)	1088 (99.5)
Other Histology[d]	2 (0.4)	3 (0.5)	5 (0.5)
Number of Metastatic Organ Systems, n (%)			
1 organ system	51 (9.4)	50 (9.1)	101 (9.2)
2 organ systems	193 (35.4)	193 (35.2)	386 (35.3)
>2 organ systems	301 (55.2)	304 (55.5)	605 (55.3)
Sites of Metastatic Disease, n (%)			
Bone	120 (22.0)	131 (23.9)	251 (23.0)
Brain	28 (5.1)	30 (5.5)	58 (5.3)
Liver	109 (20.0)	117 (21.4)	226 (20.7)
Lung	453 (83.1)	453 (82.7)	906 (82.9)
Lymph Nodes	431 (79.1)	451 (82.3)	882 (80.7)
Peritoneal	20 (3.7)	17 (3.1)	37 (3.4)
Pleural	149 (27.3)	155 (28.3)	304 (27.8)
Skin	9 (1.7)	8 (1.5)	17 (1.6)
Soft Tissue	23 (4.2)	21 (3.8)	44 (4.0)
Other	156 (28.6)	146 (26.6)	302 (27.6)

Abbreviations: AJCC = American Joint Committee on Cancer; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; NSCLC = non-small cell lung cancer; SD = standard deviation.

a Duration of disease is the time from initial diagnosis until date of randomization.

b Per AJCC Staging Manual, edition effective at the time of randomization (Sixth or Seventh Edition).

c Includes patients with Stage IIIb disease with malignant pleural effusion, defined as Stage IV under AJCC7.

d No confirmation of squamous NSCLC (considered as major protocol deviation; see Section 10.3).

Source: Section 14.1, Table JFCC.14.12 and Table JFCC.14.13.

Table 23: Anticancer Treatments Prior to Study Entry (ITT Population) – SQUIRE study

	GC+N N = 545 n (%)	GC N = 548 n (%)	Total N = 1093 n (%)
Any Prior Surgery	117 (21.5)	106 (19.3)	223 (20.4)
Any Prior Radiotherapy	42 (7.7)	46 (8.4)	88 (8.1)
Any Prior (Adjuvant/Neoadjuvant) Systemic Therapy	23 (4.2)	17 (3.1)	40 (3.7)
Carboplatin-Paclitaxel	7 (1.3)	5 (0.9)	12 (1.1)
Cisplatin-Docetaxel	1 (0.2)	4 (0.7)	5 (0.5)
Cisplatin-Gemcitabine	3 (0.6)	0	3 (0.3)
Cisplatin-Vinorelbine	9 (1.7)	4 (0.7)	13 (1.2)
Docetaxel	2 (0.4)	0	2 (0.2)
Other	5 (0.9)	7 (1.3)	12 (1.1)

Abbreviations: GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category.

Source: Section 14.1, Table JFCC.14.14 and Table JFCC.14.15.

Table 24. Overview of Post-Study Systemic Anticancer Therapy (ITT Population) – SQUIRE study

	GC+N N = 545 n (%)	GC N = 548 n (%)
Any Therapy[a]	**258 (47.3)**	**245 (44.7)**
Carboplatin/Paclitaxel	15 (2.8)	14 (2.6)
Cisplatin/Docetaxel	1 (0.2)	4 (0.7)
Cisplatin/Gemcitabine	9 (1.7)	14 (2.6)
Gemcitabine/Vinorelbine	2 (0.4)	0
Paclitaxel/Cisplatin	2 (0.4)	0
Cisplatin/Vinorelbine	4 (0.7)	1 (0.2)
Docetaxel	167 (30.6)	127 (23.2)
Erlotinib	57 (10.5)	75 (13.7)
Gemcitabine	16 (2.9)	12 (2.2)
Pemetrexed	4 (0.7)	1 (0.2)
Vinorelbine	40 (7.3)	33 (6.0)
None	0	1 (0.2)
Other	76 (13.9)	86 (15.7)
Any Later Line Therapy		
Any Third-Line Therapy	84 (15.4)	83 (15.1)
Any Fourth-Line Therapy	28 (5.1)	19 (3.5)

Abbreviations: GC =gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; ITT = intent-to-treat; N = number of patients; n = number of patients in category.

[a] Patients may have received more than 1 regimen.

Source: Section 14.3.1, Table JFCC.14.201.

About 46 % of the patients received post-study systemic anticancer therapy. In the GC + N arm, 51 % of patients continued with single agent Necitumumab after completing chemotherapy. Use of post study systemic therapy was similar in the 2 arms (47.3 % in the Portrazza+GC arm and 44.7 % in the GC arm).

Table 25: Patient Disposition ITT Population – SQUIRE study

	GC+N N = 545 n (%)	GC N = 548 n (%)	Total N = 1093 n (%)
Treated	538 (98.7)	541 (98.7)	1079 (98.7)
Never Treated	7 (1.3)	7 (1.3)	14 (1.3)
On-Treatment[a]	9 (1.7)	0	9 (0.8)
Reason for Discontinued from Treatment[a,b]	**529 (97.1)**	**541 (98.7)**	**1070 (97.9)**
Due to Radiographically Documented PD	314 (57.6)	104 (19.0)	418 (38.2)
Due to Symptomatic Deterioration	18 (3.3)	23 (4.2)	41 (3.8)
Due to Death	35 (6.4)	30 (5.5)	65 (5.9)
Due to Withdrawal of Consent[c]	44 (8.1)	33 (6.0)	77 (7.0)
Due to an Adverse Event	74 (13.6)	80 (14.6)	154 (14.1)
Due to Completion of Therapy	0	235 (42.9)	235 (21.5)
Due to Loss to Follow-Up	5 (0.9)	0	5 (0.5)
Due to Other Reasons	39 (7.2)	36 (6.6)	75 (6.9)
Off Treatment but On Study Evaluation[a,d]	**7 (1.3)**	**9 (1.6)**	**16 (1.5)**
Discontinued from Study[a,d]	**529 (97.1)**	**539 (98.4)**	**1068 (97.7)**
Due to Radiographically Documented PD	371 (68.1)	348 (63.5)	719 (65.8)
Due to Symptomatic Deterioration	20 (3.7)	31 (5.7)	51 (4.7)
Due to Death	63 (11.6)	71 (13.0)	134 (12.3)
Due to Withdrawal of Consent[c]	39 (7.2)	35 (6.4)	74 (6.8)
Due to Loss to Follow-Up	3 (0.6)	3 (0.5)	6 (0.5)
Due to Other Reasons	33 (6.1)	51 (9.3)	84 (7.7)

Abbreviations: GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; N = number of randomized patients; n = number of patients in category; PD = progressive disease.

a As of data cutoff date 17 June 2013.

b Primary reason for discontinuation as assigned by the investigator; for this analysis, adverse events, progression of disease, and death are considered as separate events.

c Includes patients who withdrew from treatment but permitted subsequent follow-up as well as those who withdrew from treatment and subsequent follow-up.

d Discontinuation of all assessments following PD or for other reasons.

Numbers analysed

Table 26: Analysis populations – SQUIRE study

	GC+N	GC	Total
ITT Population, N	545	548	1093
Per Protocol Population[a], n (%)	535 (98.2)	537 (98.0)	1072 (98.1)
Safety Population (As Treated)[b]	538	541	1079
TR Population[c], n (%)	486 (89.2)	496 (90.5)	982 (89.8)

Abbreviations: EGFR = epidermal growth factor receptor; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; SAP = statistical analysis plan.

a Includes randomized patients who received at least 1 cycle of study therapy, and did not have any major protocol violations (defined prior to database lock in the SAP, provided as an appendix to this report [Documentation of Statistical Methods]) during the study.

b Includes all patients who received any quantity of study therapy.

c Includes all patients who: (1) were in the safety population; (2) had a valid non-missing result for EGFR H-Score.

Outcomes and estimation

Primary efficacy endpoints

Overall Survival

Table 27: Overall Survival (ITT Population) – SQUIRE study

	GC+N N =545	GC N = 548
Number of deaths, n (%)	418 (76.7)	442 (80.7)
Number censored, n (%)	127 (23.3)	106 (19.3)
Log-rank p-value (two-sided) Stratified*	.0120	
Hazard ratio[b] (95% CI[b]) Stratified*	0.842 (0.736, 0.962)	
Median OS[a] – months (95% CI[a])	11.5 (10.4, 12.6)	9.9 (8.9, 11.1)
Survival rate[a] % (95% CI)[a]		
6-month	78.9 (75.2, 82.1)	72.3 (68.3, 75.9)
1-year	47.7 (43.3, 51.9)	42.8 (38.5, 47.0)
18-month	28.9 (25.0, 32.9)	24.3 (20.7, 28.1)
2-year	19.9 (16.3, 23.7)	16.5 (13.2, 20.1)

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; OS = overall survival.

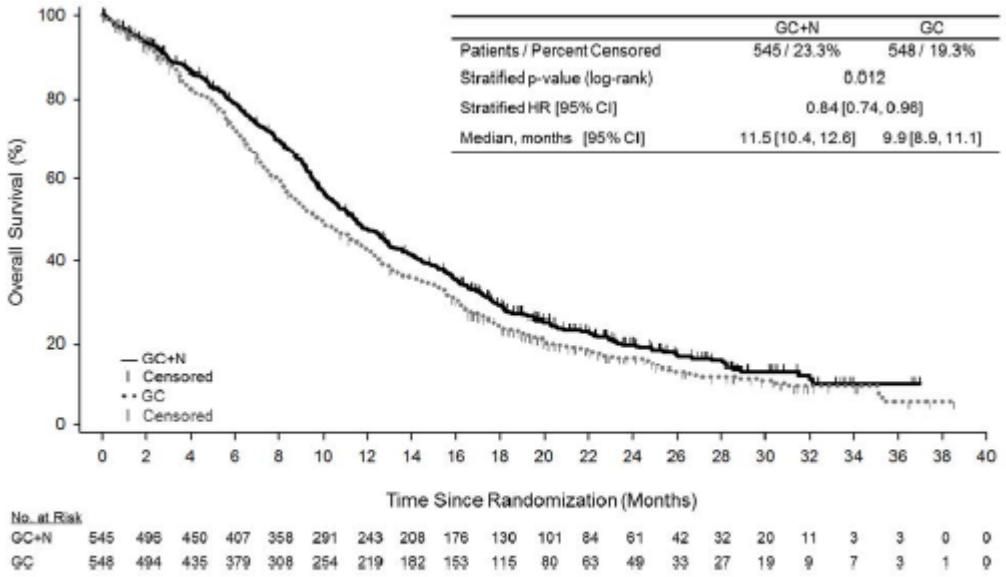
* Stratified by the randomization strata (ECOG PS [0-1 vs. 2], and geographic region [North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia]).

a Estimated by the Kaplan-Meier method.

b Hazard ratio is expressed as treatment/control and estimated from Cox model.

Source: Section 14.2, Table JFCC.14.18.

Table 28: Kaplan-Meier curve for overall survival (ITT Population) – SQUIRE study



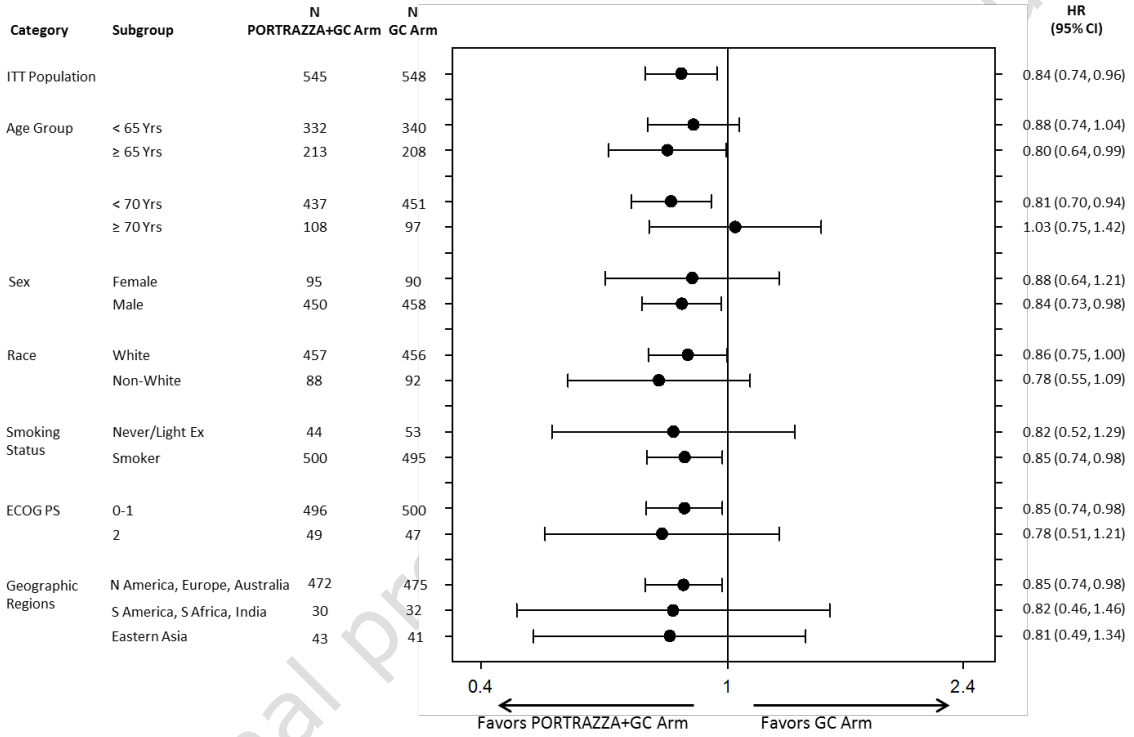
Abbreviations: CI = confidence interval; cis = cisplatin; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; gem = gemcitabine; HR = hazard ratio; ITT = intent-to-treat; neci = necitumumab; No. = number.

Table 29: Overall Survival – Pre-specified Sensitivity Analyses– SQUIRE study

	HR (95% CI)	p-Value
Primary Analysis		
IVRS strata – 860 events	0.842 (0.736, 0.962)	.0120
Sensitivity Analyses		
PP Population – Stratified	0.847 (0.740, 0.970)	.0167
PP Population – Unstratified	0.857 (0.749, 0.981)	.0250
Unstratified analysis	0.850 (0.744, 0.972)	.0176
Exactly 844 events	0.833 (0.727, 0.953)	.0081
Adjusting for potential prognostic factors	0.850 (0.742, 0.973)	.0184
Using CRF strata	0.834 (0.729, 0.954)	.0080

Abbreviations: CI = confidence interval; CRF = case report form; HR = hazard ratio; ITT = intent-to-treat; IVRS = interactive voice/web response system; N = number of randomized patients; n = number of patients in category; PP = per-protocol.

Table 30: Forest plot of hazard ratio for subgroup analysis of OS (ITT Population) – SQUIRE study



Abbreviations: C = cisplatin; G = gemcitabine; ITT = intent-to-treat.

The overall number of events in the study at the time of the analysis is about 79 %.

Secondary efficacy endpoints

Progression-Free Survival

Per protocol, tumour response was assessed with imaging intervals of six (±3 days) weeks for both arms until documentation of PD.

Table 31: Progression-Free Survival (ITT Population) – SQUIRE study

	GC+N N =545	GC N = 548
Number of events, n (%)	431 (79.1)	417 (76.1)
Number censored, n (%)	114 (20.9)	131 (23.9)
Log-rank p-value (two-sided) Stratified*	.0201	
Hazard ratio[b] (95% CI[b]) Stratified*	0.851 (0.743, 0.975)	
Median PFS – months (95% CI[a])	5.7 (5.6, 6.0)	5.5 (4.8, 5.6)
PFS rate[a] % (95% CI)[a]		
3-month	79.3 (75.5, 82.6)	72.5 (68.4, 76.3)
6-month	44.6 (40.0, 49.0)	37.2 (32.7, 41.6)

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; GC =gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; PFS = progression-free survival.

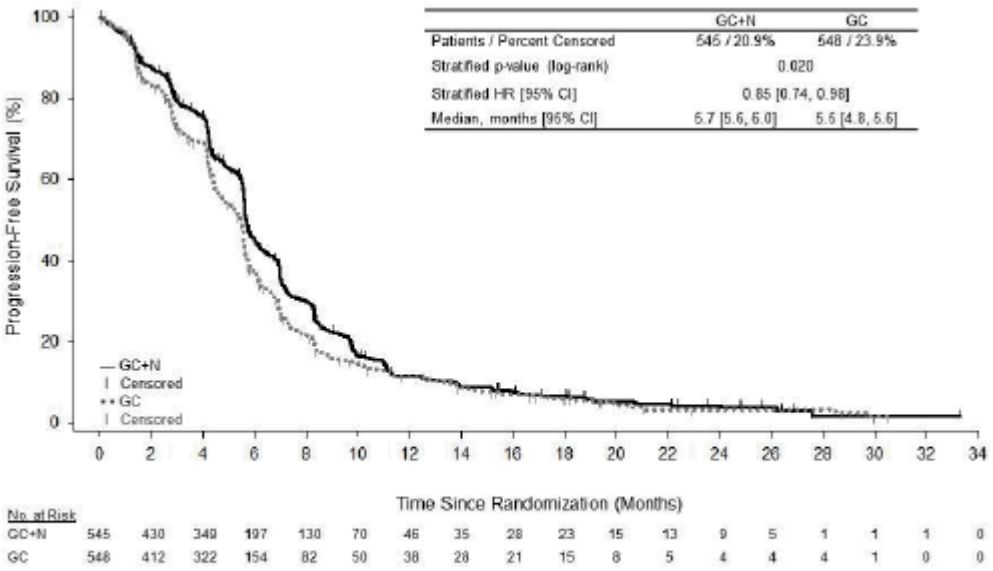
* Stratified by the randomization strata (ECOG performance status [0-1 vs. 2], and geographic region [North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia]).

a Estimated by the Kaplan-Meier method.

b Hazard ratio is expressed as treatment/control and estimated from Cox model.

Source: Section 14.2, Table JFCC.14.26.

Table 32: Kaplan-Meier curve for progression-free survival (ITT Population) – SQUIRE study



Abbreviations: cis = cisplatin; GC =gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; gem = gemcitabine; ITT = intent-to-treat; neci = necitumumab; No. = number.

Table 33: PFS – Prespecified Sensitivity Analyses – SQUIRE study

	HR (95% CI)	p-Value
Primary Analysis		
ITT Population	0.851 (0.743, 0.975)	.0201
Sensitivity Analyses		
PP Population – Stratified	0.856 (0.747, 0.981)	.0254
PP Population – Unstratified	0.857 (0.749, 0.982)	.0257
Unstratified analysis	0.852 (0.744, 0.975)	.0196
Adjusting for potential prognostic factors	0.831 (0.725, 0.952)	.0077
Sensitivity Analysis 1[a]	0.849 (0.743, 0.970)	.0161
Sensitivity Analysis 2[b]	0.857 (0.749, 0.980)	.0237
Sensitivity Analysis 3[c]	0.851 (0.746, 0.969)	.0147
Sensitivity Analysis 4[d]	0.849 (0.742, 0.972)	.0177
Sensitivity Analysis 5[e]	0.859 (0.750, 0.984)	.0277
Using CRF strata	0.847 (0.740, 0.971)	.0169

Abbreviations: CI = confidence interval; CRF = case report form; GC+N Arm = necitumumab in combination with gemcitabine and cisplatin; HR = hazard ratio; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category.

a Including symptomatic deterioration in the definition for progression (along with radiographically documented progressive disease) and death.

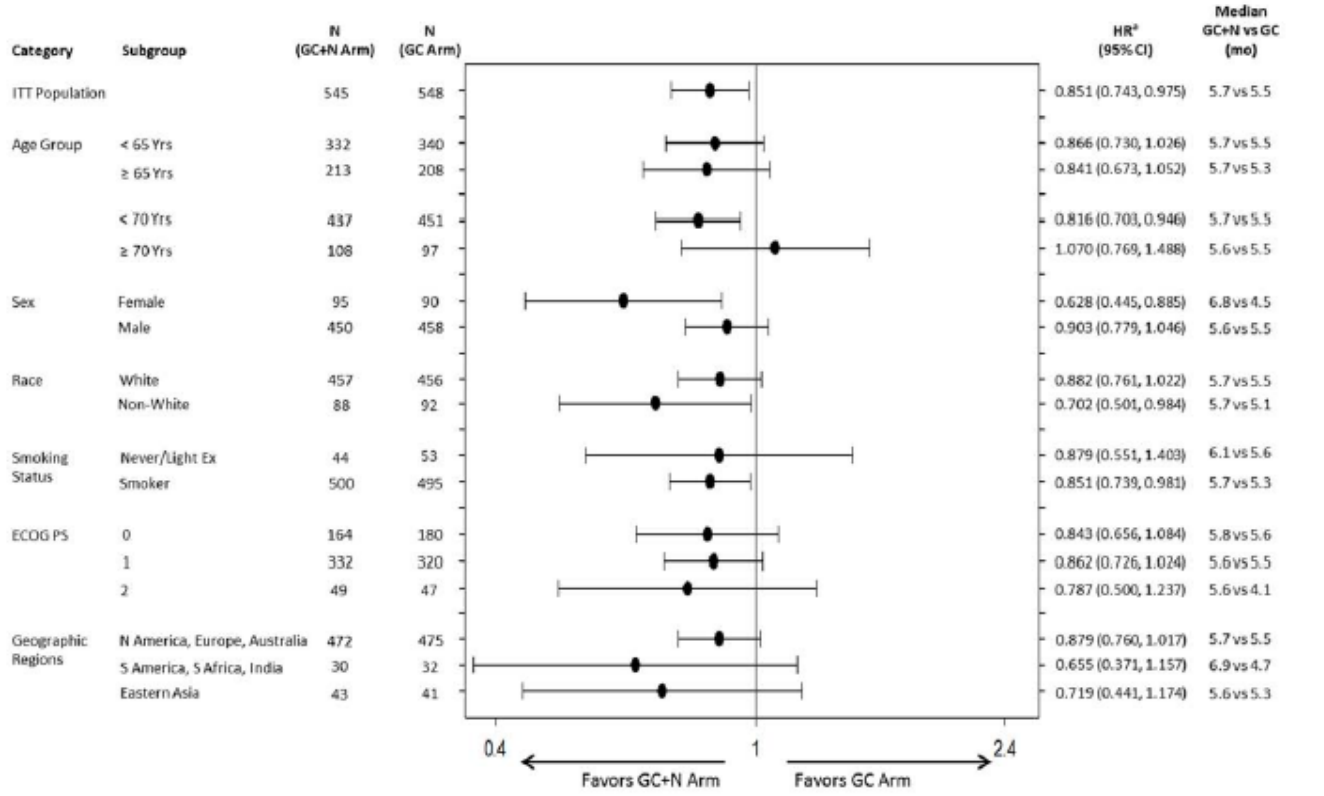
b Removing censoring for new anticancer therapy.

c Treating progression or death after ≥2 missing assessments as progression at the first missing assessment.

d Treating loss to follow-up as progression at the next scheduled visit after last tumor assessment.

e Treating loss to follow-up as progression for the GC+N Arm at the next scheduled visit after last tumor assessment.

Table 34: Forest plot of hazard ratio for subgroup analysis of PFS (ITT Population) – SQUIRE study



Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; GC Arm = gemcitabine and cisplatin; GC+N Arm = necitumumab in combination with gemcitabine and cisplatin; HR = hazard ratio; ITT = intent-to-treat; mo = months; N = number of patients in category.

a Stratified HR for ITT population; unstratified HR for subgroups.

Objective Response Rate and Disease Control Rate

Table 35: Overall Response (ITT Population) – SQUIRE study

	GC+N N = 545	GC N = 548	p-Value[a]
Best Overall Response n (%)			
CR	0	3 (0.5)	
PR	170 (31.2)	155 (28.3)	
SD	276 (50.6)	264 (48.2)	
PD	41 (7.5)	55 (10.0)	
NE	4 (0.7)	12 (2.2)	
NA	54 (9.9)	59 (10.8)	
Objective response rate[b] n (%) (95% CI)[c]	170 (31.2) (27.4, 35.2)	158 (28.8) (25.2, 32.8)	.3997
Disease control rate[d] n (%) (95% CI)[c]	446 (81.8) (78.4, 84.8)	422 (77.0) (73.3, 80.3)	.0433

Abbreviations: CI = confidence interval; CR = complete response; GC =gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; NA = no assessment; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

a Derived from two-sided Cochran-Mantel-Haenszel test adjusting for the randomization strata: Eastern Cooperative Oncology Group performance status (0-1 vs. 2) and geographic region (North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia).

b Response rate = CR + PR.

c Estimated using the Wilson formula.

d Disease control rate = CR + PR+ SD.

Source: Section 14.2, Table JFCC.14.37.

Table 36: Summary of efficacy by selected subgroups, ITT population – SQUIRE study

	Overall Survival			Progression-free Survival			Objective Response			Disease Control	
	GC+N	GC	HR	GC+N	GC	HR	GC+N	GC		GC+N	GC
Subgroup	Median (mo)		p-value	Median (mo)		p-value	ORR		OR	DCR	
ITT Population	N = 545	N =548	0.84	N = 545	N =548	0.85	N = 545	N =548	1.12	N = 545	N = 548
	11.5	9.9	p = 0.0120	5.7	5.5	p = 0.0201	31.2	28.8		81.8	77.0
Patients with ECOG PS 2	N = 49	N = 47	0.78	N = 49	N = 47	0.79	N = 49	N = 47	0.48	N = 49	N = 47
	9.5	6.9	p = 0.2748	5.6	4.1	p = 0.2923	10.2	19.1		65.3	59.6
Patients with 3 risk factors[a]	N = 47	N = 50	0.86	N = 47	N = 50	0.82	N = 47	N = 50	0.48	N = 47	N = 50
	6.5	7.2	p = 0.5014	4.2	3.2	p = 0.4049	17.0	30.0		59.6	64.0
Patients enrolled in Hungary	N = 43	N = 41	1.18	N = 43	N = 41	0.88	N = 43	N = 41	0.51	N = 43	N = 41
	10.2	11.4	p = 0.4942	5.7	5.6	p = 0.6284	20.9	34.1		69.8	70.7
Patients enrolled in Poland	N = 69	N = 59	1.04	N = 69	N = 59	1.27	N = 69	N = 59	0.64	N = 69	N = 59
	9.9	10.2	p = 0.8219	5.6	5.5	p = 0.2243	26.1	35.6		87.0	89.8

Abbreviations: DCR = disease control rate; ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; HR = hazard ratio; ITT = intent to treat; mo = month; N = number of patients; OR = odds ratio; ORR = objective response rate.

a Risk factors include: leukocytes >11,000/µL (11 x 10^9/L), BMI <18.5 kg/m^2 or BMI ≥35 kg/m^2, haemoglobin <11.5 g/dL, Platelets ≥350 x 10^9/L.

Time to Treatment Failure

Table 37: Time to Treatment Failure (ITT Population) – SQUIRE study

	GC+N N =545	GC N = 548
Number of events, n (%)	529 (97.1)	528 (96.4)
Disease progression	312 (57.2)	280 (51.1)
Death	1 (0.2)	30 (5.5)
Early discontinuation of study treatment for any reason other than 'completed treatment' (for GC Arm)	214 (39.3)	202 (36.9)
Initiation of new anti-cancer therapy	2 (0.4)	16 (2.9)
Number censored, n (%)	16 (2.9)	20 (3.6)
Alive without treatment failure	9 (1.7)	13 (2.4)
No treatment received	7 (1.3)	7 (1.3)
Stratified log-rank p-Value (2-sided)	.0061	
Stratified HR[b] (95%CI)	0.844 (0.747, 0.953)	
Median TTF[a], months (95% CI)[a]	4.3 (4.2, 4.8)	3.6 (3.3, 4.1)

Abbreviations: CI = confidence interval; GC =gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; HR = hazard ratio; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; TTF = time to treatment failure.

a Estimated by the Kaplan-Meier method.

b Hazard ratio is expressed as treatment/control and estimated from Cox model.

Note: Stratified log-rank test, as well as the hazard ratio from a stratified proportional hazard model, is stratified by the randomization strata: ECOG performance status (0-1 vs. 2) and geographic region (North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia).

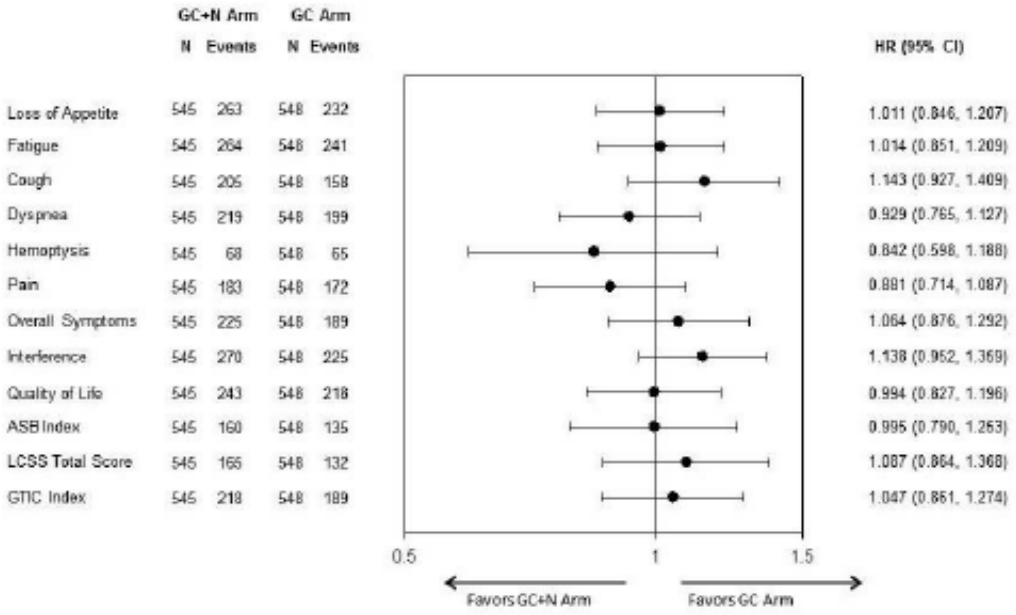
At the time of the analysis virtually all patients had had an event. Over 50 % was due to disease progression. An estimated reduction in the risk of treatment failure of 16% in GC+N Arm was observed with a median gain of close to a month.

Health Status

- Lung Cancer Symptom Scale (LCSS)

Of the 545 patients in the GC+N Arm, 481 (88.3%) had a baseline and at least one completed post-baseline LCSS assessment. In the GC Arm, 482 (88%) of the 548 patients had a baseline and at least one completed post-baseline LCSS assessment.

Table 38: Forest plot of hazard ratio and the 95% CI for time to deterioration of LCSS scores– SQUIRE study

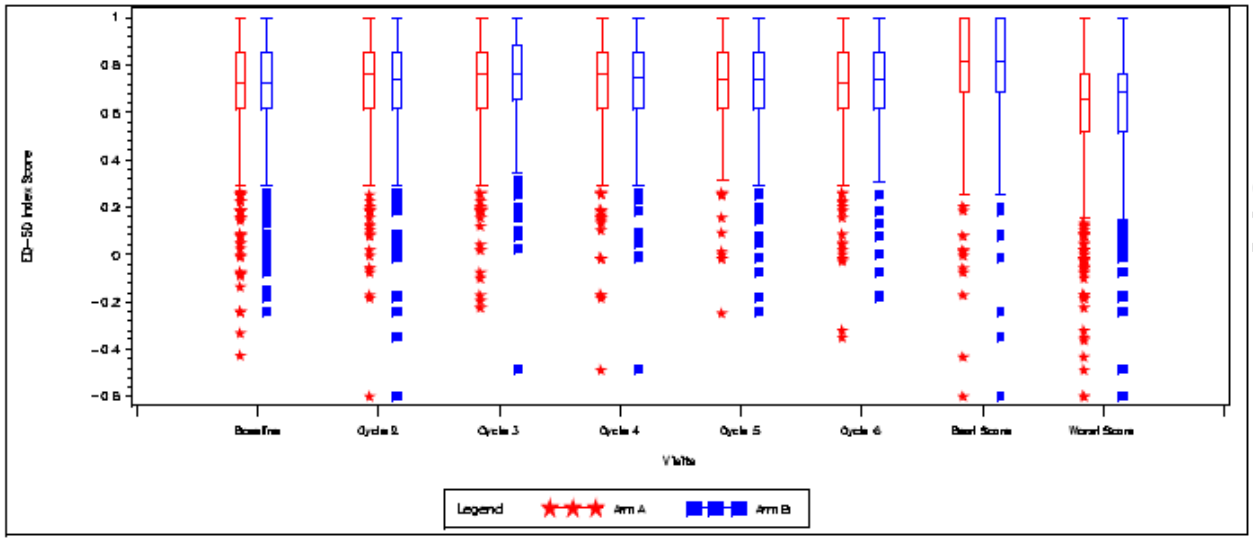


Abbreviations: CI = confidence interval; GC Arm = gemcitabine and cisplatin; GC+N Arm = necitumumab plus gemcitabine and cisplatin; HR = hazard ratio; LCSS = Lung Cancer Symptom Scale; N = number of patients.

- EQ-5D

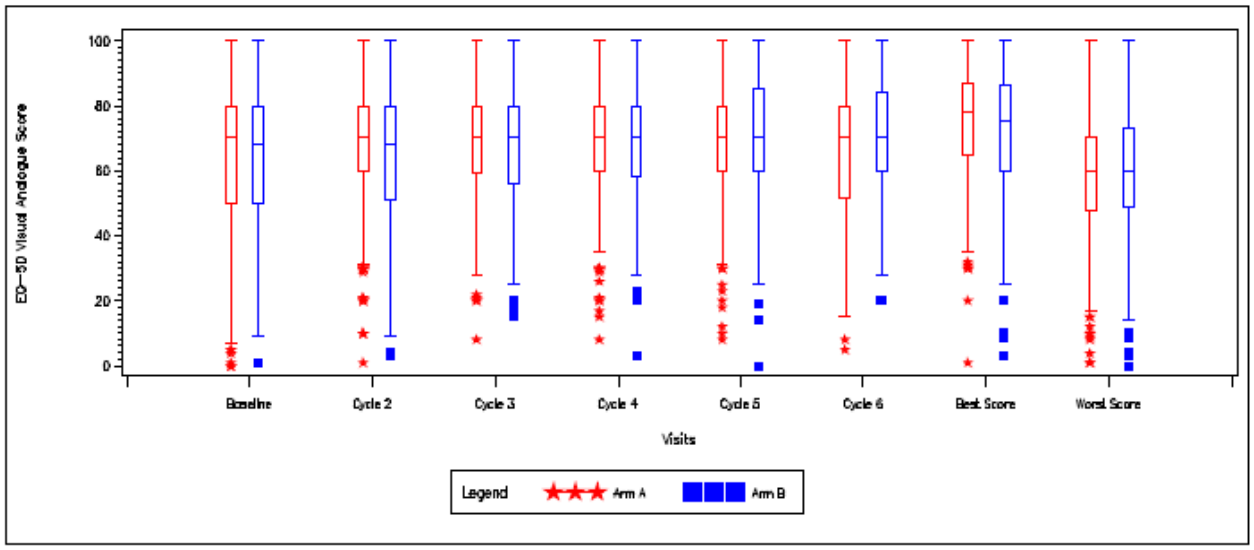
Of the 545 patients in the GC+N Arm, 484 (88.8%) had a baseline and at least one completed post-baseline EQ-5D assessment. In the GC Arm, 489 (89.2%) of the 548 patients had a baseline and at least one completed post-baseline EQ-5D assessment.

Figure 39: EQ-5D Index Score by Time Point for Chemotherapy Phase (ITT Population) – SQUIRE study



Arm A: Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab Arm B: Gemcitabine-Cisplatin Chemotherapy Alone
Using UK weights, the index score is calculated from the 5 dimension responses and ranges from -0.594 (worst) to 1.000 (best).

Figure 40: EQ-5D Visual Analogue Score by Time Point for Chemotherapy Phase (ITT Population) – SQUIRE study



Arm A: Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab Arm B: Gemcitabine-Cisplatin Chemotherapy Alone

Ancillary analyses

Evaluation of the relationship between EGFR protein expression and key efficacy parameters (OS and PFS) was performed as a pre-specifiedexploratory analysis.

EGFR membrane staining at the cellular level was recorded via H-score, which is a derived measure taking into account the percentages of cells with the corresponding staining intensity. This measure is calculated as follows:

H-score = [0×(% cells with no staining)+1×(% cells with staining intensity of+1)+2×(% cells with staining intensity of+2)+3×(% cells with staining intensity of+3)], where % cells ranges from 0 to 100 and staining

intensity takes on one of the four categories (0, +1, +2, +3, corresponding to no, weak, moderate or strong staining respectively). This results in a possible continuous range of H-score from 0 to 300.

Archived tumour tissue was available for 1060 of 1093 patients in the ITT population (97.0%). A total of 982 patients (89.8% of the ITT population) were evaluable for a prespecified exploratory EGFR protein expression analysis by immunohistochemistry (IHC) using Dako EGFR PharmDx Kit. This included 486 patients in the GC+N Arm and 496 patients in the GC Arm.

A tumour was considered to be EGFR-expressing if at least one stained cell could be identified. The large majority of patients (95.2%) had tumour samples expressing the target (that is, EGFR protein expression); only 4.8% had tumours that were not detectable for EGFR protein expression (that is, H-score = 0). The H-score cut-off at 200 was defined by a cetuximab add-on to chemotherapy study in NSCLC (the FLEX study; Pirker et al Lancet Oncology 2012).

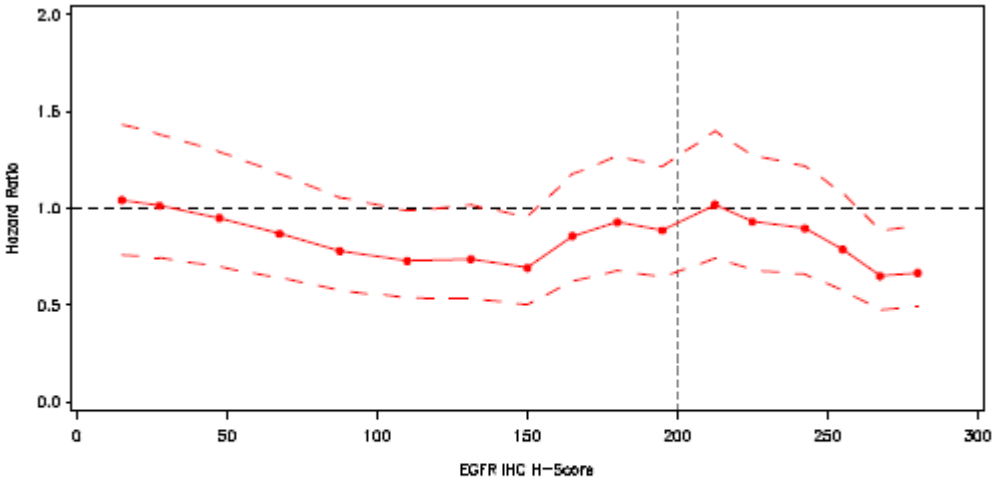
Table 41: H-Score Distribution (TR Population)

	GC+N N = 486 n (%)	GC N = 496 n (%)	Total N = 982 n (%)
H-score Category			
0	24 (4.9)	23 (4.6)	47 (4.8)
>0	462 (95.1)	473 (95.4)	935 (95.2)
<200[a]	295 (60.7)	313 (63.1)	608 (61.9)
≥200	191 (39.3)	183 (36.9)	374 (38.1)

Abbreviations: GC =gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; N = number of randomized patients; n = number of patients in category; TR = translational research.

a The category of patients with H-score <200 includes patients with H-score of 0.

Source: Section 14.2, Table JFCC.14.59.



Hazard ratio greater than 1 indicates increasing hazard with GC+N compared to GC.

Abbreviations: EGFR = epidermal growth factor receptor; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; IHC = immunohistochemistry; N = number of patients in population; TR = translational research.

Figure 20: Subpopulation treatment effect pattern plot of hazard ratios for analysis of OS (TR Population; N=982); sliding window of targeted window size and overlap of 200 and 160 patients, respectively

Table 42: Summary of Efficacy Parameters by H-Score (≥200 vs. <200)

	H-score ≥200		H-score <200	
	GC+N N = 191	GC N = 183	GC+N N = 295	GC N = 313
Overall Survival				
p-value[a]	0.018		0.170	
Stratified*				
HR (95% CI)[b]	0.76 (0.60, 0.95)		0.88 (0.74, 1.06)	
Stratified*				
Median – months	11.96	9.69	11.07	10.94
Progression-free Survival				
p-value[a]	0.277		0.038	
Stratified*				
HR (95% CI)[c]	0.88 (0.69, 1.11)		0.82 (0.69, 0.99)	
Stratified*				
Median– months	5.68	5.45	5.68	5.52

Abbreviations: CI = confidence interval; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; HR = hazard ratio; N = number of randomized patients.

* Stratified by the randomization strata (ECOG PS [0-1 vs. 2], and geographic region [North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia]).

a p-Value obtained from log-rank test of significance.

b Hazard ratio for death from any cause comparing GC+N to GC within protein expression subgroup. Hazard ratio greater than 1 indicates increasing hazards with GC+N compared to GC within protein expression subgroup.

c Hazard ratio for death from any cause or progressive disease comparing GC+N to GC within protein expression subgroup. Hazard ratio greater than 1 indicates increasing hazards with GC+N compared to GC within protein expression subgroup.

In addition, given that the target of necitumumab is EGFR, an additional analysis was performed to evaluate patients with no detectable EGFR protein expression.

Table 43: Summary of Efficacy Parameters by H-Score (>0 vs. 0)

	H-score >0		H-score=0	
	GC+N N = 462	GC N = 473	GC+N N = 24	GC N = 23
Overall Survival				
p-value[a]	0.002		0.253	
Stratified*				
HR (95% CI)[b]	0.79 (0.69, 0.92)		1.52 (0.74, 3.12)	
Stratified*				
Median – months	11.73	9.99	6.47	17.35
Progression-free Survival				
p-value[a]	0.018		0.428	
Stratified*				
HR (95% CI)[c]	0.84 (0.72, 0.97)		1.33 (0.65, 2.70)	
Stratified*				
Median– months	5.72	5.49	4.24	5.59

Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; GC = gemcitabine and cisplatin; GC+N = necitumumab plus gemcitabine and cisplatin; HR = hazard ratio; N = number of patients.

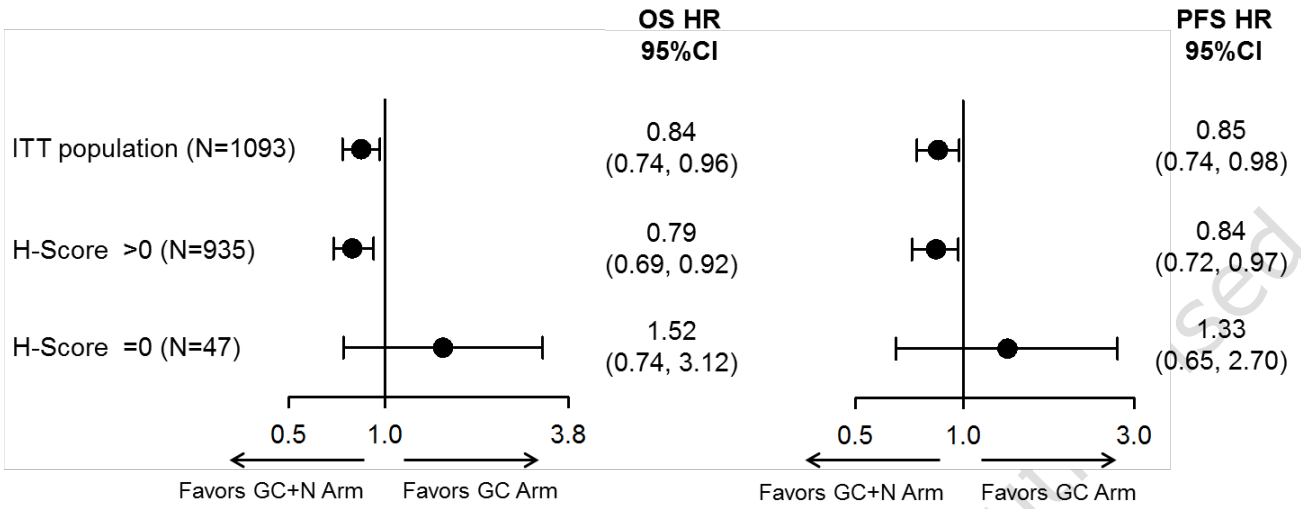
* Stratified by the randomization strata (ECOG PS [0-1 vs. 2], and geographic region [North America, Europe, and Australia vs. South America, South Africa, and India vs. Eastern Asia]).

a p-value obtained from log-rank test of significance.

b Hazard ratio for death from any cause comparing GC+N to GC within protein expression subgroup. Hazard ratio greater than 1 indicates increasing hazards with GC+N compared to GC within protein expression subgroup.

c Hazard ratio for death from any cause or progressive disease comparing GC+N to GC within protein expression subgroup. Hazard ratio greater than 1 indicates increasing hazards with GC+N compared to GC within protein expression subgroup.

In patients with no detectable EGFR protein expression, no improvement in overall survival was observed (hazard ratio [HR] = 1.52 [0.74, 3.12]).



Abbreviations: CI = confidence interval; GC Arm = gemcitabine and cisplatin; GC+N Arm = necitumumab plus gemcitabine and cisplatin; HR = hazard ratio; ITT = intent-to-treat; N = number of patients; OS = overall survival; PFS = progression-free survival.
Note: Stratified HR.

Figure 21: Forest plots of OS and PFS by EGFR IHC H-score: 0 / >0.

Summary of main study

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

Table 44: Summary of efficacy for trial SQUIRE

Title: A Randomized, Multicenter, Open-Label Phase 3 Study of Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab (IMC-11F8) Versus Gemcitabine-Cisplatin Chemotherapy Alone in the First-Line Treatment of Patients with Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC)		
Study identifier	SQUIRE; 14X-IE-JFCC; IMCL CP11-0806	
Design	Pivotal Phase 3, Randomized, Open-label, Active control	
	Duration of main phase:	until radiographic documentation of PD, toxicity requiring cessation, protocol non-compliance or patient consent withdrawal
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Superiority	
Treatments groups	N+GC	Necitumumab 800 mg on days 1 and 8 + Gemcitabine 1250 mg/m^2 IV on days 1 and 8 + Cisplatin 75 mg/m^2 IV on day 1, every 3 weeks (max 6 cycles). After 6 cycles, patients without PD continued to receive necitumumab alone until criteria for withdrawal were met. 545 patients randomized.

	GC		Gemcitabine 1250 mg/m^2 IV on days 1 and 8 + Cisplatin 75 mg/m^2 IV on day 1, every 3 weeks (max 6 cycles 548 patients randomized.
Endpoints and definitions	Primary endpoint	OS	Time from the date of randomization to the date of death for any cause.
	Secondary endpoints	PFS	Time from randomization until the first radiographic documentation of objective progression (RECIST 1.0) or death on study due to any cause, whichever occurred first.
		TTF	Time from randomization to first observation of progressive disease, death due to any cause, early discontinuation of treatment, or in initiation of new anticancer therapies.
		ORR	Proportion of patients achieving a best overall response of confirmed partial or complete response (PR+CR), according to RECIST 1.0, from the start of the treatment until PD/recurrence.
		DCR	Proportion of patients achieving a best overall response of CR, PR, or stable disease CR, PR or stable disease (CR+PR+SD), according to RECIST 1.0.
Data cut-off date Data lock	17 June 2013 19 July 2013		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent To Treat		
Descriptive statistics and estimate variability	Treatment group	N+GC	GC
	Number of subject	545	548
	Primary endpoint		
	OS N. of events n(%)	418 (76.7)	442 (80.7)
	Median OS months (95% CI)	11.5 (10.4, 12.6)	9.9 (8.9, 8.2)
	Stratified Hazard Ratio (95% CI)	0.842 (0.736, 0.962)	
	p-value (two-sided, stratified Log-Rank Test)	0.0120	
	Secondary endpoints		
	PFS N. with events n(%)	431 (79.1)	417 (76.1)
	Median PFS months (95% CI)	5.7 (5.6, 6.0)	5.5 (4.8, 5.6)

	Stratified Hazard Ratio (95% CI)	0.851 (0.743, 0.975)	
	p-value (two-sided stratified Log-Rank Test)	0.020	
	TTF N. events n (%)	529 (97.1)	528 (96.4)
	Median TTF months (95% CI)	4.3 (4.2, 4.8)	3.6 (3.3, 4.1)
	Stratified Hazard Ratio (95% CI)	0.844 (0.747, 0.953)	
	p-value (two-sided stratified Log-Rank Test)	0.0061	
	ORR (CR+PR) n(%) (95% CI)	170 (31.2) (27.4, 35.2)	158 (28.8) (25.2, 32.8)
	p-value (2-sided Cochran-Mantel-Haenszel test adjusting for randomization strata)	0.399	
	DCR (CR+PR+SD) n(%) (95% CI)	446 (81.8) (78.4, 84.8)	422 (77.0) (73.3, 80.3)
	p-value (2-sided Cochran-Mantel-Haenszel test adjusting for randomization strata)	0.043	
	TTF N. events n (%)	529 (97.1)	528 (96.4)
	Median TTF months (95% CI)	4.3 (4.2, 4.8)	3.6 (3.3, 4.1)
	Stratified Hazard Ratio (95% CI)	0.844 (0.747, 0.953)	
	p-value (two-sided stratified Log-Rank Test)	0.0061	

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

Not applicable.

Clinical studies in special populations

Paediatric population

No paediatric data for necitumumab are available.

Elderly patients

No dedicated studies have been performed in elderly patients. Population PK analysis showed no impact of age on necitumumab disposition.

Table 45: Elderly subjects treated in clinical trials supporting efficacy and safety of necitumumab

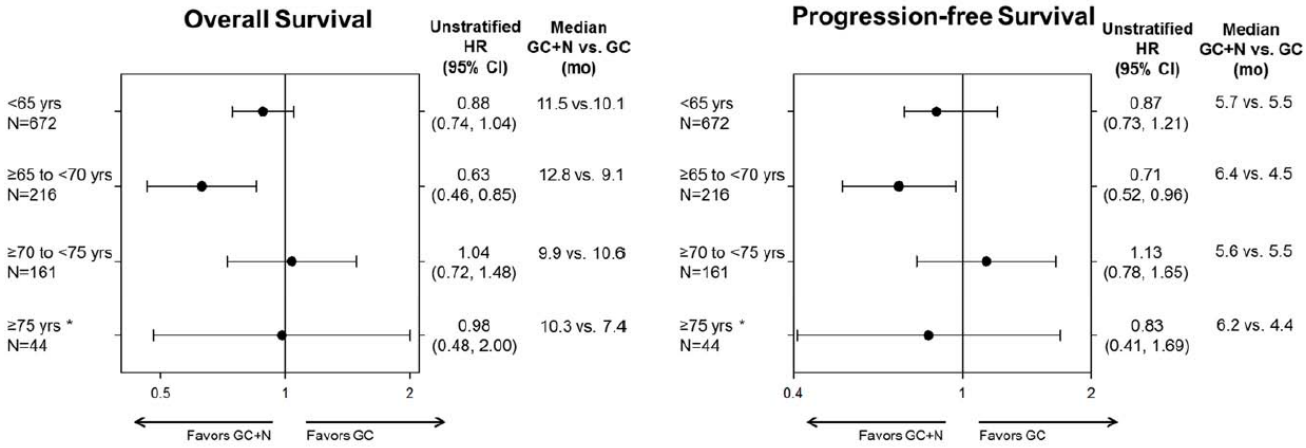
	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials			
SQUIRE	377/1093	43/1093	1/1093
INSPIRE	186/634	28/634	1/634
JFCL	66/167	24/167	2/167
Total	629/1894	95/1894	4/1894
Noncontrolled Trials			
JFCA	5/15	1/15	0
JFCD	13/44	9/44	0
JFCE	16/59	1/59	0
JFCK	38/77	5/77	0
JFCJ	6/35	3/35	0
Total	78/230	19/230	0

Age distribution among the patient populations in the controlled studies was about a third in the age group 65-74 and 5 % in the age group 75-84. Overall, patients ≥ 65 of age, constitute 38 % of the pooled population in the controlled studies. Similar proportion is noted in the non-controlled studies (age 65-74: 34 %; age 75-84: 8 % ; age ≥ 65: 42 %).

The applicant further investigated the influence of age (<70 and ≥70 years) on necitumumab efficacy in the SQUIRE study.

About 200 patients 70 years of age and above participated in SQUIRE and showed poorer outcome in terms of OS and PFS.

Based on a multivariate model for OS, including treatment and prognostic factors, the adjusted OS HR in the ≥70 years patient group was 0.92 (HR = 1.03 in the unadjusted analysis).



Abbreviations: CI = confidence interval; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; HR = hazard ratio; mo = month; ITT = intent-to-treat; N = number of patients; yrs = years.
* ad-hoc analysis

Figure 22: Forest plots for overall survival (left) and progression-free survival (right) by age categories (<65 years, 65 to <70 years, ≥70 to <75 years, and ≥75 years), ITT population, SQUIRE.

In patients ≥70 years with detectable EGFR protein expression, the hazard ratio for overall survival was 0.93 (0.65, 1.33).

Patients with hepatic or renal impairment

No dedicated studies have been performed in hepatic or renally impaired patients.

Supportive studies

Study I4X-MC-JFCK (JFCK)

This is a single-arm, open-label, Phase 2 study conducted in 61 patients with Stage IV squamous NSCLC.

Eligible patients received first-line treatment of necitumumab (800-mg absolute dose on Days 1 and 8) plus gemcitabine (1250 mg/m^2 on Days 1 and 8) and cisplatin (75 mg/m^2 on Day 1) for a maximum of six 3-week cycles. Patients with at least SD continued with necitumumab until PD, toxicity requiring cessation, protocol noncompliance, withdrawal of consent, or other discontinuation criteria.

The primary objective of the study was evaluation of objective response rate (ORR). Evaluation of OS, PFS, DCR, change in tumour size (CTS), safety, PK and immunogenicity of necitumumab were the study's secondary objectives. Response assessments were based on investigator evaluation.

As of the database cut-off date of 13 August 2014, 7 patients (11.5%) remained on study treatment, with a total of 54 patients (88.5%) who had discontinued study treatment.

The majority of patients in this study were Caucasian (n=48; 78.7%). Eligible patients were required to have an ECOG PS of 0-1 and the majority of patients at baseline presented with a PS of 1 (n=51; 83.6%). The median age was 65 years with patients ranging from 43 to 84 years. There were 49 males (80.3%) and 12 (19.7%) females.

Fifty four of the 61 patients treated were assessable for response (a post-baseline radiographic assessment was not available for 7 patients).

Table 46: Overall Tumour Response Safety Population - Study JFCK

	GC+N N=61 n (%)
Best Overall Response	
Complete Response	0 (0)
Partial Response	26 (42.6)
Stable Disease	18 (29.5)
Progressive Disease	9 (14.8)
Not Evaluable[a]	1 (1.6)
Not Assessable	7 (11.5)
DCR (CR+PR+SD)[1]	44/54 (81.5) [95% CI:* 68.57, 90.75]
Objective Response Rate (CR+PR)[1]	26/54 (48.1) [95% CI:* 34.34, 62.16]
DCR (CR+PR+SD)	44/61 (72.1) [95% CI:* 59.17, 82.85]
Objective Response Rate (CR +PR)[2]	26/61 (42.6) [95% CI:* 30.04, 55.94]

Abbreviations: CI = confidence interval; CR = complete response; CSR = clinical study report; DCR = disease control rate; GC+N = gemcitabine/cisplatin plus necitumumab; N = number of patients; n = number of patients in category; PR = partial response; SD = stable disease.

* Exact confidence interval.

a = this patient was considered not evaluable because this patient had a radiographic assessment (of stable disease) that was performed earlier than 6 weeks from the first dose.

Note: 1. The denominator includes each patient enrolled who received any amount of study drug, and who had a complete radiographic assessment at baseline and at least one complete radiographic assessment postbaseline.

2. The denominator includes each patient enrolled who received any amount of study drug.

At the time of data cut-off, a total of 44 (72.1%) PFS events and 27 (44.3%) OS events occurred, with a median PFS of 5.6 months (95% CI: 3.68, 6.87), a median OS of 11.7 months (95% CI: 7.59, NA), and the 1-year survival rate of 47.6% (95% CI: 30.20, 63.08).

There were 25 patients (41.0%) who received post-study systemic anticancer therapy including 15 (24.6%) treated with docetaxel.

The rate of anti-drug antibody (ADA)-positive responses was 14.8%. Four patients (6.6%) were treatment emergent antibody positive. Neutralizing antibodies were detected in 3 patients (5.6%) post-baseline. Overall, the rate of ADA formation in this trial was comparable to the rates observed in previous necitumumab trials.

Study I4X-MC-JFCL (JFCL)

This is a randomised (2:1), two-arm, open-label, Phase 2 study conducted in 167 patients (110: necitumumab plus paclitaxel and carboplatin arm; 57: paclitaxel and carboplatin) with Stage IV squamous NSCLC.

Eligible patients received first-line treatment of necitumumab (800-mg absolute dose on Days 1 and 8) plus paclitaxel (200 mg/m^2 on Day 1) and carboplatin (AUC 6 on Day 1) for a maximum of six 3-week cycles. Patients with at least SD continued with necitumumab until PD, toxicity requiring cessation, protocol noncompliance, withdrawal of consent, or other discontinuation criteria.

The primary objective of the study was evaluation of ORR, with the final analysis to be conducted when a minimum of 98 OS events occurred. Evaluation of OS, PFS, DCR, CTS, safety, PK and immunogenicity of necitumumab, and relationship between EGFR protein expression and efficacy outcomes were the study's secondary objectives. No formal hypothesis testing was performed. Response assessments were based on investigator evaluation. Analyses are ongoing, and the applicant is recommended to submit the final study results when available.

As of the database cut-off date of 11 May 2015, 3 patients (1.8%) remained on study treatment. Progressive disease was the most common reason for study treatment discontinuation (85 patients; 50.9%).

The majority of patients in both arms were male, had ≥2 sites of metastasis at the time of study entry, and presented with a baseline ECOG PS of 1. The treatment arms were well-balanced in terms of demographic and baseline characteristics.

The final analysis of the primary outcome (ORR) occurred when 99 OS events were observed. Of the 167 patients randomized, 144 were assessable for response.

Table 47: Overall response intent to treat population - Study JFCL

	Necitumumab + Paclitaxel-Carboplatin N = 110	Paclitaxel-Carboplatin N = 57
Best Overall Response[a], n (%)		
CR	0	1 (1.8)
PR	46 (41.8)	19 (33.3)
SD	36 (32.7)	22 (38.6)
PD	11 (10.0)	6 (10.5)
NE	1 (0.9)	2 (3.5)
NA	16 (14.5)	7 (12.3)
Objective Response Rate n/N (%) (95% CI*)[1]	46/94 (48.9) (38.5, 59.5)	20/50 (40.0) (26.4, 54.8)
Disease Control Rate n/N (%) (95% CI*)[1]	82/94 (87.2) (78.8, 93.2)	42/50 (84.0) (70.9, 92.8)
Objective Response Rate n/N (%) (95% CI*)[2]	46/110 (41.8) (32.5, 51.6)	20/57 (35.1) (22.9, 48.9)
Disease Control Rate n/N (%) (95% CI*)[2]	82/110 (74.5) (65.4, 82.4)	42/57 (73.7) (60.3, 84.5)

Abbreviations: CI = confidence interval; CR = complete response; DCR = disease control rate; N = number of patients; n = number of patients in category; PR = partial response; SD = stable disease.

* Exact confidence interval.

a The denominator for best overall response is the intent to treat population.

Note: 1. Primary analysis: The denominator includes each patient randomised who received at least one dose of the assigned study drug and who had a complete radiographic assessment at baseline and at least one complete radiographic assessment post-baseline.

2. The denominator includes all randomised patients.

At the time of data cut-off, a total of 145 PFS events and 99 OS events had occurred. Median PFS was 5.4 months in the necitumumab plus paclitaxel-carboplatin arm and 5.6 months in the paclitaxel-carboplatin arm (HR = 1.00; 95% CI: 0.71, 1.42). A sensitivity analysis resulted in a median PFS of 5.4 months vs 5.6 months (HR = 0.99; 95% CI: 0.68, 1.46). Median OS was 13.2 months in the necitumumab plus paclitaxel-carboplatin arm and 11.2 months in the paclitaxel-carboplatin arm (HR = 0.83; 95% CI: 0.55, 1. 52). The Kaplan-Meier curves cross at approximately 4 months, and there are more events occurring in the first 4 months on the necitumumab arm.

There was a numerical difference in the use of post-study systemic anticancer therapy in favour of the control arm (47 patients [42.7%] in the necitumumab arm and 29 patients [50.9%] in the control arm received post-study systemic anticancer therapy).

Study I4X-IE-JFCB: INSPIRE

This is a randomised multicentre Phase III study to investigate necitumumab in combination with Pemetrexed and cisplatin (PC) versus PC as first line treatment of stage IV (AJCC7) non-squamous NSCLC patients.

Randomization was stratified by smoking history (non-smoker vs. ex-light smoker vs. smoker); ECOG PS (0-1 vs. 2); disease histology (adeno/large cell carcinoma vs. other); and geographic region (North America, Europe, and Australia vs. South America, South Africa, and Asia [India]). A treatment cycle was defined as 3 weeks. The primary objective of the study was OS. Secondary objectives included PFS, ORR, TTF, health status, and association between EGFR protein expression and efficacy variables.

After enrolment of 633 patients, the Independent Data Monitoring Committee (IDMC) overseeing this trial recommended early closure of enrolment in INSPIRE. The IDMC reached this decision using data on non-fatal and fatal thromboembolic events from the safety database as well as the overall number of deaths from all causes (all deaths) shown in the clinical database. The additional data showed increasing and persistent evidence of an excess of thromboembolic and fatal thromboembolic SAEs on the investigational arm in INSPIRE, which accounted for an excess of deaths from all causes on this arm. For patients in the PC+N Arm, necitumumab treatment was discontinued in patients who had not completed 2 cycles of study treatment. Other patients in the PC+N Arm continued per protocol. The final sample size was 633 patients. This allowed detection of an HR of 0.80, with a one-sided log-rank test at the 0.025 significance level and a power of 67.6%. Final analysis was planned when at least 474 OS events (deaths) were observed.

The primary objective was not met for this study. There was no statistically significant or clinically relevant difference between arms in terms of OS (stratified HR = 1.01 [0.84, 1.21]; p = 0.9561), with a median OS of 11.3 months in the PC+N Arm and 11.5 months in the PC Arm.

Table 48: Summary of Overall Survival (ITT Population) - INSPIRE

	PC+N N=315 n (%)	PC N=318 n (%)	Inter-Group Comparison
Number of deaths, n (%)	236 (74.9)	246 (77.4)	
Number censored, n (%)	79 (25.1)	72 (22.6)	
Stratified[a] Log-rank p-value[b]			0.9561
Stratified[a] Hazard Ratio 95% CI			1.01 (0.84, 1.21)
Median OS – months[a] (95% CI)	11.3 (9.5, 13.4)	11.5 (10.1, 13.1)	
Survival rate % (95% CI)			
6-month	70.1 (64.6, 74.9)	74.2 (68.9, 78.7)	
1-year	47.3 (41.5, 52.8)	48.5 (42.8, 53.9)	

Abbreviations: CI = confidence interval; N = number of randomized patients; n = number of patients in category.
Note: Median and survival rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Hazard ratio and 95% CI (Wald) were estimated using the Cox model.
[a] Stratified log-rank test as well as the hazard ratio from a stratified proportional hazard model are stratified by the randomization strata: smoking history (never smoker vs. light ex-smoker vs. smoker), ECOG performance status (0-1 vs. 2), disease histology (adeno/large cell carcinoma vs. other), and geographic region (North America, Europe, and Australia/New Zealand vs. Central/South America, South Africa, and India).
[b] Derived from a two-sided test

In the secondary endpoint analyses, there were also no statistically significant or clinically relevant differences between arms in terms of PFS (HR = 0.96 [95% CI: 0.80, 1.16; p=0.6647], with a median of 5.6 months in each arm), ORR (31.1% vs. 32.1%), or DCR (73.3% vs. 73.9%).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The protocol of the pivotal SQUIRE study was amended six times and it is agreed that the amendments and protocol violations are unlikely to have a relevant impact on the integrity of the study.

No CHMP/SAWP advice has been sought by the Applicant in terms of clinical aspects of the MAA.

The study enrolled 1093 patients whom were randomised 1:1 to the respective treatment arms (545 in the GC+N arm vs. 548 in the GC arm).

The dose of necitumumab (800 mg flat dose administered IV over 60 minutes on Days 1 and 8 of each 3 week cycle) was established in the dose-escalation study I4X-IE-JFCE and seems reasonably well justified. Exposure/OS analyses in the pivotal study however, indicate that as many as 40% of the patients might be under-dosed. It is clinically unlikely that this represents a non-confounded association.

The choice of (cis) platinum-based doublet chemotherapy as part of the experimental triplet and as comparator are supported. Platinum-based doublet chemotherapy is in line with the current treatment recommendations in this setting and gemcitabine in combination with cisplatin is approved for 1st line treatment in locally advanced or metastatic NSCLC in EU. The chosen dose levels of both cisplatin and gemcitabine are non-controversial, but four instead of six cycles of chemotherapy is recommended.

The inclusion- and exclusion criteria are considered adequately reflecting the target population for the proposed indication.

Median age was 62 years of age. As commonly observed in clinical studies, the median age among the enrolled patients is lower than the median age in the clinical setting which in the case of squamous NSCLC is found to be around 70 years. It is acknowledged that median age varies between regions, e.g. higher in Western vs. Eastern Europe. The vast majority of patients were Caucasians, males and/or smokers.

Apart from the lower median age, the baseline disease characteristics well reflect the intended target population i.e. an advanced squamous NSCLC patient population.

With the exception of one patient in the GC+N arm, no patients had received any 1st line treatment prior to enrolment. Hence, the population studied is in line with the proposed indication.

There were no relevant differences in the distribution of demographics, disease characteristics, or the use of post-study systemic therapy between the subset of patients with detectable EGFR protein expression and the ITT population.

Type of post-study systemic anticancer therapy is reasonably balanced between the two arms.

In conclusion, there are no major concerns identified with respect to the conduct of the pivotal study. The population studied is considered representative of the target population and the claimed indication.

Efficacy data and additional analyses

The primary endpoint was OS. The study met its primary objective with an estimated reduction of death of 16 % in the experimental arm (HR = 0.84 [0.736, 0.962]; p=.012). Results on the secondary endpoint PFS showed an estimated reduction of 15 % in the risk of progression or death in favour of the GC+N arm (HR = 0.85 [0.743, 0.975]; p= 0.02).

Subgroup analyses of both endpoints were reasonably consistent in favour of the experimental arm with the exception of the age group ≥70 years which encompassed about 19 % of the study population (HR 1.03 for OS and 1.07 for PFS). Based on a multivariate model for OS, including treatment and prognostic factors, the adjusted OS HR in the ≥70 year patient group was 0.92. No overall differences in efficacy between arms were observed in patients above 70 years of age (see SmPC section 5.1).

The overall number of events in the study at the time of the analysis (data cut-off date 17 June 2013) was about 79 % for OS and 78 % for PFS. A satisfactory level of data maturity is considered reached.

The vast majority of patients were evaluable for LCSS score and the EQ-5D but no significant differences between treatment arms were detected.

The evaluation of the relationship between EGFR protein expression and efficacy parameters (OS and PFS) was performed as a pre-planned exploratory analysis.

In the SQUIRE study, the H-score as defined could point towards a predictive value in terms of OS (HR 0.76 for H-score ≥ 200 vs. 0.88 for H-score < 200). This was not seen in the corresponding analysis for PFS (HR 0.88 for H-score ≥ 200 vs. 0.82 for H-score < 200) and importantly a "sliding window" analyses showed a pattern compatible with absence of significance association. This is also in line with results obtained from the INSPIRE study. A correlation between levels of EGFR expression (neither as ICH H-score nor percent positive cells) and a treatment benefit has not been established and a biomarker for selecting the patient population that may derive the most benefit from the experimental treatment remains to be identified.

Patients whose tumours lacked detectable EGFR protein (24 in GC+N Arm; 23 in GC Arm), did not appear to benefit in terms of OS (HR = 1.52) or PFS (HR = 1.33) from the addition of necitumumab to gemcitabine and cisplatin compared to gemcitabine and cisplatin alone. The indication was therefore limited to patients expressing EGFR.

In the SQUIRE study the following biomarkers were investigated in the exploratory analyses:EGFR protein expression by IHC; HER2 protein expression by IHC; HER3 protein expression by IHC; EGFR copy number gain (CNG) by FISH; FGFR1 CNG by SISH; e-Cadherin protein expression by IHC; and FCγR single nucleotide polymorphisms (SNP). Given the fact that EGFR-activating mutations, KRAS mutations, and ALK translocations are rare in squamous NSCLC, these markers were not tested.

The results obtained from these analyses were overall inconclusive. Additional exploratory biomarker analyses will be performed (see RMP).

2.5.4. Conclusions on the clinical efficacy

The demonstrated benefit of necitumumab as add-on to platinum-based chemotherapy formally rests on one pivotal study.

A statistically significant effect in terms of OS and PFS has been observed in favour of GC+N as compared to GC alone with HR 0.84 and 0.85 respectively with a median gain of 1.6 months for OS.

Results from the biomarker analysis provided were inconclusive. Therefore the CHMP considers that the results of the additional exploratory analyses of biomarker status in the necitumumab clinical development programme of 4 Phase 1b/2 clinical trials should be provided post-authorisation (see RMP, Category 3 study)

2.6. Clinical safety

Patient exposure

The integrated safety population consists of 996 patients who received at least 1 dose of necitumumab in the trials included in this application. The SQUIRE and INSPIRE trials contribute to the safety population with 538 and 304 patients, respectively (54% and 30%). The safety findings from the additional studies (n=154) make up for 15.46% of the safety population.

In the main trial, of 1093 randomized patients, 1079 received at least one dose of study therapy, including 538 in the GC+N arm and 541 in the GC arm.

The median duration of therapy in the GC arm was around 17 weeks (median number of cycles=5). For the GC+N arm, the median duration of therapy was 18 weeks for GC and 20 weeks for N (median number of cycle=6), with a median duration of 12 weeks exposure to necitumumab after completing GC schedule in 275 patients (51% of the GC+N arm).

In INSPIRE, of the 633 randomized patients (of 947 planned), 616 received at least one dose of study therapy, including 304 in the PC+N arm and 312 in the PC arm. The median dose intensity for both pemetrexed and cisplatin was higher than for gemcitabine and cisplatin in SQUIRE. The median duration of necitumumab therapy was 14 weeks, due to enrollment stop by Sponsor at IDMC recommendation in February 2011 based on the increased rate of serious thromboembolic (TE) events (in particular fatal TE events and fatal events with a potential relationship to thromboembolism) reported in the necitumumab arm, assessed within the context of the overall death rates between treatment arms. The median number of necitumumab cycles was accordingly lower (n=4) than in SQUIRE.

The safety database was updated at the request of the CHMP, mainly with data from patients still on treatment at data cutoff. Overall, 29 patients were being treated at that point: 9 in SQUIRE, 7 in INSPIRE and 13 in JFCJ protocol. No new SAEs were reported in SQUIRE. Two serious TEs originated from JFCJ (1 grade 2 cerebral ischaemia and 1 grade 3 PE). No new safety signals emerged from this analysis.

Adverse events

In SQUIRE, the incidences of serious, severe (Grade ≥3), and fatal events were numerically higher among patients in the GC+N Arm.

Table 49: Overview of Treatment-Emergent Adverse Events

Adverse Event	GC+N Overall N = 538 n (%)	GC+N Ctx Phase N = 538 n (%)	GC N = 541 n (%)
Patients with ≥1 TEAE	533 (99.1)	533 (99.1)	529 (97.8)
Patients with ≥1 treatment-emergent SAE	257 (47.8)	229 (42.6)	203 (37.5)
Patients with ≥1 TEAE Grade ≥3	388 (72.1)	364 (67.7)	333 (61.6)
Patients with any TEAE with outcome death[a]	66 (12.3)	50 (9.3)	57 (10.5)
Patients with a TEAE with outcome death (excluding fatal cases of disease progression)	42 (7.8)	32 (5.9)	37 (6.8)

Abbreviations: Ctx = chemotherapy; GC = gemcitabine and cisplatin; GC+N = necitumumab plus gemcitabine and cisplatin; N = number of treated patients; n = number of patients in category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Includes fatal cases of disease progression.

In INSPIRE, similarly to SQUIRE, while patients in the Pemetrexed+Cisplatin (PC) arm were allowed to receive chemotherapy for up to 6 cycles, the ones enrolled in the PC+N arm with a tumour response of SD or better after 6 cycles could receive necitumumab monotherapy until withdrawal criteria were met. The AE pattern is similar to SQUIRE, though with more TEAEs with outcome death (16.1 vs. 10.3% including the fatal rate of disease progression), partially due to increased thromboembolic fatalities.

Adverse reactions in SQUIRE

The applicant applied scientific and medical judgement to an initial list of ADRs identified via screening criteria from the SQUIRE trial. In addition, studies INSPIRE JFCE, JFCA, JFCJ, and JFCD were reviewed to identify any potential signals not observed in SQUIRE or potential ADRs occurring at a higher rate than that observed in SQUIRE.

Table 50: ADRs reported in ≥ 1 % of necitumumab treated patients in SQUIRE

System organ class	Frequency	ADR[a]	Portrazza + GC[b] (N=538)		GC (N=541)	
			Any grade (%)	Grade ≥ 3 (%)	Any grade (%)	Grade ≥ 3 (%)
Infections and infestations	Common	Urinary tract infection	4.1	0.2	1.7	0.2
Nervous system disorders	Common	Headache	8.6	0	5.7	0.4
	Common	Dysgeusia	5.9	0.2	3.3	0
Eye disorders	Common	Conjunctivitis	5.6	0	2.2	0
Vascular disorders	Common	Venous thromboembolic events	8.2	4.3	5.4	2.6
	Common	Arterial thromboembolic events	4.3	3.0	3.9	2.0
	Common	Phlebitis	1.7	0	0.4	0
Respiratory, thoracic and mediastinal disorders	Common	Haemoptysis	8.2	0.9	5.0	0.9
	Common	Epistaxis	7.1	0	3.1	0.2
	Common	Oropharyngeal pain	1.1	0	0.7	0
Gastrointestinal disorders	Very common	Vomiting	28.8	2.8	25.0	0.9
	Very common	Stomatitis	10.4	1.1	6.3	0.6
	Common	Dysphagia	2.2	0.6	2.2	0.2
	Common	Mouth ulceration	1.5	0	0.4	0
Skin and subcutaneous tissue disorders	Very common	Skin reactions	77.9	6.3	11.8	0.6
	Common	Hypersensitivity reactions/infusion-related reactions	1.5	0.4	2.0	0
Musculoskeletal and connective tissue disorders	Common	Muscle spasms	1.7	0	0.6	0
Renal and urinary disorders	Common	Dysuria	2.4	0	0.9	0
General disorders and administration site conditions	Very common	Pyrexia	12.3	1.1	11.1	0.4
Investigations	Very common	Hypomagnesaemia[c]	81.3	18.7	70.2	7.2
	Very common	Albumin-corrected hypocalcaemia[c]	33.0	4.2	22.9	2.3
	Very common	Hypophosphataemia[c]	28.9	6.3	22.7	5.7

	Very common	Hypokalaemia[c]	23.6	4.4	17.6	3.2
	Very common	Weight decreased	12.1	0.6	6.3	0.6

Abbreviations: GC = gemcitabine and cisplatin alone; Portrazza+GC = necitumumab plus gemcitabine and cisplatin; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; TEAE = treatment-emergent adverse event.
a MedDRA preferred term (Version 16).
b The table reflects the frequency of ADRs during the chemotherapy phase of study treatment in which Portrazza+GC was directly compared with GC.
c Based on laboratory assessments. Only patients with baseline and at least one post-baseline result are included.

Common AEs by SOC and PT

Necitumumab-related TEAEs occurring in >5% of patients in the experimental arms:

Generally, necitumumab adds toxicity to the chemotherapy backbone in a pattern largely expected for an IgG1mab targeting EGFR. 'Skin' disorders (rash, dermatitis acneiform, acne, dry skin, paronychia, pruritus), hypomagnesemia, neutropenia, gastrointestinal symptoms (nausea, vomiting, diarrhoea, stomatis) and alterations of the general condition (fatigue, asthenia) are expected adverse events when necitumumab is added to the gemcitabine-cisplatin chemotherapy (SQUIRE). The 12 week necitumumab maintenance in the 275 subjects did not significantly alter the TEAE pattern seen in the chemotherapy phase in SQUIRE.

A similar trend was observed in INSPIRE: skin reactions [such as rash (33.2%), dermatitis acneiform (13.2%), dry skin (7.2%), generalized rash (5.9%), and paronychia (5.9%)], and hypomagnesemia (7.6%).

A cumulative analysis of selected AEs based on duration and outcome of events was provided by the Applicant, regarding those reported in a higher proportion in the GC+N arm (e.g. rash, hypomagnesaemia) and with higher difference between arms in terms of AEs gr≥3 (e.g. vomiting, pulmonary embolism). As expected, the results of the analysis showed that the addition of necitumumab to the GC chemotherapy backbone affected the safety findings in terms of rate, grade and median duration of events.

Adverse events of special interest (AESI)

Hematologic toxicity, skin and eye toxicity, fatigue, hypersensitivity reactions, hypomagnesemia, interstitial lung disease, and thromboembolism are events identified based on safety data known for other monoclonal anti-EGFR antibodies and/or clinical experience with necitumumab as being of special interest.

The analysis of all AESI by treatment cycle, TEs included, in order to observe event chronology, did not elicit findings inconsistent with the profile of an anti-EGFR MoAb; as expected, more events were observed during the combined necitumumab-chemotherapy phase of SQUIRE; their duration and outcome seem not to diverge from previous data with necitumumab/other anti-EGFR.

A. Thromboembolic events (TEs)

Thromboembolic events and events potentially related to thromboembolism were identified as AESI by the Applicant as signal from the INSPIRE trial and as a class-effect of anti-EGFR MoAbs in combination with cisplatin-based chemotherapy in NSCLC. The review of the baseline risk factors for both SQUIRE and INSPIRE studies did not reveal any relevant imbalances between arms.

In January 2011, the IDMC for INSPIRE reviewed unblinded SAE data. Due to an increased rate of serious TEs (in particular fatal TE events and fatal events with a potential relationship to thromboembolism) and an overall imbalance in deaths from all causes (all deaths) observed in patients randomized to receive therapy with necitumumab in combination with pemetrexed and cisplatin as compared to pemetrexed and cisplatin alone, the

IDMC recommended that enrolment into the study be stopped and necitumumab treatment be discontinued in patients who had not completed 2 cycles of treatment. The sponsor halted enrolment on 02 February 2011.

An analysis of time to occurrence of VTEs in SQUIRE discerned no pattern for these events, in contrast with the early VTEs observed in INSPIRE.

The data showed increasing and persistent evidence of an excess of TEs and fatal TE SAEs on the investigational arm in INSPIRE. The excess of fatal TEs was predominantly caused by those classed as undiagnosed or "potential" TEs in the analyses (that is, events where there was no definite diagnosis made but with potential relationship to thromboembolism [mainly cases of unexplained death]).

The IDMC reviewed data from study CP11-0806 / I4X-IE-JFCC (SQUIRE) concurrently with data from INSPIRE; taking into account data from both studies, the IDMC recommended continuing the SQUIRE trial as planned.

In SQUIRE (see table below), VTEs were reported in 49 patients (9.1%) in the GC+N arm and 29 patients (5.4%) in the GC arm. The corresponding rates of Grade ≥3 events were 5.0% and 2.6%. The most common events were pulmonary embolism (4.8% in the GC+N arm vs. 2.4% in the GC arm) and deep vein thrombosis (1.9% vs. 0.9%).

Arterial TEs occurred more often in the necitumumab arm than in the control arm (5.4% [3.9% Grade ≥3] vs. 3.9% [2.0% Grade ≥3]). The observed imbalance was mainly due to events affecting the cerebrovascular system: ischemic stroke (n = 4 in the GC+N arm vs. n = 0 in the GC arm) and cerebral ischemia (n = 3 in the GC+N arm vs. n = 0 in the GC arm).

No relevant differences between treatment arms with respect to fatal venous thromboembolism (0.2% in both arms) or fatal arterial thromboembolism (0.6% in the GC+N Arm vs. 0.2% in the GC Arm).

Table 51: AESI- Thromboembolic events - SQUIRE

	GC+N N = 538 n (%)				GC N = 541 n (%)	
	Overall		Ctx Phase Only		Overall	
AESI[a]	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Venous Thromboembolic Events	**49 (9.1)**	**27 (5.0)**	**44 (8.2)**	**23 (4.3)**	**29 (5.4)**	**14 (2.6)**
Pulmonary Embolism	26 (4.8)	19 (3.5)	24 (4.5)	17 (3.2)	13 (2.4)	10 (1.8)
Deep Vein Thrombosis	10 (1.9)	5 (0.9)	8 (1.5)	4 (0.7)	5 (0.9)	0
Thrombosis	4 (0.7)	1 (0.2)	4 (0.7)	1 (0.2)	3 (0.6)	0
Mesenteric Vein Thrombosis	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Pulmonary Artery Thrombosis	2 (0.4)	0	2 (0.4)	0	2 (0.4)	1 (0.2)
Pulmonary Venous Thrombosis	2 (0.4)	1 (0.2)	1 (0.2)	0	0	0
Venous Thrombosis Limb	2 (0.4)	0	1 (0.2)	0	0	0
Arterial Thromboembolic Events	**29 (5.4)**	**21 (3.9)**	**23 (4.3)**	**16 (3.0)**	**21 (3.9)**	**11 (2.0)**
Ischaemic Stroke	4 (0.7)	4 (0.7)	4 (0.7)	4 (0.7)	0	0
Cerebral Ischaemia	3 (0.6)	2 (0.4)	2 (0.4)	1 (0.2)	0	0
Acute Myocardial Infarction	2 (0.4)	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Aortic Thrombosis	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)	1 (0.2)	0
Cerebral Infarction	2 (0.4)	1 (0.2)	0	0	0	0
Myocardial Infarction	2 (0.4)	2 (0.4)	1 (0.2)	1 (0.2)	3 (0.6)	2 (0.4)
Peripheral Arterial Occlusive Disease	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)	1 (0.2)	0
Peripheral Artery Thrombosis	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)
Transient Ischaemic Attack	2 (0.4)	2 (0.4)	2 (0.4)	2 (0.4)	3 (0.6)	3 (0.6)

Table 52: AESI- Thromboembolic events - INSPIRE

	PC+N N=304 n (%)				PC N=312 n (%)	
	Overall		Ctx Phase Only		Overall	
AESI[a]	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Venous TEE	40 (13.2)	23 (7.6)	32 (10.5)	18 (5.9)	26 (8.3)	11 (3.5)
With fatal outcome	3 (1.0)	3 (1.0)	2 (0.7)	2 (0.7)	4 (1.3)	4 (1.3)
Arterial TEE	13 (4.3)	8 (2.6)	12 (3.9)	8 (2.6)	18 (5.8)	11 (3.5)
With fatal outcome	3 (1.0)	3 (1.0)	3 (1.0)	3 (1.0)	5 (1.6)	5 (1.6)

Abbreviations: AESI = adverse event of special interest; N = number of treated patients; n = number of patients in category; TEE = thromboembolic event

In INSPIRE, severe VTEs were reported in approximately 6 % of patients treated with necitumumab in combination with pemetrexed and cisplatin (versus 4 % in the pemetrexed and cisplatin alone arm). Severe ATEs were reported in approximately 3 % of patients treated with necitumumab in combination with pemetrexed and cisplatin (versus 4 % in the pemetrexed and cisplatin alone arm).

The submission of emerging safety data from ongoing phase II studies in first-line squamous NSCLC was also required. In study JFCK, 61 patients received at least one dose of study treatment and all of them experienced at least 1 TEAE. TEAEs ≥ grade 3 were observed in 53/61 (86.9%), in comparison with 72% in SQUIRE. TEAEs with outcome of death, excluding fatal cases of disease progression, were 11.5%, compared with 7.8% in SQUIRE.

Table 53: Frequency of any grade and grade ≥3 ATEs and VTEs (studies JFCK and SQUIRE)

	JFCK		SQUIRE	
	Any grade	Gr≥3	Any grade	Gr≥3
ATE	16.4%	6.6%	5.4%	3.9%
VTE	11.5%	4.9%	9.1%	5.4%

The applicant analysed the distribution of baseline risk factors in study JFCK and observed that in comparison with SQUIRE and INSPIRE, a higher percentage of patients in Study JFCK were ≥65 years, had a haemoglobin <10 g/dL, and had a Khorana high risk score of 3.

Table 54: Summary of Baseline Risk Factors Safety Population Study JFCK, SQUIRE, and INSPIRE

	Study JFCK Squamous NSCLC	SQUIRE Squamous NSCLC	INSPIRE Non-squamous NSCLC
	GC+N N = 61 n (%)	GC+N N = 538 n (%)	PC+N N = 304 n (%)
Risk Factors for Venous TEE			
Age ≥65	33 (54.1)	210 (39.0)	111 (36.5)
History of venous TEE	1 (1.6)	21 (3.9)	22 (7.2)
ECOG PS 2	2 (3.3)	48 (8.9)	16 (5.3)
Platelets ≥350000/µL	27 (44.3)	219 (40.7)	121 (39.8)
Leukocytes >11000/µL	22 (36.1)	171 (31.8)	100 (32.9)
Hb < 10g/dL	6 (9.8)	25 (4.6)	12 (3.9)
BMI ≥35 kg/m^2	3 (4.9)	19 (3.5)	6 (2.0)
Current smoking status: smokers[a]	NA	496 (92.2)	232 (76.3)
Khorana Risk Score (Khorana et al. 2008)			
Intermediate Risk	41 (67.2)	410 (76.2)	240 (78.9)
Score 1	25 (41.0)	252 (46.8)	138 (45.4)
Score 2	16 (26.2)	158 (29.4)	102 (33.6)
High Risk	20 (32.8)	128 (23.8)	64 (21.1)
Score 3	18 (29.5)	109 (20.3)	55 (18.1)
Score 4	2 (3.3)	18 (3.3)	9 (3.0)
Score 5	0	1 (0.2)	0
Risk Factors for Arterial TEE			
Age ≥65	33 (54.1)	210 (39.0)	111 (36.5)
History of hypertension	27 (44.3)	218 (40.5)	120 (39.5)
History of arterial TEE	7 (11.5)	71 (13.2)	33 (10.9)
History of arteriosclerosis	5 (8.2)	70 (13.0)	25 (8.2)
History of hyperlipidemia / hypercholesterolemia	21 (34.4)	68 (12.6)	46 (15.1)
History of diabetes mellitus	14 (23.0)	77 (14.3)	40 (13.2)
Platelets ≥350000/µL	27 (44.3)	219 (40.7)	121 (39.8)
Leukocytes >11000/µL	22 (36.1)	171 (31.8)	100 (32.9)
Hb < 10g/dL	6 (9.8)	25 (4.6)	12 (3.9)
BMI ≥35 kg/m^2	3 (4.9)	19 (3.5)	6 (2.0)
Current smoking status: smokers[a]	NA	513 (95.4)	255 (83.9)

Abbreviations: BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; Hb = hemoglobin; GC+N = necitumumab in combination with gemcitabine and cisplatin; N = number of treated patients; n = number of patients in category; NSCLC = non-small cell lung cancer; PC+N = necitumumab in combination with pemetrexed and cisplatin; TEE = thromboembolic event.
Note: Identification of these risk factors was based on a literature search (Scappaticci et al. 2007; Khorana et al. 2008; Choueiri et al. 2010; Hurwitz et al. 2011; Petrelli et al. 2012; Lyman et al. 2013b).
Note: All study patients had a Khorana Risk Score of at least 1 due to diagnosis of NSCLC.
a Smoking history was not collected in Study JFCK, and therefore is not included in the risk factors.

To further assess the thromboembolic events observed in Study JFCK, exploratory analyses examining possible risk factors for VTEs and ATEs were performed demonstrating a similar pattern as seen in SQUIRE, suggesting the most predictive risk factor for metastatic squamous NSCLC patients experiencing a thromboembolic event during treatment with necitumumab plus platinum-based therapy was a history of a previous event.

The analysis of baseline risk factors in SQUIRE suggested a history of VTE as the primary predictor for subsequent VTEs.

Analysis of bleeding events

With thromboprophylaxis, the risk of bleeding is higher in patients with cancer than the general population. Cases of pulmonary bleeding events in SQUIRE were evaluated. For grade 3-4 haemoptysis, an incidence of 1.3% and 0.9% was observed for the GC+N Arm and GC Arm, respectively.

Table 55: Summary of Treatment-Emergent Pulmonary Bleeding Events, Safety Population, SQUIRE

	GC+N N = 538 n (%)				GC N = 541 n (%)	
	Overall		Chemotherapy Phase			
Preferred Term	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Haemoptysis	53 (9.9)	7 (1.3)	44 (8.2)	5 (0.9)	27 (5.0)	5 (0.9)
Pulmonary Haemorrhage	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	5 (0.9)	5 (0.9)
Respiratory Tract Haemorrhage	0	0	0	0	2 (0.4)	2 (0.4)

Abbreviations: GC = gemcitabine plus cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; N = number of treated patients; n = number of patients in category.

Fatal events related to pulmonary bleeding occurred with higher incidence in the GC Arm compared to the GC+N Arm, including events of haemoptysis (0.7% [n=4] vs. 0.9% [n=5]), pulmonary haemorrhage (0.2% [n=1] vs. 0.7% [n=4]), and respiratory tract haemorrhage (0.0% vs. 0.4% [n=2]).

B. Hypersensitivity/Infusion-Related Reactions

Table 56: Hypersensitivity/Infusion-related reactions

Hypersensitivity/Infusion-Related Reactions	
Frequency with 95% CI	**Incidence rate (all grades) in patients treated with necitumumab + gemcitabine + cisplatin:** SQUIRE (N=538) 1.5% (8/538) 95% CI: 0.6, 2.9 **Incidence rate (all grades) in patients treated with necitumumab + pemetrexed + cisplatin:** INSPIRE (N=304) 2.0% (6/304) 95% CI: 0.7, 4.2
Seriousness/outcomes	**Patients treated with necitumumab + gemcitabine + cisplatin:** SQUIRE (N=538) Fatal: 0.0% (0/538) Recovered/Resolved: 1.5% (8/538) Not Recovered/Not Resolved: 0.0% (0/538) **Patients treated with necitumumab + pemetrexed + cisplatin:** INSPIRE (N=304) Fatal: 0.0% (0/304) Recovered/Resolved: 2.0% (6/304) Not Recovered/not Resolved: 0.0% (0/304)
Severity and nature of risk	**Patients treated with necitumumab + gemcitabine + cisplatin:** SQUIRE (N=538) Grade: 3-5 0.4% (2/538) Grade 3 0.4% (2/538) Grade 4 0.0% (0/538) Grade 5 0.0% (0/538) **Patients treated with necitumumab + pemetrexed + cisplatin:** INSPIRE (N=304) Grade 3-5 0.0% (0/304) Grade 3 0.0% (0/304) Grade 4 0.0% (0/304) Grade 5 0.0% (0/304)

C. Severe skin reactions

Table 57: Severe skin reactions

Severe Skin Reactions	
Frequency with 95% CI	Overall, skin reactions, all grades, have been very commonly reported in patients treated with necitumumab-containing combination chemotherapy. For the purpose of this RMP, in the sections below, skin reactions (all Grades) are presented under Seriousness/outcomes, and severe skin reactions (Grade ≥3) are presented under Severity and nature of the risk. We consider only skin reactions with Grade ≥3 to rise to the level of an Important Potential Risk.
Seriousness/outcomes	**Patients treated with necitumumab + gemcitabine + cisplatin:** SQUIRE (N=538) Fatal: 0.0% (0/538) 95% CI: 0.0, 0.7 Recovered/Resolved: 38.1% (205/538) 95% CI: 34.0, 42.4 Not Recovered/Not Resolved: 40.7% (219/538) 95% CI: 36.5, 45.0 **Patients treated with necitumumab + pemetrexed + cisplatin:** INSPIRE (N=304) Fatal: 0.0% (0/304) 95% CI: 0.0, 1.2 Recovered/Resolved: 40.8% (124/304) 95% CI: 35.2, 46.5 Not Recovered/Not Resolved: 37.2% (113/304) 95% CI: 31.7, 42.9
Severity and nature of risk	**Patients treated with necitumumab + gemcitabine + cisplatin:** SQUIRE (N=538) Grade 3-5 8.2% (44/538) Grade 3 8.2% (44/538) Grade 4 0.0% (0/538) Grade 5 0.0% (0/538) **Patients treated with necitumumab + pemetrexed + cisplatin:** INSPIRE (N=304) Grade 3-5 16.1% (49/304) Grade 3 15.8% (48/304) Grade 4 0.3% (1/304) Grade 5 0.0% (0/304)

Skin-related disorders (all MedDRA terms) dominate the safety profile of necitumumab, with 40.7% (219/538) of cases not resolved in the main trial, while 38.1% (205/538) subjects recovered. Skin reactions are mainly presented as acneiform rash, dermatitis acneiform, dry skin, pruritus, skin fissures, paronychia and palmar-plantar erythrodysaesthesia syndrome. Severe skin reactions were reported in approximately 6 % of patients while 1.7 % of patients discontinued due to skin reactions. The majority of skin reactions developed during the first cycle of treatment and resolved within 17 weeks after onset. Dermatologic involvement is a known class-effect of anti-EGFR treatment. No cases of skin necrosis, SJS/TEN have so far been observed with necitumumab.

Infusion-related reactions were reported in 1.5 % of patients and mainly present as chills, fever or dyspnoea. Severe infusion-related reactions were reported in 0.4 % of patients. The majority of infusion-related reactions developed after the first or second administration of necitumumab.

Isolated cases of Grade 1 trichomegaly have been reported in patients treated with necitumumab.

D. Electrolyte disorders

Hypomagnesemia is by far the leading electrolyte disorder caused by necitumumab. As a potential contribution of hypomagnesaemia to the risk of sudden death could not be ruled out in presence of hypokalaemia, this relationship was explored by the Applicant. No correlation between electrolyte abnormalities and sudden/unexplained deaths could be established after analyses of studies SQUIRE, INSPIRE and JFCI.

E. Other AESI and events from the Consolidated Term Analysis

Table 58: Other AESI and events from the consolidated term analysis

	GC+N N = 538 n (%)				GC N = 541 n (%)	
	Overall		Ctx Phase Only		Overall	
AESI Category[a]	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neutropenia	235 (43.7)	131 (24.3)	235 (43.7)	131 (24.3)	248 (45.8)	149
Febrile Neutropenia	6 (1.1)	4 (0.7)	4 (0.7)	3 (0.6)	8 (1.5)	7 (1.3)
Anemia	225 (41.8)	57 (10.6)	216 (40.1)	56 (10.4)	248 (45.8)	59 (10.9)
Thrombocytopenia	117 (21.7)	55 (10.2)	116 (21.6)	55 (10.2)	146 (27.0)	58 (10.7)
Fatigue	229 (42.6)	39 (7.2)	219 (40.7)	37 (6.9)	230 (42.5)	38 (7.0)
Hypomagnesaemia	168 (31.2)	50 (9.3)	162 (30.1)	48 (8.9)	85 (15.7)	6 (1.1)
Skin Reactions	424 (78.8)	44 (8.2)	419 (77.9)	34 (6.3)	64 (11.8)	3 (0.6)
Rash[b]	410 (76.2)	38 (7.1)	405 (75.3)	30 (5.6)	55 (10.2)	2 (0.4)
Hypersensitivity/IRR	8 (1.5)	2 (0.4)	8 (1.5)	2 (0.4)	11 (2.0)	0
Eye Disorders	40 (7.4)	2 (0.4)	30 (5.6)	0	12 (2.2)	0
Interstitial Lung Disease	5 (0.9)	2 (0.4)	4 (0.7)	1 (0.2)	4 (0.7)	3 (0.6)

Eye disorders were more common in the GC+N arm than in the GC arm (7.4% vs. 2.2%); there were, however, only 2 patients (0.4%) with events of Grade ≥3 (both in the GC+N arm).

Incidences of fatigue and of events pooled under the category of ILD, including incidences of events of Grade ≥3, were similar in both arms.

Events related to hematologic toxicity, pooled under the composite terms of neutropenia, febrile neutropenia, anaemia, and thrombocytopenia, were similar between arms, with a trend toward more common in the GC arm than in the GC+N arm, including events of Grade ≥3.

Serious adverse event/deaths/other significant events

SAEs

In both SQUIRE and INSPIRE, treatment-emergent SAEs were more common among patients in the necitumumab arm than with chemotherapy alone.

The most common treatment-emergent SAE in both arms of SQUIRE study was NSCLC (disease progression reported as SAE), while in INSPIRE NSCLC incidence was higher in the PC+N arm (7.2 overall and 5.3% Ctx phase) than in the PC arm (3.2%).

In SQUIRE, the SAEs for which incidence in the GC+N arm was ≥1% than in the control arm were vomiting (2.2% vs. 0.4%), pulmonary embolism (3.5% vs. 1.7%) and anaemia (4.1% vs. 3.1%). Neutropenia and thrombocytopenia occurred with higher incidence in the GC arm as compared to the GC+N arm.

When considering the same ≥1% absolute difference between arms in INSPIRE, in the PC+N arm the following PT are observed: pneumonia (4.3 vs 1.9%), diarrhoea (3.3 vs 1.6%), neutropenia (3.0 vs 1.6%), thrombocytopenia (2.6 vs 1.6%), asthenia (2.6 vs 0.6%), anorexia (2.0 vs 1.0%), general physical health deterioration (2.0 vs 1.0%) and medication error (2.0 vs 0.6%).

Deaths

Deaths are summarized by primary cause of death as assigned by the investigator. For the assignment of the primary cause of death, progression of disease (PD) was considered separate from AEs. Overall, in SQUIRE,

most patients in both arms died primarily due to PD, with a higher rate in the control arm compared to the GC+N (339 patients [63.0%] in the GC+N vs. 367 patients [67.8%] in the GC arm).

Among the patients who died while on treatment or within 30 days of the last dose of study therapy, the most common primary cause of death in both arms was assigned as an AE. A total of 35 patients (6.5%) in the GC+N arm and 38 patients (7.0%) in the GC arm died with an AE as the primary cause of death. An additional 5 patients in the GC+N and 5 patients in the GC arm died with an AE as the primary cause of death more than 30 days after the last dose of study therapy.

The findings are similar in INSPIRE. Most patients in both arms died primarily due to PD, with a higher rate in the control arm compared to the PC+N arm (185 patients [60.9%] in Arm A versus 206 patients [66.0%] in the PC Arm). Among the patients who died while on treatment or within 30 days of the last dose of study therapy, the most common primary cause of death in both arms was assigned as AE. A total of 23 patients (7.6%) in the PC+N arm and 19 patients (6.1%) in the PC arm died with an AE as the primary cause of death. An additional 5 patients in the PC+N arm and 4 patients in the PC arm died with any AE, regardless of causality, as the primary cause of death more than 30 days after the last dose of study therapy.

A head-to-head analysis of all deaths/sudden deaths/thromboembolic deaths in SQUIRE and INSPIRE is provided below:

Table 59: Summary of deaths in SQUIRE and INSPIRE studies

	SQUIRE		INSPIRE	
	GC+N % (n=538)	**GC % (n=541)**	**PC+N % (n=304)**	**PC % (n=312)**
Deaths	77	81	75.3	77.6
Disease progression	63	67.8	60.9	66
AE leading to death	12.3	10.5	16.1	10.3
Death on treatment or <30 days	11.2	10.5	14	9

Table 60: Sudden deaths and deaths cause unknown on treatment or within 30 days of last dose in SQUIRE and INSPIRE studies

SQUIRE		INSPIRE	
GC+N	**GC %**	**PC+N %**	**PC %**
15/538 = 2.8%	3/541 = 0.6%	4/304 = 1.3%	1/312 = 0.3%

In SQUIRE, there were 12 sudden/ NOS deaths (10 in the GC+N Arm, 2 in the GC Arm) and 6 deaths due to cardiac/cardio-respiratory arrest (5 in the GC+N Arm, 1 in the GC Arm) (see table 62). Of them, at least four have documented grade 2 or 3 hypomagnesaemia.

Table 61: Summary of deaths with primary cause of death as assigned by the investigator – Squire study

	NECI+Gem-Cis N=538 n (%)	Gem-Cis N=541 n (%)
Event Category	Grade 5	Grade 5
All Deaths	414 (77.0)	437 (80.8)
- Patients with death on treatment	66 (12.3)	57 (10.5)
- Death NOS	8 (1.5)	2 (0.4)
- Sudden death	2 (0.4)	0
- Cardiac arrest / Cardio-respiratory arrest	5 (0.9)	1 (0.2)

In SQUIRE, 12 of the 15 patients died within 30 days of the last dose of necitumumab and had comorbid conditions including history of coronary artery disease (n=3), hypomagnesemia (n=4), chronic obstructive pulmonary disease (n=7), and hypertension (n=5). Eleven of the 12 patients had an unwitnessed death.

Hypomagnesemia may enhance diarrhoea-induced hypokalaemia, thus contributing to possible QT prolongation / deleterious cardiac effects. Hypokalaemia was also observed in SQUIRE (Grade 3 or 4 in the GC+N Arm was 4.6% vs. 3.2% in the GC Arm). In terms of concurrent presence of Grade 3 or 4 hypomagnesaemia and Grade 3 or 4 hypokalaemia, there were overall cases from 10 patients (GC+N Arm: 8, GC Arm: 2) reported. No clinically significant abnormal ECG results were reported in these patients.

Electrolytes for the total of these 18 patients with sudden/unexplained deaths were reviewed to assess whether there was a concurrent presence of hypomagnesaemia and hypokalaemia at any time point during the course of treatment. None of these patients had concurrent presence of Grade 3 or 4 hypomagnesaemia and Grade 3 or 4 hypokalaemia. In 4 patients in the GC+N Arm with sudden/unexplained death, Grade 3 hypomagnesaemia was reported. Of these, 1 patient reported concurrent hypomagnesaemia (Grade 3) and hypokalaemia (Grade 1), and 3 patients reported hypomagnesaemia (Grade 3) and hyperkalaemia (any grade).

Laboratory findings

Haematology

In SQUIRE, changes from a baseline grade 0-2 to a worst grade 3 on study were observed with higher incidence in the GC arm than in the GC+N arm for low neutrophils and low leukocytes; changes for other parameters were similar between arms. Shifts to grade 4 were similar between arms for all parameters.

In INSPIRE, the same type of changes were seen more frequently in the PC arm than in the PC+N Arm for low neutrophils; shifts for other parameters were similar between arms. Shifts to grade 4 were more frequent in the PC+N arm for low neutrophils.

Chemistry

Findings were similar between the two studies, with consistent hypomagnesemia shifts to grade 3 or 4 in the necitumumab arms in comparison to no-necitumumab.

Safety in special populations

No dedicated studies have been performed in hepatic or renally impaired patients. However, PopPK analysis shows no correlation of necitumumab disposition to renal function (as assessed by Cockcroft-Gault creatinine clearance [range investigated 11-250 mL/min]) or hepatic function (as assessed by alanine aminotransferase [2 - 615 U/L], aspartate transaminase [1.2 - 619 U/L], and total bilirubin [0.1 - 106 µmol/L] markers.

No dedicated studies have been performed in elderly patients.

The patients >70 years of age discontinued treatment earlier. No relevant differences between age groups with regard to reasons for discontinuation could be observed. Overall, no ADR patterns could be discerned between different age groups.

Table 62: Summary of ADRs of necitumumab by age interval for elderly patients safety population – SQUIRE study

MedDRA Terms	Age <65 (N=328) n(%)	Age 65-74 (N=185) n(%)	Age 75-84 (N=25) n(%)	Age 85+ (N=0) n(%)
Total ADRs	304 (92.7)	168 (90.8)	23 (92.0)	0
Arterial Thromboembolic Events (ATE)	19 (5.8)	9 (4.9)	1 (4.0)	0
Conjunctivitis	18 (5.5)	18 (9.7)	4 (16.0)	0
Dysgeusia	21 (6.4)	11 (5.9)	1 (4.0)	0
Dysphagia	11 (3.4)	5 (2.7)	0	0
Dysuria	12 (3.7)	4 (2.2)	0	0
Epistaxis	19 (5.8)	20 (10.8)	1 (4.0)	0
Haemoptysis	32 (9.8)	18 (9.7)	3 (12.0)	0
Headache	36 (11.0)	21 (11.4)	0	0
Hypersensitivity/Infusion Related Reaction (IRR)	6 (1.8)	2 (1.1)	0	0
Hypocalcaemia	9 (2.7)	16 (8.6)	2 (8.0)	0
Hypokalaemia	15 (4.6)	25 (13.5)	1 (4.0)	0
Hypomagnesaemia	99 (30.2)	56 (30.3)	13 (52.0)	0
Hypophosphataemia	7 (2.1)	4 (2.2)	0	0
Mouth ulceration	6 (1.8)	1 (0.5)	1 (4.0)	0
Muscle spasms	5 (1.5)	5 (2.7)	1 (4.0)	0
Oropharyngeal pain	5 (1.5)	2 (1.1)	1 (4.0)	0
Phlebitis	3 (0.9)	6 (3.2)	0	0
Pyrexia	38 (11.6)	32 (17.3)	4 (16.0)	0
Skin Reactions	261 (79.6)	144 (77.8)	19 (76.0)	0
Stomatitis	33 (10.1)	23 (12.4)	3 (12.0)	0
Urinary tract infection	13 (4.0)	13 (7.0)	2 (8.0)	0
Venous Thromboembolic Events (VTE)	24 (7.3)	23 (12.4)	2 (8.0)	0
Vomiting	93 (28.4)	59 (31.9)	5 (20.0)	0
Weight decreased	39 (11.9)	30 (16.2)	3 (12.0)	0
Serious ADRs - Total	60 (18.3)	34 (18.4)	2 (8.0)	0
Fatal	5 (1.5)	3 (1.6)	0	0
Hospitalization/prolong existing hospitalization	47 (14.3)	23 (12.4)	1 (4.0)	0
AE leading to drop-out	66 (20.1)	38 (20.5)	5 (20.0)	0
Psychiatric disorders (SOC)	35 (10.7)	30 (16.2)	2 (8.0)	0
Nervous system disorders (SOC)	114 (34.8)	81 (43.8)	8 (32.0)	0
Accidents and injuries (SMQ)	7 (2.1)	9 (4.9)	2 (8.0)	0
Cardiac disorders (SOC)	27 (8.2)	22 (11.9)	3 (12.0)	0
Vascular disorders (SOC)	43 (13.1)	38 (20.5)	4 (16.0)	0
Cerebrovascular disorders (SMQ)	11 (3.4)	4 (2.2)	1 (4.0)	0
Infections and infestations (SOC)	108 (32.9)	88 (47.6)	11 (44.0)	0
Quality of life decreased (PT)	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	30 (9.1)	34 (18.4)	4 (16.0)	0

No paediatric data for necitumumab are available.

Safety related to drug-drug interactions and other interactions

No clinically relevant interaction has been identified between necitumumab and gemcitabine and cisplatin.

Discontinuation due to adverse events

Table 63: MedDRA SOC of TEAEs leading to treatment delay/modification (safety population) – SQUIRE study

	GC+N N = 538 n (%)			GC N = 541 n (%)		
	Pts. with AE leading to delay/modification of			Pts. with AE leading to delay/modification of		
System Organ Class	Any Therapy	Ctx	Neci	Any Therapy	Ctx	Neci
Patients with any event	**321 (59.7)**	**303 (56.3)**	**239 (44.4)**	**312 (57.7)**	**312 (57.7)**	**NA**
Blood and Lymphatic System Disorders	214 (39.8)	210 (39.0)	122 (22.7)	227 (42.0)	227 (42.0)	NA
Infections and Infestations	54 (10.0)	36 (6.7)	51 (9.5)	46 (8.5)	46 (8.5)	NA
Investigations	53 (9.9)	50 (9.3)	24 (4.5)	51 (9.4)	51 (9.4)	NA
General Disorders & Administration Site Conditions	42 (7.8)	31 (5.8)	37 (6.9)	31 (5.7)	31 (5.7)	NA
Skin and Subcutaneous Tissue Disorders	40 (7.4)	9 (1.7)	39 (7.2)	2 (0.4)	2 (0.4)	NA
Metabolism and Nutrition Disorders	33 (6.1)	28 (5.2)	26 (4.8)	30 (5.5)	30 (5.5)	NA
Gastrointestinal Disorders	32 (5.9)	26 (4.8)	27 (5.0)	26 (4.8)	26 (4.8)	NA

With regard to SOC of TEAEs leading to necitumumab treatment delay/modification, in SQUIRE they were mainly attributable to the SOC 'blood' (22.7%), followed by 'infections' (9.5%); in INSPIRE 'skin' leads with 13.8%, followed by 'blood' (9.9%).

Table 64: MedDRA SOC of TEAEs leading to discontinuation of study therapy (safety population) – SQUIRE study

	GC+N N = 538 n (%)				GC N = 541 n (%)			
	Pts. with a TEAE leading to discontinuation of:				Pts. with a TEAE leading to discontinuation of:			
System Organ Class	Any Therapy	Any Ctx	Neci	All	Any Therapy	Any Ctx	Neci	All
Patients with any event	**168 (31.2)**	**135 (25.1)**	**109 (20.3)**	**63 (11.7)**	**133 (24.6)**	**133 (24.6)**	**NA**	**80 (14.8)**
Blood and Lymphatic System Disorders	55 (10.2)	52 (9.7)	15 (2.8)	12 (2.2)	48 (8.9)	48 (8.9)	NA	15 (2.8)
General Disorders & Administration Site Conditions	21 (3.9)	15 (2.8)	12 (2.2)	5 (0.9)	16 (3.0)	16 (3.0)	NA	11 (2.0)
Investigations	18 (3.3)	15 (2.8)	9 (1.7)	4 (0.7)	19 (3.5)	19 (3.5)	NA	14 (2.6)
Respiratory, Thoracic, and Mediastinal Disorders	18 (3.3)	11 (2.0)	16 (3.0)	8 (1.5)	10 (1.8)	10 (1.8)	NA	9 (1.7)
Skin and Subcutaneous Tissue Disorders	14 (2.6)	2 (0.4)	14 (2.6)	2 (0.4)	1 (0.2)	1 (0.2)	NA	1 (0.2)
Neoplasms Benign, Malignant, and Unspecified	9 (1.7)	7 (1.3)	8 (1.5)	5 (0.9)	4 (0.7)	4 (0.7)	NA	3 (0.6)
Nervous System Disorders	9 (1.7)	8 (1.5)	8 (1.5)	7 (1.3)	6 (1.1)	6 (1.1)	NA	3 (0.6)
Renal and Urinary Disorders	9 (1.7)	9 (1.7)	7 (1.3)	7 (1.3)	13 (2.4)	13 (2.4)	NA	11 (2.0)
Gastrointestinal Disorders	8 (1.5)	6 (1.1)	6 (1.1)	4 (0.7)	6 (1.1)	6 (1.1)	NA	5 (0.9)
Metabolism and Nutrition Disorders	8 (1.5)	8 (1.5)	4 (0.7)	3 (0.6)	12 (2.2)	12 (2.2)	NA	5 (0.9)
Vascular Disorders	8 (1.5)	4 (0.7)	8 (1.5)	3 (0.6)	1 (0.2)	1 (0.2)	NA	1 (0.2)
Cardiac Disorders	6 (1.1)	4 (0.7)	5 (0.9)	3 (0.6)	8 (1.5)	8 (1.5)	NA	8 (1.5)
Ear and Labyrinth Disorders	6 (1.1)	6 (1.1)	2 (0.4)	2 (0.4)	5 (0.9)	5 (0.9)	NA	2 (0.4)
Infections and Infestations	5 (0.9)	5 (0.9)	5 (0.9)	5 (0.9)	9 (1.7)	9 (1.7)	NA	6 (1.1)
Injury, Poisoning, and Procedural Complications	3 (0.6)	1 (0.2)	3 (0.6)	1 (0.2)	1 (0.2)	1 (0.2)	NA	1 (0.2)
Muscoloskeletal and Connective Tissue Disorders	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)	1 (0.2)	1 (0.2)	NA	1 (0.2)

While in INSPIRE the SOC contributing to most TEAEs leading to discontinuations was 'skin', in SQUIRE was 'blood' (however, those leading directly necitumumab discontinuation are only 2.8%, compared to chemotherapy, 9.7%, and 10.2%, any therapy). They are followed in both studies by 'general disorders' and 'investigations'.

The delay/reduction of necitumumab dose due to AEs resulted in a lower re-occurence of the same adverse event, also in most cases with a reduced severity.

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

EGFR-directed monoclonal antibodies evaluated in clinical trials in patients with NSCLC include cetuximab, necitumumab, matuzumab and panitumumab (Curr Opoin Oncol 2015, 27:87-93).

From a mechanism of action perspective with implications on the safety profile, cetuximab (Erbitux) is the most relevant drug to compare necitumumab with, as both are IgG1 MoAbs blocking EGFR.

The safety profile of anti-EGFR MoAbs in general, and in the NSCLC context in particular, is largely known. With regard to cetuximab-related AEs, grade 3 or 4 leukopenia, grade 3 or 4 acne-like rash, febrile neutropenia, septic events, fatigue, diarrhoea and infusion-related reactions are more frequently seen in the chemotherapy + cetuximab arms in comparison with chemotherapy alone. 'Skin' disorders and hypomagnesemia dominate the spectrum of AEs for necitumumab.

The addition of necitumumab to the chemotherapy backbone did not reduce the median relative dose intensity for gemcitabine or for cisplatin, which indicates that the combination therapy in most cases can be administered without adjusting the individual components. The extent of chemotherapy exposure is balanced between the two arms.

VTE and ATE, including fatal cases, were observed with necitumumab in combination with gemcitabine and cisplatin (see sections 4.4 and 4.8 of the SmPC). The platinum-based chemotherapy, which is the standard treatment for the proposed indication, is thrombogenic per se. About 18% of patients who receive cisplatin-based chemotherapy for any type of malignancy develop a thromboembolic event either during treatment or within four weeks of their last cisplatin dose (Moore et al., J Clin Onc 2011). A recent meta-analysis of the risk of venous and arterial thromboembolic events in 11 clinical trials (Petrelli et al., Annals of Onc 2012) concluded that cetuximab and panitumumab are associated with a significant increase in the risk of venous, but not arterial, thromboembolism in solid tumours. The incidence of ATEs with necitumumab as add-on to cisplatin chemotherapy, as reflected in this submission, is numerically higher than the previously reported in the literature for cetuximab and panitumumab. In SQUIRE, arterial thromboembolic events occurred more often in the necitumumab arm than in the control arm (5.4% [3.9% Grade ≥3] vs. 3.9% [2.0% Grade ≥3]). The same trend, albeit less pronounced, was seen in the INSPIRE trial.

When compared to SQUIRE, 'any grade' VTEs increased by 2.4%, while grade ≥3 VTEs remained at 5% in the JFCK trial; the incidence of 'any grade' ATEs has tripled, while grade ≥3 almost doubled. In comparison with SQUIRE and INSPIRE, a higher percentage of patients in Study JFCK were ≥65 years, had a haemoglobin <10 g/dL, and had a Khorana high risk score of 3. The incidence of TEs was higher in the non-squamous (adenocarcinoma) population.

Despite the identified risk of VTE with EGFR MoABs and platinum-based chemotherapy, thromboprophylaxis is still debated and currently limited to patients at risk at baseline, even if some data suggest that LMW-heparin can reduce the risk of VTEs in certain types of cancer. For cetuximab and panitumumab, the thrombotic risk seems not correlated with the longer duration of therapy in the experimental arms. No pattern for VTEs occurrence has been discerned in SQUIRE, in contrast with the early events registered in INSPIRE.

The risk of TE events was further discussed by the applicant during a CHMP oral explanation. As a result, section 4.4 of the SmPC was amended to better define the specific patient subgroups at high risk and improve recommendations to prescribers (see below).

Administration of necitumumab should be carefully considered in those patients with a history of thromboembolic events (such as pulmonary embolism, deep vein thrombosis, myocardial infarction, stroke) or preexisting risk factors for thromboembolic events (such as advanced age, patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with acquired or inherited thrombophilic disorders). The relative risk of VTE or ATE was approximately three-fold higher in patients with a reported history of VTE or ATE. Necitumumab should not be administered to patients with multiple risk factors for thromboembolic events unless the benefits outweigh the risks to the patient.

Thromboprophylaxis should be considered after careful assessment of a patient's risk factors (including the increased risk of serious bleeding in patients with tumour cavitation or tumour involvement of large central blood vessels). Patients and physicians should be aware of signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling.

Discontinuation of necitumumab in patients who experience a VTE or ATE should be considered after a thorough benefit risk assessment for the individual patient.

In the INSPIRE study in advanced non-squamous NSCLC, patients experienced an increased rate of serious thromboembolic events (including fatal events) in the necitumumab plus pemetrexed and cisplatin arm as compared to the pemetrexed and cisplatin arm. The addition of necitumumab did not improve the efficacy outcome over pemetrexed and cisplatin alone in advanced non-squamous NSCLC. Administration of necitumumab in combination with pemetrexed and cisplatin is not recommended (see sections 4.4 and 4.8 of the SmPC).

An increased frequency of cardiorespiratory arrest or sudden death was observed with necitumumab. Cardiorespiratory arrest or sudden death was reported in 2.8% (15/538) of patients treated with necitumumab in combination with gemcitabine and cisplatin compared to 0.6% (3/541) of patients treated with chemotherapy alone. Patients with significant coronary artery disease, myocardial infarction within 6 months, uncontrolled hypertension, and uncontrolled congestive heart failure were not enrolled in the pivotal study. The incremental risk of cardiopulmonary arrest or sudden death in patients with a history of coronary artery disease, congestive heart failure, or arrhythmias as compared to those without these comorbid conditions is not known.

In study JFCL investigating the same patient populationthan SQUIRE, but with a different backbone chemotherapy (paclitaxel + carboplatin), there were no differences in the rate of deaths due to adverse events between the two arms (9.4% vs 9.1%). However, deaths within 30 days of last dose were more frequently observed in the necitumumab arm (14.2% vs 5.5%), with an excess of deaths due to AE in the necitumumab vs the control arm (8.5% vs 5.5%). AEs with outcome death included acute respiratory failure, lung infection, septic shock, circulatory collapse, respiratory failure, pulmonary embolism, brain death and cardiac arrest in one patient, hypovolemic shock, cardiac failure congestive, and pneumonia. The possible relationship of the events with the administration of necitumumab cannot be excluded, and the additional data provided reinforces the concerns on the safety profile of necitumumab in the target population.

In conclusion, the data provided by SQUIRE and INSPIRE suggest an increased risk of sudden death/death NOS when necitumumab is added to a cisplatin-based regimen (see sections 4.4 and 4.8 of the SmPC).

Progressively decreasing serum magnesium levels occur frequently and may lead to severe hypomagnesaemia. Hypomagnesaemia may reoccur at the same grade or worse after a dose delay. Patients should be carefully monitored for serum electrolytes, including serum magnesium, potassium, and calcium, prior to each necitumumab administration and after completion of necitumumab treatment, until within normal limits. Prompt electrolyte repletion is recommended, as appropriate (see sections 4.4 and 4.8 of the SmPC).

The potential of monoclonal antibodies to cause a QT effect via direct mechanisms is uncertain. Recently, an analysis of the QT effects of MoAbs and 2 antibody drug conjugates was presented (ASCO 2014, abstract 2600) and so far data suggest that MoAbs are unlikely to cause QT/QTc interval prolongation. The conducted QT study showed individual increases (and corresponding decreases) in QTc compatible with increased variability and not a pharmacological effect of the MoAb.

During the CHMP oral explanation, the applicant was also requested to further discuss severe cardiac disorders/sudden deaths which have been reported.

The discussion resulted in the request to perform a Post authorisation safety study (PASS) to monitor adverse events of interest. A study outline was submitted by the Applicant and considered informative (see RMP section).

As with all therapeutic proteins, there is the potential for immunogenicity. Overall, there was a low incidence of both treatment emergent anti-drug antibodies and neutralizing antibodies among necitumumab treated patients, and no correlation with safety outcomes in these patients. Hypersensitivity/ IRRs were reported with necitumumab. The onset of events usually occurred after the first or second administration of necitumumab. Patients should be monitored during and following the infusion for signs of hypersensitivity and infusion-related reactions with resuscitation equipment and appropriate medical resources readily available. In patients who have experienced a previous Grade 1 or 2 hypersensitivity or infusion related reaction to necitumumab, premedication with a corticosteroid and an antipyretic in addition to an antihistamine is recommended.

There was no relationship between immunogenicity and IRRs or treatment emergent adverse events.

Probably as a result of the different glycosylation process than for cetuximab (different murine structures, NS0 vs Sp2/0), hypersensitivity reactions were less frequent with necitumumab (historical comparison).

Skin reactions were reported with necitumumab. The onset of events occurred mainly during the first cycle of treatment. Pre-emptive skin treatment including skin moisturiser, sun screen, topical steroid cream (1 % hydrocortisone) and an oral antibiotic (e.g. doxycycline) may be useful in the management of dermatologic reactions as clinically appropriate. Patients may be advised to apply moisturiser, sunscreen and topical steroid cream to face, hands, feet, neck, back and chest. Dermatologic involvement is a known class-effect of anti-EGFR treatment.

The analysis of all AESI by treatment cycle, TEs included, in order to observe event chronology, did not elicit findings inconsistent with the profile of an anti-EGFR MoAb. As expected, more events were observed during the combined necitumumab + chemotherapy phase of SQUIRE; their duration and outcome seem not to diverge from previous data with necitumumab/other anti-EGFR.

The delay/reduction of necitumumab dose due to AEs resulted in a lower re-occurence of the same adverse event, also in most cases with a reduced severity. However, hypomagnesemia may reoccur at the same grade or worse after dose delay (see section 4.4. of the SmPC).

The Applicant discussed the overall tolerability of the proposed regimen (triggered by the fact that 31 % in the GC+N arm discontinued any therapy vs. 25 % in the GC arm) in terms of longer treatment period in the experimental arm, hence more discontinuations expected. When only considering events observed in the

'chemotherapy phase', the incidence rates of AEs leading to discontinuation are closer (approximately 28% vs 25%).

A sufficient representation of patients >65 and >70 years has been included in the SQUIRE trial. However no overall differences in efficacy between arms were observed in patients above 70 years of age. Cardiovascular comorbidities, performance status and the likely tolerability to chemotherapy with add-on necitumumab should therefore be thoroughly evaluated prior to the initiation of treatment in patients above 70 years of age. No dose reductions other than those recommended for all patients are necessary (see section 5.1 of the SmPC).

There are no data on the effect of necitumumab on human fertility or in pregnant women. However based on its mechanism of action and animal models where EGFR expression is disrupted, necitumumab may cause foetal harm or developmental anomalies. Women of childbearing potential should be advised to avoid becoming pregnant while on necitumumab and should be informed of the potential hazard to the pregnancy and foetus. Effective contraception has to be used during necitumumab treatment and up to 3 months after last administration of necitumumab treatment. Contraceptive measures or abstinence are recommended (see sections 4.4 and 4.6 of the SmPC). Necitumumab should not be used during pregnancy or in women not using effective contraception, unless the potential benefit justifies the potential risk to the foetus. It is unknown whether necitumumab is excreted in human milk. Excretion in milk and oral absorption is expected to be low. A risk to newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with necitumumab and for at least 4 months after the last dose.

There has been limited experience with necitumumab overdose in human clinical trials. The highest dose of necitumumab studied clinically in a human dose-escalation Phase 1 study is 1,000 mg once a week or once every other week. Adverse events observed included headache, vomiting and nausea and were consistent with the safety profile at the recommended dose. There is no known antidote for necitumumab overdose.

Necitumumab has no known influence on the ability to drive and use machines. If patients experience treatment-related symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

This medicinal product contains 244 mg sodium per dose which has to be taken into consideration by patients on a controlled sodium diet (see sections 4.4 and 4.8 of the SmPC).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety data are considered comprehensive for a new anti-cancer compound at the time of MAA and allow for a proper assessment of the risks related to necitumumab administration. Necitumumab exhibits the safety profile largely expected from a new IgG1 anti-EGFR MoAb. The 'skin' and 'electrolyte' disorders are the main contributors to the spectrum of common necitumumab-related AEs. In addition, the data provided by SQUIRE and INSPIRE suggest an increased risk of sudden death/death NOS when necitumumab is added to a cisplatin-based regimen. An increased incidence of TEs, some fatal, was observed with the addition of necitumumab to the platinum-doublet in both SQUIRE and INSPIRE studies. These risks have to be considered when prescribing necitumumab and appropriate recommendations have been included in the SmPC.

2.7. Risk Management Plan

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

The PRAC considered that the risk management plan version 1.0 (dated 27 November 2014) could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur RMP updated assessment report dated 10 April 2015.

The CHMP endorsed this advice.

The Applicant implemented all the changes to the RMP as requested by PRAC and CHMP.

The CHMP approved the RMP version 8.0 (dated 15 December 2015) with the following contents:

Safety concerns

Table 65- Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Venous Thromboembolic Events (VTEs) • Infusion-Related Reactions/Hypersensitivity • Arterial Thromboembolic Events (ATEs) • Severe Hypomagnesaemia • Severe Skin Reactions
Important potential risks	• Development and Reproductive Toxicity (DART) • Cardiorespiratory Disorders
Missing information	• Use in Pregnancy and Lactation • Activity in Biomarker-defined tumour subtypes (EGFR and KRAS and other downstream markers)

Pharmacovigilance Plan

Table 66- On-going and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Study/Activity Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
Physician/Oncologist knowledge survey (Category 3)	Assessment of physician/oncologist understanding of the key conditions for the safe use of necitumumab	Primarily: • Thromboembolic events • Cardiorespiratory disorders In addition: • Hypersensitivity/infusion related reactions • Severe skin reactions	Planned	Final report will be submitted within 12 months of end of data collection. This will be dependent on launch timings and market uptake.

		• Severe electrolyte abnormalities		
Observational Prospective PASS (Category 3)	Assessment of the incidence, severity, and sequelae of the targeted safety concerns	All serious life-threatening identified and potential risks for necitumumab treatment in the approved indication	Planned	Final report will be submitted within 12 months of end of data collection.
Exploratory analyses of biomarker status in the necitumumab clinical development programme of 4 Phase 1b/2 clinical trials (Category 3)	Assessment of EGFR protein expression status and EGFR and/or KRAS mutation status of patients in the studies	Address missing information on activity in biomarker defined subtypes	Planned	Q4 2018 (3 clinical trials) July 2019 (1 clinical trial)

Abbreviations: EGFR = epidermal growth factor receptor; KRAS = Kirsten rat sarcoma; PASS = Post-authorisation Safety Study; Q = quartile.

The PRAC also considered that routine pharmacovigilance not is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 67- Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
All safety concerns	**SmPC, Section 4.2:** Prescription only status and product administered under the supervision of a physician qualified in the use of anti-cancer chemotherapy.	None proposed
Important Identified Risks		
Venous Thromboembolic Events	SmPC wording in Section 4.4	A physician/oncologist communication will be distributed for launch. The key conditions for the safe use of necitumumab will be communicated including information on thromboembolic events and the need to consider prophylactic treatment on an individual basis in patients at high risk of thromboembolism.
Infusion-related Reactions/Hypersensitivity	SmPC wording in Section 4.2 and 4.4	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Arterial Thromboembolic Events	SmPC wording in Section 4.4	A physician/oncologist communication will be distributed for launch. The key conditions for the safe use of necitumumab will be communicated including information on thromboembolic events and the need to consider prophylactic treatment on an individual basis in patients at high risk of thromboembolism.
Severe Hypomagnesaemia	SmPC wording in Section 4.4	None proposed
Severe Skin Reactions	SmPC wording in Sections 4.2, 4.4, 4.8.	None proposed
Developmental and Reproductive Toxicity (DART)	SmPC wording in Sections 4.4, 4.6	None proposed
Cardiorespiratory Disorders	SmPC wording in Section 4.4	A physician/oncologist communication will be distributed for launch. The key conditions for the safe use of necitumumab will be communicated including information on cardiorespiratory disorders.
Use in Pregnancy and Lactation	SmPC wording in Section 4.6	None proposed
EGFR and KRAS Biomarker Activity (and other downstream markers)	None proposed	None proposed

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Portrazza (necitumumab) is included in the additional

monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

- It has obligations for stricter recording/monitoring of suspected adverse drug reactions; [REG Art 9(4)(cb), DIR Art 21a(c)];

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The SQUIRE study met its primary objective of statistically (p=0.012) improved OS for GC+N over GC in the overall population with a 16 % risk reduction of death (HR 0.84 [0.736, 0.962]; p=.0120). Also the secondary endpoint PFS showed an estimated reduction of 15 % in the risk of progression or death in favour of the GC+N arm (HR 0.85; p=0.02). All sensitivity analyses of OS and of PFS yielded a similar HR in favour of the experimental arm (HR 0.83-0.86). Apart from the age group ≥70 years (19 % of the ITT population), subgroup analyses of both endpoints were reasonably consistent in favour for the GC+N combination.

However, the OS benefit was a median of a modest 1.6 months for the experimental arm (11.5 months in the GC+N arm and 9.9 months in the GC arm).

No statistically significant differences were observed between the two treatment arms in relation to the health status assessments (LCSS and EQ-5D).

Uncertainty in the knowledge about the beneficial effects.

An OS and PFS benefit of the experimental arm over the comparator has not been demonstrated in patients ≥70 years of age (HR 1.03 and 1.07 respectively). Based on a multivariate model for OS, including treatment and prognostic factors, the adjusted OS HR in the ≥70 years patient group was 0.92. Section 4.4 and 5.1 of the SmPC adequately reflect this uncertainty.

In contrast to FLEX, SQUIRE enrolled also patients with EGFR expression negative tumours (by IHC). In this small group of patients, about 5%, no add-on activity of necitumab was demonstrated in pre-planned exploratory analysis. This is mechanistically expected and was furthermore observed in the BR 21 study conducted with erlotinib, an EGFR-TK inhibitor. This is reflected in the indication.

Several biomarkers were investigated in exploratory analyses (EGFR protein expression by IHC; HER2 protein expression by IHC; HER3 protein expression by IHC; EGFR CNG by FISH; FGFR1 CNG by SISH; eCadherin protein expression by IHC; and FCγR SNP. KRAS mutations and ALK translocations were not tested given their rarity in squamous NSCLC. The results obtained from these analyses were overall inconclusive. The plan of exploratory biomarker analyses included in the necitumumab clinical development program is considered

acceptable and the results will be submitted by 31 December 2018 for 3 clinical trials and by 31 July 2019 for an additional clinical trial (see RMP).

Risks

Unfavourable effects

Anti-EGFR class effects:

The 'skin' and 'electrolyte' disorders (class-effects of anti-EGFR MoAbs) are the main contributors to the spectrum of common necitumumab-related AEs. Even if cases of Stevens-Johnsons / toxic epidermal necrolysis syndrome have not been observed, 8-16% of skin disorders are severe (≥ grade 3) and lead to dose reductions/discontinuations; approximately half of them do not recover in a period of 28 days. Pre-emptive treatment for skin disorders is now proposed in the SmPC.

Sudden death/death NOS:

The data provided by SQUIRE and INSPIRE suggest an increased risk of sudden death/death NOS [i.e. 15 (2.8%) vs 3 (0.6%) in SQUIRE] when necitumumab is added to a cisplatin-based regimen (see SmPC section 4.4).

Thromboembolism:

An increased incidence of VTEs, some fatal, was observed with the addition of necitumumab to the platinum-doublet in both SQUIRE and INSPIRE studies. The incidence was higher in the non-squamous (adenocarcinoma) population; it was an early safety signal in INSPIRE (cycles 1 and 2) and led to IDMC termination of the study due to increased number of deaths of all causes and deaths possibly due to TEs in the necitumumab arm.

Uncertainty in the knowledge about the unfavourable effects

While there is an increased risk of electrolyte imbalances associated to the use of necitumumab, based on available data, no clear pattern of association can be hypothesized between electrolyte imbalances (i.e, hypomagnesaemia and hypokalaemia), QTc prolongation and mortality (sudden/unexplained deaths).The SmPC has been extensively revised to better define the specific patient subgroups at high thromboembolic risk and improve recommendations to prescribers.

The Applicant will also conduct an observational prospective PASS study comparing AEs between necitumumab+GC and GC treatment. The events of interest to be captured are mainly thromboembolism (including the extent and effect of thromboprophylaxis) and severe cardiac disorders/sudden deaths (see sections 4.4 and 4.8 of the SmPC).

Benefit-risk balance

Importance of favourable and unfavourable effects

Survival is considered the ultimate endpoint in cancer trials as it captures efficacy as well as safety, but tolerability should always be weighed in. The observed difference in median OS of 1.6 months associated with necitumumab was considered of modest clinical relevance. There was no detriment in terms of health status.

Benefit-risk balance

The overall B/R of Portrazza is positive and the RMP adequately reflects the PASS to be conducted by the applicant.

Discussion on the benefit-risk balance

SQUIRE enrolled also patients with EGFR expression negative tumours (by IHC). In this small group of patients, about 5%, no add-on activity of necitumab was demonstrated. This is mechanistically expected and was furthermore observed in the BR 21 study conducted with erlotinib, an EGFR-TK inhibitor. The indication has therefore been restricted to patients with EGFR positive status (see section 4.1 of the SmPC).

A numerical excess of sudden/unexplained deaths was observed in the necitumumab arm vs the control arm [i.e. 15 (2.8%) vs 3 (0.6%)], thereof 14 within 30 days from last dose. This raised concerns with respect to QT prolongation. The conducted QT study showed individual increases (and corresponding decreases) in QTc compatible with increased variability and not a pharmacological effect of the MoAb. Increased variability is expected in the target population of older patients with a history of smoking. Mechanistically, severe electrolyte disturbances are more likely to cause cardiac arrhythmias, but this was not demonstrated in the analyses conducted. Electrolyte disturbances due to the combined effects of cisplatin and necitumumab (or cetuximab) therapy remain an issue but are well captured in the SmPC.

No effect has been shown in patients above 70 years of age. Cardiovascular comorbidities, performance status and the likely tolerability to chemotherapy with add-on necitumumab should therefore be thoroughly evaluated prior to the initiation of treatment in patients above 70 years of age.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Portrazza in combination with gemcitabine and cisplatin chemotherapy for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) expressing squamous non-small cell lung cancer who have not received prior chemotherapy for this condition is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

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.

- **Additional risk minimisation measures**

Prior to launch of Portrazza (necitumumab) in each Member State the MAH must agree about the content and format of the educational material, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Portrazza (necitumumab) is marketed, all physicians (i.e. oncologists) are notified about the key conditions for the safe use of necitumumab. The materials will address the risks concerning arterial / venous thromboembolic events and cardiorespiratory disorders.

Key elements of the physician educational material:

- Importance of assessing the risks before starting treatment with necitumumab
- Description of thromboembolic events including incidence rates from clinical trials
- Advice that patients and physicians should be aware of signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms of thromboembolism such as shortness of breath, chest pain, arm or leg swelling.
- The need to carefully consider use of necitumumab in patients with a history of thromboembolic events or pre-existing risk factors for thromboembolic events
- Information on relative risk of VTE or ATE in patients with a history of VTE or ATE
- Advice that necitumumab should not be administered to patients with multiple risk factors for thromboembolic events unless the benefits outweigh the risks to the patient
- The need to consider thromboprophylaxis after careful assessment of a patient's risk factors
- Discontinuation of necitumumab in patients who experience a VTE or ATE should be considered after a thorough benefit risk assessment for the individual patient.
- Description of cardiorespiratory disorders including incidence rates from clinical trials
- Information that the incremental risk of cardiopulmonary arrest or sudden death in patients with a history of coronary artery disease, congestive heart failure, or arrhythmias as compared to those without these comorbid conditions is not known.
- Instruction for healthcare professionals to read the materials in conjunction with the SmPC.

The physician educational material package should also contain:

- The Summary of Product Characteristics
- Patient Information Leaflet

- **Obligation to complete post-authorisation measures**

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that necitumumab is qualified as a new active substance.