IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Necitumumab (lung cancer) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Necitumumab – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 12 August 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ASBI	average symptom burden index
ATE	arterial thromboembolic event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LCSS	Lung Cancer Symptom Scale
NSCLC	non-small cell lung cancer
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale
VTE	venous thromboembolic event

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug necitumumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 30 March 2016.

Research question

The aim of the present report was to assess the added benefit of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin as appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) expressing squamous non-small cell lung cancer (NSCLC) who have not received prior chemotherapy for this stage of the disease.

Table 2 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of necitumumab

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	In combination with gemcitabine and cisplatin chemotherapy for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor expressing squamous non-small cell lung cancer who have not received prior chemotherapy for this stage of the disease	**Cisplatin** in combination with a third-generation cytostatic agent (vinorelbine or **gemcitabine** or docetaxel or paclitaxel) in accordance with the approval status
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

Following the G-BA's specification, the company chose cisplatin in combination with gemcitabine from the ACT options presented in Table 2.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Results

One relevant study of direct comparison (study SQUIRE) was available for the benefit assessment.

Study characteristics

The SQUIRE study was a randomized, open-label, controlled study on the comparison of necitumumab in combination with gemcitabine and cisplatin versus gemcitabine and cisplatin. Adult patients with stage IV squamous NSCLC were included in the study. The patients were not allowed to have received prior chemotherapy (first-line treatment) for the advanced stage of the disease.

A total of 1093 patients were randomly assigned in a ratio of 1:1 to treatment with necitumumab + gemcitabine + cisplatin (545 patients) or to treatment with gemcitabine + cisplatin (548 patients). According to the Summary of Product Characteristics (SPC), necitumumab is only approved for patients with EGFR-expressing squamous NSCLC, however. This population – hereinafter referred to as "EGFR+ population" – included 462 patients in the intervention arm and 473 patients in the comparator arm. The company consistently conducted the benefit assessment on the basis of the EGFR+ population.

It was additionally assumed for the benefit assessment that patients with stage IIIB to IV NSCLC are candidates for treatment with necitumumab. Since only patients with metastatic NSCLC (stage IV) were included in the SQUIRE study, no conclusions on the added benefit can be derived for patients with locally advanced NSCLC (stage IIIB) from the data of the SQUIRE study.

In the intervention arm, the randomized study treatment with necitumumab was conducted in compliance with the SPC without maximum treatment duration until disease progression, unacceptable toxicity, protocol violation, or withdrawal of consent. Administration of gemcitabine and cisplatin in both treatment arms was restricted to a maximum of 6 cycles of 21 days.

Different treatment phases in the SQUIRE study resulted from the study design. The first study phase, in which chemotherapy consisting of gemcitabine and cisplatin was administered in both arms, is referred to as "combination therapy phase". In the following phase, the patients in the intervention arm continued treatment with necitumumab ("necitumumab monotherapy phase"), whereas the patients in the control arm received no further anticancer therapy ("post-therapy phase"). The total treatment phase included the combination phase and the necitumumab monotherapy phase in the intervention arm, and the combination and post-therapy phase in the comparator arm.

The primary outcome of the study was overall survival. Patient-relevant secondary outcomes were symptoms, health status, and adverse events (AEs).

Risk of bias

The risk of bias at study level for the SQUIRE study was rated as low.

The risk of bias for the outcome "overall survival" was rated as low. The outcomes in the category "morbidity" (symptoms and European Quality of Life-5 Dimensions visual analogue scale [EQ-5D VAS]) were rated as high, particularly due to the open-label study design and the missing or presumably directly censored values.

Due to the open-label study design, there was a high risk of bias for the outcomes in the category "non-serious/non-severe side effects" (conjunctivitis, skin reaction, discontinuation due to AEs). A low risk of bias was assumed for the outcomes in the category "serious/severe side effects" (serious adverse events [SAEs], severe AEs [Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3], arterial thromboembolic events [ATEs], venous thromboembolic events [VTEs]) for the analysis selected (relative risk for the combination therapy phase).

Results

Mortality

A statistically significant difference in favour of necitumumab in combination with gemcitabine and cisplatin was shown for the outcome "overall survival". Overall, there was an indication of an added benefit of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin for the total population.

Morbidity

- Symptoms (LCSS ASBI)

No statistically significant difference between the treatment arms was shown for the analysis of the time to deterioration of symptoms recorded with the average symptom burden index (ASBI) of the Lung Cancer Symptom Scale (LCSS).

In addition, there was proof of an effect modification by the characteristic "ethnicity" for this outcome. For Caucasians, there was no hint of an added benefit of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; an added benefit for Caucasians is therefore not proven. For non-Caucasians, there was a statistically significant difference in favour of necitumumab in combination with gemcitabine and cisplatin. As the patients of Caucasian origin represent the main ethnicity for the health care area of the present benefit assessment, the subgroup of non-Caucasians was not considered further in the assessment.

- EQ-5D VAS

No statistically significant difference between the treatment arms was shown for the outcome "health status measured with the EQ-5D VAS". This resulted in no hint of an added benefit of

necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; an added benefit for this outcome is therefore not proven.

Health-related quality of life

The study did not record data on health-related quality of life. For health-related quality of life, there was therefore no hint of an added benefit of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; an added benefit for this outcome is therefore not proven.

Side effects

- Serious adverse events

In the combination therapy phase, there was no statistically significant difference between the treatment arms for the outcome "serious adverse events (SAEs)". This resulted in no hint of greater or lesser harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; greater or lesser harm for this outcome is therefore not proven.

- Severe adverse events (CTCAE grade ≥ 3)

In the combination therapy phase, a statistically significant difference to the disadvantage of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". Overall, there was an indication of greater harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin.

- Discontinuation due to AEs

In the combination therapy phase, there was no statistically significant difference between the treatment arms for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; greater or lesser harm for this outcome is therefore not proven.

- Arterial thromboembolic events

In the combination therapy phase, there was no statistically significant difference between the treatment arms for the outcome "ATEs". This resulted in no hint of greater or lesser harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; greater or lesser harm for this outcome is therefore not proven.

- Venous thromboembolic events

In the combination therapy phase, a statistically significant difference to the disadvantage of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin was shown for the outcome "VTEs".

In addition, there was an indication of an effect modification by the characteristic "Eastern Cooperative Oncology Group Performance Status (ECOG PS)" for this outcome. There was an indication of greater harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin for patients with an ECOG PS between 0 and 1. For patients with an ECOG PS of 2, there was no hint of greater or lesser harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; greater or lesser harm for this patient group is therefore not proven.

- Conjunctivitis

In the combination therapy phase, a statistically significant difference to the disadvantage of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin was shown for the outcome "conjunctivitis". Overall, there was a hint of greater harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin for the total population.

- Skin reaction

In the combination therapy phase, a statistically significant difference to the disadvantage of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin was shown for the outcome "skin reaction". Overall, there was an indication of greater harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug necitumumab compared with the ACT is assessed as follows:

Overall, there were one positive and several negative effects. The positive effect was an indication of considerable added benefit of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin for the outcome "overall survival". The positive effect was accompanied by negative effects in the categories "serious/severe side effects" and "non-serious/non-severe side effects". The negative effects varied in their extent (at most "considerable") and partly only applied to individual subgroups. Overall, the negative effects were not so large as to completely outweigh the survival advantage of

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

necitumumab in combination with gemcitabine and cisplatin. They resulted in a downgrading of the extent of added benefit, however.

In summary, there is an indication of a minor added benefit of necitumumab in combination with gemcitabine and cisplatin versus the ACT gemcitabine and cisplatin for patients with metastatic (stage IV) EGFR-expressing squamous NSCLC. It is unclear whether the observed effects in the SQUIRE study can be transferred to patients with stage IIIB NSCLC.

Table 3 presents a summary of the extent and probability of the added benefit of necitumumab.

Table 3: Necitumumab – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
In combination with gemcitabine and cisplatin chemotherapy for the treatment of adult patients with locally advanced or metastatic EGFR-expressing squamous non-small cell lung cancer who have not received prior chemotherapy for this stage of the disease[b]	**Cisplatin** in combination with a third-generation cytostatic agent (vinorelbine or **gemcitabine** or docetaxel or paclitaxel) in accordance with the approval status	Indication of minor added benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: According to the SPC, necitumumab is approved for patients with locally advanced or metastatic NSCLC (stage IIIB and IV). The study population of the included study for the assessment of the added benefit (only patients with stage IV NSCLC) therefore does not completely cover the therapeutic indication. It remains unclear whether the observed effects can be transferred to patients with stage IIIB NSCLC.
ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; SPC: Summary of Product Characteristics

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin as ACT in adult patients with locally advanced or metastatic EGFR-expressing squamous NSCLC who have not received prior chemotherapy for this stage of the disease.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of necitumumab

Research question	Therapeutic indication	Appropriate comparator therapy[a]
1	In combination with gemcitabine and cisplatin chemotherapy for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor expressing squamous non-small cell lung cancer who have not received prior chemotherapy for this stage of the disease	**Cisplatin** in combination with a third-generation cytostatic agent (vinorelbine or **gemcitabine** or docetaxel or paclitaxel) in accordance with the approval status
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

Following the G-BA's specification, the company chose cisplatin in combination with gemcitabine from the ACT options presented in Table 4.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on necitumumab (status: 22 February 2016)
- bibliographical literature search on necitumumab (last search on 3 February 2016)
- search in trial registries for studies on necitumumab (last search on 1 February 2016)

To check the completeness of the study pool:

- search in trial registries for studies on necitumumab (last search on 8 April 2016)

No additional relevant study was identified from the check.

2.3.1 Studies included

The study listed in Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
I4X-IE-JFCC (SQUIRE[b])	Yes	Yes	No
a: Study for which the company was sponsor. b: In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of necitumumab in combination with gemcitabine and cisplatin consisted of the SQUIRE study and concurred with that of the company.

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SQUIRE	RCT, open-label, parallel	Adult patients with squamous stage IV NSCLC without prior chemotherapy for this disease[b], ECOG PS: 0–2	▪ Necitumumab + gemcitabine + cisplatin (N = 545) ▪ gemcitabine + cisplatin (N = 548) Relevant subpopulation thereof[c]: ▪ necitumumab + gemcitabine + cisplatin (n = 462) ▪ gemcitabine + cisplatin (n = 473)	▪ Screening: ≤ 21 days before randomization ▪ Treatment: ▫ gemcitabine and cisplatin: max 6 cycles of 3 weeks ▫ necitumumab: no max treatment duration, cycles of 3 weeks until disease progression, unacceptable toxicity, protocol violation, or withdrawal of consent ▪ Follow-up: every 2 months until death or end of study (regarding survival status and subsequent systemic antitumour treatments)	184 centres in 26 countries: Australia, Austria, Belgium, Brazil, Canada, Croatia, France, Germany, Greece, Hungary, Italy; Republic of Korea, Philippines, Poland, Portugal, Romania, Russia, Serbia, Singapore, Slovak Republic, South Africa, Spain, Taiwan, Thailand, United Kingdom, USA 1/2010–7/2013 Data cut-off of the analysis presented: 17 June 2013	Primary: overall survival Secondary: symptoms, health status, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Stratified by ECOG PS (0–1 or 2) and geographical region (North America, Europe and Australia vs. South America, South Africa and India vs. Eastern Asia).
c: Study participants with detectable EGFR expression in the tumour tissue (EGFR+ population).

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; n: relevant subpopulation; N: number of randomized (included) patients; NSCLC: non-small cell lung cancer; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin

Study	Intervention	Comparison
SQUIRE	Necitumumab: 800 mg (absolute dose, IV) on day 1 and 8 of a 3-week cycle[a] (no max treatment duration) + gemcitabine: 1250 mg/m^2 BSA IV on day 1 and 8 of a 3-week cycle (max 6 cycles)[b] + cisplatin: 75 mg/m^2 BSA IV on day 1 of a 3-week treatment cycle (max 6 cycles)[b]	gemcitabine: 1250 mg/m^2 BSA IV on day 1 and 8 of a 3-week cycle (max 6 cycles)[b] + cisplatin: 75 mg/m^2 BSA IV on day 1 of a 3-week treatment cycle (max 6 cycles)[b] Subsequent administration of systemic antitumour treatment was not allowed until disease progression was determined.
	Premedication ▪ necitumumab: not routinely mandated, but preventive skin treatment was allowed after the beginning of the second cycle (e.g. moisturizers or topical steroid creams) ▪ cisplatin: adequate hydration (8–12 hours before administration of cisplatin until 24 hours afterwards) according to local practice ▪ cisplatin/gemcitabine: antiemetics according to local practice (e.g. dexamethasone + serotonin receptor antagonist + aprepitant if applicable) **Pretreatment and concomitant treatment** <u>Non-permitted pretreatment[c]:</u> ▪ prior antitumour treatment with monoclonal antibodies, signal transduction inhibitors, or any therapies targeting the EGFR or VEGF receptor ▪ prior chemotherapy[d] <u>Concomitant treatment:</u> all patients received concomitant supportive treatments (e.g. analgesics, antidiarrhoeal drugs, antiemetics, haematopoietic growth factors) <u>Non-permitted concomitant treatment:</u> additional antitumour treatments (e.g. chemotherapy, radiotherapy[e], further investigational drugs)	

a: Dose modifications or possibly discontinuation of treatment according to the SPC were allowed to manage hypersensitivity and infusion-related reactions as well as skin reactions [3].
b: According to the study protocol, 2 dose reductions were allowed after occurrence of toxic reactions. Further toxicities and discontinuation of a study medication for more than 6 weeks led to cessation of the drug.
c: Pretreatment of advanced disease.
d: Adjuvant chemotherapy that was administered at least 12 months before randomization was allowed.
e: Palliative radiation for symptom relief was allowed.

BSA: body surface area; EGFR: epidermal growth factor receptor; IV: intravenous; max: maximum; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; VEGF: vascular endothelial growth factor; vs.: versus

Study design

The SQUIRE study was a randomized, open-label, controlled study on the comparison of necitumumab in combination with gemcitabine and cisplatin versus gemcitabine and cisplatin. The study was conducted in 184 centres in 26 countries.

Adult patients with stage IV squamous NSCLC were included in the study. The patients were not allowed to have received prior chemotherapy (first-line treatment) for the advanced stage of the disease. Patients were required to have an ECOG PS of 0, 1 or 2 at the time point of randomization.

A total of 1093 patients were randomly assigned in a ratio of 1:1 to treatment with necitumumab + gemcitabine + cisplatin (545 patients) or to treatment with gemcitabine + cisplatin (548 patients). Allocation was stratified by ECOG PS (0–1 or 2) and geographical region (North America, Europe and Australia vs. South America, South Africa and India vs. Eastern Asia). According to the SPC, necitumumab is only approved for patients with EGFR-expressing squamous NSCLC, however [3]. This population – hereinafter referred to as "EGFR+ population" – included 462 patients in the intervention arm and 473 patients in the comparator arm, thus comprising about 85% of the total population of the SQUIRE study. The company consistently conducted the benefit assessment on the basis of the EGFR+ population (see Section 2.7.2.4.1 of the full dossier assessment).

It was additionally assumed for the benefit assessment that patients with stage IIIB to IV NSCLC are candidates for treatment with necitumumab. Since only patients with metastatic NSCLC (stage IV) were included in the SQUIRE study, no conclusions on the added benefit can be derived for patients with locally advanced NSCLC (stage IIIB) from the data of the SQUIRE study (see Section 2.7.2.4.1 of the full dossier assessment).

The drugs necitumumab, gemcitabine, and cisplatin used in the study were administered largely without relevant deviations from the SPCs [3-5].

However, according to the SPC, cisplatin is not allowed to be administered in patients with pre-existing renal insufficiency (creatinine clearance < 60 mL/min) because cisplatin is nephrotoxic [5]. According to the inclusion criteria of the SQUIRE study, patients had to have a creatinine clearance of > 50 mL/min so that individual patients might have been treated outside the approval status of cisplatin. The study documents contained no information on the creatinine clearance at study entry of the patients included in the study so that it was unclear how many patients were actually concerned.

Furthermore, cisplatin should not be used in patients with hearing impairment because cisplatin is neurotoxic (in particular ototoxic) [5]. It was not clear from the study documents whether patients with hearing impairment were included in the study. These patients were not explicitly excluded. However, overall only few severe AEs (CTCAE grade ≥ 3) from the SOC "ear and labyrinth disorders" (intervention arm: 0.9%; comparator arm: 0.4%) and only few AEs from the SOC „ear and labyrinth disorders" leading to study discontinuation (intervention arm: 1.1%; comparator arm: 0.9%) occurred in the SQUIRE study.

Overall it could be assumed that the proportion of patients with impaired renal function or hearing impairment in the study population was below 20% so that this was not a reason against the inclusion of the study.

In the intervention arm, the randomized study treatment with necitumumab was conducted in compliance with the SPC without maximum treatment duration until disease progression, unacceptable toxicity, protocol violation, or withdrawal of consent. Administration of gemcitabine and cisplatin was restricted to a maximum of 6 cycles of 21 days.

The patients in the control arm received gemcitabine and cisplatin for a maximum of 6 cycles of 21 days. Subsequent administration of further systemic antitumour treatment (maintenance treatment) was not allowed until disease progression was determined. Switching from the comparator arm to the intervention arm was not provided for.

Limiting first-line treatment with gemcitabine and cisplatin to 4 to 6 cycles concurred with current guideline recommendations [6-8]. These guidelines also point out the possibility of maintenance treatment for individual patients – they do not provide a clear recommendation for this, however.

The primary outcome of the study was overall survival. Patient-relevant secondary outcomes were symptoms, health status, and AEs.

Different treatment and observation phases in the SQUIRE study resulted from the study design (see Figure 1). The first study phase, in which chemotherapy consisting of gemcitabine and cisplatin was administered in both arms, is hereinafter referred to as “combination therapy phase”. In the following phase, the patients in the intervention arm continued treatment with necitumumab (“necitumumab monotherapy phase”), whereas the patients in the control arm received no further anticancer therapy (“post-therapy phase”). The total treatment phase included the combination phase and the necitumumab monotherapy phase in the intervention arm, and the combination and post-therapy phase in the comparator arm. The dossier contained 2 different analyses for the outcomes on AEs, which were only followed up for 30 days after the end of treatment (see Table 8): on the one hand, analyses on the comparison of the respective combination therapy phases of both treatment arms, on the other, analyses comparing the total treatment phase of the necitumumab arm (combination therapy phase plus necitumumab monotherapy phase) with the combination phase of the comparator arm.

It would be meaningful for a benefit assessment to follow up on AEs (as on other outcomes) also beyond the end of treatment until the end of the study. This would allow an adequate comparison of AEs and an adequate balancing of benefit and harm. These data were not available, however. The fact that in oncological studies AEs are usually only observed until the end of treatment, which results in different observation periods in the study arms, is also criticized by the European Medicines Agency (EMA) in its current draft of the *Guideline on evaluation of anticancer medicinal products in man* [9]. EMA therefore consistently

recommends observation of the outcomes beyond the end of treatment to achieve an adequate benefit-risk assessment.

Alternatively, a comparison of the respective total treatment phases would be meaningful for the present benefit assessment. These data were also not available, however, because no AEs were recorded in in the comparator arm in the post-therapy phase. For the present benefit assessment, the data of the combination therapy phase were used for the outcomes in the category "side effects" (see Section 2.7.2.4.2 of the full dossier assessment). As a result, the events that occurred in the necitumumab monotherapy phase were not considered in the analysis. Considering the side effects under inclusion of the events in the necitumumab monotherapy phase – without consideration of the events in the post-therapy phase in the comparator arm (which were not recorded) – would introduce bias into the result (in this case to the disadvantage of the intervention). Consideration of the combination therapy phases, in contrast, allows unbiased estimation (regarding the observation period), albeit for a less relevant research question than the comparison of the total treatment phases. As an approximation of the comparison of the total treatment phases, an analysis is conceivable that compares the total treatment phase of the necitumumab arm (without 30 days of follow-up) with the combination phase of the comparator arm (including 30 days of follow-up). Since the necitumumab monotherapy phase was about 4 weeks, this can lead to a similar observation period in the treatment arms. These data were not available in the dossier, however.

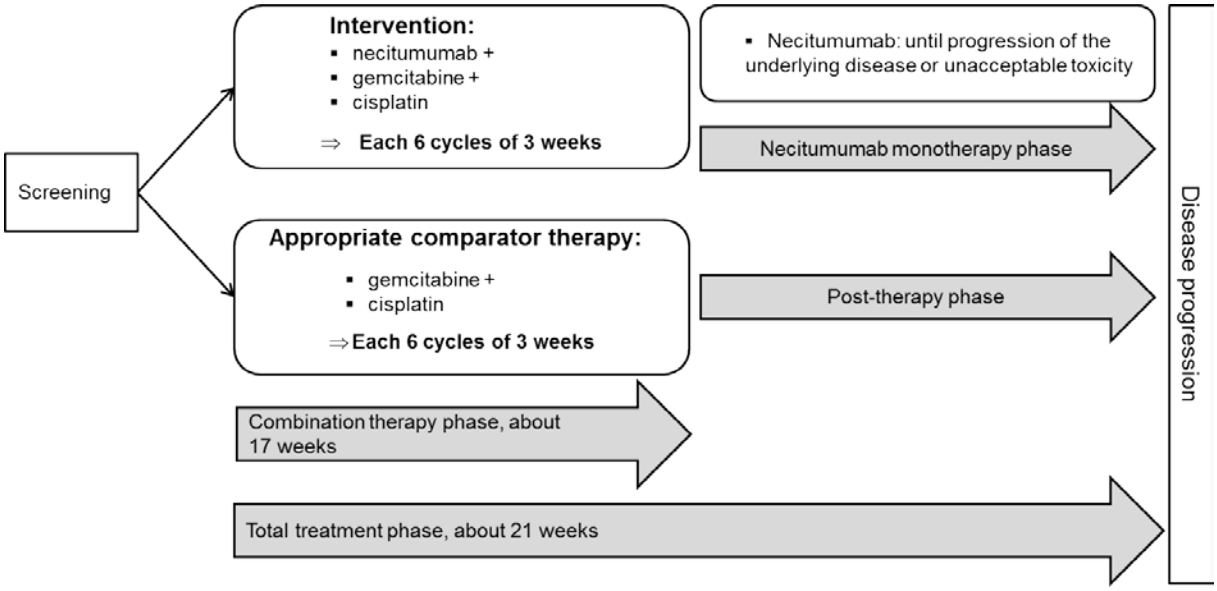

Figure 1: Design of the SQUIRE study

Table 8 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 8: Planned duration of follow up – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin

Study **Outcome category** **Outcome**	**Planned follow-up**
SQUIRE	
Mortality	
Overall survival	Every 2 months (± 7 days) until death or end of study[a]
Morbidity	
Symptoms (LCSS ASBI)	At the start of each cycle (cycle 1 to 6), then every 6 weeks (± 3 days) until disease progression
Health status (EQ-5D VAS)	At the start of each cycle (cycle 1 to 6), then every 6 weeks (± 3 days) until disease progression
Side effects	
All outcomes in the category "side effects"	About 30 days after the end of treatment[b]

a: The end of study was defined as the time point at which no patient was receiving treatment in the framework of the study anymore, the 30-day follow-up examination and the analysis of the safety data after administration of the last treatment dose in the framework of the study was completed for all patients, and the primary outcome could be analysed.
b: At least 30 and at most 37 days after the end of treatment.
ASBI: average symptom burden index; EQ-5D: European Quality of Life-5 Dimensions; LCSS: Lung Cancer Symptom Scale; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

Of the outcomes included, only overall survival was followed-up after a period of 2 months until death or until the end of study. The final data cut-off for the SQUIRE study was planned for the time point when at least 844 patients had died and was conducted on 17 June 2013. 860 patients had died at this time point. The present analyses of the SQUIRE study were based on this data cut-off. Further data cut-offs were not planned in the study.

The recording of other data was conducted outcome-specific beyond the end of treatment: Data on the outcomes "symptoms" and "health status" were recorded after the end of the combination therapy phase every 6 weeks until occurrence of disease progression. AE outcomes were recorded up to 30 days after the last treatment with the study medication.

Patient characteristics

Table 9 shows the characteristics of the patients in the studies included.

Table 9: Characteristics of the study population – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin (EGFR+ population)

Study Characteristics Category	**Necitumumab + gemcitabine + cisplatin**	**Gemcitabine + cisplatin**
SQUIRE	N[a] = 462	N[a] = 473
Age [years]		
Mean (SD)	62 (8)	62 (8)
< 65 years, n (%)	285 (61.7)	296 (62.6)
≥ 65 years, n (%)	177 (38.3)	177 (37.4)
< 70 years, n (%)	380 (82.3)	396 (83.7)
≥ 70 years, n (%)	82 (17.7)	77 (16.3)
Sex [F/M], %	18/82	15/85
ECOG PS, n (%)		
0	138 (29.9)	158 (33.4)
1	280 (60.6)	278 (58.8)
2	44 (9.5)	37 (7.8)
Ethnic origin, n (%)		
Caucasian	388 (84.0)	396 (83.7)
Asian	36 (7.8)	38 (8.0)
Other	38 (8.2)	39 (8.2)
Geographical region		
North America, Europe, Australia	400 (86.6)	407 (86.0)
South America, South Africa, India	47 (10.2)	50 (10.6)
Eastern Asia	15 (3.2)	16 (3.4)
Disease duration[b, c] [months], mean (SD)	3.8 (10.7)	3.4 (10.0)
Disease stage at study entry[c, d], n (%)		
Stage IIIB (without malignant pleural effusion)	1 (0.2)	1 (0.2)
Stage IV[e]	543 (99.6)	546 (99.6)
Unknown	1 (0.2)	1 (0.2)
Smoking history, n (%)		
Non-smoker or former light smoker	37 (8.0)	43 (9.1)
Smoker	424 (91.8)	430 (90.9)
Unknown	1 (0.2)	0 (0.0)
Organs/tissues with metastases, n (%)		
1	42 (9.1)	45 (9.5)
2	164 (35.5)	175 (37.0)
> 2	256 (55.4)	253 (53.5)

(continued)

Table 9: Characteristics of the study population – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin (EGFR+ population) (continued)

Study Characteristics Category	Necitumumab + gemcitabine + cisplatin	Gemcitabine + cisplatin
SQUIRE	N[a] = 462	N[a] = 473
Sites of metastases (at study entry), n (%)		
Bone	103 (22.3)	108 (22.8)
Brain	20 (4.3)	24 (5.1)
Liver	89 (19.3)	96 (20.3)
Lung	381 (82.5)	391 (82.7)
Lymph nodes	368 (79.7)	389 (82.2)
Peritoneal	14 (3.0)	12 (2.5)
Pleural	126 (27.3)	135 (28.5)
Skin	9 (1.9)	6 (1.3)
Soft tissue	22 (4.8)	19 (4.0)
Other	134 (29.0)	121 (25.6)
Treatment discontinuation[f], n (%)[g]	448 (97.0)	468 (98.9)
Study discontinuation[h], n (%)	447 (96.8)	466 (98.5)

a: Number of patients in the EGFR+ population. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Time from first diagnosis to randomization.
c: This information is only available for the total ITT population of the study (intervention arm: 545 patients, comparator arm: 548 patients).
d: Classification of the patients by tumour stage according to the AJCC, seventh edition [10].
e: Including stage IIIB patients with malignant pleural effusion, who are classified as having stage IV according to the seventh edition of the AJCC staging manual.
f: The most common reason for treatment discontinuation in the intervention arm was disease progression (62.1%) and in the comparator arm, end of treatment (44.4%).
g: Institute's calculation.
h: The most common reason for study discontinuation in both treatment arms was disease progression (72.9% in the intervention arm and 69% in the comparator arm).
AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; F: female; ITT: intention to treat; M: male; n: number of patients in the category; N: number of included patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The patient characteristics in the SQUIRE study were balanced between the treatment arms for the EGFR+ population relevant for the assessment. The mean age in both study arms was 62 years. Corresponding to the higher prevalence of lung cancer in men [11], the vast majority of the patients in both study arms was male (> 82%). Similarly, the majority of the patients included were of Caucasian origin (about 84%) and was in good or only slightly restricted general condition (ECOG PS 0 or 1, > 90%).

A majority of the patients in both study arms were from North America, Europe, or Australia (about 86%); in the intervention and in the comparator arm, the disease had first been diagnosed about 3.5 months before. According to the inclusion criteria, almost all patients had stage IV disease (99.6%). The proportion of smokers in the study was > 90% in both treatment arms.

The majority of the patients included (> 53%) had metastases in > 2 organs/tissues. Metastases were particularly common in lymph nodes (about 80%) and lung (about 83%).

Thromboembolic events

Table 10 shows the risk factors for thromboembolic events in the patients in the SQUIRE study.

Table 10: Risk factors for thromboembolic events in the SQUIRE study

Study	Necitumumab + gemcitabine + cisplatin n (%)	Gemcitabine + cisplatin n (%)
SQUIRE	N[a] = 538	N[a] = 541
Risk factors for venous thromboembolic events		
Age ≥ 65	210 (39.0)	207 (38.3)
History of relevant venous thromboembolic events	21 (3.9)	18 (3.3)
ECOG PS 2	48 (8.9)	46 (8.5)
Smoking status: current smoker	496 (92.2)	490 (90.6)
Risk factors for arterial thromboembolic events		
Age ≥ 65	210 (39.0)	207 (38.3)
History of hypertension	218 (40.5)	209 (38.6)
History of arterial thromboembolic events	71 (13.2)	65 (12.0)
History of arteriosclerosis	70 (13.0)	68 (12.6)
History of hyperlipidaemia/hypercholesterolaemia	68 (12.6)	68 (12.6)
History of diabetes mellitus	77 (14.3)	77 (14.2)
Smoking status: current smoker/ex-smoker	531 (95.4)	515 (95.2)
Khorana Risk Score (Khorana et al. 2008 [12])		
Intermediate risk	410 (76.2)	412 (76.2)
Score 1	252 (46.8)	222 (41.0)
Score 2	158 (29.4)	190 (35.1)
High risk	128 (23.8)	129 (23.8)
Score 3	109 (20.3)	122 (22.6)
Score 4	18 (3.3)	7 (1.3)
Score 5	1 (0.2)	0 (0)

a: These values are only available for the safety population of the SQUIRE study (no restriction to the EGFR+ population).
ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; n: number of patients in the category; N: number of included patients

The SPC of necitumumab notes that VTEs and ATEs, including fatal cases, were observed with necitumumab in combination with gemcitabine and cisplatin [3]. One of the reasons why another RCT (INSPIRE [13,14]), which compared necitumumab in combination with pemetrexed and cisplatin versus pemetrexed and cisplatin in patients with advanced squamous NSCLC, was stopped prematurely was that fatal and nonfatal thromboembolic events occurred more frequently under necitumumab treatment [15]. Therefore, 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 pre-existing risk factors for thromboembolic events (such as advanced

age, prolonged periods of immobilization, severe hypovolaemia, acquired or inherited thrombophilic disorders). Necitumumab should therefore not be administered to patients with multiple risk factors for thromboembolic events, except in cases where the advantages outweigh the risks for the patient [3]. It was not clear from the study documents in how far individual balancing was performed in the patients in the SQUIRE study.

As can be seen in Table 10, also patients with (multiple) risk factors for thromboembolic events were included in the study. According to the Khorana Score, which is used to estimate the individual risk of thrombosis in tumour patients [12], about 76% of the patients included in the SQUIRE study had an intermediate risk, and about 24% of the patients even had a high risk of thrombosis. The risk of thrombosis was evenly distributed in both treatment arms.

Overall it should be noted that all patients in the study had a risk of thromboembolic events that was at least intermediate. It is unclear in how far the advantages of necitumumab administration outweighed the risk in these patients, and whether including a large number of patients at high risk of thrombosis might have affected the study results.

Table 11 shows the median treatment duration of the patients and the follow-up period for individual outcomes.

Table 11: Information on the course of the study – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin

Study **Duration of the study phase** **Outcome category**	**Necitumumab + gemcitabine + cisplatin**	**Gemcitabine + cisplatin**
SQUIRE	N = 456[a]	N = 468[a]
Treatment duration [weeks]		
Gemcitabine		
Median [Q1; Q3]	17.9 [10.8; 19.0]	17.0 [9.0; 18.4]
Mean (SD)	14.6 (6.0)	14.1 (6.0)
Cisplatin		
Median [Q1; Q3]	18.0 [11.0; 19.0]	17.2 [9.3; 18.9]
Mean (SD)	14.8 (5.9)	14.2 (5.9)
Necitumumab		
Median [Q1; Q3]	21.0 [11.0; 32.1]	–
Mean (SD)	25.0 (21.3)	–
Observation duration		
Overall survival, morbidity, side effects	ND	ND

a: Safety population (patients with at least one dose of the study medication) within the EGFR+ population.
b: Estimated with the Kaplan-Meier method.
c: These values were only available for the safety population of the total study population (545 patients in the intervention arm and 548 patients in the comparator arm).
EGFR: epidermal growth factor receptor; N: number of analysed patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The treatment duration of the population in the SQUIRE study differed between the 2 treatment arms. Due to the study design, patients in the intervention arm were treated longer (about 21 weeks) than in the comparator arm (about 17 weeks) (see Figure 1).

No information was available on the actual observation period for the outcomes from the areas of morbidity and side effects. The observation period can differ between the individual outcomes because of the different criteria for follow-up (see Table 8). The observation period for AEs could be estimated on the basis of the data on median treatment duration because AEs were predefined to be recorded up to 30 days (about 4 weeks) after the last study medication. Under the assumption that all patients exhausted the specified follow-up period, the resulting median observation period was approximately 25 weeks in the intervention arm versus approximately 21 weeks in the comparator arm.

For the outcomes from the category "morbidity", which were at most recorded until disease progression, the observation period could be estimated considering the data on progression-free survival (PFS). The median PFS was 5.7 months in the intervention arm and 5.5 months in the comparator arm so that a comparable median observation period could be assumed for the outcomes of the category "morbidity".

Due to the shorter observation periods for the outcomes from the categories "morbidity" (only until disease progression) and "side effects" (30 days after the end of treatment), no reliable conclusion was possible for these outcomes over the total study period. Recording these outcomes – as overall survival – over the total study period would have been necessary for this.

Table 12 shows the risk of bias at study level.

Table 12: Risk of bias at study level – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
SQUIRE	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for the SQUIRE study was rated as low. This concurs with the company's assessment.

Limitations resulting from the open-label study design are described in Section 2.4.2 with the outcome-specific risk of bias.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the LCSS ASBI
  - health status measured with the EQ-5D VAS
- Health-related quality of life
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 13 shows for which outcomes data were available in the studies included.

Table 13: Matrix of outcomes – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin

Study	Outcomes										
	Overall survival	**Symptoms (LCSS ASBI)[a]**	**Health status (EQ-5D VAS)**	**Health-related quality of life**	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade ≥ 3)**	**Arterial thromboembolic events[b]**	**Venous thromboembolic events[b]**	**Conjunctivitis[b]**	**Skin reaction[b]**
SQUIRE	Yes	Yes	Yes	No[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a: LCSS items 1 to 6 (questions 1 to 6 record characteristic symptoms of lung cancer patients: loss of appetite, fatigue, cough, dyspnoea, haemoptysis, and pain).
b: Summary of several PTs (chosen by the company to represent this specific AE).
c: Outcome not recorded (the LCSS symptom score ASBI is allocated to morbidity; the LCSS total score and the GTIC [mean value of the LCSS items 7 to 9] are not validated for quality of life; see Section 2.7.2.4.3 of the full dossier assessment).

AE: adverse event; ASBI: average symptom burden index; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; GTIC: global three-item composite index; LCSS: Lung Cancer Symptom Scale; PT: Medical Dictionary for Regulatory Activities Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 14 shows the risk of bias for the relevant outcomes.

Table 14: Risk of bias at study and outcome level – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin

Study	Study level	Outcomes										
		Overall survival	Symptoms (LCSS ASBI)	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Arterial thromboembolic events	Venous thromboembolic events	Conjunctivitis	Skin reaction
SQUIRE	L	L	H[a]	H[a, b]	-[c]	L	H[d]	L	L	L	H[d]	H[d]

a: Patient-reported outcome in open-label study, > 10% missing values.
b: Potential selective reporting due to post-hoc definition of the chosen response criterion (see Section 2.7.2.4.3 of the full dossier assessment).
c: Outcome not recorded (the LCSS symptom score ASBI is allocated to morbidity; the LCSS total score and the GTIC [mean value of the LCSS items 7 to 9] are not validated for quality of life; see Section 2.7.2.4.3 of the full dossier assessment).
d: These are mainly non-severe/non-serious events or discontinuations due to AEs with documentation of the AEs having subjective components. Hence in the open-label study design, this leads to a high risk of bias.
AE: adverse event; ASBI: average symptom burden index; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; GTIC: global three-item composite index; H: high; L: low; LCSS: Lung Cancer Symptom Scale; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias for the outcome “overall survival” was rated as low. This concurs with the company’s assessment.

Concurring with the company, the risk of bias for the outcomes in the category “morbidity” (symptoms and EQ-5D VAS) was rated as high, particularly due to the open-label study design and the missing or presumably directly censored values. The outcome “EQ-5D VAS” had a high risk of bias also because the chosen response criterion was chosen post hoc (see Section 2.7.2.4.3 of the full dossier assessment).

Due to the open-label study design, there was a high risk of bias for the outcomes in the category “non-serious/non-severe side effects” (conjunctivitis, skin reaction, and discontinuation due to AEs) because the documentation as AEs had subjective components. A low risk of bias was assumed for the outcomes in the category “serious/severe side effects” (SAEs, severe AEs [CTCAE grade ≥ 3], ATEs, VTEs) for the analysis selected (relative risk for the combination therapy phase) (for detailed explanation, see Section 2.7.2.4.2 of the full dossier assessment). This partly deviates from the company’s approach, which assumed a high risk of bias for the included outcomes of the category “side effects”.

2.4.3 Results

Table 15 and Table 16 summarize the results on the comparison of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin in patients with metastatic EGFR-expressing squamous NSCLC who have not received prior chemotherapy for this stage of the disease. Since only patients with metastatic NSCLC (stage IV) were included in the SQUIRE study, no results were available for patients with locally advanced NSCLC (stage IIIB) (see Section 2.7.2.4.1 of the full dossier assessment).

The Kaplan-Meier curve on overall survival is presented in Appendix A of the full dossier assessment. No Kaplan-Meier curves were available for the outcomes "symptoms (LCSS ASBI)" and "EQ-5D VAS". Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

In the benefit assessment, the data of the combination therapy phase were used for the outcomes of the category "side effects" because the risk of bias for the data cut-off at the end of the combination therapy phase was rated as low (see Section 2.7.2.4.2 of the full dossier assessment). The events of the total treatment phase in the intervention arm are presented as additional information, but not considered in the interpretation of the results because they were biased to the disadvantage of the necitumumab arm and could therefore not be interpreted in a meaningful way.

Table 15: Results (time to first event) – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin (EGFR+ population)

Study **Outcome category** **Outcome** **Items**	**Necitumumab + gemcitabine + cisplatin**		**Gemcitabine + cisplatin**		**Necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value**
SQUIRE					
Mortality					
Overall survival	462	11.7 [10.7; 12.9] 348 (75.3)	473	10.0 [8.9; 11.4] 389 (82.2)	0.79 [0.69; 0.92]; 0.002[a]
Morbidity – time to deterioration					
Symptoms (LCSS ASBI)[b]	462	19.1 [10.0; NA] 126 (27.3)	473	NA [12.5; NA] 122 (25.8)	0.86 [0.67; 1.10]; 0.222[c]
Health status (EQ-5D VAS)[d]	414	8.4 [7.2; 31.5] 170 (41.1)	412	6.9 [5.7; 7.0] 142 (34.5)	0.97 [0.77; 1.22]; 0.766[c]
Health-related quality of life					
Outcome not recorded					

a: The p-value was determined with the log-rank test; HR and p-value were stratified by ECOG PS (0–1 vs. 2) and geographical region (North America, Europe and Australia vs. South America, South Africa and India vs. Eastern Asia).
b: Calculated as mean of the 6 LCSS symptom scales (loss of appetite, fatigue, cough, dyspnoea, haemoptysis, and pain). A (mean) increase in score by at least 15 points compared with baseline was considered as deterioration.
c: The p-value was calculated with unstratified log-rank test.
d: A decrease in score by at least 12 points compared with baseline was considered as deterioration.

ASBI: average symptom burden index; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; LCSS: Lung Cancer Symptom Scale; N: number of analysed patients; n: number of patients with (at least) one event; NA: not achieved; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

Table 16: Results (dichotomous outcomes) – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin (EGFR+ population), combination therapy phase[a]

Study Outcome category Outcome Treatment phase	Necitumumab + gemcitabine + cisplatin N	Patients with event n (%)	Gemcitabine + cisplatin N	Patients with event n (%)	Necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin RR [95% CI]; p-value[b]
SQUIRE					
Side effects					
AEs (supplementary information)					
Combination therapy phase	456	451 (98.9)	468	456 (97.4)	
Total treatment phase		451 (98.9)			
SAEs					
Combination therapy phase	456	190 (41.7)	468	181 (38.7)	1.08 [0.92; 1.26]; 0.530
Total treatment phase		215 (47.1)			
severe AEs (CTCAE grade ≥ 3)					
Combination therapy phase	456	303 (66.4)	468	281 (60.0)	1.11 [1.00; 1.22]; 0.045
Total treatment phase		323 (70.8)			
Discontinuation due to AEs					
Combination therapy phase	456	127 (27.9)	468	118 (25.2)	1.10 [0.89; 1.37]; 0.530
Total treatment phase		139 (30.5)			
Arterial thromboembolic events					
Combination therapy phase	456	21 (4.6)	468	18 (3.8)	1.20 [0.65; 2.22]; 0.601
Total treatment phase		26 (5.7)			
Venous thromboembolic events					
Combination therapy phase	456	42 (9.2)	468	25 (5.3)	1.72 [1.07; 2.78]; 0.024
Total treatment phase		46 (10.1)			
Conjunctivitis					
Combination therapy phase	456	27 (5.9)	468	12 (2.6)	2.31 [1.18; 4.50]; 0.011
Total treatment phase		37 (8.1)			
Skin reaction					
Combination therapy phase	456	361 (79.2)	468	54 (11.5)	6.86 [5.32; 8.86]; < 0.001
Total treatment phase		365 (80.0)			

a: The data of the combination therapy phase were used for the analysis of the outcomes from the category "side effects" (see Section 2.7.2.4.2 of the full dossier assessment).
b: Institute's calculation, unconditional exact test (CSZ method according to [16]).
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EGFR: epidermal growth factor receptor; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Mortality

Overall survival

A statistically significant difference in favour of necitumumab in combination with gemcitabine and cisplatin was shown for the outcome "overall survival".

Overall, there was an indication of an added benefit of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin for the total population.

This concurs with the company's assessment.

Morbidity

Symptoms (LCSS ASBI)

No statistically significant difference between the treatment arms was shown for the analysis of the time to deterioration of symptoms recorded with the LCSS ASBI.

In addition, there was proof of an effect modification by the characteristic "ethnicity" for this outcome (see Section 2.4.4). For non-Caucasians, there was a hint of an added benefit of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin. For Caucasians, there was no hint of an added benefit of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; an added benefit for this patient group is therefore not proven.

This deviates from the company's assessment, which derived no hint of an added benefit for the total population and did not consider the effect modification.

Health status (EQ-5D VAS)

No statistically significant difference between the treatment arms was shown for the outcome "time to deterioration of health status measured with the EQ-5D VAS". This resulted in no hint of an added benefit of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; an added benefit for this outcome is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life

The study did not record data on health-related quality of life.

For health-related quality of life, there was therefore no hint of an added benefit of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; an added benefit for this outcome is therefore not proven.

This concurs with the company's assessment.

Side effects

Serious adverse events

In the combination therapy phase, there was no statistically significant difference between the treatment arms for the outcome "SAEs". This resulted in no hint of greater or lesser harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; greater or lesser harm for this outcome is therefore not proven.

This concurs with the company's assessment.

Severe adverse events (CTCAE grade ≥ 3)

In the combination therapy phase, a statistically significant difference to the disadvantage of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". Overall, there was an indication of greater harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin for the total population.

This deviates from the company's assessment, which derived no greater harm on the basis of the consideration of the time to event in the total treatment phase.

Discontinuation due to adverse events

In the combination therapy phase, there was no statistically significant difference between the treatment arms for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; greater or lesser harm for this outcome is therefore not proven.

This concurs with the company's assessment.

Arterial thromboembolic events

In the combination therapy phase, there was no statistically significant difference between the treatment arms for the outcome "ATEs". This resulted in no hint of greater or lesser harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; greater or lesser harm for this outcome is therefore not proven.

This concurs with the company's assessment.

Venous thromboembolic events

In the combination therapy phase, a statistically significant difference to the disadvantage of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin was shown for the outcome "VTEs".

In addition, there was an indication of effect modifications by the characteristic "ECOG PS" (see Section 2.4.4). There was an indication of greater harm of necitumumab in combination

with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin for patients with an ECOG PS of 0 to 1. For patients with an ECOG PS of 2, there was no hint of greater or lesser harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; greater or lesser harm for this patient group is therefore not proven.

This deviates from the company's assessment, which derived a hint of greater harm on the basis of the total population.

Conjunctivitis

In the combination therapy phase, a statistically significant difference to the disadvantage of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin was shown for the outcome "conjunctivitis". Overall, there was a hint of greater harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin for the total population.

This concurs with the company's assessment.

Skin reaction

In the combination therapy phase, a statistically significant difference to the disadvantage of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin was shown for the outcome "skin reaction".

A high risk of bias was derived for this outcome of the category "non-serious/non-severe side effects" because of the open-label study design. Due to the effect size it was not assumed that the effect or the size of the effect could be explained by bias. Overall, there was an indication of greater harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin for the total population.

This deviates from the company's assessment, which derived a hint of greater harm.

2.4.4 Subgroups and other effect modifiers

In order to uncover possible differences between patient groups, the following subgroup characteristics were investigated (see also Section 2.7.2.4.3 of the full dossier assessment).

- age (< 65 years/≥ 65 years to < 70 years/≥ 70 years)
- sex (men/women)
- ECOG PS (0, 1/2)
- smoking history (non-smoker or former light smoker/smoker)
- ethnic origin (Caucasian/non-Caucasian)
- countries (Germany/other countries)

The company presented subgroup analyses for all outcomes it included.

For the subgroup analyses, analogous to the total population, the data of the combination therapy phase were used for the outcomes of the category “side effects” because the risk of bias for the data cut-off at the end of the combination therapy phase was rated as low (see Section 2.7.2.4.2 of the full dossier assessment).

In the present assessment, only the results on subgroups and outcomes are presented in which there was at least an indication of an interaction between treatment effect and subgroup characteristic. Subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The prerequisite for proof of different subgroup effects is a statistically significant interaction test ($p < 0.05$). A p-value of ≥ 0.05 and < 0.2 provides an indication of an effect modification.

Table 17 and Table 18 summarize the subgroup results of necitumumab in combination with gemcitabine and cisplatin in comparison with the ACT gemcitabine and cisplatin. Where necessary, the data from the dossier were supplemented by the Institute’s calculations.

Table 17: Subgroups (time to first event) – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin (EGFR+ population)

Study **Outcome category** **Outcome**	**Necitumumab + gemcitabine + cisplatin**		**Gemcitabine + cisplatin**		**Necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin**	
Characteristic **Subgroup**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)[a]**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)[a]**	**HR [95% CI]**	**p-value**
SQUIRE						
Mortality						
Overall survival						
Geographical region						
Germany	42	12.4 [8.7; 22.2] 29 (69.0)	54	8.4 [5.9; 13.2] 47 (87.0)	0.59 [0.37; 0.94]	0.026[b]
Other countries	420	11.6 [10.5; 12.9] 319 (76.0)	419	10.3 [9.1; 11.6] 342 (81.6)	0.84 [0.72; 0.97]	0.022[b]
					Interaction	0.135[c]
Morbidity						
Symptoms (LCSS ASBI) – time to deterioration[d]						
Ethnicity						
Caucasian	388	19.1 [10.0; NA] 107 (27.6)	396	NA [12.5; NA] 93 (23.5)	0.99 [0.75; 1.31]	0.946[b]
Non-Caucasian	74	NA [5.6; NA] 19 (25.7)	77	4.7 [2.2; NA] 29 (37.7)	0.43 [0.24; 0.78]	0.004[b]
					Interaction	0.018[c]

a: Institute's calculation.
b: Unstratified log-rank test.
c: p-value of the interaction based on the Wald test of the treatment for each subgroup; interaction test based on unstratified Cox model.
d: Calculated as mean of the 6 LCSS symptom scales (loss of appetite, fatigue, cough, dyspnoea, haemoptysis, and pain). A (mean) increase in score by at least 15 points compared with baseline was considered as deterioration.

ASBI: average symptom burden index; CI: confidence interval; EGFR: epidermal growth factor receptor; HR: hazard ratio; LCSS: Lung Cancer Symptom Scale; N: number of analysed patients; n: number of patients with (at least) one event; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Table 18: Subgroups (dichotomous outcomes) – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin (EGFR+ population), combination therapy phase[a]

Study Outcome category Outcome	Necitumumab + gemcitabine + cisplatin		Gemcitabine + cisplatin		Necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin	
Characteristic Subgroup	N	Patients with event, n (%)	N	Patients with event, n (%)	RR [95% CI]	p-value
SQUIRE						
Side effects						
Severe AEs (CTCAE grade ≥ 3)						
Sex						
Women	79	53 (67.1)	72	52 (72.2)	0.93 [0.75; 1.15]	0.536[b]
Men	377	250 (66.3)	396	229 (57.8)	1.15 [1.03; 1.28]	0.015[b]
					Interaction:	0.083[c]
Age						
< 70 years	376	258 (68.6)	391	231 (59.1)	1.16 [1.04; 1.29]	0.006[b]
< 65 years	*282*	*192 (68.1)*	*292*	*167 (57.2)*	*1.19 [1.05; 1.35]*	*0.007[b]*
≥ 65 years – < 70 years	*94*	*66 (70.2)*	*99*	*64 (64.6)*	*1.09 [0.89; 1.32]*	*0.531[b]*
≥ 70 years	80	45 (56.3)	77	50 (64.9)	0.87 [0.67; 1.12]	0.276[b]
					Interaction:	0.087[c, d]
Smoking status						
Never smoker/ former smoker	35	19 (54.3)	41	28 (68.3)	0.79 [0.55; 1.15]	0.232[b]
Smoker	421	284 (67.5)	427	253 (59.3)	1.14 [1.03; 1.26]	0.013[b]
					Interaction:	0.066[c]
Venous thromboembolic events						
ECOG PS						
0/1[e]	413	42 (10.2)	432	22 (5.1)	2.00 [1.21; 3.29]	0.005[b]
2	43	0 (0)	36	3 (8.3)	0.12 [0.01; 2.25]	0.062[b]
					Interaction:	0.064[c]
Conjunctivitis						
ECOG PS						
0/1[e]	413	27 (6.5)	432	11 (2.5)	2.57 [1.29; 5.11]	0.005[b]
2	43	0 (0)	36	1 (2.8)	0.28 [0.01; 6.68]	0.353[b]
						0.181[c]
Skin reaction						
Sex						
Women	79	62 (78.5)	72	14 (19.4)	4.04 [2.49; 6.55]	< 0.001[b]
Men	377	299 (79.3)	396	40 (10.1)	7.85 [5.83; 10.58]	< 0.001[b]
					Interaction:	0.022[c]

(continued)

Table 18: Subgroups (dichotomous outcomes) – RCT, direct comparison: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin (EGFR+ population), combination therapy phase[a] (continued)

a: The data of the combination therapy phase were used for the analysis of the outcomes from the category "side effects" (see Section 2.7.2.4.2 of the full dossier assessment).
b: Institute's calculation, unconditional exact test (CSZ method according to [16]).
c: Institute's calculation, Cochran's Q test.
d: The p-value refers to the interaction test for the subgroups < 65, ≥ 65 years – < 70 years, and ≥ 70 years.
e: Institute's calculation; ECOG PS 0 and 1 were considered jointly for the dossier assessment (see Section 2.7.2.4.3 of the full dossier assessment).
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Mortality

Overall survival

The subgroup analysis on the outcome "overall survival" showed an indication of an effect modification by the characteristic "geographical region (Germany/other countries)".

A statistically significant difference in favour of necitumumab in combination with gemcitabine and cisplatin was shown both for patients from Germany and for patients from other countries, but with different extent.

This resulted in an indication of an added benefit of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin both for patients from Germany and from other countries. Since Germany is the decisive geographical region for the health care area of the present benefit assessment and the effect of patients from Germany did not contradict the effect in the total population (neither in extent nor in probability), hereinafter only the effect of the total population is considered.

This concurs with the company's assessment.

Morbidity

Symptoms (LCSS ASBI)

Proof of an effect modification by the characteristic "ethnicity" (Caucasian/non-Caucasian) was shown in the subgroup on the outcome "symptoms" (LCSS ASBI).

For Caucasians, there was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; an added benefit for Caucasians is therefore not proven.

For non-Caucasians, there was a statistically significant difference in favour of necitumumab in combination with gemcitabine and cisplatin. As the patients of Caucasian origin represent the main ethnicity for the health care area of the present benefit assessment, the subgroup of non-Caucasians was not considered further in the assessment.

This deviates from the company's assessment, which derived no hint of an added benefit for the total population and did not consider the effect modification.

Side effects

Severe adverse events (CTCAE grade ≥ 3)

Indications of an effect modification by the characteristics "sex", "age", and "smoking status" were shown for the outcome "severe AEs (CTCAE grade≥ 3)". Since no information on possible dependencies between the subgroup characteristics was available, the subgroup results could not be interpreted, however.

This concurs with the company's assessment, which did also not consider the subgroup results.

Venous thromboembolic events

An indication of an effect modification by the characteristic "ECOG PS (0, 1/2) was shown for the outcome "VTEs".

For patients with an ECOG PS of 0 to 1, there was a statistically significant difference to the disadvantage of necitumumab in combination with gemcitabine and cisplatin. This resulted in an indication of greater harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin for patients with an ECOG PS of 0 to 1.

No statistically significant difference between the treatment arms was shown for patients with ECOG PS 2. This resulted in no hint of greater or lesser harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin; greater or lesser harm for patients with ECOG PS 2 is therefore not proven.

This deviates from the company's assessment, which did not consider the effect modification.

Conjunctivitis

An indication of an effect modification by the characteristic "ECOG PS (0, 1/2) was shown for the outcome "conjunctivitis". Due to the low number of events in the group of patients with ECOG PS 2 (one event in the comparator arm), no further interpretation of the subgroup results was conducted, however.

Overall, there was a hint of greater harm of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin for the total population.

This concurs with the company's assessment.

Skin reaction

There was proof of an effect modification by the characteristic "sex" (men/women) for the outcome "skin reaction".

A statistically significant difference to the disadvantage of necitumumab in combination with gemcitabine and cisplatin was shown both for men and for women. This resulted in an indication of greater harm (of the same extent) in both cases so that this subgroup analysis had no effect on the conclusion on the added benefit for this outcome.

This deviates from the company's assessment, which derived a hint of greater harm for the total population.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

Since only patients with metastatic NSCLC (stage IV) were included in the SQUIRE study, no conclusions on the added benefit can be derived for patients with locally advanced NSCLC (stage IIIB) from the data of the SQUIRE study (see Section 2.7.2.4.1 of the full dossier assessment).

The data presented in Section 2.4 resulted in the following assessments for necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin in patients with metastatic NSCLC (stage IV):

- an indication of an added benefit for the outcome "overall survival"
- an indication of greater harm for the outcome "severe AEs (CTCAE grade ≥ 3)"
- an indication of greater harm for the outcome "VTEs" (ECOG PS: 0, 1)
- a hint of greater harm for the outcome "conjunctivitis"
- an indication of greater harm for the outcome "skin reaction"

Determination of the outcome category for the outcomes of the category "side effects"

The proportion of severe AEs (CTCAE grade ≥ 3) was above 50% in both outcomes "ATEs" and "VTEs". They were therefore allocated to the outcome category "severe/serious side effects".

In the outcomes "conjunctivitis" and "skin reaction", the majority of the events were non-severe (CTCAE grade < 3). These outcomes were therefore allocated to the category of non-serious/non-severe side effects.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 19). In each case, the effect and the confidence interval of the combination therapy phase was used for the derivation of the extent of the outcomes of the category "side effects".

Table 19: Extent of added benefit at outcome level: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin (EGFR+ population)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin** **Median time to event or proportion of events** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Total population: 11.7 vs. 10.0 months HR: 0.79 [0.69; 0.92]; p = 0.002 probability: "indication"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
Morbidity		
Symptoms (LCSS ASBI) Ethnicity		
Caucasian[c]	19.1 vs. NA months HR: 0.99 [0.75; 1.31]; p = 0.946	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	8.4 vs. 6.9 months HR: 0.97 [0.77; 1.22]; p = 0.766	Lesser benefit/added benefit not proven
Health-related quality of life		
	No data available	
Side effects		
SAEs	41.7% vs. 38.7% RR: 1.08 [0.92; 1.26]; p = 0.530	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	66.4% vs. 60.0% RR: 1.11 [1.003; 1.22] RR[d]: 0.90 [0.82; 0.997] p < 0.045 probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Discontinuation due to AEs	27.9% vs. 25.2% RR: 1.10 [0.89; 1.37]; p = 0.530	Greater/lesser harm not proven

(continued)

Table 19: Extent of added benefit at outcome level: necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin (EGFR+ population) (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Necitumumab + gemcitabine + cisplatin vs. gemcitabine + cisplatin** **Median time to event or proportion of events** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
Arterial thromboembolic events	4.6% vs. 3.8% RR: 1.20 [0.65; 2.22]; p = 0.601	Greater/lesser harm not proven
Venous thromboembolic events ECOG PS	9.2% vs. 5.3% RR: 1.72 [1.07; 2.78]; p = 0.024	
0/1	10.2% vs. 5.1% RR: 2.00 [1.21; 3.29] RR[d]: 0.5 [0.30; 0.82] p = 0.005 probability: "indication"	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
2	0% vs. 8.3% RR: 0.12 [0.01; 2.25]; p = 0.062	Greater/lesser harm not proven
Conjunctivitis	5.9% vs. 2.6% RR: 2.31 [1.18; 4.50] RR[d]: 0.43 [0.22; 0.85] p < 0.011 probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ greater harm, extent: "minor"
Skin reaction	79.2% vs. 11.5% RR: 6.86 [5.32; 8.86] RR[d]: 0.15 [0.11; 0.19] < 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

a: Probability provided if statistically significant and relevant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Subgroup relevant for the health care area of the present benefit assessment.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; ASBI: average symptom burden index; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; LCSS: Lung Cancer Symptom Scale; NA: not achieved; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 20 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 20: Positive and negative effects from the assessment of necitumumab + gemcitabine + cisplatin in comparison with gemcitabine + cisplatin (EGFR+ population)

Positive effects	**Negative effects**
Mortality ▪ overall survival: indication of an added benefit – extent: "considerable"	Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): indication of greater harm – extent: "minor" ▪ venous thromboembolic events ▫ ECOG PS 0/1: indication of greater harm – extent: "considerable"
	Non-serious/non-severe side effects ▪ conjunctivitis: hint of greater harm – extent: "minor" ▪ skin reaction: indication of greater harm – extent "considerable"
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; SAE: serious adverse event	

Overall, there were one positive and several negative effects. The positive effect was an indication of considerable added benefit of necitumumab in combination with gemcitabine and cisplatin in comparison with gemcitabine and cisplatin for the outcome "overall survival". The positive effect was accompanied by negative effects in the categories "serious/severe side effects" and "non-serious/non-severe side effects". The negative effects varied in their extent (at most "considerable") and partly only applied to individual subgroups. Overall, the negative effects were not so large as to completely outweigh the survival advantage of necitumumab in combination with gemcitabine and cisplatin. They resulted in a downgrading of the extent of added benefit, however.

There was an uncertainty in the interpretation of the results because all patients in the SQUIRE study had at least an intermediate risk of thromboembolic events (see Section 2.3.2). Necitumumab is only approved for these patients if the advantages outweigh the risk. It is unclear in how far the administration of necitumumab was adequate in this respect for all patients included in the SQUIRE study, and whether including a large number of patients at high risk of thrombosis might have affected the study results.

In summary, there is an indication of a minor added benefit of necitumumab in combination with gemcitabine and cisplatin versus the ACT gemcitabine and cisplatin for patients with metastatic (stage IV) EGFR-expressing squamous NSCLC. It is unclear whether the observed effects in the SQUIRE study can be transferred to patients with stage IIIB NSCLC.

The result of the assessment of the added benefit of necitumumab in comparison with the ACT is summarized in Table 21.

Table 21: Necitumumab – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
In combination with gemcitabine and cisplatin chemotherapy for the treatment of adult patients with locally advanced or metastatic EGFR-expressing squamous non-small cell lung cancer who have not received prior chemotherapy for this stage of the disease[b]	**Cisplatin** in combination with a third-generation cytostatic agent (vinorelbine or **gemcitabine** or docetaxel or paclitaxel) in accordance with the approval status	Indication of minor added benefit
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: According to the SPC, necitumumab is approved for patients with locally advanced or metastatic NSCLC (stage IIIB and IV). The study population of the included study for the assessment of the added benefit (only patients with stage IV NSCLC) therefore does not completely cover the therapeutic indication. It remains unclear whether the observed effects can be transferred to patients with stage IIIB NSCLC. ACT: appropriate comparator therapy; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; NSCLC: non-small cell lung cancer; SPC: Summary of Product Characteristics		

This deviates from the company's approach, which derived an indication of considerable added benefit.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6 List of included studies

SQUIRE

Eli Lilly. First-line treatment of participants with stage IV squamous non-small cell lung cancer with necitumumab and gemcitabine-cisplatin (SQUIRE): full text view [online]. In: ClinicalTrials.gov. 11.11.2014 [Accessed: 15.04.2016]. URL: https://ClinicalTrials.gov/show/NCT00981058.

Eli Lilly. 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 CP11-0806; JFCC clinical study report amendment [unpublished]. 2015.

Eli Lilly. 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 CP11-0806; translational research (EGFR immunohistochemistry) statistical analysis plan [unpublished]. 2014.

Eli Lilly. 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 IMVL CP11-0806; Zusatzanalysen [unpublished]. 2016.

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ImClone. 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) [online]. In: EU Clinical Trials Register. [Accessed: 15.04.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-013838-25.

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Please see full dossier assessment for full reference list.

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