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Sponsor Briefing Document

Necitumumab

Eli Lilly and Company

ADVISORY COMMITTEE BRIEFING MATERIALS:

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1. Overview

Patients with advanced squamous non-small cell lung cancer (NSCLC) have fewer first-line treatment options and a poorer prognosis than patients with other forms of NSCLC. Necitumumab, a second-generation recombinant human monoclonal antibody directed against the epidermal growth factor receptor, is being developed by Eli Lilly and Company to address the pressing need for new effective treatments in this setting. In the pivotal, randomized Phase 3 trial SQUIRE, the addition of necitumumab to gemcitabine and cisplatin resulted in a statistically significant and clinically meaningful improvement in survival in patients with metastatic squamous NSCLC in the first-line setting.

Most lung cancer patients are determined to have locally advanced (30%) or metastatic (45%) disease at the time of first diagnosis and have multiple comorbidities, in particular co-existing chronic obstructive pulmonary disease and cardiovascular conditions (Janssen-Heijnen et al. 1998; Bonomi 2004; Morgensztern et al. 2009; Young et al. 2009). These patients face an imposing disease and symptom burden with very poor prognosis; the 5-year survival rate for patients with metastatic disease is less than 5% (Howlader et al. 2014).

While the majority of NSCLC patients have nonsquamous tumors (including adenocarcinoma), approximately 30% of patients are determined to have squamous cell tumors (Erickson and Wistuba 2010). Despite some common features, squamous and nonsquamous NSCLC are two distinctly different diseases. Differences in histopathology and genetic profile between the two determine prognosis and influence treatment selection (Schnabel et al. 2012; Chen et al. 2014; Gandara et al. 2015). These distinct patient populations also differ by baseline comorbidities, disease-related symptoms, and risk factors for complications during treatment. Patients with squamous NSCLC tend to be male, have a history of heavy smoking, and have high disease burden and poor prognosis.

There are many first-line treatment options currently available for patients with nonsquamous disease. The approvals of pemetrexed and bevacizumab have improved survival and widened the choice of treatment options for these patients over standard platinum doublets. As a result, median overall survival (OS) for patients with nonsquamous disease has increased from 8 months to up to 14 months with these new treatment options (Schiller et al. 2002; Manegold et al. 2008; Scagliotti et al. 2008, 2009; Reck et al. 2010; Sandler et al. 2010; Patel et al. 2012; Socinski et al. 2012, 2013; Hoang et al. 2013).

In a subset of patients with nonsquamous NSCLC - almost exclusively in patients with adenocarcinomas - recurrent somatic tumor mutations (epidermal growth factor receptor [EGFR]-activating mutations or anaplastic lymphoma kinase [ALK] translocations) have been identified. Pathway-directed therapies including erlotinib, afatinib, crizotinib, and ceritinib are now approved for selected patients whose tumors harbor these mutations, offering them a chance for significantly longer survival over historical chemotherapy regimens (Tarceva package insert [PI], Gilotrif PI, Xalkori PI, Zykadia PI).

However, patients with squamous NSCLC are not candidates to receive treatment with pemetrexed or bevacizumab, and EGFR mutations and ALK translocations are very rare among patients with squamous NSCLC (Perez-Moreno et al. 2012; Rekhtman et al. 2012; Rose-James and Sreelekha 2012; Gerber et al. 2014). Accordingly, agents targeting these mutations do not play a role in the treatment of squamous NSCLC and therefore routine testing for these genetic aberrations is not recommended for patients with squamous NSCLC (American Society for Clinical Oncology [ASCO] and National Comprehensive Cancer Network [NCCN] guidelines).

In the past 6 months, ramucirumab was approved in December 2014 in combination with docetaxel, for treatment of metastatic NSCLC (both squamous and nonsquamous) with disease progression on or after platinum-based chemotherapy, and nivolumab was approved in March 2015 for patients with squamous NSCLC with progression on or after platinum-based chemotherapy. However, these drugs are only approved in the second-line setting and few data are available to evaluate the safety or efficacy of either of these agents in the front-line setting, either alone or in combination with chemotherapy. Thus, available first-line regimens for squamous NSCLC have remained unchanged over the last 2 decades.

The current standard first-line treatment for patients with advanced squamous NSCLC therefore continues to be a platinum-based doublet of cisplatin or carboplatin combined with gemcitabine, vinorelbine, or a taxane (ASCO and NCCN guidelines). Numerous Phase 3 trials have failed to show a survival advantage for novel agents when added to platinum doublets (Herbst et al. 2009). More recently, trials conducted specifically in patients with squamous NSCLC, or including a predefined subset analysis for patients with squamous NSCLC, have not been successful (Goss et al. 2010; Scagliotti et al. 2010, 2012; Sanofi press release 2013; Langer et al. 2014; Laurie et al. 2014).

In the Phase 3 FLEX study, the addition of cetuximab, a chimeric EGFR monoclonal antibody (mAb), to cisplatin-vinorelbine resulted in a statistically significant improvement in survival for patients with advanced EGFR-positive NSCLC (Pirker et al. 2009). Despite an unfavorable benefit/risk due to chemotherapy-associated hematologic toxicities, this study showed a pronounced survival effect in the subgroup of patients with squamous NSCLC. These results suggested that inhibition of the EGFR pathway in squamous NSCLC, using a monoclonal antibody, is an important anticancer strategy requiring further investigation. EGFR mAbs are a well-characterized class of drugs, and have been approved and used widely by practicing oncologists for patients with colorectal (*K-Ras* wild-type only) and squamous head and neck cancers (Erbitux PI, Vectibix PI).

These data informed the necitumumab development strategy in first-line NSCLC, in which two separate Phase 3 trials were conducted for patients with squamous versus nonsquamous histology. One of these two trials, the Phase 3 trial SQUIRE (Thatcher et al. 2015) demonstrated that the addition of necitumumab - a human EGFR mAb - to the standard first-line chemotherapy doublet of gemcitabine and cisplatin resulted in a significant improvement in OS. This translates to a 16% reduction in risk of death, compared to chemotherapy alone, in patients with squamous NSCLC. In contrast, the second trial, INSPIRE (Study JFCB), did not show a survival

difference when necitumumab was administered in combination with pemetrexed and cisplatin to patients with nonsquamous NSCLC.

The significant survival outcome observed in SQUIRE was supported by a consistent improvement in progression-free survival (PFS), as well as consistent efficacy across the majority of prespecified subgroups in favor of the necitumumab arm. The control arm of SQUIRE performed well compared to historical data for gemcitabine and cisplatin (Sandler et al. 2000; Scagliotti et al. 2002, 2008; Schiller et al. 2002; Gatzemeier et al. 2007; Hoang et al. 2013). The safety profile for necitumumab was consistent with the well-characterized safety profile of EGFR mAbs (Erbitux PI, Vectibix PI). Thus, the SQUIRE primary survival results confirmed the histology subgroup findings from the FLEX study, verifying the efficacy of an EGFR mAb in patients with metastatic squamous NSCLC.

SQUIRE is the first and only randomized Phase 3 study conducted specifically in patients with advanced squamous NSCLC to demonstrate a significant survival benefit in the first-line setting. The totality of evidence supports the conclusion that necitumumab combined with gemcitabine and cisplatin is effective in the first-line treatment of patients with squamous NSCLC. The favorable benefit/risk assessment of the SQUIRE results represents a meaningful advance beyond standard-of-care chemotherapy for patients with squamous NSCLC, and supports approval for the proposed indication:

> *Necitumumab in combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced or metastatic squamous NSCLC.*

2. Necitumumab Development Rationale in Lung Cancer

EGFR is highly expressed in a variety of tumors, including squamous head and neck, breast, lung, colorectal, prostate, kidney, pancreas, ovary, brain, and bladder cancer (Salomon et al. 1995). Expression of EGFR correlates with poor response to treatment, disease progression, and poor survival (Baselga 2002).

Necitumumab, a second-generation recombinant human immunoglobulin G subclass 1 (IgG1) mAb, binds EGFR with high affinity, competing with natural ligands and thereby preventing receptor activation and downstream signaling. Necitumumab induces EGFR internalization and degradation in vitro. In vivo studies in mouse xenograft models of human squamous NSCLC suggested that necitumumab has antitumor activity both as a single agent and in combination with gemcitabine and cisplatin (Appendix 4).

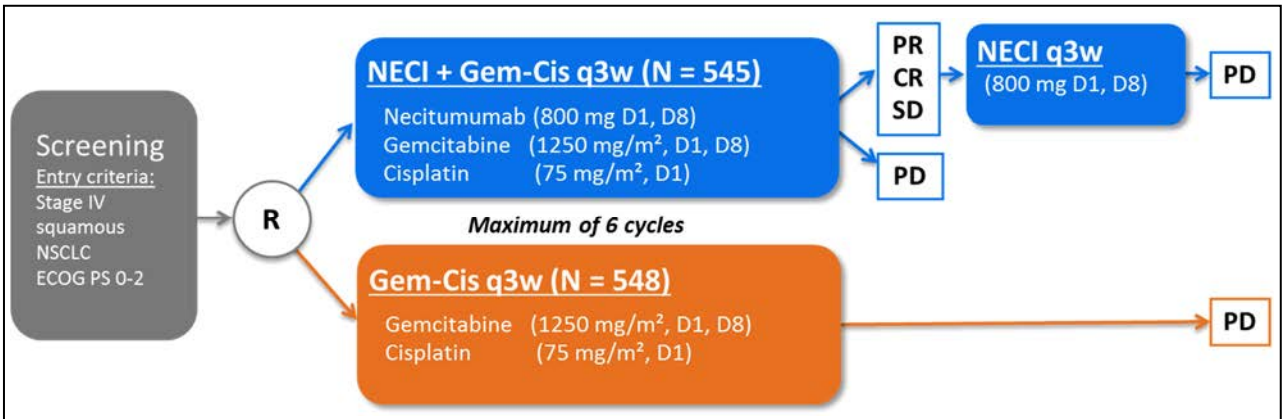
Two anti-EGFR mAbs, the chimeric mAb cetuximab and the human mAb panitumumab, are approved for treatment in combination with chemotherapy or as a single agent for patients with advanced/metastatic *K-Ras* wild-type colorectal cancer (cetuximab, panitumumab) and for patients with squamous cell head and neck cancer (cetuximab) (Erbitux PI, Vectibix PI).

EGFR is expressed in approximately 85% to 90% of patients with metastatic NSCLC (Fontanini et al. 1995; Pirker et al. 2009), and is expressed in the majority of squamous NSCLC tumors (Salomon et al. 1995). In the FLEX trial, the addition of the EGFR mAb cetuximab to cisplatin and vinorelbine was shown to statistically significantly improve OS (median OS cetuximab plus vinerolbine-cisplatin 11.3 vs. vinerolbine-cisplatin 10.1 months; hazard ratio [HR]: 0.87; 95% confidence interval [CI]: 0.76 to 1.00) in patients with EGFR-expressing advanced NSCLC (Pirker et al. 2009). A prespecified subgroup analysis showed a more pronounced survival effect for the subgroup of patients with squamous NSCLC (median OS 10.2 vs. 8.9 months; HR: 0.80; 95% CI: 0.64 to 1.00) than adenocarcinoma (median OS 12.0 vs. 10.3 months; HR: 0.94; 95% CI: 0.77 to 1.15). However, the combination was associated with an increased rate of chemotherapy-induced hematologic adverse events (AEs), notably febrile neutropenia.

Results of another pivotal Phase 3 trial investigating pemetrexed and cisplatin versus gemcitabine and cisplatin in patients with advanced/metastatic NSCLC (Scagliotti et al. 2008 study) suggested that selection of optimal chemotherapeutic regimens for these patients depends on the histology of their NSCLC tumors. Patients in the Scagliotti study with tumors of nonsquamous histology derived greater benefit from pemetrexed and cisplatin compared to gemcitabine and cisplatin (median OS pemetrexed and cisplatin 11.8 months vs. gemcitabine and cisplatin 10.4 months; HR: 0.81; 95% CI: 0.70 to 0.94), in contrast to the findings for patients with squamous NSCLC (median OS pemetrexed and cisplatin 9.4 months vs. gemcitabine and cisplatin 10.8 months; HR: 1.23; 95% CI: 1.00 to 1.51) (Scagliotti et al. 2008).

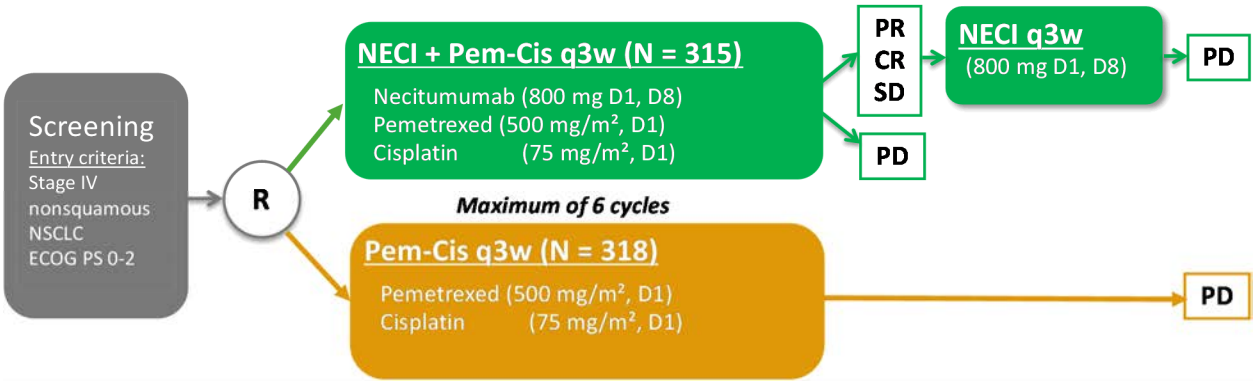
Among currently available platinum doublets, gemcitabine and cisplatin is considered a standard-of-care treatment regimen for patients with squamous NSCLC (ASCO and NCCN guidelines). Informed by the results from the FLEX and Scagliotti studies, and considering that squamous and nonsquamous NSCLC are distinct diseases, the Phase 3 development program for

necitumumab was designed to investigate necitumumab in two separate trials (SQUIRE and INSPIRE [hereafter referred to as Study JFCB]). SQUIRE (Figure 2.1) was conducted in patients with Stage IV squamous NSCLC with necitumumab in combination with gemcitabine and cisplatin, while Study JFCB (Figure 2.2) was conducted in patients with Stage IV nonsquamous NSCLC with necitumumab in combination with pemetrexed and cisplatin. Both studies were similar in design and enrolled a majority of patients from North America and Western Europe.



Abbreviations: CR = complete response; D = day; ECOG PS = Eastern Cooperative Oncology Group performance status; Gem-Cis = gemcitabine and cisplatin; N = number of randomized patients; Neci = necitumumab; NSCLC = non-small cell lung cancer; PD = progressive disease; PR = partial response; q3w = every 3 weeks; R = randomize; SD = stable disease.

Figure 2.1. SQUIRE study schema - squamous NSCLC.



Abbreviations: CR = complete response; D = day; ECOG PS = Eastern Cooperative Oncology Group performance status; Pem-Cis = pemetrexed and cisplatin; N = number of randomized patients; Neci = necitumumab; NSCLC = non-small cell lung cancer; PD = progressive disease; PR = partial response; q3w = every 3 weeks; R = randomize; SD = stable disease.

Figure 2.2. Study JFCB (INSPIRE) study schema - nonsquamous NSCLC.

Patients in the necitumumab arms of these studies with a response of stable disease (SD) or better after 6 combined chemotherapy cycles could continue to receive single-agent necitumumab until disease progression. Physicians were instructed to monitor patients on both study arms for AEs a minimum of 30 days following the completion of treatment. As a result, the safety observation period was disproportionately longer on the necitumumab arm (treatment until progressive disease [PD]) compared to the control arm (treatment up to 6 cycles). This must be taken into account when comparing rates of AEs between study arms, especially those AEs for which the underlying disease is a risk factor.

The SQUIRE study started enrollment in the beginning of 2010 and completed enrollment in the beginning of 2012 (N=1093). The study met its primary endpoint, showing a statistically significant improvement in OS for patients with Stage IV squamous NSCLC in favor of the experimental arm (OS HR: 0.84; 95% CI: 0.74 to 0.96; Figure 3.1). This was supported by a statistically significant improvement in PFS (PFS HR: 0.85; 95% CI: 0.74 to 0.98), and a favorable benefit/risk assessment. SQUIRE is the pivotal Phase 3 trial supporting the proposed indication for necitumumab in the front-line treatment setting for patients with locally advanced or metastatic squamous NSCLC in combination with gemcitabine and cisplatin. Detailed efficacy and safety results are presented below in Section 3.

In contrast to SQUIRE, the independent data monitoring committee (IDMC) recommended to stop enrollment to Study JFCB (N=633) early due to an observed imbalance in Grade 5 thromboembolic events and deaths of all causes between study arms. The IDMC determined that it would be highly unlikely, given these observations, that Study JFCB would confirm a positive survival result at the completion of the trial. The final analyses of OS and PFS for Study JFCB confirmed the IDMC interim assessment; the addition of necitumumab to pemetrexed and

cisplatin did not prove effective in patients with Stage IV nonsquamous NSCLC (OS HR: 1.01; 95% CI: 0.84 to 1.21; PFS HR: 0.96; 95% CI: 0.80 to 1.16) (as discussed in Section 3.5).

In addition to these studies, necitumumab continues to be investigated as first-line treatment in patients with squamous NSCLC (Appendix 5). Two randomized studies are currently ongoing in this indication: the Phase 1b/2 study (Study I4X-IE-JFCM) of necitumumab in combination with gemcitabine-cisplatin versus chemotherapy alone in Japanese patients, and the Phase 2 study of necitumumab in combination with paclitaxel-carboplatin versus chemotherapy alone (Study I4X-MC-JFCL).

Lilly is committed to continuing investigation of additional treatment options with necitumumab for patients with lung cancer. New trials are being initiated this year, including studies of necitumumab combined with a PD-L1 inhibitor (pembrolizumab), a CDK4/6 inhibitor (abemaciclib), and a PI3K/mTOR inhibitor, which are relevant to oncogenic pathways in squamous NSCLC.

3. SQUIRE: Survival Benefit for Necitumumab in Patients with Squamous NSCLC

Lilly designed the Phase 3 study SQUIRE as a focused effort to address the unmet needs of patients with metastatic squamous NSCLC, for whom prognosis remains poor and available first-line treatment options remain limited to platinum-based doublet regimens.

3.1. SQUIRE Study Design and Statistical Plan

SQUIRE was a well-designed, randomized, multicenter, Phase 3 study enrolling patients with Stage IV squamous NSCLC (Figure 2.1). Randomization was stratified by ECOG PS and geographic region. Additional anticancer therapy (post-study therapy) was permitted for patients only after radiographic documentation of disease progression.

Overall survival was selected as the primary endpoint because it can be measured objectively, represents a direct benefit to the patient, and is considered an optimal endpoint for registration trials in advanced NSCLC (FDA 2015). Secondary objectives included PFS, objective response rate (ORR), safety, and patient-reported outcomes. Exploratory objectives included evaluation of relationships between tumor EGFR protein expression and clinical outcomes.

The IDMC assessed safety during the course of the SQUIRE study on a regular basis and recommended to continue the study without modification; no interim efficacy analyses were performed.

Given that the occurrence of acne-like rash, a class effect of EGFR mAbs, would be expected to unblind most patients and investigators to treatment assignment, both studies were conducted open-label; however, Lilly had no unblinded access to aggregate data from the clinical database during study conduct, in order to preserve the integrity of each study. To monitor safety during the course of each study, one IDMC was established to monitor both studies; no interim efficacy analyses were performed.

Patients in both study arms underwent radiographic assessment of disease status every 6 weeks until radiographic documentation of PD according to the Response Evaluation Criteria in Solid Tumors, Version 1.0 (RECIST v1.0). Assessments were performed according to this schedule regardless of any treatment delays, allowing balanced tumor assessments between the treatment arms. Response assessment for the secondary study endpoints of PFS and ORR was based on investigator evaluation.

An estimated sample size of 1080 patients (844 events) allowed for detection of an HR of 0.80 with necitumumab in combination with gemcitabine and cisplatin (GC+N), with a two-tailed log-rank test at the 0.05 significance level and a power of 90%.

For the primary and secondary analyses, OS and PFS were estimated using the Kaplan-Meier method and were compared between treatment arms using the log-rank test, stratified by the randomization strata. Hazard ratios and 95% CIs for GC+N versus GC were estimated from stratified Cox proportional hazards models. The ORR in each treatment arm was compared using the Cochran-Mantel-Haenszel test, stratified by the stratification variables. Type 1 “alpha”

error was controlled across the endpoints OS, PFS, and ORR, by testing the primary endpoint of OS first, and only if this was statistically significant, testing the secondary endpoints of PFS and ORR according to the Hochberg method.

3.2. SQUIRE Study Population

Patients 18 years or older with histologically or cytologically confirmed Stage IV (per American Joint Committee on Cancer, edition 7 [AJCC7]) squamous NSCLC were eligible for SQUIRE. Other key inclusion criteria included adequate organ function and the availability of tumor tissue for exploratory biomarker analysis; patients with nonsquamous NSCLC or previous chemotherapy for advanced NSCLC or symptomatic brain metastases were excluded.

In order to ensure a study population better representing that seen and treated in clinical practice, SQUIRE was designed to enroll patients with ECOG PS 2 in addition to PS 0-1.

Patients were not preselected on the basis of EGFR protein expression because EGFR protein expression is not an established predictive marker, and because the vast majority of squamous NSCLC tumors express EGFR (Salomon et al. 1995; Pirker et al. 2009). However, because of the relevance of the EGFR pathway in NSCLC, the mechanism of action of necitumumab, and hypotheses generated from previous EGFR mAb studies, tumor samples were collected and tested for EGFR protein expression using the Dako Pharm-Dx kit.

A total of 1093 patients (intent-to-treat [ITT] population) were randomized (GC+N: 545; GC: 548). Seven patients in each arm did not receive study treatment, resulting in a safety population of 1079 patients. Patient demographics and disease characteristics were well balanced between treatment arms (Table 3.1). The ITT population was predominantly male with a high disease burden and strong history of smoking. The SQUIRE demographics reflect a representative population of patients who are eligible for platinum doublet chemotherapy in current US practice; in addition, 90% of patients had metastases to 2 or more organ systems and 9% had an ECOG PS of 2.

Table 3.1. Patient Demographic[a] and Disease Characteristics at Baseline
ITT Population
SQUIRE

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)[b]	96 (8.8)[b]
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[c]	40 (7.3)	44 (8.0)	84 (7.7)
Smoking History, n (%)			
Ex-Light Smoker[d]	18 (3.3)	26 (4.7)	44 (4.0)
Non-Smoker[e]	26 (4.8)	27 (4.9)	53 (4.8)
Smoker	500 (91.7)	495 (90.3)	995 (91.0)
Geographic Region, n (%)			
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)
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)

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 As reported on the case report form.

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

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

d Ceased smoking at least 15 years before Day 1 of study treatment and 10 packs or fewer.

e Fewer than 100 cigarettes lifetime.

3.3. Overview of SQUIRE Efficacy Results

SQUIRE met its primary endpoint by demonstrating a statistically significant improvement in survival (HR = 0.84; p = 0.012), with a 16% reduction in the risk of death (Table 3.2).

Table 3.2. Summary of Efficacy ITT Population SQUIRE

Measure	GC+N N = 545	GC N = 548
Overall Survival		
Log-rank p-value (two-sided), stratified*	0.0120	
HR (95% CI)[a], stratified*	0.842 (0.736, 0.962)	
Median, months (95% CI)[b]	11.5 (10.4, 12.6)	9.9 (8.9, 11.1)
Survival rate*, % (95% CI)*		
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)
Progression-Free Survival		
Log-rank p-value (two-sided), stratified*	0.0201	
HR (95% CI)[a], stratified*	0.851 (0.743, 0.975)	
Median, months (95% CI)[b]	5.7 (5.6, 6.0)	5.5 (4.8, 5.6)
Objective Response Rate[c]		
ORR, % (95% CI)[d]	31.2 (27.4, 35.2)	28.8 (25.2, 32.8)
p-value[e]	0.3997	
Disease Control Rate[f]		
DCR, % (95% CI)[d]	81.8 (78.4, 84.8)	77.0 (73.3, 80.3)
p-value[e]	0.0433	

Abbreviations: CI = confidence interval; CR = complete response; DCR = disease control rate; 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; ORR = objective response rate; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors; SD = stable disease.

* Stratified by 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]).

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

b Estimated by the Kaplan-Meier method.

c Response rate is described for patients with a CR or PR according to RECIST 1.0.

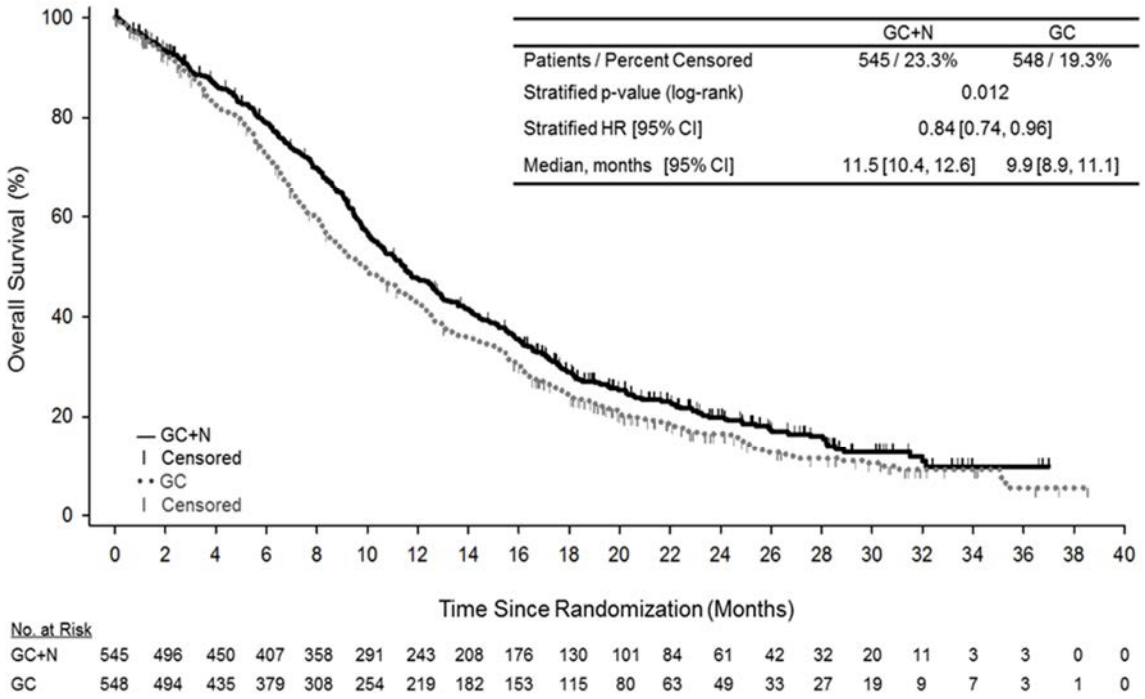
d Confidence interval calculated using the Wilson formula.

e Derived from two-sided Exact Cochran-Mantel-Haenszel test, stratified by the randomization strata.

f Disease control rate is described for patients with a CR, PR, or SD according to RECIST 1.0.

The Kaplan-Meier plot for OS shows an early separation and onset of treatment effect in favor of necitumumab that is sustained throughout the course of the study (Figure 3.1), with improvements in median survival at the 6-month, 1-year, 18-month, and 2-year time points

(Table 3.2). At the time of OS analysis (860 events), the dataset was mature, as shown by the percentage of patients who had died (GC+N Arm: 76.7%; GC Arm: 80.7%) and the median survival follow-up times (GC+N Arm: 25.2 months; GC Arm: 24.8 months) between treatment arms.



Abbreviations: CI = confidence interval; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; HR = hazard ratio; ITT = intent-to-treat.

Figure 3.1. Kaplan-Meier curves for overall survival (ITT population), SQUIRE.

The overall use of post-study anticancer therapies as well as any subsequent third- and fourth-line therapies were balanced between treatment arms (Table 3.3). In addition, the type of post-study treatment was generally balanced between the arms. A minor numerical difference in the use of post-study docetaxel did not have an impact on the OS results, as shown by a sensitivity analysis for OS that censored patients at the start of docetaxel use (HR= 0.80) (Table APP.1.1).

Table 3.3. Overview of Post-Study Systemic Anticancer Therapy
ITT Population
SQUIRE

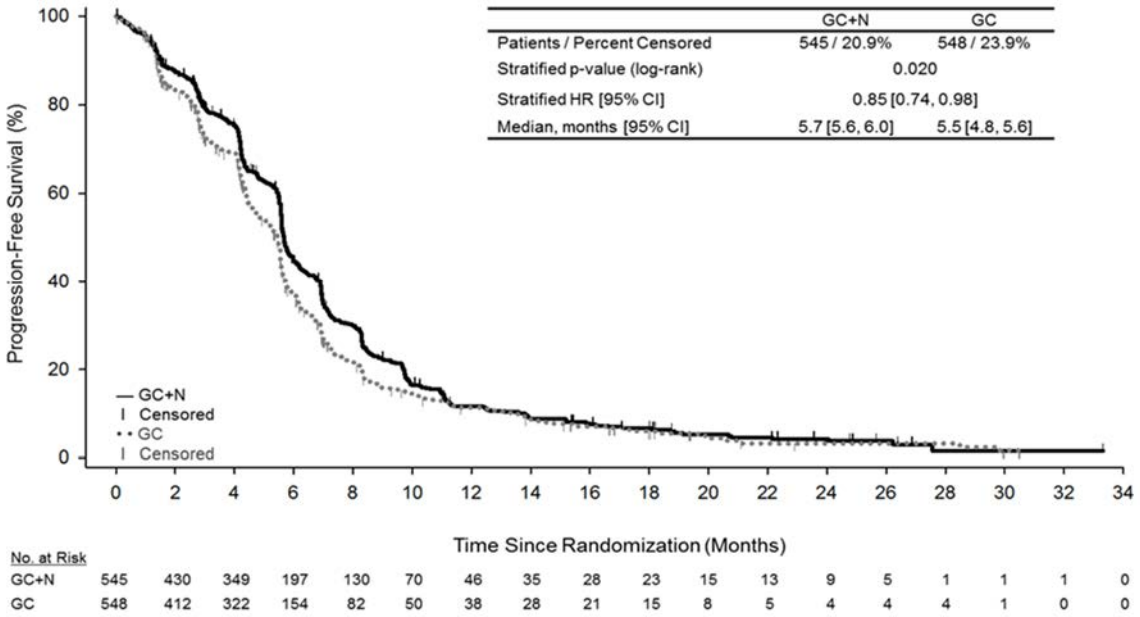
	GC+N N = 545 n (%)	GC N = 548 n (%)
Any Post-Study Therapy[a]	**258 (47.3)**	**245 (44.7)**
Docetaxel	167 (30.6)	127 (23.2)
Erlotinib	57 (10.5)	75 (13.7)
Vinorelbine	40 (7.3)	33 (6.0)
Paclitaxel/Carboplatin	15 (2.8)	14 (2.6)
Gemcitabine	16 (2.9)	12 (2.2)
Other[b]	92 (16.9)	100 (18.2)
Any Third-Line Therapy	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.

b "Other" includes less frequently used regimens including gemcitabine/cisplatin, cisplatin/docetaxel, paclitaxel/cisplatin, pemetrexed, vinerolbine/cisplatin, gemcitabine/vinorelbine, or other regimens.

The robustness of the survival results are supported by the PFS analysis; treatment with GC+N resulted in a statistically significant improvement in PFS (p=0.020), with a 15% reduction in the risk of progression or death compared with GC (Table 3.2). The Kaplan-Meier PFS curves show an early separation and continue to be separated, and show a typical "stair step" pattern, dropping at regular intervals corresponding to the imaging time points (every 6 weeks per protocol) (Figure 3.2).



Abbreviations: CI = confidence interval; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; HR = hazard ratio; ITT = intent-to-treat.

Figure 3.2. **Kaplan-Meier curves for progression-free survival (ITT population), SQUIRE.**

While the HRs for OS and PFS are similar, the difference in median PFS between the arms is small. Corresponding with the timing of radiologic assessments, the Kaplan-Meier curves for PFS by treatment arm (Figure 3.2) show substantial drops roughly every 6 weeks. Consequently, the horizontal difference between the curves is sensitive to the point chosen. While the difference at the 50th percentile, that is the median, is 0.2 months, the difference at the 40th and 60th percentiles is about 1 month, which is more consistent with expectations given the PFS HR. The PFS rates at 3, 6, and 9 months were 79.3% versus 72.5% (GC+N vs. GC), 44.6% versus 37.2%, and 22.3% versus 15.7%, respectively.

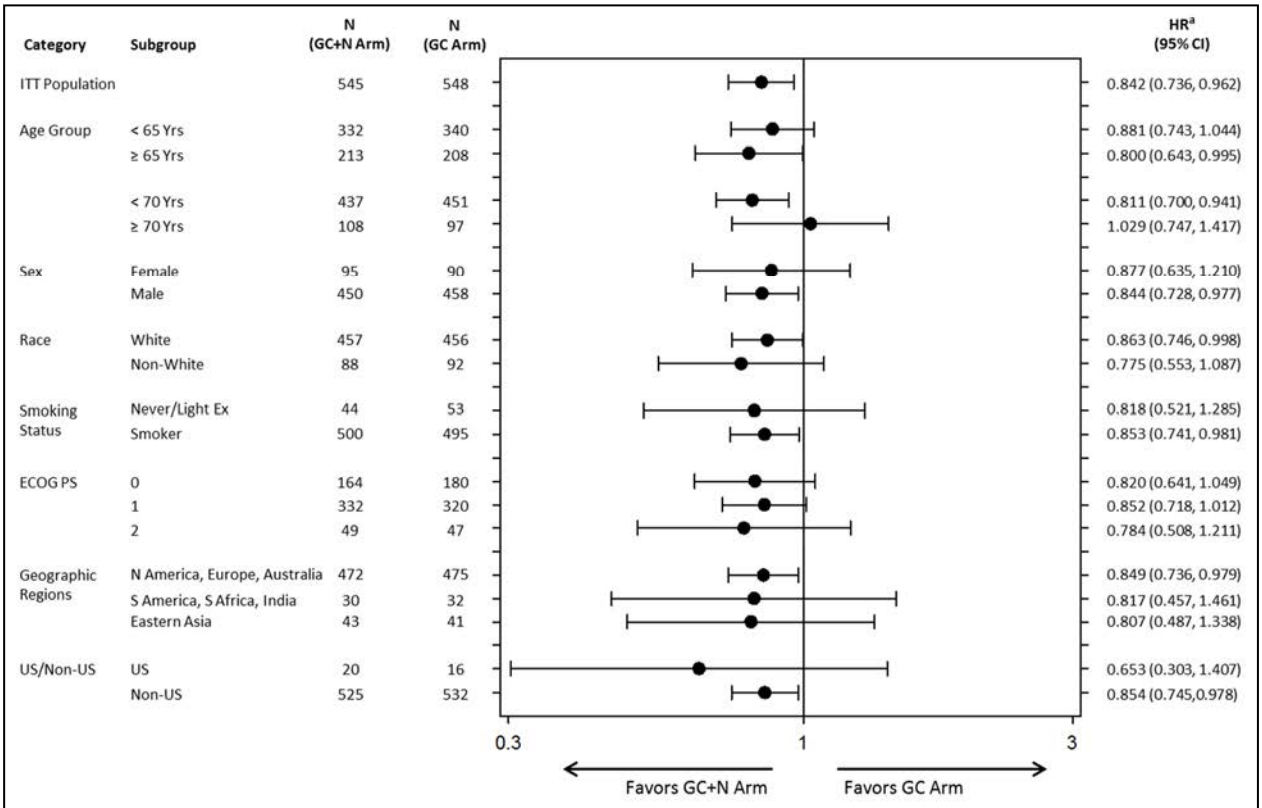
The evaluation of data also included objective response rate and disease control rate. Objective responses were seen in 31.2% of patients in the GC+N Arm and 28.8% of patients in the GC Arm (p=0.3997) (Table 3.2). The disease control rate was significantly higher in the GC+N Arm: 81.8% versus 77.0%, respectively (p=0.0433).

The median OS and PFS in the control arm were consistent with historical data for gemcitabine and cisplatin chemotherapy in squamous NSCLC (Appendix 2). In SQUIRE, the median survival in the subgroup of patients with ECOG PS 0 or 1 (10.4 months; 95% CI: 9.2, 11.7) was similar to the squamous subgroup in the Scagliotti trial (2008) that enrolled only patients with an ECOG PS of 0 or 1 (10.8 months; 95% CI: 9.5, 12.1).

The survival benefit that necitumumab demonstrated in combination with gemcitabine and cisplatin is convincing, given this control arm performance and lack of imbalances in systemic post-study anticancer therapy between study arms.

The results from all prespecified sensitivity analyses of OS and PFS confirmed consistent HRs and p-values favoring the GC+N Arm (Table APP.1.1, Table APP.1.2), further supporting the significance, magnitude of treatment effect, and robustness of the primary OS and the PFS analyses.

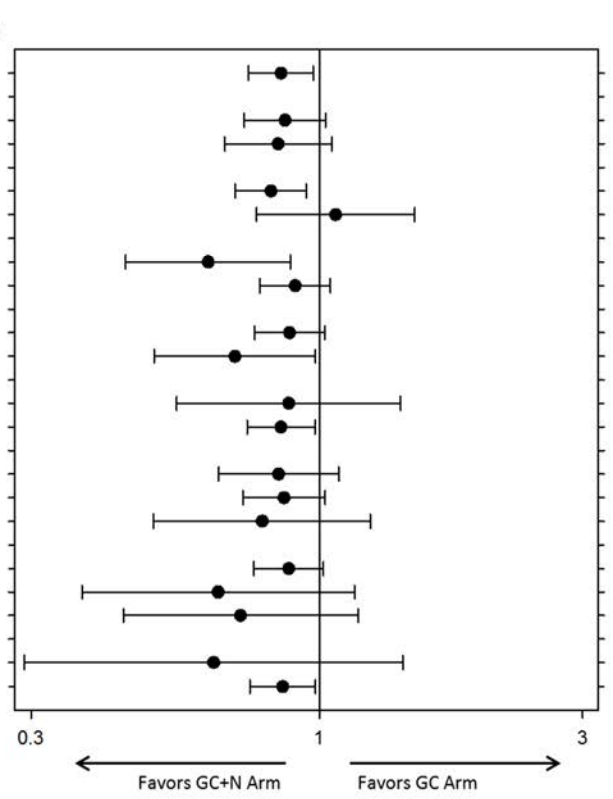
Prespecified subgroup analyses for OS and PFS included these key subgroups: age, sex, race, smoking status, ECOG PS, and geographic region. Improvements in OS and PFS were consistently observed in favor of the necitumumab arm (HR <1.0) across these prespecified subgroups except for the subgroup of patients with age ≥70 years (OS HR: 1.03; PFS HR: 1.07) (Figure 3.3, Figure 3.4).



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; HR = hazard ratio; ITT = intent to treat; N = number of patients.

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

Figure 3.3. Forest plot for subgroup analysis of overall survival (ITT population), SQUIRE.



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; HR = hazard ratio; ITT = intent to treat; N = number of patients.

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

Figure 3.4. Forest plot for subgroup analysis of progression-free survival (ITT population), SQUIRE.

There was no significant treatment-by-age subgroup (<70 and ≥70 years) interaction for either OS (p=0.153) or PFS (p=0.157). As age was not a stratification factor, there was the potential for some imbalances in baseline characteristics; the OS HR in the ≥70 year age group was 0.92 after adjusting for various baseline factors (Table APP.1.3); the baseline factors included in the model were those prespecified in the statistical analysis plan for the ITT multivariate model. In addition, when looking at HRs for OS across the age categories, <65, ≥65 to <70, and ≥70, there is no continuous linear trend to suggest decreasing treatment effect with increasing age (Figure APP.1.1). The lack of significant interaction, the covariate-adjusted OS HR, and the lack of linearity suggest that the finding of an unadjusted HR >1 in the ≥70 years subgroup may be a chance finding.

The safety profile in elderly patients (≥70 years) is consistent with the safety profile in younger patients (<70 years) (Table APP.1.4). The median number of chemotherapy cycles was lower in both arms in the ≥70 age subgroup compared with the <70 age subgroup (Table APP.1.5),

consistent with historical data (Siu et al. 1996). Population PK analysis did not indicate any effect of age on PK (Figure APP.1.2).

3.3.1. Patient-Reported Outcomes

Over 88% of patients completed a baseline and at least 1 postbaseline assessment using the Lung Cancer Symptom Scale (LCSS). Analyses of health status did not suggest a relevant difference between the treatment arms. Time to deterioration for the 6 major symptoms associated with lung malignancies, as measured by the LCSS, was generally similar between the 2 arms (Figure APP.1.3), which indicates that the addition of necitumumab to gemcitabine and cisplatin was not associated with deterioration in patient health-related quality of life.

3.3.2. EGFR Protein Expression

In SQUIRE, a prospective exploratory analysis was conducted to test the hypothesis that high EGFR protein expression (tumor immunohistochemistry [IHC] H-score ≥200) may be predictive of OS outcomes with necitumumab, as supported by historical data with cetuximab (Pirker et al. 2012). Analyses were also prespecified to evaluate efficacy in patients whose tumors did not have detectable EGFR protein expression by IHC.

Archived tumor tissue was collected for 1060 of 1093 patients in the ITT population (97.0%). Tissue samples from 982 (89.8%) of 1093 patients were evaluable by IHC for EGFR protein expression level. The large majority of patients tested (95.2%) had tumor samples expressing the target (that is, EGFR protein expression); only 4.8% had tumors without detectable EGFR protein (Table APP.1.6).

Patients with tumors with high EGFR expression (H-score ≥200) had a more favorable OS (HR = 0.75) compared to patients with low EGFR expression (H-Score <200; HR = 0.90) (Figure APP.1.4); however, an opposite trend was seen for PFS (HR = 0.88 vs. HR = 0.83, respectively; Figure APP.1.4). Interaction test results for both OS and PFS were not statistically significant, indicating that an H-score threshold of 200 did not predict a differential effect for necitumumab with gemcitabine and cisplatin in patients with squamous NSCLC.

An additional prespecified analysis of OS and PFS was performed to evaluate patients with no detectable EGFR protein expression (H-score = 0) (Figure APP.1.5). The small subgroup of SQUIRE patients whose tumors lacked detectable EGFR protein (24 in GC+N Arm; 23 in GC Arm) did not appear to benefit from the addition of necitumumab to gemcitabine and cisplatin compared to gemcitabine and cisplatin alone (OS HR = 1.86; PFS HR = 1.19).

3.4. Overview of SQUIRE Safety Results

Analysis of safety data from SQUIRE revealed a pattern of events that was both predictable for the combination of gemcitabine and cisplatin with necitumumab and manageable. The addition of necitumumab did not appear to exacerbate the known toxicities associated with the chemotherapeutic backbone (for example, hematologic AEs and fatigue), and the occurrence and severity of AEs typically associated with EGFR mAbs such as necitumumab (for example, rash, hypomagnesemia) were consistent with that observed with other agents of this class.

Exposure to chemotherapy was similar between treatment arms (Table APP.1.7). A total of 55% and 53% of patients in the GC+N Arm completed at least 6 cycles of therapy with gemcitabine and cisplatin, respectively; the corresponding percentages for the GC Arm were 48% and 46%. Median relative dose intensity of chemotherapy was similar between treatment arms.

The median number of necitumumab cycles (combination and continuation) was 6.0. Approximately 59% of patients completed 6 cycles of necitumumab. Two hundred seventy-five patients (51%) continued with single-agent necitumumab after the end of chemotherapy; the median number of additional cycles of necitumumab in the continuation phase was 4.

3.4.1. Adverse Events of Special Interest

In order to conduct a focused evaluation of the safety profile of necitumumab in combination with gemcitabine and cisplatin, Lilly defined a series of adverse events of special interest (AESIs), including individual preferred terms (PTs) as well as consolidated terms grouping PTs by medical concept (Table 3.4). AESIs were selected based on the known safety profiles of gemcitabine, cisplatin, and/or other EGFR mAbs, as well as clinical experience with necitumumab.

Based on the study design (Figure 2.1), the treatment period (and hence safety observation period) was longer on the necitumumab arm than the control arm. For the evaluation of AEs, data for the GC+N Arm are presented both for the overall treatment period and also for the equivalent control arm monitoring period (chemotherapy [Ctx] phase) to permit appropriate assessments relative to the control arm.

Table 3.4. Adverse Events of Special Interest
Safety Population
SQUIRE – Squamous NSCLC

	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
Neutropenia	235 (43.7)	131 (24.3)	235 (43.5)	131 (24.3)	248 (45.8)	149 (27.5)
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)
Hypomagnesemia (TEAEs)	168 (31.2)	50 (9.3)	162 (30.1)	48 (8.9)	85 (15.7)	6 (1.1)
Hypomagnesemia (laboratory data)	383 (83.1)	92 (20.0)	375 (81.3)	86 (18.7)	321 (70.2)	33 (7.2)
Skin Rash	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
Conjunctivitis	40 (7.4)	2 (0.4)	30 (5.6)	0	12 (2.2)	0
Interstitial lung disease (ILD)	5 (0.9)	2 (0.4)	4 (0.7)	1 (0.2)	4 (0.7)	3 (0.6)
Arterial thromboembolic events[b]	29 (5.4)	21 (3.9)	23 (4.3)	16 (3.0)	21 (3.9)	11 (2.0)
Venous thromboembolic events[b]	49 (9.1)	27 (5.0)	44 (8.2)	23 (4.3)	29 (5.4)	14 (2.6)

Abbreviations: AESI = adverse event of special interest; Ctx = chemotherapy; GC = gemcitabine and cisplatin; GC+N = necitumumab plus gemcitabine and cisplatin; Gr. = grade; IRR = infusion-related reaction(s); N = number of treated patients; n = number of patients in category; TEAE = treatment-emergent adverse event.

a AESIs include individual preferred terms or terms grouped by medical concept identified by Lilly.

b Table APP.1.9 provides the summary of thromboembolic events (including all preferred terms reported for 2 or more patients in the GC+N Arm), including the rates of Grade ≥3 events.

The first set of AESIs in this table (hematologic toxicities and fatigue) reflects the known hematologic side effects of gemcitabine and cisplatin; there were no differences in these events between arms, such that necitumumab did not exacerbate the known toxicities of this chemotherapy doublet, notably neutropenia. The incidence of febrile neutropenia was low overall, and balanced between treatment arms.

The second set of AESIs (hypomagnesemia, rash, infusion-related reaction [IRR], conjunctivitis, and interstitial lung disease [ILD]) reflect the known side effect profile of necitumumab; these were therefore increased on the experimental arm, however these were primarily low grade, and are well-known and managable side effects of EGFR mAbs. Preventive treatment for skin toxicity was not permitted per protocol during the first cycle of treatment, and the incidence and severity expected in clinical practice may be lower if effective prophylactic rash strategies are used by treating physicians (Melosky et al. 2009; Lacouture et al. 2010).

Hypomagnesemia is an expected consequence of treatment with cisplatin (Lajer and Daugaard 1999; Saif 2008); however, as observed with other EGFR mAbs (Schrag et al. 2005; Maliakal and Ledford 2010; Petrelli et al. 2012b), there was a 13% increase in hypomagnesemia events (by laboratory assessment) with the addition of necitumumab (83.1% vs. 70.2%). Although hypersensitivity / IRRs are generally expected with mAb treatment (Martinelli et al. 2009; Song et al. 2012), in SQUIRE the incidence of IRRs was low and similar between treatment arms as expected for a human monoclonal antibody.

The third set of AESIs present thromboembolic events; these are a well-described complication associated with metastatic cancer, particularly for patients with NSCL C who are treated with cisplatin-based chemotherapy, and have other predisposing risk factors including cardiac disease, history of smoking, and concurrent treatment with transfusions or erythropoeitin (Blom et al. 2004; Bennett et al. 2008; Chew et al. 2008; Khorana et al. 2008; Hicks et al. 2009; Moore et al. 2011; Corrales-Rodriguez and Blais 2012; Petrelli et al. 2012a; Alexander et al. 2014; Kadlec et al. 2014). Despite these risk factors, arterial thromboembolic events (ATEs) and venous thromboembolic events (VTEs) were observed infrequently on both study arms. There was a numeric increase in any-grade ATEs and VTEs with the addition of necitumumab to gemcitabine and cisplatin, as would be expected with an EGFR mAb; however, there were very few fatal cases of ATEs (GC+N vs. GC: 3 vs. 1 patients, 0.6% vs. 0.2%) or VTEs (1 patient on each arm, 0.2% in both arms) (Table APP.1.8).

The population of patients enrolled in SQUIRE was at risk for thromboembolic events due to their underlying disease and as a result of receiving platinum-based therapy (Petrelli et al. 2012a). Based on risk factor analyses in SQUIRE, the most predictive risk factor for metastatic squamous NSCLC patients experiencing a VTE or ATE during study treatment with gemcitabine and cisplatin, with or without necitumumab, is a history of previous VTE or ATE (Figure APP.1.6, Figure APP.1.7).

These data demonstrate that the overall safety profile for necitumumab is acceptable, particularly within the context of the significant survival benefit observed on this study. Lilly has proposed labeling to inform treating physicians about the higher risk of skin toxicities, hypomagnesemia, and thromboembolic events associated with necitumumab, and that a thorough benefit-risk assessment for patients should be carefully considered in making individual treatment decisions. Interventions to minimize these side effects may be informed by prescriber experience with currently approved EGFR mAbs for patients with advanced solid tumors, including rash management strategies, serum electrolyte supplementation, and early evaluation of potential thromboembolic events.

3.4.2. Additional Safety Analyses from SQUIRE

Analysis of events of special interest was supplemented by detailed analyses of all reported treatment-emergent adverse events (TEAEs). Please see Appendix 1 for additional data displays, including TEAEs reported for >5% of patients in the GC+N Arm (Table APP.1.10), all Grade ≥3 TEAEs reported for ≥2% of patients in the GC+N Arm (Table APP.1.11), and serious adverse

events reported for ≥2% of patients in the GC+N Arm (Table APP.1.12). Analysis of these data did not reveal any additional safety concerns.

Treatment-emergent adverse events leading to discontinuation of at least one study drug were reported for 31.2% of patients in the GC+N Arm and 24.6% patients in the GC Arm (Table APP.1.15). Regardless of treatment arm, the most common reasons for discontinuation of any therapy were events related to hematologic events (neutropenia, anemia, or thrombocytopenia).

Adverse events with an outcome of death (excluding those related to disease progression) were reported for 7.8% of patients in the GC+N Arm (Ctx Phase: 5.9%) and 6.8% patients in the GC Arm (Table APP.1.13). These included reports of unexplained or sudden death, where no additional information was available to determine the specific cause of death. In some of these cases, the patients were known to have a cardiac history and/or a preceding episode of untreated hypomagnesemia. Because hypomagnesemia is a well-characterized risk associated with both cisplatin and EGFR mAbs, it cannot be ruled out as a contributing factor for these deaths. To ensure safe administration of necitumumab similar to other approved EGFR mAbs, prescribers must be informed of the importance of monitoring and supplementing magnesium, particularly in patients with a cardiac history.

The incidence of TEAEs of any grade was similar across subgroups (Table APP.1.14). Notably, there was no evidence for increased safety risk due to necitumumab for patients with ECOG PS of 2, or elderly patients (patients ≥65 years of age, or patients >70 years of age). The respective overall rates of Grade ≥3 TEAEs in the GC+N Arm versus the GC Arm were in line with those seen in the ITT population across major subgroups.

In conclusion, the analyses of TEAEs, AEs leading to discontinuation, AEs with outcome of death, as well as analyses of subgroups, support the findings of the AESI analysis as outlined above. The SQUIRE safety results characterize a safety profile consistent with approved EGFR mAbs (rash, hypomagnesemia, and thromboembolic events). The addition of necitumumab to gemcitabine/cisplatin did not increase chemotherapy-associated AEs (hematologic AEs and febrile neutropenia). The results of SQUIRE demonstrate an acceptable safety profile for the combination of necitumumab with gemcitabine and cisplatin in patient s with Stage IV squamous NSCLC.

3.5. Study JFCB (INSPIRE) Safety and Efficacy Results

As described in Section 2, Study JFCB (INSPIRE) was a second Phase 3 study in the necitumumab NSCLC clinical development program. Study JFCB was conducted in a distinctly different patient population than SQUIRE (that is, in patients with nonsquamous [predominantly adenocarcinoma] NSCLC tumors, rather than squamous NSCLC) and utilized a different chemotherapy backbone (pemetrexed-cisplatin rather than gemcitabine-cisplatin). Detailed efficacy and safety results for this trial are provided in Appendix 3.

A total of 633 patients (of 947 planned) were randomized into Study JFCB; this included 315 randomized to receive pemetrexed and cisplatin plus necitumumab (PC+N) and 318 to

receive pemetrexed and cisplatin only (PC). At an interim analysis for safety, the IDMC recommended that enrollment be stopped due to an observed imbalance, predominantly during the first 2 cycles, in fatal thromboembolic events and fatal events that were evaluated by the IDMC as "potentially related to thromboembolism" (mainly cases of unexplained death) between the 2 arms. The IDMC determined that the study would not be able to confirm a significant improvement in survival, given this observed difference in deaths between arms. Following the enrollment stop, the trial continued with 633 patients.

The final analysis for efficacy showed no benefit for patients with nonsquamous NSCLC who received necitumumab combined with pemetrexed and cisplatin (OS; see Figure APP.3.1, Table APP.3.1) (Paz-Ares et al. 2015). As a result, Lilly ceased development of necitumumab in combination with platinum doublets for the treatment of nonsquamous NSCLC.

Because of the clear differences in NSCLC disease between patients with squamous and nonsquamous NSCLC, and the different chemotherapy regimens used to treat these patients, there is a strong clinical rationale for differentiating the safety and efficacy results from SQUIRE and Study JFCB. Unlike Study JFCB, the SQUIRE study enrolled to completion and demonstrated a significant survival benefit, acceptable safety profile, and a favorable benefit/risk in patients with squamous NSCLC.

Adverse events of special interest reported in Study JFCB are shown in Table APP.3.2.

4. Favorable Benefit/Risk for Necitumumab

In the US, approximately 221,200 new patients will be diagnosed with squamous NSCLC in 2015 (ACS 2015). Because of differences in histopathology and genetic profile, which determine prognosis and treatment selection, squamous NSCLC is a distinctly different disease compared to nonsquamous NSCLC. Patients with Stage IV squamous NSCLC continue to have a poor prognosis, and their first-line treatment options remain limited to platinum-based doublets. The results of the SQUIRE study confirm the conclusions from the FLEX study, that the EGFR pathway is particularly relevant in squamous NSCLC and EGFR mAbs are effective in this setting. The addition of necitumumab to chemotherapy represents a clear improvement over the current standard of care in the treatment of patients with advanced squamous NSCLC, for whom there have been no significant therapeutic advancements in 2 decades.

Modest survival improvements have historically served as the foundation for advancing outcomes for patients with advanced NSCLC, building upon cisplatin as a highly effective agent in this setting (Breathnach et al. 2001; Vincent 2014; Gandara et al. 2015). Numerous novel agents have been tested in combination with first-line chemotherapy in advanced NSCLC; however, no trials have been able to show significant prolongation of survival in squamous NSCLC. Importantly, the SQUIRE study has demonstrated a meaningful survival benefit for necitumumab combined with chemotherapy over chemotherapy alone in patients with squamous NSCLC.

Advancements have been made for patients with second-line squamous NSCLC. However, many patients are not able to receive second-line therapy. Therefore, the improvement of clinical outcomes in the first-line setting is critical.

The significant primary survival results of the SQUIRE study were supported by consistent improvements in secondary endpoints and across subgroups, and an early and sustained separation of survival curves throughout the duration of the study. Although the additive survival benefit with necitumumab may appear modest, the observed benefit is robust and clinically relevant, especially given the lack of new treatment options for this patient population. In addition, the results of LCSS did not suggest a detrimental effect on patient-reported outcomes as a result of the addition of necitumumab to chemotherapy.

There were no imbalances in baseline prognostic factors or post-study treatment that influenced the interpretation of efficacy in the SQUIRE study. The use of overall survival as a primary endpoint ensures that the observed benefit is objectively and accurately measured, as well as meaningful to the individual patient, making it an optimal endpoint in this context (FDA 2015). The chemotherapy backbone (gemcitabine and cisplatin) used in the trial is a well-established, efficacious standard first-line treatment for squamous NSCLC, and was administered at the recommended dose and schedule in both arms. The control arm in SQUIRE performed strongly and in line with recent historical data, and the patient population and chemotherapy regimen are relevant to US clinical practice.

Importantly, the observed efficacy of necitumumab in combination with gemcitabine and cisplatin was associated with a safety profile that was acceptable, consistent across subgroups, and in line with expectations for an EGFR mAb. The addition of necitumumab to gemcitabine and cisplatin was associated with a higher incidence of Grade ≥3 TEAEs. Rates of skin reactions and hypomagnesemia were increased with necitumumab; however, these are well-known and clinically manageable side-effects associated with EGFR mAbs in current clinical practice. Management strategies include topical and systemic therapies to prevent and treat skin reactions (Melosky et al. 2009; Lacouture et al. 2010), and close monitoring with adequate supplementation of serum electrolytes (Schrag et al. 2005; Saif 2008; Petrelli et al. 2012b). No increase in hypersensitivity/IRR was observed with the addition of necitumumab to gemcitabine and cisplatin.

Venous thromboembolic events (VTEs) and arterial thromboembolic events (ATEs) were more common in the GC+N Arm compared with the control arm. Thromboembolic events are commonly observed in patients with NSCLC; the risk of venous thrombosis in lung cancer patients is notably increased compared to the general population (Blom et al. 2004; Lyman et al. 2007; Khorana et al. 2008; Hicks et al. 2009). Cisplatin-based regimens are also associated with increased incidence of thromboembolic events in cancer patients (Moore et al. 2011). The rates of VTEs and ATEs in the necitumumab arm of SQUIRE were consistent with meta-analyses that demonstrated that the use of cetuximab or panitumumab with platinum-based chemotherapy is associated with an increased risk of thromboembolic events (Petrelli et al. 2012a).

Notably, necitumumab did not exacerbate hematologic toxicities associated with gemcitabine and cisplatin (including neutropenia, febrile neutropenia, anemia, and thrombocytopenia). There were also no clinically relevant differences in the rates of Grade 5 thromboembolic events between SQUIRE treatment arms. The observed imbalance in unexplained deaths is outweighed by the overall survival advantage with necitumumab; OS is an endpoint that by definition incorporates all causes of death.

While Study JFCB did not show a positive benefit-risk profile for the addition of necitumumab to pemetrexed and cisplatin in patients with nonsquamous NSCLC, results of SQUIRE demonstrated significant efficacy outcomes with an acceptable safety profile as a result of the addition of necitumumab to gemcitabine and cisplatin as first-line treatment in patients with advanced squamous NSCLC.

The development of mAbs targeting the EGFR has resulted in a well-characterized safety profile for this class of drugs, providing treatment options in multiple solid tumors, notably, for patients with *K-Ras* wild-type colorectal cancer, and squamous cell carcinoma of head and neck. Similar to product labeling for other approved EGFR mAbs, physicians must be informed of the risk, potential consequences, and clinical management of rash, hypomagnesemia, and venous and arterial thromboembolic events associated with necitumumab. Lilly has proposed labeling to inform prescribers of these events, and is committed to working with FDA to label necitumumab appropriately for both patients and prescribers, to ensure safe and effective use.

In order to address the unique and complex needs of individual patients with squamous NSCLC, more first-line treatment options are needed. Necitumumab offers a clear survival advantage and favorable benefit/risk when combined with standard of care chemotherapy. If approved, necitumumab will provide an important advancement for patients in this setting.

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Appendix 1. SQUIRE Additional Analyses

Table APP.1.1. Overall Survival – Prespecified and Post-hoc Sensitivity Analyses SQUIRE

	HR (95% CI)	p-Value
Primary Analysis		
IVRS strata – 860 events	0.842 (0.736, 0.962)	.0120
Prespecified 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[a]	0.850 (0.742, 0.973)	.0184
Using CRF strata	0.834 (0.729, 0.954)	.0080
Post-hoc Sensitivity Analysis		
Censoring for post-study docetaxel use	0.798 (0.678, 0.938)	.0062

Abbreviations: BMI = body mass index; CI = confidence interval; CRF = case report form; ECOG PS = Eastern Cooperative OncologyGroup performance status; 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.

a Adjusted for potential prognostic factors: sex, race, smoking history, ECOG PS at baseline, baseline leukocytes, baseline hemoglobin, baseline platelets, baseline BMI, pooled risk factor group.

Table APP.1.2. Progression-Free Survival – Prespecified Sensitivity Analyses SQUIRE

	HR (95% CI)	p-Value
Primary Analysis		
ITT Population	0.851 (0.743, 0.975)	.0201
Prespecified 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 APP.1.3. Overall Survival by Age Group – Adjusted for Potential Prognostic Factors at Baseline
ITT Population
SQUIRE

	Gemcitabine-Cisplatin Chemotherapy Plus Necitumumab			Gemcitabine-Cisplatin Chemotherapy Alone				
Age (Years)	N	Events	Median (95% CI)	N	Events	Median (95% CI)	HR (95% CI)	Log-rank p-value
< 65	332	258	11.5 (10.2,12.9)	340	277	10.1 (8.6,11.9)	0.820 (0.689,0.976)	0.4948
>=65 and < 70	105	79	12.8 (10.7,16.0)	111	94	9.1 (7.9,11.4)	0.635 (0.464,0.868)	0.0024
>=70	108	81	10.0 (9.0,12.5)	97	71	9.7 (7.4,12.6)	0.922 (0.648,1.311)	0.1059

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

Adjusted for potential prognostic factors at baseline: Sex, Race, Smoking History, ECOG PS at Baseline, Baseline Leukocytes, Baseline Hemoglobin, Baseline Platelets, Baseline BMI and geographic region (North America, Europe, and Australia vs. South America, South Africa and India vs. Eastern Asia).

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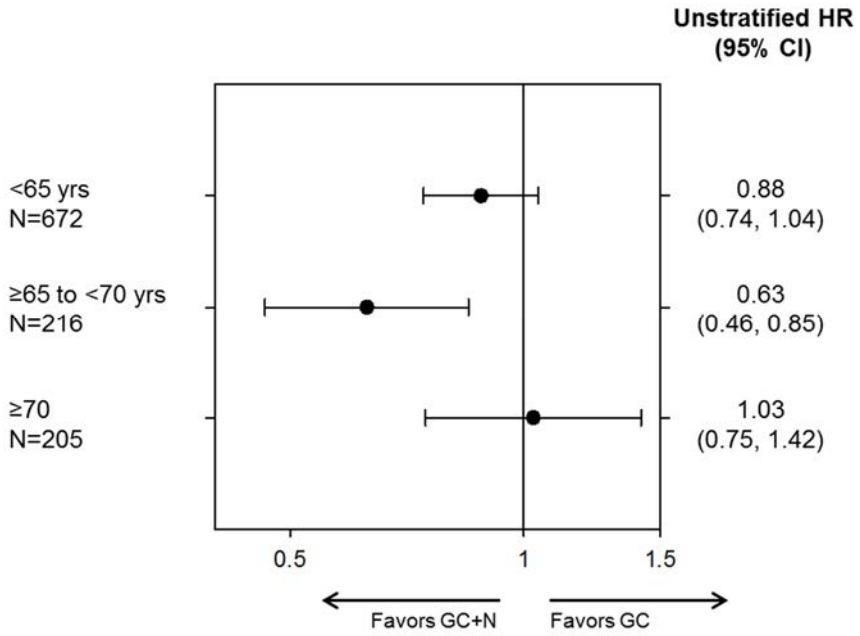


Abbreviations: CI = confidence interval; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; HR = hazard ratio; ITT = intent to treat; N = number of patients; yrs = years.

Figure APP.1.1. Forest plot for subgroup analysis of overall survival by age categories, SQUIRE (ITT population).

**Table APP.1.4. Extent of Exposure (Selected Parameters)
Safety Population (<70 years vs. ≥70 years)
SQUIRE**

	<70 years		≥70 years	
	GC+N	**GC**	**GC+N**	**GC**
Gemcitabine				
N	432	444	106	97
Median duration of therapy (weeks)	17.95	17.10	15.45	13.70
Median number of infusions (n)	10.0	9.0	8.0	7.0
Median number of cycles (n)	6.0	6.0	5.0	4.0
Q1-Q3	3.0-6.0	3.0-6.0	3.0-6.0	2.0-6.0
Median relative dose intensity (%)	87.1	87.5	84.7	78.5
Cisplatin				
N	432	444	106	97
Median duration of therapy (weeks)	18.00	17.40	15.35	13.30
Median number of infusions (n)	6.0	5.0	5.0	4.0
Median number of cycles (n)	6.0	5.0	5.0	4.0
Q1-Q3	3.0-6.0	3.0-6.0	3.0-6.0	2.0-6.0
Median relative dose intensity (%)	95.5	96.0	93.0	91.5
Necitumumab (Overall)				
N	432		106	
Median duration of therapy (weeks)	21.00		18.00	
Median number of infusions (n)	13.0		11.0	
Median number of cycles (n)	7.0		6.0	
Q1-Q3	3.0-10.0		3.0-8.0	
Median relative dose intensity (%)	95.1		91.6	
Necitumumab (Continuation Phase only)				
N	229		46	
Median duration of therapy (weeks)	13.00		10.50	
Median number of infusions (n)	8.0		6.5	
Median number of cycles (n)	4.0		3.5	
Q1-Q3	2.0-8.0		2.0-6.0	
Median relative dose intensity (%)	98.7		95.5	

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

Table APP.1.5. Adverse Events of Special Interest
Safety Population (<70 years vs. ≥70 years)
SQUIRE

	<70 years				≥70 years			
	GC+N N = 432 n (%)		GC N = 444 n (%)		GC+N N = 106 n (%)		GC N = 97 n (%)	
AESI category[a]	**Any Grade**	**Gr≥3**	**Any Grade**	**Gr≥3**	**Any Grade**	**Gr≥3**	**Any Grade**	**Gr≥3**
Neutropenia	187 (43.3)	109 (25.2)	198 (44.6)	121 (27.3)	48 (45.3)	22 (20.8)	50 (51.5)	28 (28.9)
Febrile neutropenia	4 (0.9)	3 (0.7)	5 (1.1)	4 (0.9)	2 (1.9)	1 (0.9)	3 (3.1)	3 (3.1)
Anemia	173 (40.0)	45 (10.4)	201 (45.3)	46 (10.4)	52 (49.1)	12 (11.3)	47 (48.5)	13 (13.4)
Thrombocytopenia	85 (19.7)	36 (8.3)	119 (26.8)	45 (10.1)	32 (30.2)	19 (17.9)	27 (27.8)	13 (13.4)
Fatigue	181 (41.9)	31 (7.2)	186 (41.9)	28 (6.3)	48 (45.3)	8 (7.5)	44 (45.4)	10 (10.3)
Hypomagnesemia (TEAE)	135 (31.3)	41 (9.5)	69 (15.5)	5 (1.1)	33 (31.1)	9 (8.5)	16 (16.5)	1 (1.0)
Skin rash	336 (77.8)	33 (7.6)	47 (10.6)	2 (0.5)	74 (69.8)	5 (4.7)	8 (8.2)	0
Hypersensitivity/infusion-related reaction	7 (1.6)	2 (0.5)	10 (2.3)	0	1 (0.9)	0	1 (1.0)	0
Conjunctivitis	31 (7.2)	1 (0.2)	10 (2.3)	0	9 (8.5)	1 (0.9)	2 (2.1)	0
Interstitial lung disease (pneumonitis)	4 (0.9)	2 (0.5)	3 (0.7)	3 (0.7)	1 (0.9)	0	1 (1.0)	0
Arterial thromboembolic events	23 (5.3)	15 (3.5)	15 (3.4)	7 (1.6)	6 (5.7)	6 (5.7)	6 (6.2)	4 (4.1)
Venous thromboembolic events	36 (8.3)	21 (4.9)	25 (5.6)	11 (2.5)	13 (12.3)	6 (5.7)	4 (4.1)	3 (3.1)

Abbreviations: AESI = adverse event of special interest; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; Gr = grade; N = number of treated patients; n = number of patients in category.

a AESIs include individual preferred terms or terms grouped by medical concept, identified by Lilly according to treatment relevance.

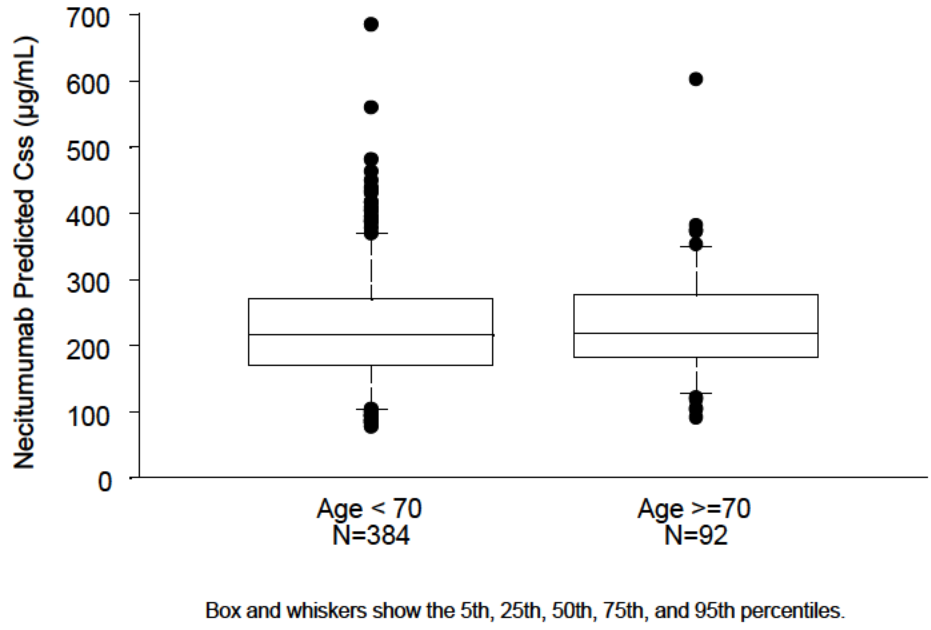


Figure APP.1.2. **$C_{ss,ave}$ predictions in SQUIRE stratified by patient age.**

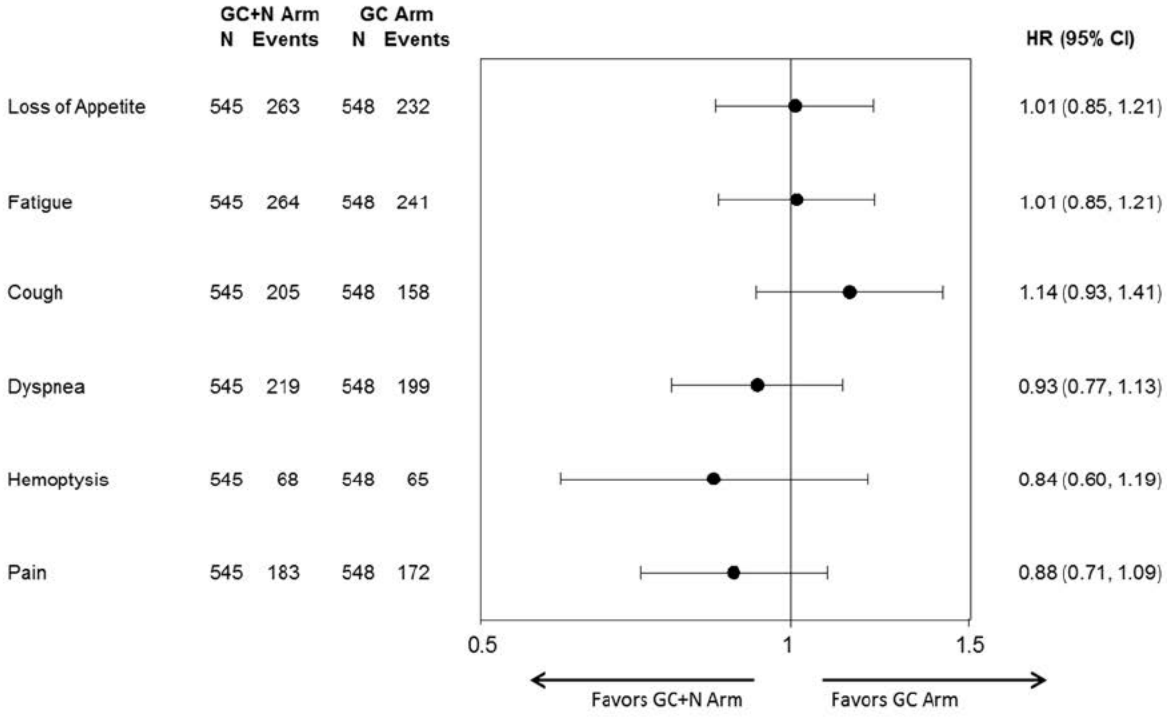


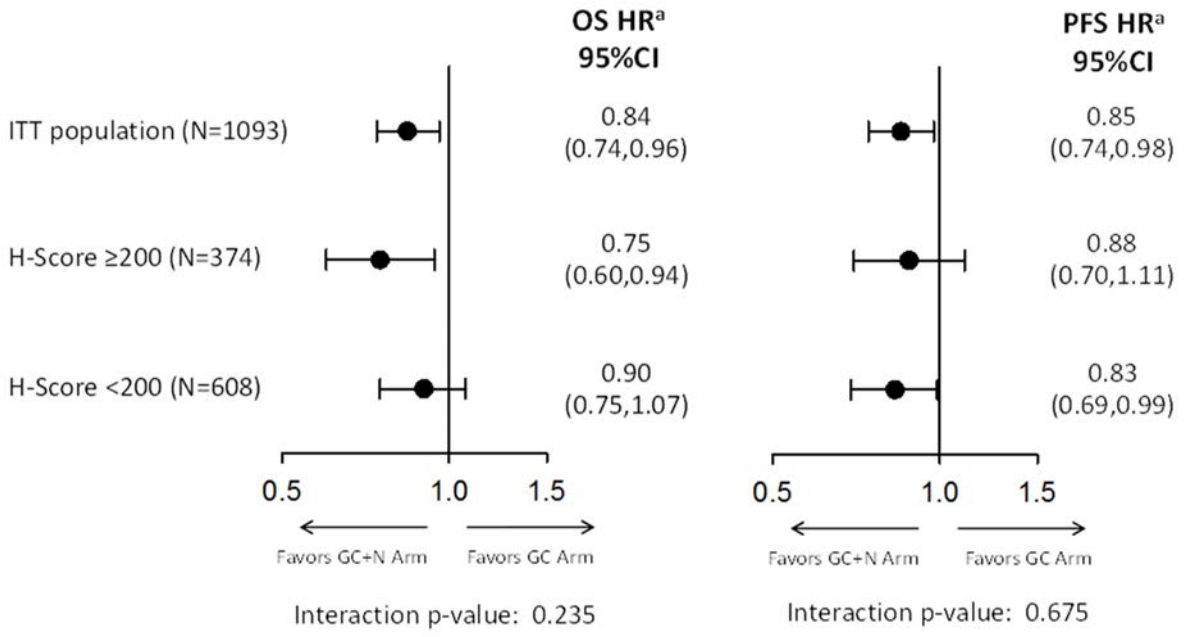
Figure APP.1.3. **Forest plot for time to deterioration of LCSS scores, SQUIRE (ITT population).**

Table APP.1.6. H-Score Distribution TR Population SQUIRE

	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.

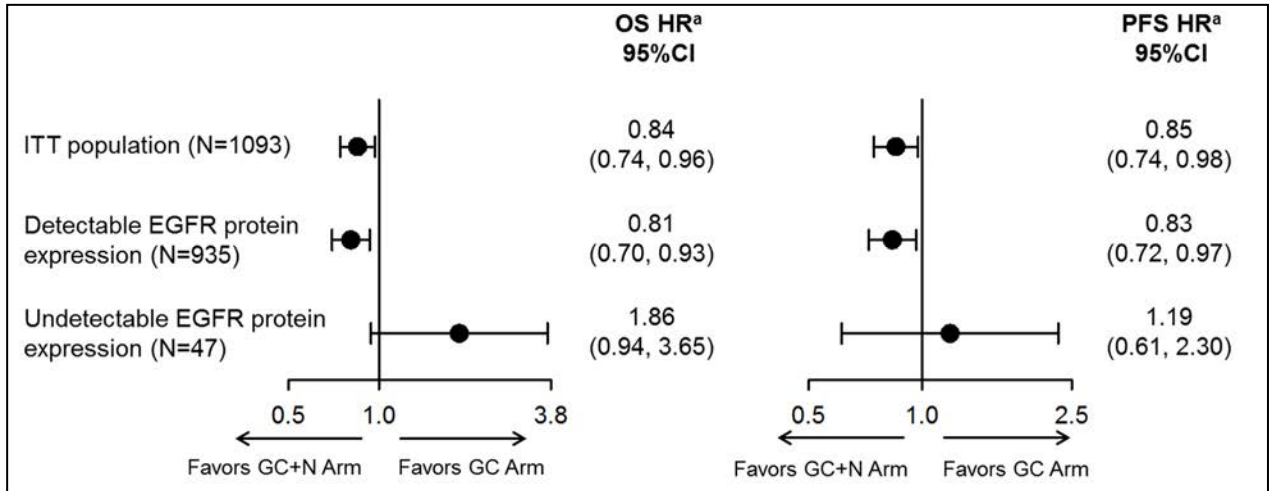
a The category of patients with H-score <200 includes patients with H-score of 0.



Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; HR = hazard ratio; IHC = immunohistochemistry; ITT = intent-to-treat; N = number of patients in population; OS = overall survival; PFS = progression-free survival; TR = translational research.

[a] Stratified HR for ITT population; unstratified HR for H-Scores ≥200 and <200.

Figure APP.1.4. Forest plots of overall survival and progression-free survival by EGFR IHC H-score (≥200 / <200) (TR population), SQUIRE.



Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; GC = gemcitabine and cisplatin; GC+N = necitumumab in combination with gemcitabine and cisplatin; HR = hazard ratio; ITT = intent-to-treat; N = number of patients in population; OS = overall survival; PFS = progression-free survival; TR = translational research.

[a] Stratified HR for ITT population; unstratified HR for EGFR protein expression (>0 [detectable] / =0 [undetectable]).

Figure APP.1.5. Forest plots of overall survival and progression-free survival by EGFR protein expression (>0 [detectable] / =0 [undetectable]) (TR population), SQUIRE.

Table APP.1.7. Extent of Exposure (Selected Parameters)
Safety Population
SQUIRE

	GC+N	GC
Gemcitabine		
N	538	541
Median duration of Therapy (weeks)	17.90	17.00
Median number of Cycles (n)	6.0	5.0
Completed 6 Cycles of Therapy (%)	54.6	47.9
Median relative dose intensity (%)	86.40	86.20
Cisplatin		
N	538	541
Median duration of Therapy (weeks)	18.00	16.90
Median number of Cycles (n)	6.0	5.0
Completed 6 Cycles of Therapy (%)	53.2	46.0
Median relative dose intensity (%)	95.10	95.30
Necitumumab (Overall)		
N	538	NA
Median duration of Therapy (weeks)	20.00	NA
Median number of Cycles (n)	6.0	NA
Completed 6 Cycles of Therapy (%)	58.7	NA
Median relative dose intensity (%)	94.40	NA
Necitumumab (Continuation Phase Only)		
N	275	NA
Median duration of Therapy (weeks)	12.10	NA
Median number of Cycles (n)	4.0	NA
Median relative dose intensity (%)	98.40	NA

Abbreviations: GC = gemcitabine and cisplatin; GC+N = necitumumab plus gemcitabine and cisplatin; NA = not applicable; N = number of treated patients; n = number of patients in category; Q = quartile.

Table APP.1.8. Adverse Events of Special Interest, Grade 3, 4, and 5 Reported Separately
Safety Population (Overall)
SQUIRE

	GC+N N = 538 n (%)				GC N = 541 n (%)			
AESI Category[a]	**Any Grade**	**Gr. 3**	**Gr. 4**	**Gr. 5**	**Any Grade**	**Gr. 3**	**Gr. 4**	**Gr. 5**
Neutropenia	235 (43.7)	97 (18.0)	34 (6.3)	0	248 (45.8)	106 (19.6)	43 (7.9)	0
Febrile neutropenia	6 (1.1)	3 (0.6)	1 (0.2)	0	8 (1.5)	6 (1.1)	1 (0.2)	0
Anemia	225 (41.8)	55 (10.2)	2 (0.4)	0	248 (45.8)	56 (10.4)	3 (0.6)	0
Thrombocytopenia	117 (21.7)	38 (7.1)	17 (3.2)	0	146 (27.0)	35 (6.5)	23 (4.3)	0
Fatigue	229 (42.6)	38 (7.1)	1 (0.2)	0	230 (42.5)	36 (6.7)	2 (0.4)	0
Hypomagnesemia (TEAE)	168 (31.2)	37 (6.9)	13 (2.4)	0	85 (15.7)	6 (1.1)	0	0
Skin Rash	410 (76.2)	38 (7.1)	0	0	55 (10.2)	2 (0.4)	0	0
Hypersensitivity/IRR	8 (1.5)	2 (0.4)	0	0	11 (2.0)	0	0	0
Conjunctivitis	40 (7.4)	2 (0.4)	0	0	12 (2.2)	0	0	0
Interstitial lung disease	5 (0.9)	1 (0.2)	0	1 (0.2)	4 (0.7)	3 (0.6)	0	0
Arterial thromboembolic events	29 (5.4)	13 (2.4)	5 (0.9)	3 (0.6)	21 (3.9)	8 (1.5)	2 (0.4)	1 (0.2)
Venous thromboembolic events	49 (9.1)	19 (3.5)	7 (1.3)	1 (0.2)	29 (5.4)	5 (0.9)	8 (1.5)	1 (0.2)

Abbreviations: AESI = adverse event of special interest; GC = gemcitabine and cisplatin; GC+N = necitumumab plus gemcitabine and cisplatin; Gr. = grade; IRR = infusion-related reaction(s); N = number of treated patients; n = number of patients in category.

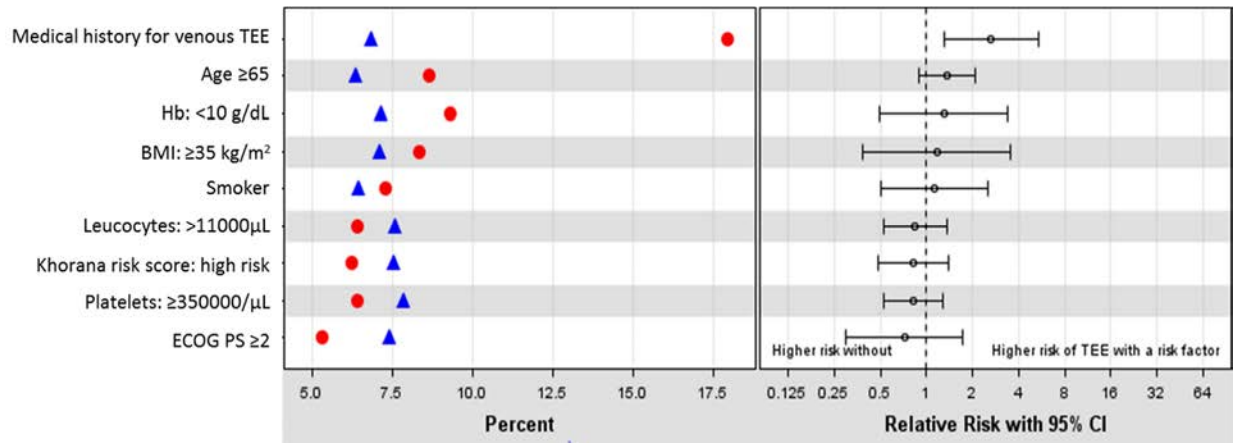
a AESIs include individual preferred terms or terms grouped by medical concept, identified by Lilly according to treatment relevance.

Table APP.1.9. Treatment-Emergent Adverse Events of Special Interest – Thromboembolic Events (Including All Preferred Terms Reported for 2 or More Patients in the GC+N Arm)
Safety Population
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)

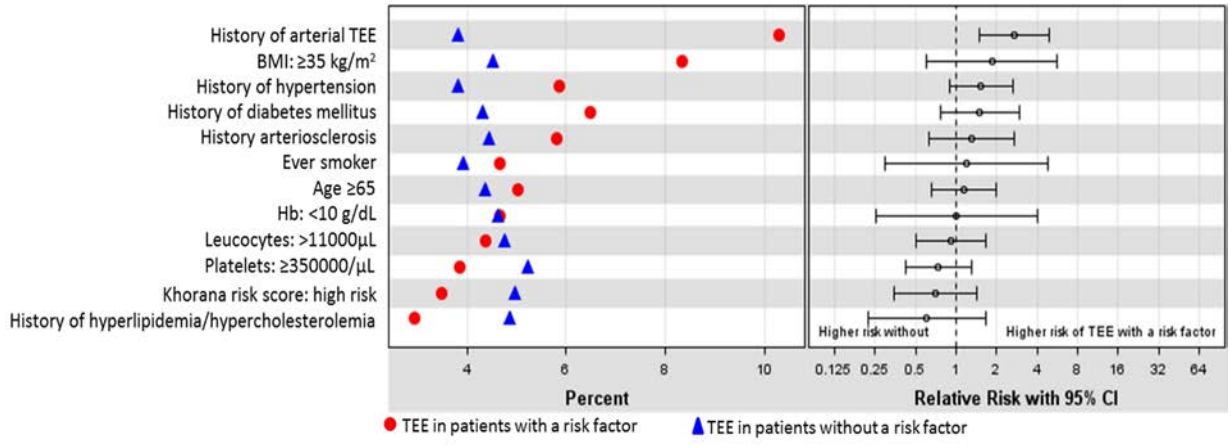
Abbreviations: AESI = adverse event of special interest; Ctx = chemotherapy; GC = gemcitabine and cisplatin; GC+N = necitumumab plus gemcitabine and cisplatin; MedDRA™ = Medical Dictionary for Regulatory Activities; N = number of treated patients; n = number of patients in category

a MedDRA™ preferred term based on progression event recorded as an AE by the investigator.



Abbreviations: BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; Hb = hemoglobin; TEE = thromboembolic event.

Figure APP.1.6. Risk factors for venous thromboembolic events based on AESI definition sorted by relative risk, pooled treatment arms of gemcitabine and cisplatin with and without necitumumab (safety population, SQUIRE).



Abbreviations: BMI = body mass index; CI = confidence interval; Hb = hemoglobin; TEE = thromboembolic event.

Figure APP.1.7. Risk factors for arterial thromboembolic events based on AESI definition sorted by relative risk, pooled treatment arms of gemcitabine and cisplatin with and without necitumumab (safety population, SQUIRE).

Table APP.1.10. Treatment-Emergent Adverse Events Occurring in >5% of Patients in the GC+N Arm, by MedDRA™ Preferred Term
Safety Population
SQUIRE

	GC+N Overall N = 538 n (%)		GC+N Ctx Phase N = 538 n (%)		GC N = 541 n (%)	
Preferred Term	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Patients with any AE	**533 (99.1)**	**388 (72.1)**	**533 (99.1)**	**364 (67.7)**	**529 (97.8)**	**333 (61.6)**
Nausea	267 (49.6)	15 (2.8)	266 (49.4)	15 (2.8)	283 (52.3)	14 (2.6)
Rash	235 (43.7)	20 (3.7)	228 (42.4)	16 (3.0)	30 (5.5)	1 (0.2)
Neutropenia	228 (42.4)	128 (23.8)	228 (42.4)	128 (23.8)	242 (44.7)	146 (27.0)
Anaemia	223 (41.4)	56 (10.4)	214 (39.8)	55 (10.2)	248 (45.8)	59 (10.9)
Decreased Appetite	159 (29.6)	5 (0.9)	150 (27.9)	5 (0.9)	151 (27.9)	8 (1.5)
Hypomagnesaemia	159 (29.6)	47 (8.7)	153 (28.4)	45 (8.4)	82 (15.2)	6 (1.1)
Vomiting	157 (29.2)	15 (2.8)	155 (28.8)	15 (2.8)	135 (25.0)	5 (0.9)
Asthenia	125 (23.2)	23 (4.3)	121 (22.5)	21 (3.9)	113 (20.9)	20 (3.7)
Fatigue	114 (21.2)	17 (3.2)	107 (19.9)	17 (3.2)	122 (22.6)	18 (3.3)
Constipation	111 (20.6)	3 (0.6)	102 (19.0)	3 (0.6)	98 (18.1)	1 (0.2)
Thrombocytopenia	110 (20.4)	53 (9.9)	109 (20.3)	53 (9.9)	132 (24.4)	54 (10.0)
Cough	87 (16.2)	0	67 (12.5)	0	69 (12.8)	3 (0.6)
Dyspnoea	87 (16.2)	15 (2.8)	66 (12.3)	11 (2.0)	79 (14.6)	21 (3.9)
Diarrhoea	84 (15.6)	9 (1.7)	76 (14.1)	8 (1.5)	61 (11.3)	8 (1.5)
Alopecia	76 (14.1)	0	75 (13.9)	0	70 (12.9)	0
Dermatitis Acneiform	81 (15.1)	7 (1.3)	80 (14.9)	7 (1.3)	3 (0.6)	0
Pyrexia	74 (13.8)	6 (1.1)	66 (12.3)	6 (1.1)	60 (11.1)	2 (0.4)
Leukopenia	73 (13.6)	22 (4.1)	72 (13.4)	22 (4.1)	87 (16.1)	36 (6.7)
Weight Decreased	72 (13.4)	4 (0.7)	65 (12.1)	3 (0.6)	34 (6.3)	3 (0.6)
Stomatitis	59 (11.0)	6 (1.1)	56 (10.4)	6 (1.1)	34 (6.3)	3 (0.6)
Dizziness	58 (10.8)	2 (0.4)	53 (9.9)	1 (0.2)	42 (7.8)	2 (0.4)
Headache	57 (10.6)	0	46 (8.6)	0	31 (5.7)	2 (0.4)
Haemoptysis	53 (9.9)	7 (1.3)	44 (8.2)	5 (0.9)	27 (5.0)	5 (0.9)
Blood Creatinine Increased	52 (9.7)	0	48 (8.9)	0	41 (7.6)	1 (0.2)
Acne	47 (8.7)	2 (0.4)	46 (8.6)	2 (0.4)	3 (0.6)	0
Oedema Peripheral	43 (8.0)	1 (0.2)	39 (7.2)	1 (0.2)	41 (7.6)	0
Epistaxis	40 (7.4)	0	38 (7.1)	0	17 (3.1)	1 (0.2)
Back Pain	39 (7.2)	6 (1.1)	27 (5.0)	4 (0.7)	28 (5.2)	4 (0.7)
Hypokalemia	38 (7.1)	16 (3.0)	34 (6.3)	15 (2.8)	28 (5.2)	8 (1.5)
Pruritus	38 (7.1)	1 (0.2)	31 (5.8)	0	5 (0.9)	1 (0.2)
Dry Skin	35 (6.5)	0	29 (5.4)	0	8 (1.5)	0
Paronychia	36 (6.7)	2 (0.4)	21 (3.9)	2 (0.4)	1 (0.2)	0

	GC+N Overall N = 538 n (%)		GC+N Ctx Phase N = 538 n (%)		GC N = 541 n (%)	
Preferred Term	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Dysguesia	33 (6.1)	1 (0.2)	32 (5.9)	1 (0.2)	18 (3.3)	0
Abdominal Pain Upper	32 (5.9)	1 (0.2)	26 (4.8)	1 (0.2)	28 (5.2)	0
Insomnia	28 (5.2)	0	24 (4.5)	0	27 (5.0)	1 (0.2)
Rash Generalised	28 (5.2)	5 (0.9)	28 (5.2)	3 (0.6)	2 (0.4)	0
Urinary Tract Infection	28 (5.2)	1 (0.2)	22 (4.1)	1 (0.2)	9 (1.7)	1 (0.2)

Abbreviations: AE = adverse event; Ctx = chemotherapy; GC = gemcitabine and cisplatin; GC+N = necitumumab plus gemcitabine and cisplatin; MedDRA™ = Medical Dictionary for Regulatory Activities; N = number of treated patients; n = number of patients in category.

Table APP.1.11. Treatment-Emergent Adverse Events of Grade ≥3, Occurring in ≥2% of Patients in the GC+N Arm, by Worst NCI-CTCAE Grade
Safety Population (Overall)
SQUIRE

	GC+N N = 538 n (%)			GC N = 541 n (%)		
Preferred Term	**Gr.≥3**	**Gr.4**	**Gr.5**	**Gr.≥3**	**Gr.4**	**Gr.5**
Patients with any TEAE	**388 (72.1)**	**74 (13.8)**	**66 (12.3)**	**333 (61.6)**	**75 (13.9)**	**57 (10.5)**
Neutropenia	128 (23.8)	34 (6.3)	0	146 (27.0)	43 (7.9)	0
Anaemia	56 (10.4)	2 (0.4)	0	59 (10.9)	3 (0.6)	0
Thrombocytopenia	53 (9.9)	17 (3.2)	0	54 (10.0)	21 (3.9)	0
Hypomagnesaemia	47 (8.7)	13 (2.4)	0	6 (1.1)	0	0
Non-Small Cell Lung Cancer[a]	26 (4.8)	0	24 (4.5)	22 (4.1)	0	19 (3.5)
Pulmonary Embolism	19 (3.5)	6 (1.1)	1 (0.2)	10 (1.8)	8 (1.5)	0
Asthenia	23 (4.3)	1 (0.2)	0	20 (3.7)	1 (0.2)	0
Leukopenia	22 (4.1)	2 (0.4)	0	36 (6.7)	5 (0.9)	0
Rash	20 (3.7)	0	0	1 (0.2)	0	0
Hyponatraemia	20 (3.7)	1 (0.2)	0	22 (4.1)	3 (0.6)	0
Fatigue	17 (3.2)	0	0	18 (3.3)	1 (0.2)	0
Hypokalaemia	16 (3.0)	5 (0.9)	0	8 (1.5)	1 (0.2)	0
Nausea	15 (2.8)	0	0	14 (2.6)	0	0
Vomiting	15 (2.8)	1 (0.2)	0	5 (0.9)	0	0
Dyspnoea	15 (2.8)	0	0	21 (3.9)	1 (0.2)	0

Abbreviations: GC = gemcitabine and cisplatin; GC+N = necitumumab plus gemcitabine and cisplatin; Gr. = grade; MedDRA™ = Medical Dictionary for Regulatory Activities; N = number of treated patients; n = number of patients in category; NCI-CTCAE = National Cancer Instititute Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event.

a MedDRA™ preferred term based on progression event recorded as an adverse event by the investigator.

Table APP.1.12. Treatment-Emergent Serious Adverse Events, Occurring in ≥2% of Patients in the GC+N Arm
Safety Population (Overall)
SQUIRE

	GC+N N = 538 n (%)		GC N = 541 n (%)
Preferred Term	**Overall**	**Ctx Phase Only**	**Overall**
Patients with any treatment-emergent SAE	**257 (47.8)**	**229 (42.6)**	**203 (37.5)**
Non-small cell lung cancer	26 (4.8)	18 (3.3)	23 (4.3)
Anaemia	22 (4.1)	22 (4.1)	17 (3.1)
Neutropenia	20 (3.7)	20 (3.7)	33 (6.1)
Pulmonary Embolism	19 (3.5)	17 (3.2)	9 (1.7)
Thrombocytopenia	17 (3.2)	17 (3.2)	20 (3.7)
Vomiting	12 (2.2)	12 (2.2)	2 (0.4)
Medication Error[a]	12 (2.2)	11 (2.0)	21 (3.9)
Pneumonia	11 (2.0)	10 (1.9)	19 (3.5)
Haemoptysis	11 (2.0)	10 (1.9)	9 (1.7)

Abbreviations: GC = gemcitabine and cisplatin; GC+N = necitumumab plus gemcitabine and cisplatin; MedDRA™ = Medical Dictionary for Regulatory Activities; N = number of treated patients; n = number of patients in category; SAE = serious adverse event.

a Per the study protocol, medication errors were to be reported as SAEs regardless of medical relevance or seriousness outcome.

Table APP.1.13. Treatment-Emergent Adverse Events with an Outcome of Death Occurring in ≥2 Patients in Either Treatment Arm
Safety Population (Overall)
SQUIRE

	GC+N N = 538 n (%)		GC N = 541 n (%)
Preferred Term	**Overall**	**Ctx Phase Only**	**Overall**
Patients with any AE	**66 (12.3)**	**50 (9.3)**	**57 (10.5)**
Excluding Fatal Cases of Disease Progression	*42 (7.8)*	*32 (5.9)*	*37 (6.8)*
Death[a]	8 (1.5)	6 (1.1)	2 (0.4)
Haemoptysis	4 (0.7)	3 (0.6)	5 (0.9)
Pneumonia	4 (0.7)	3 (0.6)	3 (0.6)
Cardio-Respiratory Arrest	3 (0.6)	2 (0.4)	1 (0.2)
Sudden Death[a]	2 (0.4)	1 (0.2)	0
Cardiac Arrest	2 (0.4)	2 (0.4)	0
Myocardial Infarction	2 (0.4)	1 (0.2)	1 (0.2)
Upper Respiratory Tract Infection Bacterial	2 (0.4)	1 (0.2)	0
Pulmonary Hemorrhage	1 (0.2)	1 (0.2)	4 (0.7)
Septic Shock	0	0	2 (0.4)
Respiratory Tract Hemorrhage	0	0	2 (0.4)
Cardiac Failure	0	0	2 (0.4)
Encephalopathy	0	0	2 (0.4)

Abbreviations: AE = adverse event; Ctx = chemotherapy; GC = gemcitabine and cisplatin; GC+N = necitumumab plus gemcitabine and cisplatin; N = number of treated patients; n = number of patients in category.

a Cases of death with unspecified cause.

Table APP.1.14. Subgroup Analysis of Any Treatment-Emergent Adverse Events Safety Population (Overall) SQUIRE

	GC+N n (%)			GC n (%)		
	N	Any Grade	Gr. ≥3	N	Any Grade	Gr. ≥3
Age						
< 65 years	328	325 (99.1)	237 (72.3)	334	325 (97.3)	195 (58.4)
≥ 65 years	210	208 (99.0)	151 (71.9)	207	204 (98.6)	138 (66.7)
< 70 years	432	429 (99.3)	315 (72.9)	444	435 (98.0)	267 (60.1)
≥ 70 years	106	104 (98.1)	73 (68.9)	97	94 (96.9)	66 (68.0)
Sex						
Male	446	443 (99.3)	323 (72.4)	452	441 (97.6)	267 (59.1)
Female	92	90 (97.8)	65 (70.7)	89	88 (98.9)	66 (74.2)
Race						
White	452	447 (98.9)	317 (70.1)	452	442 (97.8)	273 (60.4)
Non-white	86	86 (100)	71 (82.6)	89	87 (97.8)	60 (67.4)
ECOG PS						
0-1	490	487 (99.4)	355 (72.4)	495	485 (98.0)	307 (62.0)
2	48	46 (95.8)	33 (68.8)	46	44 (95.7)	26 (56.5)

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

Table APP.1.15. Most Frequent Treatment-Emergent Adverse Events Leading to Discontinuation of Any Study Drug Safety Population SQUIRE

	GC+N N = 538 n (%)	GC N = 541 n (%)
Patients with any event	**168 (31.2)**	**133 (24.6)**
Hematologic adverse events	56 (10.4)	48 (8.9)
Arterial thromboembolic events	13 (2.4)	7 (1.3)
Venous thromboembolic events	11 (2.0)	2 (0.4)
Progressive disease	9 (1.7)	4 (0.7)
Skin rash	9 (1.7)	0
Hypomagnesemia	3 (0.6)	0
Hypersensitivity/Infusion-related reactions	2 (0.4)	0
Conjunctivitis	1 (0.2)	0

Abbreviations: GC = gemcitabine and cisplatin; GC+N = necitumumab plus gemcitabine and cisplatin; NA = not applicable; N = number of treated patients; n = number of patients in category.

Appendix 2. Efficacy in the Control Arm: SQUIRE versus Study JMDB

Efficacy in the Control Arm: SQUIRE versus Study JMDB

Study *Population*	N	Median OS Mo (95% CI)	Median PFS Mo (95% CI)
SQUIRE (JFCC)			
GC (ITT)	548	9.9 (8.9, 11.1)	5.5 (4.8. 5.6)
GC, ECOG PS 0-1 (ITT)	500	10.4 (9.2, 11.7)	5.5 (5.1, 5.6)
JMDB[a]			
Squamous subgroup, ECOG PS 0-1[b]	229	10.8 (9.5, 12.1)	5.5 (4.6, 5.9)

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine and cisplatin; ITT = intent-to-treat; Mo = months; N = number of treated patients; OS = overall survival; PFS = progression-free survival.

a Scagliotti et al. 2008, 2009.

b Patients with ECOG PS 2 were excluded from Study JMDB.

Appendix 3. Study JFCB Analyses

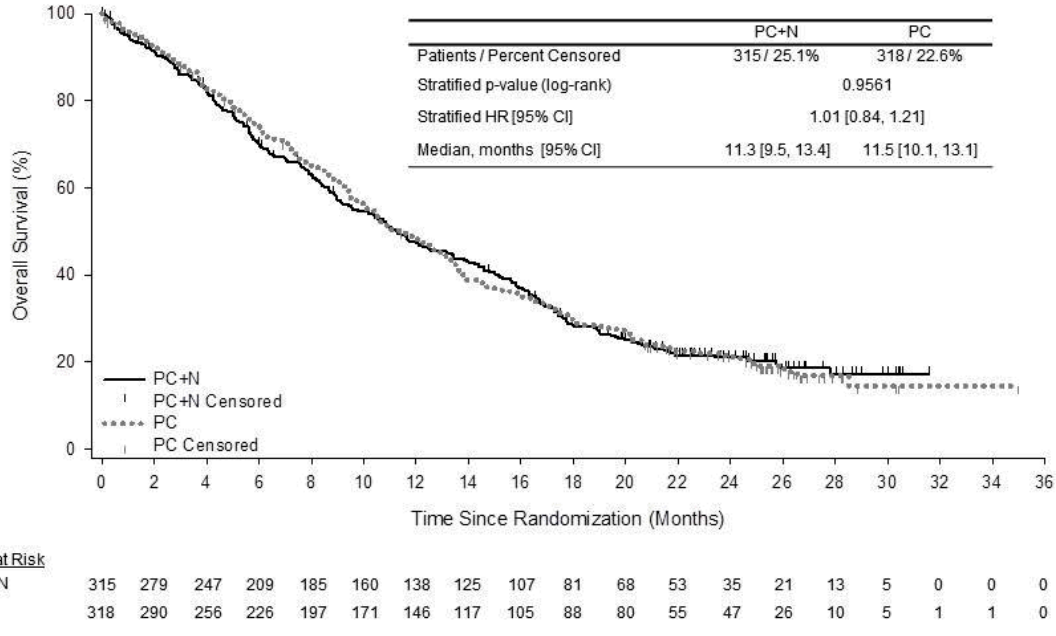


Figure APP.3.1. Kaplan-Meier plot of overall survival (ITT Population) – Study JFCB

Table APP.3.1. Secondary Efficacy Endpoints
ITT Population
Study JFCB – Nonsquamous NSCLC

	PC+N N=315 n (%)		PC N=318 n (%)
Progression-Free Survival			
Stratified[a] Log-rank p-value [b]		0.6647	
Stratified[a] Hazard Ratio		0.96	
95% CI		(0.80, 1.16)	
Median PFS – months[a]	5.6		5.6
95% CI	(5.1, 6.0)		(4.8, 5.7)
Objective Response Rate			
Disease Control, n (%)	231 (73.3)		235 (73.9)
95% CI for DCR[c]	(68.2, 77.9)		(68.8, 78.4)
Objective Response, n (%)	98 (31.1)		102 (32.1)
95% CI for ORR[c]	(26.3, 36.4)		(27.2, 37.4)
p-value[d]		0.7945	

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.

b Derived from a two-sided test

c Estimated using the Wilson formula.

d Derived from two-sided Cochran-Mantel-Haensel test adjusting for the randomization strata.

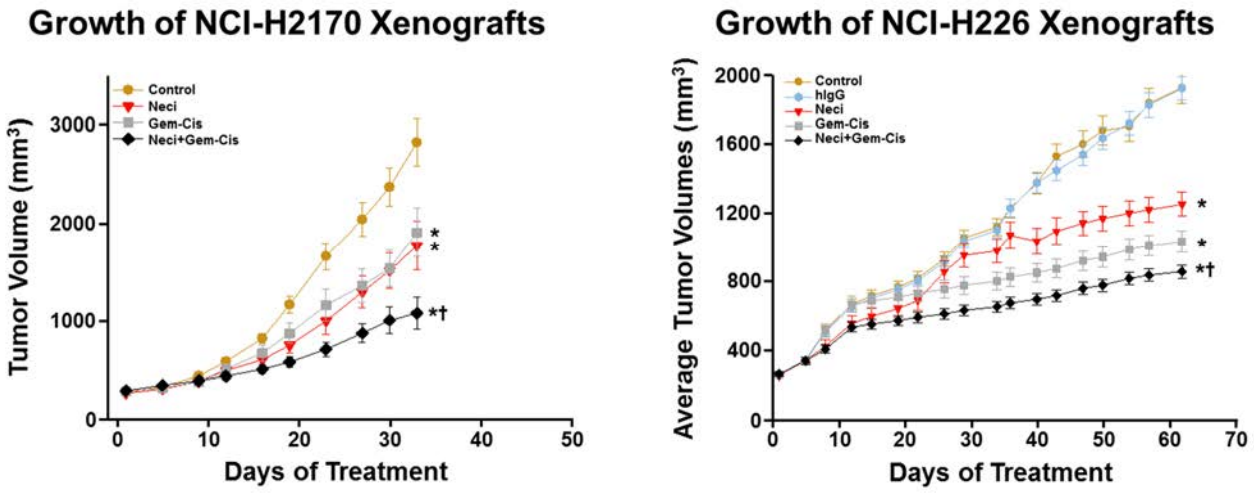
Table APP.3.2. Adverse Events of Special Interest
Safety Population
Study JFCB – Nonsquamous NSCLC

	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
Neutropenia	97 (31.9)	55 (18.1)	97 (31.9)	55 (18.1)	101 (32.4)	57 (18.3)
Febrile neutropenia	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)	3 (1.0)	1 (0.3)
Anemia	79 (26.0)	23 (7.6)	74 (24.3)	20 (6.6)	98 (31.4)	24 (7.7)
Thrombocytopenia	31 (10.2)	15 (4.9)	31 (10.2)	15 (4.9)	29 (9.3)	12 (3.8)
Fatigue	169 (55.6)	34 (11.2)	160 (52.6)	34 (11.2)	159 (51.0)	19 (6.1)
Hypomagnesemia	81 (26.6)	23 (7.6)	78 (25.7)	23 (7.6)	40 (12.8)	7 (2.2)
Hypomagnesemia (laboratory data)	185 (75.2)	42 (17.1)	184 (74.8)	41 (16.7)	138 (53.7)	12 (4.7)
Skin Rash	230 (75.7)	45 (14.8)	227 (74.7)	40 (13.2)	49 (15.7)	1 (0.3)
Hypersensitivity/IRR	6 (2.0)	0	6 (2.0)	0	4 (1.3)	0
Conjunctivitis	49 (16.1)	0	45 (14.8)	0	36 (11.5)	1 (0.3)
Interstitial lung disease	4 (1.3)	0	2 (0.7)	0	3 (1.0)	2 (0.6)
Arterial thromboembolic events	13 (4.3)	8 (2.6)	12 (3.9)	8 (2.6)	18 (5.8)	11 (3.5)
Venous thromboembolic events	40 (13.2)	23 (7.6)	32 (10.5)	18 (5.9)	26 (8.3)	11 (3.5)

Abbreviations: AESI = adverse event of special interest; Ctx = chemotherapy; Gr. = grade; IRR = infusion-related reaction(s); N = number of treated patients; n = number of patients in category; PC = pemetrexed and cisplatin; PC+N = necitumumab in combination with pemetrexed and cisplatin.

a AESIs include individual preferred terms or terms grouped by medical concept, identified by Lilly according to treatment relevance.

Appendix 4. Preclinical Data



Abbreviations: Gem-Cis = gemcitabine and cisplatin; Neci+Gem-Cis = necitumumab in combination with gemcitabine and cisplatin; Neci = necitumumab.

* Significant difference vs. control

† Significant difference vs. gemcitabine + cisplatin and necitumumab alone.

Figure APP.4.1. Activity of necitumumab in combination with gemcitabine and cisplatin in squamous non-small cell lung cancer xenografts.

Appendix 5. Summary of Necitumumab Development Program

Necitumumab Clinical Studies in the Necitumumab Clinical Development Program

Study	Objectives	Study Design *Diagnosis*	Description and Duration of Treatment	Number of Pts
Necitumumab Clinical Studies in NSCLC				
SQUIRE (I4X-IE-JFCC; IMCL CP11-0806) *Completed Study*	Primary OS Secondary PFS; ORR; TTF; safety profile; PK profile (GC+N Arm only); immunogenicity profile (GC+N Arm only); health status Exploratory Relationship between biomarkers (in tumor tissue, whole blood, and plasma) and efficacy and safety	Phase 3 Randomized, open-label, active control *Stage IV squamous NSCLC* *(first-line)*	GC+N Arm (treatment) • Neci (800 mg I.V. D1 and D8 of 3-wk cycle) • Gem (1250 mg/m^2 I.V. D1 and D8 of 3-wk cycle) • Cis (75 mg/m^2 I.V. D1 of 3-wk cycle) GC Arm (control) • Gem (1250 mg/m^2 I.V. D1 and D8 of 3-wk cycle) • Cis (75 mg/m^2 I.V. D1 of 3-wk cycle)	Planned: 1080 Randomized: 1093 Treated: 1079
INSPIRE (I4X-IE-JFCB; IMCL CP11-0805) *Completed Study*	Primary OS Secondary PFS; ORR; TTF; safety profile; PK profile (PC+N Arm only); immunogenicity profile (PC+N Arm only); health status; relationship between EGFR protein expression and efficacy Exploratory Relationship between biomarkers (in tumor tissue, whole blood, and plasma) and efficacy and safety	Phase 3 Randomized, open-label, active control *Stage IV nonsquamous NSCLC* *(first-line)*	PC+N Arm (treatment) • Neci (800 mg I.V. D1 and D8 of 3-wk cycle) • Pem (500 mg/m^2 I.V. D1 of 3-wk cycle) • Cis (75 mg/m^2 I.V. D1 of 3-wk cycle) PC Arm (control) • Pem (500 mg/m^2 I.V. D1 of 3-wk cycle) • Cis (75 mg/m^2 I.V. D1 of 3-wk cycle)	Planned: 947 Randomized: 633 Treated: 616
I4X-MC-JFCK *Completed Study*	Primary ORR Secondary OS; PFS; DCR; CTS; safety profile; PK profile; immunogenicity profile	Phase 2 Open-label, single-arm, uncontrolled *Stage IV squamous NSCLC* *(first-line)*	All Patients • Neci (800 mg I.V. D1 and D8 of 3-wk cycle) • Gem (1250 mg/m^2 I.V. D1 and D8 of 3-wk cycle) Cis (75 mg/m^2 I.V. D1 of 3-wk cycle)	Planned: 60 Treated: 61

Necitumumab Clinical Studies in the Necitumumab Clinical Development Program (continued)

Study	Objectives	Study Design *Diagnosis*	Description and Duration of Treatment	Number of Pts
Necitumumab Clinical Studies in NSCLC (continued)				
I4X-MC-JFCL *Enrollment complete*	Primary ORR Secondary Relationship between EGFR protein expression (as measured by IHC) and each of several efficacy measures: OS, PFS, best tumor response, DCR, and CTS; OS; PFS; DCR; CTS; safety profile; PK profile (Arm A only); immunogenicity profile (Arm A only)	Phase 2 Randomized, open-label, active control *Stage IV squamous NSCLC* *(first-line)*	Arm A: • Necitumumab (800 mg I.V. D1 and D8 of 3-wk cycle) • Paclitaxel (200 mg/m^2 I.V. D1 of 3-wk cycle) • Carboplatin (AUC=6 I.V. D1 of 3-wk cycle) Arm B: • Paclitaxel (200 mg/m^2 I.V. D1 of 3-wk cycle) Carboplatin (AUC=6 I.V. D1 of 3-wk cycle)	Planned: 162 Treated: 161
I4X-JE-JFCM *Ongoing Study*	Primary Phase 1b: tolerability Phase 2: OS Secondary Phase 1b: safety profile; anti-tumor effect; PK; immunogenicity Phase 2: safety profile; PFS; ORR; TTF; PK; QOL (PRO); relationship between EGFR protein expression and efficacy; immunogenicity Exploratory Phase 2: biomarkers related to necitumumab, gemcitabine and cisplatin mechanism of action	Phase 1b/2 Phase 1b Open-label, single-arm, dose escalation Phase 2 Randomized, open-label, active control *Stage IV squamous NSCLC* *(first-line)*	Phase 1b • Necitumumab (800 mg I.V. D1 and D8 of 3-wk cycle) (Cohorts 1 and 2) • Gemcitabine (1000 mg/m^2 I.V. D1 and D8 of 3-wk cycle) (Cohort 1); (1250 mg/m^2 I.V. D1 and D8 of 3-wk cycle) (Cohort 2) • Cisplatin (75 mg/m^2 I.V. D1 of 3-wk cycle) (Cohorts 1 and 2) Phase 2 Arm A: • Necitumumab (800 mg I.V. D1 and D8 of 3-wk cycle) • Gemcitabine (1250 mg/m^2 I.V. D1 and D8 of 3-wk cycle) • Cisplatin (75 mg/m^2 I.V. D1 of 3-wk cycle) Arm B: • Gemcitabine (1250 mg/m^2 I.V. D1 and D8 of 3-wk cycle) • Cisplatin (75 mg/m^2 I.V. D1 of 3-wk cycle)	Phase 1b Planned: Cohort1: 3 to 9 Cohort 2: 6 to 9 Phase 2 Planned: Arm A: 90 Arm B: 90 Treated: 99

Necitumumab Clinical Studies in the Necitumumab Clinical Development Program (continued)

Study	Objectives	Study Design *Diagnosis*	Description and Duration of Treatment[a]	Number of Pts
Necitumumab Clinical Studies in Advanced Solid Tumors				
I4X-IE-JFCE; IMCL CP11-0401 *Completed Study*	Primary Safety profile and determination of MTD Secondary PK profile; immunogenicity profile; antitumor activity	Phase 1 Open-label, two-arm dose escalation study *Advanced solid tumors*	PK Sampling Period (prior to Treatment Cycle 1 only): One infusion of necitumumab at assigned dose level, followed by 2-wk sampling period Arm A Necitumumab (100, 200, 400, 600, 800, or 1000 mg I.V. once a week for 6 wks) Arm B Necitumumab (100, 200, 400, 600, 800, or 1000 mg I.V. every other week for 6 wks)	Planned: 60 Treated: 60
I4X-IE-JFCA; IMCL CP11-0907 *Completed Study*	Primary Safety and PK profile Secondary Immunogenicity profile Exploratory Antitumor activity	Phase 1 Open-label, single-arm, dose-escalation study *Advanced solid tumors*	Necitumumab 600 or 800 mg I.V. D1 and D8 every 3 wk of 6-wk cycle, or 800 mg I.V. every 2 wk of 6-wk cycle	Planned: up to 18 Treated: 15
I4X-IE-JFCI; IMCL CP11-1114 *Enrollment complete*	Primary Effect of necitumumab on corrected QT interval Secondary Other ECG parameters; safety, tolerability, and immunogenicity; PK profile; antitumor activity Exploratory: Use a concentration-QT correlation approach to assess risk of QT prolongation with necitumumab	Phase 2 Single-arm, open-label, non-randomized Baseline value will serve as control for each individual patient. *Advanced solid tumors*	Necitumumab 800 mg I.V. every week of a 6-wk cycle	Planned: 60 Treated: 75

Necitumumab Clinical Studies in the Necitumumab Clinical Development Program (concluded)

Study	Objectives	Study Design *Diagnosis*	Description and Duration of Treatment	Number of Pts
Necitumumab Clinical Studies in Advanced Solid Tumors (concluded)				
I4X-IE-JFCJ; IMCL CP11-1115 *Completed Study*	Primary Cohort 1 only: PK of necitumumab in combination with gemcitabine and cisplain and drug-drug interactions between necitumumab and gemcitabine and cisplatin. Secondary Both cohorts: Safety profile; PK profile (Processes C and D drug products); immunogenicity profile; antitumor activity	Phase 2 Open-label, 2-cohort*non-controlled *Cohort 1 received necitumumab Process C drug product; Cohort 2 received necitumumab Process D drug product *Advanced solid tumors*	Necitumumab 800 mg I.V. D3 of a 3-wk PK run-in period and D1 and D8 of each 3-wk cycle thereafter Gemcitabine 1250 mg/m^2 I.V. D1 of 3-wk PK run-in period and D1 and D8 of each 3-wk cycle thereafter Cisplatin 75 mg/m^2 I.V. D1 of 3-wk PK run-in period and D1 of each 3-wk cycle thereafter	Planned: 30 Treated : 35 (Cohort 1: 18; Cohort 2: 17)
Necitumumab Clinical Studies in Other Indications				
I4X-IE-JFCD; IMCL CP11-0602 *Completed Study*	Primary ORR Secondary OS; PFS; duration of response; safety profile; PK profile; immunogenicity profile; association between response and *KRAS* mutation status	Phase 2 Single-arm, open-label *Locally advanced unresectable or metastatic adenocarcinoma of the colon or rectum* *(first-line)*	Necitumumab 800 mg I.V. D1 of every 2-wk cycle Oxaliplatin 85 mg/m^2 I.V. D1 of every 2-wk cycle Folinic Acid 400 mg/m^2 I.V. D1 of every 2-wk cycle 5-Fluorouracil 400 mg/m^2 I.V. bolus injection, D1 of every 2-wk cycle 5-Fluorouracil 2400 mg/m^2 Continuous I.V. infusion over 46 hours beginning D1 of every 2-wk cycle	Planned: 40 Treated: 44

Abbreviations: CSR = clinical study report; CTS = change in tumor size; D = day; DCR = disease control rate; DDI = drug-drug interaction; Gem = gemcitabine; I.V. = intravenously; Neci = necitumumab; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; SD = stable disease; TTF = time to treatment failure.