The Effect of Necitumumab in Combination with Gemcitabine plus Cisplatin on Tolerability and on Quality of Life: Results from the Phase 3 SQUIRE Trial

Martin Reck, MD, PhD, a,a* Mark A. Socinski, MD, b Alexander Luft, MD, c Aleksandra Szczesna, MD, d Mircea Dediu, MD, e Rodryg Ramla, MD, PhD, f György Losonczy, MD, DSc, g Olivier Molinier, MD, h Christian Schumann, MD, PhD, i,j Richard J. Gralla, MD, k Philip Bonomi, MD, l Jacqueline Brown, PhD, m Victoria Soldatenkova, MS, n Nadia Chouaki, MD, o Coleman Obasaju, MD, PhD, p Patrick Peterson, PhD, p Nick Thatcher, MD, PhD q

aDepartment of Thoracic Oncology, LungenClinic Grosshansdorf, Airway Research Center North, Grosshansdorf, Germany
bLung Cancer Section, Division of Hematology/Oncology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania
cLeningrad Regional Clinical Hospital, St. Petersburg, Russia
dMazowieckie Centrum Leczenia Chorób Pluc, Otwock, Poland
eInstitute of Oncology “Alexandru Trestioreanu,” Bucharest, Romania
fPoznan University of Medical Sciences, Poznań, Poland
gSemmelweis University Department of Pulmonology, Budapest, Hungary
hCentre Hospitalier Le Mans, Le Mans, France
iDepartment of Internal Medicine II, University Hospital of Ulm, Ulm, Germany
jClinic for Pneumology, Thoracic Oncology, Sleep- and Respiratory Critical Care, Kempten-Oberallgaeu Hospitals, Kempten, Germany
kAlbert Einstein College of Medicine, Bronx, New York
lRush University Medical Center, Chicago, Illinois
mEli Lilly and Company, Earl Wood, United Kingdom
nEli Lilly and Company, Bad Homburg, Germany
oEli Lilly and Company, Paris, France
pEli Lilly and Company, Indianapolis, Indiana
qThe Christie Hospital, Manchester, United Kingdom

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ABSTRACT

Introduction: Necitumumab, a second-generation, recombinant human immunoglobulin G1 epidermal growth factor receptor antibody in the phase 3 SQUIRE trial (NCT00981058), increased survival benefit for patients randomized to receive necitumumab plus gemcitabine-cisplatin compared with those who received gemcitabine-cisplatin. Here we characterize health-related quality of life (HRQoL) and tolerability results.

Methods: A total of 1093 patients with stage IV squamous non–small cell lung cancer were randomized 1:1 to receive necitumumab (800 mg absolute dose intravenously [IV]) plus gemcitabine-cisplatin (gemcitabine = 1250 mg/m² IV on days 1 and 8; cisplatin = 75 mg/m² IV on day 1) or gemcitabine-cisplatin alone (every 21 days) for up to six cycles. Patients receiving necitumumab plus gemcitabine-cisplatin without disease progression continued necitumumab until progression. HRQoL was measured by Eastern Cooperative Oncology Group performance status, the Lung Cancer Symptom Scale (LCSS), and the European Quality of Life Five-Dimensions questionnaire. Efficacy and LCSS...
Introduction

The majority of patients with non–small cell lung cancer (NSCLC) present with locally advanced unresectable or metastatic disease and nearly all present with serious symptoms, including fatigue, loss of appetite, dyspnea, cough, and pain. In addition, compared with patients with NSCLC characterized by nonsquamous histologic features, patients with squamous NSCLC tend to be older and report a higher prevalence of concomitant diseases. Thus, avoiding a heavy toxicity burden and detrimental effects on patients’ health-related quality of life (HRQoL) are important considerations in developing new treatments for patients with squamous NSCLC.

Squamous and nonsquamous NSCLC differ in terms of genetics and some therapeutic options. Whereas many first-line treatment options exist for patients with nonsquamous disease, the first-line options for patients with squamous NSCLC are limited and have remained essentially unchanged over the past two decades. The recommended first-line therapy for squamous NSCLC is generally a platinum doublet chemotherapy regimen (including cisplatin or carboplatin and a chemotherapy agent such as gemcitabine, a taxane, or vinorelbine).

Patients with advanced or metastatic squamous NSCLC treated with current standard first-line chemotherapy options have a median survival time in the range of 9.5 to 10.8 months, which is somewhat shorter than the median overall survival described for patients with advanced or metastatic nonsquamous NSCLC (10.3–12.4 months).

Necitumumab is a second-generation, recombinant human immunoglobulin G1 epidermal growth factor receptor (EGFR) antibody. In the phase 3 SQUIRE trial, the addition of necitumumab to the standard first-line chemotherapy doublet of gemcitabine and cisplatin resulted in a statistically significant improvement in overall survival in patients with squamous NSCLC (stratified hazard ratio [HR] = 0.84, 95% confidence interval [CI]: 0.74–0.96; p = 0.01, median survival 11.5 months [10.4–12.6] versus 9.9 months [8.9–11.1], respectively). Here we present HRQoL results from the SQUIRE trial and focus on patient-reported symptoms and health status as measured by the Lung Cancer Symptom Scale (LCSS) and the European Quality of Life Five-Dimensions (EQ-5D) questionnaire, respectively, as well as physician-reported Eastern Cooperative Oncology Group performance status (ECOG PS) and drug tolerability.

Patients and Methods

Patient Population, Study Design, and Treatment

Full details of the SQUIRE study design and patient eligibility criteria have been previously published. Briefly, patients with ECOG PS 0–2 and stage IV squamous NSCLC were randomized 1:1 to receive necitumumab (800 mg absolute dose intravenously [IV] on days 1 and 8) plus gemcitabine-cisplatin (gemcitabine = 1250 mg/m² IV on days 1 and 8; cisplatin = 75 mg/m² IV on day 1) or gemcitabine-cisplatin alone (every 21 days) for up to six cycles. Patients treated with necitumumab plus gemcitabine-cisplatin with no disease progression continued necitumumab single-agent therapy until disease progression. The primary end point was overall survival. Secondary end points included evaluation of patient-reported symptoms, health status, and safety profile. The study was conducted in compliance with the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable local regulations. The protocol was approved by the ethics committees of all participating centers, and all patients provided written informed consent before study entry.

Health-Related Quality of Life

The HRQoL analyses focused on patient-reported symptoms as measured by the LCSS and a broader...
assessment of health status as measured by the EQ-5D, in addition to physician-reported ECOG PS.19–21 LCSS, EQ-5D, and ECOG PS scores were analyzed for all patients in the intention-to-treat population with a baseline and at least one post-baseline assessment.

ECOG PS was evaluated in both arms by a physician at baseline (before treatment), before the start of each cycle, at the end of treatment, and during a 30-day safety follow-up visit. ECOG PS results were summarized using frequency distributions at baseline for cycles 1 to 6 and at the end of therapy. Time to first deterioration of ECOG PS by at least one level from baseline was estimated using a Cox proportional hazards model. For each patient who was not known to have had a deterioration, time to deterioration was censored at the last ECOG PS assessment date.

The LCSS and EQ-5D were administered in both arms at baseline, at the beginning of every cycle (2–6), and every 6 weeks thereafter until disease progression. At each scheduled assessment, the LCSS was completed before the EQ-5D. LCSS and EQ-5D data were analyzed by visit as assessments were performed whether a visit was for treatment (cycle) or for follow-up for disease progression.

The LCSS consists of nine items regarding the severity of six major lung cancer symptoms (loss of appetite, fatigue, cough, dyspnea, hemoptysis, and pain) and three global measures (interference with normal activity, quality of life, overall lung cancer symptoms). For each of the nine LCSS items, the patient’s response is scored from 0 to 100, with lower scores representing lower severity. In addition to the nine individual items’ scores, three summary indices were calculated: the average symptom burden index, which was defined as the mean across the six symptom-specific items; the global three-item composite index, which was defined as the mean of the three global items; and the LCSS total score, which was defined as the mean score over all nine items (if any of the nine items were not completed, the total score was treated as missing). For each of the LCSS items, mean values with standard deviations were estimated for each visit. In addition, for each of the LCSS variables, changes from baseline scores for every post-baseline assessment were obtained. On the basis of work by de Marinis et al.,22 a clinically meaningful change was defined for each visit as at least a 15-mm change from baseline, which is also consistent with one-half the standard deviation of baseline scores.23,24 Therefore, worsening was defined as at least a 15-mm increase from baseline, and an improvement was defined as at least a 15-mm decrease. Stable was defined as a change less than 15 mm or no change.

Time to deterioration was estimated using the Kaplan-Meier method and compared between treatment arms using a log-rank test. Additionally, HR and its 95% CI were estimated from the Cox proportional hazards model.25 For each patient who was not known to have had a deterioration, time to deterioration was censored at the date of the patient’s last LCSS assessment.

The EQ-5D comprises a descriptive system, a three-level assessment (no problem, some problem, and severe problem) of five dimensions (mobility, pain and discomfort, anxiety and depression, self-care, and usual activities), plus a visual analogue scale (VAS) rating of the patient’s overall health state on a scale of 0 to 100, where 0 is the worst imaginable health state and 100 is the best imaginable health state. The mean VAS scores with standard deviations and the frequencies of patients experiencing no problems, some problems, and severe problems for each of the EQ-5D dimensions were summarized descriptively by visit.

In addition to the LCSS analyses already described, a novel analysis was undertaken to evaluate the outcomes of patients with more severe baseline LCSS scores relative to those of patients with less severe baseline LCSS scores. This analysis defined the maximum severity score (MSS) for each LCSS assessment as the maximum (worst) score among the nine individual LCSS items. MSS at baseline was used to categorize patients into two groups: those with high LCSS severity (MSS ≥ median) and those with low severity (MSS < median).26 Variables for mean maximum improvement in MSS and other LCSS items over baseline were compared between treatment arms by least squares means (analysis of covariance).

**Tolerability**

Tolerability was determined by study treatment exposure, the percentage of patients receiving necitumumab continuation therapy, reported adverse events (according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0), and discontinuation of treatment for adverse events. Tolerability was evaluated in the safety population. Patients were assessed regularly for potential occurrence of adverse events from the time the patient signed the informed consent document until 30 days after the last dose of study therapy, or until resolution or stabilization of a serious adverse event or study therapy-related adverse event.

Tolerability and hospitalization results are presented by phase of treatment. Chemotherapy phase refers to the period during which patients received chemotherapy in both arms; continuation refers to the period after discontinuation of chemotherapy when patients on the necitumumab plus gemcitabine-cisplatin arm continued single-agent necitumumab.
Results

Patient and Disease Characteristics

The intention-to-treat population comprised 1093 patients who were randomly assigned to receive necitumumab plus gemcitabine-cisplatin (n = 545) or gemcitabine-cisplatin (n = 548). Seven patients in each group did not receive the study treatment; thus, the safety population comprised 1079 patients. Baseline patient and disease characteristics were well balanced between treatment arms and have been previously reported.\textsuperscript{18}

Health-Related Quality of Life

Results are shown through visit 14; after visit 14 only a small number of patients were available for the analysis.

ECOG PS. Of the 1093 patients in SQUIRE, 96 (9%) had a baseline ECOG PS of 2.\textsuperscript{18} The percentage of patients with an ECOG PS of 0–1 or 2 at each cycle was comparable between arms of the trial during the chemotherapy phase (see Supplementary Fig., Supplementary Digital Content 1). Most patients maintained their baseline ECOG PS throughout chemotherapy, with only a small percentage of patients (6.2% in the necitumumab plus gemcitabine-cisplatin arm and 3.9% patients in the gemcitabine-cisplatin arm) deteriorating from an ECOG score of 0–1 to 2.

LCSS. Of the 545 patients in the necitumumab plus gemcitabine-cisplatin arm, 481 (88.3%) had a baseline assessment and at least one completed post-baseline LCSS assessment. In the gemcitabine-cisplatin arm, 482 (88.0%) of the 548 patients had a baseline assessment and at least one completed postbaseline LCSS assessment. Compliance by visit can be found in Supplementary Digital Content 2. The median baseline LCSS scores shown in Table 1 suggest that patients generally reported moderate-to-high symptoms, interference with normal activities, and impact on quality of life, which may be seen as typical of first-line squamous NSCLC. Patients with an ECOG PS of 2 reported numerically higher symptoms for all LCSS variables, with the exception of hemoptysis (which occurred infrequently at all PS levels and on both study arms). Figure 1 shows LCSS response by assessment time point (visit). Over time, of those patients still in the study, most in both of the study arms had stable symptoms compared to baseline, and a similar pattern of response was seen for LCSS global items and LCSS total score. The proportion of patients with improved or stable scores compared with the baseline versus deterioration or missing was greater for the pain item in the necitumumab plus gemcitabine-cisplatin arm than in the gemcitabine-cisplatin arm at visits 5 (p = 0.0281) and 6 (p = 0.0325); otherwise, the responses were similar between treatment arms.

Figure 2 shows the forest plot of HRs and 95% CIs for time to deterioration over the entire assessment period for each of the 12 LCSS variables as well as for ECOG PS. None of the 95% CIs excluded an HR of 1.0, suggesting no compelling differences between the two trial arms.

EQ-5D. Of the 545 patients in the necitumumab plus gemcitabine-cisplatin arm, 484 (88.8%) had a baseline

Table 1. Responses for Individual LCSS Items at Baseline by ECOG Performance Status

<table>
<thead>
<tr>
<th>ECOG PS 0–1</th>
<th>Gem-Cis n = 500</th>
<th>Neci + Gem-Cis n = 496</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Median (Q1–Q3)</td>
<td>n</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>482</td>
<td>25.0 (7.0–48.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>482</td>
<td>34.0 (12.0–53.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>482</td>
<td>23.0 (7.0–51.0)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>482</td>
<td>21.0 (6.0–50.0)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>482</td>
<td>0.0 (0.0–5.0)</td>
</tr>
<tr>
<td>Pain</td>
<td>482</td>
<td>9.0 (1.0–37.0)</td>
</tr>
<tr>
<td>Average symptom burden index</td>
<td>482</td>
<td>22.5 (13.7–38.2)</td>
</tr>
<tr>
<td>Overall lung cancer symptoms</td>
<td>482</td>
<td>23.0 (6.0–49.0)</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>482</td>
<td>28.0 (7.0–51.0)</td>
</tr>
<tr>
<td>Quality of life today</td>
<td>482</td>
<td>38.0 (15.0–53.0)</td>
</tr>
<tr>
<td>Global three-item composite index</td>
<td>482</td>
<td>31.0 (15.0–50.0)</td>
</tr>
<tr>
<td>LCSS total score</td>
<td>482</td>
<td>53.5 (28.0–84.0)</td>
</tr>
<tr>
<td>MSS</td>
<td>482</td>
<td>50.0 (25.0–75.0)</td>
</tr>
</tbody>
</table>

LCSS, Lung Cancer Symptom Scale; ECOG, Eastern Cooperative Oncology Group; Neci + Gem-Cis, necitumumab + gemcitabine-cisplatin; Gem-Cis, gemcitabine-cisplatin; MSS, maximum severity score.
In the gemcitabine-cisplatin arm, 489 (89.2%) of the 548 patients had a baseline assessment and at least one completed post-baseline EQ-5D assessment. Compliance by visit can be found in Supplementary Digital Content 3. Mean EQ-5D VAS scores were generally consistent between treatment groups at baseline and at subsequent visits (see Supplementary Digital Content 4A). Supplementary Digital Content 4B shows the percentage of patients experiencing no problems, some problems, and severe problems for each of the EQ-5D dimensions (mobility, pain and discomfort, anxiety and depression, self-care, and usual activities). At baseline, the severity of problems was similar in both arms of the study and relatively few patients (≤6.2% in both arms) experienced severe problems. The percentages of patients experiencing no problems, some problems, and severe problems were also broadly similar between treatment groups at subsequent visits (see Supplementary Digital Content 4B).

Outcomes by Baseline LCSS Severity. The median baseline MSS on each study arm was 60. Baseline prognostic factors were generally similar for the subgroups of patients with a median baseline MSS of at least 60 and MSS less than 60 (see Supplementary Table, Supplementary Digital Content 5). The overall survival HRs for the necitumumab plus gemcitabine-cisplatin arm versus the gemcitabine-cisplatin arm were 0.67 (p < 0.001) for patients with a baseline MSS of at least 60 and 1.06 (p = 0.547) for patients with a baseline MSS less than 60 (Fig. 3A). The respective
progression-free survival HRs were 0.69 ($p < 0.001$) for patients with a baseline MSS of at least 60 and 1.07 ($p = 0.493$) for patients with a baseline MSS less than 60 (Fig. 3B).

Among patients with a baseline MSS of at least 60, the maximum improvement over baseline in the dyspnea, pain, and quality of life items of the LCSS was statistically significantly greater for the necitumumab plus gemcitabine-cisplatin arm than for the gemcitabine-cisplatin arm (see Supplementary Table, Supplementary Digital Content 6). Also among patients with a baseline MSS of at least 60, the addition of necitumumab to gemcitabine-cisplatin statistically significantly delayed both the first worsening of pain (median 16.6 versus 5.7 months) and dyspnea (median 9.3 versus 5.7 months) as compared to the gemcitabine-cisplatin arm. Among patients with a baseline MSS less than 60, there were no significant differences in the corresponding items. For other LCSS items not shown in Supplementary Digital Content 6, there were no statistically significant differences observed in either MSS group.
Tolerability

Treatment Exposure. Data for the necitumumab plus gemcitabine-cisplatin arm are presented for the chemotherapy phase (maximum of six cycles) and for the necitumumab continuation phase separately to allow for appropriate comparison with the gemcitabine-cisplatin arm. Exposure to chemotherapy was similar in both treatment arms (see Supplementary Table, Supplementary Digital Content 7). The proportion of patients completing six cycles of therapy with gemcitabine was 55% in the necitumumab plus gemcitabine-cisplatin arm and 48% in the gemcitabine-cisplatin arm; with cisplatin, the proportion was 53% in the necitumumab plus gemcitabine-cisplatin arm and 46% in the gemcitabine-cisplatin arm. Of the 538 patients who received necitumumab plus gemcitabine-cisplatin, 275 (51%) continued on necitumumab continuation monotherapy. The maximum number of cycles of necitumumab reached by the cutoff date was 45.

Reported Adverse Events. During the chemotherapy phase of the trial, 68% of patients in the necitumumab plus gemcitabine-cisplatin arm and 62% of patients in the gemcitabine-cisplatin arm experienced grade 3 or higher adverse events; during the necitumumab continuation phase of the trial, 29% of patients experienced grade 3 or higher adverse events. Rates of treatment discontinuation due to adverse events in the chemotherapy phase of the trial were slightly higher in the necitumumab plus gemcitabine-cisplatin arm than in the gemcitabine-cisplatin arm (28% versus 25%, respectively) and low in the necitumumab continuation phase (6%) (see Supplementary Table, Supplementary Digital Content 8). Rates of adverse events with an outcome of death (excluding fatal cases of disease progression) during the chemotherapy phase were slightly lower in the necitumumab plus gemcitabine-cisplatin arm than in the gemcitabine-cisplatin arm (6% versus 7%, respectively).

To further explore safety in the chemotherapy and necitumumab continuation phases of the trial, adverse events of interest were defined on the basis of the known safety profiles of other EGFR antibodies and/or prior clinical experience with necitumumab (Table 2). More patients in the necitumumab plus gemcitabine-cisplatin arm had grade 3 or 4 hypomagnesemia (8.9% of patients in the necitumumab plus gemcitabine-cisplatin arm versus 1.1% in the gemcitabine-cisplatin arm) and grade 3 rash (5.6% versus 0.4%) during the chemotherapy phase of the trial. The grade 4 adverse events occurring at the highest rates during the chemotherapy phase of the trial were neutropenia and thrombocytopenia. The incidences of both were slightly

![Figure 2. Forest plot of hazard ratios and 95% confidence intervals for time to deterioration for the Lung Cancer Symptom Scale and Eastern Cooperative Oncology Group performance status.](https://example.com/figure2.png)
higher in the gemcitabine-cisplatin arm than in the necitumumab plus gemcitabine-cisplatin arm (neutropenia 7.9% versus 6.1%; thrombocytopenia 4.3% versus 3.2%, respectively). There were no clinically relevant differences in the rate of fatal venous or arterial thromboembolic events between treatment arms during the chemotherapy phase of the trial.

Hospitalizations. Table 3 summarizes hospitalizations of patients during both the chemotherapy and necitumumab continuation phases of the study. The percentage of patients hospitalized in general was slightly higher in the necitumumab plus gemcitabine-cisplatin arm than in the gemcitabine-cisplatin arm during the chemotherapy phase. During the necitumumab continuation phase of the trial, the percentage of patients hospitalized was much lower than during the chemotherapy phase of the trial.

Treatment-Emergent Adverse Events Leading to Hospitalization. Treatment-emergent adverse events leading to hospitalization during both the chemotherapy and necitumumab continuation phases of the trial are presented in Supplementary Digital Content 9. The percentage of patients with treatment-emergent adverse events leading to hospitalization was slightly higher in the necitumumab plus gemcitabine-cisplatin arm than in the gemcitabine-cisplatin arm (32.5% versus 29.2%). Notably, the percentage of patients with treatment-emergent adverse events leading to hospitalization in the necitumumab continuation phase of the trial was low (14.2%).

Discussion
Prolongation of life along with maintenance of HRQoL and palliation of symptoms are the major goals for treatment of advanced squamous NSCLC. The SQUIRE trial established that in a patient population with a heavy metastatic disease burden (approximately 55% of patients with metastases to >2 organ systems), generally moderate to high symptoms, and an ECOG PS of 0–2, the addition of necitumumab to first-line chemotherapy improved overall survival in patients with advanced squamous NSCLC. The findings
presented here demonstrate that the survival benefit provided by the addition of necitumumab to gemcitabine-cisplatin in the SQUIRE trial was not accompanied by impairment of patient outcomes in terms of HRQoL or tolerability. In this study, most patients in both arms of the trial were able to maintain their ECOG PS. Analysis of time to worsening of symptoms, as measured by the LCSS data and the patient-reported EQ-5D analysis, did not support a consistent or compelling difference between the two trial arms. Although the validity of HRQoL data is often threatened by missing data,27 this trial reported a high rate of compliance for completion of both assessments. The additional analyses of outcomes by baseline LCSS severity suggested that the addition of necitumumab to gemcitabine-cisplatin provided the greatest survival benefit in patients with more severe baseline LCSS scores. Moreover, the addition of necitumumab to gemcitabine-cisplatin improved key LCSS items among patients with a higher severity of baseline LCSS scores. This

### Table 2. Select Treatment-Emergent Adverse Events of Special Interest Occurring in the SQUIRE Safety Population

<table>
<thead>
<tr>
<th>Event Categorya</th>
<th>Chemotherapy Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr 1</td>
<td>Gr 2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4.1</td>
<td>15.2</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Anemia</td>
<td>5.9</td>
<td>23.8</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5.2</td>
<td>6.1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15.6</td>
<td>18.2</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>9.5</td>
<td>11.7</td>
</tr>
<tr>
<td>Skin reactions</td>
<td>39.2</td>
<td>32.3</td>
</tr>
<tr>
<td>Rash</td>
<td>39.6</td>
<td>30.1</td>
</tr>
<tr>
<td>Hypersensitivity/infusion related reaction</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>3.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Interstitial lung disease (pneumonitis)</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Arterial thromboembolic events</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Venous thromboembolic events</td>
<td>1.3</td>
<td>2.6</td>
</tr>
</tbody>
</table>

aAdverse events of possible relevance to treatment, according to either composite categories or preferred terms (febrile neutropenia only).

SQUIRE, First-Line Treatment of Participants With Stage IV Squamous Non–Small Cell Lung Cancer With Necitumumab and Gemcitabine-Cisplatin; Neci + Gem-Cis, necitumumab + gemcitabine-cisplatin; Gem-Cis, gemcitabine-cisplatin; Grade.

### Table 3. Summary of Hospitalizations in the SQUIRE Safety Population

<table>
<thead>
<tr>
<th>Chemotherapy Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neci + Gem-Cis (n = 538)</td>
</tr>
<tr>
<td>No. patients hospitalized, n (%)</td>
<td>196 (36.4)</td>
</tr>
<tr>
<td>Hospitalizations due to an AE</td>
<td>167 (31.0)</td>
</tr>
<tr>
<td>Total duration of hospitalization for any reason, d</td>
<td>14.4 (14.08)</td>
</tr>
<tr>
<td>Median</td>
<td>11.0</td>
</tr>
<tr>
<td>Total duration of hospitalization due to AEs, d</td>
<td>12.8 (11.34)</td>
</tr>
<tr>
<td>Median</td>
<td>9.0</td>
</tr>
<tr>
<td>No. hospitalizations due to AEs, n (%)</td>
<td>114 (21.2)</td>
</tr>
<tr>
<td>2</td>
<td>40 (7.4)</td>
</tr>
<tr>
<td>3</td>
<td>9 (1.7)</td>
</tr>
<tr>
<td>≥4</td>
<td>4 (0.7)</td>
</tr>
</tbody>
</table>

aEach patient may have more than one hospitalization.

SQUIRE, First-Line Treatment of Participants With Stage IV Squamous Non–Small Cell Lung Cancer With Necitumumab and Gemcitabine-Cisplatin; Neci + Gem-Cis, necitumumab + gemcitabine-cisplatin; Gem-Cis, gemcitabine-cisplatin; SD, standard deviation; AE, adverse event.
symptomatic efficacy is of particular interest for the squamous lung cancer patient population as these patients tend to experience a high level of co-morbidities.\textsuperscript{3,28}

The balance among toxicity, efficacy, and quality of life plays a critical role in determining a clinically meaningful treatment outcome.\textsuperscript{8} It is of note that patients in the gemcitabine-cisplatin arm of this study were permitted to undergo study treatment for a maximum of six cycles, whereas patients in the necitumumab plus gemcitabine-cisplatin arm could receive a maximum of six cycles of chemotherapy in combination with necitumumab, and patients with a response of stable disease or better could continue to receive single-agent necitumumab until withdrawal criteria were met. As a result, the treatment period was longer in the necitumumab plus gemcitabine-cisplatin arm. The addition of necitumumab to chemotherapy did not affect the administration of chemotherapy at the recommended dose and schedule, did not cause an increase in the rate of discontinuation due to drug-related toxicities, and did not cause an increase in adverse events (with the exception of expected EGFR inhibitor class effects—skin reactions/rash and hypomagnesemia).\textsuperscript{29–32} Furthermore, there were no notable differences between arms of the trial in the rates of grade 4 adverse events, which are of particular interest because they tend to incur higher cost owing to their association with hospitalizations and other resource use.

This report combines physician-reported adverse event collection (an objective evaluation of disease- and symptom-related toxicities), ECOG PS and patient-reported outcomes (a reflection of symptom burdens and functional changes directly experienced by patients) to capture a comprehensive profile of the impact of necitumumab treatment. The well-tolerated safety profile and the LCSS and EQ-5D analyses show that adding necitumumab to gemcitabine-cisplatin did not have an impact, overall, on the deterioration of patients’ HRQoL and suggest that the most benefit is obtained by patients with higher severity of symptoms or poorer overall quality of life at the start of treatment.

Acknowledgments

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2016.03.002.

References


