Original Study

An Open-Label, Randomized, Controlled Phase II Study of Paclitaxel-Carboplatin Chemotherapy With Necitumumab Versus Paclitaxel-Carboplatin Alone in First-Line Treatment of Patients With Stage IV Squamous Non–Small-Cell Lung Cancer

David R. Spigel,[1] Alexander Luft,[2] Henrik Depenbrock,[3] Rodryg Ramlau,[4] Mazen Khalil,[5] Joo-Hang Kim,[6] Carlos Mayo,[7] Grace Yi Chao,[7] Coleman Obasaju,[8] Ronald Natale[9]

Abstract

This open-label, randomized, phase II study was intended to compare paclitaxel-carboplatin with necitumumab versus paclitaxel-carboplatin alone for the first-line treatment of advanced squamous non–small-cell lung cancer. The combination of necitumumab with chemotherapy resulted in an objective response rate of 48.9% versus 40.0% for chemotherapy alone. There were no unexpected safety concerns for an epidermal growth factor receptor monoclonal antibody.

Background: The combination of necitumumab with gemcitabine-cisplatin significantly improved overall survival (OS) in patients with stage IV squamous non–small-cell lung cancer (NSCLC), in the phase III SQUamous NSCLC treatment with the Inhibitor of EGF REceptor (SQUIRE) trial. Paclitaxel-carboplatin was selected as an alternative standard of care in the current phase II study. **Patients and Methods:** Patients were randomized (stratified according to Eastern Cooperative Oncology Group performance status and sex) 2:1 to $\leq$ six 3-week cycles (Q3W) of paclitaxel and carboplatin with or without necitumumab. Chemotherapy was paclitaxel 200 mg/m^2 on day 1 Q3W and carboplatin area under the curve 6 on day 1 Q3W. Necitumumab 800 mg, on days 1 and 8, was continued until disease progression or intolerable toxicity occurred. The primary end point was objective response rate (ORR) on the basis of Response Evaluation Criteria In Solid Tumors version 1.1. **Results:** One hundred sixty-seven patients were randomized to the necitumumab-containing arm (n = 110) or the chemotherapy-only arm (n = 57). The combination of necitumumab with chemotherapy resulted in an ORR of 48.9% versus 40.0%. Median progression-free survival and OS were 5.4 versus 5.6 months (hazard ratio [HR], 1.0) and 13.2 versus 11.2 months (HR, 0.83; P = .379) in each treatment arm, respectively. Disease control rate was 87.2% versus 84.0%. Grade $\geq$ 3 adverse events typically associated with epidermal growth factor receptor (EGFR) monoclonal antibodies showing a $>$ 2% increase were hypomagnesemia (5.7% vs. 0) and rash (2.8% vs. 0). Any Grade thromboembolic events occurred in $<$ 4% of patients in either arm. **Conclusion:** The results of our study support previously reported results that the combination of necitumumab with chemotherapy improves survival in patients with advanced squamous NSCLC and shows a safety profile consistent with that of EGFR monoclonal antibodies.

Clinical Lung Cancer, Vol. ■, No. ■, ■-■ © 2017 Published by Elsevier Inc.
Keywords: Anti-EGFR, Efficacy, Monoclonal antibody, Safety, Targeted therapy

ClinicalTrials.gov: NCT01769391.

[1]Sarah Cannon Research Institute, Nashville, TN
[2]Leningrad Regional Clinical Hospital, St Petersburg, Russia
[3]Lilly Deutschland, Bad Homburg, Germany
[4]Department of Oncology, Poznań University of Medical Sciences, Poznań, Poland
[5]Clopton Clinic, Jonesboro, AR
[6]CHA Bundang Medical Center, CHA University, Gyeonggi-do, Korea
[7]Eli Lilly and Company, Bridgewater, NJ
[8]Eli Lilly and Company, Indianapolis, IN
[9]Cedars-Sinai Medical Center, Los Angeles, CA

Submitted: Dec 1, 2016; Revised: Feb 8, 2017; Accepted: Feb 21, 2017

Address for correspondence: David R. Spigel, MD, Medical Oncology, Sarah Cannon Research Institute, 250 25th Ave N Ste 110, Nashville, TN 37203
Fax: 615-340-1542; e-mail contact: dspigel@tnonc.com

1525-7304/$ - see frontmatter © 2017 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.cllc.2017.02.002

Introduction

Patients with squamous cell carcinoma represent approximately 25% to 30% of all patients affected by non–small-cell lung cancer (NSCLC) and have a particularly poor prognosis.[1,2] In contrast to advancements seen in the treatment of nonsquamous NSCLC over the past 2 decades, therapeutic progress in advanced squamous cell NSCLC has remained mostly unchanged and represents a high unmet medical need.[3,4] First-line therapy for patients with squamous cell NSCLC remains in general a platinum-based doublet of cisplatin or carboplatin combined with gemcitabine, vinorelbine, or a taxane.

The combination of bevacizumab with carboplatin and paclitaxel significantly improved the overall survival (OS) of patients with NSCLC,[5] but because of early safety concerns, bevacizumab is not indicated for patients with squamous histology.[6] Bevacizumab and pemetrexed are currently available for first-line and/or maintenance treatment of nonsquamous cell NSCLC, having been associated with significant survival benefits.[7,8] Recently, the Food and Drug Administration (FDA) approved nivolumab, pembrolizumab, and ramucirumab in combination with docetaxel as additional second-line treatment options for patients with squamous cell NSCLC whose disease progresses after first-line therapy.[9-13] However, the proportion of patients who continue to second-line treatment can be less than 50%.[14,15]

The identification of numerous molecular targets in the tumors of patients with squamous cell NSCLC has largely not resulted in regulatorily approved molecular-targeted agents.[2-4] However, mutations in the epidermal growth factor receptor (EGFR) have proven to be predictive of outcome in response to EGFR tyrosine kinase inhibitors.[16,17] Whereas mutations in the EGFR occur in approximately 19% to 48% of adenocarcinoma cases, they occur in less than 5% of squamous cell NSCLC tumors.[18] Gene amplification and overexpression of EGFR protein tend to be at least as common in squamous cell NSCLC as in the nonsquamous population.[19] The chimeric EGFR antibody cetuximab when combined with cisplatin and vinorelbine improved response rates and OS in patients with NSCLC, with the greatest survival benefit observed in the subgroup of patients with squamous histology (hazard ratio [HR], 0.8; 95% confidence interval [CI], 0.64-1.00).[20] However, the combination of cetuximab was accompanied by a higher incidence of Grade 3 or 4 febrile neutropenia than cisplatin and vinorelbine alone. Cetuximab treatment was not approved for a NSCLC indication by the European Medicines Agency (EMA) because of a lack of a positive benefit/risk profile.[21] Cetuximab treatment has also not been approved for this indication elsewhere.

Necitumumab is a second-generation recombinant, human immunoglobulin (Ig) G1 anti-EGFR monoclonal antibody that binds to the EGFR with high affinity, competitively inhibiting ligand binding and thereby preventing receptor activation and downstream signaling. In the phase III SQUamous NSCLC treatment with the Inhibitor of EGF REceptor (SQUIRE) trial, patients with stage IV metastatic squamous cell NSCLC showed a statistically significant improvement in OS (HR, 0.84; $P = .01$) with a median survival of 11.5 months when receiving necitumumab in combination with gemcitabine and cisplatin as a first-line treatment, versus 9.9 months for those treated with chemotherapy alone.[22] On the basis of this trial, the FDA and EMA approved necitumumab for the treatment of advanced squamous cell NSCLC.[23,24]

In this phase II study, we assess the efficacy and safety of necitumumab combined with paclitaxel and carboplatin as first-line treatment for patients with advanced squamous cell NSCLC. This study enabled necitumumab to be studied with a different platinum doublet, from that investigated in the SQUIRE trial, and hence facilitates the generation of data with a taxane-platinum doublet.

Patients and Methods

Eligibility Criteria

Chemotherapy-naive patients (18 years of age or older) with histologically or cytologically confirmed stage IV (American Joint Committee on Cancer Staging Manual, 7th edition) squamous cell NSCLC were eligible. Other inclusion criteria included measurable disease at time of study entry defined according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, an estimated life expectancy $\geq$ 12 weeks, and, in the judgement of the investigator, the ability to complete at least 2 cycles of treatment. Patients were required to have National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0, Grade $\leq$ 1 for all clinically significant toxic effects of previous chemotherapy, surgery, radiotherapy, or hormonal therapy (with the exception of alopecia). Adequate hepatic (total bilirubin $\leq$ 1.5 times the upper limit of normal [ULN], and aspartate transaminase and alanine transaminase $\leq$ 5.0 times the ULN in the presence of liver metastases or $\leq$ 2.5 times the ULN in the absence of liver metastases), renal (serum creatinine $\leq$ 1.2 times the ULN or calculated creatinine clearance $\geq$ 50 mL/min), and hematological (white blood cell count $\geq$ 3000/μL, absolute neutrophil cell count $\geq$ 1500/μL, hemoglobin $\geq$ 9.5 g/dL, and platelets $\geq$ 100,000/μL) functions were also required. The availability of archived tumor tissue for the analysis of biomarkers was also an inclusion criterion.

Key exclusion criteria were: previous anticancer therapy with monoclonal antibodies, signal transduction inhibitors, or any therapies targeting the EGFR, vascular endothelial growth factor (VEGF), or VEGF receptor, major surgery in the 4 weeks before randomization, chest irradiation within the 12 weeks before randomization (except palliative irradiation of bone lesions), the presence of brain metastases that were symptomatic or required ongoing treatment with steroids or anticonvulsants, history of arterial or venous embolism, or myocardial infarction within 6 months before randomization, clinically relevant coronary artery disease or uncontrolled congestive heart failure (New York Heart Association III or IV), NCI-CTCAE Grade $\geq$ 2 peripheral neuropathy, history of drug allergy, lactation/pregnancy, concomitant infections, and any other serious uncontrolled medical disorders that could limit the patient's ability to consent to or complete the study. Patients with active malignancy other than adequately treated basal cell carcinoma of the skin or preinvasive carcinoma of the cervix, or previous history of malignancy other than NSCLC were eligible, provided freedom from disease for $\geq$ 3 years.

The study protocol was approved by ethical review boards at each of the participating investigational sites and was conducted in