An Open-Label, Multicenter, Randomized, Phase II Study of Cisplatin and Pemetrexed With or Without Cixutumumab (IMC-A12) as a First-Line Therapy in Patients With Advanced Nonsquamous Non-Small Cell Lung Cancer

Silvia Novello, MD, PhD, Giorgio Scagliotti, MD, PhD, Gilberto de Castro, Jr., MD, PhD, Murat Kiyik, MD, Rubén Kowalszyn, MD, MSc, Karl-Matthias Deppermann, MD, Edurine Arriola, MD, PhD, Lionel Bosquee, MD, Ruslan D. Novosiydly, MD, PhD, Tuan S. Nguyen, PhD, Amelie Forest, MSc, Shande Tang, PhD, Siva Rama Prasad Kambhampati, PhD, Jan Cosaert, MD, Martin Reck, MD, PhD

Abstract

Introduction: Type 1 insulin-like growth factor receptor is deregulated in solid tumors. Cixutumumab, a monoclonal antibody that inhibits the activity of type 1 insulin-like growth factor receptor, was investigated in combination with pemetrexed/cisplatin in the frontline setting.

Methods: In this open-label, phase II study, patients with stage IV nonsquamous NSCLC and a performance status of 0 to 1 were randomized (1:1) to receive 20 mg/kg cixutumumab, 500 mg/m² pemetrexed, and 75 mg/m² cisplatin (cixutumumab [n = 87]) or pemetrexed and cisplatin (control [n = 85]). Eligible patients received...
pemetrexed-based maintenance therapy with cixutumumab (cixutumumab arm) or without it (control arm). The primary end point was progression-free survival. Secondary end points assessed overall survival, objective response rate, and safety. Survival was analyzed by the Kaplan-Meier method and Cox proportional hazard model. Exploratory correlative analyses were also performed.

Results: The mean age of the intent-to-treat population (n = 172) was 59 years (range 32–83). Median progression-free survival was 5.45 months with cixutumumab versus 5.22 months in the control (hazard ratio = 1.15, 95% confidence interval: 0.81–1.61; p = 0.44). Median overall survival was 11.33 months with cixutumumab versus 10.38 months in the control (hazard ratio = 0.93, 95% confidence interval: 0.64–1.36). Objective response rate did not differ between treatments (p = 0.338). Grade 3 or 4 hyperglycemia occurred at a higher rate with cixutumumab than in the control (9.4% versus 1.2%). One death possibly related to cixutumumab occurred.

Conclusions: Efficacy was not improved in patients with nonsquamous NSCLC when cixutumumab was added to pemetrexed/cisplatin. Combination therapy was well tolerated and no new safety concerns were reported.

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Keywords: Cixutumumab; IMC-A12; First-line therapy; Pemetrexed; NSCLC

Introduction

Nonsquamous (NSq) NSCLC accounts for most patients with NSCLC and often presents as advanced/metastatic disease at diagnosis. On average, the median survival time of untreated patients with advanced NSq NSCLC is approximately 4 months after diagnosis. However, for patients with good performance status, first-line platinum-based chemotherapy improves both survival and quality of life.1

Platinum-based doublets have shown no significant differences in objective response rate (ORR), progression-free survival (PFS), or overall survival (OS).2,3 Other clinical factors not considered with traditional chemotherapy, such as histologic subtype, may also influence clinical outcome. Patients with advanced NSCLC with a nonsquamous histologic subtype benefited more from pemetrexed/cisplatin than cisplatin/gemcitabine in terms of OS (hazard ratio [HR] 0.81; p = 0.005), whereas PFS was similar between arms.4 This evidence provided a rationale for the current patient population in addition to the need for effective treatments for patients with NSq NSCLC who may not have oncogenic alterations.

It is clear that type 1 insulin-like growth factor (IGF-I) receptor (IGF-IR) has significant implications in NSCLC. Cixutumumab (IMC-A12 [Eli Lilly and Company, Indianapolis, IN]), a human immunoglobulin G monoclonal antibody, blocks IGF-IR activity and inhibits tumor survival and growth in numerous solid tumor types, including lung cancer, and in human tumor xenograft models in vivo, both alone5 and combined with chemotherapy.6 However, the clinical benefit of adding cixutumumab to chemotherapy in patients with advanced NSq NSCLC is unknown.

This open-label, multicenter, randomized phase II study assessed whether adding cixutumumab to pemetrexed/cisplatin was superior to pemetrexed/cisplatin as first-line therapy in patients with advanced NSq NSCLC. Biomarkers potentially predictive of cixutumumab efficacy were also evaluated.

Materials and Methods

Patients and Study Design

An overview of the study design and treatment plan has been fully described in Figure 1. Before enrollment, an institutional review board reviewed and approved the study protocol. Patients who met the eligibility criteria (Fig. 1) were enrolled in the study. Intravenous (IV) cixutumumab infusions were administered first, followed by an IV pemetrexed infusion 1 hour later and an IV cisplatin infusion 30 minutes after pemetrexed. All patients received vitamin B12, folic acid supplementation, and prophylactic dexamethasone. Patients continued maintenance therapy until disease progression, unacceptable toxicity, noncompliance, or withdrawal of consent.

Statistical Analysis

A superiority test comparing PFS was planned for the patients (n = 156). A median PFS of 5.3 months in the control arm was assumed with an expected median PFS of 7.16 months in the cixutumumab arm (HR of cixutumumab/control for PFS = 0.74). With a power of 80% (one-sided significance level of 20%, 1:1 ratio) to detect an HR of 0.74, 125 events were required for analysis.

The HR of cixutumumab/control for PFS was determined using the Cox’s proportional hazard model. PFS, OS, and time to progressive disease were estimated using the Kaplan-Meier method and differences assessed by log-rank test. The ORRs were compared using Fisher’s exact test. Radiographic imaging assessed the percentage change in tumor size from baseline to the end of cycle 2; comparisons were analyzed using a t test. Safety was assessed using the Common Terminology Criteria for Adverse Events, version 4.0.
Exploratory correlative research and a pharmacokinetics (PK) analysis of cixutumumab were also performed (see Supplemental Digital Content for analysis methods).

Results

Clinical Efficacy

A total of 172 patients were randomized (cixutumumab [n = 87] versus control [n = 85]). Patients discontinued treatment in the cixutumumab and control arms because of progressive disease (40% and 37%, respectively), adverse events (AEs) (20% and 15%, respectively), and death (11% for both arms). Baseline patient and disease characteristics (Table 1) of the intent-to-treat population were similar between arms.

The median PFS was 5.45 months with cixutumumab and 5.22 months with control (HR = 1.15, 95% confidence interval [CI]: 0.81–1.61), with no statistically significant difference between arms (Fig. 2A). Similarly, no statistically significant difference in OS between arms was observed, but the median OS (Fig. 2B) was numerically higher with cixutumumab than control (11.33 months versus 10.38 months, HR = 0.93, 95% CI: 0.64–1.36).

The ORR rates were 37.9% and 30.6% with cixutumumab and control, respectively (p = 0.338). Best tumor responses were similar between arms (Table 2), with more patients experiencing a partial response (37.9% versus 30.6%) or progressive disease (16.1% versus 12.9%) with cixutumumab than control. There was a similar percentage of clinical benefit responders between arms (p = 0.511).

Safety

The safety analyses included 166 patients (cixutumumab [n = 85] versus control [n = 81]). As shown in Table 3, grade 3 or 4 treatment-emergent AEs possibly related to treatment occurred more frequently with cixutumumab (56.5%) than control (43.2%). As expected, hyperglycemia (all grades) occurred at a higher rate with cixutumumab (41.2%) than control (7.4%). Dehydration (all grades), a known effect of cisplatin treatment, was also more frequently reported with cixutumumab (17.7%) than control (6.2%).

Rates of discontinuation due to serious AEs (SAEs) possibly related to any study drug were similar between arms (cixutumumab, 7.1%; control, 8.6%). Three patients

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**Table 1**

**Inclusion Criteria**
- ≥ 18 years of age
- Histologic or cytologic NSq-NSCLC diagnosis
- ECOG PS 0 or 1
- Diagnosis of Stage IV NSq-NSCLC or metastatic, recurrent disease
- Adequate bone marrow reserve, renal and hepatic function, and fasting serum glucose and hemoglobin A1c levels

**Exclusion Criteria**
- Other cancer diagnoses
- Previous chemotherapy
- Treatment with pemetrexed or other IGF-IR/EGFR agents
- Pregnancy
- Leptomeningeal disease
- Diabetes mellitus
- Other intercurrent illnesses/infections
experienced SAEs possibly related to cixutumumab that led to discontinuation (one SAE each of myocardial infarction, pancytopenia, and sepsis). Four patients in each arm died and the deaths were considered possibly related to any study drug; one death (due to sepsis) was possibly cixutumumab related.

PK

PK analysis of cixutumumab was performed using available serum concentration–time data (n = 83 [see Supplementary Text]). Overall, serum concentrations of cixutumumab increased after each cixutumumab infusion and accumulation of cixutumumab was observed (Supplementary Fig. 1). Cixutumumab clearance was low (0.02 L/h) and it had a long terminal elimination half-life (8 days [see Supplementary Table 1]).

Exploratory Correlative Analyses

Circulating and tumor-specific candidate biomarkers were also evaluated (Supplementary text and Supplementary Tables 2–5). No statistically significant interactions were demonstrated; however, compared with the control arm, numerically longer PFS, OS, or both PFS and OS were observed in cixutumumab-treated patients with low circulating total IGF-I levels (25th percentile cutoff), tumor protein p53 gene (TP53) mutations, and high type 1 insulin-like growth factor receptor/insulin receptor ratio (75th percentile cutoff) in tumor tissue, respectively.

Discussion

This phase II study failed to support the hypothesis that adding cixutumumab to pemetrexed/cisplatin was superior to pemetrexed/cisplatin alone as first-line therapy in patients with advanced, metastatic NSq NSCLC. No new safety concerns were reported. Similarly, studies of cixutumumab combined with other chemotherapies as a first-line therapy in other solid tumors have also found little to no benefit from adding cixutumumab.7–8

The lack of efficacy observed may be due, at least in part, to the administration sequence of IGF-IR inhibitors and chemotherapeutic agents.9 In breast cancer cells, growth inhibition improves when chemotherapy (doxorubicin and gemcitabine) is administered before IGF-IR inhibition, and an opposite effect occurs with the reverse administration10,11 Here, cixutumumab was administered first followed by pemetrexed/cisplatin, all on the same day.

The addition of cixutumumab to pemetrexed/cisplatin chemotherapy did not lead to any significant increase in toxicity, except for hyperglycemia, which is common among patients receiving cixutumumab. Similar safety profiles have been observed when cixutumumab was combined with mitotane7 and gemcitabine and erlotinib.12 Dose-limiting toxicities were reported when erlotinib and cixutumumab were combined in patients with NSCLC, a finding supported when other anti–IGF-IR monoclonal antibodies were unsuccessfully combined with full-dose erlotinib in patients with NSCLC.8

Clinical biomarkers may also predict clinical outcomes for IGF-IR–directed therapy. Because IGF-IR monoclonal antibodies failed to demonstrate significant clinical benefit in general patient populations,13 studies are exploring the relationship between circulating biomarkers and clinical outcome. Elevated insulin-like growth factor binding protein-1 correlated with improved PFS (p = 0.009) and OS (p = 0.003) in patients with advanced hepatocellular
carcinoma who were administered cixutumumab. In addition, low IGF-I baseline levels were associated with significantly shorter OS with a figitumumab combination therapy regimen versus control ($P = 0.01$), whereas patients with high baseline levels of glycosylated hemoglobin had a lower median OS with combined figitumumab therapy versus control ($p = 0.05$). On the basis of our exploratory biomarker analysis, numerically longer PFS, OS, or both PFS and OS were recorded in cixutumumab-treated patients with low circulating total IGF-I levels, TP53 mutations, and high tumor IGF-IR/IR ratio, respectively. Of note, the biomarker analysis was limited due to the small sample size in subgroups that were defined by marker class by treatment and a high censoring rate in OS.

Figure 2. (A) Progression-free survival and (B) overall survival Kaplan-Meier curves for the cixutumumab (red) and control (blue) treatment arms in the intent-to-treat population. vs, versus; HR, hazard ratio; CI, confidence interval.
In summary, cixutumumab added to pemetrexed/cisplatin does not improve clinical outcome as measured in PFS in patients with NSq NSCLC as a first-line therapy. Our findings corroborate the work of others and suggest that IGF-IR inhibition is largely ineffective in patients with NSq NSCLC. However, because none of the IGF-IR clinical studies enriched for a specific biomarker population, it is plausible that only select patients with NSq NSCLC benefit from the anti–IGF-IR antibodies. The predictive potential of the IGF-IR/IR ratio, TP53 mutational status, and total IGF-I levels warrant further investigation in clinical trials with a biomarker-driven design.

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Table 2. Best Overall Tumor Response

<table>
<thead>
<tr>
<th>Response</th>
<th>Cixutumumab Arm (n=87)</th>
<th>Control Arm (n=85)</th>
<th>p Value (Fisher’s Exact Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response, n</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Partial response, n</td>
<td>33 (37.9 (27.7-48.1)</td>
<td>26 (30.6 (20.8-40.4))</td>
<td>-</td>
</tr>
<tr>
<td>Stable disease, n</td>
<td>25 (28.7 (19.2-38.2)</td>
<td>35 (41.2 (30.7-51.6))</td>
<td>-</td>
</tr>
<tr>
<td>Progressive disease, n</td>
<td>14 (16.1 (8.4-23.8)</td>
<td>11 (12.9 (5.8-20.1))</td>
<td>-</td>
</tr>
<tr>
<td>Not assessed, n (%)</td>
<td>15 (17.2)</td>
<td>13 (15.3)</td>
<td>-</td>
</tr>
<tr>
<td>Overall response rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR + PR responders, n</td>
<td>33 (37.9 (27.7-49.0)</td>
<td>26 (30.6 (21.0-41.5))</td>
<td>0.338</td>
</tr>
<tr>
<td>% (95% CI, exact method)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease control rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR+PR+ stable disease, n</td>
<td>58 (66.7 (55.7-76.4))</td>
<td>61 (71.8 (61.0-81.0))</td>
<td>0.511</td>
</tr>
<tr>
<td>% (95% CI, exact method)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; CR, complete response, PR, partial response.

Table 3. Treatment-Emergent AEs Possibly Related to Any Treatment Reported in at Least 10% of Patients (Safety Population)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cixutumumab Arm (n=85)</th>
<th>Control Arm (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 TEAE</td>
<td>82 (96.5)</td>
<td>39 (45.9)</td>
</tr>
<tr>
<td>CTCAE Term</td>
<td>All Grades</td>
<td>Grade</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Anemia</td>
<td>24 (28.2)</td>
<td>8 (9.4)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>23 (27.1)</td>
<td>6 (7.1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (16.5)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Creatinine level increased</td>
<td>8 (9.4)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>15 (17.7)</td>
<td>4 (4.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (17.7)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33 (38.8)</td>
<td>7 (8.2)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>35 (41.2)</td>
<td>7 (8.2)</td>
</tr>
<tr>
<td>Mucositis, oral</td>
<td>22 (25.9)</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>18 (21.2)</td>
<td>4 (4.7)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>25 (29.4)</td>
<td>12 (14.1)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>15 (17.6)</td>
<td>4 (4.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30 (35.3)</td>
<td>7 (8.2)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>10 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>11 (12.9)</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Data are reported as n (%) for the highest-grade treatment-emergent adverse event per patient. AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.
**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.2016.07.013.

**References**


