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Randomized phase II trial of cixutumumab alone or with cetuximab for refractory recurrent/metastatic head and neck squamous cell carcinoma☆

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ABSTRACT

Objectives: Cixutumumab (CIX) and cetuximab (CET) monoclonal antibodies block ligand-binding to insulin-like growth factor-1 receptor (IGF-1R) and epidermal growth factor receptor (EGFR) respectively. The objective of this study was to assess the efficacy of CIX alone or combined with CET in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) patients.

Methods: In this open-label phase II trial, 91 R/M HNSCC patients who progressed within 90 days of platinum-based chemotherapy, were randomized to CIX 10 mg/kg alone or with CET 500 mg/m^2 every 2 weeks. Patients were stratified by prior CET use. The primary endpoint was median progression-free survival (PFS). Exploratory biomarker assessments included relevant markers on archival tumor and serial cytokine/angiogenic-factor profiles in blood.

Results: Forty-seven patients were treated with CIX monotherapy and 44 with combination. The median PFS was 1.9 and 2.0 months and clinical benefit rate (complete or partial responses and stable disease) was 5.9% and 15.3%, respectively. There was no exacerbation of CET toxicity by concurrent CIX exposure. Higher tumor expression of IGF-1 was associated with improved PFS in the CIX + CET arm while increased p-EGFR expression correlated with shorter PFS in patients receiving single agent CIX. Higher serum baseline levels of IGF-1 and IGFBP-3 correlated with improved PFS and overall survival (OS) in the CIX arm. Neither regimen resulted in improved PFS or OS compared to historical data with CET alone.

Conclusion: The results of this study do not support the use of cixutumumab alone or with cetuximab in unselected patients with R/M HNSCC.

Introduction

Cetuximab, a human-murine monoclonal antibody targeting the epidermal growth factor receptor (EGFR), is the only targeted therapy that has shown meaningful clinical activity and is approved for the treatment of head and neck squamous cell carcinoma (HNSCC). In the recurrent/metastatic (R/M) setting, it can be used in first line combined with platinum and 5-fluorouracil, or as single agent after progression on

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first line platinum-based chemotherapy, leading to an overall response rate (ORR) of 13% and disease control rate of 46% [1]. To date, no predictive biomarkers of response to cetuximab have been identified, however, there is nonclinical evidence that the activation of the insulin-like growth factor (IGF) axis represents a mechanism of resistance to this agent [2,3].

The IGF axis, composed of the IGF type 1 receptor (IGF-1R), its ligands IGF-1 and IGF-2, and a family of six ligand-binding proteins regulates cell survival, proliferation, migration and differentiation [4,5]. Dysregulated signaling through IGF-1R has been linked to proliferation, survival, angiogenesis, and invasion in cancer cells [6–8]. The IGF-1R shares common intracellular signaling pathways with the EGFR and IGF-1R signaling has been shown to mediate resistance to EGFR targeted drugs in histologically diverse human cancer cell lines. In HNSCC, IGF-1R blockade leads to an increase in apoptosis *in vitro*, and the combination of IGF-1R and EGFR inhibitors results in an enhanced anti-neoplastic effect as compared to either drug alone [7,9–11].

Cixutumumab (IMC-A12) is a fully human IgG1 monoclonal antibody targeted against IGF-1R. Its biological activities include blocking of IGF-1 and IGF-2 binding and signaling through the receptor. Cixutumumab (CIX) binding to IGF-1R also leads to a reduction in cell surface receptor density due to internalization and degradation of the complex [12]. In nonclinical studies, CIX has demonstrated antiproliferative activity in human cancer cell lines and xenograft models. In phase 1 clinical studies, CIX has shown clinical benefit in patients with malignancies unresponsive to standard therapy [13,14]. The current study was designed to test the hypothesis that inhibiting IGF-1R with CIX, either alone, or in combination with CET would be more effective than CET alone in patients with R/M HNSCC.

Patients and methods

Patient selection

Patients with histologically confirmed R/M squamous cell carcinoma of the oropharynx, hypopharynx, larynx, or oral cavity were eligible. Recurrence must have occurred during or within 90 days after previous platinum-based chemotherapy. Previous cetuximab was permitted if the patient had responded to this treatment and time to recurrence from prior cetuximab was > 90 days. Patients were required to have measurable disease, adequate hematologic and organ function, a life expectancy > 3 months, an ECOG performance status of 0–2, and a fasting serum glucose level of < 120 mg/dL.

Study design and treatment schedule

This was an open-label, multicenter, safety and activity estimating phase II, parallel group, two-arm study of patients with R/M HNSCC. All patients signed informed consent before study entry. Patients were randomly allocated to CIX monotherapy or CIX plus CET combination with stratification by prior CET therapy. The primary endpoint was median progression-free survival (PFS), using the historical PFS of 3 months with CET-based therapy in patients with R/M HNSCC as the control [15,16]. Both drugs were given intravenously every 2 weeks and a treatment cycle was defined as 2 successive infusions. CIX was administered at 10 mg/kg and CET administered at 500 mg/m^2. Treatment was continued until evidence of progressive disease, unacceptable toxicity, or consent withdrawal.

Treatment evaluation

Safety assessments including physical exam, vital signs, and adverse event monitoring were made every 2 or 4 weeks, at treatment discontinuation, and at a 30-day post-treatment follow-up visit.

The National Cancer Institute Common Toxicity Criteria of Adverse Events (NCI-CTCAE) v3.0 was used for the classification of adverse events. CIX toxicity of grade 4 was managed with dose delay and resumption at a lower dose, as was CIX grade 3 toxicity not adequately controlled with supportive care. Discontinuation of treatment was mandatory after recurrence of grade 4 non-hematologic toxicity despite dose reduction, after two recurrences of grade 3 toxicity with successive dose reductions, or after any first instance of grade ≥ 3 hypersensitivity.

For hyperglycemia, oral hypoglycemic agents were used for grade 1–2. For grade 3, CIX was held until glucose was < 300 mg/dL and symptoms resolved. Dose of CIX was reduced to 8 mg/kg if the glucose remained between 200 and 300 after stabilization. For grade 4, CIX was held until glucose was consistently < 300 mg/dL on a stable insulin regimen and symptoms resolved. CIX was then resumed at 8 mg/kg. For grade 1–3 acneiform rash, full dose CET continued with addition of supportive treatment. For grade 4 acneiform rash, CET was delayed until improvement to < grade 3. For other grade 3–4 non-hematologic toxicity from CET, therapy was held until recovery to grade 1 with dose reduction at re-treatment. A safety monitoring committee (at Eli Lilly) examined study data at regular intervals. Tumor assessments were made every 8 weeks by CT or MRI imaging. Patients were evaluated for response according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0).

Statistical methods

We utilized the data from the initial report of cetuximab monotherapy with median progression-free survival (PFS) of 85 days as the historical control for this trial [17]. The final publication of these data reported a median PFS of 70 days [1]. The protocol was in final version when these data became available and was not re-designed. The primary study objective was to demonstrate an improvement in median PFS with either regimen from 3.0 months (with CET alone) to 4.5 months. With a 1-sided 5% type I error rate, and assuming an exponential distribution for PFS, a minimum of 45 patients would need to be enrolled in a study arm to achieve 80% power to detect this difference. The primary efficacy analysis was performed according to a modified Intent-to-Treat principle, and included all randomized patients who received either treatment regardless of eligibility. The Kaplan-Meier method was used to calculate medians and confidence intervals for PFS. In addition, a comparison between treatment arms was performed using the log-rank test, although the study was underpowered for detecting a difference. Secondary endpoints were ORR, 6-month PFS rate, median overall survival (OS), 6-month survival rate, and duration of overall response (DoR). For secondary endpoints, informal comparisons between treatment arms was calculated using the log-rank test, or in the case of ORR and 6-month PFS, using Fisher's exact test. ORR was calculated with 90% confidence intervals. The safety analysis included all patients who received any treatment.

Biomarker evaluation

Blood samples were collected for biomarker analysis before drug administration on cycle 1 days 1 and 15, on cycle 2 day 1, and at the end of treatment. Serum cytokines and angiogenic factors (CAFs) and IGF axis proteins profiling were performed with a multiplex bead assay and enzyme linked immunosorbent assay (ELISA). Markers were analyzed by mean, median, and quartiles.

Archival tumor specimens were obtained either at the time of diagnosis or at recurrence. Tumor biomarkers were assessed by immunohistochemistry (IHC) using histology sections obtained from FFPE samples as detailed in the Supplement Material. The immunostainings were quantified using a 4-value intensity score (0, 1+, 2+, and 3+) and the percentage (0–100%) of tumor cells with reactivity in each core. The final score was obtained by multiplying the intensity and reactivity extension values (range, 0–300) (H score). The pathologist also scored the samples for necrosis (measured in percentage of cells).