Research Article

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A phase II study of cixutumumab (IMC-A12, NSC742460) in advanced hepatocellular carcinoma

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Background & Aims: IGF-IR is implicated in hepatic carcinogenesis. This and preliminary evidence of biological activity of anti-IGF-1R monoclonal antibody cixutumumab in phase I trials prompted this phase II study.

Methods: Patients with advanced HCC, Child-Pugh A-B8, received cixutumumab 6 mg/kg weekly, in a Simon two-stage design study, with the primary endpoints being 4-month PFS and RECIST-defined response rate. Tissue and circulating markers plus different HCC scoring systems were evaluated for correlation with PFS and OS.

Results: As a result of pre-specified futility criteria, only stage 1 was accrued: N = 24: median age 67.5 years (range 49–83), KPS 80% (70–90%), 20 males (83%), 9 stage III (37%)/15 stage IV (63%), 18 Child-Pugh A (75%), 11 HBV (46%)/10 HCV (42%)/11 alcoholic cirrhosis (46%)/2 NASH (8%), 11 (46%) diabetic. Median number of doses: 7 (range 1–140). Grade 3/4 toxicities >10% included: diabetes, elevated liver function tests, hyponatremia, and lymphopenia. Four-month PFS was 30% (95% CI 13–48), and there were no objective responses. Median overall survival was 8 months (95% CI 5.8–14). IGF-R1 staining did not correlate with outcome. Elevated IGFBP-1 correlated with improved PFS (1.2 [95% CI 1–1.4]; p 0.009) and OS (1.2 [95% CI 1.1–1.4]; p 0.003).

Conclusions: Cixutumumab monotherapy did not have clinically meaningful activity in this unselected HCC population. Grade 3–4 hyperglycemia occurred in 46% of patients. Elevated IGFBP-1 correlated with improved PFS and OS.

Keywords: Cixutumumab (IMC-A12, NSC742460); Hepatocellular Carcinoma; IGF-IR; Free IGF1; IGF2; IGFBP 1; IGFBP 3; Diabetes.

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Abbreviations: IgG1, Immunoglobulin 1; IGF-1R, Insulin growth factor 1 receptor; IGF-1, Insulin growth factor 1; MAP, Mitogen activated protein; ADCC, Antibody-dependent complement-mediated cytotoxicity; CDC, Complement-dependent cytotoxicity; IGF-2, Insulin growth factor 2; HCC, Hepatocellular carcinoma; LOH, Loss of heterozygosity; IGF-2R, Insulin growth factor 2 receptor; CTEP/NCI, Cancer Therapy Evaluation Program (CTEP)/National Cancer Institute; IRB, Institutional Review Board; RECIST, Response evaluation criteria in solid tumors; KPS, Karnofsky performance status; mcl, Cells per microliter; PT/INR, Prothrombin time/International normalized ratio; mg/dl, Milligram/deciliter; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; units/L, Units/Liter; ml/min, Milliliter per minute; HIV, Human immunodeficiency virus; mg/kg, milligram/kilogram; PFS, progression free survival; OS, Overall urvival; CTCAE, Common terminology criteria for adverse events; CC1, Cell conditioning 1; IGFBP 1, Insulin-like growth factor binding protein 1; IGFBP 3, Insulin-like growth factor binding protein 3; ELISA, Enzyme-linked immunosorbent assay; AJCC, American Joint Committee on Cancer; NASH, Non-alcoholic steatohepatitis; HR, Hazard ratio; CALGB, Cancer Leukemia Group B.

Introduction

Cixutumumab is a fully human IgG1 monoclonal antibody that binds with high specificity to IGF-R1 [1]. IGF-1 binding activates the tyrosine kinase domain of IFG-R1 [2]. Phosphotyrosine residues in turn activate the MAP kinase proliferation pathway and the Akt survival pathway [3]. Cixutumumab effectively blocks ligand-induced phosphorylation, resulting in growth inhibition and apoptosis of tumor cells in a human tumor xenograft model [4]. It also reduces the number of IGF-R1 receptors expressed on the surface of tumor cells through receptor internalization and degradation. Being an IgG class 1 immunoglobulin, cixutumumab also has the potential to mediate immune effector functions, such as antibody-dependent complement-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

The dysregulated autocrine or paracrine production of IGF-1 and IGF-2, as well as overexpression of IGF-IR, has been implicated in human hepatic carcinogenesis [5–9]. IGF-2 is

overexpressed in 16–40% HCC cells, and LOH or reduction of IGF-2R expression has been reported in 80% of HCC in a series of HCC patients [5]. Recent data have shown IGF-2 overexpression to be most noticeable in the histologically advanced tumors [9]. Blockade of IGF-1R activity with an IGF-1R inhibitor or anti-IGF-1R monoclonal antibody was shown to induce growth inhibition, apoptosis, and cell cycle arrest in preclinical models of HCC [10–12].

Most patients with HCC either present with or ultimately develop advanced disease [13]. Despite the reported 2.8 month median improvement in survival using sorafenib [14], there remains a clear continued need for new drugs or a combination of to help improve outcome. Thus we performed a phase II study evaluating cixutumumab in patients with advanced HCC.

Patients and methods

This was a single-institutional, open label study sponsored by the CTEP/NCI phase II N01 institutional grant. Cixutumumab was provided through the Clinical Trial Agreement between CTEP/NCI and ImClone/Lilly. The Institutional Review Board (IRB) of Memorial Sloan Kettering Cancer Center reviewed the protocol. Informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The study was registered with www.clinicaltrials.gov identifier NCT00639509.

Patients' eligibility

Men and women ⩾18 years of age, of any racial or ethnic background with advanced-stage, histologically confirmed, unresectable locally advanced, or metastatic HCC with at least one measurable lesion by RECIST [15], who received no prior systemic therapy with the exception of sorafenib, were eligible. Unresectability was based on but not limited to, extent of disease, vascular involvement, liver function, performance status, and co-morbid conditions. Previous local therapy, e.g., hepatic artery embolization was allowed with evidence of progression of disease by RECIST criteria evident on protocol entry. Patients were required to have an Karnofsky performance status (KPS) of 70–100%; a Child-Pugh score of A5-B8; with adequate hematologic function (absolute neutrophil count ⩾1500/mcl, platelets ⩾75,000/mcl, and PT/INR ⩽1.7 times upper limit of normal); fasting serum glucose ⩽125 mg/dl; adequate hepatic function (total bilirubin ⩽2 mg/dl, and AST/ALT ⩽93 units/L) and adequate renal function (creatinine <1.5 mg/dl or creatinine clearance ⩾60 ml/min for patients with creatinine levels equal or above 1.5).

Diabetic patients were allowed to participate provided that their blood glucose is within normal range (fasting <120 mg/dl or below upper limit of normal) and that they are on a stable dietary or therapeutic regimen for this condition. Patients with serious inter-current illnesses including known brain metastases and/or clinical encephalopathy, and/or known HIV infection were excluded. The study also excluded pregnant women and patients with other malignancies that might have affected patient's outcome.

Treatment plan

Patients received single-agent cixutumumab 6 mg/kg intravenously over one hour weekly. Treatment continued until progression of disease, unacceptable toxicity, or withdrawal of consent. Clinical evaluation occurred weekly for four weeks then every two weeks thereafter. Radiologic assessment was performed every 8 weeks.

Study objectives

The primary endpoints of the study were four-month PFS, and best overall response using RECIST 1.0 criteria.

Progression-free survival was defined as the time from first date of first treatment on the study until such time as progressive disease (RECIST criteria) was confirmed or upon patient death if disease progression was not evident at that time. The response was defined as the best response from the start of the treatment until disease progression/recurrence.

Secondary objectives included the evaluation of median OS and assessment of safety, tolerability, and adverse events using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Correlative studies

IGF-1R expression by immunohistochemistry on pre-treatment biopsies was measured and evaluated for correlation with outcome endpoints. Ventana automation (Discovery XT platform-Ventana Medical Systems, Inc, Tucson, AZ) with standard streptavidin-biotin immunoperoxidase method and DAB detection system was used as a staining method, using IGF-1R antibody, clone G11, prediluted, rabbit monoclonal antibody from the same vendor. Antigen recovery was conducted using heat and CC1 conditioning solution. Positive tissue control used was a previously tested positive for colon cancer and provided by the core research facility at Memorial Sloan-Kettering Cancer Center. The stains were scored based on the degree of staining relative to the total amount of tumor in the studied section, and were ranked based on a standard reference from 0 to 3+.

Similarly, levels of free IGF1, IGF2, IGFBP-1, and IGFBP-3 by ELISA (Beckman Coulter/DSL) on pre-treatment stored serum plus the IGF-1/IGFBP-1 and IGF-1/IGFBP-3 indices were evaluated for correlations with staging and clinical outcomes.

Statistical analyses

Historical data shows the 4-month progression-free survival for placebo to be 42% and response rate 2%, from the double-blinded, randomized, phase III clinical trial of sorafenib *vs.* placebo in patients with advanced HCC [12]. A Simon's optimal two-stage design was used with the following assumptions: a 4-month PFS of 62% is considered acceptable while a 4-month PFS of 42% is not; and an overall response rate of more than 20% is of interest and a overall response rate less than 5% is not. Maximum trial size would be set at 50 evaluable patients, with 25 patients to be enrolled in the first stage. If no more than 11 patients (no more than 44%) were observed to be progression-free for at least 4 months and no more than 2 responses (no more than 8%) were observed, among the initial 25 patients, the study would be terminated early and declared negative. If the study continues and at least 26 patients (at least 52%) were observed to survive progression-free for at least 4 months, or at least 7 responses (at least 14%) were observed, among the 50 evaluable patients, cixutumumab would be considered worthy of further testing in HCC. Assuming that overall response rate and PFS are independent, the over-all type 1 error would be 0.10 and the probability of early termination is 0.57 for 5% true overall response rate and 42% true 4-month PFS. The type 1 error decreases very slightly and the probability of early termination increases towards 0.66 if overall response rate and PFS are positively correlated.

Survival curves were estimated using the Kaplan-Meier methodology. Associations between the biomarkers and OS and PFS were assessed using univariate Cox regression models with the biomarkers treated as continuous predictors. Due to the small sample size only univariate analyses were conducted. The safety, tolerability, and adverse events were summarized using descriptive statistics. All analyses of outcome were based on an intent to treat. Patients who received at least one dose of cixutumumab were evaluable for toxicity.

Results

Demographics

Between March 26, 2008 and January 13, 2009, 24 patients were enrolled at Memorial Sloan Kettering Cancer Centers. Nineteen patients were previously untreated and were offered sorafenib as standard of care but elected to join the clinical trial as first line treatment. Five patients had previously received sorafenib; 3 progressed and 2 could not tolerate it, one due to allergic reaction, and the other due to significant fatigue. Median age was 67.5 years (range 49–83), with KPS 80% (70–90%). There were twenty men (83%). Nine patients had AJCC stage III (37%), and 15 stage IV (63%) disease. Eighteen patients (75%) had Child-Pugh score A and 6 (25%) had a Child-Pugh score B. Eleven patients had hepatitis B (46%), 10 had hepatitis C (42%), 11 had alcoholic cirrhosis (46%), and 2 had non-alcoholic steatohepatitis (NASH)