European Journal of Cancer (2015) **51**, 1714–1724

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

A randomised non-comparative phase II trial of cixutumumab (IMC-A12) or ramucirumab (IMC-1121B) plus mitoxantrone and prednisone in men with metastatic docetaxel-pretreated castration-resistant prostate cancer

Maha Hussain [a,1,*], Dana Rathkopf [b,1], Glenn Liu [c,1], Andrew Armstrong [d,1], Wm. Kevin Kelly [e], Anna Ferrari [f], John Hainsworth [g], Adarsh Joshi [h], Rebecca R. Hozak [i], Ling Yang [h], Jonathan D. Schwartz [h,2], Celestia S. Higano [j,1]

[a] *University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, United States*
[b] *Memorial Sloan-Kettering, New York, NY, United States*
[c] *University of Wisconsin, Carbone Cancer Center, Madison, WI, United States*
[d] *Duke Cancer Institute and Duke Prostate Center, Duke University, Durham, NC, United States*
[e] *Thomas Jefferson University, Philadelphia, PA, United States*
[f] *New York University Clinical Cancer Center, New York, NY, United States*
[g] *Sarah Cannon Research Institute, Nashville, TN, United States*
[h] *Eli Lilly and Company, Bridgewater, NJ, United States*
[i] *Eli Lilly and Company, Indianapolis, IN, United States*
[j] *University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA, United States*

Received 11 February 2015; received in revised form 27 April 2015; accepted 10 May 2015
Available online 13 June 2015

KEYWORDS
Ramucirumab
Cixutumumab
Mitoxantrone
Prednisone
Prostate cancer

Abstract ***Background:*** Cixutumumab, a human monoclonal antibody (HuMAb), targets the insulin-like growth factor receptor. Ramucirumab is a recombinant HuMAb that binds to vascular endothelial growth factor receptor-2. A non-comparative randomised phase II study evaluated cixutumumab or ramucirumab plus mitoxantrone and prednisone (MP) in metastatic castration-resistant prostate cancer (mCRPC).

Previously presented: Presented in part at the Innovative Minds in Prostate Cancer Today (IMPaCT) conference, March 9–12, 2011, Orlando, FL and the American Society of Clinical Oncology Annual Genitourinary Cancers Symposium, February 2–4, 2012, San Francisco, CA (abstr 97). *ClinicalTrials.gov identifier:* NCT00683475.

* *Corresponding author at:* University of Michigan Comprehensive Cancer Center, 7314 Cancer Center, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5946, United States. Tel.: +1 734 936 8906; fax: +1 734 615 2719.
E-mail address: mahahuss@umich.edu (M. Hussain).

[1] Members of the Prostate Cancer Clinical Trials Consortium (PCCTC), a program of the Prostate Cancer Foundation and the Department of Defense Prostate Cancer Research Program (DOD PCRP).

[2] Current affiliation: Stemline Therapeutics, Inc., New York, NY, United States.

http://dx.doi.org/10.1016/j.ejca.2015.05.019

Patients and methods: Men with progressive mCRPC during or after docetaxel therapy received mitoxantrone 12 mg/m^2 on day 1 and prednisone 5 mg twice daily and were randomised 1:1 to receive either cixutumumab or ramucirumab 6 mg/kg intravenously weekly in a 21-day cycle. Primary end-point was composite progression-free survival (cPFS). Secondary end-points included safety, response, radiographic progression-free survival (PFS) and overall survival (OS). Sample size was based on a 50% increase in median cPFS from 2.6 (MP) to 3.9 months (either combination).

Results: 132 men were treated (66 per arm). Median cPFS was 4.1 months (95% confidence interval (CI), 2.2–5.6) for cixutumumab and 6.7 months (95% CI, 4.5–8.3) for ramucirumab. Median time to radiographic progression was 7.5 months for cixutumumab and 10.2 months for ramucirumab, with a median OS of 10.8 and 13.0 months, respectively. Fatigue was the most frequent adverse event (AE). Incidence of most non-haematologic grade 3–4 AEs was <10% on both arms. Grade 3 cardiac dysfunction occurred in 7.6% of patients on ramucirumab.

Conclusion: Combinations of cixutumumab or ramucirumab plus MP were feasible and associated with moderate toxicities in docetaxel-pretreated men with mCRPC. Of the two regimens, the ramucirumab regimen is worthy of further testing based on the observed cPFS relative to the historical control.

1. Introduction

Despite significant progress in therapy development for patients with metastatic castration-resistant prostate cancer (mCRPC), survival is limited and better treatments are needed [1–3]. Insulin-like growth factor (IGF) and type-1 receptor (IGF-IR)-mediated signalling can potentiate androgen-receptor activation [4], and IGF-IR signalling contributes to proliferation, tumour-stromal interactions, invasion and metastasis [5–9] in preclinical models of prostate cancer (PC). Anti–IGF-IR antibodies, IGF-IR kinase inhibitors and antisense oligonucleotides to IGF-IR inhibit PC growth *in vitro* and *in vivo* [10–12].

Cixutumumab (IMC-A12) is a human immunoglobulin G, subclass 1 (IgG1) monoclonal antibody (MAb) with high affinity and specificity for IGF-IR and is an antagonist of IGF-I and IGF-II ligand binding and signalling [13,14]. Cixutumumab inhibits the proliferation and growth of a variety of human tumour cell lines, both *in vitro* and *in vivo* [13]. Cixutumumab inhibited growth of androgen-dependent and androgen-independent xenograft prostate tumours and growth inhibition was enhanced when cixutumumab was co-administered with docetaxel in CRPC models [14,15]. Preclinical data suggest that cixutumumab monotherapy inhibits but does not completely arrest tumour growth, with the most profound effects observed when IGF-IR inhibitors are combined with other agents [16]. In a phase II study of cixutumumab monotherapy in mCRPC patients, 9 of 31 (29%) had disease stabilisation for at least 6 months and cixutumumab was found to be well tolerated [17].

Vascular endothelial growth factor (VEGF) is up-regulated in PC, and higher expression has been associated with higher grade [18], more advanced disease, rapid progression and shorter survival [19–22]. Microvessel density and VEGF expression are increased in PC and higher levels of circulating and tumour VEGF are associated with aggressive clinical and preclinical PC phenotypes [18,20–22]. Inhibition of VEGF receptor-2 (VEGFR-2) with the antibody DC101 inhibits PC growth and bone metastasis in murine models [23]. Ramucirumab is a recombinant human IgG1 MAb that binds specifically and with high affinity to VEGFR-2, and inhibits receptor activation [24]. Preclinical cellular and animal models of solid and liquid tumours have demonstrated that ramucirumab attacks its intended target with inhibition of VEGF-induced VEGFR-2 activation and inhibition of VEGF-stimulated cellular migration and proliferation, and efficacy has been demonstrated in phase I trials, particularly in heavily pretreated refractory patients [25].

At the time of the study design, mCRPC patients progressing on docetaxel had no life-prolonging therapy choices and the only available treatment was the combination of mitoxantrone and prednisone, which was approved for pain palliation [26].

Based on the biological and preclinical data, we hypothesised that cixutumumab or ramucirumab would enhance the activity of mitoxantrone and prednisone in men with docetaxel-pretreated mCRPC. The study was designed and completed before the regulatory approvals of cabazitaxel, abiraterone, enzalutamide and radium-223 in the post-docetaxel setting. Thus, we conducted a randomised, open-label, non-comparative phase II study of cixutumumab or ramucirumab plus mitoxantrone and prednisone in patients with mCRPC.