European Journal of Cancer (2012) **48**, 527–537

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Cediranib monotherapy in patients with advanced renal cell carcinoma: Results of a randomised phase II study ☆

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Available online 28 January 2012

KEYWORDS
Cediranib
Monotherapy
Renal cell carcinoma
Phase II

Abstract *Background:* Cediranib is a highly potent vascular endothelial growth factor (VEGF) signalling inhibitor with activity against VEGF receptors 1, 2 and 3. This Phase II, randomised, double-blind, parallel-group study compared the efficacy of cediranib with placebo in patients with metastatic or recurrent clear cell renal cell carcinoma who had not previously received a VEGF signalling inhibitor.

Methods: Patients were randomised (3:1) to cediranib 45 mg/day or placebo. The primary objective was comparison of change from baseline in tumour size after 12 weeks of therapy. Secondary objectives included response rate and duration, progression-free survival (PFS) and safety and tolerability. Patients in the placebo group could cross over to open-label cediranib at 12 weeks or earlier if their disease had progressed. This study has been completed and is registered with ClinicalTrials.gov, number NCT00423332.

☆ Previous presentations: 2008 International Kidney Cancer Symposium (poster presentation); 2009 joint congress of the European Cancer Organisation and European Society for Medical Oncology (oral presentation); 2009 European Multidisciplinary Meeting on Urological Cancers (oral presentation).

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doi:10.1016/j.ejca.2011.12.022

Findings: Patients ($n = 71$) were randomised to receive cediranib ($n = 53$) or placebo ($n = 18$). The primary study outcome revealed that, after 12 weeks of therapy, there was a significant difference in mean percentage change from baseline in tumour size between the cediranib (–20%) and placebo (+20%) arms ($p < 0.0001$). Eighteen patients (34%) on cediranib achieved a partial response and 25 (47%) experienced stable disease. Cediranib treatment prolonged PFS significantly compared with placebo (hazard ratio (HR) = 0.45, 90% confidence interval: 0.26–0.76, $p = 0.017$; median PFS 12.1 versus 2.8 months). The most common adverse events in patients receiving cediranib were diarrhoea (74%), hypertension (64%), fatigue (58%) and dysphonia (58%).

Interpretation: Cediranib monotherapy demonstrated significant evidence of antitumour activity in patients with advanced renal cell carcinoma. The adverse event profile was consistent with previous studies of cediranib 45 mg.

1. Introduction

In 2010, cancer of the kidney and renal pelvis was estimated to account for approximately 13,000 deaths in the United States alone.[1] Clear-cell renal cell carcinoma (RCC) is the most common form of kidney cancer and is characterised by mutations in the *von Hippel-Lindau* (*VHL*) gene. In normoxic conditions, VHL breaks down hypoxia-inducible factor (HIF); however, when *VHL* is mutated, HIF is not degraded and increased levels result in overexpression of vascular endothelial growth factor (VEGF).[2] Small-molecule tyrosine kinase inhibitors (TKIs) that target the VEGF signalling pathway have been approved as monotherapy for the treatment of RCC.[3]

Cediranib (AZD2171) is a once-daily oral VEGF signalling inhibitor of all three VEGF receptors (VEGFR-1, -2, and -3).[4–6] The IC_{50} for cediranib versus VEGFR-2 in *in vitro* kinase assays is <1 nM, compared with 9 nM (sunitinib),[7] 30 nM (pazopanib)[8] and 90 nM (sorafenib)[9] for VEGFR TKIs approved for the treatment of patients with RCC. Early clinical data demonstrated encouraging antitumour activity across a broad range of tumours, both as monotherapy[6,10–14] and in combination with certain chemotherapy regimens.[15–18] Common adverse events reported with cediranib include hypertension, diarrhoea and fatigue.

This Phase II, randomised, double-blind, parallel-group study (ClinicalTrials.gov identifier NCT00423332; AstraZeneca study code 2171IL0030) compared cediranib with placebo in patients with advanced RCC who had not received previous anti-VEGF therapy.

2. Methods

2.1. Study objectives

The primary objective was to determine the efficacy of cediranib versus placebo by comparing changes from baseline in tumour size after 12 weeks of therapy (or at progression if before 12 weeks). Change in tumour size was considered a more sensitive endpoint than objective tumour response rate to assess efficacy for this type of agent in this disease setting based on previous clinical data.[19] Secondary objectives included assessments of overall best change in tumour size (defined as the smallest post-baseline tumour size), objective response rate and duration, progression-free survival (PFS), safety and tolerability, steady-state pharmacokinetic parameters and angiogenesis biomarkers.

2.2. Patients

Adult patients with histological/cytological confirmation of metastatic or recurrent clear-cell RCC/adenocarcinoma were eligible. Patients were required to have one or more lesions measurable by Response Evaluation Criteria In Solid Tumours (RECIST)[20] and a World Health Organisation (WHO) performance status of 0–2. Brain metastases were permitted if asymptomatic and either did not require corticosteroid treatment or were clinically/radiologically stable for $\geqslant$10 days after discontinuation of steroid treatment. Exclusion criteria included previous VEGF-signalling inhibitor therapy; >1 previous immunotherapy; prior cytotoxic chemotherapy for RCC (except 5-fluorouracil used in combination with immunotherapy). The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and the AstraZeneca policy on Bioethics. Each patient provided written informed consent.

2.3. Randomisation and masking

Treatment was randomised using standard software for the generation of random numbers. In order to achieve balance across this study, the randomisation schedule was stratified by country. Study personnel were blinded to treatment until either the start of open-label treatment at week 13, or at progression if this occurred before week 12.

2.4. Study design

In this double-blind study, patients were randomised 3:1 to cediranib 45 mg/day or placebo (Fig. 1). After