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Original Research

Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update

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KEYWORDS
Cabozantinib;
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Abstract ***Background:*** The randomised phase 2 CABOSUN trial comparing cabozantinib with sunitinib as initial therapy for advanced renal cell carcinoma (RCC) of intermediate or poor risk met the primary end-point of improving progression-free survival (PFS) as assessed

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by investigator. We report PFS by independent radiology review committee (IRC) assessment, ORR per IRC and updated overall survival (OS).

Patients and methods: Previously untreated patients with advanced RCC of intermediate or poor risk by IMDC criteria were randomised 1:1 to cabozantinib 60 mg daily or sunitinib 50 mg daily (4 weeks on/2 weeks off). Stratification was by risk group and presence of bone metastases.

Results: A total of 157 patients were randomised 1:1 to cabozantinib (n = 79) or sunitinib (n = 78). Median PFS per IRC was 8.6 months (95% confidence interval [CI] 6.8–14.0) versus 5.3 months (95% CI 3.0–8.2) for cabozantinib versus sunitinib (hazard ratio [HR] 0.48 [95% CI 0.31–0.74]; two-sided p = 0.0008), and ORR per IRC was 20% (95% CI 12.0–30.8) versus 9% (95% CI 3.7–17.6), respectively. Subgroup analyses of PFS by stratification factors and MET tumour expression were consistent with results for the overall population. With a median follow-up of 34.5 months, median OS was 26.6 months (95% CI 14.6–not estimable) with cabozantinib and 21.2 months (95% CI 16.3–27.4) with sunitinib (HR 0.80 [95% CI 0.53–1.21]. The incidence of grade 3 or 4 adverse events was 68% for cabozantinib and 65% for sunitinib.

Conclusions: In this phase 2 trial, cabozantinib treatment significantly prolonged PFS per IRC compared with sunitinib as initial systemic therapy for advanced RCC of poor or intermediate risk.

Trial Registration Number: NCT01835158.

1. Introduction

Despite many available treatment options, advanced renal cell carcinoma (RCC) remains essentially incurable. International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria were developed in the era of targeted therapy to classify patients into prognostic groups based on the number of established risk factors (poor risk: 3–6, intermediate risk: 1–2, and favourable risk: 0) [1]. Patients with intermediate or poor risk disease (70–80% of all patients with advanced RCC) have shorter survival duration compared with favourable risk patients and have the greatest need for more effective therapies.

VEGFR-targeted therapy is the current standard first-line treatment for patients with advanced RCC based on improvements in progression-free survival (PFS) in phase 3 clinical trials, with sunitinib and pazopanib as the most commonly used therapies [2]. Patients eventually develop disease progression, with median PFS ranging from 8 to 11 months for sunitinib and pazopanib in populations that include patients of all risk groups [3–5]. Duration of PFS is shorter in intermediate and poor risk patients; for example, in a mixed population of intermediate or poor risk patients treated with targeted therapy, median PFS can be less than 6 months, based on data from the IMDC [6].

The VEGF-signalling pathway is upregulated in clear cell RCC due to inactivation of the VHL tumour suppressor gene [7], providing a molecular rationale for the use of VEGF-targeted therapies in this setting. Targeting oncogenic pathways involved in RCC in addition to VEGF-signalling might result in therapeutic benefit. Two relevant targets are MET and AXL, as both are upregulated as a result of VHL loss and have been associated with tumour progression, resistance to VEGF-pathway inhibition in preclinical models, and poor prognosis in patients with RCC [8–11].

Cabozantinib is an oral inhibitor of MET, AXL, and VEGFR2 [12] that is approved for treatment of patients with advanced RCC after prior antiangiogenic therapy based on results from the phase 3 METEOR trial [13,14]. The randomised, open-label phase 2 CABOSUN trial (Alliance for Clinical Trials in Oncology study A031203) compared cabozantinib versus sunitinib as initial targeted therapy in patients with metastatic RCC of intermediate or poor risk by IMDC criteria. The CABOSUN study met the primary end-point of improving investigator-assessed PFS with cabozantinib compared with sunitinib; median PFS per investigator was 8.2 months with cabozantinib versus 5.6 months with sunitinib (hazard ratio [HR] = 0.66, 95% confidence interval [CI] 0.46–0.95, one-sided log-rank p = 0.012) [15]. A retrospective analysis of PFS and objective response rate (ORR) by a central, blinded independent radiology review committee (IRC) was performed to determine if independent assessment supports the investigator results.

We report results of independent assessment of PFS and ORR as well as updated overall survival (OS) for the CABOSUN trial in patients with advanced RCC of intermediate or poor risk. Subgroup analyses of PFS based on stratification factors and tumour MET expression level are also presented.

2. Methods

2.1. Study design and participants

CABOSUN (Alliance for Clinical Trials in Oncology A031203) is a randomised, phase 2 trial conducted at 77 investigative centres in the United States. Eligible patients were 18 years of age or older with advanced or