Cabozantinib versus sunitinib for untreated patients with advanced renal cell carcinoma of intermediate or poor risk: Subgroup analysis of the Alliance A031203 CABOSUN trial

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Cabozantinib Versus Sunitinib for Untreated Patients with Advanced Renal Cell Carcinoma of Intermediate or Poor Risk: Subgroup Analysis of the Alliance A031203 CABOSUN trial

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Cabozantinib treatment prolonged progression-free survival (PFS) and improved objective response rate (ORR) compared with sunitinib in patients with advanced renal cell carcinoma (RCC) of intermediate or poor risk by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria in the phase II CABOSUN trial (NCT01835158). In the trial, 157 patients were randomized 1:1 to receive cabozantinib or sunitinib, stratified by IMDC risk group and presence of bone metastases. Here, PFS and ORR, both determined by independent radiology committee (IRC), were analyzed by subgroups of baseline characteristics. Cabozantinib treatment was generally associated with improved PFS and ORR versus sunitinib across subgroups, including in groups defined by IMDC risk group, bone metastases, age, and tumor burden. Clinical trial identification number. NCT01835158. The Oncologist 2019;24:1497–1501

Introduction

Cabozantinib is an oral inhibitor of MET, AXL, and vascular endothelial growth factor (VEGF) receptors [1]. The phase II CABOSUN trial (Alliance for Clinical Trials in Oncology A031203) compared cabozantinib with sunitinib as initial treatment in patients with advanced renal cell carcinoma (RCC) of intermediate or poor International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk [2, 3]. The study met the primary endpoint of improved progression-free survival (PFS) per investigator with cabozantinib versus sunitinib. Retrospective analysis of PFS per independent radiology committee (IRC) also showed significant prolongation of PFS with cabozantinib. Median PFS per IRC was 8.6 months (95% confidence interval [CI], 6.8 – 14.0) with cabozantinib versus 5.3 months (95% CI, 3.0 – 8.2) with sunitinib (hazard ratio [HR], 0.48; 95% CI, 0.31 – 0.74; two-sided p = .0008), and objective response rate (ORR) per IRC was 20% (95% CI, 12.0 – 30.8) versus 9% (95% CI, 3.7 – 17.6), respectively. With the growing number of therapies for first-line RCC [4, 5], information on efficacy based on patient characteristics may help to select optimal use. Here, PFS per IRC and ORR per IRC were analyzed by subgroups of baseline characteristics for CABOSUN.

Materials and Methods

The CABOSUN trial and retrospective analysis of PFS and ORR by IRC have been previously described [2, 3]. Eligible patients were ≥18 years of age with advanced or metastatic clear-cell RCC without previous systemic treatment. Additional study requirements included intermediate- or poor-risk disease per IMDC criteria, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate organ function.

Patients were randomly assigned 1:1 to receive cabozantinib (60 mg once daily) or sunitinib (50 mg once daily for 4 weeks, followed by a 2-week break), stratified by IMDC risk group (intermediate or poor) and bone metastases (yes or no). Tumor assessments by magnetic resonance imaging or...
computed tomography were performed at baseline and every 12 weeks thereafter until progression or until 5 years after randomization. MET tumor expression levels were analyzed by immunohistochemistry using archival or recently biopsied tumor tissue.

The primary endpoint was PFS per investigator; secondary endpoints were ORR per investigator, overall survival (OS), and safety [2, 3]. Tumor response and PFS were retrospectively assessed based on a blinded IRC review using Response Evaluation Criteria in Solid Tumors version 1.1. This analysis used a data cutoff of September 15, 2016. Subgroup analyses by stratification factors and MET tumor expression were prespecified and have been reported previously [2, 3]. Subgroup analyses focused on PFS and ORR, as the study was not powered for determination of the secondary endpoint of OS, and were post hoc. PFS and ORR subgroup analyses were per IRC. The Cox proportional hazards model and logistic regression analysis were performed; both analyses used treatment groups and the subgroups as independent variables. No adjustments for multiplicity were made.

| Subgroup | Patients | Events | Median PFS (mo) | HR (95% CI) |
|----------|---------|--------|----------------|------------|
| All patients | 79/78 | 43/49 | 8.6 | 0.48 (0.31–0.74) |
| Age, years | | | | |
| <65 | 45/42 | 26/28 | 6.9 | 0.47 (0.28–0.81) |
| ≥65 | 34/36 | 17/21 | 12.4 | 0.51 (0.26–0.97) |
| Sex | | | | |
| Male | 66/57 | 35/35 | 11.0 | 0.53 (0.33–0.85) |
| Female | 13/21 | 8/14 | 6.8 | 0.43 (0.17–1.04) |
| IMDC risk group | | | | |
| Intermediate | 64/63 | 34/38 | 11.4 | 0.52 (0.32–0.82) |
| Poor | 15/15 | 9/11 | 6.8 | 0.31 (0.11–0.92) |
| Bone metastases | | | | |
| Yes | 29/28 | 18/19 | 5.5 | 0.51 (0.26–0.99) |
| No | 50/50 | 25/30 | 11.4 | 0.30 (0.29–0.85) |
| MET status* | | | | |
| Positive | 32/30 | 17/19 | 13.8 | 0.32 (0.16–0.63) |
| Negative | 39/30 | 23/20 | 6.9 | 0.67 (0.37–1.33) |
| ECOG performance status | | | | |
| 0 | 36/36 | 16/22 | 14.0 | 0.36 (0.19–0.70) |
| 1 | 43/42 | 27/27 | 5.5 | 0.69 (0.40–1.17) |
| Diagnosis to randomization | | | | |
| <1 year | 61/57 | 32/40 | 8.3 | 0.49 (0.31–0.78) |
| ≥1 year | 18/21 | 11/9 | 11.4 | 0.54 (0.22–1.33) |
| Prior nephrectomy | | | | |
| Yes | 57/60 | 34/38 | 8.6 | 0.55 (0.35–0.89) |
| No | 22/18 | 9/11 | 8.4 | 0.30 (0.12–0.76) |
| SoD | | | | |
| <median | 41/36 | 19/21 | 13.8 | 0.46 (0.25–0.87) |
| ≥median | 37/40 | 24/27 | 6.8 | 0.59 (0.34–1.04) |
| Metastatic sites | | | | |
| 1 | 17/26 | 5/14 | NE | 8.2 | 0.32 (0.11–0.90) |
| 2 | 37/20 | 23/13 | 8.3 | 0.76 (0.38–1.51) |
| ≥3 | 25/32 | 15/22 | 9.0 | 0.42 (0.21–0.84) |
| Nodal metastases | | | | |
| Yes | 45/42 | 26/27 | 9.0 | 0.53 (0.31–0.91) |
| No | 34/36 | 17/22 | 8.4 | 0.48 (0.25–0.92) |
| Visceral metastases | | | | |
| Yes | 61/56 | 35/36 | 8.6 | 0.50 (0.31–0.80) |
| No | 18/22 | 8/13 | 9.0 | 0.55 (0.22–1.34) |
| Lung metastases | | | | |
| Yes | 55/54 | 32/35 | 8.3 | 0.53 (0.33–0.86) |
| No | 24/24 | 11/14 | 9.0 | 0.47 (0.21–1.05) |

Figure 1. Forest plot of progression-free survival by subgroups. All analyses are per independent radiology committee. Hazard ratios are unstratified with the exception of the analysis for all patients. Metastatic sites are per investigator.

*Eight patients in the cabozantinib group and 18 patients in the sunitinib group had unknown MET status.
†Ten patients in the cabozantinib group and 10 patients in the sunitinib group were Eastern Cooperative Oncology Group (ECOG) 2.

Abbreviations: CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; NE, not estimable; PFS, progression-free survival; SoD, sum of diameters.
RHs and odds ratios are unstratified and considered exploratory.

**Results**

A total of 157 patients were randomized to receive cabozantinib (n = 79) or sunitinib (n = 78). Baseline characteristics have been reported previously and were generally balanced between treatment groups [2, 3]. Eighty-one percent of patients were intermediate risk and 19% were poor risk by IMDC criteria, 45% were ≥65 years, 78% were male, 54% were ECOG 1 or 2, and 36% had bone metastases. Tumor MET status was determined in 131 of 157 (83%) patients; of these, 47% were MET positive.

As of the data cutoff for PFS and ORR, median duration of follow-up was 25.0 months (interquartile range, 21.9–30.9).

The HR for PFS favored cabozantinib over sunitinib across all subgroups analyzed, including those defined by stratification.

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**Figure 2.** Forest plot of objective tumor response by subgroups. All analyses are per independent radiology committee. Metastatic sites are per investigator.

*Eight patients in the cabozantinib group and 18 patients in the sunitinib group had unknown MET status.

†Ten patients in the cabozantinib group and 10 patients in the sunitinib group were Eastern Cooperative Oncology Group (ECOG) 2.

Abbreviations: CI, confidence interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; SoD, sum of diameters.
DISCUSSION AND SUMMARY

In the randomized phase II CABOSUN trial, cabozantinib treatment prolonged PFS and improved the ORR compared with sunitinib as initial treatment in patients with advanced RCC of intermediate or poor IMDC risk. Subgroup analyses of PFS per IRC by baseline characteristics favored cabozantinib over sunitinib (HR <1) in all groups analyzed, including groups defined by age, IMDC risk group, bone metastases, MET status, and tumor burden. Furthermore, analyses of ORR per IRC by baseline characteristics were generally consistent with those for the overall population.

The study was not designed to determine outcomes in subgroups, and results presented here are considered exploratory and hypothesis generating. In this context, positive MET status may be associated with a greater treatment benefit with cabozantinib versus sunitinib, although patients benefited with cabozantinib irrespective of MET status. Further prospective validation of this finding is warranted.

The treatment landscape for first-line RCC is rapidly evolving, with approval of the combination of nivolumab and ipilimumab for patients with advanced RCC of intermediate or poor IMDC risk and ongoing trials of VEGF pathway and checkpoint inhibitor combinations [4–8]. Additional prospective clinical trials would be needed to better determine outcomes for cabozantinib compared with sunitinib or other first-line therapies based on baseline characteristics. Nonetheless, results presented here suggest that cabozantinib treatment was generally associated with improved PFS and ORR versus sunitinib across subgroups of baseline characteristics, consistent with results for the overall population.

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DISCLOSURES

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See http://www.TheOncologist.com for supplemental material available online.

For Further Reading:
Ai-Ping Zhou, Yuxian Bai, Yan Song et al. Anlotinib Versus Sunitinib as First-Line Treatment for Metastatic Renal Cell Carcinoma: A Randomized Phase II Clinical Trial. The Oncologist 2019;24:e702–e708.

Implications for Practice:
This study evaluated the efficacy and safety of anlotinib for the first-line treatment of metastatic renal cell carcinoma. Anlotinib, which was developed independently in China, is a new tyrosine kinase inhibitor inhibiting multiple kinases involved in angiogenesis and tumor proliferation. Results indicated that the efficacy of anlotinib is comparable to and the safety is better than that of sunitinib.