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Submission Request  
National Comprehensive Cancer Network

**Re: Clinical Evidence in Support of Cabozantinib Use in Treatment-Naïve Patients with Advanced Renal Cell Carcinoma**

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NCCN Panel: Kidney Cancer

On behalf of Exelixis, I respectfully request that the NCCN Kidney Cancer Guidelines Panel review the enclosed data for potential inclusion in the kidney cancer guidelines.

Specific Changes: Recommend the addition of cabozantinib as a first-line treatment option for advanced renal cell carcinoma (RCC) patients with clear cell component.

FDA Clearance: CABOMETYX™ (cabozantinib tablets) is approved for the treatment of patients with advanced renal cell carcinoma who have received prior antiangiogenic therapy. The approved dose for this indication is 60 mg daily.

Rationale: The CABOSUN study, a randomized phase 2 study comparing cabozantinib with sunitinib in patients with treatment-naïve advanced clear cell RCC, has demonstrated a statistically-significant improvement in progression-free survival (PFS), an improvement in objective response rate (ORR), and a trend toward improved overall survival (OS) for cabozantinib-treated patients.

Clinical Evidence: CABOSUN is a two-arm randomized open-label phase 2 study comparing cabozantinib (60 mg daily) with sunitinib (50 mg daily for 4 weeks followed by a 2 week break) in treatment-naïve patients with advanced RCC and clear cell component who were intermediate or poor risk by the International Metastatic RCC Database Consortium (IMDC) criteria<sup>1</sup>. Patients were stratified based on IMDC risk group (intermediate, poor) and presence of bone metastases (yes, no). The primary endpoint was the comparison of PFS between the two treatment arms, and secondary endpoints were ORR, OS, and safety assessment. Crossover between treatment arms was not included in the study design. The trial was conducted by the Alliance for Clinical Trials in Oncology in partnership with the National Cancer Institute's Cancer Therapy Evaluation Program (NCT01835158).

A total of 157 subjects were enrolled. Baseline demographics were balanced between the two arms, and demonstrated substantial rates of poor prognosis baseline characteristics, including IMDC poor risk (19%), ECOG performance status of 2 (13%), presence of bone metastases (36%), and lack of prior nephrectomy (26%).<sup>1</sup> The study met its primary endpoint, demonstrating a statistically-significant improvement of PFS for the cabozantinib arm compared with the sunitinib arm (median PFS of 8.2 months for cabozantinib versus 5.6 months for sunitinib; hazard ratio [HR]=0.66, p=0.012)<sup>1</sup> (**Table 1**). In addition, a higher objective response rate was observed for cabozantinib-treated patients compared with sunitinib-treated patients (46% of patients with

confirmed responses in the cabozantinib arm vs 18% in the sunitinib arm)<sup>1</sup> (**Table 2**). The OS analysis was immature with approximately 16 months minimum follow up. The HR for OS favored the cabozantinib arm (HR=0.80, 95% CI 0.50-1.26) but was not statistically significant; median survival for the cabozantinib arm was 30.3 months versus 21.8 months for the sunitinib arm<sup>1</sup>

**Table 1. Progression-Free Survival**

	Median (months)	Hazard Ratio (95% CI)	P-value (one-sided)
Cabozantinib (N=79)	8.2	0.66 (0.46-0.95)	0.012
Sunitinib (N=78)	5.6		

**Table 2. Tumor Response**

	ORR (95% CI)	Any Tumor Reduction*
Cabozantinib (N=79)	46% (34%–57%)	87%
Sunitinib (N=78)	18% (10%–28%)	44%

ORR, objective response rate; \*Percentage of patients with any reduction in the sum of target lesion diameters

The incidence of adverse events (any grade) regardless of causality was 99% for both arms, and the incidence of all-causality adverse events of grade 3 or 4 was 67% with cabozantinib and 68% with sunitinib. The most common grade 3 or 4 adverse events with cabozantinib were hypertension (28%), diarrhea (10%), palmar-plantar erythrodysesthesia (8%) and fatigue (6%), and with sunitinib were hypertension (22%), fatigue (15%), diarrhea (11%) and thrombocytopenia (11%). Dose reductions occurred in 58% of patients treated with cabozantinib, and in 49% of patients treated with sunitinib. The rate of treatment discontinuation due to adverse events was 20% and 21% in the cabozantinib and sunitinib arms, respectively.

Additional supportive data is found in the randomized phase 3 METEOR study<sup>2</sup>, in which statistically-significant improvement in PFS, OS, and ORR was demonstrated in the cabozantinib arm compared with the everolimus arm in patients with clear-cell RCC and prior treatment with antiangiogenic inhibitors. The improvements in PFS and ORR along with the trend toward an OS benefit in CABOSUN, along with the supportive data from the METEOR study, support expanding the use of cabozantinib to treatment-naïve RCC patients.

#### Literature Support

<sup>1</sup>Choueiri TK, Halabi S, Sanford BL, et al: Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203 CABOSUN trial. J Clin Oncol, 2016. Published online DOI: 10.1200/JCO.2016.70.7398.

<sup>2</sup>Choueiri TK, Escudier B, Powles T, et al: Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 17:917-27, 2016