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June 6, 2016

Submission Request
National Comprehensive Cancer Network

Re: Additional Clinical Evidence in Support of Cabozantinib in Patients with Advanced Clear-Cell Renal Cell Carcinoma Who Have Received Prior Treatment with a VEGFR-Targeted Tyrosine Kinase Inhibitor

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Date of Request:	June 6, 2016
NCCN Guidelines Panel:	Kidney Cancer

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

Specific Changes: We recommend the revision of the evidence block for cabozantinib as a treatment for patients with advanced renal cell carcinoma after prior anti-angiogenic therapy, changing the Efficacy rating from 3 to 4, based on recent demonstration of significantly improved overall survival for patients treated with cabozantinib in the METEOR trial. We also recommended inclusion of reference 2 (Choueiri et al, 2016) in the References section of the guidelines.

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 60mg daily.

Rationale: The METEOR study, a randomized phase 3 study comparing cabozantinib with everolimus in patients with advanced clear cell RCC who had received one or more prior VEGFR-targeted TKIs, has demonstrated a statistically-significant improvement of overall survival for patients treated with cabozantinib.

Clinical Evidence: METEOR is a two-arm randomized open-label phase 3 study comparing cabozantinib (60 mg daily) with everolimus (10 mg daily) in patients with advanced clear-cell RCC who had received one or more prior VEGFR-targeted TKIs¹. Patients were stratified based on MSKCC risk group (favorable, intermediate, poor) and number of prior VEGFR TKIs (1, ≥2). A total of 658 subjects were enrolled. The primary endpoint was the comparison of PFS between the two treatment arms in the first 375 subjects enrolled. Secondary efficacy endpoints were objective response rate and overall survival in the entire study population. No crossover between study arms was allowed. Minimum follow up for the first 375 patients at the time of data analysis was 11 months. The study met its primary endpoint demonstrating a statistically-significant improvement of progression-free survival for the cabozantinib arm compared with the everolimus arm (7.4 months for cabozantinib versus 3.8 months for everolimus; HR=0.58 [95% CI 0.45–0.75]; p<0.001)¹. A statistically-significant increase in the objective response rate was also seen (cabozantinib arm: 17%, everolimus arm 3%; p<0.001)². At the time of the primary analysis, an interim analysis of overall survival was performed¹. A strong



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trend for improved overall survival was demonstrated for the cabozantinib arm with a hazard ratio of 0.67 and a P-value of 0.005; however the P-value of ≤ 0.0019 required to achieve statistical significance at the interim analysis was not reached.

Final analysis of overall survival in METEOR has now been performed, with a 31 December 2015 data cut-off date and a 13-month minimum follow-up for the entire study population². The final analysis included 320 deaths: 140 in the cabozantinib arm, and 180 in the everolimus arm. There was a statistically-significant increase in overall survival in the cabozantinib arm² (**Table 1**). Median overall survival was 21.4 months for cabozantinib-treated patients, and 16.5 for everolimus-treated patients; HR=0.66 (95%CI 0.53-0.83), P=0.00026. A consistent improvement in overall survival in favor of cabozantinib was also demonstrated for each pre-specified subgroup as well².

Table 1. Overall Survival (Final Analysis)

	Median (months)	Hazard Ratio (vs Everolimus)	P-value (vs Everolimus)
Everolimus (N=328)	16.5	--	--
Cabozantinib (N=330)	21.4	0.66 (0.53-0.83)	0.00026

After additional follow-up, the adverse event profile of cabozantinib in patients with advanced renal cell carcinoma was similar to that reported previously^{1,2}. Dose reductions occurred in 62% of patients treated with cabozantinib, and in 25% of patients treated with everolimus. The rate of treatment discontinuation due to adverse events not related to RCC was 12% and 11% in the cabozantinib and everolimus groups, respectively.

Literature Support

¹Choueiri TK, Escudier B, Powles T, et al. (2015). Cabozantinib versus everolimus in advanced renal cell carcinoma. *N Engl J Med*. 373:1814-1823.

²Choueiri TK, Escudier B, Powles T, et al. (2016). Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. Published online 5 June 2016. [http://dx.doi.org/10.1016/S1470-2045\(16\)30107-3](http://dx.doi.org/10.1016/S1470-2045(16)30107-3).