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210 East Grand Avenue
South San Francisco, CA
94080
650.837.7000 main

September 26, 2015

Submission Request
National Comprehensive Cancer Network

Re: 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

Name: Douglas Clary, PhD
Company/Organization: Exelixis, Inc.
Address: 210 East Grand Blvd.
South San Francisco, CA 94080
Phone: (650) 837-7661
Email: dclary@exelixis.com
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NCCN Guidelines Panel: Kidney Cancer

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

Specific Changes: Recommend the addition of cabozantinib as a potential treatment for patients with advanced renal cell carcinoma (RCC) with predominant clear cell histology who have received at least one prior VEGFR-targeted tyrosine kinase inhibitor (TKI).

FDA Clearance: COMETRIQ® (cabozantinib capsules) is approved for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). The approved dose for this indication is 140mg 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, demonstrated a statistically-significant improvement of progression-free survival (PFS) and a trend toward improved overall survival (OS) for the cabozantinib arm compared to the everolimus arm.

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 TKIs^{1,2}. 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 endpoints included objective response rate (ORR) in the first 375 patients enrolled, and safety and OS 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 PFS for the cabozantinib arm compared with the everolimus arm (Table 1). A statistically-significant increase in the objective response rate was also seen (cabozantinib arm: 21%, everolimus arm 5%; p<0.001). A strong trend for improved overall survival was also demonstrated for the cabozantinib arm (Table 2) 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. Follow-up for the overall survival endpoint is ongoing.



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Table 1. Progression-Free Survival

	Median (months)	Hazard Ratio (vs Everolimus)	P-value (vs Everolimus)
Everolimus (N=188)	3.8	--	--
Cabozantinib (N=187)	7.4	0.58 (0.45-0.75)*	<0.001

*95% confidence interval

Table 2. Overall Survival (Interim Analysis)

	Median (months)	Hazard Ratio (vs Everolimus)	P-value (vs Everolimus)
Everolimus (N=328)	NR	--	--
Cabozantinib (N=330)	NR	0.67 (0.51-0.89)*	0.005 [†]

NR, not reached *95% confidence interval [†]did not cross the interim boundary ($p \leq 0.0019$) to achieve statistical significance at the interim analysis

The incidence of adverse events (any grade) regardless of causality was 100% with cabozantinib and >99% with everolimus, and the incidence of adverse events of grade 3 or 4 was 68% with cabozantinib and 58% with everolimus. The most common grade 3 or 4 adverse events with cabozantinib were hypertension (15%), diarrhea (11%), and fatigue (9%), and with everolimus were anemia (16%), fatigue (7%), and hyperglycemia (5%). Dose reductions occurred in 60% 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 9% and 10% in the cabozantinib and everolimus groups, respectively.

Cabozantinib Formulations: Currently COMETRIQ capsules are commercially available at 2 dose strengths (80 mg and 20 mg) supplied in blister packs. Patients prescribed a COMETRIQ dose of 60 mg take three 20 mg capsules daily. METEOR was conducted using cabozantinib tablets at a dose of 60 mg in the cabozantinib monotherapy arm with 20 mg tablets available to manage dose reductions. The tablet formulation is currently not available commercially. In a single-dose healthy volunteer study comparing a dose of 140 mg as capsules (one 80 mg capsule + three 20 mg capsules) with 140 mg as tablets (one 100 mg tablet + two 20 mg tablets), the AUC for the tablets was 8% higher than capsules³. C_{max} was approximately 19% higher with the tablets compared with capsules and the upper limit of the 90% confidence interval around the ratio of least-squares means for C_{max} (131.65%) was outside the 80.00%-125.00% accepted bioequivalence range. Therefore, the capsule and tablet formulations cannot be considered to be bioequivalent.

Literature Support

¹Choueiri T, Escudier B, Powles T, et al. (2015). Cabozantinib versus everolimus in patients with advanced renal cell carcinoma: Results of the randomized phase 3 METEOR trial. The European Cancer Conference, Vienna, Abstract 4LBA.

²Choueiri TK, Escudier B, Powles T, et al. (2015). Cabozantinib versus everolimus in advanced renal cell carcinoma. *N Engl J Med*. Advance online publication 25 Sept 2015. DOI: 10.1056/NEJMoa1510016.

³Exelixis internal report, data on file