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Submission Request
National Comprehensive Cancer Network: Panel – Kidney Cancer**Re: Update to Clinical Evidence in Support of Cabozantinib Use in Patients with Advanced Renal Cell Carcinoma**

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With the recent U.S. Food and Drug Administration (FDA) approval of an expanded CABOMETYX[®] (cabozantinib tablets) label,¹ and recent publication of updated results from a trial of first-line use of cabozantinib in patients with advanced renal cell carcinoma (RCC),² we respectfully request on behalf of Exelixis, that the NCCN Kidney Cancer Guidelines Panel review the following information as it considers potential changes to the kidney cancer guidelines

CABOMETYX Indication: CABOMETYX is a kinase inhibitor indicated for the treatment of patients with advanced RCC.¹

FDA Clearance: CABOMETYX was initially approved by the U.S. Food and Drug Administration (FDA) in 2016 for the “treatment of patients with advanced RCC who have received prior anti-angiogenic therapy” based on results from the phase 3 METEOR trial which compared cabozantinib to everolimus. Results from CABOSUN, a randomized phase 2 study which compared CABOMETYX with sunitinib as first-line therapy, served as the basis of the December 19, 2017 FDA approval of the expanded indication “for the treatment of patients with advanced RCC”.¹

Current Placement of Cabozantinib in the NCCN Clinical Practice Guidelines for Kidney Cancer: Cabozantinib is listed as a Category 2A first-line option for intermediate- and poor-risk group RCC patients with predominant clear cell histology. Cabozantinib is also listed as a Category 1, preferred option for subsequent therapy in patients with relapsed or stage IV and surgically unresectable, predominant clear cell histology,³ and Category 2A for patients with relapsed or stage IV and surgically unresectable non-clear cell histology.³

Specific Changes and Rationale:

- Request that the Guidelines Panel consider reclassification of cabozantinib from a Category 2A to a **Category 1, preferred first-line option for intermediate- and poor-risk group RCC patients with predominant clear cell histology**. Cabozantinib demonstrated a statistically significant increase in median PFS relative to sunitinib in CABOSUN (NCT 01835158) which compared the two agents as first-line therapy in patients with intermediate- or poor risk advanced RCC with clear cell histology.^{1,2} (Additional results from this trial provided below).
- Request that the Guidelines Panel consider including cabozantinib as a **first-line option for favorable-risk RCC patients with predominant clear cell histology**. CABOMETYX is indicated for the treatment of patients with advanced RCC. The label does not restrict use to intermediate- and poor-risk patients. Although first-line use of cabozantinib in favorable-risk patients was not evaluated in CABOSUN, there is strong biological rationale for cabozantinib to provide clinical benefit to patients in all risk groups. Cabozantinib possesses potent inhibitory activity against MET, VEGFR2, and AXL which are known to influence tumor growth, metastasis, and angiogenesis.¹ Antiangiogenic drugs that target VEGF and its receptors have demonstrated significant improvements in PFS in their respective registrational studies in patients with RCC, regardless of risk factors. Inactivation of the von Hippel-Lindau (VHL) tumor suppressor protein characterizes clear cell tumors and results in the upregulation of the VEGF signaling pathway.^{4,5} Both MET and AXL are also upregulated in VHL-deficient cells.⁶⁻⁹ In VHL-deficient RCC cell lines, targeting either MET or AXL results in reduced cell viability and invasive properties, indicating that both MET and AXL may play important roles in driving oncogenesis in RCC.⁷⁻⁹ Elevated expression of MET or AXL has been shown to be associated with poor prognosis in RCC patients.^{10,11} Given the known oncogenic potential of the MET and AXL signaling pathways and

their upregulation as part of the underlying pathobiology of RCC, targeting these two oncoproteins in addition to VEGFRs may provide additional anticancer effects in RCC over more selective VEGFR inhibition strategies. This is supported by the observed clinical efficacy of cabozantinib in previously untreated patients with intermediate- or poor-risk disease^{1,3} and the efficacy observed in patients of all risk categories, including those with favorable risk, who had previously received anti-angiogenic therapy in the METEOR trial.^{1,12-13} Given the biology of RCC and mechanism of action of cabozantinib, it would be expected that when administered to first-line, favorable-risk patients, cabozantinib would maintain the antitumor activity it demonstrated in first-line intermediate- and poor-risk patients and favorable-, intermediate-, and poor-risk refractory patients.

Clinical Evidence:

First-Line RCC: CABOSUN, a phase 2 randomized, open-label, multicenter study conducted by The Alliance for Clinical Trials in Oncology (The Alliance), as part of Exelixis' collaboration with the National Cancer Institute's Cancer Therapy Evaluation Program (NCI-CTEP), compared cabozantinib (60mg once daily) with sunitinib (50mg once daily for 4 weeks on/2 weeks off) as first-line therapy in patients with advanced RCC of intermediate- or poor-risk by International Metastatic RCC Database Consortium (IMDC) criteria. Patients were stratified based on IMDC risk group and the presence/absence of bone metastases. The primary efficacy measure was investigator-assessed PFS and secondary endpoints included investigator-assessed objective response rate (ORR), overall survival (OS), and safety. CABOSUN data were subjected to retrospective review by a blinded independent radiology committee (BIRC), as well as FDA censoring rules, to support the filing of an sNDA for use of cabozantinib as first-line therapy in advanced RCC.

A total of 157 subjects were enrolled in CABOSUN (127 intermediate-risk and 30 poor-risk). Baseline demographics were balanced between the two arms.² Per the BIRC analysis, a statistically-significant improvement in PFS was demonstrated favoring the cabozantinib arm compared with the sunitinib arm, median PFS of 8.6 months for cabozantinib versus 5.3 months for sunitinib (adjusted hazard ratio [HR]=0.48, 95% CI, 0.31-0.74, two-sided P=0.0008).^{1,2} In addition, a higher objective response rate was observed for cabozantinib-treated patients compared with sunitinib-treated patients, cabozantinib 20% and sunitinib 9%.^{1,2} The median OS was longer for patients treated with cabozantinib relative to those treated with sunitinib, 26.6 months compared to 21.1 months, and the HR for OS favored cabozantinib (HR=0.80, 95% CI 0.53-1.21).² These data are summarized in Table 1 below.

Table 1: CABOSUN – Progression-Free Survival, Overall Survival, Tumor Response

Endpoint	Cabozantinib (n=79)	Sunitinib (n=78)	HR (95% CI)
PFS ^a	8.6 mos	5.3 mos	0.48 (0.31-0.74) P= 0.0008 (2-sided)
OS ^b	26.6 mos	21.2 mos	0.80 (0.53-1.21)
ORR ^a	20% (95% CI 12.0-30.8)	9% (95% CI 3.7-17.6)	

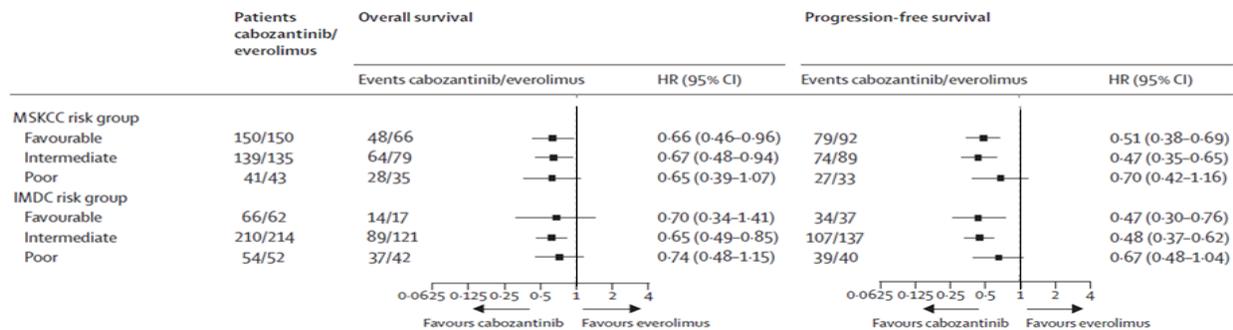
^aData Cut-Off September 15, 2016; ^bData Cut-Off July 1, 2017

The most frequent Grade 3-4 adverse reactions (≥ 5%) in patients treated with cabozantinib in CABOSUN were hypertension, diarrhea, hyponatremia, hypophosphatemia, palmar-plantar erythrodysesthesia, fatigue, ALT increased, decreased appetite, stomatitis, pain, hypotension, and syncope.¹

Subsequent Therapy RCC – Favorable Risk Patients: METEOR, a phase 3 randomized, open-label, multicenter study evaluated the safety and efficacy of cabozantinib (60mg once daily) versus everolimus (10mg once daily) in 658 patients with advanced RCC (clear cell component) who had previously received VEGFR-targeted therapy. Patients were stratified by Memorial Sloan-Kettering Cancer Center (MSKCC) risk group, favorable, intermediate, or poor. Statistically significant improvements in the primary endpoint of PFS (as assessed by BIRC), and the secondary endpoints of OS and BIRC-assessed ORR were demonstrated for cabozantinib relative to everolimus.¹ Among the 658 patients enrolled in METEOR, 46% were classified as MSKCC favorable risk. Figure 1 (below) presents a subgroup analysis of OS and PFS outcomes based on MSKCC and IMDC risk groups. The hazard ratios for PFS and OS among MSKCC favorable-risk patients were 0.51 (0.38-0.69) and 0.66 (0.46-0.96), respectively and the hazard ratios for PFS and OS among IMDC favorable-risk patients were 0.47 (0.30-0.76) and 0.70 (0.34-1.41), respectively.¹² Long-term follow-up of OS was recently published by Motzer et al.¹³ (See Figure 2 of the enclosed publication for the forest plot of OS according to MSKCC risk group, including favorable-risk patients.)¹³

Figure 1: METEOR - Forest Plots of OS and PFS Based on MSKCC and IMDC Risk Groups

Adapted from Choueiri et al. *Lancet Oncol.* 2016



Note: All 658 randomly assigned patients were included in the analyses of OS (data cut-off of Dec 31, 2015).

Abbreviation: OS=overall survival; PFS=progression-free survival; MSKCC=Memorial Sloan Kettering Cancer Center; IMDC=International Metastatic Renal Cell Carcinoma Database Consortium.

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