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Submission Request

National Comprehensive Cancer Network: Panel – Kidney Cancer

Clinical Evidence in Support of Cabozantinib in Patients with Non-Clear Cell Renal Cell Carcinoma

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On behalf of Exelixis, we respectfully request that the NCCN Kidney Cancer Guidelines Panel review the following data as it considers potential changes to the guidelines related to the management of patients with non-clear cell renal cell carcinoma (nccRCC).

CABOMETYX® (cabozantinib tablets) Indication:

CABOMETYX is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC) and patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.¹

FDA Clearance:

CABOMETYX was initially approved by the U.S. Food and Drug Administration (FDA) in April 2016 for the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy. Results from a study that compared CABOMETYX with sunitinib as first-line therapy, served as the basis of FDA approval for the expanded indication of treatment of patients with advanced RCC in December 2017. On January 14, 2019, CABOMETYX was approved for the treatment of patients with HCC who have been previously treated with sorafenib. Exelixis recommends that CABOMETYX only be used in accordance with the approved product labeling.¹

Placement of Cabozantinib in Current NCCN Kidney Cancer Guidelines:

Cabozantinib is listed as a Category 2A systemic therapy “other recommended regimen” for patients with relapsed or stage IV non-clear cell histology in Version 3.2019 of the NCCN Kidney Cancer Guidelines.²

Specific Changes:

Per the NCCN Kidney Cancer Guidelines, the Category 2A “other recommended regimen” listing for cabozantinib is based upon retrospective data and real world data reports.² One of the retrospective studies referenced, but not described in the guidelines, has since been published as a full manuscript and includes results from a larger number of patients than originally described in the referenced abstract.³ In addition, interim results from an ongoing,

prospective, Phase 2 study of cabozantinib in collecting duct RCC have been presented.⁴ We respectfully request that the NCCN Kidney Cancer Guidelines Panel review the following information as it considers potential changes to the guidelines for the treatment of nccRCC.

Rationale:

In a retrospective analysis examining the efficacy and safety of cabozantinib in 112 patients with metastatic nccRCC, cabozantinib treatment resulted in an objective response rate of 27% (95% CI: 19-36), median overall survival of 12 months (95% CI: 9.2-17 months), and median progression-free survival of 7 months (95% CI: 5.7-9 months).³ In a Phase 2, prospective, ongoing study in 9 cabozantinib-treated patients with metastatic collecting duct RCC, 2 patients achieved a partial response and 2 patients experienced stable disease.⁴

Clinical Evidence:

Martínez-Chanzá et al. conducted a multicenter, retrospective analysis to examine the clinical activity and safety of cabozantinib in patients with metastatic nccRCC. One hundred and twelve patients with nccRCC of the following histologies were included: papillary (n=66), Xp11.2 translocation (n=17), unclassified (n=15), chromophobe (n=10), and collecting duct (n=4). Sarcomatoid features were noted in 27% of tumors. Eighty-three percent of patients received cabozantinib 60 mg daily while a reduced dose of cabozantinib 40 mg was initiated in 17% of patients; 2 patients were dose-increased to 60 mg daily later in their treatment course.³

Patients had predominantly intermediate-risk (63%) or poor-risk (26%) disease and were heavily pre-treated; cabozantinib was 2nd-line or greater in 81% of patients. Of those who received previous treatment, prior therapies included other tyrosine kinase inhibitors (TKIs) (35%), immunotherapy (IO) (11%), or both TKI and IO (32%).³

At a median follow-up of 11 months, the objective response rate across all subtypes of nccRCC was 27% (95% CI: 19-36), including 1 complete response in a papillary RCC patient and 29 partial responses (PRs). In addition, 74% of patients achieved a clinical benefit (defined as an objective response plus stable disease). Median progression-free survival was 7 months (95% CI: 5.7-9 months) and the median overall survival was 12 months (95% CI: 9.2-17 months). Please refer to Table 2 within the Martínez-Chanzá manuscript, as the data also demonstrate strong activity of cabozantinib across all histologies, prior therapies, and IMDC risk groups.³

Among the overall patient population, 19 patients (17%) had a Grade 3 adverse event (AE). The most frequent Grade 3 AEs included skin toxicity (4%) and hypertension (4%). Dose reduction occurred in 46% of patients, and only 5 patients discontinued therapy. No deaths related to cabozantinib were reported.³

In addition to this analysis, interim results from a prospective, ongoing, Phase 2 study of cabozantinib 60 mg as first-line treatment in patients with metastatic collecting duct carcinoma have also been reported (NCT03354884). Of 9 patients treated, 2 patients experienced a PR and 2 achieved stable disease. All patients reported at least one Grade 1-2 AE. The most common included asthenia, diarrhea, anorexia and nausea, hand-foot syndrome, hypertension, and dysgeusia.⁴

References

- ¹ CABOMETYX® (cabozantinib tablets) [package insert]. Alameda, CA. Exelixis, Inc. January 2019.
- ² NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Kidney Cancer V.3.2019. National Comprehensive Cancer Network. 2019. Available at: https://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf
- ³ Martínez-Chanzá N, Xie W, Bilen MA, et al. Cabozantinib in advanced non-clear-cell renal cell carcinoma: a multicenter, retrospective, cohort study. Lancet Oncol. 2019. Epub. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30827746>
- ⁴ Procopio G, Ratta R, Colecchia M, et al. A phase II study of cabozantinib as first-line treatment in metastatic collecting ducts carcinoma: the BONSAI trial. J Clin Oncol 2019;37:578. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2019.37.7_suppl.578

Enclosure

Martínez-Chanzá N, Xie W, Bilen MA, et al. Cabozantinib in advanced non-clear-cell renal cell carcinoma: a multicenter, retrospective, cohort study. Lancet Oncol. 2019. Epub.