EXELIXIS®

210 E. Grand Avenue
South San Francisco
CA 94080

650.837.7000 MAIN
650.837.8205 FAX
www.exelixis.com

July 13, 2018

Submission Request
National Comprehensive Cancer Network

Re: Clinical Evidence in Support of Cabozantinib Use in Patients with Hepatocellular Carcinoma

Name	Sandra Wiejowski, PharmD	William J. Berg, MD
Phone	(650) 837-8172	(845) 587-2193
Email	swiejows@exelixis.com	wberg@exelixis.com
Company	Exelixis, Inc. 1851 Harbor Bay Parkway, Alameda, CA 94502	

Please replace the Exelixis submission dated January 24, 2018 with this submission as new information has recently become available.

On behalf of Exelixis, we respectfully request that the NCCN Hepatobiliary Cancer Guidelines Panel review the following information as it considers potential changes to the guidelines as they relate to the management of patients with hepatocellular carcinoma (HCC).

Current Placement of Cabozantinib in the NCCN Clinical Practice Guidelines for Hepatobiliary Cancer: Cabozantinib is not currently listed as a treatment option for patients with HCC in the Hepatobiliary Cancer Guidelines.

CABOMETYX® (cabozantinib tablets) Indication and Mechanism of Action: CABOMETYX is a kinase inhibitor indicated for the treatment of patients with advanced RCC.[1] *In vitro* biochemical and/or cellular assays have shown that cabozantinib inhibits the tyrosine kinase activity of multiple targets, including MET, AXL, and VEGFR.[1]

FDA Clearance/Regulatory Status: 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." Results from a study that compared CABOMETYX with sunitinib as first-line therapy, served as the basis of FDA approval of the expanded indication of "treatment of patients with advanced RCC" in December 2017. Based on results from the CELESTIAL trial (NCT 01908426), Exelixis submitted a supplemental New Drug Application (sNDA) to the FDA for CABOMETYX as a treatment for patients with previously treated advanced HCC.[2] A Prescription Drug User Fee Act (PDUFA) action date of January 14, 2019 has been assigned.[3] Cabozantinib was granted orphan designation for the treatment of HCC by the FDA in March 2017.[4] *Note: CABOMETYX is not approved for the treatment of patients with HCC. Exelixis recommends that CABOMETYX only be used in accordance with approved product labeling.*

Specific Changes: Request that the Guidelines Panel reviews the following information and considers the inclusion of cabozantinib as a Category 1 treatment option for HCC patients who have received prior systemic therapy.

Rationale: CELESTIAL compared cabozantinib with placebo in patients with advanced HCC who had received one or two prior systemic regimens, including sorafenib. Additional prior systemic therapies received included: regorafenib, lenvatinib, tivantinib, ramucirumab, anti-PD-1/PD-L1, cytotoxic chemotherapy, and investigational agents. (See Table S1 of the enclosed Supplementary Appendix for details). Cabozantinib significantly improved overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) in patients with advanced HCC after prior systemic anticancer therapy.

Clinical Evidence: CELESTIAL, a phase 3 randomized, double-blind, multicenter study, compared cabozantinib (60mg orally once daily) with placebo (orally once daily) as second- or third-line therapy in >700 patients with advanced HCC, Child-Pugh A. Patients were required to have a pathologic diagnosis of HCC not amenable to curative treatment. They were required to have received prior sorafenib, to have progressed following at least one prior systemic treatment for HCC, and could have received up to two prior systemic regimens. Patients were randomized 2:1 to cabozantinib or placebo and were stratified based on disease etiology (HBV, HCV, other), region (Asia, other), presence of macrovascular invasion and/or extrahepatic spread of disease (yes, no). Tumor assessments were performed every 8 weeks according to RECIST 1.1. Treatment continued until loss of clinical benefit or intolerable toxicity. The primary efficacy measure was OS and secondary endpoints were PFS and ORR. Crossover prior to the analysis of OS was not allowed. At the second interim analysis, 707 patients were analyzed, the primary endpoint met the critical p-value, and the study was stopped early for efficacy. Results are presented below.

Baseline demographics were balanced between the two arms. The study met its primary endpoint, demonstrating a statistically-significant improvement in OS for the cabozantinib arm compared with the placebo arm (median OS of 10.2 months for cabozantinib versus 8 months for placebo; [HR=0.76, 95% CI, 0.63-0.92, P=0.005]). A significantly longer PFS was observed for cabozantinib (5.2 months for cabozantinib vs 1.9 months for placebo; [HR=0.44, 95% CI 0.36-0.52]). A significantly higher ORR was observed for cabozantinib (4% for cabozantinib, 0.4% for placebo; P=0.009; all partial responses). Results are shown in Table 1.

Table 1: CELESTIAL – Efficacy Results[5]

Endpoint	Cabozantinib (n=470)	Placebo (n=237)	HR (95% CI)
mOS, months	10.2 (9.1-12.0)	8.0 (6.8-9.4)	0.76 (95% CI, 0.63-0.92); P=0.005
mPFS, months	5.2 (4.0-5.5)	1.9 (1.9-1.9)	0.44 (95% CI, 0.36-0.52); P<0.001
ORR,% (all partial responses)	4	<1	P=0.009
Complete Response	0	0	
Partial Response	4	<1	
Stable Disease	60	33	
Progressive Disease	21	55	
Not Evaluable or Missing	15	11	

Patients enrolled in CELESTIAL received treatment until loss of clinical benefit or intolerable toxicity. The median duration of exposure was 3.8 months and 2.0 months for the cabozantinib and placebo groups, respectively. The median average daily dose was 35.8mg cabozantinib and 58.9mg placebo. Sixty-two and 13% of the cabozantinib and placebo groups, respectively, required one or more dose reductions and 16% and 3% of the two groups discontinued therapy due to an adverse event (AE) deemed treatment-related.

The most frequent (≥ 5%) all causality Grade 3-4 AEs in patients treated with cabozantinib in CELESTIAL were palmar-planter erythrodysesthesia, hypertension, aspartate aminotransferase increased, fatigue, diarrhea, asthenia, decreased appetite, and alanine aminotransferase level increased.

References

[1]CABOMETYX® (cabozantinib) [package insert]. South San Francisco, CA. Exelixis, Inc. December 2017.

[2]Exelixis (March 15, 2018). Exelixis Submits U.S. Supplemental New Drug Application for CABOMETYX (cabozantinib) for Previously Treated Advanced Hepatocellular Carcinoma [Press Release]. Available at: http://ir.exelixis.com/phoenix.zhtml?c=120923&p=irol-newsArticle&ID=2338226

[3]Exelixis (May 29, 2018). Exelixis announces U.S. FDA accepts supplemental new drug application for CABOMETYX (cabozantinib) in previously treated advanced hepatocellular carcinoma. [Press Release]. Available at: http://ir.exelixis.com/phoenix.zhtml?c=120923&p=irol-newsArticle&ID=2351111

[4]Exelixis (March 6, 2017). Exelixis' cabozantinib granted orphan drug designation for the treatment of hepatocellular carcinoma [Press Release]. Available at: http://ir.exelixis.com/phoenix.zhtml?c=120923&p=irol-newsArticle&ID=2336592

[5]Abou-Alfa GK, Meyer T, Cheny AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018;379:54-63.

Encl:

- CABOMETYX® (cabozantinib tablets) Prescribing Information
- N Engl J Med 2018 article
- Supplementary appendix to N Engl J Med 2018 article