Exelixis Announces New Recommendations for CABOMETYX® (Cabozantinib) Tablets in Updated National Comprehensive Cancer Network Clinical Practice Guidelines

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– CABOMETYX recommended for the treatment of previously untreated advanced renal cell carcinoma across all patient risk groups –

ALAMEDA, Calif.--(BUSINESS WIRE)--Sep. 7, 2018-- Exelixis, Inc. (NASDAQ:EXEL) today announced that the National Comprehensive Cancer Network (NCCN) updated its Clinical Practice Guidelines to include new recommendations for CABOMETYX® (cabozantinib) tablets. With the updates, CABOMETYX is recommended by the NCCN for the treatment of advanced renal cell carcinoma (RCC) regardless of patient risk status (favorable-, intermediate-, and poor-risk).

Key CABOMETYX-related highlights from the updated NCCN Clinical Practice Guidelines for Kidney Cancer include:[1]

- CABOMETYX is the only preferred tyrosine kinase inhibitor (TKI) treatment option for first-line patients in the poor- and intermediate-risk groups (Category 2A)
- CABOMETYX is a recommended first-line treatment option for favorable-risk patients (Category 2B)
- CABOMETYX is the only preferred TKI treatment option for previously treated patients (Category 1)

“CABOMETYX is the only TKI indicated for the treatment of advanced kidney cancer with NCCN-preferred status for intermediate- and poor-risk groups in the first-line setting and the only TKI with preferred status for patients who have progressed on prior therapy,” said Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis. “We welcome these updated recommendations, which recognize the significance of the CABOSUN trial data included in our label as an important advance in the care of patients with this disease.”

The NCCN Clinical Practice Guidelines are the recognized standard for clinical policy in cancer care and are developed through review of evidence and recommendations from physicians and oncology researchers. The NCCN kidney cancer panel’s decision to include CABOMETYX as a Category 2A preferred option for the treatment of patients with previously untreated advanced RCC with poor- or intermediate-risk disease was based on the results of the phase 2 CABOSUN trial.

Additionally, in its recent update to the Clinical Practice Guidelines for Hepatobiliary Cancers, the NCCN added cabozantinib as a Category 1 option for the treatment of patients with hepatocellular carcinoma (HCC) (Child-Pugh Class A only) who have been previously treated with sorafenib.[2] CABOMETYX is not FDA-approved for previously treated advanced HCC. On May 29, 2018, the U.S. FDA accepted the supplemental New Drug Application for CABOMETYX in previously treated advanced HCC and assigned it a Prescription Drug User Fee Act (PDUFA) action date of January 14, 2019.

Please see Important Safety Information below and full U.S. prescribing information at **https://cabometyx.com/downloads/CABOMETYXUSPI.pdf**.

About the CABOSUN Study

On May 23, 2016, Exelixis announced that the phase 2 CABOSUN study met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in PFS compared with sunitinib in patients with advanced intermediate- or poor-risk RCC as determined by investigator assessment. The CABOSUN study was conducted by The Alliance for Clinical Trials in Oncology and was sponsored by the National Cancer Institute-Cancer Therapy Evaluation Program (NCI-CTEP) under the Cooperative Research and Development Agreement with Exelixis for the development of cabozantinib. These results were first presented by Dr. Toni Choueiri at the European Society for Medical Oncology (ESMO) 2016 Congress, and published in the *Journal of Clinical Oncology* (Choueiri, *JCO*, 2016).[3] In June 2017, a blinded independent radiology review committee (IRC) confirmed that cabozantinib provided a clinically meaningful and statistically significant improvement in the primary efficacy endpoint of investigator-assessed PFS. Results from the IRC review were presented by Dr. Toni Choueiri at the ESMO 2017 Congress.

CABOSUN was a randomized, open-label, active-controlled phase 2 trial that enrolled 157 patients with advanced RCC determined to be intermediate- or poor-risk by the IMDC criteria. Patients were randomized 1:1 to receive cabozantinib (60 mg once daily) or sunitinib (50 mg once daily, 4 weeks on followed by 2 weeks off). The primary endpoint was PFS. Secondary endpoints included overall survival, objective response rate and safety. Eligible patients were required to have locally advanced or metastatic clear-cell RCC, ECOG performance status 0-2 and had to be intermediate- or poor-risk per the IMDC criteria (Heng, *JCO*, 2009).[4] Prior systemic treatment for RCC was not permitted.

About Advanced Renal Cell Carcinoma

The American Cancer Society’s 2018 statistics cite kidney cancer as among the top ten most commonly diagnosed forms of cancer among both men and women in the U.S.[5] Clear cell RCC is the most common type of kidney cancer in adults.[6] If detected in its early stages, the five-year survival rate for RCC is high; for patients with advanced or late-stage metastatic RCC, however, the five-year survival rate is only 12 percent, with no identified cure for the disease.[7] Approximately 30,000 patients in the U.S. and 68,000 globally require treatment, and an estimated 14,000 patients in the U.S. each

year are in need of a first-line treatment for advanced kidney cancer.[7]

The majority of clear cell RCC tumors have lower than normal levels of a protein called von Hippel-Lindau, which leads to higher levels of MET, AXL and VEGF.[8,9] These proteins promote tumor angiogenesis (blood vessel growth), growth, invasiveness and metastasis.[10,11,12,13] MET and AXL may provide escape pathways that drive resistance to VEGF receptor inhibitors.[9,10]

About HCC

Liver cancer is the second-leading cause of cancer death worldwide, accounting for more than 700,000 deaths and nearly 800,000 new cases each year.[14] In the U.S., the incidence of liver cancer has more than tripled since 1980.[5] HCC is the most common form of liver cancer, making up about three-fourths of the estimated nearly 42,000 new cases in the U.S. in 2018.[5] HCC is the fastest-rising cause of cancer-related death in U.S.[15] Without treatment, patients with advanced HCC usually survive less than 6 months.[16]

About CABOMETYX® (cabozantinib)

CABOMETYX tablets are approved in the United States for the treatment of patients with advanced RCC. CABOMETYX tablets are also approved in the European Union, Norway, Iceland, Australia, Switzerland and South Korea for the treatment of advanced RCC in adults who have received prior VEGF-targeted therapy, and in the European Union for previously untreated intermediate- or poor-risk advanced RCC. In March 2017, the FDA granted orphan drug designation to cabozantinib for the treatment of advanced HCC. On March 28, 2018, Ipsen announced that the European Medicines Agency validated its application for a new indication for cabozantinib as a treatment for previously treated advanced HCC in the European Union. In 2016, Exelixis granted Ipsen exclusive rights for the commercialization and further clinical development of cabozantinib outside of the United States and Japan. In 2017, Exelixis granted exclusive rights to Takeda Pharmaceutical Company Limited for the commercialization and further clinical development of cabozantinib for all future indications in Japan.

U.S. Important Safety Information

- **Hemorrhage**: Severe and fatal hemorrhages have occurred with CABOMETYX. In two RCC studies, the incidence of Grade ≥ 3 hemorrhagic events was 3% in CABOMETYX-treated patients. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.
- **Gastrointestinal (GI) Perforations and Fistulas:** In RCC studies, fistulas were reported in 1% of CABOMETYX-treated patients. Fatal perforations occurred in patients treated with CABOMETYX. In RCC studies, gastrointestinal (GI) perforations were reported in 1% of CABOMETYX-treated patients. Monitor patients for symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula which cannot be appropriately managed or a GI perforation.
- **Thrombotic Events:** CABOMETYX treatment results in an increased incidence of thrombotic events. In RCC studies, venous thromboembolism occurred in 9% (including 5% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX-treated patients. Fatal thrombotic events occurred in the cabozantinib clinical program. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.
- **Hypertension and Hypertensive Crisis:** CABOMETYX treatment results in an increased incidence of treatment-emergent hypertension, including hypertensive crisis. In RCC studies, hypertension was reported in 44% (18% Grade ≥ 3) of CABOMETYX-treated patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy. Discontinue CABOMETYX if there is evidence of hypertensive crisis or severe hypertension despite optimal medical management.
- **Diarrhea:** In RCC studies, diarrhea occurred in 74% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **Palmar-Plantar Erythrodysesthesia (PPE):** In RCC studies, palmar-plantar erythrodysesthesia (PPE) occurred in 42% of patients treated with CABOMETYX. Grade 3 PPE occurred in 8% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPE or Grade 3 PPE until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.
- **Embryo-fetal Toxicity** may be associated with CABOMETYX. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during CABOMETYX treatment and for 4 months after the last dose.
- **Adverse Reactions:** The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, hypertension, PPE, weight decreased, vomiting, dysgeusia, and stomatitis.
- **Strong CYP3A4 Inhibitors**: If concomitant use with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage.

- **Strong CYP3A4 Inducers:** If concomitant use with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage.
- **Lactation:** Advise women not to breastfeed while taking CABOMETYX and for 4 months after the final dose.
- **Hepatic Impairment:** In patients with mild to moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see accompanying full Prescribing Information https://cabometyx.com/downloads/CABOMETYXUSPI.pdf.

About Exelixis

Founded in 1994, Exelixis, Inc. (Nasdaq: EXEL) is a commercially successful, oncology-focused biotechnology company that strives to accelerate the discovery, development and commercialization of new medicines for difficult-to-treat cancers. Following early work in model genetic systems, we established a broad drug discovery and development platform that has served as the foundation for our continued efforts to bring new cancer therapies to patients in need. We discovered our three commercially available products, CABOMETYX® (cabozantinib), COMETRIQ® (cabozantinib) and COTELLIC® (cobimetinib), and have entered into partnerships with leading pharmaceutical companies to bring these important medicines to patients worldwide. Supported by revenues from our marketed products and collaborations, we are committed to prudently reinvesting in our business to maximize the potential of our pipeline. We are supplementing our existing therapeutic assets with targeted business development activities and internal drug discovery - all to deliver the next generation of Exelixis medicines and help patients recover stronger and live longer. In July 2018, Exelixis was added to the Standard & Poor's (S&P) MidCap 400 index, which measures the performance of profitable mid-sized companies. For more information about Exelixis, please visit www.exelixis.com, follow @ExelixisInc on Twitter or like Exelixis, Inc. on Facebook.

Exelixis, the Exelixis logo, CABOMETYX, COMETRIQ and COTELLIC are registered U.S. trademarks.

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