Exelixis Initiates Phase 3 Pivotal Trial (COSMIC-311) of Cabozantinib in Patients with Radioiodine-Refractory Differentiated Thyroid Cancer Who Have Progressed after Prior VEGFR-Targeted Therapy

October 8, 2018

– Thyroid cancer is the most rapidly increasing cancer in the U.S., with incidence tripling over the past 30 years –

ALAMEDA, Calif.--(BUSINESS WIRE)--Oct. 8, 2018-- Exelixis, Inc. (Nasdaq: EXEL) today announced the initiation of a phase 3 pivotal trial (COSMIC-311) of single-agent cabozantinib in patients with radioiodine-refractory differentiated thyroid cancer (DTC) who have progressed after up to two prior vascular endothelial growth factor receptor (VEGFR)-targeted therapies. The co-primary endpoints for the trial are progression-free survival and objective response rate.

"Cabozantinib has demonstrated encouraging clinical activity in patients with radioiodine-refractory differentiated thyroid cancer in phase 1 and 2 studies, suggesting it may be a promising treatment option for patients who have progressed after prior VEGFR-targeting therapy," said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. "We look forward to enrolling patients in this global trial to learn more about the potential of cabozantinib for this intractable form of thyroid cancer."

COSMIC-311 is a multicenter, randomized, double-blind, placebo-controlled phase 3 pivotal trial that aims to enroll approximately 300 patients at approximately 150 sites globally. Patients will be randomized in a 2:1 ratio to receive either cabozantinib 60 mg or placebo once daily.

"With the incidence of thyroid cancer increasing more rapidly than any other type of cancer in the U.S., and limited options available to patients whose disease has progressed following anti-VEGFR therapy, there is an urgent need for new treatments," said Marcia Brose, M.D., Ph.D., Associate Professor of Otorhinolaryngology: Head and Neck Surgery and Director of the Center for Rare Cancers and Personalized Therapy at the Abramson Cancer Center of the University of Pennsylvania, and principal investigator of the trial. "Given the positive results from earlier stage trials, we are eager to learn more from this phase 3 study about cabozantinib's potential benefit in this patient population."

More information about this trial is available at ClinicalTrials.gov.

About Differentiated Thyroid Carcinoma

Thyroid cancer is commonly diagnosed at a younger age than most other adult cancers and is the most rapidly increasing cancer in the U.S., tripling in incidence in the past three decades.[1] Approximately 54,000 new cases of thyroid cancer will be diagnosed in the U.S. in 2018.[1] Nearly three out of four of these cases will be in women.[1] Cancerous thyroid tumors include differentiated, medullary and anaplastic forms.[1]

Differentiated thyroid tumors, which make up about 90 percent of all thyroid cancers, are typically treated with surgery followed by ablation of the remaining thyroid with radioiodine.[2] Approximately 5 to 15 percent of differentiated thyroid tumors are resistant to radioiodine treatment.[3] For these patients, life expectancy is only three to six years from the time metastatic lesions are detected.[4,5,6]

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; in the European Union for previously untreated intermediate- or poor-risk advanced RCC; and in Canada for adult patients with advanced RCC who have received prior VEGF targeted therapy. In March 2017, the FDA granted orphan drug designation to cabozantinib for the treatment of advanced HCC. In May 2018, the FDA accepted Exelixis' supplemental New Drug Application for CABOMETYX as a treatment for patients with previously treated HCC and assigned it a Prescription Drug User Fee Act action date of January 14, 2019. 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; on September 20, 2018 the CHMP provided a positive opinion for CABOMETYX as a monotherapy for the treatment of HCC in adults who have been previously treated with sorafenib. 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.

CABOMETYX is not indicated for radioiodine-refractory DTC.

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

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.

Forward-Looking Statement Disclaimer

This press release contains forward-looking statements, including, without limitation, statements related to: the potential of cabozantinib as a treatment option for patients with radioiodine-refractory differentiated thyroid cancer who have progressed after prior VEGFR-targeting therapy; and Exelixis' plans to reinvest in its business to maximize the potential of the company's pipeline, including through targeted business development activities and internal drug discovery. Any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements and are based upon Exelixis' current plans, assumptions, beliefs, expectations, estimates and projections. Forward-looking statements involve risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in the forward-looking statements as a result of these risks and uncertainties, which include, without limitation: risks and uncertainties related to regulatory review and

approval processes and Exelixis' compliance with applicable legal and regulatory requirements; the potential failure of cabozantinib to demonstrate safety and/or efficacy in COSMIC-311; uncertainties inherent in the product development process, including evolving regulatory requirements, slower than anticipated patient enrollment or inability to identify a sufficient number of clinical trial sites; the costs of conducting clinical trials, including Exelixis' dependence on third-party vendors for the development, manufacture and supply of cabozantinib; Exelixis' ability to protect its intellectual property rights; market competition; changes in economic and business conditions; and other factors affecting Exelixis and its development programs discussed under the caption "Risk Factors" in Exelixis' Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 1, 2018, and in Exelixis' future filings with the SEC. All forward-looking statements in this press release are based on information available to Exelixis as of the date of this press release, and Exelixis undertakes no obligation to update or revise any forward-looking statements contained herein.

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

[1] American Cancer Society. Key Statistics for Thyroid Cancer. https://www.cancer.org/cancer/thyroid-cancer/about/key-statistics.html. Accessed October 2018.

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