Exelixis Announces U.S. FDA Approval of CABOMETYX® (cabozantinib) for Patients with Previously Treated Radioactive Iodine-Refractory Differentiated Thyroid Cancer

September 17, 2021

– FDA approval based on phase 3 COSMIC-311 pivotal trial, which demonstrated significant improvement in progression-free survival with CABOMETYX versus placebo –

– Exelixis is prepared to fully support expanded indication immediately –

– Application approved well ahead of Prescription Drug User Fee Act target action date of December 4, 2021 –

ALAMEDA, Calif.--(BUSINESS WIRE)--Sep. 17, 2021-- Exelixis, Inc. (Nasdaq: EXEL) today announced that the U.S. Food and Drug Administration (FDA) approved CABOMETYX® (cabozantinib) for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior vascular endothelial growth factor receptor (VEGFR)-targeted therapy and who are radioactive iodine-refractory or ineligible. The FDA granted Breakthrough Therapy designation and Priority Review to CABOMETYX and its approval comes more than two months ahead of the Prescription Drug User Fee Act (PDUFA) target action date of December 4, 2021. DTC is the most common type of thyroid cancer in the U.S., and patients who are resistant to radioactive iodine treatment face a poor prognosis.[1,2,3,4]

“Before today, patients with radioactive iodine-refractory differentiated thyroid cancer who have progressed following prior VEGFR-targeted therapy were facing aggressive disease and no standard treatment option,” said Marcia S. Brose, M.D., Ph.D., Chief, Cancer Center Operation Sidney Kimmel Cancer Center at Jefferson Torresdale Hospital, Co-Director, Community Based Clinical Trials, Sidney Kimmel Cancer Center at Thomas Jefferson University, and principal investigator of COSMIC-311. “In the COSMIC-311 pivotal phase 3 trial, CABOMETYX extended the time patients live without progression of their cancer. The FDA approval of CABOMETYX is an important advancement for these patients who are badly in need of new treatment options.”

The approval is based on results from COSMIC-311, a phase 3 pivotal trial evaluating CABOMETYX versus placebo in patients with radioactive iodine-refractory DTC who progressed after up to two prior VEGFR-targeted therapies. At a planned interim analysis, CABOMETYX significantly reduced the risk of disease progression or death versus placebo ($p<0.0001$) in the intent-to-treat population. At a follow-up analysis with a median follow-up of 10.1 months, the median progression-free survival (PFS) as assessed by blinded independent radiology committee was 11.0 months for patients treated with CABOMETYX (n=170) compared with 1.9 months for patients treated with placebo (n=88); hazard ratio (HR): 0.22; 95% confidence interval (CI): 0.15–0.31. These results will be presented at the 2021 European Society of Medical Oncology (ESMO) Congress this month.

“This approval of CABOMETYX builds on our existing legacy of delivering transformational medicines for patients with difficult-to-treat forms of cancer,” said Michael M. Morrissey, Ph.D., President and Chief Executive Officer, Exelixis. “We would like to thank the clinical trial participants, the physicians and their staff who participated in the COSMIC-311 trial and to acknowledge the team at the FDA for their collaboration during the quick review of our application.”

The most common adverse events (AEs) reported in at least 25% of patients treated with CABOMETYX were diarrhea, palmar-plantar erythrodysesthesia, fatigue, hypertension and stomatitis. Grade 3/4 AEs that occurred in at least 5% of patients were palmar-plantar erythrodysesthesia, hypertension, fatigue, diarrhea and stomatitis. Serious AEs occurred in 34% of patients who received CABOMETYX, and the most common serious AEs reported in at least 2% of patients included diarrhea, pleural effusion, pulmonary embolism and dyspnea. Fatal AEs occurred in 1.6% of patients treated with CABOMETYX arm, including arterial hemorrhage (0.8%) and pulmonary embolism (0.8%). Dose reductions were required in 56% of patients treated with CABOMETYX, and 22% of patients required a second dose reduction. AEs leading to discontinuation of CABOMETYX occurred in 5% of patients.

“Patients with differentiated thyroid cancer who have progressed following prior therapy and are radioactive iodine-refractory often face a poor prognosis and have limited treatment options,” said Gary Bloom, Executive Director of ThyCa: Thyroid Cancer Survivors’ Association. “We are excited about the latest approval of CABOMETYX, which will offer hope for patients with this type of thyroid cancer.”

About COSMIC-311

COSMIC-311 was a multicenter, randomized, double-blind, placebo-controlled phase 3 pivotal trial that enrolled 258 patients at 164 sites globally. Patients were randomized in a 2:1 ratio to receive either CABOMETYX 60 mg or placebo once daily. The primary endpoints were PFS and objective response rate. Exelixis is sponsoring COSMIC-311, and Ipsen is co-funding the trial. More information about this trial is available at ClinicalTrials.gov.

About DTC

Approximately 44,000 new cases of thyroid cancer will be diagnosed in the U.S. in 2021.[5] Nearly three out of four of these cases will be in women, and the disease is more commonly diagnosed at a younger age compared to most other adult cancers.[1] While cancerous thyroid tumors include differentiated, medullary and anaplastic forms, differentiated thyroid tumors make up about 90% of cases.[1] These include papillary, follicular and Hürthle cell cancer.[1] DTC is typically treated with surgery followed by ablation of the remaining thyroid tissue with radioiodine, but approximately 5% to 15% of cases are resistant to radioiodine treatment.[1,6] For these patients, life expectancy is only three to five years from the time metastatic lesions are detected.[2,3,4]

About CABOMETYX® (cabozantinib)

In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced RCC; for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib; for patients with advanced RCC as a first-line treatment in combination with nivolumab; and for adult and pediatric patients 12 years of age and older with locally advanced or metastatic DTC that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible. CABOMETYX tablets have also received regulatory approvals in the European Union and additional countries and regions worldwide. In 2016, Exelixis granted Ipsen exclusive rights for the commercialization and further clinical development of cabozantinib outside of the U.S. 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. Exelixis holds the exclusive rights to develop and commercialize cabozantinib in the U.S.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 62% of CABOMETYX patients. Grade 3 diarrhea occurred in 10% of CABOMETYX patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 45% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Hepatotoxicity: CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone.

Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

Proteinuria: Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw (ONJ): ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

Impaired Wound Healing: Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic findings on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Thyroid Dysfunction: Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients.

Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

Hypocalcemia: CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN.

In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients.

Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.

ADVERSE REACTIONS

The most common (≥20%) adverse reactions are:

CABOMETYX as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, constipation.

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

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

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

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 system genetics, 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. Our discovery efforts have resulted in four commercially available products, CABOMETYX® (cabozantinib), COMETRIQ® (cabozantinib), COTELLIC® (cobimetinib) and MINNEBRO® (esaxerenone), and we 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. Exelixis is a member of the Standard & Poor's (S&P) MidCap 400 index, which measures the performance of profitable mid-sized companies. In November 2020, the company was named to *Fortune*'s 100 Fastest-Growing Companies list for the first time, ranking 17th overall and the third-highest biopharmaceutical company. For more information about Exelixis, please visit www.exelixis.com, follow @ExelixisInc on Twitter or like Exelixis, Inc. on Facebook.

Forward-Looking Statements

This press release contains forward-looking statements, including, without limitation, statements related to: the therapeutic potential of CABOMETYX for patients with radioactive iodine-refractory DTC who have progressed following prior VEGFR-targeted therapy; Exelixis' plans to present data from COSMIC-311 at the 2021 ESMO Congress; 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: the degree of market acceptance that CABOMETYX may achieve in the territories where it is approved and availability of coverage and reimbursement for CABOMETYX; Exelixis' ability to invest in the resources necessary to successfully commercialize CABOMETYX in the territories where it is approved and to execute its commercial strategy; Exelixis' ability to maintain and scale adequate sales, marketing, market access and product distribution capabilities for its products or to enter into and maintain agreements with third parties to do so; Exelixis' continuing compliance with applicable legal and regulatory requirements; the availability of data at referenced times; the continuing COVID-19 pandemic and its impact on Exelixis' commercial activities; Exelixis' ability to protect its intellectual property rights; Exelixis' dependence on third-party vendors for the development, manufacture and supply of cabozantinib; market competition, including the potential for competitors to obtain approval for generic versions of CABOMETYX; changes in economic and business conditions; and other factors affecting Exelixis and its commercial programs and partnerships discussed under the caption "Risk Factors" in Exelixis' Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 5, 2021, 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, except as required by law.

[1] Cooper DS, et al. 2009. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 19:1167–1214.

[2] Fugazzola L, et al. 2019. 2019 European Thyroid Association Guidelines for the Treatment and Follow-Up of Advanced Radioiodine-Refractory Thyroid Cancer. *Eur Thyroid J*. 8:227–245.

[3] Pacini F, et al. 2012. Radioactive iodine-refractory differentiated thyroid cancer: unmet needs and future directions. *Expert Rev Endocrinol Metab*. 7:541–554

[4] Durante C, et al. 2006. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab*. 91:2892–2899

[5] American Cancer Society. About Thyroid Cancer. Available at: https://www.cancer.org/cancer/thyroid-cancer/about.html. Accessed September 2021.

[6] Worden F. 2014. Treatment strategies for radioactive iodine-refractory differentiated thyroid cancer. *Ther Adv Med Oncol*. 6:267–279.

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Investors:
Susan Hubbard
EVP, Public Affairs and Investor Relations
Exelixis, Inc.
(650) 837-8194
shubbard@exelixis.com

Media:
Lindsay Treadway
Executive Director, Public Affairs and Advocacy Relations
Exelixis, Inc.
(650) 837-7522
ltreadway@exelixis.com

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