Exelixis Announces Final Results from Phase 3 COSMIC-311 Pivotal Trial of CABOMETYX® in Patients with Previously Treated Radioactive Iodine-Refractory Differentiated Thyroid Cancer Presented at ESMO 2021

September 20, 2021

– At a median follow-up of 10.1 months, median progression-free survival was 11.0 months for CABOMETYX compared with 1.9 months for placebo –

– Results served as a basis for the recent U.S. FDA approval of CABOMETYX for adult and pediatric patients 12 and older with locally advanced or metastatic DTC that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible –

ALAMEDA, Calif.--(BUSINESS WIRE)--Sep. 20, 2021-- Exelixis, Inc. (Nasdaq: EXEL) today announced final results from the phase 3 COSMIC-311 pivotal trial of CABOMETYX® (cabozantinib) in patients with previously treated radioactive iodine-refractory differentiated thyroid cancer (DTC). Following a previous announcement that the trial met one of the two primary endpoints of significant improvement versus placebo in progression-free survival (PFS) assessed by blinded independent radiology committee (BIRC; p<0.0001), the results of the final analysis are being presented during the Mini Oral Session – NETs and Endocrine Tumours at 5:30 p.m. CEST on Monday, September 20 at the 2021 European Society of Medical Oncology (ESMO) Congress (LBA67). At a median follow-up of 10.1 months, the significant improvement in PFS with CABOMETYX was maintained, with consistent benefit in subgroups based on prior treatment.

“Given the urgent need for new treatments for differentiated thyroid cancer, I’m encouraged to see that cabozantinib benefited patients in COSMIC-311 both at a longer follow-up and across prior therapy subgroups,” said Jaume Capdevila, M.D., Ph.D., Medical Oncologist at Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, and a COSMIC-311 study investigator. “These strong findings, which formed the basis for the recent U.S. FDA approval, further support cabozantinib as an important new treatment option for patients with radioactive iodine-refractory differentiated thyroid cancer who previously had no standard of care following disease progression on anti-VEGFR therapy.”

At a median follow-up of 10.1 months, CABOMETYX reduced the risk of disease progression or death versus placebo (hazard ratio [HR]: 0.22; 96% confidence interval [CI]: 0.15–0.32) in the intent-to-treat (ITT) population. Median PFS as assessed by BIRC was 11.0 months for patients treated with CABOMETYX (n=170) compared with 1.9 months for patients treated with placebo (n=88). Subgroup analyses demonstrated that CABOMETYX improved PFS versus placebo irrespective of prior exposure to lenvatinib and/or sorafenib:

- Prior sorafenib/no lenvatinib: median PFS was 16.6 months for patients treated with CABOMETYX (n=63) compared with 3.2 months for placebo (n=33) (HR: 0.13; 95% CI: 0.06–0.26).
- Prior lenvatinib/no sorafenib: median PFS was 5.8 months for patients treated with CABOMETYX (n=68) compared with 1.9 months for placebo (n=34) (HR: 0.28; 95% CI: 0.16–0.48).
- Prior sorafenib and lenvatinib: median PFS was 7.6 months for patients treated with CABOMETYX (n=39) compared with 1.9 months for placebo (n=21) (HR: 0.27; 95% CI: 0.13–0.54).

An updated analysis for the primary endpoint of objective response rate (ORR) as assessed by BIRC in the ITT population favored CABOMETYX at 11%, including one complete response, versus 0% for placebo. Median overall survival, an additional endpoint, was 19.4 months for patients treated with CABOMETYX and not estimable for patients treated with placebo (HR: 0.76; 95% CI: 0.45–1.31).

The safety profile was consistent with that previously observed for CABOMETYX, and adverse events (AEs) were managed with dose modifications. The discontinuation rate due to treatment-emergent AEs was 8.8% for CABOMETYX versus 0% for placebo. Rates of grade 3/4 treatment-emergent AEs were 62% for CABOMETYX versus 28% for placebo, with no treatment-related deaths. Dose reductions due to AEs were required in 67% of patients treated with CABOMETYX versus 5% for placebo.

“Following the recent U.S. FDA approval, we are pleased to share these detailed results at this year’s ESMO which show CABOMETYX continued to benefit these patients with advanced differentiated thyroid cancer in the trial at a longer follow-up,” said Michael M. Morrissey, Ph.D., President and Chief Executive Officer, Exelixis. “This patient population faces a poor prognosis and previously had very limited treatment options. We are thrilled that eligible patients in the U.S. now have CABOMETYX as an approved treatment option and will continue to work with our partners on their efforts to bring CABOMETYX to even more patients worldwide.”

Results from COSMIC-311 served as the basis for the September 17, 2021 U.S. Food and Drug Administration (FDA) approval of CABOMETYX for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic DTC that has progressed following prior vascular endothelial growth factor receptor (VEGFR)-targeted therapy and who are radioactive iodine-refractory or ineligible. The application was approved well ahead of the Prescription Drug User Fee Act (PDUFA) target action date of December 4, 2021.

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 ORR. 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.[1] 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.[2] While cancerous thyroid tumors include differentiated, medullary and anaplastic forms, differentiated thyroid tumors make up about 90% of cases.[2] These include papillary, follicular and Hürthle cell cancer.[2] 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. [2,3] For these patients, life expectancy is only three to five years from the time metastatic lesions are detected.[4,5,6]

About CABOMETYX® (cabozantinib)
In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced renal cell carcinoma (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 presentation of data from the COSMIC-311 pivotal trial at ESMO 2021; the therapeutic potential of CABOMETYX for patients with radioactive iodine-refractory DTC; Exelixis' plans to work with its partners to bring CABOMETYX to more eligible patients worldwide; 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 availability of data at the referenced times; complexities and the unpredictability of the regulatory review and approval processes in the U.S. and elsewhere; Exelixis' continuing compliance with applicable legal and regulatory requirements; the potential failure of CABOMETYX to demonstrate safety and/or efficacy in future trials; unexpected concerns that may arise as a result of the occurrence of adverse safety events or additional data analyses of clinical trials evaluating CABOMETYX; Exelixis' dependence on third-party vendors for the development, manufacture and supply of cabozantinib; Exelixis' ability to protect its intellectual property rights; market competition, including the potential for competitors to obtain approval for generic versions of CABOMETYX; changes in economic and business conditions, including as a result of the COVID-19 pandemic; 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 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] American Cancer Society. About Thyroid Cancer. Available at: https://www.cancer.org/cancer/thyroid-cancer/about.html. Accessed September 2021.
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[3] Worden F. 2014. Treatment strategies for radioactive iodine-refractory differentiated thyroid cancer. *Ther Adv Med Oncol*. 6:267–279.
[4] 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.
[5] Pacini F, et al. 2012. Radioactive iodine-refractory differentiated thyroid cancer: unmet needs and future directions. *Expert Rev Endocrinol Metab*. 7:541–554.
[6] 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.

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