Exelixis Announces U.S. FDA Approval of CABOMETYX® (cabozantinib) for Patients with Previously Treated Advanced Neuroendocrine Tumors

March 26, 2025

– FDA approval based on the phase 3 CABINET pivotal trial, which demonstrated a statistically significant and clinically meaningful improvement in progression-free survival versus placebo –

– CABOMETYX is now the first and only systemic treatment that is FDA approved for previously treated neuroendocrine tumors regardless of primary tumor site, grade, somatostatin receptor expression and functional status –

– Exelixis is prepared to immediately support these new indications –

ALAMEDA, Calif.--(BUSINESS WIRE)--Mar. 26, 2025-- Exelixis, Inc. (Nasdaq: EXEL) today announced that the U.S. Food and Drug Administration (FDA) has approved CABOMETYX® (cabozantinib) for the treatment of 1) adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors (pNET); and 2) adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated extra-pancreatic NET (epNET). NET are heterogeneous tumors that arise from the neuroendocrine cells of the digestive tract and other organs, such as the lung and pancreas. Most patients with advanced disease face a poor prognosis.[1,2,3,4]

“The characteristics of NET vary widely from patient to patient, and very few treatment options have demonstrated the ability to improve outcomes across such a heterogeneous population,” said Jennifer Chan, M.D., M.P.H., study chair for the CABINET trial, Clinical Director of the Gastrointestinal Cancer Center and Director of the Program in Carcinoid and Neuroendocrine Tumors at Dana-Farber Cancer Institute. “It was encouraging to see that cabozantinib resulted in significant delays in disease progression in the CABINET trial—regardless of primary tumor site and grade. This FDA approval marks a meaningful advancement, which may establish an important new treatment option for patients, without limitations based on somatostatin receptor expression and functional status.”

The FDA approval—adding to five previous approvals for CABOMETYX—is based on results from CABINET, a phase 3 pivotal trial evaluating CABOMETYX compared with placebo in two cohorts of patients with previously treated NET: advanced pNET and advanced epNET. Final progression-free survival results were presented at the 2024 European Society for Medical Oncology Congress and published in *The New England Journal of Medicine.* In January 2025, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Neuroendocrine and Adrenal Tumors were updated to include cabozantinib as a category 1 preferred regimen for the majority of well-differentiated advanced NET following specific treatments, and as a category 2A preferred regimen for other forms of advanced NET, depending on tumor grade and different requirements for prior therapy.

“As a company committed to improving the standard of care for people living with advanced, difficult-to-treat cancers, we are proud to bring CABOMETYX to patients with previously treated advanced neuroendocrine tumors,” said Amy Peterson, M.D., Executive Vice President, Product Development & Medical Affairs, and Chief Medical Officer, Exelixis. “I would like to extend our sincere gratitude to the Alliance for Clinical Trials in Oncology for conducting the CABINET trial, to the FDA for their collaboration on the review of this application and to all the patients and physicians who participated in this important study. Looking forward, we are doubling down on our commitment to the NET community as we prepare to initiate our STELLAR-311 pivotal trial examining zanzalintinib versus everolimus in the first half of 2025.”

The safety profile of CABOMETYX observed in each CABINET cohort was consistent with its known safety profile. No new safety signals were identified; however, the incidence of hypertension, regardless of treatment arm, was higher in NET patients compared to other approved tumor types. A majority of patients treated with CABOMETYX required dose modifications or reductions to manage adverse events.

"As a person who has lived with neuroendocrine tumors for over 14 years—and who has met many patients and caregivers in that time—I know that there are many challenges that come with this diagnosis, including the need to closely monitor the disease and adapt your treatment approach if faced with progression,” said Cindy Lovelace, co-founder of The Healing NET Foundation. “As very few targeted therapies have been approved for advanced NET in recent years, I am excited that CABOMETYX brings new hope to the patients in our community who have been in need of effective new treatment options.”

About CABINET (Alliance A021602)
CABINET (Randomized, Double-Blinded Phase III Study of **CAB**ozantinib versus Placebo **I**n Patients with Advanced **NE**uroendocrine **T**umors After Progression on Prior Therapy) is sponsored by the National Cancer Institute (NCI), part of the National Institutes of Health, and is being led and conducted by the NCI-funded Alliance for Clinical Trials in Oncology with participation from the NCI-funded National Clinical Trials Network as part of Exelixis’ collaboration through a Cooperative Research and Development Agreement with the NCI’s Cancer Therapy Evaluation Program.

CABINET is a multicenter, randomized, double-blinded, placebo-controlled phase 3 pivotal trial that had enrolled a total of 298 patients in the U.S at the time of the final analysis. Patients were randomized 2:1 to cabozantinib (60 mg) or placebo in two separately powered cohorts (pNET, n=99; epNET, n=199). The epNET cohort included patients with the following primary tumor sites: gastrointestinal (GI) tract, lung, unknown primary sites and other organs. Each cohort was randomized separately and had its own statistical analysis plan. Patients must have had measurable disease per RECIST 1.1 criteria and must have experienced disease progression or intolerance after at least one U.S. FDA-approved line of prior systemic therapy other than somatostatin analogs. The primary endpoint in each cohort was PFS per RECIST 1.1 by blinded independent central review. Secondary endpoints included overall survival, objective response rate and safety. More information about this trial is available at ClinicalTrials.gov.

About NET

NET are cancers that begin in the specialized cells of the body's neuroendocrine system. [1] These cells have traits of both hormone-producing endocrine cells and nerve cells.[1] In 2024, the estimated prevalence of NET in the U.S. was more than 380,000 people.[5] It is estimated that 161,000 to 192,000 people are living with unresectable, locally advanced or metastatic NET.[5] The number of people diagnosed with NET has been increasing in recent decades.[6] Functional NET release peptide hormones that can cause debilitating symptoms, like diarrhea, hypertension and flushing which may require focused treatment, while symptoms of non-functional NET are related primarily to tumor growth.[7,8,9,10,11] Most NET take years to develop and grow slowly, but eventually all patients with advanced or metastatic NET will develop refractory and progressing disease.[12,13]

NET can develop in any part of the body, but most commonly start in the GI tract or in the lungs, where they have historically been referred to as carcinoid tumors and are more recently called epNET.[1] The five-year survival rates for advanced GI and lung NET tumors are 68% and 55%, respectively.[2,3] NET can also start in the pancreas, where they tend to be more aggressive, with a five-year survival rate of only 23% for advanced disease.[1,4] For advanced NET patients, treatment options include somatostatin analogs, chemotherapy, molecular targeted therapy and peptide-receptor radionuclide therapy.[14]

About CABOMETYX® (cabozantinib)
In the U.S., CABOMETYX tablets are approved as monotherapy for the treatment of patients with advanced renal cell carcinoma (RCC) and in combination with nivolumab as a first-line treatment for patients with advanced RCC; for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib; for adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible; for the treatment of adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors (pNET); and adult and pediatric patients 12 years of age and older with previously treated, unresectable, locally advanced or metastatic, well-differentiated extra-pancreatic NET (epNET). CABOMETYX tablets have also received regulatory approvals in over 65 countries outside the U.S. and Japan, including the European Union. In 2016, Exelixis granted Ipsen Pharma SAS 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: CABOMETYX can cause severe and fatal hemorrhages. The incidence of Grade 3-5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3-4 hemorrhage and before surgery. Do not administer to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, and gastrointestinal (GI) perforations, including fatal cases, each occurred in 1% of CABOMETYX patients. Monitor for signs and symptoms, and discontinue CABOMETYX in patients with Grade 4 fistulas or GI perforation.

Thrombotic Events: CABOMETYX can cause arterial or venous thromboembolic event. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events have occurred. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events.

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. In CABINET (n=195), hypertension occurred in 65% (26% Grade 3) 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; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with antihypertensive therapy or for hypertensive crisis.

Diarrhea: CABOMETYX can cause diarrhea and it occurred in 62% (10% Grade 3) of treated 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): CABOMETYX can cause PPE and it occurred in 45% of treated patients (13% Grade 3). Withhold CABOMETYX until PPE resolves or decreases to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Hepatotoxicity: CABOMETYX in combination with nivolumab in RCC can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. Monitor liver enzymes before initiation of treatment and periodically. Consider more frequent monitoring as compared to when the drugs are administered as single agents. Consider withholding CABOMETYX and/or nivolumab, initiating corticosteroid therapy, and/or permanently discontinuing the combination for severe or life-threatening hepatotoxicity.

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. 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. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

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): CABOMETYX can cause ONJ and it occurred in <1% of treated patients. 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. Withhold CABOMETYX for development of ONJ until complete resolution; resume at a reduced dose.

Impaired Wound Healing: CABOMETYX can cause impaired wound healing. Withhold CABOMETYX for at least 3 weeks prior to elective surgery.

Do not administer 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): CABOMETYX can cause RPLS. Perform evaluation for RPLS and diagnose by characteristic finding on MRI any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Thyroid Dysfunction: CABOMETYX can cause thyroid dysfunction, primarily hypothyroidism, and it occurred in 19% of treated patients (0.4% Grade 3). Assess for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitor for signs and symptoms during treatment.

Hypocalcemia: CABOMETYX can cause hypocalcemia, with the highest incidence in DTC patients. Based on the safety population, hypocalcemia occurred in 13% of CABOMETYX patients (2% Grade 3 and 1% Grade 4).

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

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception during treatment with CABOMETYX 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, and 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 or Moderate CYP3A4 Inducers: If coadministration with strong or moderate 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.

Pediatric Use: Physeal widening has been observed in children with open growth plates when treated with CABOMETYX. Physeal and longitudinal growth monitoring is recommended in children (12 years and older) with open growth plates. Consider interrupting or discontinuing CABOMETYX if abnormalities occur. The safety and effectiveness of CABOMETYX in pediatric patients less than 12 years of age have not been established.

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
Exelixis is a globally ambitious oncology company innovating next-generation medicines and regimens at the forefront of cancer care. Powered by drug discovery and development excellence, we are rapidly evolving our product portfolio to target an expanding range of tumor types and indications with our clinically differentiated pipeline of small molecules, antibody-drug conjugates and other biotherapeutics. This comprehensive approach harnesses decades of robust investment in our science and partnerships to advance our investigational programs and extend the impact of our flagship commercial product, CABOMETYX® (cabozantinib). Exelixis is driven by a bold scientific pursuit to create transformational treatments that give more patients hope for the future. For information about the company and its mission to help cancer patients recover stronger and live longer, visit www.exelixis.com, follow @ExelixisInc on X (Twitter), like Exelixis, Inc. on Facebook and follow Exelixis on LinkedIn.

Forward-Looking Statements
This press release contains forward-looking statements, including, without limitation, statements related to: the therapeutic potential of CABOMETYX for patients with previously treated advanced neuroendocrine tumors; Exelixis' ability or plans to immediately support these new indications; Exelixis' commitment to improving the standard of care for people living with advanced, difficult-to-treat cancers, including within the NET community; timing of plans to initiate the STELLAR-311 pivotal trial examining zanzalintinib versus everolimus; and Exelixis' scientific pursuit to create transformational treatments that give more patients hope for the future. 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 of CABOMETYX in the territories where it is approved and availability of coverage and reimbursement for this product; 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; 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 detailed from time to time under the caption "Risk Factors" in Exelixis' most recent Annual Report

on Form 10-K and subsequent Quarterly Reports on Form 10-Q, and in Exelixis' other future filings with the Securities and Exchange Commission. 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.

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