Exelixis Announces Results from Subgroup Analysis of Phase 3 CABINET Pivotal Study Evaluating Cabozantinib in Advanced Gastrointestinal Neuroendocrine Tumors Presented at ASCO GI 2025

January 24, 2025

– Cabozantinib reduced the risk of disease progression or death by 50 percent compared with placebo in patients with advanced gastrointestinal neuroendocrine tumors –

– Supplemental New Drug Application under review with the U.S. FDA for cabozantinib for the treatment of patients with advanced neuroendocrine tumors based on findings from CABINET –

ALAMEDA, Calif.--(BUSINESS WIRE)--Jan. 24, 2025-- Exelixis, Inc. (Nasdaq: EXEL) today announced results from a subgroup analysis of the phase 3 CABINET pivotal study of patients with extra-pancreatic neuroendocrine tumors (epNET) arising in the gastrointestinal (GI) tract. The analysis showed cabozantinib was associated with an improvement in progression-free survival (PFS) compared with placebo in patients with advanced GI neuroendocrine tumors (NET), which was a subgroup of the epNET cohort. These results are being presented today during Poster Session B: Cancers of the Pancreas, Small Bowel, and Hepatobiliary Tract, at 11:30 a.m. PT on January 24 at the American Society of Clinical Oncology 2025 Gastrointestinal Cancers Symposium (ASCO GI 2025).

“Treating neuroendocrine tumors after disease progression can be challenging, including for those with tumors in the gastrointestinal tract, as treatment options are limited,” said Jonathan Strosberg, M.D., President Emeritus, North American Neuroendocrine Tumor Society and Chair, GI Research Program, Moffitt Cancer Center and Research Institute. “This subgroup analysis from the CABINET study showed that cabozantinib improved progression-free survival for patients with tumors arising in the GI tract and provides a more detailed picture of how patients with the most common form of this cancer may benefit from this treatment. As a physician, I’m encouraged by these findings, as they suggest cabozantinib has potential to become a standard of care for patients greatly in need of new options.”

This subgroup analysis included 116 of the 203 patients in the epNET cohort. The most common primary tumor locations were ileum/cecum (54%), small intestine with location not specified (20%), non-cecum colon or rectum (11%), stomach (4%), duodenum (3%), jejunum (3%) and non-specified midgut site (3%).

Cabozantinib was associated with improved PFS by blinded independent central review compared with placebo for patients with GI NET (hazard ratio: 0.50; 95% confidence interval: 0.28-0.88; one-sided stratified log-rank P=0.007). Median PFS was 8.5 months with cabozantinib compared with 5.6 months with placebo. Cabozantinib demonstrated potential benefit across clinical factors, including grade, functional status, concurrent somatostatin agent use, and prior therapy with Lu-177 dotatate or everolimus. One patient achieved a partial response with cabozantinib versus none with placebo, and 48 versus 30 patients, respectively, achieved stable disease.

“These new data add to the robust results from the CABINET trial that demonstrate the benefits of cabozantinib across a wide range of patients with neuroendocrine tumors and further underscore the potential of cabozantinib to become a much-needed new option for those with GI NET, which accounts for the majority of real-world patients with this tumor type,” said Amy Peterson, M.D., Executive Vice President, Product Development & Medical Affairs, and Chief Medical Officer, Exelixis. “We look forward to continuing to work with the U.S. FDA as they review our regulatory application for cabozantinib for the treatment of patients with previously treated advanced neuroendocrine tumors.”

The safety profile of cabozantinib observed in patients with GI NET was consistent with its known safety profile; no new safety signals were identified. The most frequent grade 3/4 adverse events included hypertension (19% of patients receiving cabozantinib and 4% receiving placebo), diarrhea (13% and 4%, respectively) and fatigue (10% and 4%). Three grade 5 events occurred in the cabozantinib arm possibly related to cabozantinib: one due to cardiac arrest and two not specified.

As announced in August 2023, the Alliance for Clinical Trials in Oncology independent Data and Safety Monitoring Board unanimously recommended that the CABINET trial be stopped early and unblinded due to the substantial improvement in PFS observed at an interim analysis. Final PFS results were presented at the 2024 European Society of Medical Oncology Congress and published concurrently in the *New England Journal of Medicine*. In August 2024, Exelixis announced that the U.S. Food and Drug Administration (FDA) had accepted the supplemental New Drug Application (sNDA) for cabozantinib for the treatment of previously treated, advanced NET and assigned a Prescription Drug User Fee Act target action date of April 3, 2025.

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 (pancreatic NET, n=95; epNET, n=203). The epNET cohort included patients with the following primary tumor sites: 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.[2] It is estimated that 161,000 to 192,000 people are living with unresectable, locally advanced or metastatic NET.[2] The number of people diagnosed with NET has been increasing in recent decades.[3] 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.[4,5] Most NET take years to develop and grow slowly, but eventually all patients with advanced or metastatic NET will develop refractory and progressing disease.[6,7]

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.[8,9] 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.[1,10] For advanced NET patients, treatment options include somatostatin analogs, chemotherapy, molecular targeted therapy and peptide-receptor radionuclide therapy.[11]

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 for patients 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, and; 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. 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.

CABOMETYX is not indicated as a treatment for NET.

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, 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 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 http://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 presentation of detailed results from the CABINET trial at ASCO GI 2025; the therapeutic potential of cabozantinib as a treatment across a wide range of patients with neuroendocrine tumors and the potential of cabozantinib to become a much-needed new option for those with GI NET; the regulatory review process with respect to Exelixis' sNDA for cabozantinib in previously treated advanced NET, including the Prescription Drug User Fee Act target action date assigned by the FDA; 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 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 cabozantinib to demonstrate safety and/or efficacy in future clinical testing; unexpected concerns that may arise as a result of the occurrence of adverse safety events or additional data analyses of clinical trials evaluating cabozantinib; the costs of conducting clinical trials; 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; and other factors affecting Exelixis and its development programs 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' 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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