Exelixis Highlights Positive Results for CABOMETYX® (cabozantinib) in Patients with Metastatic Papillary Renal Cell Carcinoma in SWOG S1500/PAPMET Study at ASCO GU

February 13, 2021

– Results of phase 2 trial show CABOMETYX significantly improved progression-free survival versus current guideline-preferred therapy –

***– Data to be presented during the 2021 American Society of Clinical Oncology's Genitourinary Cancers Symposium and simultaneously published in* The Lancet –**

ALAMEDA, Calif.--(BUSINESS WIRE)--Feb. 13, 2021-- Exelixis, Inc. (NASDAQ: EXEL) today announced positive phase 2 results for CABOMETYX® (cabozantinib) compared with sunitinib, the current preferred therapy according to U.S. cancer treatment guidelines,[1] in patients with metastatic papillary renal cell carcinoma (PRCC), a form of kidney cancer. The data from the S1500 trial (also called "PAPMET"), which was designed and managed by SWOG Cancer Research Network, will be presented on Saturday, February 13th during the Oral Abstract Session: Renal Cell Cancer at 10:00 – 11:15 a.m. PT at the 2021 American Society of Clinical Oncology's Genitourinary Cancers Symposium (ASCO GU), which is being held virtually, February 11-13, 2021. The findings will be simultaneously published in *The Lancet*.

"This is the first randomized trial specific to metastatic papillary renal cell carcinoma to show a clinically and statistically significant benefit with a targeted therapy, CABOMETYX, over an existing standard of care," said Dr. Sumanta Pal, Clinical Professor and Co-Director of the Kidney Cancer Program, City of Hope, and SWOG's principal investigator for the study. "The progression-free survival benefit seen in this trial is a meaningful improvement for patients with this form of kidney cancer. Based on these findings, there is strong evidence for the use of CABOMETYX in this setting."

"The PAPMET trial was sponsored by the National Cancer Institute's drug development program in the Cancer Therapy Evaluation Program, which facilitates collaborations between pharmaceutical companies as well as collaborations between companies and academic investigators. In the case of PAPMET, the National Cancer Institute brought Exelixis, AstraZeneca and Pfizer together with oncologists from SWOG to organize this trial to define which of the tested therapies is most effective for patients with papillary renal cell carcinoma," said Dr. John Wright, Associate Branch Chief, Investigational Drug Branch, CTEP, NCI.

In the new findings, CABOMETYX demonstrated significant improvement in progression-free survival (PFS), the trial's primary endpoint, and objective response rate (ORR) compared with sunitinib. Median PFS was 9.0 months (95% CI: 6-12) with CABOMETYX (n=44) versus 5.6 months (95% CI: 3-7) with sunitinib (n=46) (hazard ratio [HR] 0.60; 95% confidence interval [CI]: 0.37 to 0.97; p=0.019). ORR was 23% for CABOMETYX versus 4% for sunitinib (p=0.010). Median overall survival was 20.0 months for cabozantinib and 16.4 months for sunitinib (HR 0.84; 95% CI: 0.47 to 1.51; p=0.28), which did not reach statistical significance. Enrollment into additional arms of the study examining the use of crizotinib or savolitinib was halted early based on predefined interim futility analyses comparing these agents with the sunitinib arm.

"We're excited to build on the demonstrated history of CABOMETYX's clinically meaningful and statistically significant benefits for patients with renal cell carcinoma with these data that support its efficacy in patients with papillary renal cell carcinoma, who are often not the focus of major clinical trials for kidney cancer," said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. "The ability of CABOMETYX to inhibit MET, which is frequently altered in this tumor type, encouraged additional research into its potential benefits. It's gratifying to see these positive results of the PAPMET trial, which may help physicians choose an appropriate therapy for their patients with advanced papillary renal cell carcinoma."

The discontinuation rate of study medications due to treatment-related adverse events was 24% for sunitinib and 23% for CABOMETYX. The most common grade 3 or 4 adverse events with CABOMETYX were hypertension (32%), hand-foot syndrome (20%) and fatigue (13%). The most common grade 3 or 4 adverse events with sunitinib were hypertension (17%), anemia (13%) and decrease in white blood cell count (11%). One death, secondary to a thromboembolic event, within 30 days of the last dose of study medication was reported for a patient receiving CABOMETYX.

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

About the SWOG S1500 Clinical Trial

SWOG S1500 (NCT02761057), also called PAPMET, was a randomized phase 2 trial comparing cabozantinib, crizotinib and savolitinib to sunitinib, a VEGF-directed multikinase inhibitor and current standard of care for patients with advanced or metastatic PRCC. The study was supported by the National Cancer Institute (NCI), part of the National Institutes of Health, designed and led by the SWOG Cancer Research Network under the leadership of Dr. Pal, and conducted through the NCI National Clinical Trials Network. The goal of the trial was to determine whether MET-directed therapy improves clinical outcomes relative to conventional VEGF-directed agents. Exelixis provided the cabozantinib for the trial under a Cooperative Research and Development Agreement with the NCI.

Patients with pathologically verified PRCC (type I, II, or not otherwise specified) were randomized 1:1:1:1 to the control arm of sunitinib or one of three investigational arms: CABOMETYX, crizotinib and savolitinib. CABOMETYX was orally administered at 60 mg daily, with dose reductions to 40 mg and 20 mg permitted. Enrolled patients could have received up to one prior therapy. Prior therapy was received by 10 patients (7%), and the most common prior therapy was the combination of nivolumab with ipilimumab (4 patients). The primary endpoint was PFS, defined as the time from randomization to the time of radiographic or clinical progression, symptomatic deterioration or death from any cause, whichever occurred first. Secondary endpoints included objective response rate and overall survival, defined as the time from randomization to death from any cause, and safety evaluation.

About Papillary Renal Cell Carcinoma

PRCC accounts for about 15% of all renal cell carcinomas.[2,3] Genomic and molecular characterization of PRCC has implicated MET signaling as a key driver of this cancer.[2,4] Targeting VEGFR and other tyrosine kinases, including MET and AXL, has led to improved outcomes in RCC as compared with sunitinib, and further supported the investigation of MET targeting tyrosine kinase inhibitors in PRCC.

The American Cancer Society's 2021 statistics cite kidney cancer as among the top ten most commonly diagnosed forms of cancer among both men and women in the U.S.[5] If detected in its early stages, the five-year survival rate for RCC is high; for patients with advanced or late-stage metastatic RCC, however, the five-year survival rate is only 13%.[4] Approximately 32,000 patients in the U.S. and 71,000 worldwide will require systemic treatment for advanced kidney cancer in 2021.[6]

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 (HCC) who have been previously treated with sorafenib; and for patients with advanced RCC as a first-line treatment in combination with nivolumab. 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 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. Exelixis holds the exclusive rights to develop and commercialize cabozantinib in the United States.

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 and HCC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. 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 36% (17% 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. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 44% 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.

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 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 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. 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.

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 is observed. 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.

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, decreased appetite, PPE, nausea, hypertension, vomiting, weight decreased, constipation, and dysphonia.

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 PAPMET study at ASCO GU and simultaneous publication of such data in *The Lancet*; the therapeutic potential of CABOMETYX for patients with advanced papillary RCC; the potential for the PAPMET data results to help inform physician treatment plans for patients with advanced papillary RCC; 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; the potential failure of cabozantinib 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' continuing compliance with applicable legal and regulatory requirements; 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' Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on February 10, 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.

Exelixis, the Exelixis logo, CABOMETYX, COMETRIQ and COTELLIC are registered U.S. trademarks. MINNEBRO is a Japanese trademark.

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[1] NCCN Guidelines Version 2.2021 Kidney Cancer. Available at: https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed February 2021.

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[3] Cancer Genome Atlas Research Network, Linehan WM, Spellman PT, et al. Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma. N Engl J Med 2016;374(2):135–45.

[4] Pal SK, Ali SM, Yakirevich E, et al. Characterization of Clinical Cases of Advanced Papillary Renal Cell Carcinoma via Comprehensive Genomic Profiling. Eur Urol 2018;73(1):71–8.

[5] American Cancer Society: Cancer Facts & Figures 2021. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf. Accessed February 2021.

[6] Decision Resources Report: Renal Cell Carcinoma. October 2014 (internal data on file).

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