Exelixis Announces Final Phase 1 Results from Clinical Trial Sponsored by the National Cancer Institute at ASCO GU for Cabozantinib in Combination with Nivolumab with or without Ipilimumab in Patients with Refractory Metastatic Genitourinary Tumors

February 12, 2021

– Study demonstrated objective response rates of 38% in all patients, 62.5% in patients with renal cell carcinoma and 42.4% in patients with urothelial carcinoma –

– Data to be presented during the 2021 American Society of Clinical Oncology's Genitourinary Cancers Symposium –

ALAMEDA, Calif.--(BUSINESS WIRE)--Feb. 12, 2021-- Exelixis, Inc. (NASDAQ: EXEL) today announced positive final data for a phase 1 trial sponsored and conducted by the U.S. National Cancer Institute (NCI), including seven expansion cohorts, evaluating cabozantinib in combination with either nivolumab or nivolumab plus ipilimumab in patients with refractory metastatic genitourinary (GU) tumors. The data will be presented as part of the Rapid Abstract Session: Urothelial Carcinoma and Rare Tumors from 2:15 p.m. – 3:05 p.m. PT on Friday, February 12 at the 2021 American Society of Clinical Oncology's Genitourinary Cancers Symposium (ASCO GU), which is being held virtually, February 11-13, 2021.

In the study, cabozantinib in combination with either nivolumab alone (n=64) or nivolumab plus ipilimumab (n=56) demonstrated an objective response rate (ORR) for all evaluable patients (n=108) of 38%, with an 11.1% complete response (CR) rate per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

For the 33 patients with previously treated metastatic urothelial carcinoma (UC), the ORR was 42.4%, and the CR rate was 21%. The ORR for the 16 patients with previously treated metastatic renal cell carcinoma (RCC) was 62.5%. The ORR was 20% for patients with urachal adenocarcinoma (n=15), 85.7% for squamous cell carcinoma of the bladder (n=7) and 44.4% for penile carcinoma (n=9).

The median overall survival for the entire population was 15.9 months. Median progression-free survival was 5.5 months, and median duration of response was 22.8 months.

"We see a significant level of anti-tumor activity with an acceptable tolerability profile for the combination of cabozantinib with nivolumab or nivolumab and ipilimumab for this early phase trial across a broad range of GU malignancies," said Andrea Apolo, M.D., Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health and the principal investigator of the trial. "This phase 1 study's early results provided important information for the development of the phase 3 CheckMate -9ER study sponsored by Bristol Myers Squibb, of cabozantinib plus nivolumab versus sunitinib that recently reported improved progression-free survival, overall response, and overall response rate, leading to last month's U.S. approval of the combination therapy of cabozantinib and nivolumab in first-line advanced renal cell carcinoma. The additional activity seen in other GU tumors support further research into the potential of cabozantinib combinations with immune checkpoint inhibitors in other advanced, intractable GU cancers."

"These clinical data were the result of a productive collaboration between the investigators leading the trial, NCI-CTEP, the trial sponsor, and both Exelixis and Bristol Myers Squibb. We would like to thank the patients who generously agreed to participate in the trial," said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. "The combination of cabozantinib with immune checkpoint inhibitors continues to demonstrate positive outcomes for patients with difficult-to-treat advanced genitourinary malignancies such as renal cell and urothelial carcinomas. Going forward, we will continue our work to uncover the potential of cabozantinib in combination with immunotherapies to provide further treatment options to patients with cancer in need."

Treatment-related grade 3 or 4 adverse events (>5% of patients) observed in the doublet cabozantinib and nivolumab group included fatigue (13%), hypertension (13%), dehydration (6%) and thromboembolic event (6%). Immune-related grade 3 or 4 adverse events (>5% of patients) were not observed in this group. Treatment-related grade 3 or 4 adverse events (>5% of patients) observed in the triplet cabozantinib plus nivolumab and ipilimumab group included fatigue (16%), hypertension (11%), dehydration (5.3%) and thromboembolic event (5.3%). Immune-related grade 3 or 4 adverse events (>5% of patients) for this group included hepatitis (7%) and colitis (7%).

About the Trial

The trial was sponsored by the U.S. NCI through Cooperative Research and Development Agreements between the NCI's Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis, and both Exelixis and Bristol Myers Squibb. Andrea Apolo, M.D., of the NCI's Genitourinary Malignancies Branch, is the principal investigator. The trial was conducted by the NCI and includes centers from its Experimental Therapeutics Clinical Trials Network.

This open label, non-randomized phase 1 trial was divided into two parts: a dose-escalation phase and an expansion cohort phase. The primary endpoint of the phase 1 trial was to determine the dose-limiting toxicity and recommended doses of the doublet and triplet combinations for later stage clinical studies. The secondary endpoint is ORR as assessed per RECIST version 1.1.

Once the recommended doses were determined for the combinations of cabozantinib plus nivolumab and of cabozantinib plus nivolumab and ipilimumab, the trial enrolled seven subsequent expansion cohorts. The cabozantinib plus nivolumab expansion cohorts included patients with UC, RCC, bladder adenocarcinoma and other rare metastatic GU tumors. The cabozantinib plus nivolumab and ipilimumab expansion cohorts included UC, RCC and penile carcinoma. The objectives of the trial were to determine the clinical activity, safety and tolerability of both combinations in multiple metastatic GU tumors.

The recommended phase 2 doses determined for the combination of cabozantinib plus nivolumab were cabozantinib 40 mg daily and 3 mg/kg of nivolumab every two weeks. The recommended phase 2 doses determined for the combination of cabozantinib plus nivolumab and ipilimumab were cabozantinib 40 mg daily, 3 mg/kg of nivolumab every two weeks and 1 mg/kg ipilimumab every three weeks.

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

About Genitourinary Cancers

Genitourinary cancers are those that affect the urinary tract, bladder, kidneys, ureter, prostate, testicles, penis or adrenal glands — parts of the body involved in reproduction and excretion — and include RCC, castration-resistant prostate cancer (CRPC) and UC[1].

The American Cancer Society's (ACS) 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.[2] Clear cell RCC is the most common type of kidney cancer in adults.[3] 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%.[2] Approximately 32,000 patients in the U.S. and over 71,000 worldwide will require systemic treatment for advanced kidney cancer in 2021, with nearly 15,000 patients in need of a first-line treatment in the U.S.[4]

According to the ACS, in 2021, approximately 250,000 new cases of prostate cancer will be diagnosed, and 34,000 people will die from the disease.[2] Prostate cancer that has spread beyond the prostate and does not respond to androgen-suppression therapies — a common treatment for prostate cancer — is known as metastatic CRPC[5]. Researchers estimate that in 2020, 43,000 people were diagnosed with metastatic CRPC, which has a median survival of less than two years.[6,7,8]

Urothelial cancers encompass carcinomas of the bladder, ureter and renal pelvis at a ratio of 50:3:1, respectively.[9] Bladder cancer occurs mainly in older people, with 90% of patients aged 55 or older.[10] With an estimated 84,000 new cases expected to be diagnosed in 2021, bladder cancer accounts for about 5% of all new cases of cancer in the U.S. each year.[11] It is the fourth most common cancer in men.[2]

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; 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 a phase 1 study evaluating cabozantinib in combination with either nivolumab or nivolumab plus ipilimumab in patients with refractory metastatic GU tumors at ASCO GU; the therapeutic potential of cabozantinib combinations with immune checkpoint inhibitors in advanced, intractable GU cancers; 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.

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