Exelixis Announces Updated Phase 1 Trial Results for Cabozantinib in Combination with Nivolumab with or without Ipilimumab in Refractory Genitourinary (GU) Tumors

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– Results among 19 previously treated metastatic urothelial carcinoma (mUC) patients demonstrated a 42% objective response rate (ORR), 12.8 month median progression-free survival (mPFS), and 77% overall survival (OS) at 12 months, with 7/8 responders progression free with 15.7 months median follow-up –

– In the cohort of 13 previously treated metastatic renal cell carcinoma (mRCC) patients, a 54% ORR and 100% disease control rate (DCR) was observed –

– These initial results suggest that further evaluation of cabozantinib in combination with nivolumab with or without ipilimumab is warranted for mUC –

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Feb. 7, 2018-- Exelixis, Inc. (NASDAQ:EXEL) today announced updated data from expansion cohorts in a phase 1 trial of cabozantinib in combination with either nivolumab or nivolumab plus ipilimumab in patients with refractory genitourinary tumors. The primary endpoint of the trial is to determine the dose-limiting toxicity and recommended phase 2 doses of the doublet and triplet combinations. The findings will be presented during a poster session (Abstract #515) on February 9 at the 2018 American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO-GU), which is being held in San Francisco, California, February 8-10, 2018.

The updated data reported results from 78 patients treated with cabozantinib and nivolumab with or without ipilimumab. The initial part of the study determined the recommended dose for each treatment at four dose levels. In all, 49 patients were treated with the doublet combination of cabozantinib and nivolumab and 29 patients were treated with the triplet combination of cabozantinib, nivolumab and ipilimumab. Nineteen patients with mUC were evaluable for response with a median follow up of 15.7 months. Thirteen patients with previously treated mRCC were evaluable for response.

For the mUC cohort, the ORR across all treatment groups was 42 percent (2 CRs and 6 PRs of 19 patients) and the DCR (DCR = CR, PR and SD) was 84 percent. Seven of eight (88 percent) mUC patients with an objective response had not progressed at the time of the data cut-off. Median PFS in this patient population was 12.8 months and the overall survival rate at 12 months was 77 percent. Among the 13 patients with mRCC who were evaluable for response, ORR was 54 percent (7 PRs of 13 patients) and the DCR was 100 percent.

In the overall study, the ORR in 64 evaluable patients was 36 percent (3 CRs and 20 PRs) with a median duration of response (DOR) of 24 months. 78 patients were included in the safety analysis. Expected immune-related events including colitis, meningitis, hepatitis, pneumonitis and endocrine disorders occurred at a low frequency.

“The updated analysis of this trial shows that cabozantinib, in combination with nivolumab or in combination with nivolumab plus ipilimumab, demonstrates an acceptable tolerability profile and encouraging rates of durable responses in the previously treated metastatic urothelial carcinoma and metastatic renal cell carcinoma cohorts,” said Andrea Apolo, M.D., Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, and principal investigator of the trial. “Evidence of clinical activity, including encouraging progression free survival in a patient population that has a significant unmet need, gives us motivation to further evaluate these combination therapies.”

No dose-limiting toxicity was observed in the study. Based on general tolerability, the recommended cabozantinib dose for the expanded dose cohorts and for future late stage evaluation has been determined as cabozantinib at 40 mg daily oral dose combined with nivolumab at 3 mg/kg every 2 weeks and ipilimumab at 1 mg/kg every 3 weeks for 4 doses.

Treatment-related grade 3 or 4 adverse events (>5 percent of patients) observed in the doublet combination included lipase increased (16 percent), hypophosphatemia (14 percent), neutrophil count decreased (12 percent), hypertension (8 percent), fatigue (6 percent) and infection (6 percent). Grade 3 or 4 adverse events (>5 percent of patients) observed in the triplet combination included hypophosphatemia (21 percent), lymphocyte count decreased (14 percent), lipase increased (14 percent), ALT increased (10 percent), AST increased (10 percent), hypertension (10 percent), diarrhea (10 percent), hypokalemia (10 percent), fatigue (7 percent), hyponatremia (7 percent) and amylase increased (7 percent). Grade 3 or 4 immune-related adverse events for the doublet combination included colitis, aseptic meningitis and hepatitis (one patient each) and for the triplet combination were colitis (one patient) and hepatitis (two patients). There were no treatment-related deaths.

“We greatly value our collaboration with NCI-CTEP on this study, which suggests that the combination of cabozantinib with immune checkpoint inhibitors may have the potential to improve outcomes for patients with genitourinary malignancies, including urothelial and renal cell carcinoma,” said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. “These phase 1 results have informed the current phase 3 trial of such combination therapy in previously untreated advanced or metastatic renal cell carcinoma, as well as future studies exploring these combinations across a range of advanced genitourinary cancers including urothelial cancer.”

About the Trial

The trial is sponsored by the U.S. National Cancer Institute (NCI) through Cooperative Research and Development Agreements between the NCI’s Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis, and both Bristol-Myers Squibb and Exelixis. Andrea Apolo,

M.D., of the NCI's Genitourinary Malignancies Branch, is the principal investigator. The trial is being conducted by the NCI and includes centers from its Experimental Therapeutics Clinical Trials Network.

The updated data report on findings from 78 patients with previously treated genitourinary malignancies. Forty-nine patients were treated with the doublet combination of cabozantinib and nivolumab at four dose levels and 29 patients were treated with the triplet combination of cabozantinib, nivolumab and ipilimumab at four dose levels.

The primary endpoint of the phase 1 trial is to determine the dose-limiting toxicity and recommended doses of the doublet and triplet combinations for later stage clinical studies. The secondary endpoint is clinical response rate as assessed by RECIST 1.1. The initial part of the study included four dosing levels: cabozantinib 40 mg daily plus nivolumab 1 mg/kg once every 2 weeks; cabozantinib 40 mg daily plus nivolumab 3 mg/kg once every 2 weeks; cabozantinib 60 mg daily plus nivolumab 1 mg/kg once every 2 weeks; and cabozantinib 60 mg daily plus nivolumab 3 mg/kg once every 2 weeks.

The study also included an additional four dosing levels: cabozantinib 40 mg daily, nivolumab 1 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 doses, then nivolumab 1 mg/kg every 2 weeks; cabozantinib 40 mg daily, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 doses, then nivolumab 3 mg/kg every 2 weeks; cabozantinib 60 mg daily, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 doses, then nivolumab 3 mg/kg every 2 weeks; and cabozantinib 40 mg daily, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for 4 doses, then nivolumab 1 mg/kg every 2 weeks.

Data from the study evaluating the combination of cabozantinib with nivolumab with or without ipilimumab in patients with previously treated genitourinary tumors were previously presented by Dr. Apolo at the European Society for Medical Oncology (ESMO) 2017 Congress in Madrid.

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 renal cell carcinoma (RCC) and urothelial carcinoma.[1]

The American Cancer Society's 2018 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 12 percent, with no identified cure for the disease.[4] Approximately 30,000 patients in the U.S. and 70,000 globally require treatment.[5]

Urothelial cancers encompass carcinomas of the bladder, ureter and renal pelvis at a ratio of 50:3:1, respectively.[6] Urothelial carcinoma occurs mainly in older people; 90 percent of patients with bladder cancer are 55 years or older.[7] Bladder cancer is the fourth most common cancer in men and accounts for about five percent of all new cases of cancer in the U.S. each year.[7,8] In 2014, an estimated 696,440 people were living with bladder cancer in the U.S.[8]

About CABOMETYX® (cabozantinib)

CABOMETYX tablets are approved in the United States for the treatment of patients with advanced RCC. CABOMETYX tablets are also approved in the European Union, Norway, Iceland, Australia and Switzerland for the treatment of advanced RCC in adults who have received prior vascular endothelial growth factor (VEGF)-targeted therapy. Ipsen also submitted to European Medicines Agency (EMA) the regulatory dossier for cabozantinib as a treatment for first-line advanced RCC in the European Union on August 28, 2017; on September 8, 2017, Ipsen announced that the EMA validated the application. 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, including RCC.

CABOMETYX is not indicated for the treatment of refractory mUC and other genitourinary tumors.

Please see Important Safety Information below and full U.S. prescribing information at **https://cabometyx.com/downloads/cabometyxuspi.pdf**.

U.S. Important Safety Information

- **Hemorrhage**: Severe and fatal hemorrhages have occurred with CABOMETYX. In two RCC studies, the incidence of Grade ≥ 3 hemorrhagic events was 3% in CABOMETYX-treated patients. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.
- **Gastrointestinal (GI) Perforations and Fistulas:** In RCC studies, fistulas were reported in 1% of CABOMETYX-treated patients. Fatal perforations occurred in patients treated with CABOMETYX. In RCC studies, gastrointestinal (GI) perforations were reported in 1% of CABOMETYX-treated patients. Monitor patients for symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula which cannot be appropriately managed or a GI perforation.
- **Thrombotic Events:** CABOMETYX treatment results in an increased incidence of thrombotic events. In RCC studies, venous thromboembolism occurred in 9% (including 5% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX-treated patients. Fatal thrombotic events occurred in the cabozantinib clinical program. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.
- **Hypertension and Hypertensive Crisis:** CABOMETYX treatment results in an increased incidence of treatment-emergent hypertension, including hypertensive crisis. In RCC studies, hypertension was reported in 44% (18% Grade ≥ 3) of CABOMETYX-treated patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with

anti-hypertensive therapy. Discontinue CABOMETYX if there is evidence of hypertensive crisis or severe hypertension despite optimal medical management.

- **Diarrhea:** In RCC studies, diarrhea occurred in 74% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **Palmar-Plantar Erythrodysesthesia (PPE):** In RCC studies, palmar-plantar erythrodysesthesia (PPE) occurred in 42% of patients treated with CABOMETYX. Grade 3 PPE occurred in 8% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPE or Grade 3 PPE until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.
- **Embryo-fetal Toxicity** may be associated with CABOMETYX. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during CABOMETYX treatment and for 4 months after the last dose.
- **Adverse Reactions:** The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, hypertension, PPE, weight decreased, vomiting, dysgeusia, and stomatitis.
- **Strong CYP3A4 Inhibitors**: If concomitant use with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage.
- **Strong CYP3A4 Inducers:** If concomitant use with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage.
- **Lactation:** Advise women not to breastfeed while taking CABOMETYX and for 4 months after the final dose.
- **Hepatic Impairment:** In patients with mild to moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see accompanying full Prescribing Information https://cabometyx.com/downloads/cabometyxuspi.pdf.

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 genetic systems, 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. We discovered our lead compounds, cabozantinib and cobimetinib, and advanced them into clinical development before entering into partnerships with leading biopharmaceutical companies in our efforts to bring these medicines to patients globally. We are steadfast in our commitment to prudently reinvest in our business to maximize the potential of our pipeline. We intend to supplement 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 recently earned a spot on Deloitte's Technology Fast 500 list, a yearly award program honoring the 500 fastest-growing companies over the past four years. For more information about Exelixis, please visit www.exelixis.com or follow @ExelixisInc on Twitter.

Exelixis Forward-Looking Statement Disclaimer

This press release contains forward-looking statements, including, without limitation, statements related to: the clinical and therapeutic potential of the combination of cabozantinib with immune checkpoint inhibitors for patients with genitourinary malignancies, including urothelial and renal cell carcinoma; potential future studies exploring the combination of cabozantinib with immune checkpoint inhibitors across a range of advanced genitourinary cancers, including urothelial cancer; and Exelixis' commitment to reinvesting in its business to maximize the potential of its pipeline, including supplementing its existing therapeutic assets through targeted business development activities and internal drug discovery. Words such as "potential," "future," "commitment," "intend," or other similar expressions identify forward-looking statements, but the absence of these words does not necessarily mean that a statement is not forward-looking. In addition, any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements. These forward-looking statements 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: Exelixis' ability and the ability of its collaborators to conduct clinical trials of cabozantinib in combination with immune checkpoint inhibitors sufficient to achieve a positive completion; the potential failure of cabozantinib in combination with immune checkpoint inhibitors to demonstrate safety and efficacy in clinical testing; the complexities and challenges associated with regulatory review and approval processes; the level of costs associated with Exelixis' commercialization, research and development and other activities; competition in the area of business development activities and the inherent uncertainty of the drug discovery process; Exelixis' dependence on its relationships with its cabozantinib collaboration partners, including, the level of their investment in the resources necessary to successfully commercialize cabozantinib in the territories where it is approved; Exelixis' dependence on its relationship with Genentech/Roche with respect to cobimetinib and Exelixis' ability to maintain its rights under the collaboration; market acceptance of CABOMETYX, COMETRIQ, and COTELLIC and the availability of coverage and reimbursement for these products; Exelixis' dependence on third-party vendors for the development, manufacture and supply of its products; Exelixis' ability to protect the company's intellectual property rights; market competition; changes in economic and business conditions, and other factors discussed under the caption "Risk Factors" in Exelixis' quarterly report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 1, 2017, and in Exelixis' future filings with the SEC. The forward-looking statements made in this press release speak only as of the date of this press release. Exelixis expressly disclaims any duty, obligation or undertaking to release publicly any updates or revisions to any forward-looking statements

contained herein to reflect any change in Exelixis' expectations with regard thereto or any change in events, conditions or circumstances on which any such statements are based.

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