Exelixis Announces Amendment to Clinical Research Protocol for Phase 1b Trial of Cabozantinib in Combination with Atezolizumab in Patients with Locally Advanced or Metastatic Solid Tumors

January 4, 2018

– Four new trial cohorts, including non-small cell lung cancer (NSCLC) and castration-resistant prostate cancer (CRPC) cohorts, added to expansion phase of combination trial; anticipated to begin enrolling in first half of 2018 –

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Jan. 4, 2018-- Exelixis, Inc. (NASDAQ:EXEL) today announced an amendment to the protocol for the phase 1b trial of cabozantinib in combination with atezolizumab (TECENTRIQ®) in patients with locally advanced or metastatic solid tumors. The amendment adds four new expansion cohorts to the trial, which will now include patients with NSCLC and CRPC, in addition to previously included patients with renal cell carcinoma (RCC) and urothelial carcinoma (UC). The primary objective in the expansion stage of this trial remains to determine the objective response rate in each cohort.

New expansion cohorts include the following:

- patients with advanced non-squamous NSCLC without a defined tumor genetic alteration (EGFR, ALK, ROS1, or BRAF) who have not received prior therapy with an immune checkpoint inhibitor
- patients with NSCLC without a defined tumor genetic alteration who have progressed following treatment with an immune checkpoint inhibitor
- patients with UC who have progressed following treatment with an immune checkpoint inhibitor
- patients with CRPC who have previously received enzalutamide and/or abiraterone acetate and experienced radiographic disease progression in soft tissue

The original trial protocol included four expansion cohorts, which will remain in the amended study:

- patients with RCC with clear cell histology who have not had prior systemic anticancer therapy
- patients with UC who have progressed on or after platinum-containing chemotherapy
- patients with UC who are ineligible for cisplatin-based chemotherapy and have not received prior systemic chemotherapy for inoperable, locally advanced or metastatic disease
- patients with UC who are eligible for cisplatin-based chemotherapy and have not received prior systemic chemotherapy for inoperable, locally advanced or metastatic disease

“Patients with advanced non-small cell lung cancer or castration-resistant prostate cancer are in need of additional therapies that can slow disease progression,” said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. “We are pleased to announce that this phase 1b trial will now include additional tumor types, as well as advanced kidney and bladder cancers. Since clinical and preclinical observations indicate that cabozantinib may promote an immuno-permissive environment, we believe that its use in combination with immune checkpoint inhibitors such as atezolizumab may offer potential synergistic effects for both checkpoint inhibitor-naïve or previously treated patients.”

This multicenter, phase 1b, open-label study is divided into two parts: a dose-escalation phase and an expansion cohort phase. The dose-escalation phase is enrolling up to 36 patients either with advanced RCC with or without prior systemic therapy or with inoperable, locally advanced, metastatic or recurrent UC (including renal, pelvis, ureter, urinary bladder and urethra) after prior platinum-based therapy. The primary objective is to determine the optimal dose and schedule of daily oral administration of cabozantinib when given in combination with atezolizumab to inform the trial’s subsequent expansion stage. Cabozantinib doses of 40 mg daily and 60 mg daily are being evaluated. All patients will receive the standard atezolizumab dosing regimen (1200 mg infusion once every 3 weeks).

Once the recommended dose and schedule are determined — anticipated to occur in the first half of 2018 — the trial will begin to enroll the eight expansion cohorts. Each expansion cohort will initially enroll approximately 30 participants, although up to 80 may enroll in the cohorts of patients with UC or NSCLC who have been previously treated with an immune checkpoint inhibitor, for a total of up to 340 patients.

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

TECENTRIQ® (atezolizumab) is a registered trademark of Genentech, a member of the Roche Group.

About Exelixis’ Collaboration with Ipsen

On February 29, 2016, Exelixis and Ipsen jointly announced an exclusive licensing agreement for the commercialization and further development of cabozantinib indications outside of the United States, Canada and Japan. On December 21, 2016, this agreement was amended to include

commercialization rights for Ipsen in Canada. Ipsen has opted in to participate in the funding of the phase 1b trial in patients with locally advanced or metastatic UC, RCC, CRPC or NSCLC. They may also participate in future studies at their choosing and would have access to the results to support potential future regulatory submissions.

About Exelixis' Collaboration with Takeda

On January 30, 2017, Exelixis and Takeda jointly announced an exclusive licensing agreement for the commercialization and further development of cabozantinib indications in Japan. Takeda may also participate in this and future studies and have access to the results to support potential future regulatory submissions in their territories, if they opt into their funding obligations under the respective collaboration agreements.

Exelixis holds the exclusive rights to develop and commercialize cabozantinib in the United States.

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 (UC)[1].

Kidney cancer is among the top ten most commonly diagnosed forms of cancer among both men and women in the U.S., according to the American Cancer Society's 2017 statistics. [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.[2] Approximately 30,000 patients in the U.S. and 68,000 globally require treatment.[4]

Prostate cancer is the second most common cause of cancer death in men, behind only skin cancer.[5] There is a high survival rate for patients when prostate cancer is detected early, but once the disease has spread to other parts of the body the five-year survival rate is just 28 percent.[6] Approximately 3,085,000 men were living with prostate cancer in the U.S. in 2014,[7] and an estimated 160,000 new cases will be diagnosed this year.[5]

Urothelial cancers encompass carcinomas of the bladder, ureter and renal pelvis at a ratio of 50:3:1, respectively.[8] Urothelial carcinoma occurs mainly in older people, with 90 percent of patients aged 55 or older.[9] 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.[9] In 2014, an estimated 696,440 people were living with bladder cancer in the U.S.[10]

About Lung Cancer

Lung cancer is the number one cause of cancer-related deaths worldwide, leading to 1.6 million deaths annually.[11] NSCLC accounts for 80 to 85 percent of all cases of lung cancer.[12] Survival rates for lung cancer vary widely depending on how advanced the disease is at diagnosis. For those diagnosed at an early stage, more than 55 percent survive for five years, but that number drops to 29 percent if the disease has spread locally and less than 5 percent if it has spread to distant locations.[13] Unfortunately, nearly 80 percent of lung cancer cases are diagnosed only after the disease has spread at least locally.[13]

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 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.

CABOMETYX is not indicated for the treatment of locally advanced or metastatic UC, NSCLC or CRPC.

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 them 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.

Forward-Looking Statement Disclaimer

This press release contains forward-looking statements, including, without limitation, statements related to: the clinical and therapeutic potential of cabozantinib, including that it may promote an immune-permissive environment; Exelixis belief that cabozantinib's use in combination with immune checkpoint inhibitors such as atezolizumab may offer potential synergistic effects for both checkpoint inhibitor-naïve or previously pre-treated patients; the timing for determining the recommended dose and schedule for the phase 1b trial and for enrollment of the eight expansion cohorts, each anticipated to occur in the first half of 2018; the potential for Ipsen's and Takeda's participation in future cabozantinib studies under their respective collaborations and to have access to the results to support potential future regulatory submissions in their territories; 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; and Exelixis' mission to deliver the next generation of Exelixis medicines and help patients recover stronger and live longer. Words such as "may," "believe," "anticipated," "commitment," "potential," "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 and cobimetinib both alone and in combination with other therapies sufficient to achieve a positive completion; risks related to the potential failure of cabozantinib and cobimetinib both alone and in combination with other therapies, to demonstrate safety and efficacy in clinical testing; the availability of data and planned enrollment efforts to occur at the referenced time; risks and uncertainties related to regulatory review and approval processes and Exelixis' compliance with applicable legal and regulatory requirements; 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.

Exelixis, the Exelixis logo, CABOMETYX, COMETRIQ and COTELLIC are registered U.S. trademarks.

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