# Exelixis Announces Clinical Trial Collaboration with Roche to Evaluate Cabozantinib and Atezolizumab in Locally Advanced or Metastatic Solid Tumors

February 27, 2017

***– Study will evaluate the potential of this novel combination in multiple solid tumors, including advanced renal cell carcinoma and urothelial carcinoma –***

***– Expect to begin patient enrollment mid-year 2017 –***

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Feb. 27, 2017-- Exelixis, Inc. (NASDAQ:EXEL) today announced a new collaboration with Roche on a phase 1b dose escalation study that will evaluate the safety and tolerability of cabozantinib, Exelixis' tyrosine kinase inhibitor (TKI), in combination with atezolizumab, Roche's anti-PD-L1 immunotherapy, in patients with locally advanced or metastatic solid tumors. Enrollment is scheduled to begin mid-year 2017; Exelixis will be the sponsor of the trial, and Roche will provide atezolizumab.

Based on the dose-escalation results, the trial has the potential to enroll up to four expansion cohorts, including a cohort of patients with previously untreated advanced clear cell renal cell carcinoma (RCC) and three cohorts of urothelial carcinoma (UC), namely platinum eligible first-line patients, first- or second-line platinum ineligible patients, and patients previously treated with platinum-containing chemotherapy. Ipsen, Exelixis' global partner for cabozantinib, except in the United States and Japan, will participate in this study and have access to the results for potential future development in its territories. Takeda may also participate in these 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 agreement.

"People with advanced genitorurinary malignancies are in need of additional treatment options that can improve clinical outcomes," said Sumanta Kumar Pal, M.D., co-director, Kidney Cancer Program at City of Hope, and principal investigator in the study. "The combined approach of tyrosine kinase inhibition with cabozantinib alongside immune-checkpoint inhibition has already shown promise in an early phase 1 clinical trial. We look forward to further examining this potential with cabozantinib plus atezolizumab to treat a range of genitourinary and other tumors."

"We are pleased to collaborate with Roche to study the potential of atezolizumab in combination with cabozantinib, our lead medicine that is the subject of a broad development program across a variety of cancers," said Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis. "Although several therapies have recently received regulatory approval to treat advanced kidney and bladder cancers, survival continues largely to be measured in months, not years. Evaluating how cabozantinib may positively impact treatment when paired with immunotherapy is central to our goal of improving therapeutic outcomes for patients with these and other cancers."

The rationale for the collaboration is based on clinical and preclinical observations consistent with the ability of cabozantinib to promote an immunopermissive environment, which might present an opportunity for synergistic effects from combination treatment with immune checkpoint inhibitors and other immunotherapies.[1,2] In an ongoing phase 1 clinical trial in subjects with refractory metastatic UC and other genitourinary tumors, cabozantinib has been evaluated in combination with nivolumab, a monoclonal antibody to PD-1. The combination was well-tolerated among all enrolled subjects, no dose-limiting toxicities were reported, and the recommended phase 2 dose was determined to be 40 mg qd for cabozantinib with 3 mg/kg of nivolumab (intravenous [IV], once every two weeks).[3] Updated results from this part of the study as well as results from a second part evaluating the combination of cabozantinib, nivolumab and ipilimumab were presented during the poster session (Abstract #293) on February 17 at the American Society of Clinical Oncology 2017 Genitourinary Cancers Symposium, which was held in Orlando, Florida, February 16 – 18, 2017.

Exelixis' cabozantinib is a potent inhibitor of multiple receptor tyrosine kinases known to play important roles in tumor cell proliferation and/or tumor neovascularization including MET, VEGFR, AXL and RET. Some of these receptors have also been implicated in promoting an immunosuppressive tumor microenvironment. Cabozantinib has demonstrated broad preclinical and clinical activity across several tumor types. Cabozantinib tablets (60 mg) are approved as CABOMETYX™ inthe United States and Europe for patients with advanced RCC who have received prior anti-angiogenic/VEGF-targeted therapy, and cabozantinib capsules (140 mg) are approved as COMETRIQ® for the treatment of progressive, metastatic medullary thyroid cancer (MTC) in the United States and Europe.

**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 and urothelial carcinoma.[4]

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 2016 statistics. [5] Clear cell RCC is the most common type of kidney cancer in adults.[6] 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.[5] Approximately 30,000 patients in the U.S. and 68,000 globally require treatment.[7]

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 2013, an estimated 587,426 people were living with bladder cancer in the U.S.[10]

**About CABOMETYX™ (cabozantinib)**

CABOMETYX is the tablet formulation of cabozantinib. Its targets include MET, AXL and VEGFR-1, -2 and -3. In preclinical models, cabozantinib has been shown to inhibit the activity of these receptors, which are involved in normal cellular function and pathologic processes such as tumor angiogenesis, invasiveness, metastasis and drug resistance.

CABOMETYX is available in 20 mg, 40 mg or 60 mg doses. The recommended dose is 60 mg orally, once daily.

On April 25, 2016, the FDA approved CABOMETYX tablets for the treatment of patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. On September 9, 2016, the European Commission approved CABOMETYX tablets for the treatment of advanced renal cell carcinoma in adults who have received prior vascular endothelial growth factor (VEGF)-targeted therapy in the European Union, Norway and Iceland. 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. On January 30, 2017, Exelixis and Takeda jointly announced an exclusive licensing agreement for the commercialization and further development of cabozantinib indications in Japan.

**U.S. Important Safety Information**

**Hemorrhage:** Severe hemorrhage occurred with CABOMETYX. The incidence of Grade ≥3 hemorrhagic events was 2.1% in CABOMETYX-treated patients and 1.6% in everolimus-treated patients. Fatal hemorrhages also occurred in the cabozantinib clinical program. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.

**Gastrointestinal (GI) Perforations and Fistulas:** Fistulas were reported in 1.2% (including 0.6% anal fistula) of CABOMETYX-treated patients and 0% of everolimus-treated patients. GI perforations were reported in 0.9% of CABOMETYX-treated patients and 0.6% of everolimus-treated patients. Fatal perforations occurred in the cabozantinib clinical program. Monitor patients for symptoms of fistulas and perforations. Discontinue CABOMETYX in patients who experience a fistula that cannot be appropriately managed or a GI perforation.

**Thrombotic Events:** CABOMETYX treatment results in an increased incidence of thrombotic events. Venous thromboembolism was reported in 7.3% of CABOMETYX-treated patients and 2.5% of everolimus-treated patients. Pulmonary embolism occurred in 3.9% of CABOMETYX-treated patients and 0.3% of everolimus-treated patients. Events of arterial thromboembolism were reported in 0.9% of CABOMETYX-treated patients and 0.3% of everolimus-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. Hypertension was reported in 37% (15% Grade ≥3) of CABOMETYX-treated patients and 7.1% (3.1% Grade ≥3) of everolimus-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:** Diarrhea occurred in 74% of patients treated with CABOMETYX and in 28% of patients treated with everolimus. Grade 3 diarrhea occurred in 11% of CABOMETYX-treated patients and in 2% of everolimus-treated patients. 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. Dose modification due to diarrhea occurred in 26% of patients.

**Palmar-Plantar Erythrodysesthesia Syndrome (PPES):** Palmar-plantar erythrodysesthesia syndrome (PPES) occurred in 42% of patients treated with CABOMETYX and in 6% of patients treated with everolimus. Grade 3 PPES occurred in 8.2% of CABOMETYX-treated patients and in <1% of everolimus-treated patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPES or Grade 3 PPES until improvement to Grade 1; resume CABOMETYX at a reduced dose. Dose modification due to PPES occurred in 16% of patients.

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** 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:** CABOMETYX can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

**Adverse Reactions:** The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, PPES, hypertension, vomiting, weight decreased, and constipation.

**Drug Interactions: Strong CYP3A4 inhibitors and inducers:** Reduce the dosage of CABOMETYX if concomitant use with strong CYP3A4 inhibitors cannot be avoided. Increase the dosage of CABOMETYX if concomitant use with strong CYP3A4 inducers cannot be avoided.

**Lactation:** Advise a lactating woman not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

**Reproductive Potential: Contraception—**Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose. **Infertility —**CABOMETYX may impair fertility in females and males of reproductive potential.

**Hepatic Impairment:** Reduce the CABOMETYX dose in patients with mild (Child-Pugh score [C-P] A) or moderate (C-P B) hepatic impairment. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

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

**About Exelixis**

Exelixis, Inc. (Nasdaq: EXEL) is a biopharmaceutical company committed to the discovery, development and commercialization of new medicines to improve care and outcomes for people with cancer. Since its founding in 1994, three products discovered at Exelixis have progressed through clinical development, received regulatory approval, and entered the marketplace. Two are derived from cabozantinib, an inhibitor of multiple tyrosine kinases including MET, AXL and VEGF receptors: CABOMETYX™ tablets approved for previously treated advanced kidney cancer and COMETRIQ® capsules approved for progressive, metastatic medullary thyroid cancer. The third product, Cotellic®, is a formulation of cobimetinib, a selective inhibitor of MEK, is marketed under a collaboration with Genentech (a member of the Roche Group), and is approved as part of a combination regimen to treat advanced melanoma. Both cabozantinib and cobimetinib have shown potential in a variety of forms of cancer and are the subjects of broad clinical development programs. For more information on Exelixis, please visit www.exelixis.com or follow @ExelixisInc on Twitter.

**Forward-looking Statements**

This press release contains forward-looking statements, including, without limitation, statements related to: the expectation that enrollment for the planned study to evaluate the safety and tolerability of cabozantinib in combination with atezolizumab in patients with locally advanced or metastatic solid tumors is scheduled to begin mid-year 2017; the potential for the trial to enroll up to four expansion cohorts; the potential for Takeda to participate in the planned study and the potential for both Ipsen and Takeda to participate in future studies under the clinical collaboration and have access to the results to support potential future regulatory submissions in their territories; the potential of the cabozantinib and atezolizumab combination to treat a range of genitourinary and other tumors; Exelixis' commitment to the discovery, development and commercialization of new medicines with the potential to improve care and outcomes for people with cancer; Exelixis' focus on advancing cabozantinib; and the continued development of cobimetinib. Words such as “will,” “potential,” “may,” “look forward,” “goal,” “committed,” “focused,” 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 atezolizumab sufficient to achieve a positive completion; risks related to the potential failure of the combination of these compounds to demonstrate safety and efficacy in clinical testing; Exelixis' dependence on its collaboration partners, including, the level of their investment in the resources necessary to successfully develop cabozantinib in combination with atezolizumab; the complexities and challenges associated with regulatory review and approval processes; the degree of market acceptance of CABOMETYX and the availability of coverage and reimbursement for CABOMETYX; the risk that unanticipated developments could adversely affect the commercialization of CABOMETYX; Exelixis' dependence on third-party vendors; 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 3, 2016, 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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