# Exelixis Announces Phase 1 Trial Results for Cabozantinib in Combination with Nivolumab in Advanced Genitourinary Tumors

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***-- 43 percent ORR across diverse range of GU tumors --***

***-- Encouraging tolerability, 40 mg cabozantinib plus 3 mg/kg nivolumab defined as dose for subsequent phase 2 trials --***

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Oct. 7, 2016-- Exelixis, Inc. (NASDAQ:EXEL) today announced results from a phase 1 trial of cabozantinib in combination with nivolumab in patients with previously treated genitourinary tumors. The findings will be presented during a poster discussion session (Abstract #774PD) on October 9 at the European Society for Medical Oncology (ESMO) 2016 Congress, which is being held in Copenhagen, October 7 – 11, 2016.

“The treatment landscape for advanced, intractable cancers such as metastatic urothelial carcinoma is continuously evolving and the use of combination therapies may improve outcomes for patients in need of new options,” said Andrea Apolo, M.D., Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, the principal investigator of the trial. “Our previous correlative studies have demonstrated that cabozantinib has immunomodulatory properties that may counteract tumor-induced immunosuppression, providing the rationale for this trial.[1,2] These promising early stage clinical findings support further investigation of cabozantinib in combination with nivolumab in a number of genitourinary tumors.”

Between July 2015 and September 2016, 24 patients were accrued with metastatic urothelial carcinoma (n=7), urachal adenocarcinoma (n=4), squamous cell carcinoma of the bladder or urethra (n=3), germ cell tumor (n=4), castration-resistant prostate cancer (n=4), renal cell carcinoma (n=1), or trophoblastic tumor (n=1) and were treated in Part I of the study, which evaluated the combination of cabozantinib and nivolumab at four dose levels. The median number of prior systemic therapies was 3, and 10 patients had received 4 or more prior therapies. The objective response rate was 43 percent among the 23 patients who were evaluable for response, with one complete response and nine partial responses. Four of six patients (67 percent) with urothelial cancer achieved a response. The recommended doses for the ongoing expansion cohorts were determined to be cabozantinib at 40 mg daily and nivolumab at 3 mg/kg once every 2 weeks. Part II of the phase 1 trial examining the use of the triplet combination of cabozantinib, nivolumab, and ipilimumab is also ongoing.

“Cabozantinib has demonstrated clinical activity as a single agent in several tumors, and we are interested in further examining its potential in combination with immunotherapies to treat a variety of genitourinary and other cancers,” said Michael M. Morrissey, Ph.D., president and chief executive officer of Exelixis. “We are encouraged by these preliminary phase 1 data and look forward to results from the ongoing expansion cohorts in this trial in patients with metastatic urothelial carcinoma and renal cell carcinoma.”

Common grade 1/2 adverse events observed in more than 30 percent of patients were fatigue, diarrhea, anorexia, dysgeusia, hoarseness, and oral mucositis. Grade 3 adverse events observed in more than 10 percent of patients, included neutropenia, fatigue, and thromboembolic events. There was one grade 4 adverse event of lipase elevation. No grade 5 toxicities were observed.

In addition to Part I, the study also has enrolled 15 patients in Part II, which is evaluating the triplet combination of cabozantinib, nivolumab, and ipilimumab. Expansion cohorts assessing cabozantinib and nivolumab are currently being accrued with bladder, renal and rare genitourinary cancer patients. Data from these patients will be reported at a later date.

**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.[3]

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. [4] Clear cell renal cell carcinoma is the most common type of kidney cancer in adults.[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 12 percent, with no identified cure for the disease.[4] Approximately 30,000 patients in the U.S. and 68,000 globally require treatment.[6]

Prostate cancer is the second most common cause of cancer death in men, behind only skin cancer.[7] 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.[8] Approximately 2,850,000 men were living with prostate cancer in the U.S. in 2013,[9] and 180,000 new cases are diagnosed each year.[7]

Urothelial cancers encompass carcinomas of the bladder, ureter and renal pelvis at a ratio of 50:3:1, respectively.[10] Urothelial carcinoma occurs mainly in older people, with 90 percent of patients aged 55 or older.[11] 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.[11] In 2013, an estimated 587,426 people were living with bladder cancer in the U.S.[12]

**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.

**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 with the potential to improve care and outcomes for people with cancer. Since its founding in 1994, three medicines discovered at Exelixis have progressed through clinical development to receive regulatory approval. Currently, Exelixis is focused on advancing cabozantinib, an inhibitor of multiple tyrosine

kinases including MET, AXL and VEGF receptors, which has shown clinical anti-tumor activity in more than 20 forms of cancer and is the subject of a broad clinical development program. Two separate formulations of cabozantinib have received regulatory approval to treat certain forms of kidney and thyroid cancer and are marketed for those purposes as CABOMETYX™ tablets (U.S. and EU) and COMETRIQ® capsules (U.S. and EU), respectively. Another Exelixis-discovered compound, COTELLIC® (cobimetinib), a selective inhibitor of MEK, has been approved in major territories including the United States and European Union, and is being evaluated for further potential indications by Roche and Genentech (a member of the Roche Group) under a collaboration with Exelixis. For more information on 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 therapeutic potential of cabozantinib and the further examination of cabozantinib in combination with immunotherapies to treat a variety of genitourinary and other cancers; future data results from the ongoing expansion cohorts of the phase 1 trial of cabozantinib in combination with nivolumab in patients with metastatic urothelial carcinoma and renal cell carcinoma and from Part II of the trial evaluating the triplet combination of cabozantinib, nivolumab and ipilimumab; 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 "may," "further," "potential," "look forward," "will," "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 sufficient to achieve a positive completion; risks related to the potential failure of cabozantinib to demonstrate safety and efficacy in clinical testing; the availability of data at the referenced times; risks and uncertainties related to regulatory review and approval processes and Exelixis' compliance with applicable legal and regulatory requirements; 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 its relationship with Ipsen, including, the level of Ipsen's 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; 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 August 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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