



Exelixis Announces Phase 1 Trial Results for Cabozantinib in Combination with Nivolumab with or without Ipilimumab in Refractory Metastatic Urothelial Carcinoma and Other Genitourinary Tumors

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– Recommended doses for ongoing expansion cohorts and future potential trials identified for doublet and triplet combinations based on encouraging tolerability, safety and activity profile –

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Feb. 17, 2017-- Exelixis, Inc. (NASDAQ:EXEL) today announced results from 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 (DLT) and recommended phase 2 doses of the doublet and triplet combinations. The findings were presented during a poster session (Abstract #293) on February 17 at the 2017 Genitourinary Cancers Symposium, which is being held in Orlando, Florida, February 16 – 18, 2017.

Between July 22, 2015 and December 31, 2016, 48 patients were accrued with previously treated metastatic urothelial carcinoma (mUC, n=19), urachal adenocarcinoma (n=4), squamous cell carcinoma of the bladder or urethra (n=2), germ cell tumor (n=4), castration-resistant prostate cancer (n=9), renal cell carcinoma (n=4), trophoblastic tumor (n=1), sertoli cell tumor (n=1) or penile squamous cell carcinoma (n=4) and treated in two parts. In Part I, 30 patients were treated with the doublet combination of cabozantinib and nivolumab at four dose levels. In Part II, 18 patients were treated with the triplet combination of cabozantinib, nivolumab and ipilimumab at three dose levels.

Among the 43 patients who were evaluable for response, the objective response rate (ORR) for all tumor types was 30 percent (38 percent for the doublet dosing schedule and 18 percent for the triplet dosing schedule), with a 7 percent complete response (CR) rate and a 23 percent partial response (PR) rate. Stable disease (SD) was reported in 56 percent of patients. The ORR for patients with mUC was 38 percent, and 2 of 16 patients achieved a CR, while 2 patients with squamous cell carcinoma of the bladder had objective responses (1 CR and 1 PR). In the mUC cohort, 15 of 16 patients had a CR, PR or SD as their best response.

Grade 3 adverse events (>5 percent of patients) observed in the doublet combination included neutropenia (17 percent), hypophosphatemia (13 percent), hypertension (10 percent), lipase increase (7 percent), fatigue (7 percent), diarrhea (7 percent) and dehydration (7 percent). Grade 3 adverse events (>5 percent of patients) observed in the triplet combination included hypertension (17 percent), hypophosphatemia (17 percent), fatigue (13 percent), hyponatremia (13 percent), lipase increase (13 percent), nausea (13 percent) and rash (6 percent). There were limited numbers of grade 4 adverse events (10 percent including thrombocytopenia and lipase increase in the doublet combination, and 6 percent (lipase increase) in the triplet combination), and no grade 5 adverse events observed in either part of the trial.

"There is a significant unmet need for treatment regimens that can slow tumor progression in advanced, intractable cancers such as metastatic urothelial carcinoma. The use of combination therapies may be a strategy that could increase anti-tumor activity in these patients," said Andrea Apolo, M.D., Genitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, the principal investigator of the trial. "Previously reported data from Part I of the trial showed that cabozantinib in combination with nivolumab provided an encouraging objective response rate and tolerability profile across a diverse range of genitourinary tumors. Data from Part II also demonstrate that using cabozantinib with two immunotherapy agents is well-tolerated with promising early activity. These results support the further evaluation of both regimens in these tumor types."

The recommended doses for the ongoing expansion cohorts were determined to be cabozantinib 40 mg daily plus nivolumab 3 mg/kg once every 2 weeks for the doublet and 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 for the triplet.

"These early clinical results generated by our collaborators at the NCI-CTEP suggest that the combination of cabozantinib with either nivolumab or nivolumab and ipilimumab in patients with genitourinary malignancies is associated with an encouraging tolerability, safety and activity profile," said Michael M. Morrissey, Ph.D., president and Chief Executive Officer of Exelixis. "With these results in hand, we are committed to further examining the potential of cabozantinib in combination with a variety of immunotherapies to treat a broad range of genitourinary and other cancers."

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 primary endpoint of the phase 1 trial is to determine the dose limiting toxicity (DLT) and recommended phase 2 doses of the doublet and triplet combinations. The secondary endpoint is clinical response rate as assessed by RECIST 1.1. Part I 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.

Part II of the study included three 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; and 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.

Data from Part I of the study evaluating the combination of cabozantinib with nivolumab in patients with previously treated genitourinary tumors were presented by Dr. Apolo at the European Society for Medical Oncology 2016 Congress. 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.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 2016 statistics.² Clear cell renal cell carcinoma 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 2,850,000 men were living with prostate cancer in the U.S. in 2013,⁷ and 180,000 new cases are diagnosed each 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 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 Pharmaceutical Company Limited announced an exclusive licensing agreement for the commercialization and further clinical development of cabozantinib for all future indications in Japan, including RCC.

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

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 ($\geq 25\%$) 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 promotion of new medicines with the potential to improve care and outcomes for people with cancer. Since its founding in 1994, three products 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 further evaluation of cabozantinib in combination with immunotherapies to treat a variety of genitourinary tumors; future data results from expansion cohorts assessing cabozantinib and nivolumab in bladder, renal and rare genitourinary cancer patients; 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," "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 relationships with Ipsen and Takeda, 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; 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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