Exelixis Announces Initiation of Phase 1b Trial of Cabozantinib in Combination with Atezolizumab in Patients with Locally Advanced or Metastatic Solid Tumors

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SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Jun. 12, 2017-- Exelixis, Inc. (NASDAQ:EXEL) today announced the initiation of the dose-escalation stage of a phase 1b trial of cabozantinib in combination with atezolizumab (TECENTRIQ®) in patients with locally advanced or metastatic urothelial carcinoma (UC) or renal cell carcinoma (RCC). 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.

"Patients with locally advanced or metastatic urothelial or renal cell carcinoma are in need of additional therapies that can slow disease progression," said Sumanta Kumar Pal, M.D., Co-director, Kidney Cancer Program at City of Hope, and Principal Investigator of the study. "As new investigational and approved therapies become available, research into their use in combination with other treatments may be a productive avenue for improving clinical outcomes in patients with these tumor types. Identifying the appropriate dose for cabozantinib when paired with the immunotherapy atezolizumab is the first step in examining this potential combination therapy."

This multicenter phase 1b, open-label study is divided in two parts: a dose-escalation phase and an expansion cohort phase. The dose-escalation phase will enroll 9 to 36 patients with inoperable, locally advanced, metastatic or recurrent UC (including renal, pelvis, ureter, urinary bladder and urethra) after prior platinum-based therapy or RCC with or without prior systemic therapy. The starting dose of cabozantinib will be 40 mg daily and may be increased to 60 mg daily or decreased to 20 mg daily. All patients will receive the standard atezolizumab dosing regimen (1200 mg infusion once every 3 weeks).

The secondary objectives of the dose-escalation stage are to evaluate the plasma pharmacokinetics of daily oral administration of cabozantinib when given in combination with atezolizumab and to assess safety of the combination therapy through the evaluation of incidence and severity of adverse events, including immune-related adverse events. Exploratory endpoints include the correlation of clinical outcome with immune cell, tumor cell and blood biomarker analyses.

Once the recommended dose and schedule are determined, the trial will enroll four expansion cohorts, each with up to 30 patients, for a total of up to 120 patients with advanced or metastatic UC or RCC. The primary objective in the expansion stage of the trial is to determine the objective response rate in each cohort. The three UC expansion cohorts will enroll: 1) patients who have progressed on or after platinum-containing chemotherapy; 2) patients who are ineligible for cisplatin-based chemotherapy and have not received prior systemic chemotherapy for inoperable, locally advanced or metastatic disease; and 3) patients who are eligible for cisplatin-based chemotherapy and have not received prior systemic chemotherapy for inoperable, locally advanced or metastatic disease. The RCC expansion cohort will enroll patients with clear cell histology who have not had prior systemic anticancer therapy.

"There is a strong rationale for combining cabozantinib with immunotherapies, including clinical and preclinical observations consistent with the ability of cabozantinib to promote an immuno-permissive environment, which might present an opportunity for synergistic effects from combination treatment with immune checkpoint inhibitors and other immuno-oncology agents," said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. "We are excited to evaluate the combination of cabozantinib plus atezolizumab and look forward to the determination of a recommended phase 2 dose and to further examining this combination regimen to treat advanced cancers."

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 or RCC. 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 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 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 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.

Cabozantinib is not indicated for the treatment of locally advanced or metastatic UC.

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 Statement Disclaimer

This press release contains forward-looking statements, including, without limitation, statements related to: the potential of the cabozantinib and atezolizumab combination to treat patients with locally advanced or metastatic UC or RCC; the potential opportunity for synergistic effects from the combination of cabozantinib with immune checkpoint inhibitors and other immune-oncology agents; the potential for Takeda to participate in the funding of the phase 1b trial 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; Exelixis' commitment to the discovery, development and promotion 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 "potential," "might," "look forward," "may," "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 May 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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