# Exelixis Updates Phase 1b COSMIC-021 Trial of Cabozantinib in Combination With Atezolizumab in Patients With Advanced Solid Tumors

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***– Original metastatic castration-resistant prostate cancer and immunotherapy-refractory non-small cell lung cancer cohorts expanded to 80 subjects –***

***– Four cohorts added for metastatic castration-resistant prostate cancer based on encouraging early data –***

ALAMEDA, Calif.--(BUSINESS WIRE)--Jul. 15, 2019-- Exelixis, Inc. (NASDAQ: EXEL) today announced that two original cohorts are being expanded and four new cohorts are being added to the protocol for COSMIC-021, the phase 1b trial of cabozantinib (CABOMETYX®) in combination with atezolizumab (TECENTRIQ®) in patients with locally advanced or metastatic solid tumors.

Based on preliminary encouraging activity, as determined by response assessment per Response Evaluation Criteria in Solid Tumors (version 1.1) (RECISTv1.1), and safety data, the original immunotherapy-refractory non-small cell lung cancer (NSCLC) and metastatic castration-resistant prostate cancer (CRPC) cohorts are being expanded to 80 patients each. Additionally, four new cohorts consisting of two expansion and two exploratory cohorts are being added to COSMIC-021. The two new expansion cohorts will evaluate the combination of cabozantinib and atezolizumab in patients with metastatic CRPC who have received prior enzalutamide or abiraterone therapy, with or without prior docetaxel therapy. The two new exploratory arms evaluating single-agent cabozantinib and single-agent atezolizumab in patients with metastatic CRPC are being added to determine the individual contribution of each therapy.

“There is an urgent need for new treatments to improve outcomes for patients with NSCLC refractory to immunotherapies and patients with metastatic CRPC,” said Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis. “Following encouraging early efficacy and safety data from the original lung and prostate cancer cohorts in COSMIC-021, we look forward to exploring the combination of cabozantinib and atezolizumab further in these expanded and newly added cohorts as we advance our plans to expand the broader late-stage development plan for cabozantinib.”

With these additions, the trial now includes 20 expansion cohorts and four exploratory cohorts and aims to enroll up to 1,732 patients with advanced or metastatic solid tumors such as renal cell carcinoma (RCC) and urothelial carcinoma (UC), among others. The primary objective in the expansion stage of this trial remains to determine the objective response rate in each cohort.

Detailed descriptions of the expanded and new cohorts are outlined below:

**Immunotherapy-Refractory NSCLC:**

- After reviewing the safety and efficacy data, as determined by response assessment per RECISTv1.1, of patients enrolled in the immunotherapy-refractory NSCLC cohort, 50 additional patients (80 total) with stage IV non-squamous NSCLC who have radiographically progressed on or after treatment with one prior immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1) for metastatic disease will be enrolled at the recommended dose of cabozantinib 40 mg plus atezolizumab 1,200 mg.

- An exploratory single-agent cabozantinib cohort was previously added to the protocol. This cohort evaluates the activity of cabozantinib (60 mg daily) in 30 patients with stage IV non-squamous NSCLC who have radiographically progressed on or after treatment with one prior immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1) for metastatic disease.

**Metastatic CRPC:**

- After reviewing the safety and efficacy data, as determined by response assessment per RECISTv1.1, of patients enrolled in the metastatic CRPC cohort, 50 additional patients with metastatic CRPC (80 total) who have histologically or cytologically confirmed adenocarcinoma of the prostate are being enrolled at the recommended dose of cabozantinib 40 mg plus atezolizumab 1,200 mg. Prior treatment with one novel hormonal therapy (NHT) for castration-sensitive prostate cancer (CSPC) or metastatic CRPC is permitted. Patients may have previously received docetaxel for metastatic CSPC but no other approved or experimental systemic therapies apart from one poly (ADP-ribose) polymerase (PARP) inhibitor for metastatic prostate cancer.

- A combination-therapy expansion cohort with 30 patients with metastatic CRPC who have histologically or cytologically confirmed adenocarcinoma of the prostate after prior treatment with one NHT for CSPC or metastatic CRPC are being added. Patients may have previously received docetaxel for metastatic CSPC but no other approved or experimental systemic therapies apart from one PARP inhibitor for metastatic prostate cancer.

- 30 patients with metastatic CRPC who have histologically or cytologically confirmed adenocarcinoma of the prostate who received docetaxel for metastatic CRPC and at least one NHT for CSPC or metastatic CRPC will be enrolled in a new combination-therapy expansion cohort at the recommended dose of cabozantinib 40 mg plus atezolizumab 1,200 mg.

- An exploratory single-agent cabozantinib cohort and exploratory single-agent atezolizumab cohort with patients with metastatic CRPC who have histologically or cytologically confirmed adenocarcinoma of the prostate after prior treatment with one NHT for CSPC or metastatic CRPC are being added. Patients may have previously received docetaxel for metastatic CSPC but no other approved or experimental systemic therapies apart from one PARP inhibitor for metastatic prostate cancer. The single-agent cabozantinib cohort will initially enroll up to 30 patients, and the single agent atezolizumab cohort will initially enroll up to 10 patients.

More information about the currently enrolling cohorts in this trial is available at ClinicalTrials.gov.

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

**About the COSMIC-021 Study**

COSMIC-021 is a multicenter, phase 1b, open-label study that is divided into two parts: a dose-escalation phase and an expansion cohort phase. The dose-escalation phase was designed to enroll 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. Ultimately, all patients enrolled in this stage of the trial were patients with advanced RCC. The dose-escalation phase of the study determined the optimal dose of cabozantinib to be 40 mg daily when given in combination with atezolizumab (1200 mg infusion once every 3 weeks). These results were presented at the European Society for Medical Oncology 2018 Congress.

In the expansion phase, the trial is enrolling 20 expansion cohorts in 12 tumor types: RCC, UC, NSCLC, CRPC, triple-negative breast cancer, epithelial ovarian cancer, endometrial cancer, hepatocellular carcinoma, gastric or gastroesophageal junction adenocarcinoma, colorectal adenocarcinoma, head and neck cancer, and differentiated thyroid cancer. Up to a total of 1,720 patients may enroll in this phase of the trial: each expansion cohort will initially enroll approximately 30 patients, and up to 10 cohorts may expand enrollment up to 1,000 additional patients in the expansion phase.

In three exploratory cohorts, approximately 30 patients each with advanced UC, CRPC, or NSCLC will be treated with cabozantinib as a single-agent. In a fourth exploratory cohort, approximately 10 patients with advanced CRPC will be treated in a single-agent atezolizumab cohort. Exploratory cohorts have the option to be expanded up to 80 patients (cabozantinib) and 30 patients (atezolizumab) total.

**About CABOMETYX® (cabozantinib)**

In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced RCC and for the treatment of patients with HCC who have been previously treated with sorafenib. CABOMETYX tablets have also received regulatory approvals in the European Union and additional countries and regions worldwide. In 2016, Exelixis granted Ipsen exclusive rights for the commercialization and further clinical development of cabozantinib outside of the United States and Japan. In 2017, Exelixis granted exclusive rights to Takeda Pharmaceutical Company Limited for the commercialization and further clinical development of cabozantinib for all future indications in Japan.

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 occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

- **Perforations and Fistulas:** Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula that cannot be appropriately managed or a GI perforation.

- **Thrombotic Events:** CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic event requiring medical intervention.

- **Hypertension and Hypertensive Crisis:** CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension occurred in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

- **Diarrhea:** Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2

diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.

- **Palmar-Plantar Erythrodysesthesia (PPE):** PPE occurred in 44% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.
- **Proteinuria:** Proteinuria occurred in 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.
- **Osteonecrosis of the Jaw (ONJ):** ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 28 days prior to scheduled dental surgery or invasive dental procedures. Withhold CABOMETYX for development of ONJ until complete resolution.
- **Wound Complications:** Wound complications were reported with CABOMETYX. Stop CABOMETYX at least 28 days prior to scheduled surgery. Resume CABOMETYX after surgery based on clinical judgment of adequate wound healing. Withhold CABOMETYX in patients with dehiscence or wound healing complications requiring medical intervention.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients 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. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.
- **Adverse Reactions:** The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, and vomiting.
- **Strong CYP3A4 Inhibitors:** If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.
- **Strong CYP3A4 Inducers:** If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.
- **Lactation:** Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.
- **Hepatic Impairment:** In patients with 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**.**

**AboutExelixis**

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 system genetics, 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. Our discovery efforts have resulted in four commercially available products, CABOMETYX® (cabozantinib), COMETRIQ® (cabozantinib), COTELLIC® (cobimetinib) and MINNEBRO™ (esaxerenone), and we have entered into partnerships with leading pharmaceutical companies to bring these important medicines to patients worldwide. Supported by revenues from our marketed products and collaborations, we are committed to prudently reinvesting in our business to maximize the potential of our pipeline. We are supplementing 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 is a member of Standard & Poor's ( S&P) MidCap 400 index, which measures the performance of profitable mid-sized companies. For more information about Exelixis, please visit www.exelixis.com, follow @ExelixisInc on Twitter or like Exelixis, Inc. on Facebook.

**Forward-Looking Statements**

This press release contains forward-looking statements, including, without limitation, statements related to: Exelixis' intention to explore the combination of cabozantinib and atezolizumab further in the expanded and newly added COSMIC-021 cohorts as it advances plans to expand the broader late-stage development plan for cabozantinib; and Exelixis' plans to reinvest in its business to maximize the potential of the company's pipeline, including through targeted business development activities and internal drug discovery. Any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements and 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: risks and uncertainties related to regulatory review and approval processes and Exelixis' compliance with applicable legal and regulatory requirements; the potential failure of the combination of cabozantinib and atezolizumab or of cabozantinib and atezolizumab as single-agent therapies to demonstrate safety and/or efficacy in COSMIC-021; uncertainties inherent in the product development process, including evolving regulatory requirements, slower than anticipated patient enrollment or inability to identify a sufficient number of clinical trial sites; the costs of conducting clinical trials, including the ability or willingness of Exelixis' collaboration partners to invest in the resources necessary to complete the trials; Exelixis' dependence on third-party vendors for the development, manufacture and supply of cabozantinib; Exelixis' ability to protect its intellectual property rights; market competition; changes in economic and business conditions; and other factors affecting Exelixis and its development programs 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, 2019, and in Exelixis' future filings with the SEC. All forward-looking statements in this press release are based on information available to Exelixis as of the date of this press release, and Exelixis undertakes no obligation to update or revise any forward-looking statements contained herein.



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