Exelixis Announces Results From Two Renal Cell Carcinoma Cohorts of the COSMIC-021 Trial of Cabozantinib in Combination With Atezolizumab

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– Cabozantinib in combination with atezolizumab demonstrated promising preliminary efficacy and a favorable safety profile in cohorts of patients with clear cell and non-clear cell renal cell carcinoma –

– Data presented during the European Society for Medical Oncology Virtual Congress 2020 –

ALAMEDA, Calif.--(BUSINESS WIRE)--Sep. 21, 2020-- Exelixis, Inc. (NASDAQ: EXEL) today announced positive phase 1b clinical trial results for the combination of cabozantinib (CABOMETYX®) and atezolizumab (TECENTRIQ®) in patients with locally advanced or metastatic solid tumors. Data from two expansion cohorts of the COSMIC-021 trial was presented during the European Society for Medical Oncology (ESMO) Virtual Congress 2020. Results from the clear cell renal cell carcinoma (RCC) cohort are being presented in the GU Proffered Paper Session on September 21, 2020, and results from the non-clear cell RCC cohort were presented as a poster available on demand for registrants beginning September 17, 2020 at 9:00 a.m. CEST.

"Given the broad experience with cabozantinib as monotherapy for advanced kidney cancer, it's very exciting to see the growing body of clinical evidence that demonstrates encouraging tolerability and clinical activity when combining cabozantinib with atezolizumab in this disease," said Dr. Sumanta Pal, Clinical Professor, City of Hope, the principal investigator for the COSMIC-021 study. "We are especially encouraged to see a durable objective response in more than 50% of patients with previously untreated clear cell RCC, paired with an acceptable safety profile at both cabozantinib dose levels evaluated in combination with atezolizumab. We look forward to learning more about the potential of this combination regimen to improve outcomes for patients with advanced kidney cancer from the ongoing phase 3 CONTACT-03 trial."

Clear Cell RCC Expansion Cohort (abstract 702O):

Initial results from the clear cell RCC expansion cohort (cohort 1) are being presented by Dr. Pal. The analysis included 70 RCC patients with clear cell histology who had not received prior systemic therapy. Patients received atezolizumab in combination with either a 40 mg or 60 mg daily dose of cabozantinib.

At a median follow-up of 25.8 months for the cabozantinib 40 mg dose group, the objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1, the trial's primary endpoint for the expansion cohorts, was 53%, with one complete response; disease control rate was 94%. Median progression-free survival (PFS) was 19.5 months (95% confidence interval [CI] 11.0–NR) with 17 events observed among 34 patients. Median duration of response was not yet reached.

At a median follow-up of 15.3 months for the cabozantinib 60 mg dose group, ORR per RECIST v. 1.1 was 58%, with four complete responses; disease control rate was 92%. Median PFS was 15.1 months (95% CI 8.2–22.3) with 19 events observed among 36 patients. Median duration of response for all responding patients was 15.4 months.

For both dose groups combined, positive PD-L1 status at baseline and higher levels of CD8+ T cells each showed a significant positive association with overall response.

In the 40 mg dose group, treatment-related grade 3/4 adverse events (AEs) occurring in ≥5% of patients were diarrhea (9%), fatigue (6%), hypertension (24%) and hypophosphatemia (15%); the discontinuation rate for either cabozantinib or atezolizumab due to treatment-related AEs was 24%, and 15% discontinued both study treatments due to treatment-related AEs. In the 60 mg dose group, treatment-related grade 3/4 were diarrhea (19%), fatigue (6%), hypertension (14%), alanine aminotransferase (ALT) increased (14%), aspartate aminotransferase (AST) increased (6%), lipase increased (8%) and mucosal inflammation (6%); the discontinuation rate for either study treatment due to treatment-related AEs was 19%, and 6% discontinued both study treatments due to treatment-related AEs.

Non-Clear Cell RCC Expansion Cohort (abstract 709P):

Initial results from the non-clear cell expansion cohort (cohort 10) were presented by Dr. Bradley A. McGregor, Clinical Director, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute. The analysis included 30 patients with non-clear cell RCC who could have received one prior VEGFR-TKI therapy but could not have been previously treated with an immune checkpoint inhibitor or chemotherapy. Four patients (13%) had received prior VEGFR-TKI therapy. All patients received cabozantinib 40 mg daily in combination with atezolizumab.

At a median follow-up of 13 months, ORR per RECIST v1.1 was 33%, and disease control rate was 93%. Median PFS was 9.5 months (95% CI 5.5-NE), and median duration of response was 8.3 months.

Treatment-related grade 3/4 AEs occurred in 37% of patients, and hypophosphatemia (13%) was the most common grade 3/4 AE. Seventeen percent of patients discontinued either study treatment for treatment-related AEs, and 3% discontinued both study treatments for treatment-related AEs.

"Following on our pivotal CheckMate -9ER data, we are thrilled to share these additional findings at the ESMO Virtual Congress 2020 that speak to the potential of cabozantinib in combination with immune checkpoint inhibitor therapy for the treatment of advanced kidney cancer," said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. "The encouraging durable objective response and disease control rates demonstrated in both of these cohorts build on the positive results we've seen for cabozantinib in combination with atezolizumab in other difficult-to-treat tumor types and support the further evaluation of this regimen for the treatment of renal cell carcinoma."

More information about COSMIC-021 is available at ClinicalTrials.gov (NCT03170960).

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 urothelial carcinoma (UC), (including renal, pelvis, ureter, urinary bladder and urethra) after prior platinum-based therapy. Ultimately, all 12 patients enrolled in this stage of the trial were patients with advanced RCC. The dose-escalation phase of the study determined that both 40 mg and 60 mg daily doses of cabozantinib in combination with atezolizumab (1200 mg infusion once every 3 weeks) were safe and tolerable without dose-limiting toxicities. These results were presented at the European Society for Medical Oncology 2018 Congress.

In the expansion phase, the trial is enrolling 24 cohorts in 12 tumor types: RCC, UC, non-small cell lung cancer (NSCLC), castrate-resistant prostate cancer (CRPC), hepatocellular carcinoma (HCC), triple-negative breast cancer, epithelial ovarian cancer, endometrial cancer, gastric or gastroesophageal junction adenocarcinoma, colorectal adenocarcinoma, head and neck cancer, and differentiated thyroid cancer. Up to 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 further expand enrollment, resulting in up to 1,000 patients across such potential additional expansion cohorts.

Four of the cohorts are exploratory: three are enrolling approximately 30 patients each with advanced UC, CRPC or NSCLC to be treated with cabozantinib as a single agent, and one is enrolling approximately 10 patients with advanced CRPC to be treated with single-agent atezolizumab. Exploratory cohorts have the option to be expanded up to 80 patients (cabozantinib) and 30 patients (atezolizumab) total.

Exelixis is the study sponsor of COSMIC-021. Both Ipsen and Takeda have opted in to participate in the trial and are contributing to the funding for this study under the terms of the companies' respective collaboration agreements with Exelixis. Roche is providing atezolizumab for the trial.

About RCC

The American Cancer Society's 2020 statistics cite kidney cancer as among the top ten most commonly diagnosed forms of cancer among both men and women in the U.S.[1] Clear cell RCC is the most common type of kidney cancer in adults.[2] 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%.[2] Approximately 32,000 patients in the U.S. and 71,000 worldwide will require systemic treatment for advanced kidney cancer in 2020.[3]

About 70% of RCC cases are known as "clear cell" carcinomas, based on histology. [4] The majority of clear cell RCC tumors have below-normal levels of a protein called von Hippel-Lindau, which leads to higher levels of MET, AXL and VEGF.[5,6] These proteins promote tumor angiogenesis (blood vessel growth), growth, invasiveness and metastasis.[7,8,9,10] MET and AXL may provide escape pathways that drive resistance to VEGF receptor inhibitors.[6,7]

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.

Important Safety Information

Warnings and Precautions

Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC and HCC studies. 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 Grade 4 fistula 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 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution.

Impaired Wound Healing: Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing is observed. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic findings 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.

Drug Interactions

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.

USE IN SPECIFIC POPULATIONS

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**.**

About Exelixis

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 the 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: the potential of cabozantinib in combination with immune checkpoint inhibitor therapy for the treatment of advanced RCC; 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: complexities and the unpredictability of the regulatory review and approval processes in the U.S. and elsewhere; Exelixis' and Roche's continuing compliance with applicable legal and regulatory requirements; the potential failure of the combination of cabozantinib and atezolizumab to demonstrate safety and/or efficacy in CONTACT-03; uncertainties inherent in the product development process; the continuing COVID-19 pandemic and its impact on Exelixis' research and development operations, including Exelixis' ability to initiate new clinical trials and clinical trial sites, enroll clinical trial patients, conduct trials per protocol, and conduct drug research and discovery operations and related activities; 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, including the potential for competitors to obtain approval for generic versions of CABOMETYX; 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 August 6, 2020, 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, except as required by

law.

Exelixis, the Exelixis logo, CABOMETYX, COMETRIQ and COTELLIC are registered U.S. trademarks. MINNEBRO is a Japanese trademark.

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

[1] American Cancer Society: Cancer Facts & Figures 2020. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf. Accessed September 2020.

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