Exelixis Announces Encouraging Results for Cabozantinib in Combination With Atezolizumab in Metastatic Castration-Resistant Prostate Cancer

February 10, 2020

Data from the COSMIC-021 trial will be presented on Thursday, February 13, 2020 at the American Society of Clinical Oncology's Genitourinary Cancers Symposium

ALAMEDA, Calif.--(BUSINESS WIRE)--Feb. 10, 2020-- Exelixis, Inc. (NASDAQ:EXEL) today announced encouraging results from the metastatic castration-resistant prostate cancer (CRPC) cohort of COSMIC-021, the phase 1b trial of cabozantinib (CABOMETYX®) in combination with atezolizumab (TECENTRIQ®) in patients with locally advanced or metastatic solid tumors. The data will be presented on Thursday, February 13th during Poster Session A: Prostate Cancer at 11:30 a.m. – 1:00 p.m. PT and 5:30 – 6:30 p.m. PT at the 2020 American Society of Clinical Oncology's Genitourinary Cancers Symposium (ASCO GU 2020), which is being held in San Francisco, California, February 13 – 15, 2020.

Upon enrollment, patients had to have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST v. 1.1) and had progressed on prior novel hormone therapy and could have received prior docetaxel for hormone sensitive disease. Forty-four patients were included in this interim analysis. The median follow up was 12.6 months. The objective response rate (ORR) per RECIST v. 1.1, the trial's primary endpoint, was 32%, including two complete responses and 12 partial responses. Disease control rate was 80%. Among the 36 patients with high-risk clinical features including visceral metastases and/or extra-pelvic lymph node metastases, the ORR was 33%. Median duration of response for all responding patients was 8.3 months. Among 12 patients who had an objective response and at least one post-baseline prostate-specific antigen (PSA) evaluation, 67% had a PSA decline of at least 50%.

"Given the poor prognosis for men with metastatic castration-resistant prostate cancer, measurable visceral disease and/or extra-pelvic lymph node metastases who have progressed on novel hormone therapies, we are excited to observe clinically meaningful activity with the combination of cabozantinib and atezolizumab in this COSMIC-021 cohort," said Neeraj Agarwal, M.D., Professor, Huntsman Cancer Center, University of Utah, and an investigator of the trial. "Emerging data suggests a tolerable safety profile and encouraging efficacy for this combination that may hold promise for these patients with limited treatment options, potentially providing patients with more time before the need for treatment with chemotherapy. We look forward to additional results as the trial progresses."

The median treatment duration was 6.3 months (range 1 to 18 months). No new safety signals were identified in this combination cohort. Treatment-related grade 3/4 adverse events (AEs) occurring in ≥5% of patients were fatigue (7%), diarrhea (7%) and hyponatremia (7%). One treatment-related grade 5 AE of dehydration was reported in a 90-year-old patient. The discontinuation rate of study treatment for adverse events unrelated to disease progression was low at 7%.

Exelixis announced on January 7, 2020 that metastatic CRPC cohort 6 of COSMIC-021 had been expanded to enroll up to 130 patients. Based on regulatory feedback from the U.S. Food & Drug Administration (FDA), and if supported by the clinical data from the recently expanded existing cohort and added metastatic CRPC cohorts, Exelixis intends to file with the FDA for accelerated approval in a metastatic CRPC indication as early as 2021.

"We're happy to share these encouraging results from the metastatic CRPC cohort from COSMIC-021, our first trial evaluating the combination of cabozantinib and atezolizumab," said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. "We look forward to receiving data from the most recent expansion of this CRPC cohort while we are also preparing for the initiation of a phase 3 pivotal trial in this indication. We are excited about the emerging data in metastatic CRPC and elsewhere and the potential of combining cabozantinib with immunotherapies in this and other difficult-to-treat tumor types."

More information about this trial is available at ClinicalTrials.gov.

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 renal cell carcinoma (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 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 24 cohorts in 12 tumor types: RCC, UC, non-small cell lung cancer (NSCLC), 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. Ipsen has opted in to participate in the trial and is contributing to the funding for this study under the terms of the companies' collaboration agreement. Roche is providing atezolizumab for the trial.

About CRPC

According to the American Cancer Society, approximately 192,000 new cases of prostate cancer will be diagnosed and 33,000 people will die from the disease this year.[1] Prostate cancer that has spread beyond the prostate and does not respond to androgen-suppression therapies — a common treatment for prostate cancer — is known as metastatic CRPC.[2] Researchers estimate that in 2020, 43,000 people with prostate cancer will progress to metastatic CRPC, which has a median survival of less than two years.[3,4,5]

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: Exelixis' expectation that data from the CRPC cohort of the COSMIC-021 trial will be presented at ASCO GU 2020; the therapeutic potential of cabozantinib in combination with atezolizumab for patients with CRPC and other difficult-to-treat tumor types; Exelixis' intention to file with the FDA for accelerated approval of the combination of cabozantinib and atezolizumab in a metastatic CRPC indication as early as 2021, based on regulatory feedback from the FDA and if supported by the clinical data; Exelixis' plans to initiate a phase 3 pivotal trial in metastatic CRPC; 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: 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 potential failure of the combination of cabozantinib and atezolizumab to demonstrate safety and/or efficacy in future trials; uncertainties inherent in the product development process; 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 October 30, 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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[1] American Cancer Society. Key Statistics for Prostate Cancer. Available at: https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html. Accessed February 2020.

[2] American Society of Clinical Oncology. Cancer.Net. Treatment of Metastatic Castration-Resistant Prostate Cancer. September 8, 2014. Available at: https://www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/treatment-metastatic-castration-resistant-prostate-cancer. Accessed February 2020.

[3] Scher, H.I., Solo, K., Valant, J., Todd, M.B., Mehra, M. Prevalence of Prostate Cancer Clinical States and Mortality in the United States: Estimates Using a Dynamic Progression Model. *PLOS ONE*. 2015; 10: e0139440.

[4] American Urological Association. Prostate Cancer: Castration Resistant Guideline. 2018. Available at: https://www.auanet.org/guidelines/prostate-cancer-castration-resistant-guideline. Accessed February 2020.

[5] Moreira, D. M., Howard, L. E., Sourbeer, K. N., et al. Predicting Time From Metastasis to Overall Survival in Castration-Resistant Prostate Cancer: Results From SEARCH. *Clin Genitourin Cancer*. 2017; 15: 60–66.e2.

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