Exelixis Announces Detailed Results of Phase 3 CONTACT-02 Pivotal Trial Evaluating Cabozantinib in Combination with Atezolizumab in Metastatic Castration-Resistant Prostate Cancer Presented at ASCO GU 2024

January 25, 2024

– Cabozantinib in combination with atezolizumab reduced the risk of disease progression or death by 35% in patients with metastatic castration-resistant prostate cancer –

– Findings to be presented during an oral presentation at ASCO GU 2024 –

ALAMEDA, Calif.--(BUSINESS WIRE)--Jan. 25, 2024-- Exelixis, Inc. (Nasdaq: EXEL) today announced detailed results from CONTACT-02, a phase 3 pivotal study evaluating cabozantinib (CABOMETYX®) in combination with atezolizumab compared with a second novel hormonal therapy (NHT) in patients with metastatic castration-resistant prostate cancer (mCRPC) and measurable extra-pelvic soft tissue disease who have progressed on one prior NHT. The detailed findings are being presented during Oral Abstract Session A: Prostate Cancer at 7:55 a.m. PST on January 25 at the American Society of Clinical Oncology 2024 Genitourinary Cancers Symposium (ASCO GU).

“Patients with metastatic castration-resistant prostate cancer with prior progression on a novel hormone therapy and who have measurable soft tissue metastasis experience the worst outcomes among advanced prostate cancer patients and have limited treatment options,” said Neeraj Agarwal, M.D., FASCO, Senior Director for Clinical Research at Huntsman Cancer Institute at the University of Utah and the global lead investigator of the trial. “CONTACT-02 is the only phase 3 study evaluating a tyrosine kinase inhibitor and an immune checkpoint inhibitor to show a statistically significant improvement in progression-free survival and a trend for overall survival in these patients. I am encouraged by these results and the potential for cabozantinib plus atezolizumab to be a widely available treatment option for our patients.”

As announced in August 2023, CONTACT-02 met one of its primary endpoints, demonstrating a statistically significant improvement in progression-free survival (PFS) as assessed by a blinded independent radiology committee (BIRC) and per RECIST 1.1. The PFS analysis was conducted in the first 400 randomized patients in the intent-to-treat (PFS ITT) population and per protocol. Similar results were observed for all patients.

Detailed results presented at ASCO GU show that at a median follow-up of 14.3 months for the PFS ITT population, the hazard ratio (HR) was 0.65 (95% confidence interval [CI]: 0.50-0.84; p=0.0007); the median PFS (mPFS) was 6.3 months for cabozantinib in combination with atezolizumab compared with 4.2 months for second NHT. This was nearly identical to the PFS for the ITT population (n=507): HR was 0.64 (95% CI: 0.50-0.81, p=0.0002); mPFS was 6.3 months for cabozantinib in combination with atezolizumab and was 4.2 months for second NHT. At a median follow-up of 12.0 months for the ITT population, the median overall survival (OS) was 16.7 months for cabozantinib in combination with atezolizumab compared with 14.6 months for second NHT (HR: 0.79; 95% CI: 0.58-1.07; p=0.13). While a trend toward OS improvement was observed, the data were immature and did not meet the threshold for statistical significance. The study will continue to the next analysis of OS, anticipated in 2024.

The PFS benefit and the trend for an OS benefit were observed across subgroups of high-risk populations, as presented in Table 1.

TABLE 1	**Liver metastasis**		**Prior docetaxel for mCSPC**		**Bone metastasis**	
	Cabozantinib + atezolizumab	**Second NHT**	**Cabozantinib + atezolizumab**	**Second NHT**	**Cabozantinib + atezolizumab**	**Second NHT**
Median PFS per BIRC, months (95% CI)	6.2 (4.0-9.1)	2.1 (2.0-2.3)	8.8 (6.2-9.2)	4.1 (2.3-4.3)	6.3 (6.0-8.8)	4.1 (2.8-5.7)
Patients, n	51	48	45	44	162	155
PFS HR (95% CI)	0.43 (0.27-0.68)		0.57 (0.34-0.97)		0.67 (0.50-0.88)	
Median OS, months (95% CI)	16.4 (8.3-NE)	9.8 (5.5-11.3)	20.9 (10.1-NE)	11.3 (9.0-NE)	16.4 (11.4-18.8)	11.4 (10.4-14.6)
Patients, n	59	60	57	58	206	196
OS HR (95% CI)	0.60 (0.35-1.02)		0.56 (0.29-1.08)		0.74 (0.54-1.02)	

BIRC = blinded independent radiology committee; CI = confidence interval; HR = hazard ratio; mCSPC = metastatic castration-sensitive prostate cancer; NE = not evaluable; NHT = novel hormone therapy; OS = overall survival; PFS = progression-free survival

Treatment-emergent adverse events (AEs) occurred in 97% of patients treated with cabozantinib in combination with atezolizumab (n=248) compared with 87% of patients treated with a second NHT (n=253), 48% and 23% of which were grade 3/4, respectively. Grade 5 treatment-emergent AEs occurred in 8% of patients treated with the combination regimen compared with 12% of patients treated with a second NHT; no grade 5 treatment-related AEs occurred in either arm. Treatment-related AEs led to the discontinuation of any treatment component in 13% of patients treated with the combination regimen and 2% of patients treated with a second NHT. For all treatment components, the treatment-related AEs leading to discontinuation were 5% vs. 2%, respectively.

“Given there are limited options after progression on novel hormonal therapy, we recognize the need for a regimen that can delay disease progression, that has an acceptable tolerability profile and that is widely available to patients who may not have the means or desire to travel to specialized centers for other therapies,” said Amy Peterson, M.D., Executive Vice President, Product Development & Medical Affairs, and Chief Medical Officer, Exelixis. “Our decision to conduct CONTACT-02, based upon a signal we observed in COMET-01, underscores our commitment to patients with advanced prostate cancer and to improving their standard of care. We look forward to discussing these important results with the U.S. Food and Drug Administration, and to learning more in the next analysis of overall survival, anticipated this year.”

About CONTACT-02

CONTACT-02 is a global, multicenter, randomized, phase 3, open-label study that randomized 507 patients 1:1 to the experimental arm of cabozantinib in combination with atezolizumab and the control arm of a second NHT (either abiraterone and prednisone or enzalutamide). The two primary endpoints of the trial are PFS and OS. The study included patients with mCRPC who have measurable extra-pelvic soft tissue metastasis and who have progressed on one prior NHT. The secondary endpoint is objective

response rate per BIRC. The trial is sponsored by Exelixis and co-funded by Ipsen, Roche and Takeda Pharmaceutical Company Limited (Takeda). Takeda is conducting the trial in Japan. More information about CONTACT-02 is available at ClinicalTrials.gov.

About CRPC

According to the American Cancer Society, approximately 299,000 new cases of prostate cancer will be diagnosed in the U.S., and over 35,000 people will die from the disease in 2024.[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 mCRPC.[2] Men diagnosed with mCRPC often have a poor prognosis, with an estimated survival of 1-2 years.[3,4]

About CABOMETYX® (cabozantinib)

In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced renal cell carcinoma (RCC); for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib; for patients with advanced RCC as a first-line treatment in combination with nivolumab; and for adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible. CABOMETYX tablets have also received regulatory approvals in the European Union and additional countries and regions worldwide. In 2016, Exelixis granted Ipsen Pharma SAS exclusive rights for the commercialization and further clinical development of cabozantinib outside of the U.S. and Japan. In 2017, Exelixis granted exclusive rights to Takeda for the commercialization and further clinical development of cabozantinib for all future indications in Japan. Exelixis holds the exclusive rights to develop and commercialize cabozantinib in the U.S.

CABOMETYX in combination with atezolizumab is not indicated as a treatment for mCRPC.

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, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of fistulas and perforations, 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 events that require medical intervention.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% 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. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Diarrhea: Diarrhea occurred in 62% of CABOMETYX patients. Grade 3 diarrhea occurred in 10% of CABOMETYX patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 45% 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.

Hepatotoxicity: CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone.

Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

Proteinuria: Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria; resume CABOMETYX at a reduced dose. 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, resume at a reduced dose.

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. 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.

Thyroid Dysfunction: Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in

19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients.

Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

Hypocalcemia: CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN.

In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients.

Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

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 common (≥20%) adverse reactions are:

CABOMETYX as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, and constipation.

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

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. Avoid CABOMETYX in patients with severe hepatic impairment.

Please see accompanying full Prescribing Information
https://www.cabometyx.com/downloads/CABOMETYXUSPI.pdf.

You are encouraged to report negative side effects of prescription drugs to the FDA.

Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

About Exelixis

Exelixis is a globally ambitious oncology company innovating next-generation medicines and regimens at the forefront of cancer care. Powered by drug discovery and development excellence, we are rapidly evolving our product portfolio to target an expanding range of tumor types and indications with our clinically differentiated pipeline of small molecules, antibody-drug conjugates and other biotherapeutics. This comprehensive approach harnesses decades of robust investment in our science and partnerships to advance our investigational programs and extend the impact of our flagship commercial product, CABOMETYX® (cabozantinib). Exelixis is driven by a bold scientific pursuit to create transformational treatments that give more patients hope for the future. For information about the company and its mission to help cancer patients recover stronger and live longer, visit www.exelixis.com, follow @ExelixisInc on X (Twitter), like Exelixis, Inc. on Facebook and follow Exelixis on LinkedIn.

Forward-Looking Statements

This press release contains forward-looking statements, including, without limitation, statements related to: the presentation of detailed results from the CONTACT-02 trial at ASCO GU 2024; the therapeutic potential of cabozantinib in combination with atezolizumab as an additional and readily available treatment option for patients with mCRPC and measurable extra-pelvic soft tissue disease who have progressed on one prior NHT; Exelixis' commitment to patients with advanced prostate cancer and to improving their standard of care; Exelixis' plans to discuss the CONTACT-02 results with the U.S. Food and Drug Administration, and Exelixis' anticipation that the next analysis of overall survival will be available in 2024; and Exelixis' scientific pursuit to create transformational treatments that give more patients hope for the future. 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; complexities and the unpredictability of the regulatory review and approval processes in the U.S. and elsewhere; Exelixis' continuing compliance with applicable legal and regulatory requirements; the potential failure of cabozantinib in combination with atezolizumab to demonstrate safety and/or efficacy in future clinical testing; unexpected concerns that may arise as a result of the occurrence of adverse safety events or additional data analyses of clinical trials evaluating cabozantinib; the costs of conducting clinical 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 detailed from time to time under the caption "Risk Factors" in Exelixis' most recent Annual Report on Form 10-K and subsequent Quarterly Reports on Form 10-Q, and in Exelixis' future filings with the Securities and Exchange Commission. 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.

[1] Cancer Facts & Figures 2024. ACS website. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2024/2024-cancer-facts-and-figures-acs.pdf. Accessed January 2024.

[2] Prostate Cancer: Types of Treatment. Cancer.Net. Available at: https://www.cancer.net/cancer-types/prostate-cancer/types-treatment. Accessed January 2024.

[3] Moreira, D. M., *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.

[4] Freedland, S. J., et al. Real-world treatment patterns and overall survival among men with Metastatic Castration-Resistant Prostate Cancer (mCRPC) in the US Medicare population. *Prostate Cancer Prostatic Dis*. 2023.

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