Exelixis Presents Final Overall Survival Results from Phase 3 CONTACT-02 Pivotal Study Evaluating Cabozantinib in Combination with an Immune Checkpoint Inhibitor in Metastatic Castration-Resistant Prostate Cancer at ESMO 2024

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ALAMEDA, Calif.--(BUSINESS WIRE)--Sep. 15, 2024-- Exelixis, Inc. (Nasdaq: EXEL) today announced detailed final overall survival (OS) results from CONTACT-02, a phase 3 pivotal study evaluating cabozantinib (CABOMETYX®) in combination with atezolizumab (Tecentriq®) 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. These data are being presented today at the 2024 European Society for Medical Oncology Congress (ESMO 2024) during the Proffered Paper Session: GU Tumours, Prostate at 2:45 p.m. CEST.

“Despite recent advancements, outcomes remain poor for patients with metastatic castration-resistant prostate cancer whose disease progresses after novel hormonal therapy – particularly those with liver metastases,” 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. “I believe there is a critical need for novel agents with a new mechanism of action that are broadly accessible to patients and can delay disease progression. The positive results from CONTACT-02, especially in the subset of patients with liver metastasis, reinforce the therapeutic potential of cabozantinib in combination with atezolizumab for these patients.”

The two primary endpoints for CONTACT-02 were progression-free survival (PFS) and OS. At a median follow-up of 24.0 months, the final analysis of OS showed a numerical but not statistically significant improvement favoring cabozantinib in combination with atezolizumab (hazard ratio: 0.89; 95% confidence interval: 0.72-1.10; *P*=0.296). An improvement in OS was observed in multiple clinical subgroups, notably in patients with bone or liver metastases, with the latter category representing a population whose disease may be evolving away from androgen receptor signaling. Additional OS efficacy findings are included in Table 1 below.

TABLE 1	ITT population	Bone metastases	Liver metastases
Patients, n	575	446	132
HR **(95% CI)** **P-value**	0.89 (0.72, 1.10) *P*=0.30	0.79 (0.63, 1.00) *P*=0.046	0.68 (0.47, 1.00) *P*=0.051
Median OS (C+A); months	14.8 (13.4, 16.7)	13.8 (11.9, 16.3)	12.2 (8.8, 13.8)
Median OS (NHT); months	15.0 (13.0, 18.5)	11.6 (10.5, 14.1)	7.1 (5.3, 10.4)

C+A: cabozantinib + atezolizumab; CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; NHT: novel hormonal therapy; OS: overall survival

“Within the current treatment landscape, there is a growing population of patients with metastatic castration-resistant prostate cancer with extra-pelvic soft tissue metastases whose disease has progressed after novel hormonal therapy, leaving a high unmet need for effective, widely available treatments for these patients,” said Amy Peterson, M.D., Executive Vice President, Product Development & Medical Affairs, and Chief Medical Officer, Exelixis. “Collectively, the results from the CONTACT-02 trial suggest that there are patients who could benefit from cabozantinib in combination with atezolizumab and that this regimen could be a valuable addition to the treatment landscape for patients with advanced prostate cancer.”

Treatment-related grade 3-4 adverse events (AEs) occurred in 40% of patients receiving cabozantinib in combination with atezolizumab and 8% of those receiving NHT. Treatment-related AEs leading to discontinuation of all treatment components were similar (5% for cabozantinib in combination with atezolizumab and 2% of those receiving NHT). The time to clinically meaningful deterioration in quality of life was similar between arms, and the combination of cabozantinib and atezolizumab did not impair quality of life relative to generally well-tolerated NHT.

As previously announced, CONTACT-02 met one of its two primary endpoints, demonstrating a statistically significant benefit in PFS in the predefined PFS ITT population (i.e., the first 400 randomized patients). Detailed results were presented at the American Society of Clinical Oncology 2024 Genitourinary Cancers Symposium in January 2024. Exelixis intends to submit a supplemental New Drug Application with the U.S. Food and Drug Administration for cabozantinib in combination with atezolizumab for mCRPC later this year.

About CONTACT-02
CONTACT-02 is a global, multicenter, randomized, phase 3, open-label study that randomized 575 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 blinded independent radiology committee. 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. 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 as monotherapy for the treatment of patients with advanced renal cell carcinoma (RCC) and in combination with nivolumab as a first-line treatment for patients with advanced RCC; for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib; 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 over 65 countries outside the U.S. and Japan, including the European Union. 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 Pharmaceutical Company Limited 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 is not indicated as a treatment for CRPC.

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 final OS results from the CONTACT-02 trial at ESMO 2024; the therapeutic potential of cabozantinib in combination with atezolizumab to benefit patients with mCRPC and measurable extra-pelvic soft tissue disease who have progressed on one prior NHT, especially in the subset of patients with liver metastasis, and Exelixis' belief that this combination regimen could be a valuable addition to the treatment landscape for patients with advanced prostate cancer; Exelixis' plans to submit a supplemental New Drug Application with the U.S. Food and Drug Administration for cabozantinib in combination with atezolizumab for mCRPC later this year; 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; unexpected concerns that may arise as a result of the occurrence of adverse safety events or additional data analyses of clinical trials evaluating cabozantinib; Exelixis' dependence on its relationships with its cabozantinib commercial collaboration partners, including the level of their investment in the resources necessary to pursue regulatory approvals and successfully commercialize cabozantinib in the territories where approved; 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. 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 September 2024.

[2] Patient education: Treatment for advanced prostate cancer (Beyond the Basics). UpToDate website. Available at: https://www.uptodate.com/contents/treatment-for-advanced-prostate-cancer-beyond-the-basics. Accessed September 2024.

[3] 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.

[4] 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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