Exelixis Announces Encouraging Results from Expansion Cohort of Phase 1b STELLAR-001 Trial Evaluating Zanzalintinib in Patients with Advanced Kidney Cancer at IKCS 2023

November 10, 2023

– Results for Exelixis' next-generation tyrosine kinase inhibitor demonstrated an objective response rate of 38% and a disease control rate of 88% –

– Anti-tumor activity was observed in patients who had progressed on prior VEGFR-tyrosine kinase inhibitors, including cabozantinib –

ALAMEDA, Calif.--(BUSINESS WIRE)--Nov. 10, 2023-- Exelixis, Inc. (Nasdaq: EXEL) today announced initial results from an expansion cohort of STELLAR-001 evaluating single-agent zanzalintinib in patients with previously treated clear cell renal cell carcinoma (ccRCC). STELLAR-001 is a phase 1b trial evaluating zanzalintinib alone and in combination with atezolizumab in patients with locally advanced or metastatic solid tumors. The findings are being presented today at 2:35 p.m. CST during the Oral Abstracts session at the 2023 International Kidney Cancer Symposium (IKCS): North America.

"Following promising activity in the dose-escalation stage, I am further encouraged by the anti-tumor activity observed in the monotherapy expansion cohort suggesting that zanzalintinib may be an effective therapy following disease progression after prior treatments," said Sumanta Pal, M.D., Clinical Professor, City of Hope Comprehensive Cancer Center, who is presenting the findings. "Many of these patients with advanced kidney cancer have exhausted their treatment options, having progressed on both immune checkpoint inhibitors and tyrosine kinase inhibitors including cabozantinib, so these results showing strong response rates and durable responses are encouraging for this group of patients."

In this ccRCC cohort, 97% of patients had received prior immunotherapy and 81% had received prior VEGFR-tyrosine kinase inhibitor (TKI), including 53% who had received cabozantinib. Eighty-one percent of patients were intermediate risk by International Metastatic RCC Database Consortium.

At a median follow-up of 8.3 months, 12 of the 32 patients enrolled in the expansion cohort had a confirmed partial response for an objective response rate of 38%; the disease control rate was 88%. Additional efficacy outcomes by prior therapy subgroups are shown in Table 1.

		All patients		Patients who received a prior VEGFR-TKI	
TABLE 1	**Overall (n=32)**	**Cabozantinib-exposed (n=17)**	**Cabozantinib-naïve (n=14)**	**Any VEGFR-TKI, including cabozantinib (n=26)**	**Non-cabozantinib VEGFR-TKI (n=8)**
Objective response rate, %	38	24	57	35	63
Disease control rate, %	88	94	86	92	100

Subgroups are not mutually exclusive. Prior cabozantinib exposure was unknown for one patient.
VEGFR-TKI: vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

At data cutoff, 50% of patients were continuing treatment. The median duration of response was 7.4 months for the cabozantinib-naïve group and not estimable for the cabozantinib-exposed group.

"These findings underscore the potential zanzalintinib may hold for patients with refractory kidney cancer, including those who have previously progressed on cabozantinib," said Amy Peterson, M.D., Executive Vice President, Product Development & Medical Affairs, and Chief Medical Officer, Exelixis. "As STELLAR-001 and our phase 3 STELLAR trials progress, we look forward to elucidating the potential of zanzalintinib in kidney cancer as well as in other advanced solid tumors."

The safety population (n=81) included 32 patients from the ccRCC expansion cohort treated at 100 mg plus 49 patients across different solid tumors from the dose-escalation stage who received single-agent zanzalintinib at doses ranging from 10-140 mg. The safety profile was similar between the ccRCC cohort and the safety population. Discontinuations due to treatment-related adverse events (AEs) occurred in 9% of patients in the ccRCC cohort and 12% of patients in the safety population. There were three grade 5 treatment-emergent AEs in the ccRCC cohort and two more in the safety population; none were treatment-related, nor was the single grade 4 event. Of note, the rate of palmar plantar erythrodysesthesia was low with zanzalintinib (9% in the ccRCC cohort and 12% in the safety population, all grade 1-2).

About STELLAR-001

STELLAR-001 (NCT03845166) is a global, open-label phase 1b/2 study of zanzalintinib as a single agent or in combination with atezolizumab in patients with inoperable locally advanced or metastatic solid tumors. The trial is divided into two parts: a dose-escalation stage and an expansion cohort stage. The expansion cohorts evaluating zanzalintinib as a single agent or in combination with atezolizumab include patients with: ccRCC, non-clear cell RCC, breast cancer that is hormone receptor-positive and HER-2 negative, castration-resistant prostate cancer and colorectal cancer. More information about the trial is available at ClinicalTrials.gov.

About Zanzalintinib

Zanzalintinib is a next-generation oral TKI that inhibits the activity of receptor tyrosine kinases implicated in cancer growth and spread, including VEGF receptors, MET, AXL and MER. These receptor tyrosine kinases are involved in both normal cellular function and in pathologic processes such as oncogenesis, metastasis, tumor angiogenesis and resistance to multiple therapies, including immune checkpoint inhibitors. With zanzalintinib, Exelixis sought to build upon its extensive experience with the target profile of cabozantinib, the company's flagship medicine, while improving key characteristics, including pharmacokinetic half-life. Zanzalintinib is currently being developed for the treatment of advanced solid tumors, including genitourinary, colorectal and head and neck cancers.

Zanzalintinib is not approved for ccRCC.

About RCC

Kidney cancer is among the top 10 most commonly diagnosed forms of cancer among both men and women in the U.S.[1] An estimated 81,800 Americans will be diagnosed with kidney cancer in 2023.[1] The most common type of kidney cancer in adults is ccRCC.[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 15%.[3] In 2022, approximately 32,200 patients with advanced kidney cancer required systemic therapy in the U.S., with over 20,000 patients receiving first-line treatment.[4]

About CABOMETYX® (cabozantinib)

In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced 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 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 bi-coastal centers of 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: Exelixis' presentation of data from STELLAR-001 during the Oral Abstracts session at the 2023 IKCS: North America; the therapeutic potential of zanzalintinib to treat patients with refractory ccRCC, including those who have previously progressed on cabozantinib; Exelixis' plans to continue studying the therapeutic potential of zanzalintinib in kidney cancer as well as in other advanced solid tumors; 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 zanzalintinib, both alone and in combination with other therapies, to demonstrate safety and/or efficacy in future clinical testing; uncertainties inherent in the product development process; the costs of conducting clinical trials; Exelixis' dependence on third-party vendors for the development, manufacture and supply of zanzalintinib; 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 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.

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[1] Key Statistics About Kidney Cancer. American Cancer Society website. Available at: https://www.cancer.org/cancer/kidney-cancer/about/key-statistics.html. Accessed November 2023.

[2] What Is Kidney Cancer? American Cancer Society website. Available at https://www.cancer.org/cancer/kidney-cancer/about/what-is-kidney-cancer.html. Accessed November 2023.

[3] Survival Rates for Kidney Cancer. American Cancer Society website. Available at https://www.cancer.org/cancer/kidney-cancer/detection-diagnosis-staging/survival-rates.html. Accessed November 2023.

[4] Citeline's Datamonitor Healthcare: Renal Cell Carcinoma. March 2023 (internal data on file).

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