Exelixis Announces Final Five-Year Follow-up Results from CheckMate -9ER Trial Evaluating CABOMETYX® (cabozantinib) in Combination with Opdivo® (nivolumab) in Patients with Advanced Kidney Cancer at ASCO GU 2025

February 15, 2025

– After more than five years of follow-up, CABOMETYX in combination with Opdivo continued to show survival benefit compared with sunitinib –

– Long-term efficacy seen across subgroups, including site of metastases –

ALAMEDA, Calif.--(BUSINESS WIRE)--Feb. 15, 2025-- Exelixis, Inc. (Nasdaq: EXEL) today announced final results from the phase 3 CheckMate -9ER pivotal trial evaluating CABOMETYX® (cabozantinib) in combination with Opdivo® (nivolumab) versus sunitinib for patients with previously untreated advanced renal cell carcinoma (RCC). After more than five years of follow-up, the findings demonstrated that efficacy benefits with CABOMETYX in combination with Opdivo were sustained long term. These results, including subgroup analyses, will be presented at 8:10 a.m. PT on February 15 during Oral Abstract Session C: Renal Cell Cancer and Testicular Cancer at the American Society of Clinical Oncology 2025 Genitourinary Cancers Symposium (ASCO GU).

“In this evolving treatment landscape for renal cell carcinoma, patients are looking for options that have shown improved survival time in the long-term,” said Robert J. Motzer, M.D., Kidney Cancer Section Head, Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center. “These final five-year results from CheckMate -9ER demonstrated the durable clinical benefits of cabozantinib in combination with nivolumab —including for those with organ metastases or intermediate- or poor-risk disease classifications—and continue to support this combination regimen as a valuable first-line option for this patient population.”

At a median follow-up of 67.6 months, CABOMETYX in combination with Opdivo improved progression-free survival (PFS; hazard ratio [HR]: 0.58; 95% confidence interval [CI]: 0.49-0.70) and overall survival (OS; HR: 0.79; 95% CI: 0.65-0.96) compared with sunitinib in the intent-to-treat population. A subgroup analysis by International Metastatic RCC Database Consortium (IMDC) risk showed PFS and objective response rates (ORR) favored CABOMETYX in combination with Opdivo versus sunitinib regardless of IMDC risk group. Detailed results are shown in Table 1.

Table 1	CABOMETYX + Opdivo	Sunitinib
ITT population (n=651)		
Median PFS, mo	16.4	8.3
PFS HR (95% CI)	0.58 (0.49-0.70)	
Median OS, mo	46.5	35.5
OS HR (95% CI)	0.79 (0.65-0.96)	
ORR, %	55.7	27.4
DOR, mo	22.0	15.2
Favorable IMDC risk (n=146)		
Median PFS, mo	21.4	12.8
PFS HR (95% CI)	0.67 (0.46-0.97)	
Median OS, mo	53.7	58.9
OS HR (95% CI)	1.08 (0.70-1.66)	
ORR, %	66.2	43.1
Intermediate/poor IMDC risk (n=505)		
Median PFS, mo	15.4	7.1
PFS HR (95% CI)	0.56 (0.46-0.69)	
Median OS, mo	43.9	29.2
OS HR (95% CI)	0.74 (0.60-0.92)	
ORR, %	52.6	23.0

CI: confidence interval; DOR: duration of response; HR: hazard ratio; IMDC: International Metastatic RCC Database Consortium; ITT: intent-to-treat; ORR: objective response rate; OS: overall survival; PFS: progression-free survival

In an analysis by baseline metastases sites, PFS, OS and ORR favored the combination regimen versus sunitinib in all three subgroups (liver, bone and lung). Detailed results are shown in Table 2.

Table 2	Liver	Bone	Lung

	CABOMETYX + Opdivo (n=73)	Sunitinib (n=56)	CABOMETYX + Opdivo (n=79)	Sunitinib (n=75)	CABOMETYX + Opdivo (n=241)	Sunitinib (n=251)
Median PFS, mo	10.9	6.2	13.8	5.3	16.4	8.3
PFS HR (95% CI)	0.55 (0.37-0.82)		0.43 (0.30-0.64)		0.56 (0.46-0.69)	
Median OS, mo	37.6	22.1	34.8	20.7	47.5	32.4
OS HR (95% CI)	0.65 (0.43-0.97)		0.66 (0.45-0.95)		0.75 (0.60-0.94)	
ORR, %	52.1	21.4	49.4	9.3	57.3	27.9

CI: confidence interval; HR: hazard ratio; IMDC: ORR: objective response rate; OS: overall survival; PFS: progression-free survival

"With now more than five years of follow-up, these results continue to support CABOMETYX in combination with Opdivo as a treatment regimen that can have enduring survival benefits for patients with previously untreated advanced kidney cancer," said Amy Peterson, M.D., Executive Vice President, Product Development & Medical Affairs, and Chief Medical Officer, Exelixis. "The efficacy was sustained across multiple subgroups, further underscoring the potential of this regimen to benefit a broad population with variable disease burden. We are proud to have established such a compelling standard of care for this community and remain committed to developing much-needed treatment options for all patients living with advanced cancers."

Safety and tolerability with long-term follow-up were manageable and consistent with previous analyses. No new safety signals were reported. Grade 3/4 adverse events (AEs) occurred in 68% of patients treated with CABOMETYX in combination with Opdivo versus 55% of patients treated with sunitinib, with the most frequent being diarrhea (7% versus 5%, respectively), palmar-plantar erythrodysesthesia (8% versus 8%), hypertension (13% versus 13%), fatigue (3% versus 5%), thrombocytopenia (<1% versus 5%) and alanine aminotransferase increased (6% versus 1%). One treatment-related death per investigator occurred with CABOMETYX in combination with Opdivo versus three with sunitinib. Treatment-related AEs leading to discontinuation occurred in 28% of patients treated with CABOMETYX in combination with Opdivo versus 11% of patients treated with sunitinib.

About CheckMate -9ER

CheckMate -9ER is an open-label, randomized, multi-national phase 3 trial evaluating patients with previously untreated advanced or metastatic RCC. A total of 651 patients (23% favorable risk, 58% intermediate risk, 20% poor risk; 25% tumor PD-L1≥1%) were randomized to receive CABOMETYX in combination with Opdivo (n=323) versus sunitinib (n=328). The primary endpoint is PFS. Secondary endpoints include OS and ORR. The primary efficacy analysis is comparing the doublet combination versus sunitinib in all randomized patients. The trial is sponsored by Bristol Myers Squibb and Ono Pharmaceutical Co. and co-funded by Exelixis, Inc., Ipsen Pharma SAS and Takeda Pharmaceutical Company Limited.

About RCC

Kidney cancer is among the top ten most commonly diagnosed forms of cancer among both men and women in the U.S.[1] An estimated 80,980 Americans will be diagnosed with kidney cancer in 2025.[1] 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 18%.[2] In 2024, approximately 33,200 patients with advanced kidney cancer required systemic therapy in the U.S., with over 21,000 patients receiving first-line treatment.[3]

About CABOMETYX® (cabozantinib)

In the U.S., CABOMETYX tablets are approved as monotherapy for the treatment of patients with advanced 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.

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 final results from the CheckMate -9ER trial at ASCO GU 2025; the therapeutic potential of cabozantinib in combination with nivolumab and Exelixis' belief that the regimen may provide enduring survival benefits for patients with previously untreated advanced kidney cancer; Exelixis' belief in the ability of the regimen to benefit a broad population with variable disease burden; Exelixis' commitment to developing much-needed treatment options for all patients living with advanced cancers; 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' and Bristol Myers Squibb's continuing compliance with applicable legal and regulatory requirements; the potential failure of cabozantinib in combination with nivolumab 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' and Bristol Myers Squibb's ability to protect their respective 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.

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[1] Cancer Facts & Figures 2025. ACS. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2025/2025-cancer-facts-and-figures-acs.pdf. Accessed February 2025.

[2] Survival Rates for Kidney Cancer. ACS. Available at: https://www.cancer.org/cancer/types/kidney-cancer/detection-diagnosis-staging/survival-rates.html. Accessed February 2025.

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

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