



Exelixis and Ipsen Announce Cabozantinib in Combination with an Immune Checkpoint Inhibitor Significantly Improved Progression-Free Survival in Phase 3 COSMIC-312 Pivotal Trial in Patients with Previously Untreated Advanced Liver Cancer

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ALAMEDA, Calif. & PARIS--(BUSINESS WIRE)--Jun. 28, 2021-- [Exelixis, Inc.](#) (NASDAQ: EXEL) and Ipsen (Euronext: IPN; ADR: IPSEY) today announced that COSMIC-312, the ongoing phase 3 pivotal trial evaluating cabozantinib (CABOMETYX[®]) in combination with atezolizumab versus sorafenib in patients with previously untreated advanced hepatocellular carcinoma (HCC), met one of the primary endpoints, demonstrating significant improvement in progression-free survival (PFS) at the planned primary analysis. A prespecified interim analysis for the second primary endpoint of overall survival (OS), conducted at the same time as the primary analysis for PFS, showed a trend favoring the combination of cabozantinib and atezolizumab but did not reach statistical significance. Based on the preliminary OS data, Exelixis anticipates that the probability of reaching statistical significance at the time of the final analysis is low. The trial will continue as planned to the final analysis of OS; results are anticipated in early 2022.

In the analysis of the primary endpoint of PFS in the PFS intent-to-treat population, cabozantinib in combination with atezolizumab significantly reduced the risk of disease progression or death by 37% compared with sorafenib (hazard ratio: 0.63; 99% confidence interval: 0.44-0.91; P=0.0012). Safety for the combination appeared to be consistent with the known safety profiles of the individual medicines, and no new safety signals were identified. Exelixis plans to discuss the trial results and next steps for a potential regulatory filing with the U.S. Food and Drug Administration (FDA).

"While we are encouraged by the data supporting the potential for the combination of cabozantinib and atezolizumab to reduce the risk of disease progression or death, we are disappointed by the interim result of lack of significant improvement on overall survival versus the comparator arm," said Michael M. Morrissey, Ph.D., Exelixis' President and Chief Executive Officer. "As these data continue to mature, we are working to understand the potential impact of various contributing factors on the results, including patient demographics, subsequent anti-cancer therapy and the impact of COVID-19 on the trial. We anticipate presenting the results at a future medical conference."

About COSMIC-312

COSMIC-312 is a global, multicenter, randomized, controlled phase 3 pivotal trial that aimed to enroll approximately 840 patients at up to 200 sites globally. Patients were randomized approximately 2:1:1 to one of three arms: cabozantinib (40 mg) in combination with atezolizumab, sorafenib, or cabozantinib (60 mg). Exelixis is sponsoring COSMIC-312, and Ipsen is co-funding the trial. Genentech, a member of the Roche Group, is providing atezolizumab for use in this trial. More information about COSMIC-312 is available at [ClinicalTrials.gov](#).

About HCC

More than 900,000 new cases of liver cancer, 90% of which are HCC, are diagnosed worldwide each year.^{1,2} HCC is a leading cause of cancer-related death, expected to cause 1 million global deaths annually by 2030.³ In the U.S., HCC is the fastest-rising cause of cancer-related death.⁴ Median survival for patients with symptomatic advanced HCC who are treated with systemic therapies is just 1 to 1.5 years.²

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 HCC who have been previously treated with sorafenib; and for patients with advanced RCC as a first-line treatment in combination with nivolumab. Outside of the U.S., CABOMETYX is approved in 58 countries, including in the European Union, the U.K., Norway, Iceland, Australia, New Zealand, Switzerland, South Korea, Canada, Brazil, Taiwan, Hong Kong, Singapore, Macau, Jordan, Lebanon, Russian Federation, Ukraine, Turkey, United Arab Emirates, Saudi Arabia, Serbia, Israel, Mexico, Chile, Peru, Panama, Guatemala, Dominican Republic, Ecuador, Thailand and Malaysia for the treatment of advanced RCC in adults who have received prior VEGF-targeted therapy; in the European Union, the U.K., Norway, Iceland, Canada, Australia, Brazil, Taiwan, Hong Kong, Singapore, Lebanon, Jordan, Russian Federation, Ukraine, Turkey, United Arab Emirates, Saudi Arabia, Israel, Mexico, Chile, Peru, Panama, Guatemala, Dominican Republic, Ecuador, Thailand and Malaysia for previously untreated intermediate- or poor-risk advanced RCC; and in the European Union, the U.K., Norway, Iceland, Canada, Australia, New Zealand, Switzerland, Saudi Arabia, Serbia, Israel, Taiwan, Hong Kong, South Korea, Singapore, Jordan, Russian Federation, Ukraine, Turkey, Lebanon, United Arab Emirates, Peru, Panama, Guatemala, Chile, Dominican Republic, Ecuador, Thailand and Malaysia for HCC in adults who have previously been treated with sorafenib. In the European Union, CABOMETYX is also approved in combination with nivolumab as first line treatment for patients living with advanced RCC. 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. Exelixis holds the exclusive rights to develop and commercialize cabozantinib in the United States.

CABOMETYX is not indicated as a treatment for previously untreated advanced HCC.

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 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: 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 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.

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.

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 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 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 common (≥20%) adverse reactions are:

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

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://cabometryx.com/downloads/CABOMETRYXUSPI.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.

EUROPEAN UNION IMPORTANT SAFETY INFORMATION

For detailed recommendations on the use of CABOMETYX in the European Union, please see the [Summary of Product Characteristics](#).

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. In November 2020, the company was named to *Fortune's* 100 Fastest-Growing Companies list for the first time, ranking 17th overall and the third-highest biopharmaceutical company. For more information about Exelixis, please visit www.exelixis.com, follow [@ExelixisInc](#) on Twitter or like [Exelixis, Inc.](#) on Facebook.

About Ipsen

Ipsen is a global mid-size biopharmaceutical company with a focus on transformative medicines in Oncology, Rare Disease and Neuroscience. Ipsen also has a well-established Consumer Healthcare business. With total sales over €2.5 billion in 2020, Ipsen sells more than 20 drugs in over 110 countries, with a direct commercial presence in more than 30 countries. Ipsen's R&D is focused on its innovative and differentiated technological platforms located in the heart of the leading biotechnological and life sciences hubs (Paris-Saclay, France; Oxford, UK; Cambridge, US; Shanghai, China). The Group has about 5,700 employees worldwide. Ipsen is listed in Paris (Euronext: IPN) and in the United States through a Sponsored Level I American Depositary Receipt program (ADR: IPSEY). For more information on Ipsen, visit www.ipсен.com.

Exelixis Forward-Looking Statements

This press release contains forward-looking statements, including, without limitation, statements related to: Exelixis' expectations regarding the timing and results for final analysis of OS data from COSMIC-312; Exelixis' plans to discuss the trial results and next steps for a potential regulatory filing with the FDA; Exelixis' continuing analysis of the potential impact of various factors on the COSMIC-312 trial results and anticipation it will present the trial results at a future medical conference; 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: 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 efficacy in clinical testing; uncertainties inherent in the product development process; Exelixis' dependence on its relationships with its cabozantinib collaboration partners, including the level of their investment in the resources necessary to successfully commercialize cabozantinib or atezolizumab or the combination of these two drugs in the territories where approved; the continuing COVID-19 pandemic and its impact on Exelixis' product development and commercial activities; 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 May 6, 2021, 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, except as required by law.

Ipsen—Cautionary Note Regarding Forward-Looking Statements

The forward-looking statements, objectives and targets contained herein are based on the Group's management strategy, current views and assumptions. Such statements involve known and unknown risks and uncertainties that may cause actual results, performance or events to differ materially from those anticipated herein. All of the above risks could affect the Group's future ability to achieve its financial targets, which were set assuming reasonable macroeconomic conditions based on the information available today. Use of the words "believes," "anticipates" and "expects" and similar expressions are intended to identify forward-looking statements, including the Group's expectations regarding future events, including regulatory filings and determinations. Moreover, the targets described in this document were prepared without taking into account external growth assumptions and potential future acquisitions, which may alter these parameters. These objectives are based on data and assumptions regarded as reasonable by the Group. These targets depend on conditions or facts likely to happen in the future, and not exclusively on historical data. Actual results may depart significantly from these targets given the occurrence of certain risks and uncertainties, notably the fact that a promising product in early development phase or clinical trial may end up never being launched on the market or reaching its commercial targets, notably for regulatory or competition reasons and also taking into consideration assessment delays of certain clinical trials in light of the ongoing COVID-19 pandemic. The Group must face or might face competition from generic products that might translate into a loss of market share. Furthermore, the Research and Development process involves several stages each of which involves the substantial risk that the Group may fail to achieve its objectives and be forced to abandon its efforts with regards to a product in which it has invested significant sums. Therefore, the Group cannot be certain that favorable results obtained during pre-clinical trials will be confirmed subsequently during clinical trials, or that the results of clinical trials will be sufficient to demonstrate the safe and effective nature of the product concerned. There can be no guarantees a product will receive the necessary regulatory approvals or that the product will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements. Other risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the Group's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the Group's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions. The Group also depends on third parties to develop and market some of its products which could potentially generate substantial royalties; these partners could behave in such ways which could cause damage to the Group's activities and financial results. The Group cannot be certain that its partners will fulfill their obligations. It might be unable to obtain any benefit from those agreements. A default by any of the Group's partners could generate lower revenues than expected. Such situations could have a negative impact on the Group's business, financial position or performance. The Group expressly disclaims any obligation or undertaking to update or revise any forward-looking statements, targets or estimates contained in this press release to reflect any change in events, conditions, assumptions or circumstances on which any such statements are based, unless so required by applicable law. The Group's business is subject to the risk factors outlined in its registration documents filed with the French Autorité des Marchés Financiers. The risks and uncertainties set out are not exhaustive and the reader is advised to refer to the Group's 2020 Registration Document available on www.ipsen.com.

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¹ International Agency for Research on Cancer. GLOBOCAN 2020. Liver Fact Sheet. Available at: <http://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf>. Accessed June 2021.

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³ Kim, E., Viatour, P. Hepatocellular carcinoma: old friends and new tricks. *Exp Mol Med*. 2020;52:1898–1907.

⁴ Rawla, P., Sunkara, T., Muralidharan, P., et al. Update in global trends and aetiology of hepatocellular carcinoma. *Contemporary oncology (Pozn)*. 2018;22(3):141–150.

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Investors Contact:

Susan Hubbard
EVP, Public Affairs and
Investor Relations
Exelixis, Inc.
(650) 837-8194
shubbard@exelixis.com

Media Contact:

Lindsay Treadway
Executive Director, Public Affairs
and Advocacy Relations
Exelixis, Inc.
(650) 837-7522
ltreadway@exelixis.com

Ipsen Investor Contact:

Craig Marks
Vice President, Investor Relations
+44 7584 349 193

Ipsen Media Contact:

Emma Roper
Global Franchise Communications Manager
+44 7711 766 517

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