



Exelixis and Ipsen Initiate Phase 3 Pivotal Trial (COSMIC-312) of Cabozantinib in Combination with Atezolizumab versus Sorafenib in Previously Untreated Advanced Hepatocellular Carcinoma

December 5, 2018

– Clinical trial will also explore single-agent activity of cabozantinib in the first-line setting –

ALAMEDA, Calif. & PARIS--(BUSINESS WIRE)--Dec. 5, 2018-- [Exelixis, Inc.](#) (Nasdaq:EXEL) and Ipsen (Euronext:IPN; ADR:IPSEY) today announced the initiation of COSMIC-312, a phase 3 pivotal trial of cabozantinib (CABOMETYX[®]) in combination with atezolizumab (TECENTRIQ[®]) versus sorafenib in previously untreated advanced hepatocellular carcinoma (HCC). The co-primary endpoints of the trial are progression-free survival and overall survival. An exploratory arm will also evaluate cabozantinib monotherapy in this first-line setting.

"Liver cancer is the fastest-rising cause of cancer-related death in the U.S., underscoring the need for new treatment options for this patient community," said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. "Based on past evidence of potential synergistic effects with cabozantinib and immune checkpoint inhibitors, the combination offers promise for patients with advanced liver cancer who have not received prior treatment."

COSMIC-312 is a multicenter, randomized, controlled phase 3 pivotal trial that aims to enroll approximately 640 patients at up to 200 sites globally. Patients will be randomized 6:3:1 to one of three arms: cabozantinib (40 mg) and atezolizumab, sorafenib, or cabozantinib (60 mg).

Exelixis is sponsoring COSMIC-312, and Ipsen will co-fund the trial. Ipsen will have access to the results to support potential future regulatory submissions outside of the U.S. and Japan. Genentech, a member of the Roche Group, is providing atezolizumab for use in this trial.

"With more than 800,000 new diagnoses of liver cancer worldwide each year and a poor prognosis for patients with advanced disease, there is an urgent need to identify new treatment options," said R. Kate Kelley, M.D., Associate Professor of Clinical Medicine, Division of Hematology/Oncology, University of California, San Francisco, and lead investigator on COSMIC-312. "We look forward to learning whether the combination of cabozantinib and atezolizumab may improve outcomes for previously untreated patients."

More information about this trial is available at [ClinicalTrials.gov](#).

About HCC

Liver cancer is the second-leading cause of cancer death worldwide, accounting for more than 700,000 deaths and 800,000 new cases each year.¹ In the U.S., the incidence of liver cancer has more than tripled since 1980.² HCC is the most common form of liver cancer, making up about three-fourths of the estimated nearly 42,000 new cases in the U.S. in 2018.² HCC is the fastest-rising cause of cancer-related death in the U.S.³ According to the GLOBOCAN data, it is estimated that across the European Union (EU-28) nearly 60,000 new patients will be diagnosed with liver cancer in 2020.⁴ Without treatment, patients with advanced HCC usually survive less than 6 months.⁵

About CABOMETYX[®] (cabozantinib)

CABOMETYX tablets are approved in the United States for the treatment of patients with renal cell carcinoma (RCC). On May 29, 2018, Exelixis announced that the U.S. Food and Drug Administration (FDA) accepted for filing the supplemental New Drug Application for CABOMETYX for previously treated advanced HCC and assigned a Prescription Drug User Fee Act action date of January 14, 2019. In March 2017, the FDA granted orphan drug designation to cabozantinib for the treatment of advanced HCC.

CABOMETYX tablets are also approved in: the European Union, Norway, Iceland, Australia, Switzerland, South Korea, Canada, Brazil and Taiwan for the treatment of advanced RCC in adults who have received prior VEGF-targeted therapy; in the European Union for previously untreated intermediate- or poor-risk advanced RCC; in Canada for adult patients with advanced RCC who have received prior VEGF targeted therapy; and in the European Union, Norway and Iceland for HCC in adults who have previously been treated with sorafenib.

CABOMETYX is not indicated for previously untreated advanced HCC.

About Exelixis' Collaboration with Ipsen

On February 29, 2016, Exelixis and Ipsen jointly announced an exclusive licensing agreement for the commercialization and further development of cabozantinib indications outside of the United States, Canada and Japan. On December 21, 2016, this agreement was amended to include commercialization rights for Ipsen in Canada. Ipsen has opted to participate in this phase 3 trial in first-line advanced HCC and will have access to the results to support potential future regulatory submissions. They may also participate in future studies at their choosing.

About Exelixis' Collaboration with Takeda

On January 30, 2017, Exelixis and Takeda jointly announced an exclusive licensing agreement for the commercialization and further development of cabozantinib indications in Japan. Under the parties' collaboration agreement, if Takeda opts to participate in funding this phase 3 trial, or future

studies, Takeda will have access to the respective study results to support potential future regulatory submissions in their territory.

Exelixis holds the exclusive rights to develop and commercialize cabozantinib in the United States.

Please see Important Safety Information below and full U.S. prescribing information at <https://cabometyx.com/downloads/CABOMETYXUSPI.pdf>.

U.S. Important Safety Information

- **Hemorrhage:** Severe and fatal hemorrhages have occurred with CABOMETYX. In two RCC studies, the incidence of Grade ≥ 3 hemorrhagic events was 3% in CABOMETYX-treated patients. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.
- **Gastrointestinal (GI) Perforations and Fistulas:** In RCC studies, fistulas were reported in 1% of CABOMETYX-treated patients. Fatal perforations occurred in patients treated with CABOMETYX. In RCC studies, gastrointestinal (GI) perforations were reported in 1% of CABOMETYX-treated patients. Monitor patients for symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula which cannot be appropriately managed or a GI perforation.
- **Thrombotic Events:** CABOMETYX treatment results in an increased incidence of thrombotic events. In RCC studies, venous thromboembolism occurred in 9% (including 5% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX-treated patients. Fatal thrombotic events occurred in the cabozantinib clinical program. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.
- **Hypertension and Hypertensive Crisis:** CABOMETYX treatment results in an increased incidence of treatment-emergent hypertension, including hypertensive crisis. In RCC studies, hypertension was reported in 44% (18% Grade ≥ 3) of CABOMETYX-treated patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy. Discontinue CABOMETYX if there is evidence of hypertensive crisis or severe hypertension despite optimal medical management.
- **Diarrhea:** In RCC studies, diarrhea occurred in 74% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **Palmar-Plantar Erythrodysesthesia (PPE):** In RCC studies, palmar-plantar erythrodysesthesia (PPE) occurred in 42% of patients treated with CABOMETYX. Grade 3 PPE occurred in 8% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPE or Grade 3 PPE until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS),** a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.
- **Embryo-fetal Toxicity** may be associated with CABOMETYX. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during CABOMETYX treatment and for 4 months after the last dose.
- **Adverse Reactions:** The most commonly reported ($\geq 25\%$) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, hypertension, PPE, weight decreased, vomiting, dysgeusia, and stomatitis.
- **Strong CYP3A4 Inhibitors:** If concomitant use with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage.
- **Strong CYP3A4 Inducers:** If concomitant use with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage.
- **Lactation:** Advise women not to breastfeed while taking CABOMETYX and for 4 months after the final dose.
- **Hepatic Impairment:** In patients with mild to moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

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

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 genetic systems, 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. We discovered our three commercially available products, CABOMETYX® (cabozantinib), COMETRIQ® (cabozantinib) and COTELLIC® (cobimetinib), and 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 Standard & Poor's (S&P) MidCap 400 index, which measures the performance of profitable mid-sized companies. For more information about Exelixis, please visit www.exelixis.com, follow [@ExelixisInc](https://twitter.com/ExelixisInc) on Twitter or like [Exelixis, Inc.](https://www.facebook.com/ExelixisInc) on Facebook.

About Ipsen

Ipsen is a global biopharmaceutical group focused on innovation and specialty care. The group develops and commercializes innovative medicines in three key therapeutic areas - Oncology, Neuroscience and Rare Diseases. Its commitment to Oncology is exemplified through its growing portfolio of key therapies for prostate cancer, neuroendocrine tumors, renal cell carcinoma and pancreatic cancer. Ipsen also has a well-established Consumer Healthcare business. With total sales over €1.9 billion in 2017, Ipsen sells more than 20 drugs in over 115 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). The Group has about 5,400 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: the potential of the combination of cabozantinib and atezolizumab, or of cabozantinib as a monotherapy, as treatment options for patients with previously untreated advanced HCC; 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: risks and uncertainties related to regulatory review and approval processes and Exelixis' compliance with applicable legal and regulatory requirements; the potential failure of the combination of cabozantinib and atezolizumab, or of cabozantinib as a monotherapy, to demonstrate safety and/or efficacy in COSMIC-312; uncertainties inherent in the product development process, including evolving regulatory requirements, slower than anticipated patient enrollment or inability to identify a sufficient number of clinical trial sites; the costs of conducting clinical trials, including the ability or willingness of Exelixis' collaboration partners to invest in the resources necessary to complete the 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; 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 November 1, 2018, 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.

Ipsen Forward-Looking Statement

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. 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 fulfil 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 2017 Registration Document available on its website (www.ipсен.com).

Exelixis, the Exelixis logo, CABOMETYX, COMETRIQ and COTELLIC are registered U.S. trademarks.

TECENTRIQ® (atezolizumab) is a registered trademark of Genentech, a member of the Roche Group.

The information stated above was prepared by Exelixis Inc. and Ipsen and reflects solely the opinion of Exelixis and Ipsen. Nothing in this statement shall be construed to imply any support or endorsement of Exelixis or Ipsen, or any of its products, by the Regents of the University of California, its officers, agents and employees.

¹ International Agency for Research on Cancer. GLOBOCAN 2018. Liver Fact Sheet. Available at: <http://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf>. Accessed November 2018.

² American Cancer Society: Cancer Facts and Figures 2018. Available at: <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf>. Accessed November 2018.

³ Mittal S, El-Serag HB. Epidemiology of HCC: Consider the Population. *Journal of Clinical Gastroenterology*. 2013. 47:S2-S6.

⁴ GLOBOCAN International Agency for Research on Cancer (IARC). Cancer Tomorrow. Accessed November 2018: http://globocan.iarc.fr/Pages/burden_sel.aspx

⁵ Weledji E, Orock G, Ngowe M, NsaghaD. How grim is hepatocellular carcinoma? *Annals of Medicine and Surgery*. 2014. 3:71-76.

View source version on businesswire.com: <https://www.businesswire.com/news/home/20181204006141/en/>

Source: Exelixis, Inc.

Investors:

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

Media:

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

Investors:

Eugenia Litz
Vice President, Investor Relations
Ipsen
+44 (0) 1753 627721
eugenia.litz@ipson.com

Media:

Ian Weatherhead
Vice President, Corporate External Communications
Ipsen
+44 (0) 1753 627733
ian.weatherhead@ipson.com