

**Ipsen announces positive topline results from pivotal Phase III CheckMate -9ER trial evaluating CABOMETYX<sup>®</sup> (cabozantinib) in combination with Opdivo<sup>®</sup> (nivolumab) in previously untreated advanced renal cell carcinoma**

- Study met primary endpoint of significantly improving progression-free survival, and secondary endpoints of overall survival and objective response rate vs. sunitinib
- CABOMETYX in combination with Opdivo demonstrates clinically meaningful efficacy results across all endpoints and preliminary assessment showing a favorable safety profile
- Trial co-funded by Bristol Myers Squibb, Exelixis, Ipsen and Takeda

**PARIS, France, 20 April 2020** — Ipsen (Euronext: IPN; ADR: IPSEY) announced today that CheckMate -9ER, a pivotal Phase III trial evaluating CABOMETYX<sup>®</sup> (cabozantinib) in combination with Opdivo<sup>®</sup> (nivolumab) compared to sunitinib in previously untreated advanced or metastatic renal cell carcinoma (RCC), met its primary endpoint of progression-free survival (PFS) at final analysis, as well as the secondary endpoints of overall survival (OS) at a pre-specified interim analysis, and objective response rate (ORR).

The safety profiles of CABOMETYX and Opdivo observed in the trial reflect the known safety profiles of the immunotherapy and tyrosine kinase inhibitor components in first-line RCC.

“We are delighted that this pivotal CheckMate -9ER trial met its key efficacy measures of progression-free survival as well as overall survival for previously untreated kidney cancer patients, with a favorable safety profile. These positive topline results support the growing body of data that shows CABOMETYX<sup>®</sup> may create a more immune-permissive tumor environment that could enhance the response to immune checkpoint inhibitors,” said Dr. Howard Mayer, Executive Vice President and Head of Research and Development at Ipsen. “We look forward to discussing these results with global health authorities with the aim to bring this new combination regimen to previously untreated kidney cancer patients, a population that, despite recent advances, remains in need of additional therapeutic options that extend survival.”

“CheckMate -9ER marks an important milestone in our partnership with Exelixis to further develop CABOMETYX<sup>®</sup> and our shared vision to progress the treatment for cancers and indications with high unmet need. If approved, this combination may become an important new first-line option for patients with this cancer,” said Bartek Bednarz, Senior Vice President, Global Product & Portfolio Strategy at Ipsen. “We would like to thank the patients, their families and the healthcare professionals involved in the trial and we look forward to presenting detailed results of the study at an upcoming congress.”

For more information on the details of the trial results, please see the Exelixis Form 8-K on file [here](#).

The companies plan to submit detailed results of CheckMate -9ER for presentation at an upcoming medical conference. More information about this trial is available at [ClinicalTrials.gov](https://ClinicalTrials.gov).

### **About the trial**

CheckMate -9ER is an open-label, randomized, multi-national Phase III trial evaluating patients with previously untreated advanced or metastatic renal cell carcinoma. Patients are randomized 1:1 to Opdivo and CABOMETYX or sunitinib. The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival (OS) and objective response rate (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, Ipsen and Takeda Pharmaceutical Company Limited.

### **About renal cell carcinoma**

There are over 400,000 new cases of kidney cancer diagnosed worldwide each year.<sup>1</sup> Of these, renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for approximately 90% of cases.<sup>2</sup> It is twice as common in men, and male patients account for over two thirds of deaths.<sup>1</sup> If detected in the early stages, the five-year survival rate is high, but for patients with advanced (aRCC) or late-stage metastatic RCC, the survival rate is much lower, around 12%, with no identified cure for this disease.<sup>4,5</sup>

### **About Ipsen products**

This press release mentions investigational uses of Ipsen products. Product indications and approvals for use vary by jurisdiction; please see SmPC/PI for full indications and safety information.

### **About CABOMETYX® (cabozantinib)**

CABOMETYX® is marketed by Exelixis, Inc. in the United States. Ipsen has exclusive rights for the commercialization and further clinical development of CABOMETYX® outside of the United States and Japan.

CABOMETYX® 20 mg, 40 mg and 60 mg film-coated unscored tablets

Active ingredient: Cabozantinib (S)-malate 20 mg, 40 mg and 60 mg

Other components: Lactose

Indications: CABOMETYX® is currently approved in 51 countries, including in the European Union, the U.K., Norway, Iceland, Australia, 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 and Panama 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, Jordan, Russian Federation, Turkey, United Arab Emirates, Saudi Arabia, Serbia, Israel, Mexico, Chile and Panama for previously untreated intermediate- or poor-risk advanced RCC; and in the European Union, the U.K., Norway, Iceland, Canada, Australia, Switzerland, Saudi Arabia, Serbia, Israel, Taiwan, Hong Kong, South Korea, Singapore, Jordan, Russian Federation, Turkey, United Arab Emirates and Panama for HCC in adults who have previously been treated with sorafenib.

CABOMETYX® is not indicated for previously untreated advanced HCC.

Dosage and administration: The recommended dose of CABOMETYX® is 60 mg once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of CABOMETYX® therapy. For dose modification, please refer to full SmPC. CABOMETYX® is for oral use. The tablets should be swallowed whole and not crushed. Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking CABOMETYX®.

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

Special warnings and precautions for use:

Monitor closely for toxicity during first 8 weeks of therapy. Events that generally have early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, palmar-plantar erythrodysesthesia syndrome (PPES), proteinuria, and gastrointestinal (GI) events.

Perforations and fistulas: serious gastrointestinal perforations and fistulas, sometimes fatal, have been observed with cabozantinib. Patients with inflammatory bowel disease, GI tumor infiltration or complications from prior GI surgery should be evaluated prior to therapy and monitored; if perforation and unmanageable fistula occur, discontinue cabozantinib.

Thromboembolic events: use with caution in patients with a history of or risk factors for thromboembolism; discontinue if acute myocardial infarction (MI) or other significant arterial thromboembolic complication occurs.

Hemorrhage: not recommended for patients that have or are at risk of severe hemorrhage.

Wound complications: treatment should be stopped at least 28 days prior to scheduled surgery (including dental).

Hypertension: monitor blood pressure (BP); reduce with persistent hypertension and discontinue should uncontrolled hypertension or hypertensive crisis occur.

Palmar-plantar erythrodysesthesia (PPES): interrupt treatment if severe PPES occurs.

Proteinuria: discontinue in patients with nephrotic syndrome.

Reversible posterior leukoencephalopathy syndrome (RPLS): discontinue in patients with RPLS.

QT interval prolongation: use with caution in patients with a history of QT prolongation, those on antiarrhythmics or with pre-existing cardiac disease.

Excipients: do not use in patients with hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Drug interactions: Cabozantinib is a CYP3A4 substrate. Potent CYP3A4 inhibitors may result in an increase in cabozantinib plasma exposure (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice). Coadministration with CYP3A4 inducers may result in decreased cabozantinib plasma exposure (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort). Cabozantinib may increase the plasma concentration of P-glycoprotein substrates (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan). MRP2 inhibitors may increase cabozantinib plasma concentrations (e.g., cyclosporine, efavirenz, emtricitabine). Bile salt sequestering agents may impact absorption or reabsorption resulting in potentially decreased cabozantinib exposure. No dose adjustment when co-administered with gastric pH modifying agents. A plasma protein displacement interaction may be possible with warfarin. INR values should be monitored in such a combination.

Women of childbearing potential/contraception in males and females: Ensure effective measures of contraception (oral contraceptive plus a barrier method) in male and female patients and their partners during therapy and for at least 4 months after treatment.

Pregnancy and lactation: CABOMETRYX® should not be used during pregnancy unless the clinical condition of the woman requires treatment. Lactation – discontinue breast-feeding during and for at least 4 months after completing treatment. Drive and use machines: Caution is recommended

Adverse reactions:

The most common serious adverse reactions are hypertension, diarrhea, PPES, pulmonary embolism, fatigue and hypomagnesaemia. Very common (>1/10): anemia, lymphopenia neutropenia, thrombocytopenia, hypothyroidism, dehydration, decreased appetite, hyperglycemia, hypoglycemia, hypophosphatasemia, hypoalbuminemia, hypomagnesaemia, hyponatremia, hypokalemia, hyperkalemia, hypocalcemia, hyperbilirubinemia, peripheral sensory neuropathy, dysgeusia, headache, dizziness, hypertension, dysphonia, dyspnea, cough, diarrhea, nausea, vomiting, stomatitis, constipation, abdominal pain, dyspepsia, oral pain, dry mouth, PPES, dermatitis acneiform, rash, rash maculopapular, dry skin, alopecia, hair color change, pain in extremity, muscle spasms, arthralgia, proteinuria, fatigue, mucosal inflammation, asthenia, weight decreased, serum ALT, AST, and ALP increased, blood bilirubin increased, creatinine increased, triglycerides increased, white blood cell decreased, GGT increased, amylase increased, blood cholesterol increased, lipase increased. Common (>1/100 to <1/10): abscess, tinnitus, pulmonary embolism, pancreatitis, abdominal pain upper, gastro-esophageal reflux disease, hemorrhoids, pruritus, peripheral edema, wound complications. Uncommon (>1/1000 to <1/100): convulsion, anal fistula, hepatitis cholestatic, osteonecrosis of the jaw. Selected adverse event (AEs): GI perforation, fistulas, hemorrhage, RPLS.

Prescribers should consult the SPC in relation to other adverse reactions.

For more information, see the regularly updated registered product information on the European Medicine Agency [www.ema.europa.eu](http://www.ema.europa.eu)

In the U.S., CABOMETYX® tablets are approved for the treatment of patients with advanced RCC and for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. Please see full U.S. Prescribing Information [here](#).

### **About Ipsen**

Ipsen is a global specialty-driven 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 €2.5 billion in 2019, 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 5,800 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](http://www.ipсен.com).

### **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 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 2018 Registration Document available on its website ([www.ipsen.com](http://www.ipsen.com)).

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