



## PRESS RELEASE

### European Commission approves Cabometyx® in combination with Opdivo® as a first-line treatment for patients living with advanced renal cell carcinoma

- Approval based on pivotal Phase III CheckMate -9ER trial data, also recently published in the *New England Journal of Medicine*<sup>1</sup>
- Trial data showed Cabometyx® (cabozantinib) in combination with Opdivo® (nivolumab) doubled median progression-free survival and significantly improved overall survival and disease control rates with a lower rate of discontinuation versus sunitinib<sup>1</sup>
  - These data showed consistent efficacy benefits across key subgroups of patients<sup>1</sup>

**PARIS, FRANCE, 31 March 2021** – Ipsen (Euronext: IPN; ADR: IPSEY) today announced that the European Commission (EC) has approved Cabometyx® (cabozantinib) in combination with Bristol Myers Squibb's Opdivo® (nivolumab) for the first-line treatment of advanced renal cell carcinoma (aRCC). This decision marks the first approval for Cabometyx in combination with another therapy in Europe and the third indication of Cabometyx in renal cell carcinoma (RCC).

"Today's EC approval for the use of Cabometyx in combination with Opdivo® provides an important new first-line treatment option for patients living with advanced renal cell carcinoma," said Howard Mayer, Executive Vice President and Head of Research and Development, Ipsen. "At Ipsen, we're proud that this, now approved, treatment option not only addresses key efficacy benefits, but also the need to maintain quality of life for patients. We look forward to collaborating with a broad range of European stakeholders to bring this unique combination to eligible patients living with advanced renal cell carcinoma."

The EC approval is based on results from the pivotal Phase III CheckMate -9ER trial, presented during a Presidential Symposium at the European Society for Medical Oncology (ESMO) Virtual Congress 2020 and [published](#) in the *New England Journal of Medicine* (NEJM) on 3 March 2021. In the trial, Cabometyx in combination with Opdivo® demonstrated significant improvements across all efficacy endpoints. In patients receiving the combination, median progression-free survival (PFS), the trial's primary endpoint, was doubled compared to those receiving sunitinib alone: 16.6 months vs. 8.3 months respectively (HR: 0.51; 95% CI: 0.41–0.64;  $p < 0.0001$ ).<sup>1</sup> Overall survival (OS) also demonstrated statistically significant improvements, reducing the risk of death by 40% versus sunitinib (HR: 0.60 [98.89% CI: 0.40-0.89];  $p = 0.001$ ; median OS not reached in either arm).<sup>1</sup> In addition, Cabometyx in combination with Opdivo® demonstrated a superior objective response rate (ORR), with twice as many patients responding compared to sunitinib (55.7% vs. 27.1%;  $p < 0.0001$ ) and 8.0% vs. 4.6% achieved a complete response respectively.<sup>1</sup> Key efficacy results were consistent across the pre-specified International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk and PD-L1 subgroups.<sup>1</sup> The combination was well tolerated and reflected the known safety profiles of the immunotherapy and tyrosine kinase inhibitor components in first-line aRCC.<sup>1</sup>

Additional data from the CheckMate -9ER trial were also presented in February at the recent American Society of Clinical Oncology 2021 Genitourinary Cancers Symposium (ASCO GU). These data highlighted sustained superior efficacy of Cabometyx in combination with Opdivo® versus sunitinib for the first-line treatment of aRCC with a median follow-up of 23.5 months, as well as data suggesting significantly improved health-related quality of life (HRQoL) outcomes for the combination versus sunitinib.<sup>2,3</sup> These HRQoL data, also included as part of the recently published NEJM publication, demonstrated that the combination was associated with a lower treatment burden, a decline in the risk of confirmed deterioration in HRQoL and a reduction of disease-related symptoms compared to sunitinib.<sup>1,3</sup>

“The combination of nivolumab and cabozantinib pairs two proven agents for advanced renal cell carcinoma that together have shown superior efficacy across key endpoints and subgroups of patients compared to sunitinib in the CheckMate -9ER trial. Additionally, the combination’s safety profile was manageable with known protocols, leading to a low rate of treatment-related discontinuations.” said Marc-Oliver Grimm, M.D., Professor of Medicine and Urology Department Head, Jena University Hospital. “With today’s approval, clinicians in the EU will be able to offer patients with advanced renal cell carcinoma an additional combination therapy that may help them achieve early control of their disease and improve survival outcomes.”

This approval allows for the marketing of Cabometyx in combination with Opdivo® in this indication in all 27 member states of the European Union, Norway, Liechtenstein and Iceland. The U.S. Food and Drug Administration approved Cabometyx for patients with aRCC as a first-line treatment in combination with Opdivo® in January 2021.

Ipsen thanks the patients and investigators involved in the CheckMate -9ER clinical trial.

### **About renal cell carcinoma**

There are over 400,000 new cases of kidney cancer diagnosed worldwide each year.<sup>4</sup> Of these, renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for approximately 90% of cases.<sup>5,6</sup> It is twice as common in men, and male patients account for over two thirds of deaths.<sup>4</sup> If detected in the early stages, the five-year survival rate is high, but for patients with advanced or late-stage metastatic RCC the survival rate is much lower, around 12%, with no identified cure for this disease.<sup>7,8</sup>

### **About the CheckMate -9ER trial**

CheckMate -9ER is an open-label, randomized, multi-national Phase III 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% PD-L1  $\geq$ 1%) were randomized to Cabometyx plus Opdivo® (n= 323) versus sunitinib (n= 328). 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 Cabometyx (cabozantinib)**

Cabometyx is currently approved in 57 countries, including in the European Union, the U.K., Norway, Iceland, Liechtenstein, 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 and Thailand for the treatment of advanced RCC in adults who have received prior VEGF-targeted therapy; in the European Union, the U.K., Liechtenstein, 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 and Thailand for previously untreated intermediate- or poor-risk advanced RCC; and in the European Union, the U.K., Liechtenstein, Norway, Iceland, Canada, Australia, 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 and Thailand for HCC in adults who have previously been treated with sorafenib.

The detailed recommendations for the use of Cabometyx® are described in the [Summary of Product Characteristics](#) (SmPC) and in the [U.S. Prescribing Information](#) (PI).

Cabometyx is marketed by Exelixis, Inc. in the United States and by Takeda Pharmaceutical Company Limited in Japan. Ipsen has exclusive rights for the commercialization of Cabometyx outside of the U.S. and Japan. Cabometyx is a registered trademark of Exelixis, Inc.

### **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 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; 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](http://www.ipсен.com)

Opdivo® is a registered trademark of Bristol-Myers Squibb Company.

### **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.ipсен.com](http://www.ipсен.com)).

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### **References**

1. Choueiri TK *et al.* Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2021; 384:829-841 DOI: 10.1056/NEJMoa2026982.

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2. Motzer et al., ASCO-GU 2021. Nivolumab + cabozantinib (NIVO+CABO) vs sunitinib (SUN) as first-line therapy for advanced renal cell carcinoma (aRCC): extended follow-up and outcomes in the sarcomatoid subgroup of CheckMate -9ER.
3. Cella et al., ASCO-GU 2021. Patient-reported outcomes (PROs) of patients (pts) with advanced renal cell carcinoma (aRCC) treated with first-line (1L) nivolumab plus cabozantinib (NIVO+CABO) vs sunitinib (SUN): the randomized phase 3 CheckMate -9ER trial.
4. Kidney Cancer Factsheet. GLOBOCAN 2018. Accessed: March 2021. Available: <https://gco.iarc.fr/today/data/factsheets/cancers/29-Kidney-fact-sheet.pdf>.
5. Kidney Cancer. Mayo Clinic. Accessed: March 2021. Available: <https://www.mayoclinic.org/diseases-conditions/kidney-cancer/symptoms-causes/syc-20352664>.
6. Infographic: Kidney Cancer. Mayo Clinic. Accessed: March 2021. Available: <https://www.mayoclinic.org/diseases-conditions/kidney-cancer/multimedia/kidney-cancer-infographic/ifg-20441505>.
7. Survival rates for kidney cancer. American Cancer Society. Accessed: March 2021. Available: <https://www.cancer.org/cancer/kidney-cancer/detection-diagnosis-staging/survival-rates.html>.
8. Orlin, I et al. Renal cell carcinomas epidemiology in the era of widespread imaging. *Journal of Clinical Oncology*. 2019; 37:15. DOI: [https://ascopubs.org/doi/10.1200/JCO.2019.37.15\\_suppl.e13083](https://ascopubs.org/doi/10.1200/JCO.2019.37.15_suppl.e13083).