PRESS RELEASE

New data from pivotal Phase III CheckMate -9ER trial of Cabometyx® in combination with Opdivo® showed significantly improved QoL benefits and sustained superior efficacy versus sunitinib in patients living with aRCC

- With a median follow-up of two years, Cabometyx® in combination with Opdivo® continues to demonstrate superior progression-free survival, overall survival and objective response rate compared to sunitinib[1]
- Patients treated with Cabometyx® in combination with Opdivo® report significantly improved health-related quality of life outcomes versus sunitinb in a separate analysis from CheckMate -9ER[2]
- The expanding evidence base for Cabometyx® is also highlighted in a comparative, retrospective real-world evidence study suggesting that Cabometyx® is associated with a significantly higher response rate and a lower discontinuation rate versus other tyrosine kinase inhibitors (TKIs) after treatment with checkpoint inhibitors (CPI)[3]

PARIS, FRANCE, 8 February 2021 – Ipsen (Euronext: IPN; ADR: IPSEY) today announced the first presentation of new analyses from the pivotal Phase III CheckMate -9ER trial demonstrating clinically meaningful, sustained efficacy benefits as well as quality of life improvements with the combination of Cabometyx® (cabozantinib) and Opdivo® (nivolumab) compared to sunitinib in the first-line treatment of advanced renal cell carcinoma (RCC).[1] These data will be presented in two posters at the virtual American Society of Clinical Oncology 2021 Genitourinary Cancers Symposium (ASCO GU) from 11 – 13 February 2021 and featured in the Poster Highlights Session on 13 February 2021 from 9:00 a.m. – 9:45 a.m. EDT.[4]

In a new analysis from the CheckMate -9ER trial (Abstract #308) with a median follow-up of two years (23.5 months), Cabometyx® in combination with Opdivo® continued to show superior progression-free survival (PFS), objective response rate (ORR) and overall survival (OS) versus sunitinib, with a low rate of treatment-related adverse events (TRAEs) leading to discontinuation.[1] No new safety signals were identified with extended follow-up. Across the full study population, the combination doubled median PFS (17.0 months vs. 8.3 months, respectively; HR 0.52; 95% CI: 0.43 to 0.64), the trial's primary endpoint, compared to sunitinib. The ORR indicated that nearly twice as many patients responded to Cabometyx® in combination with Opdivo® vs. sunitinib (54.8% vs. 28.4) and the combination maintained improvements in OS, demonstrating a 34% reduction in the risk of death compared to sunitinib (HR: 0.66; 95% CI: 0.50 to 0.87). In an exploratory analysis, the combination was associated with a disease control rate (including complete response, partial response and stable disease) of 88.2% vs. 69.9% with sunitinib and a complete response rate of 9.3% compared to 4.3% with sunitinib. Among patients treated with Cabometyx® in combination with Opdivo®, 6.6% discontinued both agents due to TRAEs, 9.7% discontinued Opdivo® only and 7.2% discontinued Cabometyx® only.[1]

In an exploratory subgroup analysis of 75 patients with sarcomatoid features, the combination of Cabometyx® with Opdivo® showed benefit in this population typically associated with a poor prognosis, reducing the risk of death by 64% vs. sunitinib (HR 0.36; 95% CI: 0.17 to 0.79) and demonstrating both superior PFS (10.3 months vs. 4.2 months) and ORR (55.9% vs. 22.0%).[1]

"There is a continued need for new therapies that show benefit across subgroups of patients with advanced renal cell carcinoma," said Robert Motzer, M.D., Kidney Cancer Section Head, Genitourinary Oncology Service, and Jack and Dorothy Byrne Chair in Clinical Oncology, Memorial Sloan Kettering Cancer Center. "In CheckMate -9ER, nivolumab in combination with cabozantinib doubled progression-free survival, increased overall survival and response rate and, in an exploratory analysis, showed impressive disease control, and these promising efficacy results were sustained with extended follow-

up. Also, of note, patients in this study reported significant quality of life improvements, which are important for patients undergoing treatment for this challenging disease"

In a second analysis from the CheckMate -9ER trial (Abstract #285) conducted with 18.1 months of median follow-up, patients treated with the combination of Cabometyx® and Opdivo® reported statistically significant health-related quality of life (HRQoL) benefits.[2] Treatment with Cabometyx® in combination with Opdivo® was associated with a lower treatment burden, decreased the risk of confirmed deterioration in HRQoL and a reduction of disease-related symptoms compared to sunitinib. These exploratory outcomes were measured using Functional Assessment of Cancer Therapy Kidney Symptom Index-19 (FKSI-19), a quality of life tool specific to kidney cancer, and EQ-5D-3L instruments.[2]

"As the advances in treatments for kidney cancer transform outcomes for patients, the goals of therapy have expanded from increasing survival to improving quality of life," said Dr. Cristina Suárez, Medical Oncologist at the Vall d´Hebron University Hospital, Barcelona, Spain and a lead investigator on the Phase III CheckMate -9ER trial. "The additional analyses presented at ASCO GU mean that physicians treating people living with advanced renal cell carcinoma can consider this combination at diagnosis as a first-line option to improve patient outcomes and significantly reduce the risk of deterioration in health-related quality of life scores for their patients. This, in addition to the extended follow-up outcomes data including patients with sarcomatoid features, point to this combination becoming an important treatment approach."

Cabometyx® in combination with Opdivo® is under review with health authorities globally following the combination's approval for the first-line treatment of advanced RCC by the U.S. Food and Drug Administration (FDA) in January 2021.

"We're pleased to share these positive results at ASCO GU, building on the growing body of data for the use of Cabometyx® in first- and second-line settings. These data further support the importance of research investigating outcomes which really matter to patients," said Prof. Dr. Steven Hildemann, Executive Vice President, Chief Medical Officer, Head of Global Medical Affairs and Patient Safety, Ipsen. "The validations of the type II variation applications to the European Medicines Agency (EMA) for Cabometyx® in combination with Opdivo® last year brought this new combination regimen one step closer to the previously untreated kidney cancer patient population. Despite recent advances, these patients remain in need of more therapeutic options that extend survival and improve quality of life."

A further notable presentation at ASCO GU evaluated the use of Cabometyx® versus other TKIs after CPI treatment in the real-world management of patients with metastatic renal cell carcinoma (mRCC) (Abstract #293).[3]

A retrospective observational cohort study evaluating outcomes associated with Cabometyx® or other TKIs (axitinib, lenvatinib, pazopanib, sorafenib, sunitinib) in patients with mRCC following CPI treatment[3]

	Cabometyx® (*n = 187)*	Other TKI (*n=60)*	*p* value
6-month response rate ($RR_{6months}$, primary)	50.8%	33.3%	<0.001
Overall response rate (ORR)	53.5%	38.3%	0.041
Overall survival (OS) (95% CI) 6 months 12 months 18 months	 81.9 (75.5, 86.8) 61.5 (53.5, 68.4) 51.7 (43.1, 59.6)	 75.1 (61.5, 84) 59.6 (44.7, 71.8) 45.9 (29.6, 60.7)	 0.765
Time to treatment discontinuation (TTD, median months)	6.2	3.1	0.015
Dose reductions	47.1%	41.7%	0.466
Discontinuation due to adverse events (AEs)	31.3%	40.4%	

Findings from the study suggest that Cabometyx® is an effective and well tolerated option, associated with a significantly higher response rate and a lower discontinuation rate versus other TKIs included in the study, after treatment with CPIs.[3]

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About renal cell carcinoma
There are over 400,000 new cases of kidney cancer diagnosed worldwide each year.[5] Of these, renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for approximately 90% of cases.[6,7] It is twice as common in men, and male patients account for over two thirds of deaths.[5] 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.[8,9]

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 ≥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 54 countries, including in the European Union, the U.S., 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, Panama and New Zealand 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, Israel, Mexico, Chile, Panama and New Zealand for previously untreated intermediate- or poor-risk advanced RCC; and in the European Union, the U.S., 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, Ukraine, Lebanon and Panama 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 and further clinical development of Cabometyx® outside of the U.S. and Japan. Cabometyx® is a registered trademark of Exelixis, Inc.

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. 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 5,700 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.ipsen.com

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

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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).

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