PRESS RELEASE

Cabometyx® in combination with nivolumab shows durable survival benefits at over three-years' follow-up in first-line advanced renal cell carcinoma

- Three-year data – with a median follow-up of 44 months – from the Phase III CheckMate -9ER trial demonstrate maintained overall survival benefits with Cabometyx plus nivolumab compared to sunitinib regardless of IMDC risk score[1]
- Data represent the longest reported follow-up in any Phase III trial with a tyrosine kinase inhibitor-immunotherapy regimen in this population
- CheckMate -9ER data to be presented at ASCO GU alongside six additional abstracts supporting the use of Cabometyx either alone or in combination with immunotherapy in advanced renal cell carcinoma[2,3,4,5,6,7]

PARIS, FRANCE Ipsen (Euronext: IPN; ADR: IPSEY) today announced three-year minimum, 44-month median, follow-up results from the Phase III CheckMate -9ER trial showing that Cabometyx® (cabozantinib) in combination with nivolumab provides survival and response rate benefits after three-years in the first-line treatment of advanced renal cell carcinoma (aRCC), compared to sunitinib.[1] These findings are being presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO GU) from 16–18 February 2023.

RCC is the most common type of kidney cancer, accounting for approximately 90% of cases.[8] If detected in the early stages, the five-year survival rate is high, but for people living with advanced or late-stage metastatic RCC the survival rate is much lower, at around 12%.[9]

"Despite the progress made through science and medicine, there remains a need for treatment options that can durably extend survival for patients with metastatic renal cell carcinoma, especially for those classified as higher risk," said Mauricio Burotto, M.D., medical director, Bradford Hill Clinical Research Center, Santiago, Chile. "With these updated results from CheckMate -9ER, we've now seen nivolumab in combination with cabozantinib durably extend survival and sustain response benefits compared to sunitinib for over three years, regardless of patients' risk classification. These results reinforce the importance of this immunotherapy-tyrosine kinase inhibitor regimen for patients and its potential to help change survival expectations for patients with this challenging cancer."

In the CheckMate -9ER trial, OS (overall survival) benefits were maintained at over three-years of follow-up. [1] Median OS was significantly higher for patients on Cabometyx in combination with nivolumab versus sunitinib, at 49.5 versus 35.5 months respectively [hazard ratio (HR) 0.70 [95% confidence interval (CI) 0.56–0.87], p=0.0014)], demonstrating a 30% reduction in the risk of death.[1] Additionally, median OS improved by 11.8 months since the previous data cut at 32.9 months median follow-up.[1]

Patients treated with Cabometyx in combination with nivolumab, versus those on sunitinib, also experienced benefits in terms of progression-free survival (PFS) and objective response rate (ORR; cancer shrinking with treatment): [1]

- Median PFS was almost doubled at 16.6 versus 8.4 months for Cabometyx in combination with nivolumab versus sunitinib respectively (HR 0.58 [95% CI 0.48–0.71], p<0.0001).
- ORR was doubled with Cabometyx in combination with nivolumab versus sunitinib (95% CI, 56% [50–61] versus 28% [24–34]). Responses also continued to be more durable with the combination, with a median DoR (duration of response) of 23.1 months compared to 15.2 months with sunitinib.
- Complete Response (CR) more than doubled for patients receiving Cabometyx in combination with nivolumab (12%) compared to those receiving sunitinib (5%).
- The safety profile identified in the CheckMate -9ER trial was consistent with that previously observed.

- Results were also assessed by the following International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk scores: favorable, intermediate, intermediate/poor and poor. Benefits were seen with Cabometyx in combination with nivolumab across all efficacy measures (OS, PFS, ORR and CR), regardless of IMDC risk.[1]

"At Ipsen, our goal is for people to live longer and live well with cancer and these results reinforce the value Cabometyx can bring to patients with advanced RCC when combined with immunotherapy in the first-line setting," said Steven Hildemann, M.D. PhD, Executive Vice President, Chief Medical Officer, Head of Global Medical Affairs and Global Patient Safety. "The results from the CheckMate -9ER study continue to demonstrate sustained, now three-year long-term benefits for people living with advanced renal cell carcinoma across the most meaningful efficacy measures and risk scores, adding to the body of evidence we have for Cabometyx plus nivolumab. We sincerely thank the patients who participated in the trial, their families and their healthcare teams."

Six additional abstracts will be presented at ASCO GU assessing the benefits of Cabometyx in aRCC and non-clear cell renal cell carcinoma (nccRCC). These include:

- The CaboCombo trial, which is a prospective, international, non-interventional study of first-line Cabometyx plus nivolumab for the treatment of patients with aRCC. This study will gather real-world evidence on the first-line use of Cabometyx plus nivolumab and demonstrates Ipsen's commitment to advancing the evidence base on treatment options for people living with aRCC.[3]
- Cohort 10 of the COSMIC-021 trial, which evaluates Cabometyx in combination with atezolizumab in nccRCC, and further assesses Cabometyx's potential when combined with immune checkpoint inhibitors.[7]
- A biomarker analysis from the CheckMate -9ER trial showing that at 44-month median follow-up, median PFS and OS were improved with Cabometyx plus nivolumab versus sunitinib, regardless of PD-L1 status.[4]

ENDS

More information can be found during the presentation sessions outlined below:

Lead author/Presenter	**Indication**	**Abstract title**	**Presentation number/timing (PST)**
Laurence Albiges	aRCC	CaboPoint: Interim results from a Phase II study of cabozantinib after checkpoint inhibitor (CPI) therapy in patients with advanced renal cell carcinoma (RCC)[2]	**Oral and Poster** *Abstract #606* Sat 18 Feb 8:25 – 8:20 AM Rapid Abstract Session: Renal and Rare Tumors
Philippe Barthélémy	aRCC	CaboCombo: a prospective international non-interventional study of first-line cabozantinib plus nivolumab for the treatment of patients with advanced renal cell carcinoma[3]	**Poster** *Abstract #TPS740* Sat 18 Feb 7:00 – 8:00 AM; 12:30 – 2:00 PM Trials in Progress Poster Session C: Renal Cell Cancer; Adrenal, Penile, Urethral, and Testicular Cancers
Mauricio Burotto	aRCC	Nivolumab plus cabozantinib versus sunitinib for first-line treatment of advanced renal cell carcinoma (aRCC): 3-year follow-up from the Phase III CheckMate -9ER trial**Erreur ! Signet non défini.**	**Oral** *Abstract #603* Sat 18 Feb 2:10 – 2:20 PM Oral Abstract Session C: Renal and Rare Tumors

Toni K. Choueiri	aRCC	Biomarker analysis from the Phase III CheckMate -9ER trial of nivolumab + cabozantinib (N+C) v sunitinib (S) for advanced renal cell carcinoma (aRCC)[4]	**Poster** *Abstract #608* Sat 18 Feb 7:00 – 8:00 AM Poster Session C: Renal Cell Cancer; Adrenal, Penile, Urethral and Testicular Cancers
Paul Nathan, presented by Anand Sharma	aRCC	CARINA interim analysis: a non-interventional study of real-world treatment sequencing and outcomes in patients with advanced renal cell carcinoma initiated on first-line checkpoint inhibitor-based combination therapy[5]	**Poster** *Abstract #626* Sat 18 Feb 7:00 – 8:00 AM; 12:30 – 2:00 PM Poster Session C: Renal Cell Cancer; Adrenal, Penile, Urethral, and Testicular Cancers
Antoine Thiery Vuillemin	aRCC	Study of cabozantinib in second line under real-life setting in patients with advanced renal cell carcinoma (aRCC): study design of a French, retrospective, multicenter study (OCTOPUS)[6]	**Poster** *Abstract #TPS744* Sat 18 Feb 7:00 – 8:00 AM; 12:30 – 2:00 PM Trials in Progress Poster Session C: Renal Cell Cancer; Adrenal, Penile, Urethral, and Testicular Cancers
Bradley McGregor	Non clear cell RCC	Cabozantinib in combination with atezolizumab in non-clear cell renal cell carcinoma: extended follow-up results of cohort 10 of the COSMIC-021 study[7]	**Poster** *Abstract #684* Sat 18 Feb 7:00 – 8:00 AM; 12:30 – 2:00 PM Poster Session C: Renal Cell Cancer; Adrenal, Penile, Urethral and Testicular Cancers

Notes to editors

About renal cell carcinoma (RCC)
There were over 400,000 new cases of kidney cancer diagnosed worldwide in 2020.[10] Of these, RCC is the most common type of kidney cancer, accounting for approximately 90% of cases.[8] It is almost twice as common in men, and male patients account for over two thirds of deaths.[9,10] At diagnosis, up to 30% of patients present with advanced or metastatic RCC.[11] If detected in the early stages, the five-year survival rate is high, but for people living with advanced or late-stage metastatic RCC, the survival rate is much lower, around 12%, with no identified cure for this disease.[9]

About the CheckMate -9ER trial[12]
CheckMate -9ER is an open-label, randomized, multi-national Phase III trial evaluating people living 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 nivolumab (n= 323) versus sunitinib (n= 328). The primary endpoint is progression-free survival (PFS). The secondary endpoints include overall survival (OS) and objective response rate (ORR). The primary efficacy analysis compared 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 the CaboCombo trial[13]
CaboCombo is a prospective, international, real-world non-interventional study to evaluate the effectiveness and tolerability of Cabometyx and nivolumab in combination as a first-line treatment in adults with aRCC with clear cell-component, according to real-world clinical practice. A total of 311 patients will be enrolled across 70 centers in countries where the Cabometyx and nivolumab combination has marketing authorization and reimbursement. The decision to prescribe the combination will be made prior to, and independently from, the decision to enroll patients in the trial. The primary endpoint is real-world landmark overall survival assessed 18 months after the combination initiation. The CaboCombo study is sponsored by Ipsen.

About the COSMIC-021 trial[14]
COSMIC-021 is a multicenter, Phase Ib, open-label study that was divided into two parts: a dose-escalation phase and an expansion cohort phase. In the expansion phase, the trial enrolled 24 cohorts in 12 tumor types: non-small cell lung cancer (NSCLC), RCC, urothelial carcinoma (UC), castration-resistant prostate cancer, hepatocellular carcinoma, triple-negative breast cancer, epithelial ovarian cancer, endometrial cancer, gastric or gastroesophageal junction adenocarcinoma, colorectal adenocarcinoma, head and neck cancer, and differentiated thyroid cancer (DTC). Exelixis is the study sponsor of COSMIC-021. Both Ipsen and Takeda Pharmaceutical Company Limited (Takeda) have opted in to participate in the trial and are contributing to the funding for this study under the terms of the companies' respective collaboration agreements with Exelixis. Roche is providing atezolizumab for the trial.

About Cabometyx (cabozantinib)
Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), including VEGFRs, MET, RET and the TAM family (TYRO3, MER, AXL). These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis (the growth of new blood vessels that tumors need to grow), drug resistance, modulation of immune activities and maintenance of the tumor microenvironment.

Exelixis granted Ipsen exclusive rights for the commercialization and further clinical development of Cabometyx outside of the U.S. and Japan. Exelixis granted exclusive rights to Takeda for the commercialization and further clinical development of Cabometyx for all future indications in Japan. Exelixis holds the exclusive rights to develop and commercialize Cabometyx in the U.S.

In over 60 countries outside of the United States and Japan, including in the European Union (E.U.), Cabometyx is currently indicated as:

- Monotherapy for advanced renal cell carcinoma:
  - as first-line treatment of adult patients with intermediate or poor risk
  - in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy
- In combination with nivolumab for the first-line treatment of advanced renal cell carcinoma in adults
- Monotherapy for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy
- Monotherapy for the treatment of hepatocellular carcinoma (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 (EU SmPC) and in the U.S. Prescribing Information (USPI).

About Ipsen
Ipsen is a global mid-sized biopharmaceutical company focused on transformative medicines in Oncology, Rare Disease and Neuroscience. With Specialty Care sales of €3.0bn in FY 2022, Ipsen sells medicines in over 100 countries. Alongside its external-innovation strategy, the company's research and development efforts are focused on its innovative and differentiated technological platforms located in the heart of leading biotechnological and life-science hubs: Paris-Saclay, France; Oxford, U.K.; Cambridge, U.S.; Shanghai, China. Ipsen has around 5,000 colleagues worldwide and is listed in Paris (Euronext: IPN) and in the U.S. through a Sponsored Level I American Depositary Receipt program (ADR: IPSEY). For more information, visit ipsen.com

Ipsen's Forward-Looking Statements

The forward-looking statements, objectives and targets contained herein are based on Ipsen'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 Ipsen'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 Ipsen'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 Ipsen. 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. Ipsen 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 Ipsen 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, Ipsen cannot be certain that favorable results obtained during preclinical 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; Ipsen'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 Ipsen's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions. Ipsen 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 Ipsen's activities and financial results. Ipsen 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 Ipsen's partners could generate lower revenues than expected. Such situations could have a negative impact on Ipsen's business, financial position or performance. Ipsen 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. Ipsen'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 Ipsen's 2020 Universal Registration Document, available on ipsen.com.

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