PRESS RELEASE

Ipsen presents Phase I/II clinical data evaluating liposomal irinotecan (Onivyde®) as an investigational first-line combination treatment for metastatic pancreatic cancer at the ESMO World Congress on Gastrointestinal Cancer

Ipsen has initiated the NAPOLI-3 Phase III clinical study (NCT04083235) comparing the safety and efficacy of liposomal irinotecan + 5-fluorouracil/leucovorin (5-FU/LV) + oxaliplatin (OX) (NALIRIFOX) to gemcitabine + nab-paclitaxel in the first-line setting

Ipsen has been granted Fast Track Designation by the FDA for investigational liposomal irinotecan + 5-FU/LV + OX (NALIRIFOX) for the first-line treatment of patients with metastatic pancreatic cancer

PARIS, FRANCE, 01 July 2020 – Ipsen (Euronext: IPN; ADR: IPSEY), today announced the primary analysis of the Phase I/II study evaluating the investigational use of irinotecan liposome injection (Onivyde®) in combination with 5-fluorouracil/leucovorin (5-FU/LV) and oxaliplatin (OX) together, known as NALIRIFOX in study patients with previously untreated, unresectable, locally advanced and metastatic pancreatic ductal adenocarcinoma (PDAC) during a late-breaking oral presentation at the ESMO World Congress on Gastrointestinal Cancer (WCGI), 1–5 July 2020. The results include safety and efficacy analyses from the multicenter, open-label, study consisting of dose-exploration safety run-in (traditional 3+3 design) to confirm the maximum tolerated dose and appropriate dose regimen for NALIRIFOX in the dose-expansion phase.[1]

No new safety signals were observed in the 32 patients evaluated from the recommended NALIRIFOX 50/60 mg/m^2 dose (primary endpoint). Study patients achieved median progression-free survival of 9.2 months and median overall survival of 12.6 months (secondary endpoints).[1]

These data, in addition to promising anti-tumor activity highlighted by secondary endpoints, have led to the initiation of patient enrollment for the international Phase III NAPOLI-3 clinical study investigating the safety and efficacy of NALIRIFOX versus gemcitabine + nab-paclitaxel in the first-line setting.[2] On 5 June 2020, Ipsen was granted Fast Track designation from the U.S. Food and Drug Administration (FDA) to facilitate the development and potentially expedite the review of NALIRIFOX in this indication. Programs with Fast Track designation may benefit from early and frequent interactions with the FDA over the course of drug development. In addition, the Fast Track designation program allows for the eligibility for accelerated approval and priority review if relevant study criteria are met and enables a company to submit individual sections of a New Drug Application (NDA) for review on a rolling-submission basis.

“Pancreatic cancer is aggressive, and we continue to investigate opportunities to improve outcomes for more patients that can extend survival. Unfortunately, current treatments, including immunotherapies that are transforming outcomes for patients with other solid tumors, have not demonstrated similar success in pancreatic cancer.” said Zev Wainberg, M.D., lead investigator and associate professor of medicine, University of California Los Angeles. “The initial median progression-free and overall survival data from our Phase I/II trial are promising and we look forward to seeing how this investigational first-line treatment compares to gemcitabine + nab-paclitaxel in the Phase III trial now underway.”

“A year following the read out of the preliminary Phase I/II study, we remain encouraged by the data, which demonstrated no new safety signals and continued to show anti-tumor activity,” said Howard Mayer, M.D., Executive Vice President, Head of Research and Development at Ipsen. “Ipsen is committed to patients with pancreatic cancer. We are currently enrolling patients in our NAPOLI-3 Phase III clinical study across the U.S. and in other countries to gain a better understanding of the role of liposomal irinotecan as a potential first-line combination treatment for locally advanced and metastatic pancreatic cancer.”

The Phase I/II, open-label trial (NCT02551991) was designed to assess the safety, tolerability and dose-limiting toxicities (DLTs) of NALIRIFOX for the first-line dosing of study participants with locally advanced and metastatic pancreatic cancer. Secondary objectives were to assess clinical efficacy, defined by median progression-free survival (PFS) and median overall survival (OS), best overall response rate, overall response

rate (ORR), disease control rate at 16 weeks (DCR) and duration of response (DoR).[1]

The final analysis as of the data cut off on 26 February 2020 included all study participants from the pooled population (n=32: Part 1A-cohort B dose exploration phase n=7; Part 1B-dose expansion phase n=25) who received the maximum tolerated dose of liposomal irinotecan 50 mg/m^2 [free-base], LV 400 mg/m^2, 5-FU 2400 mg/m^2, and OX 60 mg/m^2). Patients were aged ≥ 18 years with an Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 1 and adequate organ function.[1] The preliminary results from this study were presented at the ESMO World Congress on Gastrointestinal Cancer in July 2019.

Phase I/II Safety Results[1]:

- No reported Grade 3 or higher fatigue or peripheral neuropathy.
- Treatment emergent adverse events (TEAEs) Grade 3 or higher were reported by 22 of 32 study patients and included: neutropenia (31.3%), febrile neutropenia (12.5%), hypokalemia (12.5%), anemia (12.5%), diarrhea (9.4%), nausea (9.4%) and decreased neutrophil count (9.4%); vomiting occurred in 6.3% of patients.
- 8 patients reported TEAEs leading to discontinuation of oxaliplatin alone or all four study drugs (n=8/32), with 26 study patients requiring dose adjustment due to AEs.

Phase I/II Efficacy Results[1]:

- Study patients saw a median PFS (95% CI) of 9.2 months (7.69, 11.96) and median OS of 12.6 months (8.74, 18.69).
- BOR (Best Overall Response) included: one complete response (CR; study participant diagnosed with locally advanced Stage III disease) in 3% (1/32), 10 partial responses (PR) in 31.3% (10/32) and 15 stable diseases (SD) in 46.9% (15/32) (sum of CR+PR+SD = 81.3%).
- Disease control achieved by 71.9% (23/32) of study patients at 16 weeks.

ABOUT ONIVYDE® (irinotecan liposome injection)

Ipsen has exclusive commercialization rights for the current and potential future indications for Onivyde® in the U.S. Servier is responsible for the commercialization of Onivyde® outside of the U.S. and Taiwan under an exclusive licensing agreement with Ipsen. PharmaEngine has commercial rights to Onivyde® in Taiwan.

INDICATION - UNITED STATES

Onivyde® is approved by the U.S. FDA in combination with fluorouracil (5-FU) and leucovorin (LV) for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. Limitation of Use: Onivyde® is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

IMPORTANT SAFETY INFORMATION – UNITED STATES

BOXED WARNINGS: SEVERE NEUTROPENIA and SEVERE DIARRHEA

Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with 5-FU and LV.
Withhold ONIVYDE for absolute neutrophil count below 1500/mm3 or neutropenic fever. Monitor blood cell counts periodically during treatment.

Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with 5-FU/LV. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2–4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

CONTRAINDICATION

ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl.

Warnings and Precautions

Severe Neutropenia: See Boxed WARNING. In patients receiving ONIVYDE/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients

Severe Diarrhea: See Boxed WARNING. Severe and life-threatening late-onset (onset >24 hours after chemotherapy [9%]) and early-onset diarrhea (onset ≤24 hours after chemotherapy [3%], sometimes with other

symptoms of cholinergic reaction) were observed

Interstitial Lung Disease (ILD): Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE I patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD

Severe Hypersensitivity Reactions: Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction

Embryo-Fetal Toxicity: ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during and for 1 month after ONIVYDE treatment

Adverse Reactions

- The most common adverse reactions (≥20%) were diarrhea (59%), fatigue/asthenia (56%), vomiting (52%), nausea (51%), decreased appetite (44%), stomatitis (32%), and pyrexia (23%)
- The most common Grade 3/4 adverse reactions (≥10%) were diarrhea (13%), fatigue/asthenia (21%), and vomiting (11%)
- Adverse reactions led to permanent discontinuation of ONIVYDE in 11% of patients receiving ONIVYDE/5- FU/LV; The most frequent adverse reactions resulting in discontinuation of ONIVYDE were diarrhea, vomiting, and sepsis
- Dose reductions of ONIVYDE for adverse reactions occurred in 33% of patients receiving ONIVYDE/5 FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia
- ONIVYDE was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia
- The most common laboratory abnormalities (≥20%) were anemia (97%), lymphopenia (81%), neutropenia (52%), increased ALT (51%), hypoalbuminemia (43%), thrombocytopenia (41%), hypomagnesemia (35%), hypokalemia (32%), hypocalcemia (32%), hypophosphatemia (29%), and hyponatremia (27%)

Drug Interactions

- Avoid the use of strong CYP3A4 inducers, if possible, and substitute non-enzyme inducing therapies ≥2 weeks prior to initiation of ONIVYDE
- Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors ≥1 week prior to starting therapy

Special Populations

- Pregnancy and Reproductive Potential: See WARNINGS & PRECAUTIONS. Advise males with female partners of reproductive potential to use condoms during and for 4 months after ONIVYDE treatment
- Lactation: Advise nursing women not to breastfeed during and for 1 month after ONIVYDE treatment

Please see full U.S. Prescribing Information and Boxed WARNING for ONIVYDE.

About the Phase I/II Study

The Phase I/II, open-label, comparative trial is designed to assess the safety, tolerability and dose-limiting toxicities of investigational irinotecan liposomal injection (Onivyde®) in combination with 5-fluorouracil/leucovorin (5-FU/LV) and oxaliplatin (OX) as a potential first-line treatment for metastatic pancreatic ductal adenocarcinoma cancer patients. The study has enrolled 56 patients at 15 sites across the United States, Spain and Australia. It is being conducted in two parts:

- Part 1a: a safety run-in as initial dose exploration
- Part 1b: dose expansion of the liposomal irinotecan + 5-FU/LV + oxaliplatin regimen

The study's primary endpoint is safety and tolerability. Secondary assessments of clinical efficacy include overall response rate, disease control rate and best overall response. For more information visit clinicaltrials.gov and use identifier NCT02551991.[3]

About the NAPOLI-3 Phase III Study

The NAPOLI-3 clinical trial is an open-label, randomized, multicenter, Phase III study of irinotecan liposome injection (Onivyde®) in combination with oxaliplatin (OX) and 5-fluorouracil/leucovorin (5-FU/LV) versus nab-paclitaxel plus gemcitabine in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas. The purpose of this study is to look at the efficacy and safety of

investigational irinotecan liposome injection in combination with other FDA-approved drugs used for cancer therapy compared to nab-paclitaxel + gemcitabine treatment in improving the overall survival of patients not previously treated for metastatic pancreatic cancer. The study's primary endpoint is Overall survival (OS), with secondary outcome measures defined as Progression free survival (PFS) and Overall Response Rate (ORR).

Ipsen is currently enrolling patients. To learn more about the study contact clinical.trials@ipsen.com or visit clinicaltrials.gov and use identifier NCT04083235.[2]

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.ipsen.com

Ipsen's 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, and the outcome of this study or other studies. 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 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 6 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 2019 Universal

Registration Document available on its website (www.ipsen.com).

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