



**MERRIMACK**

October 11, 2016

## **Final Results of NAPOLI-1 Study Confirm Overall Survival and Progression-Free Survival Benefit for the ONIVYDE® Regimen for Patients with Metastatic Pancreatic Cancer**

**- ONIVYDE® in combination with fluorouracil (5-FU) and leucovorin establishes a new standard of care for patients with metastatic pancreatic cancer who have progressed on gemcitabine-based therapy**  
**- Disease control achieved in twice as many patients treated with ONIVYDE in combination with 5-FU and leucovorin (52%) compared to 5-FU and leucovorin alone (24%)**

CAMBRIDGE, Mass., Oct. 11, 2016 /PRNewswire/ -- Merrimack Pharmaceuticals, Inc. (NASDAQ: MACK) today announced final results from the pivotal Phase 3 NAPOLI-1 study validating the use of ONIVYDE® (irinotecan liposome injection) in combination with fluorouracil (5-FU) and leucovorin, which represents a new standard of care for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) following treatment with gemcitabine-based therapy. The final NAPOLI-1 results were presented in a poster discussion session and a separate analysis of NAPOLI-1 safety-over-time data was presented in a poster session at the European Society for Medical Oncology 2016 Congress in Copenhagen.

"The final results of the NAPOLI-1 study provide a high level of clinical evidence establishing the ONIVYDE regimen as a meaningful treatment option for patients with metastatic pancreatic cancer," said Prof. Li-Tzong Chen, M.D., Ph.D., corresponding author, Investigator on the NAPOLI-1 trial and Director, National Institute of Cancer Research, National Health Research Institutes in Tainan, Taiwan. "Pancreatic cancer is a devastating disease with a poor prognosis. In a patient population with few treatment options, the ONIVYDE regimen provides an opportunity for extended overall survival while maintaining baseline quality-of-life and represents a new standard of care. We thank all of the patients, caregivers and investigators who participated in this pivotal study."

The extended data cutoff occurred at final database lock in November 2015 after 382 OS events that had occurred in the intention-to-treat (ITT) population. In this extended analysis of NAPOLI-1, the previously described overall survival advantage was maintained for ONIVYDE in combination with 5-FU and leucovorin versus 5-FU and leucovorin alone: 6.2 months versus 4.2 months ( $p=0.039$ , hazard ratio (HR) =0.75, 95% CI: [.057 - .99]). Findings also showed that one in four patients treated with the ONIVYDE combination regimen survived one year or more, a significant milestone. This was represented by a 26% probability of survival at one year for patients receiving ONIVYDE in combination with 5-FU and leucovorin versus 16% for patients who received 5-FU and leucovorin alone. Furthermore, disease control was achieved in twice as many patients treated with ONIVYDE in combination with 5-FU and leucovorin (52%) compared to 5-FU and leucovorin alone (24%). The demonstrated improvements in overall survival for the ONIVYDE combination regimen were achieved with little or no impact on quality of life over 12 weeks despite the addition of a second chemotherapeutic agent to 5-FU and leucovorin, a therapy recognized as a well-managed treatment for metastatic pancreatic cancer.

Results from a separate analysis of the NAPOLI-1 data evaluating the incidence and prevalence of gastrointestinal toxicities and neutropenia during the course of treatment with ONIVYDE plus 5-FU and leucovorin showed that the majority of these adverse events occurred early in treatment with decreased incidence and severity thereafter. Dose reductions or dose delays were commonly used to manage these adverse events and may account for the decreased incidence and/or severity that was observed.

The primary Phase 3 NAPOLI-1 data were the basis of the US Food and Drug Administration (FDA) and Taiwan FDA approvals of the ONIVYDE® (irinotecan liposome injection) combination regimen in October 2015. They were also the basis of the European Union's Committee for Medicinal Products for Human Use (CHMP) positive opinion issued in July 2016. The ONIVYDE combination is designated as a category 1 treatment option in the 2016 National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma in the United States as well as a category 2B status in the 2015 European Society for Medical Oncology (ESMO) clinical practice guidelines in the European Union.

## About Pancreatic Cancer

Pancreatic cancer is a rare and deadly disease with only 7% of all patients surviving five years or longer<sup>1</sup>. There are approximately 50,000 patients diagnosed with pancreatic cancer each year in the United States<sup>2</sup>, the overwhelming majority of which have adenocarcinoma<sup>3</sup>. Globally there are approximately 338,000 new cases each year<sup>4</sup>. Most patients receive gemcitabine-based therapy during either adjuvant/neoadjuvant treatment for locally advanced disease or during first- or second-line therapy for metastatic disease<sup>5</sup>, but are left with no standard of care therapy upon progression. ONIVYDE in combination with 5-FU and leucovorin is approved in the United States and Taiwan for these patients whose disease has progressed following gemcitabine-based therapy.

## Methodology and Results

### Final results of NAPOLI-1: A Phase 3 study of nal-IRI (MM-398) ± 5-fluorouracil and leucovorin (5-FU/LV) vs 5-FU/LV in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy (Abstract 622PD)

The final results of the NAPOLI-1 study evaluate the robustness of the previously described overall survival and progression free survival benefits of ONIVYDE in combination with 5-FU and leucovorin compared with 5-FU and leucovorin alone. This analysis also assesses the long-term safety and tolerability of the ONIVYDE combination regimen. The extended analysis is based on 382 OS events. Highlights include:

- 1 The overall survival advantage of ONIVYDE in combination with 5-FU and leucovorin versus 5-FU and leucovorin alone was maintained in this extended<sup>5</sup> analysis: 6.2 months versus 4.2 months (p=0.039, hazard ratio (HR) =0.75, 95% CI: [.057-.99]).
- 1 The probability of survival at one year was greater in the ONIVYDE combination arm of the study when compared to the 5-FU and leucovorin arm: 12-month overall survival estimates of 26% (95% CI, 18-35%) were observed in the ONIVYDE combination treatment arm compared to 16% (95% CI, 10-24%) for 5-FU and leucovorin arm.
- 1 The overall response rate (ORR) for the ONIVYDE plus 5-FU and leucovorin arm was 16% versus 1% for the 5-FU and leucovorin arm (P < 0.0001).
- 1 Treatment with ONIVYDE in combination with 5-FU and leucovorin provided a 2-fold improvement in disease control rate compared with 5-FU and leucovorin alone (52% vs 24%, respectively).
- 1 Final results suggest that patients treated with ONIVYDE in combination with 5-FU and leucovorin had no notable deterioration in quality of life at 12 weeks despite the addition of a second chemotherapeutic agent to 5-FU and leucovorin.
- 1 No new safety concerns were noted and the overall safety profile was manageable with the most common Grade ≥3 adverse events of neutropenia, diarrhea, fatigue, vomiting and asthenia.

### Time course of selected treatment emergent adverse events (TEAEs) in NAPOLI-1: A Phase 3 study of nal-IRI (MM-398) ± 5-fluorouracil and leucovorin (5-FU/LV) vs 5-FU/LV in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy

The basis of this subset analysis is to characterize the safety profile of the ONIVYDE combination regimen through the evaluation of the incidence and prevalence of adverse events across all three arms of the NAPOLI-1 study. Incidence (first occurrence of an event) and prevalence (first occurrence, ongoing event or recurrence) were analyzed by three treatment periods: 1-6 weeks, 6-12 weeks and greater than 12 weeks. Findings from the analysis suggest neutropenia, diarrhea, nausea and vomiting typically first occur early during the course of treatment with the ONIVYDE combination regimen and decrease in incidence and severity thereafter.

Data shows that the prevalence of nausea and vomiting in the ONIVYDE regimen arm decreased over time, with a greater frequency at 1-6 weeks when compared to greater than 12 weeks. During this same period, the prevalence of neutropenia increased slightly but decreased in severity. The prevalence of diarrhea was relatively consistent throughout treatment. This analysis suggests the median duration of adverse events of all grades was 5 to 11 days in the ONIVYDE combination arm of NAPOLI-1. Dose reductions and delays were used to manage adverse events and increased over time from the period 1-6 weeks and greater than 12-week period.

## About ONIVYDE® [pronounced \ 'on - ih - vide \]

ONIVYDE® (irinotecan liposome injection), also known as MM-398 or "nal-IRI," is a novel encapsulation of irinotecan in a liposomal formulation. The activated form of irinotecan is SN-38, which functions by inhibiting topoisomerase I (an essential enzyme involved in DNA transcription and replication) and promoting cell death. ONIVYDE was approved by the U.S. FDA in combination with fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. For full prescribing information, including Boxed WARNING,

please visit [www.ONIVYDE.com](http://www.ONIVYDE.com).

## IMPORTANT SAFETY INFORMATION - United States

### INDICATION

ONIVYDE® (irinotecan liposome injection) is indicated, 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.

#### WARNING: 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 fluorouracil (5-FU) and leucovorin (LV). Withhold ONIVYDE for absolute neutrophil count below 1500/mm<sup>3</sup> 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

ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In a clinical study, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in 1/117 patients in the ONIVYDE/5-FU/LV arm and 1/147 patients receiving ONIVYDE as a single agent. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE/5-FU/LV vs 2% of patients receiving 5-FU/LV. Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

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

ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction. Severe and life-threatening late-onset (onset > 24 hours after chemotherapy) and early-onset diarrhea (onset ≤24 hours after chemotherapy, sometimes with other symptoms of cholinergic reaction) were observed. An individual patient may experience both early- and late-onset diarrhea.

In a clinical study, Grade 3/4 diarrhea occurred in 13% of patients receiving ONIVYDE/5-FU/LV vs 4% receiving 5-FU/LV. Grade 3/4 late-onset diarrhea occurred in 9% of patients receiving ONIVYDE/5-FU/LV vs 4% in patients receiving 5-FU/LV; the incidences of early-onset diarrhea were 3% and no Grade 3/4 incidences, respectively. Of patients receiving ONIVYDE/5-FU/LV, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea.

#### Interstitial Lung Disease (ILD)

Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE in 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

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during and for 1 month after ONIVYDE treatment.

### ADVERSE REACTIONS

- The most common (≥20%) adverse reactions in which patients receiving ONIVYDE/5-FU/LV experienced a ≥5% higher incidence of any Grade vs the 5-FU/LV arm, were diarrhea (any 59%, 26%; severe 13%, 4%) (early diarrhea [any 30%, 15%; severe 3%, 0%], late diarrhea [any 43%, 17%; severe 9%, 4%]), fatigue/asthenia (any 56%, 43%; severe 21%, 10%), vomiting (any 52%, 26%; severe 11%, 3%), nausea (any 51%, 34%; severe 8%, 4%), decreased appetite (any 44%, 32%; severe 4%, 2%), stomatitis (any 32%, 12%; severe 4%, 1%), pyrexia (any 23%, 11%; severe 2%, 1%).
- Of less common (< 20%) adverse reactions, patients receiving ONIVYDE/5-FU/LV who experienced Grade 3/4

adverse reactions at a  $\geq 2\%$  higher incidence of Grade 3/4 toxicity vs the 5-FU/LV arm, respectively, were sepsis (3%, 1%), neutropenic fever/neutropenic sepsis (3%, 0%), gastroenteritis (3%, 0%), intravenous catheter-related infection (3%, 0%), weight loss (2%, 0%), and dehydration (4%, 2%).

- 1 The laboratory abnormalities in which patients receiving ONIVYDE/5-FU/LV experienced a  $\geq 5\%$  higher incidence vs the 5-FU/LV arm, were anemia (any 97%, 86%; severe 6%, 5%), lymphopenia (any 81%, 75%; severe 27%, 17%), neutropenia (any 52%, 6%; severe 20%, 2%), thrombocytopenia (any 41%, 33%; severe 2%, 0%), increased alanine aminotransferase (any 51%, 37%; severe 6%, 1%), hypoalbuminemia (any 43%, 30%; severe 2%, 0%), hypomagnesemia (any 35%, 21%; severe 0%, 0%), hypokalemia (any 32%, 19%; severe 2%, 2%), hypocalcemia (any 32%, 20%; severe 1%, 0%), hypophosphatemia (any 29%, 18%; severe 4%, 1%), hyponatremia (any 27%, 12%; severe 5%, 3%), increased creatinine (any 18%, 13%; severe 0%, 0%).
- 1 ONIVYDE can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early-onset diarrhea. Grade 1/2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE-treated patients.
- 1 Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE administration were reported in 3% of patients receiving ONIVYDE or ONIVYDE/5-FU/LV.
- 1 The most common serious adverse reactions ( $\geq 2\%$ ) of ONIVYDE were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

## DRUG INTERACTIONS

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

## USE IN SPECIFIC POPULATIONS

### Pregnancy and Reproductive Potential

Advise pregnant women of the potential risk to a fetus. Advise males with female partners of reproductive potential to use effective contraception during and for 4 months after ONIVYDE treatment.

### Lactation

Advise nursing women not to breastfeed during and for 1 month after ONIVYDE treatment.

### Pediatric

Safety and effectiveness of ONIVYDE have not been established in pediatric patients.

## DOSAGE AND ADMINISTRATION

The recommended dose of ONIVYDE is 70 mg/m<sup>2</sup> intravenous (IV) infusion over 90 minutes every 2 weeks, administered prior to LV and 5-FU. The recommended starting dose of ONIVYDE in patients known to be homozygous for the UGT1A1\*28 allele is 50 mg/m<sup>2</sup> administered by IV infusion over 90 minutes. There is no recommended dose of ONIVYDE for patients with serum bilirubin above the upper limit of normal. Premedicate with a corticosteroid and an anti-emetic 30 minutes prior to ONIVYDE. Withhold ONIVYDE for Grade 3/4 adverse reactions. Resume ONIVYDE with reduced dose once adverse reaction recovered to  $\leq$ Grade 1. Discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction and in patients with a confirmed diagnosis of ILD.

Do not substitute ONIVYDE for other drugs containing irinotecan HCl.

Please see full U.S. [Prescribing Information](#) for ONIVYDE.

## Global Partnerships

In 2014, Merrimack and Shire plc (LSE: SHP, NASDAQ: SHPG) entered into an exclusive licensing agreement for the development and commercialization of ONIVYDE outside of the United States and Taiwan. Shire's marketing authorization application for the treatment of patients with metastatic adenocarcinoma of the pancreas who have been previously treated with gemcitabine-based therapy is currently under review with the European Medicines Agency. PharmaEngine, Inc. (Taipei, Taiwan) holds the rights to commercialize ONIVYDE in Taiwan and received the Taiwan FDA approval of ONIVYDE in October 2015.

## About Merrimack

Merrimack is a fully integrated biopharmaceutical company that views cancer as a complex engineering challenge. Through systems biology, which brings together the fields of biology, computing and engineering, Merrimack aims to decrease uncertainty in drug development and clinical validation, and move discovery efforts beyond trial and error. Such an approach has the potential to make individualized treatment of patients a reality. Merrimack's first commercial product, ONIVYDE® (irinotecan liposome injection), was approved by the U.S. FDA in October 2015. With four additional candidates in clinical studies, several in preclinical development and multiple biomarkers designed to support patient selection, Merrimack is building one of the most robust oncology pipelines in the industry. For more information, please visit

Merrimack's website at [www.merrimack.com](http://www.merrimack.com) or connect on Twitter at @MerrimackPharma.

## Forward-Looking Statements

To the extent that statements contained in this press release are not descriptions of historical facts, they are forward-looking statements reflecting the current beliefs and expectations of management made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements include any statements about Merrimack's strategy, future operations, future financial position and future expectations and plans and prospects for Merrimack, and any other statements containing the words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," "hope" and similar expressions. In this press release, Merrimack's forward-looking statements include statements about the potential effectiveness and safety profile of ONIVYDE and quality of life of patients receiving ONIVYDE. Such forward-looking statements involve substantial risks and uncertainties that could cause Merrimack's clinical development programs, future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, availability of data from ongoing clinical trials, expectations for regulatory approvals, development progress of Merrimack's companion diagnostics and other matters that could affect the availability or commercial potential of Merrimack's drug candidates or companion diagnostics. Merrimack undertakes no obligation to update or revise any forward-looking statements. Forward-looking statements should not be relied upon as representing Merrimack's views as of any date subsequent to the date hereof. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to Merrimack's business in general, see the "Risk Factors" section of Merrimack's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 4, 2016 and other reports Merrimack files with the SEC.

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<sup>1</sup> American Cancer Society. Cancer Facts and Figures 2016. Atlanta: American Cancer Society; 2016

<sup>2</sup> American Cancer Society. Cancer Facts and Figures 2016. Atlanta: American Cancer Society; 2016

<sup>3</sup> American Cancer Society. Cancer Facts and Figures 2016. Atlanta: American Cancer Society; 2016

<sup>4</sup> World Health Organization. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012; Lyon, Fr.: International Agency for Research on Cancer; 2012

<sup>5</sup> Data presented at ASCO 2014 (Abrams et al.)

To view the original version on PR Newswire, visit:<http://www.prnewswire.com/news-releases/final-results-of-napoli-1-study-confirm-overall-survival-and-progression-free-survival-benefit-for-the-onivyde-regimen-for-patients-with-metastatic-pancreatic-cancer-300342298.html>

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