

IDENTIFYING DISEASE PROGRESSION IN METASTATIC PANCREATIC CANCER PATIENTS

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.

IMPORTANT SAFETY INFORMATION

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 5-FU and LV. Withhold ONIVYDE for absolute neutrophil count below $1500/\text{mm}^3$ 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

5-FU=fluorouracil; LV=leucovorin.

Please see Important Safety Information for ONIVYDE® throughout, including Boxed WARNING on Severe Neutropenia and Severe Diarrhea, and accompanying full Prescribing Information as well as complete reference list in the pocket.

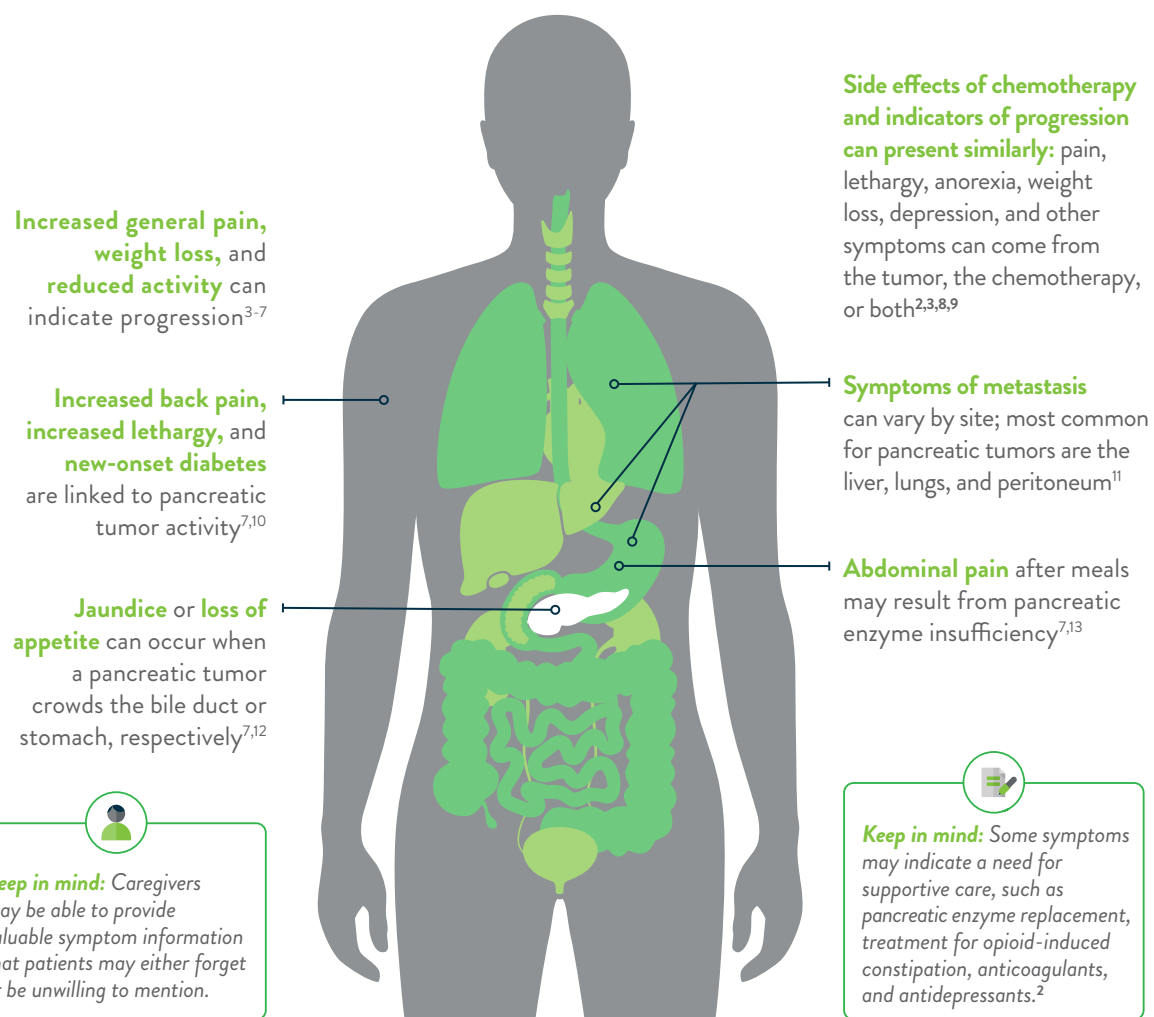
 onivyde®
(irinotecan liposome injection)

METASTATIC PANCREATIC CANCER— A UNIQUE CANCER FOR PROGRESSION

Since metastatic pancreatic cancer can progress rapidly, it's important to *closely monitor patients* for signs and symptoms of progression, which may present *before scan results*.^{1,2}

“Patients with advanced disease may have abrupt changes in clinical status. Therefore, if treatment is begun, it should proceed with close follow-up.”²

—NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Pancreatic Adenocarcinoma



TO IDENTIFY PROGRESSION IN METASTATIC PANCREATIC CANCER, CONSIDER THE 3Cs

CLINICAL SIGNS AND SYMPTOMS

- Potentially the earliest evidence for mPC progression²
- Monitor patients for pain, weight changes, and activity level
- Closely assess at every visit¹⁴

CA 19-9 BIOMARKER TESTS

- Indicate tumor activity; a *high, nondecreasing* CA 19-9 level, as well as an *increasing* level, may be a sign of progression¹⁵⁻¹⁷
- Ideally check every month

CT/PET SCANS

- Imaging at 2-3 months is recommended by ASCO^{14,18}
- Worsening clinical signs/symptoms and/or CA 19-9 levels may be “red flags” to prompt an earlier scan; however, a stable scan result along with clinical signs/symptoms plus high/rising CA 19-9 may *still indicate clinical progression*^{2,16}

Monitoring patients frequently and closely may help you detect progression earlier. A patient can then be switched to another therapy if eligible, and before their medical status deteriorates so far that another therapy is no longer feasible.

For your patients who progress on gemcitabine-based therapy, consider ONIVYDE[®] + 5-FU/LV, proven to extend overall survival (median OS: 6.1 months vs 4.2 months for 5-FU/LV alone).^{19*}

*NAPOLI-1 was a global, phase 3, randomized, open-label, multicenter trial in patients (N=417) with metastatic adenocarcinoma of the pancreas whose disease had progressed following gemcitabine-based therapy. Patients were initially randomized to receive ONIVYDE[®] (100 mg/m² every 3 weeks) or 5-FU/LV. After 63 patients were enrolled, a third arm, ONIVYDE[®] (70 mg/m² every 2 weeks) + 5-FU/LV, was added. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint, median OS, was assessed with 2 pair-wise comparisons: ONIVYDE[®] (n=151) vs 5-FU/LV (n=149) and ONIVYDE[®] + 5-FU/LV (n=117) vs 5-FU/LV (n=119, post-protocol amendment). There was no improvement in OS for ONIVYDE[®] vs 5-FU/LV (HR=1.00, p=0.97 [2-sided log-rank]). Additional efficacy endpoints were PFS and ORR.^{19,20}

PFS=progression-free survival; ORR=overall response rate; OS=overall survival.

IMPORTANT SAFETY INFORMATION (CONTINUED) 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

Please see Important Safety Information for ONIVYDE[®] throughout, including Boxed WARNING on Severe Neutropenia and Severe Diarrhea, and accompanying full Prescribing Information as well as complete reference list in the pocket.



REFERENCES

1. Oberstein PE, Olive KP. Pancreatic cancer: why is it so hard to treat? *Ther Adv Gastroenterol*. 2013;6(4):321-337.
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pancreatic Adenocarcinoma V.1.2020. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed November 26, 2019. To view the most recent and complete version of the guideline, go online to [NCCN.org](https://www.nccn.org). NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
3. Kluetz PG, Slagle A, Papadopoulos EG, et al. Focusing on core patient-reported outcomes in cancer clinical trials: symptomatic adverse events, physical function, and disease-related symptoms. *Clin Cancer Res*. 2016;22(7):1553-1558.
4. Reeve BB, Mitchell SA, Dueck AC, et al. Recommended patient-reported core set of symptoms to measure in adult cancer treatment trials. *J Natl Cancer Inst*. 2014;106(7):1-8.
5. Lee V, Cheng H, Li G, Saif MW. Quality of life in patients with pancreatic cancer: highlights from the “2012 ASCO Gastrointestinal Cancers Symposium.” San Francisco, CA. January 19-21, 2012. *J Pancreas*. 2012;13(2):182-184.
6. Hendifar AE, Petzel MQB, Zimmers, TA. Pancreas cancer-associated weight loss. *Oncologist*. 2019;24(5):691-701.
7. Kuroczycki-Saniutycz S, Grzeszczuk A, Zwierz ZW, et al. Prevention of pancreatic cancer. *Contemp Oncol (Pozn)*. 2017;21(1):30-34.
8. Mayo Clinic website. Pancreatic Cancer. <https://www.mayoclinic.org/diseases-conditions/pancreatic-cancer/symptoms-causes/syc-20355421>. Accessed November 22, 2019.
9. Mayo Clinic website. Cancer. <https://www.mayoclinic.org/diseases-conditions/cancer/symptoms-causes/syc-20370588>. Accessed November 26, 2019.
10. Keane MG, Horsfall L, Rait G, Pereira SP. A case-control study comparing the incidence of early symptoms in pancreatic and biliary tract cancer. *BMJ Open*. 2014;4(11):e005720.
11. Deeb A, Haque S-U, Olowokure O. Pulmonary metastases in pancreatic cancer, is there a survival influence? *J Gastrointest Oncol*. 2015;6(3):E48-E51.
12. Johns Hopkins Medicine. Pancreatic cancer symptoms. <https://www.hopkinsmedicine.org/health/conditions-and-diseases/pancreatic-cancer/pancreatic-cancer-symptoms>. Accessed November 22, 2019.
13. Chun C. Healthline. Understanding pancreatic cancer pain: how to find relief. <https://www.healthline.com/health/pancreatic-cancer-pain-management>. Accessed November 22, 2019.
14. Sohal DPS, Kennedy EB, Khorana A, et al. Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36(24):2545-2556.
15. Columbia University Irving Medical Center. The Pancreas Center. Symptoms of pancreatic cancer. <https://columbiasurgery.org/pancreas/symptoms-pancreatic-cancer>. Accessed November 22, 2019.
16. National Cancer Institute. Pancreatic cancer treatment (adult) (PDQ®)-health professional version. <https://www.cancer.gov/types/pancreatic/hp/pancreatic-treatment-pdq>. Accessed December 5, 2019.
17. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol*. 2006;24(33):5313-5327.
18. Ducreux M, Cuhna ASa, Caramella C, et al; on behalf of the ESMO Guidelines Committee. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(suppl 5):v56-v68.
19. ONIVYDE [package insert]. Basking Ridge, NJ. Ipsen Biopharmaceuticals, Inc.; 2017.
20. Wang-Gillam A, Li C-P, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomized, open-label, phase 3 trial. *Lancet*. 2016;387:545-557.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS

- **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:** 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 ($\geq 20\%$) 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 ($\geq 10\%$) 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 ($\geq 20\%$) 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

USE IN SPECIFIC 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 Important Safety Information for ONIVYDE[®] throughout, including **Boxed WARNING** on Severe Neutropenia and Severe Diarrhea, and accompanying full Prescribing information as well as complete reference list in the pocket.

FOR MORE INFORMATION VISIT ONIVYDE.COM