

Submitted by:

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Date of Request: January 20, 2023

NCCN® Guidelines Panel: Pancreatic Adenocarcinoma Panel

On behalf of Ipsen, we respectfully request the NCCN Guidelines Panel for Pancreatic Adenocarcinoma to consider the enclosed data for liposomal irinotecan (ONIVYDE®) in combination with 5-fluorouracil/leucovorin and oxaliplatin (NALIRIFOX) for patients not previously treated for metastatic pancreatic adenocarcinoma (mPDAC), which have been recently presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium 2023.

Specific change request

Based on the enclosed data, we request the below change to the current NCCN Guidelines for Pancreatic Adenocarcinoma:

- On page PANC-F (4 of 9) of version 2.2022, that liposomal irinotecan in combination with 5-fluorouracil/leucovorin and oxaliplatin be added as a preferred regimen for first-line therapy in patients with metastatic pancreatic adenocarcinoma disease.
- On page PANC-F (4 of 9) include in the footnote that NALIRIFOX is reasonable in patients with ECOG of 0–2.
- On page PANC-F (3 of 9) of version 2.2022, that liposomal irinotecan in combination with 5-fluorouracil/leucovorin and oxaliplatin be added as a preferred regimen for first-line therapy in patients with locally advanced pancreatic adenocarcinoma.
- On page PANC-F (3 of 9) include in the footnote that NALIRIFOX is reasonable in patients with ECOG of 0–2.

US Food and Drug Administration status

ONIVYDE® (liposomal irinotecan injection), in combination with fluorouracil and leucovorin, is approved for the treatment of patients with metastatic pancreatic adenocarcinoma after disease progression following gemcitabine-based therapy.¹ ONIVYDE® is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.¹ ONIVYDE is not indicated, alone or in combination, for the treatment of patients who have not been previously treated for metastatic adenocarcinoma of the pancreas.

Rationale

NAPOLI 3 was a randomized, open-label, phase III trial (NCT04083235) investigating the efficacy and safety of liposomal irinotecan (ONIVYDE®) in combination with 5-fluorouracil/leucovorin and oxaliplatin (NALIRIFOX) versus nab-paclitaxel + gemcitabine in first-line therapy in patients with mPDAC. Overall, 770 patients (NALIRIFOX, n = 383; Gem+NabP, n = 387) were included. Baseline characteristics were well balanced between arms with a median

follow-up of 16.1 months. The study met its primary endpoint demonstrating a clinically meaningful and statistically significant improvement in overall survival (OS) compared to gemcitabine and nab-paclitaxel in patients with mPDAC in the front-line setting.²

The median OS was 11.1 months in the NALIRIFOX arm as compared with 9.2 months in the Gem+NabP arm (HR 0.83 [95% CI 0.70–0.99]; p = 0.04)

The secondary endpoint of progression-free survival (PFS) was also significantly improved. The median PFS for the NALIRIFOX regimen was 7.4 months versus 5.6 months for gemcitabine/nab-paclitaxel, (hazard ratio 0.69 [95% CI 0.58-0.83]; p=0.0001). The ORR for NALIRIFOX was 41.8% versus 36.2% for gemcitabine/nab-paclitaxel (Table 1).²

Table 1. Tumor Response in the phase III NAPOLI 3 study²
N = 770

	Liposomal irinotecan plus 5-fluorouracil/leucovorin and oxaliplatin (n=383)	Gemcitabine plus nab-paclitaxel (n=387)
mOS (months)	11.1	9.2
	Hazard ratio: 0.83 95% confidence interval: 0.70-0.99 p = 0.04	
mPFS (months)	7.4	5.6
	Hazard ratio: 0.69 95% confidence interval: 0.58-0.83 p <0.0001	
ORR	41.8%	36.2%

mOS, median overall survival; mPFS, median progression-free survival; ORR, Objective Response Rate

Safety results were consistent with the known profile of liposomal irinotecan, 5-fluorouracil/leucovorin and oxaliplatin, as observed in the phase I/II study (NCT02551991) for patients with previously untreated metastatic pancreatic adenocarcinoma.³ Additionally, grade 3 hematologic and neuropathic adverse events were significantly lower in the NALIRIFOX regimen compared to those treated with gemcitabine and nab-paclitaxel making the treatment more manageable (Table 2)²

Table 2. Any-cause Treatment-Emergent Adverse Event's (TEAEs) in ≥10% of patients

	NALIRIFOX (N = 370)	Gem + NabP (N = 379)
	Grade 3 – 4	Grade 3 – 4
Hematologic		
Neutropenia / Neutrophil count decreased / Febrile neutropenia	14.1 / 9.7 / 2.4	24.5 / 18.7 / 2.6
Anemia / Thrombocytopenia / Platelet count decreased	10.5 / 0.8 / 0.8	17.4 / 3.7 / 2.4
Nonhematologic		
Diarrhea	20.3	4.5
Nausea	11.9	2.6
Vomiting	7.0	2.1
Hypokalemia	15.1	4.0

	NALIRIFOX (N = 370)	Gem + NabP (N = 379)
	Grade 3 – 4	Grade 3 – 4
Peripheral neuropathy	3.2	5.8
Peripheral sensory neuropathy	3.5	2.9
Paresthesia	0.3	0.5
Pyrexia	0.8	1.6

We deeply appreciate the Panel's consideration. In the event of any questions, please contact us at the provided phone numbers and/or email addresses.

Sincerely,

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Please find the following enclosures in support of this submission.

1. Ipsen Biopharmaceuticals, Inc. Prescribing Information, ONIVYDE® (irinotecan liposome injection). US Food and Drug Administration, 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207793lbl.pdf (Accessed January 2023).
2. Wainberg Z, Melisi D, Macarulla T, et al. A randomized, open-label phase 3 study of liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin (NALIRIFOX) versus nab-paclitaxel + gemcitabine in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma: NAPOLI 3. Presented at: American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI); January 18-21; San Francisco, CA.
3. Wainberg Z, Bekai-Saab T, Boland P, et al. First-line liposomal irinotecan with oxaliplatin, 5-fluorouracil and leucovorin (NALIRIFOX) in pancreatic ductal adenocarcinoma: A phase I/II study. Eur J Cancer. 2021 Jul;151:14-24. doi: 10.1016/j.ejca.2021.03.028. Epub 2021 May 4. PMID: 33957442.