

Submitted by:

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Date of Request: 9/12/2023**NCCN® Guidelines Panel:** Pancreatic Adenocarcinoma Panel

On behalf of Ipsen, we are pleased to present the recent *Lancet* publication¹ of the Phase 3 NAPOLI-3 trial of liposomal irinotecan (ONIVYDE®) in combination with 5-fluorouracil/leucovorin and oxaliplatin (NALIRIFOX) for patients not previously treated for metastatic pancreatic adenocarcinoma (mPDAC) that supports category 1 and preferred status for NALIRIFOX (**request 1**).^{1,2} This letter also includes published evidence³ on total cost of care relevant to the new footnote i (**request 2**).

Specific change request 1

Based on the enclosed Phase 3 NAPOLI-3 publication in *Lancet*¹, we respectfully request:

- PANC-F (3 of 12), Locally advanced disease, PS 0-1, and PANC-F (5 of 12), First-line metastatic disease, PS 0-1
 - Please assign Category 1 to NALIRIFOX based on published Phase 3 study
 - Please assign NALIRIFOX as preferred based on significant OS and PFS benefits over NCCN-Preferred regimen gemcitabine and nab-paclitaxel (Gem+NabP)
 - Please place NALIRIFOX above Gem+NabP based on superiority in direct head-to-head comparison
- PANC-F (4 of 12), Locally advanced disease, PS 2, and PANC-F (6 of 12), First-line metastatic disease, PS 2
 - Please assign Category 2A to NALIRIFOX based on benefits over Gem+NabP
 - Please assign NALIRIFOX as preferred based on significant OS and PFS benefits over NCCN-Preferred regimen Gem+NabP
 - Please place NALIRIFOX above Gem+NabP based on superiority in direct head-to-head comparison
- PANC-F (11 of 12), please update reference 16 to the *Lancet* publication¹

Rationale for request 1

The published global, Phase 3, randomized controlled NAPOLI-3 trial¹ (N=770) satisfies NCCN category 1 requirement. It also supports preferred status for NALIRIFOX as it is the only study that has demonstrated superiority of triplet therapy (using liposomal irinotecan) over Gem+NabP, an NCCN-preferred regimen for first-line mPDAC. Highlights include:

- NALIRIFOX demonstrated statistically significant and clinically meaningful improvements in median OS and PFS compared with Gem+NabP (Figures 1 and 2)
- Updated results presented at ASCO 2023:² 12-month and 18-month OS (12-mo: 45.6% vs 39.5%; 18-mo: 26.2% vs 19.3%) and PFS (12-mo: 27.4% vs 13.9%; 18-mo: 11.4% vs 3.6%) confirmed the favorability of NALIRIFOX over Gem+NabP
- OS and PFS benefits were consistent across key prespecified subgroups (ECOG performance status, liver metastases, age)

- ORR was also higher with NALIRIFOX (41.8%) than with Gem+NabP (36.2%)
- NALIRIFOX showed comparable tolerability with a different safety profile from Gem+NabP
- Less grade ≥ 3 hematologic and neuropathic adverse events (AE) with NALIRIFOX
- Similar rates of grade ≥ 3 treatment-related AEs (70.8% vs 68.1%); AE-related discontinuation was with 14.1% NALIRIFOX and 23.8% with Gem+NabP
- NALIRIFOX was associated with a low rate of peripheral neuropathy (grade 3-4: 6.7%); it uses a lower dose of oxaliplatin (60 mg/m²) than FOLFIRINOX (85 mg/m²)
- NAPOLI-3 had no age restrictions and was a truly global trial, with a mixture of community and academic sites

Figure 1. OS of NALIRIFOX and Gem+NabP in NAPOLI-3.¹

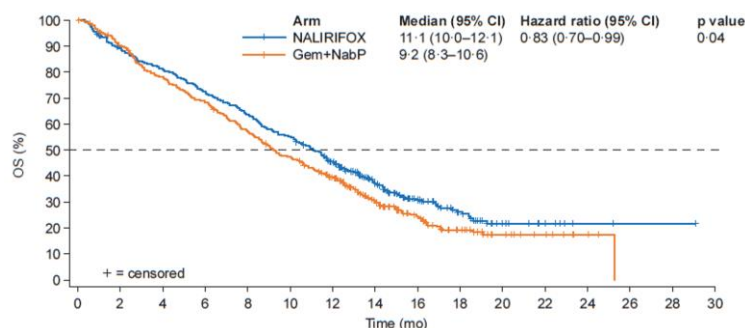
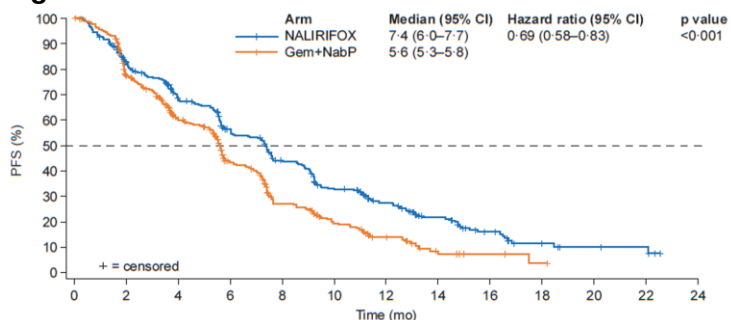


Figure 2. PFS of NALIRIFOX and Gem+NabP in NAPOLI-3.¹



Clinical Literature¹

NAPOLI 3 was a randomized, open-label, phase III trial (NCT04083235) investigating the efficacy and safety of NALIRIFOX versus Gem+NabP in first-line therapy in patients with mPDAC.¹ 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 Gem+NabP. The secondary endpoint of progression-free survival (PFS) was also significantly improved. See Table 1 for a summary of efficacy outcomes.¹

Table 1. Key efficacy outcomes in the phase III NAPOLI 3 study¹

	NALIRIFOX (n=383)	Gem + NabP (n=387)	Hazard ratio; 95% CI
mOS (months)	11.1	9.2	0.83; 0.70-0.99 (P=0.04)
18-month OS	26.2%	19.3%	--
mPFS (months)	7.4	5.6	0.69; 0.58-0.83 (P<0.0001)
18-month PFS	11.4%	3.6%	--
ORR	41.8%	36.2%	--
DCR	67.6%	62.3%	--

mDOR (months)	7.3	5.0	--
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mOS, median overall survival; mPFS, median progression-free survival; ORR, Objective Response Rate; DCR, disease Control Rate; mDOR, median Duration of Response.

Safety results were consistent with the known profile of the NALIRIFOX regimen, as observed in the phase I/II study for patients with previously untreated mPDAC.⁵ Grade 3 hematologic and neuropathic adverse events were significantly lower in the NALIRIFOX regimen compared to those treated with gemcitabine and nab-paclitaxel (Table 2).¹

Table 2. Grade 3-4 treatment-emergent AEs (TEAEs) in ≥5% of patients.¹

	Grade 3 – 4 TEAE	
	NALIRIFOX (N = 370)	Gem + NabP (N = 379)
Overall treatment-related TEAEs	70.8%	68.1%
Hematologic		
Neutropenia/ Febrile neutropenia	23.8 / 2.4	38.0 / 2.4
Anemia/ Thrombocytopenia	10.5 / 1.6	17.4 / 6.1
Nonhematologic		
Diarrhea	20.3	4.5
Nausea	11.9	2.6
Vomiting	7.0	2.1
Hypokalemia	15.1	4.0
Peripheral neuropathy	3.2	5.8

Specific change request 2

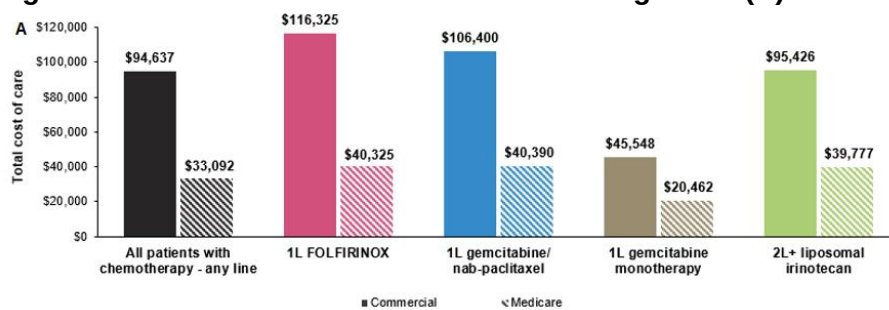
Based on publication³ on total cost of care related to adverse events (AEs):

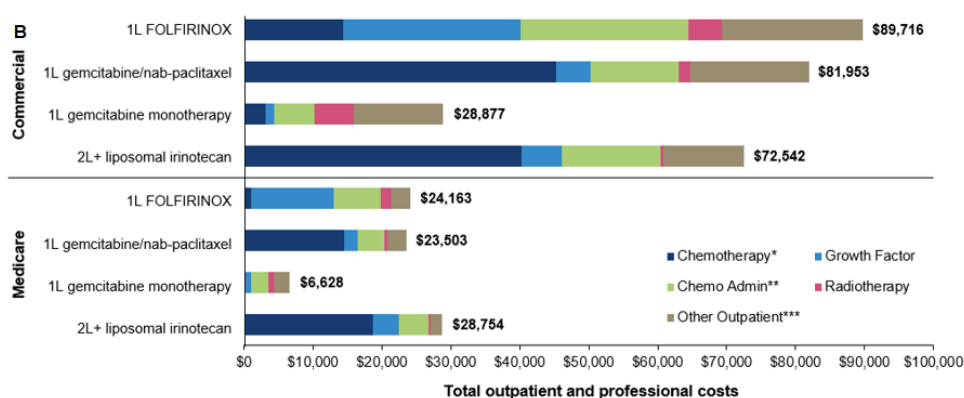
- Modify Footnote i to: “While NCCN recognizes that there is high-level evidence supporting the use of NALIRIFOX over gemcitabine and albumin-bound paclitaxel, it should be recognized that this regimen has not been directly compared with FOLFIRINOX”

Rationale for request 2

Unlike FOLFIRINOX, NALIRIFOX has an established dose regimen optimized for efficacy-to-safety ratio. Although FOLFIRINOX acquisition cost is low, its hematologic AEs result in high supportive care costs involving growth factors and outpatient care. Based on an analysis on 3,904 patients with commercial coverage and 28,063 Medicare patients, the total cost of care of FOLFIRINOX is similar to or more than other therapies (gemcitabine ± nab-paclitaxel, liposomal irinotecan) in mPDAC treatment (Figure 3).³

Figure 3. Mean total cost of care of mPDAC regimens (A) and cost breakdown (B).³





US Food and Drug Administration status

ONIVYDE® (liposomal irinotecan injection), in combination with fluorouracil and leucovorin, is approved for the treatment of patients with mPDAC after disease progression following gemcitabine-based therapy.⁴ ONIVYDE is not indicated, alone or in combination, for the treatment of patients who have not been previously treated for mPDAC.

Sincerely,

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Please find the following enclosures in support of this submission.

1. Wainberg ZA, Melisi D, Macarulla T, et al. NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial. *Lancet*. Published online September 11, 2023 [https://doi.org/10.1016/S0140-6736\(23\)01366-1](https://doi.org/10.1016/S0140-6736(23)01366-1)
2. O'Reilly EM, Melisi D, Macarulla T, et al. Liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin (NALIRIFOX) versus nab-paclitaxel + gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): 12- and 18-month survival rates from the phase 3 NAPOLI 3 trial. Presented at: 2023 ASCO Annual Meeting. June 2-6, 2023; Chicago, IL. Abstract 4006.
3. Tomicki S, Dieguez G, Latimer H, et al. Real-world cost of care for commercially insured versus Medicare patients with metastatic pancreatic cancer who received guideline-recommended therapies. *Am Health Drug Benefits*. 2021;14(2):70-78.
4. Ipsen Biopharmaceuticals, Inc. Prescribing Information, ONIVYDE® (irinotecan liposome injection). US Food and Drug Administration, 2017.
5. 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.