Characteristics of long-term survivors and impact of dose adjustments in first-line NALIRIFOX treatment for metastatic pancreatic ductal adenocarcinoma: *post hoc* analyses of NAPOLI 3

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KEY LEARNINGS

- In NAPOLI 3, among patients from North America treated with NALIRIFOX who had long-term survival (OS ≥ 18 months), a substantial proportion had ≥ 3 metastatic sites at baseline, but they otherwise had a good clinical profile.
- Across all patients treated with NALIRIFOX at North American centers (including long-term survivors), tolerability-guided dose modifications did not adversely affect OS.

BACKGROUND

- NALIRIFOX (liposomal irinotecan in combination with 5-fluorouracil/leucovorin plus oxaliplatin) is an approved option for first-line (1L) treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC).[1–3]
- Approval was based on the results of the phase 3 NAPOLI 3 trial (NCT04083235) in which NALIRIFOX significantly improved survival outcomes compared with nab-paclitaxel plus gemcitabine (Gem+NabP) in patients with previously untreated mPDAC.[4]
- In NAPOLI 3, related treatment-emergent adverse events led to dose reductions in 198 patients (54%) who received NALIRIFOX, and in 184 patients (49%) who received Gem+NabP.[4] At the time of the primary analysis of NAPOLI 3, the impact of dose modifications on overall survival (OS) was not evaluated.
- In addition, a subgroup of patients in NAPOLI 3 achieved long-term survival (≥ 18 months);[5] the characteristics of this subgroup are of interest to guide informed treatment selection.

OBJECTIVE

- This *post hoc* analysis of the North American population from NAPOLI 3 aims to describe the characteristics and dosing patterns of long-term survivors treated with NALIRIFOX and to explore the impact of dose reductions of liposomal irinotecan and/or oxaliplatin dose reductions on OS with NALIRIFOX.

CONCLUSIONS

- This *post hoc* analysis of patients treated with NALIRIFOX at North American centers in NAPOLI 3 found the following.
  - A substantial proportion of long-term survivors had ≥ 3 metastatic sites at baseline, but they otherwise had a good clinical profile: younger (vs typical mPDAC diagnosis[6]), few tumors in the head or tail of the pancreas, a good performance status and reasonably low CA 19-9 levels.
  - The majority of long-term survivors also experienced dose reductions of liposomal irinotecan and/or oxaliplatin.
    - These patients had prolonged exposure and high cumulative doses of both drugs.
  - More widely, in the North American NALIRIFOX safety population, the occurrence of dose modifications was associated with prolonged OS.
- The results suggest that tolerability-guided liposomal irinotecan or oxaliplatin dose reductions do not adversely affect OS among patients with mPDAC receiving NALIRIFOX treatment.

METHODS

Study design and patients

- NAPOLI 3 was an open-label, randomized, phase 3 trial conducted at 187 sites in 18 countries worldwide.[4]
- Patients with mPDAC (N = 770) were randomized 1:1 to receive 1L treatment with NALIRIFOX or Gem+NabP (Figure 1).
- These *post hoc* analyses included patients treated with NALIRIFOX at North American centers participating in NAPOLI 3 (70 sites; 120 patients).
  - Baseline characteristics and NALIRIFOX dosing patterns for long-term survivors were evaluated in the subgroup of the North American intention-to-treat (ITT) population that survived for ≥ 18 months after NALIRIFOX initiation.
  - The impact of dose reduction of liposomal irinotecan or oxaliplatin was assessed in the North American NALIRIFOX safety population (patients who received ≥ 1 dose of study treatment).

Statistical analysis

- All analyses were purely descriptive; no comparisons or statistical tests were performed.

RESULTS

Population

- Of the 120 patients randomized to receive NALIRIFOX at North American centers (ITT population), 15 (12.5%) had an OS ≥ 18 months (long-term survivors).
- Of the 112 patients in the North American NALIRIFOX safety population, 63 (56.3%) had a reduction in their liposomal irinotecan dose and 72 (64.3%) in their oxaliplatin dose.
- Demographic and clinical characteristics are reported below for long-term survivors; characteristics for the North American NALIRIFOX safety population are included in the Supplementary Materials, stratified by dose modification status (any/none) (Supplementary Table S1; please scan QR code).

Characteristics of long-term survivors

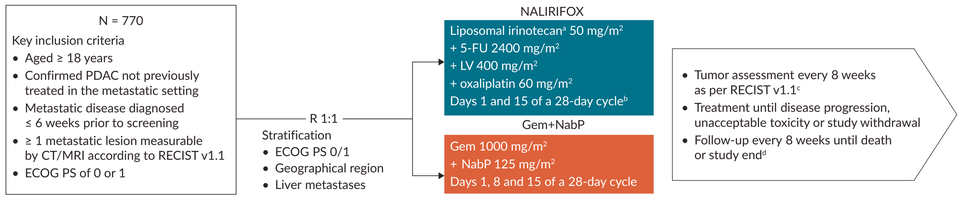
- The median age of the long-term survivor subgroup was 61.0 (interquartile range [IQR]: 49.0–70.5) years, 46.7% were female, 66.7% were white (Table 1).
- At baseline, 53.3% had a baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 and had the main pancreatic tumor located in the body of the pancreas; median carbohydrate antigen 19-9 (CA 19-9) level was 166.8 (IQR: 32.7–1728.4) U/mL, and most had metastatic disease at diagnosis (86.7%) (Table 1).
  - 53.3% of patients had ≥ 3 metastatic sites, most commonly in the liver (66.7% of patients) (Table 1).
  - Most long-term survivors (73.3%) were UGT1A1*28 non-homozygous (Table 1).

Overall survival

Long-term survivors

- Median OS (mOS) for the North American ITT population was 11.1 (IQR: 5.6–14.6) months; among the long-term survivor subgroup, mOS was 19.5 (IQR: 18.8–22.6) months (Figure 2).

Figure 1. NAPOLI 3 study design



[a]Dose expressed as irinotecan free base equivalent. [b]Administered sequentially as a continuous infusion over 46 hours (dose delays and oxaliplatin discontinuation were permitted). [c]Until progressive disease. [d]The study was complete once all patients had discontinued the study treatment or ≥ 543 OS events had occurred.
5-FU, 5-fluorouracil; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Gem, gemcitabine; LV, leucovorin; MRI, magnetic resonance imaging; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 1. Baseline demographics and disease characteristics of long-term survivors treated with NALIRIFOX at North American centers in NAPOLI 3

Baseline characteristic	OS ≥ 18.0 months (n = 15)	ITT (n = 120)
Age		
Median (IQR), years	61.0 (49.0–70.5)	65.0 (59.0–71.0)
< 65 years, n (%)	8 (53.3)	56 (46.7)
≥ 65 years, n (%)	7 (46.7)	64 (53.3)
Sex, n (%)		
Female	7 (46.7)	49 (40.8)
Race, n (%)		
Asian	1 (6.7)	4 (3.3)
Black or African American	2 (13.3)	11 (9.2)
White	10 (66.7)	99 (82.5)
Multiple	0 (0)	1 (0.8)
Other	2 (13.3)	3 (2.5)
ECOG PS score, n (%)		
0	8 (53.3)	46 (38.3)
1	7 (46.7)	74 (61.7)
Stage at diagnosis, n (%)		
Metastatic	13 (86.7)	105 (87.5)
Resectable	0 (0)	5 (4.2)
Locally advanced	2 (13.3)	8 (6.7)
Borderline resectable	0 (0)	2 (1.7)
Liver metastases in eCRF, n (%)		
No	5 (33.3)	26 (21.7)
Yes	10 (66.7)	94 (78.3)
Number of metastatic sites, n (%)		
1	3 (20.0)	34 (28.3)
2	4 (26.7)	39 (32.5)
≥ 3	8 (53.3)	47 (39.2)
Metastatic site, n (%)		
Liver	6 (40.0)	60 (50.0)
Liver, lung	4 (26.7)	33 (27.5)
Lung	3 (20.0)	12 (10.0)
Unknown	2 (13.3)	15 (12.5)
Main pancreatic cancer tumor location, n (%)		
Head	5 (33.3)	48 (40.0)
Body	8 (53.3)	38 (31.7)
Tail	2 (13.3)	33 (27.5)
Unknown	0 (0)	1 (0.8)
CA 19-9, U/mL		
Median (IQR)	166.8 (32.7–1728.4)	2948.8 (153.8–8000.0)
***UGT1A1*28* allele status, n (%)**		
Homozygous	3 (20.0)	13 (10.8)
Non-homozygous	11 (73.3)	104 (86.7)
Missing	1 (6.7)	3 (2.5)

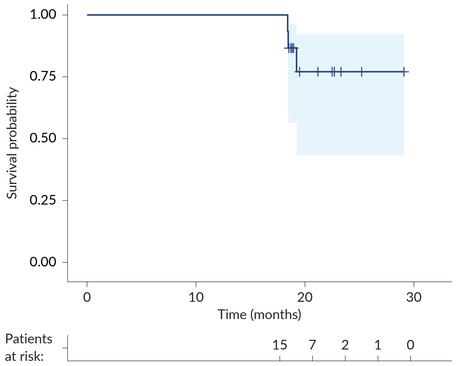
CA 19-9, carbohydrate antigen 19-9; ECOG PS, Eastern Cooperative Oncology Group Performance Status; eCRF, electronic case report form; IQR, interquartile range; ITT, intention-to-treat; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; OS, overall survival.

Table 2. Cumulative dose and duration of exposure of liposomal irinotecan and oxaliplatin

	Safety population (n = 112)		ITT (n = 120)	
	Dose not reduced	Dose reduced	Long-term survivors	Overall
Liposomal irinotecan	**n = 49**	**n = 63**	**n = 15**	**n = 120**
Dose reduction, n (%)	0	63 (56.3)	10 (66.7)	63 (52.5)
Duration of exposure at any dose, weeks, median (IQR)	18.1 (4.1–35.0)	25.3 (15.1–53.7)	65.1 (40.1–89.0)	23.1 (10.9–44.8)
Cumulative dose, mg/m², median (IQR)	403.5 (102.1–809.4)	460.1 (245.9–966.9)	1229.4 (821.9–1513.9)	429.3 (202.7–860.1)
Oxaliplatin	**n = 40**	**n = 72**	**n = 15**	**n = 120**
Dose reduction, n (%)	0	72 (64.3)	12 (80.0)	72 (60.0)
Duration of exposure at any dose, weeks, median (IQR)	12.1 (3.6–24.7)	25.2 (15.1–43.8)	39.9 (26.6–76.4)	21.8 (10.9–37.6)
Cumulative dose, mg/m², median (IQR)	327.6 (121.6–628.5)	653.8 (304.9–974.8)	962.3 (655.0–1470.3)	481.9 (242.7–920.9)

IQR, interquartile range; ITT, intention-to-treat.

Figure 2. Overall survival of long-term survivors (intention-to-treat population)



Dose modification subgroups

- Patients who received dose reductions of liposomal irinotecan or oxaliplatin had a longer median (95% confidence interval) OS than those without dose reductions:
  - Liposomal irinotecan: 13.0 (8.6–15.4) months vs 10.9 (7.7–13.9) months, respectively
  - Oxaliplatin: 14.4 (11.5–15.9) months vs 8.3 (5.9–11.2) months, respectively.
- mOS by lowest dose of liposomal irinotecan and oxaliplatin in the global safety population is reported in Supplementary Table S2; please scan QR code.

Treatment exposure and cumulative dose

Long-term survivors

- Most long-term survivors experienced dose reductions of both liposomal irinotecan (66.7%) and oxaliplatin (80%) (Table 2).
- Median (IQR) cumulative dose of liposomal irinotecan was 1229.4 (821.9–1513.9) mg/m² for long-term survivors and median cumulative dose of oxaliplatin was 962.3 (655.0–1470.3) mg/m² (Table 2).
  - Median (IQR) duration of exposure was 65.1 (40.1–89.0) weeks for liposomal irinotecan and 39.9 (26.6–76.4) weeks for oxaliplatin (Table 2).

Dose modification subgroups

- In the safety population, median duration of exposure and cumulative dose were longer among patients who received a dose reduction than among those who did not, for both liposomal irinotecan and oxaliplatin (Table 2).
  - Median (IQR) cumulative dose of liposomal irinotecan was 460.1 (245.9–966.9) mg/m² for patients who received a dose reduction and median cumulative dose of oxaliplatin was 653.8 (304.9–974.8) mg/m².
  - Median (IQR) duration of exposure was 25.3 (15.1–53.7) weeks for liposomal irinotecan and 25.2 (15.1–43.8) weeks for oxaliplatin.
- Reasons for dose reduction and discontinuation (in the safety population) are included in the Supplementary Materials (please scan QR code).

Abbreviations 1L, first-line; 5-FU, 5-fluorouracil; CA 19-9, carbohydrate antigen 19-9; CI, confidence interval; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group Performance Status; eCRF, electronic case report form; Gem, gemcitabine; Gem+NabP, nab-paclitaxel plus gemcitabine; IQR, interquartile range; ITT, intention-to-treat; LV, leucovorin; mOS, median overall survival; mPDAC, metastatic pancreatic ductal adenocarcinoma; MRI, magnetic resonance imaging; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

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