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NAPOLI 3 phase 3 trial of NALIRIFOX in metastatic pancreatic ductal adenocarcinoma: characteristics of long-term survivors

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KEY LEARNINGS

Judicious dose modifications (reductions/delays) enabled prolonged treatment exposure and long-term survival (OS, ≥ 18 months; mOS, 19.5 months) in a subgroup of North American patients treated with NALIRIFOX in NAPOLI 3; a substantial proportion of the long-term survivor subgroup had ≥ 3 metastatic sites at baseline, but otherwise had a good clinical profile.

BACKGROUND

- Metastatic pancreatic ductal adenocarcinoma (mPDAC) is an aggressive malignancy.
- Median overall survival (mOS) with chemotherapy regimens ranges from 8.5 months to 11.1 months in the clinical trial setting,[1,2] but a subgroup of patients can achieve long-term survival (≥ 18 months).[3]
- Understanding the clinical and demographic profile of patients with mPDAC who achieve long-term survival may help to tailor treatment decisions to optimize clinical outcomes.
- NALIRIFOX (liposomal irinotecan in combination with 5-fluorouracil/leucovorin plus oxaliplatin) is a US Food and Drug Administration and European Medicines Agency approved first-line (1L) treatment option for mPDAC,[4,5] based on the results of the phase 3 NAPOLI 3 trial (NCT04083235).[6]
- At a median follow-up of 16.1 months, mOS in NAPOLI 3 for the NALIRIFOX treatment arm was 11.1 months;[6] the characteristics of long-term survivors in NAPOLI 3 have not been previously reported.

OBJECTIVE

- To describe the characteristics of long-term survivors among the North American population treated with NALIRIFOX in the NAPOLI 3 trial and to explore clinical and pathological factors that might be associated with prolonged survival.

CONCLUSIONS

- This *post hoc* analysis investigated the demographic and clinical characteristics and dosing patterns among long-term survivors from North America treated with NALIRIFOX in NAPOLI 3.
- 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), few tumors in the head or tail of the pancreas, a good performance status and reasonably low CA 19-9 levels.[7]
- Dose reductions and/or treatment delays occurred in the majority of long-term survivors, enabling prolonged exposure, high cumulative doses of both liposomal irinotecan and/or oxaliplatin drugs and an overall mOS of 19.5 months.
- Owing to the small sample size, these results should be interpreted with caution.

METHODS

Study design

- NAPOLI 3 was a randomized, open-label, phase 3 trial conducted at 187 sites in 18 countries worldwide.[1]
- Patients with mPDAC (N = 770) were randomized 1:1 to receive 1L treatment with NALIRIFOX or nab-paclitaxel plus gemcitabine (Figure 1).
- In this *post hoc* analysis of patients enrolled from centers in North America (70 sites), baseline characteristics and NALIRIFOX dosing patterns were evaluated for individuals who survived for 18 months or longer (long-term survivors).

Analysis

- The analysis was purely descriptive, no comparisons or statistical tests were performed.
- Kaplan–Meier methods were used to estimate mOS (interquartile range [IQR]).

RESULTS

Demographic characteristics of long-term survivors

- Of the 120 patients from centers in North America who were randomized to receive NALIRIFOX in NAPOLI 3 (intention-to-treat [ITT] population), 15 (12.5%) had an overall survival (OS) of ≥ 18 months and were considered to be long-term survivors (Table 1).
- Long-term survivors had a median age of 61.0 years (IQR: 49.0–70.5 years) at baseline, 46.7% were female and 66.7% were of white race (Table 1).

Disease characteristics of long-term survivors

- At baseline, approximately half (53.3%) of the long-term survivor group had an Eastern Cooperative Oncology Group Performance Score (ECOG PS) 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 U/mL (IQR: 32.7–1728.4 U/mL) (Table 2).

Table 1. Patient demographics of long-term survivors treated with NALIRIFOX at North American centers in NAPOLI 3

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)
Ethnicity, n (%)		
Hispanic or Latino	2 (13.3)	11 (9.2)
Not Hispanic or Latino	13 (86.7)	105 (87.5)
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)

IQR, interquartile range; ITT, intention-to-treat; OS, overall survival.

- Most long-term survivors had metastatic disease at diagnosis (86.7%). Approximately half of patients (53.3%) had ≥ 3 metastatic sites, most commonly (66.7% of patients) in the liver (Table 2).
- Most long-term survivors (73.3%) were *UGT1A1*28* non-homozygous (Table 2).

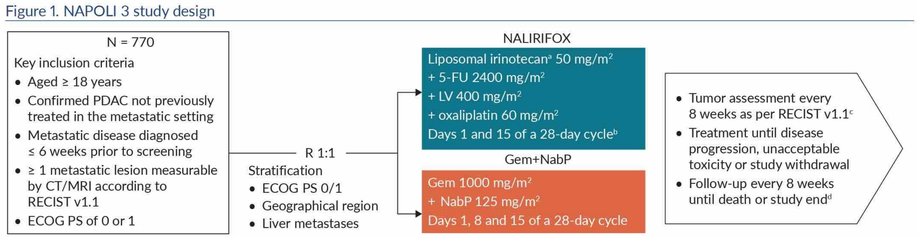
Overall survival

- Among the long-term survivors, mOS was 19.5 months (IQR: 18.8–22.6 months) (Figure 2).

Treatment patterns among long-term survivors

- Most long-term survivors experienced dose reductions and dose delays of both liposomal irinotecan (66.7% and 86.7%, respectively) and oxaliplatin (80% both) (Table 3).

Figure 1. NAPOLI 3 study design



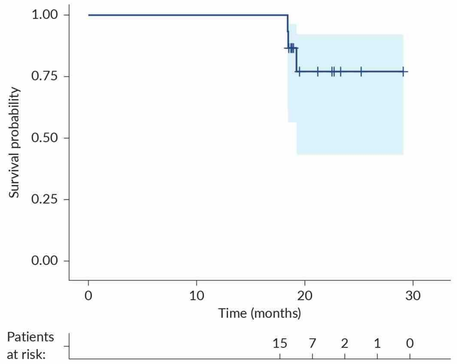
[a]Dose expressed as irinotecan free base equivalent. [b]Administered sequentially as a continuous infusion over 46 hours (dose delays and oxaliplatin discontinuation were permitted). [c]Until progressive disease. [d]The study was complete once all patients had discontinued the study treatment or ≥ 543 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 2. Baseline 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)
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)
Histological grade, n (%)		
Well differentiated	1 (6.7)	6 (5.0)
Moderately differentiated	4 (26.7)	37 (30.8)
Poorly differentiated	3 (20.0)	18 (15.0)
Undifferentiated	1 (6.7)	1 (0.8)
Unknown	6 (40.0)	58 (48.3)
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; OS, overall survival.

Figure 2. Overall survival of long-term survivors



- Median cumulative dose of liposomal irinotecan was 1229.4 mg/m² (IQR: 821.9–1513.9 mg/m²) for long-term survivors and median cumulative dose of oxaliplatin was 962.3 mg/mL (655.0–1470.3 mg/mL) (Table 3).
- Median duration of exposure was 65.1 weeks (IQR: 40.1–89.0 weeks) for liposomal irinotecan and 39.9 weeks (26.6–76.4 weeks) for oxaliplatin (Table 3).

Table 3. Treatment patterns among long-term survivors treated with NALIRIFOX at North American centers in NAPOLI 3

Treatment characteristic	OS ≥ 18.0 months (n = 15)	ITT (n = 120)
Liposomal irinotecan		
Dose reduction, n (%)	10 (66.7)	63 (52.5)
Dose delay, n (%)	13 (86.7)	84 (70.0)
Duration of exposure, weeks		
Median (IQR)	65.1 (40.1–89.0)	23.1 (10.9–44.8)
Cumulative dose, mg/m²		
Median (IQR)	1229.4 (821.9–1513.9)	429.3 (202.7–860.1)
Oxaliplatin		
Dose reduction, n (%)	12 (80.0)	72 (60.0)
Dose delay, n (%)	12 (80.0)	83 (69.2)
Duration of exposure, weeks		
Median (IQR)	39.9 (26.6–76.4)	21.8 (10.9–37.6)
Cumulative dose, mg/m²		
Median (IQR)	962.3 (655.0–1470.3)	481.9 (242.7–920.9)

IQR, interquartile range; ITT, intention-to-treat; OS, overall survival.

Abbreviations 1L, first line; 5-FU, 5-fluorouracil; CA 19-9, carbohydrate antigen 19-9; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; eCRF, electronic case report form; Gem, 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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