Effect of dose adjustments on overall survival in patients with metastatic pancreatic ductal adenocarcinoma treated with NALIRIFOX: a *post hoc* analysis of NAPOLI 3

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KEY LEARNINGS

These data indicate that, in patients who received NALIRIFOX in the NAPOLI 3 trial, dose reductions of liposomal irinotecan or oxaliplatin did not negatively impact OS. This finding supports the potential for treatment optimization in patients who receive first-line NALIRIFOX for the treatment of mPDAC.

BACKGROUND

- NALIRIFOX (liposomal irinotecan in combination with 5-fluorouracil/leucovorin plus oxaliplatin) is an FDA-approved, EMA-approved, and NCCN Category 1-recommended option for the first-line treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC).[1–3]
- Approval was based on the results of the NAPOLI 3 trial (NCT04083235; N = 770), in which NALIRIFOX significantly improved overall survival (OS; 11.1 vs 9.2 months) and progression-free survival (7.4 vs 5.6 months) in patients with previously untreated mPDAC compared with nab-paclitaxel plus gemcitabine (Gem+NabP).[4]
- In the NAPOLI 3 trial, related treatment-emergent adverse events led to a dose reduction in 198 patients (54%) who received NALIRIFOX and 184 patients (49%) who received Gem+NabP.[4]
- The impact of NALIRIFOX dose reductions on OS has not previously been reported.

AIM

- To examine the impact of liposomal irinotecan and oxaliplatin dose reductions on OS in NAPOLI 3.

METHODS

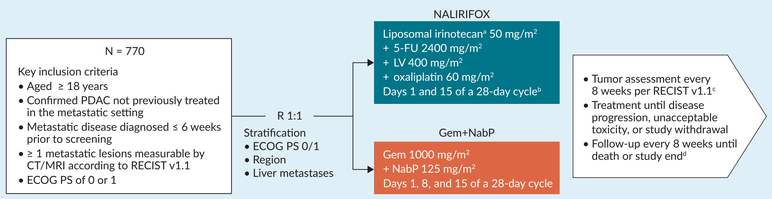
Study design and patients

- NAPOLI 3 was an open-label, randomized, phase 3 trial conducted at 187 sites in 18 countries worldwide (Figure 1).[4]
- The exploratory endpoint for this *post hoc* analysis was OS in patients with and without dose reduction of liposomal irinotecan or oxaliplatin.

Statistical analysis

- OS was defined as time from randomization to death or censoring date and was evaluated using the Kaplan–Meier method; no statistical tests were performed.
- Dose reductions were recorded for the safety population and were analyzed descriptively.

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 and ≥ 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; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

CONCLUSIONS

- The results of this *post hoc* analysis suggest that liposomal irinotecan or oxaliplatin dose reductions do not adversely affect OS.
- Patients with dose reductions of liposomal irinotecan and oxaliplatin had a longer OS, duration of exposure, and higher cumulative dose compared with those who did not.
  - Longer OS may be related to longer time on therapy and an increased likelihood of dose adjustment.
- These data suggest a path forward to further optimize the OS of patients with mPDAC receiving NALIRIFOX.

RESULTS

Patients

- Of the 370 patients who received NALIRIFOX in NAPOLI 3 (safety population), 194 and 217 received dose reductions of liposomal irinotecan and oxaliplatin, respectively (Table 1).

Table 1. Selected demographic and disease characteristics by dose reduction of liposomal irinotecan and oxaliplatin (safety population)

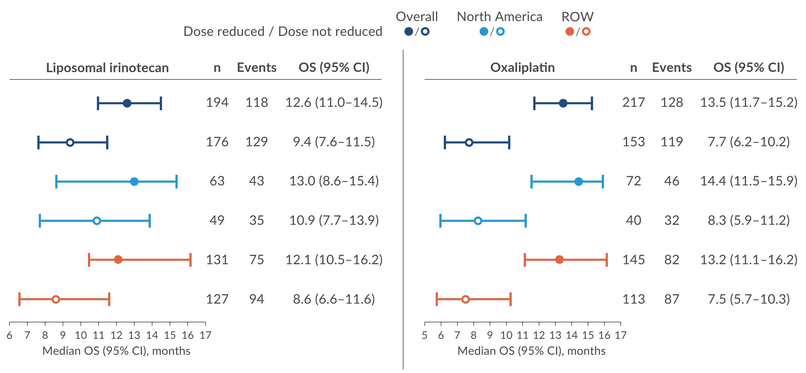
	Overall		North America		Rest of the world	
	Dose not reduced	Dose reduced	Dose not reduced	Dose reduced	Dose not reduced	Dose reduced
Liposomal irinotecan	**n = 176**	**n = 194**	**n = 49**	**n = 63**	**n = 127**	**n = 131**
Age, years, median (range)	64.0 (36.0–81.0)	65.0 (20.0–85.0)	63.0 (43.0–77.0)	66.0 (47.0–85.0)	64.0 (36.0–81.0)	64.0 (20.0–80.0)
Women	70 (39.8)	104 (53.6)	15 (30.6)	32 (50.8)	55 (43.3)	72 (55.0)
ECOG PS score 0	61 (34.7)	94 (48.5)	17 (34.7)	27 (42.9)	44 (34.6)	67 (51.1)
Liver metastases per eCRF	147 (83.5)	148 (76.3)	39 (79.6)	47 (74.6)	108 (85.0)	101 (77.1)
≥ 3 metastatic sites	74 (42.0)	71 (36.6)	23 (46.9)	22 (34.9)	51 (40.2)	49 (37.4)
Oxaliplatin	**n = 153**	**n = 217**	**n = 40**	**n = 72**	**n = 113**	**n = 145**
Age, years, median (range)	64.0 (36.0–81.0)	64.0 (20.0–85.0)	64.0 (43.0–77.0)	65.0 (45.0–85.0)	64.0 (36.0–81.0)	64.0 (20.0–80.0)
Women	58 (37.9)	116 (53.5)	13 (32.5)	34 (47.2)	45 (39.8)	82 (56.6)
ECOG PS score 0	50 (32.7)	105 (48.4)	14 (35.0)	30 (41.7)	36 (31.9)	75 (51.7)
Liver metastases per eCRF	129 (84.3)	166 (76.5)	32 (80.0)	54 (75.0)	97 (85.8)	112 (77.2)
≥ 3 metastatic sites	63 (41.2)	82 (37.8)	17 (42.5)	28 (38.9)	46 (40.7)	54 (37.2)

Data are n (%) unless otherwise stated.
ECOG PS, Eastern Cooperative Oncology Group performance status; eCRF, electronic case report form.

Overall survival

- Patients with dose reductions of liposomal irinotecan or oxaliplatin had longer OS than those without dose reductions; similar results were observed in patients who received treatment in North America and in the rest of the world (Figure 2).
- Median OS was shortest among patients who did not receive a dose reduction of liposomal irinotecan (9.1 months) or oxaliplatin (7.9 months) (Table 2).

Figure 2. Overall survival in patients with and without dose reduction of liposomal irinotecan and oxaliplatin (safety population)



CI, confidence interval; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; OS, overall survival; ROW, rest of world.

Table 2. Median overall survival by lowest dose of liposomal irinotecan and oxaliplatin (safety population)

	Overall survival		
	n	Events	Median (95% CI), months
Lowest dose of liposomal irinotecan			
50 mg/m² (starting dose)	173	129	9.1 (7.5–11.5)
40 mg/m²	118	74	11.8 (10.0–14.4)
32.5 mg/m²	56	30	16.9 (10.4–NE)
25 mg/m²	23	14	13.5 (10.3–NE)
Lowest dose of oxaliplatin			
60 mg/m² (starting dose)	150	117	7.9 (6.3–10.2)
48 mg/m²	116	77	11.7 (9.4–13.9)
39 mg/m²	73	36	17.1 (11.8–NE)
30 mg/m²	30	16	14.4 (12.2–NE)

CI, confidence interval; NE, not estimable.

Treatment exposure and cumulative dose

- Median duration of exposure was longer and cumulative dose was higher among patients who received a dose reduction than among those who did not, for both liposomal irinotecan and oxaliplatin; similar results were observed in patients who received treatment in North America and in the rest of the world (Table 3).

Table 3. Cumulative dose and duration of exposure of liposomal irinotecan and oxaliplatin (safety population)

	Overall		North America		Rest of the world	
	Dose not reduced	Dose reduced	Dose not reduced	Dose reduced	Dose not reduced	Dose reduced
Liposomal irinotecan	**n = 176**	**n = 194**	**n = 49**	**n = 63**	**n = 127**	**n = 131**
Cumulative dose, median (IQR), mg/m²	248.9 (100.0–760.0)	536.0 (295.6–870.1)	403.5 (102.1–809.4)	460.1 (245.9–966.9)	200.9 (99.7–755.0)	544.9 (320.0–824.4)
Duration of exposure at any dose, median (IQR), weeks	10.6 (3.9–35.6)	31.7 (17.1–51.7)	18.1 (4.1–35.0)	25.3 (15.1–53.7)	8.3 (3.0–36.3)	32.1 (18.0–50.1)
Oxaliplatin	**n = 153**	**n = 217**	**n = 40**	**n = 72**	**n = 113**	**n = 145**
Cumulative dose, median (IQR), mg/m²	239.9 (119.1–595.5)	635.6 (360.5–907.3)	327.6 (121.6–628.5)	653.8 (304.9–974.8)	238.1 (60.3–595.4)	635.6 (410.7–860.3)
Duration of exposure at any dose, median (IQR), weeks	8.1 (2.9–23.0)	30.0 (17.3–40.1)	12.1 (3.6–24.7)	25.2 (15.1–43.8)	8.0 (2.1–21.3)	30.1 (18.0–39.7)

IQR, interquartile range.

Reasons for dose reduction and discontinuation

- The most common adverse event (any grade) leading to dose reduction of liposomal irinotecan and oxaliplatin was diarrhea (40% and 36% of patients with dose reductions, respectively).
- The proportion of patients with grade ≥ 3 diarrhea events leading to dose reduction of liposomal irinotecan or oxaliplatin was higher in North America (38% and 35%, respectively) than in the rest of the world (24% and 23%, respectively).
- Among patients who did not receive dose reductions of liposomal irinotecan and oxaliplatin, the most common reasons for treatment discontinuation were disease progression per RECIST (38% and 35%, respectively) and adverse events (19% and 21%, respectively).

Abbreviations EMA, European Medicines Agency; FDA, US Food and Drug Administration; Gem+NabP, nab-paclitaxel plus gemcitabine; mPDAC, metastatic pancreatic ductal adenocarcinoma; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; NCCN, National Comprehensive Cancer Network; OS, overall survival; RECIST, Response Evaluation Criteria in Solid Tumors.

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