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Original Research

Perioperative NALIRIFOX in patients with resectable pancreatic ductal adenocarcinoma: The open-label, multicenter, phase II nITRO trial☆

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ABSTRACT

Background: Upfront surgery followed by postoperative treatment is a commonly adopted treatment for resectable pancreatic ductal adenocarcinoma (rPDAC). However, the risk of positive surgical margins, the poor recovery that often impairs postoperative treatments, and the risk of recurrence might limit the outcome of this strategy. This study evaluated the safety and the activity of liposomal irinotecan 50 mg/m^2 + 5-fluorouracil 2400 mg/m^2 + leucovorin 400 mg/m^2 + oxaliplatin 60 mg/m^2 (NALIRIFOX) in the perioperative treatment of patients with rPDAC.

Methods: Eligible patients had a rPDAC with $< 180°$ interface with major veins' wall. Patients received 3 cycles before and 3 cycles after resection with NALIRIFOX, days 1 and 15 of a 28-day cycle. The primary endpoint was the proportion of patients undergoing an R0 resection.

Results: 107 patients began preoperative treatment. Nine patients discontinued the treatment because of related or unrelated adverse events. Disease-control rate was 92.9%. 87 patients underwent surgical exploration, 11 had intraoperative evidence of metastatic disease, and 1 died for surgical complications. R0 resection rate was 65.3%. 49 patients completed the three postoperative cycles. The most common grade ≥ 3 adverse events were diarrhea and neutropenia. Median overall survival (OS) of ITT patients was 32.3 months (95% CI 27.8–44.3). Median disease-free and OS from surgery of resected patients were 19.3 (95% CI 12.6–34.1) and 40.3 months (95% CI 29-NA), respectively.

Conclusion: Perioperative NALIRIFOX was manageable and active, and deserves further investigation in randomized trials comparing it with standard upfront surgery followed by adjuvant therapy.

☆ Trial registration: ClinicalTrials.gov Identifier: NCT03528785

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1. Introduction

The most commonly adopted treatment for patients diagnosed with resectable pancreatic ductal adenocarcinoma remains initial surgical resection followed by postoperative chemotherapy, whereas there is limited evidence to recommend specific neoadjuvant regimens outside clinical studies. [1] However, despite using the most effective postoperative combination regimen such as mFOLFIRINOX, recurrence of the disease remains common with only a 26.1% disease-free survival (DFS) rate at 5-years. [2] The frequent recurrence of this disease can be attributed mainly to its common and early metastatic diffusion, as well as the fact that a significant number of patients receive an incomplete R1 resection, an event that postoperative treatments cannot mitigate. [3] Furthermore, these results do not represent the overall population of patients diagnosed with resectable disease. It is expected that only around one-third of patients undergoing initial surgical resection receive a postoperative treatment, leading to a large overestimation of the effectiveness of this treatment paradigm. [4].

Therefore, there is a growing interest in challenging the current treatment paradigm by investigating perioperative treatments for patients with resectable pancreatic ductal adenocarcinoma. [5] Recently, three trials have explored the efficacy of standard regimens for the metastatic setting as perioperative treatments for patients with resectable disease, the NEONAX, [6] the SWOG 1505, and the NORPACT-1 study. [7] Although these trials did not meet their primary hypotheses, they provided evidence supporting the safety and effectiveness of perioperative treatments for patients with resectable pancreatic ductal adenocarcinoma. Most importantly, these results highlighted the need for novel and more active treatment regimens to be implemented in this setting.

Liposomal irinotecan (ONIVYDE®, Ipsen) is a nanoliposomal formulation that encapsulates irinotecan hydrochloride in a lipid bilayer vesicle. The nanoliposomal formulation provides an improved therapeutic index if compared to standard free irinotecan at equivalent doses by achieving higher and more sustained levels of the active metabolite SN-38 within the tumors. [8,9] Recently, the combination regimen of liposomal irinotecan with 5FU/LV plus oxaliplatin (NALIRIFOX) showed a clinically meaningful and statistically significant improvement in median overall survival (OS) and progression-free survival (PFS), as well as a manageable safety profile, compared to nab-paclitaxel plus gemcitabine in previously untreated patients with metastatic pancreatic ductal adenocarcinoma in the randomized phase 3 study, NAPOLI 3. [10] These findings support the NALIRIFOX regimen as a new possible reference regimen for the first-line treatment of metastatic pancreatic ductal adenocarcinoma. Consequently, NALIRIFOX has been included in the most recent National Comprehensive Cancer Network guidelines as one of the recommended regimens for the treatment of unresectable pancreatic ductal adenocarcinoma. [1].

The nITRO study was a prospective multicentre phase 2 clinical trial that assessed the safety and the activity of the NALIRIFOX regimen in the perioperative treatment of resectable pancreatic ductal adenocarcinoma with the aim to reduce primary tumor size thereby improving the likelihood of a complete R0 resection, initiate an early treatment of occult micrometastatic disease by administering systemic therapy to a higher percentage of patients and with an improved tolerance compared to a fully postoperative treatment, prevent unnecessary resections in rapidly progressing and chemoresistant diseases, and ultimately enhance survival for patients affected by this disease.

2. Material and methods

2.1. Patients

nITRO was an investigator-initiated, single-arm, phase 2 trial done in two centers in Italy. Eligible patients were aged 18 years or older and had a histological or cytological diagnosis of surgically resectable pancreatic ductal adenocarcinoma, different or mixed histologies were excluded.

Resectability was defined by specialized abdominal radiologists using multiphase spiral contrast-enhanced computed tomography (CT) scans of the chest, abdomen, and pelvis, and magnetic resonance imaging (MRI) scans of the abdomen obtained within 28 days before dosing. Resectable disease was defined as no contact of the major arteries (celiac axis, superior mesenteric artery, or common hepatic artery), no contact with the superior mesenteric vein or portal vein or $\leq 180^{\circ}$ contact without vein contour irregularity, and no metastases (no visceral lesions, no lymphadenopathy outside the surgical basin).

Patients were required to have a Karnofsky performance score (KPS) ≥ 60, adequate bone marrow and liver and renal function. A full list of the eligibility criteria is provided in the study protocol (Supplement 2). All patients provided written informed consent, and the protocol was approved by the ethics committee of the Azienda Ospedaliera Universitaria Integrata di Verona. The study was conducted in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki.

2.2. Treatment and procedures

Patients received a perioperative treatment with three cycles before and three cycles after surgical resection. Every cycle included administration of liposomal irinotecan 50 mg/m^2, oxaliplatin 60 mg/m^2, LV 200 mg/m^2 and 5-FU 2400 mg/m^2 administered sequentially as a continuous infusion over 46 h on days 1 and 15 of a 28 day-cycle.

Patients achieving stable disease or radiological response underwent surgical resection 4–8 weeks after completion of the first three cycles of treatment. Within 4–8 weeks following pancreatectomy, patients received additional three cycles of the same regimen, if they were fit and in the absence of signs of progression.

All patients completed a follow-up assessment after end of the study treatment or permanent discontinuation, after which they entered long-term follow-up (every 3 months) during which survival status was monitored until 36 months after the end of treatment, death, lost to follow-up, withdrawal of consent or study closure.

Tumor response was assessed according to RECIST 1.1. Disease was assessed as defined in the study protocol (Supplement 2). Safety was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [11].

2.3. Outcomes

The primary endpoint was the proportion of patients receiving a margin-free (R0) resection among those undergoing surgical resection. R0 resection has been defined according to the International Study Group of Pancreatic Surgery (ISGPS) and The Royal College of Pathologists (RCPath) guidelines as a resection margin > 1 mm (www.rcpath.org). Tumor clearance was given by pathologists blinded to the treatment for all of the following margins: anterior, posterior, medial, or superior mesenteric groove, superior mesenteric artery, pancreatic transection, bile duct, and enteric. [12] Secondary endpoints are defined in the study protocol (Supplement 2).

2.4. Statistical analysis

A Simon's two-stage design has been used. The target sample size was calculated to be 72 to detect an absolute improvement in R0 resection rate of 15% compared with the local historical rate of 40% by using the same guidelines. In the first stage, 39 patients underwent surgical resection. If there were 17 or fewer R0 resections in these patients, the futility threshold would be reached and the study would be stopped. Otherwise, additional patients would be accrued for a total of 72 resections. The null hypothesis would be rejected if 36 or more R0 resections were observed in 72 patients undergoing resection. This design yields a type I error rate of 0.05 and power of 0.8 when the true

R0 resection rate is 55%.

DFS, OS, and 95% confidence interval (CI) were estimated using the Kaplan-Meier method. Median follow-up time was calculated using the reverse Kaplan-Meier method. For the survival analysis, patients without a recorded death or progression were censored on the date of the last follow-up visit.

All statistical analyses were performed using "survival" package in R version 4.2.2 (https://www.r-project.org). This study is registered with clinicaltrials.gov, NCT03528785, and enrolment is completed.

3. Results

3.1. Patients and treatment

Between May 2018 and May 2022, 107 patients were enrolled and formed the intention-to-treat population. The overall recruitment rate for the study was 2.27 patients per month, and was not significantly affected by the Covid-19 pandemic emergency (Supplementary Fig. 1).

The median age of the patients was 63 years (range 31–77); the large majority of them had an optimal performance status (KPS≥90%= 96.2%) and had an adenocarcinoma of the head of the pancreas (85.9%). Further baseline demographics and clinical characteristics are shown in Table 1. Sixty-nine patients (64.4%) at diagnosis or during the preoperative phase presented with jaundice which was palliated with the placement of a plastic (21.7%) or metallic (60.0%) stent.

In the intention-to-treat population, 98 (91.6%) patients received at least 3 doses of preoperative NALIRIFOX to be considered evaluable, and 86 (80.4%) completed all the three planned preoperative cycles (6 doses) (Fig. 1).

Nine patients discontinued the treatment before radiological reassessment in the preoperative phase. Two patients discontinued because of toxicities related to the treatment, and then were found to be homozygous for the UGT1A1 * 28 allele. One patient died because of febrile neutropenia and sepsis related to the treatment, he was then found to be heterozygous for the UGT1A1 * 28 allele. Two patients discontinued because of recurrent cholangitis, and two patients died because of complication related to the biliary drainage. One patient died for complication not related to the treatment. One patient withdrew the consent to the study.

Among the 98 radiologically evaluable patients, 1 (1.0%) patient obtained a complete response, 22 (22.4%) a partial response, and 68 (69.4%) a stable disease, accounting for a disease control rate of 92.9%.

Table 1
Demographic and disease characteristics at baseline in the intention-to-treat and the resected populations. KPS= Karnofsky performance status. BMI= body mass index.

Baseline characteristics		intention-to-treat (n = 107)	resected (n = 75)
Sex, n (%)	male	58 (54.3)	35 (46.7)
	female	49 (45.8)	40 (53.3)
Age (y), median (range)		63 (31–77)	62 (31–77)
KPS, n (%)	≥ 90	103 (96.2)	72 (96)
	< 90	4 (3.8)	3 (4)
Pancreatic tumor location, n (%)	Head	92 (85.9)	62 (82.7)
	Body/ tail	15 (14.1)	14 (17.3)
BMI (kg/m2)	Median	24.7	24.7
Ca19.9 (U/mL)	Median	119 (2–5710)	82 (8–2191)
Ca19.9 (U/mL), n (%)	≥ 39	76 (71.0)	51 (68)
	< 39	31 (29.0)	24 (32)
Clinical T stage	1	20 (18.9)	15 (20)
	2	81 (75.8)	58 (77.3)
	3	6 (5.6)	2 (2.7)
Clinical N stage	0	66 (61.6)	44 (58.7)
	1	41 (38.4)	31 (41.3)
	2	0	0

Seven (7.1%) patients showed progressive disease at the preoperative radiological assessment.

Among the 68 patients with a stable disease, 1 showed a clinical progression and 3 were defined as not resectable by surgeons at imaging re-evaluation because of a tumor volume increase not sufficient to qualify as a RECIST progressive disease.

Within the population of evaluable patients, 87 underwent surgical exploration. Eleven patients had intraoperative evidence of unresectable or metastatic disease, and 1 died for intraoperative complications. Ultimately, 75 patients underwent tumor resection, and 49 achieved a R0 resection accordingly to the stringent guidelines adopted, accounting for an R0 resection rate of 65.3% (95% CI 54.5–76.1), largely exceeding the alternative hypothesis of 55% (Table 2). Most of resected tumors were pT1 or pT2, and about one third had negative lymph nodes. Further pathological characteristics are shown in Table 2.

Fifty-nine patients (78.7% of total resected patients) started the postoperative treatment and 49 (65.3% of total resected patients) completed all the three pre-planned cycles. Median time from surgery to start of postoperative phase was 56 days. Subsequent adjuvant radiotherapy was per protocol permitted and was performed in 12 of those 26 patients who received an R1 resection.

3.2. Efficacy

Estimating OS in the intention-to-treat population, a total of 51 events occurred during a median follow-up period of 33.1 months (IQR 23.1–43.6). Median OS duration calculated from the date of enrollment in this population was 32.3 months (95% CI 27.8–44.3) and the 2-years survival was 83.3% (95% CI 74.7%−92.9%, Fig. 2A). Median PFS was 17.2 months (95% CI 14.6–24.1). Median DFS and OS of resected patients calculated from the date of surgery were 19.3 (95% CI 12.6–34.1) and 40.3 months (95% CI 29-NA), respectively (Fig. 2B and C). To estimate the impact of resection and R status on survival, we employed a landmark analysis at 5 months, when approximately 85% of resections had already been performed. PFS and OS in patients who did not undergo surgery, were 8.0 (95% CI 5.7–10.7) and 13.8 months (95% CI 6.7–23.9), respectively (Supplementary Fig. 2A and 2B,). Median DFS after R0 or R1 resections were 30.8 and 12.6 months, respectively (log-rank test $P = 0.02$; (Supplementary Fig. 3A). Median OS was not reached in R0 group, and 24 months OS was 82.2% (95% CI 70.9%−95.3%) for R0 patients and 63.9% (95% CI 46.5%−87.8%) for R1 patients (log-rank test $P = 0.07$; Supplementary Fig. 3B). We measured a significant association between Ca19.9 at baseline and the risk of death (Supplementary Table 1 and Supplementary Fig. 4).

3.3. Safety

In the intention-to-treat population, the most common grade ≥ 3 adverse events were diarrhea (10.3%), neutropenia (13.1%), hypokalemia (7.5%), cholangitis (7.5%) and mucositis (6.5%) in the preoperative phase. Similarly, in the postoperative phase, grade ≥ 3 neutropenia, mucositis, hypokalemia and diarrhea were found in 10.2%, 8.5%, 6.8% and 5.1% of the patients, respectively (Table 3). One patient died for treatment-related neutropenia and sepsis in the preoperative phase. Granulocyte colony-stimulating factors were needed in sixty out of 107 (72.0%) patients in the preoperative and 37 out of 59 (62.7%) patients in the postoperative phase.

4. Discussion

The nITRO trial was designed to test the hypothesis that the perioperative treatment with the novel regimen NALIRIFOX could increase the rate of a complete R0 resection compared to a historical control in patients with resectable pancreatic ductal adenocarcinoma undergoing resection. This investigator-initiated, single-arm, phase 2 trial met its primary endpoint by demonstrating an R0 resection rate of 65.3%

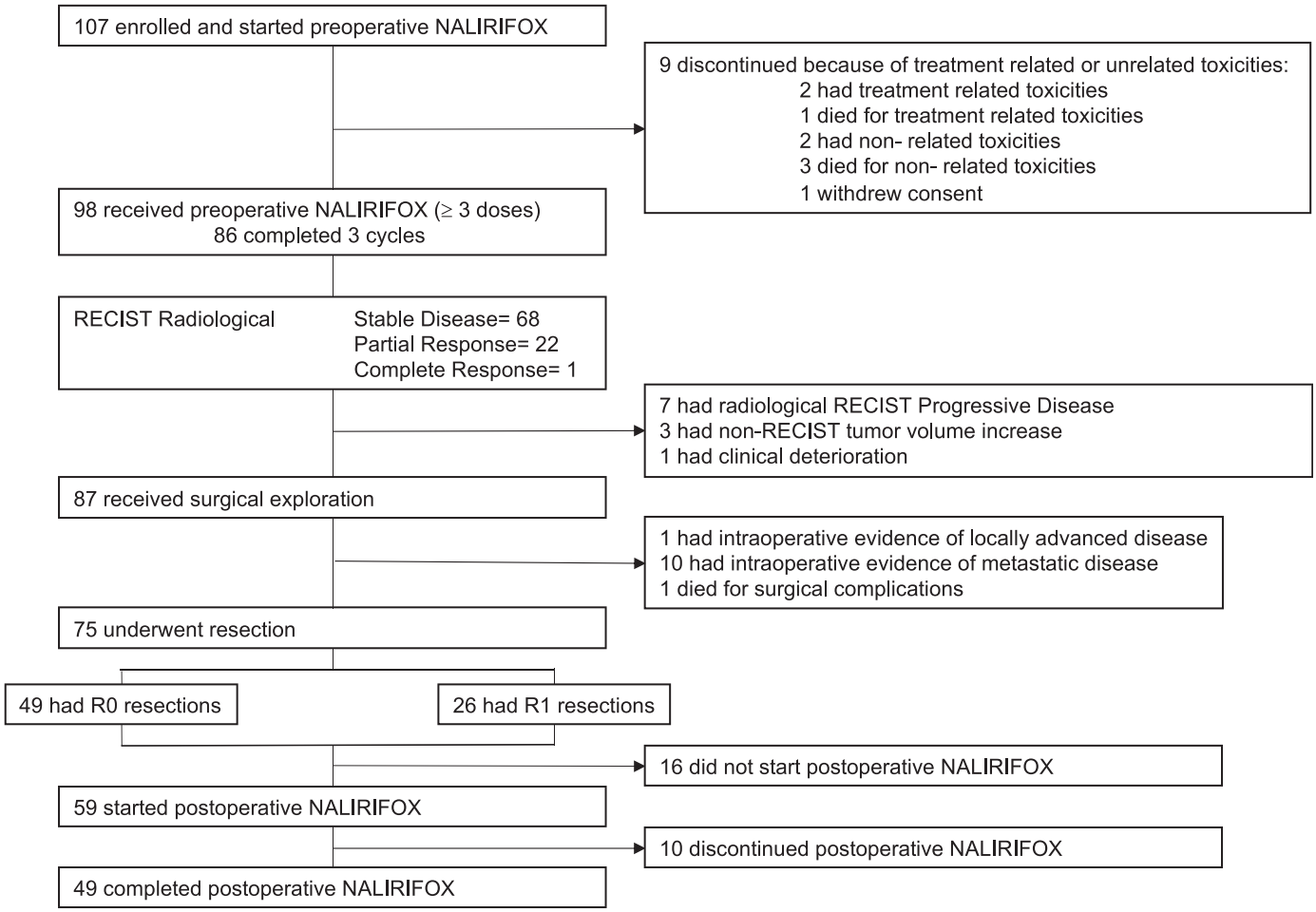

Fig. 1. Trial profile. NALIRIFOX= liposomal irinotecan plus 5-fluorouracil/ leucovorin and oxaliplatin. RECIST= Response Evaluation Criteria in Solid Tumours. R0 = resection margin ≥ 1 mm. R1 = resection margin < 1 mm. CT, computer tomography. MRI, magnetic resonance imaging.

Table 2
Surgical characteristics, resection margin status, and pathological stage in patients with successful resection. PP-DCP= Pylorus Preserving DuodenoCephaloPancreasectomy.

		n (%)
Surgery	Open	73 (96%)
	Robotic	3 (4%)
Vascular resection	Yes	13 (17.1%)
	No	63 (82.9%)
Type of operation	PP-DCP	61 (80.2%)
	Distal pancreatectomy	14 (18.4%)
	Total pancreatectomy	1 (1.3%)
Resection margin	R0	49 (65.3)
	R1	26 (34.7)
Tumor staging	pT0	3 (4)
	pT1	30 (40.0)
	pT2	35 (46.7)
	pT3	4 (5.3)
	pT4	3 (4)
Lymph node staging	pN0	24 (32.0)
	pN1	29 (38.7)
	pN2	22 (29.3)

accordingly to the stringent ISGPS/RCPath guidelines adopted.

Several aspects that limit the effectiveness of the conventional approach of using upfront surgery followed by postoperative therapy might be overcome by a perioperative strategy. [13] However, two are the main concerns regarding this approach. Firstly, there is the risk that tumor progression during these treatments could render the more chemoresistant tumor unresectable, thus eliminating the possibility of surgical intervention. Secondly, patients may experience clinical deterioration or encounter toxicities that could result in missing the opportunity for resection, thereby depriving them of a chance for a cure. [14] Among the 107 patients who started preoperative NALIRIFOX, 20 patients (18.7%) did not undergo surgical exploration. Among these patients, 7 had a radiological progression according to RECIST criteria, and 3 had a tumor volume increase not sufficient to be qualified as a progressive disease. It is conceivable that these patients developing tumor progression within the first 3 cycles of preoperative treatment with this active regimen would have a chemoresistant disease the invariably had a limited chance of a curative resection and a poor prognosis in preventing or treating any recurrent disease. These results compare favorably with those reported in SWOG 1505 trial, which is the most closely comparable study that investigated the use of mFOLFIRINOX or gemcitabine plus nab-paclitaxel with a perioperative schedule and in a similar population of patients with resectable pancreatic ductal adenocarcinoma. In SWOG 1505 trial, 22.6% of patients starting mFOLFIRINOX and 28.9% of those starting gemcitabine plus nab-paclitaxel did not receive a surgical exploration for toxic effects, clinical deterioration, or progression during the preoperative treatment period. [15] The response rates for mFOLFIRINOX and gemcitabine plus nab-paclitaxel were 9% and 21%, respectively. In the radiologically evaluable patients for this present study, a response rate of 23.4% was observed after 3 cycles of NALIRIFOX. Nonetheless, it is important to acknowledge that nine patients discontinued the treatment before radiological reassessment in the preoperative phase because of treatment-related or unrelated toxicities,

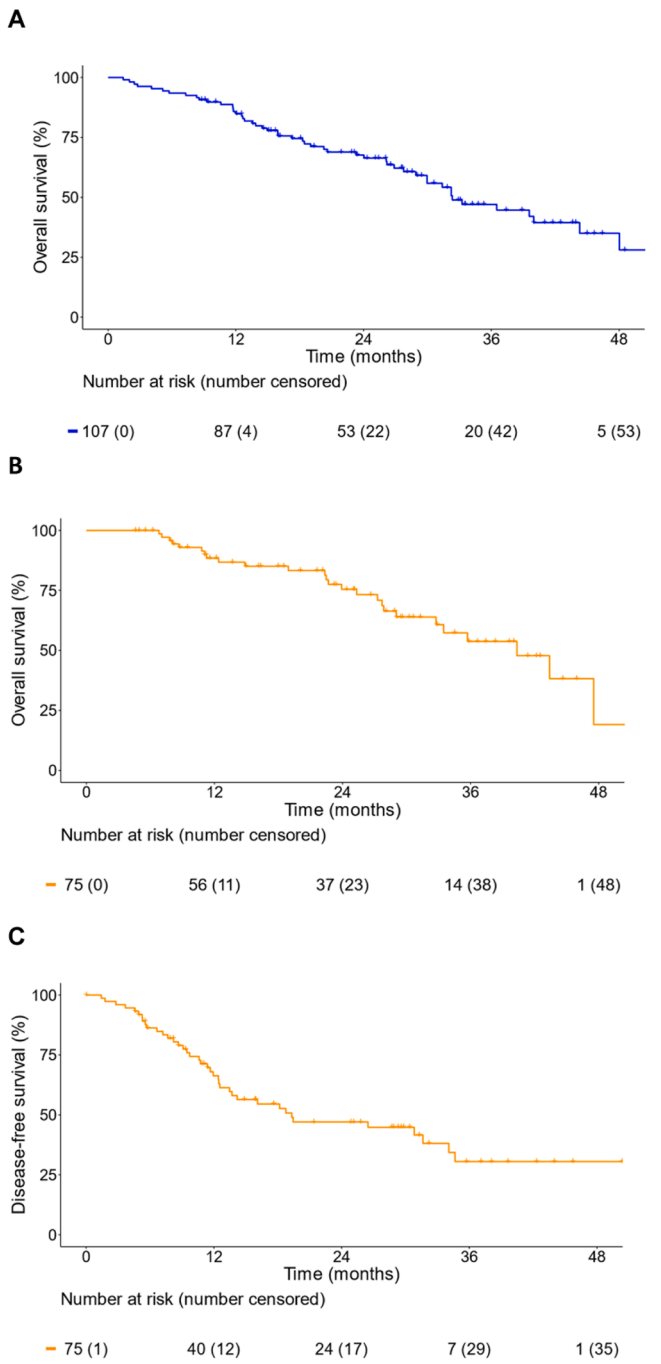

Fig. 2. Kaplan-Meier plots of A. overall survival in the intention-to-treat population; B overall survival, and C. disease-free survival from date of surgery in patients underwent resection. Cross symbols indicate censoring.

and one patient had a clinical deterioration that excluded the surgical exploration. Among these patients, two patients discontinued the treatment, and two patients died because of complication related to the biliary drainage. These adverse events correlated to biliary drainage represent however only the 5.8% of patients presenting or developing jaundice, thus we cannot generalize that icteric patients should be excluded by preoperative strategies. Nevertheless, particular attention should be given to the utilization of metallic stents instead of plastic ones in order to minimize these complications. Among the 9 patients who discontinued preoperative treatment, two were identified as heterozygous for the UGT1A1 * 28 allele. One patient who was found to be homozygous for the *UGT1A1 * 28* allele died because of febrile

Table 3
Adverse events on study. Adverse events of any cause with an incidence > 5% in patients receiving NALIRIFOX in the preoperative and postoperative phase in the safety population.

Toxicity	Preoperative phase		Postoperative phase	
	Any grade – n (%)	G3-G4 – n (%)	Any grade – n (%)	G3-G4 – n (%)
Diarrhea	45 (42.1)	11 (10.3)	13 (22)	3 (5.1)
Neutropenia	39 (36.4)	14 (13.1)	15 (25.4)	6 (10.2)
Fatigue	35 (32.7)	5 (4.7)	6 (10.2)	3 (5.1)
Nausea	28 (26.2)	4 (3.7)	8 (13.6)	2 (3.4)
Hypokaliemia	21 (19.6)	8 (7.5)	11 (18.6)	4 (6.8)
Mucositis	18 (16.8)	7 (6.5)	9 (15.3)	5 (8.5)
Fever	16 (15.0)	2 (1.9)	-	-
Jaundice	13 (12.1)	4 (3.7)	-	-
Abdominal pain	12 (11.2)	1 (0.9)	4 (6.8)	0
Cholangitis	8 (7.5)	8 (7.5)	-	-
ALT increase	8 (7.5)	3 (2.8)	3 (5.1)	1 (1.7)
Vomiting	6 (5.6)	1 (0.9)	4 (6.8)	0
Asthenia	-	-	6 (10.2)	0
Steatorrhea	-	-	4 (6.8)	0
AST increase	-	-	4 (6.8)	0

neutropenia and sepsis related to the treatment. The *UGT1A1 * 28* heterozygous and homozygous genotypes are associated to a reduced expression of UGT1A1. However current prescribing guidelines recommend the same starting dose of 50 mg/m^2 liposomal irinotecan for homozygous patients, as used in this study. [16].

The primary endpoint chosen for this current trial was the rate of R0 resections, that is an indicator of activity for the regimen investigated and has a recognized prognostic value. [3] Reported rates for microscopic tumor involvement of the resection margin can vary widely across different studies due to differences in the definition of pathologic criteria for tumor involvement used. While the American Joint Commission on Cancer (AJCC) 7th edition criteria define positive resection margins only when tumor cells are present at the edges of the specimen (tumor clearance 0 mm), [17,18] the European criteria of the ISGPS/RCPath require a microscopic tumor clearance of at least 1 mm in all transections and circumferential margins to confirm radicality. [12] When this last criteria is applied, the rate for negative resection margins in retrospective and prospective studies is usually lower than 30%. [19] In this present study we adopted the more stringent criteria of the ISGPS/RCPath and measured a meaningful R0 resection rate of 65.3%. In comparison, the R0 resection rates measured in patients treated in the SWOG 1505 trial using the AJCC criteria were 85%. [20] However, the limited prognostic value of this pathologic criteria is reflected by the modest median DFS of patients treated with mFOLFIRINOX or gemcitabine plus nab-paclitaxel of 10.9 and 14.2 months, respectively. [15] In our study, we measured a median DFS in the population of patients who underwent resection of 19.3 months and of 30.8 months in those achieving a margin negative R0 resection, indicating an important prognostic value for ISGPS/RCPath margins criteria. These pieces of evidence contribute to reinforcing the concept that studies that failed to find prognostic value in the resection status may have had an inadequate assessment of R0 resection. [21].

The most critical factor for enhancing the survival rate of patients who have undergone resection of pancreatic ductal adenocarcinoma is their ability to receive adjuvant chemotherapy. However, comprehensive analysis has demonstrated that initiation and completion of adjuvant chemotherapy after upfront surgical resection can occur infrequently, in only 35% and 7% of the patients, respectively. [4] Among the 107 patients included in the intention-to-treat population of this present study, 86 (80.4%) completed all the three preoperative cycles, and 49 (45.8%) completed the whole perioperative treatment. This is in line with the 49% and 40% of patients who completed all treatments in the mFOLFIRINOX or the gemcitabine plus nab-paclitaxel in the SWOG 1505 trial, respectively. [15] These results suggest that a

perioperative strategy may increase the likelihood of a greater number patients receiving and successfully completing systemic chemotherapy.

The median OS duration for patients in the intention-to-treat population in this study was 32.3 months, which compares favorably with the 23.2 and 23.6 months reported in the SWOG 1505 trial for perioperative mFOLFIRINOX or gemcitabine plus nab-paclitaxel, respectively. [15] The median OS in our study compares favorably also with the 25.1 months reported for the short-course neoadjuvant FOLFIRINOX in the NORPACT-1 trial. [7].

In previous studies in the advanced setting, NALIRIFOX demonstrated a manageable safety profile. In the NAPOLI 3 study, NALIRIFOX was responsible for an higher rate of serious gastrointestinal toxicities than did nab-paclitaxel plus gemcitabine, with diarrhea being the most common grade ≥ 3 adverse event in 20.3% of patients. [10] In the nITRO trial, diarrhea was less frequent (10.3%) with the perioperative schedule of NALIRIFOX trial than with the continuous one of NAPOLI 3 study. Of note, no patients reported grade > 2 peripheral neuropathy. This figure compares favorably with that of mFOLFIRINOX arm in the SWOG 1505 trial, where 16.1% of patients receiving the post-operative chemotherapy experienced grade ≥ 3 peripheral sensory neuropathy. [15].

One of the main limitations is that the study was not designed as a randomized controlled trial. There was no active comparator standard arm, such as upfront surgery followed by postoperative mFOLFIRINOX according to the PRODIGE 24 trial. [2] However, the size of the population enrolled in this single-arm study is comparable to that of previous randomized trials in this same setting, [6,15] which strengthens the reliability of the observations made about the safety and activity of the NALIRIFOX regimen in this setting. Another limitation is the short follow-up period of 33.1 months. While this follow-up duration is adequate to draw conclusions about the activity of the regimen, it may not be sufficient to draw definitive conclusions about long-term survival outcomes, especially in R0 resected patients.

5. Conclusions

In conclusion, this study demonstrated the safety and the activity of NALIRIFOX for patients with resectable pancreatic ductal adenocarcinoma. Perioperative NALIRIFOX allows to select those patients who may benefit from resection to the largest extent. Two phase 3 trials are currently comparing perioperative with adjuvant mFOLFIRINOX in patients with resectable PDAC (NCT04340141, NCT04927780). Perioperative NALIRIFOX deserves further investigation in randomized trials comparing it with standard upfront surgery followed by standard adjuvant mFOLFIRINOX therapy.

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Role of the funder/sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional contributions

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CRediT authorship contribution statement

Drs Melisi, Zecchetto, Merz and Fazzini had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Melisi. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Melisi, Merz, Fazzini. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Fazzini. Obtained funding: Melisi. Supervision: Melisi.

Declaration of Competing Interest

DM received honoraria as an advisory board member or consultant from Servier, Incyte, iOnctura, Eli Lilly, Evotec, Baxter; received institutional support for research project from Shire, Celgene, Incyte, iOnctura, Roche. GM received honoraria as consultant from Oncosil, and institutional support for research project from Fibrogen. MDO received honoraria as an advisory board member or consultant from Bracco Diagnostics, Siemens Healthcare Diagnostic, Hitachi, Novartis. RdR received honoraria as an advisory board member or consultant from Bracco Diagnostics and Fujifilm. AS received honoraria as an advisory board member or consultant from Incyte, MSD, Amgen, GlaxoSmithkline. All other authors have declared no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113430.

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