NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial

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For the plain language summary see Online for appendix 1

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Summary

Background Pancreatic ductal adenocarcinoma remains one of the most lethal malignancies, with few treatment options. NAPOLI 3 aimed to compare the efficacy and safety of NALIRIFOX versus nab-paclitaxel and gemcitabine as first-line therapy for metastatic pancreatic ductal adenocarcinoma (mPDAC).

Methods NAPOLI 3 was a randomised, open-label, phase 3 study conducted at 187 community and academic sites in 18 countries worldwide across Europe, North America, South America, Asia, and Australia. Patients with mPDAC and Eastern Cooperative Oncology Group performance status score 0 or 1 were randomly assigned (1:1) to receive NALIRIFOX (liposomal irinotecan 50 mg/m², oxaliplatin 60 mg/m², leucovorin 400 mg/m², and fluorouracil 2400 mg/m², administered sequentially as a continuous intravenous infusion over 46 h) on days 1 and 15 of a 28-day cycle or nab-paclitaxel 125 mg/m² and gemcitabine 1000 mg/m², administered intravenously, on days 1, 8, and 15 of a 28-day cycle. Balanced block randomisation was stratified by geographical region, performance status, and liver metastases, managed through an interactive web response system. The primary endpoint was overall survival in the intention-to-treat population, evaluated when at least 543 events were observed across the two treatment groups. Safety was evaluated in all patients who received at least one dose of study treatment. This completed trial is registered with ClinicalTrials.gov, NCT04083235.

Findings Between Feb 19, 2020 and Aug 17, 2021, 770 patients were randomly assigned (NALIRIFOX, 383; nab-paclitaxel–gemcitabine, 387; median follow-up 16·1 months [IQR 13·4–19·1]). Median overall survival was 11·1 months (95% CI 10·0–12·1) with NALIRIFOX versus 9·2 months (8·3–10·6) with nab-paclitaxel–gemcitabine (hazard ratio 0·83; 95% CI 0·70–0·99; p=0·036). Grade 3 or higher treatment-emergent adverse events occurred in 322 (87%) of 370 patients receiving NALIRIFOX and 326 (86%) of 379 patients receiving nab-paclitaxel–gemcitabine; treatment-related deaths occurred in six (2%) patients in the NALIRIFOX group and eight (2%) patients in the nab-paclitaxel–gemcitabine group.

Interpretation Our findings support use of the NALIRIFOX regimen as a possible reference regimen for first-line treatment of mPDAC.

Funding Ipsen.

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Introduction

Pancreatic ductal adenocarcinoma remains one of the most lethal malignancies, with an estimated 5-year survival of only 3% for patients diagnosed with metastatic disease.[1,2] In the past decade, two combination chemotherapy regimens, a quadruplet of fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) and a doublet, nab-paclitaxel and gemcitabine, have emerged as first-line standard of care.[3–5] However, these regimens have never been compared directly leaving uncertainty about the optimal treatment regimen. With the exception of microsatellite instability-high pancreatic cancer, immune checkpoint inhibitors have demonstrated only partial benefits, and although there has been much interest in using genomic profiling to improve outcomes, relatively few patients are eligible to receive molecularly targeted agents.[6–8] The poor prognosis and low number of treatment options available for most patients highlight the need for further research to compare efficacious and tolerable new treatment approaches, and to maximise the benefits of cytotoxic chemotherapy regimens.

Irinotecan is a topoisomerase I inhibitor acting mainly via its active metabolite, SN-38.[9] Liposomal irinotecan

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Research in context

Evidence before this study

Evidence around these trials was gathered from clinical guidelines and clinical experience; therefore no systematic search was undertaken. In the past decade, two combination chemotherapy regimens, fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) and nab-paclitaxel and gemcitabine, have emerged as first-line standard of care for patients with metastatic pancreatic ductal adenocarcinoma. In phase 3 trials, FOLFIRINOX and nab-paclitaxel and gemcitabine have each been compared with gemcitabine alone, but the two regimens have never been compared head to head, leaving uncertainty about the optimal first-line treatment option. Liposomal irinotecan is a liposomal formulation that encapsulates irinotecan, a topoisomerase I inhibitor, in a lipid bilayer vesicle. Encapsulation allows irinotecan to remain in circulation for longer than unencapsulated (free) irinotecan before conversion to its active metabolite, SN-38. Thus, at equivalent doses, liposomal irinotecan demonstrates higher and sustained intratumoural levels of irinotecan and SN-38 relative to free irinotecan. In a phase 1/2 trial (NCT02551991) liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin (NALIRIFOX), demonstrated promising antitumour activity in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma.

Added value of this study

To our knowledge, NAPOLI 3 is the first phase 3 trial, performed in community and academic centres worldwide, to compare two combination chemotherapy regimens head to head in patients with pancreatic ductal adenocarcinoma who have not previously received treatment for metastatic disease. Before NAPOLI 3, decisions as to the optimal combination chemotherapy regimen for most patients were based on cross-trial comparisons. As well as comparing with a standard-of-care regimen, NAPOLI 3 had fewer restrictions on eligibility than most phase 3 pancreatic cancer trials, for example no upper age restrictions and no exclusion for patients with clinical ascites. Before NAPOLI 3, the last trial to meet the primary endpoint of overall survival in patients with metastatic pancreatic ductal adenocarcinoma was the MPACT trial in 2013, which led to the approval of first-line nab-paclitaxel and gemcitabine with a median overall survival of 8·5 months. The NALIRIFOX regimen provides a new reference standard on which to base further improvements in the future.

Implications of all the available evidence

The findings of this study support the use of the NALIRIFOX regimen as a new possible standard of care and reference regimen for the first-line treatment of patients with metastatic pancreatic ductal adenocarcinoma.

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(ONIVYDE, ONIVYDE pegylated liposomal; historical names include nal-IRI, MM 398, or PEP02; Ipsen, Cambridge, MA, USA) is a liposomal formulation that encapsulates irinotecan in a lipid bilayer vesicle. Encapsulation allows irinotecan to remain in circulation for longer than unencapsulated (free) irinotecan before conversion to SN-38. Thus, at equivalent doses, liposomal irinotecan demonstrates higher and sustained intratumoural levels of irinotecan and SN-38 relative to free irinotecan.[10,11] Data from a pilot study of liposomal irinotecan in patients (n=13) with refractory advanced solid tumours reported five-fold higher levels of SN-38 in tumour biopsy samples than in plasma 72 h after dosing, suggesting local metabolic activation of irinotecan to SN-38.[12]

In the phase 3 NAPOLI 1 trial, liposomal irinotecan in combination with fluorouracil and leucovorin significantly prolonged overall survival versus fluorouracil and leucovorin in patients with metastatic pancreatic ductal adenocarcinoma whose disease had progressed following gemcitabine-based therapy.[13] A phase 1/2 trial (NCT02551991) demonstrated promising antitumour activity with liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin (NALIRIFOX) in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma. Median progression-free survival was 9·2 months (95% CI 7·69–11·96) and overall survival was 12·6 months (8·74–18·69).[14]

Building on these findings, the phase 3 NAPOLI 3 study (NCT04083235) aimed to compare NALIRIFOX with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma not previously treated in the metastatic setting.

Methods

Study design and participants

NAPOLI 3 was a randomised, open-label, phase 3 study conducted at 187 community and academic centres in 18 countries worldwide across Europe, North America, South America, Asia, and Australia (appendix 2 p 16). The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice and the requirements of the US Food and Drug Administration or local regulatory authorities regarding the conduct of human clinical trials. The protocol was approved by the local institutional review board and independent ethics committees of the participating centres. Protocol amendments made after the study started are described in the protocol.

See Online for appendix 2

For the **protocol** see https://s3.eu-west-2.amazonaws.com/ox.files/Protocol.pdf

Eligible participants were aged 18 years or older with histologically or cytologically (according to the eighth edition of the American Joint Committee on Cancer staging manual)[15] confirmed pancreatic ductal adenocarcinoma previously untreated in the metastatic setting. Patients who received previous treatment for pancreatic

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ductal adenocarcinoma with chemotherapy in the adjuvant setting were excluded; however, those who had received their last dose of adjuvant therapy more than 12 months before study entry and who had no persistent treatment-related toxicity were eligible. Patients had to have one or more metastatic tumours measurable with CT or MRI according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1[16] and an Eastern Cooperative Oncology Group performance status score of 0 or 1. The initial diagnosis of metastatic disease must have occurred within the 6 weeks before screening. Full eligibility criteria are provided in appendix 2 (pp 10–12). Patients provided written informed consent at screening.

Randomisation and masking

In this open-label NAPOLI 3 study, patients were randomly assigned (1:1) to receive NALIRIFOX or nab-paclitaxel and gemcitabine, stratified by geographical region (North America *vs* east Asia *vs* the rest of the world), performance status (Eastern Cooperative Oncology Group performance status score of 0 *vs* 1), and liver metastases (yes *vs* no). The randomisation scheme was prepared using block randomisation via a third party, and randomisation was performed by a third party by means of an integrated interactive voice response or web response system.

Procedures

Patients received NALIRIFOX (liposomal irinotecan 50 mg/m², oxaliplatin 60 mg/m², leucovorin 400 mg/m², and fluorouracil 2400 mg/m², administered sequentially as a continuous intravenous infusion over 46 h) on days 1 and 15 of a 28-day cycle, or nab-paclitaxel 125 mg/m² and gemcitabine 1000 mg/m², administered intravenously, on days 1, 8, and 15 of a 28-day cycle.

Tumour evaluations were performed by CT or MRI at screening (baseline) and every 8 weeks until progressive disease using RECIST version 1.1. In patients without disease progression at the time of treatment discontinuation, tumour evaluations were performed every 8 weeks during follow-up until progressive disease, or until the start of another anticancer treatment, whichever came first.

Treatment continued until radiologically determined disease progression (as per RECIST version 1.1)[16] or unacceptable toxicity as assessed by individual investigators. Patients completed a 30-day follow-up assessment after permanent discontinuation of study treatment, then entered long-term follow-up (every 2 months) during which survival status was monitored until death, loss to follow-up, withdrawal of consent, or study closure, whichever occurred first. Details are in appendix 2 (p 13). Full details of study procedures and schedules can be found in the protocol.

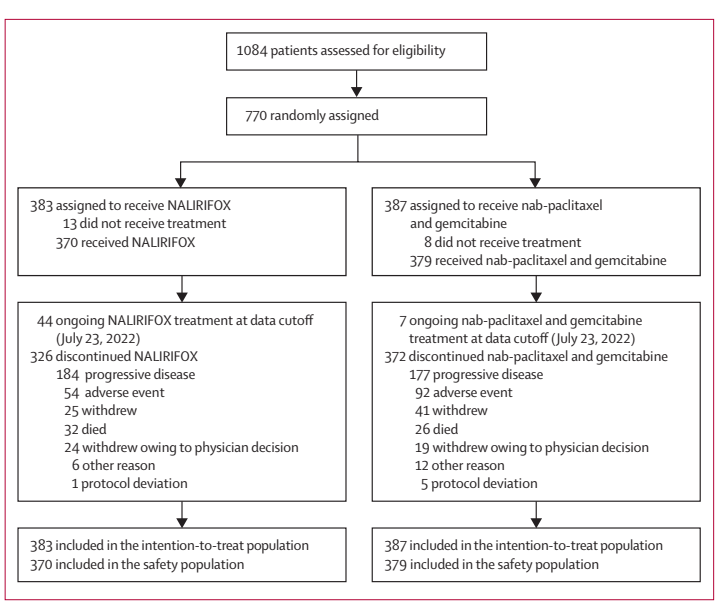

Figure 1: **Trial profile**
NALIRIFOX=liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin.

Outcomes

The primary outcome was overall survival for NALIRIFOX versus nab-paclitaxel and gemcitabine, defined as the number of months from randomisation to the date of death owing to any cause. Secondary outcomes were progression-free survival (time from randomisation to first documented disease progression using RECIST version 1.1 by investigator review or death due to any cause, whichever occurred first) and overall response rate (proportion of patients with a best overall response of partial or complete response) classified using RECIST version 1.1 by investigator review. Details of the per-protocol study endpoints are in appendix 2 (pp 13–14).

Adverse events were recorded and coded using the Medical Dictionary for Regulatory Activities (version 25.0), and severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).[17]

Statistical analysis

The primary endpoint of overall survival was evaluated when at least 543 events were observed across the two treatment groups to provide at least 90% power to detect a hazard ratio (HR) of 0·75 with an overall two-sided type one error level of 0·05. The planned sample size was 750 patients and could be increased if a review of accumulating overall survival events suggested that timing of the final analysis be extended. Assuming median overall survival was 12 months in the NALIRIFOX group and 9 months in the nab-paclitaxel and gemcitabine group,[3,4,13] a total of 543 events were needed to detect an HR of 0·75 with 90% power at a two-sided alpha level of 5%. The Hwang-Shih-DeCani method was used to control the type I error and was utilised with respective

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	NALIRIFOX (n=383)	Nab-paclitaxel and gemcitabine (n=387)
Age, years		
Mean (SD)	62·8 (9·7)	64·0 (8·3)
Median (range; IQR)	64·0 (20–85; 57–70)	65·0 (36–82; 59–70)
Sex		
Female	179 (47%)	157 (41%)
Male	204 (53%)	230 (59%)
Race		
White	315 (82%)	324 (84%)
Asian	20 (5%)	18 (5%)
Black or African American	12 (3%)	7 (2%)
Other	7 (2%)	6 (2%)
Multiple	3 (1%)	0
American Indian or Alaska Native	0	2 (1%)
Native Hawaiian or other Pacific Islander	0	1 (<1%)
Not reported	26 (7%)	29 (7%)
ECOG performance status score		
0	160 (42%)	168 (43%)
1	222 (58%)	219 (57%)
2	1 (<1%)*	0
Metastatic sites		
1	114 (30%)	138 (36%)
2	120 (31%)	108 (28%)
≥3	149 (39%)	141 (36%)
Liver metastases	307 (80%)	311 (80%)
Geographical region		
North America	120 (31%)	122 (32%)
East Asia	11 (3%)	11 (3%)
Rest of the world	252 (66%)	254 (66%)

(Table 1 continues in next column)

(Continued from previous column)

	NALIRIFOX (n=383)	Nab-paclitaxel and gemcitabine (n=387)
Main pancreatic tumour location		
Head	147 (38%)	156 (40%)
Other†	236 (62%)	231 (60%)
Baseline CA 19–9‡		
<37 U/mL	60 (16%)	71 (18%)
≥37 U/mL	321 (84%)	316 (82%)
Median (range; IQR)	1856·0 (0·6–8000·0; 178·0–8000·0)	1544·0 (0·6–8000·0; 93·7–8000·0)
Any previous anti-cancer therapy	22 (6%)	27 (7%)
Chemotherapy	14 (4%)	16 (4%)
Radiotherapy	10 (3%)	6 (2%)
Surgical procedure	18 (5%)	25 (7%)
Time from diagnosis of metastatic disease at study entry to randomisation, weeks		
Mean (SD)	3·6 (2%)	3·9 (2%)
Median (range; IQR)	3·0 (0·6–9·1; 2·1–4·7)	3·6 (0·4–10·9; 2·4–5·1)

Data are n (%), unless otherwise stated. Data are based on the intention-to-treat population. CA=carbohydrate antigen. ECOG=Eastern Cooperative Oncology Group. NALIRIFOX=liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin. *One patient was considered to have an ECOG performance status score of 2 after randomisation and continued to receive treatment. †Body, tail, or unknown location. ‡Baseline values were missing for two patients (1%) in the NALIRIFOX arm. The upper limit of detection was 8000 U/mL.

Table 1: **Baseline characteristics**

two-sided alpha allocations of 0·006 (HR<0·931) and 0·048 (HR<0·844) in the interim and final analyses. No pre-assigned definitions of minimal clinically relevant difference were applied. If the primary overall survival endpoint was statistically significant, secondary endpoints were tested in a hierarchical approach in the order of progression-free survival followed by overall response rate. Further details are in appendix 2 (pp 14–15).

Efficacy was assessed in all randomly assigned patients according to the intention-to-treat principle. Safety was assessed in all patients who received at least one dose of treatment. An independent data monitoring committee was established for this study. For time-to-event endpoints including overall survival and progression-free survival, the stratified log-rank test was used to assess between-group differences. Kaplan-Meier methods were used to estimate median (95% CI) survival and HRs (95% CI) were estimated using stratified Cox proportional hazard models. Prespecified sensitivity analyses were conducted for overall survival and progression-free survival, including subgroup analyses according to a priori stratification factors and other prognostic variables. For the overall survival analysis, patients without a recorded date of death were censored according to the last recorded date alive. For the progression-free survival analysis, patients without a recorded death or progression were censored on the date of the last evaluable tumour assessment. Overall response rate by RECIST version 1.1 according to investigator review and accompanying 95% CIs was calculated and compared between treatment groups using the Cochran–Mantel–Haenszel method, adjusted for randomisation stratification factors. Analyses were performed using SAS version 9.3 or higher. The trial was registered with ClinicalTrials.gov, NCT04083235 and EudraCT, 2018-003585-14.

Role of the funding source

The funder of the study participated in study design, data collection, data analysis, data interpretation, and review and approval of the manuscript.

Results

Between Feb 19, 2020 and Aug 17, 2021, 770 patients were randomly allocated to receive NALIRIFOX (383 patients) or nab-paclitaxel and gemcitabine (387 patients) and comprised the intention-to-treat population (figure 1,

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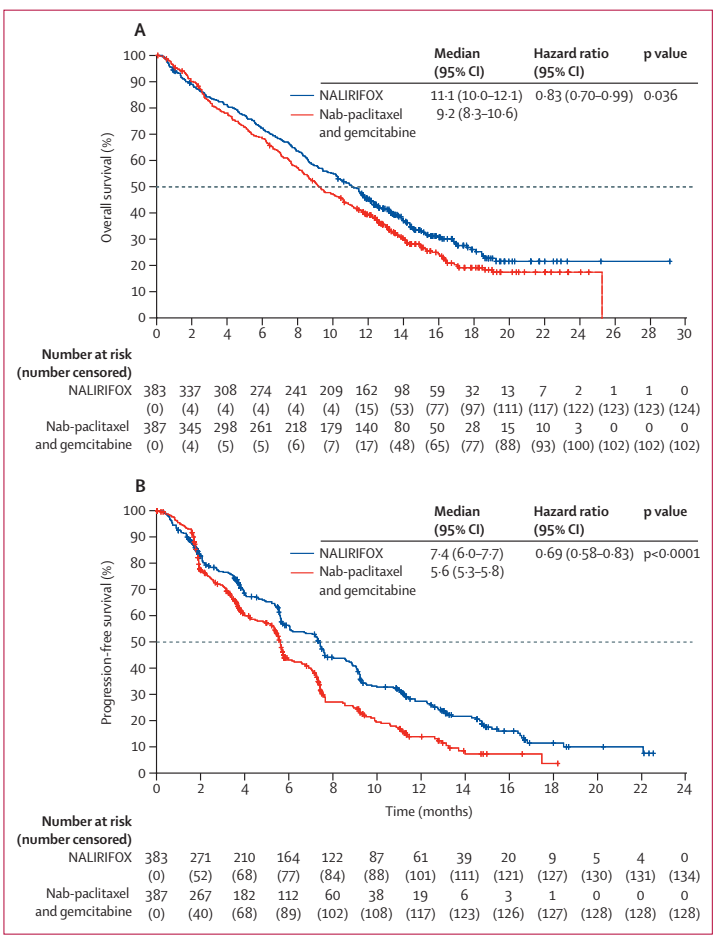

Figure 2: **Kaplan–Meier estimates of overall survival (A) and progression-free survival (B)**
NALIRIFOX=liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin.

table 1). A summary of major protocol deviations in the intention-to-treat population is in appendix 2 (p 23). The safety population comprised 749 patients (NALIRIFOX, 370 patients; nab-paclitaxel and gemcitabine, 379 patients) who had received at least one dose of any study medication. At the data cutoff (July 23, 2022), 44 patients (12%) in the NALIRIFOX group and seven (2%) in the nab-paclitaxel and gemcitabine group were still receiving the trial regimen. The most common reason for discontinuation of treatment was disease progression in 184 patients (48%) in the NALIRIFOX group and 177 patients (46%) in the nab-paclitaxel and gemcitabine group.

The survival analysis was based on 544 deaths over a median follow-up of 16·1 months (IQR 13·4–19·1). Median overall survival was 11·1 months (95% CI 10·0–12·1) in the NALIRIFOX group and 9·2 months (8·3–10·6) in the nab-paclitaxel and gemcitabine group (HR 0·83 [95% CI 0·70–0·99]; p=0·036; figure 2, table 2). Overall survival at 12 months was 45·6% (40·5–50·5) in the NALIRIFOX group and 39·5% (34·6–44·4) in the nab-paclitaxel and gemcitabine group. Overall survival at 18 months was 26·2% (20·9–31·7) for NALIRIFOX and 19·3% (14·8–24·2) for nab-paclitaxel and gemcitabine.

Median progression-free survival was 7·4 (95% CI 6·0–7·7) months in the NALIRIFOX group and 5·6 [5·3–5·8] months in the nab-paclitaxel and gemcitabine group (HR 0·69 [0·58–0·83]; p<0·0001; figure 2, table 2). Progression-free survival rates at 12 months were 27·4% (22·3–32·7) in the NALIRIFOX group and 13·9% (9·7–18·9) in the nab-paclitaxel and gemcitabine group. Progression-free survival rates at 18 months were 11·4% in the NALIRIFOX group and 3·6% in the nab-paclitaxel and gemcitabine group.

Overall survival and progression-free survival benefits with NALIRIFOX versus nab-paclitaxel and gemcitabine were generally consistent across prespecified subgroups (figure 3).

160 (42%) of 383 participants in the NALIRIFOX group had an objective response, as did 140 (36%) of 387 in the nab-paclitaxel and gemcitabine group (p=0·11; table 2). The median duration of response was 7·3 months (95% CI 5·8–7·6) in the NALIRIFOX group and 5·0 months (3·8–5·6) in the nab-paclitaxel and gemcitabine group (HR 0·67 [95% CI 0·48–0·93]; table 2).

Overall, 187 (51%) of 370 patients in the NALIRIFOX group and 206 (54%) of 379 patients in the nab-paclitaxel and gemcitabine group received subsequent systemic anticancer therapy (appendix 2 p 24). The most common subsequent therapies (appendix 2 p 25) were gemcitabine-based (153 [41%] patients) in the NALIRIFOX group and fluorouracil-based (134 [35%] patients) in the nab-paclitaxel and gemcitabine group. In a pre-planned sensitivity analysis for overall survival (censored at the time of subsequent therapy initiation or last known date of being alive, whichever occurred first), median overall survival was longer for the NALIRIFOX group than for the nab-paclitaxel and gemcitabine group (15·1 months for the NALIRIFOX group *vs* 9·2 months for the nab-paclitaxel and gemcitabine group; HR 0·71 [95% CI 0·56–0·90]; nominal p=0·0048). A pre-planned sensitivity analysis of overall survival in the per-protocol population (patients who had no major protocol deviations [appendix 2 p 26]; NALIRIFOX, n=363; nab-paclitaxel and gemcitabine, n=372) demonstrated a median overall survival of 11·5 months (10·2–12·3) in the NALIRIFOX group versus 9·3 months (8·5–10·7) in the nab-paclitaxel and gemcitabine group (HR 0·82 [0·69–0·97]; nominal p=0·022).

Among the 749 patients who received study treatment, the median duration of treatment was 24·3 weeks (IQR 8·4–42·1; median of 5·0 treatment cycles) in the NALIRIFOX group and 17·6 weeks (8·1–30·1; median of

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	NALIRIFOX (n=383)	Nab-paclitaxel and gemcitabine (n=387)	Effect size (95% CI)	p value
Overall survival				
Median overall survival, months (95% CI)	11·1 (10·0–12·1)*	9·2 (8·3–10·6)*	HR 0·83 (0·70–0·99)†	0·036
Survival rate, % (95% CI)				
6 months	72·4 (67·6–76·6)	68·4 (63·5–72·8)	··	··
12 months	45·6 (40·5–50·5)	39·5 (34·6–44·4)	··	··
18 months	26·2 (20·9–31·7)	19·3 (14·8–24·2)	··	··
Progression-free survival				
Median progression-free survival, months (95% CI)	7·4 (6·0–7·7)*	5·6 (5·3–5·8)*	HR 0·69 (0·58–0·83)†	<0·0001
Progression-free survival rate, % (95% CI)				
6 months	56·4 (50·7–61·6)	43·2 (37·6–48·6)	··	··
12 months	27·4 (22·3–32·7)	13·9 (9·7–18·9)	··	··
18 months	11·4 (7·1–16·9)	3·6 (0·5–12·3)	··	··
Response according to investigator assessment				
Overall response				
Number of patients with overall response	160	140	··	··
Rate of overall response (investigator review), % (95% CI)	41·8 (36·8–46·9)‡	36·2 (31·4–41·2)‡	OR 1·26 (0·95–1·69)§	0·11
Median duration of response, months (95% CI)¶	7·3 (5·8–7·6)*	5·0 (3·8–5·6)*	HR 0·67 (0·48–0·93)†	··
Best overall response, n (%)				
Complete response	1 (<1%)	1 (<1%)	··	··
Partial response	159 (42%)	139 (36%)	··	··
Stable disease	99 (26%)	101 (26%)	··	··
Progressive disease	38 (10%)	56 (15%)	··	··
Not evaluable‖	86 (23%)	90 (23%)	··	··

Data are based on the intention-to-treat population. NALIRIFOX=liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin. HR=hazard ratio. OR=odds ratio. *Kaplan-Meier estimate. †HRs and 95% CIs are based on a stratified Cox proportional hazards regression model, stratified by baseline Eastern Cooperative Oncology Group performance status, region, and liver metastases per interactive web response system; reference is nab-paclitaxel and gemcitabine. ‡95% CIs are calculated using the Clopper–Pearson method. §ORs, 95% CIs, and p values are obtained using the Cochran–Mantel–Haenszel method, adjusted by baseline Eastern Cooperative Oncology Group performance status, region, and liver metastases per interactive web response system; reference is nab-paclitaxel and gemcitabine. ¶Duration of response was limited to responders. ‖Included are 68 patients (18%) in the NALIRIFOX group and 64 (17%) in the nab-paclitaxel and gemcitabine group who did not have an assessment after the baseline visit.

Table 2: **Overall survival, progression-free survival, and response rates**

4·0 treatment cycles) in the nab-paclitaxel and gemcitabine group (table 3). Dose reductions per NAPOLI 3 protocol were required in 220 (60%) of 370 patients who received NALIRIFOX and 204 (54%) of 379 patients who received nab-paclitaxel and gemcitabine (table 3).

Treatment-emergent adverse events occurred in 369 (>99%) of 370 patients who received NALIRIFOX and 376 (99%) of 379 patients who received nab-paclitaxel and gemcitabine (table 3). The most common grade 3–4 treatment-emergent adverse events were neutropenia, diarrhoea, and hypokalaemia in the NALIRIFOX group and neutropenia, anaemia, and peripheral neuropathy in the nab-paclitaxel and gemcitabine group (table 3). Treatment-related treatment-emergent adverse events leading to death occurred in six (2%) of 370 patients in the NALIRIFOX group and eight (2%) of 379 patients in the nab-paclitaxel and gemcitabine group. Additional information related to adverse events, including serious treatment-emergent adverse events, is in appendix 2 (pp 28–46).

Discussion

In the NAPOLI 3 trial, the NALIRIFOX regimen demonstrated statistically significant and clinically meaningful improvements in overall survival and progression-free survival compared with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma who had not previously received treatment in the metastatic setting. The observed improvements in overall survival and progression-free survival were generally consistent regardless of baseline Eastern Cooperative Oncology Group performance status score (0 or 1), region (North America or the rest of the world), or presence of liver metastasis based on prespecified subgroup analyses. The improvement in overall survival is unlikely to be attributable to differences in subsequent therapy because similar proportions of patients received subsequent therapy in each treatment group (51% in the NALIRIFOX group and 54% in the nab-paclitaxel and gemcitabine group).

No unexpected safety concerns were identified with the use of NALIRIFOX as first-line therapy in NAPOLI 3.

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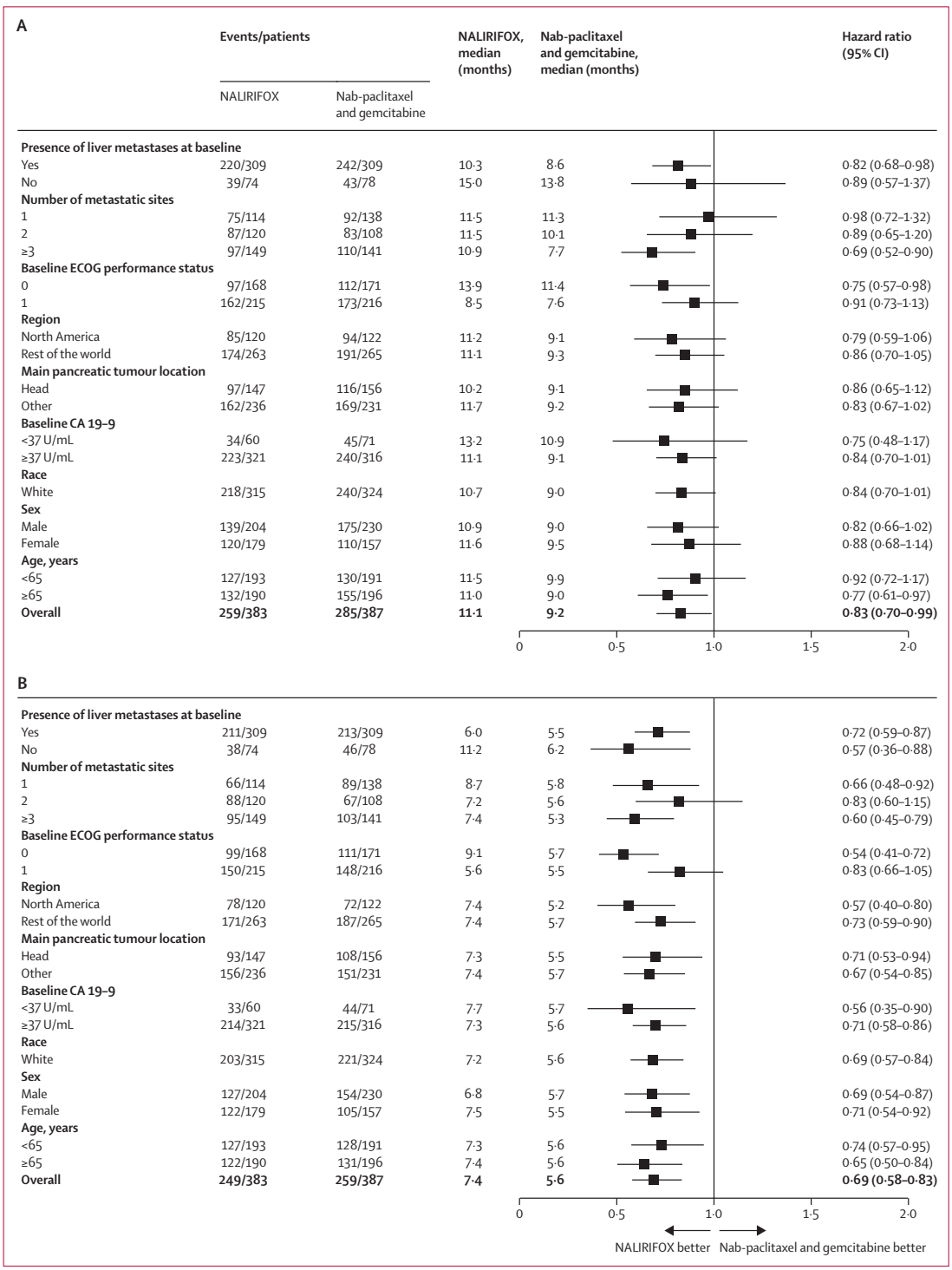

Figure 3: **Forest plot of overall survival (A) and progression-free survival (B) in selected subgroups**
The overall hazard ratio is based on stratified analysis and subgroup hazard ratios are based on unstratified analyses. CA=carbohydrate antigen. ECOG=Eastern Cooperative Oncology Group. NALIRIFOX=liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin.

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Patients remained on NALIRIFOX for a median of 6 weeks longer (1·5 treatment cycles) than those receiving nab-paclitaxel and gemcitabine, indicating that NALIRIFOX was relatively well tolerated. Furthermore, the rates of grade 3–4 peripheral neuropathy were lower in the NALIRIFOX group than in the nab-paclitaxel and gemcitabine group (3·2% *vs* 5·8%). Similar to the previous phase 1/2 study,[14] the most frequent grade 3–4 treatment-emergent adverse events in the NALIRIFOX group included neutropenia and hypokalaemia, and gastrointestinal disorders such as diarrhoea and nausea. However, rates of haematological grade 3–4 treatment-emergent adverse events including neutropenia, anaemia, and thrombocytopenia were lower with NALIRIFOX (a quadruplet combination therapy) than with nab-paclitaxel and gemcitabine group (a doublet combination therapy). The safety profile of NALIRIFOX could be related to several factors. One possibility is the use of lower doses of oxaliplatin, which help to reduce toxicities such as in cumulative peripheral neuropathy. Additional factors that include the use of the liposomal formulation of irinotecan, which was designed to maximise tumour exposure while minimising systemic toxicity, might also play a role.[18]

Although direct comparisons are not possible, it is important to consider the NAPOLI 3 results (n=770) within the context of the phase 3 PRODIGE 4/ACCORD 11 trial (n=342),[3] which compared FOLFIRINOX with gemcitabine alone and led to its use as a first-line treatment for metastatic pancreatic ductal adenocarcinoma. Enrolment in PRODIGE 4 was limited to patients aged 75 years or younger and was exclusively in France, whereas NAPOLI 3 had no age restrictions and was a global trial, with a mixture of community and academic sites. In the PRODIGE trial, FOLFIRINOX demonstrated superiority over gemcitabine alone (median overall survival 11·1 months [95% CI 9·0–13·1] *vs* 6·8 months [5·5–7·6]).[3] Indeed, NAPOLI 3 is the only study that has demonstrated superiority of quadruplet therapy (using liposomal irinotecan) over doublet therapy with nab-paclitaxel and gemcitabine. The median progression-free survival was 7·4 months (95% CI 6·0–7·7) and the overall response rate per investigator was 41·8% for NALIRIFOX in NAPOLI 3, and 6·4 (5·5–7·2) months and 31·6%, respectively, for FOLFIRINOX in PRODIGE.[3] In NAPOLI 3, rates of grade 3–4 peripheral sensory neuropathy and neutropenia with NALIRIFOX were lower than those reported for FOLFIRINOX (3·5% *vs* 9·0% and 23·8% *vs* 45·7%, respectively), probably owing to a lower cumulative dose of oxaliplatin with the NALIRIFOX regimen,[3] which was selected based on review of dose-limiting toxicities in the previous phase 1/2 dose expansion and dose exploration study.[14]

Compared with other cancers, there have been only small improvements in survival rates in patients with pancreatic ductal adenocarcinoma over the past 30 years.

	NALIRIFOX (n=370)	Nab-paclitaxel and gemcitabine (n=379)
Median duration of treatment, weeks	24·3 (0·4–100·9; 8·4–42·1)	17·6 (0·7–81·7; 8·1–30·1)
Median number of treatment cycles	5·0 (1–24; 2–10)	4·0 (1–20; 2–7)
Any dose reductions	220 (60%)	204 (54%)
TEAEs		
Any TEAE	369 (>99%)	376 (99%)
Any treatment-related TEAE	352 (95%)	352 (93%)
Grade ≥3 TEAE	322 (87%)	326 (86%)
Grade ≥3 treatment-related TEAE	262 (71%)	258 (68%)
Any TEAE leading to discontinuation	118 (32%)	112 (30%)
Any treatment-related TEAE leading to discontinuation	94 (25%)	88 (23%)
Any TEAE leading to dose reduction	208 (56%)	190 (50%)
Any treatment-related TEAE leading to dose reduction	198 (54%)	184 (49%)
Any serious TEAEs	201 (54%)	195 (52%)
Any treatment-related serious TEAEs	98 (27%)	72 (19%)
TEAEs leading to death	22 (6%)	23 (6%)
Treatment-related TEAEs leading to death	6 (2%)	8 (2%)
TEAEs of grade 3–4 occurring in ≥5% of patients in either treatment arm		
Diarrhoea	75 (20%)	17 (5%)
Nausea	44 (12%)	10 (3%)
Vomiting	26 (7%)	8 (2%)
Decreased appetite	32 (9%)	10 (3%)
Hypokalaemia	56 (15%)	15 (4%)
Fatigue	23 (6%)	20 (5%)
Asthenia	33 (9%)	19 (5%)
Neutropenia	52 (14%)	93 (25%)
Neutrophil count decreased	36 (10%)	51 (14%)
Anaemia	39 (11%)	66 (17%)
Peripheral neuropathy	12 (3%)	22 (6%)
Increased γ-glutamyltransferase	23 (6%)	21 (6%)

Data are median (range; IQR) or n (%). NALIRIFOX=liposomal irinotecan in combination with fluorouracil, leucovorin, and oxaliplatin. TEAE=treatment-emergent adverse event.

Table 3: **Duration of treatment, exposure, and overview of TEAEs in the safety population.**

Early-stage disease is undetectable in patients without symptoms, and effective screening methods are not yet available. Decisions about first-line therapy for patients with metastatic pancreatic ductal adenocarcinoma are limited by differing toxicity profiles and a lack of direct comparisons, as well as factors such as performance status, genetic alterations (eg, defective mismatch repair or homologous recombination deficiency), age, and underlying comorbidities. In NAPOLI 3, NALIRIFOX demonstrated lower rates of haematological

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treatment-emergent adverse events than nab-paclitaxel and gemcitabine. In addition, the cost of treatment and its impact on health-related quality of life are important factors in treatment decision making. Future research will be conducted to evaluate cost implications, and analyses of patient-reported quality of life outcomes from NAPOLI 3 are ongoing. Furthermore, ongoing genomic profiling evaluations on tissue and serum collected in the NAPOLI 3 trial might answer additional questions that could inform patient selection, such as whether patients with *BRCA*-mutated pancreatic cancer could have benefited from platinum exposure in the NALIRIFOX group.

Strengths of the NAPOLI 3 study include the large sample size, randomised design, and the global recruitment of patients from academic and community sites in North and South America, eastern and western Europe, Asia, and Australia. Limitations of the study include the following: the open-label study design and associated potential for outcome bias; the requirement for measurable disease and an Eastern Cooperative Oncology Group performance status score of 0 or 1 at screening; and the absence of somatic or germline profiling information.

Contributors

All authors meet the International Committee of Medical Journal Editors criteria for authorship of this Article, take responsibility for the integrity of the work, were involved in drafting, revising, and critical review of the manuscript, and approved the final version for submission. All authors conceived and designed the study, carried out the research, and analysed the data. ZAW, ZX, and HC accessed and verified the underlying data. All authors had full access to the data, final responsibility to submit for publication, and vouch for the accuracy and completeness of the data and fidelity of the trial to the protocol.

Declaration of interests

ZAW has received grants or contracts from Arcus and Bristol Myers Squibb, consulting fees from Amgen, Arcus, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Ipsen, Merck Sharp & Dohme, and Seagen, support for attending meetings or travel from Amgen, Bayer, and Merck Sharp & Dohme, and has participated on a data safety monitoring board or advisory board for Mirati and Pfizer. DM has received grants or contracts from Celgene, Evotec, Incyte, iOnctura, Roche, and Servier, consultancy fees from Incyte, iOnctura, IQVIA, Merck Sharp & Dohme, Servier, and Taiho Pharmaceutical, and has participated on a data safety monitoring board or advisory board for Incyte, Servier, Taiho Pharmaceutical, and Terumo. 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Data sharing

Qualified researchers can request access to patient-level study data that underlie the results reported in this publication. Additional relevant study documents, including the clinical study report, study protocol with any amendments, annotated case report form, statistical analysis plan, and data set specifications can also be made available. Patient-level data will be anonymised, and study documents will be redacted to protect the privacy of study participants. When applicable, data from eligible studies are available 6 months after the studied medicine and indication have been approved in the USA and EU or after the primary manuscript describing the results has been accepted for publication, whichever is later. Further details on Ipsen's sharing criteria, eligible studies, and process for sharing are available online at https://vivli.org/members/ourmembers/. Any requests should be submitted to https://vivli.org for assessment by an independent scientific review board.

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