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NALIRIFOX for metastatic pancreatic adenocarcinoma: hope or hype?

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The FDA has approved nanoliposomal irinotecan, 5-fluorouracil, leucovorin and oxaliplatin (NALIRIFOX) for patients with metastatic pancreatic adenocarcinoma on the basis of results from the NAPOLI 3 trial, in which this four-drug regimen improved overall survival relative to a doublet regimen. Here we discuss how, in the context of prior results from the PRODIGE 4 trial testing 5-fluorouracil, leucovorin, irinotecan and oxaliplatin (modified FOLFIRINOX), NALIRIFOX does not seem to raise the bar, but rather exposes patients and health-care systems to financial toxicities.

Refers to Wainberg, Z.A. et al. NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-I patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomized, open-label, phase 3 trial. *Lancet* **402**, 1272–1281 (2023).

The current first-line standard-of-care chemotherapy regimens for patients with advanced-stage or metastatic pancreatic ductal adenocarcinoma (mPDAC) include 5-fluorouracil, leucovorin, irinotecan and oxaliplatin (modified FOLFIRINOX) and gemcitabine and nab-paclitaxel, based on data from the PRODIGE 4 and MPACT trials, respectively[1,2]. The recent publication of results from the NAPOLI 3 trial and subsequent FDA approval of nanoliposomal irinotecan, 5-fluorouracil, leucovorin and oxaliplatin (NALIRIFOX) in February 2024 is the first challenge to the current standard of care for mPDAC in over a decade[3]. Here, we question whether the addition of NALIRIFOX to the therapeutic armamentarium for this disease constitutes true progress.

Compared to modified FOLFIRINOX, NALIRIFOX replaces irinotecan with nanoliposomal irinotecan and includes a lower dose of oxaliplatin (60 mg/m^2 instead of 85 mg/m^2). Data from previous studies suggest that nanoliposomal irinotecan has improved pharmacokinetic properties, including lower clearance, extended half-life and increased accumulation at tumour sites with potential for lower toxicity, although at least one small trial did not demonstrate a decrease in grade 3–4 toxicities compared to irinotecan[4]. The NAPOLI-1 and NIFTY trials demonstrated the clinical activity of this agent in previously treated patients with mPDAC and biliary tract cancers, respectively[5,6]. However, neither of these trials directly compared nanoliposomal irinotecan with an irinotecan-containing regimen and, to our knowledge, no prospective studies have been powered to enable a formal statistical comparison to show the superiority of nanoliposomal irinotecan over irinotecan.

NAPOLI 3 was a global phase III trial in which 770 patients with previously untreated mPDAC (with an ECOG performance status of PS 0–1) were randomly allocated (1:1) to receive either NALIFIROX or gemcitabine–nab-paclitaxel. The study showed a modest improvement in the primary end point of overall survival (OS) with NALIRIFOX (median durations of 11.1 months versus 9.2 months with gemcitabine–nab-paclitaxel; HR 0.83, 95% CI 0.70–0.99; $P = 0.036$). Progression-free survival was also improved (median durations of 7.4 months versus 5.6 months; HR 0.69, 95% CI 0.58–0.83; $P < 0.0001$). A numerical but not statistically significant increase in objective response rate (ORR) was reported in the NALIRIFOX group (41.8% versus 36%; $P = 0.11$)[3].

NAPOLI 3 provides strong evidence that a four-drug regimen is superior to a two-drug regimen in fit patients with mPDAC, which confirms the trend observed in a systematic analysis of real-world studies that compared modified FOLFIRINOX with gemcitabine–nab-paclitaxel in this patient population[7]. Oncologists must now decide whether to continue using modified FOLFIRINOX or switch to NALIRIFOX. NAPOLI 3 was not designed to directly compare these regimens and thus the only way to make this decision currently is by comparing the results of this trial with historical data.

The first aspect to consider is whether data from NAPOLI 3 suggest that NALIRIFOX is superior to modified FOLFIRINOX in terms of OS: we argue that they do not. The median OS of patients receiving NALIRIFOX in NAPOLI 3 is identical to that of those who received FOLFIRINOX in PRODIGE 4 (11.1 months)[1]. Considering only the advances in supportive care since the publication of PRODIGE 4 over a decade ago, we would have expected improved outcomes in NAPOLI 3. Supporters of NALIRIFOX claim that this striking similarity in median OS can be explained by the more-relaxed inclusion criteria of NAPOLI 3. Although we acknowledge that PRODIGE 4 limited enrolment to patients of ≤75 years of age, the actual enrolment of patients >75 years of age in NAPOLI 3 was marginal (8% in the NALIRIFOX arm). This small percentage does not enable us to draw any meaningful conclusions on the role of NALIRIFOX in older patients nor does it invalidate a comparison of outcomes between trials. Other differences in inclusion criteria suggest that patients enrolled in NAPOLI 3 tended to have a better prognosis than those in PRODIGE 4. NAPOLI 3 excluded patients with serum albumin levels of <3 g/dl, a restriction criterion that was not included in PRODIGE 4 (Table 1). Additionally, prior chemotherapy for early stage disease was allowed in NAPOLI 3 if it was received >12 months before enrolment, whereas PRODIGE 4 did not allow prior chemotherapy and thus restricted enrolment to patients with de novo metastatic disease (a population with inherently worse disease biology) (Table 1).

Our second concern relates to the higher ORR observed with NALIRIFOX in NAPOLI 3 compared to FOLFIRINOX in PRODIGE 4

Table 1 | Key features of NALIRIFOX versus FOLFIRINOX

Regimen and trial	Baseline patient characteristics			Efficacy outcomes			Grade ≥3 AEs			Cost per single 2-week cycle[a]
	Median age	Serum albumin levels (inclusion criteria)	Prior chemotherapy	mOS	mPFS	ORR	Diarrhoea	Neutropenia and febrile neutropenia	Neuropathy	
NALIRIFOX (NAPOLI 3)[3,9]	64 years	≥3 g/dl	4% of patients	11.1 months	7.4 months	41.8%[b]	20%	24% and 2%[c]	6.5%[d]	US $7,800
FOLFIRINOX (PRODIGE 4)[1]	61 years	No restriction	Not allowed	11.1 months	6.4 months	31.6%	13%	46% and 5%	9%	$500

[a]Approximate average wholesale cost for nanoliposomal irinotecan or irinotecan for a patient with a body surface area of 2.0 m^2. [b]No central review of images. [c]Primary prophylaxis with granulocyte colony-stimulating factor was encouraged in NAPOLI 3 and not recommended in PRODIGE 4. [d]Includes peripheral neuropathy and peripheral sensory neuropathy[9]. AE, adverse event; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan and oxaliplatin; mOS, median overall survival; mPFS, median progression-free survival; NALIRIFOX, nanoliposomal irinotecan, 5-fluorouracil, leucovorin and oxaliplatin; ORR, objective response rate.

(41.8% versus 31.6%). In NAPOLI 3, radiological responses were assessed by investigators whereas PRODIGE 4 involved central independent review by two radiologists. The lack of central review in radiological response assessment can lead to bias. Indeed, the ORR in the gemcitabine–nab-paclitaxel arm of NAPOLI 3 (36%) was higher than that observed with the same regimen in MPACT trial (21%), which involved blinded independent response assessment. This difference suggests that radiological responses might have been overestimated in NAPOLI 3 and thus that differences in ORR should not be used as an argument in favour of NALIRIFOX.

A final question is whether differences in toxicity could help to determine which regimen to use in the clinic. The incidences of grade ≥3 diarrhoea with NALIRIFOX and FOLFIRINOX in the pivotal trials were 20% versus 13% (Table 1). By contrast, the incidences of grade ≥3 neutropenia and febrile neutropenia were 24% versus 46%, and 2% versus 5%, respectively. Of note, in the phase I/II trial testing NALIRIFOX, up to 12.5% of patients had grade ≥3 febrile neutropenia at the dose tested in NAPOLI 3 (ref. 8). Prophylactic use of granulocyte colony-stimulating factor (G-CSF) was recommended in NAPOLI 3 for patients considered high risk at the investigator's discretion, although the percentage of patients who received it was not disclosed in the original publication. We note some lack of consistency in the reporting of G-CSF use compared to the phase I trial testing NALIRIFOX. According to the initial results from NAPOLI 3 presented, 6.5% of patients receiving NALIRIFOX had grade ≥3 peripheral neuropathy (3% peripheral neuropathy and 3.5% peripheral sensory neuropathy) compared to 9% of patients receiving FOLFIRINOX in PRODIGE 4, a clinically insignificant difference[9]. However, in the final publication of NAPOLI 3 the authors only included data on peripheral neuropathy (3%), which potentially underreports the true incidence of neuropathy. A recently published systematic review and meta-analysis supports our conclusion that the differences in OS between NALIRIFOX and modified FOLFIRINOX are not clinically significant and that those in neuropathy are not statistically significant[10]. Finally, we must also consider the financial toxicity of a regimen such as NALIRIFOX, which in the USA costs thousands of dollars more per cycle than modified FOLFIRINOX (Table 1).

Ideally, NALIRIFOX and modified FOLFIRINOX should be compared directly in a prospective, randomized trial. Unfortunately, motivation to conduct such a trial is unlikely owing to the costs and time involved. One could also argue that subjecting future patients with mPDAC to a trial comparing these regimens would be unethical when we could be offering enrolment in trials that evaluate novel therapies with a higher likelihood of meaningfully improving clinical outcomes. Indeed, NAPOLI 3 missed an excellent opportunity to include a third arm to enable this comparison, an approach similar to that recently tested in JCOG1611 (which compared modified FOLFIRINOX; S-1, irinotecan and oxaliplatin (S-IROX); and gemcitabine–nab-paclitaxel) (jRCTs031190009). However, we should not give up on trying to answer the question of whether NALIRIFOX truly constitutes an improvement in the standard of care for this disease. With an FDA approval, this regimen will be used in some clinics across the country over the coming years. Well-conducted studies analysing real-world data on the clinical uptake of NALIRIFOX could provide evidence that helps to settle this issue. While we look forward to the results of these future studies, whether NALIRIFOX represents true hope for our patients or just hype remains to be seen.

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Competing interests

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