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Review

Integration of liposomal irinotecan in the first-line treatment of metastatic pancreatic cancer: try to do not think about the white bear

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Davide Melisi, Simona Casalino, Silvia Pietrobono, Alberto Quinzii, Camilla Zecchetto and Valeria Merz

***Abstract*:** The approval of novel therapeutic agents remains widely reliant on evidence derived from large phase III randomized controlled trials. Liposomal irinotecan (ONIVYDE®) stands out as the only drug that has demonstrated improved survival both as a first-line therapy in combination with oxaliplatin and 5-fluorouracil/leucovorin (5FU/LV) (NALIRIFOX) compared to the standard gemcitabine plus nab-paclitaxel in the NAPOLI3 trial, and as a second-line treatment in combination with 5FU/LV compared to the standard 5FU/LV in the NAPOLI1 trial. However, just as the white bear of the Dostoevsky's paradox, the judgment of these results is invariably distracted by the intrusive thought of how different they might be if compared to similar regimens containing standard-free irinotecan as FOLFIRINOX or FOLFIRI, respectively. Here, we present and thoroughly discuss the evidence encompassing the pharmacologic, preclinical, and clinical development of liposomal irinotecan that can dispel any intrusive thoughts and foster a rational and well-considered judgment of this agent and its potential integration into the therapeutic strategies for pancreatic ductal adenocarcinoma.

Keywords: liposomal irinotecan, NALIRIFOX, pancreatic ductal adenocarcinoma

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Introduction

In 2020, around 496,000 individuals worldwide received a diagnosis of pancreatic ductal adenocarcinoma, making it the seventh most prevalent cause of cancer-related deaths, accounting for approximately 466,000 deaths.[1] When considering all stages combined, the 5-year relative survival rate is alarmingly low among solid tumors standing at just 12%.[2] In absence of any real improvement in early detection and treatment strategies, pancreatic ductal adenocarcinoma is expected to become the second leading cause of cancer-related death by 2040 in Western countries.[3] The poor prognosis for patients affected by this disease is indeed mainly attributed to the early metastatic behavior, its aggressive course, and the limited efficacy of currently approved chemotherapeutic treatments.[4]

The process of obtaining approval for novel therapeutic agents continues to strongly rely on evidence emerging from large randomized controlled trials. The randomized controlled trials are the gold standard for evaluating new therapies as they provide the most rigorous and systematic approach to studying the effectiveness and safety of therapeutic interventions.

With the exception of molecularly targeted agents designed for rare genomic alterations that can be appropriately evaluated in tumor-agnostic basket trials or molecularly selected phase II studies,[5] it is crucial that no drugs, especially cytotoxic agents or their combination regimens, be granted approval by regulatory agencies if they have never been adequately evaluated in a large randomized phase III trial or, if tested, have failed to demonstrate a clear evidence of survival improvement. Any given randomized controlled clinical trial compares a novel therapeutic intervention to a recognized standard treatment for that indication allowing researchers to assess the superiority of

Correspondence to:
Davide Melisi
Investigational Cancer Therapeutics Clinical Unit, Azienda Ospedaliera Universitaria Integrata, Verona, Italy

Digestive Molecular Clinical Oncology Research Unit, University of Verona, Piazzale L.A. Scuro, 10, Verona 37134, Italy
davide.melisi@univr.it

Simona Casalino
Silvia Pietrobono
Alberto Quinzii
Camilla Zecchetto
Digestive Molecular Clinical Oncology Research Unit, University of Verona, Verona, Italy

Valeria Merz
Digestive Molecular Clinical Oncology Research Unit, University of Verona, Verona, Italy

Medical Oncology Unit, Santa Chiara Hospital, Trento, Italy

the new therapy, and there are inherent dangers associated with any attempt to directly compare the outcomes observed in independently conducted clinical trials, often referred to as cross-trial comparisons.

'Try to pose for yourself this task: not to think of a polar bear, and you will see that the cursed thing will come to mind every minute.' (F. Dostoevsky, *Winter Notes on Summer Impressions*, 1863). The ironic process theory, also known as 'the white bear problem',[6] refers to a psychological process in which our deliberate attempts to intentionally avoid thinking certain intrusive thoughts lead to a paradoxical effect. These efforts to suppress the thoughts not only fail in their objective but, in fact, make the thoughts more likely to surface more frequently and intensely. The consequences of 'the white bear problem' include the propagation of persistent negative reactions, an increased distractibility when trying to focus on a specific topic, and most importantly, poor decision making. Intrusive thoughts can be so intense that they hinder your ability to make rational, carefully considered judgments, leading to skewed decision-making.

Liposomal irinotecan (ONIVYDE® manufacturers are IPSEN for the US market and SERVIER for the European market; also known as nal-IRI, MM-398 or PEP02) is the only drug that has ever demonstrated in more than one large randomized controlled trial an improvement in survival for patients with advanced pancreatic ductal adenocarcinoma. It showed to improve survival both as a first-line therapy in combination with oxaliplatin and 5-fluorouracil/leucovorin (5FU/LV) (NALIRIFOX) compared to the standard gemcitabine plus nab-paclitaxel,[7] and as a second-line treatment in combination with 5FU/LV compared to the standard 5FU/LV.[8] Notably, NALIRIFOX has been also included in the most recent National Comprehensive Cancer Network guidelines as one of the recommended regimens for the treatment of unresectable pancreatic ductal adenocarcinoma.[9]

However, just like in the white bear problem, the judgment of the results achieved with regimens containing liposomal irinotecan in randomized controlled trials is invariably distracted from a balanced comparison with the actual comparator arm to the intrusive thought of how different these results might be if compared to similar regimens containing standard-free irinotecan. Instead of rationally evaluating the actual results of those large randomized controlled trials, the reaction is often to make inappropriate cross-trial comparisons with the outcomes observed in different, often less statistically solid, clinical trials with similar regimens based on standard-free irinotecan.

Here, we present and discuss the evidence supporting the integration of liposomal irinotecan in the first-line treatment of metastatic pancreatic ductal adenocarcinoma, trying to avoid dwelling on the white bear of standard-free irinotecan.

What has led to all these negative phase III randomized controlled trials in metastatic pancreatic ductal adenocarcinoma throughout the past decade?

For the first-line treatment of advanced pancreatic ductal adenocarcinoma, the last phase III randomized controlled trial demonstrating the effectiveness of a novel agent was published in October 2013.[10] The MPACT trial demonstrated that adding the nanotechnologic agent nab-paclitaxel to gemcitabine, the standard of care at that time, significantly improved overall survival (OS) in patients with previously untreated metastatic pancreatic ductal adenocarcinoma. Two years before, the PRODIGE 4/ACCORD 11 established the efficacy of FOLFIRINOX regimen – oxaliplatin plus standard-free irinotecan, and 5FU/LV – compared to gemcitabine alone by prolonging OS in the same setting.[11] It was therefore almost one decade that no other agent demonstrated any further improvement for the first-line treatment of patients with metastatic pancreatic ductal adenocarcinoma.

Although a number of classic cytotoxic, molecularly targeted, or immunotherapeutic drugs have been approved in the last 10 years in the vast majority of any other solid tumors, a long list of potential novel drugs failed to demonstrate any advantage for in this disease. In this regard, it remains of the utmost urgency that the scientific community interrogates itself about the possible reasons for this long list of negative clinical trials lasting almost a decade. Because 'in all disputes the line can never be drawn so finely as not to leave a little wrong on both sides' (A. Manzoni, *The Betrothed*, 1827), the reasons for this lack in the development of drugs should be searched either in earliest phase of preclinical development, and in the conduction of clinical trials in the latest phases of clinical validation.

Several novel drugs that have recently been explored in clinical trials rely heavily on studies conducted in genetically engineered mouse models, such as $Kras^{LSL.G12D/+}$; $PdxCre^{tg/+}$ (KC)[12] or $Kras^{LSL.G12D/+}$; $p53^{R172H/+}$; $PdxCre^{tg/+}$ (KPC) mice,[13] for their mechanistic rational and preclinical validation. These genetically engineered mouse models of pancreatic ductal adenocarcinoma were expected to offer an alternative for preclinical therapeutic evaluation, replacing mouse models bearing transplanted tumors that were considered to have a limited predictive utility.[14] These murine models were intended to better mirror the biology of the human counterpart and prove more useful for studying pancreatic ductal adenocarcinoma pathogenesis and progression, and investigating the mechanisms of action and the therapeutic efficacy of cancer therapies. Most importantly, these models were intended to be used to investigate why pancreatic ductal adenocarcinoma is insensitive to chemotherapy, and develop better therapeutic strategies. A great emphasis was placed on the capacity of these models to replicate the distinctive characteristics of the tumor microenvironment in this disease, characterized by dense stromal formation and a poorly immunogenic state. Consequently, numerous agents targeting critical components of the stroma were developed and assessed across various stages of clinical trials, but they failed to demonstrate any activity. For instance, the inhibition of the hedgehog inhibitor signaling pathway was shown in these models to deplete tumor-associated stromal tissue, increase intratumoral vascular density, and enhance the delivery and efficacy of chemotherapy.[14] However, disappointingly, phase I and II studies of inhibitors targeting this signaling pathway, such as saridegib (IPI-926) or vismodegib (GDC-0449), failed to demonstrate any significant benefit for this strategy.[15,16] Similarly, degradation of hyaluronan, a major component of the pancreatic ductal adenocarcinoma extracellular matrix, was presented as a novel strategy to allow high concentrations of chemotherapy to reach the tumor, resulting in improved survival and revealing an underappreciated sensitivity of the disease to conventional cytotoxic agents in KPC murine models.[17] Encouraged by the preliminary data from phase I/II studies,[18,19] pegvorhyaluronidase alfa (PEGPH20), a PEGylated recombinant human hyaluronidase, was tested in larger randomized controlled trials, but demonstrated no efficacy in combination with nab-paclitaxel/gemcitabine.[20] Even worse, it showed a detrimental effect in combination with FOLFIRINOX.[21] These pieces of evidence raise questions about the appropriateness of these preclinical models, questioning whether they truly replicate the complexity and heterogeneity of pancreatic ductal adenocarcinoma in humans, and whether the aspects being investigated to date are genuinely the most relevant for the development of new experimental therapeutics. Moreover, the complexity involved in managing and the associated costs of using these models could have potentially slow down the entire process of discovering novel targets and developing new therapeutics.

Another crucial aspect experiencing slow and difficult development is the identification and clinical application of the different classifications proposed for molecular subtypes for pancreatic ductal adenocarcinoma.[22] The initial excitement that surrounded the results of the enormous effort put into large-scale genomic and transcriptomic analyses to identify molecular subtypes of pancreatic ductal adenocarcinoma[23–25] is now facing limitations in both the identification of novel therapeutic targets and in demonstrating a real predictive value for the different currently approved therapeutic approaches. It is evident that the reductionistic scenario that depicted two broad consensus subtypes – classical and basal-like – based on the analysis of samples from untreated resectable diseases, is instead, more much more complex and dynamic. Spatial resolved, single-cell analysis of specimens from primary or metastatic sites has revealed profound intratumoral subtype heterogeneity, with very few tumors existing as purely basal or purely classic.[26] Instead, most tumors contain a substantial fraction of cells co-expressing classical and basal markers, establishing a continuum of these two phenotypes, probably in response to gradients of cytokines secreted by tumor and stromal cells acting in a paracrine manner within different spatially confined subtumor microenvironments, or ecotypes.[27] Dissecting the molecular and cellular mechanisms in the crosstalk between neoplastic and stromal cells within these ecotypes and their modulation in response to experimental therapeutics remains of utmost importance. The secreted factors involved in these crosstalks could, indeed, potentially serve as more useful biomarkers for identifying those patients more likely to benefit from specific molecularly targeted agents. Agents that can modulate these key paracrine

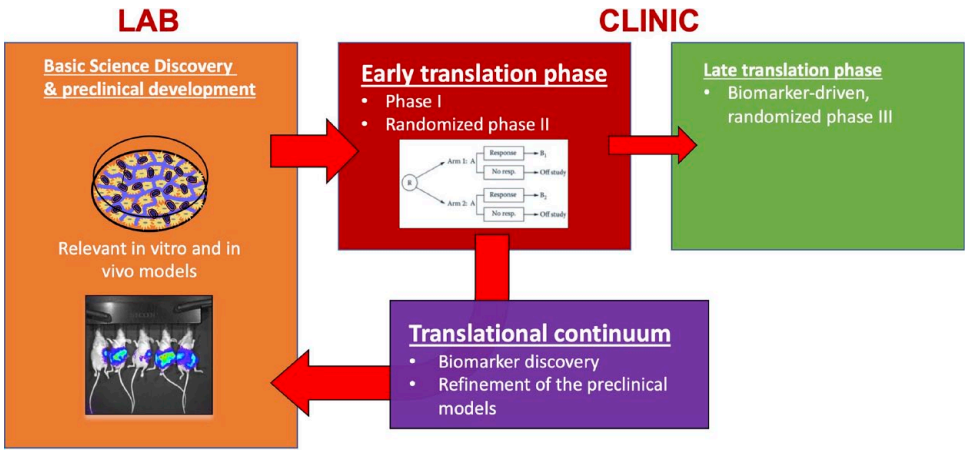

Figure 1. A possible novel paradigm for the development of experimental therapeutics for pancreatic ductal adenocarcinoma.

interactions could represent novel and effective therapies for this disease.

On the other end of the process for drug development, one of the primary reasons for the limited success in this disease could be attributed to a certain kind of 'anxiety to perform', which often leads to jumping too rapidly from limited signals of activity in phase I trials to extremely large phase III randomized controlled trials that ultimately yield completely negative results. A recent and compelling example is napabucasin (BBI608), a small molecule identified by its ability to inhibit gene transcription driven by Stat3 and cancer stemness properties. Based on the initial results of a single preclinical study demonstrating the activity of this molecule to suppress metastasis and cancer relapse in immunocompromised murine models, but not any solid antitumor activity as single-agent treatment or in combination with chemotherapy,[28] a dose-finding, phase Ib/single-arm phase II study was conducted in 59 adults with metastatic pancreatic ductal adenocarcinoma. In this early-phase clinical trial, combination treatment with napabucasin plus nab-paclitaxel with gemcitabine showed a safe toxicity profile, but a disease control rate (DCR) of 78.0%, and a median OS duration of 9.6 months,[29] very similar to those measured with standard nab-paclitaxel plus gemcitabine.[10] Without any other intermediate evaluations in randomized phase II clinical trials, the phase III CanStem111P study randomly allocated 1134 patients with previously untreated metastatic pancreatic ductal adenocarcinoma to receive napabucasin plus nab-paclitaxel with gemcitabine *versus* nab-paclitaxel with gemcitabine alone in patients. The study was terminated due to futility based on lack of OS improvement in the napabucasin plus nab-paclitaxel with gemcitabine arm (HR 1.06) at the first interim analysis.[30]

We believe that this current paradigm for the development of novel experimental therapeutics for pancreatic ductal adenocarcinoma should be challenged by giving growing importance to the fundamental step of the randomized phase II trials (Figure 1). These trial designs could solidly indicate a putative positive signal for activity without the need to involve thousands of patients, and, most importantly, permit a wide range of translational analyses on biological samples from the ultimate models – human beings. This would allow for earlier identification of those biological characteristics potentially useful as biomarkers for patients' selection. By adopting this strategy, the most promising agents could be more considerately promoted to larger randomized phase III clinical trials, possibly explored in those biomarker-selected subpopulations of pancreatic ductal adenocarcinoma patients where their activity could have the highest rationale. Moreover, the evidence emerging from these analyses would fuel a translational continuum in the laboratory, refining preclinical models to have those specific molecular characteristics to better dissect the real molecular and cellular mechanisms involved in the activity of a given agent in a biomarker-selected subtype of tumors.

Liposomal irinotecan and its white bear, standard-free irinotecan: Pharmacologic and preclinical differences

Liposomal irinotecan is a novel formulation of standard-free irinotecan that maximizes the antitumoral activity of its active form, SN-38. Irinotecan is derived from the plant Camptotheca acuminata and acts as inhibitor of topoisomerase-I, leading to double-strand DNA damage during DNA synthesis.[31] Irinotecan can be converted in SN-38, which is approximately 100–1000 times more potent in interfering with topoisomerase-I function. The hydrolysis of irinotecan and its metabolic conversion to SN-38 is primarily carried out by carboxylesterase enzymes, present in the liver, plasma, small intestine, and tumor tissue.[32]

In comparison to standard-free irinotecan, liposomal irinotecan exhibits a higher therapeutic index and improved toxicity due to its the lower accumulation in healthy tissues.[33] In this novel formulation, irinotecan molecules are encapsulated in pegylated liposomal particles with a diameter of 111 nm.[34] This encapsulation strategy prolongs the circulation of irinotecan, preventing rapid metabolic conversion to its active metabolite SN-38, thereby leading to improved pharmacokinetics. Approximately 95% of the irinotecan remains within the liposomes 24 h after administering liposomal irinotecan, allowing for high drug retention and an extended plasma half-life compared to free irinotecan.[35] Moreover, a preferential accumulation of liposomal molecules in the tumor stroma is facilitated by altered tumor vessels and abnormal lymphatic drainage, known as the enhanced permeability and retention (EPR) effect.[36] Additionally, liposomes bind circulating proteins, facilitating phagocytosis by the reticuloendothelial system.[34] In particular, tumor-associated macrophages (TAMs) actively internalize liposomal irinotecan, resulting in a continuous release of SN-38 through their own carboxylesterase activity. Tumor cells also express carboxylesterase, allowing them to act on any locally released irinotecan.[34]

Initial preclinical studies have demonstrated that liposomal irinotecan exhibits a better pharmacokinetic and toxicity profile, as well as higher tumor activity, compared to free irinotecan in models of human colon HT-29 and breast BT474 cancer xenografts.[35] Similar effects in reducing tumor burden and prolonging survival were observed in mouse xenograft models of breast cancer brain metastases.[37] Most recently, studies on patient-derived pancreatic ductal adenocarcinoma xenografts in immunocompromised mice have demonstrated that liposomal irinotecan exhibits a higher therapeutic index than standard-free irinotecan (20 *versus* 5) by achieving greater antitumor activity, histological tumor regression, and plasma levels of CPT-11 and its active metabolite SN-38 after 24 h than standard-free irinotecan.[33]

Early phase clinical trials with liposomal irinotecan

In an initial phase I study as a single-agent treatment in patients with advanced solid tumors, the maximum tolerated dose (MTD) for liposomal irinotecan at a 3-week interval was determined to be 120 mg/m^2. When comparing the results with those obtained after administering-free-form irinotecan, as reported in the literature, the dose-normalized pharmacokinetics of SN-38 after liposomal irinotecan treatment not only showed lower C max, prolonged terminal half-life, and higher area under the curve (AUC) but also exhibited significant inter-individual variation.[38] At this dose level and schedule, liposomal irinotecan was also evaluated in a multinational phase II study for patients with gemcitabine-refractory metastatic pancreatic ductal adenocarcinoma. The study successfully achieved its primary endpoint, demonstrating an OS rate of 75% at 3 months. The median progression-free survival and OS were recorded as 2.4 and 5.2 months, respectively.[39] In a different dose-finding phase I trial, the MTD for liposomal irinotecan in combination with 5-FU/LV was determined as 80 mg/m^2. The pharmacokinetic analysis revealed that liposomal irinotecan exhibited a reduced peak plasma concentration, a prolonged half-life, and a higher area under the plasma concentration-time curve from zero to time t for SN-38, in comparison to irinotecan administered at a similar dose level.[40]

The NAPOLI1 trial: Liposomal irinotecan plus 5FU/LV is the standard therapy in second-line treatment

Nearly 50% of patients who experience disease progression under a first-line treatment for metastatic pancreatic ductal adenocarcinoma receive a second-line treatment. A large chart-review study conducted on European patients treated between 2014 and 2016 indicated that gemcitabine monotherapy or gemcitabine plus nab-paclitaxel were used in 45.9% and 33.1% of patients, respectively,

who progressed under a first-line FOLFIRINOX regimen. Among those patients receiving gemcitabine plus nab-paclitaxel as first-line regimen, 39.1% had 5FU/LV plus oxaliplatin, and 23.4% had 5FU/LV monotherapy.[41] It is, however, important to notice that the evidence supporting these indications consists mainly of retrospective series or single-arm, small phase II studies, with significant heterogeneity concerning patients' populations, treatments, and outcomes.[42] The only two randomized phase III trials conducted in this setting explored the role of oxaliplatin-based chemotherapy reached conflicting results.[43,44] No randomized phase III trials have ever explored standard irinotecan-containing regimens or gemcitabine plus nab-paclitaxel in this setting, although these treatments remain widely used in clinical practice.

To date, NAPOLI1, the randomized controlled trial that explored the combination of liposomal irinotecan plus 5FU/LV, remains the largest phase III study ever conducted in second-line metastatic pancreatic ductal adenocarcinoma. NAPOLI1 included patients with metastatic pancreatic ductal adenocarcinoma progressed after previous gemcitabine-based therapy and a Karnofsky performance status score of at least 70. In the final design, 417 patients were randomized to receive liposomal irinotecan monotherapy 120 mg/m^2 every 3 weeks, weekly 5-fluorouracil 2000 mg/m^2 and folinic acid 200 mg/m^2 (5-FU/LV), or the combination of liposomal irinotecan 80 mg/m^2 plus 5-FU/LV 2400 mg/m^2 and 400 mg/m^2, respectively, every 2 weeks. Fifty-six percent of patients received the treatment in second line for metastatic disease, 32% received therapy after two or more lines and a minor fraction received it as first line, after previous treatments for local pancreatic ductal adenocarcinoma. The NAPOLI1 trial met its primary endpoint, demonstrating an OS prolongation in patients receiving the combination of liposomal irinotecan plus 5-FU/LV compared to 5-FU/VL alone (6.2 *versus* 4.2 months, respectively; HR, 0.75),[8] and there were no significant differences in quality of life assessment.[45]

Despite the evidence that NAPOLI1 is the only positive randomized controlled clinical trial in this clinical setting, the intrusive though of standard-free irinotecan struck again. Based on the argument of the lack of randomized trials comparing NAPOLI1 regimen to standard irinotecan-containing regimens such as FOLFIRI, the recommendation for marketing authorization of this regimen was limited in several European countries, including Italy, and in the United Kingdom.

Numerous initiatives have been carried out in order to corroborate the evidence supporting the effectiveness of liposomal irinotecan plus 5-FU/LV in this clinical setting. A retrospective analysis was conducted on 296 patients treated with liposomal irinotecan plus 5-FU/LV as second-line treatment after progression under mainly (79%) gemcitabine plus nab-paclitaxel as first line. These real-world data confirmed the efficacy and safety of NAPOLI1 regimen by measuring a PFS and OS of 3.2 and 7.1 months, respectively.[46] To investigate the potential efficacy of combining liposomal irinotecan with different fluoropyrimidines, the NAPAN study, a multi-center, open-label, randomized phase II trial, was conducted. This study aimed to compare the PFS outcomes between two treatment arms: liposomal irinotecan plus S-1 and liposomal irinotecan plus 5-FU/LV. The study focused on a Western population and targeted second-line treatment for pancreatic ductal adenocarcinoma. The planned enrollment of 120 patients has recently been completed, and the eagerly awaited results are forthcoming.[47]

Integrating liposomal irinotecan in first-line treatment: The NAPOLI 3 trial and the intrusive thought of FOLFIRINOX

The rationale behind incorporating liposomal irinotecan into the treatment of newly diagnosed pancreatic ductal adenocarcinoma patients was to include this agent as part of a multi-drug regimen that had already shown benefits from having a topoisomerase inhibitor among its components. In this regard, an initial phase I/II trial evaluated safety and efficacy of 5FU/LV in combination with increasing doses of liposomal irinotecan and oxaliplatin. In the initial cohort of patients, liposomal irinotecan was administered at a dose of 70 mg/m^2, and oxaliplatin was given at a dose of 60 mg/m^2. However, primary due to myelotoxicity, the doses were escalated and subsequently deescalated in subsequent cohorts. The MTD was determined to be liposomal irinotecan at 50 mg/m^2 and oxaliplatin at 60 mg/m^2. At this dose level, NALIRIFOX had a manageable safety profile and a promising activity with a median PFS and OS measured at 9.2 (95% CI: 7.69–11.96) and 12.6 (8.74–18.69) months, respectively.[48] The decision to escalate also the dose of oxaliplatin in response of an acute adverse event

as myelotoxicity was a strategic move to find a suitable dose for this agent within the NALIRIFOX regimen. The recommended dose of oxaliplatin in NALIRIFOX (60 mg/m^2) is lower than that used in the FOLFIRINOX regimen (85 mg/m^2). This dose modification contributed to one of the most compelling advantages of the NALIRIFOX regimen in terms of safety, the notably low rate of peripheral neurotoxicity, an important late adverse event that often limit the long-term use of FOLFIRINOX.

Building on these promising data, the NAPOLI3 trial was initiated as a randomized, open-label, phase III clinical trial. Its primary objective was to compare the efficacy and safety of the NALIRIFOX regimen with a standard treatment consisting of nab-paclitaxel plus gemcitabine. The trial enrolled patients with metastatic pancreatic ductal adenocarcinoma who had not received prior treatment in the metastatic setting.

Was nab-paclitaxel plus gemcitabine the most appropriate comparator for this trial? The choice of comparator for a randomized controlled trial should be based on several important scientific and ethical considerations. First, the chosen comparator should be clinically relevant and representative of real-world scenarios. Many real-world studies of patients with metastatic pancreatic ductal adenocarcinoma recently treated either in the United States[49] or Europe[50,51] have consistently demonstrated that the percentage of patients receiving nab-paclitaxel plus gemcitabine as first-line treatment is twice that of patients receiving FOLFIRINOX. Furthermore, it is important to identify the standard comparators that have been more commonly used in other studies in the same clinical setting. In this regard, nab-paclitaxel plus gemcitabine has been in the last decade the most commonly used chemotherapeutic backbone for the development of experimental therapeutics in randomized controlled trials investigating the first-line treatment of advanced pancreatic ductal adenocarcinoma patients.[52] Among the four phase III randomized controlled clinical trials actively recruiting patients with newly diagnosed metastatic pancreatic ductal adenocarcinoma, all of them have nab-paclitaxel plus gemcitabine as an active comparator in the control arm (https://clinicaltrials.gov accessed on 1st August 2023). Lastly, for deciding the most appropriate comparator for a randomized controlled trial, the ethics of clinical research requires equipoise,[53,54] a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial. From this standpoint, the design of NAPOLI3 has been the first in evaluating the outcome of starting the treatment of metastatic pancreatic ductal adenocarcinoma patients with a triple *versus* double chemotherapeutic agents combination, settling an aspect that has been among the most long-standing and widely debated topics within the scientific community since the approval of FOLFIRINOX and nab-paclitaxel plus gemcitabine regimens.

The intention-to-treat population in the NAPOLI3 trial included 770 patients from 19 countries worldwide. Patients enrolled were about 31% from North America, 3% from Asia, and 66% from Eastern and Western Europe, South America, and Australia. The patients' characteristics at baseline were well-balanced between the two arms, with a slightly higher rate of patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 1 and Ca19.9 higher than the upper normal limit in the NALIRIFOX arm. In the analysis of OS data based on 544 events during a median follow-up period of 16.1 months, the NALIFIROX group demonstrated a significantly higher median OS of 11.1 months (95% CI 10.0–12.1) compared to the nab-paclitaxel plus gemcitabine group, which had a median OS of 9.2 months (95% CI 8.3–10.6) (HR 0.83, 95% CI 0.70–0.99; $p = 0.04$). Similarly, the NALIFIROX group exhibited a significantly longer median PFS of 7.4 months (95% CI 6.0–7.7) compared to the nab-paclitaxel plus gemcitabine group with a median PFS of 5.6 months (95% CI 5.3–5.8) (HR 0.69, 95% CI 0.58–0.83; $p < 0.0001$). The PFS rates at 12 and 18 months for the NALIFIROX or the nab-paclitaxel plus gemcitabine group were 27.4% *versus* 13.9%, and 11.4% *versus* 3.6%, respectively. These results provide compelling evidence in favor of considering the NALIRIFOX regimen as a potential new standard of care for first-line treatment in patients with metastatic pancreatic ductal adenocarcinoma.

Although the analysis for OS demonstrated a statistically significant advantage for patients receiving NALIRIFOX, it is important to acknowledge that formally the trial did not achieve its pre-specified statistical goal to detect a hazard ratio for OS of 0.75 with 90% power and a 3-month difference in median OS between the treatment arms. Nonetheless, it is worth noting that the hazard

ratio was below the pre-specified final HR threshold for futility of 0.845. Ironically, the median OS of 11.1 months in the NALIRIFOX arm is exactly the same as that measured in the PRODIGE trial for patients receiving FOLFIRINOX. Despite the expected median OS in the NALIRIFOX arm being 12 months, the shadow of its white bear, FOLFIRINOX, seems to weight on the judgment of the NAPOLI3 trial results. Similarly, it could be noted that the measured median OS in the nab-paclitaxel plus gemcitabine arm of the NAPOLI3 trial [9.2 months (95% CI 8.3–10.6)] is slightly longer than that measured in the MPACT trial [8.5 months (95% CI 7.89–9.53)]. However, it is important to emphasize that these cross-trial comparisons are inappropriate speculations, and the most relevant result for interpreting a randomized controlled trial remains the estimation of significant differences in the primary endpoint outcome between the experimental and control arms.

Could subsequent treatments have potentially mitigated the difference in mOS between the two arms? A similar proportion of about 50% of patients in both arms received a second-line systemic therapy. Although specific data about the regimens received are not available thus any definitive conclusions about their impact on the OS results should be made cautiously, it is reasonable to conceive that the approval of liposomal irinotecan plus 5FU/LV as a second-line treatment after gemcitabine-containing regimens, and the widespread real-world use of nab-paclitaxel in this setting, could have acted as an unplanned crossover effect that influenced the OS results. Moreover, the PFS as a secondary endpoint, which reflects only the effect of first-line treatments, showed a more significant hazard ratio of 0.69. Additionally, the 6, 12, and 18-month PFS rates were all in favor of the NALIRIFOX regimen.

Although there was no major difference in the objective response rate between the two arms, it is worth noting that the response rate measured in patients receiving NALIRIFOX (41.8%) was the highest ever measured in a first-line randomized controlled trial. This intriguing finding may appear to be in contrast with the initial crossing of OS and PFS curves. Of note, a similar trend was also observed in the survival curves of FOLFIRINOX and gemcitabine in the PRODIGE trial.[11] This fraction of approximately 10–15% of patients seems to derive a larger benefit from a gemcitabine-containing regimen. Further translational analyses could be extremely useful in identifying these patients with particularly gemcitabine-sensitive tumors.[55]

The benefit of NALIRIFOX over gemcitabine plus nab-paclitaxel was consistently observed across all the prespecified subgroups of patients, particularly in those with a better performance status (ECOG 0) and a higher number of metastatic sites. A particularly interesting finding is the differential effect based on age, with patients older than 65 years receiving a larger benefit from treatment with NALIRIFOX. Notably, a similar effect was also observed in the PRODIGE trial, where FOLFIRINOX showed a greater benefit in older patients compared to younger patients. This effect could appear paradoxical if considered in the light of the germline mutations of BRCA1 and BRCA2, which have been demonstrated to have a clear predictive value for platinum-containing regimens. These genetic alterations are more frequently detected in younger patients or in those with early-onset metastatic pancreatic ductal adenocarcinoma.[56,57] Thus, it remains puzzling how a platinum-containing regimen would be more effective for older patients, as BRCA germline mutations are typically associated with better treatment response to these treatments. It is evident that other molecular mechanisms, beyond BRCA germline mutations, need to be explored to fully understand and explain these apparently controversial results.

In the NAPOLI3 trial, the safety profile of NALIRIFOX was found to be manageable and consistent with the profiles of the individual treatment components. When making decisions on first-line therapy between FOLFIRINOX and nab-paclitaxel plus gemcitabine during the last decade, factors such as genetic alterations, performance status, age, and underlying comorbidities have been taken into consideration. Nonetheless, the choice between the two treatment options has often been influenced by their differing toxicity profiles, with the assumption that the two-drug combination would be safer than the triple combination regimen. The NAPOLI3 trial provides a definitive answer to this long-standing debated topic. Although the incidence of treatment-related serious treatment-emergent adverse events was slightly more frequent with NALIRIFOX than with nab-paclitaxel plus gemcitabine (26.5% *versus* 19.0%), patients on NALIRIFOX remained on treatment for a median of 6 weeks longer (equivalent to 1 treatment cycle) compared to those receiving nab-paclitaxel plus gemcitabine.

Notably, adverse events were the primary reason for treatment discontinuation in 23.8% of patients receiving nab-paclitaxel plus gemcitabine, whereas only 14.1% of those receiving NALIRIFOX discontinued treatment for the same reason. The toxicity profile of these two regimens, however, were different. NALIRIFOX was associated with a higher rate of serious gastrointestinal toxicities than did nab-paclitaxel plus gemcitabine, with diarrhea being the most common grade $\geqslant 3$ adverse event in 20.3% of patients. On the other hand, serious hematologic adverse events and cumulative peripheral neuropathy, a particular concern with oxaliplatin- containing regimens, were more common in the nab-paclitaxel plus gemcitabine than in the NALIRIFOX group, likely due to a low cumulative dose of oxaliplatin with this last regimen. Furthermore, in a recent analysis of the quality of life, NALIRIFOX demonstrated a trend toward improvement in global health status from baseline and a longer time to deterioration in several EORTC QLQ-C30 subscales compared to nab-paclitaxel plus gemcitabine (Melisi *et al.* ESMO 2023). These findings indicate that NALIRIFOX may offer potential benefits in terms of quality of life and symptom management for patients undergoing treatment.

A recent meta-analysis, encompassing data from seven randomized controlled trials involving a total of 383 patients treated with NALIRIFOX, 433 with FOLFIRINOX, and 1756 with nab-paclitaxel plus gemcitabine in the first-line setting, reinforced similar conclusions.[58] Although the analysis lacked the power for a direct comparison between NALIRIFOX and FOLFIRINOX outcomes, it consistently demonstrated that patients treated with any of these three-drug combinations experienced longer PFS and OS compared to those receiving nab-paclitaxel plus gemcitabine. Importantly, the meta-analysis corroborated the distinct safety profiles observed in the NAPOLI3 trial. Notably, NALIRIFOX exhibited the most favorable toxicity profile, with significantly lower incidences of hematological toxic effects and peripheral neuropathy compared to the other regimens. Although a higher incidence of diarrhea was noted with NALIRIFOX than with nab-paclitaxel plus gemcitabine, it was not significantly different from that observed in patients treated with FOLFIRINOX.

One last aspect that will be a matter for future investigations pertains to the cost-effectiveness of NALIRIFOX regimen. The randomized design of the NAPOLI3 trail will allow a clear and prospective estimation of the cost-effectiveness of NALIRIFOX *versus* nab-paclitaxel plus gemcitabine in terms of incremental cost-effectiveness ratio and net monetary benefit. Nonetheless, the final drug costs determined through the negotiation with national reimbursement bodies will determine the actual cost-effectiveness in each country. Conversely, a cost-effectiveness estimation of NALIRIFOX *versus* FOLFIRINOX could be conducted only in the future in real-world population-based comparisons. It is important to notice that the toxicity profile of NALIRIFOX demonstrated in the NAPOLI3 study was favorable, notably with rates of G3-4 neutropenia (14.1%) largely lower than those measured with FOLFIRINOX in the PRODIGE trial (45.7%). This would lead to a lower growth factor utilization and, therefore, lower costs. An observational study among Medicare fee-for-service beneficiaries receiving FOLFIRINOX as first-line treatment found that patients receiving administrations with all four component drugs were associated with the highest incidence of adverse events as well as the highest total cost of care per administration cycle. This was notably driven by cases of neutropenia that were twice as frequent in patients receiving FOLFIRINOX with all four components compared to those receiving FOLFIRINOX with no 5-FU of any kind.[59,60] Reflective of these elements, a US study examining the total cost of care for Medicare patients found that those who received second- or third-line liposomal irinotecan had lower costs than patients who received all other regimens, notably due to the lower inpatient admission patterns of patients receiving liposomal irinotecan.[61]

Engaging in constructive distractions: The future of liposomal irinotecan in pancreatic ductal adenocarcinoma research

One of the most effective ways to manage intrusive thoughts is to find a constructive distractions that allow refocusing energy and engaging the brain. Currently, there are several clinical trials exploring liposomal irinotecan in different clinical stages. In the metastatic setting, the PRODIGE 61/FUNGEMAX phase II study is currently investigating the first-line treatment options of nab-paclitaxel plus gemcitabine *versus* liposomal irinotecan plus 5FU/LV, or the sequential use of these regimens alternately every 2 months (NCT03693677). In the phase II GIANT trial

(NCT04233866), the efficacy of liposomal irinotecan plus 5-FU/LV *versus* nab-paclitaxel plus gemcitabine is being compared in patients aged 70 years and older with metastatic, untreated pancreatic ductal adenocarcinoma. The NALPAC phase II study is evaluating the efficacy of liposomal irinotecan plus 5-FU/LV *versus* NALIRIFOX in patients progressed after a gemcitabine-based therapy (NCT05472259). For patients with locally advanced disease, two phase II single-arm trials are investigating the NALIRINOX regimen (NCT03861702) or its combination with ablative dose radiation therapy (NCT05851924) as a first-line strategy. We recently contributed to this field by conducting an investigator-initiated, Simon's two-stages, single-arm phase II study that evaluated the safety and the activity of NALIRIFOX in the perioperative treatment of 107 patients with upfront resectable pancreatic ductal adenocarcinoma. Preoperative NALIRIFOX demonstrated a radiological DCR of 92.9% and an R0 resection rate of 65·3%. This level of activity translated into a long OS durations of 32.3 months in the intention-to-treat population, and 44.3 months in the patients who underwent resection.[62] A similar regimen is being evaluated as neoadjuvant therapy in patients with resectable or borderline resectable pancreatic ductal adenocarcinoma in the phase II NEO-NalIRI study (NCT03483038).

A different constructive distraction in this field could be the identification of biomarkers for tumors that are resistant to a given treatment.[63,64] NAPOLI3, being a randomized controlled trial that allocates patients to either a gemcitabine-based or a 5FU-based chemotherapy, represents an ideal framework to explore potential predictive factors for these two different classes of treatment.

Molecular subtypes have demonstrated prognostic value, with classical tumors responding better to first-line chemotherapy compared to the more resistant basal-like ones.[65] However, these genomic and transcriptomic classifications have not shown any predictive role that could provide specific guidance on which chemotherapy agents or targeted therapies would be most effective for individual patients. Understanding the molecular and cellular mechanisms involved in the communication between neoplastic and stromal cells within the recently discovered ecotypes, as well as their potential predictive role in response to approved or experimental therapeutics, remains of paramount importance. TAMs are a crucial component of the cancer microenvironment, capable of limiting the effectiveness of chemotherapies. Research from our group and others has demonstrated that a TH_2 profile of cytokines involved in macrophage attraction and polarization serves as a significant negative prognostic factor in patients with pancreatic ductal adenocarcinoma.[66] Given their role in actively internalizing and activating liposomal irinotecan, resulting in a more efficient release of SN-38 within the tumor microenvironment, infiltration rates, and polarization of TAMs are among the most promising predictive biomarkers for this agent.

In our search for the most significant tumor-secreted protein in liposomal irinotecan-resistant pancreatic ductal adenocarcinoma models, we recently demonstrated that interleukin-8 was the circulating factor most strongly correlated with survival (plasma levels lower *versus* higher than cutoff: median overall survival (mOS) 8.9 *versus* 5.3 months, HR = 3.51, 95% CI = 0.84–6.68, $p = 4.9e\text{-}05$) in a discovery cohort of 77 patients with gemcitabine-refractory metastatic pancreatic ductal adenocarcinoma, who were prospectively enrolled to receive liposomal irinotecan plus 5-FU/LV as second or further line therapy. These findings were confirmed in a validation cohort of 50 patients.[67] These distinct cell populations and chemokines could be explored in biological samples from NAPOLI3 trial and serve as useful biomarkers to select those patients who are most likely to benefit more significantly from liposomal irinotecan.

Conclusion

The progress of science relies upon experimental evidence and not conjectures or speculations. Nanoliposomal irinotecan is the only recent therapeutic agent to date that has demonstrated a statistically significant advantage of combination regimens that included it over the standard treatments in large randomized controlled trials, either as first- or second-line treatment for metastatic pancreatic ductal adenocarcinoma. Suppositions about the possible equivalence of liposomal irinotecan with standard-free irinotecan have been dispelled by clear pharmacologic and preclinical evidence. Most importantly, liposomal irinotecan demonstrated a significant advantage where standard irinotecan failed, as seen with NAPOLI1 trial in the second-line treatment.

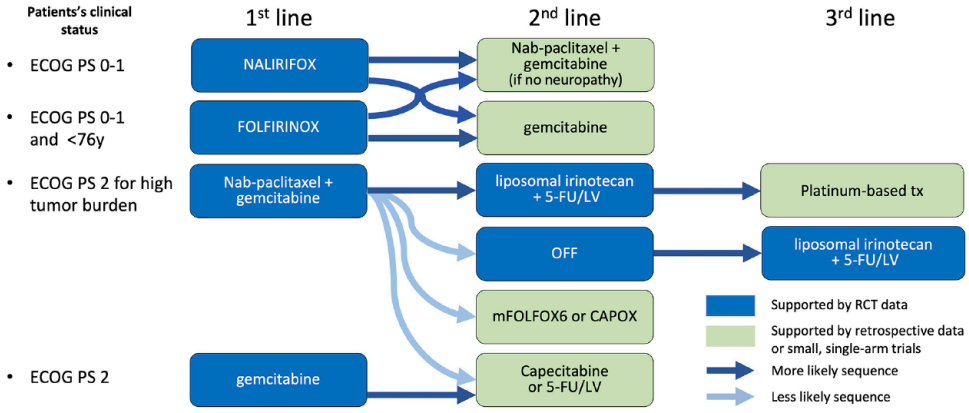

Figure 2. Optimal therapeutic sequences for metastatic pancreatic ductal adenocarcinoma upon approval of NALIRIFOX.

In the event of approval by US and European drug agencies, NALIRIFOX could become a new potential first-line choice in the therapeutic algorithm for patients with metastatic pancreatic ductal adenocarcinoma and a good performance status of 0 or 1 according to the ECOG scale (Figure 2). FOLFIRINOX might remain an option for these patients but with the age limit set at 76 years. Following these 5FU/LV-based regimens, the option of nab-paclitaxel plus gemcitabine could be considered, especially after progression on NALIRIFOX, given its significantly lower incidence of cumulative peripheral neuropathy that might limit the use of taxanes. In cases where there is a residual high grade of this toxicity, single-agent gemcitabine could be a viable alternative. Based on the NAPOLI 3 study, NALIRIFOX has demonstrated superiority over gemcitabine plus nab-paclitaxel. As a result, this double-combination regimen should be reserved for patients with a frail performance status of ECOG 2 mainly due to a large tumor burden, or with elevated bilirubin levels. If progression occurs, these patients could receive the NAPOLI1 regimen. Due to the frequent peripheral neuropathy induced by nab-paclitaxel, it is less likely for them to be considered for a platinum-containing treatment, such as the OFF regimen. For patients diagnosed with a performance status of ECOG 2 or age over 85, a sequence of monotherapies with gemcitabine, followed by capecitabine or 5FU/LV, could be considered.

Dostoyevsky was right. When we set out to avoid thinking about a white bear, it tends to persistently appear at every turn. But if we adopt a different approach, acknowledging it, embracing it, confronting it, or if we redirect our minds toward more productive ideas, we increase our chances of eventually freeing ourselves from its grip. We are hopeful that the evidence presented and discussed here can dispel any further intrusive thoughts and contribute to a rational and well-considered judgment of liposomal irinotecan and its potential integration into the therapeutic strategies for pancreatic ductal adenocarcinoma. By focusing on the scientific data and its implications, we can make informed decisions that may lead to improved treatment options and outcomes for patients with this challenging disease.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Davide Melisi: Conceptualization; Funding acquisition; Writing – original draft; Writing – review & editing.

Simona Casalino: Writing – review & editing.

Silvia Pietrobono: Writing – review & editing.

Alberto Quinzii: Writing – review & editing.

Camilla Zecchetto: Writing – review & editing.

Valeria Merz: Resources; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Not applicable.

ORCID iDs
Davide Melisi https://orcid.org/0000-0002-4031-7585

Valeria Merz https://orcid.org/0000-0002-2120-1923

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