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Oncology

A phase III randomized clinical trial of Gemcitabine and Nab-Paclitaxel as switch maintenance versus continuation of modified FOLFIRINOX as first-line chemotherapy in patients with advanced pancreatic cancer: The PANThEON Study

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ABSTRACT

Background: Advanced pancreatic ductal adenocarcinoma (PDAC) remains among the most lethal cancers, with >95 % of patients dying from the disease. Chemotherapy is the standard of care in advanced stages, with FOLFIRINOX and Gemcitabine-Nab-Paclitaxel (Gem-NabP) as the main first-line regimens. Both show moderate efficacy and significant toxicity. Except for the PASS-01 trial, no direct comparison exists, though observational studies suggest that specific subgroups may benefit differently. Given the modest outcomes and rapid clinical decline, most patients are ineligible for second-line therapy after progression. The PANThEON study evaluates whether switching from modified FOLFIRINOX (mFOLFIRINOX) to Gem-NabP after three months of induction with mFOLFIRINOX improves outcomes for PDAC.
Methods: PANThEON is a no-profit, phase III, randomized, open-label, multicenter trial. The primary endpoint is overall survival (OS). Secondary endpoints include progression-free survival (PFS), time to treatment failure (TTF), overall response rate (ORR), and quality of life (QoL). Exploratory analyses will assess tumor profiling, circulating tumor DNA (ctDNA), and radiomics to identify predictive markers. A total of 220 patients will be randomized 1:1 to Gem-NabP (arm B) or continued mFOLFIRINOX (arm A).
Discussion: The PANThEON trial addresses two challenges: improving efficacy while reducing toxicity. Switching to Gem-NabP may enhance tolerability without compromising benefit, prolonging survival and refining PDAC treatment strategies.
Trial registration: PANThEON is registered at ClinicalTrials.gov (NCT06897644) and EuCT (2024-515214-41-00).

1. Background

Pancreatic cancer is a deadly neoplasm, with >95 % of affected patients dying of their disease [1]. It is the third leading cause of cancer-related deaths in Western countries and is expected to become the second by 2030. Among the different histology subtypes of exocrine pancreatic cancer, ~95 % are represented by pancreatic ductal adenocarcinoma (PDAC), while all other subtypes represent rare histologies [2]. Surgery is the only curative treatment for PDAC, although 80 % of patients are diagnosed with an advanced unresectable stage, leading to a 5-year survival rate under 5 % [3,4].

Chemotherapy represents the standard of care for both locally advanced (LAD) and metastatic PDAC (mPDAC), with Gemcitabine + Nab-Paclitaxel (Gem-NabP) and FOLFIRINOX being standard of care for first line treatment since 2013, based on the results of MPACT [5] and ACCORD11 studies [6], respectively. Given the significant toxicity of FOLFIRINOX, a modified version (mFOLFIRINOX) was implemented and first tested in the PRODIGE 24–CCTG PA6 trial as adjuvant treatment in patients who underwent surgery for PDAC [6,7]. Later on, its activity and tolerability were confirmed in the metastatic setting [8,9].

These two combinations have not been formally compared in a clinical trial, in the western population, except for the recent PASS-01 trial [10], so that real-world observational studies and indirect evaluations (i.e. meta-analyses) tried to define which patients would benefit the most from each regimen [11,12]. At the same time, after a decade of unsuccesfull studies, the NAPOLI-3 phase III trial showed a benefit of the NALIRIFOX (fluorouracil, leucovorin, liposomal irinotecan, and oxaliplatin) regimen over Gem-NabP in terms of both progression free survival (PFS) and overall survival (OS), thus becoming a candidate new reference regimen in this setting [13]. However, recently published systematic reviews and meta-analyses showed that NALIRIFOX and FOLFIRINOX have similar PFS and OS as first-line treatment of advanced PDAC, despite significantly different costs [14,15].

Second-line therapy for PDAC is usually chosen based on prior regimens and patient condition, with Gemcitabine- and nanoliposomal-based regimens being the most widely adopted [16]. However, given the modest efficacy of current first-line regimens and the rapid clinical deterioration of patients with PDAC, the majority becomes ineligible for second-line therapy after the first disease progression. Therefore, the early administration of an active, non-cross resistant treatment after first-line therapy before disease progression, might prolong the benefit of first-line treatment and could delay clinical deterioration. Combining chemotherapy regimens in sequential or alternating strategies has been tested in trials such as the SEQUENCE and the NEOLAP-AIO-PAK-0113 studies [17,18]. The phase II SEQUENCE clinical trial evaluated Gem-NabP and mFOLFOX used in a sequential, alternating regimen, as compared to Gem-nabP. In detail, patients received one cycle of Gem-NabP (on days 1–8–15) and one cycle of mFOLFOX (on days 29–30) every six weeks (Gem-NabP/mFOLFOX), compared with standard Gem-NabP. Patients receiving Gem-NabP/mFOLFOX showed a significantly higher median OS (13.2 vs 9.7 months, HR 0.68, 95 % CI 0.48–0.95) and PFS (7.9 vs 5.2 months, HR 0.52, 95 % CI 0.36–0.73) compared to those receiving standard Gem-nabP. However, this regimen is hard to implement in clinical practice, both in terms of logistics and mostly for toxicity management, as adverse events are hard to attribute to each regimen or compounds [17]. The NEOLAP-AIO-PAK-0113 multicentric, randomized, phase II trial comparing Gem-NabP versus Gem-NabP induction followed by switch to FOLFIRINOX, showed better tolerability of the sequential regimen, though with no significant difference in terms of OS (18.5 vs. 20.7, HR 0.86, 95 % CI 0.55–1.36) in patients with locally advance disease [18]. Moreover, different phase II trials investigated sequential first-line treatment strategies. In the FIRGEM study alternating FOLFIRI and gemcitabine improved PFS compare to gemcitabine [19]. The GABRINOX phase I–II trial demonstrated that administering Gem-NabP followed by FOLFIRINOX was a safe and active first-line approach with a PFS of 10.5 months (95 % CI 6.0–12.5 months) and a median OS of 15.1 months (95 % CI 10.6–20.1 months) [20]. In contrast, the FUNGEMAX-PRODIGE 61 trial did not show superiority of fluorouracil, leucovorin, liposomal irinotecan (NAPOLI) or NAPOLI followed by Gem-

NabP over Gem-NabP alone, although it confirmed that the sequence of NAPOLI and Gem-NabP was a feasible treatment option [21].

More recently, our group reported the results of the ARMANI trial, a multicenter, Italian, no profit phase III trial, which showed that a switch maintenance with ramucirumab and paclitaxel provides a significant benefit versus continuation of first-line oxaliplatin-based chemotherapy both in terms of PFS (6.6 vs. 3.5 months, HR 0.61, 95 % CI 0.48–0.79) and OS (12.6 vs. 10.4 months, HR 0.75, 95 % CI 0.58–0.96) in patients with metastatic HER2 negative gastric or gastro-oesophageal cancer [22]. Overall, these data support the investigation of a switch maintenance strategy after first-line induction chemotherapy in patients with advanced PDAC.

Maintenance therapy after initial chemotherapy, in patients with advanced PDAC, is still under investigation, with some studies, such as ALPACA trial or PANOPTIMOX-PRODIGE 35 trial, suggesting the potential benefits of de-escalating treatment for patients who achieve stable disease to improve tolerability [23,24]. In particular the phase II PANOPTIMOX-PRODIGE 35 trial showed that maintance with fluorouracil and leucovorin after 4 months of FOLFIRINOX is an effective strategy and survival was comparable to 6 months of FOLFIRINOX [24]. Moreover, the POLO trial showed that Olaparib could be an effective maintenance therapy for patients with *BRCA1/2 or PALB2* mutations, though without a benefit in OS [25].

From a molecular standpoint, germline BRCA1/2 mutations are found in ∼3 % of western patients, within the subset of PDAC exhibiting homologous recombination deficiency (HRD), which constitutes approximately 25 % of mPDAC [26]. These subtypes demonstrate increased sensitivity to platinum-based chemotherapy and PARP inhibitors [27]. Beyond this, PDAC is characterized in over 90 % of instances by KRAS mutations, frequently co-occurring with *TP53*, *SMAD4*, and *CDKN2A* mutations as the most common genomic alterations [28]. Despite this frequent genomic homogeneity, PDAC subtypes have been identified based on transcriptomic profiling, with the classical and basal-like subtypes being the most widely validated entities [29]. These subtypes exhibit distinct responses to different chemotherapy regimens. For example, basal-like tumors show greater responsiveness to Gem-NabP, while classical tumors tend to respond better to mFOLFIRINOX [30]. However, HRD testing is not always routinely available prior to treatment initiation, and transcriptomic profiling is not standard clinical practice [26]. Therefore, exposing tumors to all available chemotherapy regimens may enhance treatment efficacy by targeting diverse subtypes. Furthermore, several transcriptomic signatures, such as *GemPred, GemCore*, and *PancreasView*, have recently been developed to predict sensitivity to gemcitabine and FOLFIRINOX components, aiming to facilitate a more personalized treatment approach [31,32]. While these signatures have shown promising results in predicting patient outcomes, primarily in the adjuvant setting, further validation is necessary, particularly in combination with Nab-Paclitaxel [33].

Based on these considerations, the PANThEON study aims at investigating whether switching first-line treatment to Gem-NabP after a mFOLFIRINOX-based 3 months induction may improve patients' OS and tolerability as compared with mFOLFIRINOX continuation.

2. Methods

2.1. Aims

The primary objective of this study is to evaluate the efficacy of switching first-line treatment to Gem-NabP (arm B) after mFOLFIRINOX-based 3 months induction compared to mFOLFIRINOX continuation (arm A). The primary study endpoint is OS, while secondary enpoints are PFS, time to treatment failure (TTF), overall response rate (ORR), quality of life (QoL), toxicities, proportion of patients not eligible to randomization and subsequent treatment line frequency.

2.2. Trial design

PANThEON is a randomized, open-label, multicenter phase III trial. This is a superiority trial evaluating Gemcitabine plus nab-paclitaxel, given as switch maintenance (arm B), versus continuation of mFOLFIRINOX (arm A), given as per standard clinical practice, in subjects with unresectable locally advanced or metastatic pancreatic adenocarcinoma without disease progression after 3 months of induction mFOLFIRINOX triplet chemotherapy.

Patients will be enrolled by their treating investigators and assigned to a treatment arm by 1:1 central randomization. Before randomization, patients will be stratified based on Easter Cooperative Oncology Group (ECOG) Performance status (PS, 0 vs 1) and disease extension (locally advanced vs metastatic with presence of liver metastases vs metastatic without presence of liver metastases). The study schema is depicted in Fig. 1.

The planned population of 220 patients will be randomized at 28 study centers in Italy (see Table 1). The study is sponsored by the Gruppo Oncologico Nord Ovest (GONO) Foundation and partially by from the Rising Tide®, Foundation for Clinical Cancer Research.

Registration, randomization and data collection procedures will be performed using the MyHealth platform, which is a secure, browser-based web application widely used by researchers offering unique features, including the randomization that can be used to conduct rigorous RCT. Investigator meetings and monthly accrual updates will be held to ensure adequate enrollment.

The sponsor GONO Foundation will be responsible for data management of this study, including quality checking of the data.

2.3. Study endpoints

The primary endpoint of the study is the **Overall Survival (OS),** defined as time from randomization to death of all causes or last follow-up for alive patients.

Additional secondary endpoints are:

- **Progression free survival (PFS)**, i.e. the time from randomization to disease progression or death from any cause;
- **Time to treatment failure** (**TTF)**, i.e. the time from randomization to discontinuation of treatment for any reason, including progressive disease, treatment toxicity and death;
- **Objective response rate (ORR)** i.e. the percentage of patients achieving a complete (CR) or partial (PR) response, according to RECIST 1.1 criteria, and **DCR**, i.e. the percentage of patients achieving a complete (CR) or partial (PR) response or a stable disease (SD), according to RECIST 1.1 criteria;
- **Quality of life (QoL),** i.e. QoL will be estimated with EORTC QLQ-C30 and the modules INFO25, PAN26, FA12, CAX24, COMU26 and CIPN20; mean score changes from baseline, proportion of patients with improved, stable, or deteriorated scores from baseline and time to deterioration in the EORTC QLQ-C30, PAN-26, CAX24, CIPN20, physical functioning, social functioning, and fatigue scores will be compared between the two arms. Time to deterioration will be defined as the time from baseline to the first onset of a 10-point or greater decrease from baseline for functional scales or a 10-point or greater increase for symptom scales, with confirmation under the right-censoring rule. All available observations will be used to calculate time to deterioration. Evaluation of the level of information will be performed with the EORTC QLQ INFO25, which is a valid self-reported instrument consisting of 25 questions. Communication

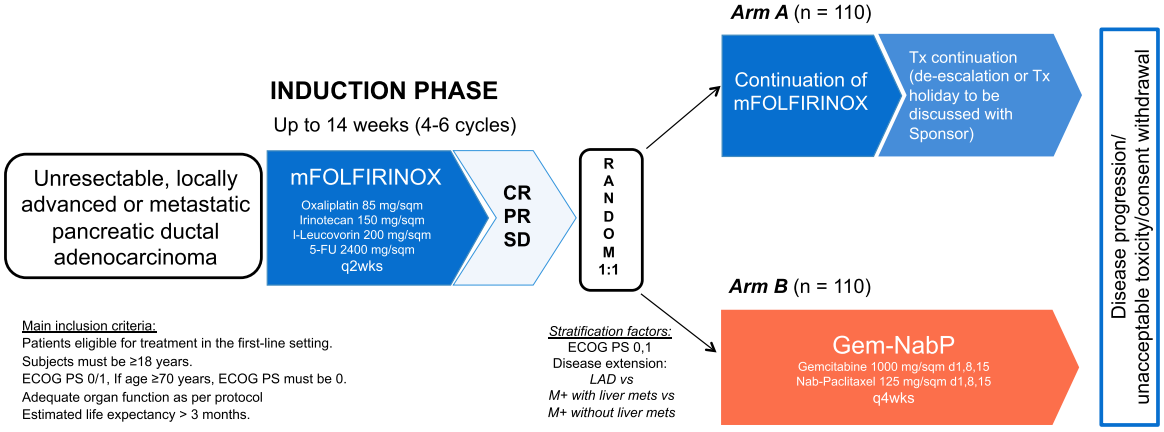

Fig. 1. PANThEON Study design.

Table 1
Participating centers.

Numero Centro	Sede Centro	Istituto	Pi
1	Milano	Fond. IRCCS Istituto Nazionale dei Tumori	Filippo Pietrantonio
2	Aviano	Centro Riferimento Oncologico	Elena Ongaro
3	Bari	A.O.U.C. Policlinico di Bari	Francesco Mannavola
4	Brescia	ASST Spedali Civili di Brescia	Giuseppina Arcangeli
5	Catania	Humanitas Istituto Clinico Catanese	Carlo Carnaghi
6	Crema	ASST Ospedale Maggiore di Crema	Gianluca Tomasello
7	Cremona	ASST di Cremona	Maria Bonomi
8	Faenza	Azienda USL della Romagna	Stefano Tamberi
9	Firenze	Az. Ospedaliero-Universitaria Careggi	Lorenzo Antonuzzo
10	Genova	IRCCS Ospedale Policlinico San Martino	Roberto Murialdo
11	Milano	Istituto Oncologico Europeo	Chiara Alessandra Cella
12	Milano	ASST Grande Ospedale Metropolitano Niguarda	Katia Bencardino
13	Milano	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico	Barbara Galassi
14	Meldola	Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.)	Ilario Giovanni Rapposelli
15	Napoli	Ospedale del Mare	Laura Attademo
16	Novara	AOU Maggiore della Carità - Novara	Laura Forti
17	Padova	I.R.C.C.S. Istituto Oncologico Veneto	Francesca Bergamo
18	Parma	Azienda Ospedaliero-Universitaria di Parma	Ingrid Garajovà
19	Pavia	IRCCS San Matteo	Salvatore Corallo
20	Pesaro-Urbino	Azienda Sanitaria Territoriale Pesaro Urbino (AST PU)	Rita Chiari
21	Pisa	Azienda Ospedaliero Universitaria Pisana	Caterina Vivaldi
22	Ponderano	Nuovo Ospedale degli Infermi	Francesco Leone
23	Prato	Nuovo Ospedale di Prato – S. Stefano	Samantha Di Donato
24	Roma	Policlinico Universitario A. Gemelli	Lisa Salvatore
25	Roma	IRCCS Istituto Nazionale Tumori Regina ELena	Emanuela Dell'Aquila
26	Rozzano	Istituto Clinico Humanitas	Silvia Bozzarelli
27	Tricase	E.E. "Card. G. Panico" - Tricase	Emiliano Tamburini
28	Udine	Presidio Ospedaliero "Santa Maria della Misericordia" di Udine	Silvio Ken Garattini

between patients and professionals will be assessed with the EORT QLC COMU26.

- **Toxicity,** i.e. the percentage of patients, relative to the total of subjects experiencing a specific adverse event, according to National Cancer Institute Common Toxicity Criteria (version 5.0).
- **Proportion of patients not eligible to randomization**, i.e. patients who started induction treatment but result not eligible due to i) clinical deterioration or treatment toxicity, ii) withdraw consent, iii) disease progression documented as best response; iv) other causes.
- **Subsequent treatment lines frequency**, i.e. the percentage of patients who undergo a systemic treatment (excluding locoregional treatments or surgical treatment of unresectable disease) after progression to first line in both arms.

Exploratory studies including Next-Generation Sequencing (NGS) in archival tumor tissues, longitudinal circulating tumor DNA (ctDNA) analysis, radiomic, radiogenomic and pathomic analyses are planned in order to predict the presence of specific molecular targets, tumor heterogeneity, and to identify patients that may achieve the best outcomes with the switch maintenance strategy with Gem-NabP compared to mFOLFIRINOX continuation.

Samples and imaging scans will be stored at the coordinating center Fondazione IRCCS Istituto Nazionale Tumori (INT) in Milan, Italy.

2.4. Clinical setting

Patients affected by histologically or cytologically confirmed unresectabled locally advanced or metastatic, eligible for treatment in the first line setting.

Other main inclusion criteria are:

- Age ≥18 years and <75 years
- ECOG PS 0–1, if age ≥ 70 years ECOG PS must be 0
- Adequate hematologic, hepatic, renal and coagulation function
- Available archival tumor tissue for exploratory research
- Presence of measurable or non-mesurable disease assessed by CT scan and/or MRI according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

- Estimated life expectancy > 3 months

Main exclusion criteria are:

- Pancreatic neuroendocrine, acinar, squamous/adenosquamous, or islet tumors
- Previous or concurrent systemic (e.g. cytotoxic or targeted or other experimental drugs) therapy for advanced pancreatic adenocarcinoma. In case of prior neo(adjuvant) chemotherapy, progression of disease must have occurred >9 months after treatment completion without any residual toxicity
- Major surgery or radiation therapy performed within <4 weeks before randomization
- Known allergy or hypersensitivity to study drugs and/or their excipients
- Unresolved toxicity ≥ CTCAE grade 2 attributed to any prior therapies (e.g. grade ≥2 peripheral neurotoxicity), excluding anemia or alopecia.
- Presence of symptomatic central nervous system (CNS) metastases, or CNS metastases that requires directed therapy (such as radiotherapy or surgery) or increasing doses of corticosteroids 2 weeks prior to study entry
- Any known additional malignancy that is progressing or requires active treatment
- Any serious underlying medical conditions (judged by the investigator), that could impair the ability of the patient to participate in the trial

2.5. Treatment

The induction chemotherapy regimen will be mFOLFIRINOX as per standard of care, with the following dose and schedule:

- Oxaliplatin 85 mg/square meter (sqm);
- Irinotecan 150 mg/sqm;
- Leucovorin 400 mg/sqm (racemic) or L-Leucovorin 200 mg/sqm;
- 5-FU 2400 mg/sqm 46-hours infusion;

every 2 weeks.

Treatment must be continued for up to a maximum of 14 weeks, corresponding to ∼ 6 bi-weekly cycles. A minimum of 4 treatment cycles administered is necessary for the patient to be evaluable for randomization.

Subjects with CR/PR/SD after induction regimen in case of measurable disease, or without progressive disease in case of non-measurable disease, will be randomized in 1:1 ratio between the two treatment arms.

- **Arm A:** Continuation of the same regimen used as induction chemotherapy.
- **Arm B:** Gemcitabine 1000 mg/sqm plus Nab-Paclitaxel 125 mg/sqm on Days 1,8,15 of every 28-day cycles.

Treatment will continue until disease progression, unacceptable toxicity, informed consent withdrawal, or patient's death in both arms, whichever comes first. For patients in arm A, treatment holiday or descalation of the treatment is permitted upon discussion with the Sponsor. In case of permanent discontinuation of one or more compounds due to unacceptable toxicity, treatment with the other agent(s) may be continued until disease progression in each arm. Second-line treatment will be at Investigator's discretion.

As defined in the study protocol, surgical resection is recommended in responsive patients with locally advanced disease. In particular it is strongly recommended to assess indication for surgery every 2 months, in the frame of a multidisciplinary group with expertise in the management of PDCA. Whenever a patient is submitted to radical resection, post-operative disease status should be re-evaluated within 8 weeks from surgery and a close post-operative follow up should be performed. Post-operative treatment is at the discretion of the investigator, according to prior treatment, performance status and surgery outcome, and must be discussed with the Sponsor.

Conversely, given the still controversial role of radiotherapy in locally advanced pancreatic ductal adenocarcinoma and the lack of a clear survival benefit compared with chemotherapy alone [34], radiotherapy is not permitted within this trial. Any potential indication for radiotherapy should therefore be evaluated on a case-by-case basis and discussed with the study team prior to administration.

2.6. Statistical methods

Sample size justification. A total of 220 subjects will be randomized 1:1 in each treatment arm over a 36-month period of uniform accrual, followed by 12 months of follow-up. To achieve this goal, about 340 subjects need to be enrolled at the start of first-line treatment, expecting a drop-out rate during or after the 3 months of induction chemotherapy of about 35 % due to disease progression (clinical and/or radiological, according to historical data), unacceptable toxicity, patient refusal, or other causes. With such a sample size and a two-sided alfa of 5 %, the study provides 80 % power to detect a hazard ratio (HR) of 0.65. Based on historical data, when the median OS from randomization in the control arm is 10 months, this HR corresponds to an increase in median OS of 5.4 months, to be regarded as a clinically meaningful effect.

2.7. Statistical analysis

Intention-to-treat (ITT) population: Patients enrolled and randomized in the trial by signing the informed consent and assigned a study identification number.

Per protocol (PP) population: ITT population excluding all the patients that did not receive maintenance treatment for any cause, severely violated protocol inclusion/exclusion criteria or have withdrawn informed consent.

Safety population: Patients who had received at least one dose of maintenance treatment.

Standard descriptive statistics will be calculated for categorical data (i.e., frequency and percentage) and continuous data (i.e., median and interquartile range) according to the ITT and PP populations.

The OS curves will be estimated with the Kaplan-Meier method and compared in the two treatment arms by using the log-rank test. The HR and the corresponding 95 % confidence interval will be estimated using a Cox model. To anticipate the study termination in case of futility, an interim analysis based on the calculation of conditional power is planned when at least 60 deaths are registered (35 % of the number of events necessary to reach the power of the study). In particular, the study will be continued if the conditional power under the observed trend is at least 30 % (indicating a promising provisional result) or stopped otherwise.

The OS, PFS and TTF curves will be estimated with the Kaplan-Meier method and compared in the two treatment arms by using the log-rank test. In the ITT and PP populations, ORR will be estimated as the percentage of patients achieving a CR or PR according to RECIST 1.1 criteria, and DCR as the percentage of patients achieving CR, PR or SD. For both OR and DCR, exact 95 % confidence intervals will be estimated, and between group comparisons will be performed using Pearson's Chi- Square test. Among exploratory analyses, the impact of transcriptomic-based tumor subtypes will be assessed on patients' outcomes.

Cox models for OS/PFS and a binary logistic model for ORR will be estimated including an interaction term between the treatment

arm and transcriptomic subtypes, in order to assess the treatment effect according to the different strata. For EORTC QLQ-C30, PAN26, CAX24, CIPN20, physical functioning, social functioning, and fatigue scores, descriptive tabular or graphical analyses will be performed. In particular, mean score changes from baseline, proportion of patients with improved, stable, or deteriorated scores from baseline and time to deterioration will be compared between the two arms. Time to deterioration will be defined as the time from baseline to the first onset of a 10-point or greater decrease from baseline for functional scales or a 10-point or greater increase for symptom scales, with confirmation under the right-censoring rule. All available observations will be used to calculate time to deterioration.

Tables of adverse event incidence and individual incidence will be produced according to the primary system-organ class (SOC) and within the category defined in the CTCAE v.5.0. The summaries will be overall (severity grades 1–5) and for grade $\geq$3 events. The analysis will be performed on the safety population.

3. Discussion

Considering the poor prognosis of patients with advanced PDAC and the limited efficacy of standard treatments, new strategies to overcome chemotherapy resistance are urgently needed.

The two most important unmet needs in treatment strategies for advanced PDAC are i) to improve the efficacy of the first-line triplet chemotherapy while reducing its toxicity, thus improving tolerability and quality of life (QoL) and ii) to increase the percentage of patients that will be eligible for an active subsequent line-therapy. In details, continuation of first-line chemotherapy until disease progression is often burdened by cumulative toxicities and occurrence of drug resistance. Currently, both FOLFIRINOX and Gemcitabine-based regimens are approved and recommended as first-line treatment options for LAD and mPDAC [5,6,35]. In the Western population, a direct comparison between the two regimens has not been tested in a clinical trial. However, the NAPOLI-3 trial showed that the triplet NALIRIFOX, a regimen very similar to FOLFIRINOX in terms of type and dosage of the drugs administered, is superior to the Gem-NabP doublet as first-line treatment of mPDAC [13]. Recent meta-analyses confirmed the superiority of FOLFIRINOX and NALIRIFOX over Gem-NabP, without a significant difference between the two triplets [14,15]. Moreover, observational studies revealed that, among possible treatment sequences, the best outcomes have been observed in patients treated with first-line mFOLFIRINOX and second-line Gemcitabine-based combinations [36]. Finally, presence of HRD is an established biomarker of higher sensitivity to platinum-based chemotherapy, but HRD status is often unknown at the time of treatment initiation and the result of the analysis, in clinical practice, takes weeks or months [26]. Therefore, upfront use of a non-platinum-based regimen may miss targeting this relevant biomarker.

Given these considerations, mFOLFIRINOX represents the best choice as upfront treatment for LAD or mPDAC. Moreover, given the significant toxicity associated with this triplet regimen, de-escalation after obtaining disease control or response may prolong treatment efficacy, while improving tolerability. The phase II PANOPTIMOX-PRODIGE 35 trial showed that, in order to impact overall survival, a short but effective induction phase is sufficient. However median overall survival remains around 10 months in both arms (maintance with fluorouracil and leucovorin after 4 months of FOLFIRINOX vs. 6 months of FOLFIRINOX) [24].

In this light, switching to an active, doublet regimen as Gem-NabP may allow patients to be exposed to all active chemotherapy regimens before clinical deterioration and inability to sustain repeated administrations and actually confer an even greater advantage; furthermore, it may avoid the cumulative toxicity of the triplet mFOLFIRINOX regime. Lastly, this strategy may allow to suspend induction chemotherapy before the tumor becomes resistant, so that the same (or similar, e.g. nanoliposomal irinotecan) compounds of mFOLFIRINOX may be newly administered in 2nd or later lines of treatment with retained efficacy. Bulding upon this rationale and the data presented above, the PANThEON study intend to propose a possible sequential regimen as a promising first line treatment strategy for mPDAC, offerering important insights for refining treatment approaches and improving patient's quality of life and survival outcomes in PDAC.

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No funds can be provided to ethical committees and single participating centers. The study will be conducted according to the current regulations.

Roles and responsibilities

The Sponsor (GONO Foundation) will be responsible for: reviewing the protocol; centralizing databases; controlling the quality of the reported data; emitting Data Query Forms; generating study program reports; generating the Statistical Analysis Plan; perform statistical analysis. Furthermore, the Sponsor provides an insurance policy in case patients suffer harm from trial participation.

Since the drugs under investigation are well characterised and know to be well tolerated, the investigators assessed that a data monitoring committee (DMC) was not needed.

Availability of data and materials

Not applicable.

Protocol version and date and version identifier

Version 1.1 – 27 Nov 2024.

Use of copyright protected materials

Not applicable.

Authors' contributions

M. Niger, F. Nichetti and F. Pietrantonio designed the study; M. Niger, F. Nichetti, C.Sciortino, S. Marchesi and F. Palermo wrote the original protocol. C. Sciortino and M. Niger drafted the manuscript. All authors are investigators in the trial and directly provided their contribution, read and approved the final manuscript.

Ethics approval and consent to participate

The study was registered at EuCT database (2024-515214-41-00) and at Clinicaltrials.gov (NCT06897644) and it is currently ongoing.

The trial was submitted to CTIS and approved by the Ethics Committee "Comitato Etico Territoriale Lombardia 4".

All study participants will provide their written informed consent after careful explanation by their treating investigators.

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. The study will comply with the requirements of the ICH E2A guideline.

Sponsor's sample Informed Consent Form will be provided to each site. Regarding exploratory analyses, the investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason. All relevant changes to study procedures or new information will be communicated to all relevant parties (investigators, IRBs, trial participants, trial registries, journals, regulators) and patients will be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy).

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in any of the study data sets. Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law. Data generated by this study must be available for inspection upon request by representatives of the national and local health authorities, Sponsor's monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Dissemination policy

The trial results will be presented at national and international conferences such as AIOM, ESMO, ESMO GI, ASCO or ASCO GI. Results will be published in top tier medical oncology journals. All Principal Investigators will be involved in the manuscript writing.

Consent for publication

Not applicable.

Declaration of competing interest

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References

[1] Park W, Chawla A, O'Reilly EM. Pancreatic cancer: a review. JAMA 2021;326:851–62.
[2] Golan T, Kanji ZS, Epelbaum R, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer 2014;111:1132–8.
[3] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA *Cancer J Clin* 2021;71:209–49.
[4] Sohal DPS, Kennedy EB, Cinar P, et al. Metastatic pancreatic cancer: ASCO guideline update. J Clin Oncol 2020;38:3217–30.
[5] Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691–703.
[6] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–25.
[7] Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or Gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med 2018;379:2395–406.
[8] Ohba A, Ozaka M, Ogawa G, et al. 1616O Nab-paclitaxel plus gemcitabine versus modified FOLFIRINOX or S-IROX in metastatic or recurrent pancreatic cancer (JCOG1611, GENERATE): a multicentred, randomized, open-label, three-arm, phase II/III trial. Ann Oncol 2023;34:S894.
[9] Philip PA, Buyse ME, Alistar AT, et al. Avenger 500, a phase III open-label randomized trial of the combination of CPI-613 with modified FOLFIRINOX (mFFX) versus FOLFIRINOX (FFX) in patients with metastatic adenocarcinoma of the pancreas. J Clin Oncol 2019;37 TPS479-TPS.
[10] Knox Jennifer J, et al. Early results of the PASS-01 trial: pancreatic adenocarcinoma signature stratification for treatment-01. JCO 2024;42 LBA4004-LBA4004.
[11] Pusceddu S, Ghidini M, Torchio M, et al. Comparative effectiveness of Gemcitabine plus Nab-Paclitaxel and FOLFIRINOX in the first-line setting of metastatic pancreatic cancer: a systematic review and meta-analysis. Cancers (Basel) 2019:11.
[12] Takumoto Y, Sasahara Y, Narimatsu H, Akazawa M. Comparative outcomes of first-line chemotherapy for metastatic pancreatic cancer among the regimens used in Japan: a systematic review and network meta-analysis. JAMA Netw Open 2022;5:e2145515.
[13] Wainberg ZA, Melisi D, Macarulla T, et al. NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial. Lancet 2023;402:1272–81.
[14] Mastrantoni L, Chiaravalli M, Spring A, et al. Comparison of first-line chemotherapy regimens in unresectable locally advanced or metastatic pancreatic cancer: a systematic review and bayesian network meta-analysis. Lancet Oncol 2024;25(12):1655–65.
[15] Nichetti F, Rota S, Ambrosini P, et al. NALIRIFOX, FOLFIRINOX, and Gemcitabine with Nab-Paclitxel as Firs-line chemotherapy for metastatic pancreatic cancer: a systematic review and meta-analysis. JAMA Netw Open 2024;7(1):e235056.
[16] Dayyani F, Macarulla T, Johnson A, Wainberg ZA. Second-line treatment options for patients with metastatic pancreatic ductal adenocarcinoma: a systematic literature review. Cancer Treat Rev 2023;113:102502.
[17] Kunzmann V, Siveke JT, Algul H, et al. Nab-paclitaxel plus gemcitabine versus nab-paclitaxel plus gemcitabine followed by FOLFIRINOX induction chemotherapy in locally advanced pancreatic cancer (NEOLAP-AIO-PAK-0113): a multicentre, randomised, phase 2 trial. Lancet Gastroenterol Hepatol 2021;6:128–38.
[18] Carrato A, Pazo-Cid R, Macarulla T, et al. Sequential nab-paclitaxel/gemcitabine followed by modified FOLFOX for first-line metastatic pancreatic cancer: the SEQUENCE trial. J Clin Oncol 2022;40:4022.
[19] Trouilloud I, Dupont-Gossard AC, Malka D, et al. Fixed-dose rate gemcitabine alone or alternating with FOLFIRI.3 (irinotecan, leucovorin and fluorouracil) in the first-line treatment of patients with metastatic pancreatic adenocarcinoma: an AGEO randomised phase II study (FIRGEM). Eur J Cancer 2014;50(18):3116–24. doi:10.1016/j.ejca.2014.09.015.
[20] Assenat E, de la Fouchardière C, Portales F, et al. Sequential first-line treatment with nab-paclitaxel/gemcitabine and FOLFIRINOX in metastatic pancreatic adenocarcinoma: GABRINOX phase Ib-II controlled clinical trial. ESMO Open 2021;6(6):100318. doi:10.1016/j.esmoop.2021.100318.
[21] Taieb J, Pernot S, Thuillier F, et al. 5-FU + Naliri, gemcitabine plus nab-paclitaxel or both regimens given sequentially for first-line treatment of metastatic pancreatic ductal adenocarcinoma: a randomized phase II comparative study (FUNGEMAX-PRODIGE 61). J Clin Oncol 2025;43(16):4184 suppl. doi:10.1200/JCO.2025.43.16_suppl.4184.
[22] Randon Giovanni, et al. Ramucirumab plus paclitaxel as switch maintenance versus continuation of first-line oxaliplatin-based chemotherapy in patients with advanced HER2-negative gastric or gastro-oesophageal junction cancer (ARMANI): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2024;25:1539–50 12. doi:10.1016/S1470-2045(24)00580-1.

[23] Dorman K, Boeck SH, Caca K, et al. Alternating application of gemcitabine/nab-paclitaxel (Gem/nab-Pac) and Gem monotherapy or continuous application of Gem/nab-Pac after induction treatment for first-line treatment of metastatic pancreatic cancer (mPC): first results from the randomized phase 2 ALPACA study from the German AIO study group (AIO-PAK-0114). J. Clin. Oncol. 2024;42:605.
[24] Dahan L, Williet N, Le Malicot K, et al. Randomized phase II trial evaluating two sequential treatments in first line of metastatic pancreatic cancer: results of the PANOPTIMOX-PRODIGE 35 trial. J Clin Oncol 2021;39(29):3242–50. doi:10.1200/JCO.20.03329.
[25] Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA–mutated metastatic pancreatic cancer. N Engl J Med 2019;381:317–27.
[26] Stossel C, Raitses-Gurevich M, Atias D, et al. Spectrum of response to platinum and PARP inhibitors in germline BRCA-associated pancreatic cancer in the clinical and preclinical setting. Cancer Discov 2023;13:1826–43.
[27] Park W, Chen J, Chou JF, et al. Genomic methods identify homologous recombination deficiency in Pancreas adenocarcinoma and optimize treatment selection. Clin Cancer Res 2020;26:3239–47.
[28] Ghafouri-Fard S, Fathi M, Zhai T, Taheri M, Dong P. LncRNAs: novel biomarkers for pancreatic cancer. Biomolecules 2021;11(11):1665.
[29] O'Kane GM, Grunwald BT, Jang GH, et al. Correction: GATA6 expression distinguishes classical and basal-like subtypes in advanced pancreatic cancer. Clin Cancer Res 2022;28:2715.
[30] Martens S, Lefesvre P, Nicolle R, et al. Different shades of pancreatic ductal adenocarcinoma, different paths towards precision therapeutic applications. Ann Oncol 2019;30:1428–36.
[31] Nicolle R, Gayet O, Duconseil P, et al. A transcriptomic signature to predict adjuvant gemcitabine sensitivity in pancreatic adenocarcinoma. Ann Oncol 2021;32:250–60.
[32] Nicolle R, Bachet JB, Harle A, et al. Prediction of adjuvant gemcitabine sensitivity in resectable pancreatic adenocarcinoma using the GemPred RNA signature: an ancillary study of the PRODIGE-24/CCTG PA6 clinical trial. J Clin Oncol 2023:JCO2202668.
[33] Fraunhoffer N, Chanez B, Teyssedou C, et al. A transcriptomic-based tool to predict gemcitabine sensitivity in advanced pancreatic adenocarcinoma. Gastroenterology 2023;164:476–80 e4.
[34] Fietkau R, Ghadimi M, Grützmann R, et al. Benefit of chemoradiotherapy versus chemotherapy after induction therapy for conversion of unresectable into resectable pancreatic cancer: the randomized CONKO-007 trial. J Clin Oncol 2025;43(30):3266–78. doi:10.1200/JCO-24-01502.
[35] Ducreux Michel, et al. PRODIGE 29-UCGI 26 (NEOPAN): a phase III randomized trial comparing chemotherapy with FOLFIRINOX or Gemcitabine in locally advanced pancreatic carcinoma. JCO 2025;43:2255–64 20.
[36] Taieb J, Seufferlein T, Reni M, et al. Treatment sequences and prognostic/predictive factors in metastatic pancreatic ductal adenocarcinoma: univariate and multivariate analyses of a real-world study in Europe. BMC Cancer 2023;23:877.