

Short-term versus long-course neoadjuvant chemotherapy for resectable and borderline resectable pancreatic ductal adenocarcinoma (PACT-21 CASSANDRA): results from the second randomisation analysis of a randomised, open-label, 2 × 2 factorial phase 3 trial



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Summary

Background The first randomisation results from the PACT-21/CASSANDRA trial demonstrated that cisplatin, nab-paclitaxel, capecitabine, and gemcitabine (PAXG) is a standard neoadjuvant treatment option for resectable/borderline resectable (R/BR) pancreatic adenocarcinoma (PDAC). Here, we report the results of the second randomisation comparing long versus short pre-operative chemotherapy.

Methods PACT-21/CASSANDRA was a 2 × 2 factorial phase 3 trial involving 17 academic hospitals across 10 regions in Italy. Eligible patients were aged 18–75 years with pathologically confirmed R/BR PDAC and were first randomly assigned to either PAXG or fluorouracil, leucovorin, irinotecan, oxaliplatin (mFOLFIRINOX). Patients without progression or limiting toxicity after 4 months were randomised to receive 2 further months of the same chemotherapy either before (long) or after (short) surgery. The trial was designed under a two-sided superiority hypothesis (H0: HR long versus short = 1.0; H1: HR ≠ 1.0). Randomisation lists were stratified according to previous chemotherapy. The primary endpoint was event-free survival (EFS) in the intention-to-treat (ITT) population. Secondary endpoints were radiological, CA19.9 and complete pathological response, R0 and N0 resections, chemotherapy dose-density, and overall survival (OS). Analyses were performed using SAS version 9.4. This trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT04793932) and EudraCT (2020-003080-26 and 2024-519031-42-00).

Findings Between Feb 23, 2021, and Sept 03, 2024, 86 patients were assigned to long and 79 to short preoperative chemotherapy. No difference in EFS was observed between the two groups in the intention-to-treat population

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(unadjusted HR 0.98; 95% CI; 0.68–1.41; $P = 0.90$). CA19-9 response (58 [97%] of 60 versus 41 [84%] of 49 patients; $P = 0.02$), pathological complete response (4 [5%] of 86 versus 0 of 79 patients; $P = 0.05$), N0 resection rate (39 [45%] of 86 versus 21 [27%] of 79 patients; $P = 0.01$), and chemotherapy dose-density were improved by longer chemotherapy. OS data are not yet mature.

Interpretation Long and short preoperative chemotherapy obtains similar EFS in R/BR PDAC. Future research should focus on more effective treatment regimens and explore the optimal post-operative therapy.

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Keywords: Neoadjuvant chemotherapy; Chemotherapy duration; Resectable PDAC; Borderline resectable PDAC; PAXG; FOLFIRINOX

Research in context

Evidence before this study

From Jan 1, 2000, to June 29, 2020, we searched PubMed using the terms ("pancreatic ductal adenocarcinoma") AND ("neoadjuvant chemotherapy" OR "neoadjuvant chemoradiotherapy" OR "neoadjuvant therapy") AND ("resectable" OR "borderline resectable") AND ("duration" OR "long" OR "short"), limited to the English language. We filtered by article type "clinical trial" and "meta-analysis". Among the results matching these search criteria, studies specifically assessing the optimal duration of neoadjuvant therapy in resectable/borderline resectable pancreatic ductal adenocarcinoma (PDAC) were not reported. Since then, only a systematic review and meta-analysis published by Hajibandeh S. et al., in 2025 evaluated the impact of neoadjuvant therapy duration on treatment outcome in non-metastatic disease. Twenty-three randomised controlled trials published by 27th May 2025 and reporting data of 1880 patients treated with heterogeneous neoadjuvant therapies were included. Neoadjuvant therapy duration ≤ 8 weeks was associated with significantly higher resection rates if compared to longer duration (>8 weeks). On the contrary, no significant differences in radiological response, R0 resection rate and 1-, 3-, and 5-years survival rates were detected. These results should be interpreted with caution in light of the high heterogeneity of neoadjuvant treatment approaches used across the analysed studies (different regimens, association with radiotherapy) and the inclusion of locally advanced PDAC patients, in addition to resectable/borderline resectable. No randomised trials directly comparing different durations of neoadjuvant therapy in resectable/borderline resectable PDAC patients were reported before the present study.

Added value of this study

PACT-21/CASSANDRA is the first randomised phase 3 trial comparing short- (4 months) versus long-course (6 months) pre-operative chemotherapy (cisplatin, nab-paclitaxel, capecitabine, and gemcitabine [PAXG] or fluorouracil, leucovorin, irinotecan, oxaliplatin [mFOLFIRINOX]) in resectable and borderline resectable PDAC. No difference in the primary endpoint of Event-Free Survival (EFS) was detected between the two chemotherapy duration arms. This finding was also validated at multivariable analysis including clinical variables and chemotherapy regimen, that was confirmed as the only factor significantly associated with EFS, as previously reported in the trial's first randomisation results. Similarly, chemotherapy duration did not significantly impact on radiological responses, overall and R0 resection rates. On the contrary, longer pre-operative chemotherapy was associated with significantly increased CA19.9 response rate, complete pathological responses, N0 resections and chemotherapy dose-density. Overall Survival data are not mature yet.

Implications of all the available evidence

Our findings show that long-course preoperative chemotherapy obtains comparable results to short-course treatment in resectable/borderline resectable PDAC. While the PAXG regimen is the most appropriate candidate for treating patients with PDAC in this setting, the choice of prolonging pre-operative chemotherapy beyond four months could be personalised based on clinical considerations in individual patients. Future research should focus on more effective treatment regimens and explore the optimal post-operative therapy.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis and, due to poorly effective and limited therapeutic options, is expected to become the third leading

cause of cancer-related death by 2030.¹ Surgical resection is a potential curative option for about 20% of patients. However, even in the most favourable clinical scenario of resection followed by adjuvant chemotherapy, fewer than

45% of patients are alive at 5 years,² and this figure may even be an overestimation.³

Neoadjuvant chemotherapy has become the standard of care in patients with borderline resectable PDAC and is increasingly considered even in those with anatomically resectable disease.^{4–10} Nonetheless, the neoadjuvant decision-making regarding the optimal chemotherapy duration has to be determined yet and ranged between 6 weeks and 4 months across prospective trials.^{4–14} Total neoadjuvant therapy, or surgery-last approach, has been proposed as well,¹⁵ but no prospective data on this topic are available.

In the recent PACT-21/CASSANDRA phase 3 randomised trial [[ClinicalTrials.gov](https://clinicaltrials.gov), NCT04793932, and EudraCT, 2020-003080-26 and 2024-519031-42-00], we compared preoperative cisplatin, nab-paclitaxel, capecitabine, and gemcitabine (PAXG) versus fluorouracil, leucovorin, irinotecan, and oxaliplatin (mFOLFIRINOX) in resectable and borderline resectable PDAC.¹⁴ A second randomisation (2 × 2 factorial design) was planned after 4 months of chemotherapy to determine whether additional 2 months of the same regimen should be given before or after surgery. Results of the first randomisation showed that PAXG was associated with a longer median Event-Free Survival (primary endpoint: 16 months versus 10.2 months; hazard ratio [HR] = 0.63), higher disease control and biologic response than mFOLFIRINOX, with similar toxicity, resection rates, and margin-free resections.¹⁴ This provided compelling evidence that PAXG is a highly active neoadjuvant regimen that outperforms mFOLFIRINOX and should serve as a new benchmark comparator in trials for resectable and borderline resectable PDAC.

Here, we report the results of the second randomisation of the PACT-21/CASSANDRA trial.

Methods

Study design and ethics

PACT-21 or CASSANDRA was an Italian, multicentre, academic, open-label, 2 × 2 randomised, phase 3 trial conducted under the auspices of the Associazione Italiana Studio Pancreas (AISP). Patients were enrolled in 17 academic hospitals from 10 regions. The first randomisation results of CASSANDRA has been published in *The Lancet*.¹⁴ Here, we report here the second randomisation of the trial, with an additional 2 months of neoadjuvant chemotherapy versus surgery plus 2 months of adjuvant chemotherapy. The study protocol is available within the [Supplementary Materials](#) (page 6).

With regards to protocol deviations, due to insufficient funding, the radiological response assessment deviated from the per-protocol plan of a central radiology review. Further, quality of life was a prespecified secondary outcome, as per study protocol; however, the study investigators deemed that it would have been methodologically weak to compare the two arms of the

second randomization due to the different timing of surgery and timing and attrition rate of chemotherapy, and we decided not to proceed with this analysis.

The trial was approved by the independent ethics committee at each participating institution and was conducted in accordance with the International Conference on Harmonisation E6 requirements for Good Clinical Practice and with the ethical principles outlined in the Declaration of Helsinki. The specific names of the authorities that granted ethical approval for the study are available in the [Supplementary Materials](#) (page 1), along with the reference numbers. All patients provided written informed consent before study initiation.

Participants

Inclusion criteria for trial enrolment have been reported elsewhere.¹⁴ Briefly, eligible participants were both females and males, aged 18–75 years, with a Karnofsky performance status score of 70 or more, and a pathologically confirmed resectable or borderline resectable PDAC according to local investigators referring to NCCN Guidelines and International consensus on the definition of borderline resectable.^{16,17} Self-reported sex (open question) data were collected at clinical review.

Procedures

At first randomisation, patients were assigned in a 1:1 ratio to receive either PAXG (oral capecitabine total daily dose of 1250 mg/m² in 625 mg/m² twice daily dosage and 30–40 min intravenous infusion of nab-paclitaxel 150 mg/m², 60–80 min intravenous infusion of gemcitabine 800 mg/m², and 60 min intravenous infusion of cisplatin 30 mg/m² every 14 days) or mFOLFIRINOX (2 h intravenous infusion of oxaliplatin 85 mg/m², 2 h intravenous infusion of leucovorin 400 mg/m², 90 min intravenous infusion of irinotecan 150 mg/m², and continuous 46 h intravenous infusion of fluorouracil 2400 mg/m² every 14 days) regimen.

Patients who were without progression or limiting toxicity after 4 months of chemotherapy were further randomised in a 1:1 ratio to receive 2 further months of the same chemotherapy either before or after surgery. Both the patient and the attending oncologist were allowed to decide whether to proceed to the second randomisation. Resection was planned in a participating institution between 4 and 8 weeks after the last intravenous chemotherapy administration. After completing trial interventions, clinical, tumour markers, and radiologic follow-up with a contrast-enhanced computed tomography of the chest and the abdomen was planned every 3 months during the first year after randomisation, every 4 months during the second year, and every 6 months from the third year on or whenever clinically indicated until disease recurrence. No central pathological review was planned because pathological assessments were performed by uninvolved pathologists in

academic, high-volume institutions, reflecting real-world practice and enhancing generalisability, with centre stratification balancing potential quality variations.

Randomisation and masking

Randomisation lists were generated using R code (Package 'randomizeR') and stratified by previously assigned chemotherapy regimen, at a 1:1 ratio in blocks of variable size, ranging from two to four. The size of blocks randomly varied to ensure a balance within strata, while preserving randomisation concealment. The list was generated at the start of the study by a consultant statistician who was not in charge of the analysis, integrated into the central clinical research organisation (CRO) independent Web-based platform, and associated with the relative centre. A randomisation button was defined in the electronic case report form structure. Based on the conditions associated with each randomisation button, the system selected a specific layer from the list and then assigned the patient to the first available free position within that layer. Patients' recruitment was overseen by the study investigator(s) at each centre, while the randomisation was performed by the local clinical trial assistant who was not otherwise involved in the trial.

Outcomes

The prespecified primary objective of the trial was to compare the efficacy of 4 months of preoperative plus 2 months of postoperative chemotherapy with that of 6 months of preoperative chemotherapy. The primary endpoint was event-free survival (EFS), defined as the interval between the date of the second randomisation and the date of the first qualifying event consisting of: a) radiological or biochemical disease progression during preoperative chemotherapy; b) radiological or biochemical disease recurrence after surgical resection; c) preoperative or intra-operative definition of unresectability; d) intra-operative metastasis detection; and e) death. Biochemical failure was defined as two consecutive increases in carbohydrate antigen 19-9 (CA19-9), each of 20% or more, separated by 4 weeks or more. Only patients with basal levels above the upper normal laboratory limit were at risk of this type of event. Patients who did not have any event at the time of final analysis were censored on the date of the latest follow-up visit.

The prespecified secondary endpoints were: a) rate of radiological responses based on the revised RECIST criteria,¹⁸ b) rate of CA19-9 responses based on previously reported criteria¹⁹ (defined as a $\geq 50\%$ reduction from the pre-first-randomisation baseline value, measured at the nadir within the entire preoperative chemotherapy period), c) rate of surgical R0–R1 tumour resections, d) rate of complete pathological responses, e) rate of absence of pathological lymph-node involvement (N0), f) rate of absence of pathological resection

margins infiltration (R0), g) rate of metastases detection during or within 3 months of surgery, h) surgical mortality s, i) surgical morbidity rate, j) treatment toxicity, k) patients reported outcomes, and l) overall survival (OS), calculated from the date of the second randomisation until death.

The exploratory secondary endpoints were: a) number of administered chemotherapy cycles; and b) chemotherapy dose-intensity.

Despite quality of life being a prespecified secondary outcome, as per study protocol, we deemed that it would have been methodologically weak to compare the two arms of the second randomization due to the different timing of surgery and timing and attrition rate of chemotherapy, and we decided not to proceed with this analysis.

Statistical analysis

Data was analysed in the intention-to-treat (ITT) population, including all randomised patients who met the eligibility criteria, and were assigned to a group at the time of the second randomisation, regardless of whether they received the planned treatment. Consistent with the pre-specified modified intention-to-treat (modified-ITT) principle (ICH-E9), patients who were randomised but found to be ineligible at central post-randomisation review of clinical documentation (disease progression already present at the time of randomisation but not recognised at the enrolling site) and patients with a final post-surgical histology incompatible with PDAC were excluded from the analytic ITT population. Efficacy evaluation regarding EFS, OS, the ratio of objective radiological and biochemical responses, complete pathological responses, resection rate, intra- and post-operative metastatic rate, N-status and R-status, and patients' characteristics, was conducted in this population. The per-protocol population (PPP) included all the randomised patients who met eligibility criteria and who did not show major protocol violations during treatment. The statistical hypothesis for the second randomisation, due to the uncertainty regarding the direction of the effect, was a two-sided superiority comparison of long-course (6 months of preoperative chemotherapy) versus short-course (4 months of preoperative chemotherapy followed by 2 months of adjuvant chemotherapy) for the primary endpoint EFS, with null hypothesis H_0 : HR (long versus short) = 1.0 and two-sided alternative H_1 : $HR \neq 1.0$ at $\alpha = 0.05$. Because no robust literature benchmark was available for this specific comparison, the overall sample-size estimation was based on the first randomisation; for the second randomisation, the 165 ITT patients effectively randomised correspond, at the data cut-off, to 80% power to detect an $HR \leq 0.65$ (or, symmetrically, ≥ 1.55), post-hoc estimated by Schoenfeld's method on 116 observed events.

This power characterisation was a post-hoc analysis; all subgroup analyses and interaction tests reported

below were pre-specified in the statistical analysis plan. Qualitative variables were compared by the chi-square test or Fisher's exact test, and quantitative variables were compared as follows: normality of distribution was assessed using the Shapiro–Wilk test and visual inspection of Q–Q plots; when normality assumptions held, between-group comparisons were performed with Student's t-test (Levene's test for equality of variances, with Welch's correction applied when variances were unequal); otherwise, the Mann–Whitney U test was used. For categorical variables, the Pearson chi-square test was applied, or Fisher's exact test when one or more expected cell counts were <5. Survival rates were estimated using the Kaplan–Meier method and compared between groups with the log-rank test. Patients without an event at the data cut-off of 31 March 2026 were censored at the date of their last documented follow-up visit. A Cox proportional hazards model stratified by chemotherapy regimen (the first-randomisation stratification factor) was used to analyse factors associated with EFS. The proportional-hazards assumption was verified using scaled Schoenfeld residuals. To assess the robustness of the primary EFS result, two pre-specified sensitivity analyses were performed: a “strict-ITT” analysis including all 171 randomised patients irrespective of eligibility and final histology, and a per-protocol analysis excluding patients with major protocol violations. Treatment heterogeneity effects in subgroups defined by prognostic factors were displayed in a forest plot,²⁰ reporting the within-level effect estimates and interaction test between the second-randomisation arm (long versus short) and each subgroup variable.²¹ The 2 × 2 factorial design assumed no qualitative interaction between chemotherapy regimen and duration; this assumption was pre-specified in the statistical analysis plan (SAP) and was formally tested by including a regimen × duration interaction term in the Cox model. OS data maturity was pre-specified as the occurrence of at least 100 death events in the ITT population of the second randomisation (corresponding to approximately 60% of events), beyond which the power for the secondary long versus short OS comparison at a clinically meaningful HR of 0.70 with two-sided $\alpha = 0.05$ exceeds 80%; an updated OS analysis is planned once this threshold is reached, or alternatively after an additional minimum year of follow-up for all patients. All calculated *P*-values were two-sided and compared against a 5% significance level. A *P*-value of less than 0.05 was considered statistically significant. The database for this analysis was locked at the clinical cut-off date of 31 March 2026. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Role of the funding source

All the trial costs were covered by donations from patients' associations MyEverest and Codice Viola. The

funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Nov 03, 2020, and April 24, 2024, 261 patients underwent the first randomisation. Between Feb 23, 2021, and Sept 03, 2024, 171 patients underwent a second randomisation to receive two additional months of the same chemotherapy to which they had been assigned by the first randomisation (*n* = 88; long-course preoperative chemotherapy group) or surgery followed by two months of adjuvant chemotherapy with the same regimen to which they had been originally assigned (*n* = 83; short-course preoperative chemotherapy group) surgery. Six patients (2 in the long-course preoperative chemotherapy group and 4 in the short-course preoperative chemotherapy group) were found to be ineligible due to pathologic diagnosis of ampullary carcinoma at final histology after surgery (*N* = 1, short preoperative group) and to disease progression that was already present before randomisation at patient's documentation review (*N* = 5) and were therefore excluded from the ITT analyses (Fig. 1). Furthermore, 13 patients, 8 in the long- and 5 in the short-course preoperative chemotherapy group, did not receive the assigned treatment; thus, the PPP consisted of 152 patients (Fig. 1). The baseline patients' characteristics are reported in Table 1.

Final EFS analysis was performed after a median follow-up of 33.4 months. Overall, 116 events occurred in 165 patients (70% of the ITT patients). No patient was lost to follow-up. Accordingly, all censoring was due to the end of follow-up. The event rate was 70% (60 of 86 patients, with 11 CA19.9 failures) in the long-course preoperative chemotherapy group and 71% (56 of 79 patients, with 7 CA19.9 failures) in the short-course preoperative chemotherapy group. In the ITT population, no significant difference in EFS was observed between the two groups (unadjusted HR 0.98; 95% Confidence Interval [CI]; 0.68–1.41; *P* = 0.90; Fig. 2A). Median EFS was 13.0 months (95% CI; 9.0–18.6 months) and 15.2 months (95% CI; 10.2–21.2 months), and 3y EFS was 27.1% (95% CI; 21.8–32.4%) and 23.6% (95% CI; 18.0–29.2%) in the long- and short-course preoperative chemotherapy arm, respectively.

Multivariable Cox regression analysis, including patient, treatment, and cancer-related variables, confirmed that preoperative chemotherapy duration was not associated with EFS (adjusted HR 0.93; 95% CI 0.64–1.35; Wald *P* = 0.69, stratified by chemotherapy regimen), whereas the chemotherapy regimen was (Table 2).

A pre-specified sensitivity “strict-ITT” analysis including all 171 randomised patients (regardless of eligibility and final histology) yielded a primary-endpoint

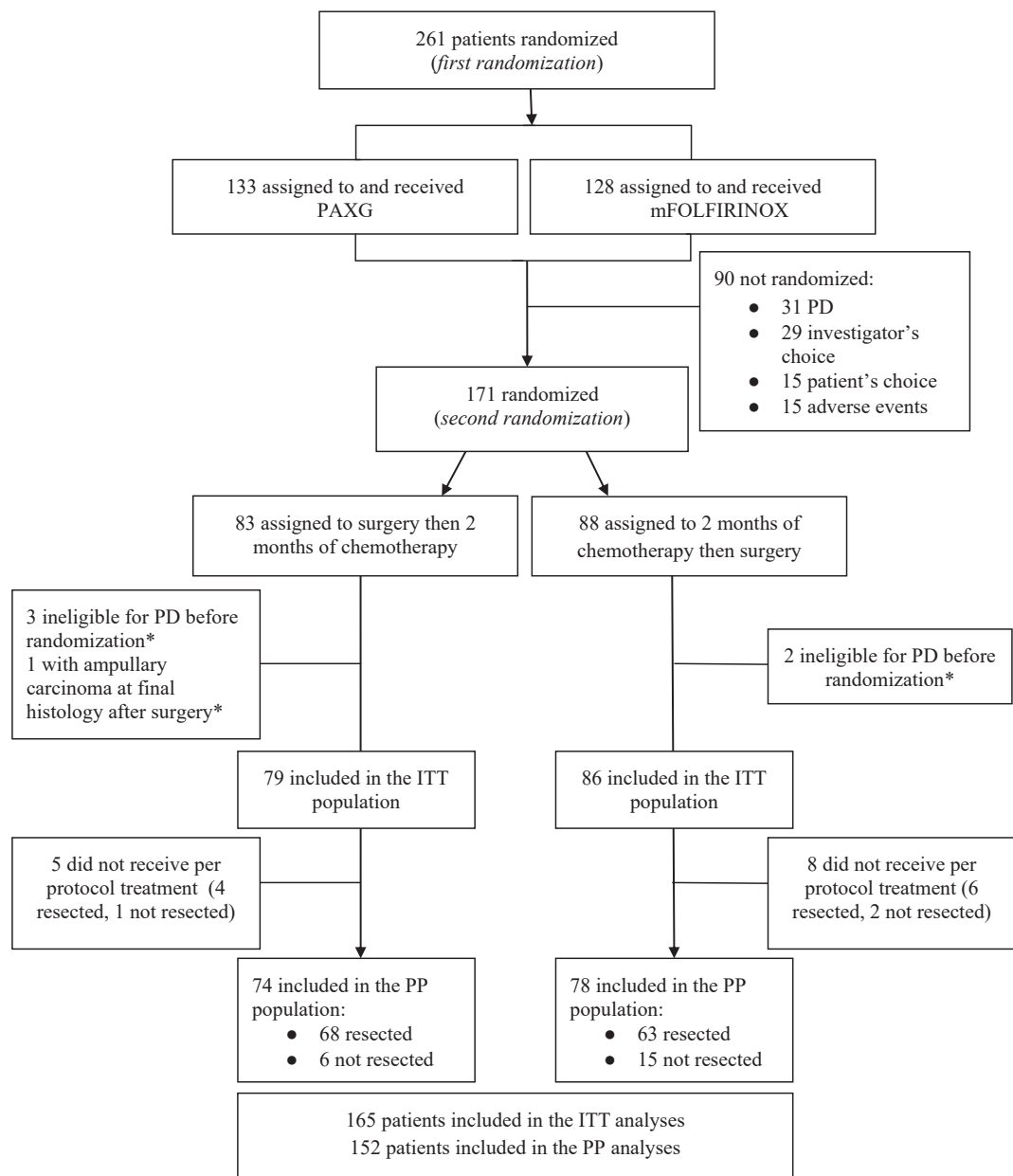


Fig. 1: Trial profile. PD = progressive disease. ITT = intention-to-treat. PPP = per protocol population. * Excluded from Intention-To-Treat population.

result essentially unchanged from the main analysis (HR 1.01; 95% CI; 0.70–1.45; log-rank $P = 0.96$).

In the PPP, no significant difference in EFS was observed between the two groups (unadjusted HR 0.92; 95% CI; 0.63–1.35; $P = 0.67$; Fig. 2B). Median EFS was 15.5 months (95% CI; 11.2–24.6 months) and 15.2 months (95% CI; 10.6–21.2 months), and 3y EFS was 30.3% (95% CI; 24.6–36.0%) and 25.8% (95% CI; 19.8–31.8%) in the long- and short-course preoperative chemotherapy arm, respectively.

Pre-specified subgroup analyses by chemotherapy regimen and by anatomical classification consistently showed no effect of chemotherapy duration on EFS, with non-significant interaction tests (Supplementary Figure S1). In the PAXG stratum ($n = 89$), the long versus short HR was 0.96 (95% CI; 0.58–1.59; $P = 0.87$); in the mFOLFIRINOX stratum ($n = 76$), HR was 1.02 (95% CI; 0.60–1.73; $P = 0.94$; Supplementary Figure S1); the regimen $\times$ duration interaction was not significant (interaction HR 0.95; 95% CI; 0.46–1.95;

	Long course N = 86	Short course N = 79
Age, years (IQR)	61 (57–67)	65 (60–70)
Sex		
Male	47 (55)	38 (48)
Female	39 (45)	41 (52)
Treatment arm		
mFOLFIRINOX	37 (43)	39 (49)
PAXG	49 (57)	40 (51)
KPS		
90–100	80 (93)	75 (95)
≤80	6 (7)	4 (5)
Anatomic classification		
Resectable	48 (56)	36 (46)
Borderline resectable ^a	38 (44)	43 (54)
CA19-9 expression		
Positive	60 (70)	51 (65)
Negative	26 (30)	28 (35)
Median (95% CI) ^b	237 (43–2732)	190 (39–6619)
<5 ULN	47 (55)	51 (65)
≥5 ULN	39 (45)	28 (35)
Clinical tumour staging		
I	46 (53)	38 (48)
II	35 (41)	36 (46)
III	5 (6)	5 (6)
Tumour location		
Head	62 (72)	61 (77)
Uncinate process	10 (12)	3 (4)
Body	8 (9)	11 (14)
Tail	6 (7)	3 (4)
Diffuse	0	1 (1)
Genetic variants ^c		
Not available	23 (27)	17 (22)
All pathogenic	4/63 (6)	14/62 (23)
BRCA1 or BRCA2 gPV	2/63 (3)	9/62 (15)
Other gPVs ^d	2/63 (3)	5/62 (8)
VUS	8/63 (13)	5/62 (8)
None	51/63 (81)	43/62 (69)

Data are presented as n (%), median (IQR), or median (95% confidence interval). Percentages may not total 100 due to rounding. IQR = interquartile range. KPS = Karnofsky Performance Status. CA19-9 = Carbohydrate Antigen 19-9. ULN = upper limit of normal. gPV = germline pathogenic variant. VUS = variant of uncertain significance. ^aPatients were included in the borderline resectable population based on both surgical and biological criteria (CA19-9 of 500 IU/ml or greater). ^bMedian values and 95% confidence intervals are calculated for the group of patients with positive CA19-9 values only. ^cGenetic testing results refer to germline variants only. Percentages are based on the tested population. ^dIncludes germline pathogenic variants in ATM, PALB2, NBN, MUTYH, and SDHB.

Table 1: Patients' baseline characteristics: intention-to-treat population.

$P = 0.89$; [Supplementary Table S1](#)). In resectable patients ($n = 84$), the long versus short HR was 1.02 (95% CI; 0.62–1.69; $P = 0.94$); in borderline resectable patients ($n = 81$), HR was 0.96 (95% CI; 0.58–1.58; $P = 0.86$); the anatomy $\times$ duration interaction P was 0.84 ([Supplementary Figure S1](#)).

Partial responses were observed in 49 of 86 (57%) and 37 of 79 (47%; $P = 0.19$) patients in the long- versus short-course preoperative chemotherapy group, respectively. A $\geq 50\%$ reduction in CA19-9 was reported significantly more often in the long-course chemotherapy group than in the short-course group (58 of 60; 97% versus 41 of 49; 84%; $P = 0.02$).

Sixty-nine patients were resected in each group (80% versus 87%, in the long- versus short-course preoperative chemotherapy group, respectively; $P = 0.22$). Among patients who received PAXG, the resection rate was 84% (41 of 49 patients) in the long-course preoperative chemotherapy group and 90% (36 of 40 patients; $P = 0.38$) in the short-course preoperative group. Among patients who received mFOLFIRINOX, the resection rate was 76% (28 of 37 patients) in the long-course preoperative chemotherapy group and 92% (36 of 39 patients; $P = 0.03$) in the short preoperative group.

Four complete pathological responses (4.7%) were observed in the long-course preoperative chemotherapy group with none in the short-course group ($P = 0.05$). The rate of N0 resections was significantly higher in the long-course preoperative chemotherapy group (45%, 39 of 86 patients; versus 27%, 21 of 79 patients; $P = 0.01$). No difference in R0 resections was observed between groups (53 of 86; 62% versus 46 of 79; 58%; $P = 0.66$).

In the PPP, 55 of 78 (71%) patients randomised to receive all the chemotherapy cycles before surgery completed the 4 planned administrations, whereas only 38 of 74 (51%) patients who were randomised to receive the last 4 chemotherapy administrations after surgery completed their treatment ($P < 0.01$).

The median relative dose-density (the percentage of the planned chemotherapy dose received in the last 4 administrations), as well as the number of chemotherapy administrations, in the long- versus short-course preoperative chemotherapy group, is summarised in [Table 3](#). The differential is entirely attributable to lower tolerability during the adjuvant phase of the short-course arm. Chemotherapy toxicity is reported in [Table 4](#) and in [supplementary Table S2](#).

OS data are not mature yet. At the time of this current analysis, 73 events occurred in 165 patients (44% of the ITT population). Median survival was 50.5 months (95% CI; 28.5 to not estimable) in the long-course preoperative chemotherapy group and 35.1 months (95% CI; 26.4–56.5 months; HR 0.88; 0.55–1.40; $P = 0.58$) in the short-course preoperative chemotherapy group. Three-year OS rates were 56.8% (95% CI; 50.8%–62.8%), in the long-course preoperative chemotherapy group, and 46.6% (95% CI; 39.6%–53.6%), in the short-course preoperative chemotherapy group.

Discussion

CASSANDRA is the first prospective phase 3 randomised trial to address the topic of preoperative

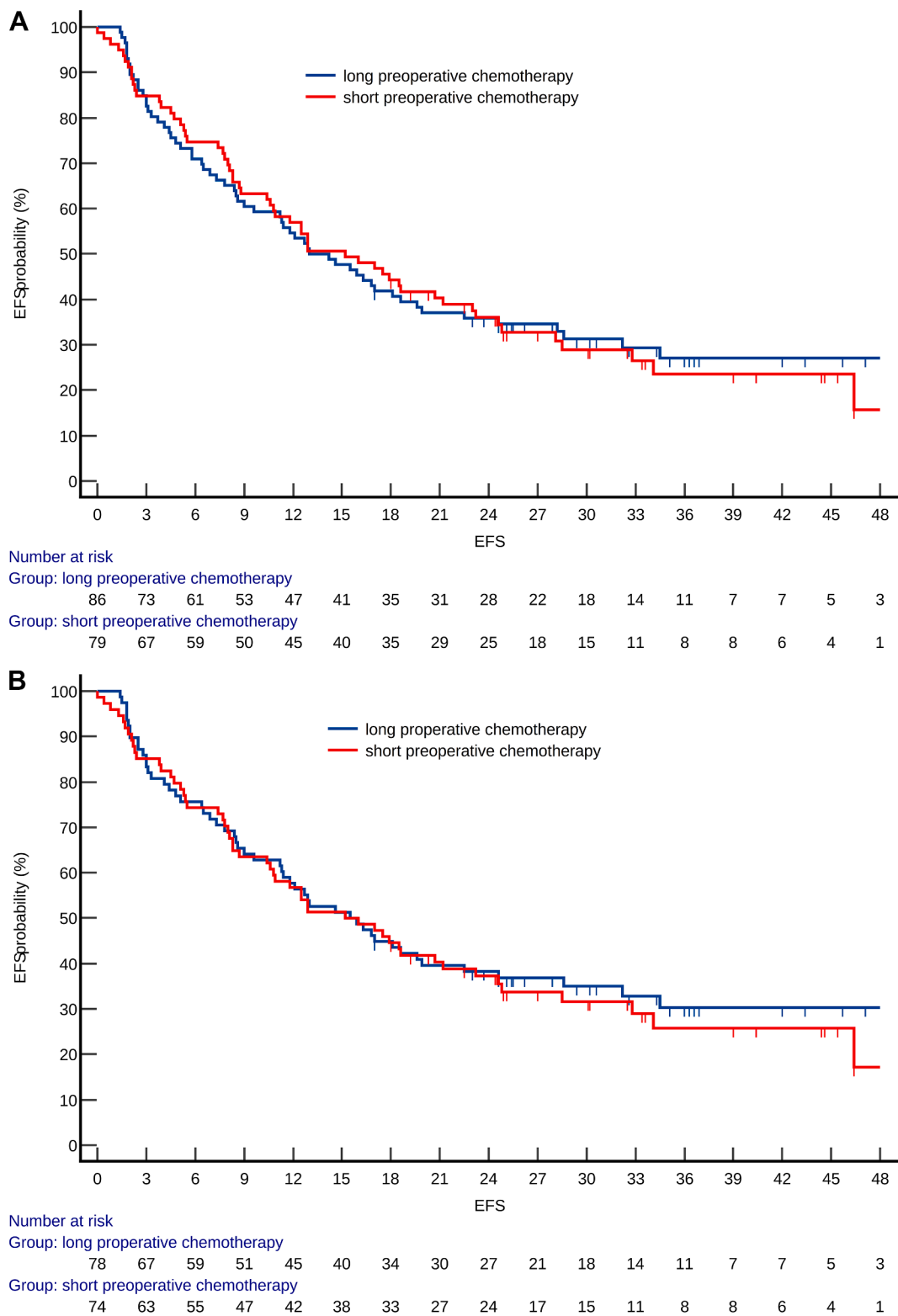


Fig. 2: Kaplan-Meier plot of event-free survival in the intention-to-treat population (A) and in the per protocol population (B). Tick marks indicate censored observations.

Covariate	HR (95% CI)	P-value
Age: >65 versus ≤65 years	1.28 (0.86–1.91)	0.225
Treatment arm: PAXG versus mFOLFIRINOX	0.67 (0.46–0.99)	0.043
Second randomisation arm: long versus short course	0.93 (0.64–1.35)	0.693
Baseline CA19-9: >5 × ULN versus ≤5 × ULN	1.33 (0.88–2.00)	0.182
KPS >80 versus ≤80	0.95 (0.43–2.11)	0.900
Anatomic classification: resectable versus borderline resectable	1.05 (0.70–1.56)	0.829
Sex: female versus male	0.86 (0.59–1.24)	0.421
Clinical stage: III versus <III	2.04 (1.00–4.10)	0.051

HR = Hazard Ratio. CI = Confidence Interval. KPS = Karnofsky Performance Status. CA19-9 = Carbohydrate Antigen 19-9. ULN = upper limit of normal.

Table 2: Multivariable cox regression analysis in the intention-to-treat population.

chemotherapy duration in patients with resectable and borderline resectable PDAC.

The second randomisation results of the CASSANDRA trial show that administering six months of preoperative chemotherapy results in an EFS comparable to that achieved with four months of preoperative plus two months of postoperative chemotherapy in patients with resectable and borderline resectable PDAC.

As per secondary endpoints, CA19-9 response, pathological complete response, as well as lymph node clearance were significantly improved by a longer preoperative chemotherapy duration. Also, radiological partial responses were numerically better (10% more) in the long preoperative chemotherapy arm. Most importantly, 20% more patients completed all the planned chemotherapy cycles, and a better dose-density was achieved in the long-course preoperative chemotherapy group. Furthermore, a higher rate of grade 3–4 neutropenia (13% versus 6%), nausea-vomiting (5% versus 2%), and of liver toxicity (5% versus none) in short- versus long-course preoperative chemotherapy group was also observed. Grade 1–2 fatigue,

neuropathy/paresthesia, hand-foot syndrome, onychopathy, dysgeusia, and constipation were more often observed in long-course group while grade 1–2 diarrhoea, nausea/vomiting, rash, pruritus, and decreased appetite were most often observed in short-course group. The difference in dose-density and in the number of administered cycles between the two arms is largely driven by the fact that, in the short arm, the last 2 months of chemotherapy are administered after surgery, during a post-operative recovery phase characterised by dose reductions and a significantly higher proportion of patients not completing the planned treatment (51% in the short arm versus 71% in the long arm; $P < 0.01$). Noteworthy, dose density has been previously suggested to be prognostic for OS in patients with resectable PDAC.^{22,23} Since none of these secondary endpoints have been formally validated as a surrogate for OS, the implications of these results should be interpreted with caution.

Assuming that early-stage PDAC is a micro-metastatic disease, the deeper biochemical, radiological, and pathological response in the long-course preoperative chemotherapy group might indicate an improved systemic tumour clearance. However, to date, this has not been translated into an EFS (or OS) benefit. As previously reported, more than 4 months of chemotherapy is required in metastatic and unresectable PDAC to achieve the maximum response.²⁴ Therefore, it is likewise theoretically implausible that short-course chemotherapy can completely neutralise micrometastatic disease in resectable and borderline resectable PDAC, and neoadjuvant chemotherapy discontinuation in 4 months or less may deprive most patients of a valuable contribution to tackling their disease, while continuing up to 6 months may allow to fully take advantage of chemotherapy therapeutic potential. Noteworthy, current data from CASSANDRA trial suggest that the potential benefit of longer chemotherapy duration may be achieved also by delaying the last two months of treatment.

On the other hand, patients who experience disease progression during the last two months of preoperative chemotherapy may be affected by biologically more aggressive and chemo-resistant tumours and can be spared from a demanding and potentially harmful surgical procedure that is unlikely to yield a survival benefit.

In line with this observation, it is reassuring that the resection rate in the CASSANDRA trial was not significantly different between the two groups and that the 7% difference in favour of the short-course preoperative chemotherapy group did not translate into prolonged EFS, suggesting that risky demolitive surgery can be spared in a subset of patients. Conversely, 6–8% more patients were event-free at 3 years in the long-course preoperative chemotherapy group as opposed to the short-course group.

Drug name	Long chemotherapy	Short chemotherapy
5-fluorouracil	83%	54%
Irinotecan	73%	51%
Oxaliplatin	75%	51%
Cisplatin	85%	61%
Nab-paclitaxel	78%	58%
Capecitabine	57%	40%
Gemcitabine	74%	54%

Data is presented as median. Relative dose-density is defined as the percentage of the planned cumulative chemotherapy dose delivered over the last four administrations. IQR: interquartile range.

Table 3: Relative chemotherapy dose-density.

	Long-course (n = 78)			Short-course (n = 59)		
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4
Haematological toxicity						
Anaemia	15 (19%)	0	0	9 (15%)	0	0
Neutrophil count decreased (neutropenia)	8 (10%)	4 (5%)	1 (1%)	3 (5%)	6 (10%)	2 (3%)
Platelet count decreased	8 (10%)	0	0	3 (5%)	0	0
Febrile neutropenia	0	1 (1%)	0	0	0	0
Non-haematological toxicity						
Peripheral neuropathy	34 (44%)	3 (4%)	0	15 (25%)	1 (2%)	0
Fatigue	26 (33%)	2 (3%)	0	14 (24%)	1 (2%)	0
Paraesthesia	16 (21%)	2 (3%)	0	8 (14%)	1 (2%)	0
Diarrhoea	10 (13%)	0	0	15 (25%)	1 (2%)	0
Nausea	7 (9%)	1 (1%)	0	13 (22%)	2 (3%)	0
Fever	10 (13%)	0	0	6 (10%)	0	0
Abdominal pain	7 (9%)	1 (1%)	0	5 (8%)	0	0
Vomiting	5 (6%)	1 (1%)	0	6 (10%)	1 (2%)	0
Hand-foot syndrome	12 (15%)	0	0	0	0	0
AST or ALT increased	3 (4%)	0	0	3 (5%)	3 (5%)	0
Dysgeusia	5 (6%)	1 (1%)	0	2 (3%)	0	0
Nail toxicity	6 (8%)	1 (1%)	0	0	0	0
Infusion-related reaction	3 (4%)	0	0	2 (3%)	1 (2%)	0
GGT increased	1 (1%)	1 (1%)	0	2 (3%)	1 (2%)	0
Hyperglycaemia	1 (1%)	0	0	1 (2%)	1 (2%)	0
Weight loss	1 (1%)	0	0	1 (2%)	1 (2%)	0
Alopecia	1 (1%)	1 (1%)	0	0	0	0
Biliary tract infection	0	2 (3%)	0	0	0	0
Pulmonary embolism	0	1 (1%)	0	0	0	0
Sepsis	0	0	0	0	1 (2%)	0

Data are n (%). Grade 1–2 treatment-related adverse events with an incidence of at least 10% in either group, and grade 3–4 events with an incidence of at least 1% in either group, are shown. All remaining events are listed in the [Supplementary Material](#) (page 4). Adverse events include those reported in treatment cycles administered after the second randomisation. AST = aspartate aminotransferase. ALT = alanine aminotransferase. GGT = gamma-glutamyl transferase.

Table 4: Summary of adverse events in the safety population.

A systematic review of the literature suggested that neoadjuvant treatment duration of 8 weeks or less is associated with a significantly higher resection rate compared to a longer course (66.7% versus 35.5%, respectively), raising concerns about missing the opportunity of curative surgery when prolonging preoperative treatment.²⁵ Such results may be influenced by several confounding factors: inclusion of patients with locally advanced PDAC, who have (by definition) very low chances of having their disease resected; high heterogeneity in the treatments and regimens used; lack of information on total treatment duration; heterogeneous definitions of anatomic resectability and R0 resection across the analysed studies. In the CASSANDRA trial ITT population, all patients were planned to receive at least 16 weeks of preoperative chemotherapy.¹⁴ Among patients with resectable disease, 94 of 126 (74.6%) underwent resection.¹⁴ This figure did not significantly differ between treatment arms, as the resection rate was 71.4% (45 of 63 patients) in the mFOLFIRINOX group and 77.8% (49 of 63 patients) in the PAXG group.¹⁴ Accordingly, concerns about a lower resection rate in the resectable population with longer preoperative

therapy duration do not appear to be justified. On the other hand, no significant difference in OS between neoadjuvant treatment duration of 8 weeks or less and of >8 weeks was reported in the general population of the systematic review, thus supporting our hypothesis that rushing to surgery does not imply an OS benefit. The 3-year OS in the systematic review was reported to be between 11.9% and 21.1%, while in the CASSANDRA trial it was 48% and 41% respectively for the PAXG and the mFOLFIRINOX group, respectively. This remarkable difference in OS between the trials included in the systematic review and the CASSANDRA trial may be related to the use of more effective preoperative treatment in the latter and suggests that contemporary chemotherapy improves the outcome by achieving better systemic disease control. Consistently, the 6% difference in resection rate between the two preoperative treatment duration groups in patients who received PAXG was not statistically significant, while in the case of mFOLFIRINOX the 16% difference was statistically significant, suggesting that more effective regimens may not only improve but also prolong disease control, maximising the potential benefit of neoadjuvant strategies.

We acknowledge the limitations of the CASSANDRA trial, including the decision of enrolling both resectable and borderline resectable disease, the absence of a central pathological and radiological response review, the conduct of the trial in high-volume academic centres, and the upper age limit at 75 years, and these have been previously discussed in the first randomisation results of CASSANDRA.¹⁴ The use of CA19-9 increases as an event may be disputable. However, no plausible mechanism would explain why this prospectively defined event measure should favour one arm over the other. Furthermore, although the impact of routine CA19-9 monitoring is still being prospectively investigated, CA19-9 elevations predict recurrence with an overall accuracy of 71–95%, with an impact on OS that is similar for CA19-9-only monitoring and imaging follow up strategies.^{26,27} Another limitation is that the sample size was calculated on the first randomisation due to the lack of a reliable benchmark in the literature for the second randomisation and to the unpredictable population composition at the time of trial start. Overall, only 165 of 260 (63%) patients in the ITT population of the first randomisation were enrolled in the second randomisation, thus limiting the statistical power for the primary endpoint of the latter. Specifically, with the 165 ITT patients effectively randomised at the data cut-off, post-hoc power calculations show that the second randomisation has 80% power to detect a long versus short HR ≤ 0.65 (or, symmetrically, ≥ 1.55) at two-sided $\alpha = 0.05$, but is underpowered for smaller, potentially clinically meaningful effect sizes. Accordingly, the patients included in the second randomisation represent a selected population who remained progression-free after 4 months of chemotherapy, tolerated treatment, and consented to further randomisation. This selection process may introduce bias and limit the generalisability of the findings that apply to a selected subgroup rather than an all-comer population.

Another limitation is that two different chemotherapy regimens were used. In fact, we cannot exclude that the outcome could have been different if only the most effective regimen had been used, as suggested by the higher resection rate in patients who received a long-course PAXG chemotherapy as opposed to those who received a long-course mFOLFIRINOX chemotherapy. The 2×2 factorial design, however, was specifically adopted to allow unconfounded estimation of the duration effect independent of the chemotherapy regimen under the assumption of no qualitative interaction. This assumption was prespecified in the SAP and was formally tested. This assumption was formally supported by a non-significant regimen $\times$ duration interaction, and pre-specified subgroup analyses within each regimen stratum consistently showed no effect of chemotherapy duration on EFS in either PAXG or mFOLFIRINOX; within-stratum power, however, is limited and these subgroup estimates should be

interpreted as exploratory. Despite the above-mentioned limitations, the number of events that may be perceived as insufficient to draw firm conclusions, and while waiting for more mature follow-up, the data provides, for the first time, useful information for preliminary inferences on current clinical practice decisions.

Overall, data from the second randomisation of the CASSANDRA trial suggests that prolonging preoperative chemotherapy, whenever possible, obtains comparable results when compared to short-duration preoperative chemotherapy for patients with resectable and borderline resectable PDAC. Accordingly, current results of CASSANDRA are reassuring with respect to the possibility of personalising treatment choices about the duration of systemic neoadjuvant treatment, taking also into account patients' preferences and clinical considerations in individual patients. While the PAXG regimen significantly prolonged EFS compared with mFOLFIRINOX and appears to be the most appropriate candidate for treating patients with PDAC in this setting, efforts to further improve chemotherapy efficacy as well as to identify reliable tools to better select patients who may be suitable candidates for surgery are eagerly awaited.

Contributors

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Data sharing statement

De-identified data that support the findings of this study will not be made publicly available for secondary use because they contain information that could compromise research participant consent. According to European and Italian regulations, any re-use of the data must be approved by the ethical committee. Access to the data will be considered upon reasonable request sent to the corresponding author and Associazione Italiana Studio Pancreas.

Declaration of interests

The authors declare the following financial interests/personal relationships. Michele Reni: Personal honoraria for consulting and advisory role from LeoPharma, Viatrix, BMS; research funding to institution from AstraZeneca; travel expenses from Daiichi Sankyo. Giuseppe Malleo: Personal honoraria for consulting role from OncoSil Medical. Letizia Procaccio: travel expenses from AstraZeneca, personal honoraria as invited speaker from Servier. Andrea Pretta: personal

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejclinm.2026.104190>.

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