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A Phase Ib-II Controlled Trial of Sequential First-Line Therapy Using Nab-Paclitaxel plus Gemcitabine Followed by FOLFIRINOX in Metastatic Pancreatic Adenocarcinoma (GABRINOX Study)

Paolo Romano[1]*, Marco Saleh[1]

[1]Department of Translational Oncology, College of Health Sciences, University of Buenos Aires, Buenos Aires, Argentina.

***E-mail** ✉ promano@hotmail.com

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ABSTRACT

The combination of nab-paclitaxel and gemcitabine (AG) as well as FOLFIRINOX (FFX) represent effective therapeutic options for metastatic pancreatic adenocarcinoma (MPA). This investigation assessed a novel initial sequential approach (AG succeeded by FFX) in MPA, potentially mitigating resistance to the initial regimen and prolonging disease control. Individuals with confirmed MPA via histology or cytology participated in a multicenter study, receiving AG on days 1, 8, and 15, then FFX on days 29 and 43. During the phase Ib portion, three escalation levels were examined to determine the maximum tolerated dose (MTD) and the recommended dose for phase II. The phase II component primarily focused on objective response rate (ORR), with additional endpoints including tolerability, progression-free survival (PFS), and overall survival (OS). In phase Ib, 33 participants were enrolled (31 evaluable), with a median age of 61 years (42-75 years) and 54.8% male. Five dose-limiting toxicities occurred, with no fatalities. Key grade 3/4 adverse events included neutropenia resolving without intervention (35.5%/32.3%), venous thromboembolism (grade 3: 22.6%), and thrombocytopenia (grade 3: 29.0%); MTD was not attained. For phase II, 58 participants were included, median age 60 years (34-72 years), 50% male, and ECOG performance status 0 in 37.9% and 1 in 62.1%. They underwent a median of 4 cycles (1-9) over 8.5 months (0.5-19.8 months). ORR reached 64.9% [95% CI 51.1%-77.1%], with notably minimal neurotoxicity. Predominant grade 3-4 events were venous thromboembolism, thrombocytopenia, neutropenia/febrile neutropenia, nausea, diarrhea, weight reduction, and fatigue, without treatment-related deaths. Responses included complete in 3.5%, partial in 61.4%, stable disease in 19.3%, and progression in 15.8%. Median PFS was 10.5 months (95% CI 6.0-12.5 months), and median OS was 15.1 months (95% CI 10.6-20.1 months). The sequential regimen of AG followed by FFX demonstrated manageable toxicity in the first-line setting, without significant neurotoxicity constraints, alongside elevated response rates and encouraging survival outcomes that support pursuit of randomized comparative studies.

Keywords: Pancreatic cancer, Adenocarcinoma, Nab-paclitaxel, Gemcitabine, FOLFIRINOX, Metastasis

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Introduction

Pancreatic adenocarcinoma continues to pose a significant oncologic difficulty and ranks among the primary causes of cancer-related mortality in developed nations [1, 2]. Its prevalence is rising swiftly, particularly across Europe and North America. Due to lack of detectable early signs and the aggressive spread of pancreatic tumor cells, as many as 80% of cases present with advanced unresectable or metastatic involvement at diagnosis [3]. Even with therapeutic progress, long-term outcomes remain poor [4-6]. In European and US populations, five-year survival rates range from only 8% to 11%. The FOLFIRINOX regimen (FFX: comprising folinic acid, fluorouracil, irinotecan, and oxaliplatin) has demonstrated superior survival over gemcitabine monotherapy and is established as a key first-line option [3, 7-9]. The PRODIGE 4/ACCORD 11 study reported median OS of 11.1

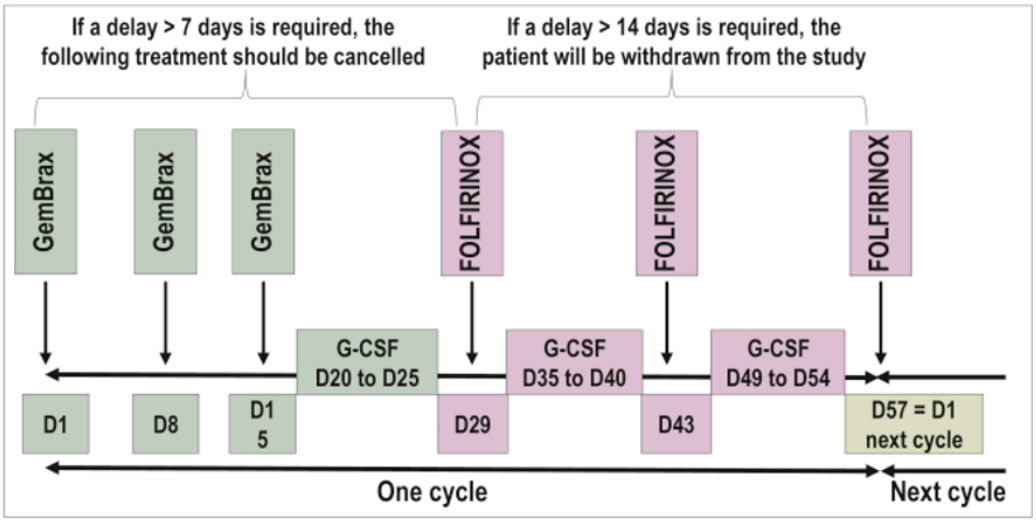
months for FFX versus 6.8 months for gemcitabine [10]. Subsequently, the MPACT phase III study [11] revealed OS benefit with AG over gemcitabine alone (8.5 vs. 6.7 months, $P < 0.001$). Patient cohorts in these landmark trials differed, with older individuals and more ECOG 2 cases in MPACT compared to PRODIGE 4/ACCORD 11. Variations also existed in ECOG 0/1 proportions (Karnofsky ≥90-100: 58% vs. 37.4%) and peritoneal involvement (4.0% vs. 19.4%). No direct head-to-head randomized comparison of FFX and AG exists, though both are accepted first-line standards. Recent propensity-matched analyses suggested FFX superiority in OS, proposing AG for subsequent lines [12, 13], a pattern seen in routine practice despite limited prospective evidence. Response rates and toxicity differed, with higher objective responses (30% vs. 20%) but greater adverse effects for FFX. Many trials adding novel agents to AG yielded negative outcomes [14].

A review by Conroy *et al*. highlighted the lack of breakthrough therapies, as early immunotherapy efforts proved ineffective [10, 15]. A German multicenter randomized phase II trial found no significant differences in resectability conversion or median OS between AG and sequential FFX, though about one-third achieved operability, requiring validation [9]. This prompted exploration of a sequenced regimen using established agents (Gemcitabine, ABraxane, IRinotecan, OXaliplatin: GABRINOX). The phase Ib-II study evaluated GABRINOX (initial AG then FFX) for response, tolerability, and effectiveness, based on the premise that nab-paclitaxel alters the stromal barrier to facilitate greater FFX tumor delivery and activity.

Materials and Methods

Study design and objectives

This prospective phase Ib-II investigation was conducted across three sites in France to examine the novel GABRINOX sequential therapy as initial treatment for metastatic pancreatic adenocarcinoma (MPA). The phase Ib (conducted at two centers) sought to establish the MTD and recommended phase II dose (RP2D) of GABRINOX in the initial cycle (monitoring window). It employed a 6 + 6 escalation scheme across four levels **(Figure 1).** The single-arm open-label phase II (multicenter) primarily assessed ORR with GABRINOX. Secondary aims included toxicity profiling (especially neuropathy), PFS, and OS. Phase II evaluations encompassed all individuals receiving RP2D and evaluable for efficacy.



a)

	GEMBRAX Day 1, 8 and 15*		FOLFIRINOX Day 29 and 43*			Number of included patients
Dose level mg/m²	Nab-Paclitaxel	Gemcitabine	Oxyplatin	Irinotecan	5-FU	
1	100	800	70	150	5-FU bolus 400	6
2a	100	800	85	180		6
2b	125	1000	70	150		6
3	125	1000	85	180	5-FU continous 2400	13
Expansion cohort	125	1000	85	180		12

* One cycle: Day 1 to day 57

b)

Figure 1. Treatment administration during phase I and phase II, irrespective of the dose level (a) and phase I dose-escalation design (b).
5-FU, 5-fluorouracil; G-CSF, granulocyte colony-stimulating factor.

Patients

Key eligibility requirements included: pathologically confirmed metastatic pancreatic adenocarcinoma with measurable lesions; metastatic diagnosis established no more than 6 weeks prior to enrollment; absence of prior therapy for advanced disease; prior adjuvant radiosensitization using fluorouracil or gemcitabine permitted if administered at least 6 months earlier without ongoing adverse effects; age 18-75 years; and ECOG/WHO performance status of 0 or 1. Primary reasons for exclusion were: documented cerebral metastases; additional malignancy within the past 5 years (excluding cured basal/squamous skin carcinoma or other malignancies disease-free for ≥5 years); exposure to cytotoxic chemotherapy beyond gemcitabine or fluorouracil in the adjuvant context; and baseline peripheral sensory neuropathy of grade 2 or higher. All participants provided written informed consent prior to participation. The protocol received approval from the relevant Ethics Committee and was conducted in compliance with Good Clinical Practice guidelines and the Helsinki Declaration (ClinicalTrials.gov identifier: NCT01964287).

Treatments

Therapy was administered in sequence. Participants initially received the AG combination [30-minute intravenous nab-paclitaxel infusion immediately followed by gemcitabine] on days 1, 8, and 15, with FFX administered on days 29 and 43 (2-hour intravenous oxaliplatin, 90-minute irinotecan, and 2-hour leucovorin after a 1-hour break, then fluorouracil bolus followed by 46-hour continuous infusion) **(Figure 1a).** Granulocyte colony-stimulating factor (G-CSF) at 263 μg/day was given as primary prophylaxis on days 20-25, 35-40, and 49-54 of each cycle. For the AG component, G-CSF served as secondary prophylaxis for 5 days prior to subsequent dosing. Dose escalation for GABRINOX is outlined in **Figure 1b.** Drugs were given per established guidelines. Individuals in the phase Ib expansion group and all phase II participants received the recommended phase II dose identified in phase Ib (level 3), using identical scheduling. Treatment consisted of up to nine 8-week cycles of GABRINOX or continued until progression, intolerable side effects, or withdrawal of consent.

Endpoints and assessments

The primary endpoint for phase II was objective response rate (complete plus partial responses), evaluated per RECIST version 1.1 with independent central review. Disease control rate represented the proportion achieving complete response, partial response, or stable disease. Toxicity was graded using NCI-CTCAE version 4.03. Progression-free survival was measured from enrollment to first progression or death from any cause, and overall survival from enrollment to death from any cause.

Statistical considerations

Phase Ib dose-escalation criteria

At least 6 patients were enrolled per dose level, with 12 at the recommended phase II dose. Dose-limiting toxicity included any grade ≥4 event or grade ≥3 symptomatic thrombocytopenia, febrile neutropenia, neutropenia

accompanied by ≥grade 3 infection, or sensory neuropathy within the initial two cycles. Escalation proceeded if fewer than 2 dose-limiting toxicities occurred in 6 patients. If 3 were observed, an additional 6 were added at that level. Escalation halted with ≥4 in 6 or ≥6 in 12 patients, prompting expansion at the prior level with 6 more patients. Maximum tolerated dose was the level with dose-limiting toxicities in ≥50% of cases. Upon identifying maximum tolerated dose, an expansion cohort of 12 additional patients (total 24) was treated at the preceding level as recommended phase II dose.

Sample size

Phase Ib required up to 60 patients (minimum 6 per level plus 24 at recommended dose). For phase II, using a single-stage A'Hern design (α=5%, β=10%, p0=30%, p1=50%), 53 evaluable patients were needed. The regimen would be deemed promising with ≥22 objective responses in 53 evaluable cases. Enrollment targeted 58 to account for approximately 10% ineligibility or unevaluability.

Statistical analyses

Safety evaluations included all treated individuals. Phase II objective and disease control rates were determined in the per-protocol group (eligible and evaluable), with remaining analyses in intent-to-treat. Frequencies and percentages described categorical data; medians and ranges summarized continuous variables. Response and control rates included percentages with 95% binomial exact confidence intervals. Kaplan–Meier estimates were used for progression-free and overall survival. Cox proportional hazards models performed multivariate assessments, reporting hazard ratios with 95% confidence intervals. Analyses utilized STATA version 16.0 (StatCorp, College Station, TX).

Results and Discussion

Phase Ib enrolled 33 patients from September 2013 to October 2015; phase II added 58, with final accrual in December 2016. All received AG followed by FFX at recommended phase II dose: nab-paclitaxel 125 mg/m² and gemcitabine 1000 mg/m² on days 1, 8, and 15, then FFX on days 29 and 43 (oxaliplatin 85 mg/m², irinotecan 180 mg/m², fluorouracil bolus 400 mg/m² plus continuous 2400 mg/m²).

In phase Ib, among 31 evaluable patients for escalation, safety, and activity, median age was 61.0 years (42-75 years), with 54.8% male **(Table 1).** ECOG/WHO status was 0 in 35.5% and 1 in 64.5%. Treatment followed assigned levels **(Figure 1b).** Five dose-limiting toxicities occurred (one at level 2a, two at 2b, two at 3), consisting of temporary grade 4 neutropenia in cycle 1 (days 8-20, prior to initial prophylactic G-CSF) resolving spontaneously. No toxicity-related fatalities were recorded. Predominant grade 3-4 events were neutropenia (grade 4: 10 patients, 32.3%; grade 3: 11, 35.5%), venous thromboembolism (grade 3: 7, 22.6%), and thrombocytopenia (grade 3: 9, 29.0%). Maximum tolerated dose was not achieved. Per protocol rules, level 3 was confirmed as recommended phase II dose (with 12-patient expansion for verification).

Table 1. Baseline Characteristics of Patients

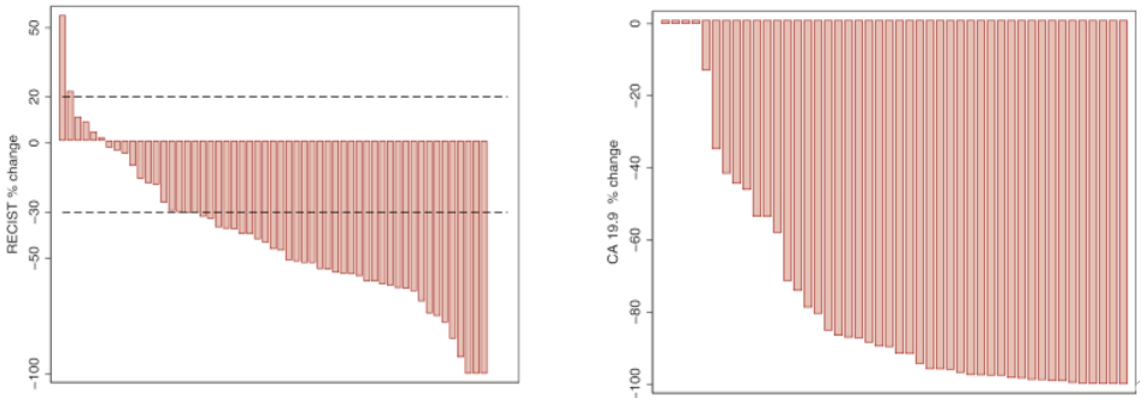
Characteristic	Phase II (n = 58)	Phase Ib (n = 31)
Age (years), median (range)	60 (34-72)	61.0 (42-75)
Sex, n (%)		
Male	29 (50.0)	17 (54.8)
Female	29 (50.0)	14 (45.2)
ECOG/WHO performance status, n (%) [a]		
0	22 (37.9)	11 (35.5)
1	36 (62.1)	20 (64.5)
Primary tumor location, n (%)		
Head of pancreas	25 (43.1)	14 (45.2)
Tail of pancreas	17 (29.3)	7 (22.5)
Body of pancreas	16 (27.6)	10 (32.3)
Prior treatment of primary tumor, n (%)		
Surgery	7 (12.1)	7 (22.6)

Radiotherapy	1 (1.7)	1 (3.2)
Adjuvant chemotherapy (gemcitabine)	6 (10.3)	5 (16.1)
Number of metastatic sites, n (%)		
1	24 (41.4)	15 (48.4)
>1	34 (58.6)	16 (51.6)
Serum CA 19-9 level [b], median (range)	849 (1-207 320)	800 (30.4-207 320)
Missing	1	4

[a] ECOG/World Health Organization performance status.
[b] Carbohydrate antigen 19-9.

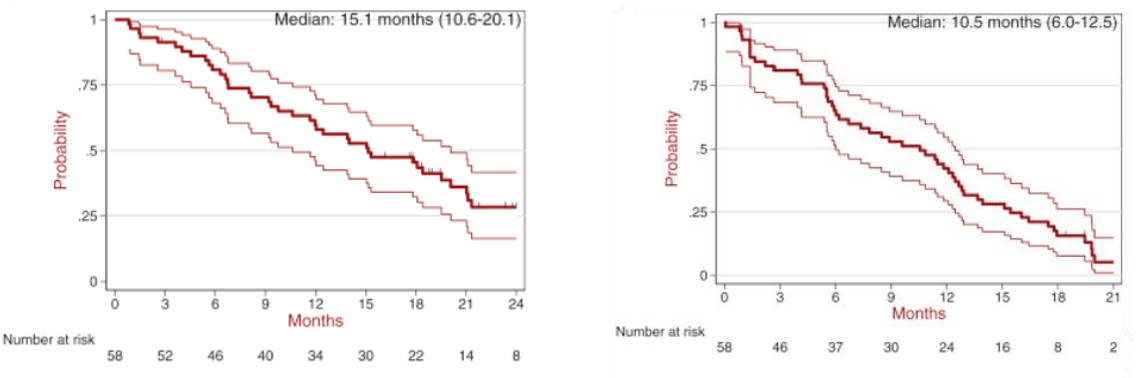
In the phase II component, participants had a median age of sixty years (range 34-72 years), with an equal distribution of males and females (50% each) **(Table 1).** ECOG/WHO performance status was rated as 0 in 37.9% and as 1 in 62.1% of cases, while 87.9% presented with synchronous metastases and 58.6% had involvement of multiple metastatic sites. A median of 4 cycles (range 1-9) were delivered over a median duration of 8.5 months (range 0.5-19.8 months).

Efficacy outcomes were based on tumor response and survival endpoints. Of 57 evaluable patients, complete response was achieved in 2 (3.5%) and partial response in 35 (61.4%), yielding an objective response rate of 64.9 percent (95 percent CI 51.1 percent to 77.1 percent). Stable disease occurred in 11 patients (19.3 percent), resulting in a disease control rate of 84.2 pecent (95 percet CI 72.1 percent to 92.5 percent) **(Figure 2a).** When restricted to the initial 53 evaluable participants, the objective response rate was 67.9 percent (95 percent CI 53.7 percent to 80.1 percent), corresponding to 36 patients with complete or partial response, thereby satisfying the predefined primary endpoint threshold of at least 22 responses among 53. A notable biochemical response was also evident in changes to serum CA 19-9 levels **(Figure 2b).** With a median follow-up of 23.7 months (95 percent CI 18.9-33.0 months), median progression-free survival reached 10.5 months (95 percent CI 6.0-12.5) **(Figure 3a),** with rates of 65.2 percent (95 percent CI 51.4 percent to 75.9 percent) at 6 months and 42.3% (95 percent CI 29.4 percent to 54.6 percent) at 12 months. Median overall survival was 15.1 months (95 percent CI 10.6-20.1 months), accompanied by rates of 80.8 percent (95 percent CI 68.1 percent to 88.9 percent) at 6 months and 59.8 percent (95 percent CI 45.9 percent to 71.1 percent) at 12 months **(Figure 3b).**



a) b)

Figure 2. Waterfall plots showing the response to treatment (a) and CA 19.9 level (b) at the end of treatment.



a) b)

Figure 3. Overall (a) and progression-free survival (b) curves with 95% confidence interval (CI).

Regarding safety, the predominant grade 3 and 4 adverse events included neutropenia (grade 3: 20 patients, 34.5%; grade 4: 13 patients, 22.4%), thrombocytopenia (grade 3: 18 patients, 31.0%; grade 4: 1 patient, 1.7%), and diarrhea (grade 3: 15 patients, 25.9%; grade 4: 1 patient, 1.7%). The incidence of febrile neutropenia remained low (grade 3: 1 patient, 1.7%; grade 4: 1 patient, 1.7%) **(Table 2).** Three fatalities occurred due to causes not attributable to protocol therapy: one from aspiration pneumonia secondary to gastrointestinal obstruction, one from respiratory failure, and one from progressive disease.

Table 2. Severe Adverse Events (Grades 1-4) in the Phase II Cohort

Adverse Event	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Neurotoxicity	30 (51.7)	17 (29.3)	3 (5.2)	0
Thrombosis	1 (1.7)	7 (12.1)	10 (17.2)	0
Thrombocytopenia	2 (3.5)	9 (15.5)	18 (31.0)	1 (1.7)
Neutropenia / Febrile Neutropenia	0 / 0	2 (3.5) / 0	20 (34.5) / 1 (1.7)	13 (22.4) / 1 (1.7)
Nausea	14 (24.1)	23 (39.7)	10 (17.2)	0
Diarrhea	14 (24.1)	19 (32.8)	15 (25.9)	1 (1.7)
Weight Loss	9 (15.5)	16 (27.6)	1 (1.7)	0
Asthenia	5 (8.6)	31 (53.5)	18 (31.0)	0

Phase II cohort (n = 58)

Furthermore, progression-free survival (PFS) and objective response rate (ORR) demonstrated strong correlations with a reduction in CA 19.9 levels exceeding 60% in the majority of cases ($P < 0.001$). Higher PFS was also linked to albumin levels above 35 g/L ($P = 0.029$), neutrophil-to-lymphocyte ratio exceeding 5 ($P = 0.053$), and prognostic nutritional index (PNI) greater than 49.6 ($P < 0.001$). Elevated lactate dehydrogenase (LDH) above 250 U/L ($P = 0.027$), neutrophil-to-lymphocyte ratio above 5 ($P = 0.017$), and PNI at or below 49.6 ($P = 0.009$) correlated with reduced PFS. Overall survival (OS) showed significant ties to LDH above 250 U/L ($P = 0.026$), albumin exceeding 35 g/L ($P = 0.021$), CA 19.9 decline over 60% ($P = 0.003$), neutrophil-to-lymphocyte ratio above 5 ($P = 0.078$), and PNI above 49.6 ($P = 0.003$). Poorer OS was associated with LDH greater than 250 U/L ($P = 0.012$) and neutrophil-to-lymphocyte ratio exceeding 5 ($P < 0.001$).

The findings highlight that a novel sequential approach (GABRINOX), involving nab-paclitaxel plus gemcitabine (AG) prior to FOLFIRINOX (FFX) in metastatic pancreatic adenocarcinoma, achieved substantial tumor response alongside improved survival outcomes and minimal neurotoxicity, suggesting strong potential for evaluation in a randomized trial. Accordingly, this phase Ib-II study yielded favorable outcomes across all key measures, confirming the practicality of the GABRINOX sequence and establishing the recommended phase II dose in an expanded patient group. In phase II, the primary goal of an ORR surpassing 50%—a challenging target for individuals with metastatic disease and unfavorable prognosis—was met, reaching 64.9%, with median PFS of 10.5 months and median OS of 15.1 months.

This ordered treatment strategy enabled extended therapy periods with negligible or mild neurotoxicity only. Notably, no instances of treatment discontinuation due to nerve-related issues occurred, and severe neurotoxicity

was rare: absent (grade 3-4) in phase Ib and limited to 5.2% grade 3 (no grade 4) in phase II, even with therapy lasting over 8 months on average. Neurotoxicity often restricts regimens like FOLFOX or FOLFIRINOX to short durations (typically 3-4 months) in metastatic settings, as well as in adjuvant treatment for stage III colorectal cancer per IDEA collaboration guidelines [16]. Similar constraints apply in metastatic colorectal cancer, where oxaliplatin is frequently de-escalated after 4 months (8 cycles) due to cumulative side effects, as seen in TRIBE1 and TRIBE2 trials [17, 18]. A comparable de-escalation to LV5FU2 maintenance after initial FOLFIRINOX was proven viable and beneficial in the PANOPTIMOX trial for disease control in metastatic pancreatic cancer [19]. The current outcomes are noteworthy, as minimizing neurotoxicity was a core rationale for the trial design: initiating with AG, then transitioning to FFX after a break from oxaliplatin and nab-paclitaxel, to curb accumulated nerve damage while preserving dose intensity and duration for better tumor management. This was reflected in prolonged therapy and sustained dosing (nab-paclitaxel relative intensity >80%; FFX >77%).

Conversely, the sequence led to notable blood-related adverse events (grade 3-4 neutropenia in 56.9% of cases). However, severe episodes (22.4% grade 4) were mostly short-lived, without symptoms, and clustered in the initial AG cycle (days 8-15) prior to growth factor support, resolving naturally without feverish complications. Following mandatory prophylactic G-CSF before FFX, severe neutropenia persisted but remained controllable, evidenced by low febrile neutropenia (3.4%) and no related fatalities. These data underscore the necessity of routine G-CSF prophylaxis in this protocol. Thromboembolic complications (17.2% grade 3, none grade 4) aligned with existing reports, prompting consideration of preventive anticoagulation [20].

A key shortfall was the omission of quality-of-life assessments. Prior work in the PRODIGE 4/ACCORD 11 trial indicated no detrimental impact on patient well-being despite toxicities from the intensive regimen [21]. Given the aggressive nature of metastatic pancreatic cancer—marked by quick decline in performance, weight reduction, cachexia, and diminished quality of life—the stable well-being in that study likely stemmed from effective disease suppression with FOLFIRINOX. Here, symptoms like nausea, vomiting, and fatigue mirrored those from standard AG or FFX [11, 21], while body weight stayed consistent, with severe weight reduction rare (1.7% grade 3). Thus, the approach proved not only effective but also tolerable for patients.

The protocol planned for 6 months of therapy, with extensions decided individually, informed by typical durations under 6 months in prior reports [10, 11]. In contrast, median duration here exceeded 8 months—unusually prolonged for this disease—and aligned with or surpassed the OS from the AG arm in the MPACT trial [11]. Efficacy was evident in robust tumor control (complete responses in 2 cases, substantial responses in 35) and survival benefits. Disease control rate reached 84.2%, with responses predominantly emerging within the initial 4 months; tumor shrinkage and CA 19.9 drops were closely aligned, consistent with patterns in FOLFIRINOX or gemcitabine therapy [22].

The 18-month OS rate of 45.5% (95% CI 32.2%-58.8%) in this unselected cohort (no molecular selection) is encouraging. Median PFS and OS outperformed historical benchmarks: 18-month OS rates of 18.6% (ACCORD 11) and 16% (MPACT), alongside medians of 11.1/6.4 months (ACCORD 11) and 8.5/5.5 months (MPACT). Direct comparisons are cautious due to the non-randomized design and potential recruitment imbalances (92.3% from two of three sites). Nonetheless, the data warrant validation in a phase III randomized setting, though challenges persist in France regarding nab-paclitaxel reimbursement. A separate French trial demonstrated viability and activity of the FIRGEMAX alternating strategy (gemcitabine/nab-paclitaxel with FOLFIRI.3) with tolerable side effects [23]. The present regimen achieved superior results using standard FFX without irinotecan escalation. Reimbursement may improve with generics. In related efforts, a phase II study (n=103, NCT04570943) is underway assessing intensified sequential GABRINOX as neoadjuvant therapy in locally advanced disease, including Stereotactic MR-guided Adaptive Radiotherapy (SMART) in stable subgroups, informed by early GABRINOX responses (partial responses 54.3% at 2 months, 73.1% at 4 months; complete 8.7%).

An open issue is optimal second-line options post-GABRINOX. Fewer than half of pancreatic cancer patients proceed to subsequent therapy. Here, progression was infrequent during active treatment, often occurring after cessation or on gemcitabine maintenance, allowing potential re-challenge with FFX given low residual neurotoxicity. The POLO trial's findings on olaparib maintenance in germline BRCA-mutated cases showed doubled PFS versus placebo, though without OS benefit at interim or quality-of-life differences; applicability is limited to ~7.5% of patients, excluding those progressing early on platinum or on prolonged chemotherapy [24]. Broader relevance in unselected metastatic cases requires more study, yet it supports PARP inhibitors as a possible follow-up approach.

Conclusion

The phase Ib-II investigation revealed elevated tumor response, manageable side effects without restrictive neurotoxicity, and enhanced survival, collectively supporting the pursuit of confirmatory randomized studies.

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Ethics Statement: None

References

1. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74:2913–2921. doi:10.1158/0008-5472.CAN-14-0155
2. Ferlay J, Partensky C, Bray F. More deaths from pancreatic cancer than breast cancer in the EU by 2017. Acta Oncol. 2016;55:1158–1160. doi:10.1080/0284186X.2016.1197419
3. Ducreux M, Cuhna AS, Caramella C, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v56–v68. doi:10.1093/annonc/mdv295
4. Huang L, Jansen L, Balavarca Y, et al. Stratified survival of resected and overall pancreatic cancer patients in Europe and the USA in the early twenty-first century: a large, international population-based study. BMC Med. 2018;16:125. doi:10.1186/s12916-018-1120-9
5. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424. doi:10.3322/caac.21492
6. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer. 2018;103:356–387. doi:10.1016/j.ejca.2018.07.005
7. Sohal DPS, Kennedy EB, Mangu PB, et al. Metastatic pancreatic cancer: ASCO guideline update. J Clin Oncol. 2020;38:3217–3230. doi:10.1200/JCO.20.01364
8. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021;19:439–457. doi:10.6004/jnccn.2021.0017
9. Kunzmann V, Siveke JT, Algül 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;6:128–138. doi:10.1016/S2468-1253(20)30330-7
10. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364:1817–1825. doi:10.1056/NEJMoa1011923
11. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369:1691–1703. doi:10.1056/NEJMoa1304369
12. Williet N, Saint A, Pointet AL, et al. FOLFIRINOX versus gemcitabine/nab-paclitaxel as first-line therapy in patients with metastatic pancreatic cancer: a comparative propensity score study. Ther Adv Gastroenterol. 2019;12:1756284819878660. doi:10.1177/1756284819878660
13. Chan KK, Guo H, Cheng S, et al. Real-world outcomes of FOLFIRINOX versus gemcitabine and nab-paclitaxel in advanced pancreatic cancer: a population-based propensity score-weighted analysis. Cancer Med. 2020;9:160–169. doi:10.1002/cam4.2705
14. Van Cutsem E, Tempero MA, Sigal D, et al. Randomized phase III trial of pegvorhyaluronidase alfa with nab-paclitaxel plus gemcitabine for patients with hyaluronan-high metastatic pancreatic adenocarcinoma. J Clin Oncol. 2020;38:3185–3194. doi:10.1200/JCO.20.00590

15. Lambert A, Schwarz L, Borbath I, et al. An update on treatment options for pancreatic adenocarcinoma. Ther Adv Med Oncol. 2019;11:1758835919875568. doi:10.1177/1758835919875568
16. André T, Meyerhardt J, Iveson T, et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration). Lancet Oncol. 2020;21:1620–1629. doi:10.1016/S1470-2045(20)30527-1
17. Cremolini C, Antoniotti C, Rossini D, et al. Upfront FOLFOXIRI plus bevacizumab versus sequential strategies in metastatic colorectal cancer (TRIBE2). Lancet Oncol. 2020;21:497–507. doi:10.1016/S1470-2045(19)30862-9
18. Rossini D, Lonardi S, Antoniotti C, et al. Treatments after progression to first-line FOLFOXIRI and bevacizumab in metastatic colorectal cancer. Br J Cancer. 2021;124:183–190. doi:10.1038/s41416-020-01089-9
19. Dahan L, Phelip JM, Le Malicot K, et al. FOLFIRINOX strategies for first-line treatment of metastatic pancreatic cancer (PRODIGE 35-PANOPTIMOX). J Clin Oncol. 2018;36:4000.
20. Frere C, Bournet B, Gourgou S, et al. Incidence of venous thromboembolism in patients with newly diagnosed pancreatic cancer. Gastroenterology. 2020;158:1346–1358.e4. doi:10.1053/j.gastro.2019.12.009
21. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in metastatic pancreatic cancer. J Clin Oncol. 2013;31:23–29. doi:10.1200/JCO.2012.44.4869
22. Robert M, Jarlier M, Gourgou S, et al. Retrospective analysis of CA19-9 decrease in metastatic pancreatic carcinoma treated with FOLFIRINOX or gemcitabine. Oncology. 2017;93:367–376. doi:10.1159/000477850
23. Rinaldi Y, Pointet AL, Khemissa Akouz F, et al. Gemcitabine plus nab-paclitaxel until progression or alternating with FOLFIRI.3 as first-line treatment (FIRGEMAX). Eur J Cancer. 2020;136:25–34. doi:10.1016/j.ejca.2020.05.018
24. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019;381:317–327. doi:10.1056/NEJMoa1903387