Sequential first-line treatment with nab-paclitaxel/gemcitabine and FOLFIRINOX in metastatic pancreatic adenocarcinoma: GABRINOX phase Ib-II controlled clinical trial

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ORIGINAL RESEARCH

Sequential first-line treatment with nab-paclitaxel/gemcitabine and FOLFIRINOX in metastatic pancreatic adenocarcinoma: GABRINOX phase Ib-II controlled clinical trial

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Available online 24 November 2021

Background: Nab-paclitaxel/gemcitabine (AG) and FOLFIRINOX (FFX) are promising drugs in metastatic pancreatic cancer (MPC). This study evaluated a new first-line sequential treatment (AG followed by FFX) in MPC that might overcome resistance to primary therapy and delay tumor progression.

Patients and methods: Patients with histologically/cytologically confirmed MPC were included in a multicentric trial receiving AG (day 1, 8 and 15) followed by FFX (day 29 and 43). In phase Ib, three dose-levels were tested for maximum tolerated dose (MTD) and recommended phase II dose. In phase II, the main outcome was the objective response rate (ORR) and secondarily safety, progression-free survival (PFS) and overall survival (OS).

Results: In phase Ib, we included 33 patients (31 assessable) of median age 61.0 years (range 42-75 years) and represented by 54.8% males. Five dose-limiting toxicities were reported without any death. The main grade 3/4 toxicities were neutropenia with spontaneous resolution (35.5%/32.3%), venous thromboembolism (grade 3: 22.6%) and thrombopenia (grade 3: 29.0%), while the MTD was not reached. In phase II, we included 58 patients of median age 60 years (range 34-72 years), 50% males and with Eastern Cooperative Oncology Group stage score 0 and 1 of 37.9% and 62.1%, respectively. They received a median of 4 (1-9) cycles in 8.5 months (0.5-19.8 months). The ORR was 64.9% [95% confidence interval (CI) 51.1% to 77.1%], and neurotoxicity was remarkably low. The main grade 3-4 toxicities were venous thromboembolism, thrombopenia, neutropenia/febrile neutropenia, nausea, diarrhea, weight loss and asthenia without any death. Tumor response was complete in 3.5% and partial in 61.4%, while disease was stable in 19.3% and progressive in 15.8% of patients. The 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).

Conclusion: Sequential AG and FFX showed acceptable toxicity as first-line treatment with no limiting neurotoxicity, while high response rate and survival justify randomized trials.

Key words: pancreatic cancer, adenocarcinoma, nab-paclitaxel, gemcitabine, FOLFIRINOX, metastasis

INTRODUCTION

Pancreatic cancer remains a major challenge in oncology and a leading cause of death in high-income countries.[1,2] Its incidence is rapidly increasing especially in Europe and North America. Because of the absence of early symptoms and high metastatic potential of pancreatic cancer cells, up to 80% of patients are diagnosed at advanced stages of unresectable tumor or metastatic disease.[3] Despite recent advances in its management, the survival rates are still low.[4-6] In Europe and the United States, only 8%-11% of patients survive 5 years after diagnosis. The FOLFIRINOX (FFX: folinic acid, fluorouracil, irinotecan and oxaliplatin) chemotherapy combination improves survival compared with gemcitabine alone and has become the standard first-line chemotherapy.[3,7-9] In PRODIGE 4/ACCORD 11 trial, the median overall survival (OS) was 11.1 months with FFX compared to

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6.8 months with gemcitabine alone.[10] Two years later, MPACT phase III trial[11] showed OS improvement with nab-paclitaxel/gemcitabine combination (AG) compared with gemcitabine alone (8.5 versus 6.7 months, $P < 0.001$). However, patients in these two pivotal trials were not fully comparable because they were older and the proportion of patients with Eastern Cooperative Oncology Group (ECOG) performance score of 2 was higher in MPACT than in PRODIGE 4/ACCORD 11 trials. Moreover, percentage of patients with ECOG performance score of 0 or 1 (Karnofsky score = 90-100) (58% versus 37.4%) and with peritoneal carcinomatosis (4.0% versus 19.4%) varied in these two trials. To our knowledge, there are no randomized trials that compared FFX and AG chemotherapy regimens, although both are considered first-line treatments. In two recent studies, a propensity score analysis supported the superiority of FFX over AG in terms of OS and indicated that AG should be used as second-line treatment.[12,13] This is actually frequently done in the clinical practice, although there are no available prospective data. The tumor response and safety profiles of these two regimens were different since adverse events and objective tumor response were higher (30% versus 20%) with FFX than with AG. Most ongoing studies evaluating the gemcitabine/nab-paclitaxel combination associated with an experimental treatment versus the combination alone have reported negative results.[14]

A recent review by Conroy et al. underlined the absence of new efficient drugs for pancreatic cancer since already tested first-generation immunotherapies failed to show satisfactory results.[10,15] A recent open-label, multicenter, randomized phase II study from 28 centers in Germany indicated that between nab-paclitaxel plus gemcitabine and the sequential FFX groups there were non-significant surgical conversion rate and median OS. Although conversion to resectability was achieved in about a third of patients, these results need further confirmation.[9] Therefore, the principle to test a sequential alternative regimen with known drugs GemcitabineABRaxaneIRInotecanOXaliplatine (GABRINOX) emerged. This phase Ib-II trial was aimed to assess GABRINOX (AG followed by FFX) response rate, safety and efficacy, starting the sequential treatment with AG and hypothesizing that nab-paclitaxel by targeting tumor microenvironment would increase FFX access to the tumor and thus would enhance its efficacy.

PATIENTS AND METHODS

Study design and objectives

This prospective phase Ib-II trial was carried out in three French centers to evaluate GABRINOX new sequential treatment as first-line treatment of metastatic pancreatic cancer (MPC) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100318). The aim of phase Ib study (bicentric) was to identify the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) of GABRINOX during the first treatment cycle (observation period). Phase Ib was designed according to 6 + 6 dose-escalation design with four dose levels (Figure 1). The primary objective of this single-arm open phase II study (multicentric) was to evaluate the objective response rate (ORR) to GABRINOX. Secondary objectives were to evaluate the safety profile (particularly neurotoxicity), progression-free survival (PFS) and OS. In phase II analysis, all patients treated with RP2D and assessable for efficacy were considered.

Patients

The main inclusion criteria were: histologically or cytologically confirmed and measurable MPC; initial definitive diagnosis of metastatic disease made $\leq$6 weeks before inclusion; no previous treatment of metastatic disease; radiation sensitizer in adjuvant setting with fluorouracil or gemcitabine allowed if the last dose was completed at least 6 months earlier and no persistent toxicity was present; age between 18 and 75 years; and ECOG/World Health Organization (WHO) performance status $\leq$1. The main exclusion criteria were: known brain metastases; history of other malignancy in the last 5 years (except *in situ* basal or squamous cell skin cancer or other cancers if disease free for at least 5 years); previous cytotoxic doses of any chemotherapy drug other than gemcitabine or fluorouracil in adjuvant setting; and $\geq$grade 2 peripheral sensory neuropathy at the beginning of the study. Patients signed an informed consent before inclusion. The study was approved by Ethics Committee and carried out according to Good Clinical Practice requirements and Helsinki Declaration (ClinicalTrials.gov number, NCT01964287).

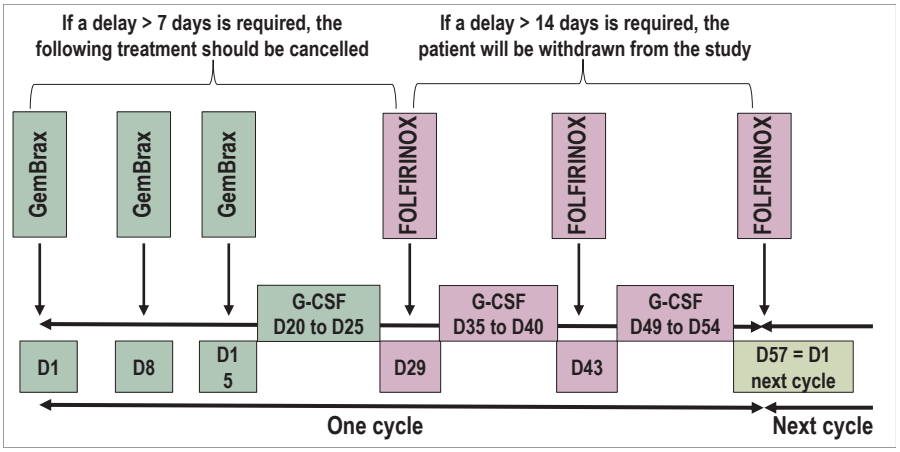
Treatments

Treatments were administered sequentially. Patients received AG [intravenous (i.v.) injection of nab-paclitaxel over 30 min followed by gemcitabine] at day 1, 8 and 15, while FFX was delivered at day 29 and 43 (i.v. injection of oxaliplatin for 2 h, irinotecan for 90 min and leucovorin for 2 h after 1-h rest, followed by fluorouracil bolus injection and then continuous 46-h infusion) (Figure 1A). From day 20 to 25, from day 35 to 40 and from day 49 to 54 of each cycle, granulocyte colony-stimulating factor (G-CSF) (263 µg/day) was prescribed as primary prophylaxis. For AG, G-CSF was prescribed as secondary prophylaxis for 5 days before the next administration. Dose-escalation levels of GABRINOX are presented in Figure 1B. Chemotherapeutic agents were administered according to standard practice. Patients included in phase Ib expansion cohort and in phase II received RP2D defined in phase Ib (dose-level 3) and with the same treatment modalities. Patients received nine cycles (8 weeks/each) of GABRINOX or until disease progression, unacceptable toxicity or patient's refusal.

Endpoints and assessments

The phase II trial primary endpoint was the ORR (i.e. complete and partial response) assessed using RECIST v1.1 criteria (central review). Disease control rate (DCR) was defined as percentage of complete or partial response or stable disease. Safety was evaluated according to the National Cancer Institute-Common Terminology Criteria

A



B

	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

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.

(NCI-CTCAE) v4.03. PFS was defined from inclusion to the date of the first documented progression or the date of death from any cause, while OS was defined from inclusion to the date of death from any cause.

Statistical considerations

Phase Ib dose-escalation rules. A minimum of 6 patients was included for each dose level and 12 patients at the RP2D. A dose-limiting toxicity (DLT) was defined as any grade $\geq$4 toxicity or grade $\geq$3 for symptomatic thrombopenia, febrile neutropenia, neutropenia with grade $\geq$3 infection or peripheral sensory neuropathy during the first two cycles. If $<$2 DLTs were observed in six patients, escalation to the next dose was permitted. If three DLTs were observed in six patients, then six additional patients were included at the same dose. If $\geq$4 DLTs in 6 patients or $\geq$6 DLTs in 12 patients were observed, dose escalation was stopped and 6 additional patients were included at the previous dose level. The MTD was defined as the dose level at which at least one DLT occurred in $\geq$50% of patients. When reaching the MTD, 12 additional patients were included in the expansion cohort (total 24 patients) at the previous dose level, i.e. the RP2D.

Sample size

A number of 60 patients were necessary in the phase Ib trial (i.e. minimum of 6 patients per dose level and 24 patients at the RPD2). For phase II, in one-stage A'Hern design (α = 5%, β = 10%, p_0 = 30% and p_1 = 50%), 53 assessable patients were necessary. The GABRINOX combination was considered sufficiently effective when there were at least 22 objective responses among 53 assessable patients. We included 58 patients considering around 10% of non-assessable patients.

Statistical analyses

The safety analysis was carried out using all treated patients. For phase II only, ORR and DCR were calculated in 'per-protocol' population (eligible and assessable patients), while other analyses were carried out in the 'intent-to-treat' population. Categorical variables were reported with numbers and frequencies and continuous variables with medians and ranges. ORR and DCR were reported using percentages and 95% confidence intervals (CIs) (binomial exact method). Event-free survival (PFS, OS) was estimated using Kaplan—Meier method. Multivariate analyses were carried out using Cox proportional hazards model. Hazard ratios were reported with 95% CI. Statistical analyses were carried out with STATA 16.0 (StatCorp, College Station, TX).

RESULTS

The phase Ib trial included 33 patients between September 2013 and October 2015, while in the phase II trial, we included 58 patients with the last inclusion in December 2016 (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100318). All patients received

Table 1. Patients' characteristics

	Phase Ib (n = 31)	Phase II (n = 58)
Age (years), median (range)	61.0 (42-75)	60 (34-72)
Sex, *n* (%)		
Male	17 (54.8)	29 (50.0)
Female	14 (45.2)	29 (50.0)
ECOG/WHO PS, *n* (%)[a]		
0	11 (35.5)	22 (37.9)
1	20 (64.5)	36 (62.1)
Primary tumor site, *n* (%)		
Head of pancreas	14 (45.2)	25 (43.1)
Tail of pancreas	7 (22.5)	17 (29.3)
Body of pancreas	10 (32.3)	16 (27.6)
Treatment of primary tumor, *n* (%)		
Surgery	7 (22.6)	7 (12.1)
Radiotherapy	1 (3.2)	1 (1.7)
Adjuvant chemotherapy (gemcitabine)	5 (16.1)	6 (10.3)
Metastatic sites, *n* (%)		
1	15 (48.4)	24 (41.4)
>1	16 (51.6)	34 (58.6)
Serum CA 19.9 level[b]		
Median (range)	800 (30.4-207 320)	849 (1-207 320)
Missing	4	1

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

AG and FFX at the RP2D: nab-paclitaxel 125 mg/m^2 and gemcitabine 1000 mg/m^2 at day 1, 8 and 15, and then FFX at day 29 and 43 (oxaliplatin 85 mg/m^2 and irinotecan 180 mg/m^2, fluorouracil bolus of 400 mg and continuous 2400 mg).

In phase Ib trial, the median age of assessable patients for dose escalation, safety and efficacy (n = 31) was 61.0 years (range 42-75 years) comprising 54.8% males (Table 1). Their ECOG/WHO performance status was 0 or 1 in proportion of 35.5% and 64.5%, respectively. They received GABRINOX according to their allocated dose level (Figure 1B). The median number of administered cycles, the mean treatment duration at each dose level and the relative dose intensities are summarized in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100318. Five DLTs were reported (n =1 in level 2a, n = 2 in level 2b and n = 2 in level 3). These patients experienced transient grade 4 neutropenia during the first treatment cycle (between day 8 and 20 and before the first prophylactic G-CSF injection) with spontaneous resolution. There was no related toxic death (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100318). The main severe (grade 3-4) toxicities were neutropenia (grade 4: n = 10, 32.3%; grade 3: n = 11, 35.5%), venous thromboembolism (grade 3: n = 7, 22.6%) and thrombopenia (grade 3: n = 9, 29.0%) (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100318). The MTD was not reached. According to the design and dose-escalation rules, level 3 was validated (12 patients were included in the expansion cohort to confirm this dose level) as the RP2D.

In phase II trial, patients' median age was 60 years (range 34-72 years) and half of them were males (Table 1). Their ECOG/WHO performance status was 0 and 1 (37.9% and 62.1%, respectively) and a proportion of 87.9% had synchronous metastatic disease with more than one metastatic site in 58.6% of patients. A median of 4 (range 1-9) cycles were administered in 8.5 months (range 0.5-19.8 months). The relative dose intensities are listed in Supplementary Tables S2 and S3, available at https://doi.org/10.1016/j.esmoop.2021.100318.

The efficacy was evaluated by tumor response and survival. Among 57 assessable patients, 2 complete responses (3.5%) and 35 partial responses (61.4%) were reported, i.e. an ORR of 64.9% (95% CI 51.1% to 77.1%). Disease was stable in 11 patients (19.3%) and the DCR was 84.2% (95% CI 72.1% to 92.5%) (Figure 2A). Considering only 53 first assessable patients, the ORR was 67.9% (95% CI 53.7% to 80.1%), i.e. 36 of 53 patients with complete or partial response. Thus, the primary objective of at least 22 of 53 responses was met. An important biological response (CA 19.9 serum concentration change) was also observed (Figure 2B). After a median follow-up of 23.7 months (95% CI 18.9-33.0 months), the median PFS was 10.5 months (95% CI 6.0-12.5) (Figure 3A). The PFS rates were 65.2% (95% CI 51.4% to 75.9%) at 6 months and 42.3% (95% CI 29.4% to 54.6%) at 12 months. The median OS was 15.1 months (95% CI 10.6-20.1 months) with OS rates of 80.8% (95% CI 68.1% to 88.9%) and 59.8% (95% CI 45.9% to 71.1%) at 6 and 12 months, respectively (Figure 3B).

Regarding toxicities, the most frequent grade 3 and 4 toxicities were neutropenia (grade 3: n = 20, 34.5%; grade 4: n = 13, 22.4%), thrombopenia (grade 3: n = 18, 31.0%; grade 4: n = 1, 1.7%) and diarrhea (grade 3: n = 15, 25.9%; grade 4: n = 1, 1.7%). The febrile neutropenia rate was low (grade 3: n = 1, 1.7%; grade 4: n = 1, 1.7%) (Table 2). Three patients died of causes unrelated to the study treatment: aspiration pneumonia due to digestive occlusion (n = 1), respiratory distress (n = 1) and disease progression (n = 1).

In addition, PFS and ORR were significantly associated with decreased CA 19.9 serum level in >60% of patients (P < 0.001). PFS was also significantly associated with albumin >35 g/l (P = 0.029), neutrophil/lymphocyte ratio >5 (P = 0.053) and prognostic nutritional index (PNI) >49.6 (P < 0.001). Lactate dehydrogenase (LDH) >250 U/l (P = 0.027), neutrophil/lymphocyte ratio >5 (P = 0.017) and PNI ≤49.6 (P = 0.009) were associated with poorer PFS (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2021.100318). OS was significantly associated with LDH >250 U/l (P = 0.026), albumin >35 g/l (P = 0.021), decreased CA 19.9 serum level >60% (P = 0.003), neutrophil/lymphocyte ratio >5 (P = 0.078) and PNI >49.6 (P = 0.003). LDH >250 U/l (P = 0.012) and neutrophil/lymphocyte ratio >5 (P < 0.001) were associated with poorer OS (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2021.100318).

DISCUSSION

We showed that an innovative and unusual sequential regimen (GABRINOX) composed of AG followed by FFX in

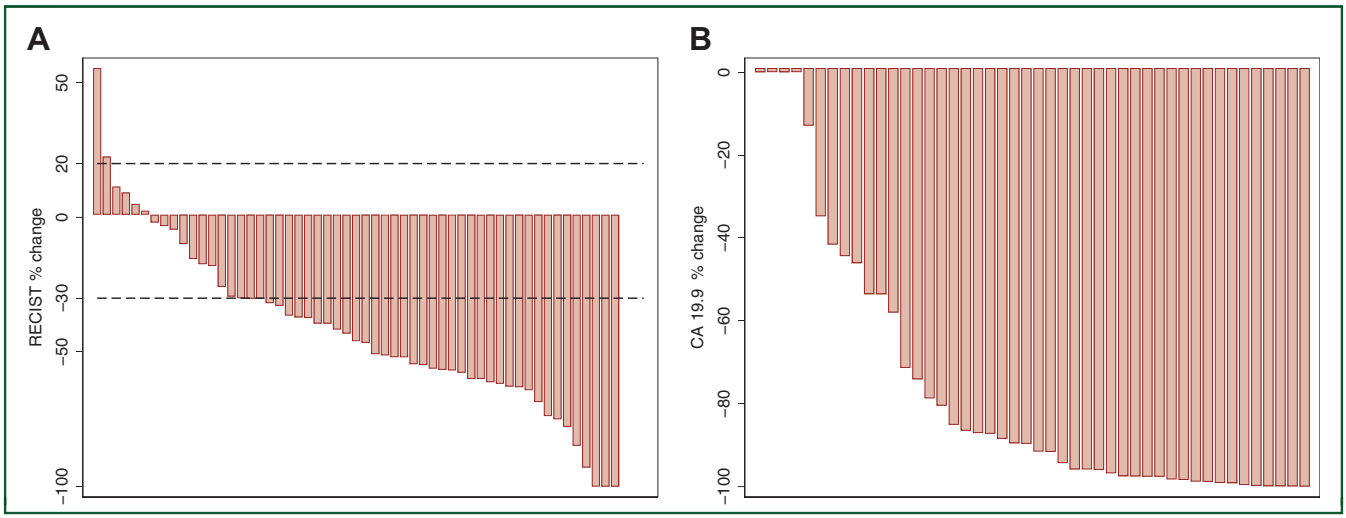


Figure 2. **Waterfall plots showing the response to treatment (A) and CA 19.9 level (B) at the end of treatment.**

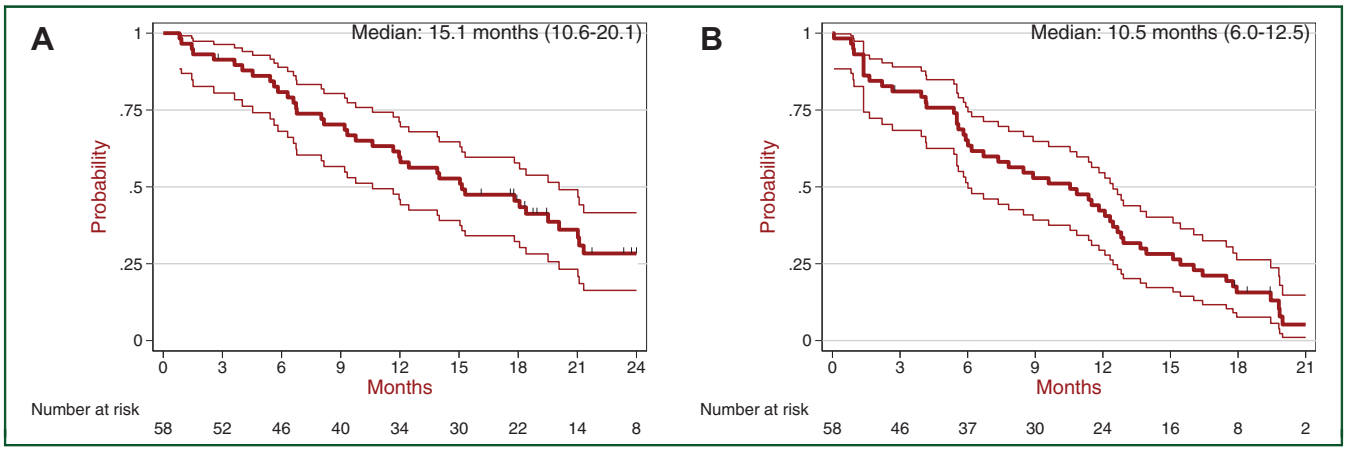


Figure 3. **Overall (A) and progression-free survival (B) curves with 95% confidence interval (CI).**

pancreatic cancer had a high response rate and, in addition, better survival rates with low neurotoxicity, all indicating promising results for a randomized study. Thus, the phase Ib-II trial showed positive results for all studied endpoints indicating the feasibility of GABRINOX sequential regimen and determined the RP2D in a large expansion cohort. The phase II revealed an ORR >50% as primary endpoint, an ambitious endpoint in patients with MPC and poor prognosis. Specifically, ORR was 64.9%, and the median PFS and OS were 10.5 and 15.1 months, respectively.

This innovative sequential regimen allowed longer treatment duration without or with only low neurotoxicity rates. Thus, no neurotoxicity-related premature treatment arrest was reported and neurotoxicity rates were low with 0% of grade 3-4 neurotoxicity in phase Ib and 5.2% of grade 3 and no grade 4 in phase II (despite median treatment >8 months). Neurotoxicity is a well-known limiting factor in FOLFOX and FOLRININOX regimens usually limiting treatments to 3-4 months in MPC but also in patients with stage III colorectal cancer (CRC) in adjuvant setting following the recommendations from the IDEA study.[16] Treatment is often limited to 3 months in adjuvant setting and for patients with metastatic CRC to 4 months (8 cycles) before oxaliplatin therapeutic de-escalation mainly because of limiting toxicities (TRIBE 1 and TRIBE 2 studies).[17,18] Such therapeutic strategy was assessed in patients with MPC in the PANOPTIMOX study, where maintenance with LV5FU2 was feasible and effective in MPC controlled after 4 months of induction chemotherapy with FOLFIRINOX.[19] Our results are encouraging because decreasing the limiting neurotoxicity was one of our hypotheses when setting up our trial. Indeed, we administered AG first followed by FFX by including an oxaliplatin and nab-paclitaxel washout period. In our hypothesis, this washout period would limit oxaliplatin cumulative toxicity and allow maintaining the doses and treatment duration for optimal disease control. Treatment duration was largely achieved as well as dose maintenance as indicated by the relative dose-intensity results (nab-paclitaxel >80% and FFX >77%).

On the other hand, this therapeutic sequence was associated with significant hematologic toxicity rates (grade 3-4 neutropenia: 56.9%). However, most of the grade 4 (22.4%) neutropenia events were transient, asymptomatic and occurred during the first AG cycle

Table 2. Severe toxicities (grade 1-4) in the phase II study

	Phase II (n = 58) n (%)
Neurotoxicity	
Grade 1	30 (51.7)
Grade 2	17 (29.3)
Grade 3	3 (5.2)
Grade 4	0
Thrombosis	
Grade 1	1 (1.7)
Grade 2	7 (12.1)
Grade 3	10 (17.2)
Grade 4	0
Thrombopenia	
Grade 1	2 (3.5)
Grade 2	9 (15.5)
Grade 3	18 (31.0)
Grade 4	1 (1.7)
Neutropenia/febrile neutropenia	
Grade 1	0/0
Grade 2	2 (3.5)/0
Grade 3	20 (34.5)/1 (1.7)
Grade 4	13 (22.4)/1 (1.7)
Nausea	
Grade 1	14 (24.1)
Grade 2	23 (39.7)
Grade 3	10 (17.2)
Grade 4	0
Diarrhea	
Grade 1	14 (24.1)
Grade 2	19 (32.8)
Grade 3	15 (25.9)
Grade 4	1 (1.7)
Weight loss	
Grade 1	9 (15.5)
Grade 2	16 (27.6)
Grade 3	1 (1.7)
Grade 4	0
Asthenia	
Grade 1	5 (8.6)
Grade 2	31 (53.5)
Grade 3	18 (31.0)
Grade 4	0

(between day 8 and 15) and before the first G-CSF administration. Moreover, they resolved spontaneously without febrile neutropenia. After prophylactic G-CSF, before FFX administration, the severe neutropenia rate was still significant but manageable, as shown by low febrile neutropenia rate (3.4%) and the absence of febrile neutropenia-related deaths. These results confirm the importance of prophylactic G-CSF administration with GABRINOX regimen. Thromboembolic event rate (17.2% of grade 3, no grade 4) was comparable with that reported in the literature raising the question of heparin prophylaxis.[20]

One limitation of our study was the lack of quality-of-life (QOL) analyses. The PRODIGE 4/ACCORD 11 study showed no negative effect on the patients' QOL despite adverse effects of the triplet chemotherapy regimen.[21] MPC is an aggressive disease with rapid deterioration of patient's general status, weight loss and cachexia and rapid alteration of QOL. The absence of QOL changes in the PRODIGE 4/ACCORD 11 studies may be due to the good control of the disease under FFX treatment. In our study, the rates of nausea, vomiting and asthenia were comparable to those reported for FFX and AG.[11,21] Moreover, body weight remained stable and only very few patients (1.7%) reported grade 3 weight loss. Therefore, this therapeutic sequence was not only efficient but also well accepted.

It was scheduled that chemotherapy would be administered for 6 months with a case-by-case decision to maintain treatment for longer periods. This choice was based on the median treatment duration (<6 months) from the literature.[10,11] In our study, the median treatment duration was >8 months, which is exceptionally long for MPC. Moreover, the median treatment duration and PFS were comparable to the median OS of the AG group in MPACT study.[11] Our study showed the efficacy of this sequential regimen both in terms of tumor response (complete response in 2 patients and major tumor response in 35 patients) and survival. The DCR (84.2%) was promising. Interestingly, tumor response was most often reported in the first 4 months of treatment and tumor and biological responses (CA 19.9) were both significant and well correlated as previously described for FOLFIRINOX or gemcitabine.[22]

In our study, the OS rate at 18 months was 45.5% (95% CI 32.2% to 58.8%), which is a promising result in an unselected population based on molecular biology criteria. The median PFS and OS compare favorably with those of previous studies: OS rate of 18.6% at 18 months (ACCORD 11 study) and 16% (MPACT study) and median OS and PFS of 11.1 and 6.4 months (ACCORD 11 study) and 8.5 and 5.5 months (MPACT study), respectively. It should be indicated that our results remain however difficult to compare to previous studies since this investigation was not randomized. Moreover, we cannot completely exclude some bias due to the unequal recruitment in various centers. Indeed, although the recruitment was initiated in three centers, the majority of patients (92.3%) were recruited in only two centers, which might bias results. Despite these considerations, our results appeared quite encouraging and deserve further confirmation in a phase III randomized study. Setting up such a study remains difficult in France where currently, nab-paclitaxel is not reimbursed by the social security system. Another phase IIR French cooperative trial showed the feasibility and efficacy of FIRGEMAX strategy (gemcitabine + nab-paclitaxel alternating with FOLFIRI.3 every 2 months) and with manageable toxicities.[23] Our study reported better results without irinotecan intensification but with a 'classical' FFX regimen. It is expected that this situation in France will change with the availability of nab-paclitaxel generics. Note that, in this context, we started a phase II trial (n = 103) (NCT04570943) to assess the efficacy of intensified and sequential GABRINOX neoadjuvant chemotherapy in patients with locally advanced pancreatic adenocarcinoma. The study will also evaluate in a sub-population of non-progressive patients after GABRINOX the feasibility of the Stereotactic Magnetic Resonance-guided Adaptive Radiotherapy (SMART). This new trial was built in this sub-population based on unpublished results of GABRINOX

phase Ib-II trial (54.3% and 73.1% of partial response at 2 and 4 months, respectively, and 8.7% of complete response).

One question that arises from our study is what would be the second-line therapy after GABRINOX. Only less than half of patients with pancreatic cancer receive second-line treatments. In our study, few patients progressed under GABRINOX treatment and progression was rather after GABRINOX arrest or during maintenance treatment with gemcitabine alone. In these cases, FFX can be administered again since none or few limiting neurotoxicity events were observed. Recent results of the Pancreas Cancer Olaparib Ongoing (POLO) trial evaluated the efficacy of poly(adenosine diphosphate—ribose) polymerase (PARP) inhibitor olaparib in a subgroup of patients with metastatic pancreatic adenocarcinoma and germline *BRCA* mutations. In this randomized study (154 patients), although no difference was found between the olaparib and placebo groups at interim analysis and no significant difference in health-related QOL, the authors reported almost twofold longer PFS under olaparib treatment. These results should be considered with caution since the maintenance treatment involved a quite low proportion (7.5%) of patients with *BRCA* mutations and did not include patients who progressed during the first 4-month platinum-based treatment or continued chemotherapy for an extended period.[24] Their significance in unselected populations with MPC needs further investigations. Nevertheless, results from POLO study are encouraging and open the possibility of the use of PARP inhibitors as a second-line strategy.

Conclusion

This phase Ib-II study showed high response rate and acceptable toxicity with no limiting neurotoxicity, which together with better survival rate, are promising results justifying new randomized trials.

ACKNOWLEDGEMENTS

The authors thank the patients and their families and Florin Grigorescu (florin.grigorescu@inserm.fr), (https://orcid.org/0000-0002-3095-5639) for editorial assistance.

FUNDING

This work was supported by CELGENE SAS (3 rue Joseph Monier, 92500 Rueil Malmaison, France) (no grant number).

DISCLOSURE

The authors have declared no conflicts of interest.

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.
2. Ferlay J, Partensky C, Bray F. More deaths from pancreatic cancer than breast cancer in the EU by 2017. *Acta Oncol Stockh Swed*. 2016;55:1158-1160.
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.
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.
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.
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.
7. Sohal DPS, Kennedy EB, Mangu PB, et al. Metastatic pancreatic cancer: ASCO guideline update. *J Clin Oncol*. 2020;38:3217-3230.
8. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw*. 2021;19:439-457.
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.
10. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364:1817-1825.
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.
12. Williet N, Saint A, Pointet A-L, 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.
13. Chan KKW, Guo H, Cheng S, et al. Real-world outcomes of FOLFIRINOX vs gemcitabine and nab-paclitaxel in advanced pancreatic cancer: a population-based propensity score-weighted analysis. *Cancer Med*. 2020;9:160-169.
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.
15. Lambert A, Schwarz L, Borbath I, et al. An update on treatment options for pancreatic adenocarcinoma. *Ther Adv Med Oncol*. 2019;11:175883591987556.
16. André T, Meyerhardt J, Iveson T, et al. Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials. *Lancet Oncol*. 2020;21:1620-1629.
17. Cremolini C, Antoniotti C, Rossini D, et al. Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol*. 2020;21:497-507.
18. Rossini D, Lonardi S, Antoniotti C, et al. Treatments after progression to first-line FOLFOXIRI and bevacizumab in metastatic colorectal cancer: a pooled analysis of TRIBE and TRIBE2 studies by GONO. *Br J Cancer*. 2021;124:183-190.
19. Dahan L, Phelip JM, Le Malicot K, et al. FOLFIRINOX until progression, FOLFIRINOX with maintenance treatment, or sequential treatment with gemcitabine and FOLFIRI.3 for first-line treatment of metastatic pancreatic cancer: a randomized phase II trial (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 and factors associated with outcomes. *Gastroenterology*. 2020;158:1346-1358.e4.
21. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol*. 2013;31:23-29.

22. Robert M, Jarlier M, Gourgou S, et al. Retrospective analysis of CA19-9 decrease in patients with metastatic pancreatic carcinoma treated with FOLFIRINOX or gemcitabine in a randomized phase III study (ACCORD11/PRODIGE4). *Oncology*. 2017;93:367-376.
23. Rinaldi Y, Pointet A-L, Khemissa Akouz F, et al. Gemcitabine plus nab-paclitaxel until progression or alternating with FOLFIRI.3, as first-line treatment for patients with metastatic pancreatic adenocarcinoma: the Federation Francophone de Cancérologie Digestive-PRODIGE 37 randomised phase II study (FIRGEMAX). *Eur J Cancer*. 2020;136:25-34.
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.