European Journal of Cancer 136 (2020) 25–34

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Clinical Trial

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)

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https://doi.org/10.1016/j.ejca.2020.05.018

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Received 23 January 2020; received in revised form 21 April 2020; accepted 9 May 2020
Available online 2 July 2020

KEYWORDS
Sequential treatment;
Pancreatic cancer;
FOLFIRI.3;
Nab-paclitaxel;
Gemcitabine

Abstract ***Background:*** Chemotherapy is effective in metastatic pancreatic adenocarcinoma (mPA), but new approaches are still needed to improve patients' survival and quality of life. We have previously published good efficacy and tolerability results on a sequential treatment strategy of gemcitabine followed by an intensified FOLFIRI (5FU+irinotecan) regimen. In the present study, we evaluated the same sequence but replaced gemcitabine by the new gemcitabine + nab-paclitaxel standard first-line combination.
Patients and methods: We randomised chemotherapy-naive patients with proven mPA, bilirubin levels ≤1.5 upper limit of normal values and performance status 0–2 to alternately receive gemcitabine + nab-paclitaxel for 2 months then FOLFIRI.3 for 2 months in arm A, or gemcitabine + nab-paclitaxel alone until progression in arm B. The primary objective was to increase the 6-month progression-free survival (PFS) rate from 40% (H_0) to 60% (H_1); using the binomial exact method, 124 patients were required. Analyses were carried out in preplanned modified intention-to-treat (mITT) and per-protocol (PP) populations.
Results: Between November 2015 and November 2016, 127 patients were enrolled. Main grade III–IV toxicities (% in arm A/B) were: diarrhoea (12.5/1.7), neutropenia (46.9/31, including febrile neutropenia: 1.6/0), skin toxicity (6.3/13.8), and peripheral neuropathy (6.3/8.6). No toxic deaths occurred. The objective response rate was 40.3% (95% confidence interval [CI]: 28.1–53.6) in arm A and 26.7% (95% CI: 16.1–39.7) in arm B. The primary end-point (6-month PFS rate) was 45.2% [one-sided 95% CI: 34.3–56.4] in arm A and 23.3% in arm B [one-sided 95% CI: 14.3–32.3] in the mITT population. In the PP population, median PFS and OS were 7.6 months and 6 months and 14.5 months and 12.2 months in arm A and B, respectively.
Conclusions: The FIRGEMAX strategy with gemcitabine + nab-paclitaxel alternating with FOLFIRI.3 every 2 months, appears feasible and effective, with manageable toxicities, in patients able to reach >2mo of treatment.
Trial registration information: EudraCT: 2014-004449-28: NCT: 0282701.

1. Introduction

Pancreatic cancer is the fourth cause of cancer-related deaths in Europe [1]. For many years, single-agent gemcitabine was the standard of care for patients with metastatic pancreatic adenocarcinoma (mPA) [2]. During the current decade two phase III trials have shown a survival benefit over gemcitabine alone, by using combination chemotherapies such as FOLFIRINOX in the PRODIGE 4/ACCORD 11 trial [3] (median overall survival (OS) of 11.1 months versus 6.8 months), and gemcitabine plus nab-paclitaxel in the MPACT study (median OS of 8.7 months versus 6.6 months) [4–7]. Considering progression-free survival (PFS), they were of 6.4 and 5.5 months with the use of FOLFIRINOX and gemcitabine+nab-paclitaxel, respectively.

Based on these results, the current National Comprehensive Cancer Network and European Society for Medical Oncology guidelines recommend combination chemotherapy with FOLFIRINOX or gemcitabine plus nab-paclitaxel as the preferred first-line treatments for patients with mPA who have good performance status (PS) [8,9].

Although adverse effects were manageable, these regimens were more toxic than gemcitabine alone, and both regimens are associated with a cumulative sensory neuropathy impairing patients' quality of life.

Therefore, new therapeutic approaches are still needed to improve patients' survival and quality of life.

Intensified irinotecan-based regimens such as the FOLFIRI.3 regimen have shown interesting clinical activity in patients with advanced PA (73% of the 40 patients enrolled were metastatic), with an objective response rate of 37.5% and a median OS of 12.1 months in a phase II trial, with an acceptable tolerability profile [10].

Sequential use of such a regimen with a gemcitabine-based regimen could enhance antitumour activity and limit cumulative toxicities as these two regimens have different antitumour modes of action and toxicity profiles. Various sequential polychemotherapy regimens have already been independently associated with better OS in patients with pancreatic cancer and other gastrointestinal tumours [11,12]. Ten years ago we conducted a randomised trial testing a sequential treatment strategy of gemcitabine followed by FOLFIRI.3 (FIRGEM study), which showed good efficacy and tolerability results and improved health-related quality of life in the sequential arm compared with the gemcitabine alone arm [13,14]. Median PFS (5.0 versus 3.4 months, hazard ratio (HR) = 0.59 [0.38–0.90]) and OS (11.0 versus 8.2 months, HR = 0.71 [0.46–1.10]) were also higher in the sequential arm.

In the present study, we evaluated the same sequence with gemcitabine + nab-paclitaxel instead of gemcitabine because the former is currently one of the two recommended first-line standard therapies along with FOLFIRINOX [8,9].

The aim of this multicenter, randomised phase II trial was to assess the efficacy and tolerability of gemcitabine + nab-paclitaxel alternating with FOLFIRI.3, every 2 months as first-line treatment for patients with mPA in comparison with gemcitabine + nab-paclitaxel alone until disease progression or unacceptable toxicity.

2. Methods

2.1. Patients

Patients with histologically or cytologically proven mPA, measurable metastatic disease (in accordance with Response evaluation criteria in solid tumours [RECIST] 1.1) [15], age between 18 and 75 years, World Health Organization PS 0, 1 or 2, and life expectancy more than 12 weeks were eligible for this study. In addition, patients had to have adequate bone marrow (granulocytes $\geq 1.5 \_ 10^9$/L; platelets $\geq 100 \_ 10^9$/L and haemoglobin ≥ 9 g/dl), liver (bilirubin ≤ 1.5 times the upper limit of normal values (ULN), ASAT and ALAT ≤ 5 ULN) and renal function (serum creatinine ≤ 120 μmol/L). The exclusion criteria were other periampullary carcinomas (e.g. extrahepatic bile duct and ampullary tumours), previous chemotherapy (adjuvant chemotherapy with gemcitabine was allowed, if completed more than 6 months before inclusion), previous radiotherapy (unless at least one measurable target lesion was present outside the irradiated fields), history of other invasive cancer, known brain, leptomeningeal or bone metastases, active uncontrolled infection, chronic diarrhoea or known inflammatory bowel disease, symptomatic intestinal obstruction, uncontrolled hypercalcaemia, uncontrolled pain, significant history of cardiac or respiratory disease, and pregnancy or breast-feeding women.

2.2. Treatments and study design

Randomization (1:1) was centralised and used a minimization technique with the following stratification criteria: center, PS 0 versus 1 versus 2, and one versus more than one metastatic site. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, ICH requirements and Good Clinical Practice guidelines; it received authorization from the French national medicines agency (ASNM), and independent ethics committee. The study was registered in clinical trials.gov (NCT02827201).

All patients provided their written informed consent before the initiation of the study. Patients were randomly assigned to arm A (FIRGEMAX - experimental arm) or arm B (standard first-line therapy). They started with 2 months of nab-paclitaxel (125 mg/m^2) I.V. for 30 min, immediately followed by gemcitabine (1000 mg/m^2) I.V. for 30 min, for a total of six doses on days 1, 8, 15, 29, 36 and 43. After these first 2 months, arm A patients switched to the FOLFIRI.3 sequence: irinotecan 90 mg/m^2 I.V. for 60 min on D1, together with folinic acid 400 mg/m^2 given as a 2-h I.V. infusion, immediately followed by continuous fluorouracil (5-FU) infusion at a dose of 2000 mg/m^2 over a 46-h period, and irinotecan, 90 mg/m^2 I.V. for 60 min repeated on D3 at the end of the 5-FU infusion. The chemotherapy cycles were repeated every 14 days for 2 months. This sequence (gemcitabine + nab-paclitaxel followed by FOLFIRI.3) was repeated until disease progression or limiting toxicity. In case of progression or limiting toxicity with one of the chemotherapy regimens, the other treatment was continued until progression, limiting toxicity, or patient refusal.

In arm B, gemcitabine + nab-paclitaxel were given until disease progression, unacceptable toxicity or patient refusal. The study design is summarised in Supplementary Fig. 1.

Protocol-specified treatment modifications were permitted in the event of predefined toxic events.

Per-protocol (PP), crossover was not allowed at any time after randomization.

2.3. Assessments

Baseline computerised tomography (CT) scan, or magnetic resonance imaging (MRI), was performed within 3 weeks before the start of treatment. In the week preceding the start of treatment, patients underwent complete medical history evaluation, physical examination, assessment of health-related quality of life (QoL), electrocardiogram, blood cell counts and chemistry, and serum carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) assays. Before each

treatment administration, patient status was assessed by physical examination, blood cell counts and biochemistry. Adverse events (AEs) were assessed and graded using the National Cancer Institute Common Terminology Criteria (AE version 4.0) [16]. Tumour assessment was performed every 2 months by CT scan (or MRI), along with serum CA 19-9 (15) and CEA assays. Tumour responses were defined using RECIST (version 1.1) and determined by investigators. Health-related QoL was evaluated every 2 months with the EORTC QLQ-C30 questionnaire, version 3.0 but will not be reported in this publication [17].

2.4. End-points

The primary end-point was the observed 6-month PFS rate based on TDM collected until 6 months (+/− 1 months). Secondary end-points were PFS calculated from the date of randomization to the date of first progression (radiological or clinical) or the date of death from any cause Alive patients free of progression were censored at the date of the last follow-up visit; response rates, OS (measured from the date of randomization until death from any cause) and safety with toxicity and treatment dose evaluations were analysed . Quality of life using QLQ-C30 questionnaires was also collected from randomization, every month during the first 4 months then every 2 or 3 months and will be reported in a separate manuscript.

2.5. Statistical analysis

This randomised noncomparative phase II trial was designed using an exact-binomial method [18]. The hypothesis was to double the 6-month PFS rate with the sequential regimen. The best reported 6-month PFS rates at the time of study design were around 30% [19]. An observed 6-month PFS rate of 40% was considered as an uninteresting rate. 60% was considered as an interesting rate for further investigation in arm A.

With a one-sided type I error of 5% and a power of 90%, 56 patients had to be included per arm. Assuming 10% of patients lost to follow-up, at least 62 patients had to be included per arm.

Primary efficacy analyses were carried out on the predefined modified intention-to-treat (mITT) (randomised patients receiving at least one dose of treatment) and PP populations (defined as mITT patients with no major protocol deviation and with at least 7 weeks of treatments). Baseline characteristics and secondary efficacy analyses were done on the ITT, mITT and PP populations. Safety analyses included all the patients who received at least one dose of study treatment(s) and analysed on real treatment received (SP: safety population).

Qualitative variables were reported as frequencies and percentages, and continuous variables as means (SD) and medians (range). The PFS rate at 6 months was described in each arm using frequency, percent and one-sided 95% confidence interval (CI). As secondary analyses, PFS, OS and time-to-event end-points were estimated using the Kaplan-Meier method, and described as the median values and rates at specific times with the corresponding 95% CI. HR and 95% CIs were carried out for exploratory purposes. Follow-up time was calculated using the reverse Kaplan-Meier method.

No p-value was carried out because this trial was not designed for comparative purposes.

3. Results

3.1. Characteristics of the patients

Between November 2015 and November 2016, 127 patients were enrolled in the trial by 36 french centres.

Table 1
Baseline characteristics.

Parameters	GN+FOLFIRI.3 (arm A) (N = 64)	GN (arm B) (N = −63)	All (N = 127)
Age in years; mean (range[a])	63.5 (38.3−76.0)	64.1 (41.0−76.0)	63.8 (38.3−76.0)
Gender *n* (%)			
Males	36 (56.3%)	29 (46.0%)	65 (51.2%)
Females	28 (43.7%)	34 (54.0%)	62 (48.8%)
ECOG PS *n* (%)			
0	24 (37.5%)	23 (36.5%)	47 (37.0%)
1	33 (51.6%)	32 (50.8%)	65 (51.2%)
2	7 (10.9%)	8 (12.7%)	11 (11.8%)
Nb of metastic sites			
1	29 (45.3%)	37 (58.7%)	66 (52.0%)
>1	35 (54.7%)	26 (41.3%)	61 (48.0%)
Previous surgery	8 (12.5%)	3 (4.5%)	11 (8.7%)
Previous radiotherapy	−	2 (3.2%)	2 (1.6%)
Previous chemotherapy	7 (10.9%)	3 (4.8%)	10 (7.9%)
CA 19.9 (UI/mL); median (range)	1346 (0.8−131600)	5575 (0.6−534806)	2048 (0.6−534806)

PS, performance status.
[a] Range: min − max.

Main baseline characteristics were balanced between arms (Table 1).

Numerically, there were fewer female patients and more patients with more than one metastatic site in arm A. At the time of this analysis, median follow-up was 27.3 months (95% CI: 24.0–29.0) and 107 patients (83%) had died at the cut-off date (5th of November 2018). Eight patients had gemcitabin as adjuvant treatment (7 in arm A and 1 in arm B). In addition, 2 patients of arm B had a neo-adjuvant treatment: 1 patient had folfox+radiotherapy and 1 patient had Gemox+radiotherapy.

In arm A, 16 patients (25%) did not receive FOLFIRI.3. Seven patients (6 in arm A and 1 in arm B) were still under treatment at the time of the analysis.

3.2. Efficacy

3.2.1. PFS rate at 6 months

In arm A (gemcitabine +nab-paclitaxel + FOLFIRI.3), 28 patients were alive and free of progression at 6 months in the mITT population, resulting in an observed 6-month PFS rate of 45.2% [one-sided 95% CI: 34.3–56.4] and 28 patients were alive and free of progression at 6 months in the PP population, resulting in an observed 6-month PFS rate of 59.6% [one-sided 95% CI: 46.5–71.7].

In arm B (gemcitabine +nab-paclitaxel), 14 patients were alive and free of progression at 6 months in the mITT population, resulting in an observed 6-month PFS rate of 23.3% [one-sided 95% CI: 14.3–32.3] and 13 patients were alive and free of progression at 6 months in the PP population, resulting in an observed 6-month PFS rate of 30.2% [one-sided 95% CI: 18.9–43.7].

Twenty-one patients died before their first disease assessment at 2 months and thus before treatment switch. Although all these patients were treated with gemcitabine+ nab-paclitaxel during these 2 months, a strong imbalance in early deaths was observed by chance between the 2 treatment arms. In fact, early death was observed in 25.8% (n = 16/62) of patients in arm A and only 8.3% (n = 5/60) in arm B. Supplementary Table 1 was also updated (Supplementary Table 1).

3.2.2. Response rate

All tumour assessments carried out between study start and D1 of the last treatment (+1.5 months) received by

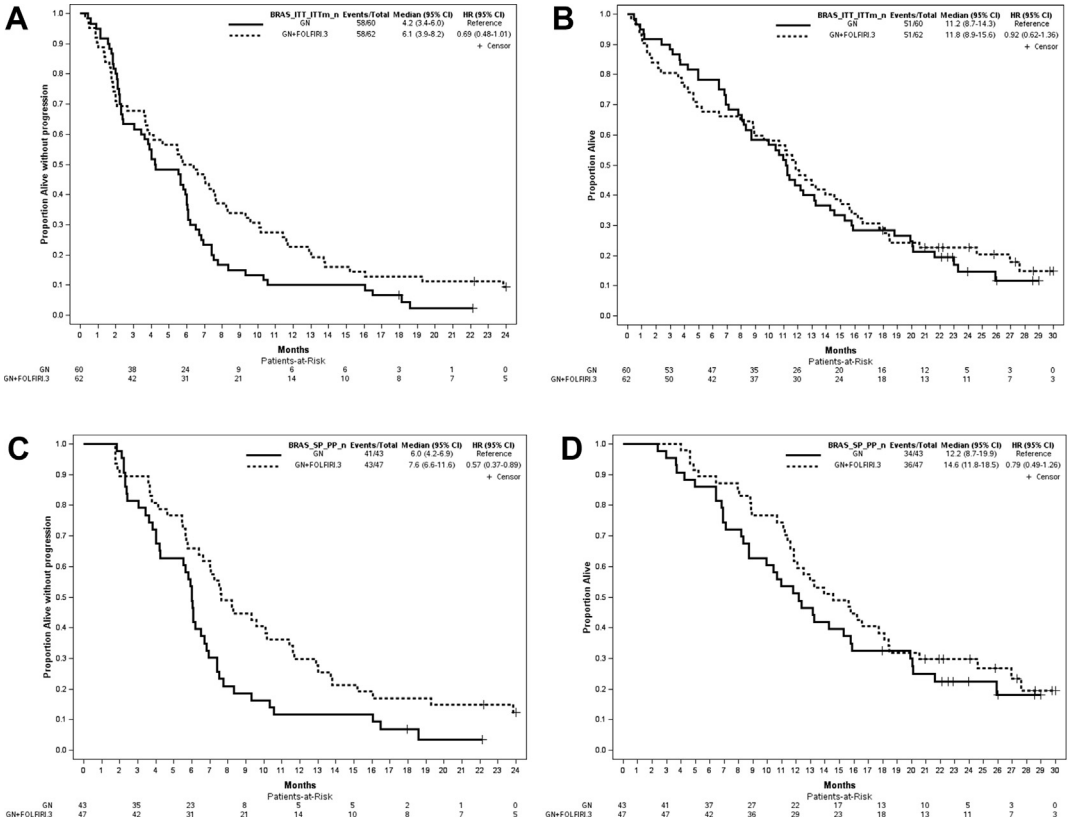

Fig. 1. A) Kaplan-Meier estimates of progression-free survival in the mITT population based on treatment arm. (B) Kaplan-Meier estimates of overall survival in the mITT population based on treatment arm, (C) Kaplan-Meier estimates of progression-free survival in the PP population based on treatment arm, (D) Kaplan-Meier estimates of overall survival in the PP population as per treatment arm. mITT, modified intention-to-treat; PP, per-protocol.

every patient in the mITT population were taken into account for the best response rate. The objective response rate was 40.3% (95% CI: 28.1–53.6) in arm A and 26.7% (95% CI: 16.1–39.7) in arm B in the mITT population. It was 53.3% (95% CI: 37.9–68.3) in arm A versus 33.3% (95% CI: 20.0–49.0) in arm B for the PP population. Progressive disease was reported in 8% of patients in arm A and 22% in arm B (Supplementary Table 1).

3.2.3. Survival

In mITT population, median PFS was 6.1 versus 4.2 months (HR = 0.69 [95% CI: 0.47–1.01]) and median OS was 11.8 versus 11.2 months (HR = 0.92 [95% CI: 0.62–1.36]) in arm A and B, respectively (Fig. 1(A) and (B)).

In PP population, median PFS was 7.6 versus 6 months (HR = 0.57 [95% CI: 0.37–0.89]) and median OS was 14.5 versus 12.2 months (HR = 0.79 [95% CI: 0.49–1.26]) in arm A and B, respectively (Fig. 1(C) and (D)).

3.3. Safety

The mean dose intensity for the patients in arm A was 97% for 5-FU, 94% for irinotecan. For gemcitabine it was 83% and 85% in arm A and B, respectively and 81% for nab-paclitaxel in both arms. The main reason for stopping treatment was disease progression in both arms. Treatment was discontinued because of toxicity in 9% of patients in arm A and 14% in arm B. There were no treatment-related deaths. All early deaths were related to rapid disease progression.

Safety data was collected for all patients who received at least one dose of study treatments, and analysed on real treatment received (n = 122). Fifty-eight patients (91%) developed gradeIII–IV toxicity in arm A versus 52 patients (90%) in arm B. Haematological AEs, diarrhoea, nausea and vomiting predominated, and were more frequent in arm A than in arm B. In contrast, skin toxicity (6.3%/13.8%) and peripheral neuropathy (6.3.7%/8.6%) were more frequent in arm B [Table 2].

Table 2
Main grade III–IV toxicities (SP: population tolerance).

Parameters	Arm A (N = 64)	Arm B (N = 58)
At least one grade ≥ III toxicity	58 (90.6%)	52 (89.7%)
Anaemia	8 (12.5%)	6 (10.3%)
Febrile neutropenia	1 (1.6%)	
Neutropenia	30 (46.9)	18 (31.0%)
Diarrhoea	8 (12.5%)	1 (1.7%)
Nausea	3 (4.7%)	1 (1.7%)
Vomiting	5 (7.8%)	
Skin toxicities	4 (6.3%)	8 (13.8%)
Venous thromboembolic event	3 (4.7%)	2 (3.4%)
Neuropathy	4 (6.3%)	5 (8.6%)

Overall, 16 (25.0%) patients in arm A and 24 (4.14%) in arm B reported at least one neurotoxic event (whatever the grade was). Thirty-six patients (56.3%) in arm A and 40 (69%) in arm B reported a skin toxicity (whatever the grade was).

Eleven patients in arm A (17%) and 14 (24%) in arm B received G-CSF as secondary prophylaxis. Grade I/II alopecia occurred in 43.8% and 41.4% of patients in arms A and B, respectively. No cases of severe stomatitis or hand-foot syndrome occurred in either arm.

4. Second- and third-line chemotherapy

At the time of statistical analysis, 68 patients in the mITT population had received second-line chemotherapy: 29 in arm A (46.8%) and 39 in arm B (65%).

Among those, 15 patients in arm A (51.7%) versus 6 in arm B (15.4%) received Folfox in second-line chemotherapy. Seven patients in arm A and 20 in arm B received a third-line chemotherapy, mainly with gemcitabine-based regimens. Altogether, Irinotecan was used in second or third line in 74% and 35% of patients from arm B.

5. Discussion

In this randomised phase II study evaluating a sequential treatment with gemcitabine +nab-paclitaxel followed by FOLFIRI.3, we observed a 6-month PFS rate of 45.2% in the experimental arm mITT population versus 23% in the gemcitabine +nab-paclitaxel control arm.

Although the number of patients alive and without progression at 6 months was doubled in the mITT population, the primary end-point was not met. This may be due to an overly ambitious hypothesis (to increase the 6-month PFS rate to 60%) and to a strong imbalance in early deaths between arms. In fact, more than twice as many early deaths were observed by chance in the experimental arm (19%, n = 12) as compared with the control arm (8%, n = 5). This underlines once more how important it is to highly select patients for clinical trials dedicated to mPA and new measures such as PS confirmation by 2 independent physicians or the use of frailty scores should be implemented in the future for this purpose. Nevertheless, when this analysis was run taking into account the prespecified PP population (with at least 7 weeks of treatments), the PFS rate was 59.6% in arm A (n = 47; 95% CI: 46.5–71.7) versus 30.2% in arm B (n = 43; 95% CI: 18.9–43.7). The PP population analysis seems justified in this context because it allows masking of the negative effect of the unfortunate early deaths (<2 months), in a study period where patients were receiving exactly the same treatment in both arms.

Table 3
Main efficacy results in recent randomised controlled trial for metastatic pancreatic cancer.

References	Type of study	Number of patients	Regimen	Overall response rate (%)	Median progression-free survival (months)	Median Ooerall survival (months)
Rocha-Lima et *al.* [23] 2004	III	342	- IrinoGem - Gem	16.6 4.4 (P < 0.001)	3.5 (TTP) 3.0 (P = 0.35)	6.3 6.6 (P = 0.79)
Louvet et *al.* [24] 2005	III	313	- GemOx - Gem	26.8% 17.3% (P = 0.04)	5.8 3.7 (P = 0.04)	9.0 7.1 (P = 0.13)
Heinemann et *al.* [25] 2006	III	195	- GemCis - Gem	11.5% 9% (P < 0.001)	5.3 3.1 (P = 0.053)	7.5 6.0 (P = 0.15)
Herrmann et *al.* [26] 2007	III	319	- GemCap - Gem	10.0% 7.8%	4.3 3.9 (P = 0.103)	8.4 7.2 (P = 0.234)
Conroy et *al.* [3] 2011	III	342	- FOLFIRINOX -Gem	31.6% 9.4% (P < 0.001)	6.4 3.3 (P < 0.001)	11.1 6.8 (P < 0.001)
Ueno et *al.* [27] 2013 (*GEST* study)	III	834	- Gem plus S1 - S1 alone - Gem alone	29.3% (P < 0.001) 21.0% (P = 0.02) 13.3%	5.7 (P < 0.001) 3.8 (P = 0.02) 4.1	10.1 (P = 0.15) 9.7 (P < 0.001) 8.8
Von Hoff et *al.* [4] 2013	III	861	- Nab-paclitaxel plus Gem - Gem	23% 7% (P < 0.001)	5.5 3.7 (P < 0.001)	8.5 6.7 (P < 0.001)
Poplin et *al.* [28] 2013	IIR	367	- CO-101 - Gem	17.1% 26.3%	3.1 3.8	5.7 6.1 (P = 0.973)
Trouilloud et *al.* [13] 2014 (*FIRGEM* study)	IIR	98	- Alternation of FOLFIRI 3 and Gem - Gem	37% 10%	5.0 3.4	11.0 8.2
Van Cutsem et *al.* [29] 2016 (MAESTRO study)	III	693	- Evofosfamide plus Gem - Gem	15.2% 8.6% (P = 0.0086)	5.5 3.7 (P = 0.004)	8.7 7.6 (P = 0.059)
Dahan et *al.* [30] 2019 (*PRODIGE 35*-Panotimox study)	IIR	276	- FOLFIRINOX - FOLFIRINOX followed LV5FU2 - Alternation of FOLFIRI 3and Gem	37.3% 38.3% 27.0%	6.3 5.7 4.5	10.1 11.0 7.3
Doherty et *al* [31,32] 2017 (HALO-109-301 study)	IIIR		- PEGPH20 plus Nab-paclitaxel plus Gem - Nab-paclitaxel plus Gem	Has not been reported	Has not been reported	11.2 11.5 (p = 0.9692)
Sonbol et al. [33] 2019 (CanStem111P study)	IIIR		- Napabucasin (BBI608) plus Nab-paclitaxel with Gemcitabine - Nab-paclitaxel with Gem	Results not yet published	Results not yet published	Results not yet published
Hammel et al. [34] 2019 (TRYbeCA-1 study)	IIIR		- Eryaspase plus Nab-paclitaxel with Gem - Eryaspase plus Irinotecan plus 5-FU plus leucovorin	Study still ongoing	Study still ongoing	Study still ongoing

(*continued on next page*)

Table 3 (*continued*)

References	Type of study	Number of patients	Regimen	Overall response rate (%)	Median progression-free survival (months)	Median Ooerall survival (months)
			- Irinotecan plus 5-FU plus leucovorin			
			- Nab-paclitaxel with Gem			
Taieb et al. [35] 2018 (*PRODIGE 37-Firgemax*)	IIR		- Alternation of FOLFIRI 3 and Nab-paclitaxel plus Gem	40.3%	6.1	11.8
			-Nab-paclitaxel plus Gem	26.67%	4.2	11.2
Golan et al. [22] 2019 (POLO study)	III	154	- Olaparib	23%	7.4	18.9
			- Placebo	12%	3.8	18.1 (P = 0.68)

With regard to secondary end-points, the response rate was improved (from 25% to 40%) by the FIRGEMAX sequential strategy in terms of median PFS in both mITT and PP populations.

For OS, a trend to a better OS was observed in the PP population but not in the mITT population, possibly owing to the 19% early deaths in the experimental arm and the trial was not powered for OS.

It is worth noting that PFS and OS observed in the FIRGEMAX regimen in the PP population (7.6 and 14.5 months, respectively) were higher than those obtained in the previous FIRGEM study (5.0 and 11 months, respectively) [13], underlining the added value of nab-paclitaxel on patient survival. Even if cross study comparisons have to be interpreted cautiously, we noticed that median PFS and median OS observed in this study with gemcitabine + nab-paclitaxel (6.0 and 12.2 months, respectively) were higher than those obtained in the princeps pivotal registration trial testing gemcitabine + nab-paclitaxel versus gemcitabine alone (5.5 and 8.5 months) [4], as well as in many other randomised trials in mPA (Table 3).

Although the rate of patients with grade IIIIV events was similar between the two treatment arms, haematological grade III-IV AEs, diarrhoea, nausea and vomiting were more frequent with the use of an intensified FOLFIRI regimen in the experimental arm, but they were all expected and manageable. In contrast, skin toxicity and peripheral neuropathy were less frequent in the experimental arm even though the median number of cycles with nab-paclitaxel received in both arms was similar (n = 6). This could be explained by the chemotherapy regimen switch every 2 months to FOLFIRI.3, giving this cumulative toxicity a rest period allowing partial recovery. Neurotoxicity can require dose reduction or even treatment hold; therefore FIRGEMAX represents a good option for better treatment compliance.

Although recent studies reported promising results in molecularly defined subgroups of pancreatic cancer such as PARP inhibitors for BRCA mutated or immunotherapy for MSI high mPA, chemotherapy remains the standard of care for most patients [20,35]. The main progress during the last decade was in fact brought about by chemotherapy intensification in the PRODIGE 4 and MPACT trials [21]. In the present noncomparative, multicenter, randomised phase II study, we tested the idea of increasing chemotherapy intensification by a sequential approach using 4 different drugs with different toxicity profiles and no cross-resistance described between them. We showed that the FIRGEMAX strategy (gemcitabine + nab-paclitaxel alternating with FOLFIRI.3 every 2 months) appears to be effective with an acceptable tolerability profile for patients with mPA. It suggests that alternating with FOLFIRI.3 every 2 months

when giving patients the standard treatment 'gemcitabine + nab-paclitaxel' increases response rates and PFS and could reduce skin and neurosensitive toxicities induced by nab-paclitaxel. However the primary end-point was not met and a larger study with better patient selection, testing this approach with 5-FU plus nanoliposomal irinotecan (PRODIGE 61), is in progress to confirm or not these promising results.

Role of funding source

The study was sponsored by the Fédération Francophone de Cancérologie Digestive (FFCD) that was responsible for the study management. This study was supported by Celgene international II Switzerland.

Conflict of interest statement

T.J. reported receiving honoraria from Merck, Roche, Amgen, Lilly, Sanofi, Samsung, MSD, Servier, Celgene, Pierre Fabre; has been a member of the consulting or advisory role for Roche, Merck KGaA, Amgen, Lilly, MSD, Servier, Pierre Fabre, Sanofi, Samsung; speakers' Bureau for Servier, Amgen, Roche, Sanofi, Merck, Lilly, Pierre Fabre. R.Y. reported receiving honoraria from Roche, Sanofi, Merck, Amgen, Bayer and Servier. B.J-.B reported receiving honoraria from Amgen, AstraZeneca, Bayer, Merck Serono, Pierre Fabre, Roche, Sanofi, Servier. All the remaining authors have declared no conflicts of interest.

Acknowledgements

The authors acknowledge all subinvestigators and the clinical staff at each hospital for their active participation and contribution to the good conduct of this study. The authors thank the FFCD operational team (data manager and CRAs): Mickael Voye, Fadil Masskouri, Marie Moreau, Caroline Choine, Florence Guiliani, Nouredine Lasmi, Guillaume Arnould, Nathan Guiet, Morgane Maury-Nègre, Hicham Fattouh, Nicolas Le Provost, Jérémie Bez, and Cécile Girault. The authors also thank the 'Ligue contre le Cancer'.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.05.018.

References

[1] 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 Canc 2018 Nov;103:356–87.
[2] Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997 Jun;15(6):2403–13.
[3] Conroy T, Desseigne F, Ychou M, et al. FOLFORINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364:1817–25.
[4] Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013 Oct 31;369(18):1691–703.
[5] Goldstein D, El-Maraghi RH, Hammel P, et al. Nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. J Natl Cancer Inst 2015 Jan 31; 107(2).
[6] Young R, Mainwaring P, Clingan P, et al. Nab-Paclitaxel plus gemcitabine in metastatic pancreatic adenocarcinoma: Australian subset analyses of the phase III MPACT trial. Asia Pac J Clin Oncol 2018 Oct;14(5).
[7] Blomstrand H, Scheibling U, Bratthäll C, et al. NO. Real world evidence on gemcitabine and nab-paclitaxel combination chemotherapy in advanced pancreatic cancer. BMC Canc 2019 Jan 8; 19(1):40.
[8] Lau SC, Cheung WY. Evolving treatment landscape for early and advanced pancreatic cancer. World J Gastrointest Oncol 2017 Jul 15;9(7):281–92.
[9] Ducreux M, Cuhna AS, Caramella C, et al. ESMO guidelines committee. Cancer of the pancreas: ESMO clinical Practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015 Sep;26(Suppl 5):v56–68.
[10] Taieb J, Lecomte T, Aparicio T, et al. FOLFIRI.3, a new regimen combining 5-fluorouracil, folinic acid and irinotecan, foradvanced pancreatic cancer: results of an Association des Gastro-Enterologues Oncologues (Gastroenterologist Oncologist Association) multicenter phase II study. Ann Oncol 2007;18: 498–503.
[11] Kelly H, Goldberg RM. Systemic therapy for metastatic colorectal cancer: current options, current evidence. J Clin Oncol 2005;23:4553–60.
[12] Klapdor R, Bahlo M, Babinsky A. Further evidence for prolongation of survival of pancreatic cancer patients by efficacy orientated sequential polychemotherapy (EOSPC) based on serial tumor marker determinations (CA 19-9/CEA). Anticancer Res 2005;25:1687–91.
[13] Trouilloud I, Dupont-Gossard AC, Malka D, et al. Fixed-dose rate gemcitabine alone or alternating with FOLFIRI.3 (irinotecan, leucovorin and fluorouracil) in the first-line treatment of patients with metastatic pancreatic adenocarcinoma: an AGEO randomised phase II study (FIRGEM). Eur J Canc 2014;50(18): 3116–24.
[14] Anota A, Mouillet G, Trouilloud I, et al. F. Sequential FOLFIRI.3+gemcitabine improves health-related quality of life deterioration-free survival of patients with metastatic pancreatic adenocarcinoma: a randomized phase II trial. PloS One 2015 May 26;10(5).
[15] Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, national cancer Institute of the United States, national cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
[16] Common Terminology criteria for adverse events v4.0 (CTCAE). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae_4_with_lay_terms.pdf.

[17] Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.
[18] Bakoyannis G. and Tououmi G. Statistical methods in medical research, http://smm.sagepub.com/content/early/2011/01/04/0962280210394479. May 16, 2012.
[19] Trouilloud I, Dubreuil O, Boussaha T, et al. Medical treatment of pancreatic cancer: new hopes after 10 years of gemcitabine. Clin Res Hepatol Gastroenterol 2011 May;35(5):364–74.
[20] Chiorean EG, Cheung WY, Giordano G, et al. Real-world comparative effectiveness of nab-paclitaxel plus gemcitabine versus FOLFIRINOX in advanced pancreatic cancer: a systematic review. Ther Adv Med Oncol 2019 May 19;11.
[21] Sahin IH, Askan G, Hu ZI, O'Reilly EM. Immunotherapy in pancreatic ductal adenocarcinoma: an emerging entity? Ann Oncol 2017 Dec 1;28(12):2950–61.
[22] Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med 2019;381(4):317–27. https://doi.org/10.1056/NEJMoa1903387.
[23] Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. J Clin Oncol 2004 Sep 15;22(18):3776–83.
[24] Louvet C, Labianca R, Hammel P, et al. GERCOR; GISCAD. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol 2005 May 20;23(15):3509–16.
[25] Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J Clin Oncol 2006 Aug 20;24(24):3946–52.
[26] Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. J Clin Oncol 2007 Jun 1;25(16):2212–7.
[27] Ueno H, Ioka T, Ikeda M, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol 2013 May 1;31(13):1640–8.
[28] Poplin E1, Wasan H, Rolfe L, et al. Randomized, multicenter, phase II study of CO-101 versus gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma: including a prospective evaluation of the role of hENT1 in gemcitabine or CO-101 sensitivity. J Clin Oncol 2013 Dec 10;31(35):4453–61.
[29] Van Cutsem Eric, Lenz Heinz-Josef, Furuse Junji, et al. Evofosfamide (TH-302) in combination with gemcitabine in previously untreated patients with metastatic or locally advanced unresectable pancreatic ductal adenocarcinoma: primary analysis of the randomized, double-blind phase III MAESTRO study. No193 Am Soc Clin Oncol 2016.
[30] Laetitia Dahan, Jean-Marc Phelip, Karine Le Malicot, 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). No 4000 ASCO presentation 2018.
[31] Doherty Gary J, Tempero Margaret, Corrie Pippa G. HALO-109–301: a Phase III trial of PEGPH20 (with gemcitabine and nab-paclitaxel) in hyaluronic acid-high stage IV pancreatic cancer. Future Oncol 23 Oct 2017;14(NO. 1). CLINICAL TRIAL PROTOCOL, Published Online:.
[32] https://www.halozyme.com/investors/news-releases/news-release-details/2019/Halozyme-Announces-HALO-301-Phase-3-Study-Fails-To-Meet-Primary-Endpoint/default.aspx.
[33] Sonbol MB, Ahn DH, Goldstein D, et al. A Phase III study of napabucasin plus nab-paclitaxel with gemcitabine. Future Oncol 2019 Apr;15(12):1295–302.
[34] Hammel Pascal, Berardi Rossana, Van Custem Eric, et al. Trybeca-1: a randomized, phase 3 study of eryaspase in combination with chemotherapy versus chemotherapy alone as second-line treatment in patients with pancreatic adenocarcinoma (NCT03665441). J Clin Oncol 2019;37(4_suppl).
[35] Taieb Julien, Rinaldi Yves, Anne-Laure Pointet, et al. Gemcitabine plus nab-paclitaxel until progression or given sequentially with 5-fluorouracile plus irinotecan (FOLFIRI.3) for first-line treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC): a randomized phase II study (PRODIGE 37-FIRGEMAX). J Clin Oncol May 20, 2018;36(15_suppl). 4107-4107.