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Gastrointestinal Cancer

FOLFIRINOX De-Escalation in Advanced Pancreatic Cancer: A Multicenter Real-Life Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. FOLFIRINOX • Maintenance treatment • Advanced pancreatic cancer • Real-life study • Quality of life

Abstract

Background. Our study describes the feasibility and efficacy of a first-line FOLFIRINOX (5-fluorouracil [5FU], folinic acid, irinotecan, and oxaliplatin) induction chemotherapy (CT) followed by de-escalation as a maintenance strategy for advanced pancreatic cancer.

Materials and Methods. This multicenter retrospective study was conducted from January 2011 to December 2018. FOLFIRINOX de-escalation was defined as stopping oxaliplatin and/or irinotecan after at least four cycles of FOLFIRINOX, without evidence of disease progression. Maintenance schedules were fluoropyrimidine monotherapy (intravenous or oral [capecitabine]), FOLFOX (5FU, oxaliplatin), or FOLFIRI (5FU, irinotecan). Primary endpoint was overall survival (OS). Secondary endpoints were first progression-free survival (PFS1), second progression-free survival (PFS2), and toxicity.

Results. Among 321 patients treated with FOLFIRINOX, 147 (45.8%) were included. Median OS was 16.1 months (95% confidence interval [CI], 13.7–20.3) and median PFS1 was 9.4 months (95% CI, 8.5–10.4). The preferred maintenance regimen was FOLFIRI in 66 (45%) patients versus 5FU monotherapy in 52 (35%) and FOLFOX in 25 (17%) patients. Among 118 patients who received maintenance CT with FOLFIRI or 5FU, there was no difference in PFS1 (median, 9.0 vs. 10.1 months, respectively; p = .33) or OS (median, 16.6 vs. 18.7 months; p = .86) between the two maintenance regimens. Reintroduction of FOLFIRINOX was performed in 20.2% of patients, with a median PFS2 of 2.8 months (95% CI, 2.0–22.3). The rates of grade 3–4 toxicity were significantly higher with FOLFIRI maintenance CT than with 5FU (41% vs. 22%; p = .03), especially for neuropathy (73% vs. 9%).

Conclusion. 5FU monotherapy maintenance appeared to be as effective as FOLFIRI, in a FOLFIRINOX de-escalation strategy, which is largely used in France. ***The Oncologist*** 2020;25:e1701–e1710

Implications for Practice: FOLFIRINOX de-escalation and maintenance is a feasible strategy in advanced pancreatic cancer that decreases chemotherapy toxicity to improve both survival and quality of life. Survivals in patients with maintenance therapy are clinically meaningful. Fluoropyrimidine monotherapy maintenance seems to be as efficient as FOLFIRI and should be a reference arm in future pancreatic cancer maintenance trials.

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Introduction

Pancreatic adenocarcinoma is expected to become the second leading cause of cancer-related death in the U.S. and Europe by 2030 [1, 2]. Despite recent progress, prognosis remains poor, with a 5-year overall survival (OS) rate, all stages combined, of 5% to 7% [3]. In 2011, substantial progress in survival was made with the use of FOLFIRINOX (5-fluorouracil [5FU] combined with folinic acid, irinotecan, and oxaliplatin) as a first-line treatment, after the results of the PRODIGE4/ACCORD11 trial in patients with metastatic pancreatic cancer (aPC) [4]. FOLFIRINOX was compared with gemcitabine and showed an improvement in median OS of 4.3 months (11.1 months vs. 6.8 months; $p < .001$) as well as in the quality of life of the patients [5]. However, triplet chemotherapy is associated with a higher burden of toxicities, including grade 3–4 neutropenia (45.7%), vomiting (14.5%), diarrhea (12.7%), and peripheral neuropathy (9%) [4]. Thus, in patients who achieve longer survival, the challenge of cytotoxic treatments is to reach a compromise between quality of life and disease control. Modified doses of FOLFIRINOX (bolus removal and reduced dose of irinotecan) did not decrease survival but resulted in fewer toxicities [6]. This protocol is the preferred first-line regimen in France, where access to gemcitabine-nab-paclitaxel, the alternative active first-line regimen, is limited because of reimbursement issues [7, 8].

The concept of maintenance generally covers the strategies of (a) therapeutic de-escalation (continuation maintenance) and (b) introducing a different molecule (switch maintenance) after a maximum response to the induction chemotherapy [9]. This concept is part of a therapeutic top-down objective, which aims to decrease the amount and therapeutic intensity while maintaining efficacy. To date, this strategy has been underevaluated in aPC but is used in other cancers such as colon [10], lung [11], and head and neck cancers [12], making it possible to maintain antitumoral pressure while reducing toxicities [9]. A few studies have addressed the maintenance in aPC: Reni et al. [13] sought to show the benefit of maintenance with sunitinib after chemotherapy, whereas Petrioli et al. [14] demonstrated that maintenance with gemcitabine after doublet chemotherapy with gemcitabine and nab-paclitaxel was feasible in older patients.

The first prospective phase II trial PRODIGE35-PANOPTIMOX investigating the feasibility of a de-escalation strategy in aPC demonstrated the feasibility of maintenance with 5-fluorouracil leucovorin (LV5FU2) after an induction strategy of eight cycles of FOLFIRINOX, without compromising survival (OS, 11.2 vs. 10.1 months) [15]. However, the study population had been selected for a clinical trial and differed from that of the clinical routine. Currently, there are no real-life data on therapeutic de-escalation practices in aPC.

We conducted a retrospective multicenter study whose main objective was to provide a descriptive overview of the feasibility and efficacy results of therapeutic de-escalation of FOLFIRINOX in aPC.

Materials and Methods

Study Design and Population

We performed a retrospective study in five French centers: three university hospitals (Lille University Hospital, St. Vincent de Paul Hospital in Lille, Besançon University Hospital) and two comprehensive centers (Oscar Lambret Centre in Lille and Eugène Marquis Centre in Rennes). The study population included all consecutive patients with aPC (locally advanced or metastatic) who received FOLFIRINOX between January 2011 and December 2018, and for whom the protocol was reduced after at least four cycles of FOLFIRINOX. De-escalation was performed using oral (capecitabine) or intravenous (LV5FU2) fluoropyrimidine, FOLFIRI (LV5FU2, irinotecan), or FOLFOX (LV5FU2, oxaliplatin). Patients under 18 years of age, those who had received less than four cycles of FOLFIRINOX, and those who had a progression disease on FOLFIRINOX were excluded. As the number of patients included in the FOLFOX group or those who had received treatment other than 5FU monotherapy or FOLFIRI was low, we focused our attention on patients who had received de-escalation with fluoropyrimidine or FOLFIRI. We investigated whether de-escalation that was performed after partial response (according to RECIST version 1.1) or stable disease (according to RECIST version 1.1) under FOLFIRINOX was sufficient to consider therapeutic decrementation. The primary endpoint was OS, and the secondary endpoints were first progression-free survival (PFS1), second progression-free survival (PFS2) in the event of FOLFIRINOX reintroduction, and toxicity.

Treatment efficacy was evaluated by computed tomography scan of the thorax, abdomen, and pelvis every 3 months. The data collected included the general characteristics of the population, metastatic or nonmetastatic status at diagnosis and at the different lines of treatment, type of treatment received, date of introduction and progression, presence and type of toxicities, notion of de-escalation, if applicable the presence of a FOLFIRINOX reintroduction, and the date of death or date of last news. A search for prognostic factors for maintenance was also performed.

The French data protection authority (Comission Nationale de l'Informatique et des Libertés agreement no. 1595361) provided a waiver of informed consent for this retrospective study and permitted the publication of anonymized data.

Statistical Analysis

Median value (interquartile range) and frequency (percentage) were provided for the description of continuous and categorical variables, respectively. Medians and proportions were compared using Student's *t* test and chi-square test (or Fisher's exact test, if appropriate), respectively. OS was calculated from the date of the first administration of first-line therapy to date of death from any cause, or the date of the last follow-up, at which point data were censored. PFS1 was defined as the time between the start of the first cycle of FOLFIRINOX and the first objective progression (RECIST version 1.1) of the tumor or death, whichever occurred first. PFS2 was defined as the time from reintroduction of FOLFIRINOX after maintenance therapy to objective tumor progression or death, whichever occurred first. Survival data were censored at the last follow-up. OS and progression-free survival were estimated using the Kaplan-Meier method, described using median or rate at specific time points with 95% confidence intervals (CIs), and compared using the log-rank test. Follow-up time was estimated using a reverse Kaplan-Meier estimation when feasible. Objective tumor

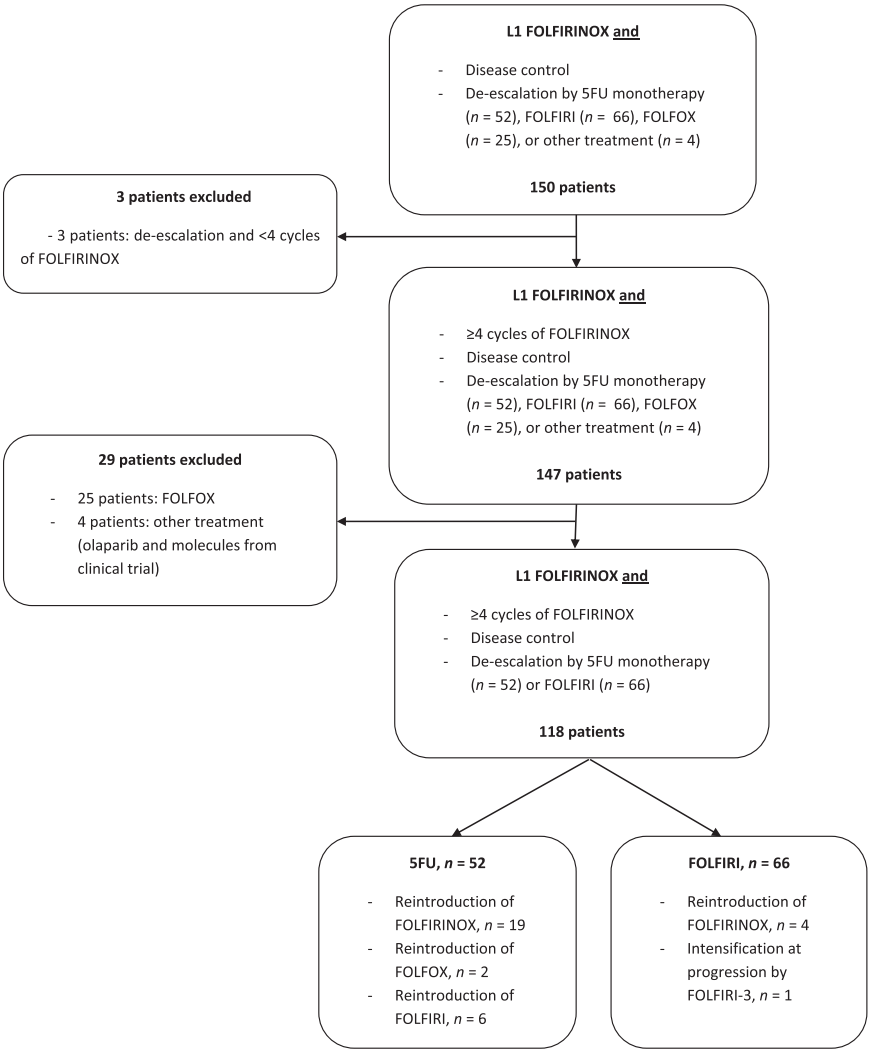

Figure 1. Flow chart. Among the 150 patients who received FOLFIRINOX for advanced pancreatic cancer and a de-escalation strategy, 147 patients were included. These patients received at least four cycles of FOLFIRINOX and received maintenance with FOLFIRI (*n* = 66), oral or intravenous 5FU (*n* = 52), FOLFOX (*n* = 25) or other type of maintenance (*n* = 4). Prognostic factors study was performed on patients who received maintenance with 5FU or FOLFIRI.
Abbreviation: 5FU, 5-fluorouracil.

response was determined according to RECIST version 1.1. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria version 4.0.

Cox proportional hazard models were performed to estimate hazard ratio and 95% confidence interval for factors associated with OS. The association of baseline parameters with OS was first assessed using univariate Cox analyses, and then parameters with *p* values of less than .05 were entered into a final multivariable Cox regression model. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary NC, USA). A value of $p < .05$ was considered statistically significant; all tests were two-sided.

Results

Population Characteristics

We included 147 (46%) patients treated with FOLFIRINOX as first-line therapy, who received therapeutic de-escalation after at least four cycles of FOLFIRINOX (Fig. 1). The median age was 60.0 years (53.1–35.7). At the initiation of FOLFIRINOX, 32 (21.8%) patients had locally advanced pancreatic cancer, and 115 (78.2%) had metastatic pancreatic cancer. The median total number of cycles of induction chemotherapy was 9.0 (6.0–11.0). Of these 147 patients, 66 (44.9%) received oral (capecitabine) or intravenous (LV5FU2) 5FU, 52 (35.4%) received FOLFIRI (5FU, folinic acid, and irinotecan), 25 (17%) received FOLFOX (5FU, folinic acid, and oxaliplatin), and 4 (2.7%) received other maintenance protocols, mainly olaparib in clinical trials. The population of the FOLFIRI group was older, and performance status (PS) was higher than that of the 5FU group (Table 1).

De-Escalation Strategy

In the de-escalation strategy population, median OS was 16.1 months (95% CI, 13.7–20.3) and median PFS1 was 9.4 months (95% CI, 8.5–10.4) (Fig. 2). There was no statistically significant improvement in OS and PFS1 depending on whether maintenance was started after 12 cycles of FOLFIRINOX or earlier (median OS, 20.5 vs. 15.0; $p = .2362$; median PFS1,

Table 1. Characteristics of the whole patient population (*n* = 147) and the population receiving FOLFIRI (*n* = 66) or 5FU maintenance (*n* = 52)

Characteristics	Overall population (*n* = 147)	FOLFIRI (*n* = 66)	5FU (*n* = 52)	*p* value
Demographic parameters				
Center, *n* (%)				
Besançon	60 (40.8)	20 (30.3)	20 (38.5)	
Lille	55 (37.4)	36 (54.6)	11 (21.1)	
Rennes	32 (21.8)	10 (15.1)	21 (40.4)	
Age, median [IQR], years	60.0 [53.1–65.7]	66.2 [55.1–65.4]	56.4 [51.2–64.7]	.0411
Gender, *n* (%)				.9748
Male	80 (54.4)	37 (56.1)	29 (55.8)	
Female	67 (45.6)	29 (43.9)	23 (44.2)	
Familial history of cancer, *n* (%)				.9497
No	46 (42.2)	19 (43.2)	17 (42.5)	
Yes	63 (57.8)	25 (56.8)	23 (57.5)	
Missing	38	22	12	
Personal history of cancer, *n* (%)				.0605
No	123 (86.0)	53 (82.8)	49 (94.2)	
Yes	20 (14.0)	11 (17.2)	3 (5.8)	
Missing	4	2	0	
Pathologic parameters				
Stage at diagnosis, *n* (%)				.2323
Localized	21 (14.3)	12 (18.2)	4 (7.7)	
Locally advanced	35 (23.8)	12 (18.2)	9 (17.3)	
Metastatic	91 (61.9)	42 (63.6)	39 (75.0)	
Primary tumor site, *n* (%)				.0908
Head	79 (56.7)	29 (43.9)	31 (59.6)	
Body and/or tail	68 (46.3)	37 (56.1)	21 (40.4)	
Histological grade, *n* (%)				.7230
Well or moderately differentiated	52 (78.8)	27 (84.4)	17 (77.3)	
Poorly differentiated or undifferentiated	14 (21.2)	5 (15.6)	5 (22.7)	
Missing	81	34	30	
Tumor extension				
Stage at chemotherapy initiation, *n* (%)				.8508
Locally advanced	32 (21.8)	11 (16.7)	8 (15.4)	
Metastatic	115 (78.2)	55 (83.3)	44 (84.6)	
Number of metastatic sites, *n* (%)				.9811
0	32 (21.8)	11 (16.7)	8 (15.4)	
1	87 (59.2)	41 (62.1)	33 (63.5)	
≥2	28 (19.0)	14 (21.2)	11 (21.1)	
Lymph node metastases, *n* (%)				.1604
No	133 (90.5)	57 (86.4)	49 (94.2)	
Yes	14 (9.5)	9 (13.6)	3 (5.8)	
Liver metastases, *n* (%)				.7166
No	57 (38.8)	22 (33.3)	19 (36.5)	
Yes	90 (61.2)	44 (66.7)	33 (63.5)	
Peritoneal metastases, *n* (%)				.5576
No	124 (84.4)	56 (84.9)	42 (80.8)	
Yes	23 (15.6)	10 (15.1)	10 (19.2)	
Lung metastases, *n* (%)				.9780
No	129 (88.8)	57 (86.4)	45 (86.5)	
Yes	18 (12.2)	9 (13.6)	7 (13.5)	

(continued)

Table 1. (continued)

Characteristics	Overall population (*n* = 147)	FOLFIRI (*n* = 66)	5FU (*n* = 52)	*p* value
Other metastases, *n* (%)				.6294
No	143 (97.3)	63 (95.5)	51 (98.1)	
Yes	4 (2.7)	3 (4.5)	1 (1.9)	
Clinical parameters				
Performance status (WHO), *n* (%)				.0258
0	56 (38.6)	22 (34.4)	25 (48.1)	
1	85 (58.6)	41 (64.1)	25 (48.1)	
≥2	4 (2.8)	1 (1.5)	2 (3.8)	
Missing	2	2	0	
Body mass index, kg/m^2	23.1 [20.7–25.6]	23.0 [20.4–25.7]	23.2 [21.2–26.2]	.3500
Missing, *n* (%)	2	2	0	
Pain, *n* (%)				.7355
No	90 (63.8)	45 (70.3)	33 (67.4)	
Yes	51 (36.2)	19 (29.7)	16 (32.6)	
Missing	6	2	3	
Jaundice, *n* (%)				.9999
No	135 (94.4)	59 (92.2)	47 (94.0)	
Yes	8 (5.6)	5 (7.8)	3 (6.0)	
Missing	4	2	2	
Ascites, *n* (%)				.6938
No	136 (95.8)	60 (93.8)	48 (96.0)	
Yes	6 (4.2)	4 (6.2)	2 (4.0)	
Missing	5	0	2	
Biological parameters				
Albumin, median [IQR], g/L	40.0 [35.0–43.0]	39.3 [35.5–42.1]	41.0 [38.5–44.0]	.1266
<35	18 (20.7)	9 (22.5)	2 (7.1)	.1083
≥35	69 (79.3)	31 (77.5)	26 (92.9)	
Missing	60	26	24	
Lymphocytes, median [IQR], mm^3	1,530.0 [1,270.0–2,100.0]	1,510.0 [1,200.0–2,184.0]	1,540.0 [1,280.0–1,720.0]	.6683
<1,000	9 (9.5)	6 (12.8)	2 (6.1)	.4595
≥1,000	86 (90.5)	41 (87.2)	31 (93.9)	
Missing	52	19	19	
Neutrophil-to-lymphocyte ratio, median [IQR]	2.93 [2.13–4.46]	2.95 [2.14–5.85]	3.06 [2.13–4.30]	.7150
<5	74 (77.9)	34 (72.3)	27 (81.8)	.3268
≥5	21 (22.1)	13 (27.7)	6 (18.2)	
Missing	52	19	19	
CA19-9, median [IQR], UI/mL	605.0 [69.0–4,756.0]	310.0 [25.0–3,528.0]	562.5 [238.0–4,000.0]	.3818
<37	30 (23.1)	19 (32.2)	8 (17.4)	.0849
≥37	100 (76.9)	40 (67.8)	38 (82.6)	
Missing	17	7	6	
Previous treatment				
Primary tumor resection, *n* (%)				.1883
Yes	22 (15.0)	12 (18.2)	5 (9.6)	
No	125 (85.0)	54 (81.8)	47 (90.4)	
Adjuvant chemotherapy, *n* (%)				.4294
Yes	17 (11.6)	8 (12.1)	48 (92.3)	
No	130 (88.4)	58 (87.9)	4 (7.7)	
Radiotherapy, *n* (%)				.9999
Yes	2 (1.4)	1 (1.5)	0 (0.0)	
No	145 (98.6)	65 (98.5)	52 (100.0)	

(continued)

Table 1. (continued)

Characteristics	Overall population (*n* = 147)	FOLFIRI (*n* = 66)	5FU (*n* = 52)	*p* value
First-line chemotherapy				
Number of cycles of FOLFIRINOX, median [IQR]	9.0 [6.0–11.0]			.1056
<8 cycles		16 (24.2)	6 (11.5)	
8–11 cycles		29 (44.0)	32 (61.6)	
>12 cycles		21 (31.8)	14 (26.9)	
Regimen after FOLFIRINOX, *n* (%)				
FOLFIRI	66 (44.9)			
FP monotherapy (capecitabine or LV5FU2)	52 (35.4)			
FOLFOX	25 (17.0)			
Other	4 (2.7)			
RECIST best response, *n* (%)				.3339
Complete or partial response	69 (51.9)	31 (50.0)	31 (60.8)	
Stability	61 (45.9)	29 (46.8)	20 (39.2)	
Progression	3 (2.2)	2 (3.2)	0 (0.0)	
Missing	14	4	1	
Toxicity of grade 3 or 4, *n* (%)				.0302
No	88 (62.4)	37 (58.7)	39 (78.0)	
Yes	53 (37.6)	26 (41.3)	11 (22.0)	
Digestive	21 (39.6)	0 (0.0)	3 (27.3)	
Hematology	8 (15.1)	1 (3.9)	5 (45.5)	
Neurology	16 (30.2)	19 (73.1)	1 (9.1)	
Other	8 (15.1)	6 (23.1)	2 (18.2)	
Missing	6	3	2	
Reason for discontinuation, *n* (%)				.8714
Progression	107 (73.3)	49 (75.4)	42 (80.8)	
Toxicity	7 (4.8)	3 (4.6)	2 (3.8)	
Other	32 (21.9)	13 (20.0)	8 (15.4)	
Missing	1	1	0	
Reintroduction of oxaliplatin and/or irinotecan, *n* (%)				<.001
No		61 (92.4)	25 (48.1)	
Yes		5 (7.6)	27 (51.9)	
FOLFIRINOX		4 (80.0)	19 (70.4)	
FOLFIRI or FOLFIRI-3		1 (20.0)	6 (22.2)	
FOLFOX		0 (0.0)	2 (7.4)	
Second-line chemotherapy administration, *n* (%)				.3059
No		15 (22.7)	27 (51.9)	
Yes		51 (77.3)	25 (48.1)	
Gemcitabine		43 (84.3)	24 (96.0)	
FOLFIRI		2 (3.9)	0 (0.0)	
FOLFOX		3 (5.9)	0 (0.0)	
Cisplatin		2 (3.9)	1 (4.0)	
GEMOX		1 (2.0)	0 (0.0)	

The population of the FOLFIRI group was older and performance status was higher than those of the 5FU group.
Abbreviations: 5FU, 5-fluorouracil; CA19-9, cancer antigen 19-9; FP, fluoropyrimidine; GEMOX, gemcitabin oxaliplatin; IQR, interquartile range; LV5FU2, 5-fluorouracil leucovorin; WHO, World Health Organization.

13.2 vs. 8.8 months; p = .4234) (supplemental online Fig. 1). Patients who received maintenance with FOLFIRI and 5FU had similar survivals (median OS, 18.7 vs. 16.6 months; p = .8678; median PFS1, 9.0 vs. 10.1, respectively; p = .3327) (supplemental online Fig. 2). On the other hand, there appeared to be a decrease in OS and PFS1 when de-escalation was performed with FOLFOX, compared with FOLFIRI or 5FU (median OS, 11.8 vs. 18.7 and 16.6 months; p = .5590; PFS1, 6.7 vs. 9.0 and 10.1 months; p = .0265) (Fig. 3). PFS1 was similar whether there was a response or stability under FOLFIRINOX, regardless of the chemotherapy regimen (5FU or FOLFIRI) (p = .5857) (Fig. 4).

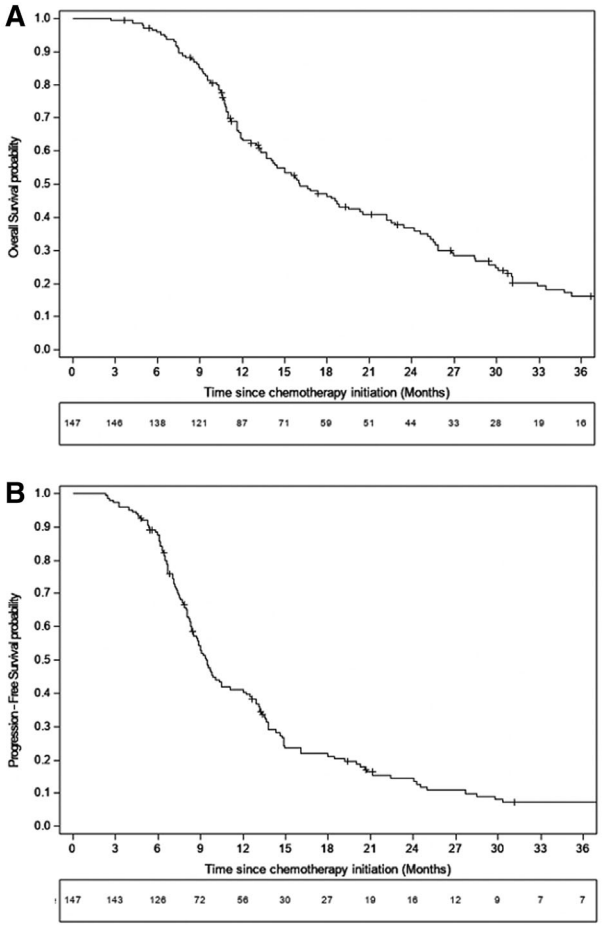

Figure 2. Assessment of overall survival and first progression-free survival (PFS1) under maintenance therapy. **(A):** Overall survival was 16.1 months (95% confidence interval [CI], 13.7–20.3). **(B):** Median PFS1 was 9.4 months (95% CI, 8.5–10.4).

Discontinuation of de-escalation therapy was mostly due to disease progression (*n* = 108 [74%]). Six (4.1%) patients stopped the treatment because of grade 3–4 toxicities, and 32 (21.9%) stopped treatment for other reasons, such as altered general condition or in relation to the oncologist's assessment (Table 1).

Adverse Events

In de-escalation population, 53 (37.6%) patients had grade 3–4 toxicities, most of which were digestive (*n* = 21 [39.6%]) and neurological (*n* = 16 [30.2%]). Eight (15.1%) patients had hematological toxicity (Table 2).

Among the 118 patients who received maintenance with FOLFIRI or 5FU, 37 (31.4%) had grade 3–4 toxicities, including 26 (41.3%) in the FOLFIRI group and 11 (22%) in the 5FU group. Toxicities in the FOLFIRI maintenance group were mainly neurological (*n* = 19 [73.1%]). In the 5FU group, toxicities were hematological (*n* = 5 [45.5%]) and digestive (*n* = 3 [27.3%]) (Table 2).

FOLFIRINOX Reintroduction

After progression under maintenance therapy by 5FU or FOLFIRI, reintroduction by triplet (FOLFIRINOX) or doublet of chemotherapy was performed in 28.1% of patients; that is, 5 (7.6%) received de-escalation with FOLFIRI, and 27 (51.9%) received de-escalation with 5FU. In the FOLFIRI regimen, four patients had reintroduction by FOLFIRINOX, and one had intensification by FOLFIRI-3 (irinotecan 100 mg/m^2 Day 1 and Day 3, folinic acid 400 mg/m^2 Day 1, continuous 5FU 2,000 mg/m^2 Day 1-Day 2). In the 5FU maintenance group, 19 patients (70.4%) had reintroduction by FOLFIRINOX, 6 (22.2%) by FOLFIRI, and 2 (7.4%) by FOLFOX (Table 1). The median PFS2 in the 5FU maintenance group was 2.8 months (95% CI, 2.0–20.5). Data were not available in the FOLFIRI group (p = .2934) (Fig. 5).

Prognostic Factors

The search for prognostic factors was carried out by univariate analysis on the 118 patients who received de-escalation with 5FU or FOLFIRI. Demographic parameters and tumor characteristics at diagnosis, whether clinical, radiological, or biological, were not associated with increased survival (supplemental online Table 1). Similarly, the number of FOLFIRINOX cycles received, best response to FOLFIRINOX, and the presence of grade 3 or 4 toxicities were not significant prognostic factors.

Discussion

We aimed to describe the conditions of maintenance therapy in advanced pancreatic cancer in France. In our study, a large proportion of patients received therapeutic de-escalation after at least four cycles of FOLFIRINOX, showing that this strategy is widely used by French oncologists. Considering the limitations of a retrospective study, 5FU maintenance seems to be as effective as FOLFIRI. Previously, Reure et al. [16] showed that de-escalation of FOLFIRINOX after four to eight cycles with capecitabine was feasible. The median OS was 17 months and median PFS1 was 5 months. Franck et al. [17] analyzed survival in patients who received a maintenance strategy with FOLFIRI after 2 to 6 months of treatment with FOLFIRINOX regimen. In this cohort of 22 patients, the median PFS1 (considering FOLFIRINOX induction and subsequent FOLFIRI maintenance therapy) was 11 months. Another retrospective study published by Hann et al. [18] showed a PFS1 of 10.6 months (95% CI, 6.7–14.4) and an OS of 18.3 months (95% CI, 14.8–21.8) in a cohort of 13 cases in which patients received de-escalation treatment with 5FU after FOLFIRINOX regimen. Our results were obtained in a real-life population with inclusion starting before the presentation of the first results of the PRODIGE35 trial [15]. In this phase II trial, patients were randomized into three arms: 12 cycles of FOLFIRINOX (arm A), 8 cycles of FOLFIRINOX followed by maintenance with 5FU and leucovorin (LV5FU2) with the possibility of reintroducing FOLFIRINOX at disease progression (arm B), and sequential treatment with gemcitabine and FOLFIRI-3 (arm C). Progression-free survival at 6 months in arms A and B (47% and 44%) and median OS (10.1 and 11.2 months) were similar, whereas arm C appeared inferior. However, the neurotoxicity rate was higher in arm B after 6 months of treatment, mainly because of the higher number of oxaliplatin cycles received by the patients in this arm with FOLFIRINOX reintroduction. We observed different results in our study, with a significantly higher grade 3–4 toxicity rate with FOLFIRI maintenance than that with 5FU (41% vs. 22%; p = .03), especially for the

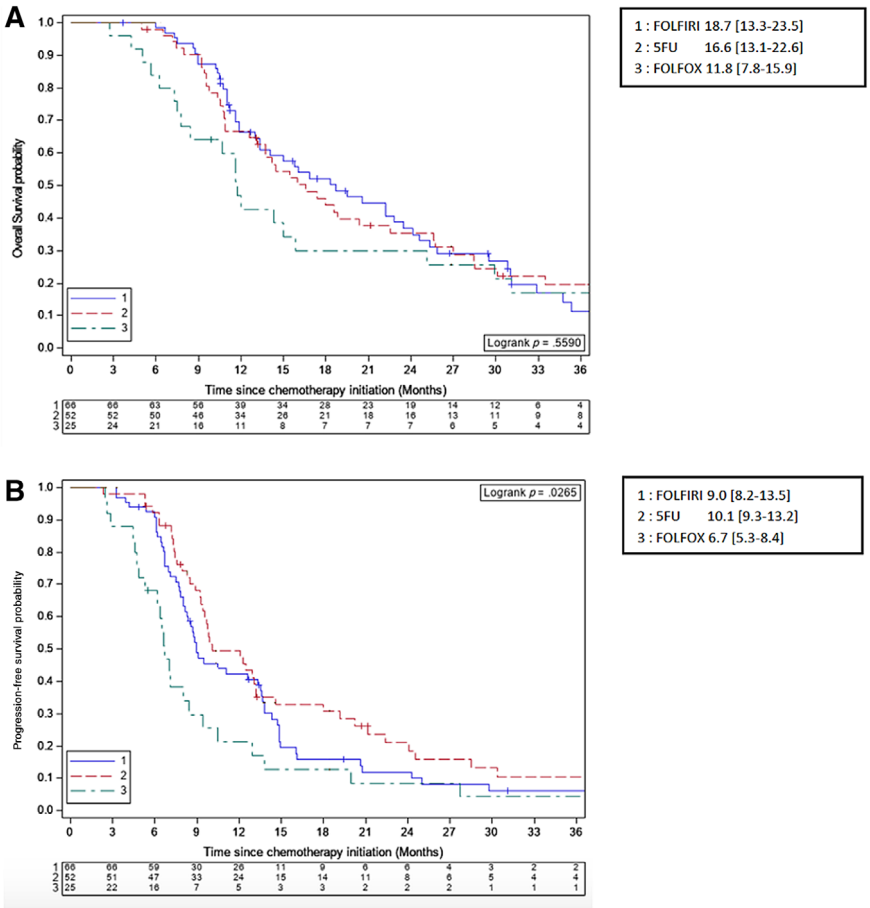

Figure 3. Overall survival and first progression-free survival (PFS1) curves in the FOLFIRI maintenance group (1), 5FU maintenance group (2), and FOLFOX maintenance group (3). **(A):** Overall survival. **(B):** Progression-free survival. There is no statistically significant difference of overall survival or PFS1 between the FOLFIRI and 5FU arms. On the other hand, there seems to be a decrease of PFS1 and overall survival in the FOLFOX group.
Abbreviation: 5FU, 5-fluorouracil.

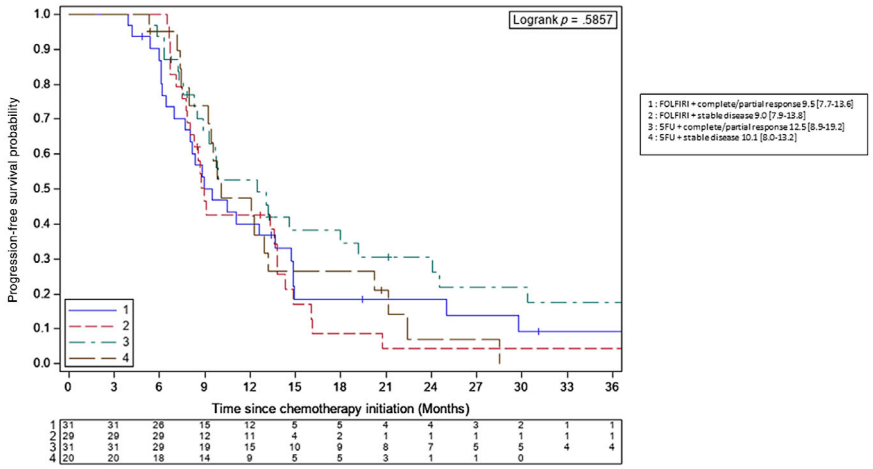

Figure 4. Analysis of first progression-free survival (PFS1) under de-escalation by FOLFIRI or 5FU depending on the response under FOLFIRINOX (n = 118). PFS1 was similar whether there was a response or stability under FOLFIRINOX, regardless of the chemotherapy regimen (5FU or FOLFIRI) (p = .5857).
Abbreviation: 5FU, 5-fluorouracil.

neuropathy (73% vs. 9.1%; p = .03). These toxicities must be associated with FOLFIRINOX induction chemotherapy, especially with oxaliplatin for neuropathy.

In colorectal cancer, de-escalation of LV5FU2 treatment in responder patients after six cycles of FOLFOX reduced toxicities in OPTIMOX trials. This strategy also improved

Table 2. Descriptive analysis of toxicities in patients who had a de-escalation strategy

Toxicity of grade 3 or 4[a]	De-escalation therapy (*n* = 147), *n* (%)	FOLFIRI (*n* = 66), *n* (%)	5FU (*n* = 52), *n* (%)
No	88 (62.4)	37 (58.7)	39 (78.0)
Yes	53 (37.6)	26 (41.3)	11 (22.0)
Digestive	21 (39.6)	0 (0.0)	3 (27.3)
Hematological	8 (15.1)	1 (3.9)	5 (45.5)
Neurological	16 (30.2)	19 (73.1)	1 (9.1)
Other	8 (15.1)	6 (23.1)	2 (18.2)
Missing	6	3	2

There was more neurotoxicity in patients who received maintenance with FOLFIRI than those who received 5FU.
[a]$p = .0302$.
Abbreviation: 5FU, 5-fluorouracil.

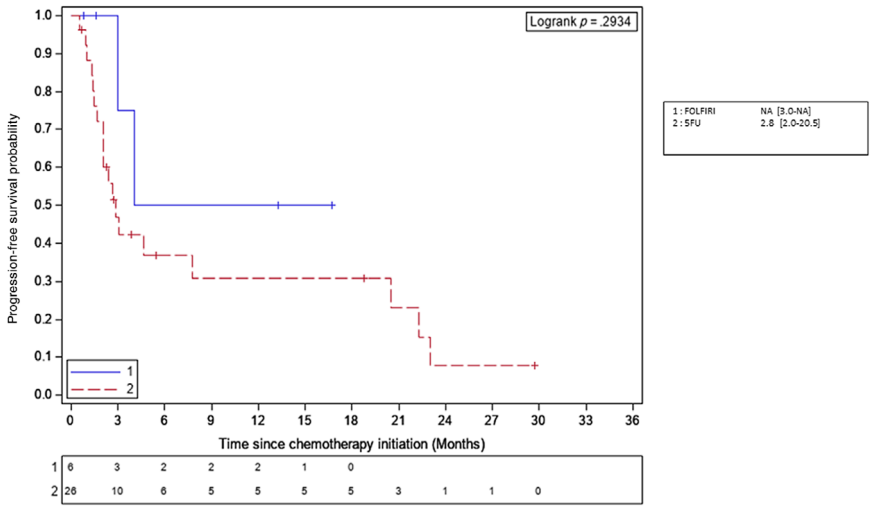

Figure 5. Analysis of second progression-free survival (PFS2), which assesses survival on FOLFIRINOX reintroduced after progression under maintenance therapy by FOLFIRI (1) or 5FU (2). PFS2 was not available in the FOLFIRI group because of because of the low number of patients, and PFS2 was 2.8 months (95% confidence interval, 2.0–20.5) in the 5FU group.
Abbreviations: 5FU, 5-fluorouracil; NA, not available.

progression-free survival compared with patients in whom treatment was suspended after six to eight cycles [19, 20]. In our study, the median OS (from the beginning of FOLFIRINOX) for all de-escalation regimens (i.e., 5FU, FOLFIRI, FOLFOX) was 16.4 months (95% CI, 13.7–20.3), and the median PFS1 was 8.8 months (95% CI, 8.3–9.7). These survivals were greater than those presented in the PRODIGE4/ACCORD11 trial as well as in the PRODIGE35-PANOPTIMOX trial [15] and similar to those shown in the retrospective study by Reure et al. [16]. The major limitation was the exclusion of early progressing patients, who were not able to receive a de-escalation regimen. Furthermore, our study included patients with both locally advanced and metastatic aPC (vs. only patients with metastatic aPC in PRODIGE4/ACCORD11 and PRODIGE35-PANOPTIMOX), whereas the OS of locally advanced pancreatic cancer was expected to be more favorable (even if this was not observed in our study), which introduces a new bias for the interpretation of OS [21].

An interesting finding was the no obvious difference in survival between the FOLFIRI and 5FU maintenance groups, although patients' characteristics were not in favor of FOLFIRI (older and higher PS). Oral or intravenous 5FU is classically better tolerated than a FOLFIRI regimen, which is an additional argument to encourage oncologists to consider a therapeutic de-escalation by 5FU. There was more reintroduction in 5FU group than in FOLFIRI group (51.9% vs. 7.6%; $p < .0001$) suggesting that this schedule was better tolerated than FOLFIRI. However, the higher reintroduction rate was not associated with higher survival. We also observed that patients with stable disease and those with objective response had similar survival outcomes, suggesting that FOLFIRINOX de-escalation with 5FU or FOLFIRI was appropriate whatever the tumor response, once disease control has been achieved after at least four cycles of induction chemotherapy. Finally, we did not find any prognostic factors that would allow better patient selection; however, these prognostic and predictive factors of response to maintenance should be studied prospectively by conducting ancillary studies of robust clinical trials such as PRODIGE35. Nevertheless, these interesting data from clinical practice support the development of further prospective maintenance studies, either de-escalation or switch maintenance, in order to improve therapeutic strategies for patients with aPC, maintaining tumor control while reducing toxicities. Thus, the 5FU arm may be a reasonable reference arm in future randomized maintenance trials in aPC [22].

Conclusion

We have shown that the de-escalation and maintenance strategy in aPC is currently widely accepted by French oncologists. In this trial, 5FU monotherapy de-escalation under FOLFIRINOX appeared to have similar results as those of FOLFIRI and may be an option in clinical routine and as a reference arm in maintenance trials. Maintenance trials should be encouraged in aPC to establish this therapeutic strategy in order to improve both therapeutic efficacy and quality of life of patients.

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Disclosures

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