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Reintroduction of palliative intent FOLFIRINOX chemotherapy in a real world pancreatic cancer cohort

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ABSTRACT

Background: FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan) can improve the prognosis of advanced pancreatic ductal adenocarcinoma (PDAC). Upon progression after a therapy-free interval it is not uncommon to reintroduce FOLFIRINOX, depending on the response and progression free interval after first-line FOLFIRINOX. The aim of this study is to provide an overview of the use and effectiveness of FOLFIRINOX reintroduction in daily practice.

Patients and methods: Patients with locally advanced and metastatic PDAC, diagnosed between 2015 and 2018, who started systemic treatment with palliative intent were selected from the Netherlands Cancer Registry (NCR). Overall and progression free survival (OS, PFS) were evaluated using Kaplan-Meier curves with log-rank tests.

Results: In this cohort of 2092 patients, most were treated with first-line FOLFIRINOX (1381; 66 %). The median OS was 9.0 months. A total of 388 patients (28 %) received subsequent systemic therapy after first-line FOLFIRNOX; 119 (30.7 %) patients were re-treated with FOLFIRINOX after a minimum of 3 months treatment interruption while 269 patients received other therapies, mostly gemcitabine/nab-paclitaxel or gemcitabine monotherapy. The median therapy-free interval between first-line FOLFIRINOX and FOLFIRINOX reintroduction was 7.0 months (p25-p75: 4,6–10,6). Patients underwent a median of 5 cycles (range: 1–32) during initial treatment and 5 cycles (range: 1–28) during FOLFIRINOX reintroduction. Median OS after FOLFIRINOX reintroduction was 23.4 months, and median progression-free survival was 6.8 months.

Conclusion: Reintroduction of FOLFIRINOX after at least 3 months therapy-free interval is used in daily practice and seems a reasonable treatment option based on a favorable OS and PFS in a small subset of patients.

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1. Introduction

The prognosis of pancreatic ductal adenocarcinoma (PDAC) is poor [1,2] and ranks among the leading causes of cancer mortality

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in the EU [3]. Patients are frequently diagnosed in an advanced stage [4] in which palliative chemotherapy is the only treatment available. Compared to historic gemcitabine monotherapy [5], both FOLFIRINOX (oxaliplatin, irinotecan and fluorouracil in combination with leucovorin) and gemcitabine + nab-paclitaxel combination therapy have shown a significant overall survival (OS) improvement, both in clinical studies [6,7] and according to real world data [8]. ESMO and NCCN guidelines for pancreatic cancer [9,10] recommend FOLFIRINOX as the preferred first line treatment both in the locally advanced and metastatic setting for patients in a good clinical condition.

There is no consensus on the optimal duration of FOLFIRINOX in patients with a response or disease control, but the number of cycles is typically maximized to 12 (6 months) based on recommendations in the Prodige study [6]. After initial chemotherapy with FOLFIRINOX a chemotherapy holiday or maintenance treatment can be considered according to the NCCN Guidelines for PDAC [10]. In daily practice, chemotherapy holidays are frequently used to preserve quality of life (QOL) after 1st line FOLFIRINOX [11]. For patients who experienced clinical benefit (defined as stable disease or response) and manageable toxicity of first line FOLFIRINOX, reintroduction of FOLFIRINOX can be considered when disease progresses after a > 3months therapy-free interval. However, there is no clinical evidence that addresses this issue or help guide this clinical treatment decision.

Therefore the aim of this study was to present a comprehensive overview of the utilization, OS and progression free survival (PFS) of FOLFIRINOX reintroduction in routine daily practice.

2. Patients and methods

2.1. Patient selection

All adult patients newly diagnosed with PDAC between 2015 and 2018 who started systemic treatment were identified in the Netherlands Cancer Registry (NCR) for inclusion in this retrospective cohort study. The NCR is a population based database, hosted by the Netherlands Comprehensive Cancer Organization (IKNL) and covers all patients with a newly diagnosed malignancy in the total Dutch population of 17.2 million people in 2018. Notification sources were the Dutch nationwide pathology databank (PALGA) and supplemented with the Dutch National Hospital Care Registration (LBZ). In order to select patients who were treated with palliative intent, we excluded patients who underwent resection of the primary tumor or another local treatment with curative intent, e.g. neoadjuvant chemoradiotherapy in the PREOPANC trial [12], and patients with a documented curative intent treatment plan at diagnosis based on arterial and venous involvement criteria of the primary tumor and TNM tumor stage [12]. Patient characteristics (sex, age, performance status, previous cancer diagnosis, comorbidities), tumor (TNM stage, tumor histology, location of metastases), treatment (systemic treatment, radiotherapy, other local therapy) were recorded from the hospital's electronic health record system by trained registrars of the NCR. Response data were also recorded from the hospital's electronic health record system when available. Vital status was obtained by annual linkage to the Municipal Personal Records Database. This study was designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [13]. The scientific committees of the Dutch Pancreatic Cancer Group (DPCG) and the Netherlands Cancer Registry (NCR) approved the study. Medical ethical approval was not required.

2.2. Palliative systemic therapy

In the selected patient group, type and timing of cancer treatments between diagnosis and death (or up to 3 years after diagnosis) were collected from the NCR database, as well as date(s) of progression. Systemic therapy regimens were classified as follows: FOLFIRINOX, gemcitabine + nab-paclitaxel, gemcitabine monotherapy, and other less commonly used regimens. Reintroduction of FOLFIRINOX was defined as a second treatment episode (minimum one cycle) with FOLFIRINOX after a minimum of 3 months (90 days) without any systemic treatment (“ therapy-free interval” or “chemotherapy holiday”) after first line FOLFIRINOX. Second line therapy was defined as treatment with agents not used in first line. Treatment duration intervals were calculated from start until stop date of the specific regimen. When patients continued fluorouracil-based therapy in a monotherapy or doublet regimen with oxaliplatin/irinotecan within 90 days after FOLFIRINOX, the stop date of the last agent in this regimen was used as the stop date of the FOLFIRINOX treatment. Retreatment with fluorouracil and oxaliplatin/irinotecan in a monotherapy or doublet regimen after a 3 months therapy-free interval was not classified as FOLFIRINOX reintroduction. Clinical benefit was defined as a documented radiologic complete or partial response (CR, PR) or stable disease (SD).

2.3. Statistical analysis

Data in this study were analyzed using SPSS statistics 28 (IBM). OS was defined as the interval from diagnosis until death from any cause or otherwise noted, censored at last follow up date, updated on February 1, 2022. PFS was defined from start of reintroduction of FOLFIRINOX to documented progression. Data on progression were not available for all patients. In patients without documented progression of FOLFIRINOX reintroduction (n = 36), time to progression was censored at time of last visit. However, several of these patients deceased within 30 days after the last visit or deceased (in the hospital) on the same day as the last hospital visit. Sensitivity analysis was performed with death within 30 days after the last hospital visit defined as a progression event. Median OS and PFS were analyzed using Kaplan Meier curves. A log rank test (Mantel-Cox) was used to compare OS differences in treatment groups. In addition, patients who deceased or stopped treatment within 30 days after FOLFIRINOX reintroduction were compared with other patients with reintroduction.

3. Results

3.1. First line systemic therapy

A total of 2092 patients who received systemic treatment with palliative intent for PDAC were included. Median age was 65 years (range 25–87). The majority of patients had distant metastases at time of diagnosis (74.7 %) and the primary tumor was histologically or cytologically confirmed in 93 % (Table 1). Patients in this cohort were treated with first line FOLFIRINOX (n = 1381, 66 %), gemcitabine monotherapy (n = 360, 17 %), gemcitabine + nab-paclitaxel (n = 250, 12 %) or other/unknown regimens (n = 101, 5 %). Six percent of patients were treated with a local therapy in addition to chemotherapy (stereotactic radiotherapy (SRT), radiofrequency ablation (RFA) or irreversible electroporation (IRE)). The majority of patients had died at the time of analysis (n = 2066, 99 %). Median OS from diagnosis differed significantly between patients who were treated with first line FOLFIRINOX (9.0 months; 95 % confidence

Table 1
Baseline patient characteristics in subsequent patient groups: all patients with palliative systemic treatment, first line FOLFIRINOX, FOLFIRINOX reintroduction after >3 months therapy-free interval after first line FOLFIRINOX, second line nab-paclitaxel + gemcitabine after first line FOLFIRINOX and second line gemcitabine monotherapy after first line FOLFIRINOX. *Two patients treated with capecitabine-oxaliplatin-irinotecan were also considered as FOLFIRINOX. Abbreviations: SRT, stereotactic radiotherapy; RFA, radiofrequent ablation; *IRE,* Irreversible electroporation.

Baseline characteristics	palliative systemic treatment (total)	palliative FOLFIRINOX as first systemic treatment*	After FOLFIRINOX as first systemic treatment		
			FOLFIRINOX reintroduction	Second line Nab-paclitaxel + gemcitabine	Second line Gemcitabine Monotherapy
N	2092	1381	119	155	67
Median age (y, range)	65 (25–87)	63 (25–83)	64 (39–79)	61 (25–80)	63 (43–82)
Age >70y (%)	563 (26,9)	229 (16,6)	25 (21)	22 (14,2)	12 (17,9)
Male (%)	1138 (54,2)	760 (54,9)	58 (48,7)	88 (56,8)	34 (50,7)
distant metastasis (%)	1563 (74,7)	1014 (73,2)	68 (57,1)	99 (63,9)	53 (79,1)
WHO PS (%) rowhead					
0–1	1357 (64,9)	983 (71,2)	96 (80,7)	118 (76,2)	51 (76,1)
2	210 (10,0)	90 (6,5)	8 (6,7)	9 (5,8)	2 (3)
3–4	32 (1,5)	14 (10,1)	–	2 (1,2)	1 (1,5)
Missing	493 (23,6)	294 (21,3)	15 (12,6)	26 (16,8)	13 (19,4)
No co-morbidity (%)	1057 (50,5)	778 (56,3)	66 (55,5)	85 (54,8)	37 (55,2)
Local treatment (%)	125 (6,0)	112 (8,1)	36 (30,3)	17 (11)	2 (3)
SRT	71 (3,4)	65 (4,7)	14 (11,8)	9(5,8)	1 (1,5)
RFA	26 (1,2)	22(1,6)	8 (6,7)	6 (3,9)	1 1,5)
IRE	28 (1,3)	25 (1,8)	14 (11,8)	2 (1,3)	

interval (CI), 8.5 to 9.4), gemcitabine + nab-paclitaxel (7.0 months; 95 % CI, 6.1 to 7.9) and gemcitabine monotherapy (4.8 months; 95 % CI, 4.3 to 5.2) ($p < 0.001$). First line treatment was administered for a median of 2.6 months (range 0–21.2; n = 1373, missing in 7), 2.3 (range 0–21.5; n = 249, missing in 1) and 1.4 months (range 0–18.4; n = 357, missing in 3) for respectively FOLFIRINOX, gemcitabine + nab-paclitaxel and gemcitabine monotherapy. A minority of patients (58 of 1381; 4,2 %) received >12cycles of FOLFIRINOX in the first line. The best response during the different chemotherapy treatments is described in Table 2.

3.2. Subsequent systemic therapy after first line FOLFIRINOX

Subsequent systemic therapy after first line FOLFIRINOX was started in 388 patients (28 % of 1381). A total of 119 patients (31 % of 388) received FOLFIRINOX reintroduction (>3 months treatment interruption after first line FOLFIRINOX); 155 patients (40 %) were treated with second line gemcitabine + nab-paclitaxel and 67 patients (17 %) with gemcitabine monotherapy (Table 1). Other second line treatments were started in 46 patients (12 %). The 119 patients who were treated with FOLFIRINOX reintroduction received a median of 4,6 months (range 1,2–12.0) FOLFIRINOX in first line versus 2,6 months for all patients who were treated with first line FOLFIRINOX as mentioned above. The number of FOLFIRINOX cycles for each treatment group is shown in Table 3. The median OS from diagnosis until death was 23.4 months (95 %CI, 21.0 to 25.8), 15.7 months (95 %CI, 13.4 to 18.0) and 11.5 months (95 %CI, 10.0 to 13.1) for patients treated with FOLFIRINOX reintroduction, gemcitabine + nab-paclitaxel and gemcitabine monotherapy in second line respectively Fig. 1a, $p < 0.01$). All patients (response unknown in 12/119) who received FOLFIRINOX reintroduction experienced clinical benefit during first line FOLFIRINOX compared to 51,6 % and 53,7 % of patients who received second line gemcitabine + nab-paclitaxel and gemcitabine monotherapy (response unknown in 33/155 and 14/67 patients).

3.3. FOLFIRINOX reintroduction

3.3.1. Incidence and treatment

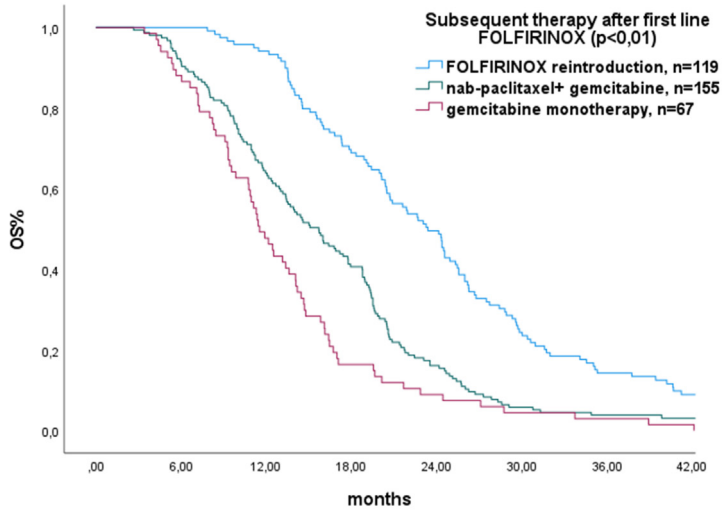
The 119 patients who received FOLFIRINOX after >3 months treatment interruption had a median age of 64 years and 57.1 % presented with metastatic disease. The median therapy-free interval between the end of first line FOLFIRINOX and reintroduction was 7.0 months (range 3.1–35.7 months; p25-p75: 4.6–10.6 months). Patients received a median of 5 cycles during FOLFIRINOX reintroduction (range 1–28 cycles). While for each treatment episode the first treatment adjustment (if applicable) was documented, further information on dose reductions at the start of

Table 2
Best response for patients during different treatments: during first line FOLFIRINOX (all patients), during first line FOLFIRINOX (subgroup of patients who received subsequent FOLFIRINOX reintroduction), during FOLFIRINOX reintroduction, during first line nab-paclitaxel + gemcitabine and during first line gemcitabine monotherapy (CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease).

Best response	n	n	n	n	n
	First line FOLFIRINOX (%)	First line FOLFIRINOX-reintroduction group (%)	FOLFIRINOX reintroduction (%)	First line nab-paclitaxel + gemcitabine (%)	first line gemcitabine (%)
CR	5 (0,4)	4 (3)	1 (1)	1 (0,4)	–
PR	341 (25)	62 (52)	23 (19)	53 (21)	20 (6)
SD	344 (25)	41 (35)	46 (39)	52 (21)	57 (16)
PD	353 (26)	–	25 (21)	59 (24)	133 (37)
unknown	338 (25)	12 (10)	24 (20)	85 (34)	150 (42)
total	1381	119	119	250	360

Table 3
FOLFIRINOX cycles during first line and reintroduction.

	First line palliative FOLFIRINOX				FOLFIRINOX reintroduction
	all patients	FOLFIRINOX reintroduction group	Second line Nab-paclitaxel + gemcitabine group	Second line gemcitabine monotherapy group	
N	1381	119	155	67	119
Median FOLFIRINOX cycles	5 (range 1–32)	8 (range 2–19)	8 (range 1–31)	7 (range 1–20)	5 (range 1–28)
patients with >8 cycles (%)	379 (27,4)	58 (48,7)	71 (43,8)	24 (35,8)	23 (20)
patients with >1 cycle (%)	1126 (81,5)	116 (100)	144 (92,9)	62 (92,5)	102 (88,7)
missing (n)	31	3	3	–	4



Numbers at risk (n) months	0	6	12	18	24	30	36	42
FOLFIRINOX reintroduction	119	119	112	82	59	29	17	10
Nab-paclitaxel gemcitabine	155	142	99	63	25	9	6	4
Gemcitabine monotherapy	67	59	32	11	6	3	2	1

a.

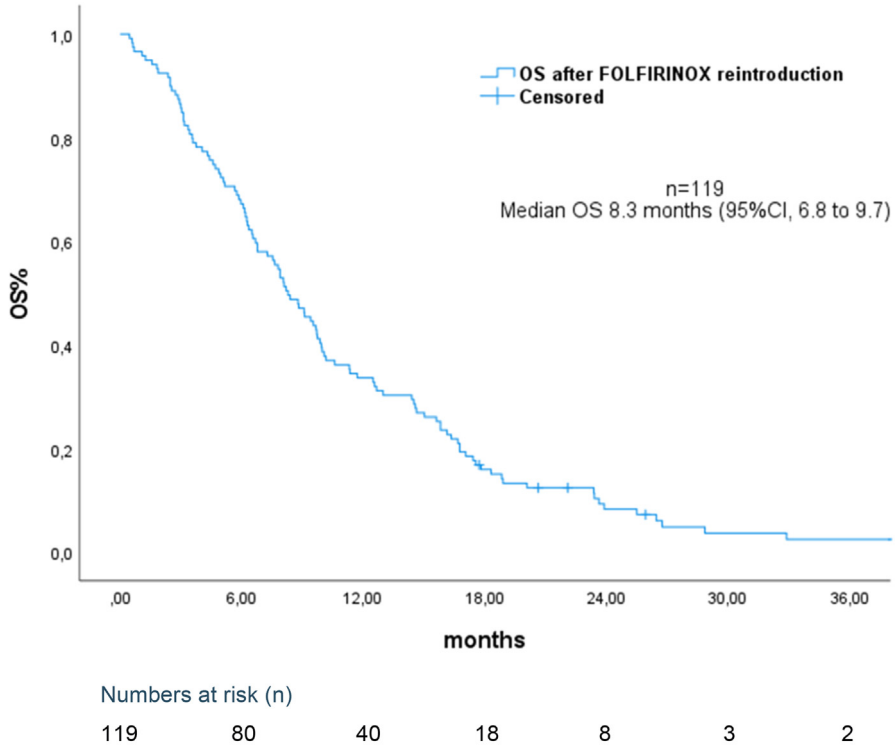
Fig. 1. a. OS (from diagnosis) by subsequent treatment group; FOLFIRINOX reintroduction, nab-paclitaxel + gemcitabine and gemcitabine monotherapy.
b. OS after start of FOLFIRINOX reintroduction.
c. PFS after start of FOLFIRINOX reintroduction.

treatment, dose intensity, and toxicity of treatment were not documented. At least 64 of 119 patients (53.8 %) needed a dose reduction after FOLFIRINOX reintroduction, compared to 73 of 119 patients (61.3 %) during first line FOLFIRINOX. 36 (30.3 %) patients who were retreated with FOLFIRINOX previously received local therapy, the majority of those patients had locally advanced disease (LAPC n = 34, 94.4 %).

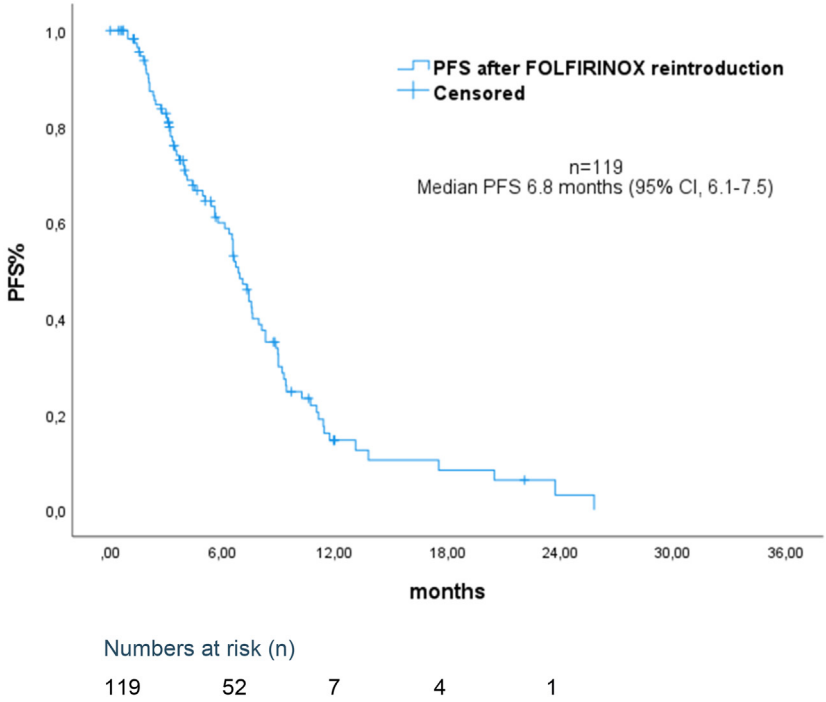
3.3.2. OS, PFS and response

Patients who presented with or without metastatic disease had a similar median OS from diagnosis until death after FOLFIRINOX reintroduction (22.7 months (95 %CI, 19 to 26.4) versus 24.4 months (95 %CI, 21.7 to 27.1) (p = 1.0)). The median OS from start of FOLFIRINOX reintroduction until death was 8.3 months (95 %CI, 6.8 to 9.7)(Fig. 1b) while the median OS from stop of FOLFIRINOX reintroduction until death was 4.4 months (95 % CI, 3.2 to 5.6). Median PFS after start of FOLFIRINOX reintroduction (n = 119) was 6.8 months (95 % CI, 6.1 to 7.5) (Fig. 1c). More than half of the patients (n = 70, 58.8 %) experienced clinical benefit during FOLFIRINOX reintroduction (Table 2). To identify patients who had no benefit of

FOLFIRINOX reintroduction we analyzed which patients died or stopped shortly after start of FOLFIRINOX reintroduction. Twenty-four of 119 patients (20.2 %) deceased (n = 4) or stopped FOLFIRINOX (n = 20) within 30 days after start of FOLFIRINOX reintroduction. For patients who either died or ceased treatment within 30 days after reintroduction of FOLFIRINOX, compared to those who did not, the median therapy-free interval from first line FOLFIRINOX until first FOLFIRINOX reintroduction was 5.4 months



b.



c.

Fig. 1. (*continued*).

(range 3.1–35.7 months; <6 months in n = 13/24, 54.2 %) compared to 7.1 months (range 3.1–31.7 months; <6 months in n = 32/95, 33.7 %). A small group of patients (n = 15, 53 % metastatic disease) was even treated with a second reintroduction of FOLFIRINOX without any other systemic therapy in between and had a median OS of 31 months from diagnosis and 17.4 months from start of first reintroduction.

4. Discussion

This retrospective cohort study investigated the use of FOLFIRINOX reintroduction after a minimum of 3 months therapy-free interval following first line palliative FOLFIRINOX for advanced PDAC. Patients who were treated with FOLFIRINOX reintroduction (119 of 1381 patients who received first line FOLFIRINOX) had a favorable median OS of 23 months from diagnosis and 8.3 months from reintroduction of FOLFIRINOX with a median therapy-free interval of 7 months between first line and FOLFIRINOX reintroduction.

Combination chemotherapy is the established standard treatment for PDAC, administered until adverse events or until disease progression necessitate a therapeutic change [14]. To our knowledge this is the first study that focuses on reintroduction of FOLFIRINOX after a treatment interruption following first line palliative FOLFIRINOX, although a maintenance approach after induction chemotherapy is explored in several studies. Support was found in the PANOPTIMOX-PRODIGE trial for maintenance fluorouracil-leucovorin after 4 months induction FOLFIRINOX for metastatic PDAC, although this strategy did not reduce chemotherapy-induced neurotoxicity [15]. Another maintenance strategy for patients with metastatic disease was investigated in the randomized SEQUENCE phase I/II trial, exploring standard gemcitabine/nab-paclitaxel versus an alternating maintenance schedule of gemcitabine-nab-paclitaxel and modified FOLFOX, resulting in improved OS (13.2 v 9.7 months; HR, 0.68; p = 0.02) for the alternating approach (ASCO 2022) [16]. In a retrospective study, maintenance fluorouracil monotherapy after FOLFIRINOX was associated with an OS of 18.3 months without OS or PFS difference between fluorouracil or FOLFIRI maintenance [17]. The OS of patients in our cohort that could be retreated with FOLFIRINOX without maintenance therapy does not seem detrimental compared to the survival rates in the maintenance studies, although these data cannot be directly compared. To specify maintenance treatment to the tumor biology, olaparib maintenance can be considered for patients with a germline BRCA1/2 mutation, but unfortunately without a significant OS benefit [18]. The 3 patients who received olaparib in our study were excluded from the FOLFIRINOX reintroduction cohort.

The optimal approach after first line FOLFIRINOX is not known. A second line cohort study reported an OS of 7.5 months after start of second line gemcitabine + nab-paclitaxel following 5FU based combinations [19]. After first-line FOLFIRINOX, an OS of 18.0 months was reported following second-line treatment with gemcitabine + nab-paclitaxel, compared to 14.3 months after second-line gemcitabine alone [20]. In a previous Dutch NCR cohort the median OS was 11.2 months for patients who were treated with any type of systemic second line therapy [8]. However, comparing these data with ours is not feasible because patients in our study who underwent FOLFIRINOX reintroduction had initially derived clinical benefit from first-line FOLFIRINOX in contrast to FOLFIRINOX-resistant disease. Our study has several limitations. As a non-randomized retrospective cohort design, it is subject to biases in patient and treatment selection. Consequently, we are unable to compare outcomes across different treatment strategies following first-line FOLFIRINOX, due to the differences between patients with initially FOLFIRINOX-sensitive and FOLFIRINOX-resistant disease. For example the survival curves of the different treatments after first line FOLFIRINOX in this real-world cohort shows a survival time bias for patients reintroduced to FOLFIRINOX who start with a minimum 3-month interval after first-line treatment, whereas patients who received second-line chemotherapy after progression on first-line FOLFIRINOX started treatment immediately.

In the Prodige study the median number of FOLFIRINOX cycles administered was 10 (range 1–47) compared to 5 cycles (range 1–32) of first line FOLFIRINOX in our cohort [6]. A substantial number of patients in our cohort (n = 226, 16,7 %) was only treated with 1 cycle of first line FOLFIRINOX, suggesting not all patients in our cohort would have been eligible for the landmark study. Patients who are eligible for FOLFIRINOX reintroduction are a selection of patients with clinical benefit on first line FOLFIRINOX, limited residual toxicity and a sufficient clinical condition. For example, patients in our cohort who could be treated with FOLFIRINOX reintroduction or other subsequent therapies were treated with more cycles of FOLFIRINOX in first line compared to all first line FOLFIRINOX patients. In addition, patients treated with FOLFIRINOX reintroduction less frequently presented with metastatic disease at diagnosis (57 vs. 73 % all first line FOLFIRINOX patients). One can envision that this difference translates into more patients being in a sufficient condition to be retreated with FOLFIRINOX. Second, information on WHO performance status and treatment response was missing in many patients in this real world cohort without structured mandatory reporting like in randomized clinical trials. Third, the exact moment of disease progression (according to RECIST) was not structurally reported in the medical charts. This may have influenced PFS intervals, as detection of progressive disease may have been omitted in case of clinical deterioration. After sensitivity analysis, with death shortly after FOLFIRINOX termination redefined as a progression event, PFS was reduced by more than a month. Fourth, only the type of the first therapy adjustment (e.g. delay or dose reduction) after start of systemic treatment was registered for each treatment episode. No data were available about dose reductions at the start of treatment, dose intensity and toxicity separately which makes it difficult to draw conclusions about safety. At last, we cannot rule out a beneficial effect on OS of a local treatment. Patients who were treated with a FOLFIRINOX reintroduction more often were treated with an additional local therapy compared to patients who were treated with second line gemcitabine plus nab-paclitaxel and gemcitabine monotherapy (30 vs 11 and 3 %). We found a favorable OS but also a large range of survival and treatment cycles after FOLFIRINOX reintroduction in our nationwide database. For example, one fifth of patients stopped FOLFIRINOX or died soon after start of FOLFIRINOX reintroduction, while others were treated for many months. In the patients with poor results after FOLFIRINOX reintroduction, the therapy-free interval after first line FOLFIRINOX was shorter (5.4 vs. 7.1 months) compared to patients who were treated >30 days with FOLFIRINOX reintroduction.

The findings of this study can be used as background information (in absence of RCTs for second line treatments after FOLFIRINOX) when reintroduction of FOLFIRINOX is considered in patients experiencing clinical benefit during first line FOLFIRINOX.

5. Conclusion

The present study provides a nationwide overview about the use of reintroduction of FOLFIRINOX in routine daily practice after at least a 3 months therapy-free interval in patients with advanced PDAC. Despite all the limitations of a retrospective cohort study, the results of this study can be used as background information to provide answers of real world outcomes to patients who are

eligible and consider retreatment with FOLFIRINOX. Also the knowledge that a drug holiday of many months is used in selected patients with reasonable outcomes can be useful in daily practice.

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Declaration of competing interest

None declared.

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