FOLFIRINOX De-Escalationin Advanced Pancreatic Cancer: A MulticenterReal-LifeStudy

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FOLFIRINOX de-escalation in advanced pancreatic cancer: a multicenter real-life study

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Implications for practice

FOLFIRINOX de-escalation and maintenance is a feasible strategy in advanced pancreatic cancer which decrease chemotherapy toxicity in order to improve both patients' 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.

ABSTRACT

BACKGROUND

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

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, oxapliplatin), 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%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%), vs. 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=0.33) or OS (median: 16.6 vs. 18.7 months, P=0.86) 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=0.03), 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.

1. Introduction

Pancreatic adenocarcinoma is expected to become the second leading cause of cancer-related death in the United States 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 (L1), following the results of the PRODIGE4/ACCORD11 trial in metastatic pancreatic cancer (aPC) patients [4]. FOLFIRINOX was compared to gemcitabine and showed an improvement in median OS of 4.3 months (11.1 months vs. 6.8 months, $p<0.001$) 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 due to reimbursement issues [7][8].

The concept of maintenance generally covers the strategies of (i) therapeutic de-escalation (continuation maintenance) and (ii) 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 under evaluated 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 anti-tumoral 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, while 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 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.

2. Materials and methods

2.1 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) Fluoropyrimidin, FOLFIRI [LV5FU2, irinotecan], FOLFOX [LV5FU2, oxaliplatin]. Patients under 18 years of age, those who had received less than four cycles of FOLFIRINOX, or 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 FP or FOLFIRI. We investigated whether de-escalation should be performed after partial response (according to RECIST 1.1) or stable disease (according to RECIST 1.1) under FOLFIRINOX was sufficient to consider therapeutic decrementation. The primary endpoint was overall survival (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 TAP CT-scan every three months. The data collected included the general characteristics of the population, metastatic or non-metastatic 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, notion, and date of death. The search for prognostic factors for maintenance was also performed.

French Data Protection Authority (CNIL agreement n°1595361) provided a waiver of informed consent for this retrospective study and permitted the publication of anonymized data.

2.2 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 L1 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 v1.1) 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 PFS were estimated using the Kaplan-Meier method and 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 response was determined according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria v4.0.

Cox proportional hazard models were performed to estimate hazard ratio (HR) 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 0.05 were entered into a final multivariable Cox regression model. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary NC, USA). $P < 0.05$ was considered statistically significant; all tests were two-sided.

3. Results

3.1 Population characteristics

We included 147 (46%) of 321 aPC patients treated with FOLFIRINOX as L1 therapy, who received therapeutic de-escalation after at least four cycles of FOLFIRINOX (Figure 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 (PC) and 115 (78.2%) had metastatic PC. 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 performans status (PS) was higher than those of the 5FU group (Table 1).

3.2 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) (Figure 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=0.2362; median PFS1: 13.2 vs. 8.8 months, P=0.4234) (Appendix, Figure 1). Patients who received maintenance with FOLFIRI and 5FU had similar survivals (median OS: 18.7 vs. 16.6 months, P=0.8678; median PFS1: 9.0 vs. 10.1, respectively, P=0.3327) (Appendix, Figure 2). On the other hand, there appeared to be a decrease in OS and PFS1 when de-escalation was performed with FOLFOX, compared to FOLFIRI or 5FU (median OS: 11.8 vs. 18.7 and 16.6 months, P=0.5590; PFS1: 6.7 vs. 9.0 and 10.1 months, P=0.0265) (Figure 3). PFS1 was similar whether there was a response or stability under FOLFIRINOX, regardless of the chemotherapy regimen (5FU or FOLFIRI) (P=0.5857) (Figure 4).

Discontinuation of de-escalation therapy was mostly due to disease progression (n=108 [74%]). Six (4.1%) patients stopped the treatment due to 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).

3.3 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).

3.4 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, i.e., 5 (7.6%) received de-escalation with FOLFIRI and 27 (51.9%) received de-escalation with 5FU. In the FOLFIRI regimen, 4 patients had reintroduction by FOLFIRINOX and 1 had intensification by FOLFIRI-3 (Irinotecan 100 mg/m² J1 and J3, folinic acid 400 mg/m² J1, continuous 5FU 2000 mg/m² J1-J2). 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=0.2934) (Figure 5).

3.5 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, tumor characteristics at diagnosis, whether clinical, radiological, or biological, were not associated with increased survival (Appendix 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.

4. Discussion

We aimed to describe the conditions of maintenance therapy in advanced pancreatic cancer in France. In our study, 46% 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 two to six 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). PFS at six months in arms A and B (47% and 44%) and median OS (10.1 and 11.2 months) were similar, while arm C appeared inferior. However, the neurotoxicity rate was higher in arm B after six months of treatment, mainly due to 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=0.03), especially for the neuropathy (73% vs. 9.1%, P=0.03).

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 PFS compared to patients in whom treatment was suspended after 6-8 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 Reure *et al* retrospective study [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 both locally advanced and metastatic aPC (vs. metastatic patients only in PRODIGE4/ACCORD11 and PRODIGE35-PANOPTIMOX), while the OS of locally advanced PC was expected to be more favourable (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 IV 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<0.0001) 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, 5FU arm may be a reasonable reference arm in future randomized maintenance trials in aPC [22].

5. Conclusions

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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CONFLICT OF INTERESTS

- Hortense Chevalier: None

- Anthony Turpin has served in a consulting/advisory role and or received honoraria for Amgen, Merck, Servier, Mylan and has received travel, accommodations, and expenses from Astra-Zeneca, Pfizer, Sanofi

- Astrid Lièvre have received honoraria for lectures from AAA, Amgen, Bayer, BMS, Celgene, HalioDx, Ipsen, Lilly, Merck, Novartis, Pierre Fabvre, Roche, Sandoz and Servier ; honoraria for consulting/advisory relationship from AAA, Amgen, Bayer, Incyte, Ipsen, Merck, Novartis, Pierre Fabvre, Sandoz and Servier ; travel support from AAA, bayer, Ipsen, Merck, Novartis, Pfizer, Roche and Servier ; research funding from Novartis, Intergragen, Incyte.

- Farid El Hajbi served in consulting/advisory role and/or received honoraria from Ipsen, Merck, Servier; has received travel accommodations and expenses from BMS, MSD, Ipsen, Sanofi

-Other Authors: None

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FIGURE LEGENDS

Figure 1: Flow chart. Among the 321 patients who received FOLFIRINOX for advanced pancreatic cancer, 147 patients were included**.** These patients received at least four cycles of FOLFIRINOX and received maintenance with FOLFIRI (N=66), oral or intraveinous 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. 5FU, 5-fluorouracil.

Figure 2: Assessment of overall survival and PFS1 under maintenance therapy. Overall survival was 16.1 months (95%CI=13.7-20.3) and median PFS1 was 9.4 months (95%CI=8.5-10.4). PFS1, first progression-free survival.

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

Figure 4: Analysis of 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=0.5857). PFS1, first progression-free survival; 5FU, 5-fluorouracil.

Figure 5: Analysis of 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%CI =2.0-20.5) in the 5FU group. PFS2, second progression-free survival; 5FU, 5-fluorouracil.

Table 1: Characteristics of the whole patient population (N=147) and the population receiving FOLFIRI (N=66) or 5FU maintenance (N=52). The population of the FOLFIRI group was older and performans status was higher than those of the 5FU group. 5FU, 5-fluorouracil; WHO, World Health Organization.

Characteristics	**Overall population N=147**	**FOLFIRI N= 66**	**5FU N=52**	**P**
Demographic parameters				
Centre, 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]	0.0411
Gender, N (%)				0.9748
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 (%)				0.9497
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 (%)				0.0605
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 (%)				0.2323
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 (%)				0.0908
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 (%)				0.7230
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 (%)				0.8508
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 (%)				0.9811
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 (%)				0.1604
No	133 (90.5)	57 (86.4)	49 (94.2)	
Yes	14 (9.5)	9 (13.6)	3 (5.8)	
Liver metastases, N (%)				0.7166
No	57 (38.8)	22 (33.3)	19 (36.5)	
Yes	90 (61.2)	44 (66.7)	33 (63.5)	
Peritoneal metastases, N (%)				0.5576
No	124 (84.4)	56 (84.9)	42 (80.8)	
Yes	23 (15.6)	10 (15.1)	10 (19.2)	
Lung metastases, N (%)				0.9780
No	129 (88.8)	57 (86.4)	45 (86.5)	
Yes	18 (12.2)	9 (13.6)	7 (13.5)	
Other metastases, N (%)				0.6294
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 (%)				0.0258
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, N (%), kg/m^2	23.1 [20.7 – 25.6]	23.0 [20.4 – 25.7]	23.2 [21.2 – 26.2]	0.3500
Missing	2	2	0	
Pain, N (%)				0.7355
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 (%)				1.0000
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 (%)				0.6938
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]	0.1266
< 35	18 (20.7)	9 (22.5)	2 (7.1)	0.1083
≥ 35	69 (79.3)	31 (77.5)	26 (92.9)	
Missing	60	26	24	
Lymphocytes, median [IQR], mm^3	1530.0 [1270.0 – 2100.0]	1510.0 [1200.0 – 2184.0]	1540.0 [1280.0 – 1720.0]	0.6683
< 1000	9 (9.5)	6 (12.8)	2 (6.1)	0.4595
≥ 1000	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]	0.7150
< 5	74 (77.9)	34 (72.3)	27 (81.8)	0.3268
≥ 5	21 (22.1)	13 (27.7)	6 (18.2)	
Missing	52	19	19	
CA19-9, median [IQR], UI/mL	605.0 [69.0 – 4756.0]	310.0 [25.0 – 3528.0]	562.5 [238.0 – 4000.0]	0.3818
< 37	30 (23.1)	19 (32.2)	8 (17.4)	0.0849
≥ 37	100 (76.9)	40 (67.8)	38 (82.6)	
Missing	17	7	6	
Previous treatment				
Primary tumor resection, N (%)				0.1883
Yes	22 (15.0)	12 (18.2)	5 (9.6)	
No	125 (85.0)	54 (81.8)	47 (90.4)	
Adjuvant chemotherapy, N (%)				0.4294
Yes	17 (11.6)	8 (12.1)	48 (92.3)	
No	130 (88.4)	58 (87.9)	4 (7.7)	
Radiotherapy, N (%)				1.0000
Yes	2 (1.4)	1 (1.5)	0 (0.0)	
No	145 (98.6)	65 (98.5)	52 (100.0)	
First-line chemotherapy				
Number of cycles of FOLFIRINOX, median [IQR]	9.0 [6.0 – 11.0]			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 (%)				0.3339
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 (%)				0.0302
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 (%)				0.8714
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 (%)				<0.001
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 (%)			0.3059
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)*	
CISPLATINE	*2 (3.9)*	*1 (4.0)*	
GEMOX	*1 (2.0)*	*0 (0.0)*	

Table 2: Descriptive analysis of toxicities in patients who had a de-escalation strategy. There was more neurotoxicity in patients who received maintenance with FOLFIRI than those who received 5FU. 5FU, 5-fluorouracil.

Toxicity of grade 3 or 4, N (%)		**De-escalation therapy (N=147)**	**FOLFIRI (N=66)**	**5FU (N=52)**	**p=0.0302**
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)	
	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	

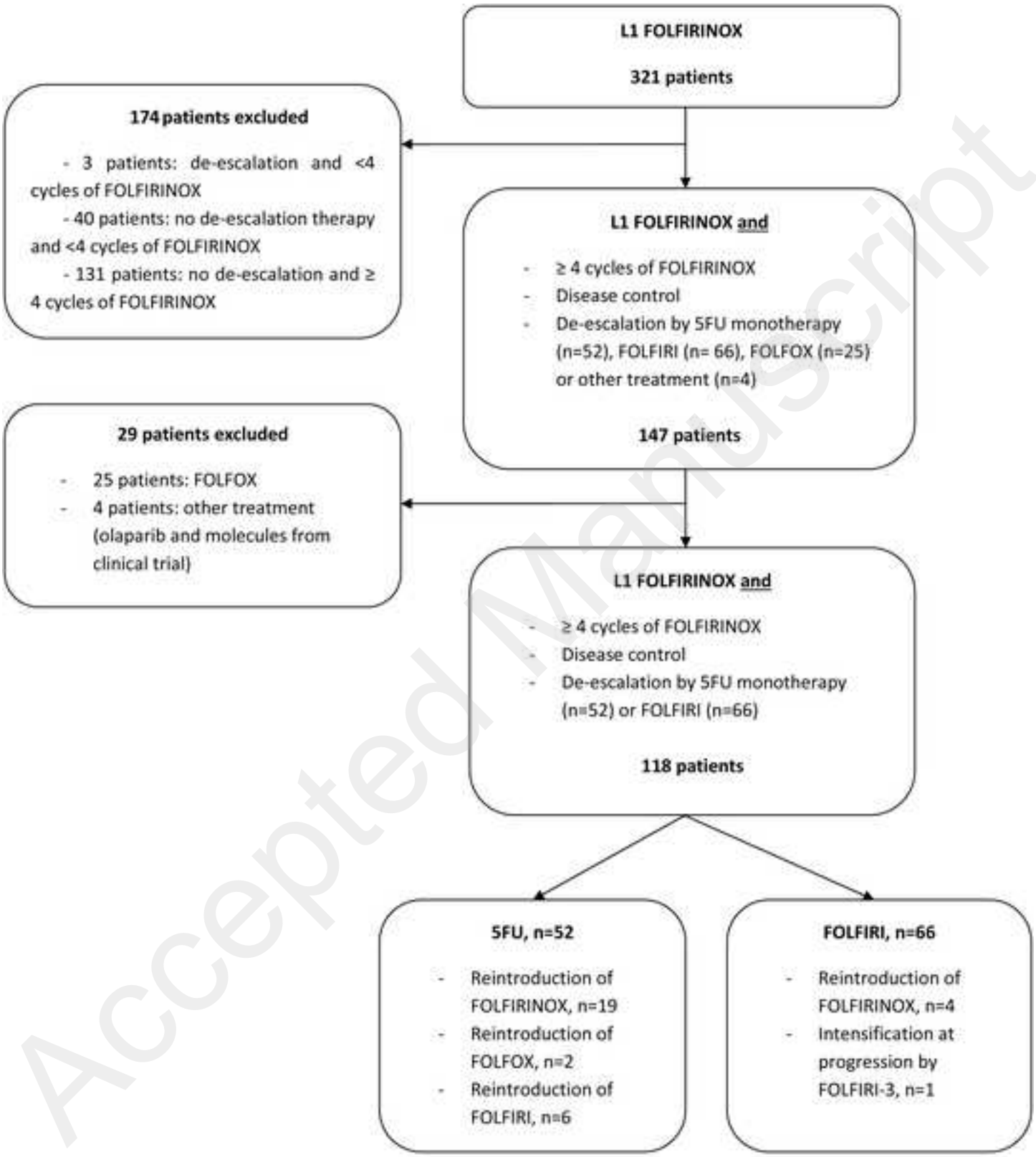
APPENDIX

Appendix Figure 1: Assessment of overall survival and PFS1 according to the number of FOLFIRINOX cycles received before therapeutic de-escalation. Overall survival and PFS1 were not significantly higher when patients received at least 12 cycles of FOLFIRINOX than those who received less than 12 cycles. PFS1, first progression-free survival.

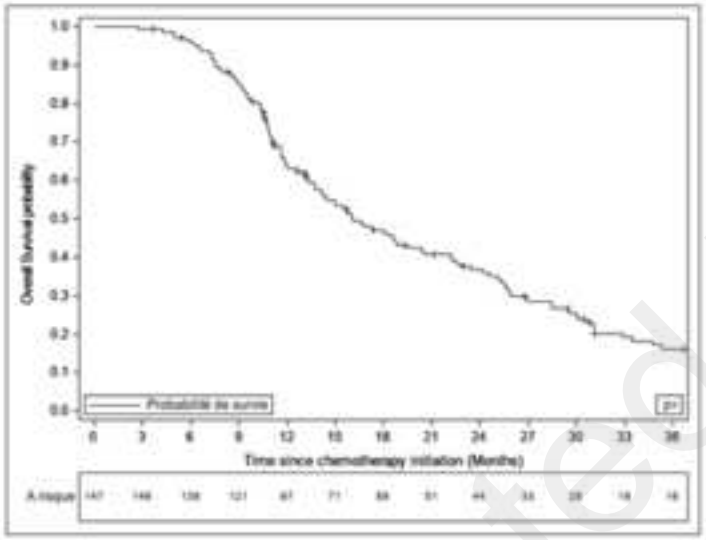
Appendix Figure 2: Overall survival and PFS1 curves in FOLFIRI maintenance group (1) and 5FU maintenance group (2) (n=118). There is no difference of survival between these two treatment (P=0.8676 and P=0.3327 respectively). PFS1, first progression-free survival; 5FU, 5-fluorouracil.

Appendix Table 1: Assessment in univariate analysis of prognostic factors related to therapeutic de-escalation (univariate analysis, N=118). There is no prognostic factor associated with increased survival.

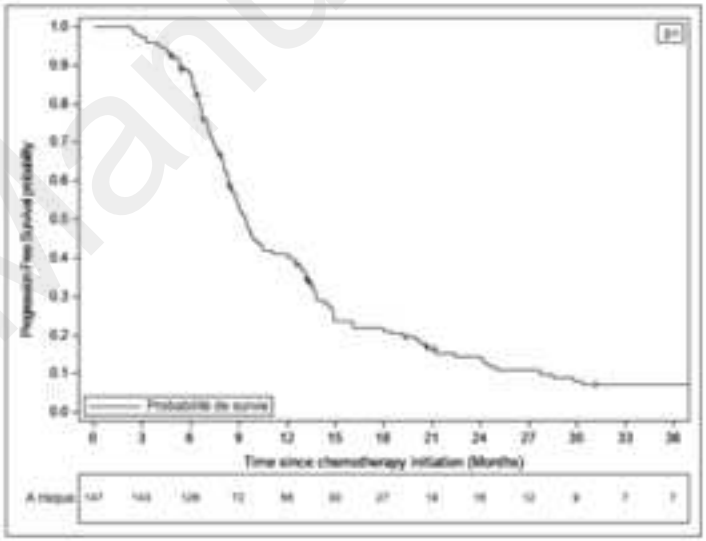
Figure



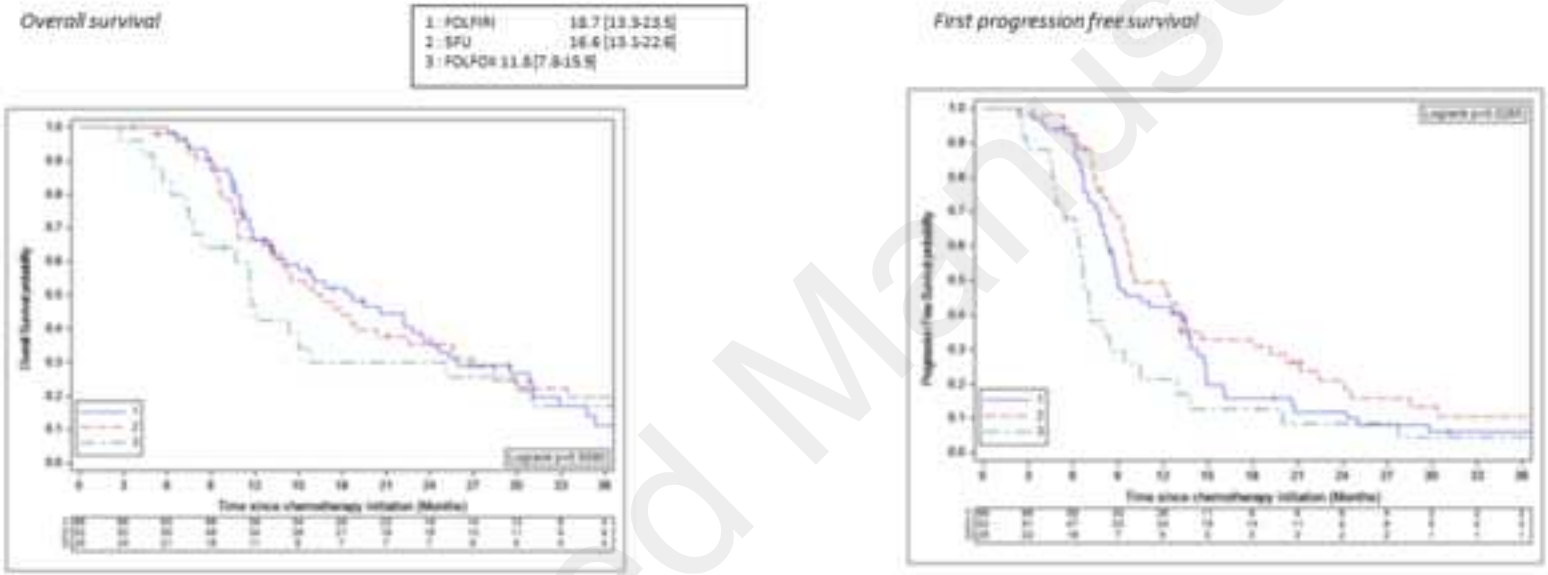
Overall survival



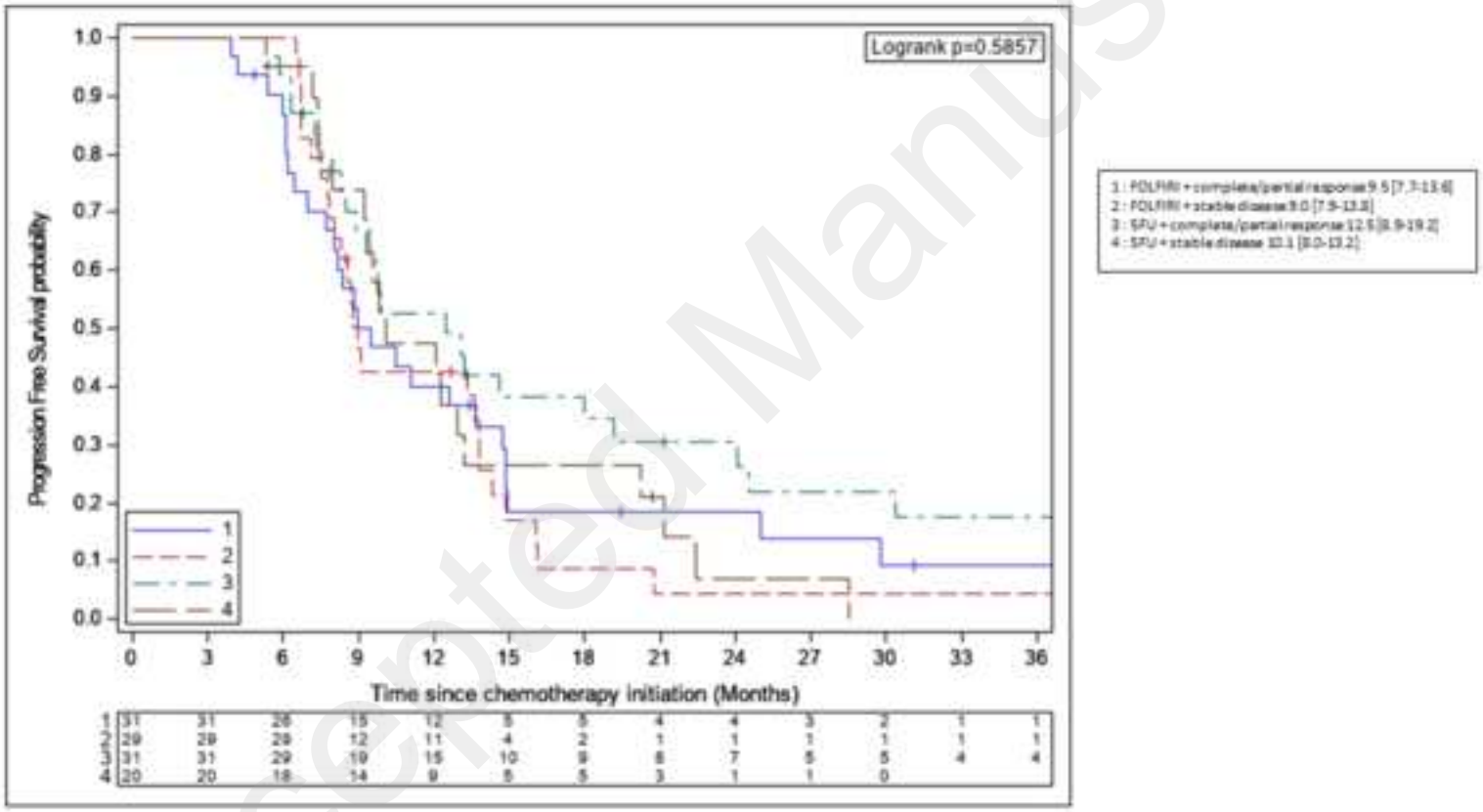
First progression free survival

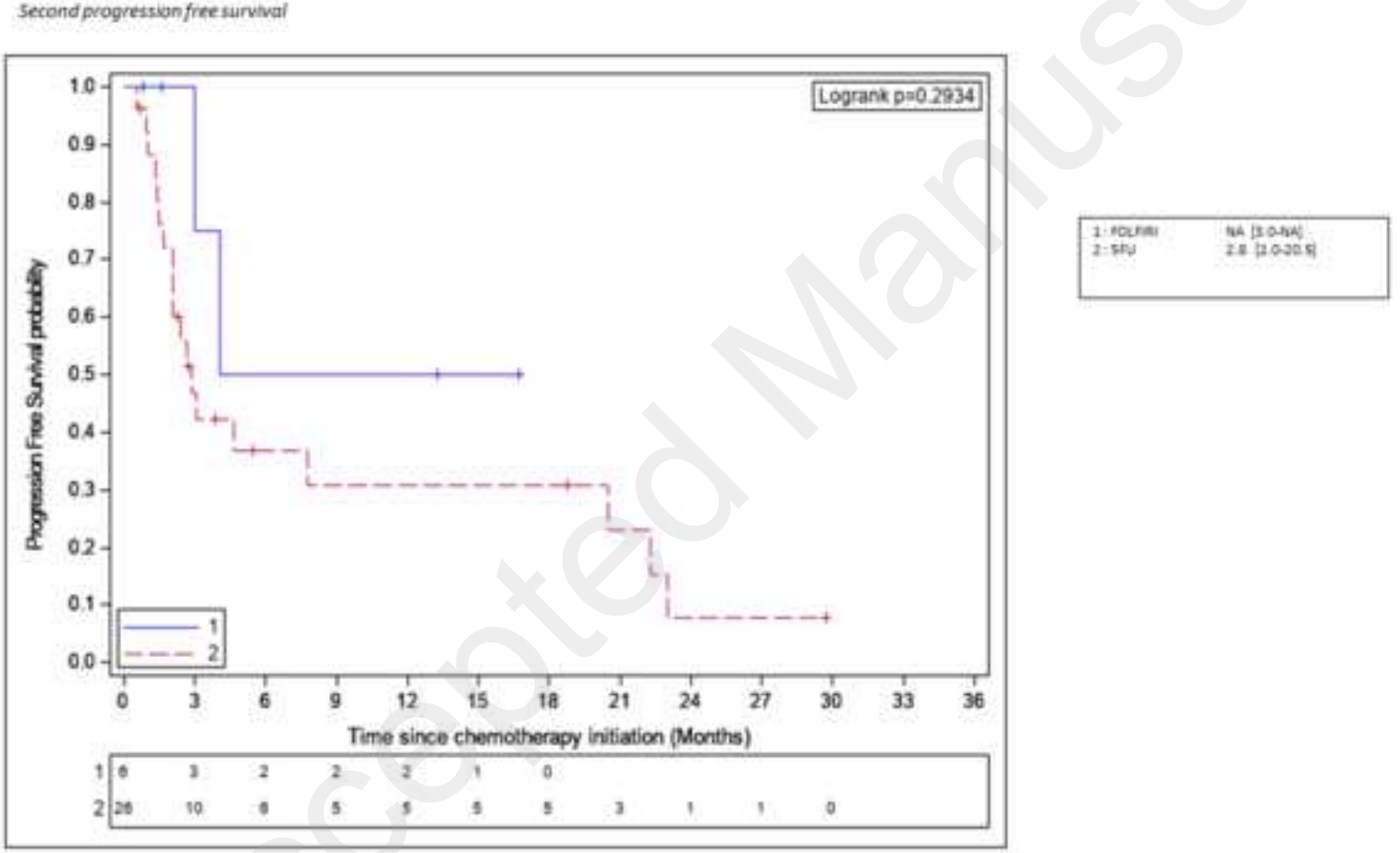


Figure



Figure





Appendix Table 1

Parameters	HR (95% CI)	P
Demographic parameters		
Age, years	1.009 (0.988 – 1.030)	0.4040
Gender		
Male	1.00 (Reference)	
Female	1.132 (0.766 – 1.674)	0.5330
Family history of cancer		
No	1.00 (Reference)	
Yes	1.260 (0.791 – 2.007)	0.3297
Personal history of cancer		
No	1.00 (Reference)	
Yes	0.913 (0.508 – 1.640)	0.7604
Pathologic parameters		
Stage at diagnosis		
Localized	1.00 (Reference)	
Locally advanced	1.127 (0.545 – 2.328)	
Metastatic	1.221 (0.658 – 2.268)	0.8029
Primary tumor site		
Head	1.00 (Reference)	
Body and/or Tail	1.018 (0.691 – 1.500)	0.9292
Histological grade		
Well or moderately differentiated	1.00 (Reference)	
Poorly differentiated or undifferentiated	0.884 (0.422 – 1.850)	0.7433

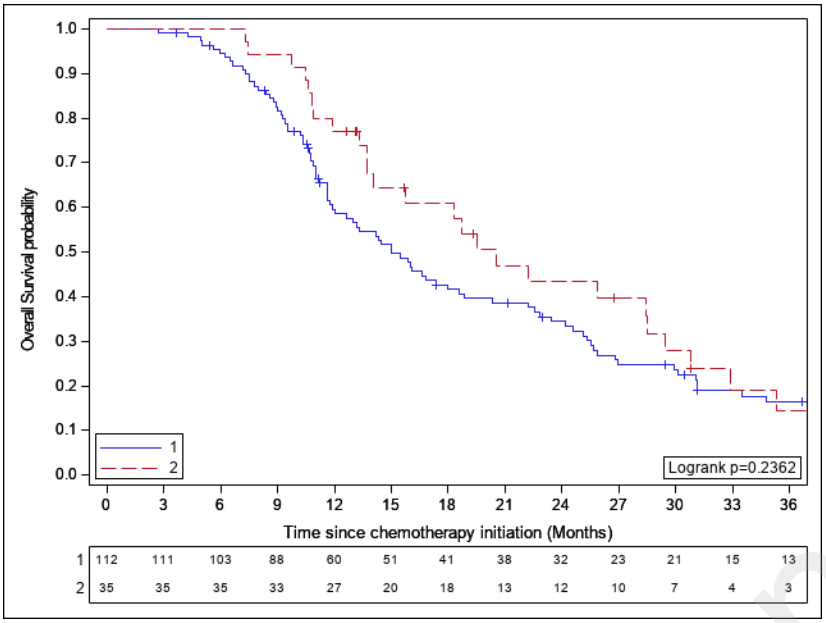
Tumor extension		
Stage at chemotherapy initiation		
Locally advanced	1.00 (Reference)	
Metastatic	1.090 (0.653 – 1.819)	0.7419
Number of metastatic sites		
0	1.00 (Reference)	
1	1.172 (0.690 – 1.991)	
≥ 2	0.924 (0.499 – 1.711)	0.5842
Lymph node metastases		
No	1.00 (Reference)	
Yes	0.876 (0.467 – 1.643)	0.6803
Liver metastases		
No	1.00 (Reference)	
Yes	1.300 (0.863 – 1960)	0.2098
Peritoneal metastases		
No	1.00 (Reference)	
Yes	0.645 (0.373 – 1.117)	0.1178
Lung metastases		
No	1.00 (Reference)	
Yes	0.940 (0.543 – 1.630)	0.8269
Other metastases		
No	1.00 (Reference)	
Yes	0.930 (0.341 – 2.538)	0.8881
Clinical parameters		

Performance status (WHO)		
0	1.00 (Reference)	
1	0.973 (0.653 – 1.452)	
≥ 2	0.888 (0.214 – 3.683)	0.9810
Body mass index, kg/m^2	1.020 (0.973 – 1.069)	0.4191
Pain		
No	1.00 (Reference)	
Yes	0.989 (0.641 – 1.524)	0.9592
Jaundice		
No	1.00 (Reference)	
Yes	0.901 (0.416 – 1.954)	0.7925
Ascites		
No	1.00 (Reference)	
Yes	1.358 (0.590 – 3.126)	0.4721
Biological parameters		
Albumin, g/L	1.006 (0.962 – 1.052)	0.7907
<35	1.00 (Reference)	
≥35	1.311 (0.615 – 2.794)	0.4837
Lymphocytes, mm^3		
<1000	1.548 (0.702 – 3.414)	0.2789
≥1000	1.00 (Reference)	
Neutrophil-to-lymphocyte ratio	0.978 (0.913 – 1.048)	0.5325
<5	1.00 (Reference)	
≥5	0.800 (0.468 – 1.368)	0.4150

CA19-9, UI/mL		
<37	1.00 (Reference)	
≥37	1.135 (0.688 – 1.872)	0.6206
Previous treatment		
Primary tumor resection		
Yes	1.00 (Reference)	
No	1.359 (0.757 – 2.441)	0.3043
Adjuvant chemotherapy		
Yes	1.00 (Reference)	
No	1.101 (0.554 – 2.190)	0.7838
Radiotherapy		
Yes	1.00 (Reference)	
No	1.658 (0.230 – 11.947)	0.6158
First-line chemotherapy		
Number of cycles of FOLFIRINOX		
<8 cycles	1.365 (0.764 – 2.440)	
8-11 cycles	1.143 (0.735 – 1.778)	
≥12 cycles	1.00 (Reference)	0.5725
RECIST best response		
Complete or partial response	1.00 (Reference)	
Stability	0.988 (0.660 – 1.479)	0.9545
Toxicity of grade 3 or 4		
No	1.00 (Reference)	
Yes	1.089 (0.715 – 1.659)	0.6915

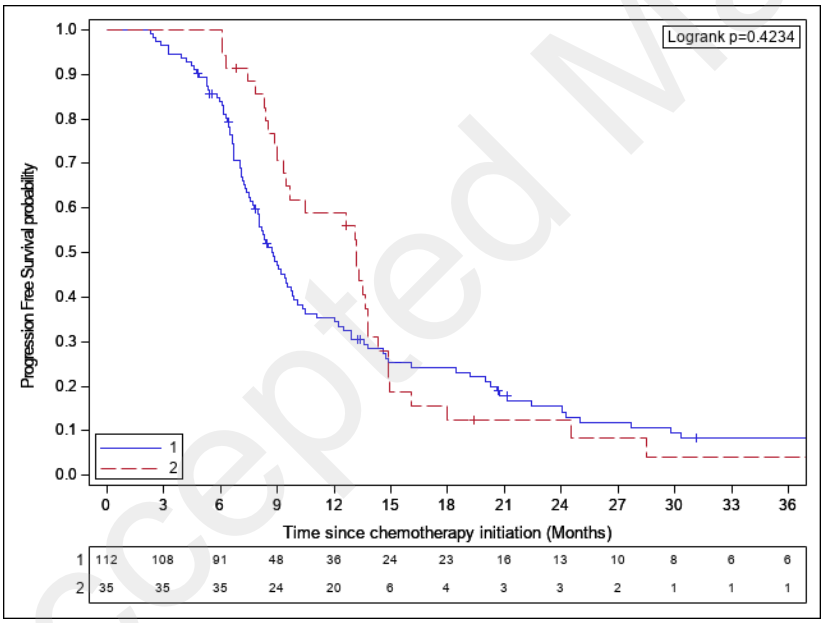
Figure S1

Overall survival



1 : <11 cycles : 15.0 [11.9-18.6]
2 : ≥12 cycles : 20.5 [13.7-28.5]

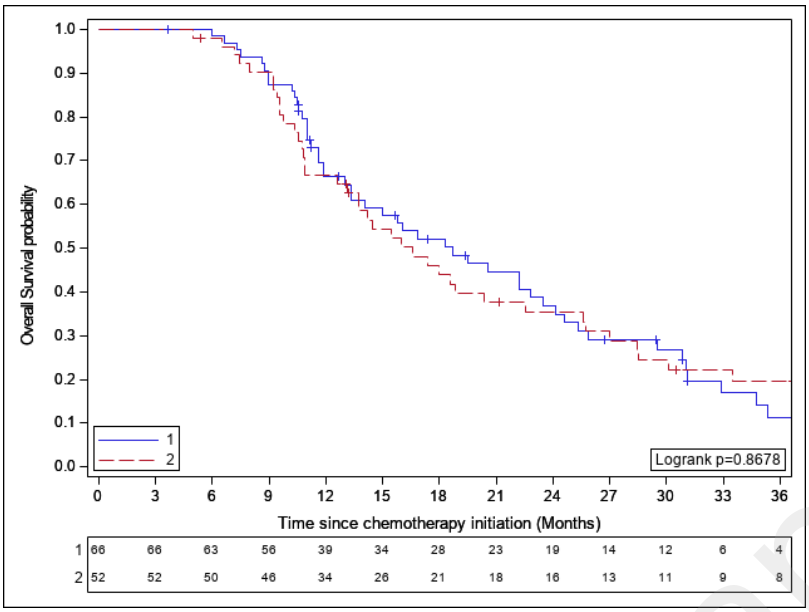
First progression free survival



1 : <11 cycles : 8.8 [7.8-9.8]
2 : ≥12 cycles : 13.2 [9.3-13.8]

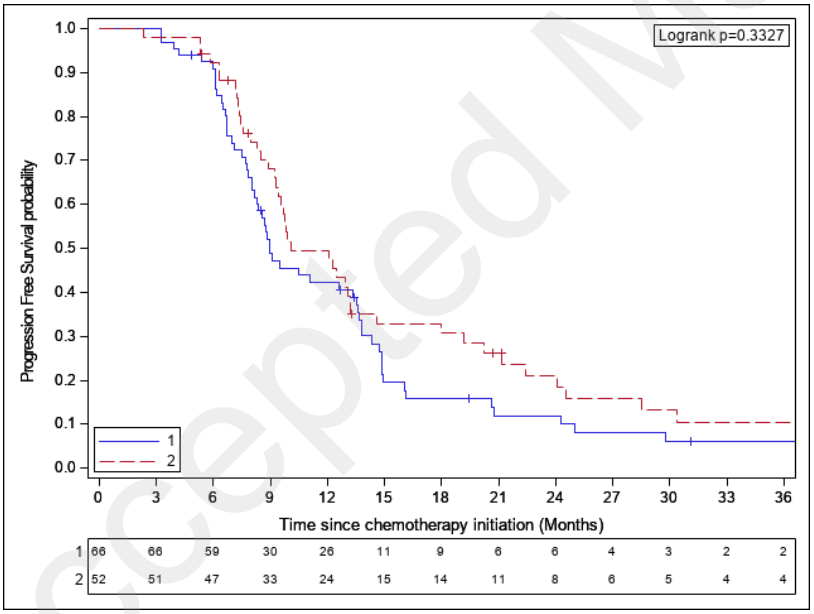
Figure S2

Overall survival



1 : FOLFIRI 16.6 [13.1-22.6]
2 : 5FU 18.7 [13.3-23.5]

First progression free survival



1 : FOLFIRI 10.1 [9.3-13.2]
2 : 5FU 9.0 [8.2-13.5]