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ORIGINAL RESEARCH

Second-Line Treatment for Advanced Pancreatic Adenocarcinoma: Is There a Role for Gemcitabine?

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Abstract

Purpose Advanced pancreatic adenocarcinoma (PA) is an aggressive disease that has poor prognosis and frequently interferes with patient's quality of life. There has been progress in first-line regimens; however, there is no standard second-line regimen. The aim of this study is to analyze second-line gemcitabine after first-line fluorouracil (FU) + leucovorin (LV) + irinotecan + oxaliplatin (FOLFIRINOX) regimen.

Methods This study included consecutive patients with advanced PA treated at Hospital Sirio-Libanês from 2011 to 2016. The patients received FOLFIRINOX as first-line treatment and upon progression, received gemcitabine alone. Survival analysis was performed using the Kaplan-Meier method.

Results A total of 54 patients were evaluated. Most patients were male (61.1%) and most had an ECOG performance status of 0 or 1 prior to the beginning of second-line treatment (66.6%). The mean number of gemcitabine cycles was 3.4. Most patients had disease progression as the best response to treatment (75.9%), 11.1% had stable disease, and 9.3% experienced a partial response. The median progression-free survival was 1.7 months, and the median overall survival was 6.8 months.

Conclusions Gemcitabine alone did not show meaningful clinical benefit as second-line treatment after FOLFIRINOX.

Keywords Gemcitabine · FOLFIRINOX · Second-line treatment · Pancreatic

Introduction

Pancreatic adenocarcinoma (PA) is one of the most lethal neoplasms of the gastrointestinal tract. At the time of diagnosis, less than 20% of the cases are resectable, and most patients harbor metastatic or inoperable disease [1]. Early detection and surgical treatment are the only curative options; however, the recurrence rate is approximately 80% and the overall 5-year survival for these patients is only 14% [1]. In the metastatic scenario or that of inoperable tumor, the disease is fatal, and even with the incorporation of new regimens in the last decade, the median overall survival (OS) remains less than 1 year [2].

Chemotherapy is a feasible option for patients with inoperable or metastatic disease, and the benefit for OS over best supportive care (BSC) is well established [3]. The clinical benefit of gemcitabine as first-line treatment was demonstrated by Burris et al. [4], and this was the preferred regimen until 2011 when Conroy et al. [2] showed the superiority of the fluorouracil (FU) + leucovorin (LV) + irinotecan + oxaliplatin (FOLFIRINOX) regimen over gemcitabine alone (median OS, 11.1 versus 6.8 months, respectively; $p < 0.001$). Later, Von Hoff et al. [5] also demonstrated that nab-paclitaxel associated with gemcitabine had better OS than gemcitabine alone (median OS, 8.5 versus 6.7 months, respectively; $p < 0.001$).

While some advances in first-line regimens were achieved in the last decade, second-line regimens have little prospective data available in the literature. Three phase III trials have evaluated second-line regimens with fluorouracil associated with either oxaliplatin or nanoliposomal irinotecan after progression on first-line gemcitabine [6–8]. However, since these drugs are frequently used today as first-line treatment with FOLFIRINOX, there is no standard second-line regimen after progression on FOLFIRINOX. Therefore, most oncologists

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use other active drugs not used in the first-line treatment, such as gemcitabine.

The aim of our study was to retrospectively evaluate the efficacy of gemcitabine as second-line treatment for patients with metastatic or inoperable PA who progressed after first-line treatment with FOLFIRINOX.

Methods

Patients

We identified, via the electronic medical records of the Hospital Sirio-Libanês-Brazil, all consecutive patients with metastatic or inoperable PA treated between June 2011 and December 2016. Patients were eligible if they had received FOLFIRINOX as first-line treatment and upon progression or intolerable toxicity, received gemcitabine as second-line treatment. Patients were required to have histologically or cytologically confirmed PA, be 18 years or older, have radiological evidence of metastatic or inoperable disease and have presented with an Eastern Cooperative Oncology Group (ECOG) status of 0–2. All patients were required to have documented progression or intolerance to FOLFIRINOX. Patients who received adjuvant chemotherapy with gemcitabine, had not relapsed during treatment, and had upon relapse received FOLFIRINOX as first-line treatment followed by gemcitabine as second-line treatment were still considered for analysis. The data on clinical characteristics, such as age, sex, and performance status and radiological data were obtained from medical records.

Treatment Regimen

FOLFIRINOX was administered in accordance with the study regimen proposed by Conroy et al. [2], which consists of a bolus of 85 mg/m^2 oxaliplatin, 180 mg/m^2 irinotecan, 400 mg/m^2 leucovorin, and 400 mg/m^2 5-FU followed by 2400 mg/m^2 5-FU given as a continuous infusion for 46 h every 2 weeks. Gemcitabine was given as 1000 mg/m^2 weekly for the first 3 weeks over a 4-week interval. The number of cycles and the rates of dose reduction or treatment interruptions were evaluated. Treatment was provided until disease progression or unmanageable toxicity occurred.

Objectives and Statistical Analysis

Our primary objective was to evaluate the median OS of patients who received gemcitabine as second-line treatment following FOLFIRINOX. Survival was defined as the time from the first dose of chemotherapy until death from any cause. Our secondary objective was to access toxicity, progression-free survival (PFS), and response rate (RR). PFS was defined from the beginning of treatment to the date when disease progression occurred or death. Surviving patients were censored at the date of last follow-up. RR was evaluated by follow-up imaging—either computed tomography scans or magnetic resonance imaging—and retrospectively assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [9]. OS and PFS were estimated using the Kaplan-Meier method. We also analyzed the efficacy of second-line gemcitabine according to the response to the FOLFIRINOX regimen. Patients with stable disease (SD) or partial response (PR) as a best response to first-line FOLFIRINOX were evaluated in one group compared with those who presented with progressive disease (PD). This study was approved by the local institutional review board and was conducted in accordance with state and federal regulations.

Data Availability The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Results

Patient Characteristics

A total of 54 eligible patients who were treated between June 2011 and December 2016 were included in our analysis. The patient characteristics are shown in Table 1. There were 21 (38.9%) men and 33 (61.1%) women. The mean age at diagnosis was 65.2 years (standard deviation, 10.3 years). By the time of diagnosis, most patients were classified as TNM stage IV disease (74%) and the rest were stage III (16.7%) or IIB (9.3%). Among those patients with stage IIB or III disease, nine were diagnosed with locally advanced and irresectable disease, and five underwent tumor resection and experienced relapse after surgery. The five patients treated with surgery received gemcitabine as adjuvant treatment and did not experience disease relapse during the adjuvant treatment. Most patients (59.3%) presented with an elevation of CA 19.9 beyond the upper limit at diagnosis. At the time of gemcitabine treatment initiation, most patients were classified according to the Eastern Cooperative Oncology Group performance status (ECOG-PS) as 0 or 1 (66.6%), and 15 (27.8%) patients were ECOG 2.

First-Line FOLFIRINOX Outcomes

All patients received FOLFIRINOX as a first-line treatment for metastatic, relapsed, or inoperable disease, and the results are shown in Table 2. The mean number of cycles of FOLFIRINOX was 9.4 with a standard deviation of 6.0. Thirty-five patients (64.8%) experienced interrupted treatment when disease progression was detected. Fourteen

Table 1 Patient characteristics ($N = 54$)

Age at diagnosis (years)	
Median	65.2
SD	10.3
Sex (No. (%))	
Male	33 (61.1)
Female	21 (38.9)
ECOG performance status (No. (%))	
0	16 (29.6)
1	20 (37.0)
2	15 (27.8)
3	0 (0.0)
NA	3 (5.6)
TNM stage group (No. (%))	
IIB	5 (9.3)
III	9 (16.7)
IV	40 (74.0)
CA 19.9 elevation (No. (%))	
Yes	32 (59.3)
No	8 (14.8)
NA	14 (25.9)
Smoking (No. (%))	
Yes	21 (38.9)
No	30 (55.5)
NA	3 (5.6)
Alcoholism (No. (%))	
Yes	11 (20.4)
No	39 (72.2)
NA	4 (7.4)

Abbreviation: *NA*, not available

Table 2 Treatment outcomes ($N = 54$)

First-line FOLFIRINOX	
Number of cycles	
Mean	9.4
SD	5.9
Reasons for treatment interruption (No. (%))	
Maximum benefit	14 (25.9)
Disease progression	35 (64.8)
Intolerable toxicity	5 (9.3)
Best response (No. (%))	
Complete response	0 (0.0)
Partial response	27 (50.0)
Stable disease	7 (13.0)
Disease progression	17 (31.5)
NA	3 (5.5)
Second-line gemcitabine	
Number of cycles	
Mean	3.4
SD	2.2
Reasons for treatment interruption (No. (%))	
Maximum benefit	2 (3.7)
Disease progression	49 (90.7)
Intolerable toxicity	1 (1.8)
Ongoing	1 (1.8)
Lost to follow-up	1 (1.8)
Best response (No. (%))	
Complete response	0 (0.0)
Partial response	5 (9.3)
Stable disease	6 (11.1)
Disease progression	41 (75.9)
NA	2 (3.7)
Dose reductions (No. (%))	
Yes	17 (31.5)
No	31 (57.4)
NA	6 (11.1)
Treatment delays for more than seven days (No. (%))	
Yes	10 (18.5)
No	37 (68.5)
NA	7 (13.0)

Abbreviations: *NA*, not available; *SD*, standard deviation

patients (25.9%) experienced interrupted treatment after a considered maximum benefit was achieved by the treating physician. Eleven of these patients were followed without any chemotherapy and started on second-line gemcitabine when disease progression was documented by imaging. Three patients were reexposed to FOLFIRINOX after a chemotherapy-free interval, and upon new progression, treatment was switched to gemcitabine. One patient who received nine cycles was reexposed to another 3 cycles of FOLFIRINOX; another patient received 12 cycles and was reexposed to another 3 cycles of FOLFIRINOX; and one patient was reexposed to another 4 cycles after receiving 12 cycles of FOLFIRINOX. Five patients (9.3%) stopped treatment because of intolerable toxicity. FOLFIRINOX was interrupted in three of these patients due to severe hematological toxicity and in two patients due to limiting gastrointestinal toxicities. The best response to FOLFIRINOX was PR in 27 patients (50%), SD in 7 patients (13%), and PD in 17 patients (31.5%). No patient had a complete response (CR).

Second-Line Gemcitabine Outcomes

The median follow-up was 13.4 months (95% CI, 7.3–19.6) since the beginning of FOLFIRINOX. The median OS with second-line gemcitabine was 6.8 months (95% CI, 2.6–11.0) (Fig. 1). The median PFS was 1.7 months (95% CI, 0.98–2.42) (Fig. 2). The mean number of cycles of gemcitabine was 3.4 with a standard deviation of 2.2. Most patients (90.7%) experienced interrupted gemcitabine because of disease progression. Two patients (3.7%) experienced

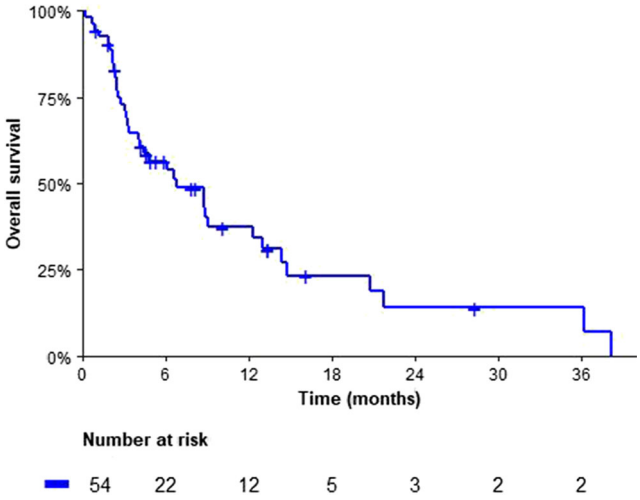

Fig. 1 Kaplan-Meier curve of overall survival with second-line gemcitabine

interruption because maximum benefit was achieved. These two patients were followed and upon progression, one patient received paclitaxel as third-line treatment and the other received a combination of capecitabine and gemcitabine. One patient (1.8%) experienced interrupted second-line gemcitabine because of intolerable hematological toxicity. Most patients (75.9%) had PD as the best response to treatment, six (11.1%) had SD, five (9.3%) experienced a PR and no patient had a CR. Seventeen (31.5%) patients required dose reductions because of toxic effects and ten (18.5%) required treatment delays of more than seven days because of adverse events (Table 2).

Five patients (9.6%) that were treated with second-line gemcitabine had used that same regimen as adjuvant treatment after radical surgery. Four of these patients had PD as the best response to treatment and only one experienced a PR. All five patients interrupted gemcitabine because of disease

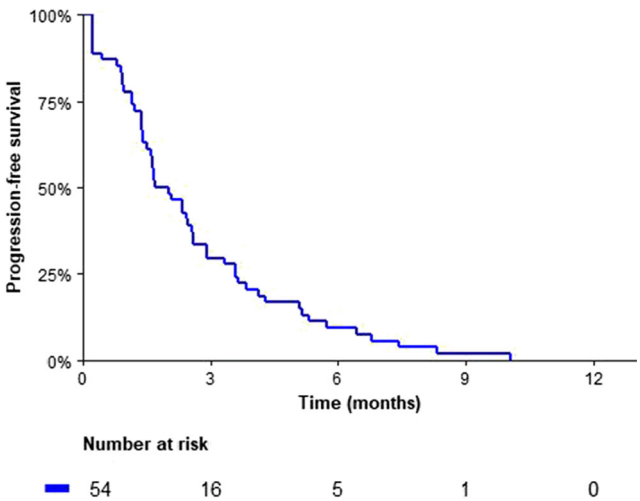

Fig. 2 Kaplan-Meier curve of progression-free survival with second-line gemcitabine

progression. We analyzed gemcitabine outcomes according to the response observed during FOLFIRINOX treatment. Patients who were refractory to FOLFIRINOX (resistant disease) had worse outcomes with gemcitabine than those who had SD or a PR with FOLFIRINOX (controlled disease) (Table 3). For those with primary resistance to FOLFIRINOX, the RR was 5.9% and the disease control (DC) rate was 11.7 versus 8.1 and 23.4%, respectively, for those with controlled disease. The median OS was higher for patients with controlled disease than for those with primary resistance (8.8 versus 3.3 months), although this difference was not significant ($p = 0.144$) (Fig. 3). The median PFS was also numerically higher, but the difference was not significant (2.0 versus 1.4 months; $p = 0.235$) (Fig. 4).

Third-Line Treatments

Twenty-five patients (46.3%) received a third-line treatment post progression on gemcitabine. Most of these patients (60%) received paclitaxel alone, three patients (12%) capecitabine alone, two (8%) a FOLFOX regimen (fluorouracil + oxaliplatin), one patient (4%) gemcitabine with nab-paclitaxel, one patient trametinib, one patient lapatinib + erlotinib, and another patient carboplatin with paclitaxel and bevacizumab.

Discussion

There is a lack of phase III trials evaluating second-line treatments for PA in the literature, and no standard regimen is consolidated. A few studies have evaluated chemotherapy regimens after failure on first-line gemcitabine: The CONKO-003 trial demonstrated that the OFF regimen, which consisted of FU and LV, associated with oxaliplatin, had better OS than FU/LV alone (median OS of 5.9 versus 3.3 months; hazard ratio (HR), 0.66, $p = 0.010$) [6]. The PANCREOX trial also evaluated the combination of oxaliplatin with FU/LV versus FU/LV alone. In contrast with the results of the previous trial, no survival benefit was observed in the combination arm for PFS (median of 3.1 months for the combination arm versus 2.9 months for the FU/LV arm; $p = 0.99$), and OS was inferior in the experimental arm (median of 6.1 versus 9.9 months; $p = 0.02$) [7]. More recently, the NAPOLI-1 trial evaluated FU/LV with nanoliposomal irinotecan versus FU/LV alone. The experimental arm had better median OS than the control arm (6.1 versus 4.2 months; HR, 0.67; $p = 0.012$), demonstrating that this combination could be an option for patients who fail gemcitabine [8].

Since the pivotal study of Conroy et al. [2], FOLFIRINOX has become the treatment of choice for patients with metastatic or inoperable PA with good performance status (PS). A few years later, Von Hoff et al. demonstrated the superiority of the combination of nab-paclitaxel with gemcitabine over gemcitabine alone

Table 3 Correlation between gemcitabine outcomes and response to FOLFIRINOX

FOLFIRINOX	Gemcitabine			
	Response rate (%)	Disease control rate (%)	mPFS (months)	mOS (months)
Controlled disease ($N = 34$)	8.1	23.5	2.0	8.8
Resistant disease ($N = 17$)	5.9	11.7	1.4	3.3

Abbreviations: *mPFS*, median progression-free survival; *mOS*, median overall survival

for first-line treatment [5]. There has been no head-to-head comparison between FOLFIRINOX and gemcitabine-nab-paclitaxel regimens. Gemcitabine alone as first-line treatment is reserved today for specific situations, such as for patients with poor ECOG-PS or older patients for whom a combination treatment is not appropriate. These changes in the first-line scenario raised questions about what the preferred second-line treatment would be. In the Conroy study, 46.8% of patients who received first-line FOLFIRINOX were exposed to a second-line treatment, and among those patients, the most common regimen was gemcitabine in 82.5%. In our country, gemcitabine alone is the most common second-line treatment after FOLFIRINOX in clinical practice.

To the best of our knowledge no prospective data have evaluated second-line gemcitabine. Our data are consistent with other retrospective studies. We demonstrated an RR of only 9.3%, a median PFS of 1.7 months and a median OS of 6.8 months. A trial published by Viaud et al. that evaluated 96 patients found a similar median PFS (2.1 months) and RR (10%) and a shorter OS (3.7 months) [10]. That trial evaluated prognostic factors and found that the ECOG-PS was significantly associated with OS (> 1 versus ≤ 1; HR = 2.40; $p < 0.0001$), which could explain why our patients had higher OS: in our trial, 66.6% of patients had an ECOG-PS of 0 or 1 prior to beginning second-line treatment versus 47% in the Viaud study [10]. Gilabert et al. described 72 patients and evidenced similar results with an RR of 11%. In this trial, the median PFS was 2.5 months and the median OS was 13.6 months for the entire cohort including OS during first-line FOLFIRINOX [11]. Sarabi et al. analyzed 42 patients and found similar results with a median of 4.5 infusions of gemcitabine yielding a DC rate after 2 months of treatment of only 26.2%. The median OS in this trial was 3.6 months [12]. Another retrospective study evaluated 20 patients and found a median PFS of 2.0 months and a median OS of 5.7 months [13].

Our results show that patients refractory to FOLFIRINOX had worse outcomes with gemcitabine than patients who experienced DC with the first-line treatment (Table 3). This observation is in accordance with the findings of Gilabert et al. [11] that showed worse OS for patients with primary resistance to FOLFIRINOX (8.6 versus 14.3 months; $p = 0.02$); however, these results differed from those of Sarabi et al. [12], which evidenced that patients with primary resistance to FOLFIRINOX had a higher probability of responding to gemcitabine (54.5% for patients with primary resistance versus 21.4% for those whose disease manifested some control (PR or SD); $p = 0.061$). To our point of view, it is unlikely that a disease that was primarily resistant to a triplet regimen such as FOLFIRINOX would be associated with a higher

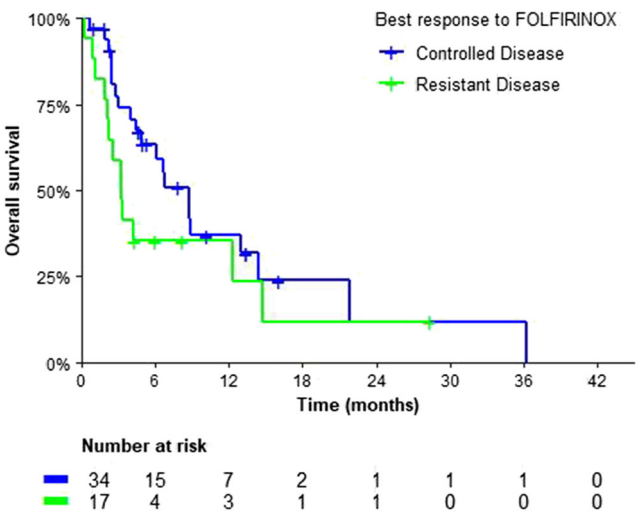

Fig. 3 Kaplan-Meier curve of overall survival according to the response observed during first-line FOLFIRINOX treatment

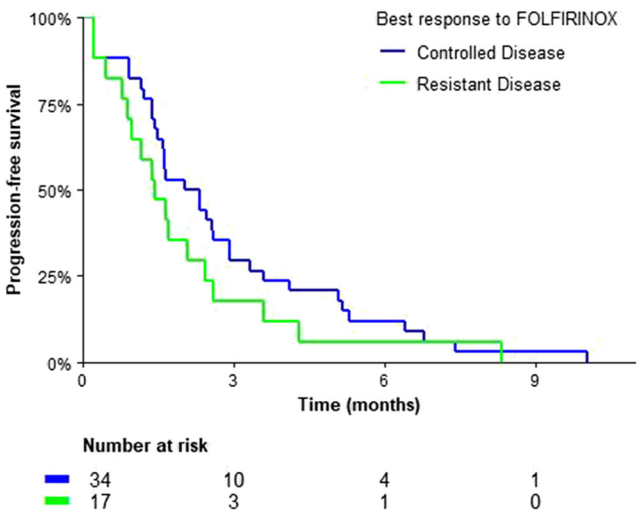

Fig. 4 Kaplan-Meier curve of progression-free survival according to the response observed during first-line FOLFIRINOX treatment

probability of benefit with gemcitabine as the second-line treatment. More intense chemotherapy regimens could be a reasonable option for patients who maintain a good PS, especially for those who were primarily resistant to the FOLFIRINOX regimen.

After the results of Von Hoff et al. [5] demonstrated that the combination of gemcitabine with nab-paclitaxel achieved better OS and RR than gemcitabine alone, some authors considered using this combination as second-line treatment. A phase II trial of the AGEO group investigated nab-paclitaxel plus gemcitabine after FOLFIRINOX failure. In this trial that selected 57 patients, the median OS was 8.8 months and the median PFS was 5.1 months. The RR was 17.5% and disease control rate was 58% [14]. Similar results were reported in retrospective trials [15–17]. Zhang et al. evaluated 28 patients and found that the time to treatment failure was 12 weeks, and the median OS was 23 weeks. The RR was 19.9% and DC was observed in 46.5% [15]. Bertocchi et al. reported data of 23 patients from a single institution and demonstrated a median OS of 5 months and disease control in 43.5% of the patients [16]. Nguyen et al. evaluated 30 patients and reported a median PFS of 3.7 months and a median OS of 12.4 months. The RR was 17%, and the CB rate was 57% [17].

We acknowledge that our study has limitations. Data collection from medical reports is subject to the quality of the information described by the medical staff. We had great difficulty collecting data on side effects of gemcitabine, and therefore, this information could not be described and analyzed in the present study. Additionally, the small number of patients and the retrospective design have certainly led to selection bias and may have influenced the results. In fact, our study has a great number of patients with an ECOG-PS of 0 and 1 (66.6%) which may have influenced the survival results and may have compromised the external validation since we would expect a smaller percentage of these patients after progression to first-line FOLFIRINOX.

In conclusion, gemcitabine alone as second-line treatment after FOLFIRINOX has shown dismal survival results and small clinical benefit. Our data showed consistency with other retrospective trials and evidenced that patients with primary resistance to FOLFIRINOX could have more aggressive disease with decreased prospects of any benefit with gemcitabine alone in a second-line setting. A more intense regimen for second-line treatment using the combination of nab-paclitaxel with gemcitabine seems to achieve better results than gemcitabine alone, and this strategy deserves to be further explored in larger and prospective trials.

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Compliance with Ethical Standards

Conflict of Interest Gustavo dos Santos Fernandes has received grants for consulting or Advisory Role from Roche, has received a speaker honorarium from Roche, has provided expert testimony for Novartis, and received travel accommodations and expenses from Roche. The rest of the authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

References

1. Popp FC, Popp MC, Zhao Y, Betzler C, Kropf S, Garlipp B, et al. Protocol of the PANCALYZE trial: a multicenter, prospective study investigating the tumor biomarkers CXCR4, SMAD4, SOX9 and IFIT3 in patients with resected pancreatic adenocarcinoma to predict the pattern of recurrence of the disease. BMC Cancer. 2017;17(1):229.
2. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25.
3. Yip D, Karapetis C, Strickland A, Steer CB, Goldstein D. WITHDRAWN: chemotherapy and radiotherapy for inoperable advanced pancreatic cancer. Cochrane Database Syst Rev. 2009;07(4):CD002093.
4. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, 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 Off J Am Soc Clin Oncol. 1997;15(6):2403–13.
5. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703.
6. Oettle H, Riess H, Stieler JM, Heil G, Schwaner I, Seraphin J, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol Off J Am Soc Clin Oncol. 2014;32(23):2423–9.
7. Gill S, Ko YJ, Cripps C, Beaudoin A, Dhesy-Thind S, Zulfiqar M, et al. PANCREOX: a randomized phase III study of 5-fluorouracil/Leucovorin with or without Oxaliplatin for second-line advanced pancreatic Cancer in patients who have received gemcitabine-based chemotherapy. J Clin Oncol Off J Am Soc Clin Oncol. 2016;34:3914–20.
8. Wang-Gillam A, Li C-P, Bodoky G, Dean A, Shan YS, Jameson G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase III trial. Lancet. 2016;387:545–57.
9. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.
10. Viaud J, Brac C, Artru P, Le Pabic E, Leconte B, Bodère A, et al. Gemcitabine as second-line chemotherapy after Folfirinox failure in advanced pancreatic adenocarcinoma: a retrospective study. Dig Liver Dis. 2017;49(6):692–6. https://doi.org/10.1016/j.dld.2017.02.007.

11. Gilabert M, Chanez B, Rho YS, Giovanini M, Turrini O, Batist G, et al. Evaluation of gemcitabine efficacy after the FOLFIRINOX regimen in patients with advanced pancreatic adenocarcinoma. Medicine (Baltimore). 2017;96(16):e6544. https://doi.org/10.1097/MD.0000000000006544.
12. Sarabi M, Mais L, Oussaid N, Desseigne F, Guibert P, Fouchardiere C. Use of gemcitabine as a second-line treatment following chemotherapy with FOLFIRINOX for metastatic pancreatic adenocarcinoma. Oncol Lett. 2017;13:4917–24. https://doi.org/10.3892/ol.2017.6061.
13. Da Rocha Lino A, Abrahão CM, Brandão RM, Gomes JR, Ferrian AM, Machado MCC, et al. Role of gemcitabine as second-line therapy after progression on FOLFIRINOX in advanced pancreatic cancer: a retrospective analysis. J Gastrointest Oncol. 2015;6(5):511–5. https://doi.org/10.3978/j.issn.2078-6891.2015.041.
14. Portal A, Pernot S, Tougeron D, Arbaud C, Bidault AT, Fouchardière C, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after Folfirinox failure: an AGEO prospective multicentre cohort. Br J Cancer. 2015;113:989–95.
15. Zhang Y, Hochster H, Stein S, Lacy J. Gemcitabine plus nab-paclitaxel for advanced pancreatic cancer after first-line FOLFIRINOX: single institution retrospective review of efficacy and toxicity. Exp Hematol Oncol. 2015;4:29.
16. Bertocchi P, Abeni C, Meriggi F, Rota L, Rizzi A, Di Biasi B, et al. Gemcitabine plus nab-paclitaxel as second-line and beyond treatment for metastatic pancreatic cancer: a single institution retrospective analysis. Rev Recent Clin Trials. 2015;10:142–5.
17. Nguyen KT, Kalyan A, Beasley HS, Singhi AD, Sun W, Zeh HJ, et al. Gemcitabine/nab-paclitaxel as second-line therapy following FOLFIRINOX in metastatic/advanced pancreatic cancer—retrospective analysis of response. J Gastrointest Oncol. 2017;8(3):556–65. https://doi.org/10.21037/jgo.2017.01.23.