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REVIEW

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Maintenance chemotherapy in advanced and metastatic pancreatic cancer, a narrative review and case series

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Abstract

Limited data exist on the management of patients with locally advanced (aPC) or metastatic pancreatic (mPC) cancer who achieve stable disease/response after first-line chemotherapy. In this setting, maintenance therapy is important to minimize toxicity while preserving survival benefits. The aim of this study is to conduct a narrative review of the evidence available on the topic and present the results of a retrospective case series of patients with aPC or mPC who received maintenance therapy following a good response to induction chemotherapy. Olaparib is the only drug approved for maintenance therapy in patients with metastatic pancreatic cancer and germline Breast Cancer gene mutation. Data from several trials, including the phase II PANOPTIMOX-PRODIGE35 trial, showed clinical benefit from the use of 5-fluorouracil (5-FU) as maintenance. We also conducted a case series including 12 patients who received FOLFIRINOX as induction chemotherapy for aPC or mPC followed by fluorouracil (5-FU) or FOLFIRI maintenance therapy. Median progression-free survival is 22.13 months which is higher than that reported in the literature, which ranges between 5 and 10.6 months. Although further conclusions cannot be drawn because of the small sample size, the results are promising and encourage further exploration of this topic in larger prospective trials.

KEYWORDS
combination chemotherapy, maintenance, maintenance chemotherapy, pancreatic neoplasms

1 | INTRODUCTION

Pancreatic cancer is the 11th most common cancer in the US, accounting for 3% of all cancers as well as the 12th most common in the world. It is also the 4th most fatal cancer, responsible for 7% of all cancer deaths in the US and is 7th in the world.[1,2] Patients most often present at a late stage, which typically worsens the disease course, and as such, pancreatic cancer unfailingly ranks last when it comes to prognostic outcomes.[3] Thus, treatment is usually not as effective, driving research toward finding new approaches. In terms of first-line management, for patients with good performance status, FOLFIRINOX/modified FOLFIRINOX (fluorouracil, oxaliplatin, irinotecan, and leucovorin) or gemcitabine plus nab-paclitaxel is currently the standard treatment plan.[4] The PRODIGE 4/ACCORD 11 randomized trial compared 171 patients taking FOLFIRINOX with 171 patients on gemcitabine. It effectively established the use of FOLFIRINOX in treating metastatic pancreatic cancer with an improved survival rate and objective response rate, and a significant reduction in quality of life (QoL) impairment when compared to gemcitabine, despite a worse toxicity profile.[5,6] These results align with those of the PRODIGE 24/ACCORD phase III trial, which found that modified FOLFIRINOX had significantly higher disease-free survival (DFS) and overall survival (OS) than gemcitabine, however with a higher incidence of adverse events and toxicity rate.[7] Moving forward, for patients who retain a good performance

status after completing a first-line treatment, maintenance therapy is usually considered as the next option for optimal disease control and QoL.[8] Maintenance therapy strategies can be broadly categorized into "continuation maintenance" or "switch maintenance".[9,10] In the continuation approach, the number of chemotherapeutic agents used for induction is reduced; an example would be FOLFIRI (fluorouracil, leucovorin, and irinotecan) or 5-fluorouracil (5-FU)/capecitabine maintenance after FOLFIRINOX. PANOPTIMOX-PRODIGE35, a phase II randomized trial, showed that the use of leucovorin plus 5-FU, after 4 months of FOLFIRINOX, was clinically beneficial for patients with metastatic pancreatic cancer.[11] In the second approach of "switch maintenance", another agent is used with a different mechanism of action, like using the poly adenosine diphosphate-ribose polymerase (PARP) inhibitor olaparib following a platinum-based regimen in patients with Breast Cancer gene (BRCA) mutations.[10] In the POLO phase III randomized trial, olaparib administration following platinum-based chemotherapy exhibited a higher progression-free survival (PFS) than placebo in patients with metastatic pancreatic cancer and a germline BRCA mutation,[12] which led to the Food and Drug Administration (FDA) approval of the drug in this setting.

The aim of this study is to evaluate the outcomes of patients with locally advanced or metastatic pancreatic cancer who received maintenance therapy following a good response to induction chemotherapy with FOLFIRINOX and present a comprehensive review of the available evidence in the literature.

2 | METHODS

This is a combined narrative review and retrospective case study. We included patients above 18 years old, diagnosed with locally advanced or metastatic pancreatic adenocarcinoma who have received induction chemotherapy for at least 8 cycles with no evidence of disease progression, followed by maintenance, between January 2014 and October 2021, at the American University of Beirut Medical Center, a tertiary care hospital in Lebanon. Patients who had disease progression on induction chemotherapy were excluded. After obtaining Institutional Review Board approval, the patients' charts were reviewed and data on the patient's characteristics, tumor characteristics, treatment, and response were collected.

Numerical variables were summarized by their mean and categorical variables were described by counts and relative frequencies. PFS was calculated from the time of starting maintenance chemotherapy to disease progression with the Kaplan Meier method using SPSS software IBM v.25.

In addition, an extensive literature search was carried out to identify all literature and systematic reviews, retrospective and prospective studies, and randomized controlled trials in the English language up to February 2022 dealing with maintenance therapies in pancreatic cancer. The following bibliographic databases were searched: PubMed, Ovid Medline, and Google Scholar were systematically investigated for English studies published in peer-reviewed journals. A combination of the following keywords was used: *irinotecan*, *antineoplastic combined chemotherapy protocols*, *fluorouracil*, *oxaliplatin*, *leucovorin*, *pancreatic neoplasms*, *maintenance chemotherapy*, *maintenance*, *QoL*, *toxicity*. Keywords were combined using the Boolean operators **OR** and **AND**. Bibliography lists from all eligible articles were also hand-searched to identify additional papers potentially relevant for inclusion. In addition, ongoing clinical trials studying the role of maintenance therapy in pancreatic cancer were identified from the official NIH website Clinicaltrials.gov.

3 | RESULTS

3.1 | Patient characteristics

Twelve patients were included in this retrospective case report. The mean age of the population was 66 years, and the mean age at diagnosis was 62 years. The majority were males. Table 1 shows the alcohol intake, smoking status, and family history of these patients.

3.2 | Tumor characteristic and treatment

Eleven patients had ductal adenocarcinoma with one signet ring subtype, and one patient had pancreatic ampullary adenocarcinoma. Ten patients had metastasis, mostly to the liver and lung, and in one patient to the bone, and two had locally advanced disease (Table 2). Five patients have undergone Whipple resection. Molecular testing was performed for three patients, and the decision was made at the discretion of their oncologists. Patient 12 only had *BRAF* gene mutations analysis and no mutations were detected. FoundationOne CDx test was performed on the tissue samples of patients 5 and 11. Patient 5 had *KRAS* G12A amplification, *CDKN2A/B* p16INK4a D84G alteration, and *TP53* V73fs*76 alteration. Patient 11 had *AKT2* amplification, *KRAS* G12C mutation, *CCNE1* amplification, *CDKN2A/B* p16INK4a E69* and p14ARF G83V alterations and *TP53* C176W alteration. All patients received FOLFIRINOX as induction chemotherapy, and the median duration was 5.13 months. Oxaliplatin was dropped for two patients because of the development of neurotoxicity. With respect to maintenance therapy, seven patients received 5-FU, four patients FOLFIRI and one patient received FOLFIRI as de-escalation from FOLFIRINOX followed by 5-FU. The median duration of maintenance therapy irrespective of the regimen used was 15.2 months. The duration of induction and maintenance chemotherapy of individual patients is presented in Figure 1.

3.3 | Survival outcomes

By the time of analysis, two of the patients have died. Six patients (including those who died) had disease progression on maintenance therapy and were switched to another line of treatment, while the rest are still receiving maintenance therapy by the time of analysis

TABLE 1 Patients' characteristics

Age at diagnosis, mean (median, years)	62 (61)
Population age, mean (median, years)	66 (67)
Gender *n* (%)	
Male	10 (83.3%)
Female	2 (16.7%)
Alcohol intake	
Yes	3 (27%)
No	8 (73%)
Smoking	
Current smoker	9 (75%)
Ex-smoker	2 (16.7%)
Non-smoker	1 (8.3%)
Family history of pancreatic cancer	
Yes	1 (8.3%)
No	11 (91.7%)
Family history of other cancers	
None	9
Breast cancer	2
Gastric cancer	1
Liver cancer	1

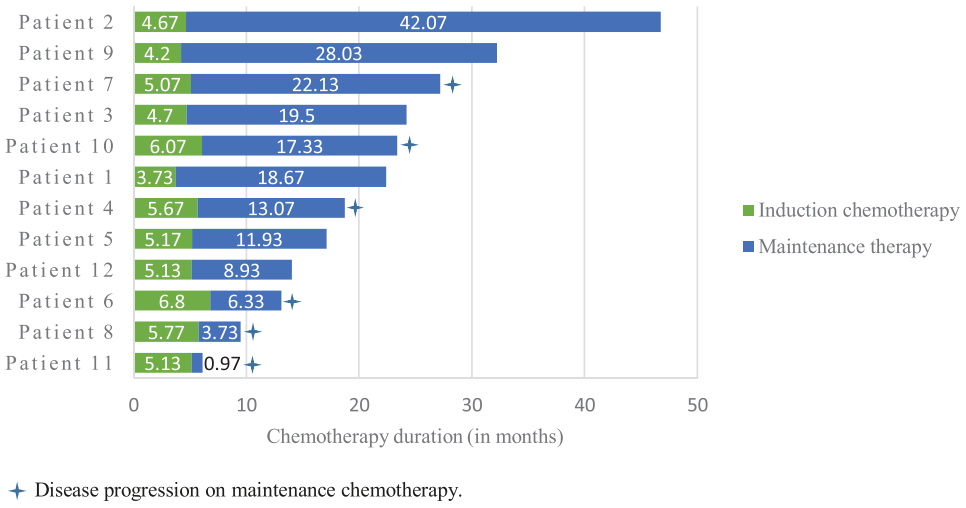

FIGURE 1 Bar graph showing induction and maintenance chemotherapy duration (months) of individual patients

(Figure 1). Three of the patients who progressed were restarted on FOLFIRINOX, one patient received gemcitabine and nab-paclitaxel, one patient received radiotherapy for local recurrence followed by palliative surgery and pembrolizumab, and one patient received radiotherapy for local recurrence then continued maintenance therapy with 5-FU. The overall median PFS was 22.13 months (95% confidence interval [CI]; 10.99–33.26). In one patient, the maximal PFS reached was 42.1 months (Figure 2).

3.4 | Narrative review of the literature and discussion

Exploring maintenance therapy strategies in advanced pancreatic cancer is gaining more attention, especially that the breakthrough of new-line therapies has produced a paradigm shift in management with improved PFS and OS, albeit at the cost of greater toxicity. Perhaps the first study implicitly implying the use of maintenance

TABLE 2 Tumor characteristics and treatments

Tumor location	
Head	9 (75.1%)
Body	1 (8.3%)
Tail	1 (8.3%)
Ampullary	1 (8.3%)
Histology	
Ductal adenocarcinoma	11 (91.7%)
Signet ring subtype	1
Ampullary adenocarcinoma	1 (8.3%)
Tumor grade	
Grade I	1 (8.3%)
Grade II	3 (25%)
Grade III	1 (8.3%)
Unknown	7 (58.3%)
T stage	
T2	1 (8.3%)
T3	4 (33.3%)
T4	3 (25%)
Unknown	4 (33.3%)
N stage	
N1	6
N2	1
Unknown	5
Disease stage	
Locally advanced	2 (16.7%)
Metastatic	10 (83.3%)
Liver	6
Lung	3
Bone	1
Induction chemotherapy	
FOLFIRINOX	12 (100%)
Maintenance chemotherapy	
5-FU	7 (58.3%)
FOLFIRI	4 (33.3%)
FOLFIRI/5-FU	1 (8.3%)

chemotherapy was published in 1985. The aim of the study was to evaluate the efficacy of adjuvant chemoradiotherapy post-Whipple procedure, and the patient in the experimental arm received two cycles of radiotherapy and 5-FU, which was continued for 2 years or until disease progression. The results showed a statistically significant longer median survival in the experimental arms compared to controls (20 vs. 11 months, $p = .03$).[13] As of 2016, studies have emerged to investigate the use of different regimens for maintenance chemotherapy in advanced and metastatic pancreatic cancer, aiming to maintain survival benefits while minimizing toxicity. Table 3 provides a summary of the studies available on this topic. In this study, we report on our experience with the use of maintenance chemotherapy for advanced/metastatic pancreatic cancer, which we started applying following the results of the PRODIGE35-PANOPTIMOX trial. All of our patients have received induction chemotherapy with FOLFIRINOX followed by maintenance with either 5-FU or FOLFIRI.

The feasibility of 5-FU/capecitabine maintenance after FOLFIRINOX induction chemotherapy was first studied by Reure et al. Maintenance capecitabine, the prodrug of 5-FU was given to 30 patients with

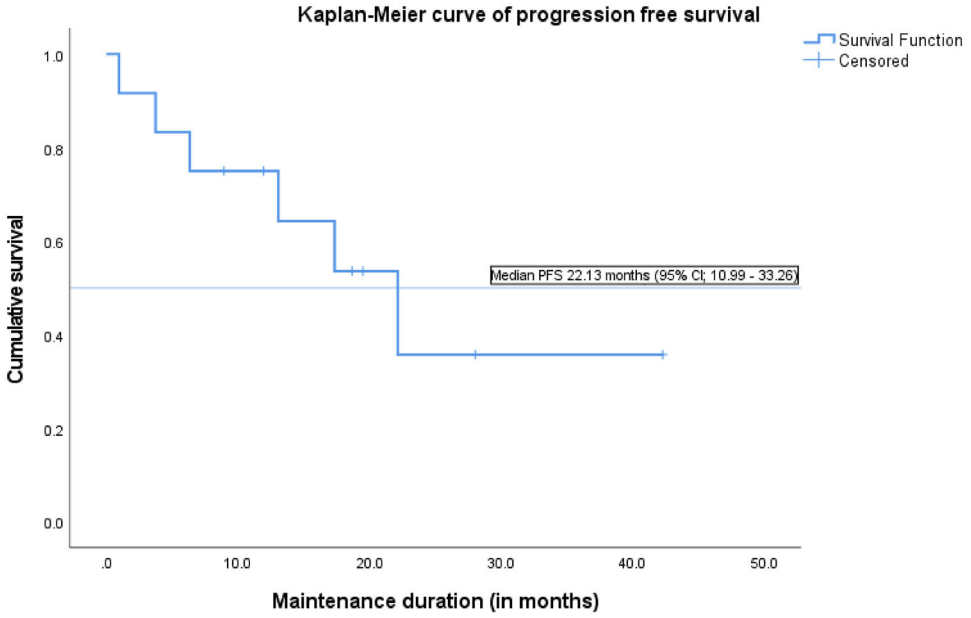

FIGURE 2 Kaplan-Meier curve of progression-free survival among patients with locally advanced or metastatic pancreatic cancer on maintenance therapy

TABLE 3 Literature review summary on maintenance therapy for locally advanced and metastatic pancreatic cancer

Study	Population	Arms/intervention	PFS 1[1] (months)	OS (months)
Dahan et al.[11]	mPC[2]	Arm A: FOLFIRINOX 12 cycles; arm B: FOLFIRINOX and 5-FU maintenance; arm C: FILGREM [3]	Arm A: 6.3; arm B: 5.7; arm C: 4.5	Arm A:10.1; arm B: 11.2; arm C: 7.33
Chevalier et al.[9]	aPC[4] and mPC	Induction with FOLFIRINOX then de-escalation to capecitabine/5-FU; FOLFIRI; FOLFOX	Capecitabine/5-FU: 10.1; FOLFIRI: 9; FOLFOX: 6.7 (p = .0265)	Capecitabine/5-FU : 16.6; FOLFIRI : 18.7; FOLFOX: 11.8 (p = .5590)
Reure et al.[14]	mPC	FOLFIRINOX followed by capecitabine maintenance	5	17
Franck et al.[16]	Non-resectable PC (aPC and mPC)	FOLFIRINOX followed by de-escalation to FOLFIRI maintenance	8	46
Hann et al.[15]	aPC and mPC	Induction FOLFIRINOX followed by 5-FU maintenance vs control (FOLFIRINOX with no other 2nd line or gemcitabine 2nd line)	Maintenance: 10.6 (95% CI; 6.7–14.4); control: 4.9 (95% CI; 3.2–6.6)	Maintenance: 18.3 (95% CI; 14.8–21.8); control: 8.7 (95% CI; 6.5–11)
Reni et al.[18]	mPC	Arm A: observation; arm B: sunitinib	6-months PFS: 3.6% for arm A and 22.2% for arm B (95% CI: 6.2%–38.2%; p < .01)	2-year OS: 7.1%(95% CI: 0–16.8%) for arm A and 22.9% for arm B (95% CI: 5.8%–40.0%; p = .11)
Golan et al.[12]	mPC with a deleterious germline BRCA mutation	Induction platinum-based chemotherapy followed by olaparib maintenance vs placebo	Olaparib group: 7.4; placebo group: 3.8 (HR for disease progression or death, 0.53; 95% CI, 0.35–0.82; p = .004)	Olaparib group: 19; placebo group: 19.2 (HR 0.83 favoring olaparib; 95% CI 0.56–1.22; p = .3487)

[1]PFS 1: progression-free survival 1.
[2]mPC: metastatic pancreatic cancer.
[3]FILGREM: fluorouracil, leucovorin, and irinotecan (FOLFIRI.3) and gemcitabine.
4PC: advanced pancreatic cancer.

metastatic pancreatic cancer whose disease was stable after FOLFIRINOX induction. Median PFS1 during capecitabine maintenance was 5 months, and 96.7% of the patients progressed.[14] In another retrospective study, Hann et al. compared the outcomes of patients with advanced or metastatic pancreatic cancer who have received 5-FU maintenance following FOLFIRINOX vs. controls (who received FOLFIRINOX with no other second-line treatment or gemcitabine second-line). PFS1 was 10.6 months (95% CI; 6.7–14.4 months) in the maintenance group, which is significantly higher compared to 4.9 months (95% CI; 3.2-6.6) in the control group, and significant survival benefit was also demonstrated with OS of 18.3 months for the maintenance group and 8.7 months for the control group. In addition, four patients had treatment pause during maintenance therapy based on their own wishes, and this did not negatively affect PFS. A possible explanation for the difference in PFS and OS between the two groups is that patients who had progressed during induction chemotherapy were not eligible to receive maintenance. Although both studies showed a similar OS, a higher proportion of patients in the study by Reure required dose reduction of capecitabine compared to 5-FU, which could account for the difference in PFS between the two studies.[15] The PANOPTIMOX-PRODIGE35 was the first randomized phase II trial that investigated the role of maintenance chemotherapy in previously untreated patients with metastatic pancreatic cancer. It included three arms; arm A received FOLFIRINOX until disease progression, arm B took FOLFIRINOX followed by maintenance with 5-FU, and arm C received sequential treatment with FILGREM (sequential treatment alternating gemcitabine and fluorouracil, leucovorin, and irinotecan every 2 months). Median PFS1 was similar between arms A and B, and shorter in arm C (6.3, 5.7, and 4.5 months, respectively), and median OS followed a similar trend. Arm C did not meet the study's predetermined efficacy threshold, and the study concluded that maintenance with 5-FU was feasible and effective in metastatic pancreatic cancer. However, neurotoxicity was higher in the maintenance arm possibly due to a higher cumulative dose of oxaliplatin. Despite this, a longer median time to deterioration of QoL was observed in the maintenance arm compared to the other two, which favors maintenance therapy.[11]

FOLFIRI was also explored as a maintenance option. Franck et al. investigated the safety and efficacy of FOLFIRI maintenance after FOLFIRINOX induction, in 22 patients with advanced pancreatic cancer. Median PFS under FOLFIRI was 8 months,[16] which is higher than the interval achieved using 5-FU/capecitabine in the two previous studies by Reure et al. and PANOPTIMOX-PRODIGE35, but lower than the PFS observed in the study by Hann et al. Chevalier et al. have conducted a real-life study in which patients with advanced or metastatic pancreatic cancer underwent treatment de-escalation from FOLFIRINOX induction to capecitabine/5-FU, FOLFIRI or FOLFOX. The study found that patients who received maintenance therapy with FOLFIRI and 5-FU had similar PFS1 and OS, but had better outcomes than those who received FOLFOX de-escalation (median PFS1 9, 10.1, and 6.7 months, respectively, and median OS 18.7, 16.6, and 11.8 months, respectively).[9] Patients' outcomes were similar to the study by Reure et al. and better than the PANOPTIMOX-PRODIGE35 trial.

In our study, we report a higher PFS compared to the literature, however, the small sample size of our population prevents us from drawing further conclusions. Molecular profiling of two patients showed that they both have *KRAS* G12C and *CDKN2A/B* alterations, which correlate with short survival in patients with pancreatic ductal adenocarcinoma.[17] The PFS of these two patients was shorter than the median of the population.

One of the important goals of maintenance therapy is to decrease the toxicity resulting from prolonged chemotherapy. Paradoxically, this was not demonstrated in the PANOPTIMOX-PRODIGE35 trial, which found a higher rate of grade 3/4 neurotoxicity in arm B (maintenance arm) compared to arm A (FOLFIRINOX arm) (19.8% vs. 10.2%, respectively). This was attributed to the higher median dose intensity of oxaliplatin in the maintenance group. Nevertheless, the median time to deterioration in the QoL score was longer in arm B because neurotoxicity occurred later compared to arms A and C, which favors the maintenance therapy.[11] The study by Chevalier et al. demonstrated higher neurotoxicity in the FOLFIRI maintenance arm compared to the 5-FU maintenance arm, the latter having mainly hematologic and gastrointestinal toxicities.[9] As for maintenance with capecitabine, the significant toxicities were gastrointestinal and dermatological. In particular, hand-foot syndrome occurred in 16.6% of the patients, and 35% required dose reduction,[14] compared to only a 9% rate of dose reduction in the infusion 5-FU maintenance study.[15]

Apart from cytotoxic agents, researchers have also explored the efficacy of targeted agents in maintenance therapy for pancreatic cancer. As an example, Sunitinib, which targets several receptor tyrosine kinases that are over-expressed in pancreatic cancer, was evaluated in the PACT-12 trial. Fifty-six patients who were disease-free after induction chemotherapy were randomized to receive Sunitinib vs. observation, until disease progression. Six-month PFS, median PFS, and median OS were higher in the Sunitinib arm compared to the observation arm.[18] Although the study population was small and highly selected, the results are promising for further evaluation of this regimen. In the phase III POLO trial, the PARP inhibitor olaparib almost doubled the median PFS compared to the placebo (7.4 months vs. 3.8 months) in 154 patients with metastatic pancreatic cancer and germline BRCA 1/2 mutation.[12] Based on these results, maintenance therapy with olaparib is now a preferred regimen by NCCN following first-line platinum-based chemotherapy in this patient population.[4]

Finally, several clinical trials are being conducted on different therapeutic agents such as PARP inhibitors, PD-1 blockers, receptor tyrosine kinase inhibitors (lenvatinib), and CXCR1/2 chemokine receptor inhibitors (SX-682) as possible maintenance therapy in pancreatic cancer (Table 4). Two studies are investigating cancer vaccines in combination with chemotherapeutic agents alone or with a PD-1 blocker (durvalumab) in patients with pancreatic cancer who achieved stable disease or response following chemotherapy. OSE2101 is a multi-epitope vaccine limited for HLA-A2 positive patients, targeting tumor-associated antigens that are expressed in pancreatic adenocarcinoma (carcinoembryonic antigen [CEA], HER2, MAGE2, MAGE3, and TP53), and has already received orphan drug designation by FDA for use in non-small cell lung cancer.[19] Another cancer vaccine that

TABLE 4 Ongoing clinical trials on maintenance therapy in locally advanced and metastatic pancreatic cancer

Study	Identifier	Actual enrollment	Intervention/Arms	Primary objective(s)	Estimated completion date
21)	NCT03806309	106 with aPC[1] or mPC[2].	Experimental arm: OSE2101 plus FOLFIRI. Comparator arm: FOLFIRI.	1 year OS in patients with SD[3] or tumor response after first-line chemotherapy.[4]	2023
22	NCT04887805	28 with aPC or mPC.	Experimental arm: pembrolizumab and lenvatinib,	PFS in patients with PR[5] or SD after first or second-line therapy.	2023
23	NCT04477343	20 patients with mPC.	Experimental arm: SX-682[6] and nivolumab.	Maximum tolerable dose in patients who completed at least 16 weeks of first-line chemotherapy.	2023
24	NCT03331562	24 patients with mPC.	Active comparator: pembrolizumab and paricalcitol. Placebo Comparator: Pembrolizumab and normal saline.	Radiologic disease progression in patients with at least PR or SD after first-line chemotherapy.	Recruitment completed, pending results.
25	NCT04300114	136 patients with mPC.	Experimental arm: fluzoparib. Comparator arm: placebo.	PFS in patients with germline BRCA1/2 or PALB2 mutation and no progression following platinum-based chemotherapy.	2022
26	NCT02184195	154 with mPC.	Experimental arm: olaparib. Comparator arm: placebo.	PFS in patients with germline BRCA1/2 mutation and no progression on platinum-based first-line treatment.	2022
27	NCT03140670	50 patients with aPC or mPC.	Experimental arm: rucaparib.	Adverse events over 4 years in patients with germline BRCA1/2 mutation and no progression on platinum-based treatment.	2023
28	NCT03376659	Eight patients with mCC[7] or PC[8].	Phase I[§]: MVA-BN-CV01 (prime), FPV-CV01 (boost), durvalumab and capecitabine.	Phase II dose of durvalumab.	2023
			Phase II[§§]: MVA-BN-CV301 (prime, FPV-CV301 (boost), durvalumab, and capecitabine.	PFS in patients with SD or response after first-line treatment.	

[1]aPC: advanced pancreatic cancer.
[2]mPC: metastatic pancreatic cancer.
[3]Stable disease.
[4]FOLFIRINOX or modified FOLFIRINOX.
[5]Partial response.
[6]Allosteric inhibitor to human CXCR1 and CXCR2 receptor.
[7]Metastatic colon cancer.
[8]Pancreatic cancer.
[§]Safety.
[§§]Pancreatic cancer experimental arm.

is being investigated is BN-CV301 which is composed of MVA-BN-CV301 prime and FPV-CV301 boost. It contains transgenes encoding for the tumor-associated antigens mucin 1 and CEA, in addition to three costimulatory molecules.[20]

4 | CONCLUSION

There are limited data to guide the management of patients with locally advanced or metastatic pancreatic cancer who achieved disease control after first-line induction chemotherapy. However, emerging studies are supporting the use of maintenance therapy with different agents that can maintain survival benefits in such patients with minimal side effects. Although so far only olaparib is approved for maintenance therapy in patients with the germline BRCA mutation, larger prospective studies are needed to validate the use of other agents such as 5-FU and FOLFIRI in non-genetically selected cases.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

FUNDING INFORMATION

No funding was required.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are stored in a secured server, in a manner that the data is not publicly available but restricted to the acknowledged study personnel as per study protocol.

ETHICS STATEMENT

The study protocol was approved by the Institutional Review Board at the American University of Beirut Medical Center.

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