Chapter

Current Systemic Treatment Options for Metastatic and Unresectable Pancreatic Cancer

Christian Caglevic, Mauricio Mahave, Cristobal Sanhueza and Luis Ubillos

Abstract

Metastatic and local advanced unresectable pancreatic cancers are lethal conditions that always carry a poor prognosis with rare exceptions. Currently, the mainstay of therapy is cytotoxic chemotherapy plus best supportive care. First-line therapy for patients with a good performance status includes FOLFIRINOX or gemcitabine plus nab-paclitaxel regimens. Patients carrying a deleterious germline BRCA mutation can be treated with maintenance olaparib after FOLFIRINOX. Patients with a poor performance status, but still fit enough for chemotherapy, may be treated with single agent gemcitabine. Second-line therapy will depend on previous therapy and current performance status. Options for patients treated with gemcitabine-based regimens are 5-fluorouracil plus leucovorin plus either nanoliposomal irinotecan, irinotecan or oxaliplatin. Patients that were treated with first line FOLFIRINOX may benefit from a gemcitabine-based chemotherapy, but evidence from randomized trials is lacking. Other options like immunotherapy and targeted therapies yield benefit only in very selected cases, and it is still an area of research.

Keywords: metastatic pancreatic cancer, unresectable pancreatic cancer, local advanced pancreatic cancer, FOLFIRINOX, nab-paclitaxel, gemcitabine, nanoliposomal irinotecan, olaparib, BRCA pancreatic cancer

1. Introduction

Advanced exocrine pancreatic cancer (PC) is one of the most lethal malignancies among all types of solid tumors. According to data from United States of America (USA) registries, 29% of the patients will debut with locally advanced disease, and 53% will have metastases at diagnosis [1]. Even in the cases when resection is feasible, long-term survival rates are among 3.9 and 9.3%, meanwhile 5 years-overall survival for stage IV is lesser than 3% [1, 2]. The late stage at presentation and the particular microenvironment characterized by predominant desmoplastic tissue and immunosuppressive cells explain why PC poses such a challenge [3].

Historically, median overall survival (mOS) for advanced stages was around 6 months when the patient was treated with gemcitabine or gemcitabine-based

combinations but new chemotherapy regimens and better understanding of the tumor biology has led to improved, yet still poor, survival [4].

Unlike other cancers, target therapy has yielded only modest benefit in PC. There are only two targeted agents than historically have got approval for metastatic or unresectable PC: erlotinib and olaparib. Erlotinib, a tyrosine kinase inhibitor (TKi) targeting the epidermal grow factor receptor (EGFR), in combination with gemcitabine, when compared with gemcitabine alone, showed a statistically significant, but clinically modest benefit in OS [5]. Just recently, the US Food and Drug Administration (FDA) approved the PARP inhibitor olaparib for PC in patients with deleterious or suspected deleterious germline BRCA mutations [6], which are present only in approximately 5% of pancreatic cancer patients.

Immunotherapy has showed great advances in melanoma and lung cancer among others, has not yield any promising results in PC. The site agnostic FDA approval for checkpoint inhibitors for mismatch repair deficient tumors (dMMR) or tumors with high microsatellite instability (MSI-H) has modest impact in PC [7], given that those abnormalities are infrequent in pancreatic adenocarcinoma.

Current research is looking for development of new drugs with different mechanisms of action in order to overcome chemotherapy resistance wishing to improve survival and quality of life in advanced PC patients.

Considering that pancreatic cancer is mainly a systemic disease we have focused this chapter in systemic treatments addressed to unrecoverable patients and we will not refer here to local treatments such as radiation therapy or chemoradiation that can be curative in a very small amount of patients but that do not have a real impact in survival in the metastatic or micrometastatic scenario.

2. First steps: chemotherapy development in metastatic or unresectable pancreatic adenocarcinoma

Earlier tested in gastric cancer by the Southwest Oncology Group the combination of 5-Fluoruracil, Adriamycin and Mitomycin C (FAM) was later assessed in advanced PC patients and published in 1980. Smith et al. reported a 37% of partial responses (PR) and 11% of stable disease (SD) among 27 patients that were treated with this regimen and had measurable disease, with a median duration of response (mDOR) of 9 months. Patients with better performance status were more likely to response (55%) and patients with Performance Status (PS)2–3 only achieved a 29% of response rate (RR) ($p < 0.15$). Median OS was higher in patients that responded (12 months) when compared with nonresponders (3.5 months) ($p < 0.01$). Myelosuppression was the most relevant toxicity reported in this trial [8].

In 1985, a multicenter phase 3 clinical trial that compared 5-Fluoruracil (5FU) alone or in combination with Adriamycin (FA) or in combination with Adriamycin plus Mitomycin C (FAM) in treating advanced pancreatic and gastric carcinoma was published. This trial that included 144 PC patients from 11 centers of the United States with advanced or metastatic adenocarcinoma of the pancreas, did not show any benefit of both combination arms when compared with 5-FU alone in terms of median OS, median time to progression (TTP), objective response rate (ORR) and parameters of palliation, however, the reported hematological and nonhematological toxicities were higher in the FA and FAM arms when compared with 5 FU alone [9]. This clinical trial led to a decreasing use of FAM regimen and for the increasing need to look for new treatments for these population of patients.

3. Gemcitabine: a new era for pancreatic cancer

One decade later, gemcitabine, a nucleoside analogue that exhibits antitumor activity, started to show promising results in PC patients.

Conducted as a phase 2 trial by former concepts, Casper et al. reported their experience of treating 44 PC patients, all of them with confirmed adenocarcinoma, not amenable to curative surgical treatment, performance status 0–1, and measurable disease (32 patients with metastatic disease and 12 patients with local advanced PC). The initial dose of gemcitabine was 800 mg/m^2 weekly for 3 weeks and 1 week off. Thirty-five patients received two or more cycles of Gemcitabine. Median TTP was 16 weeks. Five patients (11%) achieved a major response according to the radiological criteria used in the trial, the median duration of response for those patients was 13 months but only 5.6 months for all the treated population. Reported one-year survival was 23%. Most of the patients presented mild toxicity to gemcitabine including hematological, cutaneous toxicity, alopecia, nausea, vomiting and diarrhea. Some of these patients were treated with increasing doses of Gemcitabine, 1000 mg/m^2 then 1250 mg/m^2 and 2 patients up to 1500 mg/m^2; however, those last patients needed a reduction of their doses due to flu-like syndrome [4].

In a phase 3 randomized clinical trial Gemcitabine was compared head to head with 5 FU. This study included 126 patients from Canada and the United States with locally-advanced-unresectable or metastatic PC. Despite the known limited benefit of 5-FU in PC the investigators that designed the trial decided to use it as control arm instead of a placebo arm. The primary end point for this trial was "Clinical Benefit" (considering analgesic consumption, pain intensity, performance status and weight); secondary end points included response rate, time to disease progression and survival. Gemcitabine was given as a 1000 mg/m^2 intravenous regimen weekly for 7 weeks and 1 week of rest, followed by 1000 mg/m^2 weekly during 3 weeks with 1 week of rest during the rest of the treatment. 5-FU was given weekly in a fixed dose of 600 mg/m^2 intravenously. Primary end point was met, and this resulted in a positive trial achieving a clinical benefit of 23.8% in the gemcitabine arm and only 4.8% in the 5 FU arm. Median OS and TTP were 5.6 months and 9 weeks for gemcitabine arm versus 4.4 months and 4 weeks for 5FU arm, reported 12-months survival was 18 and 2% for gemcitabine and 5FU respectively ($p = 0.0025$). Among gemcitabine treated patients only a 5.4% achieved a radiological response but none from the 5 FU arm did, 39 and 19% of SD was reported for both arms. When compared responders versus nonresponder median OS was 10.7 months versus 4.8 months regardless of the treatment arm. Grade 3–4 neutropenia was higher in the gemcitabine arm (25.9% versus 4.9% for 5-FU, $p < 0.001$), No severe infections were reported in either arms but grade 3 and 4 anemia was 9.7% in gemcitabine arm and 0% in 5 FU arm, grade 1–2 fever was higher in gemcitabine arm 30.1% versus 16% for 5-FU, rashes 23.8 versus 12.9%, grade 3–4 nausea vomiting 9.5 and 3.2% versus 4.8 and 0% respectively. For both arms there were no survivors after 19 months since starting treatment [10]. This trial led to FDA to approve Gemcitabine as a first line of treatment for unresectable or metastatic pancreatic cancer in 1996.

Due to the positive results of gemcitabine in patients with advanced PC many combinations of gemcitabine-based treatments were tested looking to improve OS and progression free survival (PFS), most of them did not show improvement in overall survival as shown in HU's meta-analysis [11]: gemcitabine—5-FU combination (conducted by J. D. Berlin); gemcitabine—irinotecan combination (trials conducted by G. Rocha Lima and by G.P. Stathopoulos); gemcitabine—oxaliplatin (trials conducted by C. Louvet and by E. Poplin); gemcitabine—pemetrexed

(conducted by H Oettle); gemcitabine—exatecan (conducted by G. Abou-Alfa); gemcitabine—cisplatin (trials conducted by V. Heinemann and by G. Colucci); gemcitabine—capecitabine (conducted by D. Cunningham); gemcitabine—bevacizumab (conducted by H. Kindler); gemcitabine—cetuximab (conducted by P. Philip); gemcitabine—axitinib (conducted by H. Kindler). Gemcitabine—sorafenib combination also resulted in negative trials in terms of overall survival [12].

Despite those several negative clinical trials, a meta-analysis conducted by Ciliberto aimed to evaluate the role of gemcitabine-based combination therapy when compared with gemcitabine alone. Including more than 10.600 patients from 34 randomized trials, the combination treatments showed marginal superiority in terms of survival, overall response, and disease control rate but with higher toxicity rates mainly diarrhea, nausea, neutropenia, thrombocytopenia. One of the interpretations of the authors was that combination regimens gemcitabine-based should be reserved only for well selected patient populations [13]. In an Asiatic population study, a 3-arms clinical trial was conducted to compare gemcitabine alone, gemcitabine plus S-1 combination or S-1 alone in local advanced and in metastatic pancreatic patients. The combination arm did not show superiority when compared with gemcitabine alone, however, S-1 showed noninferiority against gemcitabine with a good tolerability profile [14].

From PC biopsies Fjallskog et al. found and reported that 55% of tumor samples studied stained positive for Epidermal Growth Factor Receptor (EGFR) [15]. In a murine model of pancreatic adenocarcinoma adding erlotinib highly inhibited gemcitabine-induced MAP kinase signaling regardless of the activation of KRAS by maintaining high levels of ERBB2 protein [16]. A multicenter phase 3 double blind international trial assessed gemcitabine plus erlotinib combination versus gemcitabine plus placebo [5]. About 569 patients with unresectable or metastatic adenocarcinoma of the pancreas, ECOG 0–2 were randomized in a 1:1 ratio to receive either gemcitabine alone or gemcitabine plus erlotinib. Gemcitabine was given intravenously 1000 mg/m^2 weekly for 7 weeks and 1 week off, then 1000 mg/m^2 weekly for 3 weeks and 1 week off during the next cycles (28 days cycle). Erlotinib was orally given in a 100 mg dose and increased to 150 mg in a Canadian cohort. The primary end point was OS, secondary end points included PFS, ORR, duration of response, correlation of EGFR expression with outcomes, quality of life and toxicity. Reported median survival and one-year survival were 6.24 months and 23% for the gemcitabine—erlotinib arm versus 5.9 months and 17% for the gemcitabine-placebo arm. PFS was improved in the combination arm. Despite these positive results in statistical terms, the clinical value was marginal and the reported toxicity significantly higher in the combination arm, including 6 deaths protocol-related all of them in patients in the gemcitabine-erlotinib arm including interstitial pneumonitis, sepsis, stroke and neutropenic sepsis. Immunohistochemical analysis and correlation with response did not show any improvement among EGFR positive patients. Interestingly, patients that developed skin rash grade 2 or higher lived longer when compared with whom did not (10.5 months for grade 2 versus 5.8 months and 5.3 months for grade 1 and 0 respectively), 1-year survival was 16% for rash grade, 0, 9% for rash grade 1 and 43% for rash grade 2 or higher ($p < 0.001$).

A German trial that compared erlotinib in combination with either capecitabine or gemcitabine as the front-line treatment for advanced pancreatic cancer patients allowing cross over after failure showed a low toxicity rate for both arms and not deaths treatment-related [17].

Despite that gemcitabine-erlotinib combination got FDA approval for metastatic or unresectable PC, considering its minimal benefit in terms of survival when compared with gemcitabine alone and also due to the higher toxicity profile of the combination, it is not considered as a "first option of treatment" in advanced pancreatic adenocarcinoma patient by different authors and international guidelines [18, 19].

4. 2020: current first-line options for the treatment of metastatic and or unresectable adenocarcinoma of the pancreas and their historical development

Based on the knowledge from preclinical assays and clinical studies that had showed synergist activity of irinotecan, oxaliplatin and 5-FU combination, a phase 1 trial assessed a regimen that combined 5-FU, leucovorin. Irinotecan and oxaliplatin [20]. This trial included 34 patients with different malignancies, 6 of them with pancreatic advanced cancer. Among pancreatic cancer patients one partial response and one complete response were achieved. For all the patients treated main grade 3–4 toxicities included 78% neutropenia (12% febrile neutropenia), 41% asthenia, 37% peripheral neuropathy, 27% diarrhea and 24% nausea and vomiting, 6% thrombocytopenia and 5% anemia. 51% of the patients required granulocyte colony stimulating factor (G-CSF).

FOLFIRINOX regimen (oxaliplatin 85 mg/m^2 + Irinotecan 180 mg/m^2 + Leucovorin 400 mg/m^2 + 5-FU 400 mg/m^2 in bolus and 5-FU 2400 mg/m^2 in 46 hours in continuous infusion) every 2 weeks was evaluated in a phase 2 French clinical trial that included 46 patients with advanced or metastatic pancreatic adenocarcinoma that had not received previous treatment (chemotherapy, radiotherapy or chemoradiation), with ages between 18 and 70 years, performance status 0–1, adequate bone marrow function, total bilirubin not superior than 1.5 times the upper normal level (UNL), AST – ALT and alkaline phosphatases <3 ULN (5 < ULN in patients with liver metastasis) and an adequate renal function were some of the selection criteria [21]. Patients with brain or leptomeningeal disease were excluded. Primary end point of the trial was response rate end according to former WHO criteria; secondary end points included safety, quality of life and clinical benefit assessment. Treatment was given until progression of disease or unacceptable toxicity for up to 6 months of chemotherapy in case of benefit. According to protocol atropine was allowed to be administered to diminish the risk of severe cholinergic syndrome in patients that presented it in a previous cycle. Antiemetic prophylaxis treatment was permitted at investigator's discretion. Loperamide was allowed for patients with delayed diarrhea and oral fluroquinolones in case that diarrhea lasted more than 2 days. After cycle 1 of treatment G-CSFs were also allowed to be used in case of need. The median of age of patients was 56 years, 65% were male and 76% stage IV B, doses reductions were indicated in the 14% of the total of cycles for all the patients. Most of delays for new cycles were due to hematological toxicities. By investigators assessment and after a median follow up of 33 months, the overall response rate was 26% (all partial responses) and 39% of patients achieved stable disease, the median duration of response was 10.4 months, PFS was 5.6 months, median OS was 10.2 months (9.5 months for metastatic patients and 15.7 months for locally advanced disease), 1-year survival was 43%. Grade 3–4 neutropenia occurred in the 52% of patients but only 4% of febrile neutropenia was reported, 8% of treated patients need hospitalization due to diarrhea, grade 3 and 4 vomiting was 20 and 17%, grade 3 and 4 asthenia was 20 and 21%, grade 2 and 3 peripheral neuropathy was 13 and 15% respectively and 7 patients were discontinued of treatment for this last toxicity. Concerning quality of life 18% of patients reported worsening and 37% reported improvement in quality of life.

By those days, the standard of care for advanced PC gemcitabine was compared head to head against FOLFIRINOX regimen in a first line of treatment, multicenter phase 2–3 clinical trial designed by the same French group [22]. About 342 patients were randomized in a 1:1 ratio to receive either FOLFIRINOX every 2 weeks at the same doses than in the phase 2 trial or gemcitabine that was given intravenously 1000 mg/m^2 weekly during 7 weeks and 1 week off, then 1000 mg/m^2 weekly

during 3 weeks and 1 week of rest. Main inclusion criteria were age 18 years or older, histologically or cytologically confirmed adenocarcinoma of the pancreas, measurable disease, ECOG 0–1 and adequate hepatic, renal and bone marrow function. Exclusion criteria included but were not limited to an age older than 76 years, previous radiotherapy for measurable lesions, brain metastases and others.

OS was the primary end point of this trial. Secondary end points included PFS, tumor response, safety and quality of life. The median number of cycles was 10 for FOLFIRINOX arm (range 1–47) and 6 for Gemcitabine (range 1–26) ($p < 0.001$). With a median follow up of 26 months median OS was 11.1 months for FOLFIRINOX arm and 6.8 months for Gemcitabine arm (HR 0.57; $p < 0.001$). Reported survival rates at 6–12-18 months were 57.6–20.6% and 6% for gemcitabine arm and 75.9, 48.4, 18.6% for FOLFIRINOX arm. According to RECIST criteria there was a 31.6% of responses among the FOLFIRINOX treated patients including 1 complete response but also 38.6% of stable disease as the best response. For the gemcitabine arm it was reported a 41.5% of stable disease and only a 9.4% of partial responses. Median PFS was 6.4 months and 3.3 months for FOLFIRINOX and Gemcitabine arms respectively (HR 0.47; $p < 0.001$). Patients that received a second line of therapy had a median OS de 4.4 months in each group since new treatment started. Grade 3 and 4 toxicities were more frequent in the FOLFIRINOX arm including neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, peripheral neuropathy and also grade 2 alopecia. ALT elevations were significatively higher among gemcitabine treated patients. 42% of the FOLFIRINOX-treated patients required G-CSF but only 5% of the patients of the gemcitabine arm. At a 6 months period 66% of gemcitabine treated patients and 31% in the FOLFIRINOX arm had a decrease in the scores of quality of life (HR 0.47; $p < 0.01$). Later reports from the same group remarked about the risk of worsening in quality of life among patients treated with FOLFIRINOX regimen when compared with gemcitabine-treated patients [23].

Based on the results of this French trial, FOLFIRINOX has shown to be superior in terms of OS, PFS and ORR, and it is currently worldwide accepted as a first line option of treatment for patients with advanced PC, however, it is necessary to remember that this regimen was approved in patients younger of 76 years old and it was assessed only in French population.

Some authors have reported their experiences in patients using some modifications of the FOLFIRINOX regimen (known as modified FOLFIRINOX or mFOLFIRINOX). Considering a significant dispersion of results among them, some retrospective analysis and meta- analysis showed similar results in terms of survival but with less toxicity when compared with the results from the pivotal study mentioned above [24]. Avoiding 5-FU bolus and using hematopoietic growth factors also seems to be safe in mFOLFIRINOX regimen when it is used in metastatic pancreatic cancer [25].

Before FOLFIRINOX was recognized as the first option of treatment for advanced disease the standard of treatment was gemcitabine. Gemcitabine has lower efficacy but a better toxicity profile when compared with FOLFIRINOX and it can still be used in the first line of treatment among patients that are not amenable to receive FOLFIRINOX or gemcitabine-nab paclitaxel combination. Nab-paclitaxel is a derivate, solvent-free, albumin bound form of paclitaxel with some relevant advantages over paclitaxel including a significant lower hypersensitivity reactions profile and a shorter infusion time. Its formulation with albumin also allows nab-paclitaxel to reach the tumor microenvironment by using endogenous albumin transport pathways [26]. A glycoprotein that has been related in the carcinogenesis of several solid tumors, SPARC (secreted protein acidic and rich in cysteine), has been found in high levels in the tumor stroma of pancreatic cancer, mainly in

peritumoral fibroblasts and it has been linked with bad prognosis. In complete resected patients 5-year survival has been reported to be worse among pancreatic cancer patients that express stromal SPARC and it might be considered as a prognostic marker [27]. Tumor stroma's SPARC seems to facilitate that nab-paclitaxel penetrates the tumor microenvironment hypothesizing that this drug may have a significant potential role in the pancreatic cancer control [28].

As earlier mentioned in this chapter, gemcitabine was combined with several other drugs looking to improve survival and quality of life in advanced PC, unfortunately those trials` outcomes were mostly negative. One exception was gemcitabine plus Nab-paclitaxel combination that is currently another recommended first-line treatment option in the metastatic setting of patients harboring adenocarcinoma of the pancreas. Comparing nab-paclitaxel with other chemotherapy agents, there is evidence of synergism in a mouse model when gemcitabine was combined with nab-paclitaxel by reducing cytidine deaminase levels that involves gemcitabine's metabolism [29].

A phase 1–2 clinical trial was conducted to define the maximum tolerated dose (MTD) of gemcitabine plus Nab-paclitaxel combination in previously untreated metastatic PC patients. The regimen was then finally defined as gemcitabine 1000 mg/m^2 plus nab paclitaxel 125 mg/m^2 weekly for 3 weeks every 28 days. Reported dose limiting toxicities were mainly neutropenia and sepsis. Outcomes from patients treated with the MTD showed a 1-year survival of 48%, with a median OS of 12.2 months and a response rate of 48%. Interestingly, as part of this trial FDG PET CT response was also assessed and showed that patients with complete metabolic response had a longer overall survival of 20.1 months versus 10.3 months in patients that did not achieve a metabolic complete response ($p = 0.01$) [30].

Von Hoff et al., following the previous phase 1–2 trial, designed an international multicenter open label phase 3 clinical trial to compare gemcitabine plus nab-paclitaxel combination with gemcitabine alone in patients with advanced PC (MPACT trial) [31]. The study arm used the same doses of gemcitabine and nab-paclitaxel suggested by the previous phase1–2 trial. The control arm, gemcitabine alone was given in a dose of 1000 mg/m^2 weekly for 7 weeks in an 8 weeks cycle (defines as protocol as cycle 1) and then 1000 mg/m^2 weekly for 3 weeks every 4 weeks. The primary end point was OS and secondary end points included PFS and ORR. Inclusion criteria included patients with a confirmed metastatic adenocarcinoma of the pancreas with measurable disease by RECIST 1.0, Karnofsky score of 70–100, chemotherapy naive (patients that received previous gemcitabine or 5-FU as radiosensitizers were allowed to participate in the trial), adequate renal, bone marrow and liver function as defined by protocol. Patients that had received adjuvant chemotherapy and patients with locally advance disease were excluded. Stratification was according to Karfnofsky score, presence or not of liver metastases and geographical region. Randomization was performed in a 1:1 ratio and the trial included 861 patients (63% from North America, 15% from Eastern Europe, 14% from Australia and 9% from western Europe). 10% of patients were older than 75 years and 8% of patients had ECOG 2. The primary end point of the trial was met, median OS was 8.5 months for the combination arm and 6>7 months for the gemcitabine alone group (HR 0.72; $p < 0.001$). 1 and 2-year survival were higher for the gemcitabine plus nab-paclitaxel combination arm (35 and 9%) arm when compared with gemcitabine alone (9 and 4%). Patients that underwent a second line of treatment lived longer if they had been treated with the combination treatment (9.4 months for gemcitabine-nab paclitaxel versus 6.8 months for gemcitabine alone, HR 0.68; $p < 0.001$). PFS, ORR and disease control rate (DCR) were also higher in the combination arm: PFS 5.5 months versus 3.7 months

(HR 0.69, p < 0.001), ORR 23% versus 7% (p < 0.001) and DCR of-16 weeks-or-longer 48% versus 33% respectively (p < 0.001). In addition, patients that had a decrease in basal CA 19–9 of 90% or more irrespective of the treatment arm live longer when compared with patients that reached a decrease of this biomarker lower than 90% (13.5 months versus 8.2 months, HR 0.53; p < 0.001). 15% of patients from gemcitabine arm and 32% of the combination arm received at least 6 months of treatment. Reported grade 3–4 toxicities were higher among gemcitabine-nab paclitaxel arm (neutropenia 38 vs. 27%, leukopenia 31 vs. 16%, fatigue 17 vs. 7%, peripheral neuropathy 17 vs. 1%, diarrhea 6 vs. 1%). Discontinuation of nab paclitaxel due to peripheral neuropathy grade 1–3 was 8% and no grade 4 neuropathy was reported. 3% of patients in the combination arm developed febrile neutropenia and 26% receipted G-CSF versus 1 and 15% for gemcitabine arm respectively. There was a 4% of fatal events in each group but sepsis and pneumonitis related deaths were more frequent among gemcitabine plus nab paclitaxel treated patients.

Un update of the long-term survival of this trial was later published [32]. The median OS for the gemcitabine-nab paclitaxel combination was 8.7 months versus 6.6 months for the gemcitabine arm (HR 0.72; p < 0.001). Patients that lived 3 years or longer was only a 4% and they all had been treated with the combination treatment. Higher CA 19–9 and neutrophil to lymphocyte ratio > 5 were associated with worse survival and there was a trend for more benefit in those poor prognosis subgroups.

The phase 2 multicenter, international, single arm LAPACT trial was addressed to assess the efficacy and safety of gemcitabine plus Nab-paclitaxel combination in patients with locally advanced, unresectable nonmetastatic, previously untreated pancreatic cancer [33]. Primary end point was time to treatment failure (TTF). This study was designed for all the patients to be treated in a "induction phase" with gemcitabine 1000 mg/m^2 plus nab-paclitaxel 125 mg/m^2 weekly for 3 weeks in a 28 days cycle for a total of 6 cycles. After this induction period, patients without disease progression, by investigator choice, were treated with the same chemotherapy regimen or chemoradiation or surgery (patients with responses before this 6 cycles period could undergo surgery without have to end the complete all pre-programmed chemotherapy treatment). Only ECOG 0–1 patients were allowed to be enrolled. A total of 106 patients were evaluable. Median TTF was 8.6 months and PFS 10.2 months. Main reasons for discontinuing treatment were adverse events (18%) and progressive disease (7%). Grade 3 or higher toxicity reported included 42% neutropenia, 11% anemia, 10% fatigue and 4% of peripheral neuropathy. Respecting to efficacy to treatment 32.7% of patients had a partial response and 57.9% stable disease as the best reported response. 43% of patients continue treatment with gemcitabine plus nab paclitaxel after induction treatment, 16% underwent chemoradiation and 15% of patients underwent surgery (n 16). Of the 16 patients that underwent surgery, 7 patients achieved a R0 resection and 9 patients a R1 resection.

This chemotherapy regimen, gemcitabine plus nab-paclitaxel combination, is currently also an option to consider for unresectable patients, with a very low curative option, in tumors that have a real minor chance to undergo a R0 resection, as it has already been already described for FOLFIRINOX and chemoradiation [34, 35].

No phase 3 clinical trial has compared the efficacy of FOLFIRINOX and gemcitabine plus nab-paclitaxel combination, for this reason selection of patients for either treatment must consider the differences between both phase 3 pivotal trials. The phase 2 trial LAPACT also provide us some information for unresectable patients that underwent gemcitabine- nab paclitaxel treatment looking for a neoadjuvant option considering that phase 3 trial MPACT only enrolled metastatic patients. MPACT trial allowed the inclusion of patients older than 75 years (10%)

and poorer performance status (8% ECOG 2), in the FOLFIRINOX phase 3 trial patients older than 75 years were not allowed and ECOG was limited to <2. Despite that FOLFIRINOX trial was a multicenter only included French sites, however, MPACT included patients from North America, Europe, and Australia.

A systematic meta-analysis aimed to answer if there is superiority of FOLFIRINOX or gemcitabine-nab paclitaxel combination in the first line of treatment for metastatic or advanced PC. Based on 16 retrospective studies that included 2123 gemcitabine plus nab-paclitaxel treated patients and 1690 FOLFIRINOX treated patients, no statistical significantly differences were found in terms of overall risk of death, PFS and RR. Toxicity was in line of the pivotal trials [36]. These results may help to conclude that despite of the numerically superiority in OS of the phase 3 FOLFIRINOX trial when it is compared with MPACT trial, and in the absence of a comparative head to head phase 3 trial for these 2 regimens, clinicians may use any of those according with their experience but also taking account of the medical conditions and biography of each patient to be treated.

BRCA 1–2 mutations have been found between the 5% and 12.8% of pancreatic cancer patients among different patient populations [6]. In a retrospective observational study that analyzed the outcomes in 71 PC patients harboring BRCA 1–2 germline mutations, OS was statistically higher among stage 3–4 patients that were treated with platinum-based chemotherapy when compared with patients that did not use platin compounds as part of their treatment (22 versus 9 months, $p = 0.039$) [37].

Recently published, the POLO study (Pancreas Cancer Olaparib Ongoing) was a phase 3 multicenter doble blinded in patients with metastatic PC and BRCA1–2 germline mutations that had received at least 16 weeks of a platinum-based palliative chemotherapy and had no disease progression during the treatment, then patients were assigned to receive olaparib (300 mg twice daily) or placebo in a 2:1 ratio [38]. The primary end point of the trial was PFS by a blinded independent central review. 154 patients were randomized (3315 patients screened). 86% of the olaparib group and 81% of the placebo group had been treated with FOLFIRINOX regimen and 2 and 5% with gemcitabine cisplatin combination, respectively. Primary end point, PFS was met showing longer median PFS among patients treated with olaparib versus placebo (7.4 versus 3.8 months, HR 0.53, $p = 0.004$), however, no benefit in overall survival was found for 18.9 months in olaparib arm and 18.1 months in placebo arm ($p = 0.68$). 23% of patients olaparib-treated had response (including 2 patients that achieved a complete response) vs. 12% in the placebo arm by blinded independent central review, with a median duration of response of 24.9 versus 3.7 months respectively. Considering that POLO trial resulted in a positive trial achieving to meet its primary end point PFS, FDA in December 2019 got the approval for the use of olaparib for the maintenance treatment of adult patients with germline BRCA-mutated metastatic adenocarcinoma of the pancreas without disease progression on at least 16 weeks of a first-line platinum-based chemotherapy regimen such as FOLFIRINOX and cisplatin-based chemotherapy. This way, olaparib became the first drug to be approved as a maintenance treatment for pancreatic cancer and currently is a new weapon to improve PFS among BRCA-mutated PC patients.

5. Second-line systemic therapy for metastatic or local advanced unresectable adenocarcinoma of the pancreas

After progression to a first-line therapy, subsequent treatment will depend greatly on the patient performance status and which drugs were or not given before.

Other factors to take in account are molecular abnormalities like dMMR/MSI-H or mutations that can be targeted (druggable mutations).

Patient that received gemcitabine-based chemotherapy as the first-line therapy can be treated with a combination of 5-FU and nanoliposomal irinotecan (nal-IRI). The phase III Napoli-1 trial showed an overall survival difference of 1.9 months (6.1 versus 4.2) when compared with 5-fluorouracil monotherapy (HR 0.67) [39]. 45% of the patients had received 5-FU treatment as a previous line, but only 10% of the patients had received irinotecan previously. A subgroup analysis showed that the benefit was maintained in patients that had received 5-FU but not in those previously treated with irinotecan. A recent update of this trial showed an estimated 1-year survival of 26% for nanoliposomal irinotecan plus 5-FU combination versus 16% for 5 FU alone [40].

Nanoliposomal irinotecan is not yet widely available. Phase two trials have shown than irinotecan plus 5-fluorouracil and leucovorin (FOLFIRI) has modest activity, but comparable to nal-Iri, in patients previously treated with gemcitabine, with an overall response rate of 15% and 35% of stable disease, time to progression 3.7 months and median OS of 6 months [41, 42]. The 2018 American Society of Clinical Oncology (ASCO) guidelines for treatment of metastatic PC endorses the use of FOLFIRI in countries were nal-Iri is not available [43].

Oxaliplatin-containing regimens such as FOLFOX or oxaliplatin plus 5-FU have yielded mixed results as a second line in this setting, with poor accrual and modest benefit. The multicenter German phase III Conko-003 trial compared OFF regimen (oxaliplatin, folinic acid and fluorouracil) against fluorouracil and folinic acid (FF) in patients that had disease progression after gemcitabine treatment. This trial resulted positive in terms of overall survival (median overall survival 5.9 months for OFF regimen and 3.3 months for FF regimen, HR 0.66 p = 0.01) and in terms of time to progression (2.9 months for OFF and 2.0 months for FF respectively, HR 0.68, p = 0.19). Reported neurotoxicity grade 1–2 was higher among OFF- treated patients (38% versus 7% in FF group) [44]. Conversely, the phase III PANCREOX trial failed to show benefit for FOLFOX as second line therapy as compared to 5FU single therapy [45]. With those results, oxaliplatin based regimens are less preferred than nal-Iri or irinotecan-based regimens, but still an option in patients who cannot receive the latter for any circumstances and are still fit and willing to pursue further therapy.

When the combination of irinotecan, oxaliplatin, leucovorin and 5FU (FOLFIRINOX) regimen is given as a first line therapy, patient in good shape could be treated with a gemcitabine-based regimen. Reports have shown feasibility of this regimen [46, 47], but there are no phase III trials supporting this recommendation. As a result, from first line chemotherapy toxicity and declined performance status, it is advisable to use an attenuated regimen in this situation, reducing doses or changing schedules to biweekly administration [48].

Patients with poor performance status, but still fit enough and willing to receive further therapy, should not receive multiagent regimens. Gemcitabine or 5-FU single drug could represent an option for those patients, given the toxicities associated with more intense regimens and modest benefit.

An analysis that included 1503 patients from 34 trials for the second line of treatment for pancreatic cancer showed a median overall survival of 6 months among treated patients and 2.8 months for patients that underwent best supportive care but no chemotherapy (p = 0.013). Patients treated with either gemcitabine or platinum-based chemotherapy showed better outcomes when compared with other regimens, reported progression free survival was 4 months versus 1.6 months (p 0.059) and reported median overall survival was 6 months versus 5.3 months (p = 0.1), respectively [49].

Immunotherapy may represent an option in a very selected group of patients. A phase II trial showed promising activity of pembrolizumab, a PD-1 blocking antibody, in gastrointestinal cancers with deficiency of mismatch repair (dMMR) or high microsatellite instability (MSI-H) [50]. These finding lead to the site agnostic FDA approval for checkpoint inhibitors for dMMR/MSI-H tumors. ASCO 2018 guidelines for metastatic pancreatic cancer recommends dMMR/MSI-H testing to all patients with metastatic PC seeking for second line therapy, although this has modest real impact in PC, given that those abnormalities are present in only percent less than one percent of the patients [7].

Multiple gene testing with next generation sequencing test can lead to the identification of potentially target therapy that can be helpful for patients with metastatic PC, but there is no trial showing clear benefit of using this strategy. There are ongoing randomize trials exploring these options, making it a better option when available.

Stromal-depleting agents such as PEGPH20 have shown promising results in a phase 2 trial in untreated patients when combining with gemcitabine-Nab-paclitaxel in high hyaluronic acid population. These results have not been reproduced when PEGPH20 has been combined with FOLFIRINOX [51].

6. Conclusions

Pancreatic cancer is one of the most lethal malignancies among solid tumors and unfortunately most of the times it is diagnosed as a metastatic or unresectable disease with null chances of cure.

First systemic treatments for advanced pancreatic carcinoma were controversial in results and poor outcomes were historically reported.

In the 90's decade gemcitabine became the standard of care for advanced disease, with a mild improve in survival and in response rates. Looking to improve survival, response rate and quality of life several gemcitabine-based chemotherapy combinations were assessed in clinical trials but most of them failed in their primary end points. Despite, gemcitabine- erlotinib combination resulted in a positive trial in statistical terms when compared with gemcitabine alone, allowing to get FDA approval, the clinical significance was poor and currently it is not a recommended treatment as a first option.

No relevant advances were reported until 2011 when a phase 3 French clinical trial in advanced PC showed that FOLFIRINOX when compared with gemcitabine improved OS and response rate in advanced PC but with higher toxicity. 2 years later, in 2013, the publication of another phase clinical trial showed that gemcitabine plus nab-paclitaxel combination was superior than gemcitabine in terms of survival and responses, including patients older than 75 years and with worse performance status (0–2) than the French trial (0–1). Nevertheless, no phase 3 clinical trials have been conducted in order to answer which treatment is better than the other. Meta-analysis that have included both treatments show that apparently both regimens are similar in efficacy.

A recent publication showed that among BRCA-mutated advanced-PC adding olaparib as a maintenance treatment, in patients without disease progression after FOLFIRINOX, improves progression free survival but until now no benefit in overall survival has been reported.

Second-line therapy will depend on previous therapy and current performance status. Options for patients treated with gemcitabine-based regimens are 5-fluorouracil plus leucovorin plus either nanoliposomal irinotecan, irinotecan or oxaliplatin. Patients that were treated with first line FOLFIRINOX may benefit from a

gemcitabine-based chemotherapy, but evidence from randomized trials is lacking. Other options like immunotherapy and targeted therapies yield benefit only in very selected cases, and it is still an area of research.

Conflict of interest

None of the authors received payments or any benefit for participating in this publication. This chapter has not been sponsored neither influenced for any pharmaceutical company, organization, or institution. Authors freely declare any personal potential conflict of interest that could be related or not with this manuscript.

Dr. Christian Caglevic: Honoraria: Andes Biotechnologies. Speaker: MSD, BMS, Lilly. Principal Investigator: MSD, GSK, Bayer, Boehringer Ingelheim, Astellas, Roche, Astra Zeneca, BMS, Novartis. Advisory and Consulting: MSD, BMS, Roche, Boehringer Ingelheim. Sponsored Educational Program (including travel, accommodations, and expenses): BMS, MSD, Roche.

Dr. Mauricio Mahave: no conflicts of interest.

Dr. Cristobal Sanhueza: Expert testimony: Tecnofarma. Travel-accommodations and expenses: Roche, Tecnofarma.

Dr. Luis Ubillos: Advisory and Consulting: Tecnofarma.

Author details

Christian Caglevic[1*], Mauricio Mahave[2], Cristobal Sanhueza[3] and Luis Ubillos[4]

1 Clinical Trials Unit, Cancer Research Department, Instituto Oncologico Fundacion Arturo Lopez Perez, Santiago, Chile

2 Medical Oncology Service, Instituto Oncologico Fundacion Arturo Lopez Perez, Santiago, Chile

3 Oncology Department, Facultad de Medicina, Clinica Alemana Santiago, Universidad del Desarrollo, Santiago, Chile

4 Medical Oncology, Hospital Britanico and Hospital de Clinicas UDELAR, Montevideo, Uruguay

*Address all correspondence to: christian.caglevic@falp.org

References

[1] Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2016. Bethesda, MD: National Cancer Institute. 2019. Available from: https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site April 2019

[2] Paniccia A, Hosokawa P, Henderson W, et al. Characteristics of 10-year survivors of pancreatic ductal adenocarcinoma. JAMA Surgery. 2015;**150**(8):701-710. DOI: 10.1001/jamasurg.2015.0668

[3] Liu Q, Liao Q, Zhao Y. Chemotherapy and tumor microenvironment of pancreatic cancer. Cancer Cell International. 2017;**17**:68. DOI: 10.1186/s12935-017-0437-3. eCollection 2017

[4] Casper ES, Green MR, Kelsen DP, et al. Phase II trial of gemcitabine (2,2′-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Investigational New Drugs. 1994;**12**(1):29-34. DOI: 10.1007/BF00873232

[5] Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada clinical trials group. Journal of Clinical Oncology. 2007;**25**(15):1960-1966. DOI: 10.1200/JCO.2006.07.9525

[6] Golan T, Sella T, O'Reilly EM, et al. Overall survival and clinical characteristics of BRCA mutation carriers with stage I/II pancreatic cancer. British Journal of Cancer. 2017;**116**(6):697-702. DOI: 10.1038/bjc.2017.19

[7] Macherla S, Laks S, Naqash A, et al. Emerging role of immune checkpoint blockade in pancreatic cancer. International Journal of Molecular Sciences. 2018;**19**(11):3505. DOI: 10.3390/ijms19113505

[8] Smith FP, Hoth DF, Levin B, et al. 5-fluorouracil, Adriamycin, and mitomycin-C (FAM) chemotherapy for advanced adenocarcinoma of the pancreas. Cancer. 1980;**46**(9):2014-2018. DOI: 10.1002/1097-0142(19801101)46:9<2014::aid-cncr2820460920>3.0.co;2-d

[9] Cullinan SA, Moertel CG, Fleming TR. PhD; et al. a comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. JAMA. 1985;**253**(14):2061. DOI: 10.1001/jama.1985.03350380077025

[10] Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. Journal of Clinical Oncology. 1997;**15**(6):2403-2413. DOI: 10.1200/JCO.1997.15.6.2403

[11] Hu J, Zhao G, Wang H-X, et al. A meta-analysis of gemcitabine containing chemotherapy for locally advanced and metastatic pancreatic adenocarcinoma. Journal of Hematology & Oncology. 2011;**4**:11. Published online 2011 Mar 26. DOI: 10.1186/1756-8722-4-11

[12] Goncalves A, Gilabert M, Francois E, et al. BAYPAN study: A double-blind phase III randomized trial comparing gemcitabine plus sorafenib and gemcitabine plus placebo in patients with advanced pancreatic cancer. Annals of Oncology. 2012;**23**(11):2799-2805. DOI: 10.1093/annonc/mds135. Epub: 05 July 2012

[13] Ciliberto D, Botta C, Correale P, et al. Role of gemcitabine-based combination therapy in the management of advanced pancreatic cancer: A meta-analysis of randomised trials. European Journal of Cancer;**49**(3):593-603.

DOI: 10.1016/j.ejca.2012.08.019. Epub: 16 September 2012

[14] Ueno H, Ioka T, Ikeda M, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. Journal of Clinical Oncology. 2013;**31**(13):1640-1648. DOI: 10.1200/JCO.2012.43.3680. Epub: 01 April 2013

[15] Fjällskog M-LH, Lejonklou MH, Öberg KE, et al. Expression of molecular targets for tyrosine kinase receptor antagonists in malignant endocrine pancreatic tumors. Clinical Cancer Research. 2003;**9**(4):1469-1473

[16] Miyabayashi K, Ijichi H, Mohri D, et al. Erlotinib prolongs survival in pancreatic cancer by blocking gemcitabine-induced MAPK signals. Cancer Research. 2013;**73**(7):2221-2234. DOI: 10.1158/0008-5472.CAN-12-1453

[17] Boeck S, Vehling-Kaiser U, Waldschmidt D, et al. Erlotinib 150 mg daily plus chemotherapy in advanced pancreatic cancer: An interim safety analysis of a multicenter, randomized, cross-over phase III trial of the 'Arbeitsgemeinschaft Internistische Onkologie'. Anti-Cancer Drugs. 2010;**21**(1):94-100. DOI: 10.1097/CAD.0b013e32833123ed

[18] Caglevic C, Gallardo J, de la Torre M, et al. Recommendations for the management of pancreatic cancer type adenocarcinoma: A consensus statement reached during the 2015 Latin American Symposium on Gastroenterological Oncology. Revista Médica de Chile. 2016;**144**(10):1305-1318. DOI: 10.4067/s0034-98872016001000010

[19] Miksad RA, Schnipper L, Goldstein M. Does a statistically significant survival benefit of Erlotinib plus gemcitabine for advanced pancreatic cancer translate into clinical significance and value? Journal of Clinical Oncology;**25**(28):4506-4507. DOI: 10.1200/JCO.2007.13.0401

[20] Ychou M, Conroy T, Seitz JF, et al. An open label phase I study assessing the feasibility of the triple combination: Oxaliplatin plus irinotecan plus leucovorin/5-fluorouracil every 2 weeks in patients with advanced solid tumors. Annals of Oncology. 2003;**14**:481-489. DOI: 10.1093/annonc/mdg119

[21] Conroy T, Paillot B, Francois E, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer -- a Groupe Tumeurs digestives of the Fédération Nationale des Centres de Lutte Contre le cancer study. Journal of Clinical Oncology. 2005;**23**:1228-1236. DOI: 10.1200/JCO.2005.06.050

[22] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. The New England Journal of Medicine. 2011;**364**(19):1817-1825. DOI: 10.1056/NEJMoa1011923

[23] Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: Results from the PRODIGE 4/ACCORD 11 randomized trial. Journal of Clinical Oncology. 2013;**31**(1):23-29. DOI: 10.1200/JCO.2012.44.4869. Epub: 03 December 2012

[24] Tong H, Fan Z, Liu B, et al. The benefits of modified FOLFIRINOX for advanced pancreatic cancer and its induced adverse events: A systematic review and meta-analysis. Scientific Reports. 2018;**8**:8666. DOI: 10.1038/s41598-018-26811-9

[25] Mahaseth H, Brutcher E, Kauh J, et al. Modified FOLFIRINOX regimen with improved safety and maintained

efficacy in pancreatic adenocarcinoma. Pancreas. 2013;**42**(8):1311-1315. DOI: 10.1097/MPA.0b013e31829e2006

[26] Kundranda MN, Niu J. Albumin-bound paclitaxel in solid tumors: clinical development and future directions. Drug Design, Development and Therapy. 2015;**9**:3767-3777. Published 2015 Jul 24. DOI: 10.2147/DDDT.S88023

[27] Murakawa M, Aoyama T, Miyagi Y, et al. The impact of SPARC expression on the survival of pancreatic ductal adenocarcinoma patients after curative resection. Journal of Cancer. 2019;**10**(3):627-633. DOI: 10.7150/jca.28660

[28] Vaz J, Ansari D, Sasor A, Andersson R. SPARC: A potential prognostic and therapeutic target in pancreatic cancer. Pancreas. 2015;**44**(7):1024-1035. DOI: 10.1097/MPA.0000000000000409

[29] Frese KK, Neesse A, Cook N, et al. Nab-paclitaxel potentiates gemcitabine activity by reducing cytidine deaminase levels in a mouse model of pancreatic cancer. Cancer Discovery. 2012;**2**(3):260-269. DOI: 10.1158/2159-8290.CD-11-0242

[30] Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: A phase I/II trial. Journal of Clinical Oncology. 2011;**29**(34):4548-4554. DOI: 10.1200/JCO.2011.36.5742

[31] Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. The New England Journal of Medicine. 2013;**369**(18):1691-1703. DOI: 10.1056/NEJMoa1304369

[32] Goldstein D, El-Maraghi RH, Hammel P, et al. nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: Long-term survival from a phase III trial. Journal of the National Cancer Institute. 2015;**107**(2):pii: dju413. DOI: 10.1093/jnci/dju413. Print 2015 Feb

[33] Hammel P, Lacy J, Portales F, et al. Phase II LAPACT trial of nab-paclitaxel (nab-P) plus gemcitabine (G) for patients with locally advanced pancreatic cancer (LAPC). Journal of Clinical Oncology. 2018;**36**(4_suppl):204-204. DOI: 10.1200/JCO.2018.36.4_suppl.204

[34] Caglevic C, Panay S, Gallardo C, et al. Neoadjuvant treatment for nonmetastatic pancreatic cancer. In: Rodrigo L, editor. Advances in Pancreatic Cancer. Chapter 9. 2018. pp. 179-194. DOI: 10.5772/intechopen.75739

[35] Caglevic C, Panay S, Reyes FC, et al. Is neoadjuvant an option for the treatment of non-metastatic pancreatic cancer patients? Gastroenterol Hepatol Open Access. 2018;**9**(5):177-179. DOI: 10.15406/ghoa.2018.09.00321

[36] Pusceddu S, Ghidini M, Torchio M, et al. Comparative effectiveness of gemcitabine plus nab-paclitaxel and FOLFIRINOX in the first-line setting of metastatic pancreatic cancer: A systematic review and meta-analysis. Cancers (Basel). 2019;**11**(4):484. Published 2019 Apr 5. DOI: 10.3390/cancers11040484

[37] Golan T, Kanji Z, Epelbaum R, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. British Journal of Cancer. 2014;**111**:1132-1138. DOI: 10.1038/bjc.2014.418

[38] Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-mutated metastatic pancreatic cancer. The New England Journal of Medicine. 2019;**381**(4):317-327. DOI: 10.1056/NEJMoa1903387. Epub: 02 June 2019

[39] Wang-Gillam A, Li CP, Bodoky 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 3 trial. Lancet. 2016;**387**(10018):545-557. DOI: 10.1016/S0140-6736(15)00986-1. Epub: 29 November 2015

[40] Wang-Gillam A, Hubnerb RA, Siveke JT, et al. NAPOLI-1 phase 3 study of liposomal irinotecan in metastatic pancreatic cancer: Final overall survival analysis and characteristics of long-term survivors. European Journal of Cancer. 2019;**108**:78-87. DOI: 10.1016/j.ejca.2018.12.007. Epub: 14 January 2019

[41] Zaniboni A, Aitini E, Barni S, et al. FOLFIRI as second-line chemotherapy for advanced pancreatic cancer: A GISCAD multicenter phase II study. Cancer Chemotherapy and Pharmacology. 2012;**69**(6):1641-1645. DOI: 10.1007/s00280-012-1875-1. Epub: 11 May 2012

[42] Gebbia V, Maiello E, Giuliani F, et al. Irinotecan plus bolus/infusional 5-fluorouracil and leucovorin in patients with pretreated advanced pancreatic carcinoma: A multicenter experience of the Gruppo Oncologico Italia Meridionale. American Journal of Clinical Oncology. 2010;**33**(5):461-464. DOI: 10.1097/COC.0b013e3181b4e3b0

[43] Sohal DPS, Kennedy EB, Khorana A, et al. Metastatic pancreatic cancer: ASCO clinical practice guideline update. Journal of Clinical Oncology. 2018;**36**(24):2545-2556. DOI: 10.1200/JCO.2018.78.9636. Epub: 23 May 2018

[44] Oettle H, Riess H, Stieler JM, 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. Journal of Clinical Oncology. 2014;**32**(23):2423-2429. DOI: 10.1200/JCO.2013.53.6995. Epub: 30 June 2014

[45] Gill S, Ko Y-J, Cripps C, et al. PANCREOX: A randomized phase III study of fluorouracil/leucovorin with or without oxaliplatin for second-line advanced pancreatic cancer in patients who have received gemcitabine-based chemotherapy. Journal of Clinical Oncology. 2016;**34**(32):3914-3920. DOI: 10.1200/JCO.2016.68.5776. Epub: 30 September 2016

[46] Nguyen KT, Kalyan A, Beasley HS, et al. Gemcitabine/nab-paclitaxel as second-line therapy following FOLFIRINOX in metastatic/advanced pancreatic cancer—Retrospective analysis of response. Journal of Gastrointestinal Oncology. 2017;**8**(3):556-565. DOI: 10.21037/jgo.2017.01.23

[47] Zhang H, Kellett C, Lambert P, Kim CA. Efficacy and tolerability of second-line nab-paclitaxel and gemcitabine after failure of first-line FOLFIRINOX for advanced pancreas cancer: A single-institution experience. Clinical Colorectal Cancer. 2018;**17**(3):e451-e456. DOI: 10.1016/j.clcc.2018.03.003. Epub: 08 March 2018

[48] Ahn DH, Krishna K, Blazer M, et al. A modified regimen of biweekly gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer is both tolerable and effective: A retrospective analysis. Therapeutic Advances in Medical Oncology. 2017;**9**(2):75-82. DOI: 10.1177/1758834016676011. Epub: 02 November 2016

[49] Rahma OE, Duffy A, Liewehr DJ, et al. Second-line treatment in advanced pancreatic cancer: A comprehensive analysis of published clinical trials. Annals of Oncology.

2013;**24**(8):1972-1979. DOI: 10.1093/annonc/mdt166. Epub: 12 May 2013

[50] Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. The New England Journal of Medicine. 2015;**372**(26):2509-2520. DOI: 10.1056/NEJMoa1500596

[51] Mohammad A. Advanced pancreatic cancer: The standard of care and new opportunities. Oncology Reviews. 2018;**12**:370. DOI: 10.4081/oncol.2018.370