Review

From First Line to Sequential Treatment in the Management of Metastatic Pancreatic Cancer

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Abstract

The current management of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) is based on systemic chemotherapy. The results of the MPACT and PRODIGE clinical trials have demonstrated that the combination of nab-paclitaxel and gemcitabine (GEM) as well as FOLFIRINOX regimen result in improvement in overall survival when compared to GEM alone. Treatment guidelines now recommend either one of these two regimens as first line treatment for fit patients with mPDAC. Because no head-to-head comparison between the two regimens exists, the selection of one versus the other is based on clinical criteria. The design and eligibility criteria of these two clinical trials are dissimilar, making the results of the MPACT trial more applicable to the general population of patients with mPDAC. In addition, the combination of nab-paclitaxel and GEM is better tolerated and easier to administer in clinical practice than FOLFIRINOX. Furthermore, when the regimens are studied in comparable patient populations the efficacy results are very similar. Nanoliposomal irinotecan plus 5FU has recently demonstrated a significant increase in efficacy rates after a GEM-based treatment. Importantly, treatment of mPDAC should now be considered as a continuum care for patients who are fit, with second and even third line treatments. Different sequential treatment algorithms are proposed based on available data. In retrospective studies, patients who were managed with GEM-based regimens followed by fluoropyrimidine-based regimens appear to have the most favorable outcome.

Key words: pancreatic cancer, metastatic disease, chemotherapy, nab-paclitaxel + gemcitabine, FOLFIRINOX, sequential treatment

Introduction

Pancreatic ductal adenocarcinoma (PDAC), one of the most lethal solid tumors, is often diagnosed at advanced, metastatic, stage. As a result, most of the patients (80–90%) are not candidates for curative surgical resection. The most common clinical factors encountered in daily practice that should be incorporated into the treatment decision-making process to optimize patient outcomes include performance and nutritional and psychological status, patient's age, pain, and other comorbidities [1-3]. Current systemic treatment of patients with metastatic (mPDAC) is based on systemic chemotherapy. During more than twenty years, single gemcitabine (GEM) was the only approved and widely used agent [4,5]. However, over the last few years, two additional effective regimens have shown

clinically meaningful and statistically significant improvement in median survival resulting in a change in first-line treatment selection [6,7]. In addition, recently, new chemotherapy regimens have significantly improved survival in second line treatment [8,9]. The availability of different treatment options, which obviously represents an important advance, also creates uncertainty as which regimen(s) should be recommended for specific clinical situations. To address these issues, and supported by professional societies or working groups, a series of clinical guidelines have been issued [10-13].

This article reviews the different treatment options available for mPDAC patients. A thorough revision of the literature evidence as well as experts´ opinion regarding sequential treatment algorithms is also presented. The manuscript is the result of the GALLgo project, an experts´ consultant initiative carried out by the ECO Foundation.

Treatment recommendations based on European and American Medical Oncology Societies

Table 1 compares the recommendations made by the European Society of Medical Oncology (ESMO), NCCN (National Comprehensive Cancer Network), ASCO (American Society for Clinical Oncology) and SEOM (Sociedad Española de Oncología Médica) Guidelines, based on performance status (Eastern Cooperative Group Performance Status, ECOG) and other criteria. These recommendations are based on expert assessment in which the level of evidence is based on available information using standardized criteria. Experts agree that before systemic treatment is initiated it is important to resolve bile and duodenal obstruction by endoscopic stent placement as well as to have adequate pain control and nutritional status.

ESMO Guidelines recommend that patients with advanced PDAC and ECOG 0 or 1 should receive first-line treatment with either the combination of gemcitabine (GEM) and nab-paclitaxel or FOLFIRINOX [10]. As discussed below, both of these regimens have shown improvement in overall survival (OS) in randomized phase 3 studies (IA). Patients with ECOG 2 and/or bilirubin levels > 1.5 upper normal limit (UNL) should be treated with single agent GEM (IA) [14]. However, the combination of nab-paclitaxel and GEM is recommended for patients in whom the ECOG 2 is a consequence of high tumor burden (IIB). The role of other combinations based on GEM, including GEM and erlotinib, is less clear due to the clinical significance in increase in median survival of only 14 days [15,16]. For patients with ECOG 3 and 4 the recommended treatment is palliative care. For patients with DNA damage repair deficits (*BRCA* mutations) or acinar type tumors, due to a higher probability of response rate, the recommended treatment is platinum analogs [10].

Table 1. ESMO, NCCN, ASCO AND SEOM guidelines [10-13].

GUIDELINES	ECOG 0-1	ECOG 2	ECOG 3-4	OTHERS
ESMO [10]	Nab-paclitaxel + GEM (IA) or FOLFIRINOX (IA)	ECOG 2 or bilirubin levels >1.5 UNL: GEM (IA) ECOG 2 as consequence of high tumor burden: Nab-paclitaxel + GEM (IIB)	Palliative Care	*BRCA* mutations o acinar type tumor: Platinum salt treatment or platinum analogs combinations
NCCN [12]	Combination of nab-paclitaxel + GEM (category 1) or FOLFIRINOX (category 1) or Other options**	GEM (category 1) KPS ≥ 70: Combination of nab-paclitaxel + GEM (2A)	Poor performance status: GEM (category 1) or Palliative Care	
ASCO [13]	ECOG 0-1 and: Favorable comorbidity profile: FOLFIRINOX (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong) Relatively favorable comorbidity: Combination of nab-paclitaxel + GEM (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong)	ECOG 2 or a comorbidity profile that precludes more-aggressive regimens and who wish to pursue cancer-directed therapy: GEM or GEM + erlotinib or capecitabine (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate)	ECOG ≥ 3 or with poorly controlled comorbid conditions despite ongoing active medical care: They should be offered cancer-directed therapy only on a case-by-case basis. The major emphasis should be on optimizing supportive care measures (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).	
SEOM [11]	and < 75 and fit: Combination of nab-paclitaxel + GEM (IA) or FOLFIRINOX (IA)	or fit > 75 years: Combination of nab-paclitaxel + GEM (IIB) or GEM (IB)	or frail patients: Best supportive care	*BRCA* or *PALB2* mutations: Platinum-based treatments

*GEM: Gemcitabine; KPS: Karnofsky performance status; ** Other options: GEM + erlotinib (category 1); GEM-based combination therapy; GEM (category 1); Capecitabine or continuous infusion 5FU (category 2B); fluoropyrimidine + oxaliplatin (category 2B)

The NCCN guidelines recommend that patients with ECOG 0-1 participate in a clinical trial and if not feasible, either FOLFIRINOX or the combination of nab-paclitaxel + GEM (category 1) as preferred options but it also include other GEM-based combinations including GEM and erlotinib as category 1, although with a very limited benefit [12]. The combination of nab-paclitaxel + GEM is a reasonable treatment option also for patients with Karnofsky performance status ≥ 70. For patients with poor performance status (PS), the recommended treatment is either GEM (category 1) or palliative care.

The ASCO guidelines further recommend FOLFIRINOX for patients with a favorable comorbidity profile who prefer aggressive treatment and have the support system for such aggressive medical therapy while the combination of nab-paclitaxel + GEM is recommended for patients with relatively favorable comorbidity profile who prefer and have the support system for relatively less aggressive medical therapy [13]. The combination of nab-paclitaxel + GEM is less strict with regards to hematological parameters, age and PS requirements, compared to FOLFIRINOX.

Table 2. Algorithm for first line treatment for mPDAC, based on patients´ characteristics [18].

Patient´s characteristics	First line treatment recommendations
Candidates suitable for chemotherapy treatment WITHOUT limitations:	Nab-paclitaxel + GEM (IA)
ALL ítems should be met:	or
* ECOG 0-1	
* Age ≤ 75 years	FOLFIRINOX (IA)
* Bilirubin ≤ 1.5 UNL	
* Good nutritional status	
* Lack of comorbidities	
Candidates suitable for chemotherapy WITH limitations:	**ECOG 2:**
At least ONE of the ítems should be met:	Due to tumor burden: Nab-paclitaxel + GEM
* ECOG 2	Due to comorbitides: Nab-paclitaxel + GEM or GEM
* Age > 75 years	
* Mild to moderate organ dysfunction:	
- Neurological, endocrine-metabolic, renal	
- Non-obstructive reversible (dose adjustment) liver dysfunction (hyperbilirubinemia):	
> Non tumor induced (prior liver disease): Bilirubin levels: 1.5 - 3 mg/dL	
> Tumor induced (obstructive jaundice or liver infiltration): Bilirubin levels: 1.5 - ≤ 5 mg/dL	
- Cardiac dysfunction	
* Recent VTD	
* Malnutrition/tumor cachexia	
Candidates NOT suitable for chemotherapy:	* Support treatment in Palliative Care Unit
The presence of AT LEAST ONE of the following factors:	
* ECOG 3-4	
* Severe organ dysfunction	
- Neurological, endocrine-metabolic, renal...	
- Liver dysfunction (hyperbilirubinemia):	
> Non tumor-induced (prior liver disease): > 3 mg/dL	
> Tumor-induced (obstructive jaundice or liver infiltration): > 5 mg/dL	

SEOM guidelines also incorporate age and fitness in the decision making algorithm [11]. Thus,

patients with ECOG 0-1, age < 75 years and fit can be treated with either FOLFIRINOX or the combination of nab-paclitaxel + GEM. Patients with ECOG 2 or those who are fit but age > 75 years should be treated with the combination of nab-paclitaxel + GEM or GEM alone. For patients with ECOG 3-4 or frail the recommended approach is best supportive care [11]. Platinum based treatments are recommended for patients with *BRCA* or *PALB2* mutations [17].

In addition, a recent Spanish consensus has also reviewed the different therapeutic options in mPDAC based on patient's characteristics [18]. As shown in **Table 2**, for those patients that are candidates for chemotherapy treatment with no limitations, treatment options include nab-paclitaxel + GEM or FOLFIRINOX. However, for those patients that are candidates for chemotherapy treatment with limitations, treatment options include the combination of nab-paclitaxel + GEM (ECOG 2 due to tumor burden) or either the combination of nab-paclitaxel + GEM or GEM monotherapy (ECOG 2 due to comorbidities). Finally, for those patients that are not candidates for chemotherapy treatment, the only option is support treatment in Palliate Care Units [18].

MPACT vs PRODIGE in routine clinical practice

As mentioned above and for the most part, systemic treatment of patients with mPDAC is currently based on the results of two randomized clinical trials that compared first-line FOLFIRINOX or the combination of nab-paclitaxel + GEM versus GEM and demonstrated a statistically significant improvement in median OS, the primary aim of both studies [6,7]. As summarized in **Table 3**, median OS of patients treated with FOLFIRINOX compared to GEM in the PRODIGE study was 11.1 months vs. 6.8 months, respectively [7]. The combination of nab-paclitaxel + GEM resulted in an improvement in median OS (from 6.7 months to 8.7 months) compared to GEM [6]. However, these two regimens (the combination of nab-paclitaxel + GEM and FOLFIRINOX) have not been compared head to head and therefore, it is not known which one, if any, is better.

In routine clinical practice the key issue is to select, from available options, the regimen that better suits individual patients. In making this selection, a number of factors need to be considered. The clinical trial population is indeed a patient sample from the overall patient population and the goal is to apply the results from the sample to the population. Factors to consider include ECOG PS, age, disease extent, comorbidities, nutritional status, patient´s preferences, family support, efficacy of the regimen,

tolerability, treatment sequence, and finally treatment goals.

Table 3. MPACT and PRODIGE studies: Comparison of study characteristics, demographics, outcome, safety and treatment administration [6,7].

	MPACT	PRODIGE
Study Characteristics		
Study design	Phase III	Phase III
Number of patients	861	342
Continents	3	1
Countries	11	1
Number of centers	151	48
Statistical Power	90 %	80 %
Centralization	Yes	No
Demographic Characteristics		
Age (range)	62 (27-86)	61 (25-76)
ECOG		
0	16 %	37 %
2	8 %	1 %
Head of Pancreas	44 %	39 %
Biliary Stent	19 % (no limitation)	16 % (preferably not)
Median Metastatic Sites	3 or +	2
CA 19.9 > 59 x UNL	52 %	41.5 %
Outcome		
OS (median, months)	8.7	11.1
% patients alive		
12	35	48.4
18	16	18.6
24	10	NR
42	2	NR
Response Rate (%)		
Investigator assessment	29	31.6
Central review	23	NR

*OS: Overall survival

Table 4. MPACT trial: Median survival in different populations [21,24].

Populations	
	MPACT median survival
Population < 65 years	**9.6 months**
KPS of 90-100%	9.7 months
KPS of 100%	12.6 months
Western European countries	10.7 months
	YOSEMITE median survival
ECOG 0-1	Not reached in the control group (> 13.2 months in the experimental arm)

When comparing the design and population enrolled in both studies there are important differences that can affect the results achieved. **Table 3** provides a comparative summary of study design, patients´ characteristics and outcome of the studies. Multiple factors, such as age and PS, can affect outcome: For example, in the MPACT trial, the median survival of patients with KPS of 90-100% was 9.7 months [19]. In addition, the median survival with KPS 100% was 12.6 months. Likewise, patients with only one metastatic site survived 13.5 months [20]. An analysis of survival in patients from Western European countries showed 10.7 month median survival [21]. Finally, in the population < 65 years old the median survival was 9.6 months (**Table 4**). While

the studies are similar with regards to median age, gender, stage of disease and liver involvement, the percentages of elderly patients, those with high tumor burden, and those with ECOG 2 were higher in the MPACT trial. Hence, while the results with MPACT are inferior numerically, patients´ status was worse, and the results therefore are more generalizable and convenient. Recent practice patterns analysis in the US shows that the combination of nab-paclitaxel + GEM is progressively becoming the most frequently used regimen [22].

Both regimens resulted in improvement in quality of life. In the PRODIGE study, patients treated with FOLFIRINOX had a significantly lower rate of deterioration [23]. Likewise, patients with good performance status treated with the combination of nab-paclitaxel + GEM in the MPACT trial were more likely to maintain a high functional status as compared to those treated with GEM alone [24]. The combination of nab-paclitaxel + GEM treatment resulted in a 20.7% improvement in quality of life adjusted survival in mPDAC patients [25]. In addition, as discussed below, the combination of nab-paclitaxel + GEM was better tolerated in terms of toxicity (**Table 5**).

Table 5. MPACT and PRODIGE studies: Most significant toxicities [3,4].

	MPACT	PRODIGE
Fatigue	17%	23.6%
Diarrhea	6%	12.7%
Vomiting	-	14.5%
Neuropathy	17%**	9%
Ischemic cardiopathy	No limitations	Limitations (probably)
Biliary prothesis	No limitations (19%)	Preferably no biliary stent (15.8%)
VTE	No limitations	Increases VTE risk (PTE: 6.6%)
Anemia	13%	7.8%
Thrombopenia	13%	9%
Febrile neutropenia	3%	5.4%

*VTE: venous thromboembolic events; PTE: Pulmonary thromboembolism
** In the GEM + nab-paclitaxel group, the median time to the first occurrence of grade 3 neuropathy was 140 days, and the median time to improvement from grade 3 to grade 2 was 21 days and to grade 1 or resolution of the event was 29 days. Of the patients who had grade 3 peripheral neuropathy, 44% resumed treatment at a reduced dose of nab-paclitaxel within a median of 23 days after the onset of a grade 3 event.

Recently, several retrospective studies have analyzed the toxicity and efficacy of these regimens in daily clinical practice. A study that analyzed the median survival of patients treated with GEM based on their eligibility to receive either FOLFIRINOX or the combination of nab-paclitaxel + GEM showed that eligible patients had better survival than those that were not [26]. Thus, candidates to receive FOLFIRINOX had a median survival of 8.6 months vs. 4.7 months for those that were not fit to receive FOLFIRINOX ($p < 0.001$). Likewise, OS for candidates to receive the combination of nab-paclitaxel + GEM was 6.7 months compared to 4.9 months for those who

were ineligible (*p* = 0.008). Overall, double number of patients (45.2%), were potentially eligible for the combination of nab-paclitaxel + GEM vs. for FOLFIRINOX (24.7%). Poor ECOG (PS ≥2) and age (> 76 years old) were the main limiting factors for FOLFIRINOX eligibility [27]. Furthermore, in an analysis of 2,422 patients with advanced PDAC treated in routine clinical practice in the US, the median OS for FOLFIRINOX treated patients was 11.2 months vs. 10.2 for the combination of nab-paclitaxel + GEM [27]. Time to treatment discontinuation was similar in patients treated with FOLFIRINOX vs. the combination of nab-paclitaxel + GEM in community oncology settings while the overall incidence of grade 3/4 toxicity was higher (95% vs. 84%), in particular diarrhea (15% vs. 9%), and dehydration (21% vs. 14%) [28]. Thirty nine percent of FOLFIRINOX treated patients vs. 8% of patients treated with the combination of nab-paclitaxel + GEM required G-CSF support [28]. In addition to the results of retrospective studies and analysis of routine clinical practice, another evidence to support the efficacy of nab-paclitaxel + GEM comes from the analysis of recent randomized clinical trials in which the regimen was selected as the control arm. For example, the Yosemite study, recently presented, compared nab-paclitaxel and GEM with combinations of this regimen with demcizumab, an inhibitor of the DLL4 notch ligand. The overall results of the study were negative and the combination treatment did not improve the outcome of the patients. While the reasons for this negative results are not known, an interesting observation is that in this highly selected group of patients, the combination of nab-paclitaxel and GEM showed very encouraging results with an overall response rate of 41.2%, 70.6% overall clinical benefit, and PFS of 5.49 months. OS, that was 13.24 months for the experimental arm, had not been reached in the control arm at the time of the last update. A number of randomized studies in highly selected patient populations using nab-paclitaxel and GEM as the control arm are now being conducted and their results, that will be presented in the near future, will provide additional support of the role of nab-paclitaxel and GEM in highly selected patients with advanced PDAC [29].

Interestingly, elderly patients treated with the combination of nab-paclitaxel + GEM or who received the combination of nab-paclitaxel + GEM in routine clinical setting do not have worse outcome in retrospective studies but develop more toxicity including hematological toxicity, neurotoxicity, and fatigue [30,31]. No differences in survival were observed in patients with ECOG 2 or bile stents either [32].

FOLFIRINOX regimen has shown to have similar efficacy in patients > 70 years compared to younger patients in small studies, achieving OS of 11.6 and 11 months, respectively [33,34]. However, as mentioned above, and discussed below, FOLFIRINOX is associated with substantial grade 3 and 4 toxicity events. For that reason, the practical application of the published regimen is not clear. In a retrospective study of 224 patients treated with FOLFIRINOX, less than half of the patients received the full dose, almost half of the patients did not receive the 5-fluorouracil (5FU) bolus and 25% received < 70% of the full dose. In addition, 40% required G-CSF support [35].

Recent studies with modified schemas of FOLFIRINOX have shown good results with regards to OS [36-38]. The results of a retrospective study that analyzed the outcome of 137 PDAC patients treated with modified FOLFIRINOX show that those who had two or more risk factors (liver metastases, PS1 and lymphocyte ratio > 4) had a significantly lower OS (7.4 months) compared to those with one or none risk factors (11.1 vs. 17.6 months, respectively) [39]. Another retrospective study analyzed the use of FOLFIRINOX in daily clinical practice in 292 PDAC patients in Italy [40]. The results showed that 70% of the patients had ECOG 0, 9% had stage I-II and 30% of the patients had locally advanced disease. With regards to OS, those patients treated with the modified schema had a significantly longer OS compared to regular FOLFIRINOX (18 vs. 12 months) [40].

In another retrospective study, conducted on Japanese population, that compared a modified FOLFIRINOX regimen vs nab-paclitaxel + GEM in 135 patients with similar baseline characteristics showed that nab-paclitaxel + GEM resulted in higher response rate (39% vs. 27%), median OS (14 months vs. 11.5 months) and one-year survival (67% vs. 44%), and a similar toxicity profile [41].

The impact of dose modification on the combination of nab-paclitaxel + GEM has been less studied. However, the limited evidence available suggests that tolerability is similar, regardless of age, PS, as well as the presence of biliary stent. Thus, a phase 2 study of 47 patients treated with full dose of the combination of nab-paclitaxel + GEM in a biweekly schedule reported an overall median survival of 11.1 months, with only 10% grade 3-4 neutropenia and 6% grade 3-4 fatigue [42].

The exploratory analysis conducted by Scheithauer *et al.* in the MPACT trial suggested dose reductions and delays were effective when necessary to ameliorate toxicity allowing greater treatment exposure without compromising efficacy [43]. In addition, patients with biliary stent treated with the

combination of nab-paclitaxel + GEM appeared to have same outcome in retrospective studies [44].

One important clinical question is the most appropriate regimen for patients who have received adjuvant treatment with GEM after resection of a localized tumor and subsequently develop disease progression. An analysis of 90 of such patients who received the combination of nab-paclitaxel + GEM after relapse showed a median OS of 15 months. Survival changed with the disease free interval (DFI) and increased from 8.7 months in patients DFI < 6 months to 16.3 months in those with DFI > than 12 months [45].

Tolerability

An important consideration when selecting a treatment regimen is the expected frequency and severity of side effects. The occurrence of side effects is related to the patient baseline characteristics and comorbidities such as age, ECOG, and bile duct stent among others. In addition, it is also crucial to gauge the impact that any given toxicity could have in the patient overall health status; appropriate preventive measures; access to care should an event occur as well as to provide a concrete and well detailed plan on how to manage events should they occur. **Table 5** provides numerical information of the most relevant toxicity events reported with these regimens [6,7]. In this section venous thromboembolic events (VTE), cardiac toxicities and gastrointestinal complications will be reviewed.

The French physician Jean-Baptiste Bouillaud reported the association between cancer and VTE in 1823 [46]. It has been shown that cancer patients have a 4 to 7-fold increment in the risk of VTE. The prevalence of arterial ischemic events ranges from 1.5% to 3.1%, while VTE events show a 28-fold increase risk [47-49]. Cancer-related VTE accounts for increased mortality and morbidity: mortality after a discharge for VTE event is nearly doubled and the risk of death increases up to eightfold after an acute VTE in patients with cancer as compared with non-cancer patients. In addition, patients with cancer-related thrombosis have a lower survival rate than cancer patients without thrombosis [50].

In 2016, international clinical practice guidelines were released by an international consensus-working group that pooled the existing data with the intent of making the Good Clinical Practice Guidelines (GCPG) easier to use at each national level [51].

FOLFIRINOX increases the risk of VTE due to several factors including the drugs themselves (irinotecan per se and in combination with 5FU and LV); as well as due to the need to use a central line and frequent use of G-CSF [52,53]. An analysis of risk factors for VTE in 570 active cancer-associated incident VTE (cases) and 604 matched controls with active cancer identified as independent risk factors the following variables: cancer site, disease stage, liver metastasis, progesterone, being underweight or obese, hospitalization or nursing home, central venous catheter and infection [54].

Pancreas cancer diagnoses conferred the highest risk [55]. Chemotherapy treatment is associated with a 1.8-fold increase risk of VTE [52]. In a study at Memorial Sloan Kettering Cancer Center conducted from 2003 to 2005, 115 of 2,120 cancer patients being treated for advanced malignancies develop VTE [52]. The tumor location (gastrointestinal tumors) and irinotecan treatment were independent risk factors for VTE. Patients with PDAC had a 2.26 (1.06 - 4.80) hazard ratio (HR) of developing VTE. Likewise, treatment with irinotecan increased the HR to develop a VTE to 1.89 (1.29 - 3.59). Indeed, in the colorectal cancer randomized trials CALGB89803 and N9741, irinotecan treatment combined with 5FU and LV was associated with a 2.4% and 3.1% of patients experiencing treatment related death respectively [56]. In these studies, 0.8% and 1% of deaths were either induced or exacerbated by vascular events.

Other risk factors for VTE include the need of a central venous catheter and use of G-CSF in up to half of the patients [53,57,58]. Studies have shown that there is a 0.3% to 28% incidence of catheter related VTE in patients with cancer [57]. In addition, the use of G-CSF increases the risk of VTE by 1.69 (range: 1.09-2.64) [54]. With regards to the combination of nab-paclitaxel + GEM, its use has not been associated with a significant increase in the risk of VTE [6]. However, the results of the PROTECHT study have shown a significant increase in VTE risk associated to GEM [59].

With regards to cardiotoxicity, it has been long recognized than 5FU causes cardiac toxicity [60]. However, the syndrome of 5FU -associated cardiotox-icity remains poorly defined and its incidence may be underestimated. Large series suggest that clinically demonstrated 5FU-related cardiotoxicity ranges from 1.6 to 4% [60].

Importantly, the presence of prior cardiac history is not predictive as only 14% of patients have a history of heart disease and cardiac risk factors are present in only 37 % of patients. However, the probability of EKG changes in 10 fold higher in patients with prior history of cardiac diseases (15 vs. 1.5%, $p < 0.001$) [61]. Cardiac events appear to be independent of dose and are higher in patients treated with continuous infusion as compared to bolus regimens (12.5 vs. 3.5%, $p = 0.024$) [62].

Previous studies also suggest that the addition of LV to continuous infusion of 5FU results in a further increment of cardiotoxicity [60]. The pathophysiology of 5FU cardiac toxicity is not fully understood, and different alteration, such as coronary artery thrombosis, arteritis, or vasospasm have been proposed as underlying mechanisms. Direct toxicity to the myocardium and autoimmune phenomena have also been implicated. Clinically, most cases consist of ischemic events (angina myocardial infarction), and arrhythmias. Most frequent EKG changes include ischemia or ST-T segment elevation. Approximately 12% of the patients develop enzymatic changes, with a reported mortality rate of 8% [60].

With regards to the combination of nab-paclitaxel + GEM, less ischemic events have been reported, compared to FOLFIRINOX regimen. As mentioned before, this is related to the higher cardiotoxicity associated to 5FU [63-65].

Pancreatic exocrine insufficiency (PEI) is a known complication of both benign and malignant pancreatic diseases, pancreatic resection, and post-surgical alteration of the anatomy of the foregut. It is defined as inadequate pancreatic enzyme activity caused by insufficient pancreatic enzyme production/ activation, or altered enzyme deactivation. The physiologic biphasic pattern of pancreatic enzyme release is absent in patients with mPDAC [66].

Unfortunately, PEI is often overlooked in cancer patients, as the focus of attention is their baseline disease. However, PEI occurs frequently in PDAC affecting both patients with and without surgical resection [67]. A prospective trial conducted in 194 mPDAC patients found that 25% of the patients presented extreme levels PEI (levels of fecal elastase-1 < 25 μg/g), while 14% and 11% presented severe or moderate PEI [68]. The most frequent tumor location in patients with extreme PEI was the head of the pancreas. In addition, extreme PEI was significantly associated with jaundice and a with worse prognosis (median OS of 7 months vs. 11 months, p = 0.031) [68]. Given this high prevalence, physicians should focus on diagnosing and treating PEI and to optimize nutritional status and physical condition, especially for those patients undergoing palliative chemo-therapy. These issues, that are innate to mPDAC, are further exacerbated in patients treated with FOLFIRINOX because of the high incidence of grade 3 vomiting (14.5%) and diarrhea (12.7%) as compared to the combination of nab-paclitaxel and GEM (no vomiting and diarrhea 6%) [6,7].

mPDAC patients often have a decreased nutritional intake secondary to a variety of factors, including anorexia, early satiety, nausea, pain, anxiety, and depression. Eighty percent of mPDAC patients have weight loss at presentation. mPDAC patients often report a loss of approximately 15% of their pre-illness weight by the time of diagnosis, and the weight loss continues with a median loss by the time of death of 25% of pre-illness weight [69].

Sequential treatment

The availability of more effective first line treatments (the combination of nab-paclitaxel + GEM and FOLFIRINOX based on the results of phase III studies) is allowing the development of second line treatment options based on the results of phase II and phase III studies for patients with mPDAC [6-9, 70-72].

Thus, the results of the CONKO-003 study, that analyzed the efficacy of second line oxaliplatin and 5FU/LV versus 5FU/LV alone for GEM refractory pancreatic cancer, showed that the combination significantly extended the duration of OS when compared to 5FU/LV alone in patients with advanced GEM refractory pancreatic cancer [9].

On the other hand, the PANCREOX study, that compared infusional 5FU/LV vs. mFOLFOX6 (infusional 5FU/LV and oxaliplatin) did not demonstrate differences in PFS or OS between these two regimens, questioning the role of the addition of oxaliplatin for the management of patients previously treated with GEM-based-regimens [73].

Finally, the results of the NAPOLI phase III study, that analyzed the effect of nanoliposomal irinotecan (NalIRI) alone or combined with 5FU/LV in a phase 3 trial in patients with metastatic PDAC previously treated with GEM-based therapies showed that extends survival (6.1 vs 4.2 months), with a manageable safety profile [8].

Indeed, patients who receive three lines of treatment are not rare these days. Similar to other diseases like colon cancer for example, the availability of second and even third line treatments imply that the management of the disease should be viewed as a continuum of care of several lines of treatment rather than compartmentalized treatments. However, there are no clear guidelines regarding the optimal sequence of treatment in metastatic PDAC, in part due to the lack of head to head comparison between possible approaches. Factors to consider in making these decisions include the ECOG performance status, comorbidities, residual toxicities (i.e. neuropathy), prior treatments, and patient's goals and preferences. Algorithms for sequential management of patients with PDAC, based on expert opinions are emerging. **Table 6** provides a potential treatment sequencing approach for PDAC based on the review of the available literature.

Table 6. Potential treatment sequencing approach for mPDAC.

First line	Second line	Third line
Nab-paclitaxel + GEM	5FU based regimen: 5FU/LV NalIRI + 5FU/LV Oxaliplatin + 5FU/LV Capecitabine	Platinum-based regimen or NalIRI
FOLFIRINOX	GEM based-regimen	?

*GEM: Gemcitabine; 5FU: 5-fluorouracil; LV: Leucovorin; NalIRI: liposomal irinotecan

Table 7. mPDAC: Sequential treatments: Retrospective data [74-78].

Study	Treatment Strategy	N	OS (median, months)
MPACT [78]	Nab-paclitaxel + GEM, 5FU/Capecitabine	132	13.5
	Nab-paclitaxel + GEM -FOLFIRINOX	18	15.7
	Nab-paclitaxel + GEM -FOLFOX	36	13.7
Gilabert et al [74]	GEM-based followed Ox-based	16	14.9
Giordano et al [75]	Nab-paclitaxel + GEM -second Line chemotherapy	102	13.5
	Nab-paclitaxel + GEM -FOLFOL/XELOX	56	12.8
	Nab-paclitaxel + GEM -FOLFIRI	24	13.2
	Nab-paclitaxel + GEM -FOLFIRINOX	22	13.8
Braiteh et al [76]	Nab-paclitaxel + GEM -5FU based regimen	26	12.7
	FOLFIRINOX-GEM based regimen	41	8.4
Schimdt et al [77]	FOLFIRINOX- Nab-paclitaxel + GEM	20	10.8
	Nab-paclitaxel + GEM -FOLFIRINOX	6	18
	FOLFIRINOX/FOLFOX- Nab-paclitaxel + GEM	27	12.1
	Nab-paclitaxel + GEM -FOLFIRINOX/FOLFOX	10	12.2

*GEM: Gemcitabine; OX: Oxaliplati

Randomized clinical trials in second line setting are only available for patients who received GEM based chemotherapy in the first line setting (**Tables 7 and 8**) [7,74-77]. The vast majority of these patients, however, did not receive the combination of nab-paclitaxel + GEM [8,9,71,72]. Notwithstanding differences in study design and the small samples sizes of the trials, there are conflicting results for FOLFOX-like regimens with one positive and another negative trial. The most consistent data currently available is for liposomal irinotecan (NalIRI) + 5FU/LV [8]. It should be noted, however, very few of these patients received the combination of nab-paclitaxel + GEM in the first line setting, the preferred GEM combination used these days. Likewise, there is no randomized trial of second line treatment after first line treatment with FOLFIRINOX.

In the lack of randomized trials in the second line setting after the combination of nab-paclitaxel + GEM as first line, an approach to determine the results with second line treatments is to analyze the outcome of patients who received second line treatment after first line with the combination of nab-paclitaxel + GEM in the MPACT trial [78]. A total of 347, approximately 40% of patients from the MPACT trial received second line treatment. More than 60% of the patients who received a second line treatment were KPS 90-100% and the most common regimen used (78%) was 5FU based. Regardless of the second line treatment received, OS was longer for patients who had received the combination of nab-paclitaxel + GEM as compared to GEM alone (12.8 vs. 9.9 months, *p* = 0.015) in the first line setting; however, no differences in survival were noted for second line treatment based on first line results. The best OS as obtained in patients who received first line with the combination of nab-paclitaxel + GEM followed by FOLFIRINOX (15.7 months). These results are consistent with a retrospective analysis that compared the outcome of patients receiving two or more lines of chemotherapy in order to define the optimal sequence of treatments [74]. Patients were classified in two groups based on the first line treatment they had received (5FU-based, 59 patients) or GEM-based (31 patients). OS was significantly longer in patients who had received gemcitabine-based first line treatment (14.9 months vs. 13.8 months, *p* = 0.046). Similar results have been reported in other studies indicating that patients who receive second line treatment, as expected, have better survival and that results appear to be superior with the sequence of gemcitabine-based versus 5FU based in the first line. In the PRODIGE study a total of 165 patients (48.2%) of the patients received second line treatment (80 patients in the FOLFIRINOX group and in 85 patients in the GEM group) [7]. No difference in median survival was noted between the groups (4.4 months in each group) from the introduction of second-line therapy. The most common second line regimens were as follows: in the FOLFIRINOX group, GEM (in 82.5% of the patients) or a GEM-based combination (in 12.5%), and in the gemcitabine group, a combination of 5FU, LV, and oxaliplatin (FOLFOX) (in 49.4%); GEM plus oxaliplatin (in 17.6%); a regimen of 5FU and LV plus cisplatin every 2 weeks (in 16.5%); and FOLFIRINOX (in 4.7%). It is also important to mention the results a small study (n = 57) conducted in France (AGEO study) that analysed the efficacy of nab-paclitaxel + GEM in metastatic PDAC after FOLFIRINOX failure [79].

Table 8. Second line treatment: Results of randomized studies [8,9,71,72].

Reference	Study design	Number of patients	First line	Second line	PFS (median, months)	OS (median, months)
CONKO-003 [9]	Phase III	168	GEM	OFF vs 5FU/LV	2.9 vs 2.0	5.9 vs 3.3
PANCREOX [72]	Phase III	108	GEM based	FOLFOX vs 5FU/LV	3.1 vs 2.9	6.1 vs 9.9
NAPOLI-1 [8]	Phase III	417	GEM based	NalIRI +/- 5FU/LV	3.1 vs 1.5	6.1 vs 4.2
SWOG S115 [71]	Phase II	115	GEM	FOLFOX vs MK2006 + selumetinib	2.0 vs 1.5	6.9 vs 4.0

*GEM: Gemcitabine; 5FU: 5-fluorouracil; LV: Leucovorin; OFF: Oxaliplatin/5FU/LV; NalIRI: liposomal irinotecan

Disease control rate and objective response rate were 58% and 17.5% respectively. In addition, median OS and median PFS were 8.8 and 5.1 months. The reported median OS survival since the commencement of the first-line chemotherapy was 18 months. The results suggest that the administration of the combination seems to be effective, with a manageable toxicity profile, after FOLFIRINOX failure.

Treatment guidelines recommendations by ESMO, NCCN and SEOM indicate that second line treatment should be considered for patients with good performance status [10-12]. For patients who have received gemcitabine-based chemotherapy in the first line setting, the NCCN Guidelines recommend either 5FU + NalIRI (IA) or other fluoropyrimidine based treatment [9]. ESMO guidelines further specified that given the conflicting results with oxaliplatin, NalIRI, if available, should be the preferred regimen [10]. SEOM guidelines do not indicate a preference for any of the two regimens and emphasizes that none of them have been tested in patients treated with the combination of nab-paclitaxel + GEM or FOLFIRINOX in the first line [11]. For patients who have received fluoropyrimidine-based first line treatment, NCCN guidelines recommend a gemcitabine-based regimen in the second line setting [12]. **Table 9** summarizes the current approach in the treatment sequence for advanced PDAC.

Table 9. Current approaches in treatment sequencing for mPDAC.

First Line	Second Line	Third Line
GEM-based (GEM, Combination of nab-paclitaxel + GEM, GEM-erlotinib)	**PS 0-1:** Fluoropyrimidine based regimen (+/- platinum and or NalIRI); FOLFIRINOX **PS-2:** Fluoropyrimidine alone; BSC	**PS 0-1:** NalIRI or platinum based regimen (if no prior exposure)
FOLFIRINOX	**PS 0-1:** Combination of nab-paclitaxel **PS-2:** GEM monotherapy, BSC	??

*BSC: Best Supportive Care; GEM: Gemcitabine; NalIRI: liposomal irinotecan

It can be concluded that the treatment of patients with mPDAC has improved over the last few years with more effective chemotherapy regimens in first and second line settings. Both the combination of nab-paclitaxel + GEM and FOLFIRINOX showed improvement in survival in randomized phase III studies and are currently considered standard of care in the first line setting. Differences in study design, patients´ characteristics, toxicity profile, resource consumption and supportive care required, affect the clinical application of these regiments in routine clinical practice. While no comparative study exists, the combination of nab-paclitaxel + GEM appears better tolerated, easier to administer and applicable to a broader patient population. The proportion of patients that are candidates to receive second and third line regimens is increasing due to better results with achieved with front line regimens. Management of mPDAC should be considered as a continuum care rather than a compartmentalized approach. In this sense, sequential treatment algorithms that interconnect first and subsequent lines are being developed.

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Competing Interests

The authors have declared that no competing interest exists.

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