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REVIEW ARTICLE

Towards an optimal treatment algorithm for metastatic pancreatic ductal adenocarcinoma (PDA)

M. Uccello MD,* M. Moschetta PhD MD,* G. Mak MD,* T. Alam BSc (Hons),* C. Murias Henriquez MD,* and H.-T. Arkenau PhD MD *†

ABSTRACT

Chemotherapy remains the mainstay of treatment for advanced pancreatic ductal adenocarcinoma (PDA). Two randomized trials have demonstrated superiority of the combination regimens FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan) and gemcitabine plus nab-paclitaxel over gemcitabine monotherapy as a first-line treatment in adequately fit subjects. Selected PDA patients progressing to first-line therapy can receive second-line treatment with moderate clinical benefit. Nevertheless, the optimal algorithm and the role of combination therapy in second-line are still unclear. Published second-line PDA clinical trials enrolled patients progressing to gemcitabine-based therapies in use before the approval of nab-paclitaxel and FOLFIRINOX. The evolving scenario in second-line may affect the choice of the first-line treatment. For example, nanoliposomal irinotecan plus 5-fluouracil and leucovorin is a novel second-line option which will be suitable only for patients progressing to gemcitabine-based therapy. Therefore, clinical judgement and appropriate patient selection remain key elements in treatment decision. In this review, we aim to illustrate currently available options and define a possible algorithm to guide treatment choice. Future clinical trials taking into account sequential treatment as a new paradigm in PDA will help define a standard algorithm.

Key Words Pancreatic ductal adenocarcinoma, pancreatic cancer, second-line, chemotherapy, algorithm

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDA) is a challenging disease and the fourth leading cause of cancer death worldwide. It has a poor prognosis, with less than 2% of patients surviving more than five years. More than 80% of subjects are diagnosed with metastatic or unresectable disease and are mainly treated with palliative chemotherapy for symptom control and survival prolongation[1,2]. Single-agent gemcitabine has been considered the standard first-line treatment for PDA since 1997, when Burris *et al.*[3] published a randomized trial demonstrating a modest survival advantage of gemcitabine in comparison with 5-fluorouracil (5FU). Afterwards, several gemcitabine combination therapies failed to show a significant survival advantage over gemcitabine alone[4–7]. A breakthrough in the treatment of metastatic PDA was the publication of the PRODIGE/ACCORD trial[8]; the multiple drug regimen FOLFIRINOX (5FU and folinic acid, oxaliplatin, and irinotecan) substantially increased the survival in appropriately selected first-line metastatic PDA patients. Another milestone was achieved with the MPACT trial[9], demonstrating superior efficacy of the combination nab-paclitaxel plus gemcitabine versus gemcitabine alone in fit patients. Second-line treatment can be proposed to carefully selected patients, according to Eastern Cooperative Oncology Group (ECOG) performance status (PS) and other clinical variables, such as bilirubin levels and comorbidities[10,11]. Although both FOLFIRINOX and gemcitabine plus nab-paclitaxel can be regarded as preferred options in selected patients with good PS and adequate organ function, a question remains regarding the most appropriate second-line treatment after failure of optimal combination regimens. Indeed, available second-line PDA studies were conducted after failure of gemcitabine given as monotherapy or in combination with other drugs rather than nab-paclitaxel. In this article, we will focus on existing second-line treatment options and speculate about a possible treatment algorithm for metastatic PDA. We performed an extensive literature search using PubMed, Medline, and Embase

Correspondence to: Mario Uccello, 93 Harley Street, London W1G 6AD, United Kingdom.
E-mail: mario_uccello@hotmail.it **DOI:** https://doi.org/10.3747/co.25.3708

databases. We also reviewed existing guidelines (National Institute for Health and Care Excellence [NICE], National Comprehensive Cancer Network [NCCN], European Society for Medical Oncology [ESMO]).

Current Second-Line Treatment Options in Metastatic PDA

Pancreatic ductal adenocarcinoma (PDA) is a very aggressive disease, and patient deterioration can occur rapidly after disease progression to first-line treatment. Therefore, enrolling an adequate number of patients in trials exploring the use of second-line options is challenging. As a result, median survival of fit patients receiving second-line treatment within a clinical trial is around four to six months[10,12]. In 2001, the German Charité Onkologie (CONKO)-study group published the results of the first clinical trial comparing a combination regimen versus best supportive care (BSC) only for second-line advanced PDA[13]. Given the encouraging preliminary activity of the regimen shown in phase II studies, the investigators selected a schedule of moderate intensity with 5FU, leucovorin (LV), and oxaliplatin (OFF) as the experimental arm. Unfortunately, the trial was closed prematurely, as patients and physicians progressively manifested lack of acceptance of a BSC arm. Data on the 46 enrolled patients exhibited a median overall survival (OS) of 4.82 months for OFF treatment vs. 2.30 months with BSC alone ($p = 0.031$). Afterwards, the CONKO group conducted another phase III trial[14], in which 168 patients were randomly assigned to either OFF or 5FU plus LV (5FU/LV). The median OS in the OFF arm was significantly prolonged in comparison with the control group (5.9 months vs. 3.3 months, $p = 0.010$). The time to progression with OFF was also significantly increased (2.9 months vs. 2.0 months, $p = 0.019$). Both schedules showed manageable toxicity, but OFF showed an expected increased rate of mild to moderate neurotoxicity (38.2% vs. 7.1%). Given the results observed in these two studies, 5FU/LV plus oxaliplatin was regarded as the most suitable option in fit patients after failure of gemcitabine-based treatment. Conversely, the recently published PANCREOX phase III trial[15] showed a detrimental effect from the use of oxaliplatin in combination with 5FU/LV, using the classic modified FOLFOX (MFOLFOX) regimen. The trial was initially designed to randomize 128 patients with ECOG PS 0–2 to receive either 5FU/LV or MFOLFOX in a 1:1 ratio to detect a 15% improvement in the rate of progression-free survival (PFS) with a statistical power of 0.8. However, the study did not reach the target enrolment due to slow accrual, with only 54 patients per arm enrolled. Unexpectedly, no benefit was seen with regard to median PFS with the addition of oxaliplatin (3.1 months for MFOLFOX vs. 2.9 months for 5FU/LV; $p = 0.99$), and a detrimental effect was detected in the combination arm in terms of median OS (6.1 months vs. 9.9 months; $p = 0.02$). Therefore, the authors concluded that 5FU/LV might be a viable second-line treatment option.

However, the contradicting results found in the PANCREOX and CONKO study trials may be explained by better balanced patient characteristics and/or the less intense regimen adopted in the latter study. For example, the median time since the diagnosis of advanced disease in the PANCREOX trial was longer among subjects given the combination regimen. Moreover, crossover and post-progression therapy may be other confounding factors[16,17]. Other chemotherapeutic agents have been tested in phase II trials, including taxanes used as monotherapy or in combinations schedules. Nevertheless, none of them have been tested in phase III trials. Additionally, all available trials explored the use of second-line treatments after progression to gemcitabine-based treatment before the approval of nab-paclitaxel[10,12]. Therefore, the optimal schedule after progression to FOLFIRINOX or gemcitabine plus nab-paclitaxel is still not clearly defined.

Nanoliposomal Irinotecan (nal-IRI) with 5FU/LV: A New Option in Second-Line PDA

Irinotecan is widely used for the treatment of gastrointestinal cancers, but the extent of its activity is limited by toxic side effects. Irinotecan is a synthetic derivative of the plant extract camptothecin that inhibits the action of topoisomerase I. It is a prodrug that is activated by carboxylesterase enzymes, present mainly in liver and colon tissue, to the active form SN-38. The active SN-38 is then inactivated via glucuronidation by hepatic uridine diphosphonate glucuronyltransferases to form SN-38 glucuronide, which is primarily excreted through the biliary system[18,19]. In the second-line PDA, encouraging results have been reported using a modified (m) FOLFIRI (irinotecan plus 5FU/LV) regimen which was compared with a MFOLFOX regimen in a randomized phase II study[20]. Both combinations showed manageable toxicity profiles and comparable activity, without any significant differences in median OS (16.6 weeks for MFOLFIRI vs. 14.9 weeks for MFOLFOX; $p > 0.05$). A major challenge in the clinical use of traditional chemotherapeutics is maximizing the efficacy in tumours while sparing normal cells. A novel approach has been recently pursued by using a novel nanoparticle formulation of liposomal irinotecan. Liposomal delivery systems offer potential benefits, including the ability to modify pharmacokinetic and safety profiles of cytotoxic drugs to increase target drug exposure. A phase II trial[21] investigating the use of nal-IRI in 40 gemcitabine-refractory PDA patients showed encouraging anti-tumour activity and a tolerable safety profile, with an objective response rate (ORR) of 7.5% and a median PFS and median OS of 2.4 months and 5.2 months, respectively. Most frequently observed grade 3/4 adverse events were neutropenia (30%), fatigue (20%), and diarrhoea (15%). Grade 1 or 2 alopecia was reported in 42.5% of patients. Based on these results, the NAPOLI-1 phase 3 study[22] was initiated and enrolled 417 patients, who were randomly assigned to receive either nal-IRI plus 5FU/LV every 2 weeks, nal-IRI monotherapy every 3 weeks, or 5FU/LV. All randomized patients had previously received gemcitabine-based treatment, though the study population was not restricted to second-line treatment exclusively. In fact, 32% of patients had previously received two or more lines for metastatic disease prior to commencing the study. The median OS (primary endpoint) was significantly prolonged in patients who received nal-IRI plus 5FU/LV in comparison with those receiving 5FU/LV only (6.2 months vs. 4.2 months; $p = 0.012$). Of note, the survival benefit was maintained through all predefined subgroups, such as ECOG PS, albumin levels, tumour stage at diagnosis, and baseline CA19.9 levels. Other endpoints were also superior in the combination arm,

including median PFS (3.1 months vs. 1.5 months, $p = 0.0001$) and ORR (19% vs. 1%; $p < 0.0001$). Overall, the safety profile of the combination arm was manageable and in line with the previous phase II study, with commonest grade 3/4 adverse events including neutropenia (32%), fatigue (14%), diarrhoea (13%), and vomiting (11%). On the other hand, no clinical benefit was observed in patients given nal-IRI monotherapy in comparison with those receiving 5FU/LV. Furthermore, nal-IRI monotherapy showed a higher incidence of severe diarrhoea and alopecia in comparison with nal-IRI plus 5FU/LV. Therefore, nal-IRI plus 5FU/LV can be considered a new standard option in this population of pre-treated patients with good PS and organ function. Nevertheless, it remains questionable why a treatment arm receiving the classic FOLFIRI regimen was not included in the NAPOLI-1 trial.

Sequential Treatment As a New Paradigm in Metastatic PDA

Patients affected by PDA can often deteriorate quickly and face significant symptoms such as pain, jaundice, diarrhoea, gastrointestinal obstruction, weight loss, cachexia, and depression. Therefore, BSC represents an important aspect of care from an early stage. A multidisciplinary team approach integrating palliative care is essential to provide adequate assistance and improve quality of life for PDA patients. Incorporation of core members such dieticians, palliative care doctors and nurses, and psychologists will allow a prompt identification and treatment of cancer-related symptoms and complications. Palliative surgical procedures can also be offered for biliary or gastric outlet obstruction in patients with longer life expectancies. Best supportive care (BSC) without additional therapy should be considered as an option in metastatic or recurrent pancreatic cancer, primarily for patients with poor PS[23,24]. Nevertheless, a significant number of patients with no symptoms or with adequately controlled symptoms can receive the most effective standard of care or can be enrolled into clinical trials. Nowadays, combination chemotherapy is considered the gold standard first-line treatment for metastatic PDA. FOLFIRINOX[8] and gemcitabine plus nab-paclitaxel[9] can significantly extend the survival of these patients in comparison with gemcitabine monotherapy. Although these combinations have never been compared in clinical trials, FOLFIRINOX may produce slightly better outcomes at the cost of increased toxicity. FOLFIRINOX can provide an ORR of around 30%[8,25,26], which seems to be higher than the ORR commonly observed with gemcitabine plus nab-paclitaxel[9]. Case series suggest that FOLFIRINOX may also be the best option in a neoadjuvant setting, with a response rate of around 30% to 40%[27,28]. Nevertheless, the high rate of hematologic toxicity and fatigue can limit the use of a standard FOLFIRINOX regimen. Patients enrolled in the PRODIGE/ACCORD trial were a selected population with age less than 70 years, good PS, and adequate organ function, including normal bilirubin levels[8]. In a broader population, a modified FOLFIRINOX (MFOLFIRINOX) regimen (e.g., without 5FU bolus) is usually adopted with improved safety and maintained response rate[26]. Therefore, we propose the use of FOLFIRINOX for younger patients (less than 65 years old) with good PS, adequate organ function, and non-significant comorbidities (Figure 1). The use of gemcitabine plus nab-paclitaxel could be the best option in patients unable to tolerate an increased rate of toxicity and central line for continuous 5FU infusion. The indication for gemcitabine monotherapy or BSC only should be restricted to unfit patients with inadequate organ function and/or poor PS. The role of older gemcitabine-based combinations should be restricted to very few circumstances (e.g., unavailability of expensive drugs like nab-paclitaxel). In the absence of reliable criteria for patient selection, the combination of gemcitabine plus erlotinib is not considered cost-effective, in spite of the very modest increased benefit observed in terms of OS over gemcitabine monotherapy in a phase III trial[29]. There is also evidence suggesting a role for gemcitabine plus capecitabine in terms of increased PFS and ORR, but this combination failed to show a clear survival advantage over gemcitabine alone in the metastatic first-line setting[7]. However, a recent meta-analysis[30] of eight randomized clinical trials showed a longer OS in patients receiving gemcitabine plus capecitabine than in patients receiving gemcitabine monotherapy (hazard ratio, 0.87; $p = 0.03$).

Conducting randomized trials in second-line PDA remains a challenge, because most patients do not retain a good clinical condition when progressing to first-line treatment. Available data are mainly based on patients failing gemcitabine-based first line regimens before the approval of nab-paclitaxel[10,12]. The clinical scenario in a real-life setting is even worse, as was shown by the slow recruitment of the CONKO and PANCREOX trials[13–15]. Furthermore, less than 50% of patients enrolled in the PRODIGE/ACCORD trial[8] were started with a second-line treatment. Nevertheless, emerging data indicate an increased post-progression survival from the use of newer combination regimens in first-line, leading to better outcomes in a second-line setting[31–33]. An exploratory analysis[31] conducted on PDA after failure of gemcitabine or nab-paclitaxel plus gemcitabine showed that first-line combination and the use of second-line treatment were factors associated with longer post-progression survival. The longest median OS values after failure of gemcitabine plus nab-paclitaxel were observed in patients receiving 5FU-based combinations such as FOLFIRINOX and FOLFOX. Additionally, Portal *et al.*[32] reported promising data in a prospective multicentre cohort of patients treated with gemcitabine plus nab-paclitaxel after failure of FOLFIRINOX. The ORR was 17%, whereas median PFS and median OS were 5.1 months and 8.8 months, respectively. Despite the findings obtained in the PANCREOX trial, patients progressing to first-line gemcitabine treatment should be offered either OFF, MFOLFOX, or 5FU plus nal-IRI[13,14,16,22]. Modified FOLFIRINOX remains an attractive option for very fit patients[31]. Capecitabine plus oxaliplatin (XELOX) may be considered when a central line for continuous 5FU infusion is not available[34]. Despite the lack of data from phase III studies, FOLFIRI could be offered to patients unable to receive oxaliplatin or nal-IRI[20]. The role of 5FU monotherapy remains controversial, but it should not be considered the best option in patients able to receive combination regimens[14,16,22]. For patients receiving first-line FOLFIRINOX, gemcitabine can be considered the most appropriate second-line option by default. However, even in this context, gemcitabine combinations may have a potential role in fit patients[32].

Future clinical trials assessing second-line options should ideally take into account sequential treatment as an emerging paradigm in the treatment of advanced

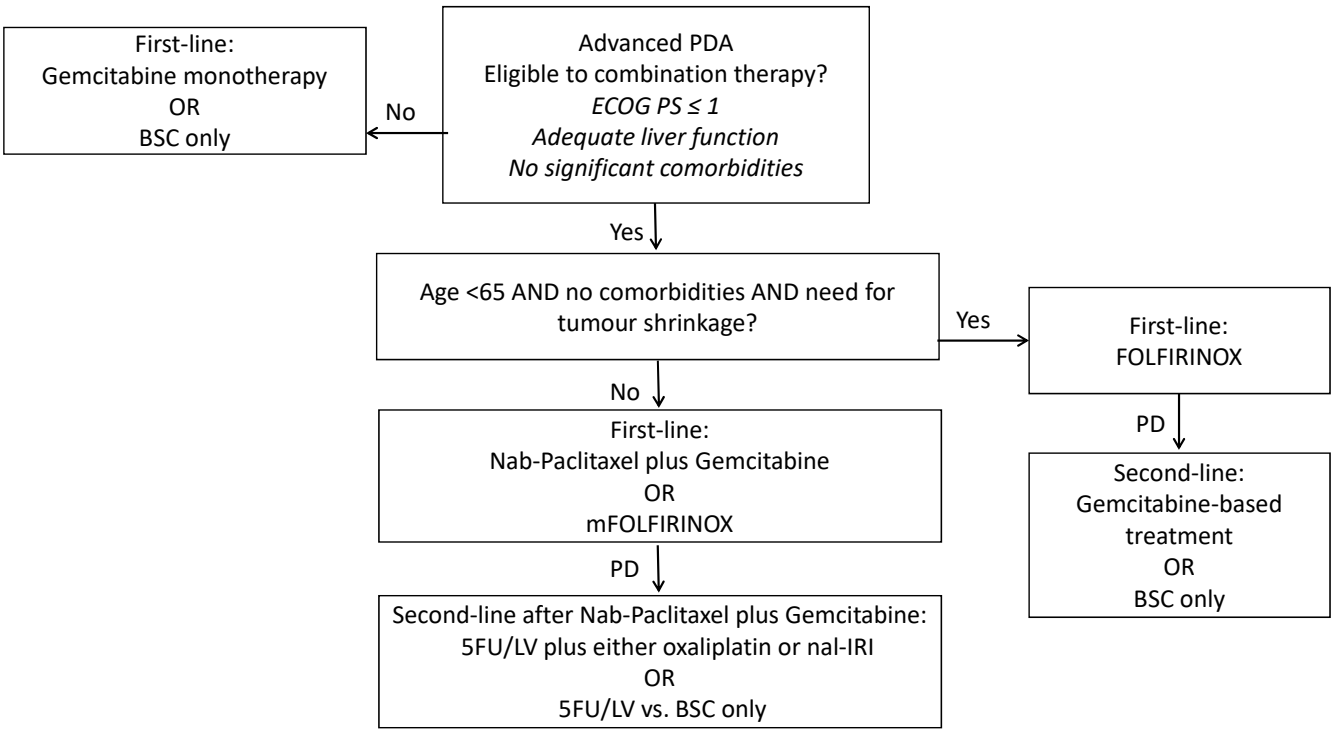

FIGURE 1 Possible algorithm to guide treatment decision in metastatic pancreatic ductal adenocarcinoma. PDA = pancreatic ductal adenocarcinoma; ECOG PS = Eastern Cooperative Group performance status; BSC = best supportive care; FOLFIRINOX = 5-fluorouracil plus leucovorin, oxaliplatin, and irinotecan; mFOLFIRINOX = modified FOLFIRINOX; 5FU/LV = 5-fluorouracil plus leucovorin; PD = progressive disease.

pancreatic cancer in order to achieve a standard of care and define a treatment algorithm. Meanwhile, several ongoing late phase trials evaluating a number of novel agents may result in significant changes in clinical practice in the coming years. Other factors may influence the choice of the best second-line option (e.g., patient preference). *BRCA* mutation carriers may be offered PARP-inhibitors and/or platinum-containing regimens[35]. Additionally, the unavailability of nab-paclitaxel in second-line, as well as a defined role for 5FU-containing regimens after failure of gemcitabine-based treatment, could potentially favour the use of gemcitabine plus nab-paclitaxel in first-line settings. Neither targeted treatments nor immunotherapy have provided significant benefit to PDA. Evaluated classes of agents have included immune checkpoint inhibitors, growth factor receptor inhibitors, tyrosine kinase inhibitors, and inhibitors of other pathways such as MEK1/2, HER-2, and PI3K[33]. In conclusion, the evolving scenario in the second-line setting may influence the choice of the best first-line treatment. We tried to define a treatment algorithm without replacing current clinical guidelines and based on an independent interpretation of literature evidence. A better understanding of the complex biological nature of the metastatic disease may lead to improved treatment options in both first- and second-line settings.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest and declare that we have none.

AUTHOR AFFILIATIONS

*Drug Development, Sarah Cannon Research Institute UK, London, United Kingdom; and †UCL Cancer Institute, University College of London, London, United Kingdom.

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