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Treatment landscape of metastatic pancreatic cancer

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive form of cancer with a dismal prognosis. The lack of symptoms in the early phase of the disease makes early diagnosis challenging, and about 80–85% of the patients are diagnosed only after the disease is locally advanced or metastatic. The current front-line treatment landscape in local stages comprises surgical resection and adjuvant chemotherapy. In Switzerland, although both FOLFIRINOX and gemcitabine plus nab-paclitaxel regimens are feasible and comparable in the first-line setting, FOLFIRINOX is preferred in the treatment of fit (Eastern Cooperative Oncology Group [ECOG] performance status [PS]: 0–1), young (<65 years old) patients with few comorbidities and normal liver function, while gemcitabine plus nab-paclitaxel is used to treat less fit (ECOG PS: 1–2) and more vulnerable patients. In the second-line setting of advanced PDAC, there is currently only one approved regimen, based on the phase III NAPOLI-1 trial. Furthermore, the use of liposomal-irinotecan in the second line is supported by real-world data. Beyond the standard of care, various alternative treatment modalities are being explored in clinical studies. Immunotherapy has demonstrated only limited benefits until now, and only in cases of high microsatellite instability (MSI-H). However, data on the benefit of poly (ADP-ribose) polymerase (PARP) inhibition as maintenance therapy in patients with germline BRCA-mutated tumors might signal of an advance in targeted therapy. Currently, there is a lack of molecular and genetic biomarkers for optimal stratification of patients and in guiding treatment decisions. Thus, identification of predictive and prognostic biomarkers and evaluating novel treatment strategies are equally relevant for improving the prognosis of metastatic pancreatic cancer patients.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the 7th leading cause of cancer-related mortality worldwide.[1,2] The highest incidence rates have been observed in Europe, North America, Australia and New Zealand, with an incidence of 7 to 10 new cases per 100,000 persons per year.[2–5] In the USA, the 5-year survival rate of pancreatic cancer patients was about 5–10% between 2008 and 2015, while in Switzerland it was about 5% in men and 6.8% in women in the period 2001–2010.[6–8] The incidence and mortality rates correlate with increasing age, with the most prevalent patient group comprising patients above 70 years of age.[4] In the USA, 57,600 new cases and 47,050 deaths have been estimated in 2019.[9] According to the most recent Swiss cancer statistics, the average annual incidence of pancreatic cancer was 715 in men and 708 in women between 2012 and 2016, while the average annual mortality was 615 and 643, respectively, in the same period.[10,11] It accounts for about 3.2% of all cancers in the country.[12,13] Moreover, pancreatic cancer accounts for 6.0% of all cancer deaths among men and 7.9% among women and the average lifetime risk of dying from pancreatic cancer is 1.5% for men and 1.6% for women.[12,13]

The number of cancer-related deaths of PDAC is predicted to increase

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by 25% by the end of 2025, which will make PDAC the second most common cause of cancer-related death worldwide by 2030.[3,4] In Europe, the projected rise in pancreatic cancer incidence is calculated to be +29.3% and mortality to be +31.6% during this period.[4] Altogether, these numbers make it imperative to find new treatment options and better diagnostic tools.

Smoking, diabetes mellitus, obesity, alcohol abuse, increased age, ethnicity, genetic factors, *Helicobacter pylori* infection, non-O blood group and chronic pancreatitis are some of the risk factors identified for pancreatic cancer.[4,8,12,14] Genetic factors play a key role in only a small proportion of pancreatic cancer cases, as most cases are attributed to environmental factors.[14]

PDAC, which represents about 95% of all pancreatic cancer cases, and pancreatic neuroendocrine tumor (Pan-NET), which is less common (>5%), are the primary subtypes of pancreatic cancer. PDAC usually manifests in the exocrine glands of the pancreas, while Pan-NET occurs in the endocrine tissue of the pancreas.[4] Furthermore, according to the 8th edition of the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) TNM staging classification, pancreatic cancer is classified into 4 subtypes based on the clinical stage of the tumor: I (no spread or resectable), the cancer is limited to the pancreas and has grown 2 cm (IA) or greater than 2 cm but greater than 4 cm (IB); II (local spread or borderline resectable), the cancer is >4 cm and is limited to the pancreas (IIA), or it has spread locally to 1–3 regional lymph nodes (IIB); III (wider spread or unresectable primary tumor), cancer may have metastasized ≥4 lymph nodes or expanded to the nearby blood vessels or nerves, but has not metastasized to distant sites; IV (metastatic), cancer has spread to distant organs.[15]

The diagnosis of pancreatic cancer is rather challenging as most cases are asymptomatic in the early stages. Thus, currently available diagnostic tests often overlook patients with early-stage disease. Upon disease progression, there is a gradual manifestation of non-specific symptoms, like jaundice, weight loss, light-colored stools, abdominal pain and fatigue. In such cases, diagnosis is established when the disease is locally advanced or metastatic, which renders 80–85% of the cases unresectable, ultimately leading to a very poor prognosis as illustrated by the low 5-year survival rate of patients.[4,16] Several factors, such as age, sex, type of cancer, staging at the time of diagnosis, tumor size, serum albumin levels, as well as other factors including overall health and lifestyle of the patient have a considerable impact on the survival rates of pancreatic cancer patients. It is noteworthy, that diagnosis at an early stage and small tumor size (<2 cm) are key prognostic factors.[4] In addition, liver metastasis is associated with a worse prognosis.[17]

Haeno et al. (2012) designed a mathematical model of pancreatic cancer progression and dissemination to investigate the dynamics of cancer cell growth and metastasis, the survival of patients, and optimum intervention strategies.[18] The authors found that pancreatic cancer growth is initially exponential. After estimating the rates of pancreatic cancer growth and dissemination, they determined that patients likely harbor metastases at diagnosis and predicted the number and size distribution of metastases as well as patient survival. Therefore, understanding the mechanistic details and temporal pattern of pancreatic cancer metastasis is critical for designing effective interventions.

The aggressive progression of the disease can be attributed to its early dissemination during the disease course, high levels of molecular heterogeneity, mostly undruggable drivers and the immunosuppressive microenvironment, which altogether lead to the development of treatment resistance. Furthermore, the lack of predictive biomarkers makes the selection of the most effective treatment challenging.[19]

The current standard of care treatment

In general, population-based screening is not recommended as the lifetime risk of developing pancreatic cancer is considerably low (about 1%) in an unselected population.[16] Primary prevention, supported by increased awareness and lifestyle change, is the most effective way of controlling the incidence and mortality rates of pancreatic cancer. However, in the case of patients with a family history of this disease, new and more effective screening techniques are currently being developed.[4] Furthermore, germline mutations in the *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *PALB2*, *PRSS1*, *STK11*, *TP53*, and the Lynch syndrome (LS) mismatch repair genes are also associated with an increased risk of pancreatic cancer. In these cases, annual magnetic resonance imaging (MRI) and/or endoscopic ultrasound surveillance in individuals with LS and one first-degree relative affected with PDAC may be considered, according to the current guidelines [20], although more supporting evidence is needed.

First-line treatment strategies

Currently, a multimodal approach with surgical resection followed by adjuvant chemotherapy with FOLFIRINOX (folinic acid [leucovorin], fluorouracil [5-FU], irinotecan and oxaliplatin) is the best available potentially curative therapy offering a 3-year overall survival of more than 60%.[21] However, this approach is possible only in a minority of patients, due to its toxicity profile (the rate of grade 3–4 adverse events: 75.9%). As an alternative, in less fit patients older than 70 years and with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2, or patients who have any contraindication to the drugs used in FOLFIRINOX, gemcitabine/capecitabine could be an option, following the ESPAC-4 data.[22] Gemcitabine alone, the first agent which demonstrated a benefit in the post-operative setting, should be used only in frail patients.[23,24]

"Borderline resectable" are those tumors that are considered resectable upon good response to neoadjuvant treatment, mainly due to contact with the superior mesenteric vein or the portal vein of >180°, or with the superior mesenteric or celiac artery of ≤180°. In these cases, no standard approach has yet been established, and randomized trials are ongoing. Chemotherapy or chemo/radiotherapy could be considered, but most recommendations are based on systematic reviews, *meta*-analyses and retrospective series. Nonetheless, recent data support the role of FOLFIRINOX as the most promising preoperative strategy in this setting. [25,26]

Despite the optimization of the adjuvant and neoadjuvant approach, long-term survival rates are generally low, with high recurrence rates making other therapeutic options the need of the hour.[16] In this respect, approximately 50% of patients present with distant metastases at the time of diagnosis. Here, systemic chemotherapy remains the predominant treatment modality aimed to palliate cancer-related symptoms and prolong life.

Gemcitabine has been an established treatment option for metastatic pancreatic adenocarcinoma for a long time.[27,28] FOLFIRINOX was compared with gemcitabine, the standard of care, in a randomized phase III trial of 342 patients with untreated metastatic pancreatic cancer.[21] The experimental arm led to improved clinical outcomes, with an extended median life expectancy of more than 4 months, from 6.8 to 11.1 months (HR: 0.57 [95% CI: 0.45–0.73]; $p < 0.001$), but has an inferior safety profile compared with gemcitabine.

Two years later, the results of another first-line phase III study were published comparing gemcitabine plus nab-paclitaxel with gemcitabine monotherapy.[29] Namely, the MPACT trial demonstrated that the combination of nab-paclitaxel and gemcitabine leads to a significantly improved median overall survival (OS) compared with gemcitabine alone (8.5 months vs 6.7 months, HR: 0.72 [95% CI: 0.62–0.83]; $p < 0.001$). Median progression-free survival (PFS) as well as independently assessed overall response rate (ORR), were also significantly improved. The combination regimen was somewhat more toxic than monotherapy, which was addressed by dose reductions and treatment delays.[30,31] In a long term (>3 years) survival analysis, the median OS was significantly longer in the nab-paclitaxel plus gemcitabine arm versus the gemcitabine alone arm (8.7 months vs 6.6 months, HR: 0.72 [95% CI: 0.62–0.83]; $p < 0.001$).[32]

According to these results, the combination of nab-paclitaxel with gemcitabine was approved in the first-line setting of locally advanced nonresectable or metastatic pancreatic adenocarcinoma.[25] However, there is a lack of clinical studies with direct head-to-head comparisons of first-line treatment options, especially with respect to efficacy, safety and quality of life (QoL). Fig. 1 summarizes the potential choices for first-line chemotherapy. Nonetheless, the wider use of FOLFIRINOX in the adjuvant setting could potentially limit its application at the time of relapse.[21]

In a real-world study, the median OS for metastatic pancreatic cancer patients was lower than in both the PRODIGE/ACCORD 11 study for FOLFIRINOX (8.2 months vs 11.1 months) and in the MPACT study for nab-paclitaxel plus gemcitabine (6.1 months vs 8.7 months).[33] Patients treated with FOLFIRINOX had less frequent all-cause emergency department visits and all-cause hospitalization but increased febrile neutropenia-related hospitalization was observed.

In Switzerland, a group of clinicians has tried to build a consensus regarding the treatment strategy in the first-line setting. Gemcitabine plus nab-paclitaxel is the most used first-line approach. In the case of young (age below 65 years) and fit (ECOG PS of 0–1) patients with normal bilirubin levels, treatment with FOLFIRINOX could be considered. In addition, FOLFIRINOX can provide an ORR of around 30%, which seems to be higher than the ORR commonly observed with gemcitabine plus nab-paclitaxel (around 20%). For this reason, this combination could be the preferred option where tumor shrinkage represents the main clinical goal. Gemcitabine monotherapy remains an option for patients whose PS or comorbidities preclude combination chemotherapy. However, in the case of frail patients with ECOG PS 3–4, best supportive care (BSC) is advised.[34]

In the optimization of the continuum of care of pancreatic cancer patients, it is essential to base the choice of first-line therapy on the availability and overlap with potential second-line options. FOLFIRINOX as a front-line treatment does not have any clinically validated second-line options, while gemcitabine plus nab-paclitaxel would allow for second-line treatment with nanoliposomal irinotecan (nal-IRI) plus 5-fluorouracil (5FU), the only second-line therapy for metastatic pancreatic cancer that has shown a survival advantage in a phase III study, after progression to a gemcitabine-based regimen.[35]

Second-line treatment strategies

Approximately 40–50% of advanced pancreatic cancer patients progress to receive second- or later-line chemotherapy.[36] Several factors, including drug availability, patient characteristics, physician preference and prior first-line therapy may affect treatment choice.[37] Furthermore, the risk:benefit ratio should be analyzed before choosing second-line therapy for pancreatic cancer patients. The evolving scenario in the second line may affect the choice of first-line treatment. For instance, nal-IRI plus 5-FU and folinic acid (leucovorin [LV]) is a novel second-line option that is suitable only for patients progressing on gemcitabine-based therapy.

It is noteworthy that in the clinical setting, this combination is also used as a third-line therapy if previously not used (Fig. 1). Nonetheless, when FOLFIRINOX therapy in the first-line fails, the combination of gemcitabine plus nab-paclitaxel may represent a second-line treatment option, despite the lack of randomized clinical trials. This combination has been shown to be more effective than gemcitabine monotherapy in small retrospective and cohort studies.[38–40]

Another treatment option in this setting, which demonstrated activity in a German phase III trial, is the combination of 5-FU plus oxaliplatin, for patients who have progressed on a gemcitabine-based treatment line.[41] In this study, a total of 168 patients were randomly assigned to folinic acid and 5-FU (FF), or oxaliplatin and FF, administered in a weekly schedule, according to the OFF regimen. The median OS in the OFF group (5.9 months [95% CI: 4.1–7.4]) versus the FF group (3.3 months [95% CI: 2.7–4.0]) was significantly improved (HR: 0.66 [95% CI: 0.48–0.91]; $p = 0.010$). Rates of adverse events were similar between treatment arms, except for grade 1–2 neurotoxicity, which was more frequent in the OFF arm, as expected. However, the results of a more recent randomized phase III trial (PANCREOX) using biweekly infusional fluorouracil, folinic acid, and oxaliplatin (FOLFOX) schedule were disappointing, with a similar PFS (3.1 vs 2.9 months; $p = 0.99$) and shorter OS (6.1 vs 9.9 months; $p = 0.02$) in the modified FOLFOX6 group versus the infusional FF alone.[42] Due to these contrasting results, the

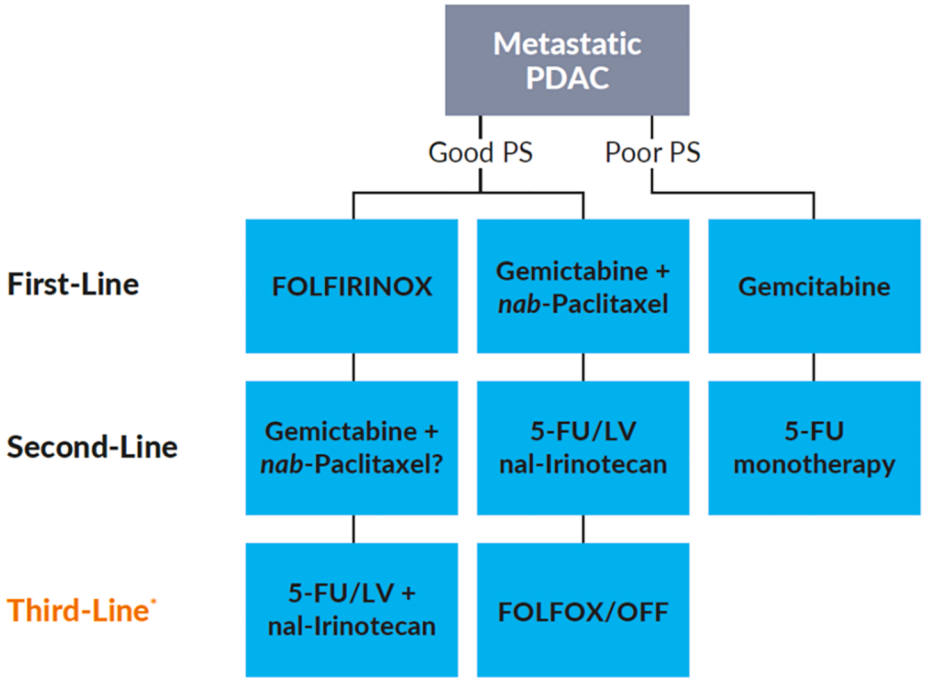

Fig. 1. Treatment strategy for first-, second- and third-line therapy in patients with metastatic pancreatic ductal adenocarcinoma (PDAC). PS, performance status.

use of oxaliplatin in the second line remains controversial.

Nal-IRI was originally developed using a system to encapsulate irinotecan within a liposomal carrier, producing a therapeutic agent with improved biodistribution and pharmacokinetic characteristics compared to the free drug. In Switzerland, nal-IRI in combination with 5-FU and folinic acid (leucovorin [LV]) is the only second-line therapy approved for the treatment of adult metastatic pancreatic adenocarcinoma patients, progressing after a gemcitabine-based first-line treatment, based on the NAPOLI-1 trial.[43,44] This phase III, open-label, multicenter, randomized trial evaluated nal-IRI with or without 5-FU/LV in metastatic pancreatic cancer patients previously treated with gemcitabine-based therapies. Median OS was 6.1 months (95% CI: 4.8–8.9) in patients treated with the combination regimen and 4.2 months (95% CI: 3.6–4.9) in those treated with 5-FU/LV only ($p = 0.012$). Further, median OS was 4.9 months (95% CI: 4.2–5.6) for patients receiving nal-IRI monotherapy compared with 4.2 months (95% CI: 3.6–4.9) for those receiving 5-FU/LV ($p = 0.94$). In a multivariate analysis, nal-IRI plus 5-FU/LV was associated with improved OS (HR: 0.58 [95% CI: 0.42–0.81]). This benefit was sustained for most patient subgroups analyzed in the NAPOLI-1 trial. Although the study showed that diarrhea and vomiting are the most prominent adverse events associated with nal-IRI, in clinical practice, neutropenia is more common. Moreover, health-related quality of life (HRQoL) was maintained, while survival was significantly extended.[45] The final OS analysis of the NAPOLI-1 trial demonstrated that the OS advantage was sustained, making nal-IRI plus 5-FU/LV the only evidence-based second-line treatment option.[46] A recent post hoc sub-analysis of the NAPOLI-1 trial population has identified several potential prognostic factors: decreased appetite at baseline (may be associated with worse survival outcomes), prior curative surgery (associated with improved median OS), the presence of liver metastases (correlating with significantly shorter median OS and median PFS), a greater number of distant metastases (prognostic of worse outcomes), and higher baseline pain and analgesic use.[47] Furthermore, age did not appear to be a prognostic factor for decreased survival in this study population after second-line treatment with nal-IRI plus 5-FU/LV, which was consistent with the results of the NAPOLI-1 trial. Indeed, colleagues at University Hospital Zurich in Switzerland recently published the case of a young, fit patient with metastatic adenocarcinoma of the pancreatic duct with liver metastases, treated with a sequence devised following the MPACT and NAPOLI-1 study protocols, demonstrating an impressive response, while maintaining QoL.[48]

A retrospective single-center analysis conducted at the Medical University of Vienna including patients with non-resectable metastatic pancreatic adenocarcinoma confirmed the efficacy and tolerability results of the NAPOLI-1 trial with nal-IRI plus 5-FU/LV and showed that it can lead to better results in comparison to the OFF protocol.[49] In contrast, a retrospective real-world study evaluating the efficacy of oxaliplatin-based (FOLFOX, GEMOX, CAPOX) versus irinotecan-based therapies (nal-IRI, FOLFIRI) in 181 advanced pancreatic cancer patients previously treated with gemcitabine plus nab-paclitaxel was recently published.[50] The results showed a clear trend for improved survival outcomes with platinum-based doublet compared with regimens including irinotecan or nal-IRI. In this specific clinical setting, head-to-head trials are still lacking, and prospective, randomized trials are needed to examine the optimal treatment sequence.

In the absence of comparative trials, potential predictive factors are required. A large-scale study analyzing real-world patient characteristics, treatment patterns, and outcomes of patients with metastatic pancreatic cancer treated with nal-IRI has shown that the effectiveness of nal-IRI in the real world may be consistent with efficacy findings in the NAPOLI-1 trial, despite differences in patient characteristics and dosing patterns.[51] Real-world data further demonstrate that only a small proportion of patients (13%) reach a third-line treatment and that ineffective first-line treatment is often detrimental to a patient's prognosis.[52] Thus, it is essential that biomarker analysis and subsequent application of precision medicine are done at the beginning of the treatment course. In this regard, interleukin-8 (IL8) has been recently identified as the most significant circulating factor for the serine/threonine kinase TGFβ-activated kinase 1 (TAK1) pathway activation in an orthotopic nude murine model.[53] Mice bearing shTAK1 tumors had significantly lower plasma levels of IL8 and experienced a significant reduction in tumor growth if treated with nal-IRI, whereas TAK1-proficient tumors were also related to higher IL8 levels and chemoresistance. In the same research, in a discovery cohort of 77 patients, IL8 was the circulating factor most significantly correlated with survival and this finding was also validated in a further cohort of 50 patients.

TAK1 is a central fulcrum integrating the most important signals from different cytokines and determining resistance to chemotherapeutic treatments through the activation of several transcription factors.[54]

Recently, a post hoc analysis of NAPOLI-1 aimed to develop a predictive nomogram for OS at 6 and 12 months.[55] The eight factors that were determined to be the most influential were the Karnofsky Performance Status, the presence of liver metastasis, randomization to nal-IRI + 5-FU/LV, albumin (g/dL), neutrophil/lymphocyte ratio, CA 19–9 (U/mL), disease stage at diagnosis, and body mass index (kg/m^2). Despite several limitations, with the most relevant being the unequal distribution of some factors, such as few patients with KPS < 70, albumin < 30 g/L, or increased bilirubin, as the study population was favorably selected, the use of this nomogram may help to distinguish between risk groups in every day clinical practice.

Genetic testing of UGT1A1 polymorphisms before treatment with nal-IRI is not routinely done. Although it is recommended, no clear guidelines regarding its applicability are available. However, it is possible to start at a lower dose level as a precaution.

Going beyond the standard of care

Current standard of care treatments only lead to a 5-year survival rate of about 10% in all pancreatic cancer patients and only 1% in the case of metastatic disease.[9] Furthermore, improvement in survival rates of unresectable and/or metastatic disease has been minimal over recent decades. Surgery, as well as currently available chemotherapy and radiotherapy merely manage to extend the survival of the patients and/or relieve their symptoms, as no curative treatment is yet available for metastatic or locally inoperable cancer, which demands further research for the development of new local and systemic therapies.[4]

Immunotherapy, which has been very successful in treating many types of cancers, has demonstrated only limited activity in pancreatic cancer. This treatment strategy (especially pembrolizumab) is effective only in a highly specific, small patient subgroup characterized by microsatellite instability-high (MSI-H) pancreatic cancer (<1% of PDAC patients).[56] The KEYNOTE 158 study further showed that even among MSI-H tumors, the response of pancreatic cancer is worse than other non-colorectal cancer entities (only 1 patient with a complete response and 3 patients with partial response out of 22 patients).[57] Furthermore, a phase I trial evaluating the combination of cabiralizumab – an inhibitor of colony-stimulating factor 1 receptor (CSF1R) – plus nivolumab with and without chemotherapy in microsatellite stable (MSS) pancreatic cancer patients demonstrated encouraging results. However, phase II and phase III trials initiated based on these results did not meet their primary endpoints.[58–60] In the phase III SEQUOIA trial, an evaluation of FOLFOX with and without pegylated IL-10 also failed to demonstrate any treatment benefit.[61] Disappointing results have also been reported in a phase II trial exploring the combination of dual immune checkpoint inhibitors (durvalumab, a human monoclonal antibody that inhibits binding PD-L1 to its receptor, and tremelimumab, which is directed against CTLA-4) and gemcitabine plus nab-paclitaxel.[62] At the final analyses, combining PD-L1 and CTLA-4 inhibition with gemcitabine and nab-paclitaxel did not improve treatment efficacy. Overall, the failure of immunotherapy in PDAC observed so far may

reside in the low immunogenicity and the low tumor mutational burden. [63] Furthermore, the abundant stroma generates a hypoxic microenvironment and drives the recruitment of immunosuppressive cells through cancer-associated fibroblast activation and transforming growth factor β (TGF β) secretion. Correlative studies to assess biomarkers that may predict immune sensitivity in this setting are under way.

The POLO trial is another groundbreaking study in pancreatic cancer that analyzed the potential of poly ADP ribose polymerase (PARP) inhibitors in the treatment of germline *BRCA*-mutated pancreatic cancer patients. The patients were treated with platinum-based chemotherapy in the first line followed by maintenance with olaparib (a PARP inhibitor) or placebo if not progressing after at least 16 weeks. This study demonstrated that olaparib maintenance led to improved median PFS (7.4 months vs 3.8 months, HR: 0.53 [95% CI: 0.35–0.82]; p = 0.0038). No difference in OS between the groups was found, although the survival data had not reached maturity at the time of publication.[64] In December 2019, olaparib was approved in the USA for use in this patient setting and became the first biomarker-based targeted therapy approved for pancreatic cancer. Recently, the agent was also authorized by the European Medical Agency (EMA).[65] In Switzerland, this drug was approved in July 2020 by Swissmedic [66], however its cost-effectiveness ratio is not fully clear.

A new randomized study presented at ASCO-GI 2020 explored platinum-based chemotherapy (gemcitabine/cisplatin) with or without PARP inhibition (veliparib) in the first line for the treatment of *BRCA* or *PALB2*-mutated pancreatic cancer patients. In both study arms, the response rates were high with a numerical advantage in favor of the triplet regimen (74.1% vs 65.2%). However, no PFS benefit and worse toxicity were observed when adding PARP inhibition to chemotherapy, which was expected based on results from ovarian cancer studies.[67] Based on the benefits demonstrated by platinum-based chemotherapy in the first-line treatment of patients with a family history of breast, ovarian or pancreatic cancer, it should be a standard in their treatment. [68]

Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), was explored as the first-line option in the CANNCIC-PA3 trial. As a result, the disease control rate, complete response, partial response, and stable disease were significantly higher with erlotinib plus gemcitabine than placebo plus gemcitabine.[69] Nonetheless, due to a survival advantage of only 3 weeks, this combination has neither been recommended nor approved in Europe. A systematic review evaluating the potential benefit of adding cetuximab, an anti-EGFR monoclonal antibody, to standard chemotherapy for pancreatic cancer revealed that this modification led to no survival benefit, increased toxicity and higher costs.[70]

Recently, another phase III study was designed to determine if the addition of pegvorhyaluronidase alfa (PEGPH20) to nab-paclitaxel/gemcitabine in patients with hyaluronan-high metastatic pancreatic ductal adenocarcinoma (PDA) can prolong overall survival, did not meet its primary endpoint. Despite the molecular selection, the addition of PEGPH20 to nab-paclitaxel/gemcitabine did not improve overall survival.[71]

The results from the US Targeted Agent and Profiling Utilization Registry (TAPUR) study have demonstrated that single-agent palbociclib, a CDKN inhibitor, has no meaningful clinical activity in patients with CDKN2A-mutated or -deleted advanced PDAC and cholangiocarcinoma.[72] Interestingly, according to preclinical data, sequential administration of CDK4/6 inhibitors after taxanes cooperates to prevent cellular proliferation in PDAC cells, patient-derived xenografts[73], suggesting broad applicability for their sequential administration after available chemotherapeutic agents.

Thus, even though a number of studies have proposed new treatment options for pancreatic cancer, further studies investigating novel treatment strategies as well as molecular and genetic stratification of patients are still required.

It is evident that there is a lack of molecular and genetic biomarkers within the treatment landscape of pancreatic cancer. However, a review by Collisson et al. (2019) discussed the finding that a large proportion of pancreatic tumors harbor targets for precision oncology.[74] Currently, molecular testing and upfront panel testing (next-generation sequencing [NGS]) are used to identify the oncogenic driver. Genomic data generated by NGS may allow the development of personalized treatment programs with targeted therapies, given the large number of gene mutations seen in PDAC.

Recently, the results from more than 1000 patients with pancreatic cancer enrolled in the real-world Know Your Tumor (KYT) program in the USA have been published.[75] This analysis focused on the OS outcomes for patients whose tumors harbored actionable molecular alterations and who received a matched targeted therapy. As a final result, the median OS of patients with advanced pancreatic cancer and actionable alterations who received matched therapy was one year longer than those with actionable alterations who received unmatched therapy, or those without actionable alterations. Thus, whereas it is not currently recommended to perform tumor multigene NGS in patients with advanced pancreatic cancer in daily practice, considering the unmet medical need and the high number of alterations ranked as level II–IV, it is recommended to propose NGS to patients with advanced pancreatic cancer in the context of molecular screening programs, to get access to clinical trials with innovative drugs.[76]

Non-HRD pancreatic cancer patients (about 85%) are currently being studied to identify predictive biomarkers for optimal chemotherapy selection. An example is the COMPASS trial, where patients underwent whole-exome and RNA sequencing, in addition to MRI, in order to correlate gene expression patterns with a response to chemotherapy. [77] Furthermore, patients were divided into basal-like and classical cancer types, based on genetic subtyping. It was shown that basal-like cancer responds much less to chemotherapy, especially FOLFIRINOX. [78] This represents a new hope for the future in that, potentially, specific biomarkers might be discovered, which would be instrumental in guiding the selection of first-line chemotherapy.

NTRK gene fusions are known to be oncogenic drivers in rare cases (1%) of PDAC and have been shown to be actionable with tropomyosin receptor kinase (TRK) inhibitors, such as larotrectinib.[79] This drug has shown marked and durable antitumor activity in patients with TRK fusion-positive cancer, regardless of tumor type, and was recently approved in Switzerland in this indication.

Future perspectives

Mutations in KRAS are a major driver of PDAC progression, but it was considered an undruggable target until only recently. In fact, there have been some advances that have exploited KRAS as a therapeutic target, with promising “targeted” therapies and the single nucleotide variant-selective KRAS G12C inhibitors.[80,81] Approximately 3% of PDACs harbor KRAS G12C mutations.[82] As recently reported in *The New England Journal of Medicine*, the phase I CodeBreaK100 trial showed in detail the activity of the oral KRAS G12C inhibitor, sotorasib (AMG 510), in heavily pretreated patients with KRAS p.G12C-mutant advanced non-small cell lung cancer (NSCLC), colorectal cancer, and other solid tumors including pancreatic cancer.[83] Sotorasib produced an objective response in 32% of patients with NSCLC. Responses were also observed in patients with colorectal cancer and other solid tumors. Among 28 patients with other tumor types, 6 out of 8 evaluable patients with pancreatic cancer achieved stable disease, and 3 had an approximate 30% reduction in tumor burden from baseline. The authors concluded that sotorasib showed encouraging anticancer activity in patients with heavily pretreated advanced solid tumors harboring the KRAS p.G12C mutation.

Adagrasib (MRTX849), another novel agent targeting KRAS G12C mutations, also demonstrated similar signs of efficacy in patients with advanced NSCLC and colorectal cancer and other primary sites, whose

tumors harbor the molecular alteration. A confirmed partial response was observed in 1 patient with pancreatic cancer.[84] Innovative research has led to clinical trials targeting RAS-driven cancers, including small molecule inhibitors and combination therapy, to improve treatment efficacy and overcome resistance.

Approximately 8–10% of PDAC cases are *KRAS* wild type. In a subset of these tumors, neuregulin 1 (*NRG1*) gene fusions have been identified as targetable oncogenic drivers, providing a novel treatment strategy for this disease. As part of a prospective clinical trial, Jones and colleagues (2019) performed whole-genome sequencing and whole transcriptome analysis on 47 patients with metastatic PDAC. In all 3 patients with *KRAS* wild-type tumors, the authors discovered translocations affecting the *NRG1* gene that were predicted to be in-frame and preserved the EGF-like domain of the NRG1 protein.[85] Given that NRG1 binds the ERBB3 receptor, which heterodimerizes with ERBB2 to activate downstream signaling pathways, the authors treated 2 patients with the pan-ERBB receptor inhibitor, afatinib, and observed partial responses to therapy. This report describes NRG1 fusion proteins as an important oncogenic driver in a subset of *KRAS* wild-type pancreatic cancers and suggests a new therapeutic strategy for patients harboring these lesions. Namely, MCLA-128 has shown promising single-agent activity in a first-in-human study across several tumor types. The clinical proof-of-concept has been achieved in metastatic breast cancer and gastric cancer in heavily pretreated patients progressing on multiple anti-HER2 therapies.[86,87] MCLA-128 is now being investigated in patients with NRG1 fusion-positive tumors in the ongoing phase II part of the study (NCT02912949).

Although immunotherapy and personalized medicine have demonstrated very limited success so far, a small subgroup of patients with HRD-positive (*BRCA* mutated) disease has been deemed eligible for treatment with platinum-based chemotherapy as well as PARP inhibitors, which might become the next standard treatment for this patient subgroup. However, in HRD-negative patients, treatment decisions are still primarily based on the preference of the treating clinician. Furthermore, cytosolic 5′-nucleotidase 1A (NT5C1A), which mediates resistance to gemcitabine by dephosphorylating gemcitabine monophosphate and thus reducing the amount of cytotoxic gemcitabine metabolites intracellularly, has also been found to be highly expressed in the epithelial compartment of a subgroup of PDAC patients. Thus, analyzing the expression levels of NT5C1A might be instrumental in identifying patient subgroups more likely to develop gemcitabine resistance.[88,89] Finally, novel therapeutic strategies like oncolytic viral therapy and gene editing technology have shown promising results in pre-clinical and early phase clinical trials, and thus are worthy of further investigation.[16]

Conclusions

There have been many significant advances in the overall treatment landscape of pancreatic cancer in the last few years. This has led to changes in the standard of care and a better understanding of the disease biology. However, the prognosis of pancreatic cancer has not dramatically improved, and pancreatic cancer remains a devastating malignancy with limited treatment options. The identification of further prognostic and predictive biomarkers for molecular stratification of patients is imperative in this situation and will lead to optimal treatment decisions and ultimately better prognoses. Thus, focusing clinical trial designs on molecular screening of patients as well as improving access and participation in clinical trials will be instrumental not only in identifying novel therapeutic strategies but also in early diagnosis and improving the prognosis of this aggressive disease.[90]

CRediT authorship contribution statement

Sara De Dosso: Conceptualization, Writing - original draft, Writing - review & editing. **Alexander R. Siebenhüner:** Writing - review & editing. **Thomas Winder:** Writing - review & editing. **Alexander Meisel:** Writing - review & editing. **Ralph Fritsch:** Writing - review & editing. **Christoforos Astaras:** Writing - review & editing. **Petr Szturz:** Writing - review & editing. **Markus Borner:** Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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