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Platinum-Based Chemotherapy in Locally Advanced or Metastatic Pancreatic Ductal Adenocarcinoma: Summary of Evidence and Application in Clinical Practice

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Abstract
Background: Different therapeutic options are available for the treatment of advanced or metastatic pancreatic ductal adenocarcinoma (PDAC). Platinum-based multi-agent chemotherapy regimens, such as FOLFIRINOX, are important elements in the multidisciplinary management of PDAC. ***Summary:*** At least one third of patients with metastatic PDAC are eligible for treatment with FOLFIRINOX. Eligibility criteria include good performance status and the absence of relevant comorbidities. However, chemotherapies can potentially be associated with serious adverse events, such as diarrhea or polyneuropathies. Here, we review relevant data from first-line, second-line, and maintenance therapy trials as well as real-world data. In addition, we address the management of possible adverse events. ***Key Messages:*** (1) Selection of a suitable treatment regime depends on patient performance status, comorbidities, and anticipated toxicity. (2) FOLFIRINOX is an appropriate treatment for patients up to 75 years of age with an ECOG PS of 0 or 1, without relevant comorbidities, normal or nearly normal bilirubin levels, and no significantly reduced DPD activity. (3) In particular, patients with germline *BRCA1/2* (g*BRCA1/2*) or *PALB2* mutations may benefit from first-line platinum-containing therapy. (4) Early and comprehensive testing of the patient's mutational status could support the first-line treatment decision-making.

Introduction

Approximately 20,000 new cases and 18,000 deaths due to pancreatic cancer occurred in Germany in 2020 [1]. Pancreatic cancer is the 6th most common type of cancer in women and the 10th most common type of cancer in men. In Germany, however, it was the 2nd most common cause of cancer-related death in 2019 [2]. The prognosis of pancreatic cancer is still poor [3]. The 5-year overall survival rate is only 9% in Germany [1]. At the time of diagnosis, more than 80% of tumors are locally advanced (LA), inoperable, or metastatic [4]. The average age at diagnosis is 76 years for women and 72 years for men [1].

The treatment of non-resectable advanced pancreatic ductal adenocarcinoma (PDAC) comprises different regimens [4, 5]. Platinum-based first-line chemotherapy is an established systemic treatment option [5]; the FOLFIRINOX regimen, for example, consists of the components irinotecan (180 mg/m^2), oxaliplatin (85 mg/m^2), folinic acid (leucovorin, 400 mg/m^2), and 5-fluorouracil

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(5-FU, 400 mg/m^2 [bolus] followed by 2,400 mg/m^2 over 46 h intravenously every 2 weeks [the bolus is often waived]). In randomized controlled trials, treatment-eligible patients had an Eastern Co-operative Oncology Group (ECOG) performance status (PS) of ≤1. In clinical practice, about one-quarter to one-third of patients receive platinum-based chemotherapy in Europe, primarily FOLFIRINOX [4, 6]. Other options include the combination of *nab*-paclitaxel plus gemcitabine and gemcitabine monotherapy [4]. The latter is mainly suitable for patients with poor PS or substantial comorbidities, preventing a more aggressive treatment.

Mutations in the DNA damage response (DDR) genes *BRCA1/2* or *PALB2* can influence the response of tumors to a platinum-based treatment. Approximately 5–7% of the overall PDAC population has a germline mutation in *BRCA1/2* or *PALB2,* leading to homologous recombination deficiency (HRD) as described below [7–9]. Tumors with HRD are more sensitive to a platinum-based chemotherapy regimen than non-HRD tumors [10].

On the other hand, platinum-containing chemotherapies such as FOLFIRINOX are also associated with a wide range of potentially serious adverse events which may affect patient-reported quality of life and require close monitoring and adequate management. The goal of this review is to provide an overview of the available data from clinical trials for first-line, second-line, and maintenance therapy of LA or metastatic PDAC (mPDAC) with a focus on platinum-based chemotherapies. In addition, we will discuss possible therapy adjustments to manage or prevent chemotherapy-induced AE.

Guideline Recommendations for First-Line Therapy and Maintenance Therapy in Advanced PDAC

In Table 1, we have summarized the PDAC treatment recommendations of the American Society of Clinical Oncology (ASCO) [3], the National Comprehensive Cancer Network® (NCCN®) [11], as well as the German S3 guideline [12].

An Overview of Chemotherapy Regimens – Focus on Platinum-Based Regimens

First-Line Treatment

The pivotal trial evaluating FOLFIRINOX in patients with mPDAC was conducted in 2011 [13]. Overall, 342 patients with mPDAC were randomized to receive FOLFIRINOX or gemcitabine monotherapy as first-line treatment. The mean age of the patients was ≤75 years, and they had an ECOG PS of 0 or 1 as well as normal bilirubin levels. Patients in the FOLFIRINOX arm had a significantly longer median overall survival (OS, 11.1 vs. 6.8 months; hazard ratio [HR] for death, 0.57; 95% confidence interval [CI], 0.45–0.73; $p < 0.001$) and median progression-free survival (PFS, 6.4 vs. 3.3 months; HR for disease progression, 0.47; 95% CI, 0.37–0.59; $p < 0.001$). Grade 3/4 AE occurred more frequently in the FOLFIRINOX arm, e.g., significantly more neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy were observed. In another small Japanese trial in which 36 chemotherapy-naive patients with mPDAC were treated with FOLFIRINOX, a similar median PFS, median OS, and rate of AE were observed [14].

To reduce treatment-related toxicity, modifications of the FOLFIRINOX scheme are widely carried out in day-to-day clinical practice. A phase-II trial provides some data supporting the use of a modified FOLFIRINOX (mFOLFIRINOX) regimen. US-American patients with LA PDAC (n = 29) and mPDAC (n = 37) received an mFOLFIRINOX regimen in which irinotecan and the 5-fluorouracil bolus were reduced by 25% [15]. Compared to the historical (full-dose) cohort of the pivotal FOLFIRINOX trial [13], significantly lower rates of neutropenia, vomiting, and fatigue were observed, whereas the efficacy was preserved. These results were confirmed by another clinical trial [16]. The study population comprised 69 untreated patients with mPDAC. Again, compared to a historical Japanese cohort receiving full-dose FOLFIRINOX [14], a more favorable safety profile with no significant differences in efficacy were observed.

Another platinum-based chemotherapy that has been studied in trials is the combination of cisplatin and gemcitabine. This combination has been shown to prolong both PFS and OS in clinical trials and has also been studied in combination with poly(ADP-ribose) polymerase (PARP) inhibitors. In a phase III trial, 195 chemotherapy-naive patients with advanced PDAC were randomized to receive cisplatin plus gemcitabine or gemcitabine alone [17]. The combination led to a numerically longer median PFS and median OS; however, no statistical significance was observed. In a further phase II study, 51 patients with advanced PDAC and germline mutations in *BRCA1/2* or *PALB2* were randomized to receive cisplatin and gemcitabine with or without the PARP inhibitor veliparib [18]. The triple combination showed no survival advantages over the double combination but a worse safety profile. Interestingly, in this selected population, treatment with cisplatin and gemcitabine resulted in a median OS of 16.4 months and a median PFS of 9.7 months, with an acceptable tolerability, supporting the concept of good efficacy of platinum-based chemotherapy in *BRCA1/2* or *PALB2* germline mutated tumors. In a further phase III trial, gemcitabine plus oxaliplatin showed no survival benefit over gemcitabine alone in patients with advanced PDAC but a higher rate of ≥ grade 3 AE such as throm-

Table 1. International guideline recommendations for first-line and maintenance treatment of advanced and metastatic pancreatic cancer [3, 11, 12]

	American Society of Clinical Oncology [3]	National Comprehensive Cancer Network [11]	German S3 guideline [12]
First-line therapy	• FOLFIRINOX[a] for patients with ECOG PS 0–1, favorable comorbidity profile[b], patient preference, and a support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services • Gemcitabine plus *nab*-paclitaxel for patients with ECOG PS 0–1, relatively favorable comorbidity profile, patient preference, and a support system for aggressive medical therapy • Gemcitabine monotherapy for patients with ECOG PS 2 or comorbidity profile that precludes more aggressive regimens • Cancer-directed therapy on a case-by-case basis for patients with ECOG PS 3 or with poorly controlled comorbid conditions	NCCN preferred regimens for LA disease: • FOLFIRINOX or modified FOLFIRINOX for patients with ECOG PS 0–1 • Gemcitabine plus albumin-bound paclitaxel for patients with ECOG PS 0–2 • FOLFIRINOX or modified FOLFIRINOX for patients with known germline *BRCA1/2* or *PALB2* mutations • Gemcitabine plus cisplatin for patients with known germline BRCA1/2 or PALB2 mutations • Gemcitabine standard dose (category 1)[c] for patients with poor performance status • Gemcitabine fixed-dose-rate (category 2B)[c] for patients with poor performance status • Capecitabine (category 2B)[c] for patients with poor performance status • Continuous infusion 5-FU (category 2B)[c] for patients with poor performance status	Chemotherapy for patients with ECOG PS 0–2 Options: • FOLFIRINOX for patients with ECOG PS 0-1, favorable comorbidity profile, patient preference, and appropriate supportive therapy • Gemcitabibe-based combinations for patients not tolerating FOLFIRINOX or not wishing to be treated with FOLFIRINOX • Gemcitabine plus *nab*-paclitaxel for patients with ECOG PS 0–1, relatively favorable comorbidity profile, patients wishing to be treated with this regimen, and access to appropriate supportive therapy • Gemcitabine + erlotinib as an alternative to gemcitabine monotherapy • Gemcitabine monotherapy for patients not tolerating combinations due to ECOG PS ≥2 and/or comorbidity profile, patient preference Platinum-based chemotherapy for patients with known germline *BRCA1* or *BRCA2* mutations
Maintenance	Olaparib or chemotherapy for patients with germline *BRCA1* or *BRCA2* mutations and no disease progression for at least 16 weeks, after platinum-based chemotherapy as first-line treatment	Olaparib for patients with germline *BRCA1* or *BRCA2* mutations and no disease progression after 4–6 months of platinum-based chemotherapy as first-line treatment	Substances that affect DNA repair mechanisms such as PARP inhibitors for patients with known germline *BRCA1* or *BRCA2* mutations

DNA, deoxyribonucleic acid; ECOG, Eastern Co-operative Oncology Group; PARP, poly(adenosine diphosphate-ribose) polymerase; PS, performance status. [a]FOLFIRINOX = irinotecan (180 mg/m^2), oxaliplatin (85 mg/m^2), folinic acid (leucovorin, 400 mg/m^2), and 5-fluorouracil (5-FU, 400 mg/m^2 (bolus) followed by 2,400 mg/m^2 over 46 h intravenously every 2 weeks. [b]Favorable comorbidity profile loosely defined as hemoglobin ≥10 g/dL and platelet count ≥100,000/mL without transfusion support; absolute neutrophil count ≥1,500/mL; bilirubin and international normalized ratio ≤1.5 times the upper limit of normal; albumin ≥3 g/dL; creatinine clearance ≥60 mL/min/1.73 m^2; and absence of comorbid conditions that require ongoing active medical care, such as congestive heart failure, chronic obstructive pulmonary disease, uncontrolled diabetes mellitus, and neurologic disorders [3]. [c]NCCN categories of evidence and consensus: category 1: based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate; category 2B: based upon lower level evidence, there is NCCN consensus that the intervention is appropriate.

bocytopenia, vomiting, and peripheral sensory polyneuropathy [19].

Non-platinum-based chemotherapies evaluated in clinical trials for treating advanced PDAC have been monotherapies with gemcitabine or 5-FU and the combination of *nab*-paclitaxel plus gemcitabine. Gemcitabine monotherapy (1,000 mg/m^2 weekly × 7 followed by 1 week of rest, then weekly × 3 every 4 weeks thereafter) was compared to the 5-FU monotherapy (600 mg/m^2 once weekly) in 126 chemotherapy-naive patients with advanced PDAC [20]. Treatment with gemcitabine led to a higher rate of sustained improvement in at least one parameter among pain, Karnofsky performance status, and weight (23.8 vs. 4.8%, $p = 0.0022$), as well as a modest survival benefit (median OS 5.65 vs. 4.41 months, $p = 0.0025$) in comparison with 5-FU. However, in the gemcitabine arm, grade 3/4 AE occurred more frequently. In a phase III trial, the combination of *nab*-paclitaxel plus gemcitabine revealed a significant survival benefit when tested versus gemcitabine (median OS 8.5 vs. 6.7 months, HR for death 0.72; 95% CI, 0.62–0.83; $p < 0.001$) at the price of higher rates of peripheral neuropathy (17 vs. 1%) and neutropenia (38 vs. 27%) [21]. AE seemed to be reversible, though.

Phase II trials aiming for a surgical conversion rate as primary end point in LA PDAC compared platinum and gemcitabine-based combination treatment/treatment sequences include the SWOG S1505, JCOG 1407, and NEOLAP-AIO trial [22–24]. Results from these trials with regard to *BRCA1/2* and *PALB2* mutations have not yet been reported.

Taken together, FOLFIRINOX is an option for first-line therapy in younger patients (≤75 years) with an ECOG PS of 0 or 1 and normal or nearly normal bilirubin

levels (level of evidence, LoE 5; grade of recommendation, GoR A) [12]. Modified FOLFIRINOX represents an alternative to reduce the risk of AE. Another first-line standard of care is the combination of *nab*-paclitaxel plus gemcitabine which is also suitable for patients with an ECOG PS of 0–2 (LoE 5; GoR A) [12]. Furthermore, the combination of cisplatin and gemcitabine is an option in patients with advanced PDAC and germline mutations in *BRCA1/2* or *PALB2* (LoE 2/4; GoR B) [12]. Gemcitabine monotherapy is an alternative for patients with poor PS or relevant comorbidities (LoE 5; GoR B) [12].

Impact of Germline BRCA1/2 or PALB2 Mutations on Efficacy of Platinum-Based Chemotherapy (Platinum Sensitivity)

Approximately 5–7% of the overall PDAC patient population carries a germline mutation in the DDR genes *BRCA1/2* or *PALB2* [7–9]. BRCA1 and BRCA2 are essential proteins in homologous recombination following DNA double strand breaks. PALB2 is in turn an important regulator of BRCA2 function. Loss of function of these genes leads to HRD. BRCAness (*BRCA* mutations and mutations causing a BRCA-like phenotype) has to be distinguished from HRDness (other somatic or germline mutations causing HR defects, including non-BRCA-related phenotypes) [25]. Tumors with HRD are likely to be more sensitive to platinum-based chemotherapy than non-HRD tumors because of higher sensitivity to DNA damage and cross-linking agents due to defective DNA repair mechanisms.

Germline mutations in *BRCA1/2* are enriched in patients with PDAC and personal or family history of BRCA-associated tumors such as ovarian, mamma, prostate, or pancreatic cancer and also in patients with early-onset PDAC (<50 years). In patients with g*BRCA1/2* mutations that meet the criteria stated above, platinum-based first-line therapy should preferably be initiated [12]. Due to low case numbers (or incidence) for other DDR genes (such as PALB2), this recommendation should be limited to gBRCA [12].

In a retrospective trial, the efficacy of mostly first-line platinum-based chemotherapy in patients with LA or mPDAC and a known g*BRCA1/2* or *PALB2* mutation was evaluated [9]. The population included 26 mutation-positive patients; each patient was matched to a cohort of platinum-treated control PDAC patients ($n = 52$). Treatments were as follows:

- FOLFIRINOX: $n = 10$ (38.5%) versus $n = 39$ (75%)
- FOLFOX: $n = 10$ (38.5%) versus $n = 11$ (21.1%)
- Cisplatin plus gemcitabine: $n = 6$ (23%) versus $n = 1$ (1.9%)
- Cisplatin plus gemcitabine plus *nab*-paclitaxel: $n = 0$ versus $n = 1$ (1.9%)

The objective response rate was significantly better in patients with DDR gene mutations ($n = 14$) versus controls ($n = 8$): 58 versus 21% ($p = 0.0022$). The median real-world PFS amounted to 10.1 months for mutation-positive patients versus 6.9 months for controls (HR 0.43; 95% CI, 0.25–0.74; $p = 0.0068$). The respective numbers for median real-world OS were 24.6 versus 18.8 months ($p = 0.0467$).

Frequency of HRD in patients with advanced PDAC was assessed in another trial [26]. Fifty (19%) out of 262 patients had an HRD – 15% ($n = 40$) germline mutations (17 monoallelic, 23 biallelic) and 4% ($n = 10$) somatic mutations (4 monoallelic, 6 biallelic). Median OS in HRD-positive patients treated with first-line platinum-based chemotherapy amounted to 25.1 months, whereas HRD-negative patients treated with or without first-line platinum-based chemotherapy had a median OS of 15.3 or 13.0 months. Median PFS was significantly longer in HRD-positive patients treated with first-line platinum-based chemotherapy versus HRD-negative patients (HR 0.44; 95% CI, 0.29–0.67; $p < 0.01$).

A trial evaluating the efficacy of platinum-based chemotherapy in g*BRCA1/2*-positive mPDAC included 71 patients [10]. The OS analysis was based on data from 58 patients, of which 43 had stage 3 ($n = 15$) or 4 ($n = 28$) disease. Twenty-two patients with stage 3 or 4 PDAC received a platinum-based therapy – mostly cisplatin plus gemcitabine. The median OS for stage 3 or 4 PDAC was 22 months if treated with platinum-based chemotherapy versus 9 months if treated with non-platinum-based chemotherapy ($p < 0.039$).

In summary, platinum-based chemotherapy should be the first choice in eligible patients with advanced PDAC and g*BRCA1/2* or *PALB2* mutations (LoE 2/4; GoR B). However, there is no evidence for efficacy in patients with advanced PDAC and somatic *BRCA1/2* or *PALB2* mutations.

Routine screening for HRD-positive tumors is currently not established in the treatment of PDAC. However, the importance of screening, e.g., with next generation sequencing, for actionable molecular alterations has been demonstrated in a retrospective analysis of the US Know Your Tumor (KYT) program [27]. This program enables PDAC patients to undergo commercially available multi-omic profiling for molecularly tailored therapy options. The results suggest that treatments specifically targeting oncogenic drivers and DNA repair mechanisms may have a substantial impact on survival and warrant further prospective evaluation.

There is a clear need to harmonize HRD definitions and to validate optimal biomarkers, including somatic and germline analyses. Clinical differences between somatic versus germline mutations, monoallelic versus biallelic inactivation, and the prediction of molecular altera-

tions to therapeutic sensitivity have to be addressed. Though extension of genes in NGS panel testing increases the probability of HRD identification, there is no evidence beyond the core *BRCA1/2* and *PALB2* genes. Especially in unresectable PDAC, formalin-fixed clinical biopsies used for sequencing are often small, so current diagnostic assays are mostly focused on the coding regions [28].

Second-Line Treatment

There is less evidence for second-line chemotherapy in patients with advanced PDAC. In the NAPOLI-1 trial, patients (n = 417) with mPDAC who progressed after previous gemcitabine-based therapy were randomized to receive either nanoliposomal irinotecan monotherapy, 5-FU plus folinic acid, or a combination of nanoliposomal irinotecan, 5-FU, and folinic acid in second or further lines [29]. Nanoliposomal irinotecan in combination with 5-FU/folinic acid showed a significant survival benefit (median OS 6.1 vs. 4.2 months) compared to 5-FU/folinic acid, with a manageable safety profile. There was no difference concerning efficacy between patients treated with nanoliposomal irinotecan and patients treated with 5-FU/folinic acid.

The CONKO-003 trial compared the triple combination of oxaliplatin, 5-FU, and folinic acid (OFF) to the dual combination of 5-FU and folinic acid (FF) [30]. The analysis was based on data of 160 patients with mPDAC and progression on first-line gemcitabine. The median PFS and median OS were significantly longer in the OFF arm versus the FF arm, whereas the tolerability was similar. Of note, both the NAPOLI-1 as well as the CONKO-003 trial included patients mainly receiving gemcitabine as a single agent in the first line.

Randomized trials assessing the combination of *nab*-paclitaxel plus gemcitabine as second-line treatment are lacking. Prospectively obtained data from the TRYbeCA-1 trial, where patients in the control subgroups received either irinotecan-5FU or gemcitabine plus *nab*-paclitaxel, depending on the prior first-line therapy, showed a median OS of 6.9 months in the gemcitabine plus *nab*-paclitaxel arm [31]. In the guidelines of the American Society of Clinical Oncology (ASCO), this combination is recommended for patients who have received a first-line treatment with FOLFIRINOX, have an ECOG PS of 0 or 1, and a relatively favorable comorbidity profile [3]. In summary, nanoliposomal irinotecan, 5-FU, folinic acid, and the OFF combination are evidence-based options for treating patients with advanced PDAC and progression after gemcitabine-based first-line treatment [32].

Maintenance Treatment after Platinum-Based First-Line Chemotherapy

Effective first-line mPDAC treatment options such as mFOLFIRINOX or *nab*-paclitaxel plus gemcitabine raise the question of maintenance therapies in patients with stable disease or an objective response [33]. In France for instance, FOLFIRINOX treatment is usually discontinued after 6 months or 12 cycles with no consecutive maintenance therapy [13]. In the retrospective PANOPTIMOX trial, 273 patients with mPDAC were included and randomized to three treatment arms [34]. Sequential therapy with 5-FU, folinic acid, and irinotecan (FOLFIRI) and gemcitabine (arm C) was not as effective as FOLFIRINOX (8 cycles) followed by maintenance therapy (arm B) or FOLFIRINOX (12 cycles) followed by no maintenance therapy (arm A). More severe neurotoxicity (sensory neuropathy) could be observed in arm B versus arm A, probably due to a higher cumulative oxaliplatin dose. In arm A, severe neurotoxicity occurred within the first 6 months of treatment. In comparison, in arm B, severe neurotoxicity set in predominantly within the first 6 months of treatment, but a considerable proportion of patients also showed the first symptoms later on.

In another retrospective study, 30 patients who had initially been treated with FOLFIRINOX and had not shown any signs of progression received maintenance therapy with capecitabine. The median OS in this patient group amounted to 17 months [35]. Considering that results of retrospective studies should be interpreted with caution, maintenance therapy post FOLFIRINOX might be effective and seems to be associated with a good tolerability. The PACT-12 phase II trial comparing sunitinib as maintenance therapy to observation only showed a significantly better PFS and numerically but not significantly longer median OS in 55 patients [36]. Grade 3/4 AE, such as neutropenia, thrombocytopenia, hand-foot-syndrome, or diarrhea, occurring in the sunitinib arm were manageable. In summary, the evidence on maintenance therapy is weak and further research is needed.

A de-escalation strategy of platinum-based chemotherapy (FOLFIRINOX) was assessed in a retrospective trial including 147 patients with mPDAC [37]. De-escalation was defined as stopping oxaliplatin and/or irinotecan after at least four cycles of FOLFIRINOX and no evidence of progression. Similar results for treatment with 5-FU compared to FOLFIRI could be obtained.

Maintenance therapy with the PARP inhibitor olaparib was evaluated in the POLO trial, the only trial so far examining active maintenance treatment in mPDAC in a prospective and randomized fashion, albeit in a particular subgroup of patients with mPDAC [38]. The population included 154 patients with mPDAC, g*BRCA1/2* mutations, and no progression after previous platinum-based chemotherapy for at least 16 weeks. Patients receiving olaparib had a significantly longer median PFS than patients receiving placebo. The median OS was not significantly different between treatment groups [39]. Grade ≥3 AE such as anemia, fatigue, or asthenia occurred more

often in the olaparib group but were manageable. In addition, a numerically better response rate and PFS2 (defined as time from randomization to second progression or death) were observed in the olaparib arm.

Before olaparib, maintenance therapies relied on chemotherapy regimens, typically including fluorouracil or gemcitabine. These treatments are often given until the patient becomes intolerant to the treatment due to toxicities. Therefore, olaparib is a welcome addition to the treatment of mPDAC, even if only in a small subgroup of patients. It is currently approved as the active maintenance treatment for g*BRCA1/2*-mutated mPDAC that has not progressed at least 16 weeks of a first-line platinum-based therapy.

Real-World Data

How are the above-mentioned platinum-based treatment options currently used in clinical practice in Germany and other European countries? Here, we summarize real-world data regarding the treatment of advanced PDAC from 2 studies. The prospective clinical cohort study *Tumorregister Pankreaskarzinom* (Tumor Registry Pancreatic Cancer) included 1,174 patients with advanced PDAC starting first-line therapy in 104 mainly outpatient German cancer centers [4]. The most common first-line therapies were the combination of *nab*-paclitaxel plus gemcitabine (42%) followed by FOLFIRINOX (24%) and gemcitabine monotherapy (23%). Patient subgroups differed considerably with regards to age, PS, and comorbidities. Older patients or more comorbid patients were more likely to receive a monotherapy with gemcitabine. The median OS and median PFS varied between 6.8 and 11.3 months and 4.6 and 6.3 months, respectively. FOLFIRINOX treatment was associated with the longest median OS (11.3 months) and PFS (6.3 months). However, this therapy was mainly administered to younger and less comorbid patients. In total, only 40% of patients starting a first-line treatment went on to receive a second-line treatment. The most common second-line regimens were *nab*-paclitaxel plus gemcitabine (28.9%), FOLFOX/OFF (folinic acid plus 5-FU plus oxaliplatin, 23.8%), gemcitabine (11.5%), FOLFIRINOX (7.9%), and 5-FU (4.1%).

A retrospective, observational chart review study was conducted to evaluate the treatment of mPDAC in five European countries: France, Germany, Italy, Spain, and the UK [6]. The analysis was based on data from 2,565 patients. Of note, the most common treatment was the FOLFIRINOX regimen (35.6%; in Germany, 33.5%). It was followed by *nab*-paclitaxel plus gemcitabine (25.7%; in Germany, 31.0%) and gemcitabine monotherapy (20.5%; in Germany, 15.9%). Other combinations with gemcitabine, including gemcitabine plus cisplatin, were used in 9.2% (in Germany, 10.5%). Again, patients ≤65 years with an ECOG PS of 0 or 1 were more likely to be treated with mFOLFIRINOX rather than with *nab*-paclitaxel plus gemcitabine. Full-dose FOLFIRINOX was more often administered than mFOLFIRINOX omitting the 5-FU bolus (28.1 vs. 7.4%). Subsequent dose modifications were less frequent with mFOLFIRINOX (26.1 vs. 6.7%). Patients reaching the longest median OS of 16 and 15 months received mFOLFIRINOX and full-dose FOLFIRINOX, respectively. Treatments with *nab*-paclitaxel plus gemcitabine or gemcitabine monotherapy led to a median OS of 12 and 9 months, respectively. Information regarding second-line treatment was available for 1,666 patients. The most common treatment was gemcitabine monotherapy (27.1%; in Germany, 16.2%). Altogether, 5-FU-based treatments were used in 44.9% (in Germany, 37.2%) and gemcitabine-based treatments were used in 53.2% (in Germany, 61.6%) of cases. It has to be considered that the local reimbursement schemes for combinations such as gemcitabine plus *nab*-paclitaxel may have impacted treatment decisions.

The presented data show that platinum-based chemotherapy is frequently used in Europe. The application is in line with current guidelines. The median OS and median PFS achieved in these real-world populations are comparable to or even better than the results of clinical trials.

Possible Modifications of Platinum-Based Chemotherapy

Taken together, platinum-containing chemotherapy with the FOLFIRINOX regimen is an option for up to one-third of patients with advanced PDAC. The clinical data presented demonstrate the efficacy of this therapy in certain patients; however, it is also associated with AE such as polyneuropathy or diarrhea. In the following part, we would like to discuss possible modifications of platinum-based chemotherapy. The discussion is driven by the results of clinical trials and our own experience with FOLFIRINOX therapy. We are focusing on how to start FOLFIRINOX treatment and how to manage AE such as polyneuropathy and diarrhea. The information is summarized in Figure 1.

Criteria for Using mFOLFIRINOX

We recommend starting mFOLFIRINOX in advanced or mPDAC if all of the following criteria are fulfilled:

- Age ≤75 years
- Good performance status – ECOG PS 0–1
- No relevant comorbidities (for details see Table 1)
- Patient preference

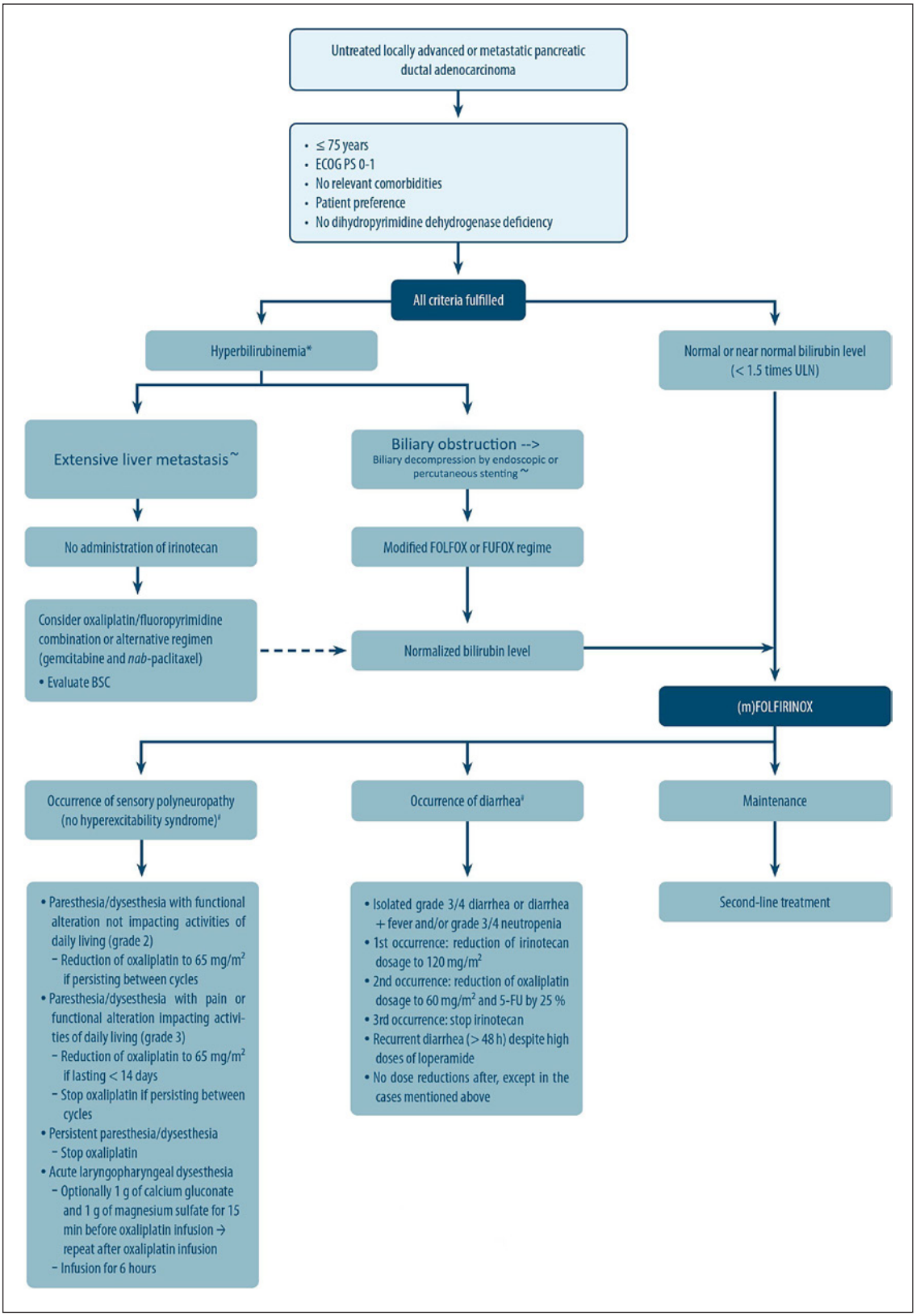

Fig. 1. Therapeutic algorithm for FOLFIRINOX treatment in LA or mPDAC (mod. from [40–42]). # Mod. [40], * Mod. [41], ~ Mod. [42]. ULN, upper limit of normal.

- Normal or near normal bilirubin level (<1.5 times the upper limit of normal)
- No dihydropyrimidine dehydrogenase deficiency (see below)

Elderly Patients

Some authors have discussed starting FOLFIRINOX in a significantly reduced dose in elderly or fragile patients with mPDAC, assuming a better tolerability of the treatment [5]. In clinical trials, dose-adjusted platinum-based chemotherapies in elderly or fragile patients with gastrointestinal cancers have been evaluated [43]. However, patients with advanced PDAC were not included. Dose-adjusted chemotherapy resulted in similar efficacy but less AE than full-dose chemotherapy in elderly or fragile patients with advanced gastroesophageal cancer.

While some of us believe that initial dose reductions in patients with advanced PDAC and reduced PS or relevant comorbidities may be beneficial, others think that the approach of starting FOLFIRINOX in a significantly reduced dose is generally not recommendable in advanced PDAC as supporting data are missing. Nevertheless, the age of a patient is not an exclusion criterion for the treatment with FOLFIRINOX. Therefore, patients older than 75 years with an ECOG PS of 0-1 and no relevant comorbidities may be treated with FOLFIRINOX in full dose (LoE 5; GoR A) [12], keeping in mind that the data this recommendation is based on derives from a trial that excluded patients over 75 years of age [13].

Dosage

As described previously, an mFOLFIRINOX regimen for the treatment of advanced or mPDAC may consist of an initial 25% reduction in 5-FU bolus and irinotecan dosing. In the adjuvant setting, an mFOLFIRINOX regimen without a 5-FU bolus and in most cases with a reduction of the irinotecan dose to 150 mg/m^2 was successfully administered [40]. We would not use a 5-FU bolus outside of trial environments, and we would also not recommend starting mFOLFIRINOX treatment with additional dose adjustments wherever possible. So far, there is no evidence that further dose adjustments are as effective as a non-dose adjusted regimen. In our opinion, the patient is probably not eligible for FOLFIRINOX therapy if the dosage needs further adjustments, i.e., modifications other than the above-mentioned, and should preferably be treated with a dual combination (i.e., *nab*-paclitaxel plus gemcitabine). Dose modifications and adjustments as well as alternative regimens could increase the proportion of platinum-eligible patients significantly. It is important that patients are involved in the treatment decision-making – when there are different treatment options and when available evidence is equivocal, especially in patients where HRD is present or not unlikely.

However, a patient with a reduced ECOG PS due to the underlying pancreatic cancer (i.e., high tumor burden) could be an indication for an mFOLFIRINOX treatment with further dose modifications. In this approach, the idea would be to first improve the PS so that an mFOLFIRINOX treatment becomes possible. An mFOLFIRINOX treatment could then be administered after two cycles of FOLFOX or dose-adjusted mFOLFIRINOX, providing that the patient has recovered.

Hyperbilirubinemia

Hyperbilirubinaemia, generally correlated with biliary obstruction, is associated with shorter overall survival in patients with pancreatic cancer [44, 45]. In addition, preconditions like Gilbert-Meulengracht's syndrome may additionally increase hyperbilirubinemia and therefore limit the treatment with irinotecan. Therefore, only patients with a normal or near to normal bilirubin concentration at baseline (<1.5 times upper limit of normal) should be treated with mFOLFIRINOX without dose adjustment. Determining the underlying cause of hyperbilirubinemia is crucial. Specifically, biliary decompression by endoscopic or percutaneous stenting may contribute to normalize bilirubin levels. For further details, see Figure 1. Careful monitoring of liver parameters during chemotherapy is warranted. *Nab*-paclitaxel and gemcitabine should also be used with caution in patients with hyperbilirubinaemia [42].

Dihydropyrimidine Dehydrogenase Deficiency

Dihydropyrimidine dehydrogenase deficiency (DPD) is associated with a higher toxicity of 5-FU treatment [46]. DPD is caused by variants of the DPD gene DPYD. We recommend testing patients for the four most common DPYD variants before starting treatment. The 5-FU dose should be adjusted in accordance with a publicly available, risk-adapted algorithm [46].

Managing Adverse Events

Polyneuropathy

Health care professionals should differentiate between hyperexcitability syndrome and dose-dependent peripheral polyneuropathy. Sensory polyneuropathy usually occurs with prolonged FOLFIRINOX treatment [13], especially due to the administration of oxaliplatin. Possible dose modifications because of polyneuropathy are summarized in Figure 1.

Some of us would recommend treating patients with mFOLFIRINOX for at least 4 months and discontinuing oxaliplatin after 4 months. Even after discontinuation of oxaliplatin, long-term survival is possible in patients, who have reached stable disease or an objective response. FOLFIRI maintenance therapy is feasible, safe, and may also be efficacious [47].

Diarrhea

Diarrhea is a common AE during treatment with mFOLFIRINOX. Recommendations for possible dose modifications can be found in Figure 1. In case of clinically relevant persisting diarrhea, lasting more than 2 days despite adequate AE management, the dose should be adapted as described in the algorithm.

Conclusion

Platinum-based therapy represents a possible therapeutic option for a specific subgroup of patients with advanced or mPDAC. Particularly for the FOLFIRINOX regimen, study results are available, indicating good efficacy and tolerability of this combination.

In our opinion, FOLFIRINOX is an appropriate treatment for patients up to 75 years of age with an ECOG PS of 0 or 1, who have no relevant comorbidities, no elevated bilirubin levels, and no DPD. Approximately one-third of patients meet these criteria. However, AE such as polyneuropathies or diarrhea may occur with this therapy, which may limit the quality of life of affected individuals.

We recommend starting FOLFIRINOX therapy without the 5-FU bolus and, if possible, considering dose modifications only if dose-limiting AE occur. In Figure 1, we have presented an algorithm for FOLFIRINOX therapy that summarizes the criteria for initiating therapy and describes a possible course of action in the presence of pre-existing hyperbilirubinemia or if side effects occur.

In conclusion, in our opinion, FOLFIRINOX remains a very important therapeutic option in the treatment of advanced PDAC and may be offered to patients, considering individual conditions and the options discussed. In particular, patients with g*BRCA1/2* or *PALB2* mutations may benefit from first-line platinum-containing therapy. This offers them the potential option of active maintenance therapy (with olaparib) if they have no progression for at least 16 weeks. Evidence is scarce though for olaparib as maintenance therapy after 16 weeks in *PALB2* mutated PDAC and tumors with somatic mutations where treatment options have to be investigated further. Early and comprehensive testing of the patient's mutational status would be desirable to support the first-line treatment decision-making.

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Conflict of Interest Statement

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Author Contributions

Anke Reinacher-Schick, Dirk Arnold, Marino Venerito, Eray Goekkurt, Anna-Lena Kraeft, and Thomas Seufferlein contributed to the content of the manuscript and provided personal clinical experience. Anke Reinacher-Schick and Thomas Seufferlein took the lead in writing the manuscript. Anke Reinacher-Schick, Dirk Arnold, Marino Venerito, Eray Goekkurt, Anna-Lena Kraeft, and Thomas Seufferlein provided critical feedback and helped shape the research, analysis, and manuscript.

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