Chemotherapy for pancreatic cancer

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Summary

Chemotherapy is an important part of multimodality pancreatic cancer treatment. After curative resection, adjuvant chemotherapy can significantly improve disease-free survival and overall survival. The current standard of care is six months adjuvant chemotherapy with modified folinic acid, 5-fluorouracil, irinotecan and oxaliplatin (mFOLFIRINOX) in patients fit enough for this protocol, otherwise six months of gemcitabine and capcitabine based on the European Study Group for Pancreatic Cancer (ESPAC)-4 study. In patients with metastatic disease, combination chemotherapy according to the FOLFIRINOX protocol or with gemcitabine plus nab-paclitaxel is an important improvement to gemcitabine monotherapy that was the standard for many years. Patients not fit for combination chemotherapy however may still benefit from gemcitabine. Patients with good performance status may benefit from second-line chemotherapy. Chemoradiation has long been used in locally advanced pancreatic cancer but is now tempered following the LAP07 study. This trial showed no difference in overall survival in those patients with stable disease after four months of gemcitabine (with or without erlotinib) randomized to either continuation of gemcitabine therapy or chemoradiation (54 Gy with capecitabine). As an alternative to radiation, other forms local therapies including radiofrequency ablation, irreversible electroporation, high-intensity focused ultrasound, microwave ablation and local anti-KRAS therapy (using siG12D-LODER) are currently under investigation. Given the systemic nature of pancreas cancer from an early stage, the success of any local approach other than complete surgical resection (with adjuvant systemic therapy) is likely to be very limited. In patients with locally advanced, resectable cancer, chemotherapy may offer the chance for secondary resection with a survival similar to patients with primary resectable disease. Downstaging regimens need to be evaluated in prospective randomized trials in order to make firm recommendations. Selection of patient groups for specific therapy including cytotoxics is becoming a reality using assays based on drug cellular transport and metabolism, and molecular signatures. Going forward, high throughput screening of different chemotherapy agents using molecular signatures based on patients’ derived organoids holds considerable promise.
Background

Pancreatic ductal adenocarcinoma (PDAC) has the worst 5-year survival of all the common malignancies [1-3]. Surgery with adjuvant chemotherapy is the only chance for cure, but most patients are diagnosed with irresectable disease, leaving palliative chemotherapy as the mainstay of treatment for most patients. Despite major advances in surgical techniques and adjuvant chemotherapy, most patients relapse after surgery and are finally also treated with palliative chemotherapy.

PDAC is relatively chemotherapy refractory. In contrast to other types of cancer, such as colon cancer or breast cancer, the survival benefits in metastatic cancer even with intensive combination chemotherapy are only very modest [4]. Even with the most effective poly-chemotherapy protocols, which can only be administered to selected patients with good performance status, the median overall survival of stage IV patients does not exceed one year [5]. Efforts to optimize symptom control in patients with advanced disease, in particular biliary drainage, pain control, and nutrition may facilitate the benefits of palliative chemotherapy. Recently albumin-bound paclitaxel (nab-paclitaxel) [6] and nanoliposomal irinotecan [7] have been licensed for metastatic pancreatic cancer [8]. In this review, we will summarize the currently available systemic therapies for:

- patients with metastatic pancreatic cancer disease;
- patients with operable cancer;
- patients with locally advanced, irresectable disease.

Chemotherapy for patients with metastatic disease

First-line chemotherapy

The first landmark study regarding palliative chemotherapy in PDAC patients was published in 1997 and compared gemcitabine (1000 mg/m² weekly for seven weeks, one week of rest, followed by weekly gemcitabine for every 3 out of 4 weeks) with weekly 5-fluorouracil (5-FU, 600 mg/m²) as first-line treatment for patients with locally advanced, irresectable disease or metastatic [9] (table 1). At that time, 5-FU was most commonly used in various doses and protocols although larger randomized studies defining the benefit of single-agent 5-FU compared to best supportive care were missing [10]. Gemcitabine treatment resulted in an increase in median overall survival from 4.41 to 5.65 months (P = 0.0025) and a superior 1-year survival of 18% versus 2%, suggesting that a proportion of patients might derive benefit from it, but, as yet, predictive biomarkers to identify these have remained elusive. Additionally, a higher percentage of patients in the gemcitabine group experienced a "clinical benefit response" that was a composite measurement of pain, Karnofsky performance status and weight status (23.8% versus 4.8%, P = 0.0022). Since gemcitabine therapy was also better tolerated than 5-FU, gemcitabine monotherapy became the standard of care. Subsequently, a variety of gemcitabine combinations with different chemotherapeutic partners, including cisplatin, oxaliplatin, and capetitabine were tested but failed to show superiority to gemcitabine monotherapy in randomized phase III trials (reviewed in [11]). Meta-analyses showed a small benefit for gemcitabine combinations with platinum analogs or fluoropyrimidines, especially in patients with good performance status [12-15]. In 2011, Conroy et al. published the results of the ACCORD11/PRODIGE4 study that represents a milestone in pancreatic cancer chemotherapy. The study recruited 342 patients with stage IV PDAC [5]. Patients receiving FOLFIRINOX, a combination therapy of oxaliplatin (85 mg/m²), irinotecan (180 mg/m²), and 5-FU (400 mg² as bolus and 2400 mg/m² as continuous infusion) achieved a median overall survival of 11.3 months. Median overall survival in the gemcitabine control group was, consistent with previous studies, about 6.8 months (hazard ratio for death 0.57, P < 0.001). The objective response rate in the FOLFIRINOX group was 31.6% compared to 9.4% in the gemcitabine group (P < 0.001); 1-year survival was 48.4% versus 20.6%. Importantly, this study only included patients that had an Eastern cooperative oncology group (ECOG) performance status of 0 or 1, were younger than 76 years, had no significant cardiac disease, and near normal bilirubin. As expected, the FOLFIRINOX group had higher rates of grade III/IV toxicities, especially neutropenia, diarrhea and peripheral neuropathy [5]. Despite these adverse effects, the quality of life was better in the FOLFIRINOX group than in the gemcitabine group, because FOLFIRINOX improved and delayed quality of life impairment due to cancer-related symptoms [16]. To reduce toxicity, several groups have reported small series of patients using modified versions of the FOLFIRINOX protocol (mFOLFIRINOX), usually with either reduction of the irinotecan dose or omission of the 5-FU bolus [17]. Although the reported efficacy results are in general similar to the ACCORD11/PRODIGE4 study, the original protocol should be still considered as the standard since direct comparisons of the mFOLFIRINOX versions with the standard protocol in randomized trials are not available.

Nab-paclitaxel is a novel albumin-bound, solvent-free and water-soluble formulation of paclitaxel. In contrast to previous castor oil-based formulations, pre-medication to avoid hypersensitivity reactions is not necessary [18]. In the randomized phase III MPACT trial, combination treatment with nab-paclitaxel (125 mg/m² weekly for three out of four weeks) and gemcitabine (1000 mg/m² weekly for three out of four weeks) was compared to gemcitabine monotherapy as first-line therapy in 861 patients with stage IV pancreatic cancer. Patients had to have a Karnofsky performance status of at least 70% and a normal serum bilirubin level. Combination treatment increased overall survival from 6.6 months to 8.7 months (P < 0.001) [6,19]. The objective response rate was 23% in the combination

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group versus 8% in the gemcitabine group (P < 0.001). The addition of nab-paclitaxel increased the rate of grade 3/4 neutropenia from 27% to 38%, but febrile neutropenia was a rare event (3% versus 1%). Other grade 3/4 adverse effects that were more common in patients in the combination group were fatigue (17% vs. 7%) and peripheral neuropathy (17% vs. 1%). Nab-paclitaxel can also be safely combined with either infusional 5-FU/leucovorin [20] or capecitabine [21], e.g. in patients with disease relapse following resection and adjuvant gemcitabine chemotherapy or with gemcitabine intolerance, although there are no data from randomized trials on efficacy. In a phase I trial of 35 patients (24 with metastatic and 11 with locally advanced disease), a combination of nab-paclitaxel with 5-FU, leucovorin and oxaliplatin (FOLFOX) has also been reported. This combination had a response rate of 60% (21 of 35 patients) and is of potential interest as an induction chemotherapy regimen in locally advanced, inoperable patients. The combination of two drugs that cause polyneuropathy (nab-paclitaxel and oxaliplatin) however will not be suitable for prolonged use in the palliative setting. Larger studies to confirm this degree of activity and to define safety/toxicity are required [22]. Recommendations for the use of gemcitabine/nab-paclitaxel in patients with hyperbilirubinemia have also been published [23]. Both FOLFIRINOX and gemcitabine/Nab-paclitaxel can be offered to patients with good performance status. The two protocols have not been directly compared in a randomized study, and interstudy comparisons naturally have severe limitations. While the superior survival in the FOLFIRINOX trial is an argument to choose this protocol for fit patients, the MPACT study had no age-limit and included some patients (7.6%) with an ECOG performance status of 2. Gemcitabine/nab-paclitaxel might therefore be preferred in older patients or patients with borderline performance status. However, both protocols should be discussed with eligible patients since other factors besides overall survival, for example adverse effects like alopecia or diarrhea or the practicability of the chemotherapy schedule are

| Table 1 | Selected randomized trials of palliative chemotherapy for pancreatic cancer |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Name            | Line of treatment | Stage | Number of patients | Treatment regimen                                    | Overall survival [months] | P-value | References |
| Gemcitabine     | First            | II/III/IV | 63               | Gemcitabine                                             | 5.65                   | 0.0025 | Burris et al., 1997 [9] |
| NCIC CTC PA.3   | First            | III/IV | 285              | Gemcitabine + erlotinib + Gemcitabine                   | 6.24                   | 0.038  | Moore et al., 2007 [54] |
| GemCap          | First            | III/IV | 267              | Gemcitabine + capecitabine + Gemcitabine                | 7.1                    | 0.08   | Cunningham et al., 2009 [15] |
| PRODIGE 4/ACCORD 11 | First  | IV     | 171              | Folinic acid + 5-FU (bolus + infusion) + irinotecan + oxaliplatin + Gemcitabine | 11.1                   | < 0.001 | Conroy et al., 2011 [5] |
| MPACT           | First            | IV     | 431              | Gemcitabine + nab-Paltaxel + Gemcitabine                | 8.7                    | < 0.001 | Von Hoff et al., 2013 [6] |
| LAP07           | First            | III    | 102              | Chemotherapy + Radiochemotherapy                       | 16.5                   | 0.83   | Hammel et al., 2016 [121] |
| CONKO-003 (1)   | Second           | III/IV | 23               | Oxaliplatin + 5-FU + folic acid (OFF) + Best supportive care | 4.82                   | 0.008  | Pelzer et al., 2011 [33] |
| CONKO-003 (2)   | Second           | III/IV | 76               | Oxaliplatin + 5-FU + folic acid (OFF) + 5-FU + folic acid | 5.9                    | 0.010  | Oettle et al., 2014 [34] |
| PANCREOX        | Second           | III/IV | 54               | Oxaliplatin + 5-FU + folic acid (mFOLFOX6) + 5-FU + folic acid | 6.1                    | 0.02   | Gill et al., 2016 [35] |
| NAPOLI-1        | Second           | IV     | 117              | Nal-irinotecan + 5-FU + folic acid + Nal-irinotecan + 5-FU + folic acid | 6.1                    | 0.012  | Wang-Gillam et al., 2016 [7] |
often important for the patient's final choice. Unfortunately, there are no routine clinical biomarkers to predict success of either protocol. Expression of secreted protein acidic and rich in cysteine (SPARC) that was investigated as predictive factor for nab-paclitaxel did not correlate with overall survival [24]. Different PDAC subtypes based on expression profiling have been described [25-28], and there is increasing evidence that subtypes of pancreatic cancer might predict response to chemotherapy, with inferior response rates for the "basal" [29] and the related "quasi-mesenchymal"/cytokeratin-81-positive subtypes [30] compared to the better responses seen in the "classical" subtype.

Pegylated recombinant human hyaluronidase (PEGPH20) degrades hyaluronan, which predominates in the stroma of metastatic pancreatic cancer and potentially decreases drug delivery. A randomized phase II trial showed an increase in median progression free survival in patients given PEGPH20 plus Nab-paclitaxel/gemcitabine compared to Nab-paclitaxel/gemcitabine (hazard ratio [HR], 0.73; IC95%: 0.53 to 1.00; P = 0.049) and is now progressing as a phase III trial but only for patients with tumors with high hyaluronan levels [31]. A phase I/II randomized study in metastatic pancreatic cancer however showed a median overall survival of 15.1 (IC95%: 10.1 to 15.7) months in patients given modified FOLFIRINOX (mFFOX) compared to only 7.6 (IC95%: 4.6 to 9.2) months in patients given PEGPH20 with mFFOX (HR = 0.48). Moreover, PEGPH20 with mFFOX caused greatly increased toxicity (mostly gastrointestinal and thromboembolic events) and decreased treatment duration compared to mFFOX alone [32].

**Second-line chemotherapy**

Although PDAC patients that progress under first-line chemotherapy frequently have a poor performance status, a proportion remains sufficiently well enough for second-line chemotherapy. The CONKO-003 multicenter phase III study randomized patients with failure of gemcitabine-based therapy to best supportive care or therapy with oxaliplatin and 5-FU [33]. Oxaliplatin (85 mg/m^2) was administered on days 8 and 15 of a six-weeks cycle, 5-FU (2000 mg/m^2 intravenously over 24 h) with leucovorin on days 1, 8, 15 and 22 (OFF protocol). The study had to be terminated early due to slow recruitment because of resistance by patients in the trial to be randomized to best supportive care. Of the forty-six patients included, the group receiving second-line therapy had a median overall survival benefit of 4.82 versus 2.30 months (P = 0.008). Subsequently, the CONKO-003 protocol was modified to include a 5-FU (2000 mg/m^2 intravenously over 24 hours) with leucovorin (folinic acid) on days 1, 8, 15 and 22 (FF) in the control arm instead of the best supportive care [34]. The OFF protocol was also superior to FF with an overall survival of 5.9 versus 3.3 months (P = 0.010). The Canadian PANCREOX trial was a larger randomized phase III study with 108 patients, that showed no benefit for the second-line combination of oxaliplatin with 5-FU/folinic acid compared to 5-FU/folinic acid alone [35]. The standard arm of infusional leucovorin 400 mg/m^2 administered over 2-hours on day 1 and 5-FU given as a bolus intravenous dose of 400 mg/m^2 on day 1 followed by a 2400 mg/m^2 continuous infusion for 46 hours, administered every 14 days. The mFOLFOX6 regimen consisted of the same plus an oxaliplatin dose of 85 mg/m^2 given as a 2-hour intravenous infusion on day 1, administered every 14 days. The group receiving mFOLFOX6 had a worse survival than the group receiving 5-FU and folinic acid (6.1 months versus 9.9 months, P = 0.02). These conflicting results remain unresolved.

One possible explanation is that toxicity of mFOLFOX6 in the second-line setting reduced exposure to chemotherapy, resulting in the unfavorable outcome. In the PANCREOX study, 63% of patients in the mFOLFOX6 group had grade 3/4 adverse events, compared to 11% in the 5-FU/folinic acid group, and 20% versus 2% withdrew from the study due to adverse events. The role of OFF and mFOLFOX6 is uncertain in the post FOLFIRINOX and post gemcitabine with nab-paclitaxel era.

The randomized phase III study NAPOLI-1 used nanoliposomal irinotecan, a new formulation of irinotecan that is supposed to increase intratumoral irinotecan levels [36]. In contrast to the CONKO-003 and PANCREOX trials, more than half of the patients had received gemcitabine-based combination treatment including gemcitabine/Nab-paclitaxel. The study initially compared 5-FU monotherapy (2000 mg/m^2 over 24 h for 4 out of 6 weeks) with nanoliposomal irinotecan monotherapy (120 mg/m^2 every three weeks), but a third arm with nanoliposomal irinotecan/5-FU combination treatment (80 mg/m^2 nanoliposomal irinotecan, 2400 mg 5-FU over 46 h biweekly) was later added per amendment. Patients in the nanoliposomal irinotecan/5-FU group had a survival of 6.1 months compared to 4.2 months in the 5-FU only group (P = 0.012). Survival in the nanoliposomal irinotecan monotherapy group was not statistically different from the 5-FU monotherapy group. Based on this study, nanoliposomal irinotecan with 5-FU was approved for second-line therapy by the FDA and European Medicines Agency. Oxaliplatin and nanoliposomal irinotecan as a partner for 5-FU have not been directly compared to each other and seem to be similarly effective. The choice for the individual patient may be based on the different potential toxicities, such as neuropathy for oxaliplatin and diarrhea for irinotecan.

There are no data from randomized trials guiding the use of second-line chemotherapy after FOLFIRINOX failure, but gemcitabine-based chemotherapy is an obvious choice. In the ACCORD11 study, nearly half of the patients received...
second-line chemotherapy, either gemcitabine monotherapy (82.5%) or gemcitabine-based combinations (12.5%). There are several small institutional series that report a median overall survival of 3.6 to 5.7 months from the start of second-line mono-
thrapy with gemcitabine [37-40], but no randomized studies have compared gemcitabine with best supportive care. Similarly, there are retrospective studies regarding the role of gemcitabine plus nab-paclitaxel after FOLFIRINOX failure, with longer median overall survival in the range of 5.3 to 12.4 months [41-44]. In the largest study with 57 patients, second-line gemcitabine plus nab-
paclitaxel resulted in a response rate of 17.5% and an overall survival of 8.8 months. Overall survival from the beginning of first-
line therapy was remarkable with 18 months, which may suggest a selection bias of patients who remain sufficiently fit for second-
line chemotherapy [41]. Second-line chemotherapy with gemci-
tabine plus nab-paclitaxel as well as gemcitabine monotherapy are currently included as therapeutic options in the American Society of Clinical Oncology Clinical Practice Guidelines for meta-
static pancreatic cancer [45].

Targeted therapy

Targeted therapies, either as monoclonal antibodies or small molecules, are very successful in many types of cancer, such as EGFR- or VEGF-directed antibodies in colorectal cancer, trastu-
zumab in Her-2 positive breast cancer or tyrosine inhibitors such as crizotinib in biomarker-selected subsets of non-small cell lung cancer. Except for erlotinib, a small molecule EGFR tyrosine kinase inhibitor, all other targeted drugs so far have failed in pancreatic cancer, including cetuximab [46], bevacizumab [47,48], sorafenib [49], axitinib [50] and aflibercept [51] (reviewed in [52,53]).

In a randomized phase III study of the National Cancer Institute of Canada that recruited 569 patients with locally advanced, irresectable or metastatic PDAC, patients treated with gemci-
tabine plus erlotinib had a survival of 6.24 months versus 5.91 months in the gemcitabine group [54]. There was no difference in objective response rate between the two groups. It is ques-
tionable whether the median difference in survival of about 10 days is clinically relevant, especially when cost-effectiveness and quality of life are taken into consideration. Patients in the erlotinib plus gemcitabine often developed a skin rash (72%), a typical side effect of EGFR-inhibition. The survival benefit in the erlotinib plus gemcitabine group was more pronounced in patients who developed a rash, being 10.5 months in those with rash grade 2 and higher. In a randomized phase II study that tested an erlotinib dose escalation protocol, the fraction of patients with rash ≥ grade 2 was successfully increased from 9.3% to 41.14%, but the dose escalation did not result in an increased survival [55]. Although inactivation of erlotinib by either basal or induced expression of cytochrome P450 3A5 in pancreatic cancer cells from a subgroup of patients has been shown [26], cytochrome P450 3A5 expression as negative pre-
dictive marker for erlotinib has not been demonstrated in patients. It is now recommended erlotinib is discontinued when there is no rash after 8 weeks as there is then no survival benefit.

The combination of gemcitabine with erlotinib followed by second-line therapy with capecitabine has comparable efficacy to capecitabine plus erlotinib followed by gemcitabine [56]. The addition of capecitabine to gemcitabine and erlotinib did not increase survival in a Spanish randomized phase II study [57]. Erlotinib (100 mg) combined with standard doses of Nab-pacli-
taxel and gemcitabine was not tolerable in a phase IIb study. The maximum tolerated doses were 1000 mg/m² gemcitabine with 75 mg/m² Nab-paclitaxel and 75 mg erlotinib [58]. In a recent study, patients that were deemed fit enough for FOLFIRINOX therapy were treated for 4 weeks with gemcitabine and erlo-
tinib. Patients that developed a skin rash of any grade (including grade 1) after 4 weeks continued treatment with gemcitabine plus erlotinib (90 out of 117 evaluable patients), whilst patients without rash were switched to FOLFIRINOX. The patients that developed a skin rash and continued with gemcitabine plus erlotinib had a median overall survival of 10.1 months, compared with 10.9 months in those without a rash and switching to FOLFIRINOX [59].

One important reason for the failure of targeted therapies in PDAC is the fact that most studies were not biomarker-driven and the “targeted” agent was given to unselected patients. However, defining molecular subgroups for targeted therapy is difficult since most PDAC patients harbor a mutation in KRAS (reviewed in [60]), which controls dominant oncogenic signaling pathways and is of itself not drug-able [61,62]. In a study of 336 patients at Memorial Sloan Kettering Cancer Center who were genetically characterized by sequencing a panel of 410 genes over 90% had KRAS-mutations, only three (1%) patients had targeted therapy, none of whom responded [63]. There were however actionable driver alterations (with tyrosine receptor kinase inhibitors) in 5.4% patients with wild-
type KRAS cancers, including fusions of the fibroblast growth factor receptor 2 (FGFR2), neurotrophin tyrosine kinase receptor 3 (NTRK3) and ROS1. Responses to entrectinib and larotrectinib therapy in pancreatic cancer patients with NTRK- and ROS1-fusions have already been reported [64,65]. Recently, in a study from Heidelberg, four tumors from 17 patients with metastatic pancreatic cancer younger than 50 years were analyzed by whole genome and transcriptome sequencing had wild-type KRAS, with fusions of the neuregulin-1 (NRG1) gene in three patients and the RET1 gene in the other. Although two patients with NRG1-rearrangements reported to afatinib or erlotinib and pertuzumab treatment, these were short-lived [66]. ERBB3-inhibition of NRG1-fusions in pancreatic cancer using a mono-
clonal antibody might be more effective than afatinib [67].
Another promising pancreatic cancer subgroup for targeted therapy of up to 24% of patients are those with tumors harboring defects in DNA damage response mechanisms with either germline or somatic mutations in BRCA1, BRCA2 or PALB2, or a mutational signature of "BRCaness" [60,68]. Several studies investigating poly-(ADP-ribose)-polymerase (PARP) inhibitors either as monotherapy or in combination with chemotherapy in pancreatic cancer patients are in progress [69,70].

Immunotherapy

Immune checkpoint inhibitors are now approved for various types of cancer such as melanoma, lung cancer, renal cell carcinoma and head and neck squamous cell carcinoma [71]. In contrast, no immunotherapy for pancreatic cancer has yet reached the clinic. Pancreatic cancer is considered to be a poorly immunogenic type of cancer, and the pancreatic cancer tumor microenvironment is thought to create an immunosuppressive milieu that is a barrier to successful immunotherapy [72,73]. Monotherapy with CTLA-4 or PD1 inhibitors are largely ineffective in pancreatic cancer but there are a number of clinical studies testing combinations such checkpoint inhibitors plus chemotherapy, vaccines and radiation and cytokine antagonists [72]. In theory, chemotherapy with clinically relevant agents such as gemcitabine and/or capecitabine should reduce the immune response, but clinical studies suggest that the immune status is largely maintained [8,74,75]. On the other hand, radiotherapy may suppress immunity in pancreatic cancer. In genetically engineered mouse models of pancreatic cancer radiation treatment caused the tumor macrophages to acquire an immune-suppressive phenotype and disabled T cell-mediated anti-tumor responses. Neutralizing antibodies against macrophage colony-stimulating factor 1 negated this effect, allowing radiation to have increased efficacy in slowing tumor growth [76]. There is a small subgroup of pancreatic cancer patients that can already be treated with immunotherapy: pembrolizumab has been approved by the FDA for the treatment of microsatellite-instable cancer independent from the type of cancer. This landmark study also included patients with pancreatic cancer [77]. Studies investigating the prevalence of microsatellite instability in pancreatic cancer have resulted in widely divergent results, but the prevalence is probably only in the range of about 1% [78-80].

Chemotherapy for patients with resectable disease

Surgery is the only potentially curative treatment for PDAC patients, but more than 90% of patients relapse after surgery alone. Therefore, adjuvant strategies to increase the fraction of patients with long-term survival have been investigated since the 1970s (reviewed in [81]).

Adjuvant chemotherapy

Current standard of care after curative pancreatic cancer resection based on large randomized clinical trials is adjuvant chemotherapy (table II). Between 1994 and 2000, the European Study Group for Pancreatic Cancer Trial 1 (ESPAC-1) randomized patients in a two-by-two factorial design to adjuvant 5-FU-based chemoradiotherapy (70 patients), chemotherapy with 5-FU (74 patients), chemoradiotherapy followed by chemotherapy (72 patients) or observation (69 patients) [82,83]. An additional 261 patients were randomized to either chemotherapy or chemoradiation versus observation outside the original design (ESPAC-1 plus). 5-FU was administered intravenously as a bolus (425 mg/m²) with folinic acid (20 mg/m²) daily for 5 days once a month over 6 months. This study demonstrated the superiority of adjuvant chemotherapy over observation and showed no role for the chemoradiation protocol used in this study. The five-year survival rate was 21% in the chemotherapy group and 8% in patients who did not receive chemotherapy (P = 0.009), establishing adjuvant chemotherapy with 5-FU as a standard therapy after R0 or R1 resection of pancreatic cancer. The CONKO-001 study recruited 368 patients with R0 or R1- resected pancreatic cancer between 1998 and 2004 to observation or adjuvant chemotherapy. In contrast to the ESPAC-1 trial, intravenous gemcitabine (1000 mg/m² on days 1, 8, and 15 every 4 weeks, 6 cycles) was used since it had recently been shown to improve overall survival and quality of life compared to bolus 5-FU in the palliative setting [9]. The median disease-free survival, the primary endpoint of the study, was 13.4 months in the gemcitabine group and 6.9 months in the control group (P < 0.001) [84]. Further follow-up showed also a significant advantage in overall survival [85]. The two different chemotherapy regimens, bolus 5-FU and gemcitabine, were compared in the ESPAC-3 study, a large randomized study with overall survival as primary endpoint that included 1088 patients [86]. The study had an initial observation arm that was discontinued when the final results of the ESPAC-1 study became available [83]. There was no statistically significant difference between the two treatment arms, with similar median overall survival (23.0 versus 23.6 months, P = 0.39), 2-year overall survival (48.1% versus 49.1%, P = 0.39) and median progression-free survival (14.1 months versus 14.3 months P = 0.53). The study demonstrated that gemcitabine and 5-FU plus folinic acid are equally effective as adjuvant treatments for resected pancreatic cancer patients. The toxicity profile of 5-FU and gemcitabine were different: gemcitabine caused more grade 3/4 leukopenia (10% vs. 6%) and thrombocytopenia (1.5% vs. 0%), while stomatitis (10% vs. 0%) and diarrhea (13% vs. 2%) were more common in the 5-FU group. When all serious side effects were combined, gemcitabine had a more favorable safety profile than 5-FU (7.5% versus 14.0%, P < 0.001) and became the preferred choice for most oncologists. Importantly, in case of contraindications against...
gemcitabine, 5-FU can still be used as an equally effective alternative treatment. The ESPAC-3 study additionally provided important data regarding the timing of adjuvant chemotherapy: there was no difference in survival for patients who started adjuvant therapy earlier than eight weeks after surgery compared to those who started between weeks 8 and 12 [87]. On the other hand, outcome was negatively affected when adjuvant chemotherapy could not be completely administered. As a conclusion, adjuvant chemotherapy should be delayed to up to 12 weeks after surgery if the patient has not yet fully recovered to improve chances that the patient is fit enough to receive the complete 6 cycles of adjuvant chemotherapy.

The JASPAC-01 trial compared the fluoropyrimidine derivative S-1 to gemcitabine in R0-resected Japanese patients [88]. S-1 is a combination of tegafur, an orally available prodrug of 5-FU, and gimeracil and oteracil, two drugs that modulate 5-FU metabolism to decrease inactivation of 5-FU and reduce gastrointestinal side effects [89]. This study demonstrated non-inferiority of S-1 compared to gemcitabine, the primary endpoint of the study, and showed a greatly improved hazard ratio for death of 0.57 ($P = 0.0001$) and an increased 5-year overall survival of 44.1% in the S-1 group compared to 24.4% in the gemcitabine group. Adjuvant therapy with S-1 is therefore a standard adjuvant therapy for Japanese and possibly other Asian patients. For Western patients, these results need to be confirmed since there are differences in S-1 pharmacokinetics between Asian and Western patients that result in different maximal tolerated doses of S-1 [90].

The recent ESPAC-4 randomized phase III adjuvant trial for patients with resected pancreatic cancer (R0 or R1) compared gemcitabine monotherapy with combination gemcitabine plus capecitabine (830 mg/m² twice daily orally for 21 days followed by 7 days’ rest) [91]. The gemcitabine-capecitabine combination had been previously tested in the palliative setting [15]. A total of 732 patients from different European countries were randomized into the two treatment arms between 2008 and 2014. Eighty percent of patients had lymph node positive disease, and 60% of patients had an R1 status defined by microscopic tumor cells within 1 mm of the resection margin. Combination treatment with gemcitabine and capecitabine

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<th>Trial</th>
<th>Number of patients</th>
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<th>Inclusion criteria</th>
<th>Treatment Regimen</th>
<th>Overall survival [months]</th>
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<td>CONKO-001</td>
<td>179</td>
<td>R0/R1</td>
<td>Karnofsky PS ≥ 50%</td>
<td>Gemcitabine</td>
<td>22.8</td>
<td>0.01</td>
<td>20.7</td>
<td>Oettle et al., 2013 [84,85]</td>
</tr>
<tr>
<td></td>
<td>175</td>
<td></td>
<td>Observation</td>
<td>Gemcitabine</td>
<td>20.2</td>
<td></td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td>ESPAC-3</td>
<td>539</td>
<td>R0/R1</td>
<td>WHO PS ≤ 2</td>
<td>Gemcitabine</td>
<td>23.6</td>
<td>0.39</td>
<td>17.5</td>
<td>Neoptolemos et al., 2010 [86]</td>
</tr>
<tr>
<td></td>
<td>551</td>
<td></td>
<td>S-FU + folinic acid</td>
<td>Gemcitabine</td>
<td>23.0</td>
<td></td>
<td>15.9</td>
<td></td>
</tr>
<tr>
<td>JASPAC-01</td>
<td>187</td>
<td>R0/R1</td>
<td>ECOG PS 0/1</td>
<td>Gemcitabine</td>
<td>46.5</td>
<td>0.0001</td>
<td>44.1</td>
<td>Uesaka et al., 2016 [88]</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td></td>
<td>5-FU</td>
<td>Gemcitabine</td>
<td>25.5</td>
<td></td>
<td>24.4</td>
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</tr>
<tr>
<td>CONKO-005</td>
<td>217</td>
<td>R0</td>
<td>Karnofsky PS ≥ 60%</td>
<td>Gemcitabine</td>
<td>26.5</td>
<td>0.61</td>
<td>20</td>
<td>Sinn et al., 2017 [95]</td>
</tr>
<tr>
<td></td>
<td>219</td>
<td></td>
<td>Gemcitabine + erlotinib</td>
<td>Gemcitabine</td>
<td>24.5</td>
<td></td>
<td>25</td>
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<tr>
<td>CONKO-006</td>
<td>65</td>
<td>R1</td>
<td>Karnofsky PS ≥ 60%</td>
<td>Gemcitabine</td>
<td>17.1</td>
<td>0.94</td>
<td>n.a.</td>
<td>Sinn et al., 2014 [96]</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td></td>
<td>(48 weeks)</td>
<td>Gemcitabine</td>
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<td></td>
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<td></td>
<td></td>
<td>Gemcitabine (48 weeks) + sorafenib (48 weeks)</td>
<td>Gemcitabine + capecitabine</td>
<td>25.5</td>
<td>0.032</td>
<td>16.3</td>
<td>Neoptolemos et al., 2017 [91]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gemcitabine + capecitabine</td>
<td>Gemcitabine</td>
<td>28.0</td>
<td></td>
<td>28.8</td>
<td></td>
</tr>
<tr>
<td>ESPAC-4</td>
<td>366</td>
<td>R0/R1</td>
<td>WHO PS ≤ 2</td>
<td>Gemcitabine</td>
<td>25.5</td>
<td>0.032</td>
<td>16.3</td>
<td>Neoptolemos et al., 2017 [91]</td>
</tr>
<tr>
<td></td>
<td>365</td>
<td></td>
<td>Gemcitabine</td>
<td>Gemcitabine</td>
<td>28.0</td>
<td></td>
<td>28.8</td>
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<tr>
<td>PRODGE-24</td>
<td>246</td>
<td>R0/R1</td>
<td>ECOG PS 0/1</td>
<td>Gemcitabine</td>
<td>35.0</td>
<td>0.003</td>
<td>n.a.</td>
<td>Conroy et al., 2018 [93]</td>
</tr>
<tr>
<td></td>
<td>247</td>
<td></td>
<td>Post-OP CA</td>
<td>Gemcitabine</td>
<td>54.4</td>
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</tr>
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</table>

*Note: ESPAC = European Study Group for Pancreatic Cancer; CONKO = Cooperative Trial for Operative Pancreatic Cancer; JASPAC = Japanese Society for Pancreatic Cancer; PRODGE = Pancreatic Cancer Research Group.*
resulted in an improved median overall survival (28.0 months versus 25.5 months, P = 0.032) and estimated 5-year survival (28.8% versus 16.3%). The differences between the treatment arms were more pronounced in the R0 patients (median overall survival 39.5 months versus 27.9 months; hazard ratio for death 0.68 [0.49–0.93]) compared to the R1 patients (23.7 months versus 23.0 months; hazard ratio for death 0.90 [0.72–1.13]). As expected, toxicity in the combination group was increased with more grade 3/4 neutropenia (38% versus 24%), diarrhea (5% versus 2%) and hand-foot-syndrome (7% versus 0%) but was manageable and acceptable. Based on the ESPAC-4 study, the combination of gemcitabine and capecitabine should be considered as a standard adjuvant treatment for patients with resected pancreatic cancer [92].

Current studies will show whether further intensification of chemotherapy is feasible in the adjuvant setting and will improve overall survival. The two protocols that have been shown to be superior to gemcitabine monotherapy in palliative patients are under investigation: FOLFIRINOX [5] and gemcitabine plus nab-paclitaxel [6]. The French-Canadian PRODIGE 24/CCTG PA.6 study (NCT01526135) randomized 493 patients to 12 cycles of biweekly modified FOLFIRINOX (150 mg instead of 180 mg/m² irinotecan and no 5-FU bolus) or 6 cycles of gemcitabine in patients with macroscopically complete resection and WHO performance status of 0 or 1 [17]. Patients with a postoperative CA 19-9 level higher than 180 KU/L were excluded. Results of this study were presented at the 2018 annual meeting of the American Society for Clinical Oncology [93]. Adjuvant modified FOLFIRINOX resulted in an improved median disease free survival (21.6 versus 12.8 months; hazard ratio 0.59, IC95%: 0.47–0.74) and median overall survival (54.4 versus 34.8 months, hazard ratio 0.66, IC95%: 0.49–0.89). Although there was a high rate of grade 3 and 4 toxicity in the mFOLFIRINOX group (75.5% versus 51.1% in the gemcitabine group), these toxicities seemed to be manageable. Modified FOLFIRINOX clearly should be offered to all resected patients fit enough to receive this protocol. Now that there is range of options for adjuvant therapy the first-line choice is largely based on performance status and liver function with second-line therapies based on disease relapse and potential toxicities (figure 1; table III). To use FOLFIRINOX there should be no clinically significant history of cardiac disease and there should be no chronic diarrhea. In the adjuvant setting, bilirubin is usually not a problem. Following recurrent disease and in the palliative

**Figure 1**
Representative algorithm for the administration of adjuvant chemotherapy based on the best current evidence in phase III trials. Once disease recurrence occurs then patients are treated with the next best alternative therapies based on evidence obtained in the advanced setting.
setting hyperbilirubinemia is mainly prohibitive for the use of irinotecan. Administration of 5-FU and oxaliplatin is usually possible in patients with nearly any bilirubin. If there is progressive or recurrent disease after some time (say at least six months) following the initial use of FOLFIRINOX, the patient can be treated with FOLFIRINOX again. If the patient has neuropathy after oxaliplatin it may not be possible to give nab-paclitaxel.

The APACT study has similar inclusion criteria as the PRODIGE 24 study, also uses gemcitabine monotherapy as control arm and compares it to combination chemotherapy with nab-paclitaxel (125 mg/m² on days 1, 8, and 15 of a 28 days cycle) and gemcitabine (1000 mg/m² on days 1, 8, and 15 of a 28 days cycle) [94]. Target accrual has been reached with sufficient events anticipated for analysis of the disease free survival endpoint in the next 12 months. The CONKO-005 study that investigated the addition of erlotinib to adjuvant gemcitabine was negative and did not show an improvement in disease free or overall survival in R0-resected pancreatic cancer patients [95]. The CONKO-006 trial also showed no difference in disease free or overall survival between patients with an R1 resection randomized to gemcitabine (with placebo) and gemcitabine with the multiple tyrosine kinase inhibitor sorafenib [96]. A recent study has found an association between increased survival after PDAC resection with an immune response against tumoral neo-epitopes that were related to microbial epitopes [97]. This raises the possibility that vaccination strategies that boost immune response to tumoral neo-epitopes could improve adjuvant therapy for pancreatic cancer.

### Adjuvant chemoradiation

Based on the evidence from several randomized phase III trials summarized above, adjuvant chemotherapy is currently the standard treatment after pancreatic cancer resection with no evidence from good quality randomized trials to support the use of chemoradiation. Consequently, the guidelines of the European Society for Medical Oncology state that no adjuvant chemoradiation should be given to pancreatic cancer patients outside of clinical trials [98]. Adjuvant chemoradiation is still used in some countries, especially the USA, and the National Comprehensive Cancer Network guideline lists adjuvant chemoradiation as an option, although no evidence level for this recommendation is provided [99]. Recommendations for adjuvant chemoradiation are often still based on the Gastrointestinal Tumor Study Group trial 9173 that was published in 1985 and compared 5-FU-based chemoradiation followed by two years of 5-FU chemotherapy to observation in R0-resected patients. The study was prematurely closed after 43 patients due to slow accrual and because of a difference in survival between the two groups (20 months in the chemoradiation/chemotherapy group versus 11 months in the observation group, P = 0.035) [100]. In contrast, a European Organisation for Research and Treatment of Cancer trial [101] and the ESPAC-1 study did not show a significant survival benefit of chemoradiation compared to observation/no chemoradiation [82]. The results and potential flaws of the various trials have been extensively debated [102], and new trials that use state-of-the-art radiation techniques and have a control arm with standard of care adjuvant chemotherapy are needed. The RTOG 0848 trial, a large randomized phase III study
with 952 patients that investigates the value of additional chemoradiation for patients with no progression after standard adjuvant chemotherapy with gemcitabine is currently ongoing [103].

**Neoadjuvant therapy in resectable or borderline resectable patients**

According to most current guidelines, patients with resectable pancreatic cancer should immediately proceed to surgery, but neoadjuvant strategies involving preoperative chemotherapy or chemoradiation are currently an active area of research and controversially discussed (reviewed in [104]). The current American Society of Oncology Clinical Practice guideline for “Potentially Curable Pancreatic Cancer” already recommends to offer neoadjuvant chemotherapy or chemoradiation to patients with “a CA 19-9 level suggestive of extrapancreatic disease” or a “radiographic interface between primary tumor and mesenteric vasculature” on cross-sectional imaging and even as an alternative treatment to upfront resection to all resectable patients [105]. In a large retrospective propensity score matched analysis [106] and a recent meta-analysis [107], neoadjuvant treatment was associated with superior survival, but evidence from randomized controlled trials also accounting for patients that progress under neoadjuvant therapy and become unresectable is mandatory to change current practice. Potential advantages of neoadjuvant treatment are an increased R0 resection rate, earlier treatment of distant micrometastases and use of more aggressive chemotherapy that might be intolerable after resection, and through a test of time/chemoresistance to spare patients with early metastatic spread what would have been a futile operation [108]. On the other hand, non-responders to chemotherapy might progress and lose the chance for curative resection, and histologic confirmation of small tumors by endosonographic biopsy that is required before neoadjuvant therapy might be challenging in many centers. Borderline resectable patients have a higher risk of R1 resection, often need more complex operations including vascular resection and have a higher risk of systemic disease [109,110], making the use of neoadjuvant therapy even more compelling. It should be noted however that phase III proof of concept studies are essentially lacking. Several trials that investigate neoadjuvant treatments, including chemotherapy with gemcitabine and nab-paclitaxel, FOLIRINOX or chemoradiation in resectable or borderline resectable patients are under way [104]. As an example, the ESPAC-5F study [ISRCTN8950674] is currently comparing upfront surgery, neoadjuvant chemotherapy with FOLIRINOX or gemcitabine/capecitabine or chemoradiation in 100 borderline resectable patients [111].

A Korean study was required to randomize 110 patients with borderline resectable disease for the 2-year survival primary outcome measure [112]. This number was however only based on a one-sided \( \alpha \) value of 0.05 (instead of a 2-sided \( \alpha \) value), which is unacceptable for a proof of concept study [112]. Only 27 patients were randomized to receive chemoradiation and 28 to upfront surgery before the trial was stopped, This was because they claimed a survival advantage of 21 months for patients treated with gemcitabine-based neoadjuvant chemoradiation versus 12 months, \( P = 0.004 \) with upfront surgery and an increased R0 resection rate of 51.8% versus 26.1% respectively. There were however only 8 and 6 patients, respectively, who actually completed the entire per-protocol treatment, thus rendering any interpretation highly unstable and inconclusive [112].

At the recent 2018 American Society of Clinical Oncology meeting, the investigators of the PREOPAC-1 trial that compared preoperative gemcitabine-based chemoradiation versus upfront surgery in resectable and borderline resectable pancreatic cancer reported a resection rate of 62% versus 72% with a median survival of 17.1 versus 13.7 months respectively [113]. This did not reach the primary end point in survival based on an intention to treat analysis. There was a rather poor survival outcome in the patients with upfront resection with a high rate of metastases at the time of surgical exploration and a median survival rate of only 16.8 months in those resected [113].

**Chemotherapy in patients with locally advanced disease**

Several phase III studies inform the use of palliative chemotherapy in stage IV patients and adjuvant chemotherapy after surgery. There is less evidence regarding the optimal treatment of patients with locally advanced, unresectable disease. While the study by Burris et al. that established gemcitabine as standard treatment included patients with locally advanced disease and patients with stage IV disease [9], the phase III studies investigating FOLFIRINOX and gemcitabine/nab-paclitaxel only included patients with metastatic disease [5,6]. However, there is little doubt that FOLFIRINOX and gemcitabine/nab-paclitaxel are also highly active in the locally advanced setting. A patient-level meta-analysis of eleven studies by Suker et al., representing 315 patients with locally advanced disease found a median overall survival of 24.2 [IC95%: 21.6 to 26.8] months [114]. The median progression free survival was 15.0 [IC95%: 13.8 to16.2] months. In 10 studies representing 490 patients, 296 grade 3 or 4 adverse events were reported (i.e. 60.4 events per 100 patients). No death was attributed to FOLFIRINOX toxicity. Although it appears that patients with locally advanced disease treated with FOLFIRINOX had a median and progression free survival superior to previously reported rates with gemcitabine intrinsic biases cannot be ruled out. The actual survival ranges vary wide in individual studies using FOLFIRINOX, ranging from 10.0 to 32.7 months for overall survival and ranging from 3.0 to 20.4 months for progression free survival. Prospective trials comparing different regimens and strategies including neoadjuvant therapy followed by attempted resection in patients with locally advanced disease are warranted.
There are multiple reports regarding successful conversion to resectability after chemotherapy with FOLFIRINOX and also gemcitabine/nab-paclitaxel in patients with irresectable cancer [115-119]. It is important to note that response evaluation by imaging is unreliable, making it necessary to discuss surgical exploration after chemotherapy [120]. Chemoradiation has long been used in locally advanced pancreatic cancer. However, the LAP07 study, a large study with 449 patients with locally advanced pancreatic cancer randomized those patients with stable disease after four months of chemotherapy with gemcitabine (with or without erlotinib) to either continuation of gemcitabine therapy or chemoradiation (54 Gy with capecitabine), showed no difference in overall survival for the two groups [121]. This study has dampened the enthusiasm for radiotherapy in the locally advanced setting. Although combination chemoradiotherapy and systemic chemotherapy may downstage locally advanced pancreatic cancer and lead to resectability in some patients, the evidence that chemoradiotherapy is required in addition to the chemotherapy is lacking [122,123]. Chemoradiotherapy might be used when intensive chemotherapy is not possible. Combination gemcitabine/nab-paclitaxel chemotherapy with subsequent chemoradiation, is currently under investigation (CONKO-007 study). As an alternative to radiation, other forms local therapies including radiofrequency ablation, irreversible electroporation, high-intensity focused ultrasound, microwave ablation and local anti-KRAS therapy (using siG12D-LODER) are currently under investigation, either as treatment during laparotomy or as percutaneous or endosonographic procedures are being tested [8,124]. Given the systemic nature of pancreatic cancer from an early stage the success of any local approach other than complete surgical resection (with adjuvant chemotherapy) is likely to be very limited [125].

**Future perspectives**

Selection of patient groups for specific therapy including cytotoxics is becoming a reality using assays based on drug cellular transport and metabolism [126-128] and molecular signatures [129]. Going forward, high throughput screening of different chemotherapy agents using molecular signatures based on patient derived organoids holds considerable promise in all of the clinical scenarios described. The Spencer and Tuveson laboratories have recently jointly described a high throughput screening system that enables the consistent production of organoids in standard flat-bottom 384- and 1536-well plates and automated cytotoxicity screening of ~3300 approved drugs [130]. The identification of molecular signatures that might predict the success of different drugs represents an important milestone toward personalized medicine. There is now existing evidence that the "basal" and "quasi-mesenchymal"/cytokeratin-81-positive PDAC subtypes [25-30] that are characterized by inferior response rates to chemotherapy could be converted to the "classical" PDAC subtype [111] with greater responsiveness to subsequent chemotherapy.

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**References**


[103] Gemcitabine hydrochloride with or without erlotinib hydrochloride followed by the same chemotherapy regimen with or without radiation therapy and capecitabine or fluorouracil in treating patients with pancreatic cancer that has been removed by surgery. ClinicalTrials.gov Identifier NCT01013649.


Chemotherapy for pancreatic cancer


