Review

Neoadjuvant treatment of pancreatic ductal adenocarcinoma: present and future

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Abstract

Pancreatic ductal adenocarcinoma is a highly aggressive malignancy with a poor prognosis. Effective treatment with acceptable outcomes is yet to be found, with chemo- and radioresistance comprising major impediments towards this goal. Although upfront surgery is the established therapeutic approach for resectable and borderline resectable disease, neoadjuvant treatment has recently monopolized the interest in clinical trials. This also applies to locally advanced pancreatic adenocarcinomas that could potentially be rendered operable. Chemotherapy and chemoradiotherapy are the most utilized therapeutic modalities in the neoadjuvant setting, while immunotherapy and targeting agents have been gaining significant attention. This critical review focuses on the clinical experience gained from retrospective and phase II/III randomized trials, reporting on the outcomes of neoadjuvant chemotherapy and chemoradiotherapy for pancreatic adenocarcinoma. Moreover, the ongoing trials, including those that involve immunotherapy and targeting agents, are summarized.

Keywords: Pancreatic cancer, neoadjuvant treatment, chemotherapy, radiotherapy, surgery, immunotherapy

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) constitutes one of the most challenging malignancies due to the high mortality rates and the lack of effective treatment. According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute of the United States of America, there were an estimated 60,430 new PDAC cases and 48,220 deaths in 2021[1]. Its increasing incidence has been attributed to numerous causative factors, including cigarette smoking, diabetes mellitus, obesity, alcohol consumption, pancreatitis, and a family history of pancreatic cancer[2]. Germline mutations concerning *BRCA2*, *BRCA1*, *PALB2*, *ATM*, *CDKN2*A, *MSH2*, *MSH6*, and *TP53* have been shown to be present in up to 9.7% of PDAC cases. Somatic alterations in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*, on the other hand, are detected in nearly all of PDAC[3]. The best-studied mutations concern *KRAS* and are thought to be responsible for the progression of pancreatic intraepithelial neoplasia to PDAC by triggering metabolic, signaling, apoptotic, and homeostatic pathways[4]. Furthermore, *BRCA1* and *BRCA2* mutations, involved in the pathogenesis of breast and ovarian cancer, also characterize familial PDAC[5]. Therefore, meticulous monitoring of patients with a familial history of the aforementioned malignancies could allow early detection of a significant proportion of PDACs and, moreover, introduce early detection genetic tests.

PDACs are usually classified as resectable (R-PDAC), borderline resectable (BR-PDAC), and unresectable-locally advanced (LA-PDAC)[6]. This classification reflects the different prognoses and therapeutic approaches applied. Although surgery is considered the backbone of therapy for R-PDAC and BR-PDAC, there has recently been a shift of focus towards neoadjuvant therapies in these two categories. Due to its extremely fast metastatic potential and subsequent unfavorable prognosis, it is believed that localized PDAC, in most cases, represents a metastatic disease in its early stages. In this context, neoadjuvant treatment could exhibit dual function. The first concerns the eradication of micrometastatic lesions and the increased probability of completion of systemic therapy, as a large proportion of patients are not fit to receive postoperative chemotherapy. The second one aims at recognizing diseases that will progress even during systemic therapy, thus suggesting a highly aggressive biological behavior. The subset of patients with PDAC bearing these adverse properties will avoid unnecessary surgical operations, which is often associated with a sharp decrease in the quality of life. Moreover, neoadjuvant chemotherapy or chemoradiotherapy (chemo-RT) could lead to tumor downstaging locally, facilitating surgery and a potential R0 resection[7-9]. The above rationale certainly applies to locally advanced disease, assumed inoperable at diagnosis, as preoperative chemotherapy and radiotherapy could down-stage the disease and allow a reappraisal of surgery.

This review focuses on the clinical experience gained from retrospective and phase II/III randomized trials, reporting on the outcomes of neoadjuvant chemotherapy and chemo-RT for PDAC. Moreover, the currently ongoing trials, including those that involve immunotherapy and targeting agents, are summarized. The literature search was performed in the EMBASE and MEDLINE databases using the text words "pancreatic adenocarcinoma", "neoadjuvant", "chemotherapy", "radiotherapy", "immunotherapy", "targeting agents", and "surgery". Phase II and III studies published between 1990 and April 2022 were retrieved. Ongoing phase II and III trials were identified on ClinicalTrials.gov.

CHEMO- AND RADIORESISTANCE

Chemoresistance is one of the most prominent challenges physicians have to face when treating different types of malignancies. As far as PDAC is concerned, genomic alterations, such as *KRAS* and *SMAD4* mutations and *TP53* inactivation, were originally believed to be the main drivers of the increased chemoresistance of PDAC. In a study by Yang *et al.*, chemosensitivity to gemcitabine and cisplatin was increased in *KRAS* shRNA knockdown pancreatic cancer cells, suggesting that *KRAS* oncogene expression

is linked with resistance to chemotherapeutic drugs[10]. Similarly, *TP53* mutations of pancreatic cancer were associated with higher resistance to chemotherapy with gemcitabine[11]. Extensive research in the field, however, has supported that additional intracellular mechanisms and tumor microenvironment are equally important factors that reduce the efficacy of chemotherapy in pancreatic malignancies[12]. Altered expression of key enzymes involved in critical metabolic cellular pathways, such as aerobic glycolysis and glutamine metabolism, appears to induce a chemoresistant phenotype in pancreatic cancer cells[13]. Moreover, epigenetic mechanisms and especially target of methylation induced silencing 1 (*TMS1*) methylation are involved in acquired chemoresistance[14]. As far as the tumor microenvironment is concerned, PDAC is characterized by a dense extracellular matrix and fibroblastic stroma, which leads to decreased bioavailability of drugs in the tumor and, subsequently, diminished efficacy of the various chemotherapy regimens[15]. Pancreatic stellate cells and cancer-associated fibroblasts contribute to this chemoresistant phenotype through various mechanisms, including the production of components of the tumor stroma and the prevention of H_2O_2-induced apoptosis[12]. Finally, a study by Amit *et al.* demonstrated the inactivation of gemcitabine by tumor-associated macrophages, implying the potential role of the innate immune system in chemoresistance[16].

Drug-specific resistance pathways may also be active in PDAC. Gemcitabine is one of the most used drugs - in combination with nab-paclitaxel - and as a deoxycytidine analog, it interferes with DNA synthesis. Suppression of the nucleoside transporter *hENT1* gene or alterations of the function of deoxycytidine kinase and ribonucleoside reductase contribute to the resistance of pancreatic cancer cells to gemcitabine[17]. Overexpression of the dihydropyrimidine dehydrogenase and thymidylate synthase is involved in the resistance to gemcitabine and 5-FU[18]. Irinotecan is also a major drug for PDAC, used in the FOLFIRINOX [5-FU/leucovorin/irinotecan/oxaliplatin (FFX)] regimen. The activity of carboxyl-esterase-2 (CES2) in cancer cells is essential for the transformation of irinotecan to the SN-38 active derivative, and low expression of CES2 has been associated with poor prognosis in BR-PDAC[19]. Furthermore, DNA repair enzymes define the resistance of pancreatic cancer cells to platinum compounds and radiation; the excision repair cross-complementing proteins (ERCC) 1, 2, and 4 render cancer cells resistant to platinum agents, although a recent study failed to show any association between these enzymes and response to FFX chemotherapy[20]. Common resistance mechanisms to paclitaxel chemotherapy include taxane-metabolizing enzyme activity (e.g., CYP1 enzymes), overexpression of multidrug resistance proteins regulating the efflux of taxanes, tubulin gene mutations, and signaling molecules (POLO kinase, Bcl-2, and the ACT pathway)[21].

Radioresistance is another impediment to the effective treatment of this extremely aggressive malignancy. PDAC is characterized by diffuse hypoxia throughout the tumor and its microenvironment[22]; thus, radiotherapy's efficacy is quite limited. Moreover, pancreatic stellate cells, as mentioned above, inhibit H_2O_2-induced apoptosis, one of the main mechanisms through which radiotherapy elicits its cytotoxic properties[23]. Finally, cancer stem cells have been associated with increased radioresistance due to their enhanced ability of DNA repair and slow proliferation[24].

NEOADJUVANT CHEMOTHERAPY FOR PDAC
Monotherapy and older chemotherapy regimens for LA-PDAC
LA-PDAC of the pancreatic head and body/tail is defined by tumor contact of more than 180° with the superior mesenteric artery (SMA) or celiac axis (CA). Body/tails tumors involving the aorta are also deemed inoperable. Finally, the inability to reconstruct the superior mesenteric vein (SMV) or portal vein (PV) due to tumor invasion or thrombus occlusion characterizes LA-PDAC[6].

The current establishment of FFX and GnP (gemcitabine/nab-paclitaxel) as preferred regimens for neoadjuvant treatment of LA-PDAC was preceded by a long period of clinical experimentation with older drugs and schedules. In 1997, a randomized trial by Burris *et al.* demonstrated moderately increased survival and improved pain palliation, achieved by gemcitabine alone over 5-FU[25]. The addition of cisplatin to gemcitabine has also been explored with conflicting results. Colucci *et al.* reported longer median time to disease progression when gemcitabine and cisplatin were combined *vs.* gemcitabine alone in patients with LA-PDAC or metastatic PDAC, while non-statistically significant better overall survival (OS) was observed[26]. On the contrary, 10 years later, the randomized phase III GIP-1 study showed that the combination of cisplatin and gemcitabine conferred no benefit[27]. A subset of LA-PDAC patients with BRCA mutations appear to be more sensitive to platinum drugs[28] and, as per the NCCN guidelines, gemcitabine-cisplatin is one of the two preferred first-line regimens for locally advanced disease alongside FFX for patients with known BRCA1/2 mutations[6]. An alternative regimen for advanced pancreatic cancer is erlotinib plus gemcitabine. Moore *et al.* reported that a statistically longer one-year OS can be achieved through these two drugs combined *vs.* gemcitabine monotherapy, although the benefit is small[29]. Another phase III trial published in 2009 compared gemcitabine monotherapy to gemcitabine plus capecitabine for the treatment of LA-PDAC and demonstrated significantly better response rates and progression-free survival (PFS), as well as a trend towards longer OS with the latter regimen[30]. Finally, a meta-analysis by Li *et al.* suggested that gemcitabine plus fluoropyrimidine drugs lead to improved OS in comparison to gemcitabine alone[31].

Towards neoadjuvant FFX and GnP for LA-PDAC

A phase II study by Conroy *et al.* introduced FFX in 2005 as an effective drug combination for the treatment of advanced pancreatic disease[32], further prompting the PRODIGE phase III trial that cemented the superiority of this regimen over gemcitabine monotherapy for metastatic PDAC as far as median OS (11.1 *vs.* 6.8 months), median PFS (6.4 *vs.* 3.3 months), and objective response rate (31.6% *vs.* 9.4%) are concerned[33]. These results have also been supported by a meta-analysis of 13 studies assessing the efficacy of FFX over gemcitabine alone with or without subsequent radiation or chemoradiation in LA-PDAC, which reported a median OS of 24.2 months when FFX was utilized *vs.* a 6-13 months OS achieved with gemcitabine[34]. In addition, FFX rendered LA-PDAC resectable in 76 out of 125 patients (60%) when analyzed retrospectively[35], thus exhibiting another potential benefit from its use. The effectiveness of GnP was originally addressed in a phase I/II study by Von Hoff *et al.*[36]. Two years later, the MPACT phase III trial, assigning patients with metastatic PDAC to either GnP or gemcitabine monotherapy, displayed longer median OS (8.5 *vs.* 6.7 months) and PFS (5.5 *vs.* 3.7 months) with the combined regimen and expanded the available and efficient chemotherapy drugs for this disease[37].

Following the favorable results obtained in advanced and metastatic PDAC, FFX and GnP were evaluated in the neoadjuvant setting. A retrospective study comparing FFX and GnP as a preoperative regimen in LA- and BR-PDAC showed a survival benefit in patients who achieved pathological response and biochemical marker regression patterns. Both regimens, however, were equally effective, although a better tolerance of GnP should be considered when treating frail patients[38]. Another smaller retrospective study confirmed the equivalence of the two regimens[39]. Neoadjuvant GnP examined in the LAPACT phase II study provided a median OS of 18.8 months[40]. The NEOLAP-AIO-PAK-0113 randomized phase II trial, published in 2021, investigated whether induction chemotherapy with GnP followed by FFX could yield better outcomes than GnP alone[41]. Sequential induction chemotherapy was proven to confer similar results to the GnP regimen. Overall, applying multidrug induction chemotherapy could be a potential means to overcome the inherent chemoresistance of this malignancy [Table 1].

Table 1. Published phase II/III trials on neoadjuvant chemotherapy for PDAC

Author (year)	Disease	Type of study	No pts	Control arm	Neoadjuvant chemotherapy	Neoadjuvant chemo-RT	Main findings
LA-PDAC							
LAPACT; Philip (2020)[40]	LA-PDAC	Phase II	107		GnP followed by surgery or chemo-RT or GnP	Optional	Median PFS 10.9 months and median OS 18.8 months
NEOLAP-AIO-PAK-0113; Kunzmann (2020)[41]	LA-PDAC	Phase II (randomized)	130	No	4 cycles of GnP 2 cycles of GnP followed by 4 cycles of FFX	No	Similar results (HR 0.86, 95%CI: 0.55-1.36, *P* = 0.53)
BR-PDAC							
Yoo (2017)[45]	BR-PDAC	Phase II	18	No	FFX	No	Median survival 16.8 months
ESPAC-5F; Ghaneh (2020)[46]	BR-PDAC	Phase II (randomized, 4 arms)	88	Upfront surgery (group A)	FFX (group B) or Gemcitabine/capecitabine (group C)	50.4 Gy, 1.8 Gy/fraction Concurrent with capecitabine (group 4)	Better 1-year survival in the neoadjuvant arms 77% *vs.* 40% (HR 0.27, 95%CI: 0.13-0.55, *P* < 0.001)
NUPAT-01; Yamaguchi (2022)[47]	BR-PDAC	Phase II (randomized)	51	No	A. FFX B. GnP	No	OS is not significantly different between groups
LA/BR-PDAC							
Lee (2012)[49]	LA-PDAC BR-PDAC	Phase I/II	43	No	Gemcitabine and capecitabine	No	Median OS 23.1 months for patients that underwent surgery
Reni (2018)[48]	LA-PDAC BR-PDAC	Phase II (randomized)	54	No	Gemcitabine, nab-paclitaxel, cisplatin and capecitabine Nab-paclitaxel followed by gemcitabine	No	1-year PFS 58% (Arm A) *vs.* 39% (Arm B) 18-month OS 69% (Arm A) *vs.* 54% (Arm B) (*P* = not significant)
Saito (2018)[50]	LA-PDAC BR-PDAC	Phase II	24	No	Gemcitabine, S-1, LV	No	Resection rate 60.9% (R0 76.5%)
BR/R-PDAC							
Motoi (2013)[54]	BR-PDAC R-PDAC	Phase II	36	No	Gemcitabine and S-1	No	Median OS 34.7 months in R0 resected patients
R-PDAC							
Heinrich (2008)[52]	R-PDAC	Phase II	28	No	Gemcitabine and cisplatin	No	Median DFS 9.2 months and median OS 26.5 months
O'Reilly (2014)[53]	R-PDAC	Phase II	38	No	Gemcitabine and oxaliplatin	No	Resectability 71% and median OS 27.2 months
Prep-02/JSAP05; Motoi (2019)[55]	R-PDAC	Phase II/III	364	Upfront surgery	Gemcitabine and S-1	No	Improved median OS (36.7 *vs.* 26.6 months)) (HR 0.72, 95%CI: 0.55-0.94, *P* = 0.015)

NEPAFOX; Al-Batran (2021)[56]	R-PDAC	Phase II/III	40	Upfront surgery followed by gemcitabine	FFX	No	Improved survival in the upfront surgery group (25.6 *vs.* 10.3 months) (HR 0.366, 95%CI: not reported, *P* = 0.0337)
SWOG S1505; Sohal *et al.* (2020)[57]	R-PDAC	Phase II (randomized)	103	No	FFX and GnP		2-year OS improvement not statistically significant (41.6% and 48.8% with FFX and GnP, respectively)
AIO-NEONAX; Ettrich *et al.* (2022)[59]	R-PDAC	Phase II (randomized)	127	Upfront surgery followed by GnP	GnP followed by surgery and adjuvant GNP	No	Longer median OS in the perioperative chemotherapy arm (25.2 *vs.* 16.7 months) (HR, *P* value not reported)
PAANACHE01-PRODIGE48; Schwarz *et al.* (20220)[60]	R-PDAC	Phase II (randomized)	146	Upfront surgery	A. FFX B. FOLFOX	No	1-year OS rates 84.1% in Arm A *vs.* 80.8% in the control arm (HR, *P* value not reported)

PDAC: Pancreatic ductal adenocarcinoma; LA: locally advanced; BR: borderline resectable; R: resectable; chemo-RT: chemoradiotherapy; OS: overall survival; PFS: progression free survival; DFS: disease free survival; FFX: 5-FU/leucovorin/irinotecan/oxaliplatin; GnP: gemcitabine/nab-paclitaxel.

There are no randomized phase III studies that have established either FFX or GnP in the neoadjuvant setting for LA-PDAC. The adoption of these regimens is mainly based on the superiority noted in trials on advanced and metastatic diseases. The choice between the two adopted regimens should be based on the expected tolerance. FFX is usually prescribed to patients with a performance status (PS) score of 0-1, while GnP has a moderately safer toxicity profile. Patients with poor PS are usually treated with gemcitabine monotherapy in a rather palliative setting, as they are unlikely to undergo surgery. In addition, gemcitabine plus cisplatin has been proven to be effective when BRCA1/2 or PALB2 mutations have been detected[6].

BR-PDAC
Briefly, BR-PDAC refers to tumors of the pancreatic head with direct contact with the common hepatic artery (CHA) without extension to CA or hepatic artery bifurcation. Encasement of SMA (pancreatic head tumors) and CA (body/tails tumors) should be less than 180°. Inferior vena cava (IVC) involvement and contact with the SMV or PV of more than 180° or vein thrombosis, the extent of which allows safe resection and reconstruction, also define BR-PDAC[6].

A retrospective study in 2008 reported the effects of neoadjuvant treatment in a cohort of patients with BR-PDAC and suggested a potential survival benefit for patients who proceeded to surgical operation[42]. FFX and GnP have been compared in terms of efficacy for BR-PDAC[43]. Patients who received FFX had a greater probability of undergoing surgery and displayed longer PFS; however, there was no statistically significant difference in OS. A meta-analysis by Janssen *et al.* of 24 studies of patients with BR-PDAC who received neoadjuvant FFX concluded on the significant impact of this regimen on OS and R0 resection rates, underlining the importance of randomized studies that could confirm these results[44]. A small phase II study utilizing neoadjuvant FFX resulted in a median OS of 16.8 months[45]. The results of the ESPAC-5F four-arm randomized phase II trial, assessing resection rates when immediate surgery was compared to neoadjuvant chemotherapy with gemcitabine plus capecitabine or FFX or neoadjuvant chemoradiation, showed no difference between arms; a significantly longer one-year OS, however, was achieved with neoadjuvant treatment (77% *vs.* 40%)[46]. Finally, neoadjuvant FOLFIRINOX and GnP were assessed in the NUPAT-01 randomized phase II trial. OS did not differ significantly between groups, with three-year OS rates reaching an overall 54.7% and R0 resections rates achieved in 67.4% of patients[47].

Other chemotherapy regimens have been applied in phase II trials for BR/LA-PDAC. A randomized phase II study on a four-drug combination (gemcitabine, nab-paclitaxel, cisplatin and capecitabine) *vs.* sequential nab-paclitaxel and gemcitabine suggested improved OS in the multidrug arm[48]. Two additional phase II studies[49,50] on gemcitabine with capecitabine or S-1 are also mentioned in Table 1, which summarizes published phase II/III trials on neoadjuvant chemotherapy for PDAC.

R-PDAC

Although R-PDAC has not been clearly defined, it is commonly accepted that it should not abut or encase the regional vascular structures, namely SMA, CHA, and CA. It is undetermined whether the involvement of SMV and PV contributes to the resectability of this tumor; in the event of contact between tumor and SMV, it should be limited to less than 180° without disrupting the venous contour in all respects[6].

Due to the lack of sufficient evidence from clinical trials and studies supporting the superiority of neoadjuvant therapy over upfront surgery, the latter is considered as a standard-of-care treatment in resectable tumors despite the high postoperative morbidity rates. Nevertheless, neoadjuvant treatment has gradually gained ground recently, thanks to some favorable results from completed trials. In a pilot study, no benefit in OS and disease-free survival (DFS) was demonstrated in patients who received neoadjuvant chemotherapy with gemcitabine and oral S-1 over patients who underwent surgical resection[51]. Heinrich *et al.* conducted a prospective phase II trial comparing neoadjuvant chemotherapy with gemcitabine and cisplatin to the resection-first option and reported an OS of 26.5 *vs.* 19.1 months, respectively, and a similar DFS between the two arms (9.2 *vs.* 9 months)[52]. O'Reilly *et al.* proved in a phase II, single-arm trial that neoadjuvant gemcitabine and oxaliplatin may offer surprisingly long OS (27.2 months) and DFS (30.6 months)[53]. Similarly, neoadjuvant gemcitabine and S-1 offered a median OS of 34.7 in R0 patients[54]. The most promising results were published in the PREP-02/JSAP05 phase II/III randomized trial, which showed that neoadjuvant chemotherapy (gemcitabine and S-1) has a statistically significant superiority in OS (36.7 *vs.* 26.6 months in the upfront surgery group)[55]. Al-Batran *et al.* reported a phase II/III randomized study (NEPAFOX trial) comparing upfront surgery with adjuvant gemcitabine-based chemotherapy (Arm A) to perioperative FFX (Arm B). The results, however, were disappointing; median OS was 25.68 (Arm A) *vs.* 10.03 (Arm B) months, respectively, while median PFS was also lower among patients who received neoadjuvant chemotherapy[56]. In 2020, the SWOG S1505 phase II trial demonstrated that neither neoadjuvant FFX nor GnP for R-PDAC was associated with a statistically significant improvement in two-year OS when compared to the a priori threshold of 40% (41.6% and 48.8% with FFX and GnP, respectively)[57]. Surgical results from the same trial display an 85% R0 resection rate in patients who underwent surgery (95%), while complete or significant pathologic response with systemic treatment was achieved in 33% of patients[58]. The final results of the NEONAX randomized phase II trial comparing neoadjuvant GnP (followed by surgery and adjuvant GnP) with upfront surgery followed by adjuvant GnP for patients with R-PDAC were published[59]. Perioperative GnP was associated with a longer median OS (25.2 *vs.* 16.7 months). The authors suggested that this difference in OS could be attributed to more patients receiving chemotherapy preoperatively and fewer patients proceeding to adjuvant chemotherapy in the upfront surgery arm. Similar to the NEONAX trial, the efficacy of neoadjuvant FOLFIRINOX for patients with R-PDAC was investigated in the PANACHE01-PRODIGE48 randomized phase II study[60]; one-year OS rates were 84.1% and 80.8% for patients who received neoadjuvant chemotherapy with FOLFIRINOX and upfront surgery, respectively, indicating that preoperative treatment for R-PDAC is a sound option and demands further investigation. The above trials are summarized in Table 1.

NEOADJUVANT CHEMO-RT FOR PDAC
Experience from definitive chemo-RT for LA-PDAC
Several randomized trials provided evidence that the addition of chemo-RT to chemotherapy is beneficial for patients with LA-PDAC. In 2011, a randomized trial conducted by ECOG reported 74 patients with LA-PDAC who received gemcitabine with or without local radiotherapy (total dose 50.4 Gy and 1.8 Gy/fraction)[61]. The quality of life achieved was similar in both groups, while a significantly improved OS (median 11.1 *vs.* 9.2 months) in the chemo-RT arm was noted. Five years later, the LAP07 randomized trial on 442 patients was published[62]. Patients were randomized to receive gemcitabine with or without erlotinib, followed by a second randomization of patients without disease progression at four months. In this latter phase of the trial, 133 patients received chemo-RT (54 Gy conventionally fractionated RT with capecitabine). After a median follow-up of 36.7 months, the median OS was similar in all groups. However, the rate of locoregional progression in the chemo-RT group was significantly lower than the one recorded for the chemotherapy group (32% *vs.* 46%). Chemo-RT was well tolerated, as no increase of grade 3-4 toxicities was recorded. Only 6% of the patients recruited in the trial had surgery after chemo-RT.

Low total dose conventionally fractionated photon RT, which applies a low dose per fraction, seems to be ineffective at suppressing the growth or eradicating PDAC, which is well-known to be radio- and chemoresistant[63,64]. Large radiotherapy fractions, the application of which has become feasible with modern radiotherapy techniques including stereotactic approaches, may be more potent against radioresistant PDAC cells. A study from the MD Anderson Cancer Center recruited a total of 200 patients in a dose escalation radiotherapy protocol using intensity modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB) to deliver a biologically effective dose of 50-70 Gy concurrently with capecitabine[65]. Patients receiving a dose above 70 Gy had a significantly better OS (median 17.8 *vs.* 15 months) and estimated two-year survival rates (36% *vs.* 19%). The locoregional relapse-free survival was almost doubled (10.2 *vs.* 6.2 months). Using biomarkers, the isolation of the group of patients with a high tendency to develop metastasis could exclude them from radiotherapy and eventually help to identify a subgroup that would benefit from the locoregional control offered by RT[66].

Densely ionizing radiation, produced by proton and heavy-ion linear accelerators, also has potential advantages. However, these rely on the superior dose distribution and the consequent sparing of normal tissues, as well as on the specific radiobiology of this type of radiation that kills cancer cells ignoring the hypoxic tumor microenvironment and the repair capacity of single DNA strand breaks[67]. Although randomized trials are not available, phase II trials have provided encouraging results, with a two-year survival of around 50%[68-70].

Neoadjuvant chemo-RT for LA/BR-PDAC
Upfront surgery of presumed operable PDACs results in high rates (up to 60%) of incomplete excisions[46]. The postoperative survival of patients with involved surgical margins is significantly worse[71]. Based on the favorable outcome of patients with rectal cancer receiving neoadjuvant chemo-RT, the hypothesis that neoadjuvant chemo-RT could also be beneficial in pancreatic cancer is sound. An analysis of 6936 patients with PDAC, collected from the National Cancer Database, identified 3185 patients who were treated with neoadjuvant chemo-RT and 3751 with neoadjuvant chemotherapy[72]. Negative resection margins were more frequent in the chemo-RT group (86.1% *vs.* 80%), but postoperative mortality rates were higher (6.4% *vs.* 3.6%). There was no survival benefit detected between the two groups.

Several retrospective studies with a relatively low number of patients have reported high resectability rates in LA/BR-PDAC treated with FFX with or without radiotherapy[8]. In 2014, a study by Kharofa *et al.*

suggested that induction chemotherapy followed by chemo-RT (total dose 50.4 Gy and 1.8 Gy/fraction with gemcitabine or capecitabine) results in 70% resectability with negative margins in 98% of cases[73]. The study comprised 39 patients with borderline resectability and 30 resectable cases. The local failure at two years was impressively low (9%), and 23% of operated patients were alive without disease at the time of analysis (median follow-up of 47 months). Another retrospective study by Katz *et al.* included 129 patients with BR-PDAC treated with gemcitabine-based chemo-RT[74]. Resectability was obtained in 66% of patients (95% R0 resection), and the median OS reached 33 months. In 2022, a report by Hill *et al.* analyzed 198 patients[75], 76 of whom had received neoadjuvant chemotherapy and 122 chemo-RT with stereotactic body radiation therapy (SBRT) technique. SBRT offered significantly higher complete resectability rates (92% *vs.* 70%) and negative node histopathology (59% *vs.* 42%). Of interest, a pathologic complete response (pCR) rate of 7% was recorded. However, there was no survival benefit from SBRT (two-year OS rate of 50.4%).

Nevertheless, phase II and a small number of phase III trials have provided encouraging results in LA/BR-PDAC[46,73-85], as shown in Table 2. In 2018, a phase II study from the Massachusetts General Hospital reported 48 patients with BR-PDAC who were treated with eight cycles of FFX[82]. Patients who achieved resolution of the vascular involvement (56%) were further treated with hypofractionated accelerated proton radiotherapy (5 Gy × 5 fractions) with capecitabine, while the rest of the patients received long course chemo-RT (total dose 50.4 Gy and 1.8 Gy/fraction) with capecitabine or 5-FU. Tumor resection was feasible in 32/48 patients, with R0 resection obtained in 97% of cases. The overall two-year PFS rate was 43%, while the median PFS for operated patients reached 48.6 months. The two-year OS rate for this latter group of patients was 72%.

A Korean study published in the same year enrolled 50 patients with BR-PDAC to receive preoperative chemo-RT with gemcitabine *vs.* upfront surgery and adjuvant chemo-RT[83]. The resectability rates were significantly higher in patients receiving neoadjuvant chemo-RT (51.8% *vs.* 26.1%) and the two-year OS rate was significantly better in the neoadjuvant arm (40.7% *vs.* 26.1%).

Early results of the ESPAC-5F multicenter randomized phase II trial were reported at the 2020 ASCO congress[46]. Patients with BR-PDAC were recruited in a four-arm study (upfront surgery *vs.* neoadjuvant gemcitabine/capecitabine *vs.* neoadjuvant FFX *vs.* neoadjuvant chemo-RT). An early analysis of 88 patients showed a benefit in the neoadjuvant arms in terms of one-year survival rate (77% *vs.* 40%). There are no data available on the role of RT yet. In contrast, the A021501 randomized phase II trial did not demonstrate a survival benefit in patients with BR-PDAC who received SBRT or hypofractionated RT after neoadjuvant mFOLFIRINOX when compared to patients that received mFOLFIRINOX alone (median OS 29.8 *vs.* 17.1 months for the chemotherapy alone and chemotherapy plus RT arms, respectively)[84].

The PREOPANC randomized trial, published in 2020, included 246 patients who were treated with preoperative chemo-RT *vs.*upfront surgery[86]. Patients had BR/R-PDAC and were randomized to receive upfront surgery *vs.* neoadjuvant chemo-RT with gemcitabine, followed by surgery and postoperative gemcitabine chemotherapy. The R0 resection rates were better in the RT group (71% *vs.* 40%). The DFS and locoregional control were also improved in the RT arm, while a benefit in survival was also noted (median OS 35.2 *vs.* 19.8 months). Long-term results of the PREOPANC study were published in 2022, and the five-year OS rate was significantly better in the chemo-RT arm (20.5% *vs.* 6.5%), despite the rather small 1.4 months difference in median survival (15.7 *vs.* 14.3 months in the chemo-RT and upfront surgery arms, respectively)[87]. Moreover, the first results of a randomized phase III trial (CONKO-007) comparing induction chemotherapy (GnP or FOLFIRINOX) followed by additional chemotherapy cycles or chemo-RT (RT + gemcitabine) for patients with advanced PDAC were reported in the 2022 ASCO Annual Meeting I.

Table 2. Published phase II/III trials on neoadjuvant chemo-RT for PDAC

Author (year)	Disease	Type of study	No pts	Control arm	Neoadjuvant chemotherapy	Neoadjuvant chemo-RT	Main findings
LA-PDAC							
Sherman (2015)[76]	LA-PDAC	Phase II	45	No	Gemcitabine, capecitabine and docetaxel	50.4 Gy, 1.8 Gy/fraction Concurrent capecitabine and gemcitabine	1-year OS: 71%
Eguchi (2018)[77]	LA-PDAC	Phase II	34	No	No	40-54 Gy, 2-1.8 Gy/fraction Concurrent gemcitabine/S1 followed by chemotherapy	Resectability 15% Median OS for operated patients 3.63 years
CONKO-007; Fietkau *et al.* (2022)[88]	LA-PDAC	Phase III	525	No	FFX (Group A)	FFX followed by chemo-RT (50.4 Gy, 1.8 Gy/fraction with concurrent gemcitabine) (Group B)	Higher R0 resections rates in the chemo-RT arm. Median PFS (HR 0.919, 95%CI: 0.702-1.203, *P* = 0.54) and OS (HR 0.964, 95%CI: 0.760-1225, *P* = 0.766) not significantly different between the two arms
BR-PDAC							
Kim (2013)[78]	R/BR/LA-PDAC	Phase II	68	No	No	30 Gy, 2 Gy/fraction Concurrent gemcitabine and oxaliplatin	Resectability 63% (R0 84%) Median OS 27.1 months for operated patients
Chakraborty (2014)[79]	BR-PDAC	Phase II	13	No	Induction chemotherapy followed by chemo-RT	50 Gy, 2.5 Gy/fraction Concurrent capecitabine	Resectability 38.4% Median survival 13 months
Katz (2016)[80]	BR-PDAC	Phase II	22	No	FFX	50.4 Gy, 1.8 Gy/fraction Concurrent capecitabine	pCR 13% Median OS 21.7 months
Fiore (2017)[81]	BR/LA-PDAC	Phase II	41	No	Gemcitabine and oxaliplatin	54 Gy, 1.8 Gy/fraction Concurrent gemcitabine	Median OS 19.2 months
Murphy (2018)[82]	BR-PDAC	Phase II	48	No	FFX before chemo-RT	25 Gy, 5 Gy/fraction or 54 Gy, 1.8 Gy/fraction Concurrent capecitabine	Resectability 66.6% R0 surgery 97% 2-year PFS 43% (all pts) 2-year PFS 72% (operated pts)
Jang (2018)[83]	BR-PDAC	Phase III	50	Upfront surgery	No	54 Gy, 1.8 Gy/fraction Concurrent gemcitabine	Higher resectability in the chemo-RT arm (51.8% *vs.* 26.1%) (*P* = 0.004) Better 2-year OS (30.7% *vs.* 26.1%) (HR 1.495, 95%CI: 0.66-3.36, *P* = 0.028)
ESPAC-5F; Ghaneh 2020[46]	BR-PDAC	Ongoing Phase III (4 arms)	88	Upfront surgery (group A)	FFX (group B) or Gemcitabine/capecitabine (group C)	50.4 Gy, 1.8 Gy/fraction Concurrent capecitabine (group D)	Better 1-year survival in the neoadjuvant arms 77% *vs.* 40% (HR 0.27, 95%CI: 0.13-0.55, *P* < 0.001)
A021501; Katz *et al.* 2021[84]	BR-PDAC	Phase II (randomized)	126	No	FFX (Group A)	FFX followed by SBRT (33-40 Gy in 5 fractions) or hypofractionated image-guided RT (25 Gy, 5 Gy/fraction) (Group B)	Chemo-RT did not improve median OS (31 months Group A *vs.* 17.1 Group B) (95%CI: 22.2-NE and 12.8-24.4 for Group A and B, respectively) (HR, *P* value not reported)
BR/R-PDAC							
Okano (2017)[85]	BR-PDAC R-PDAC	Phase II	57	No	No	30 Gy, 3 Gy/fraction Concurrent with S-1	2-year OS 83% in patients with resectable, and 58% in borderline resectable tumors
PREOPANC;	BR-PDAC	Phase III	246	Upfront	No	36 Gy, 2.4 Gy/fraction	Better 5-year OS in the chemo-RT arm (20.5% *vs.* 6.5%)

Vesteijne (2022)[87]	R-PDAC			surgery		Concurrent gemcitabine	(HR 0.73, 95%CI: 0.56 to 0.96; *P* = 0.025)
R-PDAC							
Talamonti (2006)[89]	R-PDAC	Phase II	20	No	No	36 Gy, 2.4 Gy/fraction Concurrently with seven weekly infusions of gemcitabine	Resectability 85% R0 margins 95% Lack of lymph node involvement 65%
Evans (2008)[90]	R-PDAC	Phase II	86	No	No	30 Gy, 3 Gy/fraction Concurrently with seven weekly infusions of gemcitabine	Resectability 85% R0 margins 89% Median survival 34 months in operated patients *vs.* 7 months in inoperable
Turrini (2009)[91]	R-PDAC	Phase II	102	No	No	45 Gy, 1.8 Gy/fraction Concurrently with 5-FU/Cisplatin	Resectability 74% Ro margins 92% pCR 13% Lack of lymph node involvement 76%
Varadhachary (2008)[92]	R-PDAC	Phase II	79	No	No	45 Gy, 1.8 Gy/fraction Concurrently with four bi-weekly infusions of gemcitabine and cisplatin	Resectability 65.8% Median survival 31 months
Golcher (2015)[93]	R-PDAC	Phase II (randomized)	66	Upfront surgery	No	50.4 Gy, 1.8 Gy/fraction Concurrently with four weekly cycles of gemcitabine and cisplatin	Good tolerance No difference between groups

PDAC: Pancreatic ductal adenocarcinoma; LA: locally advanced; BR: borderline resectable; R: resectable; chemo-RT: chemoradiotherapy; OS: overall survival; PFS: progression-free survival; DFS: disease-free survival; FFX: 5-FU/leucovorin/irinotecan/oxaliplatin; pCR: pathologic complete response.

Although patients in the chemo-RT arm were linked with higher R0 resection rates and pathologic complete responses, PFS and OS did not differ significantly between the two groups[88].

Neoadjuvant chemo-RT for R-PDAC

Neoadjuvant chemo-RT for R-PDAC has also been under investigation [Table 2]. A small early phase II study on 20 patients treated with chemo-RT with seven weekly infusions of gemcitabine showed 85% resectability rates (94% R0 margins) and absence of nodal involvement in 65% of specimens (five specimens with minimal residual disease)[89]. In 2008, Evans *et al.* reported a study on 86 patients with R-PDAC who received preoperative gemcitabine chemotherapy (seven weekly infusions) and radiotherapy (30 Gy in 10 fractions)[90]. Tumor resectability was obtained in 85% of patients, with a median OS of 34 months, compared to seven months for patients who were assumed inoperable. In 89% of operated patients, the histological margins were negative. Another relatively large phase II trial by Turrini *et al.* involved 101 patients with R-PDAC who were treated with neoadjuvant chemo-RT (total dose 45 Gy and 1.8 Gy/fraction) with cisplatin and 5-FU[91]. Overall, 26 out of 101 patients progressed during neoadjuvant therapy, while the remaining underwent surgery (92% R0 resections). Complete pathological responses were achieved in 13% of specimens, and a lack of nodal involvement was observed in 76% of patients. Varadhachary *et al.* reported 79 patients treated with chemo-RT with gemcitabine and cisplatin[92]. In total, 52 out of 79 (70%) underwent surgery, and their

median survival was 31 months.

More recent phase II studies continue to provide encouraging results from neoadjuvant chemo-RT. A study from Japan recruited 57 patients (33 resectable tumors)[85], treated with hypofractionated RT (total dose 30 Gy and 3 Gy/fraction) and S-1 chemotherapy. The two-year OS was 83% in resectable tumors and 58% in tumors with borderline resectability. In 2015, the first ever randomized phase II trial (University of Erlangen) was published[93]. Although this was terminated prematurely due to low recruitment rates, 66 patients were analyzed. Patients were randomized to receive primary surgery or neoadjuvant chemo-RT (total dose 50.4 Gy and 1.8 Gy/fraction) with four weekly cycles of gemcitabine and cisplatin. The study confirmed good tolerance, but there was no difference in terms of efficacy.

NEOADJUVANT TARGETED THERAPIES FOR PDAC

PDAC is a tumor with extensive activation of multiple growth and metastasis-related molecular pathways. Overall, four major pathways are active. The *KRAS* gene is frequently mutated, which leads to the overactivation of the RAF-MEK-ERK and PI3K-AKT/mTOR pathways[94]. Furthermore, mutations of the *EGFR* gene are common in PDAC. The EGFR pathway also intersects with the insulin growth factor IFG-1 pathway, both promoting growth and migration properties of the cancer cells[95,96]. Angiogenic pathways involving VEGF secretion and VEGF-receptor overexpression by the neo-vasculature also characterize a subgroup of PDACs[97]. In addition, the hepatocyte growth factor receptor (Met) pathway regulates cancer cell interactions with the tumor stroma and cancer-associated fibroblasts, promoting stromatogenesis, invasion, and metastasis[98]. Finally, a subgroup of patients with *BRCA1/2* mutations suffer from DNA repair deficiency, which is a potential target for the development of molecular therapy[99].

Targeting agents against KRAS and downstream pathways have mainly focused on RAF and MEK inhibitors. Direct inhibition of KRAS with pharmacological agents is problematic for several reasons[100]. Trametinib, a MEK inhibitor, has some potential in the treatment of PDAC, as a randomized phase II study showed benefit in combination with gemcitabine, with a longer duration of response[101]. Promising results have also been published regarding the concurrent administration of trametinib with pembrolizumab and RT in locally recurrent PDAC[102]. Moreover, the combination of trametinib with the autophagy inhibitor chloroquine is being assessed in an ongoing trial for advanced PDAC (NCT03825289), but there are no trials in the neoadjuvant setting. AKT inhibition with the MK-2206 agent has shown activity in PDAC, and two clinical studies have been completed in advanced and metastatic disease (NCT01658943, NCT01783171).

Anti-EGFR therapies have been tested against PDAC. Randomized phase III trials on the combination of cetuximab monoclonal antibody (MoAb) with different gemcitabine, irinotecan, and cisplatin combinations failed to improve the survival of patients with metastatic disease[103]. A phase III trial comparing gemcitabine with or without erlotinib showed prolongation of the PFS[29]. The GEMCAD 10-03 phase II trial published in 2018 combining neoadjuvant gemcitabine and erlotinib with RT in R-PDAC provided encouraging results, suggesting further trials should be conducted with neoadjuvant erlotinib[104]. Moreover, a recent phase I/II trial showed benefit in terms of OS when combining the IGF-1R antagonist with gemcitabine and erlotinib in advanced disease, suggesting a potential value in the neoadjuvant setting[105].

Specific anti-VEGF or anti-VEGF-receptor agents, e.g., bevacizumab and ramucirumab, respectively, have not shown any efficacy in combination with chemotherapy for PDAC[106]. Broad spectrum multitarget tyrosine kinase inhibitors (MTKIs), e.g., sunitinib, sorafenib, imatinib, and axitinib, have displayed limited activity in PDAC[107,108] . In a phase III trial, axitinib failed to show a benefit in combination with gemcitabine

in advanced PDAC[109]. Recent experimental data suggest that MTKIs may remodel the PDAC microenvironment, enhancing the efficacy of immunotherapy, which may lead to trials combining MTKIs with immune checkpoint inhibitors[110]. In the neoadjuvant setting, the NCT00557492 trial examining the combination of RT with bevacizumab and gemcitabine before surgery has been completed; there are no available results yet.

Targeting the intense desmoplastic activity of PDAC is another interesting area of research. Saridegib (IPI-926), an inhibitor of the Sonic Hedgehog pathway involved in fibroblastic proliferation, has been tested in a phase I trial together with FFX in advanced PDAC[111]. Hyaluronan depletion through the administration of pegylated hyaluronidase (PEGPH20) is also of therapeutic relevance in PDAC. A randomized trial combining PEGPH20 with GnP did not, however, improve the survival of patients with metastatic PDAC[112]. In fact, the SWOG S1313 trial showed detrimental effects[113].

In patients with BRCA mutations, DNA repair is compromised. In this subgroup of patients, poly(ADP-ribose) polymerase (PARP) compensates for the missing repair activity of BRCA. PARP inhibitors, such as olaparib, improve the survival of PDAC patients with BRCA mutations, administrated either as monotherapy or in combination with gemcitabine[114]. The POLO trial randomized patients whose disease had not progressed after platinum-based chemotherapy to maintenance olaparib or placebo; the results, although not statistically significant, displayed a trend towards longer time to subsequent chemotherapy and overall survival with olaparib treatment[115]. The ongoing APOLLO trial (NCT04858334), sponsored by the NCI, is investigating olaparib's role as a postoperative monotherapy regimen in R-PDAC, but there are no trials at the neoadjuvant level. Niraparib is also under investigation in the treatment of PDAC (NCT03553004).

Losartan is an angiotensin II receptor blocker, mostly used to treat hypertension. It was also utilized in the neoadjuvant setting as a targeting agent for LA-PDAC treatment in a single-arm phase II study by Murphy *et al.*[116]; neoadjuvant FFX combined with losartan followed by either short or long course chemo-RT was prescribed in patients with unresectable PDAC. Surgery was performed in 86% of patients, while R0 resection was achieved in 69% of them. In the subgroup of patients who underwent surgery, median PFS and OS were longer when compared to the overall median PFS and OS (21.3 and 33 months *vs.* 17.5 and 31.4 months, respectively). Losartan, together with FFX, SBRT, and nivolumab, is also under investigation in a phase II trial for LA-PDAC (NCT03563248).

ONGOING TRIALS ON NEOADJUVANT CHEMOTHERAPY AND CHEMO-RT
There are several ongoing phase II and III trials for PDAC, examining both chemotherapy [Table 3] and chemo-RT [Table 4] in the neoadjuvant setting. Selected trials are presented in this section.

LA-PDAC
Connective tissue growth factor (CTGF) promotes the growth of fibroblasts and angiogenesis[117]. The NCT03941093 phase III trial is examining the addition of an anti-CTGF MoAb to the standard FFX or GnP neoadjuvant chemotherapy, aiming at OS. Alternating electric fields have a direct inhibitory effect on tumor growth[118]. In this context, the PANOVA-3 (NCT03377491) phase III trial is actively recruiting patients to assess the effects of GnP plus alternated electric tumor treating field (TTFields), provided by an externally applied device, on OS. The Y2018-ZD-001 (NCT03673137) phase II/III trial incorporates irreversible electroporation to chemotherapy with gemcitabine, which could potentially enhance the bioavailability of drugs. Gene therapy is also being explored in the THERGAP-02 (NCT02806687) phase II trial, which randomizes patients to gemcitabine alone or gemcitabine plus intratumoral injection of CYL-02 (plasmid

Table 3. Ongoing trials on neoadjuvant chemotherapy for PDAC

ClinicalTrials.gov identifier	Country	Disease	Type of study	Control arm	Experimental arm	Primary endpoint	Status
LA-PDAC							
NCT03941093	USA	LA-PDAC	Phase III	Neoadjuvant GnP or FFX followed by surgery	Neoadjuvant GnP or FFX and Pamrevlumab anti-CTGF MoAb followed by surgery	OS and resectablity	Recruiting
NCT03377491 (PANOVA-3)	USA	LA-PDAC	Phase III	Neoadjuvant GnP	Tumor Treating Fields (TTFields -Alternated electric tumor treating fields) and GnP	OS	Recruiting
NCT03673137 (Y2018-ZD-001)	China	LA-PDAC	Phase II/III	Irreversible electroporation (IRE) followed by gemcitabine starting on day 7 after IRE treatment	Gemcitabine infusion over 30 minutes following percutaneous IRE	OS	Completed
NCT02806687 (THERGAP-02)	France	LA-PDAC	Phase II	Neoadjuvant gemcitabine	Intratumoral injection of CYL-02 plus neoadjuvant chemotherapy with gemcitabine followed by gemcitabine alone	PFS	Active, not recruiting
LA/BR-PDAC							
NCT04617821	China	LA-PDAC BR-PDAC	Phase III	Neoadjuvant FFX	Neoadjuvant GnP	OS	Recruiting
R-PDAC							
NCT01521702	France	R-PDAC	Phase III	Surgery	Neoadjuvant gemcitabine and Oxaliplatin followed by surgery	PFS	Recruiting
NCT02172976	Germany	R-PDAC	Phase II/III	Surgery followed by adjuvant gemcitabine	Neoadjuvant and adjuvant FFX	Median OS	Completed
NCT03750669	China	R-PDAC	Phase II	None	Sequential GnP and FFX before surgery	DFS	Recruiting
NCT04927780 (PREOPANC-3)	Netherlands	R-PDAC	Phase III	Upfront surgery followed by adjuvant FFX	Neoadjuvant FFX followed by surgery and adjuvant FFX	OS	Recruiting
NCT04340141	USA	R-PDAC	Phase III	Upfront surgery followed by adjuvant FFX	Neoadjuvant and adjuvant FFX	OS	Recruiting
NCT01150630 (PACT-15)	Italy	R-PDAC	Phase II	Upfront surgery followed by adjuvant gemcitabine	Neoadjuvant cisplatin, epirubicin and gemcitabine	Event free survival	
NCT02030860	USA	R-PDAC	Phase I	Neoadjuvant GnP	Neoadjuvant GnP and paricalcitol	Adverse events	Completed
NCT05268692	Japan	R-PDAC	Phase II/III	Neoadjuvant GnP	Neoadjuvant gemcitabine/S-1	OS	
NCT02919787 (NorPACT) - 1	Denmark, Finland, Norway, Sweden	R-PDAC	Phase II/III	Surgery followed by adjuvant FOFLIRINOX	Neoadjuvant FFX followed by surgery and adjuvant FFX	OS	Active, not recruiting

PDAC: Pancreatic ductal adenocarcinoma; LA: locally advanced; BR: borderline resectable; R: resectable; OS: overall survival; PFS: progression-free survival; DFS: disease-free survival; FFX: 5-FU/leucovorin/irinotecan/oxaliplatin; GnP: gemcitabine/nab-paclitaxel; MoAb: monoclonal antibody.

Table 4. Ongoing trials on neoadjuvant chemo-RT for PDAC

ClinicalTrials.gov identifier	Country	Disease	Type of study	Control arm	Experimental arm	Primary endpoint	Status
BR-PDAC							
NCT01458717	Korea	BR-PDAC	Phase II/III	Upfront surgery followed by chemo-RT with gemcitabine and maintenance gemcitabine chemotherapy	Neoadjuvant chemo-RT with gemcitabine followed by surgery and maintenance gemcitabine chemotherapy	2-year survival rate	Completed 2018
NCT02676349 (PANDAS-PRODIGE 44)	France	BR-PDAC	Phase II	Neoadjuvant FFX followed by surgery and adjuvant gemcitabine or 5FU/LV	Neoadjuvant FFX followed by chemo-RT with capecitabine, surgery and adjuvant gemcitabine or 5FU/LV	Resectability (R0 rates)	Recruiting
NCT03777462	China	BR-PDAC	Phase II	Neoadjuvant GnP followed by surgery	A Neoadjuvant GnP chemotherapy and SBRT followed by surgery B Neoadjuvant S-1/nab-paclitaxel chemotherapy and SBRT followed by surgery	OS	Recruiting
Trial NL7094 (NTR7292) (PREOPANC-2)	Netherlands	BR-PDAC	Phase III	Neoadjuvant gemcitabine-based chemo-RT followed by surgery and adjuvant gemcitabine	Neoadjuvant chemotherapy with FFX followed by surgery	OS	Completed
NCT02839343	USA	BR-PDAC	Phase II		Neoadjuvant chemotherapy with FFX followed by surgery and adjuvant chemotherapy with FOLFOX Neoadjuvant chemotherapy with FFX followed by hypofractionated RT followed by surgery and adjuvant chemotherapy with FOLFOX	OS	Active, not recruiting
R-PDAC							
NCT00335543	Germany - Austria	R-PDAC	Phase II	Surgery alone	Neoadjuvant chemo-RT with cisplatin and gemcitabine	OS	Completed

PDAC: Pancreatic ductal adenocarcinoma; LA: locally advanced; BR: borderline resectable; R: resectable; chemo-RT: chemoradiotherapy; OS: overall survival; FFX: 5-FU/leucovorin/irinotecan/oxaliplatin; GnP: gemcitabine/nab-paclitaxel; SBRT: stereotactic body radiation therapy.

gene therapy).

BR-PDAC
A Chinese phase III trial is focusing on standard regimens (FFX *vs.* GnP) (NCT04617821), with OS as the primary endpoint. PREOPANC-2 (NL7094) is a randomized phase III study consisting of two arms: (1) neoadjuvant gemcitabine-based chemo-RT followed by surgery plus adjuvant gemcitabine chemotherapy; and (2) neoadjuvant chemotherapy with eight cycles of FFX followed by surgery. Recruitment has been completed. Neoadjuvant FFX followed by chemo-RT or hypofractionated irradiation *vs.* neoadjuvant chemotherapy alone with FFX is also under investigation (NCT02839343).

R-PDAC
We expect the preliminary results of the NorPACT-1 (NCT02919787) study, which compares immediate surgery to preoperative chemotherapy using FFX, and the NEOPAC (NCT01521702) trial, which examines neoadjuvant chemotherapy with gemcitabine and oxaliplatin *vs.* upfront surgery. In addition, the SWOG S1505 (NCT02562716) trial is currently comparing neoadjuvant modified FFX to neoadjuvant GnP to determine which regimen leads to better OS. Moreover, the European NCT00335543 phase II trial compares

Table 5. Ongoing trials on neoadjuvant immunotherapy for PDAC

ClinicalTrials.gov identifier	Country	Disease	Study type	Treatment	Primary endpoint	Status
LA-PDAC						
NCT01959672	USA	LA-PDAC with High serum CA125 levels	Phase II	Gemcitabine/5-FU/leucovorin every 3 weeks plus Oregovomab anti-CA125 and nelfinavir mesylate (protease inhibitor). SBRT starts on week 11. Assessment of resectability	Response and resectability rates	Completed (has results)
NCT04327986	USA	LA-PDAC	Phase I/II	Dose escalation of M9241 (IL-12 immunocytokine) with M7824 (bi-functional anti-PD-L1 and anti-TGFβ MoAb), with or without SBRT	Safety, dose finding efficacy	Completed
NCT02446093	USA	LA-PDAC	Phase I/II	Aglatimagene besadenovec (oncolytic adenoviral vector), valacyclovir and chemo-RT followed by surgery. Control arm: chemo-RT and Surgery	Resectability safety	Recruiting
NCT03767582	USA	LA-PDAC	Phase I/II	Nivolumab and CCR2/CCR5 dual antagonist with or without GVAX and SBRT	Survival pathological responses	Recruiting
NCT03563248	USA	LA-PDAC	Phase II	FFX and SBRT with or without Losartan (inhibitor of angiotensin) with or without Nivolumab, followed by surgery	R0 resections survival	Recruiting
NCT02648282	USA	LA-PDAC	Phase II	Cyclophosphamide plus GVAX plus Pembrolizumab plus SBRT	DMFS	Active, not recruiting
LA/BR-PDAC						
NCT03983057	China	LA-PDAC BR-PDAC	Phase II	FFX *vs.* FFX and anti-PD1 MoAb	PFS	Recruiting
BR-PDAC						
NCT03970252	USA	BR-PDAC	Phase II	Nivolumab and FFX	Pathological response	Recruiting
BR/R-PDAC						
NCT02305186	USA	BR-PDAC R-PDAC	Phase I/II	Pembrolizumab and chemo-RT (capecitabine + 50.4 Gy, 1.8 Gy/fraction) *vs.* chemo-RT	Safety immunopathology study	Recruiting
NCT04940286	USA	BR-PDAC R-PDAC	Phase II	Durvalumab, oleclumab (anti-CD73 ectonucleotidase), GnP followed by surgery	Pathological response safety	Recruiting
R-PDAC						
NCT03727880	USA	R-PDAC	Phase II	Pembrolizumab and Defactinib *vs.* Pembrolizumab before surgery	Pathological responses	Recruiting
NCT02588443	USA	R-PDAC	Phase I	RO70097890 (anti-CD40) with or without GnP before surgery	Adverse event	Completed
NCT00727441	USA	R-PDAC	Phase II	A GVAX vaccination followed by surgery. Postoperative vaccination, chemo-RT with gemcitabine and 5-FU B Low dose cyclophosphamide, GVAX vaccination followed by surgery. Postoperative vaccination, chemo-RT with gemcitabine and 5-FU	Safety and OS	Completed 2020
NCT02451982	USA	R-PDAC	Phase II	A GVAX vaccine with CY followed by surgery and chemo-RT B Same as A plus Nivolumab followed by surgery and chemo-RT C Same as B plus urelumab followed by surgery and chemo-RT D BMS-986253 and Nivolumab the surgery and chemo-RT	Pathologic response and intra-tumoral immunological response evaluation	Recruiting

PDAC: Pancreatic ductal adenocarcinoma; LA: locally advanced; BR: borderline resectable; R: resectable; chemo-RT: chemoradiotherapy; OS: overall survival; PFS: progression-free survival; FFX: 5-FU/leucovorin/irinotecan/oxaliplatin; GnP: gemcitabine/nab-paclitaxel; SBRT: stereotactic body radiation therapy; DMFS: distant metastasis free survival; MoAb: monoclonal antibody.

surgery alone to neoadjuvant chemo-RT with cisplatin and gemcitabine.

NEOADJUVANT IMMUNOTHERAPY FOR PDAC

In the last decade, immunotherapy with immune checkpoint inhibitors has revolutionized the clinical practice of oncology in the majority of human carcinomas. A striking exception is PDAC. In a review by Henriksen *et al.* of 24 identified studies on the treatment of metastatic PDAC with ipilimumab and anti-PD-1/PD-L1 MoAbs with or without chemotherapy, the response rates were disappointing, and the median survival did not exceed six months[119]. The poor response to immunotherapy is related to the immunosuppressive tumor microenvironment, low percentage of PDACs with mismatch repair deficiency, high expression of arginase and IDO that promote immunological tolerance, and infiltration of the tumor stroma by regulatory T cells and myeloid cells[120].

Struggling to uncover the immuno-resistance of advanced PDAC, it is unlikely to expect the launch of neoadjuvant immunotherapy trials. A small randomized trial on preoperative administration of IL-2 did not show any benefit[121]. However, encouraging results were reported in a subsequent study on 30 patients, suggesting an improvement in PFS and OS[122]. A recent analysis identified 526 patients in the National Cancer Database who received neoadjuvant (408) or adjuvant immunotherapy (118)[123]; patients treated with neoadjuvant immunotherapy had longer survival. A phase I trial on the preoperative administration of the CD40 agonist MoAb selicrelumab demonstrated significant changes in the tumor microenvironment with less fibrosis, fewer M2-type macrophages, and increased presence of mature dendritic cells compared to cases that had received chemo-RT[124]. Furthermore, the combination of an anti-CD40 MoAb with nab-paclitaxel is under investigation in a phase I trial (NCT02588443). In 2022, the results of maintenance vaccination with the OSE2101 vaccine after induction chemotherapy with FOLFIRINOX for patients with advanced pancreatic cancer were reported; OSE2101 conferred a 12-month OS rate of 40% (*vs.* 44% in patients who continued treatment with FOLFIRINOX) and was not associated with grade 3 or higher toxicities[125]. Ongoing trials on neoadjuvant immunotherapy are shown in Table 5.

FURTHER TREATMENT APPROACHES

It is important to underline that, alongside the ongoing trials assessing the efficacy of combined treatment modalities for PDAC, new strategies are also being tested in the neoadjuvant setting. Most notably, adoptive therapy incorporates alternation between treatments according to patient tolerance and tumor response. The NeoOPTIMIZE (NCT04539808) and NCT03322995 phase II trials are focusing on the early adoption of different chemotherapy regimens or chemoradiation when the initial drug combination is associated with increased toxicity or poor clinical response. Moreover, tumor subtype-based therapy is another approach under evaluation. In the NCT04683315 phase II trial, RNA expression profiling is being used to categorize PDAC as either basal or classical. Patients with the molecular basal and classical tumor subtypes will receive GnP and FFX, respectively, and treatment response will be assessed. GATA6 expression is another biomarker which could potentially impact treatment choice (NCT04472910). Finally, circulating tumor DNA (ctDNA) is also under investigation as an early marker of tumor response or resistance to neoadjuvant chemotherapy (NCT04616131).

CONCLUSIONS

The results from retrospective studies and phase II/III randomized trials on the neoadjuvant treatment of PDAC are quite encouraging. Ongoing phase III trials investigating chemotherapy, chemo-RT, immunotherapy, targeting agents and their combinations will shed more light on the advantages of this rising clinical practice and potentially herald a new era in the treatment algorithm of non-metastatic PDAC.

DECLARATIONS

Authors' contributions
Performed search of literature, analysis of data, writing of the first draft of the study and final approval of the manuscript: Koukourakis IM, Desse D, Papadimitriou M
Made substantial contributions to conception and design of the study, interpretation, writing of the study and final approval of the manuscript: Papadimitriou C, Konstadoulakis M, Zygogianni A

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