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REVIEW

Metastatic pancreatic cancer: Is there a light at the end of the tunnel?

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Abstract

Due to extremely poor prognosis, pancreatic cancer (PDAC) represents the fourth leading cause of cancer-related death in Western countries. For more than a decade, gemcitabine (Gem) has been the mainstay of first-line PDAC treatment. Many efforts aimed at improving single-agent Gem efficacy by either combining it with a second cytotoxic/molecularly targeted agent or pharmacokinetic modulation provided disappointing results. Recently, the field of systemic therapy of advanced PDAC is finally moving forward. Polychemotherapy has shown promise over single-agent Gem: regimens like PEFG-PEXG-PDXG and GTX provide significant potential advantages in terms of survival and/or disease control, although sometimes at the cost of poor tolerability. The PRODIGE 4/ACCORD 11 was the first phase Ⅲ trial to provide unequivocal benefit using the polychemotherapy regimen FOLFIRINOX; however the less favorable safety profile and the characteristics of the enrolled population, restrict the use of FOLFIRINOX to young and fit PDAC patients. The nanoparticle albumin-bound paclitaxel (*nab*-Paclitaxel) formulation was developed to overcome resistance due to the desmoplastic stroma surrounding pancreatic cancer cells. Regardless of whether or not this is its main mechanisms of action, the combination of *nab*-Paclitaxel plus Gem showed a statistically and clinically significant survival advantage over single agent Gem and significantly improved all the secondary endpoints. Furthermore, recent findings on maintenance therapy are opening up potential new avenues in the treatment of advanced PDAC, particularly in a new era in which highly effective first-line regimens allow patients to experience prolonged disease control. Here, we provide an overview of recent advances in the systemic treatment of advanced PDAC, mostly focusing on recent findings that have set new standards in metastatic disease. Potential avenues for further development in the metastatic setting and current efforts to integrate

new effective chemotherapy regimens in earlier stages of disease (neoadjuvant, adjuvant, and multimodal approaches in both resectable and unresectable patients) are also briefly discussed.

Key words: Pancreatic cancer; Metastatic disease; Chemotherapy; Folfirinox; *nab*-Paclitaxel

Core tip: In this paper, we provide an overview on the latest progress in the systemic treatment of advanced pancreatic cancer, mostly focusing on recent findings that have set new standards in metastatic disease. Potential avenues for further development in the metastatic setting and current efforts to integrate new effective chemotherapy regimens in earlier stages of disease (neoadjuvant, adjuvant, and multimodal approaches in both resectable and unresectable patients) are also briefly discussed.

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INTRODUCTION

Pancreatic cancer ranks as the fourth leading cause of cancer-related deaths in the United States and in most Western countries[1]. With a 5-year survival rate of 6% and mortality closely approaching incidence (approximately 46000 new cases and 39000 deaths estimated in the United States in 2014), pancreatic adenocarcinoma (PDAC) remains arguably the most aggressive[1,2] and resistant among solid tumors, to either classic chemotherapeutics[3] or targeted agents[4].

Besides the dismal prognosis, PDAC patients are usually affected by a complex association of symptoms (obstructive jaundice, pain, and weight loss, *etc.*) that require prompt and frequent palliative measures in order to improve patient performance status (PS) and quality of life (QoL), regardless of the specific oncologic treatment adopted[5,6].

Before the advent of gemcitabine (Gem), fluorouracil (5-FU), in different doses, schedules, and combination regimens, has been considered the cornerstone in the palliative treatment of advanced PDAC. A Cochrane systematic review[7] demonstrated that 5-FU-based chemotherapy significantly prolongs 6- and 12-mo survival [odds ratio (OR) = 0.37, 95% confidence interval (CI): 0.25-0.57, *P* value < 0.00001 for the 12-mo comparison], compared to best supportive care, providing significant clinical benefits in at least one study[8]. However, no significant difference was found in one-year mortality for 5-FU alone *vs* 5-FU combinations (OR = 0.90, 95%CI: 0.62 -1.30)[7].

PAST: GEM AS THE CORNERSTONE OF SYSTEMIC THERAPY

Since the first demonstration of clinical benefit in 1997, Gem has been the cornerstone of first-line PDAC treatment. In a phase Ⅲ study, Burris *et al*[9] randomized 126 locally advanced or metastatic PDAC patients to receive Gem 1000 mg/m^2 (once weekly for 7 wk followed by a week of rest and then once weekly for 3 out of 4 wk) or 5-FU 600 mg/m^2 (once weekly). Patients had to be symptomatic at study entry (70% of the patients had a Karnofsky PS - KPS < 80%). Indeed, the primary study endpoint was clinical benefit response (CBR), a composite assessment of pain, analgesic consumption, KPS, and weight[10,11]. Gem demonstrated to be superior to 5-FU in terms of CBR (23.8% *vs* 4.8%, *P* = 0.0022), and relatively, unexpectedly in the secondary endpoint of overall survival (OS) (5.65 mo *vs* 4.41 mo, *P* = 0.0025). In addition, the 6-, 9-, and 12-mo survival rates were higher with Gem (46%, 24%, and 18%, respectively) than with 5-FU (31%, 6%, and 2%, respectively)[9], although the real impact of Gem, as compared to 5-FU, on OS has been questioned by subsequent meta-analyses[12].

One approach aimed at improving Gem activity has been pharmacokinetic modulation, achieved by prolonging the infusion time[13-16]. This approach is justified by the observation that deoxycytidine kinase, the enzyme that catalyzes the conversion of Gem to its active triphosphate metabolite, is rapidly saturated at plasma concentrations achieved with the standard 30-min infusion. Indeed, Gem doses of 300-350 mg/m^2 infused over 30 min have reportedly failed to result in increased intracellular accumulation of Gem triphosphate in peripheral blood mononuclear cells[17-19]. Conversely, infusion of the same Gem doses over a prolonged period at a constant dose rate of 10 mg/m^2 per minute would avoid enzyme saturation and permit greater intracellular accumulation, possibly increasing Gem antitumor activity. Fixed dose-rate (FDR) Gem infusion has proven feasible, well tolerated (even in patients with impaired liver function[20]), and has shown promising clinical activity[15,21,22]. Although, FDR-Gem failed to significantly extend survival over standard 30-min infusion in a randomized phase Ⅲ trial, pharmacokinetic Gem modulation did show a trend towards increased clinical activity and proved equivalent by adding a second chemotherapy drug (oxaliplatin) to a Gem backbone. However, FDR-Gem was administered at a higher (1500 mg/m^2) weekly dose, as compared to the standard 30-min infusion (administered at 1000 mg/m^2)[23].

Until recently, efforts to improve on single-agent Gem efficacy by combining it with either a second cytotoxic drug or a molecularly targeted agent have failed[24,25]. The addition of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, to Gem has produced a clinically negligible, albeit statistically significant, improvement in OS in advanced, inoperable PDAC[26]. Even though, the combination of Gem and erlotinib is not widely employed, particularly in Europe, currently available evidence suggests that PDAC patients who develop skin toxicity during treatment may derive substantial benefit from this approach[27-29].

The addition of oxaliplatin to Gem in the study by Louvet *et al*[30] improved response rate (ORR), progression-free survival (PFS) and CBR over single agent Gem, but no statically significant difference in OS was observed (9.0 mo *vs* 7.1 mo, respectively, $P = 0.13$). Similar results were shown in a second study on the combination of Gem/oxaliplatin, in which combination therapy was actually therapeutically equivalent to FDR-Gem alone[23]. Similarly, cisplatin plus Gem showed no statistically significant benefit in survival, with comparable tumor responses and PFS[31,32]. The Gem/capecitabine combination demonstrated a significant improvement in ORR (19.1% *vs* 12.4%, $P = 0.034$) and PFS [hazard ratio (HR) = 0.78, 95%CI: 0.66-0.93; $P = 0.004$)] but failed to increase OS (HR = 0.86, 95%CI: 0.72-1.02; $P = 0.08$)[33].

The overall negative results with Gem-based combinations have generally been attributed to a lack of statistical power to detect small differences in survival, thus prompting for cumulative analyses that could detect small survival differences with adequate statistical power. Several meta-analyses have been conducted with the aim of assessing the potential of Gem-based chemotherapy doublets to increase survival in advanced PDAC.

Our group conducted a literature-based meta-analysis on 6296 patients enrolled in 20 randomized clinical trials comparing the single agent Gem *vs* Gem-based combinations[24]. No survival benefits were observed with combination therapies [relative risk (RR) = 0.93, 95%CI: 0.84-1.03; $P = 0.17$). However, a statistically significant, albeit minimal, advantage for Gem-based combinations was found for PFS (RR = 0.91, 95%CI: 0.84-0.98; $P = 0.015$) and ORR (RR = 1.57, 95%CI: 1.31-1.86; $P < 0.0001$): this translates into a number of patients needed to treat for a single patient to benefit (NNT) of 39 patients for PFS (with a 2.6% absolute benefit) and 33 patients for ORR. None of the 4 different combination groups (Gem plus a platinum salt, Gem plus a fluoropyrimidine, Gem plus other classical cytotoxic agents, and Gem plus targeted drugs) demonstrated an OS benefit over single-agent Gem, while significant advantages in PFS (RR = 0.67, 95%CI: 0.53-0.83; $P = 0.0004$) and ORR were obtained for platinum-containing combinations[24].

Several other meta-analyses have been conducted, exploring whether adding a second drug to Gem would impact on survival of advanced PDAC patients. Sultana *et al*[12] conducted a meta-analysis on 19 studies, involving 4697 patients, and found a statistically significant, but clinically negligible, OS benefit for Gem-based combinations (HR= 0.91, 95%CI: 0.85-0.97; $P = 0.004$), particularly when Gem was combined with platinum salts. Heinemann *et al*[32] analyzed 15 randomized trials involving 4465 patients. Overall, they demonstrated a small, albeit statistically significant, survival advantage for Gem-based combinations, as compared to single-agent Gem (HR = 0.91, $P = 0.004$). The combined analysis of 5 randomized trials showed a significant prolongation in OS (HR = 0.85, $P = 0.010$) and a significant benefit in PFS and ORR for the combination of Gem with platinum salt. Meta-analytic results from 6 studies demonstrated a significant, albeit modest, improvement in survival (HR = 0.90, $P = 0.03$) for Gem/fluoropyrimidine combination, more pronounced when the association with capecitabine in 3 trials was considered (HR = 0.83, $P = 0.01$). In a subgroup analysis conducted on 1682 patients (38% of the overall population) for whom PS data were available, OS benefit for Gem-based combinations seemed to be confined to patients with good PS (HR = 0.76, $P < 0.001$)[34]. All these data are consistent with previous meta-analytic results showing no difference in 1-year mortality rate between Gem-combination and single agent Gem (OR = 0.88, 95%CI: 0.74-1.05) and a better 6-mo mortality rate for the subgroup of platinum/Gem schedules (OR = 0.59, 95%CI: 0.43-0.81; $P = 0.001$)[7]. Xie *et al*[35] evaluated 18 randomized trials involving 4237 patients and showed a reduction of 9% in the risk of death with Gem-based doublets at 6 mo (RR = 0.91, 95%CI: 0.85-0.97; $P = 0.005$) and of 4% at 1 year (RR = 0.96, 95%CI: 0.93-0.99; $P = 0.02$); Gem/capecitabine and Gem/oxaliplatin combinations significantly reduced the risk of death by 15% (RR = 0.85, 95%CI: 0.73-0.99; $P = 0.04$) and 20% (RR = 0.80, 95%CI: 0.70-0.91; $P = 0.001$), respectively. No survival benefit was shown for Gem-based combinations in the good PS group of patients and an increased risk of death was demonstrated for patients with poor PS. A further meta-analysis on thirty-five trials and a total of 9979 patients demonstrated that the Gem-based combination treatments achieved a significant benefit over single agent Gem (OS: OR = 1.15, $P = 0.011$; PFS: OR = 1.27, $P < 0.001$; ORR: OR = 1.58, $P < 0.001$). Improvement in terms of survival and ORR were especially evident when Gem was combined with fluoropyrimidines (OS: OR = 1.33, $P = 0.007$; PFS: OR = 1.53, $P < 0.001$; ORR: OR = 1.47, $P = 0.03$). Similar results were obtained for the combination with oxaliplatin (OS: OR = 1.33, $P = 0.019$; PFS: OR = 1.38, $P = 0.011$)[36]. A more recent meta-analysis provided a statistically significant, even though marginal, survival

improvement over single agent Gem (pooled HR = 0.93; 95%CI: 0.89-0.97; P = 0.001). As observed by the authors, such slight improvements were obtained at the price of a significantly greater incidence of toxic effects, notably diarrhea, nausea, neutropenia and thrombocytopenia[37]. Although slight differences were obtained in the results, overall all of these meta-analyses ultimately convey the very same message, that is summarized in the results of a recent pooled analysis, performed by our group: when the results of 7 randomized trials comparing Gem-monotherapy with the three most popular combination regimens (Gem/cisplatin, Gem/capecitabine and Gem/oxaliplatin) were pooled together, a clinically negligible, albeit statistically significant, absolute survival benefit (2%-3% at 1 year) was observed, ruling out the possibility that Gem-based combination regimens could improve 1-year survival by more than 5%[38]. Thus, the routine use of Gem-based doublets with either platinum salts or fluoropyrimidines in metastatic PDAC does not seem to be supported by available evidence.

PRESENT: FOLFIRINOX AND OTHER POLYCHEMOTHERAPY APPROACHES

The multicentre, randomized, phase Ⅱ-Ⅲ trial PRODIGE 4/ACCORD 11, comparing single-agent Gem with the polychemotherapy regimen FOLFIRINOX in patients with metastatic PDAC was published in 2011. Three hundred forty-two patients were randomly assigned to receive standard Gem 1000 mg/m^2 or FOLFIRINOX (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 180 mg/m^2, 5-FU 400 mg/m^2 administered by intravenous bolus, followed by a continuous intravenous infusion of 2400 mg/m^2 over a 46-h period), in cycles repeated every 2 wk. With a median follow-up of 26.6 mo, median OS was 11.1 mo (95%CI: 9.0-13.1) in the FOLFIRINOX group and 6.8 mo (95%CI: 5.5-7.6) in the Gem group (HR = 0.57; 95%CI: 0.45-0.73; P < 0.001); 1-year survival rate was 48.4% in the FOLFIRINOX group, as compared with 20.6% in the Gem group; HR for death remained significant when adjusted for independent adverse prognostic factors. A statistically significant difference was observed also for PFS (6.4 mo *vs* 3.3 mo, HR = 0.47; 95%CI: 0.37-0.59; P < 0.001). An impressive ORR of 31.8% in the FOLFIRINOX group was reported, as compared to 11.3% in the Gem group. Results were not influenced by second-line treatments, in fact approximately 45% of patients in both groups received second-line therapy. As expected, FOLFIRINOX's safety profile was less favorable, with a significantly higher incidence of grade 3 or 4 neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy, as well as grade 2 alopecia[39]. Nevertheless, health-related QoL analysis showed that FOLFIRINOX significantly reduces QoL impairment, as compared with Gem[40], highlighting the fact that in very aggressive diseases, such as advanced PDAC, QoL is influenced more by disease-related symptoms than treatment-related toxicity. One of the limits of Conroy's trial is that enrollment was restricted to patients younger than 76 years, with an Eastern Cooperative Oncology Group (ECOG) PS score of 0 or 1 and a bilirubin level ⩽ 1.5 times the upper normal limit; thus, the proportion of patients carrying a biliary stent was relatively low (14.3%). On these bases, the FOLFIRINOX regimen is currently recommended as a first-line treatment option for young and fit PDAC patients, with good hepatobiliary function, and dose/schedule modifications are applied by many groups, in order to avoid excessive toxicity[41-48].

Before the advent of FOLFIRINOX, other groups had shown potential advantages for polychemotherapy over single-agent Gem in advanced PDAC. In 2005, Reni *et al*[49] performed a randomized phase Ⅲ study in locally advanced or metastatic pancreatic cancer with the PEFG regimen, consisting of cisplatin 40 mg/m^2 and epirubicin 40 mg/m^2 given on day 1, Gem 600 mg/m^2 administered on days 1 and 8 and 5-fluorouracil 200 mg/m^2 per day as continuous infusion during the entire duration of chemotherapy treatment, with cycles repeated every 28 d. Primary endpoint was 4-mo PFS improvement with the four-drug combination over single-agent Gem. A previous phase Ⅱ study on the same regimen showed interesting ORR results (55% in the metastatic population), survival (median time to tumor progression 7 mo and median OS 9.5 mo), and safety profile[49]. In the phase Ⅲ trial the primary endpoint was met with a total of 99 patients enrolled (affected by either metastatic or locally advanced disease) and a median follow-up of 33.5 mo, more than 30% absolute difference in 4-mo progression-free survival was observed (4-mo PFS: 60%, 95%CI: 46-72, *vs* 28%, 95%CI: 17-42; HR = 0.46, 95%CI: 0.26-0.79; P = 0.001). Median PFS was 5.4 mo (95%CI: 2.0-9.6 mo) for the combination regimen *vs* 3.3 mo (95%CI: 2.2-5.3) for Gem (HR = 0.51, 95%CI: 0.33-0.78; P = 0.0033); the HR for death in the PEFG group compared with the Gem group was 0.65 (95%CI: 0.43-0.99; P = 0.047). Disease response was reported in 38.5% (95%CI: 25.3-51.7) in the combination group compared to 8.5% (95%CI: 0.5-16.5) in the monochemotherapy group (OR = 6.60, 95%CI: 2.11-20.60; P = 0.0008). PEFG was quite well tolerated, although more patients experienced grade 3-4 neutropenia and thrombocytopenia in the PEFG group (P < 0.0001)[50]. The small sample size and the choice of PFS as the primary endpoint may have constituted a weakness of the study, making the results difficult to generalize, leading to a general reluctance to widely adopt such a regimen as a possible standard in advanced PDAC[51]. Other concerns include the toxicity profile and the potential impairment in QoL in an already usually highly symptomatic population of patients[51]. A simplified schedule characterized by a better toxicity profile, more suitable for routine

clinical use, was indeed proposed by the authors[52,53]. Other attempts at making this regimen more easily manageable and even more active encompassed substituting the oral capecitabine for 5-FU (PEXG) and docetaxel for epirubicin (PDXG). The results of a randomized phase Ⅱ study comparing PEXG and PDXG confirmed a very high ORR (37% and 60%, respectively) and notable PFS (approximately 7.5 mo in both arms) and OS benefit (approximately 11 mo in both arms)[54].

Another multidrug regimen combining Gem, docetaxel, and capecitabine (GTX: capecitabine 750 mg/m^2 per day, days 1-14; Gem 750 mg/m^2 over 75 min on days 4 and 11 and docetaxel 30 mg/m^2 on days 4 and 11; cycles repeated every 21 d) was initially tested retrospectively in a metastatic PDAC population of 35 patients, with a reported ORR of 29% and disease stabilization in an additional 31%[55]. A subsequent analysis included 154 patients with locally advanced (73 patients; 24%) or metastatic PDAC (117 patients; 76%) treated with the GTX regimen where the majority of patients had an ECOG PS of 0 (29%) or 1 (66%) and 49% of patients had received previous chemotherapy treatment. Metastatic patients who received GTX as first-line treatment achieved a median survival of 11.3 mo; partial response and stable disease were observed in 11% and 62% of patients, respectively. Unfortunately, responses significantly correlated with toxicity, namely neutropenia, ALT elevation and hospitalizations: 9% of patients experienced grade 3-4 non-hematological toxicity and 41% experienced hematological toxicity (grade 3-4 anemia, neutropenia and thrombocytopenia in 12%, 34% and 13% of patients, respectively)[56].

PRESENT: GEM/*NAB*-PACLITAXEL

Nab-Paclitaxel is a nanoparticle albumin-bound (nab) paclitaxel characterized by a formulation of nanoparticle colloidal suspension, with an average size of 130 nm, prepared with human serum albumin. This formulation without solvents confers more favorable pharmacologic characteristics that allow the delivery of a higher dose of paclitaxel than Cremophor-paclitaxel, significantly lowering the risk of infusion hypersensitivity reactions and neutropenia and a faster recovery of peripheral neuropathy upon stopping the treatment[57]. *Nab*-Paclitaxel uptake into cells may be dependent on SPARC (secreted protein acidic and rich in cysteine) expression. SPARC is an albumin-binding protein that interacts with an extracellular matrix, influencing cell migration, proliferation, angiogenesis (especially during wound healing), matrix cell adhesion, and tissue remodeling. Pancreatic cancer is characterized by malignant epithelial cells surrounded by a rich stromal reaction, composed of extracellular matrix proteins (collagen, hyaluronic acid, SPARC) and cellular elements cancer-associated fibroblast, endothelial, immune, and inflammatory cells[58,59]. Analysis of pancreatic cancer tissue samples showed that SPARC is overexpressed[60] preferentially by stromal fibroblasts and epigenetically silenced in pancreatic cancer cells[61]. SPARC expression in peritumoral fibroblasts is a strong marker of poor prognosis in patients with resectable pancreatic adenocarcinoma, independent of common clinical parameters including tumor size, margin status, and lymph node metastasis[62-64]. As pancreatic cancer stroma may contribute to poor vascularisation and high intratumoural pressure, thereby causing decreased drug diffusion[65], SPARC represents an interesting stromal target[63] and the binding between SPARC and albumin may facilitate the tumor delivery of albumin-bound therapeutic agents[58]. Indeed, preclinical studies on PDAC stroma targeting strategies showed promising results and achieved decrease intratumor interstitial pressure, normalized vascularisation, and improved drug delivery[66-68].

This stimulated researchers' interest in testing *nab*-Paclitaxel in PDAC. A phase Ⅰ/Ⅱ study was conducted in metastatic PDAC patients that received Gem (1000 mg/m^2) with *nab*-Paclitaxel (100, 125, or 150 mg/m^2) on days 1, 8, and 15, every 28 d. In the 44 patients treated at the MTD of 125 mg/m^2 median PFS was 7.9 mo (95%CI: 5.8-1.0 mo), median OS was 12.2 mo (95%CI: 8.9-17.9 mo), and 1-year survival was 48%; ORR was 48%, with an overall disease control rate of 68%[60]. These promising results, along with the favorable safety profile prompted starting a phase Ⅲ study.

Eight-hundred-sixty-one metastatic pancreatic cancer patients were enrolled in a phase Ⅲ trial and randomized to receive *nab*-Paclitaxel at a dose of 125 mg/m^2 plus Gem (1000 mg/m^2) 3 wk on/1 wk off or single agent Gem (1000 mg/m^2). OS was significantly improved with *nab*-Paclitaxel plus Gem as compared to Gem monotherapy (8.7 mo *vs* 6.6 mo, HR = 0.72, 95%CI: 0.62-0.83; $P < 0.001$), as were the 1-year (35% *vs* 22%) and 2-year (10% *vs* 5%) survival rates. A significant improvement in PFS was also reported (5.5 mo *vs* 3.7 mo, HR = 0.69, 95%CI: 0.58-0.82; $P < 0.001$). The ORR was significantly higher with the combination treatment than with Gem (23% *vs* 7%; $P < 0.001$; response-rate ratio, 3.19). Disease control rate (DCR; confirmed response or stable disease for ⩾ 16 wk) was 48% in the *nab*-Paclitaxel/Gem population and 33% in the Gem group (ratio for disease control 1.46; 95%CI: 1.23-1.72). The difference between treatment groups could not be attributed to the use of second-line therapy[69-71]. The most common adverse events related to *nab*-Paclitaxel/Gem combination were fatigue (54%), alopecia (50%), and nausea (49%). Grade 3 or higher adverse events were neutropenia (38% in the combination group *vs* 27% in the Gem group, with 3% *vs* 1% of febrile neutropenia, respectively), fatigue (17% *vs* 7%), and peripheral

Table 1 Selected adjuvant or "strategy" (neoadjuvant *vs* adjuvant) clinical trials employing contemporary treatment regimens for resectable pancreatic adenocarcinoma

Study ID[1]	Design	Phase	Estimated accrual	Status
NCT00882310	Adjuvant Gem, Taxotere, and Xeloda	Ⅱ	32	Active, not recruiting
NCT00960284	Post-operative Gemcitabine *vs* PEFG Followed by Chemoradiation	Ⅱ/Ⅲ	102	Completed
NCT01150630	Adjuvant Gem *vs* Adjuvant PEXG *vs* Neoadjuvant/Adjuvant PEXG	Ⅱ/Ⅲ	370	Recruiting
NCT01526135	Adjuvant Gem *vs* modified FOLFIRINOX[2]	Ⅲ	490	Recruiting
NCT01660711	Neoadjuvant/Adjuvant modified FOLFIRINOX[3]	Ⅱ	21	Recruiting
NCT01845805	Adjuvant *nab*-Paclitaxel/Gem/Azacitidine	Ⅱ	80	Recruiting
NCT01964430	Adjuvant Gem *vs* *nab*-Paclitaxel/Gem (APACT)	Ⅲ	800	Recruiting
NCT02023021	Adjuvant *nab*-Paclitaxel/Gem	Ⅱ	80	Recruiting
NCT02047474	Neoadjuvant/Adjuvant modified FOLFIRINOX[4]	Ⅱ	46	Recruiting
NCT02047513	Adjuvant only *vs* Neoadjuvant/Adjuvant *nab*-Paclitaxel/Gem (NEONAX)	RⅡ[5]	166	Not yet recruiting
NCT02172976	Adjuvant Gemcitabine *vs* Neoadjuvant/Adjuvant FOLFIRINOX	Ⅱ/Ⅲ	126	Not yet recruiting

[1]ClinicalTrials.gov Identifier; [2]Oxaliplatin 85 mg/m^2, Irinotecan 165 mg/m^2, Leucovorin 400 mg/m^2, fluorouracil (5-FU) 2400 mg/m^2 c.i.v.i. over 48 h (no 5-FU bolus); [3]Oxaliplatin 85 mg/m^2, Irinotecan 180 mg/m^2, Leucovorin 400 mg/m^2, 5-FU 2400 mg/m^2 c.i.v.i. over 48 h (no 5-FU bolus); [4]Dose/schedule modifications not specified; [5]Randomized phase Ⅱ.

neuropathy (17% *vs* 1%). Median time to occurrence of G3 peripheral neuropathy in the combination group was 140 d, with a median time to recovery of such toxicity to G1 or lower of 29 d. 44% of patients could then resume combined treatment and the median OS of patients experiencing G3 peripheral neuropathy was strikingly longer (14.9 mo), as compared to that observed in the ITT population (8.5 mo).

Stromal SPARC expression, evaluated in 36 patients enrolled in the phase Ⅰ/Ⅱ trial by Von Hoff *et al*[61] was demonstrated to be a predictor factor for OS. Patients with high-SPARC expression showed a prolonged OS compared with low-SPARC expression group (median OS: 17.8 mo *vs* 8.1 mo, respectively; P = 0.0431). No significant correlation with OS was reported for the expression of SPARC in tumor cells[60]. Conversely, the exploratory analysis of the MPACT study on the prognostic significance of SPARC expression did not show any correlation with OS. Stromal SPARC was neither a prognostic factor, nor a significant, independent predictive factor for OS or secondary endpoints, such as PFS, TTF, ORR and DCR. In an additional analysis, tumor epithelial SPARC, baseline and change from baseline of plasma SPARC were similarly not predictive for OS. However, only 256 patients (30% of the ITT population) were evaluable for stromal SPARC expression, among the 860 patients enrolled in the MPACT study, and the IHC assay was different from that employed in the phase Ⅰ/Ⅱ trial, although it showed 86% concordance[72]. These two aspects, together with differences in patient characteristics and tissue of origin, may explain to some extent the failure of such exploratory analysis to highlight a significant predictive value of SPARC expression in this setting. However, a closer look at survival curves according to SPARC expression does reveal differences that may have potential biological and clinical meaning, although they do not reach statistical significance, thus supporting the continued exploration of a potential role of SPARC expression in regulating sensitivity to *nab*-Paclitaxel/Gem combinations.

FUTURE: IS THERE A RATIONALE FOR MAINTENANCE THERAPY?

Maintenance therapy refers to systemic therapy given to cancer patients who have achieved an objective response or disease stabilization after first line treatment, with the aim to extend responses or delay recurrence, eventually prolonging OS. The maintenance approach is largely used for hematologic malignancies and has been recently investigated in solid tumors, providing conflicting results. In breast cancer this strategy seems to improve PFS without OS benefit; in colorectal cancer no evidence exists in favor of continuous treatment[73]. A PFS advantage can be obtained with maintenance paclitaxel or maintenance bevacizumab in ovarian cancer, while maintenance therapy has been approved by the US Food and Drug Administration for advanced NSCLC[74-76]. With regard to pancreatic cancer, the trial recently published by Reni *et al*[77] was the first to address the role of a maintenance strategy in this disease. They performed a multicentre phase Ⅱ study in which 56 metastatic PDAC patients, who were progression-free after 6 mo from the start of first line chemotherapy, were randomized to receive sunitinib 37.5 mg/d continuously or observation only, with the primary endpoint of a 20% improvement in 6-mo PFS (PFS-6). The study met its primary endpoint: PFS-6 was 3.6% (95%CI: 0%-10.6%) in the observation group and 22.2% (95%CI: 6.2%-38.2%) in patients receiving sunitinib. Median PFS were 2.0 and 3.2 mo, respectively (P < 0.01, HR = 0.51, 95%CI: 0.29-0.89). Although differences in OS did not reach statistical significance (HR = 0.71, 95%CI: 0.40-1.26; P = 0.11), the proportion of patients who were alive at two years was tripled in the sunitinib maintenance arm (22.9% *vs* 7.1%), as compared with the observation arm. Most common grade 3-4 adverse events in the experimental arm were: thrombocytopenia, neutropenia and hand-foot syndrome (12%) and diarrhea (8%). Although

Table 2 Selected ongoing studies of contemporary "nanoparticle albumin-paclitaxel-based" systemic therapy in borderline resectable, locally advanced and metastatic pancreatic cancer

Title (Study ID[1])	Phase	Stage	Status
Randomized Phase Ⅱ Trial of Pre-Operative Gemcitabine and *nab*-Paclitaxel With or With Out Hydroxychloroquine (NCT01978184)	Phase 2	Potentially resectable	Recruiting
Phase 1/2 Safety and Feasibility of Gemcitabine and *nab*-Paclitaxel in Combination With LDE-225 as Neoadjuvant Therapy in Patients With Borderline Resectable Pancreatic Adenocarcinoma (NCT01431794)	Phase 1 Phase 2	Resectable	Recruiting
A Pilot Phase Ⅱ Multi Center Study of Gemcitabine and *nab*-Paclitaxel (Abraxane) as Preoperative Therapy for Potentially Operable Pancreatic Cancer (NCT01298011)	Phase 2	Resectable	Active, not recruiting
Phase Ⅱ Study of Preoperative FOLFIRINOX Versus Gemcitabine/*Nab*-Paclitaxel in Patients With Resectable Pancreatic Cancer (NCT02243007)	Phase 2	Resectable	Not yet recruiting
Phase Ⅱ Neoadjuvant Chemotheraphy (Gemcitabine and *nab*-Paclitaxel *vs* mFOLFIRINOX) and Sterotatic Body Radiation Therapy for Borderline Resectable Pancreatic Cancer (NCT02241551)	Phase 2	BR	Not yet recruiting
Nab-Paclitaxel Plus Gemcitabine With Concurrent MR-Guided IMRT in Patients With Locally Advanced and Borderline Resectable Pancreatic Cancer (NCT02283372)	Phase 1	BR or LA	Not yet recruiting
A Phase Ⅰ Dual Dose Escalation Study of Radiation and *nab*-Paclitaxel in Patients With Unresectable and Borderline Resectable Pancreatic Cancer (NCT02207465)	Phase 1	BR or LA unresectable	Recruiting
A Phase 2 Trial of Gemcitabine Plus *nab*-Paclitaxel With or Without FG-3019 as Neoadjuvant Chemotherapy in Locally Advanced, Unresectable Pancreatic Cancer (NCT02210559)	Phase 2	LA, unresectable	Recruiting
A Phase Ⅰ Study of Chemoradiotherapy Using Gemcitabine Plus *nab*-Paclitaxel for Unresectable Locally Advanced Pancreatic Adenocarcinoma (NCT02272738)	Phase 1	LA, unresectable	Recruiting
A Phase 1, Multicenter, Open-label, Dose-escalation Study to Investigate the Safety and Pharmacokinetics of Nab® -Paclitaxel (ABI-007) Plus Gemcitabine in Subjects With Advanced Pancreatic Cancer Who Have Cholestatic Hyperbilirubenemia Secondary to Bile Duct Obstruction (NCT02267707)	Phase 1	LA unresectable or metastatic	Not yet recruiting
Evaluation of Tumoral Perfusion Modification by Dynamic Imaging After Chemotherapy Combining Gemcitabine and *nab*-Paclitaxel (Abraxane) in Patients With Potentially Operable, Locally Advanced or Metastatic Pancreatic Adenocarcinoma (NCT01715142)	Phase 0	Stage Ⅰ-Ⅱ-Ⅲ-Ⅳ	Not yet recruiting
A Phase Ⅱ Randomized Trial Comparing a Combination of Abraxane and Gemcitabine Versus Gemcitabine Alone as First Line Treatment in Locally Advanced Unresectable Pancreatic Cancer. GAP (Gemcitabine Abraxane Pancreas) Trial (NCT02043730)	Phase 2	Stage Ⅲ	Active, not recruiting
A Multicenter Phase Ⅰ/Ⅱ Randomized Phase Ⅱ Study of Gemcitabine and *nab*-Paclitaxel With or Without NPC-1C in Patients With Metastatic or Locally Advanced Pancreatic Cancer (NCT01834235)	Phase 1 Phase 2	Stage Ⅲ-Ⅳ	Recruiting
A Phase IB Study of Erlotinib in Combination With Gemcitabine and *nab*-Paclitaxel in Patients With Previously Untreated Advanced Pancreatic Cancer (NCT01010945)	Phase 1	Stage Ⅲ-Ⅳ	Completed
A Phase 1 Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX7486 as a Single Agent and in Combination With Gemcitabine and *nab*-Paclitaxel in Patients With Advanced Solid Tumors (NCT01804530)	Phase 1	Stage Ⅲ-Ⅳ	Recruiting
An Open-Label, Phase Ⅰ Dose Escalation Trial of TH-302 in Combination With Gemcitabine and *Nab*-Paclitaxel in Previously Untreated Subjects With Metastatic or Locally Advanced Unresectable Pancreatic Adenocarcinoma (NCT02047500)	Phase 1	Stage Ⅲ-Ⅳ	Recruiting
Phase Ⅱ Study Evaluating Bi-weekly Dosing of Gemcitabine Plus *nab*-Paclitaxel in the Treatment of Surgically Unresectable/Metastatic Pancreatic Cancer (NCT01851174)	Phase 2	Stage Ⅲ-Ⅳ	Recruiting
Phase 1B Trial of ADI-PEG 20 Plus *nab*-Paclitaxel and Gemcitabine in Subjects With Advanced Pancreatic Cancer (NCT02101580)	Phase 1	Stage Ⅲ-Ⅳ	Not yet recruiting
Phase Ⅱ Trial of Abraxane® in the Treatment of Patients With Pancreatic Cancer Who Have Failed First-Line Treatment With Gemcitabine-Based Therapy (NCT00691054)	Phase 2	Stage Ⅲ-Ⅳ	Completed
A Phase Ⅰ/Ⅱ/Pharmacodynamic Study of Hydroxychloroquine in Combination With Gemcitabine/Abraxane to Inhibit Autophagy in Pancreatic Cancer (NCT01506973)	Phase 1 Phase 2	Stage Ⅲ-Ⅳ	Recruiting
BYL719 in Combination With Gemcitabine and (Nab)-Paclitaxel in Locally Advanced and Metastatic Pancreatic Cancer (NCT02155088)	Phase 1	Stage Ⅲ-Ⅳ	Recruiting
A Phase Ⅰ and Randomized, Double-Blinded Phase Ⅱ Study of *nab*-paclitaxel/Gemcitabine Plus AZD1775 or Placebo in Treatment-Naïve Metastatic Adenocarcinoma of the Pancreas (NCT02194829)	Phase 1 Phase 2	Stage Ⅲ-Ⅳ	Suspended
A Phase Ib Study of Dovitinib in Combination With Gemcitabine and *nab*-Paclitaxel in Patients With Advanced Solid Tumors and Pancreatic Cancer (NCT02048943)	Phase 1	Stage Ⅲ-Ⅳ-recurrent	Not yet recruiting
Phase Ⅰ-Ⅱ Trial of Gemcitabine Plus *nab*-Paclitaxel (GemBrax) Followed by Folfirinox as First Line Treatment of Patients With Metastatic Pancreatic Adenocarcinoma (NCT01964287)	Phase 1 Phase 2	Stage Ⅳ	Recruiting
A Phase 1b Dose Escalation Study of Vantictumab (OMP-18R5) in Combination With *nab*-Paclitaxel and Gemcitabine in Patients With Previously Untreated Stage Ⅳ Pancreatic Cancer (NCT02005315)	Phase 1	Stage Ⅳ	Recruiting
A Phase 1b Dose Escalation Study of OMP-54F28 in Combination With *nab*-Paclitaxel and Gemcitabine in Patients With Previously Untreated Stage Ⅳ Pancreatic Cancer (NCT02050178)	Phase 1	Stage Ⅳ	Recruiting
A Phase 2, Randomized, Multicenter Study of PEGPH20 (PEGylated Recombinant Human Hyaluronidase) Combined With *nab*-Paclitaxel Plus Gemcitabine Compared With *nab*-Paclitaxel Plus Gemcitabine in Subjects With Stage Ⅳ Previously Untreated Pancreatic Cancer (NCT01839487)	Phase 2	Stage Ⅳ	Recruiting
A Phase Ⅰ/Ⅱ Study of Indoximod in Combination With Gemcitabine and *nab*-Paclitaxel in Patients With Metastatic Adenocarcinoma of the Pancreas (NCT02077881)	Phase 1 Phase 2	Stage Ⅳ	Not yet recruiting
A Phase 1b/2 Study of OMP-59R5 in Combination With *nab*-Paclitaxel and Gemcitabine in Subjects With Previously Untreated Stage Ⅳ Pancreatic Cancer (NCT01647828)	Phase 1 Phase 2	Stage Ⅳ	Recruiting
Phase Ⅰ Trial of the Proapoptotic Agonist, LCL161, and Gemcitabine Plus *nab*-Paclitaxel in Patients With Metastatic Pancreatic Cancer (NCT01934634)	Phase 1	Stage Ⅳ	Recruiting

A Phase Ⅰ Study of *nab*-paclitaxel (Abraxane), Gemcitabine, and Capecitabine (Xeloda) (AGX) in Patients With Previously Untreated, Metastatic Pancreatic Adenocarcinoma (NCT01161186)	Phase 1	Stage Ⅳ	Completed
A Phase 1b/2 Pilot Trial of *nab*-Paclitaxel Plus Cisplatin Plus Gemcitabine (Nabplagem) in Patients With Previously Untreated Metastatic Pancreatic Ductal Adenocarcinoma (PDA) (NCT01893801)	Phase 1 Phase 2	Stage Ⅳ	Recruiting
A Phase Ⅰ/Ⅱ, Two-Part, Multicenter Study to Evaluate the Safety and Efficacy of M402 in Combination With *nab*-Paclitaxel and Gemcitabine in Patients With Metastatic Pancreatic Cancer (NCT01621243)	Phase 1 Phase 2	Stage Ⅳ	Recruiting
A Phase 2, Randomized, Double-blind Study of Gemcitabine And *nab*-Paclitaxel Combined With Momelotinib in Subjects With Previously Untreated Metastatic Pancreatic Ductal Adenocarcinoma Preceded by a Dose-finding, Lead-in Phase (NCT02101021)	Phase 2	Stage Ⅳ	Not yet recruiting
Phase 1/2 Study Of PF-03084014 In Combination With Gemcitabine And *nab*-Paclitaxel In Patients With Previously Untreated Metastatic Pancreatic Ductal Adenocarcinoma (NCT02109445)	Phase 1 Phase 2	Stage Ⅳ	Not yet recruiting
Phase Ⅰ/Ⅱ Study to Evaluate *nab*-Paclitaxel in Substitution of CPT11 or Oxaliplatin in FOLFIRINOX Schedule as First Line Treatment in Metastatic Pancreatic Cancer (NCT02109341)	Phase 1 Phase 2	Stage Ⅳ	Recruiting
A Randomized, Double-Blinded, Placebo-Controlled Phase Ⅱ Trial Of Gemcitabine Plus *nab*-Paclitaxel Combined With OGX-427 Or Placebo In Patients With Metastatic Pancreatic Cancer (The Rainier Trial) (NCT01844817)	Phase 2	Stage Ⅳ	Recruiting
A Phase Ⅱ Study of Gemcitabine and Nanoparticle-Bound Paclitaxel as Second Line Therapy in Patients With Metastatic Pancreatic Cancer (NCT02242409)	Phase 2	Stage Ⅳ	Recruiting
Enzalutamide in Combination With Gemcitabine and *nab*-Paclitaxel for the Treatment of Advanced Pancreatic Cancer (NCT02138383)	Phase 1	Stage Ⅳ	Recruiting
A Phase Ib/Ⅱ Study of the Selective Inhibitor of Nuclear Export (SINE) KPT-330, Gemcitabine and *nab*-Paclitaxel in Patients With Metastatic Pancreatic Cancer (NCT02178436)	Phase 1 Phase 2	Stage Ⅳ	Not yet recruiting
Phase Ⅱ Trial of *nab*-Paclitaxel Plus S-1 in First-line Treatment of Patients With Advanced Pancreatic Cancer (NCT02124317)	Phase 2	Stage Ⅳ	Recruiting
Biological Effect of *nab*-Paclitaxel Combined to Gemcitabine in Metastatic Pancreatic Cancer (NCT02174887)	Phase 1	Stage Ⅳ	Not yet recruiting
A 3-Arm Phase 2 Double-Blind Randomized Study of Gemcitabine, Abraxane® Plus Placebo Versus Gemcitabine, Abraxane® Plus 1 or 2 Truncated Courses of Demcizumab in Subjects With 1st-Line Metastatic Pancreatic Ductal Adenocarcinoma (NCT02289898)	Phase 2	Stage Ⅳ	Not yet recruiting
A Phase Ib Clinical Study of BBI608 in Combination With Gemcitabine and *nab*-Paclitaxel in Adult Patients With Metastatic Pancreatic Adenocarcinoma (NCT02231723)	Phase 1	Stage Ⅳ	Recruiting
Nab-paclitaxel Plus Gemcitabine in Chinese Patients With Advanced Pancreatic Cancer (NCT02135822)	Phase 2	Advanced	Recruiting

[1]ClinicalTrials.gov Identifier. *nab*-Paclitaxel: Nanoparticle albumin-bound paclitaxel.

the study has obvious limitations (small sample size above all), it does provide a proof of the principle that switch maintenance in appropriately selected patients may indeed be beneficial in advanced PDAC; this becomes all the more relevant now that the proportion of advanced PDAC patients who reach the 6-mo landmark without experiencing progression of their disease is up to approximately 50% with contemporary first-line chemotherapy (such as FOLFIRINOX or *nab*-Paclitaxel/Gem). Such provocative findings open up an entirely new field in the treatment of PDAC, which clearly deserves further investigation.

WHERE DO WE GO FROM HERE?

Despite twenty years of well-deserved therapeutic nihilism[24,78,79], the field of systemic therapy for advanced/metastatic pancreatic cancer is finally moving forward: in only three years the median and 1-year OS have almost doubled from the 6 mo and 20% of the Gem era to the 9-11 mo and 35%-48% achieved with *nab*-Paclitaxel/Gem and FOLFIRINOX. Such evidence clearly sets new standard(s) of systemic therapy in metastatic pancreatic cancer, so that the use of Gem monotherapy appears nowadays justified only in a minority of patients, characterized by suboptimal PS (KPS < 70%), advanced age, and/or significant comorbidities. These results also substantially raise the bar for the design of present and future clinical trials, where the use of Gem monotherapy as the standard comparator arm is no longer acceptable, except, perhaps, in specific subpopulations of unfit patients.

The first burning question is: how will such advances in systemic therapy impact on outcomes in earlier stages of disease [locally advanced (LAPC), borderline resectable (BRPC), and frankly resectable disease], where there is, theoretically, much more to be gained and patients may be rendered NED and potentially cured? FOLFIRINOX is being actively pursued as a neoadjuvant/induction chemotherapy regimen in the multimodal management of LAPC and BRPC[45,46,80-83], most often with dose modifications aimed at improving tolerability and reducing the risk of serious toxicity: with ORR ranging from 27% to 50% and resectability rates of 12%-51%, such approach appears promising, although its ultimate impact on survival endpoints (median PFS ranging from 8 to 13 mo and median OS approximately 22 mo), as compared with more traditional regimens, will need to be judged on more congruous numbers of patients with adequate follow up. The combination of *nab*-Paclitaxel and Gem is also an attractive neoadjuvant treatment strategy for LAPC and BRPC. Although, currently available data in this setting are still anecdotal (case reports and preliminary reports of small case series)[84-88], such combination is extremely interesting, particularly because of the peculiar mechanism of action, which may encompass stromal depletion, arguably much more relevant in the primary pancreatic tumor than in metastatic lesions[58]. Even more importantly, both

Table 3 Selected ongoing studies of "folfirinox-based"and other contemporary regimens in borderline resectable, locally advanced and metastatic pancreatic cancer

Title (Study ID[1])	Phase	Stage	Status
A Phase Ⅱ Study of Neoadjuvant FOLFIRINOX in Patients With Resectable Pancreatic Ductal Adenocarcinoma With Tissue Collection (NCT02178709)	Phase 2	Resectable	Recruiting
Phase Ⅱ Study of Preoperative FOLFIRINOX Versus Gemcitabine/*nab*-Paclitaxel in Patients With Resectable Pancreatic Cancer (NCT02243007)	Phase 2	Resectable	Not yet recruiting
Neoadjuvant CAPOXIRI Chemotherapy in the Treatment of Resectable, Borderline Resectable and Locally Advanced Pancreatic Adenocarcinoma Protocol (NCT01760252)	Phase 2	Resectable, BR and LA	Recruiting
GTX-RT in Borderline Resectable Pancreatic Cancer (NCT01754623)	Phase 2	BR	Active, not recruiting
Neoadjuvant FOLFIRINOX for Borderline Resectable Pancreatic Cancer - a Pilot Study (NCT02148549)	Phase 1	BR	Recruiting
Phase Ⅱ Neoadjuvant Chemotheraphy (Gemcitabine and *nab*-Paclitaxel *vs* mFOLFIRINOX) and Sterotatic Body Radiation Therapy for Borderline Resectable Pancreatic Cancer (NCT02241551)	Phase 2	BR	Not yet recruiting
Phase IB Study of FOLFIRINOX Plus PF-04136309 in Patients With Borderline Resectable and Locally Advanced Pancreatic Adenocarcinoma (NCT01413022)	Phase 1	BR or LA	Recruiting
Phase Ⅱ Single Arm Clinical Trial of FOLFIRINOX for Unresectable Locally Advanced and Borderline Resectable Pancreatic Cancer (NCT01688336)	Phase 2	BR or LA unresectable	Recruiting
Prospective Randomized Multicenter Phase Ⅱ Trial to Investigate Intensified Neoadjuvant Chemotherapy in Locally Advanced Pancreatic Cancer (NEOLAP) (NCT02125136)	Phase 2	LA	Not yet recruiting
The Effect of FOLFIRINOX and Stereotactic Body Radiation Therapy for Locally Advanced, Non-Resectable Pancreatic Cancer (BCC-RAD-13) (NCT02128100)	Phase 2	LA, unresectable	Not yet recruiting
A Phase Ⅱ, Randomized, Open Label Study of Single Dose siG12D LODER in Combination With Chemotherapy in Patients With Unresectable Locally Advanced Pancreatic Cancer (NCT01676259)	Phase 2	LA, unresectable	Not yet recruiting
A Prospective Evaluation of Neoadjuvant FOLFIRINOX Regimen in Patients With Non-metastatic Pancreas Cancer (Baylor University Medical Center and Texas Oncology Experience) (NCT01771146)	Not provided	Localized, Non-metastatic	Recruiting
Phase 1b Clinical Trial of LDE225 in Combination With Fluorouracil, Leucovorin, Oxaliplatin and Irinotecan (FOLFIRINOX) in Previously Untreated Locally Advanced or Metastatic Pancreatic Adenocarcinoma, With an Expansion Cohort at the Recommended Phase 2 Dose (NCT01485744)	Phase 1	LA unresectable or metastatic	Recruiting
A Phase Ⅰ Study of FOLFIRINOX Plus IPI-926 for Advanced Pancreatic Adenocarcinoma (NCT01383538)	Phase 1	Not provided	Active, not recruiting
Phase Ⅱ Study: Neoadjuvant Gemcitabine, Docetaxel and Capecitabine Followed by Neoadjuvant Radiation Therapy With Gemcitabine and Capecitabine in the Treatment of Stage Ⅱ and Ⅲ Pancreatic Adenocarcinoma (NCT01065870)	Phase 2 Phase 3	Stage Ⅱ-Ⅲ	Recruiting
A Phase Ⅰ-Ⅱ Study of PAXG in Stage Ⅲ-Ⅳ Pancreatic Adenocarcinoma (NCT01730222)	Phase 1-2	Stage Ⅲ-Ⅳ	Recruiting
Phase Ⅱ Study of Modified FOLFIRINOX in Advanced Pancreatic Cancer (NCT01523457)	Phase 2	Stage Ⅲ-Ⅳ	Recruiting
Ceritinib and Combination Chemotherapy in Treating Patients With Advanced Solid Tumors or Locally Advanced or Metastatic Pancreatic Cancer (NCT02227940)	Phase 1	Stage Ⅲ-Ⅳ, recurrent	Not yet recruiting
Phase 2, Multicenter Study of FOLFIRINOX Followed by Ipilimumab in Combination With Allogeneic GM-CSF Transfected Pancreatic Tumor Vaccine (GVAX) in the Treatment of Metastatic Pancreatic Cancer (NCT01896869)	Phase 2	Stage Ⅳ	Recruiting
A Phase Ⅱ Study of Induction Consolidation and Maintenance Approach for Patients With Advanced Pancreatic Cancer (NCT01488552)	Phase 1-2	Stage Ⅳ	Recruiting
A Phase Ⅰ Open-Label Dose-Escalation Clinical Trial of CPI-613 in Combination With Modified FOLFIRINOX in Patients With Metastatic Pancreatic Cancer and Good Performance Status (NCT01835041)	Phase 1	Stage Ⅳ	Recruiting
Phase Ⅰ B/Randomized Phase Ⅱ Study of Folfirinox Plus AMG-479 (Ganitumab) or Placebo in Patients With Previously Untreated, Metastatic Pancreatic Adenocarcinoma (NCT01473303)	Phase 1 Phase 2	Stage Ⅳ	Withdrawn
Phase Ⅱ Trial to Investigate the Efficacy and Safety of mFOLFIRINOX in Patients With Metastatic Pancreatic Cancer in China (NCT02028806)	Phase 2	Stage Ⅳ	Recruiting
S1313, A Phase IB/Ⅱ Randomized Study of Modified FOLFIRINOX + Pegylated Recombinant Human Hyaluronidase (PEGPH20) Versus Modified FOLFIRINOX Alone in Patients With Good Performance Status Metastatic Pancreatic Adenocarcinoma (NCT01959139)	Phase 1 Phase 2	Stage Ⅳ	Recruiting
Phase I-Ⅱ Trial of Gemcitabine Plus *nab*-Paclitaxel (GemBrax) Followed by Folfirinox as First Line Treatment of Patients With Metastatic Pancreatic Adenocarcinoma (NCT01964287)	Phase 1 Phase 2	Stage Ⅳ	Recruiting
Phase Ⅱ Study of Modified FOLFIRINOX in Advanced Pancreatic Cancer (NCT01523457)	Phase 2	Stage Ⅳ	Recruiting
Phase Ⅰ/Ⅱ Study to Evaluate *nab*-Paclitaxel in Substitution of CPT11 or Oxaliplatin in FOLFIRINOX Schedule as First Line Treatment in Metastatic Pancreatic Cancer (NCT02109341)	Phase 1 Phase 2	Stage Ⅳ	Recruiting
Phase Ⅱ Study for Inoperable Non-Metastatic Pancreatic Cancer (Stage ⅣA) With Neoadjuvant Gemzar, Taxotere and Xeloda (GTX), and Radiation With Gemzar (NCT00869258)	Phase 2	Stage Ⅳ	Active, not recruiting
Phase Ⅱ Study of Gemcitabine/Taxotere/Xeloda (GTX) in Combination With Cisplatin in Subjects With Metastatic Pancreatic Cancer (NCT01459614)	Phase 2	Stage Ⅳ	Active, not recruiting
Phase-2 Study Evaluating Overall Response Rate (Efficacy) and Autonomy Daily Living Preservation (Tolerance) of "FOLFIRINOX " Pharmacogenetic Dose Adjusted, in Elderly Patients (70 yr or Older) With a Metastatic Pancreatic Adenocarcinoma (NCT02143219)	Phase 2	Stage Ⅳ	Not yet recruiting

[1]ClinicalTrials.gov Identifier. BR: Borderline resectable; LA: Locally advanced; *nab*-Paclitaxel: Nanoparticle albumin-bound paclitaxel.

strategies (aggressive polychemotherapy with PEFG- or FOLFIRINOX-like regimens and *nab*-Paclitaxel/Gem combinations) are being tested in the adjuvant setting or in "strategy studies", comparing neoadjuvant *vs* adjuvant chemotherapy with such novel regimens, in an attempt to improve the "cure" rate obtained by surgery in resectable PDAC patients (Table 1).

The second question is: how do we build on current standards to push forward survival of advanced PDAC patients even further? In relation to this, is the question of if, and how, we can integrate promising molecularly targeted agents into current treatment paradigms. Many ongoing phase Ⅰ-Ⅱ trials (Tables 2 and 3) are aimed at making the most of both worlds (polychemotherapy approaches and *nab*-Paclitaxel) and try to incorporate *nab*-Paclitaxel into PEFG- or FOLFIRINOX-like backbones, mostly by substituting *nab*-Paclitaxel for one of the components of the original regimen[89] (see also NCT01730222 and NCT02109341, Tables 2 and 3). An "add on" strategy is also the preferred design to try incorporating biological agents into first-line treatment (Tables 2 and 3). Such a strategy, however, has many potential pitfalls in our opinion: (1) if we are to learn from past experience, twenty years of negative studies using the Gem *vs* Gem + an additional agent (either a second chemotherapy drug or a targeted agent) paradigm should have taught us that such an "add on to current standard" strategy does not pay off (*nab*-Paclitaxel/Gem being the only notable exception)[24,38]; (2) while the combination of *nab*-Paclitaxel/Gem may still constitute a reasonable backbone for "add on" strategies, FOLFIRINOX-like regimens have substantial toxicity issues (so that most groups have adopted "modified" schedules), making it very unlikely that other agents may be simply added, without modifying the original regimen (and thereby potentially diminishing its efficacy); and (3) one of the most important clinical consequences of finally having "active" first-line regimens is that an increasing proportion of patients experience prolonged disease control, which enables them to receive a second or subsequent lines of therapy with clinical benefit. Thus, if the aim is to prolong disease control across multiple lines of treatment using all or most active agents upfront may actually turn out to be detrimental over the entire course of the disease.

Although there is no easy solution to the challenge of identifying optimal development strategies in advanced PDAC, one possibility is to exploit different disease settings, as an alternative to the classical "all in first-line" or "at relapse" strategies, to test the activity of new agents. In this respect, data recently obtained in the maintenance setting, even with a relatively inactive (in first- or second-line) class of agents such as VEGF/VEGFR inhibitors[90-93], is extremely provocative. Indeed, these results raise the interesting hypothesis that targeting the VEGFR pathway, which may be of marginal relevance and insufficient to alter the natural history of the disease against a bulky and rapidly growing tumor, could still be effective against progression under conditions of maximum cytoreduction and chemotherapy-induced tumour damage As more patients achieve disease control at 6 mo and as more active agents against pancreatic cancer become available, the maintenance setting may potentially achieve even more exciting results. Another disease setting that is currently relatively unexplored as a testing arena for new drugs is neoadjuvant treatment, which would also have the advantage of being able to truly (histologically) assess response and get access to post-treatment cancer tissue and tumor microenvironment, to look for drug effects on specific pathways/tissue components.

Last, but not least, thanks to novel technologies and "omics"-based characterization efforts, the molecular classification of pancreatic cancer(s) is evolving, as in many other malignancies, towards the clusterization of individual cases in discrete subgroups, characterized by alterations in common pathways. Some of these "driver" alterations could already be exploited therapeutically, while some other will require more preclinical modeling efforts, in order to make them suitable therapeutic targets. In addition to yielding novel therapeutic targets, such efforts are expected to rapidly lead to the identification of potentially predictive biomarkers, which would help select populations of pancreatic cancer patients who would derive the most benefit from specific therapeutic approaches. While eagerly awaiting this "new wave" of biology-based improvements in pancreatic cancer care, we will continue to work together with our patients and look at the therapeutic options that have been made recently available with renewed hope.

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