

# Emerging treatments for advanced pancreatic cancer: clinical potential of albumin-bound paclitaxel

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**Abstract:** The management of pancreatic cancer has historically represented a major challenge for oncologists. The inherent aggressiveness of this tumor and the fibrotic features of the surrounding stromal tissue have significantly limited the impact of standard chemotherapy. Moreover, the paucity of available tumor tissue has hampered a better understanding of the biology of this disease as well as the development of new treatment strategies. Recently, the therapeutic landscape of metastatic pancreatic cancer has been enriched by two new combination regimens (FOLFIRINOX and gemcitabine-nab-paclitaxel) which have been demonstrated to improve the outcome in patients with good performance status. Moreover, the peritumoral stroma has been increasingly recognized as a potential therapeutic target for this disease, and several new agents targeting stromal components are currently under investigation. In this paper, we review the current treatment options for advanced pancreatic cancer, highlight the role of the peritumoral stroma, and discuss the clinical potential of nab-paclitaxel and antistromal treatment strategies.

**Keywords:** pancreatic cancer, nab-paclitaxel, stroma, SPARC

## Introduction

Pancreatic cancer is the eighth most common malignant tumor in Europe, with 103,800 estimated new cancer cases in 2012, and is the fourth most common cause of cancer-related death.<sup>1</sup> Cancer mortality predictions for the year 2013 show that pancreatic cancer remains the only major cancer type (alongside lung cancer in women) for which no improvement in mortality rate has been predicted.<sup>2</sup>

In the recent Cancer Statistics 2013 from the American Cancer Society, the 5-year overall survival rate for pancreatic cancer has been reported to be 6%.<sup>3</sup> This unfavorable outcome is largely due to the fact that, in most cases, patients are initially diagnosed with advanced disease. Approximately 40% of patients present with inoperable locally advanced tumors, while approximately 40%–45% have distant metastases at the time of diagnosis.<sup>4</sup> In these circumstances, the 5-year overall survival rates are 9% and 2%, respectively.<sup>3</sup> Only a minority of patients (10%–20%) have resectable disease at presentation. However, even when the tumor is diagnosed at an early stage and is potentially amenable to radical surgery, the prognosis remains poor; only 22% of patients undergoing curative resection are still alive at 5 years, and the median survival is 23 months.<sup>5,6</sup>

The characteristics of pancreatic cancer have historically made the management of this tumor a major challenge.<sup>7</sup> In particular, the deep and poorly accessible location of the tumor and the absence of specific and sensitive diagnostic tumor markers hamper

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early radiological detection and largely delay histological diagnosis. Moreover, the inherent low chemosensitivity of pancreatic adenocarcinoma cells coupled with difficult drug penetration through the surrounding peritumoral stromal tissue significantly limits the impact of standard cytotoxic chemotherapy agents.

Gemcitabine and fluoropyrimidines have represented the mainstay of palliative chemotherapy for locally advanced or metastatic pancreatic cancer.<sup>8–10</sup> Although targeted therapies have largely failed in pancreatic cancer,<sup>11–13</sup> new chemotherapy agents or combination chemotherapy treatments have recently proved to be effective in this setting and have significantly widened the therapeutic options for the disease.<sup>14–16</sup> Moreover, the pancreatic stroma has increasingly been recognized as a key component of the tumor–drug interaction process and emerged as an attractive therapeutic target for pancreatic cancer.<sup>17</sup>

In this paper, we review the role of the pancreatic tumor stroma and the emerging treatment options for patients with advanced disease. In particular, we focus on the clinical potential of nanoparticle albumin-bound (nab)-paclitaxel and its role within the evolving therapeutic landscape of pancreatic cancer.

## **Peritumoral stroma: hallmark of pancreatic cancer and potential therapeutic target**

The desmoplastic nature of the tumor microenvironment is probably the most important hallmark of pancreatic cancer. The tumor stroma is a complex structure that accounts for most of the tumor bulk and largely influences the disorganized tumor vasculature, low blood microvessel density, and hypoxic microenvironment surrounding pancreatic cancer.<sup>18</sup> Given the large amount of extracellular fibrotic tissue, the stroma represents a mechanical barrier, which limits the effective delivery of drugs to the tumor cells and ultimately affects the efficacy of treatment.<sup>19</sup> More interestingly, it also represents a highly dynamic structure that, through the interaction between tumor and stromal cells and the autocrine or paracrine secretion of cytokines, chemokines, and growth factors, modulates crucial processes including tumor progression, invasiveness, and metastases.<sup>20,21</sup>

The pancreatic tumor stroma is formed by extracellular matrix proteins, such as fibronectin, collagen I and III, hyaluronic acid, secreted protein acidic and rich in cysteine (SPARC), and cellular elements including pancreatic stellate cells, fibroblasts, macrophages, inflammatory cells, pericytes, and endothelial cells.<sup>22</sup> The mechanisms underlying

the development and remodeling of the stroma have not been fully elucidated. However, it is commonly recognized that pancreatic stellate cells play a central role in these processes.<sup>23–25</sup>

Pancreatic stellate cells are a subtype of highly proliferating fibroblasts that are activated by oxidative stresses, and cytokine or growth factors produced by tumor cells or other stromal cells, including activin A, interleukin-1, interleukin-6, transforming growth factor beta-1, platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor.<sup>26</sup> Once activated, pancreatic stellate cells acquire a myofibroblast-like phenotype and produce major components of the peritumoral stroma, including collagen I, collagen III, and fibronectin.

Pancreatic tumor survival and growth may be promoted through different mechanisms secondary to activation of pancreatic stellate cells and the formation of stroma.<sup>27</sup> It has been shown that the irregular production and deposition of extracellular matrix proteins may promote survival and migration of tumor cells.<sup>28,29</sup> A reduced sensitivity to antitumoral agents has been reported when pancreatic tumor cells are attached to extracellular matrix proteins.<sup>30</sup> Moreover, some studies suggest that pancreatic stellate cells can induce tumor proliferation by activating the Notch signaling pathway in pancreatic cancer cells.<sup>31</sup>

Pancreatic stellate cells also produce matrix metalloproteinases and tissue inhibitors of metalloproteinases, two regulators of matrix remodeling that lead to increased invasion and metastatic potential of pancreatic tumor cells by degrading basal membrane collagen.<sup>32,33</sup> Interestingly, the close and dynamic interaction between pancreatic cancer cells and pancreatic stellate cells does not appear to be limited to the primary tumor but is maintained during the metastatic process. Studies have shown that pancreatic stellate cells migrate to the site of metastatic tumor alongside tumor cells, thus potentially reproducing in the metastases the same mechanisms of stroma formation and remodeling observed in the primary tumor.<sup>34</sup>

The activity of the stromal component in pancreatic cancer may also be a potential prognostic marker. Erkan et al analyzed the deposition of collagen and  $\alpha$ -smooth muscle actin, a marker of pancreatic stellate cell activity, in 233 tumor tissues from a prospectively registered database of pancreatic cancer patients who underwent surgery. They defined the activated stroma index as the ratio between the  $\alpha$ -smooth muscle actin-stained area and the collagen-stained area, and identified four major patterns of collagen deposition. Interestingly, patients with the lowest activated stroma index

had the best median survival rate, while patients with the highest activated stroma index were found to have the worst outcome. Of note, the activated stroma index was shown to be an independent prognostic marker in multivariable survival analysis comparable with nodal status.<sup>35</sup>

In light of its key role in the mechanisms of oncogenesis, tumor growth, invasiveness, and metastases, the peritumoral stroma has recently emerged as an attractive therapeutic target for pancreatic cancer. The available evidence supporting the importance of dynamic stromal–epithelial interactions in the pancreatic tumor microenvironment suggests the hypothesis that targeting key components of the stroma may interfere with crucial tumor pathways and ultimately translate into significant antitumor activity. Moreover, combining targeted antistromal drugs with cytotoxic agents may also result in synergistic effects and increase the therapeutic potential of standard treatments. Several antistromal agents have been investigated in preclinical and early-stage clinical studies.

Sonic hedgehog pathway inhibitors<sup>36,37</sup> are small molecules that have been shown to reduce the dense, fibrous peritumoral stroma, increase tumor perfusion, and enhance tumoral delivery of gemcitabine.<sup>38,39</sup> However, despite the promising signals observed in preclinical and Phase I clinical studies,<sup>40,41</sup> recent randomized Phase II trials investigating the addition of Sonic hedgehog to gemcitabine have failed to demonstrate a significant survival advantage.<sup>42,43</sup> Trials investigating the addition of Sonic hedgehog inhibitors to other chemotherapy regimens including gemcitabine-nab-paclitaxel (NCT01088815)<sup>44</sup> or FOLFIRINOX (NCT01383538,<sup>45</sup> NCT01485744)<sup>46</sup> are currently ongoing.

Degradation of hyaluronic acid, an important component of the peritumoral stroma, has been shown to be a promising therapeutic approach for the treatment of pancreatic cancer. Moreover, the stromal changes resulting from enzymatic degradation of this glycosaminoglycan make this approach particularly interesting when used in association with standard chemotherapy. Indeed, administration of hyaluronidase has been reported to be associated with a reduction in interstitial pressure and an increase in diameter of tumor blood vessels, all changes that facilitate effective delivery of chemotherapy to pancreatic tumor cells.<sup>47</sup> Promising activity has been observed with PEGPH20, a pegylated human recombinant PH20 hyaluronidase, in both preclinical and early clinical studies.<sup>48</sup> The efficacy of a gemcitabine-PEGPH20 combination versus gemcitabine alone is now being evaluated in a Phase IB/II study in patients with previously untreated metastatic pancreatic cancer (NCT01453153).<sup>49</sup>

Another potentially interesting therapeutic target is represented by several key receptor tyrosine kinases, including vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and basic fibroblast growth factor receptor. Through either direct effects on pancreatic cancer cells or recruitment of endothelial cells and vascular smooth muscle cells into the stroma surrounding the tumor, these receptor tyrosine kinases promote tumor growth, control interstitial fluid pressure in the stroma, and facilitate development of metastases.<sup>50,51</sup> Preclinical studies suggest that therapeutic inhibition of these receptor tyrosine kinases may result in a significant antitumor effect.<sup>52,53</sup> The antitumor effects of these receptor tyrosine kinase inhibitors *in vivo* are currently under investigation (NCT01497392).<sup>54</sup>

## Current treatments options for metastatic pancreatic cancer

In patients with metastatic disease, the major goals of treatment are symptom control, improvement of quality of life, and prolongation of survival. Historically, systemic chemotherapy, largely 5-fluorouracil-based, was shown to be superior over best supportive care in terms of psychological measures, quality of life, and overall survival.<sup>55,56</sup> In 1997, a pivotal, randomized clinical trial (n=126) showed that gemcitabine improved the clinical benefit rate (23.8% versus 4.8%,  $P=0.0022$ ) and median overall survival (5.65 months versus 4.41 months,  $P=0.0025$ ) when compared with 5-fluorouracil as first-line treatment for patients with locally advanced or metastatic disease. The probability of surviving beyond one year in this trial was 18% for patients treated with gemcitabine and 2% for patients treated with 5-fluorouracil.<sup>8</sup>

Following the results of this study, single-agent gemcitabine represented the mainstay of treatment for advanced pancreatic cancer for many years. However, over the last decade, several studies have shown that adding a second cytotoxic agent to a gemcitabine-based chemotherapy may potentially increase the efficacy of treatment and improve the overall outcome of pancreatic cancer (Table 1).

In a randomized Phase III trial with 313 patients, the combination of gemcitabine plus oxaliplatin was demonstrated to be superior to gemcitabine alone in terms of response rate (26.8% versus 17.3%,  $P=0.04$ ), progression-free survival (5.8 months versus 3.7 months, hazard ratio [HR] 0.75,  $P=0.04$ ) and clinical benefit (38.2% versus 26.9%,  $P=0.03$ ).<sup>57</sup> However, the difference in overall survival (primary endpoint of the study) between the treatment groups did not reach statistical significance (8.8 months versus 6.9 months, HR 0.82,  $P=0.13$ ). Interestingly, no difference

**Table 1** Main Phase III studies comparing combination chemotherapy versus single-agent gemcitabine in advanced pancreatic cancer

Reference	n	Patient population	Treatment arms	Primary endpoint	Response rate (%)	Disease control (%)	Median PFS (months)	Median OS (months)
Louvet et al <sup>57</sup>	313	Locally advanced or metastatic	Gemcitabine Gemcitabine–oxaliplatin	OS	17.3 26.8 ( <i>P</i> =0.04)	26.9 38.2 ( <i>P</i> =0.03)	3.7 5.8 HR 0.75 ( <i>P</i> =0.04)	6.9 8.8 HR 0.82 ( <i>P</i> =0.13)
Heinemann et al <sup>58</sup>	195	Locally advanced or metastatic	Gemcitabine Gemcitabine–cisplatin	OS	8.2 10.2 NS	48.5 70.4 ( <i>P</i> <0.001)	3.1 5.3 HR 0.75 ( <i>P</i> =0.053)	6.0 7.5 HR 0.80 ( <i>P</i> =0.15)
Moore et al <sup>13</sup>	569	Locally advanced or metastatic	Gemcitabine Gemcitabine–erlotinib	OS	8.0 8.6 NS	49.2 57.5 ( <i>P</i> =0.07)	3.7 3.5 HR 0.77 ( <i>P</i> =0.004)	5.9 6.2 HR 0.82 ( <i>P</i> =0.038)
Poplin et al <sup>14</sup>	547	Locally advanced or metastatic	Gemcitabine Gemcitabine–oxaliplatin	OS	6.0 9.0 NS	NA	2.6 2.7 ( <i>P</i> =0.10)	4.9 5.7 HR 0.88 ( <i>P</i> =0.22)
Cunningham et al <sup>10</sup>	533	Locally advanced or metastatic	Gemcitabine Gemcitabine–capecitabine	OS	12.4 19.1 ( <i>P</i> =0.034)	41.7 48.7 NA	3.8 5.3 HR 0.78 ( <i>P</i> =0.004)	6.2 7.1 HR 0.86 ( <i>P</i> =0.08)
Colucci et al <sup>59</sup>	400	Locally advanced or metastatic	Gemcitabine Gemcitabine–cisplatin	OS	10.1 12.9 ( <i>P</i> =0.37)	NA	3.9 3.8 HR 0.97 ( <i>P</i> =0.80)	8.3 7.2 HR 1.10 ( <i>P</i> =0.38)
Conroy et al <sup>15</sup>	342	Metastatic	Gemcitabine FOLFIRINOX	OS	9.4 31.6 ( <i>P</i> <0.001)	50.9 70.2 ( <i>P</i> <0.001)	3.3 6.4 HR 0.47 ( <i>P</i> <0.001)	6.8 11.1 HR 0.57 ( <i>P</i> <0.001)
Von Hoff et al <sup>16</sup>	861	Metastatic	Gemcitabine Gemcitabine–nab-paclitaxel	OS	7.0 23.0 ( <i>P</i> <0.001)	33.0 48.0 ( <i>P</i> <0.001)	3.7 5.5 HR 0.69 ( <i>P</i> <0.001)	6.7 8.5 HR 0.72 ( <i>P</i> <0.001)

**Abbreviations:** FOLFIRINOX, 5-fluorouracil, folinic acid, irinotecan and oxaliplatin; HR, hazards ratio; NA, not available; OS, overall survival; PFS, progression-free survival.

in any outcome measure was reported for the combination of gemcitabine plus oxaliplatin versus gemcitabine alone in a subsequent Phase III trial (*n*=447) in which fixed-dose rate gemcitabine was also assessed.<sup>14</sup> In both studies, an increased risk of grade  $\geq 3$  toxicity (in particular myelosuppression, vomiting, and peripheral neuropathy) was observed in the combination arm.

Similarly, in a randomized Phase III trial of gemcitabine plus cisplatin versus gemcitabine alone (*n*=195), use of a combination treatment was associated with prolonged progression-free survival (5.3 months versus 3.1 months, HR 0.75, *P*=0.053); however, the advantage in overall survival (primary endpoint of the study) for the gemcitabine–cisplatin group (7.5 months versus 6.0 months) was not statistically significant (HR 0.80, *P*=0.15). In this trial, an increased trend towards a statistically significant benefit for the combination arm (*P*=0.051) was observed in the subgroup of patients with better performance status (Karnofsky performance status 90%–100%).<sup>58</sup> In contrast, in a larger similarly designed study (*n*=400), a different schedule of gemcitabine–cisplatin was not demonstrated to provide any clinical advantage in response rate or survival outcomes over gemcitabine alone.<sup>59</sup>

A subsequent pooled analysis of two Phase III trials showed that combination of gemcitabine with a platinum analog significantly improved progression-free survival (HR 0.75, *P*=0.003) and overall survival (HR 0.81, *P*=0.031) as compared with single-agent gemcitabine.<sup>60</sup> Moreover, an increased benefit from the doublet chemotherapy was found in patients with good performance status (HR 0.64 and HR 0.72 for progression-free survival and overall survival, respectively).

Similar results to those reported for adding a platinum compound to gemcitabine were observed with the combination of gemcitabine plus capecitabine. In a large randomized Phase III trial (*n*=533) in the UK, addition of capecitabine to single-agent gemcitabine significantly improved the objective response rate (19.1% versus 12.4%, *P*=0.034) and progression-free survival (5.3 months versus 3.8 months, HR 0.78, *P*=0.004) and did not compromise patient quality of life.<sup>10</sup> In analysis of the primary endpoint of overall survival, only a trend towards an advantage for the combination arm was observed (7.1 months versus 6.2 months, HR 0.86, *P*=0.08). However, after pooling this trial with two randomized trials of gemcitabine versus gemcitabine plus capecitabine (*n*=935),<sup>9,61</sup> a significant improvement in overall

survival was found in favor of the combination treatment (HR, 0.86,  $P=0.02$ ).<sup>10</sup>

Further support for the use of combination chemotherapy was provided by the results of several meta-analyses of randomized studies comparing single-agent gemcitabine versus gemcitabine-based doublet chemotherapy. In a large meta-analysis of 19 studies with no interstudy heterogeneity, gemcitabine-based combinations significantly improved overall survival compared with single-agent gemcitabine (HR 0.91, 95% confidence interval [CI] 0.85–0.97).<sup>62</sup> Interestingly, these results seemed to be largely driven by the comparison analysis of gemcitabine alone versus gemcitabine combined with either a platinum agent (HR 0.85, 95% CI 0.74–0.96) or capecitabine (HR 0.83, 95% CI 0.72–0.96). Indeed, in a subgroup analysis, there was insufficient evidence to suggest a survival advantage for the combination of gemcitabine with either 5-fluorouracil (HR 0.98, 95% CI 0.86–1.11) or irinotecan (HR 1.01, 95% CI 0.84–1.22). These results were confirmed in another meta-analysis where a subgroup analysis of 1,682 patients with adequate information on baseline performance status also showed that combination chemotherapy was associated with a significant survival benefit in patients with good performance status (Eastern Cooperative Oncology Group 0–1 or Karnofsky performance status 90%–100%; HR 0.76, 95% CI 0.67–0.87,  $P<0.0001$ ).<sup>63</sup> In contrast, use of combination chemotherapy did not appear to improve the outcome for patients with a baseline poor performance status (HR 1.08, 95% CI 0.90–1.29,  $P=0.40$ ).

Although associated with a clinically marginal improvement in outcome, erlotinib is the only targeted agent that has been granted US Food and Drug Administration approval for first-line treatment of advanced pancreatic cancer in combination with gemcitabine. In a randomized Phase III trial ( $n=569$ ), the combination treatment with this anti-epidermal growth factor receptor agent was demonstrated to be associated with a statistically significant improvement in overall survival over gemcitabine alone (6.24 months versus 5.91 months, HR 0.82,  $P=0.038$ ).<sup>13</sup> The one-year survival rates were 23% for the gemcitabine–erlotinib arm and 17% for the gemcitabine alone arm ( $P=0.023$ ). Combination therapy was also associated with an increase in median progression-free survival (3.75 months versus 3.55 months, HR 0.77;  $P=0.004$ ). No difference between the two treatment arms was observed in terms of objective response rate (8.6% versus 8.0%).

More recently, evidence has emerged that a more intensive treatment regimen including a combination of three cytotoxic drugs is feasible and effective in patients with metastatic

disease and a good performance status. In a randomized Phase III trial ( $n=342$ , Eastern Cooperative Oncology Group performance status 0–1), the combination of oxaliplatin, irinotecan, and fluorouracil with leucovorin (FOLFIRINOX) was demonstrated to be superior to gemcitabine alone in terms of response rate (31.6% versus 9.4%,  $P<0.001$ ), progression-free survival (6.4 months versus 3.3 months, HR 0.47,  $P<0.001$ ), and overall survival (11.1 months versus 6.8 months, HR 0.57,  $P<0.001$ ).<sup>15</sup> The investigational arm was associated with an increased risk of grade  $\geq 3$  adverse events, especially neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy. However, it is worth noting that the analysis of quality of life showed that, at 6 months, 66% of patients in the gemcitabine alone arm experienced a deterioration of quality of life compared with 31% of patients in the FOLFIRINOX arm (HR 0.47,  $P<0.001$ ). Moreover, the time to deterioration in quality of life was reported to be delayed in the investigational arm when compared with the control arm for all functional and symptom scales and with respect to appetite loss, dyspnea, and constipation.

## New formulation of taxanes and nab-paclitaxel in advanced pancreatic cancer

Taxanes have been widely tested in pancreatic cancer, either in monotherapy or as combination therapy with gemcitabine or other chemotherapy agents.<sup>64</sup> Both paclitaxel and docetaxel were associated with modest activity (response rate 0%–15%, median time to progression 1–5 months, overall survival 5–8.5 months) when given as single agents in previously untreated patients.<sup>65–68</sup> Single-arm or randomized Phase II trials including combination of a taxane plus gemcitabine showed interesting results (response rate up to 40% and median overall survival up to 9 months), possibly confirming the preclinical data suggesting a synergistic effect of this combination.<sup>69–72</sup> However, given the design of these studies, the small numbers, and the potential biases associated with patient selection, these results are difficult to interpret.

Recently, new paclitaxel formulations have been investigated in pancreatic cancer with the aim to overcome abundant fibrous desmoplasia and increase drug delivery to the tumor cells. In a single-arm study of 56 patients, monotherapy with paclitaxel-loaded polymeric micelles has been reported to achieve disease control in 60% of cases, with a progression-free survival of 2.8 months and an overall survival of 6.5 months.<sup>73</sup> In a four-arm, randomized Phase II trial ( $n=212$ ), different dosages of EndoTAG®-1 (Medigene AG,



Planegg/Martinsried, Germany), a novel formulation of charged liposomes carrying paclitaxel embedded in the cationic liposome membrane and selectively delivering the drug to the intratumoral endothelial cells, were investigated in association with gemcitabine versus gemcitabine alone.<sup>74</sup> Although the response rate was comparable across the four treatment groups (14%–16%), the median progression-free survival and overall survival were longer in the combination arms (from 4.1 to 4.6 months and from 8.1 to 9.3 months, respectively) compared with the gemcitabine alone group (2.7 months and 6.8 months, respectively). The toxicity profile of the gemcitabine plus EndoTAG®-1 combination was favorable and, interestingly, no treatment-related neuropathy was reported in the trial. These results support the hypothesis that use of new formulations of taxanes may improve the efficacy of these agents and also improve their safety profile and minimize the risk of toxicity, especially when given in association with other cytotoxic drugs.

Nab-paclitaxel (Abraxane®; Celgene, Summit, NJ, USA) is a 130 nm albumin-bound formulation of paclitaxel particles initially developed to reduce the toxicity associated with the oil-based solvents required to solubilize paclitaxel.<sup>75</sup> Moreover, this novel formulation is associated with increased delivery of the drug into tumor tissue, possibly mediated by active transport of albumin into the interstitial space via gp60-mediated transcytosis or binding of albumin to SPARC.<sup>76,77</sup> In preclinical studies conducted in murine models of pancreatic cancer, nab-paclitaxel showed antitumor activity as a single agent and synergistic activity in combination with gemcitabine.<sup>78</sup> Interestingly, nab-paclitaxel was demonstrated to increase the intratumoral concentration of gemcitabine by decreasing protein levels of the primary gemcitabine-metabolizing enzyme, cytidine deaminase.<sup>79</sup>

In a Phase I/II trial in patients with previously untreated metastatic pancreatic cancer (n=67), administering nab-paclitaxel in combination with standard-dose gemcitabine was demonstrated to be safe at the maximum tolerated dose of 125 mg/m<sup>2</sup>.<sup>78</sup> The dose-limiting toxicities were sepsis and neutropenia, and the most common treatment-related adverse events that led to treatment discontinuation were neuropathy and fatigue. Interestingly, use of this combination was associated with significant activity and promising survival outcomes. Indeed, in the group of patients treated at the maximum tolerated dose of nab-paclitaxel (n=44), the response rate was 48% and the overall disease control rate was 68%. Moreover, in the same group, median progression-free survival and overall survival were 7.9 months and 12.2 months, respectively, and the one-year survival rate was 48%.

These results were confirmed in a recent international, multicenter, open-label, randomized Phase III trial conducted in 861 patients with untreated metastatic pancreatic cancer.<sup>16</sup> In this trial, patients with a Karnofsky performance status  $\geq 70$  were randomized in a 1:1 ratio to receive nab-paclitaxel plus gemcitabine versus gemcitabine alone. Of note, the trial excluded patients who had previously received adjuvant systemic chemotherapy and did not allow crossover at the time of progressive disease. The primary endpoint of the study was overall survival. The analysis conducted in the intention-to-treat population showed a statistically significant advantage in favor of the combination treatment, with a median overall survival of 8.5 months for the experimental arm compared with 6.7 months for the control arm (HR 0.72,  $P < 0.0001$ ). The 1-year and 2-year survival rates were 35% and 9% for gemcitabine-nab-paclitaxel and 22% and 4% for gemcitabine alone, respectively. Of note, use of subsequent treatments was similar in the treatment groups and the survival advantage for the combination arm was confirmed even when data for survival were censored at the time of the initiation of second-line therapy. Similarly, addition of nab-paclitaxel was associated with longer progression-free survival (5.5 months versus 3.7 months, HR 0.69,  $P < 0.0001$ ), increased tumor response rate (23% versus 7%), and a higher rate of disease control (48% versus 33%) compared with single-agent gemcitabine.

Treatment was generally well tolerated, with patients in the investigational arm receiving 81% and 75% of the protocol-specified nab-paclitaxel and gemcitabine doses, respectively. There was no difference between the two treatment groups in term of incidence of serious adverse events (50% with nab-paclitaxel plus gemcitabine and 43% with gemcitabine) or fatal events (4% in each treatment group). Neutropenia (38% versus 27%), leukopenia (31% versus 16%), fatigue (17% versus 7%), and peripheral neuropathy (17% versus 1%) were the treatment-related grade  $\geq 3$  adverse events, which were reported to occur more frequently in the combination group than in the control group. Of note, peripheral neuropathy was cumulative but rapidly reversible after discontinuation of treatment.

Based on these data, nab-paclitaxel has recently obtained approval from both the US Food and Drug Administration and European Medicines Agency for use in combination with gemcitabine for the first-line treatment of patients with metastatic pancreatic cancer. Moreover, given the promising activity and manageable toxicity observed in this trial, the combination of gemcitabine plus nab-paclitaxel is currently being tested in different treatment settings in association with

other cytotoxic drugs or novel agents targeting the pancreatic stroma (Table 2). Other treatment schedules of gemcitabine and nab-paclitaxel (ie, biweekly dosing) are being assessed to see whether the safety profile of this combination can be improved (NCT01851174).<sup>80</sup>

The efficacy of nab-paclitaxel has also been assessed in previously treated metastatic pancreatic cancer patients. In a small Phase II trial of nab-paclitaxel monotherapy in patients who progressed on gemcitabine-based therapy (n=19), one patient had a confirmed partial response and six (32%) had stable disease as their best response. Eleven (58%) patients were alive at 6 months (primary endpoint of the study), and estimated median progression-free survival and overall survival were 1.7 months and 7.3 months, respectively.<sup>81</sup> Treatment was overall well tolerated, with grade  $\geq 3$  neutropenia, febrile neutropenia, and anemia occurring in 32%, 11%, and 11% of patients, respectively.

## Nab-paclitaxel in locally advanced pancreatic cancer

The activity of nab-paclitaxel observed in association with gemcitabine in patients with metastatic disease has prompted investigation of this combination therapy in other treatment settings. Most of the currently available data are from small Phase II trials in which gemcitabine-nab-paclitaxel was given as a preoperative treatment in patient with resectable or potentially resectable locally advanced pancreatic cancer.

In a recent pilot, multicenter Phase II trial in patients with resectable disease (n=25), administering three cycles of neoadjuvant gemcitabine-nab-paclitaxel was feasible and associated with radiological and biochemical response (16% and 60%, respectively).<sup>82</sup> Twenty of 25 patients (80%) underwent surgical resection, and in 19 cases this was a radical (R0) resection. The primary endpoint of the study was a  $>90\%$  postoperative histological tumor response (grade 3/4), and this was reported in six patients (30%).

Similar results were reported in a small cohort of patients with resectable or borderline resectable pancreatic cancer (n=16).<sup>83</sup> More interestingly, in this study, the clinical and pathological effects of two cycles of neoadjuvant gemcitabine-nab-paclitaxel were also investigated by elastography, an endoscopic ultrasound-based technique for noninvasive assessment of the tumor stroma. The authors reported that the elastography ratio value diminished significantly after treatment and correlated with improvement in the maximum standardized uptake value and carbohydrate antigen (CA19.9) response, emerging as an attractive method to monitor tumor response. Analysis of residual tumors of patients treated with nab-paclitaxel plus gemcitabine revealed a less abundant peritumoral fibrillar collagen matrix and a smaller number of cancer-associated fibroblasts compared with a control group of untreated or conventionally treated patients. Moreover, in areas of tumor regression, collagen had an amorphous structure, with a discontinuous and disorganized network of type I collagen fibers.

**Table 2** Ongoing clinical trials investigating the addition of an anti-stroma agent to the combination of gemcitabine and nab-paclitaxel in pancreatic cancer

Trial ID	Agent	Mechanism of action	Patient population	Study design
NCT02005315 <sup>106</sup>	Vantictumab (OMPI8R5)	Human mAb targeting the WNT pathway	1st line, metastatic	Phase 1b dose escalation study
NCT01431794 <sup>107</sup>	Erismodegib (LDE225)	Oral hedgehog inhibitor	Borderline resectable	Open-label Phase 1/2 randomized study
NCT01088815 <sup>108</sup>	Vismodegib (GDC-0449)	Oral hedgehog inhibitor	1st line, metastatic	Single arm Phase 2 study
NCT01839487 <sup>109</sup>	PEGPH20	PEGylated recombinant human hyaluronidase	1st line, metastatic	Open-label Phase 2 randomized study
NCT01804530 <sup>110</sup>	PLX7486-TsOH	TKI inhibitor tosylate salt	Advanced non-resectable (part 2)	Phase 1 dose-escalation study
NCT01647828 <sup>111</sup>	OMP-59R5	Anti-notch receptor mAb	1st line, metastatic	Open-label Phase 1/2 randomized study
NCT01461915 <sup>112</sup>	ODSH	Low anticoagulant heparin derivate	1st line, metastatic	Open-label Phase 2 randomized study
NCT01621243 <sup>113</sup>	M402	Heparan sulfate mimetic	Metastatic pancreatic cancer	Double-blinded Phase 1/2 randomized study
NCT01844817 <sup>114</sup>	Apatorsen (OGX-427)	Antisense oligonucleotide targeting HSP 27	1st line, metastatic	Double-blinded Phase 2 randomized study
NCT01858883 <sup>115</sup>	INCB039110	Selective Janus Kinase-1 inhibitor	Advanced or metastatic	Phase 1b study

**Abbreviations:** mAb, monoclonal antibody; TKI, tyrosine kinase inhibitor; HSP, heat shock protein; PEGPH20, (PEGylated Recombinant Human Hyaluronidase); ODSH, (2-0, 3-0 Desulfated Heparin).

The preliminary results of a pilot study assessing a sequential neoadjuvant strategy with two cycles of gemcitabine-nab-paclitaxel followed by two cycles of FOLFIRINOX in patients with locally advanced, stage III pancreatic cancer have been recently reported.<sup>84</sup> The first eight study patients completed the planned four cycles of treatment, and sequential therapy was feasible in that there were no unexpected toxicities, and administering gemcitabine-nab-paclitaxel did not appear to adversely affect the safety profile of FOLFIRINOX. Five partial responses (63%) and three cases of stable disease (37%) were observed, and three patients (37%) underwent an R0 resection. The authors reported tumor regression in all resected patients, with one pathological complete response.

Additional clinical trials are currently further investigating the clinical potential of nab-paclitaxel in other treatment settings, including a large, multicenter, randomized, Phase III study of gemcitabine-nab-paclitaxel versus gemcitabine alone as adjuvant treatment following R0 or R1 resection (Table 3). The results of these trials will certainly provide more information on the role of this novel agent within the therapeutic landscape of pancreatic cancer. In particular, it will be very interesting to see whether the antitumor effects of nab-paclitaxel observed in the presence of macroscopic disease are maintained in the setting of microscopic disease where the clinical relevance of the peritumoral stroma and the characteristics of the tumor microenvironment may be markedly different.

## SPARC and nab-paclitaxel

SPARC, also known as osteonectin or BM-40, is an albumin-binding 42 kDa multifunctional glycoprotein highly expressed during mammalian development and tissue differentiation, and usually declines after organ maturation.<sup>81</sup> SPARC expression

has been suggested to have a role in tissue remodeling during several physiological or pathological processes, including wound healing, angiogenesis, and tumorigenesis.<sup>85</sup>

In pancreatic cancer, SPARC is expressed in the tumor microenvironment in approximately 80% of cases.<sup>86,87</sup> Cytoplasmic staining for this glycoprotein is strongest in fibroblastic cells immediately adjacent to infiltrating cancer cells and significantly less common in pancreatic cancer cells.<sup>77</sup> Expression of SPARC in pancreatic cancer has been reported to correlate with poor outcome.<sup>77,88</sup> However, the biological rationale for this correlation and the mechanisms whereby expression of this glycoprotein may influence the outcome of pancreatic cancer are largely unknown.<sup>89</sup> Expression of SPARC by stromal fibroblasts may be a generic indicator of an activated fibroblast phenotype or may influence pericyte migration, collagen deposition, and ultimately facilitate development of dense collagenous stroma.<sup>89–91</sup>

More recently, SPARC has emerged as a potential biomarker in pancreatic cancer. Nab-paclitaxel was previously shown to have antitumor activity in various types of cancer that overexpress SPARC.<sup>92–100</sup> In a Phase I/II study of gemcitabine plus nab-paclitaxel in pancreatic cancer, increased expression of SPARC in stromal cells, but not in cancer cells, was found to be associated with improved overall survival.<sup>78</sup> Although only 36 study patients were assessable for SPARC; the median overall survival for patients with high-SPARC tumors was 17.8 months versus 8.1 months in the group of patients with low-SPARC tumors ( $P=0.043$ ). This finding is in contrast with historical reports on the association between SPARC expression and poor outcome, and suggested that stromal SPARC may represent a useful marker of activity for gemcitabine plus nab-paclitaxel combination regimens in pancreatic cancer. However, it is worth noting

**Table 3** Main clinical trials with gemcitabine and nab-paclitaxel in other treatment settings of pancreatic cancer

Trial ID	Indication	Patient population	Treatment arms	Study design	Primary endpoint
NCT01964430 <sup>116</sup>	Adjuvant	Resected (R0 or R1) Stage T 1–3, N 0–I, M0	Gemcitabine vs Gemcitabine nab-paclitaxel	Open-label, randomized Phase 3	Disease-free survival
NCT01978184 <sup>117</sup>	Neoadjuvant	Potentially or borderline resectable	Gemcitabine nab-paclitaxel vs Gemcitabine nab-paclitaxel plus hydroxychloroquine	Open-label Phase 2 randomized study	Histologic response
NCT01470417 <sup>118</sup>	Neoadjuvant	Resectable and borderline resectable	Low-risk resectable: Gemcitabine nab-paclitaxel followed by surgery High-risk/borderline resectable: Gemcitabine nab-paclitaxel followed by CRT and surgery	Non-randomized Phase 2 study	Biochemical response Radiologic response Pathologic downstaging R0 resection rate
NCT02024009 <sup>119</sup>	Locally advanced disease	Unresectable, locally advanced	Gemcitabine nab-paclitaxel followed by CRT (50.4 or 60 Gy) with or without Nelfinavir	Randomized Phase 2/3 study	Overall survival

**Abbreviation:** CRT, chemoradiotherapy.



that data from preclinical and clinical studies investigating the role of SPARC as a potential predictive biomarker for the benefit of nab-paclitaxel in pancreatic cancer and other types of tumors have been inconsistent.<sup>101–104</sup>

In a recent pharmacokinetic and pharmacodynamic analysis of cremophor-paclitaxel, nab-paclitaxel and a novel mouse albumin nab-paclitaxel in a genetically engineered mouse model of pancreatic cancer, Neesse et al found that circulating SPARC levels, but not stromal-derived SPARC, may influence the intravascular concentration and tissue delivery of low-dose nab-paclitaxel. However, accumulation and activity of nab-paclitaxel were largely dose-dependent and not affected by SPARC when nab-paclitaxel was administered at therapeutic doses.<sup>105</sup> The prognostic or predictive role of SPARC expression in tumor specimens from MPACT (the Metastatic Pancreatic Adenocarcinoma Clinical Trial)<sup>16</sup> is currently being investigated, and the results of these analyses are eagerly awaited.

## Conclusion

After several years during which no major changes were introduced in the routine management of advanced pancreatic cancer, the treatment paradigm for this disease has recently evolved. Two large randomized Phase III trials<sup>15,16</sup> have provided definitive evidence that more intensive treatments are feasible in patients with good performance status and are associated with better outcome. As a result, oncologists have now an increased number of treatment options for patients with advanced pancreatic cancer and can tailor therapy according to patient characteristics. Patient performance status, comorbidities, drug-related toxicities, and treatment goals are increasingly being taken into consideration in routine practice to individualize therapeutic strategies and optimize the treatment risk/benefit profile for each patient. Moreover, studies are currently investigating whether the antitumor activity and clinical benefit observed with the new combination regimens in the advanced setting can be replicated in the setting of adjuvant and neoadjuvant treatment.

Nab-paclitaxel is already being used for the treatment of metastatic pancreatic cancer in many countries. Although initially developed for a different purpose, this drug can be considered as the prototype of antitumor agents that couple inherent cytotoxic activity with an ability to overcome the mechanical barrier of the pancreatic peritumoral stroma. Moreover, its acceptable safety profile and synergistic interaction with gemcitabine suggest that the gemcitabine-nab-paclitaxel combination is not only an option for first-line treatment of patients with advanced disease but may also

represent the optimal chemotherapy backbone for evaluation of combination treatments, including standard chemotherapy agents and promising agents with alternative mechanisms of action. Identification of those patients most likely to benefit from nab-paclitaxel could certainly maximize the efficacy of this agent. Although preliminary data suggest an association between the benefit of nab-paclitaxel and expression of SPARC, further investigation is needed to validate SPARC as a clinically useful predictive biomarker.

It is undeniable that, despite the general enthusiasm associated with the recent advent of new treatment options, the overall prognosis of advanced pancreatic cancer is still poor and several challenges remain in the management of this disease. More studies are certainly needed to elucidate further the biology of pancreatic cancer and promote development of new therapeutic strategies that could overcome the inherent mechanisms of resistance to treatment.

It is now established that the peritumoral stroma plays a key role in the development of pancreatic cancer and has a strong influence on the biological behavior of this disease. Trying to better understand the interactions between tumor cells and the complex network of stromal components and define their exact role in pancreatic carcinogenesis and tumor progression are certainly some of the next and most important challenges. Several promising antistromal agents are currently under investigation, and the results of these studies will determine whether targeting the stroma is a valid therapeutic option in this disease.

## Acknowledgments

We acknowledge support from the National Institute for Health Research Biomedical Research Centre at the Royal Marsden Hospital and Institute of Cancer Research and from the Peter Stebbings Memorial Charity.

## Disclosure

Prof David Cunningham has received research funding from Roche, Amgen, Celgene, Sanofi-Aventis and Merck Serono. The authors report no other conflicts of interest in this work.

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