The winning FORMULA-tion: the development of paclitaxel in pancreatic cancer

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ABSTRACT
Paclitaxel has wide application in anti-cancer therapy but was never considered an efficacious agent in pancreatic cancer. A review of the experience with the Cremaphor (Cre) formulation hinted paclitaxel’s activity in pancreatic cancer but the early development was hampered by significant toxicities such as neutropenia and infection at clinically tolerable doses. However, such efficacy was confirmed in the recently completed phase III MPACT trial where the addition of nab-paclitaxel to gemcitabine significantly improved the survival of metastatic pancreatic cancer patients. Several other Cremaphor-free formulations of paclitaxel had also been evaluated in pancreatic cancer and the reasons for the success of the albumin nanoparticulate are examined here. In the era of biological and molecularly-targeted agents, the success of nab-paclitaxel in the recalcitrant pancreatic cancer is a timely reminder of the importance and relevance of pharmacology and novel drug delivery technology in the development of anti-cancer drugs.
INTRODUCTION

Pancreatic cancer is the 8th leading cause of cancer deaths worldwide and approximately 266,000 patients died from the disease in 2008.(1) Gemcitabine was the first anti-cancer drug to achieve meaningful survival improvement in advanced pancreatic cancer and had been the standard bearer since the 1990s.(2) Over the years, a large number of cytotoxic and molecularly-targeted drugs were evaluated in combination with gemcitabine in clinical trials but almost all failed to further improve the survival of advanced pancreatic cancer.(3-5) In some instances, this was due to low intrinsic activity of the new agent, but some others might have been due to poor clinical trial design. A meta-analysis of 15 clinical trials involving 4465 advanced pancreatic cancer patients concluded that patients with good performance status should be offered gemcitabine-containing combinations. Erlotinib, given with gemcitabine, is the only other anti-cancer drug to receive regulatory approval for the treatment of advanced disease. However, the addition of erlotinib to gemcitabine achieved only approximately 2 weeks median survival improvement compared to gemcitabine as demonstrated in the NCIC CTG PA.3 trial.(6)

The success of FOLFIRINOX, an intensive cytotoxic regimen of fluorouracil, leucovorin, irinotecan and oxaliplatin, was a major milestone in pancreatic cancer therapy, which extended the survival of metastatic pancreatic cancer patients by 4.3 months compared to gemcitabine alone.(7) However, toxicities related to FOLFIRINOX were significant and included febrile neutropenia, fatigue, diarrhea and peripheral neuropathy, and is being used selectively. As such, there remains a need for therapies more tolerable than FOLFIRINOX yet still able to achieve clinically meaningful survival improvement. Positive results from the recently announced MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial) trial showed that the nab-...
paclitaxel and gemcitabine combination may, in fact, fill this void (Table 1).(8) This review will contrast the development of nab-paclitaxel in pancreatic cancer to other paclitaxel formulations and explore the question of why the nab- formulation succeeded while others had not (Table 2). Experience on docetaxel in the context of ‘GTX’ is also reviewed briefly.

METASTATIC PANCREATIC ADENOCARCINOMA CLINICAL TRIAL (MPACT)

The MPACT study was a multi-national phase III trial launched following the encouraging result of a phase I/II trial of nab-paclitaxel plus gemcitabine in advanced pancreatic cancer.(9) In the pivotal trial, 842 metastatic pancreatic cancer patients with KPS score >= 70 were randomized to receive nab-paclitaxel 125 mg/m2 followed by gemcitabine 1000 mg/m2 on days 1, 8 and 15 every 28 days or gemcitabine 1000 mg/m2 weekly for 7 weeks followed by 1 week rest, then on days 1, 8 and 15 every 4 weeks thereafter.(8) Forty-three percent (43%) of the patients had head of pancreas tumor, 85% liver metastasis, 7% had previous Whipple procedure and 17% had biliary stent at enrollment. Patients who received nab-paclitaxel/gemcitabine did much better than the gemcitabine only arm with median survival 8.5 months vs. 6.7 months (hazard ratio 0.72; P=0.000015), 1-year survival 35% vs. 22%, 2-year survival 9% vs. 4% and objective response rate 23% vs. 7% respectively.

The nab-paclitaxel/gemcitabine combination was well tolerated; patients in the combination arm received 71% and 63% of planned nab-paclitaxel and gemcitabine doses respectively and the gemcitabine only arm received 79% of planned gemcitabine dose. The added toxicity risks from the addition of nab-paclitaxel were acceptable and manageable, and Grade 3 or worse adverse events included neutropenia, febrile neutropenia, thrombocytopenia and fatigue (Table
1). G-CSF use was 25% and 15% in the combination and control arms respectively. Grade 3 or worse peripheral neuropathy occurred in 17% of patients in the nab-paclitaxel containing arm that improved to Grade 1 or better in a median of 29 days; and, 44% resumed nab-paclitaxel following improvement of the peripheral neuropathy.

In summary, the addition of nab-paclitaxel to gemcitabine did achieve a statistical and clinically meaningful survival improvement for metastatic pancreatic cancer patients, and the added toxicity risk was acceptable and manageable including neutropenia and neuropathy. The nab-paclitaxel/gemcitabine regimen should therefore be considered in advanced pancreatic cancer patients with good physiological reserve who were not otherwise a candidate for the intensive FOLFIRINOX. Also, the more favorable toxicity profile makes nab-paclitaxel plus gemcitabine a very attractive backbone for developing novel agents.

PACLITAXEL AND PANCREATIC CANCER

Paclitaxel has broad application in oncology and causes mitotic arrest in cancer cells by disrupting microtubule function.(10) Due to the poor aqueous solubility, polyoxyethylated castor oil solvent (Cremaphor®) was used to solubilize paclitaxel for intravenous administration (Cre-paclitaxel; Taxol®). However, the formulation caused infusion hypersensitivity reaction requiring pre-medication with steroids and anti-histamines.(11,12) The Cremaphor solvent also altered paclitaxel’s pharmacology affecting the toxicity profile and anti-cancer efficacy.(13-15) A number of strategies had thus been developed to better solubilize and improve the pharmacology of paclitaxel including albumin nanoparticles, emulsions and liposomes (Figure 1).(15)
Cremaphor formulation

Cre-paclitaxel was evaluated in pancreatic cancer but failed to demonstrate significant activity in general (Table 2). A phase II trial of Cre-paclitaxel 175 mg/m2 every 3 weeks in 14 patients with chemo-naive locally advanced unresectable and metastatic pancreatic cancer was closed early when pre-planned analysis showed no response.(16) The median survival was 7.2 months. A higher dose of Cre-paclitaxel 250 mg/m2 every 3 weeks with G-CSF support was tested in chemo-naive advanced pancreatic cancer patients. Though 1 complete response was observed, the median survival was 5 months and the regimen was declared inactive in pancreatic cancer.(17) The median duration of treatment was 51 days, and 6 patients (15%) stopped due to treatment-related toxicities. Common grade 3 or worse included granulocytopenia (92%), anemia (23%), thrombocytopenia (21%), liver function anomalies (23%) and infection (21%) including 1 septic death.

A weekly schedule of Cre-paclitaxel 90 mg/m2 on days 1, 8 and 16 every 28 days was evaluated in combination with bryostatin, a protein kinase C inhibitor, in a phase II trial of 19 advanced pancreatic cancer patients (5 were first-line).(18) No confirmed response was observed and time-to-treatment failure was 1.9 months. Several other weekly schedules of Cre-paclitaxel monotherapy in gemcitabine refractory advanced pancreatic cancer patients had been reported in several retrospective reports.(19,20) However, the results were difficult to interpret due to the nature of the reports though tumor responses had been observed including 1 complete response.
Combination regimen of Cre-paclitaxel 175mg/m2 every 4 weeks and fluorouracil 1000 mg/m2 on days 1, 2 and 3 was evaluated in a single-arm phase II study of 28 gemcitabine refractory advanced disease.(21) The majority of patients (89%) received only 1 previous line of gemcitabine-containing therapy. There were 2 partial responses, though the median time-to-progression and survival were 2.5 and 7.6 months respectively. Grade 3 and worse adverse events included neutropenia (21.4%) (including one grade 4 neutropenia associated with pneumonia), thrombocytopenia (3.6%), diarrhea (7.1%) and neuropathy (3.5%).

*Albumin-bound formulation: early phase trials experience*

The albumin formulation of paclitaxel, nab-paclitaxel (Abraxane®), is approved by the United States Food and Drug Administration for the treatment of breast and lung cancers.(22) The solvent-free nab-paclitaxel is advantageous over Cre-paclitaxel with significantly lower risk of infusion hypersensitivity reactions and neutropenia, and faster recovery of peripheral neuropathy upon stopping the treatment.(23) The hint of activity of nab-paclitaxel/gemcitabine in pancreatic cancer came from a phase I/II trial.(9) Sixty-seven treatment-naive patients with advanced pancreatic cancer were treated with nab-paclitaxel dose levels 100, 125 or 150 mg/m2 in combination with gemcitabine 1000 mg/m2 on days 1, 8 and 15 every 28 days. The dose limiting toxicities were neutropenia and sepsis at the 150 mg/m2; thus, the 125 mg/m2 dose level was determined tolerable and evaluated further in the phase III MPACT trial. The single-arm study observed a respectable median survival of 12.2 months, 1-year survival 48% and overall response rate 48% in patients treated at the maximum tolerated dose.
The feasibility of combining additional cytotoxic drug to \textit{nab}-paclitaxel/gemcitabine was evaluated by Ko and colleagues.\cite{24} In the phase I trial, capecitabine was administered on days 1 to 7, and \textit{nab}-paclitaxel and gemcitabine (at fixed-dose rate infusion; FDR) on day 4 on an every 14-day cycle. Dose limiting toxicities were grade 3 neutropenia and grade 3 alanine transaminase elevation. Capecitabine 750 mg/m\textsuperscript{2} twice daily, \textit{nab}-paclitaxel 100 mg/m\textsuperscript{2} and gemcitabine FDR 750 mg/m\textsuperscript{2} was determined to be the maximum tolerated dose. Of the 14 evaluable patients, the objective response rate was 14.3\% and median survival 7.5 months. The inferior efficacy observed of this regimen compared to the above-mentioned phase I/II study was most likely due to the lower dose-intensity of component drugs.

\textit{nab}-paclitaxel monotherapy 100 mg/m\textsuperscript{2} on days 1, 8 and 15 every 28-days cycle was evaluated in 19 patients previously treated with gemcitabine-based regimens.\cite{25} The treatment was tolerable and the toxicity profile was consistent with expectation. The median survival was 7.3 months and 1 (5\%) partial response was observed. The study was closed before reaching target accrual in view of the decision to develop the \textit{nab}-paclitaxel and gemcitabine combination in first-line setting. For comparison, Oettle and colleagues reported a case series of 18 metastatic patients previously treated with gemcitabine-based therapy.\cite{20} Patients received \textit{Cre}-paclitaxel 50 mg/m\textsuperscript{2} weekly for 6 weeks followed by a week of rest and the dose was increased up to 85 mg/m\textsuperscript{2} for patients with less than grade 3 toxicities. The median dose administered was 73 mg/m\textsuperscript{2} (range 55 to 88 mg/m\textsuperscript{2}). The median survival observed was 4.4 months and 1 (5.6\%) achieved complete response. The longer survival observed in the aforementioned \textit{nab}-paclitaxel monotherapy study may be a result of improved supportive care over the decade though both
studies consistently reported tumor responses, suggesting efficacy of paclitaxel in some patients and biomarkers are needed to identify this subgroup.

**Cationic liposomal formulation**

Cationic liposomes has strong affinity for negatively charged tumor endothelial cells and is theoretically advantageous in selectively delivering paclitaxel to tumor vasculature.\(^{(26)}\) EndoTag\(^\circledR\)-paclitaxel (\(ET\)-paclitaxel) is one such formulation where paclitaxel is embedded in the cationic liposome membrane.\(^{(27)}\) The efficacy of adding \(ET\)-paclitaxel to gemcitabine was evaluated in a randomized phase II trial where 212 pancreatic cancer patients (80% metastatic and 20% locally advanced) were randomized to one of 4 arms: gemcitabine 1000 mg/m\(^2\), gemcitabine plus twice weekly \(ET\)-paclitaxel 11, 22 or 44 mg/m\(^2\) for 7 weeks. The median survival achieved were 6.8 vs. 8.1, 8.7 and 9.3 months respectively and 1-year survival were 15% vs. 21%, 35% and 30% respectively. Partial response was the best response and the rates were similar between gemcitabine alone and \(ET\)-paclitaxel containing arms. Grade 3 or worse adverse events during first cycle were observed in 24%, 22%, 32% and 40% respectively. There was a dose-dependent increase in grade 3 or worse thrombocytopenia (2% vs. 8%, 16%, 18% respectively) whilst neutropenia risk were almost comparable across all arms. Infusion-related reactions (pyrexia, chills) were more frequent in the \(ET\)-paclitaxel containing arms. The combination was reportedly planned for phase III evaluation.

**Polymeric micelle formulation**

Paclitaxel-loaded polymeric micelle (Genexol-PM\(^\circledR\))\(^{(28)}\) was evaluated as monotherapy in treatment-naive advanced pancreatic cancer in a single-arm phase II study\(^{(29)}\) The initial 11
patients were treated at 435 mg/m2 once every 3 weeks and the dose was reduced to 300 or 350 mg/m2 for the next 45 patients due to intolerance. The median survival achieved was 6.5 months and response rate 6.7% (1 complete and 2 partial responses). The 300 mg/m2 every 3 weeks was determined as the tolerable dose and toxicities were comparable to the Cremaphor formulation. The most common adverse events were neutropenia (40%), fatigue (17.8%), infection, dehydration, neuropathy (13.3% each) and abdominal pain (11.1%). The formulation was reportedly being evaluated in combination with gemcitabine in advanced pancreatic cancer (ClinicalTrials.gov #NCT00882973).

**DOCETAXEL – IN THE CONTEXT OF ‘GTX’**

Docetaxel is a semi-synthetic taxoid that also has wide application in anti-cancer therapy.(30) The dose limiting toxicity was neutropenia and the initial recommended phase II dose was 100 mg/m2 every 3 weeks though 75 mg/m2 every 3 weeks was later determined to be more tolerable.(31,32) Like Cre-paclitaxel, docetaxel monotherapy did not demonstrate significant activity in pancreatic cancer.(33-36) Several dosing schedules combining docetaxel and gemcitabine were evaluated in advanced pancreatic cancer with median survival ranging from 4.7 to 10.5 months, and response rate 6% to 30%.(37-44) However, toxicities were significant in these phase II studies including neutropenia, infection and septic death.

Fine and colleagues reported a single-arm phase II study of docetaxel, gemcitabine and capecitabine (‘GTX’) in first-line metastatic patients that achieved a median survival 14.5 months and response rate 38%; whilst the frequency of grade 3 or 4 neutropenia was 29%, febrile neutropenia 3%, anemia and thrombocytopenia 12% (Table 3).(45) A retrospective study
of 154 advanced pancreatic cancer patients treated with GTX reported a response rate 11% and median survival 11.6 months (in stage IV patients).(46) Grade 3 or worse hematological toxicities were 41%. An alternate every 28-day cycle schedule of docetaxel, gemcitabine and capecitabine was reported by Xenidis and colleagues that achieved response rate 40% and median survival 9 months.(47) Reni and colleagues evaluated an intensive 4-drug regimen by adding cisplatin to docetaxel, gemcitabine and capecitabine in first-line metastatic patients and achieved a response rate 57% but a disappointing median survival of 5.8 months.(48) The efficacy and toxicity profile of GTX seemed comparable to that reported in the phase I/II trial of *nab*-paclitaxel/gemcitabine by von Hoff and colleagues (Table 2). Unfortunately, the GTX regimen had never been properly evaluated in a randomized trial.

**THE WINNING FORMULA**

Neutropenia was a significant hurdle, in addition to infusion reaction, in the development of paclitaxel.(49) Through pharmacokinetic modeling, the risk for paclitaxel-induced neutropenia was found to correlate with the time interval which free paclitaxel concentration was above the 0.05 μM threshold.(50) Then, a recent meta-analysis of various paclitaxel formulations using population pharmacokinetic modeling showed that, at equivalent doses, this time interval by the *nab*- formulation was much shorter and correlated with a lower neutropenic risk than the Cremaphor formulation.(51) As such, the *nab*- formulation seemed to confer a more favorable pharmacological characteristic that allowed the delivery of a higher yet equitoxic dose of paclitaxel than Cremaphor. Furthermore, preclinical studies showed that the *nab*- formulation may enhance intratumoral paclitaxel accumulation through gp-60 mediated uptake of the albumin moiety and moreover, Cremaphor also inhibit paclitaxel uptake by endothelial cells.
(Figure 1).(52) These pharmacological characteristics likely contributed to the superior efficacy of nab-paclitaxel observed in clinical trials.(23)

The synergism between nab-paclitaxel and gemcitabine in pancreatic cancer was evaluated in 2 complementary preclinical models: primary patient-derived tumors and genetically engineered mice.(53) In the primary tumor xenograft model, nab-paclitaxel/gemcitabine treatment caused tumor regression in 64% of the 11 biologically distinct primary tumors versus 18% and 36% in gemcitabine and nab-paclitaxel monotherapy respectively.(9) nab-paclitaxel treatment appeared to deplete the desmoplastic stromal matrix while enhancing microvasculature in gemcitabine-resistant primary tumors. Correspondingly, the intratumoral gemcitabine concentration was 2.8 folds higher in mice treated with nab-paclitaxel/gemcitabine than gemcitabine alone. Similar synergistic anti-cancer and pharmacological effects were confirmed by Frese and colleagues using a transgenic pancreatic cancer murine model.(54) Furthermore, the group showed that paclitaxel enhanced intratumoral gemcitabine accumulation through the inactivation of cytidine deaminase, a key inactivating enzyme of gemcitabine.

SPARC (Secreted protein, acidic and rich in cysteine) was found to be epigenetically silenced in pancreatic cancer cells but preferentially expressed in adjacent stromal fibroblasts.(55) Increased SPARC expression had been associated with poorer prognosis in patients with pancreatic cancer.(56) The increased expression of the albumin-binding protein in pancreatic cancer patients stimulated the interest to initiate the phase I/II trial to evaluate nab-paclitaxel in the disease(9) Of the 36 evaluable patients from the phase I/II trial, high stromal SPRAC level was associated with longer survival in patients treated with the combination. The
role of SPARC as a predictive biomarker for benefit from \textit{nab}-paclitaxel treatment would be clarified once the investigators complete the analysis of patient tumor specimens from the MPACT trial.

In summary, the success of \textit{nab}-paclitaxel/gemcitabine was a result of multiple factors mechanistically. The favorable pharmacological characteristics of \textit{nab}- formulation enabled the delivery of a higher paclitaxel dose, which not only increased the cell kill but also synergized the effects of gemcitabine by enhancing intratumoral accumulation through several mechanisms, including depletion of stromal matrix, increasing tumor microvasculature and inhibiting the catabolism of gemcitabine metabolites.

**CONCLUSIONS**

A review of the experience with \textit{Cre}-paclitaxel hinted the drug’s activity in pancreatic cancer except the dose of paclitaxel that could be safely administered was limited by the toxicities associated with the formulation. Interestingly, the combination of \textit{Cre}-paclitaxel and gemcitabine had never been systematically evaluated in treatment-naive advanced pancreatic cancer except for a phase I study of this combination with radiation.(57) As discussed above, \textit{nab}-paclitaxel had several pharmacological advantages over the \textit{Cre} formulation that eventually translated into superior clinical efficacy when combined with gemcitabine in pancreatic cancer.

Several factors influence one’s recommendation on which regimen (\textit{nab}-paclitaxel/gemcitabine or FOLFIRINOX) to initiate in a newly diagnosed metastatic patient including the impact on quality-of-life (QoL). Unlike the PRODIGE 4/ACCORD 11 trial (58),
formal QoL assessment was not part of the MPACT trial. However, the relative tolerability of nab-paclitaxel/gemcitabine can be inferred from the fact that patients treated with nab-paclitaxel/gemcitabine maintained comparable dose intensity as the gemcitabine alone arm. In terms of drug cost, nab-paclitaxel/gemcitabine is approximately 8 to 10 times higher than FOLFIRINOX though such contrast is unlikely a deciding factor in the United States in the near future.(59)

In the era where billions of dollars are spent developing novel biological and molecular-targeted drugs, the success of nab-paclitaxel is a timely reminder that innovations to improve the pharmacological characteristics of old drugs are still important and relevant in anti-cancer drug development even though they may not be as catchy at scientific conferences.
REFERENCES


FIGURE LEGEND

Figure 1. Mechanisms-of-action by various paclitaxel formulations in pancreatic cancer. The albumin moiety of nab-paclitaxel facilitates the preferential uptake of paclitaxel by pancreatic tumor through gp-60 mediated endothelial transcytosis and binding of SPARC in tumor-associated stroma. Compared to the Cremaphor formulation, the albumin formulation also alters the pharmacokinetic behavior and improves the toxicity profile of the nab- formulation thereby allowing the administration of a higher yet equitoxic dose of paclitaxel. In the polymeric micelle formulation, paclitaxel is surrounded by polymers consisting of inward-facing hydrophobic and outward-facing hydrophilic ends. In cationic liposomal formulation, paclitaxel is embedded in liposomal membrane that is positively charged, and preferentially delivers the drug to the negatively charged tumor microvessel endothelium. Intra-tumorally, paclitaxel inhibits cytidine deaminase that leads to the accumulation of gemcitabine.
Table 1. Comparison of efficacy and safety profile between gemcitabine/nab-paclitaxel and FOLFIRINOX.

<table>
<thead>
<tr>
<th></th>
<th>nab-paclitaxel/gemcitabine*</th>
<th>FOLFIRINOX**</th>
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<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
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<tr>
<td>1-year survival</td>
<td>35%</td>
<td>48.4%</td>
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<tr>
<td>median OS</td>
<td>8.5 mo.</td>
<td>11.0 mo.</td>
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<tr>
<td>median PFS</td>
<td>5.5 mo.</td>
<td>6.4 mo.</td>
</tr>
<tr>
<td>ORR</td>
<td>23%</td>
<td>31.6%</td>
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<tr>
<td><strong>Toxicity Profile (Grade 3 or worse)</strong></td>
<td></td>
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<tr>
<td>Neutropenia</td>
<td>38%</td>
<td>45.7%</td>
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<tr>
<td>Febrile Neutropenia</td>
<td>3%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13%</td>
<td>9.10%</td>
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<tr>
<td>Diarrhea</td>
<td>6%</td>
<td>12.70%</td>
</tr>
<tr>
<td>Sensory Neuropathy</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17%</td>
<td>23.6%</td>
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</table>

**Note:** *MPACT(8); **PRODIGE 4/ACCORD 11(7); OS: overall survival; PFS: progression free survival; ORR: objective response rate; mo.: months. The gemcitabine only control arms from MPACT and PRODIGE4/ACCORD11 were similar in efficacy and toxicity risks.*
Table 2. Studies that evaluated paclitaxel in advanced pancreatic cancer patients

<table>
<thead>
<tr>
<th>Clinical Trial (year)</th>
<th>Design</th>
<th># of patients</th>
<th>Line(s) of therapy; Patient population</th>
<th>Regimen</th>
<th>Overall Response Rate</th>
<th>median survival (months)</th>
</tr>
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<tbody>
<tr>
<td>Cre-paclitaxel</td>
<td></td>
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</tr>
<tr>
<td>Gebbia (1996)</td>
<td>Phase II</td>
<td>14</td>
<td>1st-line; Stage III/IV</td>
<td>Paclitaxel 175 mg/m2 every 3 weeks</td>
<td>0%</td>
<td>7.2</td>
</tr>
<tr>
<td>Whitehead (1997)</td>
<td>Phase II</td>
<td>39</td>
<td>1st-line; Stage III/IV</td>
<td>Paclitaxel 250 mg/m2 every 3 weeks + G-CSF</td>
<td>8%</td>
<td>5</td>
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<tr>
<td>Kim (2008)</td>
<td>Phase II</td>
<td>28</td>
<td>gemcitabine-refractory; Stage III/IV</td>
<td>paclitaxel 175 mg/m2 on Day 1 every 4 weeks + fluorouracil 1000 mg/m2 iv on Days 1-3 every 4 weeks</td>
<td>10%</td>
<td>2.5</td>
</tr>
<tr>
<td>Lam (2009)</td>
<td>Phase II</td>
<td>19</td>
<td>1st-line and beyond; Stage III/IV</td>
<td>paclitaxel 90 mg/m2 weekly x3 every 4 weeks + bryostatin</td>
<td>0%</td>
<td>1.9</td>
</tr>
<tr>
<td>Oettle (2000)</td>
<td>Retrospective study</td>
<td>18</td>
<td>2nd and 3rd lines; Stage IV</td>
<td>paclitaxel 55 to 88 mg/m2 weekly</td>
<td>5%</td>
<td>4.3</td>
</tr>
<tr>
<td>Shukuya (2010)</td>
<td>Retrospective study</td>
<td>23</td>
<td>gemcitabine-refractory; Stage III/IV</td>
<td>paclitaxel 80 mg/m2 weekly x 3 every 4 weeks</td>
<td>0%</td>
<td>3.4</td>
</tr>
<tr>
<td>Maeda (2012)</td>
<td>Retrospective study</td>
<td>30</td>
<td>gemcitabine-refractory; Stage III/IV</td>
<td>paclitaxel 80 mg/m2 weekly x 3 every 4 weeks</td>
<td>10%</td>
<td>6.7</td>
</tr>
<tr>
<td>nab-paclitaxel</td>
<td></td>
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<tr>
<td>von Hoff (2011)</td>
<td>Phase I/II</td>
<td>67</td>
<td>1st-line; Stage IV</td>
<td>nab-paclitaxel 100, 125, 150 mg/m2 + gemcitabine 1000 mg/m2 weekly x3 every 4 weeks</td>
<td>46%</td>
<td>12.2</td>
</tr>
<tr>
<td>Ko (2012)</td>
<td>Phase I</td>
<td>15</td>
<td>1st-line; Stage IV</td>
<td>nab-paclitaxel 100 mg/m2 (Day 4) + gemcitabine 750 mg/m2 (Day 4) + capecitabine 750 mg/m2 twice daily (Day 1 to 7) every 14 days</td>
<td>14%</td>
<td>7.5</td>
</tr>
<tr>
<td>MPACT (2013)</td>
<td>Phase III</td>
<td>842</td>
<td>1st-line; Stage IV</td>
<td>nab-paclitaxel 125 mg/m2 +gemcitabine 1000 mg/m2 weekly x 3 every 4 weeks</td>
<td>23%</td>
<td>8.5</td>
</tr>
<tr>
<td>Hosein (2012)</td>
<td>Phase II</td>
<td>19</td>
<td>2nd and 3rd lines; Stage III/IV</td>
<td>nab-paclitaxel 100 mg/m2 weekly x 3 every 4 weeks</td>
<td>5%</td>
<td>7.3</td>
</tr>
<tr>
<td>ET-paclitaxel</td>
<td></td>
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<tr>
<td>Lohr (2012)</td>
<td>Phase II randomised</td>
<td>200</td>
<td>1st-line; Stage III/IV</td>
<td>ET-paclitaxel 11, 22, 44 mg/m2 twice-weekly + gemcitabine 1000mg/m vs gemcitabine</td>
<td>14%/ 14%/ 16%/ 14% respectively</td>
<td>4.1/ 4.6/ 4.4/ 2.7 respectively</td>
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<tr>
<td>GPM-paclitaxel</td>
<td></td>
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<tr>
<td>Saif (2010)</td>
<td>Phase II</td>
<td>2010</td>
<td>1st line; Stage III/IV</td>
<td>GPM-paclitaxel 435/300/350 mg/m2 every 3 weeks</td>
<td>7%</td>
<td>6.5</td>
</tr>
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</table>
Table 3. Studies that evaluated docetaxel in combination with gemcitabine and capecitabine in advanced pancreatic cancer patients

<table>
<thead>
<tr>
<th>Clinical Trial (year)</th>
<th>Design</th>
<th># of patients</th>
<th>Line(s) of therapy; Patient population</th>
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<th>Overall Response Rate</th>
<th>median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine (2012)</td>
<td>Phase II</td>
<td>44</td>
<td>1st-line; Stage IV</td>
<td>docetaxel 30 mg/m2 (day 4, 11) + gemcitabine 750 mg/m2 (day 4, 11) + capecitabine 750 mg/m2/day divided into 2 doses (day 1-14) every 21 days</td>
<td>38%</td>
<td>14.5</td>
</tr>
<tr>
<td>Xenidis (2012)</td>
<td>Phase II</td>
<td>40</td>
<td>1st line; Stage III/IV</td>
<td>docetaxel 50 mg/m2 (day 1, 15) + gemcitabine 1,500 mg/m2 (days 1, 15) + capecitabine 2,250 mg/m2 in 2 daily divided doses (day 1-7 and 15-21) every 28 days</td>
<td>40%</td>
<td>9.0</td>
</tr>
<tr>
<td>Reni* (2012)</td>
<td>Phase II, randomized</td>
<td></td>
<td>1st-line; Stage III/IV</td>
<td>docetaxel 25-30 mg/m2 (day 1, 15) + gemcitabine 800 mg/m2 (day 1, 15) + capecitabine 1250 mg/m2/day (day 1 to 28) + cisplatin 30 mg/m2 (day 1, 15) every 28 days</td>
<td>57%</td>
<td>5.8</td>
</tr>
<tr>
<td>De Jesus-Acosta (2012)</td>
<td>Retrospective study</td>
<td>154</td>
<td>1st and 2nd lines; Stage III/IV</td>
<td>docetaxel 30 mg/m2 (day 4, 11) + gemcitabine 750 mg/m2 (day 4, 11) + capecitabine 750 mg/m2/day divided into 2 doses (day 1-14) every 21 days</td>
<td>11%</td>
<td>11.6 (Stage IV)</td>
</tr>
</tbody>
</table>

*Reni et al (2012) included Stage III and IV patients. Data for stage IV patients in the docetaxel containing arm is presented here.
Figure 1: SPARC gp-60 mediated endocytosis. Binding of cationic liposomes to negatively charged tumor endothelium. SPARC-binding in tumor-associated stromal matrix. Gemcitabine accumulation intratumorally through cytidine deaminase inhibition by paclitaxel. Binding of cationic liposomes to negatively charged tumor endothelium.

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