nab-Paclitaxel for the treatment of pancreatic cancer

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Background: Nanoparticle albumin-bound paclitaxel (nab-P) plus gemcitabine (Gem) became a standard treatment option for metastatic pancreatic cancer (MPC) following positive results from a global phase III trial (MPACT). A large number of studies have now published results on the use of nab-P/Gem to treat advanced and early-stage disease, warranting a comprehensive review. The main goal of this systematic review is to summarize the efficacy and safety data of nab-P/Gem for the treatment of pancreatic cancer (PC).

Methods: This systematic review includes results from studies that either published results in a peer-reviewed journal or presented the results at a major oncology conference.

Results: Sixty-two studies were included (50 in the advanced/metastatic setting and 12 in the locally advanced setting). Most studies on the treatment of MPC were exclusively first-line (33/50). Nevertheless, the studies in this review comprised a broad spectrum of patients, including those <65 and ≥65 years of age and those with a Karnofsky performance status of 70–100. Median overall survival (OS) in studies of nab-P/Gem in the advanced/metastatic setting ranged from 8.7 to 13.5 months. In addition, 15 studies of patients with advanced/metastatic PC examined nab-P/Gem as a backbone on which to add a variety of agents, including cancer stem cell inhibitors, stromal disrupting agents, and immune-modulating agents (median OS, 6.9–17 months). Ongoing trials are investigating nab-P/Gem with or without other agents across disease settings.

Discussion: Studies conducted after MPACT have demonstrated that nab-P/Gem is an effective regimen for the first-line treatment of MPC for a wide range of patients. Regimens using nab-P/Gem as a backbone on which to combine additional agents are being studied actively, particularly in the advanced disease setting. Ongoing studies will yield valuable insights on the utility of nab-P-containing regimens to improve patient outcomes in PC in both earlier-stage and advanced disease.

Keywords: pancreatic cancer, nab-paclitaxel, metastatic, neoadjuvant, systematic review

Introduction

More than 50,000 new pancreatic cancer (PC) cases and >40,000 cancer-related mortalities due to PC are expected in the USA in 2016.1,2 The 5-year survival rate for all stages of PC combined is 8%. Although those with resectable disease have a more favorable prognosis (5-year survival =29%), =52% of patients are diagnosed with metastatic disease, which confers a less favorable outlook (5-year survival =3%).3 Since the approval of gemcitabine (Gem) in 1997, no phase III trial in advanced/metastatic disease had demonstrated a clinically and statistically significant improvement in overall survival (OS) over Gem alone4 until recently. The treatment landscape for metastatic
disease has evolved to include 2 key regimens: folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) and nanoparticle albumin-bound paclitaxel (nab-P) plus Gem (nab-P/Gem). The FOLFIRINOX regimen was approved based on a French multicenter phase II/III trial that reported significant improvements in OS with FOLFIRINOX versus Gem (median, 11.1 vs 6.8 months; hazard ratio [HR], 0.57; \( P < 0.001 \)), but significant adverse events were also observed.4 The nab-P/Gem regimen was approved in many countries after the phase III MPACT trial demonstrated that the addition of nab-P (Abraxane®; Celgene Corporation, Summit, NJ, USA) to Gem improved OS versus Gem (median, 8.7 vs 6.6 months; HR, 0.72; \( P < 0.001 \)).5 Currently, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) recommend treatment with FOLFIRINOX or nab-P/Gem as standards of care for patients with metastatic pancreatic cancer (MPC).6,7 Age, performance status (PS), and other clinical factors are considered when deciding which regimen to use; Gem monotherapy is currently reserved for patients ineligible to receive combination chemotherapy.8 nab-P/Gem and FOLFIRINOX have not been approved for earlier-stage disease; however, numerous trials are exploring their utility. The NCCN recommends chemotherapy for unresectable locally advanced PC (LAPC) and chemoradiation for selected patients, preferably after induction chemotherapy for tumor control.6 Currently, no clear evidence exists to support the use of nab-P/Gem over FOLFIRINOX or vice versa, and several trials are investigating their efficacy and safety.8

A population-based study of >3,000 patients showed that nab-P/Gem is the most commonly used chemotherapy regimen for the first-line treatment of MPC in the USA,9 possibly due to the toxicity profile of FOLFIRINOX, which limits its use to younger/fitter patients. The extensive use of nab-P/Gem in both academic and community settings coupled with >100 current and active clinical trials in PC warrants a comprehensive review of clinical data to gain a better understanding of how this regimen is being used for the treatment of PC and associated outcomes. The overall goal of this review is to summarize recent data regarding the safety and efficacy of regimens that include nab-P/Gem for patients with PC.

Methods

The search terms “nab-paclitaxel and (pancreatic or pancreas)” were entered in PubMed to retrieve publications from January 1, 2011 to June 30, 2016. Abstracts from the annual meetings of the American Society of Clinical Oncology (ASCO) 2011–2016, the Gastrointestinal Cancers Symposium (ASCO GI) 2011–2016, the European Cancer Organisation/ESMO 2011–2015, the ESMO World Congress on Gastrointestinal Cancer 2015 and 2016, and the Italian Association of Medical Oncology (2014) were searched using the term “nab-paclitaxel.” Clinical trials and institutional analyses of nab-P in all stages of PC were included. Duplicates, electronic abstracts, case studies, cost studies, meta-analyses, and studies of the effects of eligibility criteria were excluded. The website www.clinicaltrials.gov was searched using the terms “nab-paclitaxel” OR “Abraxane” AND “pancreatic” AND “adenocarcinoma” to identify ongoing trials without results; only open, active, phase II–III trials with a sample size ≥100 were included.

Results

Studies of nab-P in advanced/metastatic PC

Fifty studies evaluating nab-P in MPC were retrieved (Figure 1; Table 1). Approximately one-half were retrospective analyses. MPACT was the only phase III study, and all other prospective trials were phase I or II. Two-thirds of studies evaluated nab-P in the first-line setting, and approximately one-third of those studies assessed nab-P/Gem with an additional agent. nab-P was most often evaluated at a dose of

![Diagram](https://www.dovepress.com/)

**Figure 1** Schematic of method for systematically selecting studies for inclusion in the database.

**Abbreviations:** LAPC, locally advanced pancreatic cancer; nab-P, nanoparticle albumin-bound paclitaxel; PC, pancreatic cancer.
125 mg/m², which was given the first 3 of 4 weeks (qw 3/4). The tables in this systematic review cover MPC (Tables 1–3), neoadjuvant treatment or locally advanced disease (Table 4), and ongoing trials in all settings (Table 5).

**nab-P/Gem in MPC**

Ten studies reported the median OS for first-line nab-P/Gem in patients with advanced PC; 5,10–18 Table 2 lists 8 of these studies with a population ≥45 patients. The most commonly used dose and schedule were those used in the MPACT trial: nab-P 125 mg/m² plus Gem 1,000 mg/m² administered on a qw 3/4 schedule. 5,14,19,20 Patients treated with this dose and schedule experienced a median OS ranging from 8.7 to 13.5 months 5,18 and 1-year survival ranging from 35% to 62%. 5,14,19,20 Most prospective studies evaluating this dose and schedule were single-arm trials.

**nab-P/Gem in MPC – age**

It may be expected that younger patients would experience longer survival and improved tolerability compared with older patients. However, most studies, including MPACT, suggest that older patients benefit from nab-P/Gem in terms of efficacy without increased risk of toxicity. Approximately 40% of patients enrolled in MPACT were ≥65 years. 5 Median OS was 9.6 and 7.7 months for patients <65 and ≥65 years, respectively, and the toxicity profiles were similar between age groups. The combination in MPACT demonstrated significant OS benefit over Gem alone in both age groups: <65 years (HR, 0.65; P<0.001) and ≥65 years (HR, 0.80; P=0.048).

A study (N=37) including patients treated with first-line or ≥ second-line nab-P/Gem for MPC showed that OS was not significantly different between patients ≥66 years and those <66 years of age (median, 10.5 vs 9 months; P=0.49). 21 Similarly, a large Italian database review of patients (N=208) with advanced PC treated with nab-P/Gem demonstrated that age (≥75 vs <75 years) was not significantly associated with efficacy or toxicity with respect to median OS.
(11.4 vs 11 months; \(P=0.86\)), disease control rate (69\% vs 61\%; \(P=0.64\)), grade 3/4 neutropenia (25\% vs 28\%), and neutrotoxicity (9\% vs 12\%).22 Additionally, an exploratory analysis from MPACT showed that the percentages of patients requiring nab-P dose reductions were similar between age groups (42\% for patients \(\geq 65\) years vs 40\% for patients <65 years).23

**nab-P/Gem in MPC – PS**

Data on whether patients with a better PS might receive greater benefit from nab-P/Gem than patients with a poorer PS are inconclusive; however, similar to the literature in older patients, several studies suggest that less fit patients receive meaningful benefit from the regimen. Stratification of the MPACT population by Karnofsky PS (KPS) demonstrated significantly better OS in the fitter (KPS 90–100) versus less fit (KPS 70–80) group in the combination arm (median, 9.7 vs 7.6 months; HR, 0.76; \(P=0.009\)) and the Gem arm (median, 7.9 vs 4.3 months; HR, 0.57; \(P<0.001\)). In the KPS 70–80 subpopulation, nab-P/Gem extended median OS by >3 months compared with Gem alone (7.6 vs 4.3 months; HR, 0.59; \(P<0.001\)).

A small phase I/II trial examined the effect of nab-P/Gem in patients with an Eastern Cooperative Oncology Group (ECOG) PS of 2.24 The results of the phase I portion suggest that these patients were able to receive the standard dose of nab-P/Gem; the relative dose intensity was 100\% in 6 patients who received nab-P 125 mg/m\(^2\) plus Gem 1,000 mg/m\(^2\) qw 3/4.

In a retrospective analysis of 39 patients with unresectable LAPC or MPC treated with nab-P/Gem,25 patients with an ECOG PS of 1 survived longer than patients with an ECOG PS of 2 (median OS, 15 vs 7 months; \(P=0.032\)).25 Similarly, the previously mentioned Italian retrospective analysis of patients with advanced PC (N=208) treated with nab-P/Gem showed a numerically shorter OS in the ECOG PS 2 versus ECOG PS 0–1 group (median, 8.7 vs 11.2 months; \(P=0.07\)), but the difference was not significant.22 In addition, toxicities did not appear to be influenced by PS, because similar percentages of patients with PS 0–1 and PS 2 developed neutropenia (31\% and 34\%, respectively) and neurotoxicity (17\% in each group). Collectively, these studies suggest that, although PS may affect OS, nab-P/Gem seems to be effective regardless of PS.

**nab-P/Gem in MPC – real-world comparative effectiveness studies**

Although clinical trials comparing nab-P/Gem with FOLFIRINOX for the treatment of PC have not yet reported results, retrospective analyses have explored these standard-of-care regimens with one another and/or Gem for the treatment of MPC.11,12,26–29 One study reported a median OS of 10.2 months with nab-P/Gem (n=189) versus 11.2 months with FOLFIRINOX (n=666) and 7 months for Gem combined with other chemotherapies (n=1,567).11 Similar results were reported from another retrospective analysis: median OS of 11.6 months with nab-P/Gem (n=41) versus 13 months with FOLFIRINOX (n=101) and 7.5–9.1 months for Gem plus other chemotherapies (n=277).12 A real-world analysis based on electronic medical records of patients (N=202) receiving first-line treatment for advanced PC demonstrated similar comparative effectiveness for nab-P/Gem versus FOLFIRINOX (database persistence [proxy for OS], median, 8.6 months in both groups), despite patients in the FOLFIRINOX group being significantly younger.27 In addition, a retrospective analysis (N=150) of patients treated at 5 cancer centers in British Columbia, Canada, found that both nab-P/Gem and FOLFIRINOX produced similar outcomes and demonstrated longer OS versus Gem alone as treatment for unresectable PC (median, 11.6 and 11.2 vs 4.1 months, respectively; \(P<0.001\) and \(P=0.039\)).29 Patients who received FOLFIRINOX were younger (median age, 61 vs 70 years) and fitter (ECOG PS1, 91\% vs 54\%) than those who received nab-P/Gem.29 Collectively, the OS with nab-P/Gem observed in MPACT was consistent with the OS observed in real-world observational data sets, and nab-P/Gem was comparable in effectiveness to FOLFIRINOX.

**Subsequent therapies after first-line nab-P/Gem in MPC**

Many recent analyses have examined the use of second-line therapies after nab-P/Gem.27,36–33 Patients in MPACT who received second-line therapy (n=170) after nab-P/Gem experienced a numerically longer median OS than those who did not (n=250; median total OS, 12.8 and 6.3 months, respectively).30 The longest total OS values were observed in patients who received first-line nab-P/Gem followed by fluoropyrimidine-containing second-line regimens (n=132; median, 13.5 months); a small number (n=18) received second-line FOLFIRINOX and experienced a median total OS of 15.7 months.30 Another retrospective analysis from the previously described Italian registry (N=250) demonstrated similar findings, that is, a median OS of 13.5 months in patients who received second-line treatment after first-line nab-P/Gem (n=122).31 More specifically, patients who received second-line FOLFOX/XELOX (n=56), FOLFIRI (n=24), and FOLFIRINOX (n=22) had median total OS values of 12.8, 13.2, and 13.8 months, respectively.31 Consistent
findings have been observed in many other analyses, and the totality of data suggests that first-line nab-P/Gem followed by second-line therapy, particularly with regimens that contain a fluoropyrimidine, is feasible and beneficial to patients with advanced PC.27,30–33

**Future directions**

Future directions for nab-P/Gem include studies in which the regimen has been used as a backbone therapy (ie, with another agent) in MPC (Table 3) and as a doublet in locally advanced pancreatic cancer (Table 4). Table 5 displays a list of selected ongoing trials of nab-P/Gem with or without other agents as treatment for metastatic, locally advanced, and resectable disease.

**Table 3** Studies of nab-P/Gem + another agent for advanced/metastatic pancreatic cancer (no cutoff based on N)

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Type of study</th>
<th>Line of Tx</th>
<th>Agent combined with nab-P/Gem</th>
<th>N</th>
<th>MPC, %</th>
<th>Age, median, years</th>
<th>PS</th>
<th>Median OS (95% CI), months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen, 201656</td>
<td>Ph Ib</td>
<td>1st</td>
<td>Erlotinib&lt;sup&gt;b&lt;/sup&gt;</td>
<td>19</td>
<td>63</td>
<td>63</td>
<td>ECOG 0–1</td>
<td>9.3 (3.3–15.4)</td>
</tr>
<tr>
<td>Ko, 2012&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Ph I</td>
<td>1st</td>
<td>Capecitabine&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15</td>
<td>100</td>
<td>62</td>
<td>ECOG 0–2</td>
<td>7.5 (NR)</td>
</tr>
<tr>
<td>De Jesus-Acosta, 2014&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Ph II</td>
<td>1st</td>
<td>Vismodegib added in cycle 2</td>
<td>59</td>
<td>100</td>
<td>60</td>
<td>ECOG 0–1</td>
<td>10 (7.3–11)</td>
</tr>
<tr>
<td>ALPINE O’Reilly, 2015&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Ph Ib</td>
<td>1st</td>
<td>Tarextumab</td>
<td>40</td>
<td>100</td>
<td>63</td>
<td>ECOG 0–1</td>
<td>11.6</td>
</tr>
<tr>
<td>Hidalgo, 2016&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Ph Ib</td>
<td>1st</td>
<td>Demcizumab</td>
<td>56</td>
<td>70</td>
<td>65</td>
<td>NR</td>
<td>10.1 (6.5–16.2)</td>
</tr>
<tr>
<td>Hingorani, 2016&lt;sup&gt;41–43&lt;/sup&gt;</td>
<td>Ph II</td>
<td>1st</td>
<td>PEGPH20</td>
<td>74</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>12 (high-HA population)</td>
</tr>
<tr>
<td>O’Reilly, 2016&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Ph I</td>
<td>1st</td>
<td>Necuparanib</td>
<td>27</td>
<td>100</td>
<td>63 (mean)</td>
<td>ECOG 0–1</td>
<td>13.1 (4.0–16.6)</td>
</tr>
<tr>
<td>Bhattacharyya, 2015&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Inst.</td>
<td>1st</td>
<td>VT-122CM</td>
<td>20</td>
<td>65</td>
<td>62</td>
<td>Mean ECOG 1.9</td>
<td>17.0</td>
</tr>
<tr>
<td>Mahipal, 2015&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Ph I</td>
<td>1st</td>
<td>Enzalutamide</td>
<td>8</td>
<td>100</td>
<td>64</td>
<td>ECOG 1</td>
<td>NR</td>
</tr>
<tr>
<td>Reni, 2014&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Ph Ib</td>
<td>1st</td>
<td>Capicitabine + cisplatin&lt;sup&gt;d&lt;/sup&gt;</td>
<td>24</td>
<td>NR</td>
<td>63</td>
<td>KPS≤80, 13%</td>
<td>NR</td>
</tr>
<tr>
<td>Sigal, 2013&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Ph II</td>
<td>1st</td>
<td>2-O, 3-O desulfated heparin (ODSH)</td>
<td>10</td>
<td>NR</td>
<td>66</td>
<td>ECOG 0–1</td>
<td>NR</td>
</tr>
<tr>
<td>RAJINE KO, 2016&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Ph II</td>
<td>1st</td>
<td>Apatorsen</td>
<td>66</td>
<td>100</td>
<td>67</td>
<td>ECOG 0–1</td>
<td>5.3 (3.2–7.2)</td>
</tr>
<tr>
<td>El-Rayes, 2016&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Ph Ib</td>
<td>≤2nd</td>
<td>BBI-608</td>
<td>37</td>
<td>100</td>
<td>63</td>
<td>NR</td>
<td>6.9 (P=NS)</td>
</tr>
<tr>
<td>Bahary, 2016&lt;sup&gt;51&lt;/sup&gt;</td>
<td>Ph Ib</td>
<td>1st</td>
<td>Indoximod</td>
<td>15</td>
<td>100</td>
<td>68</td>
<td>KPS=70</td>
<td>NR</td>
</tr>
<tr>
<td>Borad, 2016&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Ph I</td>
<td>1st</td>
<td>Evofosfamide</td>
<td>19</td>
<td>89</td>
<td>62</td>
<td>ECOG 0–1</td>
<td>14.2 (8.5–19.4)</td>
</tr>
</tbody>
</table>

**Notes:** nab-P at 125 mg/m<sup>2</sup> the first 3 of 4 weeks (qw 3/4) unless otherwise indicated. nab-P at 75, 100, or 125 mg/m<sup>2</sup> qw 3/4. *Dose escalation of nab-P from 100 to 150 mg/m<sup>2</sup> on day 4 of a 14-day cycle, “nab-P at 100–150 mg/m<sup>2</sup> on days 1 and 14 every 4 weeks.

**Abbreviations:** CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; Gem, gemcitabine; HA, hyaluronan; Inst, institutional analysis; KPS, Karnofsky performance status; MPC, metastatic pancreatic cancer; NR, not reported; nab-P, nanoparticle albumin-bound paclitaxel; NS, not statistically significant; OS, overall survival; Ph, phase; PS, performance status; Tx, treatment.

**nab-P/Gem as a backbone regimen in MPC (studies with results)**

Because nab-P/Gem has demonstrated survival comparable to that with FOLFIRINOX and a more favorable toxicity profile, this regimen is commonly used as a chemotherapy backbone for other agents (Table 3). Agents combined with nab-P/Gem are diverse and include cancer stem cell inhibitors (demcizumab, vismodegib, tarextumab, and BBI-608), those with potential immune-modulating activities (indoximod), those directed against tumor stroma (PEGPH20 and 2-O, 3-O desulfated heparin), chemotherapies (capicitabine ± cisplatin), hormone therapy (enzalutamide), and others (erlotinib and apatorsen). In 15 studies of patients with MPC treated with nab-P/Gem combined with other agents...
(including 10 phase I trials), the median OS ranged from 6.9 to 17 months.

**nab-P/Gem as a backbone regimen in MPC (studies without results)**

Thirty ongoing phase II and III trials of nab-P in PC with a sample size of ≥100 were identified, including 16 MPC trials (all first line); most included an additional agent (Table 5). For example, the phase II/III RESOLVE trial (N=326) is evaluating nab-P/Gem, with or without the Bruton tyrosine kinase inhibitor ibrutinib, as first-line treatment of MPC. Based on promising results from phase I/II trials (Table 3), a phase III trial (N=420) is investigating PEGPH20 in combination with nab-P/Gem in patients with high levels of hyaluronan, and demecizumab with nab-P/Gem is being evaluated in the phase II YOSEMITE trial (N=201). Another noteworthy ongoing trial is a phase II study (N=260) of nab-P/Gem plus istiratumab (MM-141; a bispecific antibody

### Table 4 Locally advanced and/or earlier-stage pancreatic cancer studies of ≥15 patients that include treatment with nab-P/Gem

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Type of study</th>
<th>Regimen*</th>
<th>N</th>
<th>Stage</th>
<th>Age, median, years</th>
<th>Response data</th>
<th>Resection rate in all patients/in patients who underwent resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sueyoshi, 2015</td>
<td>Ph I</td>
<td>nab-P/Gem + radiation</td>
<td>15</td>
<td>Unresectable LAPC</td>
<td>63</td>
<td>PR=13% SD=67% PD=7%</td>
<td>NA NA</td>
</tr>
<tr>
<td>Dean, 2016</td>
<td>Retro</td>
<td>nab-P/Gem → 5-FU CRT nab-P/Gem</td>
<td>42</td>
<td>Unresectable LAPC</td>
<td>66</td>
<td>pCR=33%</td>
<td>7%/38% 12%/63%</td>
</tr>
<tr>
<td>Idrees, 2016</td>
<td>Retro</td>
<td>nab-P/Gem</td>
<td>26</td>
<td>BL resectable (77%) and LAPC (23%)</td>
<td>NR</td>
<td>pCR=15%</td>
<td>NR/86% (not given for each group)</td>
</tr>
<tr>
<td>Peterson, 2016</td>
<td>Retro</td>
<td>nab-P/Gem</td>
<td>20</td>
<td>BL resectable (70%) and unresectable (30%); patients ineligible for FOLFIRINOX</td>
<td>69</td>
<td>PR=20%</td>
<td>20%/67% NA</td>
</tr>
<tr>
<td>NEOPAX, Van Laethem, 2016</td>
<td>Ph 0</td>
<td>nab-P/Gem</td>
<td>23</td>
<td>Unresectable and borderline resectable</td>
<td>63</td>
<td>PR=35% pCR=0</td>
<td>30%/NR 26%/NR</td>
</tr>
<tr>
<td>GAIN-I; Sliesoraitis, 2014</td>
<td>Ph II</td>
<td>nab-P/Gem</td>
<td>10</td>
<td>Resectable/borderline resectable</td>
<td>68</td>
<td>60%/75%</td>
<td>20%/25%</td>
</tr>
<tr>
<td>Alvarez, 2013</td>
<td>NR</td>
<td>nab-P/Gem</td>
<td>16</td>
<td>Resectable, 44%; borderline resectable, 56%</td>
<td>58</td>
<td>PR by PET, 50%; no objective responses; I complete pathological response, 6 GRT 1, l GRT 2, 2 GRT 3</td>
<td>69%/92% 6%/8%</td>
</tr>
<tr>
<td>GAP; Barbour, 2015</td>
<td>Ph II</td>
<td>nab-P/Gem</td>
<td>41</td>
<td>Resectable</td>
<td>65</td>
<td>Pancreatic resection rate, 73%</td>
<td>37%/52% 0-mm margin: 34%/48%</td>
</tr>
<tr>
<td>MacKenzie, 2013</td>
<td>Ph II</td>
<td>nab-P/Gem</td>
<td>25</td>
<td>Resectable</td>
<td>65</td>
<td>RECIST</td>
<td>80%/95%</td>
</tr>
</tbody>
</table>

**Notes:** *nab-P at 125 mg/m² the first 3 of 4 weeks (qw 3/4) unless otherwise indicated. *nab-P at 50–125 mg/m² qw 3/4. *Dose and schedule of nab-P not reported. *nab-P at 100 mg/m² qw 3/4.

**Abbreviations:** S-FU, 5-fluorouracil; BL, baseline; CRT, chemoradiation therapy; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; Gem, gemcitabine; GRT, grade of residual tumor; LAPC, locally advanced pancreatic cancer; NA, not applicable; NR, not reported; nab-P, nanoparticle albumin-bound paclitaxel; pCR, pathological complete response; PET, positron emission tomography; Ph, phase; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; Retro, retrospective; SD, stable disease.
against ErbB3 and insulin-like growth factor-1 [IGF-1] receptor) for the first-line treatment of patients with MPC and high serum levels of free IGF-1. Finally, whether the combination of nab-P/Gem with checkpoint inhibitors will be an effective strategy for PC is an important question, because checkpoint inhibitors have recently provided breakthrough treatment options for several tumor types and are currently being explored in a number of PC trials. Data on such combinations (eg, nab-P/Gem and nivolumab) are preliminary at this point.

Neoadjuvant trials for patients with resectable, borderline resectable, or LAPC (studies with results)

Several recent studies (n=12) examined neoadjuvant nab-P/Gem as a strategy for improving R0 resection rates in resectable tumors or converting borderline resectable tumors to resectable tumors. One of the main pathologic predictors of survival after surgery is resection margin status; a negative resection margin (R0) is associated with better prognosis compared with a positive margin. Eight of the 12 studies had a total enrollment of ≥15 patients (Table 4). Noteworthy among these is a pilot phase II study in which patients with resectable PC (N=25) were treated with neoadjuvant nab-P/Gem for 3 cycles. Surgical resection was possible in 84% of patients and resulted in R0 resection in 95% of resected cases, or 80% of the intention-to-treat population. The phase II GAP study also evaluated neoadjuvant nab-P/Gem for 2 cycles in patients with resectable PC (N=41). After neoadjuvant treatment, 73% of the patients underwent pancreatic resection. Similar results were reported from another trial of neoadjuvant nab-P/Gem (administered for 2 cycles) in patients with resectable or borderline resectable tumors (N=16). Seventy-five percent of patients underwent surgery, and R0 resection was achieved in 69% of the intention-to-treat population – 92% of those who underwent surgery.

**Table 5** Selected ongoing phase II/III trials (N≥100) of nab-P/Gem ± other agents in pancreatic adenocarcinoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Planned N</th>
<th>Patient population or stage of disease</th>
<th>Regimen</th>
<th>Planned primary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOLINPAC, NCT0210688473</td>
<td>II</td>
<td>110</td>
<td>Unresectable LAPC or metastatic</td>
<td>First-line nab-P/Gem vs Gem</td>
<td>Deterioration-free QOL using EORTC QLQ-C30 OS</td>
</tr>
<tr>
<td>ALPACA, NCT0256414674</td>
<td>II</td>
<td>325</td>
<td>Metastatic</td>
<td>First-line: induction with nab-P/Gem → nab-P/Gem or alternating Gem monotherapy and nab-P/Gem</td>
<td></td>
</tr>
<tr>
<td>nab-P/Gem + other</td>
<td>III</td>
<td>430</td>
<td>Metastatic</td>
<td>First-line nab-P/Gem + momelotinib vs nab-P/Gem</td>
<td>DLT, OS</td>
</tr>
<tr>
<td>NCT0271580476</td>
<td>III</td>
<td>420</td>
<td>Metastatic</td>
<td>First-line nab-P/Gem + PEGPH20 vs nab-P/Gem + placebo</td>
<td>PFS, OS</td>
</tr>
<tr>
<td>RESOLVE, NCT0243666846</td>
<td>II/III</td>
<td>326</td>
<td>Metastatic</td>
<td>First-line nab-P/Gem + ibrutinib vs nab-P/Gem + placebo</td>
<td>PFS</td>
</tr>
<tr>
<td>CARRIE, NCT0239913746</td>
<td>II</td>
<td>260</td>
<td>Metastatic</td>
<td>First-line nab-P/Gem + MM-141 vs nab-P/Gem + placebo</td>
<td>PFS</td>
</tr>
<tr>
<td>YOSEMITE, NCT0228989845</td>
<td>II</td>
<td>201</td>
<td>Metastatic</td>
<td>First-line nab-P/Gem + placebo vs nab-P/Gem + demcizumab + placebo (truncated course of demcizumab) vs nab-P/Gem + demcizumab</td>
<td>PFS</td>
</tr>
<tr>
<td>NCT0255199177</td>
<td>II</td>
<td>168</td>
<td>Metastatic</td>
<td>First-line nab-P/Gem vs nal-IRI + S-FU + folic acid vs nal-IRI + S-FU + folic acid + oxaliplatin</td>
<td>PFS</td>
</tr>
<tr>
<td>FIRGEMAX, NCT02827220178</td>
<td>II</td>
<td>124</td>
<td>Metastatic</td>
<td>First-line nab-P/Gem alternating with FOLFIRI.3 vs nab-P/Gem</td>
<td>PFS at 6 months</td>
</tr>
</tbody>
</table>

(Continued)
### Table 5 (Continued)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Planned N</th>
<th>Patient population or stage of disease</th>
<th>Regimen</th>
<th>Planned primary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEQUENCE, NCT0250433379</td>
<td>I/II</td>
<td>180</td>
<td>Metastatic</td>
<td>First-line nab-P/Gem → recommended dose of modified FOLFOX from phase I</td>
<td>Phase I: safety, DLT Phase II: OS at 12 months</td>
</tr>
<tr>
<td>PACT-19, NCT0173022280</td>
<td>I/II</td>
<td>134</td>
<td>Advanced</td>
<td>Phase II: first-line nab-P RP2D + Gem 800 mg/m² + cisplatin 30 mg/m² + cape 1,250 mg/m² q2w every 4 weeks vs nab-P 125 mg/m² + Gem 1,000 mg/m² qw 3/4</td>
<td>Phase I: DLT Phase II: PFS for stage IV, resectability rate for stage III</td>
</tr>
<tr>
<td>NabucCO, NCT0210934180</td>
<td>I/II</td>
<td>114</td>
<td>Metastatic</td>
<td>First-line nab-P + FOLFIRI or nab-P + FOLFOX</td>
<td>MTD, DLTs, ORR</td>
</tr>
<tr>
<td>NACT0219482942</td>
<td>I/II</td>
<td>133</td>
<td>Advanced</td>
<td>First-line nab-P/Gem ± MK-1775</td>
<td>Phase I: MTD Phase II: PFS</td>
</tr>
<tr>
<td>Resectable or locally advanced nab-P/Gem only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LAPACT, NCT023011434</td>
<td>II</td>
<td>110</td>
<td>Untreated LAPC</td>
<td>nab-P/Gem</td>
<td>Time to treatment failure</td>
</tr>
<tr>
<td>APACT, NCT0196443045</td>
<td>III</td>
<td>800</td>
<td>Resected</td>
<td>Adjuvant nab-P/Gem vs Gem</td>
<td>DFS</td>
</tr>
<tr>
<td>NEONAX, NCT020475134</td>
<td>II</td>
<td>166</td>
<td>Resectable</td>
<td>Neoadjuvant and adjuvant vs only adjuvant nab-P/Gem</td>
<td>Time to DFS</td>
</tr>
<tr>
<td>S1505, NCT0256271644</td>
<td>II</td>
<td>112</td>
<td>Resectable</td>
<td>Neoadjuvant nab-P/Gem vs mFOLFIRINOX</td>
<td>OS</td>
</tr>
<tr>
<td>NCT0250684248</td>
<td>III</td>
<td>300</td>
<td>Resected</td>
<td>Second-line adjuvant nab-P 100 mg/m² + Gem 1,000 mg/m² + oxaliplatin + folic acid + 5-FU</td>
<td>OS</td>
</tr>
<tr>
<td>NCT0224300742</td>
<td>II</td>
<td>112</td>
<td>Resectable</td>
<td>Neoadjuvant FOLFIRINOX vs nab-P/Gem</td>
<td>OS at 18 months</td>
</tr>
<tr>
<td>nab-P/Gem + other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEOLAP, NCT0212513644</td>
<td>II</td>
<td>168</td>
<td>Untreated or border resectable LAPC</td>
<td>Neoadjuvant nab-P/Gem vs nab-P/Gem followed by FOLFIRINOX</td>
<td>Conversion rate to resection</td>
</tr>
<tr>
<td>“Personalized Medicine,” NCT0172658241</td>
<td>II</td>
<td>120</td>
<td>Resectable and borderline resectable</td>
<td>nab-P/Gem ± subsequent CRT with Gem or cape as neoadjuvant or adjuvant therapy or other chemotherapies in similar settings vs CRT with Gem or cape in similar settings</td>
<td>Recsectability rate</td>
</tr>
<tr>
<td>SCALOP-2, NCT0202400943</td>
<td>I/II</td>
<td>289</td>
<td>LAPC</td>
<td>Induction nab-P/Gem → nab-P/Gem + RT → cap + RT ± nelfinavir vs 6 cycles of nab-P/Gem</td>
<td>OS, PFS</td>
</tr>
</tbody>
</table>

**Abbreviations:** 5-FU, 5-fluorouracil; cape, capecitabine; CRT, chemoradiation therapy; DFS, disease-free survival; DLT, dose-limiting toxicity; EORTC, European Organisation for Research and Treatment of Cancer; FOLFIRI, folinic acid, 5-fluorouracil, and irinotecan; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; Gem, gemcitabine; LAPC, locally advanced pancreatic cancer; MTD, maximum tolerated dose; nal-IRI, nanoliposomal irinotecan; nab-P, nanoparticle albumin-bound paclitaxel; OS, overall survival; PFS, progression-free survival; QOL, quality of life; qw 3/4, first 3 of 4 weeks; RP2D, recommended phase II dose; RT, radiotherapy.

### Neoadjuvant trials for patients with resectable, borderline resectable, or LAPC (studies without results)

The phase II NEOLAP trial (N=168) will examine the ability of neoadjuvant nab-P/Gem versus FOLFIRINOX to convert unresectable LAPC or borderline resectable tumors to resectable tumors (Table 5). Additional phase II study (N=112) is comparing neoadjuvant nab-P/Gem versus FOLFIRINOX followed by resection in patients with potentially resectable tumors. The randomized phase II LAPACT study (N=110) is investigating time to treatment failure in patients with unresectable LAPC treated with nab-P/Gem.43,44
Ongoing adjuvant trials for patients with resectable PC
The ongoing phase III APACT study is evaluating nab-P/Gem versus Gem monotherapy as adjuvant treatment in patients who have undergone macroscopic complete resection for non-MPC (Table 5). Two other studies are also examining nab-P/Gem as adjuvant therapy: the phase II NEONAX study (N=166; nab-P/Gem as adjuvant only vs as neoadjuvant plus adjuvant) and a second-line adjuvant phase III trial in patients who experienced disease relapse during Gem-based adjuvant therapy (N=300).

Discussion
Multiple studies have demonstrated that first-line treatment with nab-P/Gem improves survival in patients with MPC, with OS similar to or better than that observed in MPACT. These studies have helped to confirm the dose and schedule of nab-P 125 mg/m² plus Gem 1,000 mg/m² qw3/4 as an effective and tolerable option for patients with MPC. Retrospective analyses of comparisons between nab-P/Gem and FOLFIRINOX suggested similar efficacy outcomes between the regimens, despite differences in patient populations; nab-P/Gem was used in a broader spectrum of patients.

Most studies demonstrated an OS benefit with nab-P/Gem regardless of age group; similarly, patients seem to derive substantial clinical benefit from nab-P/Gem regardless of PS. The demonstrated efficacy of first-line nab-P/Gem has led to a number of studies examining regimens afterward as second-line therapy. These studies showed that second-line treatment after nab-P/Gem is feasible and that fluoropyrimidine-containing regimens, and not exclusively FOLFIRINOX, are appropriate options in this setting.

There are currently >100 ongoing trials (combined target enrollment >9,500 patients) assessing different nab-P regimens for the treatment of PC, and these studies will provide critical information regarding optimal combinations for specific patient populations.

Conclusion
In summary, nab-P/Gem is an effective and well-tolerated regimen for patients with PC. Ongoing trials will evaluate nab-P in all stages of PC. The combination of nab-P/Gem has become a standard of care for MPC and a backbone onto which novel therapies are added in ongoing trials. Future directions in this field will revolve around improving our understanding of PC, including its molecular biology, and identifying subsets of patients that may benefit from specific treatments.

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