

# Albumin-bound paclitaxel in solid tumors: clinical development and future directions

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**Abstract:** Albumin-bound paclitaxel (*nab*-paclitaxel) is a solvent-free formulation of paclitaxel that was initially developed more than a decade ago to overcome toxicities associated with the solvents used in the formulation of standard paclitaxel and to potentially improve efficacy. *Nab*-paclitaxel has demonstrated an advantage over solvent-based paclitaxel by being able to deliver a higher dose of paclitaxel to tumors and decrease the incidence of serious toxicities, including severe allergic reactions. To date, *nab*-paclitaxel has been indicated for the treatment of three solid tumors in the USA. It was first approved for the treatment of metastatic breast cancer in 2005, followed by locally advanced or metastatic non-small-cell lung cancer in 2012, and most recently for metastatic pancreatic cancer in 2013. *Nab*-paclitaxel is also under investigation for the treatment of a number of other solid tumors. This review highlights key clinical efficacy and safety outcomes of *nab*-paclitaxel in the solid tumors for which it is currently indicated, discusses ongoing trials that may provide new data for the expansion of *nab*-paclitaxel's indications into other solid tumors, and provides a clinical perspective on the use of *nab*-paclitaxel in practice.

**Keywords:** *nab*-paclitaxel, breast, lung, pancreas, ovarian, melanoma

## *Nab*-paclitaxel development

Paclitaxel is widely used for the treatment of solid tumors;<sup>1-3</sup> however, the solvent used in the commercial formulation of solvent-based (sb)-paclitaxel, polyoxyethylated castor oil (Kolliphor<sup>®</sup> EL, formerly known as Cremophor EL; BASF SE, Ludwigshafen, Germany), is associated with severe, sometimes fatal hypersensitivity reactions.<sup>4-6</sup> To reduce the risk of hypersensitivity reactions with sb-paclitaxel, patients are routinely pretreated with corticosteroids and antihistamines.<sup>1,2</sup> Furthermore, some studies have shown that Kolliphor EL can entrap paclitaxel in solvent micelles, making the drug less available to enter tumors, thereby limiting its clinical efficacy.<sup>6-8</sup>

*Nab*-paclitaxel is a solvent-free albumin-bound form of paclitaxel.<sup>2,3,9</sup> Compared with sb-paclitaxel, *nab*-paclitaxel has several advantages, including the ability to deliver significantly higher doses of paclitaxel over a shorter infusion time (30 minutes vs 3 hours for sb-paclitaxel) and the elimination of the need for pre-medications to prevent hypersensitivity reactions. Other advantages of *nab*-paclitaxel over sb-paclitaxel include enhanced transport of paclitaxel across endothelial cells and greater delivery of paclitaxel to tumors.<sup>9</sup> Because *nab*-paclitaxel is formulated with albumin, it is postulated that the drug uses endogenous albumin transport pathways, including receptor-mediated transcytosis, to cross endothelial cell monolayers and enter tumors.<sup>9,10</sup> In a preclinical study, fourfold more *nab*-paclitaxel was transported across endothelial cells than sb-paclitaxel.<sup>9</sup> Moreover, it was found that Kolliphor EL inhibited the binding of paclitaxel to albumin and endothelial cells, potentially limiting intratumoral

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uptake of paclitaxel.<sup>9</sup> Albumin, or albumin-bound molecules such as *nab*-paclitaxel, may also find a way into the tumor microenvironment via the enhanced permeation and retention effect, which proposes that molecules are able to escape the circulation through gaps between endothelial cells resulting from leaky vasculature around tumors.<sup>11</sup> A comprehensive review of *nab*-paclitaxel's mechanism of action and delivery system has recently been published.<sup>12</sup>

Recent studies on the population pharmacokinetics (PK) and pharmacodynamics (PD) of *nab*-paclitaxel demonstrated that pharmacologic features of *nab*-paclitaxel appear to be distinct from those of *sb*-paclitaxel.<sup>13,14</sup> These distinct features likely contribute to the differences in clinical safety and efficacy between the two paclitaxel formulations.<sup>13</sup> Specifically, compared with *sb*-paclitaxel, *nab*-paclitaxel was associated with faster and deeper tissue penetration and slower elimination of paclitaxel. Tissue distribution of paclitaxel was found to be dependent on the drug carrier complex.<sup>14</sup> These results confirm preclinical findings that more paclitaxel may be able to enter the tumor when delivered as *nab*-paclitaxel<sup>9</sup> – and with more rapid distribution to tissues, the duration of high systemic exposure is shorter. This may, in turn, explain the observation of the lower frequency of some severe adverse events, such as neutropenia, with *nab*-paclitaxel than with *sb*-paclitaxel, despite that *nab*-paclitaxel demonstrates a higher paclitaxel dose intensity (26%–49% higher) than *sb*-paclitaxel.<sup>15–17</sup> Furthermore, in the population PK/PD study, a threshold plasma concentration for *nab*-paclitaxel was defined at 0.84 mM, such that the duration of time spent above this concentration predicted the probability of neutropenia.<sup>13</sup> Compared with that previously reported for *sb*-paclitaxel (0.05 mM), the threshold plasma paclitaxel concentration was nearly 17-fold higher for *nab*-paclitaxel.<sup>13</sup> Consistent with these findings, in trials to establish the maximum tolerated dose (MTD) of *nab*-paclitaxel, it was found that the albumin-bound formulation of paclitaxel allowed for a higher dose delivery of paclitaxel compared with *sb*-paclitaxel. The MTD of *nab*-paclitaxel was 71% to 88% higher than that reported for *sb*-paclitaxel for both the every-3-weeks (q3w) regimen (300 vs 175 mg/m<sup>2</sup>) and the weekly regimen (150 vs 80 mg/m<sup>2</sup>) in patients with advanced or metastatic solid tumors.<sup>18–20</sup> Dose-limiting toxicities in these trials included neutropenia, peripheral neuropathy, stomatitis, and superficial keratopathy.<sup>18–20</sup> With respect to peripheral neuropathy, a common taxane-associated side effect, the incidence of peripheral neuropathy with *nab*-paclitaxel compared to with *sb*-paclitaxel has varied across trials.<sup>15,16</sup> Differences in patient populations, dosing schedules, and adverse-event

management strategies may have played a role in the varying incidence rates. Nevertheless, the ability to deliver a higher dose of paclitaxel and the enhanced tissue distribution and tumor uptake of *nab*-paclitaxel versus *sb*-paclitaxel likely contribute to the more favorable efficacy and safety profile of the albumin-bound formulation of paclitaxel.

## ***Nab*-paclitaxel in breast cancer, non-small-cell lung cancer (NSCLC), and pancreatic cancer**

### **Breast cancer**

A Phase I dose-escalation trial of 19 patients with advanced solid tumors established the MTD of *nab*-paclitaxel at 300 mg/m<sup>2</sup> given q3w.<sup>18</sup> Dose-limiting toxicities included peripheral neuropathy, stomatitis, and superficial keratopathy, which occurred at a dose of 375 mg/m<sup>2</sup>. There were no reported hypersensitivity reactions despite the absence of steroid premedication and a short infusion time (30 minutes). The MTD and schedule were subsequently evaluated in a Phase II trial for the first- or ≥ second-line treatment of patients with metastatic breast cancer (MBC). The trial reported an overall response rate (ORR) of 48% for the intent-to-treat population of patients, with a 64% ORR in chemotherapy-naïve patients.<sup>21</sup> Time to tumor progression was 6.1 months and median overall survival (OS) was 14.6 months. These results supported the study of *nab*-paclitaxel vs *sb*-paclitaxel in a Phase III trial of patients with MBC.<sup>15</sup> In this study, the dose of *nab*-paclitaxel was reduced to 260 mg/m<sup>2</sup> q3w to lower the risk for severe toxicities, but the dose intensity was still 49% higher than that of *sb*-paclitaxel, which was dosed at 175 mg/m<sup>2</sup> q3w.<sup>15</sup> *Nab*-paclitaxel demonstrated a significantly higher ORR (33% vs 19%;  $P=0.001$ ; primary endpoint) and significantly longer time to tumor progression (5.3 vs 3.9 months;  $P=0.006$ ) compared with *sb*-paclitaxel (Table 1). OS was not significantly different between the two paclitaxel treatments for the overall population (14.9 vs 12.8 months;  $P=0.374$ ), but patients who received *nab*-paclitaxel as second-line or greater did have a significantly longer OS than those who received *sb*-paclitaxel (13.0 vs 10.7 months; hazard ratio [HR] 0.73;  $P=0.024$ ). Grade 4 neutropenia was more common with *sb*-paclitaxel than with *nab*-paclitaxel (22% vs 9%), but the incidence of grade 3 sensory neuropathy was higher with *nab*-paclitaxel than with *sb*-paclitaxel (10% vs 2%) (Table 1). Sensory neuropathy was managed with dose interruptions or reductions and improved to grade 2 or less in a median of 22 days.

Based on these positive results, *nab*-paclitaxel received its first US Food and Drug Administration (FDA) approval

**Table 1** Phase III registration trials of albumin-bound paclitaxel (*nab*-P) in breast, non-small-cell lung, and pancreatic cancers

| Phase III trial   | Patient population           | Regimen  | Efficacy      |                    |                 | Select grade $\geq 3$ AEs, % |                           |
|---|------------------------------|--|---------------|--------------------|-----------------|------------------------------|---------------------------|
|   |                              |  | ORR, %        | Median PFS, mo     | Median OS, mo   | Neutropenia                  | Neuropathy                |
| <b>Breast cancer</b><br>Gradishar et al <sup>15</sup>             | First-line (n=97)            | <i>Nab</i> -P 260 mg/m <sup>2</sup> 30-minute infusion q3w   | 33            | TTP 5.3            | 14.9            | 30                           | 10 <sup>a</sup>           |
|   | Second-line or later (n=132) | <i>sb</i> -P 175 mg/m <sup>2</sup> 3-hour infusion q3w   | 19<br>P=0.001 | TTP 3.9<br>P=0.006 | 12.8<br>P=0.374 | 45<br>P<0.05                 | 2 <sup>a</sup><br>P<0.001 |
| <b>Non-small-cell lung cancer</b><br>Socinski et al <sup>16</sup> | First-line (n=521)           | <i>Nab</i> -P 100 mg/m <sup>2</sup> 30-minute infusion on days 1, 8, and 15 followed by carbo AUC 6 mg/mL/min on day 1 q3w               | 33            | 6.3                | 12.1            | 47                           | 3 <sup>a</sup>            |
|   | First-line (n=531)           | <i>sb</i> -P 200 mg/m <sup>2</sup> 3-hour infusion + carbo AUC 6 mg/mL/min, both given q3w   | 25<br>P=0.005 | 5.8<br>P=0.214     | 11.2<br>P=0.271 | 58<br>P<0.001                | 12<br>P<0.001             |
| <b>Pancreatic cancer</b><br>Von Hoff et al <sup>35</sup>          | First-line (n=431)           | <i>Nab</i> -P 125 mg/m <sup>2</sup> 30- to 40-minute infusion followed by gem 1,000 mg/m <sup>2</sup> on days 1, 8, and 15 every 4 weeks | 23            | 5.5                | 8.5             | 38                           | 17                        |
|   | First-line (n=430)           | Gem 1,000 mg/m <sup>2</sup> weekly for 7 of 8 weeks (cycle 1) and then on days 1, 8, and 15 every 4 weeks                                | 7<br>P<0.001  | 3.7<br>P<0.001     | 6.7<br>P<0.001  | 27                           | 1                         |

Note: <sup>a</sup>Grade 3 only.

Abbreviations: AEs, adverse events; AUC, area under the concentration–time curve; carbo, carboplatin; gem, gemcitabine; mo, month; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q3w, every 3 weeks; *sb*-P, *sb*-paclitaxel; TTP, time to progression.

in 2005 for the treatment of MBC. *Nab*-paclitaxel is indicated for patients with breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.<sup>3</sup> Prior therapy should have included an anthracycline unless clinically contraindicated.

## NSCLC

A Phase II dose-finding study found that 100 mg/m<sup>2</sup> weekly *nab*-paclitaxel combined with q3w carboplatin area under the concentration–time curve (AUC) 6 provided the best clinical benefit–risk ratio compared with several other doses/schedules of *nab*-paclitaxel plus carboplatin in patients with advanced NSCLC.<sup>22</sup> This dose/schedule showed comparable efficacy to the other dosing cohorts and had the least severe adverse events. These results led to a larger Phase III trial of more than 1,000 patients with advanced NSCLC in which the mentioned dose/schedule of *nab*-paclitaxel plus carboplatin was compared with 200 mg/m<sup>2</sup> *sb*-paclitaxel plus carboplatin AUC 6 q3w.<sup>16</sup> The study met its primary endpoint with improvement in ORR for *nab*-paclitaxel plus carboplatin versus *sb*-paclitaxel plus carboplatin (33% vs 25%;  $P=0.005$ ; Table 1). However, there was no statistically significant difference in median progression-free survival (PFS) (6.3 vs 5.8 months) or median OS (12.1 vs 11.2 months) for *nab*-paclitaxel plus carboplatin versus *sb*-paclitaxel plus carboplatin (Table 1). A subset analysis of the Phase III trial based on predefined stratification factors revealed that patients with squamous histology treated with *nab*-paclitaxel plus carboplatin had a significantly higher ORR compared with those who received *sb*-paclitaxel plus carboplatin (41% vs 24%;  $P<0.001$ ). In addition, the median OS was significantly longer in patients  $\geq 70$  years of age who were treated with *nab*-paclitaxel plus carboplatin compared with *sb*-paclitaxel plus carboplatin (19.9 vs 10.4 months;  $P=0.009$ ). In the overall treated population, grade  $\geq 3$  neutropenia (47% vs 58%) and sensory neuropathy (3% vs 12%) occurred significantly less frequently with *nab*-paclitaxel plus carboplatin ( $P<0.001$ ; Table 1), while grade  $\geq 3$  thrombocytopenia (18% vs 9%) and anemia (27% vs 7%) were more common with *nab*-paclitaxel plus carboplatin than with *sb*-paclitaxel plus carboplatin ( $P<0.001$ ). The safety profiles were similar, regardless of patient age or histology.<sup>23,24</sup> Based on the findings of this Phase III trial, the FDA-approved *nab*-paclitaxel in combination with carboplatin for the first-line treatment of patients with locally advanced or metastatic NSCLC who are not candidates for curative surgery or radiation.<sup>3</sup>

## Pancreatic cancer

Gemcitabine monotherapy is one of the most widely used agents in the treatment of metastatic pancreatic cancer, based on a seminal study by Burris et al that demonstrated a median survival of  $\approx 6$  months.<sup>25</sup> A decade later and after numerous failed clinical trials, erlotinib in combination with gemcitabine was FDA approved for the treatment of locally advanced, unresectable, or metastatic pancreatic cancer,<sup>26</sup> partly based on a statistically significant 0.3-month survival advantage for erlotinib plus gemcitabine vs gemcitabine alone.<sup>27</sup> However, in routine clinical practice, this combination is very selectively used in a small subset of patients. Several other Phase III trials of gemcitabine doublets failed to demonstrate a significant survival advantage over gemcitabine alone.<sup>25,27–32</sup>

*Nab*-paclitaxel was selected as a combination partner for gemcitabine because it has been shown to synergize with gemcitabine and was associated with increased intratumoral delivery of gemcitabine and stromal depletion.<sup>33</sup> In a Phase I/II trial, the MTD of *nab*-paclitaxel in combination with 1,000 mg/m<sup>2</sup> gemcitabine was established at 125 mg/m<sup>2</sup>; both agents were given weekly for the first 3 of 4 weeks (qw 3/4) in patients with advanced pancreatic cancer.<sup>33,34</sup> For patients treated at the MTD (n=44), the ORR was 48% and median OS was 12.2 months. This led to a large multinational Phase III trial of more than 850 patients in who 125 mg/m<sup>2</sup> *nab*-paclitaxel plus 1,000 mg/m<sup>2</sup> gemcitabine qw 3/4 was compared with 1,000 mg/m<sup>2</sup> gemcitabine alone (given weekly for 7 of 8 weeks during cycle 1 and then qw 3/4 for cycle 2 and beyond) (Table 1).<sup>35</sup> Median OS (primary endpoint) was significantly longer with *nab*-paclitaxel plus gemcitabine versus gemcitabine alone (8.5 vs 6.7 months;  $P < 0.001$ ). The treatment benefit of *nab*-paclitaxel plus gemcitabine over gemcitabine alone was consistent across most prespecified subgroups, including those patients with more advanced disease (eg, poorer performance status, liver metastasis,  $\geq 3$  sites of metastatic disease, and carbohydrate antigen 19-9 levels  $59\times$  the upper limit of normal).<sup>35</sup> Grade  $\geq 3$  neutropenia (38% vs 27%), fatigue (17% vs 7%), and neuropathy (17% vs 1%) were higher with *nab*-paclitaxel plus gemcitabine versus gemcitabine alone; no patients experienced grade 4 neuropathy in either arm. As observed in other trials,<sup>15,16,36</sup> the grade 3 neuropathy associated with *nab*-paclitaxel resolved for a majority of patients and improved to grade 1 or lower in a median of 29 days.

*Nab*-paclitaxel plus gemcitabine was the first gemcitabine doublet to demonstrate a clinically meaningful benefit over gemcitabine alone in a Phase III trial of advanced/metastatic

pancreatic cancer.<sup>25,27–32</sup> In 2013, *nab*-paclitaxel plus gemcitabine became an FDA-approved regimen for the first-line treatment of patients with metastatic pancreatic cancer.<sup>3</sup>

Based on the hypothesis of secreted protein acidic and rich in cysteine (SPARC), an albumin-binding protein, playing a role in the delivery of *nab*-paclitaxel to tumors, analyses have been performed to examine the relationship between SPARC expression and outcome in patients treated with *nab*-paclitaxel plus gemcitabine. In the Phase I/II trial, high versus low stromal SPARC expression was associated with longer OS in the *nab*-paclitaxel plus gemcitabine arm (17.8 vs 8.1 months;  $P = 0.0431$ ), suggesting that SPARC may be a biomarker for pancreatic cancer that facilitates accumulation of *nab*-paclitaxel into tumors.<sup>33</sup> An analysis of SPARC status in the Phase III Metastatic Pancreatic Adenocarcinoma Clinical Trial found that stromal, tumor, and plasma SPARC were not prognostic for survival or predictive of survival in either treatment arm.<sup>37</sup>

## Clinical perspectives and future directions

### Breast cancer

Since its approval in 2005, *nab*-paclitaxel has been studied in a variety of breast cancer patient populations and with varying doses and schedules.<sup>36,38</sup> It has demonstrated efficacy in patients with poor prognostic factors and aggressive disease features,<sup>39</sup> including those with triple-negative breast cancer (TNBC).<sup>40,41</sup> Although the approved dose of *nab*-paclitaxel for the treatment of MBC is 260 mg/m<sup>2</sup> q3w, determining the optimal dose and schedule when it is used as a single agent or in combination with other agents is an ongoing effort and a source of widely varying trial outcomes. In a preliminary analysis of the Cancer and Leukemia Group B (CALGB 40502) Phase III trial, which evaluated three combination regimens for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-negative MBC (*nab*-paclitaxel 150 mg/m<sup>2</sup> qw 3/4 plus bevacizumab 10 mg/kg every 2 weeks [q2w] or *sb*-paclitaxel 90 mg/m<sup>2</sup> qw 3/4 plus bevacizumab 10 mg/kg q2w or ixabepilone 16 mg/kg qw 3/4 plus bevacizumab 10 mg/kg q2w), similar PFS (primary endpoint) was found for the *nab*-paclitaxel and *sb*-paclitaxel arms (9.2 vs 10.6 months; HR 1.19; 95% confidence interval, 0.96–1.49;  $P = 0.12$ ).<sup>42</sup> However, high rates of hematologic and non-hematologic toxicity, including peripheral neuropathy, in the *nab*-paclitaxel plus bevacizumab arm suggest that the 150 mg/m<sup>2</sup> weekly schedule of *nab*-paclitaxel in combination with bevacizumab may not have been optimal. Early discontinuations and dose reductions due to these toxicities in the

*nab*-paclitaxel arm may have led to insufficient dose intensity and duration of therapy. With bevacizumab's approval being revoked by the FDA in MBC, the more pertinent clinical question is whether weekly *nab*-paclitaxel is superior to weekly paclitaxel in the absence of bevacizumab. A head-to-head clinical trial would help to answer this question.

A recent large Phase III trial of 1,204 patients did demonstrate superiority of 150 mg/m<sup>2</sup> *nab*-paclitaxel given weekly (n=606) over 80 mg/m<sup>2</sup> sb-paclitaxel given weekly (n=598), both followed by epirubicin and cyclophosphamide, as neoadjuvant chemotherapy in patients with early breast cancer; pathological complete response (pCR) rates were 38% and 29%, respectively (odds ratio 1.53;  $P=0.001$ ).<sup>43</sup> Patients with TNBC appeared to derive the greatest benefit from *nab*-paclitaxel therapy (odds ratio 2.69;  $P<0.001$ ). The incidence of grade  $\geq 3$  neutropenia was high with both treatments, 61% and 62%, respectively ( $P=0.636$ ), whereas the incidence of grade  $\geq 3$  peripheral neuropathy was significantly higher with *nab*-paclitaxel (10%) versus sb-paclitaxel treatment (3%;  $P<0.001$ ). Of note, after 400 patients were treated in the *nab*-paclitaxel arm, the dose of *nab*-paclitaxel was reduced to 125 mg/m<sup>2</sup>. Long-term follow-up of this trial will determine if the increased pCR rates translate into improved disease-free survival and OS.

A Phase II trial of 302 patients with MBC treated in the first-line demonstrated that *nab*-paclitaxel dosed at 150 mg/m<sup>2</sup> qw 3/4 had a better efficacy and safety profile compared with another sb taxane, docetaxel, given at 100 mg/m<sup>2</sup> q3w.<sup>38</sup> The 150 mg/m<sup>2</sup> weekly dose showed significant improvement in PFS compared with docetaxel (median 12.9 vs 7.5 months;  $P=0.0065$ ) and demonstrated the longest median OS (33.8 months) compared with the other *nab*-paclitaxel regimens (22.2 months for 100 mg/m<sup>2</sup> weekly and 27.7 months for 300 mg/m<sup>2</sup> q3w) and docetaxel (26.6 months).<sup>36,38</sup> The 150 mg/m<sup>2</sup> dose was associated with more dose reductions and a higher incidence of grade 3 neuropathy than docetaxel (22% vs 12%); however, sensory neuropathy associated with *nab*-paclitaxel improved from grade 3 to grade 2 or lower in half the amount of time versus that associated with docetaxel (a median of 20 vs 41 days).

While these clinical trial results are interesting, it is not entirely clear how relevant these doses/schedules are to clinical use. According to a recent US claims study analyzing 664 eligible records of patients with MBC, a weekly schedule of *nab*-paclitaxel was dispensed more often than the q3w schedule (71% vs 29%) from January 2005 to September 2012.<sup>44</sup> Thus, it appears that the weekly dose of *nab*-paclitaxel has been widely adapted into clinical practice for the treatment

of MBC. The recommended doses and schedules of single-agent *nab*-paclitaxel by the National Comprehensive Cancer Network (NCCN) for the systemic treatment of recurrent or MBC are 260 mg/m<sup>2</sup> q3w and 100 or 150 mg/m<sup>2</sup> qw 3/4.<sup>45</sup> Currently, the NCCN does not recommend a *nab*-paclitaxel-based combination regimen for the treatment of any type of breast cancer.

Very few treatment options exist for patients with TNBC, an aggressive disease that accounts for about 20% to 25% of all breast cancer.<sup>46</sup> Patients with metastatic TNBC tend to be resistant to single-agent chemotherapy and often require combination chemotherapy.<sup>45</sup> Independent trials have demonstrated activity of *nab*-paclitaxel in combination with carboplatin, gemcitabine, or bevacizumab for the treatment of metastatic TNBC.<sup>41,42,47</sup> The Phase II/III Triple-Negative Albumin-Bound Paclitaxel Combination International Treatment Study (tnAcity; NCT01881230) will evaluate the efficacy and safety of *nab*-paclitaxel plus gemcitabine (or carboplatin) versus gemcitabine plus carboplatin as first-line treatment of patients with TNBC (Table 2).<sup>48</sup> During the Phase II portion of the trial, the best combination partner for *nab*-paclitaxel will be determined (gemcitabine or carboplatin) and carried forward into the Phase III trial where the selected *nab*-paclitaxel regimen will be compared with gemcitabine plus carboplatin. Planned enrollment for this trial is 790 patients and the primary endpoint is PFS. There are a number of other ongoing Phase III/IV trials evaluating the safety and efficacy of *nab*-paclitaxel in various breast cancer settings, and these are listed in Table 2.<sup>49-54</sup>

## NSCLC

In the USA, >70% of patients with lung cancer are 65 years of age or older and the median age of diagnosis is 70 years.<sup>55</sup> Historically, elderly patients have been underrepresented in Phase III trials of advanced NSCLC (15% to 28% of enrolled patients were  $\geq 70$  years of age),<sup>23,56-60</sup> thus application of these trial results to the elderly population has limitations. Other challenges in treating elderly patients include comorbidities and altered PK of drugs with age.<sup>61,62</sup> As a result, patients above age 70 years with lung cancer tend to be undertreated due to lack of sufficient evidence. In a subset analysis of the Phase III NSCLC trial, it was found that elderly patients who were treated with *nab*-paclitaxel plus carboplatin had a nearly 10-month improvement in OS compared with patients treated with sb-paclitaxel plus carboplatin ( $P=0.009$ ).<sup>16</sup> The safety profile of *nab*-paclitaxel plus carboplatin in the elderly population was similar to the overall trial population.<sup>23</sup> Based on this positive result, one

Table 2 Phase III/IV clinical trials of albumin-bound paclitaxel (*nab*-P)

| ClinicalTrials.gov identifier | Trial description  | Treatment   | Primary endpoint   | Planned enrollment | Planned primary completion |
|-------------------------------|--|---|--|--------------------|----------------------------|
| <b>BC</b>                     |  |   |  |                    |                            |
| NCT01881230 <sup>48</sup>     | Phase III/III tnAcity trial: evaluate risk/benefit of <i>nab</i> -P in combination with gem and carbo compared with gem and carbo in metastatic TNBC                         | <i>Nab</i> -P 125 mg/m <sup>2</sup> + gem 1,000 mg/m <sup>2</sup> qw 2/3 vs <i>nab</i> -P 125 mg/m <sup>2</sup> + carbo AUC 2 qw 2/3 vs gem 1,000 mg/m <sup>2</sup> + carbo AUC 2 qw 2/3        | PFS  | 790                | October 2015               |
| NCT01781338 <sup>49,50</sup>  | Phase III/III ADAPT trial: adjuvant dynamic marker-adjusted personalized therapy trial optimizing risk assessment and therapy response prediction in early breast cancer     | <i>Nab</i> -P 125 mg/m <sup>2</sup> qw or sb-pac 175 mg/m <sup>2</sup> q2w; both in combination with epirubicin 90 mg/m <sup>2</sup> and cyclophosphamide 600 mg/m <sup>2</sup> q2w for 8 weeks | Identification of a responder subpopulation within intermediate- and high-risk groups in any BC subtype, which due to therapy has a comparable outcome to a low-risk group | 4,936              | April 2020                 |
| NCT01822314 <sup>51</sup>     | Phase III ETNA trial: neoadjuvant chemotherapy with <i>nab</i> -P in women with HER2-negative high-risk BC   | <i>Nab</i> -p 125 mg/m <sup>2</sup> qw 3/4×4 cycles vs sb-P 90 mg/mg <sup>2</sup> qw 3/4×4 cycles; both followed by AC or EC or FEC q3w   | pCR  | 632                | September 2016             |
| NCT01690702 <sup>52</sup>     | Phase III GAIN-2 trial: study of <i>nab</i> -P in high-risk early BC   | EC + <i>nab</i> -P: 260–330 mg/mg <sup>2</sup> q2w vs EC + docetaxel  | DFS  | 2,886              | January 2016               |
| NCT02019277 <sup>53</sup>     | Phase III trial: study of pertuzumab and trastuzumab in combination with a taxane in patients with advanced HER2-positive BC   | Pertuzumab, trastuzumab, and taxane (investigators' choice of docetaxel, paclitaxel, or <i>nab</i> -P)  | Safety   | 50                 | May 2017                   |
| NCT01572038 <sup>54</sup>     | Phase III PERUSE trial: study of pertuzumab in combination with trastuzumab and a taxane in first-line treatment in patients with HER2-positive advanced BC                  | Pertuzumab, trastuzumab, and taxane (investigators' choice of docetaxel, paclitaxel, or <i>nab</i> -P)  | Safety   | 1,500              | May 2018                   |
| <b>NSCLC</b>                  |  |   |  |                    |                            |
| NCT02151149 <sup>63</sup>     | Phase IV ABOUND.70+ trial: safety and efficacy study of <i>nab</i> -P in combination with carbo to treat advanced NSCLC in the elderly                                       | <i>Nab</i> -P 100 mg/m <sup>2</sup> + carbo AUC 6 q3w vs <i>nab</i> -P 100 mg/m <sup>2</sup> + carbo AUC 6 q4w  | Incidence of peripheral neuropathy and myelosuppression  | 284                | December 2016              |
| NCT02027428 <sup>66</sup>     | Phase III ABOUND.sqm trial: safety and efficacy study of <i>nab</i> -P as maintenance therapy after <i>nab</i> -P plus carbo in first-line stage IIIB/IV squamous-cell NSCLC | Induction: <i>nab</i> -P 100 mg/m <sup>2</sup> qw + carbo AUC 6 q3w ×4 cycles<br>Maintenance: <i>nab</i> -P 100 mg/m <sup>2</sup> qw 2/3 or best supportive care                                | PFS  | 260                | May 2016                   |
| <b>PC</b>                     |  |   |  |                    |                            |
| NCT01964430 <sup>70</sup>     | Phase III APACT trial: <i>nab</i> -P and gem vs gem alone as adjuvant therapy for patients with resected PC  | <i>Nab</i> -P 125 mg/m <sup>2</sup> + gem 1,000 mg/m <sup>2</sup> qw 3/4 vs gem 1,000 mg/m <sup>2</sup> qw 3/4  | DFS  | 800                | April 2019                 |
| NCT01836432 <sup>71</sup>     | Phase III PILLAR: immunotherapy study in borderline resectable or locally advanced unresectable PC   | FOLFIRINOX or <i>nab</i> -P 125 mg/m <sup>2</sup> + gem 1,000 mg/m <sup>2</sup> qw 3/4 with or without algepantucel-L immunotherapy   | OS   | 280                | September 2015             |

**Note:** <sup>a</sup>*Nab*-P dose to be determined in a run-in phase.

**Abbreviations:** ABOUND.70+, Safety and Efficacy Study of Abraxane in Combination With Carboplatin to Treat Advanced NSCLC in the Elderly (70+); ABOUND.sqm, Safety and Efficacy Study of Abraxane as Maintenance Treatment After Abraxane Plus Carboplatin in 1st Line Stage IIIB/IV Squamous Cell Non-small Cell Lung Cancer (abound); AC, doxorubicin and cyclophosphamide; ADAPT, Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial; APACT, Adjuvant Pancreatic Adenocarcinoma Clinical Trial; AUC, area under the concentration-time curve; BC, breast cancer; carbo, carboplatin; DFS, disease-free survival; EC, epirubicin and cyclophosphamide; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; FOLFIRINOX, leucovorin, 5-fluorouracil, irinotecan, oxaliplatin; gem, gemcitabine; HER2, human epidermal growth factor receptor 2; NSCLC, non-small-cell lung cancer; OS, overall survival; PC, pancreatic cancer; pCR, pathologic complete response; PERUSE, Phase III trial of pertuzumab in combination with trastuzumab and a taxane in first-line treatment in patients with HER2-positive advanced BC; PFS, progression-free survival; Phase PILLAR, Immunotherapy Study in Borderline Resectable or Locally Advanced Unresectable Pancreatic Cancer; qw 2/3, first 2 of 3 weeks; qw 3/4, first 3 of 4 weeks; qw, weekly; q2w, every 2 weeks; q3w, every 3 weeks; q4w, every 4 weeks; sb-P, solvent-based paclitaxel; tnAcity, Triple-Negative Albumin-Bound Paclitaxel Combination International Treatment Study; TNBC, triple-negative breast cancer.

of the Albumin-Bound Paclitaxel in NSCLC (ABOUND) Phase III trials, ABOUND.70+ (NCT02151149), will evaluate the efficacy and safety of *nab*-paclitaxel plus carboplatin in elderly patients (aged  $\geq 70$  years) with advanced NSCLC (Table 2).<sup>63</sup> Patients will be randomly assigned to either 100 mg/m<sup>2</sup> weekly *nab*-paclitaxel given on day 1, 8, and 15 plus carboplatin AUC 6 given on day 1 every 21 days or the same regimen with 1 week off for a 28-day cycle. Planned enrollment is 284 patients. The primary endpoint is safety (incidence of peripheral neuropathy or myelosuppression).

Squamous NSCLC portends a poorer prognosis compared with other non-squamous subtypes, with 1- and 5-year survival rates of 14.6% and 1.6%, respectively.<sup>64</sup> Treatment options for patients with squamous NSCLC are also limited.<sup>65</sup> Pemetrexed and bevacizumab are not indicated for these patients, and the known mutations targetable by currently approved agents are rare in squamous NSCLC.<sup>65</sup> Current NCCN guidelines recommend platinum-based doublets as a category 1 option, and cisplatin plus vinorelbine in combination with cetuximab as a category 2B recommendation in patients with squamous NSCLC.<sup>65</sup> In the Phase III NSCLC trial of *nab*-paclitaxel plus carboplatin versus sb-paclitaxel plus carboplatin, patients with squamous histology treated with *nab*-paclitaxel plus carboplatin achieved an ORR that was nearly double that of patients treated with sb-paclitaxel plus carboplatin ( $P < 0.001$ ).<sup>16</sup> The safety profile of *nab*-paclitaxel plus carboplatin in patients with squamous histology was similar to the overall treated population of patients.<sup>16</sup> This intriguing outcome provided the rationale for the Phase III ABOUND squamous maintenance trial (ABOUND.sqm; NCT02027428) that will evaluate the safety and efficacy of *nab*-paclitaxel as maintenance therapy after first-line treatment with *nab*-paclitaxel plus carboplatin in patients with stage IIIB/IV squamous-cell NSCLC (Table 2).<sup>66</sup> After induction, patients will receive maintenance therapy of either *nab*-paclitaxel plus best supportive care or best supportive care alone. Planned enrollment is 260 patients and the primary endpoint is PFS.

## Pancreatic cancer

There are limited options for adjuvant therapy for pancreatic cancer and no adjuvant regimen has received regulatory approval in the USA. The NCCN guidelines recommend 5-fluorouracil (5-FU) plus leucovorin or gemcitabine as adjuvant chemotherapy options, but for chemotherapy alone, gemcitabine is preferred over 5-FU/leucovorin based on its more favorable safety profile.<sup>67</sup> Because a majority of patients receiving adjuvant gemcitabine relapse with recurrence rates in the

range of 77% to 81% in Phase III trials, better treatment options are needed.<sup>68,69</sup> The regimen used in the Phase III MPACT trial of *nab*-paclitaxel plus gemcitabine versus gemcitabine is now being evaluated in the Phase III Adjuvant Pancreatic Adenocarcinoma Clinical Trial (APACT; NCT01964430) as adjuvant therapy for patients with resected pancreatic cancer (Table 2).<sup>70</sup> Patients will be randomly assigned to receive 125 mg/m<sup>2</sup> *nab*-paclitaxel plus gemcitabine 1,000 mg/m<sup>2</sup> given on days 1, 8, and 15 of a 28-day cycle for a total of six cycles or gemcitabine alone. Planned enrollment is 800 patients and the primary endpoint is disease-free survival.

Based on the positive results of the Phase III MPACT study, there has been a significant increase in the use of *nab*-paclitaxel plus gemcitabine as a backbone regimen, and several studies are evaluating this combination with other novel therapies, including immunotherapy as in the Phase III Immunotherapy Study in Borderline Resectable or Locally Advanced Unresectable Pancreatic Cancer (PILLAR) trial (Table 2).<sup>71</sup> As we move forward with this backbone regimen, future studies will likely address whether the qw 3/4 schedule, currently the FDA-approved schedule for MPC,<sup>3</sup> will be optimal for regimens of *nab*-paclitaxel as a combination partner or as part of a novel sequence of regimens.

## Clinical benefit of *nab*-paclitaxel in other solid tumors

While *nab*-paclitaxel is currently only indicated by the FDA in three solid tumors, it is routinely used in the USA for the treatment of other solid tumors based on recommendations from the NCCN. At this time, melanoma and ovarian cancer (including fallopian tube cancer and primary peritoneal cancer) are the only solid tumors outside of the current indications in which *nab*-paclitaxel is an NCCN-recommended treatment option.<sup>72,73</sup> According to the NCCN guidelines, *nab*-paclitaxel is listed as a category 2A recommendation for the treatment of advanced or metastatic melanoma, based on positive Phase II trial data in which *nab*-paclitaxel led to response rates of 22% to 26% in chemotherapy-naïve patients with metastatic melanoma.<sup>74,75</sup> Response rates have historically been  $< 20\%$  with commonly used cytotoxics including dacarbazine, temozolomide, and sb-paclitaxel with or without carboplatin.<sup>72</sup> In a head-to-head Phase III trial of *nab*-paclitaxel 150 mg/m<sup>2</sup> qw 3/4 vs dacarbazine 1,000 mg/m<sup>2</sup> q3w for the treatment of chemotherapy-naïve patients, *nab*-paclitaxel led to a significant improvement in the primary endpoint of PFS (4.8 vs 2.5 months; HR 0.792;  $P = 0.044$ ) and a 2-month, nonsignificant improvement in OS (12.6 vs 10.5 months; HR 0.897;  $P = 0.271$ ).<sup>76</sup> Neuropathy

was a common grade  $\geq 3$  treatment-related event observed with *nab*-paclitaxel (25% vs 0% for dacarbazine); however, these events improved by  $\geq 1$  grade in a median of 28 days. Given the advent and success of immunomodulatory drugs in the treatment of melanoma, a number of Phase II trials evaluating combinations of *nab*-paclitaxel with this class of drugs are underway in metastatic melanoma.<sup>77,78</sup>

*Nab*-paclitaxel also has a category 2A recommendation for the treatment of recurrent ovarian cancer.<sup>73</sup> The NCCN recommendation for retreatment of ovarian cancer with *nab*-paclitaxel is based on a Phase II trial that showed an ORR of 64% and median PFS of 8.5 months.<sup>79</sup> Patients received *nab*-paclitaxel dosed at 260 mg/m<sup>2</sup> q3w. Neutropenia (24%) and neuropathy (9%; no grade 4) were the most common grade  $\geq 3$  events. In patients with platinum-sensitive recurrent ovarian cancer, platinum-based therapy either as a single agent or in combination is widely accepted as first-line therapy.<sup>73</sup> Although *nab*-paclitaxel has shown activity in this setting, it has not been studied in a Phase III trial of platinum-sensitive recurrent ovarian cancer to date. Unfortunately, almost all patients with platinum-sensitive ovarian cancer will develop resistance to platinum over time.<sup>80</sup> Platinum-resistant ovarian cancer is generally treated with non-platinum-based chemotherapy; however response rates are low and prognosis is poor. At least two Phase II trials examined the safety and efficacy of *nab*-paclitaxel in this setting. In a Gynecologic Oncology Group study, 47 patients with both platinum-resistant and taxane-resistant ovarian cancer were treated with *nab*-paclitaxel, 100 mg/m<sup>2</sup> days 1, 8, and 15 on a 28-day schedule.<sup>81</sup> The response rate was 23%, and 36% of patients had stable disease. A second study investigated the combination of *nab*-paclitaxel (using the same dosing schedule) plus bevacizumab (10 mg/kg given on days 1 and 15) in platinum-resistant patients.<sup>82</sup> Of 48 patients enrolled, the ORR was 50% and 29% had stable disease. Taken together, these Phase II studies indicate potential activity of *nab*-paclitaxel against platinum-resistant ovarian cancer. Further studies are needed in this population of patients with very limited options.

## Conclusion

Given the success of *nab*-paclitaxel in the treatment of MBC, advanced or metastatic NSCLC, and metastatic pancreatic cancer, the potential for *nab*-paclitaxel to improve disease outcomes in settings with an unmet need should be evaluated. Several Phase III/IV studies in select populations of patients with breast cancer, NSCLC, and pancreatic cancer are currently under investigation and may lead to expanded

indications of *nab*-paclitaxel in these disease areas (Table 2). In addition, a number of Phase II trials in other solid tumors, including urothelial,<sup>81</sup> squamous-cell carcinoma of the head and neck,<sup>83</sup> gastric cancer,<sup>84</sup> and colorectal and small bowel carcinoma,<sup>85</sup> are ongoing and should provide us with information regarding the role of *nab*-paclitaxel in the treatment of these tumor types as well. Other encapsulated (ie, liposomes and polymers) forms of paclitaxel are in development.<sup>86</sup> However, *nab*-paclitaxel is currently the only FDA- and European Medicines Agency-approved encapsulated form of paclitaxel.<sup>3,87</sup> Differences in efficacy, safety, and PK/PD properties between these paclitaxel formulations remain to be determined in clinical trials.

## Acknowledgments

Medical writing assistance was provided by Kerry R Garza, PhD, MediTech Media, Ltd, funded by Celgene.

## Disclosure

MNK has received consulting fees for advisory board participation and for lectures from Celgene. JN has received consulting fees or honoraria for advisory board participation from Celgene.

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