Overcoming Taxane Resistance in Metastatic Breast Cancer

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Target Audience
This program is intended for breast cancer specialists, medical oncologists, advanced practitioners, registered nurses, and other physicians and healthcare professionals involved in the treatment of patients with breast cancer.

Goal
The goal of this activity is to advance the science and understanding of novel approaches for the treatment of metastatic breast cancer.

Learning Objectives

- Describe recent clinical data on the treatment of patients with taxane-resistant metastatic breast cancer
- Discuss the efficacy and safety of novel paclitaxel formulations for treatment of patients with metastatic breast cancer
- Explain the biologic mechanisms of taxane resistance
Physician Continuing Medical Education

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- View the presentation
- Complete the Participant Information Form and Evaluation Form
- Complete the post test and score a 65% or above
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Introduction

The taxanes paclitaxel and docetaxel are highly active agents in the treatment of breast cancer. As such, these drugs are frequently used in both adjuvant and metastatic settings.\(^1\) The taxanes have a relatively complex mechanism of action.\(^2\) Their primary cellular target is the β subunit of tubulin. Through reversible binding to β-tubulin subunits, the taxanes stabilize microtubule complexes and promote microtubule polymerization. Formation of these long microtubule polymers disrupts normal cell division, leading to cell cycle arrest at the G2/M interface, resulting in cellular death or apoptosis.

Resistance to the taxanes can occur through several mechanisms.\(^3,4\) This module will focus on the mechanisms of taxane resistance and strategies for overcoming this resistance.

Mechanisms of Taxane Resistance

Inadequate delivery of a cytotoxic agent to tumor cells constitutes a relative form of resistance to therapy. This may be overcome through novel drug formulations or alternative delivery strategies that improve drug delivery to the tumor. Either approach can enhance delivery of the agent, resulting in increased efficacy and an improved therapeutic ratio.

Innate resistance to taxane therapy occurs at the cellular level. This type of resistance, considered true biological resistance, is the result of alterations in the target or other cellular processes that render the cell insensitive to the agent. The multidrug resistant (MDR) phenotype is an example of true biological resistance and occurs in many cancer types, including breast cancer.\(^3,4\) Circumventing MDR is another possible means to overcoming taxane resistance.

Several agents designed to overcome taxane resistance have been evaluated in the clinical setting, including novel formulations and entirely new chemical entities. Novel formulations focus on enhanced taxane delivery strategies to overcome relative resistance. New chemical entities, such as the epothilone compounds, focus on circumventing true biological taxane resistance. Both types of agents are proving to be effective in the treatment of women with breast cancer.

Novel Enhanced Taxane Delivery Mechanisms

Many of the new paclitaxel formulations are either novel compounds or agents that enhance current taxane delivery mechanisms. These include nanoparticle albumin-bound (nab) paclitaxel, paclitaxel poliglumex, and vitamin E–based paclitaxel.\(^5-7\) Nab paclitaxel (ABI-007) has been approved for clinical use by the US Food and Drug Administration (FDA) in patients with metastatic breast cancer after failure of combination chemotherapy or in patients who have relapsed within 6 months of receiving adjuvant chemotherapy. Nab paclitaxel is also currently being studied for the treatment of newly diagnosed breast cancer as well as for other solid tumors. Paclitaxel poliglumex and vitamin E–based paclitaxel are still investigational agents that have yet to be approved by the FDA.
Although paclitaxel is the active cytotoxic agent in all of these novel formulations, each of these agents utilizes a different carrier system. For nab paclitaxel, the carrier is nanoparticle human serum albumin. Paclitaxel poliglumex uses a polyglutamate carrier whereas vitamin E–based paclitaxel’s carrier is, as suggested, vitamin E. Of note, all of these novel formulations avoid the use of Cremophor EL, a main component of traditional paclitaxel formulations. Therefore, in addition to enhancing the delivery of paclitaxel, none of these agents requires steroid premedication, resulting in more convenient drug administration while avoiding steroid-related adverse effects.

**Nab Paclitaxel**

Nab paclitaxel is an albumin-bound formulation of paclitaxel. The use of albumin as a carrier has several attractive features from a biological perspective. Albumin is a natural transporter of hydrophobic molecules, with cellular transport effected via binding to the gp60 receptor. A second endothelial protein, secreted protein acid rich in cysteine, shares sequence homology with gp60 and has been shown to bind albumin. Secreted protein acid rich in cysteine, also called osteonectin, is expressed in a number of tumor types, including breast cancer. Preclinical models have shown that secreted protein acid rich in cysteine also mediates albumin uptake and may be a useful mechanism of transport not only for albumin-bound paclitaxel, but also for other albumin-bound agents.

Nab paclitaxel is formulated as 130 nm particles. These nanoparticles are inherently unstable in the circulation and rapidly disintegrate into small (approximately 10 nm) albumin-bound complexes. These small paclitaxel-albumin complexes are then available for endothelial transport, theoretically resulting in enhanced intracellular accumulation and enhanced paclitaxel cytotoxicity.

Clinical approval of nab paclitaxel was based on the results of a randomized, phase III trial comparing this formulation (nab paclitaxel 260 mg/m² every 3 weeks) with a standard regimen of traditional Cremophor-based paclitaxel (175 mg/m² every 3 weeks). The trial enrolled 460 women with stage IV breast cancer who had not received any prior taxane therapy.

Patients who received nab paclitaxel had a significantly higher overall response rate (33% vs 19%; \( P = .001 \)) and significantly longer time to tumor progression (23.0 vs 16.9 weeks; hazard ratio: 0.75; \( P = .006 \)) compared with those receiving traditional paclitaxel.

Adverse event profiles also favored the nab paclitaxel formulation. Grade 4 neutropenia occurred significantly less frequently with nab paclitaxel compared with traditional paclitaxel (9% vs 22%, respectively; \( P < .001 \)). Febrile neutropenia was uncommon in both study arms, occurring in less than 2% of patients. Grade 3 sensory neuropathy occurred more frequently with nab paclitaxel but was easily managed and tended to improve rapidly. There were no hypersensitivity reactions among the patients receiving nab paclitaxel, despite the fact that they received no premedications. Overall, nab paclitaxel improved efficacy with less toxicity than traditional paclitaxel, without requiring steroid premedication.

Recently, interim results of a phase II randomized trial comparing nab paclitaxel with docetaxel were presented at the 2006 annual San Antonio Breast Cancer Symposium (abstract 46). The 4-arm trial enrolled 300 patients with previously untreated stage IV breast cancer.
metastatic breast cancer and no prior taxane therapy. Patients were randomized to receive nab paclitaxel at a dose of either 100 mg/m² or 150 mg/m² given weekly for 3 of 4 weeks, nab paclitaxel 300 mg/m² once every 3 weeks, or docetaxel 100 mg/m² once every 3 weeks.

View the Capsule Summary of Abstract 46 at the end of this document >>

Confirmed response rates were 58% and 62% for weekly nab paclitaxel doses of 100 mg/m² and 150 mg/m², respectively, 33% for nab paclitaxel administered every 3 weeks, and 36% for docetaxel. Response rates with both of the weekly nab paclitaxel regimens were statistically superior compared with the every-3-week nab paclitaxel and with every-3-week docetaxel regimens. Preliminary progression-free survival data also statistically favored all of the nab paclitaxel regimens compared with docetaxel.

The 74% incidence of grade 4 neutropenia was significantly higher for patients on the docetaxel arm compared with any of the nab paclitaxel arms, which ranged from 3% to 7% (P < .001 for all comparisons). Among the nab paclitaxel arms, grade 3 or 4 neutropenia occurred less frequently in the 100 mg/m² weekly arm compared with either the 150 mg/m² weekly (19% vs 35%, respectively; P = .003) or the 300 mg/m² every 3 weeks (37%; P = .002) schedule. The incidence of peripheral neuropathy was comparable across all of the nab paclitaxel arms and the docetaxel arm. Among the nab paclitaxel arms, fewer grade 3 events occurred in those who received the 100 mg/m² regimen compared with the other 2 arms.

Overall, weekly nab paclitaxel 100 mg/m² was the most effective and least toxic treatment regimen.

**Vitamin E–Based Paclitaxel and Paclitaxel Polyglumex**

Another potential way to increase drug delivery to tumor cells is to design agents that exploit the alterations observed in vascular permeability in cancerous tissue. Normal healthy tissue vasculature has relatively tight cellular junctions, whereas tumor vasculature tends to be more disorganized and “leaky.” It is also recognized that the lymphatic drainage of tumor tissue may be highly impaired, which can effect drug delivery and retention.

The size and weight of macromolecule drug carriers directly influences vascular permeability. It is theoretically possible to target tumor cells by optimizing carrier size, thereby taking advantage of their leaky vasculature while limiting exposure to normal cells.

This hypothesis underlies the development of both vitamin E–based paclitaxel and paclitaxel polyglumex. The former is a sustained release oil-in-water emulsion paclitaxel. At 40 to 80 nm, the size of the vitamin E–based paclitaxel droplets are optimized to enhance tumor permeability and retention. In a phase II clinical trial of 47 women with previously untreated stage IV breast cancer, the overall response rate to vitamin E–based paclitaxel (120 mg/m² given weekly) was 49% by independent review. Based on these findings, a randomized phase III trial comparing this agent (100 mg/m² weekly) with traditional Cremophor-based paclitaxel (80 mg/m² weekly) was initiated. Eligible patients could not be HER2 positive, were allowed to have received no more than 1 prior regimen for metastatic disease, and had no taxane therapy within the past year. The study recently completed accrual of 800 patients.
Paclitaxel polyglumex is another novel macromolecule paclitaxel formulation designed to take advantage of the altered vascular permeability present in tumor tissue. This formulation links paclitaxel to a biodegradable polyglutamate polymer. The macromolecule is able to cross through the leaky junctions in the tumor vasculature to be taken up into tumor cells. Once inside, the polyglutamate polymer is cleaved, releasing free paclitaxel. Theoretically, this results in enhanced uptake in tumor tissue, increased accumulation in tumor cells, and decreased exposure to normal tissues. There is a suggestion from preclinical and early clinical studies in lung cancer patients that the metabolism of paclitaxel polyglumex may be influenced by estradiol levels. Currently, clinical data with this compound are limited, although there are several ongoing studies.

**Biologic Mechanisms of Taxane Resistance**

There are several mechanisms by which tumors cells can develop true biological resistance to taxane therapy. These include adenosine triphosphate (ATP)–binding cassette transporter abnormalities, tubulin-binding–site mutations, altered subcellular distribution or drug metabolism, and inhibition of apoptotic signaling.

P-glycoprotein (P-gp) is a well-known ATP-binding cassette transporter. Multidrug resistance is often mediated by *mdr1* gene amplification, which encodes for P-gp. Although P-gp is normally expressed in many different cell types, upregulation of P-gp has been shown to be present in 14% to 26% of cancer patients who are chemotherapy naive and in 43% to 57% of patients following chemotherapy. However, the broad range of normal P-gp expression has made it difficult to develop agents that specifically inhibit P-gp in order to enhance their cytotoxic effect.

Targeting the mechanisms involved in taxane-induced apoptosis is another means of addressing taxane resistance. However, apoptotic pathways are complex, making it difficult to affect this process by targeting specific pathway components. In addition to MDR and inhibition of apoptosis, there are other potential mechanisms of taxane resistance, including inactivation of detoxifying systems by glutathione S-transferase, decreased drug activation, redistribution of proteasomes into the nucleus, and mutations in the tubulin target. Although all of these mechanisms of taxane resistance are of current scientific interest, epothilone analogue development as a means to circumvent MDR has progressed the furthest.

**The Epothilones**

The epothilones are structurally unrelated to the taxanes. However, their function is similar, since both classes of compounds compete for tubulin binding. The epothilones have a unique tubulin binding site compared with the taxanes, and their activity is unaffected by most of the tubulin mutations that confer taxane resistance. Ixabepilone, an analogue of epothilone B, has several interesting features. The relatively increased flexibility of this compound is due in large part to its unique tubulin-binding site. This site also prevents ixabepilone from binding to ATP-binding cassette transporters, such as P-gp. Among all the epothilones currently being studied (Table 1), ixabepilone has been investigated most extensively in the treatment of breast cancer.
Table 1. Epothilones in Clinical Development

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Generic Drug Name</th>
<th>Phase of Clinical Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS-247550</td>
<td>Ixabepilone</td>
<td>II, III</td>
</tr>
<tr>
<td>BMS-310706</td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>EPO906</td>
<td>Patupilone</td>
<td>II, III</td>
</tr>
<tr>
<td>KOS-362</td>
<td>Epothilone D</td>
<td>II</td>
</tr>
<tr>
<td>KOS-1584</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZK219477</td>
<td>ZK-EPO</td>
<td>II</td>
</tr>
</tbody>
</table>

Several phase II trials have shown that single-agent ixabepilone is active in patients with metastatic breast cancer (Table 2).\[31-34\] Overall response rates ranged from 12% to 43%, and responses were reported in heavily pretreated patients. The response rate in taxane-resistant patients was 12% whereas the combined response rate in anthracycline-, taxane-, and capecitabine-resistant disease was 18%. The most common grade 3 and 4 adverse events were neutropenia, fatigue, and reversible peripheral neuropathy. Additionally, ixabepilone does not require steroid premedication because it is not Cremophor based.

Table 2. Selected Phase II Studies of Single Agent Ixabepilone in Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Ixabepilone Regimen</th>
<th>Evaluable Patients, n</th>
<th>Prior Therapy</th>
<th>Overall Response Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low et al[31]</td>
<td>6 mg/m² Days 1-5 every 3 weeks</td>
<td>37</td>
<td>Taxane</td>
<td>22</td>
</tr>
<tr>
<td>Denduluri et al[32]</td>
<td>6 mg/m² Days 1-5 every 3 weeks</td>
<td>23</td>
<td>No taxane</td>
<td>43</td>
</tr>
<tr>
<td>Conte et al[33]</td>
<td>40 mg/m² Day 1 every 3 weeks</td>
<td>49</td>
<td>Taxane resistant</td>
<td>12</td>
</tr>
<tr>
<td>Thomas et al[34]</td>
<td>40 mg/m² Day 1 every 3 weeks</td>
<td>126</td>
<td>Anthracycline, taxane, and capecitabine resistant</td>
<td>18</td>
</tr>
</tbody>
</table>

A phase I/II trial evaluated capecitabine (2000 mg/m² Days 1-14) in combination with 2 different schedules of ixabepilone (either 40.0 mg/m² on Day 1 or 13.3 mg/m² Days 1-3) administered every 3 weeks.\[35,36\] The study enrolled 62 women with breast cancer previously treated with anthracycline and taxane therapy. Visceral involvement was present in 80% of patients and 44% had received more than 2 prior therapies for metastatic disease. The overall response rate in this heavily pretreated population was 30%, with a median response duration of 6.9 months. The most common grade 3 and 4 toxicity included neutropenia, hand-foot syndrome, and sensory neuropathy.\[36\]
Two parallel phase III studies compared capecitabine (2500 mg/m² Days 1-14) with a combination of capecitabine (2000 mg/m² Days 1-14) plus ixabepilone (40 mg/m² on Day 1), and both have recently completed accrual. Although the treatment regimens were identical in both of these studies, patient eligibility criteria and primary study endpoints were different. The first of these studies enrolled 750 patients who had received prior anthracycline and taxane therapy and were classified as taxane resistant. The primary endpoint was time to disease progression. The second study enrolled 1200 patients who had received prior anthracycline and taxane therapy but were not classified as taxane resistant, and its primary endpoint was overall survival. Final results are not yet available for either study, although it is anticipated that both of these trials will be used to support ixabelipline’s application for FDA approval in the setting of metastatic breast cancer.

Conclusion

In conclusion, novel taxane formulations have been shown to be effective in enhancing drug delivery, thereby overcoming relative taxane resistance. The epothilone analogue ixabepilone has demonstrated promising activity in overcoming true biologic resistance mediated by MDR or tubulin mutations in metastatic disease. Proof of principle has already been established in phase II studies of patients with taxane-resistant disease, and the results of the 2 phase III studies discussed are eagerly anticipated.
Posttest

Click on the appropriate response below.

1. Which of the following novel taxane formulations has been approved for use by the US Food and Drug Administration for the treatment of patients with metastatic breast cancer?

   A. Paclitaxel poliglumex  
   B. Nanoparticle albumin-bound (Nab) paclitaxel  
   C. Vitamin E-based paclitaxel  
   D. All of the above

2. Ixabepilone has been studied in several phase II trials and has been associated with which of the following results?

   A. 12% response rate in patients with taxane resistance  
   B. Grade 3/4 neutropenia  
   C. 43% response rate in patients with no prior taxane therapy  
   D. 22% response rate in patients with prior taxane therapy  
   E. All of the above

3. In interim results of a phase II randomized trial comparing nab paclitaxel with docetaxel, which of the following were reported?

   A. Significantly better overall response rates for docetaxel  
   B. Superior response rates with weekly nab paclitaxel vs every-3-week dosing  
   C. Superior progression-free survival with docetaxel  
   D. Higher grade 4 neutropenia with nab paclitaxel
References


32. Denduluri N, Lee JJ, Walshe JM et al. Phase II clinical trial of ixabepilone in metastatic breast cancer (MBC) patients previously untreated with taxanes. Program and abstracts of the 42nd Annual Meeting of the American Society of Clinical Oncology; June 2-6, 2006; Atlanta, Georgia. Abstract 651.

33. Conte P, Thomas E, Martin M, Klimovsky J, Tabernero J. Phase II study of ixabepilone in patients (pts) with taxane-resistant metastatic breast cancer (MBC): final report. Program and abstracts of the 42nd Annual Meeting of the American Society of Clinical Oncology; June 2-6, 2006; Atlanta, Georgia. Abstract 10505.

34. Thomas E, Perez EA, Mukhopadhyay P, et al. Phase II trial of ixabepilone in patients with metastatic breast cancer (MBC) who are resistant to an anthracycline, a taxane and capecitabine. Program and abstracts of the 42nd Annual Meeting of the American Society of Clinical Oncology; June 2-6, 2006; Atlanta, Georgia. Abstract 660.

35. Bunnell CA, Klimovsky J, Thomas E. Final efficacy results of a phase I/II trial of ixabepilone in combination with capecitabine in patients with metastatic breast cancer (MBC) previously treated with a taxane and an anthracycline. Program and abstracts of the 42nd Annual Meeting of the American Society of Clinical Oncology; June 2-6, 2006; Atlanta, Georgia. Abstract 10511.
36. Vahdat LT, Klimonsky J, Bunnell C. Phase I/II trial in patients with metastatic breast cancer (MBC) previously treated with a taxane and an anthracycline: final safety data. Program and abstracts of the 42nd Annual Meeting of the American Society of Clinical Oncology; June 2-6, 2006; Atlanta, Georgia. Abstract 10528.


Abstract 46 - Solvent-Free Paclitaxel Shown Safer and More Effective Compared With Docetaxel in Metastatic Breast Cancer Patients

- A report on data presented at the conference

- Third interim analysis of randomized, phase II trial[^1]

Summary of Key Conclusions

- Administration of weekly albumin stabilized nanoparticle albumin-bound (nab)-paclitaxel produced highest response rates compared with nab-paclitaxel or docetaxel every 3 weeks
  - Rates comparable between low-dose and high-dose nab-paclitaxel administered weekly
- All nab-paclitaxel arms produced lower rate of neutropenia and mucositis in comparison with docetaxel
  - No significant differences in rates of peripheral neuropathy
  - In general, low-dose weekly nab-paclitaxel arm appeared least toxic
- Preliminary results suggested that weekly low-dose nab-paclitaxel the optimal regimen for further analysis in future clinical trials

Background

- Nab-paclitaxel (ABI-007)
  - Solvent-free, albumin-bound, nanometer particle of paclitaxel
  - Created to circumvent toxicity of castor oil-based solvent required for standard paclitaxel
- Numerous studies have investigated optimal formulations and delivery of taxanes
  - TAX311[^2]
    - Solvent-based docetaxel prolonged survival and time to progression compared with solvent-based paclitaxel, but at expense of greater toxicity
  - CA012[^3]
    - Solvent-free nab-paclitaxel produced higher overall response and prolonged survival compared with solvent-based paclitaxel, with less toxicity
  - Cross-trial analysis of 2 studies suggested that nab-paclitaxel and docetaxel activity possibly comparable, but that nab-paclitaxel better tolerated
  - CALGB 9840[^4]
    - Weekly vs every-3-week administration of solvent-based paclitaxel produced better clinical outcomes, but at expense of greater toxicity
  - CALGB 9342[^5]
    - No difference in efficacy between high and low doses of solvent-based paclitaxel administered every 3 weeks
• Current 4-arm study designed to compare safety and efficacy of
  o Solvent-free nab-paclitaxel vs solvent-based docetaxel
  o nab-paclitaxel every week vs every 3 weeks
  o High-dose vs low-dose nab-paclitaxel

Schematic of Study Design

Eligibility

• Inclusion criteria
  o No prior chemotherapy for metastatic disease
  o Stage IV adenocarcinoma of breast
  o Adequate liver function
Baseline Characteristics

- Baseline characteristics well balanced between treatment arms
  - No patient received prior taxane therapy

<table>
<thead>
<tr>
<th>Characteristic, %</th>
<th>Nab-paclitaxel 300 mg/m² q3w (n = 76)</th>
<th>Nab-paclitaxel 100 mg/m² qw (n = 76)</th>
<th>Nab-paclitaxel 150 mg/m² qw (n = 74)</th>
<th>Docetaxel 100 mg/m² q3w (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sites of metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>13</td>
<td>13</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>20</td>
<td>24</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>Lung/thoracic</td>
<td>70</td>
<td>64</td>
<td>67</td>
<td>78</td>
</tr>
<tr>
<td>Hepatic/liver</td>
<td>28</td>
<td>36</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>Bone</td>
<td>29</td>
<td>33</td>
<td>44</td>
<td>34</td>
</tr>
<tr>
<td>Prior adjuvant/neoadjuvant chemotherapy</td>
<td>43</td>
<td>38</td>
<td>38</td>
<td>46</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>26</td>
<td>20</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Alkylating agents</td>
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<td>38</td>
<td>36</td>
<td>46</td>
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<tr>
<td>Antimetabolites</td>
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<td>36</td>
<td>36</td>
<td>42</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Other</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

q3w, every 3 weeks; qw, weekly.

Description of Current Analysis

- Patients enrolled between November 2005 and June 2006
  - 4 interim analyses prospectively planned
  - Current study reported data from third interim analysis
- Patients assessed every 8 weeks for treatment response
- Primary endpoints
  - Treatment response
  - Toxicity
- Secondary endpoint
  - Progression-free survival
- Blinded independent radiology review currently being conducted (not reported here)

Main Findings

- 55% of patients stopped treatment by third interim analysis
- Confirmed response rates highest for patients on weekly nab-paclitaxel
  - Both doses of nab-paclitaxel weekly superior to nab-paclitaxel every 3 weeks
    - Nab-paclitaxel 100 mg/m² weekly vs nab-paclitaxel 300 mg/m² every 3 weeks (P < .001)
    - Nab-paclitaxel 150 mg/m² weekly vs nab-paclitaxel 300 mg/m² every 3 weeks (P < .001)
Both doses of nab-paclitaxel weekly superior to docetaxel
  - Nab-paclitaxel 100 mg/m² weekly vs docetaxel (P = .004)
  - Nab-paclitaxel 150 mg/m² weekly vs docetaxel (P = .016)

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>Nab-paclitaxel 300 mg/m² q3w (n = 76)</th>
<th>Nab-paclitaxel 100 mg/m² qw (n = 76)</th>
<th>Nab-paclitaxel 150 mg/m² qw (n = 74)</th>
<th>Docetaxel 100 mg/m² q3w (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed response rate</td>
<td>33</td>
<td>58</td>
<td>62</td>
<td>36</td>
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</tbody>
</table>

- Preliminary analysis of progression-free survival (33% of potential events) showed that all nab-paclitaxel doses superior to docetaxel
  - Nab-paclitaxel 300 mg/m² every 3 weeks vs docetaxel (P = .018)
  - Nab-paclitaxel 100 mg/m² weekly vs docetaxel (P = .041)
  - Nab-paclitaxel 150 mg/m² weekly vs docetaxel (P < .001)
- Most common adverse events (occurring in > 5% of patients): neutropenia, peripheral neuropathy, fatigue, stomatitis/mucositis, and arthralgias
- Severe neutropenia significantly more common in docetaxel arm vs nab-paclitaxel arms
  - Among nab-paclitaxel arms, severe neutropenia significantly more common in every-3-weeks arm and high-dose weekly arm

<table>
<thead>
<tr>
<th>Neutropenia</th>
<th>Nab-paclitaxel 300 mg/m² q3w (n = 76)</th>
<th>Nab-paclitaxel 100 mg/m² qw (n = 76)</th>
<th>Nab-paclitaxel 150 mg/m² qw (n = 74)</th>
<th>Docetaxel 100 mg/m² q3w (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 1</td>
<td>20</td>
<td>28</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>• 2</td>
<td>33</td>
<td>30</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>• 3</td>
<td>33</td>
<td>16</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>• 4</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>74</td>
</tr>
<tr>
<td>P value vs docetaxel</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>--</td>
</tr>
<tr>
<td>P value vs nab-paclitaxel, 100 mg/m² qw</td>
<td>.002</td>
<td>--</td>
<td>.003</td>
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</tr>
</tbody>
</table>

- Incidence of peripheral neuropathy comparable between docetaxel and nab-paclitaxel arms
  - Among nab-paclitaxel arms, peripheral neuropathy significantly more common in every-3-weeks arm and high-dose weekly arm

<table>
<thead>
<tr>
<th>Peripheral Neuropathy</th>
<th>Nab-paclitaxel 300 mg/m² q3w (n = 76)</th>
<th>Nab-paclitaxel 100 mg/m² qw (n = 76)</th>
<th>Nab-paclitaxel 150 mg/m² qw (n = 74)</th>
<th>Docetaxel 100 mg/m² q3w (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade, %</td>
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<td></td>
<td></td>
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<td>• 1</td>
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<td>23</td>
<td>23</td>
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<tr>
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<td>15</td>
</tr>
<tr>
<td>• 3</td>
<td>14</td>
<td>7</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>• 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P value vs docetaxel</td>
<td>.12</td>
<td>.35</td>
<td>.28</td>
<td>--</td>
</tr>
<tr>
<td>P value vs nab-paclitaxel, 100 mg/m² qw</td>
<td>.02</td>
<td>--</td>
<td>.05</td>
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</tr>
</tbody>
</table>
Fatigue significantly more common in docetaxel arm vs low-dose weekly nab-paclitaxel arm
  o Among nab-paclitaxel arms, fatigue significantly more common in every-3-weeks arm and high-dose weekly arm

<table>
<thead>
<tr>
<th></th>
<th>Nab-paclitaxel 300 mg/m² q3w (n = 76)</th>
<th>Nab-paclitaxel 100 mg/m² qw (n = 76)</th>
<th>Nab-paclitaxel 150 mg/m² qw (n = 74)</th>
<th>Docetaxel 100 mg/m² q3w (n = 74)</th>
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<tbody>
<tr>
<td>Grade, %</td>
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<tr>
<td>• 1</td>
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<td>15</td>
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<tr>
<td>• 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P value vs docetaxel</td>
<td>.13</td>
<td>&lt; .001</td>
<td>.08</td>
<td>--</td>
</tr>
<tr>
<td>P value vs nab-paclitaxel, 100 mg/m² qw</td>
<td>.01</td>
<td>--</td>
<td>.02</td>
<td>--</td>
</tr>
</tbody>
</table>

Grade 1/2 stomatitis/mucositis significantly more common in docetaxel arm vs nab-paclitaxel arms (P < .001 for all comparisons)
  o No significant differences between vs nab-paclitaxel arms

Grade 1/2 arthralgias significantly more common in every-3-weeks (P = .01) and high-dose weekly nab-paclitaxel arm (P = .03) vs docetaxel
  o Among nab-paclitaxel arms, arthralgias significantly more common in every-3-weeks arm (P = .002) and high-dose weekly arm (P = .003) vs low-dose weekly arm

References