Overview of nab-paclitaxel in Breast Cancer

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Madrid 2.2016
CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

Preferred single agents:
- Anthracyclines
  - Doxorubicin
  - Pegylated liposomal doxorubicin
- Taxanes
  - Paclitaxel
- Anti-metabolites
  - Capecitabine
  - Gemcitabine
- Other microtubule inhibitors
  - Vinorelbine
  - Eribulin

Other single agents:
- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

Chemotherapy combinations:
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab

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A concise story of nab-paclitaxel and breast cancer
Conventional taxanes, a mainstay of metastatic breast cancer treatment, balance efficacy with hypersensitivity / adverse events

**Efficacy**

- Increased systemic drug exposure
- Decreased drug clearance
- Nonlinear pharmacokinetics
- Lack of dose-dependent antitumor activity

**Toxicity**

- Hypersensitivity reactions are common
- Can sometimes lead to irreversible peripheral neuropathy associated with demyelination and axonal degeneration

Conventional Taxanes lack significant efficacy in patients with aggressive disease (e.g. HER2-negative patients)
CA012: nab-Paclitaxel Compared With Cremophor® EL Paclitaxel in Metastatic Breast Cancer Study Design and Objectives

- **Women ≥ 18 years with measurable MBC**
- **No prior taxane for metastatic disease**
- **ECOG PS 0-2**
- **Patients stratified for prior anthracycline exposure** (N = 460)

- **nab-Paclitaxel 260 mg/m²**
  - IV over 30 minutes q3w
  - No standard premedication

- **Cremophor EL Paclitaxel 175 mg/m²**
  - IV over 3 hours q3w
  - Standard premedication with dexamethasone and antihistamines

- **Primary endpoint:** ORR by RECIST
- **Secondary endpoints:** TTP, OS
- **Safety and efficacy based on ITT population:** 454 patients (229 nab-paclitaxel and 225 CrEL paclitaxel) who received ≥ 1 dose of study drug

CrEL, Cremophor EL; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat; IV, intravenous; MBC, metastatic breast cancer; ORR, overall response rate; OS, overall survival; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to tumor progression.

CA012: *nab*-Paclitaxel Compared With Cremophor® EL Paclitaxel in Metastatic Breast Cancer

**Results:**

Time to Tumor Progression for All Patients

- *nab*-Paclitaxel is associated with a significantly longer time to progression than Cremophor EL paclitaxel

\[
P = 0.006  
\text{HR} = 0.75
\]

Note: *P* value from log-rank test

**CA012: nab-Paclitaxel Compared With Cremophor® EL Paclitaxel in Metastatic Breast Cancer Results: Overall Survival in the ITT Population**

- The difference in OS in the ITT population for nab-paclitaxel and Cremophor EL paclitaxel was not statistically significant.

HR, hazard ratio; OS, overall survival.

## CA012: nab-Paclitaxel Compared With Cremophor® EL Paclitaxel in Metastatic Breast Cancer Treatment Exposure

<table>
<thead>
<tr>
<th>Treatment Exposure</th>
<th>Cremophor® EL Paclitaxel Injection 175 mg/m² Over 3 h (n = 225)</th>
<th>nab-Paclitaxel 260 mg/m² Over 30 min (n = 229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median cycles/patient</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Min, max cycles/patients</td>
<td>1, 18</td>
<td>1, 18</td>
</tr>
<tr>
<td>Mean dose intensity mg/m²/week</td>
<td>57.02</td>
<td>85.13</td>
</tr>
<tr>
<td>Mean total paclitaxel/patient/m²</td>
<td>909 mg</td>
<td>1459 mg</td>
</tr>
<tr>
<td>Patients with ≥ 1 dose delay, n (%)</td>
<td>53 (24)</td>
<td>41 (18)</td>
</tr>
</tbody>
</table>

Data on File. Celgene Corporation.
CA012: nab-Paclitaxel Compared With Cremophor® EL Paclitaxel in Metastatic Breast Cancer Safety: Sensory Neuropathy

- nab-Paclitaxel median time to improvement from grade 3 to a lesser grade: 22 days (95% CI: 17-22 days)

- Twenty-four patients (10%) in the nab-paclitaxel arm developed grade 3 sensory neuropathy compared with 5 patients (2%) in the Cremophor EL paclitaxel arm ($P < 0.001$)

CI, confidence interval.
CA024: Phase II Trial of First-Line nab-Paclitaxel vs Docetaxel in Metastatic Breast Cancer

Study Design and Objectives

- Women with pathologically confirmed MBC
- No previous chemotherapy treatment for MBC
- No parenchymal brain metastasis
- ECOG PS 0 - 2
- No grade > 1 baseline sensory neuropathy
- No concurrent immunotherapy or hormonal therapy for breast cancer

• Primary endpoint: investigator-assessed ORR (CR + PR) by RECIST
• Secondary endpoints: DCR (CR + PR + SD ≥ 16 weeks), PFS, DOR, OS, safety, tolerability

Arm A<sup>a</sup>: nab-Paclitaxel 300 mg/m<sup>2</sup> q3w  
  n = 76

Arm B: nab-Paclitaxel 100 mg/m<sup>2</sup> qw 3/4  
  n = 76

Arm C<sup>a</sup>: nab-Paclitaxel 150 mg/m<sup>2</sup> qw 3/4  
  n = 74

Arm D<sup>a</sup>: Docetaxel 100 mg/m<sup>2</sup> q3w<sup>b</sup>  
  n = 74

<sup>a</sup> Administered at the maximum tolerated dose.
<sup>b</sup> Patients treated with docetaxel received oral corticosteroid premedication.

CR, complete response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Group performance status; MBC, metastatic breast cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; qw 3/4, first 3 of 4 weeks; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

CA024: Phase II Trial of First-Line nab-Paclitaxel vs Docetaxel in Metastatic Breast Cancer

Results: Overall Response Rate

For overall comparisons, $P = .224$ for independent radiologist-assessed ORR and $< .001$ for investigator-assessed ORR.

ORR, overall response rate; q3w, every 3 week; qw 3/4, first 3 of 4 weeks.

CA024: Phase II Trial of First-Line nab-Paclitaxel vs Docetaxel in Metastatic Breast Cancer

Results: Overall Survival

- The 150 mg/m² qw 3/4 nab-paclitaxel arm resulted in the longest median OS compared with the other nab-paclitaxel regimens or docetaxel

q3w, every 3 weeks; qw 3/4, first 3 of 4 weeks.

# CA024: Phase II Trial of First-Line nab-Paclitaxel vs Docetaxel in Metastatic Breast Cancer
## Treatment Exposure

<table>
<thead>
<tr>
<th>Dose Intensity</th>
<th>nab-Paclitaxel</th>
<th>Docetaxel</th>
<th>Overall P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg/m² q3w (n = 76)</td>
<td>100</td>
<td>101</td>
<td>NA</td>
</tr>
<tr>
<td>100 mg/m² qw 3/4 (n = 76)</td>
<td>75</td>
<td>33</td>
<td>&lt; .001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>150 mg/m² qw 3/4 (n = 74)</td>
<td>101</td>
<td>25</td>
<td>34 (43)</td>
</tr>
<tr>
<td>100 mg/m² q3w (n = 74)</td>
<td>33</td>
<td>25</td>
<td>22 (30)</td>
</tr>
</tbody>
</table>

- Based on the Fisher exact test.
- One dose reduction per patient was allowed.
- Based on Kruskal-Wallis test.
- Based on investigator assessment of patients who exhibited a confirmed response.

<table>
<thead>
<tr>
<th></th>
<th>300 mg/m² q3w (n = 76)</th>
<th>100 mg/m² qw 3/4 (n = 76)</th>
<th>150 mg/m² qw 3/4 (n = 74)</th>
<th>100 mg/m² q3w (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥ 1 dose delay, n (%)</td>
<td>33 (43)</td>
<td>34 (45)</td>
<td>60 (81)</td>
<td>25 (34)</td>
</tr>
<tr>
<td>Patients with 1 dose reduction, n (%)</td>
<td>15 (20)</td>
<td>14 (18)</td>
<td>35 (47)</td>
<td>22 (30)</td>
</tr>
<tr>
<td>Cycle of dose reduction, median (range)</td>
<td>7 (2-13)</td>
<td>5 (2-13)</td>
<td>4 (1-19)</td>
<td>3 (2-13)</td>
</tr>
<tr>
<td>Cycle at best response, median (range)</td>
<td>4 (3-21)</td>
<td>2 (2-8)</td>
<td>2 (2-15)</td>
<td>5 (2-18)</td>
</tr>
<tr>
<td>Duration of treatment in weeks, median (range)</td>
<td>22 (&lt; 1-125)</td>
<td>30 (2-123)</td>
<td>38 (2-107)</td>
<td>21 (1-109)</td>
</tr>
<tr>
<td>Cycles administered, median (range)</td>
<td>8 (1-39)</td>
<td>8 (1-30)</td>
<td>10 (1-27)</td>
<td>8 (1-37)</td>
</tr>
</tbody>
</table>

### Selected Adverse Events

<table>
<thead>
<tr>
<th>Selected Adverse Events</th>
<th>nab-Paclitaxel</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300 mg/m² q3w (n = 76)</td>
<td>100 mg/m² qw 3/4 (n = 76)</td>
</tr>
<tr>
<td>Neutropenia, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>28 (37)</td>
<td>15 (20)</td>
</tr>
<tr>
<td>Grade 4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 (7)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Nadir neutrophil count, mean ± SD, × 10⁹/L</td>
<td>1.21 ± 1.00</td>
<td>1.51 ± 0.96</td>
</tr>
<tr>
<td>Sensory neuropathy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>16 (21)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>4 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Time to onset of sensory neuropathy in days, median</td>
<td>151</td>
<td>189</td>
</tr>
<tr>
<td>Time to improvement of sensory neuropathy in days, median&lt;sup&gt;b&lt;/sup&gt;</td>
<td>22</td>
<td>22</td>
</tr>
</tbody>
</table>

Note: febrile neutropenia occurred in 8% of patients in the docetaxel arm vs 1% in each nab-paclitaxel arm.

<sup>a</sup> For grade 4 neutropenia, \( P < .001 \) for all 3 nab-paclitaxel arms compared with docetaxel arm.

<sup>b</sup> To grade ≤ 2.

q3w, every 3 weeks; qw 3/4, first 3 of 4 weeks; SD, standard deviation.

CALGB 40502: sb-Paclitaxel, nab-Paclitaxel, orIxabepilone, Each ± Bev for First-Line MBC

Study Design and Objectives\textsuperscript{1,2}

- Primary endpoint: PFS\textsuperscript{1,2}
- Secondary endpoints: ORR, DoR, TTF, rate of patients progression free at 12 months, OS, toxicity\textsuperscript{2}

Measurable MBC; No prior chemotherapy for metastatic disease; ≥ 12 months from adjuvant taxanes; adequate organ function; ECOG PS 0 or 1
(N = 799)

\begin{itemize}
\item sb-Paclitaxel 90 mg/m\textsuperscript{2} qw 3/4 ± bevacizumab 10 mg/kg q2w 28-day cycles (n = 283)
\item nab-Paclitaxel 150 mg/m\textsuperscript{2} qw 3/4 ± bevacizumab 10 mg/kg q2w 28-day cycles (n = 271)
\item Ixabepilone 16 mg/m\textsuperscript{2} qw 3/4 ± bevacizumab 10 mg/kg q2w 28-day cycles (n = 245)
\end{itemize}

Patients could discontinue chemotherapy and continue bevacizumab only after cycle 6 if stable or responding disease

Stratification factors\textsuperscript{1}:
Prior adjuvant taxane use, hormone receptor status, treatment with Bev\textsuperscript{a}

\textsuperscript{a}Treatment with Bev became a stratification factor after the protocol was modified to make Bev optional (see trial modification slide).

Bev, bevacizumab; CALGB, Cancer and Leukemia Group B; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; MBC, metastatic breast cancer; ORR, overall response rate; OS, overall survival; q2w, every 2 weeks; qw 3/4, first 3 of 4 weeks; sb, solvent-based; TTF, time to treatment failure.

## Patient Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristic, %</th>
<th>sb-Paclitaxel 90 mg/m² qw 3/4 ± Bevacizumab 10 mg/kg q2w (n = 283)</th>
<th>nab-Paclitaxel 150 mg/m² qw 3/4 ± Bevacizumab 10 mg/kg q2w (n = 271)</th>
<th>Ixabepilone 16 mg/m² qw 3/4 ± Bevacizumab 10 mg/kg q2w (n = 245)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>6 57 36</td>
<td>8 54 38</td>
<td>7 57 35</td>
</tr>
<tr>
<td>&lt; 40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>78 15 7</td>
<td>79 17 3</td>
<td>84 11 5</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant taxane</td>
<td>44</td>
<td>44</td>
<td>44</td>
</tr>
</tbody>
</table>

Bev, bevacizumab; CALGB, Cancer and Leukemia Group B; MBC, metastatic breast cancer; q2w, every 2 weeks; qw 3/4, first 3 of 4 weeks; sb, solvent-based.  

## Other Grade ≥ 3 Adverse Events

<table>
<thead>
<tr>
<th>Nonhematologic Grade ≥ 3 Adverse Events</th>
<th>sb-Paclitaxel 90 mg/m² qw 3/4 ± Bevacizumab 10 mg/kg q2w (n = 262)</th>
<th>nab-Paclitaxel 150 mg/m² qw 3/4 ± Bevacizumab 10 mg/kg q2w (n = 258)</th>
<th>Ixabepilone 16 mg/m² qw 3/4 ± Bevacizumab 10 mg/kg q2w (n = 237)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>$P^a$</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>7</td>
<td>17</td>
<td>.0004</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18</td>
<td>47</td>
<td>.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8</td>
<td>7</td>
<td>ns</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
<td>16</td>
<td>.010</td>
</tr>
<tr>
<td>Pain</td>
<td>4</td>
<td>10</td>
<td>.010</td>
</tr>
<tr>
<td>Motor neuropathy</td>
<td>2</td>
<td>10</td>
<td>.0003</td>
</tr>
</tbody>
</table>

$^a$ $P$ value vs paclitaxel ± bevacizumab.
Unplanned Subset Analysis of PFS
44% adjuvant taxanes, DFI > 1 year in 66%

### ER+ Disease

**Comparison HR P-value 95% CI**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>P-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>nab vs. pac</td>
<td>1.38</td>
<td>0.0194</td>
<td>1.05 – 1.81</td>
</tr>
<tr>
<td>ixa vs. pac</td>
<td>1.60</td>
<td>0.0006</td>
<td>1.22 – 2.08</td>
</tr>
</tbody>
</table>

### Triple Negative Disease

**Comparison HR P-value 95% CI**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>P-value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>nab vs. pac</td>
<td>0.93</td>
<td>0.7354</td>
<td>0.62 – 1.40</td>
</tr>
<tr>
<td>ixa vs. pac</td>
<td>1.46</td>
<td>0.0647</td>
<td>0.98 – 2.18</td>
</tr>
</tbody>
</table>

28% of 799 ER/PR- = 225
Overall Survival (OS)

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>OS in Months, Median</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sb-P ± Bevacizumab</td>
<td>26</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>nab-P ± Bevacizumab</td>
<td>27</td>
<td>1.02</td>
<td>0.75 - 1.38</td>
<td>.92</td>
</tr>
<tr>
<td>Ixa ± Bevacizumab</td>
<td>21</td>
<td>1.28</td>
<td>0.95 - 1.72</td>
<td>.10</td>
</tr>
</tbody>
</table>

Bev, bevacizumab; CALGB, Cancer and Leukemia Group B; HR, hazard ratio; Ixa, ixabepilone; MBC, metastatic breast cancer; nab-P, nab-paclitaxel; sb-P, solvent-based paclitaxel.

Toxicity

• Grade 3+ adverse events
  – Hematologic: nab/pac/ixa
    • 51% vs 21% and 12%
  – Non hematologic: nab/pac/ixa
    • 60% vs 44% and 56%

• Sensory neuropathy
  – Grade 3+: nab/pac/ixa
    • 25% vs 16% and 25%

• Other toxicities
  – More common in both experimental arms
Nab-paclitaxel

- Role in Neoadjuvant setting?
- TNBC subset?
pCR is a Surrogate for Survival

Cortazar et al. Lancet 2014
## Carboplatin Improves pCR in TNBC

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Tumor Subtypes</th>
<th>Regimen (for TNBC)</th>
<th>Carboplatin dose/schedule</th>
<th>ypT0N0 rates TNBC</th>
</tr>
</thead>
</table>
| GeparSixto     | 588 | 1. *HER2+ 2. TNBC (315) | a) Paclitaxel/doxil/bev  
b) Paclitaxel/doxil/bev + Carbo              | AUC 2→1.5, weekly          | a)36.9%  
b)53.2% |
| CALGB 40603    | 443 | 1. TNBC        | a) Paclitaxel → ddAC +/- bev  
b) Paclitaxel/Carbo → ddAC +/- bev          | AUC6, q3wks during paclitaxel | a)41%  
b)54% |
| ISPY2          | 72  | 1. HR+/HER2- 2. HR-/HER2- | a) Paclitaxel → ddAC  
b) Paclitaxel → ddAC, Carbo/velaparib        | AUC6, q3wks x4 cycles     | a)26%  
b)52% |
| Northwestern   | 30  | 1. TNBC        | a) Eribulin + carboplatin     | AUC6, q3weks x4 cycles    | a)45.8% |

* no benefit in HER2+

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von Minckwitz Lancet Oncol 2014  
Sikov JCO 2014  
Rugol SABCS 2013  
Giordano SABCS 2013
Paclitaxel 80 mg/m² wkly x 12
Bevacizumab 10 mg/kg q2wks x 9
Carboplatin AUC 6 q3wks x 4
Paclitaxel 80 mg/m² wkly x 12
Carboplatin AUC 6 q3wks x 4
Bevacizumab 10 mg/kg q2wks x 9
Paclitaxel 80 mg/m² wkly x 12
Menstrual hormone manipulation
Surgery &
XRT*
No Adjuvant Systemic Treatment Planned*
&Research biopsies if residual tumor
*MD discretion

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CALGB 40603 – EFS by pCR Breast/Axilla

HR=0.30 (0.19-0.45), p=<0.0001

- non-pCR 3-yr=62%
- pCR 3-yr=86%

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Years from Study Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>non-pCR</td>
<td>236</td>
</tr>
<tr>
<td>pCR</td>
<td>207</td>
</tr>
</tbody>
</table>
CALGB 40603 – EFS for carboplatin vs. not

HR=0.84 (0.58-1.22), p=0.36

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>No Cb</th>
<th>Cb</th>
</tr>
</thead>
<tbody>
<tr>
<td>218</td>
<td>185</td>
<td>145</td>
</tr>
<tr>
<td>225</td>
<td>202</td>
<td>162</td>
</tr>
<tr>
<td>185</td>
<td>145</td>
<td>94</td>
</tr>
<tr>
<td>202</td>
<td>162</td>
<td>31</td>
</tr>
<tr>
<td>145</td>
<td>94</td>
<td>31</td>
</tr>
<tr>
<td>162</td>
<td>31</td>
<td>37</td>
</tr>
</tbody>
</table>

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(GeparSixto) Design for Patients with TNBC

N=315 patients with centrally confirmed TNBC

cT2, cT3, or cT4a-d or cT1 and cN+ or pN_{SLN}+

Paclitaxel (P) 80 mg/m² q1w
Non-pegylated liposomal doxorubicin (M) 20 mg/m² q1w
Bevacizumab 15 mg/kg q3w

Carboplatin (Cb) q1w
Dose of AUC 2 was reduced to AUC 1.5 after enrolment of 330 patients

von Minckwitz SABCS 2015 (with permission)
pCR Rates by Subtype

ypT0 ypN0

HER2-pos. BC

- PM: N=136
- PMCb: N=137

OR 0.84; p=0.6

TNBC

- PM: N=157
- PMCb: N=158

OR 1.94; p=0.005

Test for interaction p=0.015

von Minckwitz SABCS 2015 (with permission)
DFS: Effect of Carboplatin in TNBC

3 yrs DFS 85.8%
3 yrs DFS 76.1%

Logrank p=0.0325
HR PMCb to PM = 0.56, 95% CI (0.33, 0.96), p=0.0350

von Minckwitz SABCS 2015 (with permission)
Carboplatin in Neoadjuvant Setting

<table>
<thead>
<tr>
<th></th>
<th>CALGB 40603</th>
<th>GeparSixto</th>
</tr>
</thead>
<tbody>
<tr>
<td># with TNBC</td>
<td>443</td>
<td>315</td>
</tr>
</tbody>
</table>
| Regimen              | a)Paclitaxel → ddAC +/- bev  
b)Paclitaxel/Carbo → ddAC +/- bev | a)Paclitaxel/doxil /bev  
b)Paclitaxel/doxil /bev + Carbo |
| Carbo dosing         | AUC6, q3wks during paclitaxel | AUC 2→1.5, weekly |
| pCR rate             | a)41%  
b)54% | a)36.9%  
b)53.2% |
| 3 year DFS           | 76% vs 71% (HR 0.84, 95%CI 0.58-1.22, p=0.36) | 85.8% vs 76.1% (HR 0.56, 95%CI 0.33-0.96, p=0.035) |

- Nonstandard US regimens
- Carbo dose density?
- Increased toxicity
- May affect completion of standard therapy
- Not ready for routine use
- Encourage clinical trial participation
GeparSepto nab®-Paclitaxel at a Dose of 125 mg/m² Weekly is Equally Efficacious but Less Toxic Than at 150 mg/m²—Results From the Neoadjuvant Randomized GeparSepto Study (GBG 69)

G Von Minckwitz, M Untch, C Jackisch, A Schneeweiss, B Conrad, B Aktas, C Denkert, H Eidtmann, H Wiebringhaus, S Kümmel, J Hilfrich, M Warm, S Paepke, M Just, C Hanusch, J Hackmann, JU Blohmer, M Clemens, SD Costa, B Gerber, V Nekljudova, S Loibl

nab® is a registered trademark of Celgene Corporation.

San Antonio Breast Cancer Symposium, December 9-13, 2014

Initial Study Design

N=1200

**Core biopsy** (before study entry)

**Arm A**
- Paclitaxel 80 mg/m² weekly
- nab-Paclitaxel 150 mg/m² weekly
- Epirubicin 90 mg/m²
- Cyclophosphamide 600 mg/m²

**Arm B**
- If HER2 positive: Trastuzumab
- If HR positive: Tamoxifen, Aromatase inhibitors acc. to AGO Guidelines

12 weeks

**Core biopsy optional**

**Surgery**

*Centrally confirmed:
- Subtypes HER 2/ HR
- Ki 67
- SPARC

If HER2 positive:
- Trastuzumab 8 mg/kg (loading dose) followed by 6 mg/kg
- Pertuzumab (absolute dose per application) 840 mg (loading dose) followed by 420 mg
GeparSepto: nab-Paclitaxel 125 vs 150 mg/m² vs 80 mg/m² Paclitaxel as Neoadjuvant Treatment in Early Breast Cancer

**Background**

- The GeparSepto study showed that nab-P increased the pCR rate compared with Pac as part of sequential taxane-epirubicin/cyclophosphamide neoadjuvant treatment in early breast cancer.

- After a safety analysis found higher rates of dose reductions and treatment discontinuations with nab-P compared with Pac, nab-P dose was reduced from 150 to 125 mg/m².
### GeparSepto: nab-Paclitaxel 125 vs 150 mg/m² vs 80 mg/m² Paclitaxel as Neoadjuvant Treatment in Early Breast Cancer

#### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before Amendment</th>
<th>After Amendment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>nab-P 150 mg/m²</strong> n = 229</td>
<td>Pac 80 mg/m² n = 226</td>
<td>nab-P 125 mg/m² n = 377</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>49 (28 - 75)</td>
<td>48 (26 - 75)</td>
</tr>
<tr>
<td>cT1-3, n (valid %)</td>
<td>209 (91.7)</td>
<td>209 (92.9)</td>
</tr>
<tr>
<td>cN positive, n (valid %)</td>
<td>101 (45.5)</td>
<td>103 (46.2)</td>
</tr>
<tr>
<td>ER and/or PgR+, n (valid %)</td>
<td>144 (62.9)</td>
<td>146 (64.6)</td>
</tr>
<tr>
<td>HER2+, n (valid %)</td>
<td>56 (24.5)</td>
<td>54 (23.9)</td>
</tr>
<tr>
<td>Tumor grade G3, n (valid %)</td>
<td>123 (53.7)</td>
<td>127 (56.2)</td>
</tr>
<tr>
<td>Ductal/ductal-lobular invasive, n (valid %)</td>
<td>199 (86.9)</td>
<td>195 (86.3)</td>
</tr>
<tr>
<td>TNBC, n (valid %)</td>
<td>64 (27.9)</td>
<td>62 (27.4)</td>
</tr>
<tr>
<td>HER2−/HR+, n (valid %)</td>
<td>109 (47.6)</td>
<td>110 (48.7)</td>
</tr>
<tr>
<td>Ki-67 &gt;20%, n (valid %)</td>
<td>139 (60.7)</td>
<td>136 (60.2)</td>
</tr>
<tr>
<td>SPARC+ (IRS 6-12), n (valid %)</td>
<td>42 (18.3)</td>
<td>40 (17.7)</td>
</tr>
</tbody>
</table>

GeparSepto: nab-Paclitaxel 125 vs 150 mg/m² vs 80 mg/m² Paclitaxel as Neoadjuvant Treatment in Early Breast Cancer

**pCR Rates According to nab-Paclitaxel Dose**

- Differences in pCR rates between nab-P 125 mg/m² and Pac 80 mg/m² were greatest in the overall cohort and the TNBC subgroup.
GeparSepto: *nab*-Paclitaxel 125 vs 150 mg/m² vs 80 mg/m² Paclitaxel as Neoadjuvant Treatment in Early Breast Cancer

**Hematologic Toxicities**

<table>
<thead>
<tr>
<th>AE, n (valid %)</th>
<th>Grade</th>
<th><em>nab</em>-P 150 mg/m² n = 220</th>
<th><em>nab</em>-P 125 mg/m² n = 385</th>
<th>Pac 80 mg/m² n = 601*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Any 3/4</td>
<td>206 (93.6) 5 (2.3)</td>
<td>354 (91.9) 8 (2.1)</td>
<td>528 (88.1) 4 (0.7)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>Any 3/4</td>
<td>209 (95.0) 110 (50.0)</td>
<td>358 (93.0) 170 (44.2)</td>
<td>550 (91.8) 271 (45.2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Any 3/4</td>
<td>197 (50.0) 140 (63.9)</td>
<td>334 (86.8) 228 (59.2)</td>
<td>487 (81.3) 371 (61.9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Any 3/4</td>
<td>51 (23.2) 2 (0.9)</td>
<td>93 (24.2) 3 (0.8)</td>
<td>145 (24.2) 3 (0.5)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3/4</td>
<td>10 (4.5)</td>
<td>18 (4.7)</td>
<td>24 (4.0)</td>
</tr>
</tbody>
</table>

* For safety analysis, patients were grouped according to their dose on day 1
GeparSepto: *nab*-Paclitaxel 125 vs 150 mg/m² vs 80 mg/m² Paclitaxel as Neoadjuvant Treatment in Early Breast Cancer

**Nonhematologic Toxicities**

<table>
<thead>
<tr>
<th>AE, n (valid %)</th>
<th>Grade</th>
<th><em>nab</em>-P 150 mg/m² n = 220</th>
<th><em>nab</em>-P 125 mg/m² n = 385</th>
<th>Pac 80 mg/m² n = 601</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any nonhematologic AE</td>
<td>Any 3/4</td>
<td>220 (100.0)</td>
<td>385 (100.0)</td>
<td>600 (99.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>188 (85.5)</td>
<td>306 (79.5)</td>
<td>458 (76.2)</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>Any 3/4</td>
<td>194 (88.2)</td>
<td>320 (83.1)</td>
<td>392 (65.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32 (14.5)</td>
<td>32 (8.1)</td>
<td>16 (2.7)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>Any 3/4</td>
<td>54 (24.5)</td>
<td>117 (30.4)</td>
<td>107 (17.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 (1.4)</td>
<td>10 (2.6)</td>
<td>6 (1.0)</td>
</tr>
</tbody>
</table>

* For safety analysis, patients were grouped according to their dose on day 1

GeparSepto: *nab*-Paclitaxel 125 vs 150 mg/m² vs 80 mg/m² Paclitaxel as Neoadjuvant Treatment in Early Breast Cancer

**Taxane Treatment Exposure**

<table>
<thead>
<tr>
<th></th>
<th>nab-P 150 mg/m²</th>
<th>nab-P 125 mg/m²</th>
<th>Pac 80 mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation, %</td>
<td>26.8</td>
<td>16.6</td>
<td>13.3</td>
</tr>
<tr>
<td>Relative total dose intensity,^a^ median (range), %</td>
<td>108 (10 - 123)</td>
<td>99 (17 - 104)</td>
<td>100 (0 - 136)</td>
</tr>
</tbody>
</table>

- Taxane treatment was discontinued in 26.8% (*nab*-P 150 mg/m²), 16.6% (*nab*-P 125 mg/m²), and 13.3% (Pac 80 mg/m²) of patients, respectively.
- Median RTDI of taxane (based on *nab*-P 125 mg/m²) was 108% (10% - 123%) with *nab*-P 150 mg/m², 99% (17%-104%) with *nab*-P125 mg/m², and 100% (0%-136%) with Pac 80 mg/m².

^a^ Based on *nab*-P 125 mg/m².

**GeparSepto: nab-Paclitaxel 125 vs 150 mg/m² vs 80 mg/m² Paclitaxel as Neoadjuvant Treatment in Early Breast Cancer**

**Time to Resolution of Peripheral Sensory Neuropathy**

- Median time to resolve peripheral sensory neuropathy from grade 2 - 4 to grade ≤ 1
  - *nab-P* 125 mg/m²: 6 weeks; *nab-P* 150 mg/m²: 12.4 weeks
  - Median time to resolve from grade 3 - 4 to grade ≤ 1 was 17 and 20 weeks, respectively

---

Comparison of 12 weeks neoadjuvant Nab-Paclitaxel combined with Carboplatinum vs. Gemcitabine in triple-negative breast cancer: WSG-ADAPT TN randomized phase II trial


West German Study Group, Moenchengladbach; Bethesda Hospital, Moenchengladbach; University Hospital Schleswig-Holstein, Camus Lübeck; Institute of Pathology, MHH, Hanover; University Hospital Tübingen, Oncological practice Troisdorf, Clinics Rotkreuz, Munich, Clinics Holweide, Cologne, Marienhospital Witten; Gynecological Practice, Hildesheim, University Hospital, Essen; St. Elisabeth Clinics, Cologne, University Hospital Charite, Berlin, Diakonie Clinics, Hamburg, Clinics Essen-Mitte, Hospital Mutterhaus, Trier; Evangelical Waldkrankenhau, Berlin, St. Antonius Hospital, Eschweiler, Institute of Pathology, Viersen Ludwig Maximilian University Clinics Munich
ADAPT HR-/HER2-:
Trial Design

Standard chemotherapy (4xEC) recommended after surgery / 12-week biopsy (in case of clinical non-pCR)

03.12.2015

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ADAPT HR-/HER2-:
CONSORT Diagram

N=385 screened

N=336 randomized (ITT)

N=182 randomized
Nab-Pac/Gem

N=180 started Tx

Adverse events n=10 (5.5%)
Progress/relapse n=10 (5.4%)
Pat. decision n=2 (1%)
Other n=2 (1%)

N=158 completed Tx by protocol 87%

N=154 randomized
Nab-Pac/Carbo

N=151 started Tx

Adverse events n=6 (4%)
Progress n=2 (1.3%)
Pat. decision n=1 (0.6%)
Other n=5 (3.2%)

N=140 completed Tx by protocol 91%

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### ADAPT HR-/-HER2-: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Nab-Pac/Gem</th>
<th>Nab-Pac/Carbo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>182</td>
<td>154</td>
</tr>
<tr>
<td>Age</td>
<td>median (range)</td>
<td>50 (26-75)</td>
</tr>
<tr>
<td>cT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>68 (37.4%)</td>
<td>57 (37%)</td>
</tr>
<tr>
<td>≥2</td>
<td>114 (62.6%)</td>
<td>97 (62.9%)</td>
</tr>
<tr>
<td>cN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>135 (74.2%)</td>
<td>113 (73.4%)</td>
</tr>
<tr>
<td>≥1</td>
<td>47 (25.8%)</td>
<td>41 (26.6%)</td>
</tr>
<tr>
<td>Ki-67</td>
<td>median</td>
<td>75%</td>
</tr>
<tr>
<td>Central grade 3</td>
<td>172 (94.5%)</td>
<td>140 (90.9%)</td>
</tr>
</tbody>
</table>
ADAPT HR-/HER2-:
Safety

- Dose reductions:
  - Nab-Pac/Gem vs. Nab-Pac/Carbo:
    • 20.6% vs. 11.9%
- Patients with SAEs (all grades):
  - Nab-Pac/Gem vs. Nab-Pac/Carbo:
    • 17.2% vs. 10.6%
  - Related to therapy:
    • Nab-Pac/Gem vs. Nab-Pac-Carbo
      • 10.6% vs. 5.3%
    • 96.3% recovered without sequelae
ADAPT HR-/HER2-: Toxicity CTC ≥ grade 3

<table>
<thead>
<tr>
<th></th>
<th>Nab-Pac/Gem</th>
<th>Nab-Pac/Carbo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia/decreased neutrophils</td>
<td>15.0%</td>
<td>14.6%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Infections*</td>
<td>6.1%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Increased ALT*</td>
<td>11.7%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>0.6%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

03.12.2015  *comparison between arms significant at $\alpha = 5\%$
ADAPT HR-/HER2-: Pathological complete response

<table>
<thead>
<tr>
<th>Group</th>
<th>pCR Rate</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (nab-Pac+Gem)</td>
<td>28.7%</td>
<td>51/178</td>
</tr>
<tr>
<td>B (nab-Pac+Carbo)</td>
<td>45.9%</td>
<td>67/146</td>
</tr>
</tbody>
</table>

p<0.001
ADAPTHR-/HER2-:
pCR by early response

- n=71 (21%) with missing 3-week biopsy
- n=80 (24%) significant necrosis (<500 invasive tumor cells) in 3-week biopsy
- Combination of <500 tumor cells and/or Ki67 decrease ≥30% in 3-week biopsy was identified as an early response criterion

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ADAPT HR-/HER2-: pCR in study arms by early response

A (nab-Pac+Gem)

- Responders: 13.5%
- Non-Responders: 36.1%
- Value: 10/74

B (nab-Pac+Carbo)

- Responders: 29.5%
- Non-Responders: 52.8%
- Value: 26/72, 13/44, 38/72

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ADAPT HR-/-HER2-:
Conclusions

- Nab-Pac/Carbo is associated with less toxicity and significant superiority to Nab-Pac/Gem in terms of pCR
- Early morphological changes seem to be predictive for pCR, irrespective of treatment arm
- No predictive factors for carboplatin efficacy have been identified so far; further correlative analyses (e.g. subtypes, family history, BRCA1-ness etc.) are ongoing
- Validation of these results in larger studies seems warranted
Checkpoint Inhibitors
The next frontier!
1. Release of cancer antigens
   - Immunogenic cell death
   - Tolerogenic cell death

2. Cancer antigen presentation
   - TNF-α
   - IL-1
   - IFN-α
   - CD40L/CD40
   - CDN
   - ATP
   - HMGB1
   - TLR
   - IL-10
   - IL-4
   - IL-13

3. Priming and activation
   - CD28/B7.1
   - CD137/CD137L
   - OX40/OX40L
   - CD27/CD70
   - HVEM
   - GITR
   - IL-2
   - IL-12
   - CTLA4/B7.1
   - PD-L1/PD-1
   - PD-L1/B7.1
   - Prostaglandins

4. Trafficking of T cells to tumors
   - CX3CL1
   - CXCL9
   - CXCL10
   - CCL5

5. Infiltration of T cells into tumors
   - LFA1/ICAM1
   - Selectins
   - VEGF
   - Endothelin B receptor

6. Recognition of cancer cells by T cells
   - Reduced pMHC on cancer cells

7. Killing of cancer cells
   - IFN-γ
   - T cell granule content
   - PD-L1/PD-1
   - PD-L1/B7.1
   - IDO
   - TGF-β
   - TIM-3/phospholipids
   - LAG-3
   - Arginase
   - MICA/MICB
   - B7-H4
   - BT LA
   - VISTA

Stimulatory factors: Green
Inhibitors: Red
In a state of chronic antigen presentation, such as malignancy, the chronic presence of antigen or pro-inflammatory cytokines (IL-12, IFN gamma, etc) can upregulate PD-1 expression on the T cell; tumor clones can also select for PD-L1 expression. With PD-1-PD-L1 binding, even in the presence of the costimulatory molecule, "peripheral exhaustion" can occur.

*PD-L1: programmed death-ligand 1; CD: cluster of differentiation; PD-1: programmed cell death-1; APC: antigen-presenting cells; MHC: major histocompatibility complex; IL: interleukin; IFN gamma: interferon gamma.*
Safety and Clinical Activity pf Atezolizumab (anti-PDL1) in Combination with nab-Paclitaxel in Patients with Metastatic Triple-Negative Breast Cancer


Courtesy of Adams et al. SABCS 2015 P2-11-06
Treatment & Biopsy Schedule

- Atezolizumab
- Nab-paclitaxel

Safety Cohort:

Serial Biopsy Cohort:

Red arrow indicates biopsy. 
* A second post-dose biopsy was taken in serial biopsy cohort ≈ 4 wk after first dose of atezolizumab.

Courtesy of Adams et al. SABCS 2015 P2-11-06
<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>1L (n = 9)</th>
<th>2L (n = 8)</th>
<th>3L+ (n = 7)</th>
<th>All Patients N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>66.7% (29.9, 92.5)</td>
<td>25% (3.2, 65.1)</td>
<td>28.6% (3.7, 71.0)</td>
<td>41.7% (22.1, 63.4)</td>
</tr>
<tr>
<td>ORR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>88.9% (51.7, 99.7)</td>
<td>75.0% (34.9, 96.8)</td>
<td>42.9% (9.9, 81.6)</td>
<td>70.8% (48.9, 87.4)</td>
</tr>
<tr>
<td>CR</td>
<td>11.1%</td>
<td>0</td>
<td>0</td>
<td>4.2%</td>
</tr>
<tr>
<td>PR</td>
<td>77.8%</td>
<td>75.0%</td>
<td>42.9%</td>
<td>66.7%</td>
</tr>
<tr>
<td>SD</td>
<td>11.1%</td>
<td>25.0%</td>
<td>28.6%</td>
<td>20.8%</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>28.6%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Confirmed ORR defined as at least 2 consecutive assessments of complete or partial response.

<sup>b</sup> Including investigator-assessed unconfirmed responses.
**Table 5. Objective Response Rate by PD-L1 Expression Level**

<table>
<thead>
<tr>
<th></th>
<th>IC0 (n = 7)</th>
<th>IC1/2/3 (n = 9)</th>
<th>Unknown (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>57.1% (18.4, 90.1)</td>
<td>77.8% (40.0, 97.2)</td>
<td>75% (34.9, 96.8)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>12.5%</td>
</tr>
<tr>
<td>PR</td>
<td>57.1%</td>
<td>77.8%</td>
<td>62.5%</td>
</tr>
<tr>
<td>SD</td>
<td>42.9%</td>
<td>22.2%</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>25%</td>
</tr>
</tbody>
</table>

*Including investigator-assessed unconfirmed responses.*
Summary

• nab-paclitaxel remains an important agent for treatment of MBC
• nab-paclitaxel may be a preferred taxane in the preoperative setting
• nab-paclitaxel is frequently partnered with new agents (ie CPM) due to its anti-tumor activity and tolerability....and no steroids needed, attractive for immune strategies!