From taxanes to epothilones: Targeting microtubules in breast cancer and beyond

Slide Update 2

Slide 1
Title slide

Slide 2

Taxanes are an important component of many regimens used for the treatment of both early and advanced breast cancer. NCCN treatment guidelines recommend taxanes either as monotherapy or in combination with another cytotoxic agent or targeted therapy. Taxanes, alone or in combination, are commonly used in adjuvant and metastatic breast cancer therapy. Recent studies have evaluated combination versus sequential taxane use, and studied the impact of patient and tumor characteristics, such as hormonal and menopausal status on efficacy. Although extent of disease, disease-free interval (DFI), prior adjuvant therapy, and performance status remain of prognostic value, current recommendations also reflect individualization of treatment according to hormone receptor (HR) and HER2 status. The presence of the breast cancer susceptibility gene mutations, BRCA1 and BRCA2, may also guide therapy, since BRCA1 and BRCA2 breast cancers have an increased sensitivity to anthracyclines and platinum, but reduced sensitivity to taxanes and vinca alkaloids. Other markers may indicate an anticipated reduced response to chemotherapy; PTEN deficiency being associated with trastuzumab resistance and tau expression with paclitaxel resistance. The hypoxia regulated gene, CAIX, upregulated in basal-like breast tumors, has also been associated with chemotherapy resistance.

Since taxanes are widely used in the management of breast cancer, taxane retreatment is common. A retrospective analysis in advanced breast cancer patients (n=246) reported taxane retreatment in 50% patients (data not shown). However, this may be complicated for a variety of reasons. Modest and variable efficacy has been reported following taxane re-treatment with either the same or a different taxane; the latter indicating “cross-resistance” between agents. Seidman and colleagues reported a 27% overall response rate (ORR) in metastatic patients retreated with paclitaxel, while an ORR of 18% was reported following docetaxel use in paclitaxel-resistant metastatic patients. Taxane therapy of breast cancer is further complicated by the absence of a strict definition of “resistance” and from uncertainty as to the exact clinical significance of DFI and taxane-free interval (TFI) to drug selection.

1NCCN Clinical Practice Guidelines in Oncology, Breast Cancer V.1.2009
2Andreopoulou & Hortobagyi, J Clin Oncol 2008; 26: 3660–2
3Tan et al, Br J Cancer 2009; 100: 405–11
4Burns et al, ASCO Breast Cancer Symposium 2008; Abstract 139
5Seidman et al, J Clin Oncol 1996; 14: 1877–84
From taxanes to epothilones: Targeting microtubules in breast cancer and beyond

Slide Update 2

Adjuvant chemotherapy for HER2(-) breast cancer: NCCN recommendations for non-trastuzumab-containing regimens

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Other regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC</td>
<td>FAC / CAF</td>
</tr>
<tr>
<td>AC (dose dense) → P</td>
<td>FEC / CEF</td>
</tr>
<tr>
<td>AC → P qw</td>
<td>CMF</td>
</tr>
<tr>
<td>TC</td>
<td>AC → T q3w</td>
</tr>
<tr>
<td>AC</td>
<td>AC → P q3w</td>
</tr>
<tr>
<td>T = docetaxel; P = paclitaxel; qw = weekly; q2w = 2 weekly</td>
<td></td>
</tr>
</tbody>
</table>

NCCN Clinical Practice Guidelines in Oncology, Breast Cancer V.1.2009

Slide 3

NCCN breast cancer treatment guidelines provide recommendations for chemotherapy and non-chemotherapy treatment of early localized, locally advanced, and metastatic breast cancers.

This slide summarizes the recommended adjuvant non-trastuzumab-containing options for patients with HER2(-) breast cancer. Taxanes form an essential component of regimens used in adjuvant therapy, and are combined or sequentially administered with drugs such as anthracyclines and cyclophosphamide.

T = docetaxel, A = doxorubicin, C = cyclophosphamide, P = paclitaxel, F = fluorouracil, E = epirubicin, M = methotrexate

NCCN Clinical Practice Guidelines in Oncology, Breast Cancer V.1.2009

Slide 4

NCCN treatment recommendations are also provided for the management of breast cancer of HER2(+) subtype. Trastuzumab is recommended to be used in combination with taxanes, decreasing the potential for cardiotoxicity which can arise from concomitant use of an anthracycline. Neoadjuvant therapy, however, permits use of concomitant trastuzumab-and epirubicin 75 mg/m².

A = doxorubicin, C = cyclophosphamide, T = trastuzumab, D = docetaxel, F = fluorouracil, E = epirubicin

NCCN Clinical Practice Guidelines in Oncology, Breast Cancer V.1.2009
From taxanes to epothilones:
Targeting microtubules in breast cancer and beyond

Slide 5
Currently available microtubule-targeting drugs bind to microtubule tubulin. This binding results in microtubule stabilization or destabilization and resultant inhibition of microtubule activity/function. Taxanes block the dynamic behavior of the microtubule, by stabilizing GDP-bound tubulin in the microtubule (microtubule stabilizers) and inhibiting microtubule activity essential to spindle formation. Mitotic arrest at the G2/M mitotic stage and cell death follow (as shown).


Slide 6
This slide illustrates the role of microtubules during interphase and mitosis, and describes likely target sites for microtubule-targeting agents throughout the cell cycle. The microtubule cytoskeleton is essential to chromosome separation at mitosis, and drives the intracellular trafficking of material-ferrying organelles across the cell. The dynamic nature of microtubules increases through interphase and mitosis, allowing for the “seek and capture” of chromosomes, chromosome alignment at the metaphase plate and completion of cell division.

Microtubule-targeted drugs are categorized into; Microtubule destabilizers (microtubule polymerization inhibitors) and microtubule stabilizers (microtubule polymerization enhancers). Vinca alkaloids and the halichondrin B analog, E7389, are examples of microtubule destabilizers, while taxanes and epothilones are examples of microtubule-stabilizers.

It is probable that more than one mechanism underlies the anti-cancer activity of microtubule-targeting drugs. In addition to inhibiting mitotic microtubule activity, taxanes are also thought to interfere with microtubule function during interphase, inhibiting essential activities including intracellular trafficking and signal transduction.

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From taxanes to epothilones: Targeting microtubules in breast cancer and beyond

Slide Update 2

Why new treatment strategies and drugs are needed in breast cancer

- Incidence of breast cancer (↑ 35% cases, 2008 → 2030)¹
  - significant ↑ in patients >65 years and non-Caucasians
  - drug tolerability and racial disparities important
- Treatment should be individualized to patient and tumor characteristics
  - patient (i.e., age, menopausal status, co-morbidities)
  - tumor (i.e., site, stage, size, subtype, resistance profile)
- 40% of patients treated with curative intent progress to metastatic disease²
- Taxanes and anthracyclines remain standard of care for EBC and MBC
  - drug re-use is associated with resistance and toxicity
  - resistance accounts for treatment failure in 90% of MBC patients³

¹Smith et al, SABCS 2008; Abstract 6076
²O’Shaughnessy et al, Oncologist 2002; 7(Suppl. 6): 4–12
³Longley & Johnston, J Pathol 2005; 205: 275–92

reported race (black vs white) to have no significant influence on pathological complete response or recurrence-free survival (RFS) following adjuvant chemotherapy in triple-negative breast cancer (TNBC) patients (data not shown), other studies have described significantly increased recurrence rates and death in African-American (AA) versus Caucasian TNBC patients (n=93; AA vs Caucasian; local recurrence rate 4.30% vs 2.15%, systemic recurrence rate 19% vs 10%, death 17.2% vs 13.98%).

Since 40% of patients treated with curative intent progress to metastatic disease, and treatment failure for chemotherapy resistance is high in metastatic patients, a greater emphasis is placed upon the use of novel regimens and drug therapies in optimizing therapy.

Studies are ongoing to evaluate the influence of race on response to chemotherapy. Although Dawood and colleagues reported race (black vs white) to have no significant influence on pathological complete response or recurrence-free survival (RFS) following adjuvant chemotherapy in triple-negative breast cancer (TNBC) patients (data not shown), other studies have described significantly increased recurrence rates and death in African-American (AA) versus Caucasian (CA) patients (n=93; AA vs CA; local recurrence rate 4.30% vs 2.15%, systemic recurrence rate 19% vs 10%, death 17.2% vs 13.98%).

Slide 8

Breast cancer is a heterogenous disease and, as such, studies are currently evaluating the role of a wide range of targets and novel therapeutic approaches in breast cancer management. This slide describes targets and therapeutic approaches under pre-clinical or clinical investigation for breast cancer.

Inhibition of microtubule function is an established approach; this being fundamental to the activity of taxanes and vinca alkaloids. More recently, FDA-approval of the epothilone, ixabepilone, and of nab-paclitaxel, has provided newer therapies which differ in their efficacy and toxicity to existing microtubule-targeting breast cancer drugs.

Tan & Swain, Cancer J 2008; 14: 343–51

Adapted from Tan & Swain, Cancer J 2008; 14: 343–51
From taxanes to epothilones: Targeting microtubules in breast cancer and beyond

Slide 9
Epothilones, while structurally unrelated to taxanes, act similarly to them. Through binding to microtubule β-tubulin, epothilones interfere with microtubule dynamics to produce an increase in β-tubulin polymerization and microtubule stabilization. Epothilones and taxanes differ in their binding sites with the thiazole side-chain of epothilone A and ixabepilone occupying a unique binding site region on β-tubulin, such that only one polar contact point (C7-OH) is shared with paclitaxel. These structural and binding site disparities between epothilones and paclitaxel account in part, at least, for differences in the pre-clinical and clinical activity of the 2 drug classes.

While a number of mechanisms may be implicated in resistance to microtubule-binding drugs, differences exist between those mechanisms implicated in resistance to paclitaxel and ixabepilone. Enhanced expression and activity of the drug efflux pump, PgP, and alterations of tubulin mutation or tubulin isotype expression, are mechanisms implicated in resistance to paclitaxel in vitro. However, ixabepilone is relatively immune from these resistance mechanisms. Altered expression of proteins such as Bcl-2 and Bax, or alterations of the binding proteins stathmin and tau, may generate resistance to both paclitaxel and ixabepilone.

Differences in the mechanisms causing resistance to taxanes and ixabepilone allow for use of epothilones in paclitaxel-resistant cell lines and in paclitaxel-resistant MBC. Ixabepilone is the only FDA-approved epothilone, licensed for use in resistant MBC.

Slide 10
Epothilones in MBC: An update
From taxanes to epothilones: Targeting microtubules in breast cancer and beyond

Slide Update 2

Evolving data for epothilones in MBC

- KOS-862 (original slide resource)
- Ixabepilone
  - phase II studies
    - taxane ± anthracycline resistant MBC (original slide resource)
    - trastuzumab in HER2(+) MBC (original slide resource, slide update 2)
  - phase III studies
    - pivotal 046 trial (original slide resource)
    - confirmatory 048 trial (slide update 1)
    - subanalyses of pooled 046 and 048 data (slide update 2)
      - taxane-resistant MBC
      - first-line MBC
      - triple-negative MBC
      - symptomatic MBC
      - resolution of peripheral neuropathy (inc. 081 trial)

Data are rapidly evolving for use of epothilones in the management of MBC. This data has been reviewed in this program and is available in either the original slide resource for this program, or in the subsequent updates.

Data for KOS-862 is limited, however a 14% ORR (original slide resource, Buzdar 2005) has been reported following its study in anthracycline- and taxane-resistant MBC (n=37, 29 evaluable).

A number of phase II studies have demonstrated the efficacy of ixabepilone in taxane- and anthracycline-resistant metastatic patients, as reviewed in the original slide resource. Preliminary data have been reported for ixabepilone in combination with carboplatin and trastuzumab in 59 1st-line HER2(+) MBC patients (original slide resource, Moulder 2007). Further phase II data in HER2(+) patients are described in this update.

Phase III studies (studies 046 and 048) have described the efficacy and tolerability of ixabepilone in combination with capecitabine in anthracycline and taxane pre-treated/resistant MBC (046 original slide resource; 048 slide update 1). Subanalysis of pooled 046 and 048 study data have been performed, with data presented at SABCS 2008 reviewed in this update.

Buzdar et al, SABCS 2005; Abstract 1087
Moulder et al, SABCS 2007; Abstract 6070
Hortobagyi et al, ASCO Breast Cancer Symposium 2008; Abstract 186
Roche et al, SABCS 2008; Abstract 186
Vahdat et al, SABCS 2008; Abstract 6117
Rugo et al, SABCS 2008; Abstract 3057
Conte et al, SABCS 2008; Abstract 6114
Perez et al, SABCS 2008; Abstract 6140

Slide 11

This slide describes the study design of a phase II non-randomized evaluation of the efficacy and safety of 3-weekly ixabepilone 40 mg/m² plus trastuzumab, administered until disease progression or toxicity, in 39 HER2(+) metastatic patients. Patients were either chemotherapy or trastuzumab-naïve for MBC (Cohort 1, n=15; adjuvant trastuzumab >1 year prior to study entry permitted) or had received <2 metastatic chemotherapy regimens and 1 or 2 adjuvant or metastatic trastuzumab regimens (Cohort 2, n=24). Dose reduction for ixabepilone toxicity was permitted. HR(+) status was noted in 33% of Cohort 1 and 50% of Cohort 2 patients respectively, with ≥3 metastatic sites present in 40% and 46% patients and prior adjuvant taxane therapy in 27% and 29% patients, respectively.

Tolaney et al, SABCS 2008; Abstract 3137

Ixabepilone + trastuzumab in HER2(+) MBC: Study design

- Inclusion criteria included:
  - epothilone-naïve
  - neuropathy grade <2

Tolaney et al, SABCS 2008; Abstract 3137

Slide 12

This slide describes the study design of a phase II non-randomized evaluation of the efficacy and safety of 3-weekly ixabepilone 40 mg/m² plus trastuzumab, administered until disease progression or toxicity, in 39 HER2(+) metastatic patients. Patients were either chemotherapy or trastuzumab-naïve for MBC (Cohort 1, n=15; adjuvant trastuzumab >1 year prior to study entry permitted) or had received <2 metastatic chemotherapy regimens and 1 or 2 adjuvant or metastatic trastuzumab regimens (Cohort 2, n=24). Dose reduction for ixabepilone toxicity was permitted. HR(+) status was noted in 33% of Cohort 1 and 50% of Cohort 2 patients respectively, with ≥3 metastatic sites present in 40% and 46% patients and prior adjuvant taxane therapy in 27% and 29% patients, respectively.

Tolaney et al, SABCS 2008; Abstract 3137
From taxanes to epothilones: Targeting microtubules in breast cancer and beyond

Slide Update 2

**Ixabepilone + trastuzumab in HER2(+) MBC: Efficacy**

<table>
<thead>
<tr>
<th>Tolane 2008</th>
<th>1st-line MBC (n=15)</th>
<th>Non-1st-line MBC (n=24)</th>
<th>Overall (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (%)</td>
<td>80</td>
<td>33.3</td>
<td>51.3</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(51.9–95.7)</td>
<td>(16.6–55.3)</td>
<td>(34.8–67.6)</td>
</tr>
<tr>
<td>TTF (months)</td>
<td>5.6</td>
<td>4.6</td>
<td>NR</td>
</tr>
<tr>
<td>TTP (months)</td>
<td>NR</td>
<td>6.1</td>
<td>NR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moulder 2007**</th>
<th>1st-line MBC (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (%)</td>
<td>44</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>8.0</td>
</tr>
</tbody>
</table>

**Ixabepilone 15 mg/m² iv, + carboplatin (AUC=2) iv, d1/8/15 of 28d cycle, 6 cycles.**

**Trastuzumab 4 mg/kg then 2 mg/kg qw during chemotherapy, then at 6 mg/kg q3w to disease progression**

**Tolaney et al, SABCS 2008; Abstract 3137**

**Moulder et al, SABCS 2007; Abstract 6070**

Median results provided, NR = not reported

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**Capcitabine ± ixabepilone in anthracycline- and taxane-pre-treated, locally-advanced or MBC:**

**Study design for trials 046 and 048**

<table>
<thead>
<tr>
<th>MBC / LA Taxane + anthracycline pre-treated</th>
<th>Capcitabine 2500 mg/m² d1–14, q3w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capcitabine 2000 mg/m² d1–14, q3w + ixabepilone 40 mg/m² q3w</td>
<td></td>
</tr>
</tbody>
</table>

**Study population**

<table>
<thead>
<tr>
<th>Study 046† (n=752)</th>
<th>Study 048† (n=1221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td></td>
</tr>
<tr>
<td>A/T resistant ≤3 lines</td>
<td>A/T pre-treated ≤2 lines</td>
</tr>
<tr>
<td>Resistance criteria (disease progression within, months)</td>
<td>Resistance criteria (disease progression within, months)</td>
</tr>
<tr>
<td>Neo/adj. setting: 6 months A, 212 months T</td>
<td>Neo/adj. setting: 6 months A, 212 months T</td>
</tr>
<tr>
<td>Metastatic setting: 63 months A, 64 months T</td>
<td>Metastatic setting: 63 months A, 64 months T</td>
</tr>
<tr>
<td>Study endpoints</td>
<td></td>
</tr>
<tr>
<td>PFS (%)</td>
<td>OS (%)</td>
</tr>
<tr>
<td>A = anthracycline; T = taxane</td>
<td></td>
</tr>
</tbody>
</table>

**Study endpoints**

| A = anthracycline; T = taxane |
| OS (%) | PFS, safety |

**Study population**

<table>
<thead>
<tr>
<th>Study population</th>
<th>Study endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/T resistant ≤3 lines</td>
<td>PFS (%)</td>
</tr>
<tr>
<td>A/T pre-treated ≤2 lines</td>
<td>OS (%)</td>
</tr>
</tbody>
</table>

**Resistance criteria (disease progression within, months)**

| Neo/adj. setting: 6 months A, 212 months T | Neo/adj. setting: 6 months A, 212 months T |
| Metastatic setting: 63 months A, 64 months T | Metastatic setting: 63 months A, 64 months T |

**Study endpoints**

| A = anthracycline; T = taxane |
| OS (%) | PFS, safety |

**

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**Slide 13**

In this small study in advanced HER2(+) MBC, median ORR was 80% in 1st-line MBC, 33.3% in non-1st-line MBC, and 51.3% in the overall patient population. All responses were partial in nature. Median TTF in 1st-line and non-1st-line HER2(+) MBC was 5.6 months and 4.6 months respectively, with a median TTP of 6.1 months in the non-1st-line patients. Principle adverse effects of >grade 2 severity reported in 10% patients were; sensory neuropathy 56% (n=22), fatigue 38% (n=15), alopecia 36% (n=14), leukopenia 26% (n=10), and joint pain 26% (n=10).

Findings of this phase II study were similar to those reported following use of ixabepilone 15 mg/m² iv d1/8/15, in combination with carboplatin and trastuzumab, in 1st-line HER2(+) MBC (n=59) as reported by Moulder and colleagues.

**Tolaney et al, SABCS 2008; Abstract 3137**

**Moulder et al, SABCS 2007; Abstract 6070**

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**Slide 14**

This slide outlines the design of 2 phase III randomized, open-label studies of ixabepilone plus capecitabine versus capecitabine alone in taxane-resistant and anthracycline pre-treated/resistant locally-advanced/MBC.

Study 046 (n=752) and the confirmatory 048 study (n=1221) had differing resistance criteria; study criteria requiring 046-enrolled patients to be anthracycline- and taxane-resistant following ≤3 metastatic chemotherapy regimens, and 048 patients to be anthracycline- or taxane-pre-treated or resistant following ≤2 metastatic treatment regimens. Anthracycline resistance was defined as tumor progression during treatment or within 3 months of metastatic or within 6 months of (neo)adjuvant treatment. Taxane resistance was defined as tumor progression during treatment or within 4 months of metastatic or within 12 months of adjutant treatment. In comparison to the pivotal 046 study in which all patients met strict resistance criteria, approximately 50% patients in the confirmatory 048 trial met these criteria.

**Thomas et al, J Clin Oncol 2007; 25: 5210–7**

**Hortobagyi et al, ASCO Breast Cancer Symposium 2008; Abstract 186**

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**Thomas et al, J Clin Oncol 2007; 25: 5210–7**

**Hortobagyi et al, ASCO Breast Cancer Symposium 2008; Abstract 186**
Capecitabine ± ixabepilone in MBC: Influence of taxane-resistance on PFS (pooled 046 and 048 data)

<table>
<thead>
<tr>
<th>Resistance type</th>
<th>T-resistant group (%)</th>
<th>Overall population (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxane</td>
<td>Cap + Ixa: 615</td>
<td>Cap: 608</td>
</tr>
<tr>
<td>Anthracycline</td>
<td>52%</td>
<td>51%</td>
</tr>
<tr>
<td>Taxane + anthracycline</td>
<td>52%</td>
<td>51%</td>
</tr>
</tbody>
</table>

Median PFS (months)

- **Cap + Ixa**: HR=0.81, p=0.0004
- **Cap**: HR=0.80, p<0.0001

<table>
<thead>
<tr>
<th>Resistance type</th>
<th>T-resistant group (%)</th>
<th>Overall population (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxane</td>
<td>100%</td>
<td>69%</td>
</tr>
<tr>
<td>Anthracycline</td>
<td>52%</td>
<td>39%</td>
</tr>
<tr>
<td>Taxane + anthracycline</td>
<td>52%</td>
<td>36%</td>
</tr>
</tbody>
</table>

Roche et al, SABCS 2008; Abstract 2015

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Capecitabine ± ixabepilone in MBC: Influence of taxane-resistance on ORR and OS (pooled 046 and 048 data)

<table>
<thead>
<tr>
<th>Resistant subgroup</th>
<th>Overall population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cap + Ixa</td>
</tr>
</tbody>
</table>
| ORR (%)                   | 39%       | 22%
| CR (%)                    | 3%        | 1%
| PR (%)                    | 36%       | 38%
| OS (months)               | 13.3      | 11.6
| HR                        | 0.90      | 0.92
| p                         | 0.0886    | 0.0861

ORR calculated using data from all randomized patients in 046 and those with measurable disease in 048
Median results provided

Roche et al, SABCS 2008; Abstract 2015

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**Slide 15**
This slide describes the efficacy of ixabepilone in combination with capecitabine in a prespecified pooled subset of taxane-resistant patients from the phase III 046 and 048 studies.

Most patients in the ixabepilone-receiving arm had received prior metastatic chemotherapy (subgroup vs overall; 87% vs 85%), while significant numbers had symptomatic disease, ER+ disease or triple-negative disease (subgroup vs overall; symptomatic 32% vs 32%, ER+ 48% vs 52%, TN 24% vs 22%). All patients in the subgroup were taxane-resistant, with anthracycline resistance present in 52% of the subgroup compared with 39% of the overall population.

Consistent with results observed in the overall patient population, ixabepilone plus capecitabine provided a significant increase in PFS compared with capecitabine alone in taxane-resistant MBC (Cap+Ixa [n=615] vs Cap [n=608]; 5.1 months vs 3.7 months, HR=0.81, p=0.0004).

Roche et al, SABCS 2008; Abstract 2015

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**Slide 16**
In this taxane-resistant subgroup (n=1289), addition of ixabepilone to capecitabine increased median ORR and OS, although the latter did not attain statistical significance (Cap+Ixa vs Cap, respectively; ORR 39% vs 22%, OS 13.3 months vs 11.6 months). A majority of responses were partial in nature.

Roche et al, SABCS 2008; Abstract 2015
Capecitabine ± ixabepilone in MBC: Influence of therapy line on PFS (pooled 046 and 048 data)

<table>
<thead>
<tr>
<th>First-line MBC (%)</th>
<th>Overall population (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap + Ixa</td>
<td>Cap</td>
</tr>
<tr>
<td>n=123</td>
<td>n=111</td>
</tr>
<tr>
<td>5.6, HR=0.58, p&lt;0.0001</td>
<td>2.8, HR=0.80, p&lt;0.0001</td>
</tr>
<tr>
<td>5.6, HR=0.58, p&lt;0.0001</td>
<td>4.2, HR=0.80, p&lt;0.0001</td>
</tr>
</tbody>
</table>

\[ \text{Vahdat et al, SABCS 2008; Abstract 6117} \]

Slide 17
In this subset analysis of pooled data from studies 046 and 048, the efficacy and toxicity of capecitabine with or without ixabepilone in 293 1st-line (post-adjuvant rapidly relapsing) metastatic patients was evaluated. The subset under study had relapsed within 12 months of (neo)adjuvant anthracycline and taxane therapy. Post-adjuvant rapidly relapsing patients accounted for 15% of the overall patient population, while other baseline characteristics were consistent between the subset and overall populations (subset characteristics included; taxane resistance ~50%, ≥2 disease sites ~35%, triple-negative 40%). Addition of ixabepilone to capecitabine in 1st-line metastatic patients (post-adjuvant rapidly relapsing) significantly increased PFS (Cap+Ixa [n=123] vs Cap [n=111]; 5.6 months vs 2.8 months, HR 0.58, p<0.0001). This result was consistent with that observed in the pooled overall population.

\[ \text{Vahdat et al, SABCS 2008; Abstract 6117} \]

Slide 18
This slide describes median ORR and OS following capecitabine plus ixabepilone (n=123) versus capecitabine (n=111) alone in 1st-line MBC, following relapse on (neo)adjuvant anthracyclines and taxanes. Addition of ixabepilone to capecitabine significantly increased median ORR, a majority of best responses being partial in nature, and increased OS (Cap+Ixa vs Ixa, respectively; ORR 46% vs 24%, OS 15.1 months vs 12.5 months). In contrast to the findings from analysis of the pooled overall population, OS increase following ixabepilone-containing therapy failed to attain statistical significance (HR 0.84, p=0.2081).

\[ \text{Vahdat et al, SABCS 2008; Abstract 6117} \]
Considerations in TNBC treatment

- Triple-negative breast cancer (TNBC)
  - aggressive, metastases common (especially lung and brain)\(^1,2,3\)
  - progression will vary with presence of EGFR and CK 5/6 basalmarkers\(^4\)
  - incidence may vary with ethnicity
    - African-Americans vs Caucasians (17.6% vs 3.7%)\(^5\)

- Chemotherapy treatment of TNBC
  - targeted treatment under study (inc. EGFR / PARP inhibitors)\(^6\)
  - neoadjuvant chemotherapy effective
    - (pCR following AC: TNBC vs combined luminal 27% vs 7%)\(^7\)
  - few prospective trials of platinum compounds\(^8\)
  - adjuvant taxanes are effective\(^8\)
  - → reliance on anthracyclines / taxanes, options in resistant disease?

Patients with disease classified by "the TN definition (HER2(-)/ER(-)/PR(-))/ and those classified by the 5-biomarker definition (HER2(+), ER(+)/PR(+)/EGFR(-)/CK 5/6(-)).\(^8\) TN subtype may vary with patient ethnicity, both in terms of incidence and prognosis.\(^5\) A retrospective review of 93 newly diagnosed TNBCs showed 17.6% of cases to be in AAs and 3.7% in Caucasians, with significantly increased rates of local/systemic recurrence and death in the AA subgroup.\(^5\) Other studies, however, have shown race not to impact response to primary systemic chemotherapy (data not shown).

As with other disease subtypes, TN status must be considered alongside other patient and tumor factors in the selection of appropriate drug therapy.\(^2\) TNBC is sensitive to neoadjuvant chemotherapy resulting in improved complete pathological response rates compared with those in other TN patients. Following AC neoadjuvant chemotherapy (± endocrine therapy) in 107 patients, clinical responses were reported in 85% of patients with basal-like disease and 47% of patients with luminal disease (p=0.0001).\(^2\) pCR was also significantly increased in basal-like disease.\(^7\)

Platinum drugs and taxanes have definite antitumor activity in TNBC.\(^8,9\) CALGB 9344 reported significantly increased DFS in HER2(-)/ER(-) patients following adjuvant paclitaxel-containing chemotherapy.\(^9\) Uncertainty remains, however, as to available options for anthracycline/taxane-resistant TN metastatic patients.

**Slide 19**

Triple-negative breast cancer (TNBC) is associated with poor prognosis, since disease is typically aggressive with metastases common, especially in the lung and brain. In a retrospective analysis of patient outcomes in 369 primary breast cancer patients (14.6% triple-negative [TN]), although pathological complete response rate was higher in TN patients compared with non-TN patients (TN vs non-TN: 16.1% vs 11.6%) and clinical response rates similar (TN vs non-TN: 12.7% vs 11.3%), TN disease was associated with a higher progressive disease rate (TN vs non-TN: 17.5% vs 0.3%).\(^1\)

In this study, TN basal-like tumors were associated with poor patient prognoses (data not shown).\(^2\) Kennecke and colleagues reported a median survival of 0.5 years in EBC patients with basal-type TN disease (n=375), with brain metastasis common in these patients (13% metastasis; luminal A 2%, luminal B 13%, HER2(+)ER(+) 17%, HER2(+) ER(-) 30%, TN 27%).\(^2\) A retrospective review of survival and metastatic spread in EBC patients (n=679) further confirmed these findings, with brain metastases the first site of recurrence in 3.5% patients.\(^2\) Median survival was 2.9 months in TN patients, and 5.8 months in those with brain metastases as the first site of disease recurrence.\(^3\)

Prognoses of basal-like TN disease, following anthracycline-based adjuvant chemotherapy, has been shown to vary between patients with disease classified by “the TN definition (HER2(-)/ER(-)/PR(-))”\(^1\) and those classified by the 5-biomarker definition (HER2(+), ER(+)/PR(+)/EGFR(-)/CK 5/6(-)).\(^8\) TN subtype may vary with patient ethnicity, both in terms of incidence and prognosis.\(^5\) A retrospective review of 93 newly diagnosed TNBCs showed 17.6% of cases to be in AAs and 3.7% in Caucasians, with significantly increased rates of local/systemic recurrence and death in the AA subgroup.\(^5\) Other studies, however, have shown race not to impact response to primary systemic chemotherapy (data not shown).

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**Slide 20**

This slide describes results from a subset analysis of outcomes in TN patients taken from the phase III 046 and 048 studies. TN metastatic patients (n=443), pre-treated or resistant to anthracycline and taxane therapy, received either capecitabine monotherapy or capecitabine in combination with ixabepilone until disease progression or toxicity. A significant proportion of the pooled overall population had TN disease (22%). Baseline characteristics of the TN subgroup included: poor performance status 29%, prior (neo)adjuvant anthracycline/taxane 28%, prior metastatic chemotherapy 73%, and taxane resistance 76%.

Ixabepilone addition to capecitabine significantly improved median PFS in TN patients (Cap+Ixa vs Ixa: 4.2 months vs 1.7 months, HR 0.63, p<0.0001). This PFS increase was consistent with that reported in analysis of the overall pooled patient population. Median ORR and OS were also increased in capecitabine plus ixabepilone-treated TN patients compared with those who received capecitabine monotherapy (Cap+Ixa vs Ixa, respectively; ORR 31% vs 15%, OS 10.3 months vs 9.0 months). TN patients had reduced OS durations compared with those observed in the overall pooled population (TN vs overall; Ixa+Cap 10.3 months vs 14.6 months, Cap 9.0 months vs 13.6 months). OS in ixabepilone-treated patients attained statistical significance in the overall patient population only.
From taxanes to epothilones:
Targeting microtubules in breast cancer and beyond

Slide Update 2

Impact of performance status on chemotherapy selection in MBC

- Diminished performance status (PS) is common in MBC
- Many factors may contribute to ↓ PS in MBC
  - ↑ age and co-morbidities
  - extensive prior chemotherapy / radiotherapy (toxicities)
  - high tumor burden
- Diminished PS is associated with:
  - ↓ response to chemotherapy and poorer prognosis
  - ↑ risk of chemotherapy-related adverse events
- PS affects selection of chemotherapy regimens

Slide 21

Diminished performance status is common in patients with MBC arising from factors including: increasing age and co-morbidities, extensive prior chemotherapy/radiotherapy and high tumor burden. These patients are at an increased risk of chemotherapy-related toxicity, with consequent discontinuation of treatment regimens, drug resistance and worsened prognosis.

Slide 22

Conte and colleagues evaluated the efficacy and safety of ixabepilone in combination with capecitabine versus capecitabine alone in a subset of MBC patients with diminished performance status (KPS 70–80) from studies 046 and 048. Patients, pre-treated or resistant to anthracyclines and taxanes following ≤2 lines (048) and ≤3 lines (046) of metastatic chemotherapy, received capecitabine alone (n=257) or capecitabine plus ixabepilone (n=268) until toxicity or disease progression. Excluding KPS status, baseline characteristics of the subset population were generally consistent with those in the overall pooled population, except in that the diminished performance status subgroup contained more patients with advanced disease (≥2 metastatic sites or ≥2 prior metastatic regimens).

As shown in the slide, median PFS and ORR were increased in diminished PS patients following ixabepilone plus capecitabine therapy when compared to outcomes observed following capecitabine alone (Cap+Ixa vs Ixa; PFS 4.6 months vs 3.1 months, HR 0.76 p=0.0021; ORR 35% vs 19%). Median OS was also increased through ixabepilone addition in KPS 70–80 patients (Ixa+Cap vs Cap; 12.3 months vs 9.5 months, HR 0.75 p=0.0015).

Conte et al, SABCS 2008; Abstract 6114
From taxanes to epothilones:
Targeting microtubules in breast cancer and beyond

Slide Update 2

Summary of results from subanalysis of pooled 046 / 048 data

- Efficacy of capecitabine ± ixabepilone was comparable to that reported in the overall pooled population in patients with:
  - taxane-resistant MBC\(^1\)
  - first-line MBC\(^2\)
  - triple-negative MBC\(^3\)
  - diminished PS MBC\(^4\)

- Patients had been pre-treated or were resistant to anthracyclines and taxanes

\(^1\)Roche et al, SABCS 2008; Abstract 2015  
\(^2\)Vahdat et al, SABCS 2008; Abstract 6117  
\(^3\)Rugo et al, SABCS 2008; Abstract 3057  
\(^4\)Conte et al, SABCS 2008; Abstract 6114

Slide 23

Consistent with results observed in the overall patient populations of studies 046 and 048, PFS was significantly improved following addition of ixabepilone to capecitabine in the taxane-resistant, 1st-line, TN and diminished performance status (PS) MBC patient subgroups. ORR and OS were also increased. Patients had been pre-treated or were resistant to anthracyclines and taxanes.

Roche et al, SABCS 2008; Abstract 2015  
Vahdat et al, SABCS 2008; Abstract 6117  
Rugo et al, SABCS 2008; Abstract 3057  
Conte et al, SABCS 2008; Abstract 6114

Slide 24

Section title slide

Tolerability issues associated with microtubule-targeting agents used in breast cancer management
From taxanes to epothilones: Targeting microtubules in breast cancer and beyond

Slide 25

This slide summarizes the principal grade 3/4 toxicities observed following use of paclitaxel, nab-paclitaxel, docetaxel and vinorelbine as monotherapy, and from use of ixabepilone plus capecitabine, in the treatment of MBC.

Generally, peripheral neuropathy and neutropenia are associated with use of microtubule-targeting therapy.

O'Shaughnessy et al, J Clin Oncol 2002; 20: 2812–23
Zelek et al, Cancer 2001; 92: 2267–72

Slide 26

Peripheral neuropathy (PN) is associated with use of microtubule-targeting chemotherapy, occurring across drug classes but at varying incidence and severity. A number of factors influence PN development including: the drug, absolute and cumulative drug doses, administration schedule, and the presence of co-morbidities. Although symptoms following first-generation vinca alkaloids may be both sensory and motor in nature, sensory neuropathy is most apparent following taxane or epothilone therapy.

As microtubules play a key role in the structure and function of neurons, neuropathy is likely to follow microtubule-inhibitor use. However, these symptoms may vary in time to onset, rate of progression, severity, pattern, and reversibility between agents, and this may warrant consideration in selection of the chemotherapy regimen.
Slide 27

A number of risk factors for PN development following microtubule-targeting agents have been identified; these including increasing age, and chemotherapy exposure, and diabetes.

In an analysis of the relationship of patient and treatment factors to development of paclitaxel-related toxicity in 1048 non-1st-line MBC patients, time to onset of neurosensory/motor toxicity was significantly increased in patients >65 years. Diabetes has been determined to be a risk factor for ixabepilone-associated PN.

PN reversibility may differ by class, and may be managed through a number of therapeutic interventions. However, drug discontinuation to maintain patient QOL may be necessary.

Lichtman et al, SABCS 2008; Abstract 6112
Perez et al, SABCS 2008; Abstract 550871
Driessen et al, ESMO 2008; Abstract 909P
Lee & Swain, J Clin Oncol 2006; 24: 1633–42
Hensley et al, J Clin Oncol 2009; 27: 127–45
Wickham, J Clin Oncol Nurse 2007; 11: 361–76

Slide 28

This slide provides reported incidences of grade 3/4 peripheral neuropathy following use of vinca alkaloids, taxanes, and ixabepilone, as monotherapy in MBC. Studies are representative, since a number of non-agent factors will influence PN development.

Although nab-technology was introduced to minimize taxane-related toxicities, the significant risk of PN with nab-paclitaxel is thought to be due to the delivery of a higher taxane dose.

Slide Update 2

Principle grade 3/4 adverse events following capecitabine ± ixabepilone in anthracycline / taxane pre-treated MBC

<table>
<thead>
<tr>
<th></th>
<th>1st-line MBC</th>
<th>Triple-negative MBC</th>
<th>Taxane-resistant MBC</th>
<th>Symptomatic (KPS 70-80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>74</td>
<td>8</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>55</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Non-hematological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any peripheral neuropathy</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>22</td>
<td>19</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13</td>
<td>2</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14</td>
<td>5</td>
<td>6</td>
<td>9</td>
</tr>
</tbody>
</table>

Hematological Toxicities:
- Neutropenia: 74%, 8%, 8%, 9%
- Leukopenia: 55%, 6%, 6%, 5%

Non-hematological Toxicities:
- Any peripheral neuropathy: 23%, 23%, 23%, 23%
- Hand-foot syndrome: 22%, 19%, 14%, 16%
- Fatigue: 13%, 2%, 11%, 11%
- Diarrhea: 14%, 5%, 6%, 9%

Study 081 (Ixa) Study 046 (Cap + Ixa) Study 048 (Cap + Ixa)
Resolution (%): 76% 86% 86%
Improvement (%): 83% 89% 89%

Slide 29
This slide summarizes the most common adverse events observed at grade 3/4 severity in the subgroup analyses of phase III ixabepilone trials.

The most common hematological toxicities of neutropenia and leukopenia, and non-hematological toxicities of PN, fatigue and diarrhea, were increased following use of ixabepilone plus capecitabine in all subgroups. Patients were anthracycline/taxane-pre-treated or resistant and had received ≤3 prior chemotherapy regimens for metastatic disease. Hand-foot syndrome, associated with capecitabine use, was present in about 15–20% patients.

Although generally well tolerated in studies, ixabepilone should be used with caution in patients with pre-existing peripheral neuropathy, poor bone marrow reserve and low neutrophil counts. The prescribing information for ixabepilone should be consulted prior to ixabepilone administration.

Vahdat et al, SABCS 2008; Abstract 6117
Rugo et al, SABCS 2008; Abstract 3057
Roche et al, SABCS 2008; Abstract 2015
Conte et al, SABCS 2008; Abstract 6114

Slide 30
This retrospective analysis evaluated incidence rates, resolution/improvement times, management strategies and risk factors, for PN in metastatic patients who had received ixabepilone monotherapy (study 081) or ixabepilone plus capecitabine (study 046, study 048) following pre-treatment with anthracycline/taxane-containing chemotherapy.

Patients who developed PN were managed with either a drug treatment delay of <3 weeks if symptoms did not resolve to baseline or grade 1, dose reduction if PN was of grade 2 severity for >7 days or grade 3 for <7 days, or drug discontinuation if grade 3 PN was observed for >7 days or if grade 4 symptoms developed. Grade 3/4 PN was reported in 14% (study 081), 23% (study 046) and 25% (study 048) of patients. PN was predominantly sensory, and its development was associated with increasing cumulative exposure to ixabepilone.

Perez et al, SABCS 2008; Abstract 6140

This slide describes the percentage of patients with ixabepilone-induced PN whose symptoms either resolved or improved with intervention, and provides the median time to symptom resolution or improvement.

Persistent (>7 days) grade 2 or any grade 3 PN was reported in 26% (081), 31% (046) and 27% (048) patients, with ~70% patients continuing to receive a median 3 further cycles of ixabepilone following dose reduction. Discontinuation of ixabepilone for PN was reported in 6% (081), 21% (046) and 19% (048) patients. In a risk factor analysis for PN (n=945), PN was significantly increased by the presence of diabetes (grade 3/4 PN, diabetic vs non-diabetic; 23% vs 18%, HR 1.69, p=0.042).

Perez et al, SABCS 2008; Abstract 6140
From taxanes to epothilones: Targeting microtubules in breast cancer and beyond

**Slide Update 2**

**Incidence of grade 3/4 neutropenia following microtubule-inhibitors in MBC**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Grade 3/4 sensory neuropathy</th>
<th>Febrile neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinorelbine qw</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>Paclitaxel qw</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Nab-paclitaxel qw</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Docetaxel qw</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Ixabepilone T-naïve</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Ixabepilone T-resistant</td>
<td>53</td>
<td>6</td>
</tr>
<tr>
<td>T-naïve</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>A/T/C-resistant</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

*Representative studies provided
T = taxane; A/T/C = anthracycline / taxane / anthracycline
*Not reported
Zeke et al, Cancer 2001; 92: 2267–72

**Neutropenia and liver function:**

<table>
<thead>
<tr>
<th>Neutropenia-related deaths following Cap + Ixa (%)</th>
<th>Neutropenia-related deaths following Cap (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0/1 LFTs (n=685)</td>
<td>1.9</td>
</tr>
<tr>
<td>Grade 2/3 LFTs (n=42)</td>
<td>31</td>
</tr>
</tbody>
</table>

*Exclusion criteria for study 046 capecitabine + ixabepilone study amended to exclude all patients with liver dysfunction grade 2, irrespective of liver metastases
Liver function and baseline neutrophil count, amongst other factors, must be considered before administering ixabepilone

Ixabepilone Prescribing information

**Slide 31**

Neutropenia is a frequently reported side-effect of microtubule-inhibitor therapy in MBC patients. This slide describes rates of grade 3/4 neutropenia and reports of febrile neutropenia following administration of vinorelbine, taxanes, and ixabepilone, as monotherapy in metastatic patients. Studies are representative only, since a number of patient and treatment factors may influence the development of neutropenia. Incidence of neutropenia does differ between drug classes, and generally occurs more frequently in treatment-experienced patients. Febrile neutropenia is, however, relatively uncommon.

Zeke et al, Cancer 2001; 92: 2267–72

**Slide 32**

Ixabepilone monotherapy studies, and subsequently combination studies, have reported increased rates of severe neutropenia and febrile neutropenia, especially in patients with hepatic impairment.

Following an increase in neutropenia-related deaths in capecitabine plus ixabepilone-treated patients with grade 2 or higher baseline LFTs in study 046, study criteria were amended and caution recommended in patients with liver dysfunction and/or lower neutrophil counts at baseline. Dose adjustments may be warranted according to hematological and hepatic function. Prescribing information must be consulted prior to ixabepilone administration.

Ixabepilone Prescribing information
<table>
<thead>
<tr>
<th>From taxanes to epothilones: Targeting microtubules in breast cancer and beyond</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>From taxanes to epothilones: Targeting microtubules in breast cancer and beyond</strong></td>
</tr>
<tr>
<td>- Taxanes, alone or in combination with anthracyclines and/or cyclophosphamide, form the mainstay of adjuvant and metastatic breast cancer therapy</td>
</tr>
<tr>
<td>- Clinically, taxane cross-resistance and an absence of guidance regarding re-treatment may be problematic</td>
</tr>
<tr>
<td>- ↑ need for novel chemotherapies with differing mechanisms of action</td>
</tr>
<tr>
<td>- The epothilone ixabepilone, has demonstrated activity in anthracycline-/ taxane-pre-treated MBC</td>
</tr>
<tr>
<td><strong>From taxanes to epothilones: Targeting microtubules in breast cancer and beyond</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Summary slide</strong></td>
</tr>
<tr>
<td>- Evolving data confirm the efficacy of ixabepilone in combination with capecitabine in earlier stage MBC, TNBC, and patients with diminished PS</td>
</tr>
<tr>
<td>- Preliminary data suggest that ixabepilone in combination with trastuzumab appears effective against HER2(+) MBC</td>
</tr>
<tr>
<td>- Microtubule inhibition is associated with development of adverse events, including peripheral neuropathy and neutropenia</td>
</tr>
<tr>
<td>- Peripheral neuropathy risk and incidence is variable, and for ixabepilone may be resolved / improved with dose interruption or reduction</td>
</tr>
</tbody>
</table>
From taxanes to epothilones:
Targeting microtubules in breast cancer and beyond