Individualized Treatment Options in the Management of Metastatic Breast Cancer

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City of Hope Comprehensive Cancer Center

Objectives

Upon completion of this activity participants should be able to:

1. Compare and contrast the safety, efficacy, and survival prolongation profiles associated with current and emerging therapies in the treatment of metastatic breast cancer
2. Analyze individualized treatment strategies for patients whose metastatic breast cancer has progressed after receiving previous treatment courses
3. Discuss ASCO and NCCN Guidelines for management of patients with metastatic breast cancer
4. Develop individualized plans for selection and sequencing of the different agents for each patient with metastatic breast cancer throughout the course of their disease
5. Review strategies to detect, prevent, and appropriately manage potential adverse effects from metastatic breast cancer treatments
Outcome of patients with stage IV breast cancer

~ 40,000 deaths per year

**Median Overall survival**

- Triple negative breast cancer: 13 months
- HER+ and HR+ breast cancer: 36 – 48 months


Hormone-Receptor Positive Metastatic Breast Cancer (IHC ≥ 1%)
### First-Line Comparison of Aromatase Inhibitors vs Tamoxifen

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Patients</th>
<th>TTP/PFS months</th>
<th>P-Value</th>
<th>ORR, %</th>
<th>P-Value</th>
<th>CBR, %</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole</td>
<td>340</td>
<td>8.2</td>
<td>32.9</td>
<td>56.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>328</td>
<td>8.3</td>
<td>NS</td>
<td>32.6</td>
<td>NS</td>
<td>55.5</td>
<td>NS</td>
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<tr>
<td>Anastrozole</td>
<td>171</td>
<td>11.1</td>
<td>0.005</td>
<td>21.1</td>
<td>NS</td>
<td>59.1</td>
<td>0.0098</td>
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<tr>
<td>Tamoxifen</td>
<td>182</td>
<td>5.6</td>
<td>17.0</td>
<td>45.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letrozole</td>
<td>453</td>
<td>9.4</td>
<td>0.0001</td>
<td>32</td>
<td>0.0002</td>
<td>50</td>
<td>0.0004</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>454</td>
<td>6.0</td>
<td>21</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exemestane</td>
<td>182</td>
<td>9.9</td>
<td>NS</td>
<td>46</td>
<td>0.006</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>189</td>
<td>5.8</td>
<td>31</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TTP = time of progression; PFS = progression-free survival; ORR = overall response rate; CBR = Clinical benefit rate; NR = not reported


### Fulvestrant

- Acts through degradation of the estrogen receptor
- Equivalent to anastrozole in patients with metastatic breast cancer previously treated with tamoxifen (FDA-approved for antiestrogen-treated MBC)
- Equivalent to tamoxifen (selective estrogen receptor modulator [SERM] in first-line treatment of ER-positive MBC)
- Equivalent to exemestane in patients with MBC previously treated with non-steroidal AIs
- Dose and schedule may have been suboptimal in earlier trials

FIRST: Study Design

- Randomized, open-label phase II trial
  - Primary endpoint: CBR, defined as CR, PR, or SD for \( \geq 24 \) wks
  - Postmenopausal women with previously untreated hormone receptor-positive advanced breast cancer \( (N = 205) \)
  - Fulvestrant 500 mg by IM injection on Days 0, 14, 28, and every 28 days thereafter \( (n = 102) \)
  - Anastrozole 1 mg/day PO \( (n = 103) \)
  - Until disease progression or other event requiring discontinuation


FIRST: Efficacy Outcomes at Follow-Up Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Median, months</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP</td>
<td>Fulvestrant ( (n = 102) )</td>
<td>23.4</td>
<td>0.66 (0.47-0.92)</td>
</tr>
<tr>
<td></td>
<td>Anastrozole ( (n = 103) )</td>
<td>13.1</td>
<td>.73 (0.54-1.00)</td>
</tr>
<tr>
<td>TTP</td>
<td></td>
<td>0.64 (0.46-0.90)</td>
<td>.01</td>
</tr>
<tr>
<td>(adjusted for predefined covariates)</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; TTF = time to treatment failure; TTP = time to progression

Progression-Free Survival in S0226

All eligible patients (n=694)

Anastrozole + Fulvestrant (268 events)
Anastrozole (297 events)

Stratified log-rank p = 0.0070

Median PFS
Combination 15.0 mos (95% CI 13.2 - 18.4)
Anastrozole 13.5 mos (95% CI 12.1 - 15.1)

HR = 0.80 (95% CI 0.68 - 0.94)

Overall Survival in S0226

All eligible patients (n=694)

Anastrozole + Fulvestrant (154 deaths)
Anastrozole (176 deaths)

Stratified log-rank p = 0.049

Median OS
Combination 47.7 mos (95% CI 43.4 - 55.7)
Anastrozole 41.3 mos (95% CI 37.2 - 45.0)

HR = 0.81 (95% CI 0.65 - 1.00)
Is Fulvestrant plus Anastrozole better than single agent RX? Yes in 1 trial

• A similarly designed European trial (FACT) was negative.

• A trial in patients who progressed on an AI (SoFEA) compared fulvestrant and anastrozole, versus anastrozole alone, or exemestane alone, was also negative.

Mehta R et al. NEJM 2012 367:435-44
Who May Benefit from mTOR-targeting Therapy?

- ~ 40% of ER+ breast cancers will contain PI3K mutations
- ~ 30% will have reduced PTEN expression
- mTOR can be activated independent of the PI3K pathway
- mTOR can activate the ER receptor independent of ER

**BOLERO-2 Trial Design**

**BOLERO-2**  
N = 724  
- Postmenopausal women  
- Advanced Breast Cancer  
- NSAI-refractory disease  
  - Recurrence during/within 12 mo of adjuvant treatment or  
  - Progression during/within 1 mo of treatment for advanced disease  

**Key Baseline Characteristics**  
- Median age, years: 62  
- Race, %  
  - Caucasian: 75  
  - Asian: 20  
- Visceral involvement, %: 56  
- Bone metastases, %: 77  

**Primary Endpoint:**  
PFS by local assessment

**Postmenopausal women**  
- Advanced Breast Cancer  
- NSAI-refractory disease  
  - Recurrence during/within 12 mo of adjuvant treatment or  
  - Progression during/within 1 mo of treatment for advanced disease

**BOLERO-2 Efficacy:**  
Addition of Everolimus (EVE) to Exemestane (EXE)  
More Than Doubled Median PFS

- **PFS Local***  
  HR = 0.45 (95% CI: 0.38–0.54)  
  Log-rank P value: < 0.0001  
  EVE + EXE: 7.82 months  
  PBO + EXE: 3.19 months

- **PFS Central***  
  HR = 0.38 (95% CI: 0.31–0.48)  
  Log-rank P value: < 0.0001  
  EVE + EXE: 11.01 months  
  PBO + EXE: 4.14 months

**Final PFS Analysis: 18-month Median Follow-up**
Greater PFS Benefit With Everolimus in Patients With Minimal Alterations in PIK3CA/PTEN/CCND1 or FGFR1/2

**BOLERO-2: Most Common G3/4 AEs**

<table>
<thead>
<tr>
<th></th>
<th>Everolimus + Exemestane (N = 482), %</th>
<th>Placebo + Exemestane (N = 238), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>56</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18</td>
<td>4</td>
</tr>
<tr>
<td>Anemia</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>AST</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>12</td>
<td>3</td>
</tr>
</tbody>
</table>

AE: Adverse Event; AST: Aspartate aminotransferase

**Probability of Progression-Free Survival**

HR (95% CI): 0.27 (0.18 - 0.41)
PD 0332991 (CDK4/6 inhibitor) + Letrozole vs Letrozole: Study Design

- 2-part, randomized phase II study

**Stratified by disease site (visceral, bone only, or other); Disease-Free Interval (>12 vs ≤12 mo from end of adjuvant to recurrence or de novo advanced disease)**

Postmenopausal women with ER-positive, HER2-negative advanced breast cancer (N = 66)

PD 0332991 125 mg QD + Letrozole 2.5 mg QD

Letrozole 2.5 mg QD

**Stratified by disease site (visceral, bone only, or other); Disease-Free Interval (>12 vs ≤12 mo from end of adjuvant to recurrence or de novo advanced disease)**

women with ER-positive, HER2-negative advanced breast cancer, CCND1 amp, and/or p16 loss (N = 99)

PD 0332991 125 mg QD + Letrozole 2.5 mg QD

Letrozole 2.5 mg QD

All patients continued assigned treatment until disease progression, withdrawal of consent, or unacceptable toxicity with follow-up tumor assessment every 2 mos


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PD 0332991 Plus Letrozole vs Letrozole: PFS

- Significant improvement with PD 0332991 plus letrozole vs letrozole

<table>
<thead>
<tr>
<th>PFS</th>
<th>PD 0332991 + Letrozole (n = 84)</th>
<th>Letrozole (n = 81)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>21 (25)</td>
<td>40 (49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>26.1 (12.7-26.1)</td>
<td>7.5 (5.6-12.6)</td>
<td>0.37 (0.21-0.63)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>
CGH and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre prospective trial (SAFIR01).
Andre et al Lancet Oncol 2014

Hypothesis: Molecular analysis will reveal potential therapeutic targets which will be **case-specific**
Feasibility: 30% actionable targets

- 407 patients/14 months
- Success rate of obtaining metastatic biopsies was high (96%) and complications were rare SAE (2%)
- Assay success depends on methodology; targeted sequencing 72%, CGH 67% success rate The main reason for assay failure is the low cellularity (23%)
  - Highest rate of failure bone (78%)
- Targetable genomic alterations found in ~48% of cases with molecular results.

- Only 43 patients received targeted therapy and response rate was low (4 patients)
- Feasible, but so far not enough evidence of success: ineffective drugs, escape mechanisms, many other targets?

S1222

**FULVESTRANT ALONE VERSUS FULVESTRANT AND EVEROLIMUS VERSUS FULVESTRANT, EVEROLIMUS AND ANASTROZOLE:**

A PHASE III RANDOMIZED PLACEBO-CONTROLLED TRIAL IN POSTMENOPAUSAL PATIENTS WITH HORMONE-RECEPTOR-POSITIVE STAGE IV BREAST CANCER

*Clinical Trial and Translational Medicine Projects*

George Somlo M.D.
Daniel F. Hayes M.D
Peter Kuhn, Ph.D.
James Hicks, Ph.D.
CTC Assays

- **CellSearch:** *CTC-Endocrine Therapy Index*
- **CTC-NGS:** *CTC Genomic Characterization*

**PLAN:**
- We will determine CTC-ETI at baseline, first follow-up, and at progression.
- We will determine if:
  - # of CTC = poor prognosis/more likely to benefit from combination vs. single agent fulvestrant
  - CTC-ETI at baseline = poor response to Endocrine Therapy
  - CTC-ETI during followup gives insight into mechanisms of resistance
- We will determine if genomic fingerprint predicts response

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**NCCN Guidelines Version 3.2013**

**Invasive Breast Cancer**

**SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE**

**ER and/or PR POSITIVE; HER2 NEGATIVE OR POSITIVE**

- **Premenopausal**
  - Prior endocrine therapy within 1 y
  - Consider initial chemotherapy (See BINV-20 and BINV-21)
- **Postmenopausal**
  - Ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women
  - Ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women or Selective ER modulators or aromatase inhibitor or Selective ER modulators or selective ER down-regulator
  - Consider initial chemotherapy (See BINV-20 and BINV-21)
- **Visceral crisis**
  - Ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women or Selective ER modulators or aromatase inhibitor or Selective ER modulators or selective ER down-regulator
  - Consider initial chemotherapy (See BINV-20 and BINV-21)

**No prior endocrine therapy within 1 y**

- **Premenopausal**
  - Consider initial chemotherapy (See BINV-20 and BINV-21)
- **Postmenopausal**
  - Ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women or Selective ER modulators or aromatase inhibitor or Selective ER modulators or selective ER down-regulator
  - Consider initial chemotherapy (See BINV-20 and BINV-21)
- **Visceral crisis**
  - Ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women or Selective ER modulators or aromatase inhibitor or Selective ER modulators or selective ER down-regulator
  - Consider initial chemotherapy (See BINV-20 and BINV-21)

**See Follow-up Therapy for Endocrine Treatment of Recurrent/Stage IV Disease (BINV-22)**
HER2-Directed Therapies in Metastatic Breast Cancer (IHC 3+ of FISH-amplified)

EGFR 1 & (HER2) 2 Inhibition

Cell Division/Tumor Growth

EGFR/HER

Cetuximab

Trastuzumab

Erlotinib

Lapatinib

Gefitinib

Signaling
CT ± Trastuzumab: TTP

Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2 overexpressing metastatic breast cancer.

<table>
<thead>
<tr>
<th></th>
<th>Response Rate (%)</th>
<th>Duration of Response (mo)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbo/pac/trastuz</td>
<td>52*</td>
<td>10.7*</td>
<td>35.7</td>
</tr>
<tr>
<td>Pac/trastuzumab</td>
<td>36</td>
<td>7.1</td>
<td>32.2</td>
</tr>
</tbody>
</table>

Trastuzumab Beyond Progression Trial

Eligibility criteria:
- Progressive MBC or LABC
- HER2 overexpression
- Previous treatment with trastuzumab
- Trastuzumab-free interval < 6 weeks
- LVEF ≥ 50

Primary endpoint: time to progression
Secondary endpoints: OS, ORR, safety

* Study closed at 156 patients due to slow accrual following FDA registration of lapatinib for this indication

Von Minckwitz, Eur J Cancer 2011

Trastuzumab Beyond Progression Trial: Previous treatment and efficacy

Administered pre-treatments (N=156):
- 1st-line taxane + trastuzumab (N=111)
- Trastuzumab alone or with other 1st-line chemotherapy (N=42)
- Taxane + trastuzumab as adjuvant therapy (N=3)

<table>
<thead>
<tr>
<th></th>
<th>Capecitabine</th>
<th>Capecitabine + Trastuzumab</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TTP</td>
<td>5.6 months</td>
<td>8.2 months</td>
<td>0.69</td>
<td>.034</td>
</tr>
<tr>
<td>Median OS</td>
<td>20.4 months</td>
<td>25.5 months</td>
<td>0.76</td>
<td>.26</td>
</tr>
<tr>
<td>ORR</td>
<td>27%</td>
<td>48%</td>
<td>-</td>
<td>.011</td>
</tr>
<tr>
<td>CBR</td>
<td>54%</td>
<td>75%</td>
<td>-</td>
<td>.0068</td>
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</tbody>
</table>

ORR: Overall Response Rate (CR+PR)
CBR: Clinical Benefit Rate (CR+PR+SD >24 weeks)

Von Minckwitz, Eur J Cancer 2011
EGF100151: A Phase III Study Comparing Lapatinib/Capecitabine vs. Capecitabine in Women With Refractory Advanced or Metastatic Breast Cancer

Eligibility criteria:
- Progressive MBC or stage IIIIB/IIIC LABC with T4 lesion
- HER2 overexpression (IHC3+ or 2+ and FISH+)
- Unlimited prior therapies, but no prior capecitabine
- Prior therapies must include:
  - Trastuzumab in metastatic setting
  - Anthracycline and taxane in either metastatic or adjuvant setting

Primary endpoint: TTP
Secondary endpoints: OS, PFS, ORR

Geyer et al. NEJM 2007 355:2733-42

Time to Progession as Assessed by IRC

<table>
<thead>
<tr>
<th>Lapatinib + Capecitabine</th>
<th>Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts</td>
<td>163</td>
</tr>
<tr>
<td>Progressed or died</td>
<td>49</td>
</tr>
<tr>
<td>Median TTP, wk</td>
<td>36.7</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.49 (0.34, 0.71)</td>
</tr>
<tr>
<td>P-value (log-rank, 1-sided)</td>
<td>0.00004</td>
</tr>
</tbody>
</table>

Geyer et al. NEJM 2007 355:2733-42
Cameron et al. ESMO 2006
**Phase III trial: Lapatinib ± Trastuzumab in heavily pretreated MBC following progression on Trastuzumab**

- HER2+ (FISH+/IHC 3+)
- Progressed on anthracyclines, taxanes, and most recent trastuzumab regimen

**Randomize**

- Lapatinib (1500 mg/day PO) (N=148)
- Lapatinib (1000 mg/day PO) + Trastuzumab (4 mg/kg load → 2 mg/kg weekly) (N=148)

**Crossover if PD after 4 wk therapy (N=73)**

**Primary endpoint: Progression-free survival (PFS): Investigator**

Secondary endpoints including:
- Overall Survival
- Overall Response Rate
- Clinical Benefit Rate
- Safety

**Efficacy Outcomes at Follow-Up Analysis**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Median, months</th>
<th>Lapatinib</th>
<th>Trastuzumab</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>8.1 weeks</td>
<td>11.1 weeks</td>
<td>0.74 (0.48-0.94)</td>
<td>.011</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>9.5 months</td>
<td>14 months</td>
<td>0.74 (0.57-0.97)</td>
<td>.021</td>
<td></td>
</tr>
</tbody>
</table>

Combining Pertuzumab and Trastuzumab for More Comprehensive HER2 Blockade

- Pertuzumab targets the extracellular dimerization domain (subdomain II) of HER2
  - Blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4
- Trastuzumab binds to subdomain IV and disrupts ligand-independent HER2 signaling

CLEOPATRA: Study Design

- Primary endpoint: PFS (independently assessed)
- Secondary endpoints: PFS (investigator assessment), ORR, OS, Safety

Women with previously untreated, HER2-positive locally recurrent/metastatic breast cancer
(N = 808)

Treatment until disease progression or unacceptable toxicity

Stratified by geographic region and previous (neo)adjuvant chemotherapy

Trastuzumab 6 mg/kg q3w* + Docetaxel 75-100 mg/m² q3w† + Pertuzumab 420 mg q3w‡ (n = 402)

Trastuzumab 6 mg/kg q3w* + Docetaxel 75-100 mg/m² q3w† + Placebo q3w (n = 406)

*Trastuzumab 8 mg/kg loading dose given.
†Minimum of 6 docetaxel cycles recommended; < 6 cycles permitted for unacceptable toxicity or PD.
‡Pertuzumab 840 mg loading dose given.

## CLEOPATRA: Safety

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Trastuzumab + Docetaxel + Pertuzumab (n = 407)</th>
<th>Trastuzumab + Docetaxel + Placebo (n = 397)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>66.8</td>
<td>7.9</td>
</tr>
<tr>
<td>Alopecia</td>
<td>60.9</td>
<td>NR</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>52.8</td>
<td>48.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>42.3</td>
<td>NR</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Rash</td>
<td>33.7</td>
<td>NR</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>29.2</td>
<td>NR</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>27.8</td>
<td>NR</td>
</tr>
<tr>
<td>Asthenia</td>
<td>26.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>23.1</td>
<td>NR</td>
</tr>
<tr>
<td>Constipation</td>
<td>15.0</td>
<td>NR</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>13.8</td>
<td>13.8</td>
</tr>
<tr>
<td>Dry skin</td>
<td>10.6</td>
<td>NR</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>NR</td>
<td>12.3</td>
</tr>
</tbody>
</table>

Swain et al., Lancet Oncology 2013 14:461-71
Trastuzumab-MCC-DM1

- Binds to HER2 with affinity similar to trastuzumab
- Provides intracellular delivery of mertansine
  - Derivative of maytansine, a natural-product microtubule polymerization inhibitor
  - 20-100 more potent than vincristine

Swain et al. Lancet Oncology 2013 14:461-71; Update ESMO 2014: OS 56 vs 40 ms
EMILIA Phase III Study: T-DM1 vs Lapatinib/Capecitabine in HER2+ MBC

Stratified by world region, number of previous chemotherapy regimens for MBC or unresectable locally advanced breast cancer, presence of visceral disease

- Primary endpoint: PFS by IRF, OS, safety
- Secondary endpoints: QoL (FACT B), DOR, PFS by investigator assessment


T-DM1 vs Lapatinib/Capecitabine in HER2+ MBC (EMILIA): PFS

<table>
<thead>
<tr>
<th></th>
<th>Median, Mos</th>
<th>Events, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine/lapatinib</td>
<td>6.4</td>
<td>304</td>
</tr>
<tr>
<td>T-DM1</td>
<td>9.6</td>
<td>265</td>
</tr>
</tbody>
</table>

Stratified HR: 0.650 (95% CI: 0.55-0.77; P < .0001)

T-DM1 vs Lapatinib/Capecitabine in HER2+ MBC (EMILIA): OS (Interim Analysis)

**T-DM1 vs Lapatinib/Capecitabine in HER2+ MBC (EMILIA): Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>T-DM1 (n = 490)</th>
<th>Capecitabine + Lapatinib (n = 488)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grades ≥ 3</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>1.2</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>8.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>39.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>6.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Increased AST</td>
<td>22.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>16.9</td>
<td>2.9</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>10.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>28.0</td>
<td>12.8</td>
</tr>
</tbody>
</table>

Phase III MARIANNE Study: T-DM1 ± Pertuzumab in HER2+ MBC

- **Primary endpoints:** PFS as assessed by IRF, AEs
- **Secondary endpoints:** OS, TTF by IRF, ORR, CBR, DO

![ClinicalTrials.gov. NCT01120184.](image)

Current Therapy for Advanced HER2+ Breast Cancer

<table>
<thead>
<tr>
<th>Setting</th>
<th>Biologic Agent</th>
<th>Cytotoxic Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line</td>
<td>Pertuzumab + Trastuzumab</td>
<td>• Docetaxel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Paclitaxel</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab</td>
<td>• Paclitaxel ± carboplatin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Docetaxel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Vinorelbine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Capecitabine</td>
</tr>
<tr>
<td>Previous trastuzumab</td>
<td>T-DM1</td>
<td>• Capecitabine</td>
</tr>
<tr>
<td></td>
<td>Lapatinib</td>
<td>• Other</td>
</tr>
<tr>
<td></td>
<td>Lapatinib + trastuzumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trastuzumab</td>
<td></td>
</tr>
</tbody>
</table>

Based on NCCN clinical practice guidelines in oncology: Breast cancer (v.3.2013). www.nccn.org
SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE
ER and PR NEGATIVE; or ER and/or PR POSITIVE and ENDOCRINE REFRACTORY; HER2 NEGATIVE

ER and PR negative; or ER and/or PR positive and endocrine refractory; and HER2 negative

Bone or soft tissue only or Asymptomatic visceral

Yes → Consider additional trial of endocrine therapy, if not endocrine refractory or Chemotherapy → No response to 3 sequential regimens or ECOG performance status ≥3

No → Chemotherapy → See Endocrine Therapy (BINV-19)

Consider no further cytotoxic therapy; transition to palliative care (See NCCN Guidelines for Palliative Care)

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
- Alumunium-bound paclitaxel
- Cisplatin
- Epirubicin
- Nab-paclitaxel

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

Preferred first-line agents for HER2-positive disease:
- Pertuzumab + trastuzumab + docetaxel (category 1)

Other first-line agents for HER2-positive disease:
- Trastuzumab with:
  - Paclitaxel ± carboplatin
  - Docetaxel
  - Vinorelbine
  - Capecitabine

Preferred agents for trastuzumab-exposed HER2-positive disease:
- Ado-trastuzumab emtansine (T-OM1)

Other agents for trastuzumab-exposed HER2-positive disease:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents

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EMBRACE: Study Design

Locally recurrent or MBC
- 2-5 prior chemotherapies
- ≥2 for advanced disease
- Prior anthracycline and taxane
- Progression ≤ 6 months of last chemotherapy
- Neuropathy ≤ grade 2
- ECOG ≤ 2
N=762

Enrulbin mesylate 1.4 mg/m², 2-5 min IV d1, 8 q21d

Randomization 2:1
Treatment of physician’s choice (TPC)
Any monotherapy (chemotherapy, hormonal, biological)* or supportive care only^*

Primary objective
- OS
Secondary objectives
- PFS, ORR, safety

Stratification
- Geographical region
- Prior XELODA
- HER2 status

*Approved for treatment of cancer.
^Or palliative treatment or radiotherapy administered according to local practice, if applicable.

### EMBRACE: Adverse Events*

<table>
<thead>
<tr>
<th></th>
<th>Grade 3 Eribulin (n=508)</th>
<th>Grade 3 TPC (n=254)</th>
<th>Grade 4 Eribulin (n=508)</th>
<th>Grade 4 TPC (n=254)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic Events, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>21.1</td>
<td>14.2</td>
<td>24.1</td>
<td>6.9</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>11.7</td>
<td>4.9</td>
<td>2.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.8</td>
<td>3.2</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3.0</td>
<td>0.8</td>
<td>1.25</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Non-hematologic events, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
<td>8.2</td>
<td>10.1</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>7.8</td>
<td>2.0</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.2</td>
<td>2.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3.6</td>
<td>2.4</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>1.4</td>
<td>2.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>0.4</td>
<td>3.6</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

---

### Triple Negative Breast Cancer and BRCA-ness

- The majority of BRCA1 mutation-associated breast cancers are triple negative/basal-like subtype
- What is behind the BRCA1-ness?

**Genomic instability**
- Impaired Double strand DNA repair by homologous recombination
- BRCA carriers as well as sporadic BLBCs have reduced BRCA1 expression
  - promoter methylation defect in non-BRCA-mutated BLBCs
  - LOH
  - high levels of activity of a negative regulator of BRCA1: ID4
  - BRCA1 functional loss
- other pathway abnormalities
### PARP inhibitors

Data on single agent clinical activity with most PARP-inhibitors, especially in BRCA carriers are limited.

**Olaparib:**
*Clinical Data:* BRCA1 and 2 carriers with breast cancer
- **Response Rate:** 41% (n: 27, 400 mg BID) 22% (n:27; 100 mg BID)
- **Progression-free Survival:** 5.7 months 3.8 months

*Cell line data:* low BRCA1 and increased expression levels of MRE11, NBS1, TDG, XPA are associated with resistance, while increased expression of CHEK2 and MK2 associated with response.

**Niraparib:**
*Clinical Data:* 2 of 4 patients responded among BRCA carrier breast cancer patients (MTD 300 mg BID)


---

### Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre open-label, non-randomized study.

- Stratification by BRCA status
- Objective response rate
- 91 enrolled (65 ovarian ca vs 26 breast ca)

**Objective Response Rate**
- Overall RR: 29%
- 7/17 (41%) RR in BRCA 1 or BRCA2 carriers
- 11/46 (25%) in non-carriers

- No objective response in breast cancer (disease control rate: 38% at 8 weeks, 70% (7/10) in BRCA+ and and 19% in 3/16

Background and Rationale

Homologous recombinant DNA repair is defective in BRCA carriers. Single-strand break repair can be inhibited by poly(ADP-ribose) polymerase (PARP)-1. Platinum agents generate intra and inter-DNA cross-links impeding cell divisions.

Platinum (Gronwald, et al. JCO, 2009, abstract) and PARP inhibitors have both shown single agent activity in BRCA-associated breast cancer patients (Silver et al. J Clin Oncol 2010; Tutt et al. Lancet 2010). Precinical data suggest synergism between platinum agents and ABT-888 (Clark CC et al. Mol Cancer Ther. 2012). Clinical data on combining these two classes of agents, particularly in BRCA-associated breast cancer are limited, and the optimal dose, frequency, and duration have not been defined.

Applying the concept of synthetic lethality (Rehman et al. Nat Rev 2010), and adding a DNA-damaging agent (carboplatin) we designed a trial to treat women with BRCA-associated stage IV breast cancer and to compare carboplatin and ABT-888 vs. single agent ABT-888.

Since neither the dose-limiting toxicity (DLT) nor the maximum tolerated dose (MTD) of daily ABT-888 had been firmly established, we first conducted a phase I trial of carboplatin and escalating doses of ABT-888.
Study Design

- Veliparib (vel) at 400 mg BID daily (21-day cycles).
- Upon progression and crossing over: carboplatin IV over 30 minutes at an AUC of 5 and vel at 150 mg BID
- Dose adjustments are allowed to 50 mg BID of vel, and dose delays are allowed up to 14 days (21 days for thrombocytopenia).
- Simon’s Optimal Two-Stage Design: ≥ 2 confirmed partial responses in the first 10 patients (with separate strata for BRCA1 and BRCA2) will result in accruing 12 more patients for either/both strata (22 patients per strata).

Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Treated *</td>
<td>22</td>
<td>22</td>
<td>44</td>
</tr>
<tr>
<td>Median Age (Range)</td>
<td>42 (28-68)</td>
<td>44 (28-67)</td>
<td>43 (28-68)</td>
</tr>
<tr>
<td>ER/PgR +</td>
<td>2 (9%)</td>
<td>18 (82%)</td>
<td>20 (45%)</td>
</tr>
<tr>
<td>Prior Chemo for Mets</td>
<td>1 (0-5)</td>
<td>1 (0-3)</td>
<td>1 (0-5)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>Dominant Metastatic Site</td>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone with Lung</td>
<td>2 (9)</td>
<td>6 (27)</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Bone with Liver</td>
<td>1 (4)</td>
<td>6 (27)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Bone with nodes, other sites</td>
<td>1 (4)</td>
<td>2 (9)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Liver +/- lung</td>
<td>3 (14)</td>
<td>3 (14)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Lung</td>
<td>9 (41)</td>
<td>3 (14)</td>
<td>12 (27)</td>
</tr>
<tr>
<td>Nodes and/or soft tissue</td>
<td>5 (24)</td>
<td>1 (4)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Lung and brain</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Soft Tissue with brain</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*Excludes 1 pt who received 1 pill before insurance denial, and 1 pt who withdrew from the trial/follow-up
### Number of Cycles on Vel, Vel and Carboplatin, and Time to Failure (TTF)

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Cycles on vel alone</td>
<td>3 (1+ - 15)</td>
<td>6 (1+ - 18)</td>
<td>4 (1+ - 18)</td>
</tr>
<tr>
<td># of all treatment cycles (with early cross-over data)</td>
<td>4 (1+ - 16)</td>
<td>8 (1+ - 18)</td>
<td>5 (1+ - 18)</td>
</tr>
<tr>
<td>Median TTF on vel alone (months)</td>
<td>3.0 (95%CI 1.9-4.9)</td>
<td>5.7 (95%CI 4.0-8.3)</td>
<td>4.0 (95%CI 3.0-6.0)</td>
</tr>
<tr>
<td>Median TTF on treatment (including cross-over to carboplatin and vel^)</td>
<td>6.4 (95%CI 3.7-10.3)</td>
<td>8.3 (95%CI 6.0-8.5)</td>
<td>6.9 (95%CI 5.3-8.5)</td>
</tr>
<tr>
<td>Median TTF on our prior* Carboplatin and vel trial</td>
<td>7.9 (95%CI 5.5-11.5)</td>
<td>9.4 (95% CI 6.9-10.8)</td>
<td>8.1 (95% CI 6.5-10.1)</td>
</tr>
</tbody>
</table>

^ 20 patients are still on treatment with a median time of 2.7 months; 15 are without progression
* Phase I long-term outcome : 3 of 27 pts in CR 21+ months

### Response and Clinical Benefit Ratio on Vel and Subsequent Vel and Carboplatin, and on our Prior Combination Trial

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Vel alone</th>
<th>Vel alone</th>
<th>Vel and carboplatin</th>
<th>Vel and carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Response Rate (PR)</td>
<td>Clinical benefit (CB)</td>
<td>Response Rate (PR)</td>
<td>CB</td>
</tr>
<tr>
<td>BRCA1</td>
<td>3/20 (15%)</td>
<td>4/20 (20%)</td>
<td>1/9 (11%)</td>
<td>1/9 (11%)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>7/19 (37%)</td>
<td>8/19 (42%)</td>
<td>0/6 (0%)</td>
<td>1/6 (17%)</td>
</tr>
<tr>
<td>OUTCOME ON OUR PRIOR TRIAL OF CARBOPLATIN AND VEL</td>
<td>5/11 (45%)</td>
<td>3 CRs, 2 PRs</td>
<td>8/11 (73%)</td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>9/15 (60%)</td>
<td>1 CR, 8 PRs</td>
<td>11/15 (73%)</td>
<td></td>
</tr>
<tr>
<td>BRCA1 and 2</td>
<td>1CR (100%)</td>
<td></td>
<td>1/1 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

5 patients on ABT-888 alone are still too early to assess response since they are on cycles 1-3. One patient on ABT-888 & carboplatin too early to assess for response.
Conclusion

• ABT-888/veliparib at 400 mg BID daily, is well-tolerated and is associated with clinically relevant activity. The confirmed response and clinical benefit rates (15% and 20% in BRCA1 carriers and 37% and 42% in BRCA2 carriers) support further clinical development.

• It is too early to assess the overall benefit of crossing over to the combination of veliparib and carboplatin after progression on veliparib alone.

• Mature data from our previously completed phase I trial suggests a benefit with a strategy combining carboplatin and ABT-888 upfront, with maintenance ABT-888 upon maximum response; 5 of 27 patients so treated reached complete remission and 3 remain without recurrence at 21-23+ months, respectively.

• In the current preliminary analysis veliparib alone followed by veliparib and carboplatin on progression does not appear to achieve the same clinical benefit rate as up-front veliparib plus carboplatin followed by maintenance veliparib.

Lessons Learned

• Metastatic (Stage IV) breast cancer is still incurable, but long-term disease control is feasible, with good quality of life.

• Both progression-free and overall survival have improved over the years with the availability of newer agents.

• Establishment of tumor biology (biopsy) upon recurrence is necessary due to the heterogeneity of disease, discordance between primary and recurrent site biology, and the potential for treatment with targeting therapies.

• In addition to standard staging, tumor markers are helpful in monitoring disease progression, while the role of circulating tumor cell and circulating DNA assays is to be determined.
Lessons Learned

• HR+ breast cancer: more likely to present with bone metastasis (bisphosphonates, denosumab)
• First line treatment is anti-estrogen therapy except in cases of rapid recurrence or visceral predominant disease
• LHRH antagonists with tamoxifen in premenopausal, and aromatase inhibitors in postmenopausal patients are the choices for first line treatment; fulvestrant is an acceptable choice; the role of combining fulvestrant with an AI is unclear
• Second line options include fulvestrant, another AI, or exemestane and everolimus

Lessons Learned

• HR+ refractory or triple negative breast cancer
• Single sequential therapy is acceptable, combination therapy can be used for heavy visceral load or rapid progression
• Taxanes (weekly paclitaxel, q 3 weeks docetaxel or nab-paclitaxel)
  Other agents: see NCCN
• Triple negative breast cancer may be more sensitive to platinum compounds BRCA-carriers may benefit from PARP-inhibitors
• Unmet needs: prevention and treatment of CNS metastasis, seen up to 30% (similar to HER2+ stage IV disease)
Lessons Learned

• Further delineation of molecular genetics of both primary and metastatic tumor sites are needed inclusive of mutations, amplifications, epigenetic changes, etc.

• The role of protein/kinom analysis is to be determined

• If feasible, in addition to biopsy of first metastatic recurrence, repetitive samples may be useful

• Participation in clinical trials (whether NCI, institutional, or pharma-driven) should be available for all patients

Thank you