HER2 Biology and Treatment in Breast Cancer

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Washington Hospital Center
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Georgetown University
Washington DC
Off-Label Use Disclosure(s)

I do intend to discuss an off-label use of a product during this activity. The following products will be discussed:
1) MM-302
Disclosures

• Research to institution: BMS, Pfizer (PUMA), Genentech/Roche
• Steering Committees trials with Genentech/Roche (uncompensated)
• Honorarium: Genentech/Roche and Clinigen
Outline

• History
• EGFR/HER2 signaling pathway
• HER2 as a target for anticancer therapy
• Studies targeting HER2
  • Metastatic
  • Neoadjuvant
• SAFE-HEaRt study
Milestones of HER2/anti-HER2 therapies in Breast Cancer

1978
- EGFR discovery
- Cohen

1982
- neu oncogene discovery
- Weinberg

1983
- Her2 cloned
- Ullrich and Coussens

1984
- EGFR MoAb inhibited growth
- Mendelsohn

1985
- Her2 amplification in breast cancer
- Aaronson

1987
- Amplification of Her2/neu correlates with shorter survival
- Slamon

1998
- FDA approves single agent trastuzumab for 2nd line and in combination with paclitaxel for 1st line MBC

2006
- FDA approves pertuzumab + trastuzumab + docetaxel for MBC

2007
- FDA approves lapatinib + capecitabine for MBC

2012
- FDA approves TDM1 for MBC

2013
- FDA approves Pertuzumab + Trastuzumab neoadjuvant

MBC: metastatic breast cancer
MoAb: monoclonal antibody
EGF Receptor Family

Dimerization: Essential for Receptor Activation

Potential HER2 targets for anticancer therapy

Immune System Response to Trastuzumab

Bianchini G., Gianni L. Lancet Oncol 2014;15:e58-68
Q1: How Would You Currently Treat This Patient?

A 56-year-old woman with ER/PR+, HER2+ breast cancer now has involvement of the liver, lung, and bone marrow after receiving adjuvant AC → trastuzumab + paclitaxel, then trastuzumab for one year. It is now two years later. Which option is most likely to yield the longest PFS and OS?

1. Lapatinib / capecitabine
2. Trastuzumab / pertuzumab / docetaxel or paclitaxel
3. Lapatinib / trastuzumab
4. T-DM1
5. Everolimus / exemestane
First-Line MBC Setting
Chemotherapy Plus Trastuzumab in Metastatic Disease

<table>
<thead>
<tr>
<th></th>
<th>Slamon et al n = 469</th>
<th>Marty et al n = 186</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Arms</td>
<td>AC or T* vs AC or T→H\†</td>
<td>Docetaxel vs Docetaxel →H\†</td>
</tr>
<tr>
<td>Time to Disease Progression (mos)</td>
<td>4.6 7.4 P value &lt; 0.001</td>
<td>6.1 11.7 P value 0.0001</td>
</tr>
<tr>
<td>Response Rate</td>
<td>32% 50% P value &lt; 0.001</td>
<td>34% 61% P value 0.0002</td>
</tr>
<tr>
<td>Median Overall Survival (mos)</td>
<td>20 25 P value 0.046</td>
<td>23 31 P value 0.0325</td>
</tr>
</tbody>
</table>

* T = paclitaxel; † H = trastuzumab.

Trastuzumab and pertuzumab bind to different regions on HER2 and may have synergistic activity.

**Trastuzumab**
- Does not inhibit HER2 dimerization, thus blocking HER2:HER3
- Prevents HER2 receptor shedding
- Blocks HER2 signaling and flags cells for destruction by the immune system

**Pertuzumab**
- Inhibits HER2 from forming dimer pairs
- Flags cells for destruction by the immune system
- Does not prevent HER2 receptor shedding
Pertuzumab and trastuzumab is effective following progression on trastuzumab

Sequential use of pertuzumab and trastuzumab has beneficial effects following progression on trastuzumab alone

aloading dose

Scheuer, unpublished data, 2008
**CLEOPATRA Study Design**

**HER2-positive MBC centrally confirmed (N = 808)**

- **Randomization stratified by geographic region and neo/adjuvant chemotherapy**
- **Study dosing q3w:**
  - Pertuzumab/placebo: 840 mg loading → 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading → 6 mg/kg maintenance
  - Docetaxel: 75 mg/m² → 100 mg/m² escalation if tolerated

- * < 6 cycles allowed for unacceptable toxicity or PD; > 6 cycles allowed at investigator discretion.

HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; PD, progressive disease.

Efficacy Analysis Milestones

PFS primary analysis

Δ 6.1 months
HR 0.62 (p < 0.0001)

May 2011

HR, hazard ratio.

Efficacy Analysis Milestones

- **PFS primary analysis**
  - Δ 6.1 months
  - HR 0.62 (p < 0.0001)

- **OS 1st interim analysis**
  - HR 0.64 (p = 0.005)

Efficacy Analysis Milestones

May 2011

PFS primary analysis

Δ 6.1 months
HR 0.62 (p < 0.0001)

May 2012

OS 1st interim analysis

HR 0.64 (p = 0.005)

OS 2nd interim analysis

HR 0.66 (p = 0.0008)*

* Crossed the prespecified O’Brien-Fleming stopping boundary (HR ≤ 0.739; p ≤ 0.0138)

Efficacy Analysis Milestones

May 2011
- PFS primary analysis
  - Δ 6.1 months
    - HR 0.64 (p = 0.005)

May 2012
- OS 1st interim analysis
  - HR 0.66 (p = 0.0008)*
- Patients still on placebo offered crossover to pertuzumab
- OS 2nd interim analysis
  - HR 0.62 (p < 0.0001)
Efficacy Analysis Milestones

- **May 2011**: PFS primary analysis
  - Δ 6.1 months
  - HR 0.64 (p = 0.005)

- **May 2012**: OS 1st interim analysis
  - HR 0.62 (p < 0.0001)

- **May 2012**: OS 2nd interim analysis
  - HR 0.66 (p = 0.0008)*

- **July 2012**: Patients still on placebo offered crossover to pertuzumab

- **Feb 2014**: OS final analysis
## Baseline Characteristics

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Placebo + T + D (n = 406)</th>
<th>Pertuzumab + T + D (n = 402)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>54.0 (27–89)</td>
<td>54.0 (22–82)</td>
</tr>
<tr>
<td><strong>Region, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>128 (31.5)</td>
<td>125 (31.1)</td>
</tr>
<tr>
<td>Europe</td>
<td>152 (37.4)</td>
<td>154 (38.3)</td>
</tr>
<tr>
<td>North America</td>
<td>68 (16.7)</td>
<td>67 (16.7)</td>
</tr>
<tr>
<td>South America</td>
<td>58 (14.3)</td>
<td>56 (13.9)</td>
</tr>
<tr>
<td><strong>Hormone receptor status, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER- and/or PgR-positive</td>
<td>199 (49.0)</td>
<td>189 (47.0)</td>
</tr>
<tr>
<td>ER- and PgR-negative</td>
<td>196 (48.3)</td>
<td>212 (52.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (2.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td><strong>Disease type at screening, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonvisceral</td>
<td>90 (22.2)</td>
<td>88 (21.9)</td>
</tr>
<tr>
<td>Visceral</td>
<td>316 (77.8)</td>
<td>314 (78.1)</td>
</tr>
</tbody>
</table>

D, docetaxel; ER, estrogen receptor; PgR, progesterone receptor; T, trastuzumab.

## Prior Therapy for Breast Cancer

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Placebo + T + D (n = 406)</th>
<th>Pertuzumab + T + D (n = 402)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior neo/adjuvant chemotherapy, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>192 (47.3)</td>
<td>184 (45.8)</td>
</tr>
<tr>
<td>No</td>
<td>214 (52.7)</td>
<td>218 (54.2)</td>
</tr>
<tr>
<td><em><em>Components of neo/adjuvant therapy</em>, n (%)</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>164 (40.4)</td>
<td>150 (37.3)</td>
</tr>
<tr>
<td>Taxanes</td>
<td>94 (23.2)</td>
<td>91 (22.6)</td>
</tr>
<tr>
<td>Hormonal treatments</td>
<td>97 (23.9)</td>
<td>106 (26.4)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>41 (10.1)</td>
<td>47 (11.7)</td>
</tr>
</tbody>
</table>

* Patients could have received more than one therapy.

Final OS Analysis

**Median follow-up 50 months (range 0–70 months)**

OS (%)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Ptz + T + D</th>
<th>Pla + T + D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>402</td>
<td>406</td>
</tr>
<tr>
<td>10</td>
<td>371</td>
<td>350</td>
</tr>
<tr>
<td>20</td>
<td>318</td>
<td>289</td>
</tr>
<tr>
<td>30</td>
<td>268</td>
<td>230</td>
</tr>
<tr>
<td>40</td>
<td>226</td>
<td>179</td>
</tr>
<tr>
<td>50</td>
<td>104</td>
<td>91</td>
</tr>
<tr>
<td>60</td>
<td>28</td>
<td>23</td>
</tr>
<tr>
<td>70</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

n at risk

HR 0.68
95% CI = 0.56, 0.84
p = 0.0002

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.

CI, confidence interval; Pla, placebo; Ptz, pertuzumab.
Final OS Analysis

Median follow-up 50 months (range 0–70 months)

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.

CI, confidence interval; Pla, placebo; Ptz, pertuzumab.
OS: Predefined Subgroups

<table>
<thead>
<tr>
<th>Category</th>
<th>Subgroups</th>
<th>N</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior treatment</td>
<td>All</td>
<td>808</td>
<td>0.67</td>
<td>(0.55, 0.82)</td>
</tr>
<tr>
<td></td>
<td>De novo</td>
<td>432</td>
<td>0.64</td>
<td>(0.48, 0.85)</td>
</tr>
<tr>
<td></td>
<td>neo/adjuvant therapy</td>
<td>376</td>
<td>0.70</td>
<td>(0.53, 0.93)</td>
</tr>
<tr>
<td>Region</td>
<td>Europe</td>
<td>306</td>
<td>0.65</td>
<td>(0.47, 0.91)</td>
</tr>
<tr>
<td></td>
<td>North America</td>
<td>135</td>
<td>0.63</td>
<td>(0.37, 1.07)</td>
</tr>
<tr>
<td></td>
<td>South America</td>
<td>114</td>
<td>0.50</td>
<td>(0.30, 0.85)</td>
</tr>
<tr>
<td></td>
<td>Asia</td>
<td>253</td>
<td>0.82</td>
<td>(0.57, 1.16)</td>
</tr>
<tr>
<td>Age group</td>
<td>&lt; 65 years</td>
<td>681</td>
<td>0.70</td>
<td>(0.56, 0.87)</td>
</tr>
<tr>
<td></td>
<td>≥ 65 years</td>
<td>127</td>
<td>0.53</td>
<td>(0.31, 0.90)</td>
</tr>
<tr>
<td></td>
<td>&lt; 75 years</td>
<td>789</td>
<td>0.68</td>
<td>(0.55, 0.83)</td>
</tr>
<tr>
<td></td>
<td>≥ 75 years</td>
<td>19</td>
<td>0.85</td>
<td>(0.26, 2.73)</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>480</td>
<td>0.63</td>
<td>(0.49, 0.82)</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>30</td>
<td>0.41</td>
<td>(0.11, 1.45)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>261</td>
<td>0.82</td>
<td>(0.58, 1.17)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>37</td>
<td>0.37</td>
<td>(0.13, 1.06)</td>
</tr>
<tr>
<td>Disease type</td>
<td>Visceral</td>
<td>630</td>
<td>0.59</td>
<td>(0.48, 0.74)</td>
</tr>
<tr>
<td></td>
<td>Nonvisceral</td>
<td>178</td>
<td>1.11</td>
<td>(0.66, 1.85)</td>
</tr>
<tr>
<td>ER/PgR status</td>
<td>Positive</td>
<td>388</td>
<td>0.71</td>
<td>(0.53, 0.96)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>408</td>
<td>0.61</td>
<td>(0.47, 0.81)</td>
</tr>
<tr>
<td>HER2 IHC status</td>
<td>3+</td>
<td>721</td>
<td>0.66</td>
<td>(0.53, 0.81)</td>
</tr>
<tr>
<td>FISH status</td>
<td>FISH-positive</td>
<td>767</td>
<td>0.69</td>
<td>(0.56, 0.85)</td>
</tr>
</tbody>
</table>

ITT population. Nonstratified.
Updated PFS

*Investigator-Assessed*

**ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Ptz + T + D</th>
<th>Pla + T + D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>30</td>
<td>40</td>
<td>50</td>
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<tr>
<td>40</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>50</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>60</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>70</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>80</td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

**Ptz + T + D:** median 18.7 months

**Pla + T + D:** median 12.4 months

Δ 6.3 months

HR 0.68

95% CI = 0.58, 0.80

p < 0.0001
CLEOPATRA: Independently Assessed Progression-Free Survival by Age
Exposure to Study Treatment

<table>
<thead>
<tr>
<th>Safety population*</th>
<th>Placebo + T + D (n = 396)</th>
<th>Pertuzumab + T + D (n = 408)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time on study treatment, months (range)</td>
<td>11.4 (0.1–66.3)</td>
<td>17.4 (0.1–67.7)</td>
</tr>
<tr>
<td>Median number of docetaxel cycles (range)</td>
<td>8 (1–42)</td>
<td>8 (1–52)</td>
</tr>
</tbody>
</table>

* All patients who received any amount of study medication (pertuzumab/placebo, T, and/or D).
Adverse Events (All Grades) with ≥ 25% Incidence or ≥ 5% Difference between Groups Overall

<table>
<thead>
<tr>
<th>Safety population</th>
<th>Placebo + T + D (n = 396), %</th>
<th>Pertuzumab + T + D (n = 408), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>60.6</td>
<td>60.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48.7</td>
<td>68.4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>50.0</td>
<td>53.4</td>
</tr>
<tr>
<td>Nausea</td>
<td>42.4</td>
<td>44.9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37.4</td>
<td>38.0</td>
</tr>
<tr>
<td>Rash</td>
<td>24.0</td>
<td>37.5</td>
</tr>
<tr>
<td>Asthenia</td>
<td>30.8</td>
<td>27.7</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>26.8</td>
<td>29.7</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>28.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24.5</td>
<td>26.0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>25.0</td>
<td>24.3</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>19.9</td>
<td>27.2</td>
</tr>
<tr>
<td>Headache</td>
<td>19.2</td>
<td>25.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>25.5</td>
<td>15.9</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14.4</td>
<td>20.8</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10.1</td>
<td>17.6</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7.6</td>
<td>13.7</td>
</tr>
<tr>
<td>Dry skin</td>
<td>6.1</td>
<td>11.3</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>5.1</td>
<td>10.3</td>
</tr>
</tbody>
</table>
Grade ≥ 3 Adverse Events

*Incidence ≥ 5%*

<table>
<thead>
<tr>
<th>Safety population</th>
<th>Placebo + T + D (n = 396), %</th>
<th>Pertuzumab + T + D (n = 408), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>46.2</td>
<td>49.0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>14.9</td>
<td>12.3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7.6</td>
<td>13.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5.1</td>
<td>9.3</td>
</tr>
</tbody>
</table>

- No cumulative toxicities
## Cardiac Safety

<table>
<thead>
<tr>
<th>Safety population</th>
<th>Placebo + T + D (n = 396), %</th>
<th>Pertuzumab + T + D (n = 408), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>sLVD</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td>LVEF decline to &lt; 50% and by ≥ 10% points from baseline*</td>
<td>7.4</td>
<td>6.1</td>
</tr>
</tbody>
</table>

- One new sLVD event in the pertuzumab group after 40 months (resolved)
- LVEF declines reversed in 88% of pertuzumab patients

* In patients with post-baseline assessment; n = 378 in the placebo group and 394 in the pertuzumab group. sLVD, symptomatic left ventricular dysfunction.
## Treatment after Study Discontinuation

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Placebo + T + D (n = 369 withdrawn), %</th>
<th>Pertuzumab + T + D (n = 335 withdrawn), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>78.9</td>
<td>77.0</td>
</tr>
<tr>
<td>Any HER2-targeted treatment</td>
<td>n = 291</td>
<td>n = 258</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>71.5</td>
<td>72.9</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>41.6</td>
<td>45.3</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Trastuzumab emtansine</td>
<td>48.8</td>
<td>48.1</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>11.7</td>
<td>12.4</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>58.4</td>
<td>55.0</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>30.2</td>
<td>26.0</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>19.2</td>
<td>15.9</td>
</tr>
<tr>
<td>Taxanes</td>
<td>16.8</td>
<td>15.9</td>
</tr>
<tr>
<td>Hormonal treatments</td>
<td>19.2</td>
<td>15.1</td>
</tr>
<tr>
<td>Taxanes</td>
<td>19.2</td>
<td>26.7</td>
</tr>
</tbody>
</table>
CLEOPATRA Conclusions

• The addition of pertuzumab to standard 1L therapy significantly improved median OS by 15.7 months
  – Benefit consistent across subgroups
• Investigator-assessed PFS benefit maintained
• No new safety concerns
  – Long-term cardiac safety maintained
CLEOPATRA Conclusions

• The addition of pertuzumab to standard 1L therapy significantly improved median OS by 15.7 months
  – Benefit consistent across subgroups
• Investigator-assessed PFS benefit maintained
• No new safety concerns
  – Long-term cardiac safety maintained

The 56.5-month median OS is unprecedented in this indication and confirms the pertuzumab regimen as first-line standard of care for patients with HER2-positive MBC
Diarrhea

- At the time of starting treatment, all patients should be given a prescription for loperamide, and advised to keep the medication/prescription with them at all times. The patient should be clearly instructed to start loperamide promptly at the first signs of diarrhea.

- A dose of 4 mg loperamide must be given after first episode of diarrhea, and 2 mg every 4 hours or after every episode of unformed stool, until the patient is free from diarrhea for 12 hours. The maximum allowed daily dose of loperamide is 16 mg.
Pertuzumab Rash

- Papulopustular rash – 1,157 patients - all grades 24.6% and high grades 1.1%
- Regular moisturization
- Twice-daily application of sun-block SPF 15 or higher
- Moderate to severe (CTCAE grades 2–3) acneiform rash, treatment with a tetracycline antibiotic (doxycycline or minocycline) and a topical corticosteroid may be effective.
- For mild cases (CTCAE grade 1), treatment with a topical corticosteroid or a topical antibiotic, such as clindamycin or dapsone

CLEOPATRA

Time to CNS Metastases as first site of disease progression

HR = 0.58 (95% CI, 0.39−0.85)

$P = 0.0049$

Swain, et al Ann Oncol 2014;25: 1116-1121
**CLEOPATRA**

*Overall Survival in Patients with CNS metastases as first site of progression*

![Graph showing overall survival probability over time for Pertuzumab + trastuzumab + docetaxel compared to Placebo + trastuzumab + docetaxel.](image)

- **HR = 0.66 (95% CI, 0.39–1.11)**
- **P = 0.1139**

**n at risk**
- **Placebo arm**: 51, 51, 42, 40
- **Pertuzumab arm**: 55, 55, 54, 50

**Time (months)**
- **Placebo arm**: 30, 16, 11, 7, 0, 0
- **Pertuzumab arm**: 42, 33, 24, 12, 8, 1

Swain, et al Ann Oncol 2014;25: 1116-1121
**PIK3CA** mutation associated with poorer prognosis

**CLEOPATRA**

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Pla+T+D WT</th>
<th>Pla+T+D Mut</th>
<th>Ptz+T+D WT</th>
<th>Ptz+T+D Mut</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pla+T+D WT</strong></td>
<td>191</td>
<td>164</td>
<td>136</td>
<td>114</td>
</tr>
<tr>
<td><strong>Pla+T+D Mut</strong></td>
<td>90</td>
<td>76</td>
<td>56</td>
<td>37</td>
</tr>
<tr>
<td><strong>Ptz+T+D WT</strong></td>
<td>190</td>
<td>179</td>
<td>159</td>
<td>137</td>
</tr>
<tr>
<td><strong>Ptz+T+D Mut</strong></td>
<td>86</td>
<td>71</td>
<td>61</td>
<td>44</td>
</tr>
</tbody>
</table>

Independently-assessed PFS (%)

Time (months)

- 83 events
- 45 events
- 101 events
- 63 events

**PIK3CA** mutation associated with poorer prognosis

- Mut, mutated; WT, wild-type

*Baselga, ..Swain, J Clin Oncol 2014; 32: 3753-61*
Summary and conclusion

**CLEOPATRA BIOMARKERS**

- Our analyses confirm HER2 as the only marker for selecting patients for HER2-targeted therapy
  - This was despite comprehensive exploration of a broad panel of candidate biomarkers
  - Results were consistent with the TRYPHAENA and NeoSphere studies\(^1,2\)

- The lack of a HER2 treatment-naïve control arm may have resulted in the absence of a signal for other biomarkers in CLEOPATRA

Baselga, ..Swain, J Clin Oncol 2014; 32: 3753-61

Summary and conclusion

**PI3K**

- Mutations in *PIK3CA* were not associated with resistance to pertuzumab, as patients derived similar additional benefit independent of *PIK3CA* mutational status.

- However, the *PIK3CA* mutational status may identify patients with poorer prognoses and particular unmet medical needs:
  - Previous studies have shown mutated *PIK3CA* to be associated with lapatinib resistance\(^1\) and poorer prognosis after trastuzumab therapy\(^2\).
  - Other studies have shown good prognoses with mutated *PIK3CA*; particularly in hormone receptor-positive tumors\(^3\)–\(^5\).

- Clinical trials of HER2-targeted molecules in combination with PI3K pathway-targeted agents may therefore be justified based on our findings:


## Objective Response Rate and Clinical Benefit Rate vs. Prior Trastuzumab Use

<table>
<thead>
<tr>
<th>Response</th>
<th>Response Rate CR/PR</th>
<th>Clinical Benefit Rate CR/PR/SD6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior T</td>
<td>29%</td>
<td>39%</td>
</tr>
<tr>
<td>No Prior T</td>
<td>51%</td>
<td>71%</td>
</tr>
<tr>
<td>Adjusted Odds Ratio</td>
<td>0.39 (95% CI, 0.18-0.82)</td>
<td>0.28 (95% CI, 0.13-0.59)</td>
</tr>
<tr>
<td>P Value</td>
<td>0.038</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Overall Survival According to Trastuzumab Use (Metastatic Breast Cancer, Excluding de novo Stage IV)

Overall Survival According to Trastuzumab Use
(Metastatic Breast Cancer, Including de novo Stage IV)

No: N = 438, Median = 39 mos
Yes: N = 75, Median = 28 mos
First Line HER2+ Metastatic Breast Cancer Controlled Cohort Study

Log-rank test:
$p = .51$

<table>
<thead>
<tr>
<th>mBC/Adj T+</th>
<th>No. at risk</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mBC/Adj T+</td>
<td>68</td>
<td>87.5</td>
</tr>
<tr>
<td>mBC/Adj T-</td>
<td>21</td>
<td>60.0</td>
</tr>
</tbody>
</table>

Negri, Zambelli, Franchi et al. The Oncologist 2014;19:1209–15
Paclitaxel, Pertuzumab, Trastuzumab
Phase 2 study

N = 69
HER2 +
0-1 prior Rx
1° endpoint=6 mo PFS

Paclitaxel (T) at 80 mg/m² q week

Pertuzumab (P) at 840mg load → 420 mg q 3 weeks

Trastuzumab (H) at 8 mg/kg load → 6 mg/kg q 3 weeks

q week ........................................
q 3 weeks.................................
q 3 weeks.................................

N = 69
HER2 +
0-1 prior Rx
1° endpoint=6 mo PFS

q 3 months.................................
cardiac biomarkers every 2 cycles........................................

Dang, et al J Clin Oncol 2014;32: epub
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Total Enrolled</th>
<th>69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>53 (26-84)</td>
</tr>
<tr>
<td>ECOG 0 1 2+</td>
<td>41 (59%) 27 (39%) 1 (1%)</td>
</tr>
<tr>
<td>Measurable disease, n (%)</td>
<td>57 (83%)</td>
</tr>
<tr>
<td>Prior (neo)adjuvant therapy, n (%)</td>
<td>30 (43%)</td>
</tr>
<tr>
<td>Anthracycline</td>
<td>19 (28%)</td>
</tr>
<tr>
<td>Taxane</td>
<td>25 (32%)</td>
</tr>
<tr>
<td>Hormone</td>
<td>22 (32%)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>22 (32%)</td>
</tr>
<tr>
<td>Prior therapy in metastatic setting 0 1</td>
<td>51 (74%) 18 (26%)</td>
</tr>
</tbody>
</table>
Paclitaxel, Pertuzumab, Trastuzumab
Efficacy at 6 Months

<table>
<thead>
<tr>
<th>Efficacy at 6 months (n=69)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-free, n (%)</strong></td>
<td>54 (84%)</td>
</tr>
<tr>
<td>Complete response (CR), n (%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Partial response (PR), n (%)</td>
<td>31 (48%)</td>
</tr>
<tr>
<td>Stable disease (SD), n (%)</td>
<td>16 (25%)</td>
</tr>
<tr>
<td><strong>Progression of disease, n (%)</strong></td>
<td>10 (16%)</td>
</tr>
</tbody>
</table>

Dang, et al J Clin Oncol 2014;32: epub
### Paclitaxel, Pertuzumab, Trastuzumab

**Selected AEs of > 25%**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Grade 1 – 2</th>
<th>Grade 3 – 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>54 (81%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>53 (79%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>53 (79%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>48 (72%)</td>
<td>0</td>
</tr>
<tr>
<td>AST elevation</td>
<td>42 (63%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>37 (55%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>35 (52%)</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>37 (55%)</td>
<td>0</td>
</tr>
<tr>
<td>Acneiform rash</td>
<td>37 (55%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>33 (49%)</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>36 (54%)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>26 (43%)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>25 (37%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>26 (39%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Dang, et al J Clin Oncol 2014; 32: epub
Paclitaxel, Pertuzumab, Trastuzumab Progression-Free Survival

Med FU of 21 mo

6-mo PFS of 86%!

Med PFS = 19.5 mo

Study a success
6-mo PFS > 65%

Dang, et al J Clin Oncol 2014;32: epub
**Paclitaxel, Pertuzumab, Trastuzumab**

**Conclusions**

- Study met 1° endpoint w/ 6-month PFS of 86%
- Median PFS was 19.5 months
  - 1\textsuperscript{st} line-med PFS = 24.2 mo
  - 2\textsuperscript{nd} line-med PFS = 16.4 mo
- Well tolerated
  - No febrile neutropenia
- Paclitaxel with trastuzumab and pertuzumab is another option for patients with HER2+ metastatic breast cancer (NCCN endorsed)

Dang, et al J Clin Oncol 2014;32: epub
First Line Therapy HER2+MBC

- CARESlamon 2001 chemotherapy +/- Trastuzumab TTP, P<0.001
- M77001 Marty 2005 Docetaxel +/- Trastuzumab TTP, P =0.0001
- BCIRG 007 Valero 2011 Doc + Trastuzumab +/- carboplatin TTP, P = 0.57
- CLEOPATRA Baselga 2011 Doc + Trastuzumab +/- Pertuzumab PFS, P<0.001
Studies in the First-Line HER2+ MBC Setting
Phase III MARIANNE Study Design

Primary endpoint: PFS

RANDOMIZATION

HER2+ Progressive or recurrent locally advanced or chemotherapy-naïve MBC (N = 1092)

TRASTUZUMAB q3wk + DOCETAXEL q3wk OR PACLITAXEL qwk

T-DM1 + PERTUZUMAB q3wk

T-DM1 + PLACEBO q3wk
Roche Press Release
Dec 19, 2014

• “Roche has reported the MARIANNE study showed the three regimens helped people live without their disease worsening (PFS) for a similar amount of time, meeting its non-inferiority endpoint as assessed by an Independent Review Committee. However, neither Kadcyla-containing treatment arm significantly improved PFS compared to Herceptin and chemotherapy. Adverse events observed in the two experimental arms of the study were generally consistent with those seen in previous studies of Kadcyla and/or Perjeta”
PI3K / AKT / mTOR Pathway

- Mutation of PIK3CA
- Loss of PTEN
- Resistance to trastuzumab?
- pAKT = surrogate of an activated pathway

Lu CH. Clin Cancer Res. 2007;13:5883-5888.
Phase III Trial of Everolimus in Combination With Trastuzumab and Paclitaxel as Frontline Therapy for HER2+ MBC (BOLERO-1)

HER+ MBC
No prior anthracycline/taxane-based chemotherapy in the metastatic setting
(N = 719)

Randomization

Everolimus 10 mg PO +
Paclitaxel 80 mg/m² qwk d 1, 8, 15
+ Trastuzumab 2 mg/kg d1, 8, 15, 22

Placebo +
Paclitaxel 80 mg/m² qwk d 1, 8, 15
+ Trastuzumab 2 mg/kg d1, 8, 15, 22

Endpoint

Available at: www.clinicaltrials.gov/NCT 00876395
BOLERO-1/TRIO 019: PFS Full Population (Investigator-assessment)

Hazard Ratio = 0.89; 95% CI [0.73, 1.08]
Log rank p value = 0.1166

Median PFS
- Everolimus: 14.95 months; 95% CI [14.55, 17.91] (n/N = 271/480)
- Placebo: 14.49 months; 95% CI [12.29, 17.08] (n/N = 154/239)

Censoring times

No. of patients still at risk
- Everolimus: 480 416 365 324 289 260 217 178 151 130 122 107 94 80 72 63 58 48 42 35 26 21 17 13 10 5 3 3 0
- Placebo: 239 221 199 166 144 123 106 91 80 69 53 47 43 38 36 31 24 17 15 12 9 7 6 4 3 1 1 0

- One-sided p-value is obtained from the log-rank test stratified by prior use of trastuzumab (Y/N) and Visceral metastasis (Y/N) from IWRS.
**BOLERÓ-1/TRÍO 019: PFS HR – Subpopulation (Investigator Assessment)**

**Hazard Ratio** = 0.66; 95% CI [0.48, 0.91]

**Log rank p value** = 0.0049

**Median PFS**
- **Everolimus:** 20.27 months; 95% CI [14.95, 24.08] (n/N = 97/208)
- **Placebo:** 13.08 months; 95% CI [10.05, 16.56] (n/N = 66/103)

- One-sided p-value is obtained from the log-rank test stratified by prior use of trastuzumab (Y/N) and Visceral metastasis (Y/N) from IWRS.

**Sensitivity analysis without censoring patients at the start of new antineoplastic therapy:**
- Median PFS and 95% CIs
  - 20.27 mo (14.82, 24.08) for everolimus [n = 102]
  - 12.88 mo (10.94, 16.56) for placebo [n = 68]
- HR = 0.66 [0.48, 0.9], p = 0.0043
BOLERO-1/TRIO 019: Summary

- Primary objective of PFS was not met
- Median PFS prolonged by 7 mo in the HR-negative subpopulation (20 mo everolimus arm vs 13 mo placebo arm, HR 0.66, p=0.0049)
  - However, protocol prespecified analysis did not cross the statistical significance threshold (p=0.0044)
- Safety profile was consistent with results previously reported in BOLERO-3
- Higher rate of AE-related on-treatment deaths was reported for everolimus (3.6% vs 0% with placebo)
  - All but one AE-related on-treatment deaths occurred within 15 mo of study start
  - Proactive monitoring and early management of AEs in patients treated with everolimus and chemotherapy is critical
- OS follow-up will be ongoing until 438 events are reported
Trastuzumab-Resistant MBC
Immunoconjugate/ADC

- **T-DM1: Trastuzumab Emtansine**
  - Antibody Drug Conjugate (ADC)
  - Trastuzumab is linked to an antimicrotubule drug (maytansine or DM1) for a targeted and antineoplastic effect
  - Trastuzumab binds to HER2 cancer cells, is absorbed, and then releases DM1

![Diagram of T-DM1 structure](image-url)
Trastuzumab Emtansine (T-DM1): Mechanism of Action

EMILIA Study Design

**Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease

**Primary endpoints:** PFS by independent review, OS, and safety

**Key secondary endpoints:** PFS by investigator, ORR, DOR

**Statistical considerations:** Hierarchical statistical analysis was performed in pre-specified sequential order: PFS by independent review → OS → secondary endpoints
  - PFS analysis: 90% power to detect HR=0.75; 2-sided alpha 5%
  - OS analyses: 80% power to detect HR=0.80; 2-sided alpha 5%

HER2-positive LABC or MBC (N=980)
  - Prior taxane and trastuzumab
  - Progression on metastatic treatment or within 6 months of adjuvant treatment

T-DM1
3.6 mg/kg q3w IV

PD

Capecitabine
1000 mg/m² PO bid, days 1–14, q3w
+ Lapatinib
1250 mg/day PO qd

PD
Progression-Free Survival by Independent Review

Median (months) | No. of events
---|---
Cap + Lap | 6.4 | 304
T-DM1 | 9.6 | 265

Stratified HR=0.650 (95% CI, 0.55, 0.77)  
\(P<0.0001\)


Unstratified HR=0.66 (\(P<0.0001\)).
Overall Survival: Confirmatory Analysis

<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>No. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap + Lap</td>
<td>25.1</td>
<td>182</td>
</tr>
<tr>
<td>T-DM1</td>
<td>30.9</td>
<td>149</td>
</tr>
</tbody>
</table>

Stratified HR=0.682 (95% CI, 0.55, 0.85); \( P=0.0006 \)

Efficacy stopping boundary \( P=0.0037 \) or HR=0.727


Data cut-off July 31, 2012; Unstratified HR=0.70 (\( P=0.0012 \)).
TH3RESA Study Schema

- **Stratification factors:** World region, number of prior regimens for advanced BC, presence of visceral disease
- **Co-primary endpoints:** PFS by investigator and OS
- **Key secondary endpoints:** ORR by investigator and safety

a. Advanced BC includes MBC and unresectable locally advanced/recurrent BC.
b. TPC could have been single-agent chemotherapy, hormonal therapy, or HER2-directed therapy, or a combination of a HER2-directed therapy with a chemotherapy, hormonal therapy, or other HER2-directed therapy.
c. First patient in: Sep 2011. Study amended Sep 2012 (following EMILIA 2nd interim OS results) to allow patients in the TPC arm to receive T-DM1 after documented PD.
d. Excluding single-agent hormonal therapy.

BC, breast cancer; IV, intravenous; ORR, objective response rate; PD, progressive disease; q3w, every 3 weeks.

TH3RESA: PFS by Investigator Assessment

<table>
<thead>
<tr>
<th></th>
<th>TPC (n=198)</th>
<th>T-DM1 (n=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>3.3</td>
<td>6.2</td>
</tr>
<tr>
<td>No. of events</td>
<td>129</td>
<td>219</td>
</tr>
<tr>
<td>Stratified HR</td>
<td>0.528 (95% CI, 0.422, 0.661)</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months. Unstratified HR=0.521 (P<0.0001).

Wildiers, et al. ECCO 2013
# HER2 Beyond Progression

<table>
<thead>
<tr>
<th>Author</th>
<th>Agents</th>
<th>N</th>
<th>TTP</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Minckwitz et al</td>
<td>Capecitabine + trastuzumab vs capecitabine</td>
<td>156</td>
<td>8.2 months vs 5.6 months, P = 0.03</td>
<td>NR</td>
<td>25.5 months vs 20.4 months, P = 0.257</td>
</tr>
<tr>
<td>Geyer et al</td>
<td>Capecitabine + lapatinib vs capecitabine</td>
<td>324</td>
<td>8.4 months vs 4.4 months, P &lt; 0.001</td>
<td>8.4 months vs 4.1 months, P &lt; 0.001</td>
<td>19 months vs 16 months, P = 0.206</td>
</tr>
<tr>
<td>Blackwell et al</td>
<td>Lapatinib + trastuzumab vs lapatinib</td>
<td>296</td>
<td>NR</td>
<td>12 weeks vs 8.1 weeks, P = 0.008</td>
<td>14 months vs 9.5 months, P = 0.026</td>
</tr>
</tbody>
</table>
ASCO Guidelines for Advanced HER2+ Breast Cancer

• HER2 targeted combo for first line
• Pertuzumab + Trastuzumab + taxane for first line
• TDM1 for second line
• If no pertuzumab first line and ≥ 2nd line: offer pertuzumab
• Third line lapatinib/capecitabine, other chemo combo with lapatinib or trastuzumab or hormonal therapy

ASCO Guidelines for Advanced HER2+ Breast Cancer

• Chemotherapy for 4-6 months, continue anti-HER2 therapy until progression and may add hormonal therapy if ER positive

• If recurrence during or after adjuvant \( \leq 12 \) months treat with second line

• HER2+ and ER+
  – HER2 targeted therapy and chemo (#1 recommendation)
  – Endocrine therapy and trastuzumab or lapatinib
  – Endocrine therapy alone

SAFE-HEaRt study

A pilot study evaluating the cardiac SAFETY of HER2 targeted therapy in patients with HER2 positive breast cancer and reduced left ventricular function

Chair (PI): Sandra Swain, MD FACP
Cardiology Co-Chair: Ana Barac, MD
Fellow: Filipa Lynce, MD

Supported by Breast Cancer Research Foundation and Genentech

ClinicalTrials.gov Identifier: NCT01904903
Primary Objective

- To evaluate the cardiac safety of HER2 targeted therapy (non-lapatinib) in patients with HER2+ BC and reduced LVEF when given concomitantly with cardiac treatment
  - Cardiac dysfunction
  - Cardiac events
  - Asymptomatic LV dysfunction
Patient Selection

- Stage I-IV breast cancer
- Male or Female Age ≥ 18
- HER2+, IHC 3+ and/or FISH ≥ 2.0
- LVEF <50% and ≥ 40% on an echocardiogram done in the last 30 days.
  - Different methods such as MUGA, MRI or CT will not be accepted as an indicator of screening/baseline LVEF.
- Receiving or planning to receive trastuzumab, trastuzumab + Pertuzumab or TDM-1, for at least 3 months, alone or in combination with other systemic treatment or radiation.
- No CHF in the last 12 months nor current CHF
Patients with HER2 + BC and 40% ≤ LVEF < 50%

- Cardiac evaluation
- Echocardiogram with strain
- Ultra sensitive troponins
- Titrate Bblockers, ACEi to max tolerated dose

Start HER2 therapy (trastuzumab, trastuzumab/pertuzumab or T-DM1)
Innovative Treatments for HER2 Positive Breast Cancer
**MM-302: HER2-targeted PEGylated liposomal doxorubicin**

**anti-HER2 scFv**
- Targets liposome to HER2-overexpressing cells
- Promotes internalization
- Binds to a different epitope than trastuzumab
- Does not bind to cardiomyocytes

**Liposome**
- Extended half-life
- Stably encapsulates doxorubicin
- Passive accumulation in tumors
- Size precludes delivery to cardiac tissue

**Doxorubicin Crystals**
- Effective cytotoxic agent in breast cancer
- DNA intercalator, TOP2A inhibitor, free radical generator
MM-302 Mechanism of Action

**HER2-positive tumor**
- MM-302
- Doxorubicin
- HER2

**Heart**
- Tight vasculature
- Does not bind to cardiomyocytes

**Extravasation via leaky vasculature**
- Binding and internalization

**Cancer Cell Death**

**Trastuzumab**
- Binds to a different epitope than trastuzumab
HERMIONE Study Schema

**HER2-positive locally advanced/metastatic BC (N=250)**
- Anthracycline naive
- Prior metastatic treatment with pertuzumab and T-DM1
- Prior treatment with trastuzumab

1. **MM-302**
   - 30 mg/m², Q3W
   - + trastuzumab
   - 6 mg/kg*, Q3W

1. **Chemotherapy of Physician’s Choice**
   - (capecitabine, gemcitabine or vinorelbine)
   - + trastuzumab
   - 6 mg/kg*, Q3W

**Stratification Factors:** Geographic region, presence of visceral disease, number of prior chemotherapy regimens for metastatic disease

**Primary Endpoint:** Independently assessed PFS

**Secondary Endpoints:** Investigator assessed PFS, OS, safety, response rate

* 8 mg/kg trastuzumab loading dose
Trastuzumab-based bispecific antibody, HER2-TDB, targets HER2 and conditionally activates T cells

A 56-year-old woman with ER/PR+, HER2+ breast cancer now has involvement of the liver, lung, and bone marrow after receiving adjuvant AC→ trastuzumab + paclitaxel, then trastuzumab for one year. It is now two years later. Which option is most likely to yield the longest PFS and OS?

1. Lapatinib / capecitabine
2. Trastuzumab / pertuzumab / docetaxel or paclitaxel
3. Lapatinib / trastuzumab
4. T-DM1
5. Everolimus / exemestane