Management of HER2+ MBC
SOBO 2013

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Not all HER2+ disease is HER-E
Molecular Subtype and Therapeutic Questions

- **ER + subtypes**: Luminal A, Luminal B
- **ER - negative subtypes**: Claudin-low, Basal-like, HER2-enriched
- **Endocrine-dominant**: Hormone receptor +
- **Triple negative (ER, PR, HER2)**: Chemo-based
- **HER2+ on clinical assays (can be ER + or -)**: HER2-targeting

**Note:**
- HER2+ can be ER + or ER - on clinical assays.
HER2-Positive Breast Cancer

NCIC MA.5 (N=88)
- HER2-E: 78%
- Basal-like: 10%
- Luminal A: 9%
- Luminal B: 2%

NCIC MA.12 (N=66)
- HER2-E: 74%
- Basal-like: 12%
- Luminal A: 11%
- Luminal B: 3%

Combined microarray dataset (N=81)
- HER2-E: 56%
- Basal-like: 13%
- Luminal A: 21%
- Luminal B: 10%

Prat & Perou, Mol Oncol. 2011
Frequency of 1\textsuperscript{st} line HER2+ Breast Cancer

Frequency = \( f (\text{de novo MBC} + \text{recurrent BC}) \)

- 1\textsuperscript{st} line incidence is plummeting in US owing to impact of adjuvant trastuzumab
- 1\textsuperscript{st} line treatment is becoming a thing of the past
### Prognosis in MBC by HER2 Status and by Therapy With Trastuzumab

<table>
<thead>
<tr>
<th></th>
<th>N = 2091 (median f/u = 16.9 mo)</th>
<th>No. of Patients (%)</th>
<th>1-y Survival (95% CI)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-positive</td>
<td>118 (5.6)</td>
<td>70.2% (60.3%, 78.1%)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>HER2-negative</td>
<td>1782 (85.3)</td>
<td>75.1% (72.9%, 77.2%)</td>
<td>0.56 (95% CI 0.45-0.69, P = 0.0001)</td>
<td></td>
</tr>
<tr>
<td>HER2-positive treated with trastuzumab</td>
<td>191 (9.1)</td>
<td>86.6% (80.8%, 90.8%)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; MBC = metastatic breast cancer.

# Chemotherapy Plus Trastuzumab in Metastatic Disease

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

*T = paclitaxel; †H = trastuzumab

Chemo + trastuzumab: Lessons

- No new toxicity signals
- Almost any chemotherapy will work with trastuzumab
- Laboratory models of “synergy” were of some but not definitive help
- Probably not a process worth repeating with other anti-HER2 agents
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

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

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

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-DM1)

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

1There is no compelling evidence that combination regimens are superior to single-agent regimens.

2Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Therapies for HER2-positive breast cancer

- Trastuzumab
- Pertuzumab
- T-DM1
- Lapatinib, Neratinib
- HSP-90 Inhib

Baselga. Nat Rev Cancer 2009
Trastuzumab Beyond Progression in HER2+ Breast Cancer

N=156

HER2+ locally advanced, MBC
Progression during or after trastuzumab therapy
(within 6 weeks of prior trastuzumab)

Capecitabine 2500 mg/m²
days 1-14, 3-week cycle

Capecitabine 2500 mg/m²
days 1-14, 3-week cycle

Trastuzumab 6 mg/kg
q 3 weeks

Primary endpoint: Time to Progression
Secondary endpoints: Response Rate, Overall Survival,
Duration of Response, Safety

von Minckwitz. JCO 2009
Time To Progression

Product-Limit Survival Estimates
With Number of Subjects at Risk

X : 5.6 (4.2 - 6.3) mos
XH : 8.2 (7.3 - 11.2) mos

HR=0.69 (two-sided p=0.034;
one-sided p=0.015)

ORR 48% vs 27%, p=0.0011

median follow-up: 15.6 mos

von Minckwitz. JCO 2009
Capecitabine vs Capecitabine + Lapatinib

- Progressive, HER2+ MBC or LABC
- Previously treated with anthracycline, taxane and trastuzumab*
- No prior capecitabine

Randomize

Lapatinib 1250 mg po qd continuously + Capecitabine 2000 mg/m²/d po days 1-14 q 3 wk

Capecitabine 2500 mg/m²/d po days 1-14 q 3 wk

N=528

Stratification:
- Disease sites
- Stage of disease

*Trastuzumab must have been administered for metastatic disease

Geyer et al, NEJM 2006
Capecitabine vs Capecitabine + Lapatinib: Time to Progression

- **No. of pts**
  - Lapatinib + Capecitabine: 160
  - Capecitabine: 161
- **Progressed or died**
  - Lapatinib + Capecitabine: 28%
  - Capecitabine: 43%
- **Median TTP, wk**
  - Lapatinib + Capecitabine: 36.9
  - Capecitabine: 19.7

**HR 0.51 (0.35-0.74)**

**p=0.0016**

**Objective Response rate 22% vs 14%**

Geyer et al, NEJM 2006
Phase III Study to Test if Total HER2+ Blockade Improves Clinical Outcome

Key Inclusion
- HER2+(FISH+/ IHC3+) MBC
- Progression on
  - Anthracycline
  - Taxane
  - Trastuzumab
- Progression on most recent trastuzumab regimen

Stratification Factors
- Visceral Disease
- Hormone Receptor

Primary Endpoint: ITT PFS
Secondary Endpoints: OS, ORR, CBR, safety

RANDOMIZATION

\[ N = 296 \]

Lapatinib 1500 mg/day PO
\[ N = 148 \]

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

Lapatinib 1000 mg/day PO
Trastuzumab 2mg/kg IV qw \( N=148 \)

Median prior chemotherapy regimens; 4-5

Blackwell et al, JCO 2010
Progression-Free Survival: Lapatinib vs Lapatinib + Trastuzumab

Borderline statistically significant improvement in overall survival also seen

Blackwell et al, JCO 2010
MA.31/ EGF108919: Design

Randomize

**EXPERIMENTAL ARM**

- 24 Weeks: Lapatinib plus Taxane
- Until PD: Lapatinib

**STANDARD ARM**

- 24 Weeks: Trastuzumab plus Taxane
- Until PD: Trastuzumab

Primary Outcome: PFS

Sample Size: ~ 600 (536 centrally confirmed HER2+ patients)
Progression Free Survival Intent to Treat Analysis

Median PFS TTAX/T = 11.4 months
Median PFS LTAX/L = 8.8 months
HR = 1.33 (95% CI = 1.06 - 1.67), P = 0.01
Pertuzumab and Trastuzumab: Complementary Mechanisms of Action

Trastuzumab:
- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

Pertuzumab:
- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

Presented at: 34th Annual San Antonio Breast Cancer Symposium; December 6-11, 2011; San Antonio, TX.
**HER2:HER3 Dimers May Provide An Escape Mechanism From Trastuzumab**

**Homodimers**
- HER1:HER1
- HER2:HER2
- HER3:HER3
- HER4:HER4

**Heterodimers**
- HER1:HER2
- HER1:HER3
- HER1:HER4
- HER2:HER3
- HER2:HER4
- HER3:HER4

**Signaling activity**

Patients with HER2-positive MBC centrally confirmed (N=808)

Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)

CLEOPATRA study design

Placebo + trastuzumab

Docetaxel ≥6 cycles recommended

Pertuzumab + trastuzumab

Docetaxel ≥6 cycles recommended

Baselga et al, NEJM 2012
CLEOPATRA: Significant improvement in median PFS\(^1,2\) (and OS)\(^3\) with pertuzumab

HR = 0.62
95% CI 0.51, 0.75
p < 0.001

D, docetaxel; Ptz, pertuzumab; T, trastuzumab

1. Baselga J, et al. SABCS 2011 (Abstract S5-5);
Kaplan-Meier curves of the confirmatory overall survival analysis

- **Ptz + T + D**: 113 events; median not reached
- **Pla + T + D**: 154 events; median 37.6 months

HR=0.66
95% CI 0.52–0.84
p=0.0008
## Adverse events (all grades) with ≥25% incidence or ≥5% difference between arms

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Placebo + trastuzumab + docetaxel (n=396)</th>
<th>Pertuzumab + trastuzumab + docetaxel (n=408)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>191 (48.2)</td>
<td>278 (68.1)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>240 (60.6)</td>
<td>248 (60.8)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>197 (49.7)</td>
<td>216 (52.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>168 (42.4)</td>
<td>179 (43.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>148 (37.4)</td>
<td>155 (38.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>95 (24.0)</td>
<td>149 (36.5)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>105 (26.5)</td>
<td>121 (29.7)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>79 (19.9)</td>
<td>112 (27.5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>121 (30.6)</td>
<td>110 (27.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>97 (24.5)</td>
<td>104 (25.5)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>122 (30.8)</td>
<td>101 (24.8)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>40 (10.1)</td>
<td>68 (16.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>101 (25.5)</td>
<td>63 (15.4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>101 (25.5)</td>
<td>63 (15.4)</td>
</tr>
<tr>
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<td>63 (15.4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>101 (25.5)</td>
<td>63 (15.4)</td>
</tr>
</tbody>
</table>

Highlighted are adverse events with ≥5% higher incidence.
## Cardiac adverse events

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Placebo + trastuzumab + docetaxel</th>
<th>Pertuzumab + trastuzumab + docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data cutoff date</td>
<td>May 2011 (n=397)</td>
<td>May 2012 (n=396)</td>
</tr>
<tr>
<td>LVSD (all grades)</td>
<td>33 (8.3)</td>
<td>34 (8.6)</td>
</tr>
<tr>
<td>Symptomatic LVSD</td>
<td>7 (1.8)</td>
<td><strong>7 (1.8)</strong></td>
</tr>
<tr>
<td>LVEF decline to &lt;50% and by ≥10% points from baseline*</td>
<td>25/379 (6.6)</td>
<td>28/378 (7.4)</td>
</tr>
<tr>
<td>LVEF recovery to ≥50%*</td>
<td>18/25 (72.0)</td>
<td>25/28 (89.3)</td>
</tr>
</tbody>
</table>
Phase II Study
Paclitaxel + Trastuzumab + Pertuzumab

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

- Paclitaxel at 80 mg/m²
- Pertuzumab at 840 mg load → 420 mg q 3 w
- Trastuzumab at 8 mg/kg load → 6 mg/kg q 3 w

Every 4 cycles:
- Cardiac biomarkers every 2 cycles

ECHO w/ strain imaging

Datko F, et al, P5 18-20
Response

Best Response, Evaluable Pts with Measurable Disease (N = 26)

Best Response, Evaluable Pts with Non-Measurable Disease (N = 7)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression of disease, N</td>
<td>1 (rapid POD at 1.6mo)</td>
</tr>
<tr>
<td>Stable disease, N</td>
<td>5</td>
</tr>
<tr>
<td>Complete response, N</td>
<td>1</td>
</tr>
</tbody>
</table>
Conclusion

Taxane+Pertuzumab+Trastuzumab – preferred 1\textsuperscript{st} therapy for HER2+ MBC
Shorter median PFS observed with mutated PIK3CA while treatment effect is maintained

<table>
<thead>
<tr>
<th>PIK3CA status</th>
<th>Patients, n</th>
<th>Events</th>
<th>Median, months</th>
<th>Patients, n</th>
<th>Events</th>
<th>Median, months</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mut</td>
<td>90</td>
<td>63</td>
<td>8.6</td>
<td>86</td>
<td>45</td>
<td>12.5</td>
<td>0.64 (0.43, 0.93)</td>
</tr>
<tr>
<td>WT</td>
<td>191</td>
<td>101</td>
<td>13.8</td>
<td>190</td>
<td>83</td>
<td>21.8</td>
<td>0.67 (0.50, 0.89)</td>
</tr>
<tr>
<td>Overall</td>
<td>406</td>
<td>242</td>
<td>12.4</td>
<td>402</td>
<td>191</td>
<td>18.5</td>
<td>0.62 (0.51, 0.75)</td>
</tr>
</tbody>
</table>

- The prognostic impact of PIK3CA mutations cannot be attributed to a specific mutation, nor to mutation(s) in a specific exon, based on the available dataset
  - 182 mutations detected overall (32%)
  - Exon 7: 12; exon 9: 39; exon 20: 131

Mut, mutated; WT, wild-type

Baselga J et al, SABC 2012
Trastuzumab-DM1 in HER2+ MBC

- Potency > Vincristine or Vinblastine
- Maximal exposure of HER2+ tumors
- Minimal exposure of normal tissues
- Antitumor Properties of trastuzumab

Lewis-Phillips GD et al., Cancer Res 68:9280-9290, 2008
EMILIA Study Design

HER2+ (central) LABC or MBC (N=980)
- Prior taxane and trastuzumab
- Progression on metastatic tx or within 6 mos of adjuvant tx

T-DM1
3.6 mg/kg q3w IV

Capecitabine
1000 mg/m² orally bid, days 1–14, +
Lapatinib 1250 mg/day orally daily

- **Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease
- **Primary end points:** PFS by independent review, OS, and safety
- **Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression

Blackwell et al, ASCO 2012
Verma et al, NEJM 2012

Presented By Eric P. Winer, MD at 2013 Breast Cancer Symposium
Progression-Free Survival by Independent Review

<table>
<thead>
<tr>
<th></th>
<th>Median (mos)</th>
<th>No. events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap + Lap</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<0.0001

No. at risk by independent review:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
<th>20</th>
<th>22</th>
<th>24</th>
<th>26</th>
<th>28</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cap + Lap</strong></td>
<td>496</td>
<td>404</td>
<td>310</td>
<td>176</td>
<td>129</td>
<td>73</td>
<td>53</td>
<td>35</td>
<td>25</td>
<td>14</td>
<td>9</td>
<td>8</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>T-DM1</strong></td>
<td>495</td>
<td>419</td>
<td>341</td>
<td>236</td>
<td>183</td>
<td>130</td>
<td>101</td>
<td>72</td>
<td>54</td>
<td>44</td>
<td>30</td>
<td>18</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>0</td>
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</tbody>
</table>

Blackwell et al, ASCO 2012
Verma et al, NEJM 2012

Presented By Eric P. Winer, MD at 2013 Breast Cancer Symposium
EMILIA: Overall Survival

<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 = 0.68 (95% CI, 0.55, 0.85); P < 0.001

Efficacy stopping boundary P = 0.0037 or HR = 0.727

## Overview of Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Cap + Lap (n=488)</th>
<th>T-DM1 (n=490)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-grade AE, n (%)</td>
<td>477 (97.7)</td>
<td>470 (95.9)</td>
</tr>
<tr>
<td>Grade ≥3 AE, n (%)</td>
<td>278 (57.0)</td>
<td>200 (40.8)</td>
</tr>
<tr>
<td>AEs leading to treatment discontinuation (for any study drug), n (%)</td>
<td>52 (10.7)</td>
<td>29 (5.9)</td>
</tr>
<tr>
<td>AEs leading to death on treatment, n (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 (1.0)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>LVEF &lt;50% and ≥15-point decrease from baseline, %&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 (1.6)</td>
<td>8 (1.7)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Cap + Lap: CAD, multiorgan failure, coma, hydrocephalus, ARDS; T-DM1: metabolic encephalopathy.

<sup>b</sup>Evaluable pts: 445 (Cap + Lap); 481 (T-DM1).

Presented By Eric P. Winer, MD at 2013 Breast Cancer Symposium

**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.
## Baseline Characteristics (2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TPC (n=198)</th>
<th>T-DM1 (n=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ER and/or PR-positive, %</strong></td>
<td>52.0</td>
<td>51.5</td>
</tr>
<tr>
<td><strong>Visceral involvement, %</strong></td>
<td>75.8</td>
<td>74.8</td>
</tr>
<tr>
<td><strong>Disease extent at study entry, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>94.4</td>
<td>96.8</td>
</tr>
<tr>
<td>Unresectable locally advanced/recurrent BC</td>
<td>5.6</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Number of prior regimens for advanced BC,a</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>median (range)</strong></td>
<td>4 (1–19)</td>
<td>4 (1–14)</td>
</tr>
<tr>
<td>≤3, %</td>
<td>39.4</td>
<td>32.6</td>
</tr>
<tr>
<td>4–5, %</td>
<td>32.8</td>
<td>37.1</td>
</tr>
<tr>
<td>&gt;5, %</td>
<td>27.8</td>
<td>30.3</td>
</tr>
<tr>
<td><strong>Brain metastasis at baseline, %</strong></td>
<td>13.6</td>
<td>9.9</td>
</tr>
</tbody>
</table>

*a Two patients in the T-DM1 arm had missing information for prior treatment in the advanced BC setting: TPC, n=198; T-DM1, n=402.

ER, estrogen receptor; PR, progesterone receptor.
## TPC Treatment Category

<table>
<thead>
<tr>
<th>TPC treatment category</th>
<th>TPC (n=184&lt;sup&gt;a&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combination with HER2-directed agent, %</strong></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy&lt;sup&gt;b&lt;/sup&gt; + trastuzumab</td>
<td>68.5</td>
</tr>
<tr>
<td>Lapatinib + trastuzumab</td>
<td>10.3</td>
</tr>
<tr>
<td>Hormonal therapy + trastuzumab</td>
<td>1.6</td>
</tr>
<tr>
<td>Chemotherapy&lt;sup&gt;b&lt;/sup&gt; + lapatinib</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Single-agent chemotherapy,&lt;sup&gt;b&lt;/sup&gt; %</strong></td>
<td>16.8</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes patients who received study treatment.

<sup>b</sup> The most common chemotherapy agents used were vinorelbine, gemcitabine, eribulin, paclitaxel, and docetaxel.
Conclusions

- T-DM1 demonstrated improved efficacy and safety compared with TPC
  - Significant improvement in PFS
    - HR=0.528; $P<0.0001$
    - A clear and consistent treatment effect across subgroups
  - Interim OS favored T-DM1 but efficacy stopping boundary not crossed
    - HR=0.552; $P=0.0034$
  - Safety and ORR favored T-DM1
    - Fewer grade ≥3 AEs with T-DM1 vs TPC: 32.3% vs 43.5%
    - Fewer discontinuations and dose reductions due to AEs with T-DM1
    - ORR 31.3% vs 8.6%, $P<0.0001$

- These data reaffirm the results from the EMILIA study, demonstrating a consistent benefit with T-DM1 in patients with previously treated HER2-positive advanced BC
MARIANNE Phase III

N=1092 HER2+ MBC First-line

1° Endpoint: PFS
2° Endpoints: OS, TTF, DOR, ORR, CBR

T = paclitaxel 80 m/m weekly or docetaxel at 75-100 m/m q 3 w
H = trastuzumab 2 mg/kg q w or 6 mg/kg q 3 w
P = pertuzumab at 840 mg load → 420 mg q 3 w
TDM = trastuzumab/DM1 at 3.6 mg/kg q 3 w
HER2 Therapies in Metastatic BC

Gajria et al. Exp Rev Anticancer Ther 2011
BOLEIRO-3: Study Design

Phase 3 Study
N = 569
- Locally advanced or metastatic HER2+ breast cancer
- Prior taxane required

Treatment Groups

Everolimus (5 mg PO daily) + Vinorelbine (25 mg/m² weekly) + Trastuzumab (2 mg/kg weekly*)
(n = 284)

Placebo (PO daily) + Vinorelbine (25 mg/m² weekly) + Trastuzumab (2 mg/kg weekly*)
(n = 285)

Follow-up/Survival
Key Endpoints:
- Primary: PFS
- Secondary: OS, ORR, time to deterioration of ECOG PS, safety, DoR, CBR, and QoL

Therapy until PD or intolerable toxicity
- Stratification by prior lapatinib use (yes/no)

*Resistance to prior trastuzumab required
†Following a 4-mg/kg loading dose on day 1, cycle 1 (1 cycle = every 21 days).
Abbreviations: AE, adverse event; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; EVE, everolimus; PD, progressive disease; PO, oral; PS, performance status; QoL, quality of life; TRAS, trastuzumab.
http://www.clinicaltrials.gov/ct2/show/NCT01007942?term=BOLEIRO3&rank=1

Presented by: Ruth M. O’Regan, MD
BOLERO-3: Primary Endpoint
Progression-Free Survival by Local Assessment

Hazard ratio = 0.78; 95% CI [0.65, 0.95]
Log-rank P value: 0.0067

Median PFS
Everolimus: 7.00 months
Placebo: 5.78 months

Presented by: Rebecca Alexandra Dent, MD at 2013 ASCO Annual Meeting
Take Home Messages/Conclusions

• Multiple HER2-targeting agents are available with more on the horizon
• Treatment strategy for HER2 disease should continue to utilize HER2 agents even after progression
• Select pts can be considered for endocrine/HER2 doublets without chemotherapy
• Strategies to overcome resistance to HER2 therapy are being explored
Backup
## Second Generation TKI’s for HER2+ MBC

<table>
<thead>
<tr>
<th><strong>NERATINIB</strong></th>
<th><strong>AFATINIB</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pan HER Receptor TKI</td>
<td>Pan HER Receptor TKI</td>
</tr>
<tr>
<td>Irreversible inhibitors</td>
<td>Irreversible inhibitors</td>
</tr>
<tr>
<td>Orally administered</td>
<td>Orally administered</td>
</tr>
<tr>
<td>Phase 3 development</td>
<td>Phase 3 development</td>
</tr>
<tr>
<td>Potential to cross BBB</td>
<td>Potential to cross BBB</td>
</tr>
<tr>
<td></td>
<td>Inhibits mutated HER1</td>
</tr>
</tbody>
</table>
# HER RECEPTOR TKI’s: Efficacy

<table>
<thead>
<tr>
<th>TKI</th>
<th>1(^{st}) line Setting</th>
<th>Pre-treated Setting</th>
<th>Grade 3 Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2Lapatinib</td>
<td>24%</td>
<td>4 -7%</td>
<td>3%</td>
</tr>
<tr>
<td>3Neratinib</td>
<td>56%</td>
<td>24%</td>
<td>30%</td>
</tr>
<tr>
<td>4Afatinib</td>
<td>N/A</td>
<td>10%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Neratinib: Phase 3 NALA Trial

Eligibility:
HER2 positive MBC
≥ 2 lines of HER2-targeting regimens for MBC

Stratification:
Number of HER2 therapies 2 vs >3
Geography
Visceral vs. non visceral disease
ER/ PR status

International PI: Jose Baselga
AFATINIB: Phase 3 LUX-BREAST 1 Trial

ELIGIBILITY:
• HER2+ MBC
• POD on one line of Trastuzumab
• Prior anthracycline and taxane

Primary Endpoint: PFS
MARIANNE: Phase III study of T-DM1 with or without pertuzumab vs SOC of care in first-line HER2-positive MBC

HER2-positive progressive or recurrent locally advanced BC or previously untreated MBC (n=1092) → R →
- Trastuzumab + taxane (n=364)
- T-DM1 + pertuzumab (n=364)
- T-DM1 + placebo (n=364)

T-DM1 + pertuzumab: our new standard of care in 2015?

BC = breast cancer; MBC = metastatic breast cancer; PFS = progression-free survival

Data on file. Genentech USA, Inc., CA, USA and F Hoffmann-La Roche Ltd., Basel, Switzerland
SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE
ER and PR NEGATIVE; or ER and/or PR POSITIVE and ENDOCRINE REFRACTORY; and HER2 POSITIVE

Consider trial of endocrine therapy, if not endocrine refractory<sup>hh,nn,rr</sup> → See Endocrine Therapy (BINV-18)

ER and PR negative; or ER and/or PR positive and endocrine refractory; and HER2 positive<sup>b</sup>

Bone or soft tissue only or Asymptomatic visceral

Yes

Pertuzumab + trastuzumab + taxane (preferred)<sup>pp,rr,ss</sup> or Trastuzumab ± chemotherapy<sup>pp,rr,ss,tt</sup>

No

Continue HER2 targeted therapy, typically in combination with other chemotherapy, or trastuzumab + lapatinib

No response to 3 sequential regimens or ECOG performance status ≥ 3 → Consider no further cytotoxic therapy; transition to palliative care<sup>jj</sup>

<sup>b</sup>See Principles of HER2 Testing (BINV-A).

<sup>hh</sup>False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor-positive tumor (e.g., long disease-free interval, limited sites of recurrence, indolent disease, older age).

<sup>jj</sup>See NCCN Palliative Care Guidelines.

<sup>mm</sup>See Subsequent Endocrine Therapy for Systemic Disease (BINV-N).

<sup>pp</sup>See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-O).

<sup>rr</sup>See Principles of Monitoring Metastatic Disease (BINV-M).

<sup>ss</sup>Continued trastuzumab following progression on first-line trastuzumab-containing chemotherapy for metastatic breast cancer. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.

<sup>tt</sup>Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
### CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

#### Preferred Single Agents

**Anthracyclines**
- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin

**Taxanes**
- Paclitaxel
- Docetaxel
- Albumin-bound paclitaxel

**Anti-metabolites**
- Capecitabine
- Gemcitabine

**Other microtubule inhibitors**
- Vinorelbine
- Eribulin

#### Preferred Chemotherapy Combinations

- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- AT (doxorubicin/docetaxel; doxorubicin/paclitaxel)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)

#### Other Combinations

- Ixabepilone + capecitabine (category 2B)

#### Preferred First-line Agents For HER2-positive Disease

- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

#### Other First-line Agents For HER2-positive Disease

**Trastuzumab with:**
- Paclitaxel ± carboplatin
- Docetaxel
- Vinorelbine
- Capecitabine

#### Agents For Trastuzumab-exposed HER2-positive Disease

- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents

---

1. There is no compelling evidence that combination regimens are superior to sequential single agents.

2. Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

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