Systemic therapy for HER2+ ABC

F. Cardoso, MD
Director, Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal
ESMO Board of Directors & Director of Membership
Chair, ABC Global Alliance and ABC Guidelines
ESO Breast Cancer Program Coordinator
Financial disclosures:
*Personal financial interest in form of consultancy role for:* Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Seattle Genetics, Teva.

*Institutional financial support for clinical trials from:* Amgen, Astra-Zeneca, Boehringer-Ingelheim, Bristol-Myers-Squibb, Daiichi, Eisai, Fresenius GmbH, Genentech, GlaxoSmithKline, Ipsen, Incyte, Nektar Therapeutics, Nerviano, Novartis, Macrogenics, Medigene, MedImmune, Merck, Millenium, Pfizer, Pierre-Fabre, Roche, Sanofi-Aventis, Sonus, Tesaro, Tigris, Wilex, Wyeth.

Non-Financial disclosures:
Chair ABC Global Alliance and ABC Consensus Conference and Guidelines.
Member/Committee Member of ESMO, ESO, EORTC-BCG, IBCSG, SOLTI, ASCO, AACR, EACR, SIS, ASPIC
Treatment of ER-negative / HER2-positive ABC

Note: Include in clinical trials when available
Treatment of ER-positive / HER2-positive ABC

CLINICAL PRACTICE GUIDELINES

First line

Previously untreated with anti-HER2 therapy

ChT + trastuzumab + pertuzumab
(ChT + trastuzumab only if pertuzumab not available)

Previously treated (neo)adjuvantly with anti-HER2 therapy

ChT + pertuzumab + trastuzumab
or ChT + trastuzumab

Patients unsuitable for ChT or with long disease-free interval, minimal disease burden and/or strong ER/PgR expression

ET + anti-HER2 (trastuzumab or lapatinib)
or ET + dual HER2 blockade (trastuzumab + lapatinib or trastuzumab + pertuzumab)

No progression

ET + anti-HER2 as maintenance therapy

If complete remission, optimal duration of maintenance anti-HER2 therapy is unknown

Stopping anti-HER2 therapy after several years of complete remission may be an option

Progression

T-DM1 if available (no data available on use after dual blockade)

Trastuzumab in combination with an unused ChT agent or with ET (if appropriate)

Trastuzumab + lapatinib + ET, if not previously used

Maintenance ET + anti-HER2 therapy

Additional anti-HER2 therapy and ChT or ET

Later lines

Second lines

Note: Include in clinical trials when available

© 2018 ESMO. All rights reserved. esmo.org/Guidelines/ Breast-Cancer/4th-ESMO-International-Consensus-Guidelines-for-Advanced-Breast-Cancer-ABC-4
MANAGEMENT OF HER-2 + MBC:

• ABC: primary or metastatic HER-2 status?
• Starting early and continuing HER-2 blockade beyond progression (change of paradigm)
  • Combinations with CT and ET: when & which agents?
• Which anti-HER-2 agent? Dual blockade? Best sequence of therapies?
• Overall good safety profile of anti-HER-2 therapies but cardiac surveillance & management guidelines needed
  • Important problem of brain metastases
    • Resistance - biomarkers
    • Accessibility
MANAGEMENT OF HER-2 + MBC:

• ABC: primary or metastatic HER-2 status?

• Starting early and continuing HER-2 blockade beyond progression (change of paradigm)

  • Combinations with CT and ET: when & which agents?

  • Which anti-HER-2 agent? Dual blockade? Best sequence of therapies?

• Overall good safety profile of anti-HER-2 therapies but cardiac surveillance & management guidelines needed

  • Important problem of brain metastases

    • Resistance - biomarkers

  • Accessibility
META-ANALYSIS OF HER-2 STATUS DISCORDANCE BETWEEN PRIMARY VS. METS

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>Test</th>
<th>D/N*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsutsui</td>
<td>2002</td>
<td>IHC</td>
<td>0/76</td>
</tr>
<tr>
<td>Carlsson</td>
<td>2004</td>
<td>IHC</td>
<td>0/47</td>
</tr>
<tr>
<td>Santiago</td>
<td>2009</td>
<td>IHC</td>
<td>1/52</td>
</tr>
<tr>
<td>Cardoso</td>
<td>2001</td>
<td>IHC</td>
<td>8/370</td>
</tr>
<tr>
<td>Azam</td>
<td>2009</td>
<td>IHC</td>
<td>5/100</td>
</tr>
<tr>
<td>Santinelli (nodes)</td>
<td>2008</td>
<td>I/F</td>
<td>3/54</td>
</tr>
<tr>
<td>Simon</td>
<td>2001</td>
<td>I/F</td>
<td>8/125</td>
</tr>
<tr>
<td>Aoyama</td>
<td>2010</td>
<td>FISH</td>
<td>4/60</td>
</tr>
<tr>
<td>Cho</td>
<td>2008</td>
<td>CISH</td>
<td>6/72</td>
</tr>
<tr>
<td>Aitken</td>
<td>2010</td>
<td>IHC</td>
<td>17/190</td>
</tr>
<tr>
<td>Xu</td>
<td>2002</td>
<td>FISH</td>
<td>3/33</td>
</tr>
<tr>
<td>Masood</td>
<td>2000</td>
<td>IHC</td>
<td>0/56</td>
</tr>
<tr>
<td>Tanner</td>
<td>2001</td>
<td>CISH</td>
<td>0/46</td>
</tr>
<tr>
<td>Shimizu</td>
<td>2000</td>
<td>IHC</td>
<td>0/21</td>
</tr>
<tr>
<td>Gong</td>
<td>2005</td>
<td>FISH</td>
<td>2/60</td>
</tr>
<tr>
<td>Sekidō</td>
<td>2003</td>
<td>IHC</td>
<td>2/44</td>
</tr>
<tr>
<td>Idirisinghe</td>
<td>2010</td>
<td>IHC</td>
<td>6/117</td>
</tr>
<tr>
<td>Zidan</td>
<td>2005</td>
<td>IHC</td>
<td>8/58</td>
</tr>
<tr>
<td>Guarneri</td>
<td>2008</td>
<td>I/F</td>
<td>12/75</td>
</tr>
<tr>
<td>Edgerton</td>
<td>2003</td>
<td>IHC</td>
<td>19/112</td>
</tr>
<tr>
<td>Santinelli (LR/DM)</td>
<td>2008</td>
<td>I/F</td>
<td>14/65</td>
</tr>
<tr>
<td>Tapia</td>
<td>2007</td>
<td>FISH</td>
<td>3/105</td>
</tr>
<tr>
<td>Vincent-Salomon</td>
<td>2002</td>
<td>IHC</td>
<td>2/44</td>
</tr>
<tr>
<td>Gancberg</td>
<td>2002</td>
<td>IHC</td>
<td>6/100</td>
</tr>
<tr>
<td>Simmons</td>
<td>2009</td>
<td>FISH</td>
<td>2/25</td>
</tr>
<tr>
<td>Regitnig</td>
<td>2004</td>
<td>IHC</td>
<td>5/31</td>
</tr>
<tr>
<td>Lower</td>
<td>2009</td>
<td>IHC</td>
<td>127/382</td>
</tr>
</tbody>
</table>

Estimates with 95% confidence intervals

- 4.18 (2.45, 7.06)
- 1.42 (0.40, 4.86)
- 13.41 (7.16, 23.73)
- 9.55 (4.94, 17.67)

HER2 Discordant %

Houssami et al, Breast Cancer Res Treat, 2011
MANAGEMENT OF HER-2 + MBC:

• ABC: primary or metastatic HER-2 status?

• Starting early and continuing HER-2 blockade beyond progression (change of paradigm)
  • Combinations with CT and ET: when & which agents?
  • Which anti-HER-2 agent? Dual blockade? Best sequence of therapies?

• Overall good safety profile of anti-HER-2 therapies but cardiac surveillance & management guidelines needed
  • Important problem of brain metastases
    • Resistance - biomarkers
      • Accessibility
Anti-HER-2 therapy should be offered early to all HER-2+ MetaBC patients, except in the presence of contra-indications for use of such therapy (LoE/GoR: I/A) (98%).

Patients progressing on an anti-HER2 therapy combined with a cytotoxic or endocrine agent should be offered additional anti-HER2 therapy with subsequent treatment, except in the presence of contraindications, since it is beneficial to continue suppression of the HER2 pathway (LoE/GoR: I/A) (91%).

CHANGE IN PARADIGM IN ONCOLOGY!
Chemotherapy ± trastuzumab in the first-line treatment of ErbB2+ metastatic breast cancer

H0648g trial

- Longer OS: 25.1 vs. 20.3 ms (p=0.046)
- Longer TTP: 7.4 vs. 4.6 ms (p<0.001)
- Higher RR: 50 vs. 32% (p<0.001)
- Longer duration: 9.1 vs. 6.1 ms (p<0.001)
IMPORTANCE OF STARTING ANTI-HER-2 AGENT EARLY ON
Continuation of Trastuzumab Prolongs Time to Progression by Nearly 3 Months

HR = 0.69 (two-sided \( P = .0338 \); one-sided \( P = .0169 \))

Trastuzumab + Capecitabine (n = 78)

Capecitabine (n = 78)

*Median TTP in months

TTP, time to progression; HR hazard ratio

In patients achieving a complete remission, the optimal duration of maintenance anti-HER2 therapy is unknown and needs to be balanced against treatment toxicity, logistical burden and cost.

Stopping anti-HER2 therapy, after several years of sustained complete remission, may be considered in some patients, particularly if treatment re-challenge is available in case of progression (LoE/GoR: Expert Opinion/C) (93%).
MANAGEMENT OF HER-2 + MBC:

• ABC: primary or metastatic HER-2 status?
• Starting early and continuing HER-2 blockade beyond progression (change of paradigm)
  • Combinations with CT and ET: when & which agents?
• Which anti-HER-2 agent? Dual blockade? Best sequence of therapies?
• Overall good safety profile of anti-HER-2 therapies but cardiac surveillance & management guidelines needed
  • Important problem of brain metastases
    • Resistance - biomarkers
  • Accessibility
2 clinical trials in HER-2+/ER+ BC showing the efficacy of blocking growth factor pathway to overcome endocrine resistance

<table>
<thead>
<tr>
<th>Trial Name/Author</th>
<th>Clinical Setting</th>
<th>Trial Phase and No. of Patients</th>
<th>Study Design</th>
<th>Clinical Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnston (^1)</td>
<td>HER2+ ABC</td>
<td>III (n = 219)</td>
<td>Arm 1: LET</td>
<td>PFS: 3.0 vs 8.2 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arm 2: LET + lapatinib</td>
<td>(P = .019)</td>
</tr>
<tr>
<td>TAnDEM Kaufman (^2)</td>
<td>HER2+ ABC</td>
<td>III (n = 207)</td>
<td>Arm 1: ANA</td>
<td>PFS: 2.4 vs 4.8 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arm 2: ANA + trastuzumab</td>
<td>(P = .0016)</td>
</tr>
</tbody>
</table>

- ET alone quite bad results
- ET + anti-HER-2 did not show OS benefit

---

ET + dual blockade anti-HER-2

**Primary PFS Analysis (Stratified, ITT Population)**

<table>
<thead>
<tr>
<th></th>
<th>Pertuzumab + trastuzumab + Al (n = 129)</th>
<th>Trastuzumab + Al (n = 129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>74 (57.4)</td>
<td>92 (71.3)</td>
</tr>
<tr>
<td>Median, months</td>
<td>18.80</td>
<td>15.80</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(14.09, 27.60)</td>
<td>(11.04, 19.58)</td>
</tr>
<tr>
<td>Δ months</td>
<td>2.99</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.65 (0.44, 0.99)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0070</td>
<td></td>
</tr>
</tbody>
</table>

**Results:**
- ORR: 63 vs 56%, NS
- PFS: 3 ms benefit
- OS immature
ALTENATIVE: Secondary Endpoint
PFS in All Treatment Arms

<table>
<thead>
<tr>
<th></th>
<th>LAP+TRAS+AI n=120</th>
<th>TRAS+AI n=117</th>
<th>LAP+AI n=118</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>62 (52)</td>
<td>75 (64)</td>
<td>74 (63)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td><strong>11</strong></td>
<td><strong>5.7</strong></td>
<td><strong>8.3</strong></td>
</tr>
<tr>
<td>95% CI</td>
<td>[8.3, 13.8]</td>
<td>[5.5, 8.4]</td>
<td>[5.8, 11.2]</td>
</tr>
<tr>
<td>HR; 95% CI vs TRAS+AI</td>
<td>0.76 [0.54, 1.06]</td>
<td>-</td>
<td>0.71 [0.51, 0.98]</td>
</tr>
<tr>
<td>P-value</td>
<td>0.1041</td>
<td>-</td>
<td>0.0361</td>
</tr>
</tbody>
</table>

Subjects at risk
- LAP+TRAS+AI: 120, 109, 77, 64, 59, 39, 24, 19, 16, 12, 10, 10, 7, 7, 5, 5, 2, 1, 1, 0, 0, 0, 0, 0
- TRAS+AI: 117, 98, 57, 39, 37, 28, 19, 15, 13, 12, 7, 6, 3, 3, 3, 3, 2, 2, 0, 0, 0, 0, 0
- LAP+AI: 118, 110, 70, 47, 44, 34, 23, 16, 15, 13, 10, 8, 6, 5, 3, 3, 1, 1, 1, 1, 1, 1, 0

Presented by: William J. Gradishar
For the highly selected patients* with ER+/HER-2+ MBC, for whom ET + anti-HER2 therapy was chosen as 1st line therapy, dual anti-HER2 blockade (with either pertuzumab + trastuzumab or lapatinib + trastuzumab) can be used since it provides a benefit in PFS. This decision must be balanced against the higher side effects, higher costs and lack of OS benefit so far, as compared to ET + anti-HER2 monotherapy.

(LoE/GoR : I/B) (80%)
For patients with ER+/HER-2+ MBC, for whom CT + anti-HER2 therapy was chosen as 1st line therapy and provided a benefit, it is reasonable to use ET + anti-HER2 therapy as maintenance therapy, after stopping CT, although this strategy has not been studied in randomized trials.
Duration of maintenance therapy should be until progression, unacceptable toxicity or patient request, and needs to be evaluated in clinical trials.
(LoE/GoR: NA/B) (80%)

There is no data to decide between single agent anti-HER-2 or dual blockade, to combine with maintenance ET after stopping CT, in ER+/HER2+ ABC.
monarcHER STUDY DESIGN (for “triple positive” ABC)

**Eligibility Criteria**
- HR+, HER2+ ABC
- ≥2 prior HER2 directed therapies for ABC
- prior T-DM1 and taxane required
- CDK4 & 6 inhibitor/fulvestrant naive
- No untreated or symptomatic CNS metastases

**Stratification Factors:**
- number of previous systemic regimens (2–3 vs. >3)
- measurable vs. nonmeasurable

**Randomization**
N = 237
1:1:1

**Sample Size Calculations:**
- 165 PFS events give 80% power at 2-sided alpha of 0.20, assuming a HR of 0.667

**Arm A**
abemaciclib 150 mg PO BID +
trastuzumab IV q21d +
fulvestrant\(^a\) IM q28d

**Arm B**
abemaciclib 150 mg PO BID +
trastuzumab IV q21d

**Arm C**
trastuzumab IV q21d +
investigator’s choice chemotherapy\(^b\)

**Primary Endpoint**
- PFS\(^c\) (A vs. C, then B vs. C)

**Secondary Endpoint**
- ORR, safety, OS, PRO, PK

---

Abbreviations: ABC = advanced breast cancer, HR+ = hormone receptor-positive, HER2(+) = human epidermal growth factor receptor-2 (positive), n = number of patients, PD = progressive disease, BID= twice daily, q21d= every 21 days, PFS = Progression Free Survival, ORR = Objective Response Rate, OS = Overall Survival, PRO = Patient Reported Outcomes, PK = pharmacokinetics

\(^a\)Dosing per fulvestrant label

\(^b\)Standard-of-care single-agent chemotherapy should include approved drug in breast cancer.

\(^c\)Investigator assessed
PRIMARY ENDPOINT: PFS

Arm A = abemaciclib + trastuzumab + fulvestrant
Arm B = abemaciclib + trastuzumab
Arm C = trastuzumab + chemotherapy

- Statistically significant improvement ($\Delta = 2.6$ months A vs. C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs. C

OVERALL SURVIVAL: EXPLORATORY ANALYSIS*

Arm A = abemaciclib + trastuzumab + fulvestrant
Arm B = abemaciclib + trastuzumab
Arm C = trastuzumab + chemotherapy

- No arm with Trastuzumab + Fulvestrant
- Hypothesis: synergy between Abemaciclib + Fulvestrant

S. Tolaney et al
MANAGEMENT OF HER-2 + MBC:

• ABC: primary or metastatic HER-2 status?

• Starting early and continuing HER-2 blockade beyond progression (change of paradigm)

  • Combinations with CT and ET: when & which agents?

• Which anti-HER-2 agent? Dual blockade? Best sequence of therapies?

• Overall good safety profile of anti-HER-2 therapies but cardiac surveillance & management guidelines needed

  • Important problem of brain metastases

    • Resistance - biomarkers

    • Accessibility
Both combination and sequential single agent CT are reasonable options. Based on the available data, we recommend sequential monotherapy as the preferred choice for MBC.

Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.

(LoE/GoR: I/A) (96%)

ALL guidelines are in agreement for this recommendation
First-line treatment with trastuzumab+docetaxel and carboplatin in ErbB2+ MBC

- Study BCIRG 007
- 263 patients, first-line ErbB2+ MBC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trastuzumab +docetaxel</th>
<th>Trastuzumab +carboplatin +docetaxel</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to progression (months)</td>
<td>11.1</td>
<td>10.4</td>
<td>0.57</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>72</td>
<td>72</td>
<td>0.97</td>
</tr>
<tr>
<td>Median overall survival (months)</td>
<td>37.1</td>
<td>37.4</td>
<td>0.99</td>
</tr>
<tr>
<td>Median duration of response (months)</td>
<td>10.7</td>
<td>9.4</td>
<td>0.32</td>
</tr>
</tbody>
</table>

BCIRG, Breast Cancer International Research Group; MBC, metastatic breast cancer
PATIENTS IN THESE TRIALS WERE TAXANE-NAÏVE (Dogma even less valid for today’s 1st line population)

- Single-agent T significantly worse than single-agent A in PFS but not in RR nor OS.
- T-based significantly better than A-based combinations in RR and PFS, but not in OS.
Vinorelbine seems at least as good as taxane and significantly less toxic.

**HERNATA Trial of Docetaxel/Trastuzumab vs Vinorelbine/Trastuzumab**

- **Median PFS (months)**
  - D+T: 12.4
  - V+T: 15.3
- **P=0.67 HR 0.94 (95%CI 0.71-1.25)**

**Anderssen et al EBCC 2010**

**In press J Clin Oncol**

**N=284**

- **Docetaxel + trastuzumab**
- **Vinorelbine + trastuzumab**

**First-line MBC**

- **No prior trastuzumab**
- **Measurable Disease**

**N=81**

- **Paclitaxel or Docetaxel + Trastuzumab**
- **Vinorelbine + Trastuzumab**

**TRAVIOTA:**

**Taxane + Trastuzumab vs. Vinorelbine + Trastuzumab**

- **p=0.09**

**Vinorelbine or Capecitabine:**

**NO/LITTLE ALOPECIA**

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxane Arm</td>
<td>58%</td>
<td>6.0 months</td>
</tr>
<tr>
<td>Vinorelbine Arm</td>
<td>66%</td>
<td>8.5 months</td>
</tr>
</tbody>
</table>

First-line anti-ErbB2 treatment combined with vinorelbine or anthracyclines in ErbB2+ MBC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Dose (mg/m²)</th>
<th>n</th>
<th>OR (%)</th>
<th>Median TTP (months)</th>
<th>Cardiac toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vinorelbine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burstein et al. 2001</td>
<td>T</td>
<td>II</td>
<td>25</td>
<td>40</td>
<td>8.5</td>
<td>No symptomatic heart failure; 3 patients with grade 2</td>
</tr>
<tr>
<td>Jahanzeb et al. 2002&lt;sup&gt;a&lt;/sup&gt;</td>
<td>T</td>
<td>II</td>
<td>30</td>
<td>37</td>
<td>18.0</td>
<td>No serious cardiotoxicity</td>
</tr>
<tr>
<td>Bernardo et al. 2002&lt;sup&gt;a&lt;/sup&gt;</td>
<td>T</td>
<td>II</td>
<td>25</td>
<td>48</td>
<td>9.0</td>
<td>Mild</td>
</tr>
<tr>
<td>Chan et al. 2006&lt;sup&gt;a&lt;/sup&gt;</td>
<td>T</td>
<td>II</td>
<td>30</td>
<td>65</td>
<td>10.0</td>
<td>One grade 3 symptomatic cardiac dysfunction</td>
</tr>
<tr>
<td>Andersson et al. 2010&lt;sup&gt;a,b&lt;/sup&gt; (HERNATA)</td>
<td>T</td>
<td>III</td>
<td>30–35</td>
<td>141</td>
<td>59.3</td>
<td>15.3</td>
</tr>
<tr>
<td>Saip et al. 2011</td>
<td>L</td>
<td>II</td>
<td>20/25</td>
<td>29</td>
<td>NR</td>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Awada et al. 2009</td>
<td>N</td>
<td>I/Ii</td>
<td>25</td>
<td>34</td>
<td>NR</td>
<td>No cases of symptomatic CHF or asymptomatic LVEF decline</td>
</tr>
<tr>
<td><strong>Epirubicin-cyclophosphamide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untch et al. 2010&lt;sup&gt;a&lt;/sup&gt; (HERCULES)</td>
<td>T</td>
<td>I–II</td>
<td>E: 60/90 C: 600</td>
<td>120</td>
<td>57/60</td>
<td>12.5/10.1</td>
</tr>
<tr>
<td><strong>Nonpegylated liposomal doxorubicin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortes et al. 2009</td>
<td>T</td>
<td>I–II</td>
<td>50</td>
<td>69</td>
<td>98</td>
<td>Asymptomatic LVEF decline in 12 patients</td>
</tr>
</tbody>
</table>
Regarding the CT component of HER-2 positive MBC treatment:

When pertuzumab is not given, 1\textsuperscript{st} line regimens for HER-2 MBC can include trastuzumab combined with a vinorelbine or a taxane. \textit{(LoE/GoR: I/A) (88%)}

Differences in toxicity between these regimens should be considered and discussed with the patient in making a final decision. Other CT agents can be administered with trastuzumab but are not as well studied and are not preferred.

\textit{In manuscript:} Single agent vinorelbine in association with anti-HER-2 therapy has shown superior or equal efficacy compared to taxanes and has a better tolerability.
For later lines of therapy, trastuzumab can be administered with several CT agents, including but not limited to, vinorelbine (if not given in 1st line), taxanes (if not given in 1st line), capecitabine, eribulin, liposomal anthracyclines, platinum, gemcitabine, or metronomic CM. (LoE/GoR: II/A) (91%)

The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences, and country availability.
HER-2 POSITIVE MBC: CHEMOTHERAPY COMPONENT

CT agents to combine with a dual blockade of trastuzumab + pertuzumab are docetaxel (LoE/GoR: I/A) or paclitaxel (LoE/GoR: I/B). Also possible are vinorelbine (LoE/GoR: II/A), nab-paclitaxel (LoE/GoR: II/B) and capecitabine (LoE/GoR: II/A).

(Consensus: 86%)
MANAGEMENT OF HER-2 + MBC:

- ABC: primary or metastatic HER-2 status?
- Starting early and continuing HER-2 blockade beyond progression (change of paradigm)
  - Combinations with CT and ET: when & which agents?
    - Which anti-HER-2 agent? Dual blockade? Best sequence of therapies?
- Overall good safety profile of anti-HER-2 therapies but cardiac surveillance & management guidelines needed
  - Important problem of brain metastases
    - Resistance - biomarkers
  - Accessibility
In the 1st line setting, for HER2+ ABC previously treated (in the adjuvant setting with DFI >12 ms) or untreated with trastuzumab, combinations of CT + trastuzumab are superior to combinations of CT + lapatinib in terms of PFS and OS.

(LoE/GoR: I/A) (95%)
Progression Free Survival
Centrally-confirmed HER2+ Analysis

Median PFS TTAX/T = 13.7 months
Median PFS LTAX/L = 9.0 months
HR = 1.48 (95% CI = 1.15 – 1.92), P = 0.003

Overall Survival
Centrally-confirmed HER2 + Analysis

HR = 1.25 (95% CI = 0.81 – 1.93), P = 0.32

Gelmon, K. ASCO 2012
CEREBEL Study: A Phase III Randomized Open-Label Study of Lapatinib plus Capecitabine vs Trastuzumab + Capecitabine in HER2-Positive Metastatic Breast Cancer

Inclusion Criteria:
- Stage IV HER2+ breast cancer
- Prior anthracycline and a taxane
- Prior treatment with CT, trastuzumab, HT, RT is permitted
- LVEF ≥50%, normal organ function

Main Exclusion Criteria:
- History and/or current evidence of CNS metastases
- Prior therapy with lapatinib or ErbB2 inhibitor other than trastuzumab

EARLY CLOSURE!!
475 pts enrolled
40% completed 12 months, had PD or died

Lapatinib 1250 mg PO qd continuously +
capcitabine 2000 mg/m²/d
PO days 1-14 q3 weeks

Capecitabine 2500 mg/m² bid d1-14 q21 days

Primary endpoint: Incidence of CNS metastases at site of first relapse
Secondary endpoints: Incidence of CNS progression at any time, time to first CNS progression, PFS, OS, ORR, CBR, duration of response, toxicity, pharmacogenetics, and biomarker analysis
Primary endpoint: CNS endpoints (modified ITT)

<table>
<thead>
<tr>
<th></th>
<th>Lapatinib + capecitabine (N=251)</th>
<th>Trastuzumab + capecitabine (N=250)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS as first site of relapse, n (%)</td>
<td>8 (3)</td>
<td>12 (5)</td>
<td>0.65 (0.26, 1.63)</td>
<td>0.360</td>
</tr>
<tr>
<td>Incidence of CNS progression at any time, n (%)</td>
<td>17 (7)</td>
<td>15 (6)</td>
<td>1.14 (0.52, 2.51)</td>
<td>0.8646</td>
</tr>
<tr>
<td>Time to first CNS progression, median (range)</td>
<td>5.7 (2–17)</td>
<td>4.4 (2–27)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

TRASTUZUMAB + CAPECITABINE BETTER

OS (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>Lap + Cap (N=271)</th>
<th>Tras + Cap (N=269)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months</td>
<td>22.7</td>
<td>27.3</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.34 (0.95, 1.90)</td>
<td></td>
</tr>
<tr>
<td>Stratified log-rank p-value</td>
<td>0.095</td>
<td></td>
</tr>
</tbody>
</table>

LOW NUMBER OF BRAIN METS
QUESTION: The optimal timing to use lapatinib?

CEREBEL trial

HR: 1.70 (1.15-2.50)

MA 31 COMPLETE Trial

ALTTO Trial

ADAPTED FROM JAVIER CORTES
In case of progression on trastuzumab-based therapy, the combination trastuzumab + lapatinib is a reasonable treatment option for some patients. (LoE/GoR: I/B) (84%)

There are however, no data on the use of this combination after progression on pertuzumab or T-DM1.
EGF104900: Significant Overall Survival (OS) Benefit With Trastuzumab + Lapatinib Following Disease Progression

**Survival, %**

- **6 Month OS:** 80%
- **12 Month OS:** 56%

**Survival, %**

- **6 Month OS:** 70%
- **12 Month OS:** 41%

**Patients at risk:**
- **L:** 148
- **L+T:** 148

<table>
<thead>
<tr>
<th></th>
<th>L</th>
<th>L+T</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>148</td>
<td>148</td>
</tr>
<tr>
<td>Died, N (%)</td>
<td>113 (78)</td>
<td>105 (72)</td>
</tr>
<tr>
<td>Median, months</td>
<td>9.5</td>
<td>14.0</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>.74 (.57-.97)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P-value</td>
<td>.026</td>
<td></td>
</tr>
</tbody>
</table>

NALA study design

Inclusion criteria
• Metastatic breast cancer (MBC)
• Centrally confirmed HER2+ disease
• ≥2 lines of HER2-directed therapy for MBC
• Asymptomatic and stable brain metastases permitted

Stratification variables
• Number of prior HER2 therapies for MBC
• Disease location
• HR status
• Geographic location

Endpoints
• Co-primary: PFS (centrally confirmed) and OS
• Secondary: PFS (local), ORR, DoR, CBR, intervention for CNS metastases, safety, health outcomes

Loperamide 4 mg with first dose of neratinib, followed by 2 mg every 4 h for first 3 d, then loperamide 2 mg every 6–8 h until end of Cycle 1. Thereafter as needed

MAJOR PROBLEM:
Comparator is a suboptimal regimen
(should have been compared to trastuzumab + capecitabine)
Prespecified restricted means analysis – PFS

Mean PFS (months)     p-value
Neratinib + Capecitabine: 8.8     0.0003
Lapatinib + Capecitabine: 6.6

2.2 months

Restriction: 24 months

No. at risk:
N+C: 307, 183, 113, 69, 54, 35, 20, 13, 9, 7, 3, 2, 2
L+C: 314, 183, 82, 39, 24, 9, 8, 3, 2, 2, 2, 1

OS (co-primary endpoint)

Mean OS (months) Hazard ratio (95% CI) Log-rank p-value
Neratinib + Capecitabine: 24.0     0.88 (0.72–1.07)     0.2086
Lapatinib + Capecitabine: 22.2

1.7 months

Restriction: 48 months

No. at risk:
N+C: 307, 294, 275, 244, 220, 182, 142, 112, 82, 64, 47, 34, 28, 18, 15, 13, 6, 4, 2, 1
L+C: 314, 303, 273, 240, 208, 170, 132, 107, 84, 67, 47, 36, 27, 22, 17, 12, 8, 4, 3, 1
Time to intervention for CNS metastases

Overall cumulative incidence (Gray's test): 22.8% vs 29.2%; *p*=0.043

Patient reported outcomes

EORTC QLQ-C30 summary score
Mean score over time

EORTC QLQ-C30 Global health status
Mean score over time
Trastuzumab and Pertuzumab Bind to Different Regions on HER2 and Have Synergistic Activity

- Trastuzumab suppresses HER2 activity
- Flags cells for destruction by the immune system
- Pertuzumab inhibits HER2 heterodimerization
- Suppresses multiple HER signaling pathways
- Flags cells for destruction by the immune system
The **standard 1st line therapy** for patients **previously untreated** with anti-HER2 therapy is the combination of **CT + trastuzumab and pertuzumab**, because it has proven to be superior to **CT + trastuzumab** in terms of OS in this population.

*(LoE/GoR: I/A) (86%)*
For patients previously treated (in the (neo)adjuvant setting) with anti-HER2 therapy, the combination of CT + trastuzumab and pertuzumab is an important option for 1st line therapy.
(LoE/GoR: I/A) (76%)

Few (88) of these pts were treated in the Cleopatra trial and all with trastuzumab-free interval > 12 months.
CLEOPATRA: Median PFS and OS

CAUTION!!!!
Only 21% -26% pts had previously received (neo)adjuvant trastuzumab

**Progression-free Survival (%)**
- Ptz+T+D: 18.5 mo.
- Pla+T+D: 12.4 mo.

\[ \Delta = 6.1 \text{ mo.} \]

**Overall Survival (%)**
- Ptz+T+D: 56.5 mo.
- Pla+T+D: 40.8 mo.

\[ \Delta = 15.7 \text{ mo.} \]

HR=0.62  
\( p<0.0001 \)

HR 0.68  
\( p = 0.0002 \)

**CLEOPATRA: End-of-study OS in the ITT population***

* Crossover pts were analyzed in the Pla arm.

OS was compared between arms using the log-rank test, stratified by prior treatment status and geographic region. The Kaplan–Meier approach was used to estimate median OS, and a stratified Cox proportional hazards model was used to estimate the HR and 95% CIs.

**FINAL OS RESULTS**

HR 0.69 (95% CI = 0.58, 0.82)

Median OS: 40.8 mo (Pla) v 57.1 mo (P)

**Median FU about 8 years**

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>P + H + D</th>
<th>Pla + H + D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>402</td>
<td>406</td>
</tr>
<tr>
<td>10-20</td>
<td>381</td>
<td>350</td>
</tr>
<tr>
<td>20-30</td>
<td>269</td>
<td>289</td>
</tr>
<tr>
<td>30-40</td>
<td>228</td>
<td>230</td>
</tr>
<tr>
<td>40-50</td>
<td>188</td>
<td>181</td>
</tr>
<tr>
<td>50-60</td>
<td>165</td>
<td>149</td>
</tr>
<tr>
<td>60-70</td>
<td>150</td>
<td>115</td>
</tr>
<tr>
<td>70-80</td>
<td>137</td>
<td>88</td>
</tr>
<tr>
<td>80-90</td>
<td>120</td>
<td>75</td>
</tr>
<tr>
<td>90-100</td>
<td>71</td>
<td>44</td>
</tr>
<tr>
<td>100-110</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>110+</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

* Crossover pts were analyzed in the Pla arm.
OS was compared between arms using the log-rank test, stratified by prior treatment status and geographic region. The Kaplan–Meier approach was used to estimate median OS, and a stratified Cox proportional hazards model was used to estimate the HR and 95% CIs.

**FINAL PFS RESULTS**

HR 0.69 (95% CI = 0.59, 0.81)

Median PFS: 12.4 mo (Pla) v 18.7 mo (P)

**Median FU about 8 years**

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>P + H + D</th>
<th>Pla + H + D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>402</td>
<td>406</td>
</tr>
<tr>
<td>10-20</td>
<td>284</td>
<td>223</td>
</tr>
<tr>
<td>20-30</td>
<td>179</td>
<td>110</td>
</tr>
<tr>
<td>30-40</td>
<td>121</td>
<td>76</td>
</tr>
<tr>
<td>40-50</td>
<td>93</td>
<td>53</td>
</tr>
<tr>
<td>50-60</td>
<td>71</td>
<td>43</td>
</tr>
<tr>
<td>60-70</td>
<td>60</td>
<td>35</td>
</tr>
<tr>
<td>70-80</td>
<td>52</td>
<td>30</td>
</tr>
<tr>
<td>80-90</td>
<td>43</td>
<td>23</td>
</tr>
<tr>
<td>90-100</td>
<td>34</td>
<td>21</td>
</tr>
<tr>
<td>100-110</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>110+</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>120+</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Crossover pts were analyzed in the Pla arm.
OS was compared between arms using the log-rank test, stratified by prior treatment status and geographic region. The Kaplan–Meier approach was used to estimate median OS, and a stratified Cox proportional hazards model was used to estimate the HR and 95% CIs.
Adverse events (all grades) with ≥25% incidence or ≥5% difference between arms

<table>
<thead>
<tr>
<th></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>
<td>Febrile neutropenia</td>
<td>30 (7.6)</td>
<td>56 (13.7)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>23 (5.8)</td>
<td>44 (10.8)</td>
</tr>
</tbody>
</table>

Highlighted are adverse events with ≥5% higher incidence. **No increase in cardiac toxicity!**
1st Line Phase III MARIANNE Study

Patients with HER2 positive progressive or recurrent locally advanced breast cancer or previously untreated metastatic breast cancer

- **Primary endpoints:** PFS as assessed by IRF; Safety
- **Secondary endpoints:** OS; PFS by investigator; PRO analyses; Biomarkers
- **Superiority design with a Non-inferiority analysis** between each of the experimental arms and the control arm
- **Interim futility analysis:** Option to drop experimental arm

DID NOT SHOW SUPERIORITY OF DUAL BLOCKADE!
Only 30% of pts previously pretreated with Trastuzumab in the (neo)adjuvant setting

- **n=1092**
- Patients stratified by:
  - World region
  - Neo/Adjuvant therapy (Y/N)
  - Trastuzumab and/or lapatinib based therapy (Y/N)
  - Visceral disease (Y/N)

Trastuzumab + taxane
T-DM1 + placebo
Final Analysis of Overall Survival

WHAT WE DON’T KNOW:
How T-DM1 compares with Taxane + Trastuzumab + Pertuzumab

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>T-DM1</th>
<th>T-DM1+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>n=365</td>
<td>n=367</td>
<td>n=363</td>
</tr>
<tr>
<td>Day 1</td>
<td>365</td>
<td>367</td>
<td>363</td>
</tr>
<tr>
<td>12 Months</td>
<td>303</td>
<td>322</td>
<td>309</td>
</tr>
<tr>
<td>24 Months</td>
<td>251</td>
<td>264</td>
<td>257</td>
</tr>
<tr>
<td>36 Months</td>
<td>197</td>
<td>216</td>
<td>217</td>
</tr>
<tr>
<td>48 Months</td>
<td>155</td>
<td>176</td>
<td>172</td>
</tr>
<tr>
<td>60 Months</td>
<td>128</td>
<td>145</td>
<td>141</td>
</tr>
<tr>
<td>72 Months</td>
<td>28</td>
<td>37</td>
<td>41</td>
</tr>
<tr>
<td>Median OS (mo.)</td>
<td>50.9</td>
<td>53.7</td>
<td>51.8</td>
</tr>
<tr>
<td>Events (no.)</td>
<td>169</td>
<td>175</td>
<td>168</td>
</tr>
<tr>
<td>Stratified HR (97.5% CI) vs HT</td>
<td>—</td>
<td>0.93 (0.73–1.20)</td>
<td>0.86 (0.67–1.11)</td>
</tr>
</tbody>
</table>

Courtesy of Carlos Barrios
PHEREXA study design
NCT01026142

• HER2-positive MBC (centrally confirmed)
• Prior taxane and H
• Progression during or after H-based therapy for MBC

N = 452

Arm A:
H (8 mg/kg → 6 mg/kg) + X (1,250 mg/m²)
n = 224

Arm B:
H (8 mg/kg → 6 mg/kg) + X (1,000 mg/m²) + P (840 mg → 420 mg)
n = 228

First pt included: Jan 30, 2010
Last pt included: Aug 12, 2013
Clinical cut-off: May 29, 2015

Courtesy of Ander Urruticoechea
Primary analysis: PFS by independent review facility
ITT population

<table>
<thead>
<tr>
<th>Arm A: H + X</th>
<th>Arm B: H + X + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>mPFS (months)</td>
</tr>
<tr>
<td>(n = 224)</td>
<td>2.1</td>
</tr>
<tr>
<td>158 (71)</td>
<td>118 (74)</td>
</tr>
<tr>
<td>mPFS (months)</td>
<td>9.0</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>0.82 (0.65–1.02)</td>
</tr>
<tr>
<td>mFU (months)</td>
<td>28.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm A: H + X</th>
<th>Arm B: H + X + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>mPFS (months)</td>
</tr>
<tr>
<td>(n = 228)</td>
<td>2.1</td>
</tr>
<tr>
<td>168 (74)</td>
<td>111.1</td>
</tr>
<tr>
<td>mPFS (months)</td>
<td>9.0</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>0.82 (0.65–1.02)</td>
</tr>
<tr>
<td>mFU (months)</td>
<td>25.3</td>
</tr>
</tbody>
</table>

Stratified. CI, confidence interval; FU, follow-up.

Secondary analysis: OS
ITT population

<table>
<thead>
<tr>
<th>Arm A: H + X</th>
<th>Arm B: H + X + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>mOS (months)</td>
</tr>
<tr>
<td>(n = 224)</td>
<td>28.1</td>
</tr>
<tr>
<td>115 (51)</td>
<td>98 (43)</td>
</tr>
<tr>
<td>mOS (months)</td>
<td>28.1</td>
</tr>
<tr>
<td>Δ (months)</td>
<td>8.0</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>0.68 (0.51–0.90)</td>
</tr>
<tr>
<td>mFU (months)</td>
<td>29.5</td>
</tr>
</tbody>
</table>

Statistical significance cannot be claimed due to the hierarchical testing of OS after the primary IRF PFS endpoint

Stratified.
Comparison of patient populations
Limited prior *Adjuvant Trastuzumab* Therapy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HER2 regimens tested</td>
<td>Docetaxel/Paclitaxel</td>
<td>Docetaxel</td>
<td>Paclitaxel</td>
<td>Taxane</td>
</tr>
<tr>
<td>De novo metastatic</td>
<td>55%</td>
<td>53%</td>
<td>≈ 50%</td>
<td>43%</td>
</tr>
<tr>
<td>Prior adj. trast. (and interval &gt;1y)</td>
<td>31%</td>
<td>11%</td>
<td>10%</td>
<td>18%</td>
</tr>
</tbody>
</table>

*The results of most of these trials are relevant today only for de novo metastatic patients*

*Adapted from M. Piccart St. Gallen 2015 Presentation & R. Dent ESMO Asia 2015*
HER-2 POSITIVE MBC

There are currently no data supporting the use of dual blockade with trastuzumab + pertuzumab and CT beyond progression (i.e. continuing dual blockade beyond progression) and therefore this 3 drug regimen should not be given beyond progression outside clinical trials. (LoE: Expert Opinion/E) (86%)

There are no data on how to treat patients who have a relapse after receiving CT + trastuzumab + pertuzumab in the early setting.
HER-2 POSITIVE MBC: 2\textsuperscript{nd} line and beyond

After 1\textsuperscript{st} line trastuzumab-based therapy, T-DM1 provides superior efficacy relative to other HER-2-based therapies in the 2\textsuperscript{nd} line (vs. lapatinib + capecitabine) and beyond (vs. treatment of physician’s choice).

T-DM1 should be preferred in patients who have progressed through at least 1 line of trastuzumab-based therapy, because it provides an OS benefit.

(LoE/GoR: I/A) (88%)

However, there are no data on the use of T-DM1 after dual blockade with trastuzumab + pertuzumab.
Progression-Free Survival by Independent Review

<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>No. of 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) \(P<0.0001\)

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 \(HR=0.727\)

5 to 6 MONTHS BENEFIT IN OS

Unstratified HR=0.66 (\(P<0.0001\)).
### PFS by Investigator Assessment

#### Median follow-up:
- TPC: 6.5 months
- T-DM1: 7.2 months

#### Unstratified HR = 0.521 (P < 0.0001)

<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>
</tbody>
</table>

Stratified HR = 0.528 (95% CI, 0.422, 0.661)  P < 0.0001

#### Final OS Analysis

<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>15.8</td>
<td>22.7</td>
</tr>
</tbody>
</table>

Stratified HR = 0.68 (95% CI: 0.54–0.85)  P = 0.0007

(Pre-specified crossing boundary: HR < 0.748; P < 0.012)

#### SUPERIOR PFS

44.9% of TPC arm pts received T-DM1 crossover therapy

#### 3 ms
OS BENEFIT
TOXICITIES OF T-DM1

- **Thrombocytopenia**
  - Grade ≥3: 10% of patients; Nadir on day 8; Nadir is typically lowest in cycle 1
  - Not typically cumulative; usually manageable with dose reduction
  - Severe hemorrhage is rare, but small number of cases have been reported

- **Transaminase elevation**
  - Grade ≥3: 5% of patients; Not typically cumulative
  - Usually manageable with dose reduction; Severe hepatic dysfunction very rare

- **Pneumonitis**
  - ≈1% of pts; typically grade 1/2; T-DM1 should be discontinued

- **Nodular regenerative hyperplasia**
  - <0.5%); can lead to noncirrhotic portal hypertension
  - Requires biopsy to diagnose; T-DM1 should be discontinued

Diéras et al, SABCS 2012, Abstract P5-18-06
MANAGEMENT OF HER-2 + MBC:

• ABC: primary or metastatic HER-2 status?

• Starting early and continuing HER-2 blockade beyond progression (change of paradigm)

  • Combinations with CT and ET: when & which agents?

  • Which anti-HER-2 agent? Dual blockade? Best sequence of therapies?

• Overall good safety profile of anti-HER-2 therapies but cardiac surveillance & management guidelines needed

  • Important problem of brain metastases

  • Resistance - biomarkers

  • Accessibility
Trastuzumab suppresses HER2 activity
• Flags cells for destruction by the immune system

Pertuzumab inhibits HER2 heterodimerization
• Suppresses multiple HER signaling pathways
• Flags cells for destruction by the immune system

DUAL BLOCKADE: TRANSTUZUMAB + PERTUZUMAB

15 MONTHS BENEFIT IN OS in previously untreated patients
COST: ~ 6.500 €/cycle
Trastuzumab-DM1

Receptor-T-DM1 complex is internalized into HER2-positive cancer cell

T-DM1 binds to the HER2 protein

Potent antimicrotubule agent is released once inside the HER2-positive tumor cell

5 MONTHS BENEFIT IN OS
COST: ~ 4,000 €/cycle
HER-2 POSITIVE MBC: 1\textsuperscript{st} line

CT + trastuzumab and pertuzumab
   or
   CT + trastuzumab
   or
ET + trastuzumab +/- pertuzumab or lapatinib

HER-2 POSITIVE MBC: 2\textsuperscript{nd} line and beyond

T-DM1
   or
   CT + trastuzumab
   or
ET + trastuzumab
MANY QUESTIONS SILL UNANSWERED

- Optimal duration of anti-HER-2 therapy for ABC (indeinitely?)
- At progression should only the cytotoxic drug be changed of both the cytotoxic and the anti-HER-2 agent
- Is treatment beyond PD also true for other anti-HER-2 agents?
- Dual blockade for everyone or some?
- The role of the dual blockade without CT
- Triple blockade?
- Best sequence of anti-HER-2 therapies
- Mechanisms of resistance & ways to overcome it; predictive markers
- NEW ANTI-HER-2 AGENTS in development
Margetuximab: Fc-engineered to Activate Immune Responses

**Trastuzumab**

**Fab:**
- Binds HER2 with high specificity
- Disrupts signaling that drives cell proliferation and survival

**Fc:**
- Wild-type immunoglobulin G1 (IgG1) immune effector domains
- Binds and activates immune cells

**Margetuximab**

**Fab:**
- Same specificity and affinity
- Similarly disrupts signaling

**Fc engineering:**
- ↑ Affinity for activating FcγRIIIA (CD16A)
- ↓ Affinity for inhibitory FcγRIIB (CD32B)

**Margetuximab Binding to FcγR Variants:**

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Receptor</th>
<th>Allelic Variant</th>
<th>Relative Fc Binding</th>
<th>Affinity Fold-Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activating</td>
<td>CD16A</td>
<td>158F</td>
<td>Lower</td>
<td>6.6x ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>158V</td>
<td>Higher</td>
<td>4.7x ↑</td>
</tr>
<tr>
<td></td>
<td>CD32A</td>
<td>131R</td>
<td>Lower</td>
<td>6.1x ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>131H</td>
<td>Higher</td>
<td>↔</td>
</tr>
<tr>
<td>Inhibitory</td>
<td>CD32B</td>
<td>232I/T</td>
<td>Equivalent</td>
<td>8.4x ↓</td>
</tr>
</tbody>
</table>

H. Rugo, ASCO 2019

Study CP-MGAH22-04 (SOPHIA) Design$^{1,2}$

**Arm 1**
Margetuximab (15 mg/kg Q3W) + chemotherapy
in 3-week cycles

**Arm 2**
Trastuzumab (8 mg/kg loading → 6 mg/kg Q3W) + chemotherapy
in 3-week cycles

**Stratification:**
- Chemotherapy choice
- Prior therapies (≤2 vs >2)
- Metastatic sites (≤2 vs >2)

**HER2+ advanced breast cancer**
- ≥2 prior anti-HER2 therapies, including pertuzumab
- 1-3 prior treatment lines in metastatic setting
- Prior brain metastasis ok if treated and stable

**Investigator’s choice of chemotherapy**
(capecitabine, eribulin, gemcitabine, or vinorelbine)

**Sequential Primary Endpoints**
- PFS (by CBA; n=257; HR=0.67; α=0.05; power=90%)
- OS (n=385; HR=0.75; α=0.05; power=80%)

**Secondary Endpoints**
- PFS (Investigator assessed)
- Objective response rate (by CBA)

**Tertiary/Exploratory Endpoints**
- Clinical benefit rate (CBR), duration of response (DoR)
- Safety profile, antidrug antibody
- Effect of CD16A, CD32A, and CD32B on margetuximab efficacy

HR=hazard ratio; CBA=central blinded analysis.


H. Rugo, ASCO 2019
SOPHIA TRIAL: PFS Analysis in ITT Population

24% Risk Reduction of Disease Progression
Central Blinded Analysis (Primary Endpoint)

- PFS analysis was triggered by last randomization on October 10, 2018, after 265 PFS events occurred

ITT population: N=536. CI=confidence interval.

Margetuximab + Chemotherapy (n=266)
Trastuzumab + Chemotherapy (n=270)

# of events
130
135

Median PFS (95% CI)
5.8 months (5.52–6.97)
4.9 months (4.17–5.59)

HR by stratified Cox model, **0.76**
(95% CI, 0.59–0.98)
Stratified log-rank **P=0.033**

H. Rugo, ASCO 2019
DS-8201a: a HER2-targeting Antibody-drug Conjugate

DS-8201a Structure and Mechanism of Action

• DS-8201a was designed with the goal of improving critical attributes of an ADC

- Proprietary drug-linker
  - Payload with a different mechanism of action
  - High potency of payload
  - Payload with short systemic half-life
  - Bystander effect
  - Stable linker-payload
  - Tumor-selective cleavable linker
  - High drug-to-antibody ratio

Conjugation chemistry
The linker is connected to cysteine residue of the antibody

Payload (DXd)
Etsatecan derivative

• DS-8201 is a humanized HER2 antibody attached to a novel topoisomerase 1 inhibitor payload by a tetrapeptide-based linker
• Designed to deliver CT inside cancer cells and reduce systemic exposure in comparison to traditional CT
• Activity in HER2+ and “HER2 low”
**DS-8201a: a HER2-targeting Antibody-drug Conjugate**

### Efficacy Outcomes by Cancer Type (5.4 or 6.4 mg/kg)

<table>
<thead>
<tr>
<th></th>
<th>HER2-Positive BC (N = 111)</th>
<th>HER2-Low BC (N = 34)</th>
<th>HER2-Positive GC (N = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Confirmed ORR</em>, % (n/N)</em>*</td>
<td>54.5% (54/99)</td>
<td>50.0% (17/34)</td>
<td>43.2% (19/44)</td>
</tr>
<tr>
<td><strong>DCR, % (n/N)</strong></td>
<td>93.9% (93/99)</td>
<td>85.3% (29/34)</td>
<td>79.5% (35/44)</td>
</tr>
<tr>
<td><strong>ORR in modified ITT</strong>, % (n/N)</td>
<td>48.6% (54/111)</td>
<td>50.0% (17/34)</td>
<td>43.2% (19/44)</td>
</tr>
<tr>
<td><strong>DOR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, (95% CI), months</td>
<td>NR</td>
<td>11.0 (NA)</td>
<td>7.0 (NA)</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, (95% CI), months</td>
<td>NR</td>
<td>12.9 (NA)</td>
<td>5.6 (3.0, 8.3)</td>
</tr>
<tr>
<td>Min, max</td>
<td>1.0, 22.2+</td>
<td>0.5, 19.6+</td>
<td>1.2, 19.6+</td>
</tr>
</tbody>
</table>

*Confirmed response includes subjects who had ≥2 postbaseline scans, had progressive disease, or discontinued treatment for any reason prior to second postbaseline scan.

**Modified ITT population included all subjects who received ≥1 dose of DS-8201a at either 5.4 or 6.4 mg/kg, including those subjects who were too early to assess, but are ongoing on study.

†after value indicates censoring.

BC, breast cancer; CI, confidence interval; DCR, disease control rate; DOR, duration of response; GC, gastric/gastroesophageal junction cancer; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; NA, not available; NR, not reached; ORR, overall response rate; PFS, progression-free survival.

Data cutoff for this analysis is April 18, 2018.
New anti-HER2 agents
Where are we going?

Antibody
- Margetuximab

Bispecific antibody
- BTRC4017A
- GBR 1302
- MCLA-128
- PRS-343
- ZW-25
- ZW-49

ADC
- A166
- ARX788
- DHES0815A
- DS 8201a
- Trastuzumab deruxtecan
- SYD-985

Novel TKI
- Poziotinib
- Pyrotinib
- Tucatinib

Courtesy G. Curigliano
Treatment of HER2+ ABC: Progress over time

First-line
- CT
- CT + Trastuzumab
- D + Trastuzumab
- D + Trastuzumab + Pertuzumab

Second line
- Capecitabine
- Capecitabine + Lapatinib
- Capecitabine + Lapatinib
- T-DM1

Third / Later line
- Physicians choice
- T-DM1

Overall survival, months

References:
1 Slamon et al. NEJM 2001; 2 Swain et al. NEJM 2015; 3 Geyer et al. NEJM 2011; 4 Verma et al. NEJM 2012
5 Geyer et al. SABCS 2015. mod. from Loibl SABCS 2015
Overall survival according to subtype

Sixth International Consensus Conference

SAVE THE DATE
4-6 November 2021
Lisbon, Portugal

Coordinating Chair:
F. Cardoso, PT

Advanced Breast Cancer

Receive updates on
www.abc-lisbon.org