Systemic therapy for HER2+ ABC

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EORTC Breast Group Past-Chair
Financial disclosures:

*Personal financial interest in form of consultancy role for:* Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, 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, 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
ESO-ESMO ABC4 GUIDELINES

SPECIAL ARTICLE

4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†


1300 participants from 88 countries

www.abc-lisbon.org

https://oncologypro.esmo.org/Guidelines/
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
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  - Accessibility
A **biopsy** (preferably providing histology) of a metastatic lesion should be performed, if easily accessible, to confirm diagnosis particularly when metastasis is diagnosed for the first time. *(LoE/GoR: I/B) (98%)*

**Biological markers** (especially HR and HER-2) should be **reassessed at least once** in the metastatic setting, if clinically feasible. *(LoE/GoR: I/B) (98%)*

Depending on the metastatic site (e.g. bone tissue), technical considerations need to be discussed with the pathologist.
META-ANALYSIS OF HER-2 STATUS DISCORDANCE BETWEEN PRIMARY VS. METS

Estimates with 95% confidence intervals

Houssami et al, Breast Cancer Res Treat, 2011
If the results of tumour biology in the metastatic lesion differ from the primary tumour, it is currently unknown which result should be used for treatment-decision making.

Since a clinical trial addressing this issue is difficult to undertake, we recommend considering the use of targeted therapy (ET and/or anti-HER-2 therapy) when receptors are positive in at least one biopsy, regardless of timing  (LoE/GoR: Expert opinion/B) (87%)
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• 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

Study design: H0648g Phase III registration trial

ErbB2+ metastatic breast cancer (n=469)

- Anthracycline pretreated
  - Paclitaxel (n=96)
  - Trastuzumab + paclitaxel (n=92)

- Anthracycline naïve
  - Anthracycline (n=138)
  - Trastuzumab + anthracycline (n=143)

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)
First-line treatment of ErbB2+ metastatic breast cancer with docetaxel ± trastuzumab

Study design: M77001 trial (Phase II trial)

N=188
ErbB2+ MBC (IHC3+ and/or FISH+)

Randomisation

Docetaxel* 100 mg/m² q3w×6
n=94

Docetaxel* 100 mg/m² q3w×6+ trastuzumab 4 mg/kg → 2 mg/kg → PD
n=92

2 patients did not receive study medication

*Patients progressing on docetaxel alone could cross over to receive trastuzumab
IHC, immunohistochemistry; FISH, fluorescence in-situ hybridisation; MBC, metastatic breast cancer; PD, progressive disease; q, every

IMPORTANCE OF STARTING ANTI-HER-2 AGENT EARLY ON

First-line treatment of ErbB2+ metastatic breast cancer with docetaxel ± trastuzumab

Overall survival: M77001 trial

Median values are shown

Trastuzumab Beyond Trastuzumab: GBG-26 Study

MBC HER2-positive Progression under trastuzumab-based first-line therapy (TFI < 6 weeks) with taxane (n = 114) or monotherapy or nontaxane (n = 42)

Capecitabine 2500 mg/m² bid d1-14 q21 days + continuation of trastuzumab 6 mg/kg q3 weeks (n = 78)

Capecitabine 2500 mg/m² bid d1-14 q21 days (n = 78)

R, randomization; TFI, treatment-free interval; MBD, metastatic breast cancer

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>Johnston¹</td>
<td>HER2+ ABC</td>
<td>III (n = 219)</td>
<td>Arm 1: LET Arm 2: LET + lapatinib</td>
<td>PFS: 3.0 vs 8.2 mo $P = .019$</td>
</tr>
<tr>
<td>TAnDEM Kaufman²</td>
<td>HER2+ ABC</td>
<td>III (n = 207)</td>
<td>Arm 1: ANA Arm 2: ANA + trastuzumab</td>
<td>PFS: 2.4 vs 4.8 mo $P = .0016$</td>
</tr>
</tbody>
</table>

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

PERTAIN Study Design (Phase II Trial)

G. Arpino et al, SABCS 2016

ET + dual blockade anti-HER-2

ORR: 63 vs 56%, NS
PFS: 3 ms benefit
OS immature
ALTERNATIVE: Study Design

- Global study conducted across 112 sites, 29 countries; Data cutoff: March 11, 2016

- Stratification factors:
  - Prior TRAS in neo/adjuvant or metastatic setting
  - Investigator’s choice of AI (steroidal/nonsteroidal)

N=355

- Postmenopausal women with confirmed ER+ and/or PgR+, HER2+ MBC

R 1:1:1

LAPATINIB (1000 mg/day)+TRASTUZUMAB^a+Al^b (n=120)

TRAS^a+Al^b (n=117)

LAP (1500 mg/day)+Al^b (n=118)

Therapy until disease progression, unacceptable toxicity or death, withdrawal of consent or investigator discretion

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^aTRAS 8 mg/kg IV loading dose followed by 6 mg/kg IV q3weeks; ^bInvestigator’s choice of AI included LET (2.5 mg/day), ANA (1 mg/day) or EXE (25 mg/day).

AI, aromatase inhibitor; ER+, estrogen receptor-positive; HER2+, human epidermal growth factor receptor 2-positive; LAP, lapatinib; MBC, metastatic breast cancer; PgR+, progesterone receptor-positive; TRAS, trastuzumab.
ALTERNATIVE: Secondary Endpoint
PFS in All Treatment Arms

<table>
<thead>
<tr>
<th></th>
<th>LAP+TRAS+AI</th>
<th>TRAS+Al</th>
<th>LAP+Al</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>11</td>
<td>5.7</td>
<td>8.3</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+Al      117  98  57  39  37  28  19  15  13  12  7  6  3  3  3  3  3  2  2  0  0  0  0  0
LAP+Al       118  110  70  47  44  34  23  16  15  13  10  8  6  5  3  3  1  1  1  1  1  1  0

Proportion Alive and Progression Free

Presented by: William J. Gradishar

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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.
MANAGEMENT OF HER-2 + MBC:

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• 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: study design

Patients with ErbB2+ FISH+ MBC N=263

Trastuzumab +docetaxel 100 mg/m² n=131

Trastuzumab+docetaxel 75 mg/m² +carboplatin (AUC=6) n=131

Primary endpoint: median time to progression

AUC, area under the curve; BCIRG, Breast Cancer International Research Group; FISH, fluorescence in situ hybridisation; MBC, metastatic breast cancer
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
• 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.

PATIENTS IN THESE TRIALS WERE TAXANE-NAÏVE (Dogma even less valid for today’s 1st line population)
Vinorelbine seems at least as good as taxane and significantly less toxic.

Vinorelbine or Capecitabine: NO/LITTLE ALOPECIA

**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)

**TRAVIOTA:**
- Taxane + Trastuzumab vs. Vinorelbine + Trastuzumab

<table>
<thead>
<tr>
<th>No. at risk:</th>
<th>Docetaxel + Trastuzumab</th>
<th>Vinorelbine + Trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>D+T</td>
<td>143</td>
<td>66</td>
</tr>
<tr>
<td>V+T</td>
<td>141</td>
<td>76</td>
</tr>
<tr>
<td>Reg2_TV</td>
<td>141</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>13</td>
</tr>
</tbody>
</table>

Andersen et al EBCC 2010

In press J Clin Oncol

Vinorelbine or Capecitabine:
- NO/LITTLE ALOPECIA

**First-Line MBC**
- No prior trastuzumab
- Measurable Disease
- N = 81

**RR and TTP**

<table>
<thead>
<tr>
<th>Treatment</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>

p = 0.09

HERNATA Study:
Phase III, randomised, multicentre study comparing docetaxel + trastuzumab vs vinorelbine + trastuzumab as first-line therapy in locally advanced/HER2+ MBC

Endpoints
Primary
• TTP
Secondary
• OS
• 1-year survival
• ORR
• TTF
• Toxicity and tolerability

Patients
• Confirmed HER2+ locally advanced or MBC
• Chemotherapy and HER2-targeted treatment was allowed as (neo-)adjuvant therapy, but not for treatment of locally advanced or MBC
• Prior hormonal therapy allowed
• PS ≤ 2

• Treatment was administered every 3 weeks for until progression, intolerable toxicity, or patient withdrawal
  – Treatment after discontinuation of study medication was at the discretion of the physician

Docetaxel 100 mg/m² (Day 1) + trastuzumab 6 mg/kg* (Day 1)

Randomisation (1:1 ratio)

iv vinorelbine 30/35† mg/m² (Day 1 and 8) + trastuzumab 6 mg/kg* (Day 1)

*First cycle: trastuzumab 8mg/kg
†According to institutional-predefined preference

**HERNATA study: Summary of clinical outcomes**

<table>
<thead>
<tr>
<th>Response, n(%)</th>
<th>Docetaxel + trastuzumab (n=123)*</th>
<th>Vinorelbine + trastuzumab (n=118)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>16 (13.0)</td>
<td>13 (11.0)</td>
</tr>
<tr>
<td>PR</td>
<td>57 (46.3)</td>
<td>57 (48.3)</td>
</tr>
<tr>
<td>SD</td>
<td>20 (16.2)</td>
<td>19 (16.1)</td>
</tr>
<tr>
<td>PD</td>
<td>9 (7.3)</td>
<td>6 (5.1)</td>
</tr>
<tr>
<td>NE</td>
<td>21 (17.0)</td>
<td>23 (19.5)</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>73 (59.3)</td>
<td>70 (59.3)</td>
</tr>
<tr>
<td><strong>DCR†</strong></td>
<td>93 (75.6)</td>
<td>89 (75.4)</td>
</tr>
</tbody>
</table>

| Time-related outcomes, months |
|-------------------------------|------------------|
| Median TTF                   | 5.6 [HR 0.50; 95%CI, 0.38–0.64; p = 0.0001] | 7.7 |  
| Median TTP                   | 12.4 [HR 0.94; 95% CI, 0.71–1.25; p = 0.67] | 15.3 |
| Median OS                    | 35.7 [HR 1.01; 95% CI, 0.71–1.42; p = 0.98] | 38.8 |
| 1-year survival, % [95% CI]  | 88 [81–92] | 88 [82–93] |

*Patients with measurable disease
†Not reported in study
## 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>75</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No symptomatic heart failure; 3 patients with grade 2</td>
</tr>
<tr>
<td>Jahanzeb et al. 2002</td>
<td>T</td>
<td>II</td>
<td>30</td>
<td>37</td>
<td>78</td>
<td>18.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No serious cardiotoxicity</td>
</tr>
<tr>
<td>Bernardo et al. 2002</td>
<td>T</td>
<td>II</td>
<td>25</td>
<td>48</td>
<td>86</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Chan et al. 2006</td>
<td>T</td>
<td>II</td>
<td>30</td>
<td>65</td>
<td>63</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>One grade 3 symptomatic cardiac dysfunction</td>
</tr>
<tr>
<td>Andersson et al. 2010</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>(HERNATA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decline in LVEF to &lt;40% in 3.6%</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>5c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Awada et al. 2009</td>
<td>N</td>
<td>I/II</td>
<td>25</td>
<td>34</td>
<td>43/25</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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</td>
<td>T</td>
<td>I–II</td>
<td>E: 60/90</td>
<td>120</td>
<td>57/60</td>
<td>12.5/10.1</td>
</tr>
<tr>
<td>(HERCULES)</td>
<td></td>
<td></td>
<td>C: 600</td>
<td></td>
<td></td>
<td>Symptomatic LVEF decline in 1.7% (TEC-60), 5.0% (TEC-90) and 0 (EC-90)</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>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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. (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.

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.
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
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 CONCEPT OF DUAL BLOCKADE
Lapatinib: TKI, small molecule, acts in the intracellular domain

MAPK pathway (Ras/Raf/MEK/ERK)

PI3K/Akt pathway

Ligands
Other ErbB
ErbB2

Lapatinib

Proliferation
Cell cycle, Survival

STOP
GO
STOP
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%)
MA.31/ EGF108919 COMPLETE TRIAL: Randomized Phase III, Taxane-Based CT with Lapatinib vs. Trastuzumab; 1st line therapy; with HER-2+ MBC

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)

Gelmon, K. ASCO 2012
### Treatment Discontinuations

**OFF PROTOCOL TREATMENT**

(n = 382)

<table>
<thead>
<tr>
<th>Reason</th>
<th>LTAX/L=202</th>
<th>Number (%)</th>
<th>TTAX/T=180</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5 (2.5)</td>
<td></td>
<td>10 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Intercurrent Illness</td>
<td>3 (1.5)</td>
<td></td>
<td>3 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>143 (70.8)</td>
<td></td>
<td>121 (67.2)</td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>36 (17.8)</td>
<td></td>
<td>19 (10.6)</td>
<td></td>
</tr>
<tr>
<td>Refused Treatment</td>
<td>2 (1.0)</td>
<td></td>
<td>4 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic Progression</td>
<td>4 (2.0)</td>
<td></td>
<td>3 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (4.5)</td>
<td></td>
<td>20 (11.1)</td>
<td></td>
</tr>
</tbody>
</table>

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

• 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

**EARLY CLOSURE!!**

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

- Lapatinib 1250 mg PO qd continuously
- Capecitabine 2500 mg/m² bid d1-14 q21 days
- Trastuzumab loading dose 8 mg/kg → 6 mg/kg q3 weeks
- Capecitabine 2000 mg/m²/d PO days 1-14 q3 weeks
### 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>

**CEREBEL TRIAL**

**LOW NUMBER OF BRAIN METS**

**TRASTUZUMAB + CAPECITABINE BETTER**

![Survival曲线图](image)

- **Median OS, months**
  - Lap + Cap (N=271): 33.7
  - Tras + Cap (N=269): 37.3

- **Hazard ratio (95% CI)**
  - Lap + Cap vs Tras + Cap: 1.34 (0.95, 1.80)

- **Stratified log-rank p-value**: 0.095
NEW 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: Phase III Study Evaluated Dual HER2 Blockade

- HER2 (FISH+/IHC3+) metastatic breast cancer
- Progression on
  - Anthracycline
  - Taxane
  - Trastuzumab
- Progression on most recent trastuzumab regimen

Primary endpoint:
- Progression-free survival

Secondary endpoints:
- Overall survival
- Overall response rate
- Clinical benefit rate

Randomize

Lapatinib 1500 mg/d PO (n = 148)

Crossover allowed to lapatinib + trastuzumab if progression after at least 4 weeks on therapy

Lapatinib 1000 mg/d PO + trastuzumab 4→2 mg/kg IV weekly (n = 148)

- Staging occurred at 4, 8, 12, 16 weeks, and then every 8 weeks
- Steady state of single-agent lapatinib occurs at approximately 7 days

EGF104900: Significant Overall Survival (OS) Benefit With Trastuzumab + Lapatinib Following Disease Progression

<table>
<thead>
<tr>
<th></th>
<th>L N = 148</th>
<th>L+T N = 148</th>
</tr>
</thead>
<tbody>
<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>

HER-2 POSITIVE MBC: 1\textsuperscript{st} line

The standard 1\textsuperscript{st} 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.
Patients with HER2-positive MBC centrally confirmed (N = 808)

1:1

Placebo + trastuzumab

n=406

Docetaxel*

≥6 cycles recommended

Pertuzumab + trastuzumab

Docetaxel*

≥6 cycles recommended

n=402

• PRIMARY ENDPOINT: PFS

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

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

Baselga, J. SABCS 2011
CLEOPATRA: Median PFS and OS

CAUTION!!!!

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

Ptz+T+D: 18.5 mo. Pla+T+D: 12.4 mo. \( \Delta = 6.1 \) mo.

Ptz+T+D: 56.5 mo. Pla+T+D: 40.8 mo. \( \Delta = 15.7 \) mo.

HR = 0.62
\( p < 0.0001 \)

HR 0.68
\( p = 0.0002 \)

Overall survival subgroup analyses

- An exploratory subgroup analysis was performed for patients who had received prior neoadjuvant and/or adjuvant trastuzumab therapy (88 patients). The observed hazard ratio of 0.68 (95% CI 0.30–1.55) indicates overall survival benefit in the pertuzumab arm for this subpopulation.
### 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><strong>122 (30.8)</strong></td>
<td>101 (24.8)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>40 (10.1)</td>
<td><strong>68 (16.7)</strong></td>
</tr>
<tr>
<td>Constipation</td>
<td><strong>101 (25.5)</strong></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!**
1\textsuperscript{st} Line Phase III MARIANNE Study

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

Patients stratified by:
- World region
- Visceral disease (Y/N)

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

- 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

Trastuzumab + taxane
T-DM1 + pertuzumab
T-DM1 + placebo

n=1092
## Progression-Free Survival by IRF

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>T-DM1</th>
<th>T-DM1+P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS (mo.)</strong></td>
<td>13.7</td>
<td>14.1</td>
<td>15.2</td>
</tr>
<tr>
<td><strong>Events (no.)</strong></td>
<td>231</td>
<td>236</td>
<td>217</td>
</tr>
<tr>
<td><strong>Stratified HR vs HT</strong></td>
<td>—</td>
<td>0.91</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.73–1.13)</td>
<td>(0.69–1.08)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(P=0.31)</td>
<td>(P=0.14)</td>
</tr>
<tr>
<td><strong>Stratified HR vs T-DM1</strong></td>
<td>—</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.73–1.13)</td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing progression-free survival](image-url)
Summary of Findings From Primary Analysis

• After a median duration of follow-up of 35 months
  – T-DM1–based treatment exhibited non-inferior, but not superior, PFS relative to HT
  – Median OS was not reached in any treatment arm

• T-DM1 was better tolerated than HT

• Health-related quality of life was maintained for a longer duration with T-DM1 treatments

• We now present results from the final OS analysis conducted after approximately 20 months of additional follow-up

Final Analysis of Overall Survival

WHAT WE DON’T KNOW:
How T-DM1 compares with Taxane + Trastu + Pertu

<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>Events (no.)</td>
<td>169</td>
<td>175</td>
<td>168</td>
</tr>
<tr>
<td>Median OS (mo.)</td>
<td>50.9</td>
<td>53.7</td>
<td>51.8</td>
</tr>
<tr>
<td>Stratified HR (97.5% CI) vs HT</td>
<td>—</td>
<td>0.93</td>
<td>(0.73–1.20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.67–1.11)</td>
</tr>
</tbody>
</table>

Courtesy of Carlos Barrios
### All-Grade AEs Occurring in >20% of Patients in Any Treatment Arm With >10% Point Difference Between HT and T-DM1 Arms

<table>
<thead>
<tr>
<th>All-grade AE, %</th>
<th>HT (n = 353)</th>
<th>T-DM1 (n = 361)</th>
<th>T-DM1+P (n = 366)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>60.1</td>
<td>7.2</td>
<td>9.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>49.0</td>
<td>25.5</td>
<td>48.6</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>28.0</td>
<td>14.1</td>
<td>18.9</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>27.8</td>
<td>10.2</td>
<td>9.6</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22.1</td>
<td>11.9</td>
<td>10.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>37.1</td>
<td>48.2</td>
<td>52.5</td>
</tr>
<tr>
<td>Headache</td>
<td>22.7</td>
<td>32.1</td>
<td>32.8</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>15.0</td>
<td>31.3</td>
<td>35.2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17.0</td>
<td>27.4</td>
<td>32.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19.5</td>
<td>22.2</td>
<td>30.3</td>
</tr>
<tr>
<td>Chills</td>
<td>4.0</td>
<td>15.2</td>
<td>26.5</td>
</tr>
</tbody>
</table>
# Grade ≥3 AEs Occurring in ≥3% in Any Treatment Arm

<table>
<thead>
<tr>
<th>Adverse Event Preferred Term, Grade ≥3, %</th>
<th>HT (n = 353)</th>
<th>T-DM1 (n = 361)</th>
<th>T-DM1+P (n = 366)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>19.3</td>
<td>4.4</td>
<td>3.8</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>6.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.2</td>
<td>0.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.1</td>
<td>4.7</td>
<td>5.5</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.8</td>
<td>5.0</td>
<td>7.1</td>
</tr>
<tr>
<td>ALT increased</td>
<td>0.8</td>
<td>4.4</td>
<td>6.0</td>
</tr>
<tr>
<td>AST increased</td>
<td>0.3</td>
<td>6.9</td>
<td>3.3</td>
</tr>
<tr>
<td>GGT increased</td>
<td>0.3</td>
<td>3.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>6.6</td>
<td>9.0</td>
</tr>
</tbody>
</table>

- Greater incidence in HT arm
- Greater incidence in T-DM1 arms
Median time to progression (months)

First-line MBC

- Slamon 2001: 4.6 months
- Marty 2005: 7.4 months

Second-line MBC (trastuzumab-exposed)

- Cameron 2008: 4.3 months

Graph showing:
- Chemotherapy only
- Trastuzumab + chemotherapy
- Lapatinib + chemotherapy

Courtesy D. Cameron
Phase II Study of Pertuzumab, Trastuzumab, and Weekly Paclitaxel

- 36 evaluable pts with 1\textsuperscript{st} or 2\textsuperscript{nd} line HER2+ MBC
- ORR = 47%
- No cardiac events

Datko F et al, SABCS 2012. Abstract P5-18-20
VELVET STUDY

**Cohort 1:** *pertuzumab and trastuzumab administered sequentially in separate infusions*, followed by vinorelbine

**Cohort 2:** *pertuzumab and trastuzumab were administered in a single infusion*, followed by vinorelbine
VELVET STUDY DESIGN

- Primary endpoint: investigator-assessed objective response rate (ORR) in patients with measurable disease at baseline (RECIST v1.1)

- Secondary endpoints: time to response, duration of response (DoR) in responders, PFS, time to progression (TTP), OS, safety and tolerability, and health-related quality of life (HRQoL).

Similar results in both Cohorts for safety and efficacy
ORR: 74%
Median PFS: 14.3 months
Median DoR: 13.3 months
Median OS not reached at 2 years FU (2 year-survival: 78.3%)

**PROBLEM:**
- Non-randomized trial
- Good for accessing safety but not the best for efficacy (no cross-trials comparision)

**IMPORTANT:**
- 41.5% pts previously treated with Trastuzumab (neo/adjuvant)

**Table 2**

| Number of patients censored | 32 (30.2%) | 8 (18.2%) | 24 (38.7%) | 13 (28.9%) | 7 (28.0%) | 12 (33.3%) |

Data are reported number (%) [95% CI] for best overall response and median number of months [95% CI] or number (%) for progression-free survival. Best overall response was assessed only in patients of the intent-to-treat population with measurable disease at baseline. Progression-free survival was assessed in the intent-to-treat population. One patient had a missing progesterone receptor score and was considered as having a negative score. Overall good safety profile (diarrhea, neutropenia); few discontinuations
Safety of pertuzumab plus trastuzumab plus vinorelbine for 1st line treatment of pts with HER2+- LABC or MBC

Edith A. Perez, José Manuel López-Vega, Lucia Del Mastro, Thierry Petit, Claudio Zamagni, Ulrich Freudensprung, Lydie Bastière-Truchot, Ru Walker, Michael Andersson. SABCS 2013, Poster 2-16-10

Discussion

• A cross-study comparison of the incidence of selected AEs (Table 4) suggests that the safety profile of the combination of pertuzumab, trastuzumab, and vinorelbine observed to date in VELVET compares favorably with those seen previously in CLEOPATRA (pertuzumab, trastuzumab, and docetaxel) and HERNATA (trastuzumab and vinorelbine). However, it should be noted that it is difficult to compare results from different clinical trials.

Table 4. Cross-study comparison of the VELVET, CLEOPATRA, and HERNATA trials

<table>
<thead>
<tr>
<th>Incidence of selected AEs, %</th>
<th>VELVET</th>
<th>CLEOPATRA</th>
<th>HERNATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>14.9%</td>
<td>6.1%</td>
<td>NR</td>
</tr>
<tr>
<td>Alopecia</td>
<td>23.6%</td>
<td>50.9%</td>
<td>NR</td>
</tr>
<tr>
<td>Grade ≥ 3 neutropenia</td>
<td>23.6%</td>
<td>48.9%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3.7%</td>
<td>13.8%</td>
<td>10.8%</td>
</tr>
<tr>
<td>Grade ≥ 3 leukopenia</td>
<td>8.5%</td>
<td>12.3%</td>
<td>21%</td>
</tr>
</tbody>
</table>

* All adverse events; NR, not reported
* Pertuzumab, trastuzumab, and docetaxel arm; *Trastuzumab and vinorelbine arm; *First six cycles only; *Grade 2 or 3 only; grade 1 reported NR; *Increased neutropenia and granulocyte count decreased; pretreated arm
* Pretreated neutropenia and neutrophil blood cell count decreased; pretreated arm

Conclusions

• There was an acceptable safety profile with the combination of pertuzumab, trastuzumab, and vinorelbine, and no new safety signals were observed.

• The incidences of alopecia and of grade ≥3 hematologic AEs are currently lower than those observed previously with trastuzumab plus vinorelbine or with pertuzumab plus trastuzumab plus docetaxel. 

• Based on encouraging interim safety data, enrollment into Cohort 2 began in April 2013 and completed in September 2013. Final efficacy data from both cohorts are expected in 2015.
PHEREXA study design
NCT01026142

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

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

N = 452
Primary analysis: PFS by independent review facility
ITT population

<table>
<thead>
<tr>
<th></th>
<th>Arm A: H + X (n = 224)</th>
<th>Arm B: H + X + P (n = 228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>158 (71)</td>
<td>168 (74)</td>
</tr>
<tr>
<td>mPFS (months)</td>
<td>9.6</td>
<td>11.1</td>
</tr>
<tr>
<td>Δ (months)</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>0.82 (0.65–1.02)</td>
<td>0.07</td>
</tr>
<tr>
<td>Log-rank p-value*</td>
<td>0.07</td>
<td>2.65</td>
</tr>
<tr>
<td>mF/U (MMMs)</td>
<td>28.6</td>
<td>25.3</td>
</tr>
</tbody>
</table>

*Stratified. CI: confidence interval, FU: follow-up.

Secondary analysis: OS
ITT population

<table>
<thead>
<tr>
<th></th>
<th>Arm A: H + X (n = 224)</th>
<th>Arm B: H + X + P (n = 228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>115 (51)</td>
<td>98 (43)</td>
</tr>
<tr>
<td>mOS (months)</td>
<td>28.1</td>
<td>36.1</td>
</tr>
<tr>
<td>Δ (months)</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>0.88 (0.51–0.99)</td>
<td>29.5</td>
</tr>
<tr>
<td>mF/U (MMMs)</td>
<td>28.5</td>
<td></td>
</tr>
</tbody>
</table>

*Stratified

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

• The addition of P to H and X did not significantly improve independent review facility-assessed PFS

• An 8-month increase in mOS with P to 36.1 months was observed
  – The magnitude of OS benefit is in keeping with prior experience of P in MBC\textsuperscript{1,2}

• No new safety signals were identified

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

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemo</strong></td>
<td>Docetaxel/Paclitaxel</td>
<td>Docetaxel</td>
<td>Paclitaxel</td>
<td>Taxane</td>
</tr>
<tr>
<td><strong>Anti-HER2 regimens tested</strong></td>
<td>T-DM1 or T-DM1 + Pertuzumab</td>
<td>Trastuzumab + Pertuzumab (vs TRAS)</td>
<td>Trastuzumab + Everolimus 10mg OD (vs TRAS)</td>
<td>Lapatinib (vs TRAS)</td>
</tr>
<tr>
<td><strong>De novo metastatic</strong></td>
<td>55%</td>
<td>53%</td>
<td>≈ 50%</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Prior adj. trast. (and interval &gt;1y)</strong></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*
## Prior Trastuzumab Efficacy Data

### Adjuvant Trastuzumab DFI > 1 year

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td>10.3 months vs 15.2 months (T-DM1)</td>
<td>10.4 months vs. 16.9 months (p value not reported)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>NR</td>
<td>46.6 months vs 53.8 months (p value not reported)</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Adapted from R. Dent ESMO Asia 2015*

¹ Swain et al NEJM Correspondence 2015

But based only on 88 pts!!
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.
In a HER-2+ MBC patient, previously untreated with the combination of CT + trastuzumab + pertuzumab, it is acceptable to use this treatment after 1st line, although currently no data exists in this setting.

(LoE/GoR: II/B) (76%)
After 1st line trastuzumab-based therapy, T-DM1 provides superior efficacy relative to other HER-2-based therapies in the 2nd 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%)
**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

**1:1**

**T-DM1**
3.6 mg/kg q3w IV

**Capecitabine**
1000 mg/m² orally bid, days 1–14, q3w

+ **Lapatinib**
1250 mg/day orally qd

**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

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

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

No. at risk by independent review:
Cap + Lap: 496, 404, 310, 178, 129, 73, 53, 35, 25, 14, 9, 8, 5, 1, 0, 0
T-DM1: 495, 419, 241, 256, 183, 130, 101, 72, 54, 44, 30, 18, 9, 3, 1, 0

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).

5 to 6 MONTHS BENEFIT IN OS

EMILIA STUDY
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 STUDY**

**SUPERIOR PFS**

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

---

**Final OS Analysis**

3 ms
OS BENEFIT
TH3RESA: Treatment Choice in TPC Arm

• 80.4% of pts assigned to TPC arm received trastuzumab-containing combination regimen

<table>
<thead>
<tr>
<th>Treatment Regimen in TPC Arm, %</th>
<th>TPC (n = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination regimen including anti-HER2 agent</td>
<td>83.2</td>
</tr>
<tr>
<td>▪ Chemotherapy* + 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 + lapatinib</td>
<td>2.7</td>
</tr>
<tr>
<td>Single-agent chemotherapy*</td>
<td>16.8</td>
</tr>
</tbody>
</table>

*Most commonly used chemotherapy agents: vinorelbine, gemcitabine, eribulin, paclitaxel, docetaxel.

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
Overview: adverse events of trastuzumab

- Generally very well tolerated
- Most common side effects are mild-to-moderate infusion-related reactions with the first infusion (25% of patients)¹
- Increased risk of LVEF decline/CHF, particularly in combination with anthracyclines:
  - 3–30% incidence of LVEF decline in trials
  - <4% incidence of symptomatic CHF¹–³

USUALLY REVERSIBLE

CHF, congestive heart failure; LVEF, left ventricular ejection fraction
TOXICITIES OF T-DM1

• Thrombocytopenia
  – Grade $\geq$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 $\geq$3: 5% of patients; Not typically cumulative
  – Usually manageable with dose reduction; Severe hepatic dysfunction very rare

• Pneumonitis
  – $\approx$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
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
DUAL BLOCKADE: TRANSTUZUMAB + PERTUZUMAB

- 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

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
\hspace{1cm} or
CT + trastuzumab
\hspace{1cm} or
ET + trastuzumab +/- pertuzumab or lapatinib

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

T-DM1
\hspace{1cm} or
CT + trastuzumab
\hspace{1cm} or
ET + trastuzumab
MANAGEMENT OF HER-2 + MBC:

MANY QUESTIONS SILL UNANSWERED

- Optimal duration of anti-HER-2 therapy for ABC (indefinitely?)
- 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
Targeting HER2 in ABC

OS

First-line

CT
CT + H
D + H
D + H + P
2001
25.1 mos
40.8 mos
56.5 mos

Second line

Cape
16.2 mos
2010
Cape-Lap
18.8 mos
Cape-Lap
25.1 mos
T-DM1
30.9 mos
2012

Siamon (2001); Swain (2015)
Geyer C (2006); Verma (2012)

Courtesy of Pierfranco Conte and Valentina Guarneri


Courtesy G. Curigliano