4th ESO-ESMO Latin-American Masterclass in Clinical Oncology

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Mexico City, Mexico

Chairs:
A. Cervantes, ES - N. Pavlidis, GR
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Under the auspices of
CMO
SMEO

LATIN-AMERICA PROGRAMME

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Recommended management of HER-2+ ABC

F. Cardoso, MD
Director, Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal
ESO Breast Cancer Program Coordinator
ESMO Board of Directors & NR Committee Chair
EORTC Breast Group Past-Chair
DISCLOSURES

Consultant/Ad Board:

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
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
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: 1 B) (98%)

Biological markers (especially HR and HER-2) should be reassessed at least once in the metastatic setting, if clinically feasible. (LoE: 1 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

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: Expert opinion) (87%)
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: 1 A). (91%)

All patients with HER-2+ MBC who relapse after adjuvant anti-HER-2 therapy should be considered for further anti-HER-2 therapy, except in the presence of contraindications (LoE: 1 B) (97%)

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 (n=138)
  - Anthracyline naïve
    - 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)

MCBS: 5
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

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

Overall survival: M77001 trial

IMPORTANCE OF STARTING ANTI-HER-2 AGENT EARLY ON
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)

R

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 $P = .0169$)

*Median TTP in months

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: Expert Opinion) (93%)
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
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 Arm 2: LET + lapatinib</td>
<td>PFS: 3.0 vs 8.2 mo (P = .019)</td>
</tr>
<tr>
<td>TAnDEMG Kaufman(^2)</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

ET + dual blockade anti-HER-2

Primary PFS Analysis (Stratified, ITT Population)

<table>
<thead>
<tr>
<th>Event-Free Probability (%)</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>16.30</td>
<td>16.80</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(14.00, 27.66)</td>
<td>(11.04, 18.56)</td>
</tr>
<tr>
<td>L.M. months</td>
<td>3.99</td>
<td>3.99</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.65 (0.48, 0.89)</td>
<td>0.65 (0.48, 0.89)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0070</td>
<td>0.0070</td>
</tr>
</tbody>
</table>

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

N=355

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

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

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

LAPATINIB (1000 mg/day)+TRASTUZUMAB<sup>a</sup>+AI<sup>b</sup> (n=120)

TRAS<sup>a</sup>+AI<sup>b</sup> (n=117)

LAP (1500 mg/day)+AI<sup>b</sup> (n=118)

<sup>a</sup>TRAS 8 mg/kg IV loading dose followed by 6 mg/kg IV q3weeks; <sup>b</sup>Investigator’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

Presented by: William J. Gradishar

<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>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 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 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 1 0

Proportion Alive and Progression Free

Time Since Randomization (Months)
For the highly selected patients* with ER+/HER-2+ MBC, for whom ET + anti-HER2 therapy was chosen as 1\textsuperscript{st} 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%)

* Defined in the manuscript
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: 1 B). (96%)

ALL guidelines are in agreement for this recommendation
Cochrane meta-analysis of Combination vs. Sequential monoCT for ABC

Progression-free survival (all trials)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Combination Total</th>
<th>Sequential Total</th>
<th>Weight</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alba 2004</td>
<td>0.0296</td>
<td>0.1827</td>
<td>69</td>
<td>75</td>
<td>10.7%</td>
<td>1.03 [0.72, 1.47]</td>
</tr>
<tr>
<td>Baker 1974</td>
<td>0.239</td>
<td>0.2295</td>
<td>46</td>
<td>30</td>
<td>6.8%</td>
<td>1.27 [0.81, 1.99]</td>
</tr>
<tr>
<td>Beslija 2006</td>
<td>-0.6033</td>
<td>0.2865</td>
<td>50</td>
<td>50</td>
<td>4.3%</td>
<td>0.55 [0.31, 0.96]</td>
</tr>
<tr>
<td>Conte 2004</td>
<td>0.0862</td>
<td>0.139</td>
<td>106</td>
<td>92</td>
<td>18.5%</td>
<td>1.09 [0.83, 1.43]</td>
</tr>
<tr>
<td>Fountzilas 2001</td>
<td>0.2151</td>
<td>0.1579</td>
<td>90</td>
<td>93</td>
<td>14.3%</td>
<td>1.24 [0.91, 1.69]</td>
</tr>
<tr>
<td>Park 2010</td>
<td>0.2776</td>
<td>0.2429</td>
<td>41</td>
<td>40</td>
<td>6.0%</td>
<td>1.32 [0.82, 2.12]</td>
</tr>
<tr>
<td>Sledge 2003</td>
<td>0.2469</td>
<td>0.0962</td>
<td>230</td>
<td>453</td>
<td>38.5%</td>
<td>1.28 [1.06, 1.55]</td>
</tr>
<tr>
<td>Tomova 2010</td>
<td>-0.1625</td>
<td>0.6415</td>
<td>46</td>
<td>53</td>
<td>0.9%</td>
<td>0.85 [0.24, 2.99]</td>
</tr>
</tbody>
</table>

Total (95% CI)    | 678              | 886 | 100.0%            | 1.16 [1.03, 1.31] |

Heterogeneity: $\chi^2 = 9.41$, df = 7 ($P = 0.22$); $I^2 = 26$

Test for overall effect: $Z = 2.52$ ($P = 0.01$)

Overall survival (all trials)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Combination Total</th>
<th>Sequential Total</th>
<th>Weight</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alba 2004</td>
<td>0.2151</td>
<td>0.2634</td>
<td>69</td>
<td>75</td>
<td>4.5%</td>
<td>1.24 [0.74, 2.08]</td>
</tr>
<tr>
<td>Baker 1974</td>
<td>0.3716</td>
<td>0.2606</td>
<td>46</td>
<td>30</td>
<td>4.6%</td>
<td>1.45 [0.87, 2.42]</td>
</tr>
<tr>
<td>Beslija 2006</td>
<td>-0.6387</td>
<td>0.3182</td>
<td>50</td>
<td>50</td>
<td>3.1%</td>
<td>0.53 [0.28, 0.99]</td>
</tr>
<tr>
<td>Chlebowski 1989</td>
<td>-0.1054</td>
<td>0.1282</td>
<td>129</td>
<td>93</td>
<td>19.2%</td>
<td>0.90 [0.70, 1.16]</td>
</tr>
<tr>
<td>Conte 2004</td>
<td>0.174</td>
<td>0.2355</td>
<td>106</td>
<td>92</td>
<td>5.7%</td>
<td>1.19 [0.75, 1.89]</td>
</tr>
<tr>
<td>Fountzilas 2001</td>
<td>0.1989</td>
<td>0.1667</td>
<td>90</td>
<td>93</td>
<td>11.3%</td>
<td>1.22 [0.88, 1.69]</td>
</tr>
<tr>
<td>Park 2010</td>
<td>-0.1744</td>
<td>0.235</td>
<td>41</td>
<td>40</td>
<td>5.7%</td>
<td>0.84 [0.53, 1.33]</td>
</tr>
<tr>
<td>Sledge 2003</td>
<td>0.0488</td>
<td>0.0901</td>
<td>230</td>
<td>453</td>
<td>38.8%</td>
<td>1.05 [0.88, 1.25]</td>
</tr>
<tr>
<td>Tomova 2010</td>
<td>0.1989</td>
<td>0.211</td>
<td>46</td>
<td>53</td>
<td>7.1%</td>
<td>1.22 [0.81, 1.84]</td>
</tr>
</tbody>
</table>

Total (95% CI)    | 807              | 979 | 100.0%            | 1.04 [0.93, 1.16] |

Heterogeneity: $\chi^2 = 10.54$, df = 8 ($P = 0.23$); $I^2 = 24$

Test for overall effect: $Z = 0.76$ ($P = 0.45$)

Dear RF et al. Combination vs. sequential single agent CT for MBC (Review) 2013

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**VISCERAL CRISIS** is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease.

Visceral crisis is not the mere presence of visceral metastases but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.

*(LoE: Expert opinion) (95%)*
First-line treatment with trastuzumab+ docetaxel and carboplatin in ErbB2+ MBC

Study BCIRG 007: study design

Patients with ErbB2+ FISH+ MBC N=263

Randomisation

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
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>Vinorelbine</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. 2002a</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. 2002a</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. 2006a</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. 2010a,b</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>III</td>
<td>25</td>
<td>34</td>
<td>43/25e</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>Epirubicin-cyclophosphamide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untch et al. 2010a</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>Nonpegylated liposomal doxorubicin</td>
<td>T</td>
<td>I-II</td>
<td>50</td>
<td>69</td>
<td>98</td>
<td>NR</td>
</tr>
</tbody>
</table>
**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.
HERNATA Trial of Docetaxel/Trastuzumab vs Vinorelbine/Trastuzumab

Vinorelbine seems at least as good as taxane and significantly less toxic

Vinorelbine or Capecitabine: NO/LITTLE ALOPECIA

TRAVIOTA:
Taxane + Trastuzumab vs. Vinorelbine + Trastuzumab

Paclitaxel or Docetaxel + Trastuzumab

First-line MBC
No prior trastuzumab
Measurable Disease
N=81

Vinorelbine + Trastuzumab

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

p=0.09

Regarding the CT component of HER-2 positive MBC treatment:

When pertuzumab is not given, 1st line regimens for HER-2 MBC can include trastuzumab combined with a vinorelbine or a taxane.  
(LoE: 1 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: 2 A) 891%

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: 1 A) or paclitaxel (LoE: 1 B).

Also possible are vinorelbine (LoE: 2 A) and nab-paclitaxel (LoE: 2 B) and Capecitabine (LoE: 1 A).

(86% Consensus)
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

THE CONCEPT OF DUAL BLOCKADE

- Pertuzumab inhibits HER2 heterodimerization
- Suppresses multiple HER signaling pathways
- Flags cells for destruction by the immune system
Lapatinib: TKI, small molecule, acts in the intracellular domain

Ligands
Other ErbB
ErbB2
Lapatinib

MAPK pathway (Ras/Raf/MEK/ERK)

PI3K/Akt pathway

Proliferation
Survival

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In the 1st line setting, for HER-2+ MBC previously treated (in the adjuvant setting) or untreated with trastuzumab, combinations of CT + trastuzumab are superior to combinations of CT + lapatinib in terms of PFS and OS. (LoE: 1 A) (85%)
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

Progression Free Survival
Centrally-confirmed HER2+ Analysis

Overall Survival
Centrally-confirmed HER2+ Analysis

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 + capecitabine 2000 mg/m²/d PO days 1-14 q3 weeks

**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
<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>

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>

Subjects at risk

<table>
<thead>
<tr>
<th></th>
<th>Lap + Cap</th>
<th>Tras + Cap</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>271</td>
<td>269</td>
</tr>
<tr>
<td>1</td>
<td>194</td>
<td>207</td>
</tr>
<tr>
<td>2</td>
<td>129</td>
<td>140</td>
</tr>
<tr>
<td>3</td>
<td>79</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

LOW NUMBER OF BRAIN METS

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

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

• 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

HR 0.62
p<0.0001

HR 0.68
p = 0.0002

Ptz+T+D: 18.5 mo.
Ptz+T+D: 56.5 mo.

Pla+T+D: 12.4 mo.
Pla+T+D: 40.8 mo.

Δ=6.1 mo.
Δ=15.7 mo.

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

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
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>Median PFS (mo.)</td>
<td>13.7</td>
<td>14.1</td>
<td>15.2</td>
</tr>
<tr>
<td>Events (no.)</td>
<td>231</td>
<td>236</td>
<td>217</td>
</tr>
<tr>
<td>Stratified HR vs HT</td>
<td>—</td>
<td>0.91</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>(0.73–1.13)</td>
<td>(0.69–1.08)</td>
<td>P=0.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stratified HR vs T-DM1</td>
<td>—</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.73–1.13)</td>
</tr>
</tbody>
</table>
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 n=365</th>
<th>T-DM1 n=367</th>
<th>T-DM1+P n=363</th>
</tr>
</thead>
<tbody>
<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>

No. at Risk:
- HT: n=365
- T-DM1: n=367
- T-DM1+P: n=363

Courtesy of Carlos Barrios
PHEREXA study design
NCT01026142

1. HER2-positive MBC (centrally confirmed)
2. Prior taxane and H
3. 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
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>9.0</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></td>
</tr>
<tr>
<td>Log-rank p-value*</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>mFU (months)</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>0.68 (0.51–0.90)</td>
<td></td>
</tr>
<tr>
<td>mFU (months)</td>
<td>29.5</td>
<td>29.3</td>
</tr>
</tbody>
</table>

* Stratified.

Statistical significance cannot be claimed due to the hierarchical testing of OS after the primary IRF PFS endpoint.
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><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 <em>(vs TRAS)</em></td>
<td>Trastuzumab + Everolimus 10mg OD <em>(vs TRAS)</em></td>
<td>Lapatinib <em>(vs TRAS)</em></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*
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.

(86%)

There are no data on how to treat patients who have a relapse after receiving CT + trastuzumab + pertuzumab in the early setting.
After 1\textsuperscript{st} line trastuzumab-based therapy, \textit{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).

\textit{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 \textit{T-DM1} after dual blockade with trastuzumab + pertuzumab.
EMILIA Study Design

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

**Primary end points:** PFS by independent review, OS, and safety

**Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression

Progression-Free Survival by Independent Review

<table>
<thead>
<tr>
<th></th>
<th>No. at risk by independent review:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap + Lap</td>
<td>496 404 310 176 129 73 53 25 14 9 8 5 1 0 0</td>
</tr>
<tr>
<td>T-DM1</td>
<td>495 419 341 236 183 130 101 72 54 44 30 18 9 3 1 0</td>
</tr>
</tbody>
</table>

No. of events:
- Cap + Lap: 304
- T-DM1: 265

Stratified HR=0.650 (95% CI, 0.55, 0.77)

P<0.0001

Unstratified HR=0.66 (P<0.0001).

~5 MS BENEFIT IN OS

Overall Survival: Confirmatory Analysis

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

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

Efficacy stopping boundary P=0.0037 or HR=0.727.

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

- **HER2-positive (central) advanced BC**\(^a\)
  
  \(N=600\)

- **≥2 prior HER2-directed therapies for advanced BC**

- **Prior treatment with trastuzumab, lapatinib, and a taxane**

- **T-DM1**
  
  \(3.6 \text{ mg/kg q3w IV}\)
  
  \(n=400\)

- **Treatment of physician’s choice (TPC)**\(^b\)
  
  \(n=200\)

- **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.
PFS by Investigator Assessment

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

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

---

**Final OS Analysis**

**Median (months):**
- TPC: 15.8
- T-DM1: 22.7

**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
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: \(~ 6.500 \text{ €/cycle}\)
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 (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
Margetuximab-Fc-optimized anti-HER2 Monoclonal Ab

- Derived from 4D5, parent antibody of trastuzumab
  - Margetuximab and trastuzumab bind same epitope on HER2 with high affinity
- Fc domain modifications enhance NK cell and macrophage activation
  - Enhanced binding to low affinity variants of activating Fcγ receptor, CD16A
  - Diminished binding to inhibitory Fcγ receptor, CD32B
- Enhanced antibody dependent cell-mediated cytotoxicity \textit{in vitro}
- Patients with high affinity Fc receptors had prolonged PFS with trastuzumab
  \textit{(Musolino et al., J Clin Oncol 26: 1789-96 (2008))}
- SOPHIA will test if enhanced ADCC leads to superior outcomes in HER+ MBC

SOPHIA Study to Establish Superiority to Trastuzumab

HER2+ mBC, 1-2 lines in metastatic setting (prior trastuzumab, pertuzumab, T-DM1)

PI Choice of Chemotherapy (capecitabine, eribulin, gemcitabine or vinorelbine)

1:1 Randomization (n = 530)

Arm 1
margetuximab + chemotherapy

Arm 2
trastuzumab + chemotherapy

Sequential Primary Endpoints: Progression-Free Survival & Overall Survival:
PFS (N=257, HR=0.67, α=0.05, power=90%)
OS (N=358, HR=0.75, α=0.05, power=80%)
Targeting HER2 in ABC

OS

First-line

CT

20.3 mos

CT + H

25.1 mos

2001

D + H

40.8 mos

2015

D + H + P

56.5 mos

Second line

Cape

16.2 mos

2010

Cape-Lap

18.8 mos

T-DM1

30.9 mos

2012

Slamon (2001); Swain (2015)

Geyer C (2006); Verma (2012)

Courtesy of Pierfranco Conte and Valentina Guarneri


Courtesy G. Curigliano
ADVANCES HAVE BEEN DIFFERENT IN DIFFERENT MBC SUBTYPES

Prognosis in MBC by HER-2 Status
and by Therapy with Trastuzumab

<table>
<thead>
<tr>
<th>n = 2,091 (median f/u = 16.9 mo)</th>
<th>Patients (%)</th>
<th>1 y survival (95% CI)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-pos</td>
<td>118 (5.6%)</td>
<td>70.2% (60.3%, 78.1%)</td>
<td>--</td>
</tr>
<tr>
<td>HER2-neg</td>
<td>1,782 (85.3%)</td>
<td>75.1% (72.9%, 77.2%)</td>
<td>0.56 (0.45-0.69, p = 0.0001)</td>
</tr>
<tr>
<td>HER2-pos treated with trastuzumab</td>
<td>191 (9.1%)</td>
<td>86.6% (80.8%, 90.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Dawood et al, ASCO abstract 1018, 2008

ER and/or PR positive tumours
The median survival was 22 months & has not increase over time since the 90’s (introduction of AIs)

Trends in survival in metastatic breast cancer. Sundquist et al. EBCC 2010, abst # 453

- HER-2+ BC: the one with the major advances
- TNBC: the one with less advances
- ER+ BC: advances until the 90’s and then stalled...

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Advanced Breast Cancer

Fifth International Consensus Conference

14-16 November 2019
Lisbon, Portugal

Coordinating Chair: F. Cardoso, PT

RECEIVE UPDATES AT WWW.ABC-LISBON.ORG | #ABCLISBON

SAVE THE DATE
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
## Incidence of CNS Metastases in Trastuzumab-Treated Patients

<table>
<thead>
<tr>
<th>Case Series</th>
<th>Patient Population</th>
<th>#</th>
<th>Overall</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendell et al, 2003</td>
<td>Trastuzumab-treated</td>
<td>42</td>
<td>123</td>
<td>34</td>
</tr>
<tr>
<td>Clayton et al, 2004</td>
<td>Trastuzumab-treated</td>
<td>23</td>
<td>93</td>
<td>25</td>
</tr>
<tr>
<td>Lai et al, 2004</td>
<td>Trastuzumab-treated</td>
<td>38</td>
<td>79</td>
<td>48.1</td>
</tr>
<tr>
<td>Lower et al, 2003</td>
<td>Trastuzumab-treated</td>
<td>22</td>
<td>87</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Non-trastuzumab-treated</td>
<td>58</td>
<td>190</td>
<td>31</td>
</tr>
<tr>
<td>Pinder et al, 2007</td>
<td>Trastuzumab-treated first-line</td>
<td>95</td>
<td>231</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Non-trastuzumab-treated</td>
<td>12</td>
<td>61</td>
<td>20</td>
</tr>
<tr>
<td>Shmueli et al, 2004</td>
<td>Trastuzumab-treated</td>
<td>10</td>
<td>41</td>
<td>21</td>
</tr>
<tr>
<td>Stemmler et al, 2006</td>
<td>Trastuzumab-treated</td>
<td>42</td>
<td>136</td>
<td>30.9</td>
</tr>
<tr>
<td>Yardley et al, 2007</td>
<td>HER2-positive MBC</td>
<td>236</td>
<td>768</td>
<td>30.7</td>
</tr>
<tr>
<td>Yau et al, 2006</td>
<td>Trastuzumab-treated</td>
<td>23</td>
<td>87</td>
<td>26.4</td>
</tr>
</tbody>
</table>
High Risk of Brain Metastases in Patients with HER2+ MBC

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bendell et al,</strong></td>
<td>34%</td>
</tr>
<tr>
<td><em>Cancer</em> 2003</td>
<td></td>
</tr>
<tr>
<td><strong>Clayton et al,</strong></td>
<td>39%</td>
</tr>
<tr>
<td><em>Br J Cancer</em> 2004</td>
<td></td>
</tr>
<tr>
<td><strong>Stemmler et al,</strong></td>
<td>31%</td>
</tr>
<tr>
<td><em>Breast</em> 2006</td>
<td></td>
</tr>
<tr>
<td><strong>Kennecke et al,</strong></td>
<td>29% (ER-)</td>
</tr>
<tr>
<td><em>J Clin Oncol</em> 2010</td>
<td>15% (ER+)</td>
</tr>
<tr>
<td><strong>Brufsky et al,</strong></td>
<td>44% (ER-)</td>
</tr>
<tr>
<td><em>Clin Cancer Res</em> 2011</td>
<td>31% (ER+)</td>
</tr>
</tbody>
</table>

Courtesy N. Lin
Brain imaging should **NOT** be routinely performed in asymptomatic patients. This approach is applicable to all patients with MBC including those patients with HER-2+ and/or TNBC MBC (LoE: Expert opinion) (94%)

**BUT**

- Careful evaluation of signs and symptoms is needed since clinical manifestations of brain metastases may sometimes be quite **subtle**, particularly among patients with HER-2+ or TN MBC.

- In the setting of suggestive signs or symptoms, a lower threshold to **image** such patients should be considered given the higher pre-test probability for CNS involvement.
Patients with a single or a small number of potentially resectable brain metastasis should be treated with surgery or radiosurgery. Radiosurgery is also an option for some unresectable brain metastases. (LoE: 1 B) (92%)

If surgery/radiosurgery is performed it may be followed by whole brain radiotherapy but this should be discussed in detail with the patient, balancing the longer duration of intracranial disease control and the risk of neurocognitive effects (LoE: 1 B) (72%)

- A multi-disciplinary discussion including neurosurgeons, radiation oncologists and medical oncologists is indispensable in determining the optimal treatment for each patient.
- The treatment plan can also be a combination of these three available therapeutic approaches
Because patients with HER2+ve MBC and brain metastases can live for several years, consideration of long term toxicity is important and less toxic local therapy options (e.g. stereotactic RT) should be preferred to whole brain RT, when available and appropriate (e.g. in the setting of a limited number of brain metastases).

(LoE: 1C) (89%)
Trastuzumab Improves Survival in Patients With mCNS Disease: U S Retrospective Analysis

LANDSCAPE STUDY: a FNCLCC phase II study with lapatinib and capecitabine in pts with brain metastases from HER-2+ MBC before whole brain RT

**Primary endpoint: CNS volumetric response**

45 pts

CNS-OR: 29/43 = 67.4% (95% CI: 52-81)

<table>
<thead>
<tr>
<th>CNS volumetric change</th>
<th>N = 43 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80% reduction</td>
<td>9 (20.9)</td>
</tr>
<tr>
<td>50-%&lt;80% reduction</td>
<td>20 (46.5)</td>
</tr>
<tr>
<td>20-%&lt;50% reduction</td>
<td>6 (14)</td>
</tr>
<tr>
<td>&gt; 0-%&lt;20% reduction</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>Progression*</td>
<td>6 (14)</td>
</tr>
</tbody>
</table>

* 2 patients had extra-CNS disease progression

NSS improvement: 14/24 = 58.3% (95% CI: 36.6-77.9)

**IMP: pts previously untreated with WBRT**

Bachelot et al, ASCO 2011
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
+ capecitabine 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>

**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>

**Subjects at risk**

<table>
<thead>
<tr>
<th></th>
<th>Lap + Cap</th>
<th>Tras + Cap</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 3 months</td>
<td>271</td>
<td>269</td>
</tr>
<tr>
<td>4 – 6 months</td>
<td>194</td>
<td>207</td>
</tr>
<tr>
<td>7 – 12 months</td>
<td>129</td>
<td>140</td>
</tr>
<tr>
<td>13 – 24 months</td>
<td>79</td>
<td>97</td>
</tr>
<tr>
<td>25 – 35 months</td>
<td>48</td>
<td>61</td>
</tr>
<tr>
<td>36 – 48 months</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>49 – 60 months</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>61 – 72 months</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**LOW NUMBER OF BRAIN METS

TRASTUZUMAB + CAPECITABINE BETTER

**OS (ITT population)**
In patients with HER2 positive ABC who develop brain metastases with stable extracranial disease, systemic therapy should not be changed. (LoE: 1 C) (95%)

For patients with HER2 positive cancers where brain metastases are the only site of recurrence, the addition of CT to local therapy is not known to alter the course of the disease. It is recommended to re-start the anti-HER2 therapy (trastuzumab) if this had been stopped. (LoE: 1 C) (83%)
Phase II trial of Neratinib and Capecitabine for Patients with Human Epidermal Growth Factor Receptor 2-Positive (HER2+) Breast Cancer Brain Metastases

Translational Breast Cancer Research Consortium (TBCRC) 022
NCT01494662  Abstract #1005

Rachel A. Freedman¹, Rebecca S. Gelman¹, Michelle E. Melisko², Carey K. Anders³, Beverly Moy⁴, Kimberly L. Blackwell⁵, Roisin M. Connolly⁶, Polly A. Niravath⁷, Catherine H. Van Poznak⁸, Shannon L. Puhalla⁹, Sarah Farooq¹, Anne M. Cropp¹, Christine M. Cotter¹, Minetta Liu¹⁰, Ian E. Krop¹, Julie Nangia¹¹, Nadine Tung¹², Antonio C. Wolff⁶, Eric P. Winer¹, Nancy U. Lin¹

¹Dana-Farber Cancer Institute, ²University of California at San Francisco, ³University of North Carolina, ⁴Massachusetts General Hospital, ⁵Duke University, ⁶Johns Hopkins University, ⁷Houston Methodist Hospital ⁸University of Michigan, ⁹University of Pittsburgh, ¹⁰Mayo Clinic, ¹¹Baylor College of Medicine, ¹²Beth Israel Deaconess Medical Center

Presented by: Rachel A Freedman, MD, MPH
TBCRC 022 Study Cohorts

**All cohorts now closed to enrollment**

**HER2+ Breast Cancer and Brain Mets**

- **Progressive brain mets**
- **Craniotomy Candidates**
- **Progressive brain mets**
  - No prior lapatinib (3A)
  - Prior lapatinib (3B)

**Cohort 1 (n=40)**
- Neratinib (240 mg/day)

**Cohort 2 (n=5)**
- Neratinib (240 mg/day) until surgical resection, then Neratinib (240 mg/day)

**Cohort 3A (n=37)**
- Neratinib (240 mg/day) and Capecitabine (750 mg/m² D1-14 of 3 week cycle)

**Cohort 3B (n=11)**
- Neratinib (240 mg/day) and Capecitabine (750 mg/m² D1-14 of 3 week cycle)
TBCRC 022 Cohort 1: Neratinib Monotherapy

*CNS volumetric responses observed but did not meet pre-specified threshold to prompt further investigation as monotherapy*

Freedman et al. J Clin Oncol 2016; Table/Figure re-used with permission. © (2017) ASCO. All rights reserved.
Study Conclusions

Neratinib plus capecitabine is an active treatment combination for HER2+ disease metastatic to the CNS in pre-treated patients

- 49% CNS ORR by composite criteria
- 24% CNS ORR by RANO-BM criteria
- Median time to CNS progression = 5.5 months
- Prolonged disease control was seen in many:
  - 51% initiated 6+ cycles of therapy, 19% initiated 10+ cycles
- Although our observed median OS of 13.5 months is similar to that reported in past studies\(^1,2\), 49% study patients remain alive as of April 1, 2017