Systemic therapy for HER2+ ABC

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Chair, ABC Global Alliance and ABC Guidelines
ESMO Guidelines and Public Policy Steering Committees
ESO Scientific Committee
DISCLOSURES SLIDE

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Treatment of ER-negative / HER2-positive ABC

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

CLINICAL PRACTICE GUIDELINES

Previously untreated with anti-HER2 therapy

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

Previously treated (neo)adjuvantly with anti-HER2 therapy

ChT + pertuzumab + trastuzumab
or ChT + trastuzumab

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

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

No progression

ET + anti-HER2 as maintenance therapy

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

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

ET + anti-HER2 as maintenance therapy

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

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

Trastuzumab + lapatinib + ET, if not previously used

Maintenance ET + anti-HER2 therapy

Additional anti-HER2 therapy and ChT or ET

Note: Include in clinical trials when available

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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:

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  • Important problem of brain metastases
    • Resistance - biomarkers
      • Accessibility
META-ANALYSIS OF HER-2 STATUS DISCORDANCE BETWEEN PRIMARY VS. METS

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

• ABC: primary or metastatic HER-2 status?

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  • Important problem of brain metastases
    • Resistance - biomarkers
  • Accessibility
HER-2 POSITIVE MBC

Anti-HER-2 therapy should be offered **early** to all HER-2+ MetaBC patients, except in the presence of contra-indications for use of such therapy (LoE/GoR: I/A) (98%).

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

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

H0648g trial

- Longer OS: 25.1 vs. 20.3 ms (p=0.046)
- Longer TTP: 7.4 vs. 4.6 ms (p<0.001)
- Higher RR: 50 vs. 32% (p<0.001)
- Longer duration: 9.1 vs. 6.1 ms (p<0.001)

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MCBS: 5
Importance of starting anti-HER-2 agent early on

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

Overall survival: M77001 trial

Overall result  vs  Crossover analysis

Median values are shown

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/GoR: Expert Opinion/C) (93%).
MANAGEMENT OF HER-2 + MBC:

• ABC: primary or metastatic HER-2 status?

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

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

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

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

  • Important problem of brain metastases

  • Resistance - biomarkers

  • Accessibility
2 clinical trials in HER-2+/ER+ BC showing the efficacy of blocking growth factor pathway to overcome endocrine resistance

<table>
<thead>
<tr>
<th>Trial Name/ Author</th>
<th>Clinical Setting</th>
<th>Trial Phase and No. of Patients</th>
<th>Study Design</th>
<th>Clinical Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnston(^1)</td>
<td>HER2+ ABC</td>
<td>III (n = 219)</td>
<td>Arm 1: LET Arm 2: LET + lapatinib</td>
<td>PFS: 3.0 vs 8.2 mo (P = .019)</td>
</tr>
<tr>
<td>TAnDEM 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></th>
<th>Pertuzumab + trastuzumab + AI (n = 129)</th>
<th>Trastuzumab + AI (n = 129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>74 (57.4)</td>
<td>92 (71.3)</td>
</tr>
<tr>
<td>Median, months</td>
<td>18.80</td>
<td>15.80</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(14.09, 27.66)</td>
<td>(11.04, 16.50)</td>
</tr>
<tr>
<td>Δ months</td>
<td>3.09</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.65 (0.44, 0.98)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0070</td>
<td></td>
</tr>
</tbody>
</table>

**ORR**: 63 vs 56%, NS

**PFS**: 3 ms benefit

**OS immature**
**ALTERNATIVE: Secondary Endpoint**

PFS in All Treatment Arms

**Presented by:** William J. Gradishar

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### Kaplan-Meier Curves

#### Proportion Alive and Progression Free vs. Time Since Randomization (Months)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events, n (%)</th>
<th>Median PFS, months</th>
<th>95% CI</th>
<th>HR; 95% CI vs TRAS+AI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAP+TRAS+AI</td>
<td>62 (52)</td>
<td>11</td>
<td>[8.3, 13.8]</td>
<td>0.76 [0.54, 1.06]</td>
<td>0.1041</td>
</tr>
<tr>
<td>TRAS+AI</td>
<td>75 (64)</td>
<td>5.7</td>
<td>[5.5, 8.4]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAP+AI</td>
<td>74 (63)</td>
<td>8.3</td>
<td>[5.8, 11.2]</td>
<td></td>
<td></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 3 2 2 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

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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%)

* 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.
monarcHER STUDY DESIGN (for “triple positive” ABC)

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

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

Randomization
N = 237
1:1:1

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

Arm A
abemaciclib 150 mg PO BID +
trastuzumab IV q21d +
fulvestranta IM q28d

Arm B
abemaciclib 150 mg PO BID +
trastuzumab IV q21d

Arm C
trastuzumab IV q21d +
investigator’s choice chemotherapyb

Continue until PD

Primary Endpoint
- PFSc (A vs. C, then B vs. C)

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

Abbreviations: ABC = advanced breast cancer, HR+ = hormone receptor-positive, HER2(+) = human epidermal growth factor receptor-2 (positive), n = number of patients, PD = progressive disease, BID= twice daily, q21d= every 21 days, PFS = Progression Free Survival, ORR = Objective Response Rate, OS = Overall Survival, PRO = Patient Reported Outcomes, PK = pharmacokinetics
aDosing per fulvestrant label
bStandard-of-care single-agent chemotherapy should include approved drug in breast cancer.
cInvestigator assessed
PRIMARY ENDPOINT: PFS

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

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

OVERALL SURVIVAL: EXPLORATORY ANALYSIS*

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

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

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

- ABC: primary or metastatic HER-2 status?

- Starting early and continuing HER-2 blockade beyond progression (change of paradigm)
  
  - Combinations with CT and ET: when & which agents?

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

- Overall good safety profile of anti-HER-2 therapies but cardiac surveillance & management guidelines needed
  
  - Important problem of brain metastases
    
    - Resistance - biomarkers
    
    - Accessibility
Both combination and sequential single agent CT are reasonable options. Based on the available data, we recommend **sequential monotherapy** as the preferred choice for MBC. Combination CT should be reserved for patients with rapid clinical progression, visceral crisis, or need for rapid symptom and/or disease control.

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

TRAVIDOTA:
Taxane + Trastuzumab vs. Vinorelbine + Trastuzumab

Paclitaxel or Docetaxel + Trastuzumab

Vinorelbine + Trastuzumab

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

RR
Taxane Arm 58%
Vinorelbine Arm 66%

TTP
6.0 months
8.5 months

p=0.09
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>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>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>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><strong>Epirubicin-cyclophosphamide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andersson et al. 2010a,b</td>
<td>T</td>
<td>III</td>
<td>30</td>
<td>141</td>
<td>59.3</td>
<td>15.3</td>
</tr>
<tr>
<td>Saip et al. 2011</td>
<td>L</td>
<td>II</td>
<td>20</td>
<td>29</td>
<td>NR</td>
<td>5c</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><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>
</tbody>
</table>
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/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%)
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  • 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 **standard** 1\(^{st}\) 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.
CLEOPATRA: Median PFS and OS

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

\[ \text{HR} = 0.62 \quad \text{p} < 0.0001 \]
\[ \text{HR} = 0.68 \quad \text{p} = 0.0002 \]

Ptz+T+D: 18.5 mo. \quad \Delta = 6.1 \text{ mo.}
Pla+T+D: 12.4 mo.

Ptz+T+D: 56.5 mo. \quad \Delta = 15.7 \text{ mo.}
Pla+T+D: 40.8 mo.

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

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

- **Number at risk**
  - P + H + D: 402, 371, 318, 269, 228, 188, 155, 120, 71, 20, 0, 0
  - Pla + H + D: 406, 350, 289, 230, 181, 149, 115, 96, 88, 75, 44, 11, 1, 0

  **Median OS**:
  - (Pla) v 57.1 mo (P)

  **Landmark OS**:
  - 37% (Pla) v 23% (P)
  - Events: 235 (58.5%) v 280 (69.0%)

  **HR 0.69 (95% CI = 0.58, 0.82)**

  **Median FU about 8 years**

**FINAL OS RESULTS**

**HR 0.69 (95% CI = 0.58, 0.82)**

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

---

**FINAL PFS RESULTS**

**HR 0.69 (95% CI = 0.59, 0.81)**

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

---

**CLEOPATRA: End-of-study investigator-assessed PFS (ITT population)**

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

- **Number at risk**
  - P + H + D: 402, 284, 179, 121, 93, 71, 60, 52, 43, 34, 21, 6, 0, 0
  - Pla + H + D: 406, 223, 110, 76, 53, 43, 35, 30, 23, 21, 10, 4, 0, 0

  **Median investigator-assessed PFS**:
  - 12.4 mo (Pla) v 18.7 mo (P)

  **Events**:
  - 304 (75.6%) v 329 (81.0%)
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>Febrile neutropenia</td>
<td>30 (7.6)</td>
<td>56 (13.7)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>23 (5.8)</td>
<td>44 (10.8)</td>
</tr>
</tbody>
</table>

Highlighted are adverse events with ≥5% higher incidence

No increase in cardiac toxicity!
1st Line Phase III MARIANNE Study

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

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

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

- Patients stratified by: World region, Neo/Adjuvant therapy (Y/N), Trastuzumab and/or lapatinib based therapy (Y/N), Visceral disease (Y/N)
- n=1092
- Treatment groups:
  - Trastuzumab + taxane
  - T-DM1 + pertuzumab
  - T-DM1 + placebo
Final Analysis of Overall Survival

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

<table>
<thead>
<tr>
<th>Survival (%)</th>
<th>Day 1</th>
<th>12 Months</th>
<th>24 Months</th>
<th>36 Months</th>
<th>48 Months</th>
<th>60 Months</th>
<th>72 Months</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>HT</th>
<th>T-DM1</th>
<th>T-DM1+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT</td>
<td>365</td>
<td>303</td>
<td>251</td>
</tr>
<tr>
<td>T-DM1</td>
<td>367</td>
<td>322</td>
<td>264</td>
</tr>
<tr>
<td>T-DM1+P</td>
<td>363</td>
<td>309</td>
<td>257</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stratified HR (97.5% CI) vs HT</th>
<th>HT n=365</th>
<th>T-DM1 n=367</th>
<th>T-DM1+P n=363</th>
</tr>
</thead>
<tbody>
<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 T-DM1</td>
<td>—</td>
<td>0.93 (0.73–1.20)</td>
<td>0.86 (0.67–1.11)</td>
</tr>
</tbody>
</table>

Courtesy of Carlos Barrios
PHEREXA study design
NCT01026142

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

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

N = 452

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

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

ITT population

<table>
<thead>
<tr>
<th>Arm A: H + X (n = 224)</th>
<th>Arm B: H + X + P (n = 228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>158 (71)</td>
</tr>
<tr>
<td></td>
<td>168 (74)</td>
</tr>
<tr>
<td>mPFS (months)</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>11.1</td>
</tr>
<tr>
<td>Δ (months)</td>
<td>2.1</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>0.82 (0.65–1.02)</td>
</tr>
<tr>
<td>Log-rank p-value*</td>
<td>0.07</td>
</tr>
<tr>
<td>mFU (months)</td>
<td>28.6</td>
</tr>
<tr>
<td></td>
<td>25.3</td>
</tr>
</tbody>
</table>

Secondary analysis: OS

ITT population

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td></td>
<td>98 (43)</td>
</tr>
<tr>
<td>mOS (months)</td>
<td>28.1</td>
</tr>
<tr>
<td></td>
<td>36.1</td>
</tr>
<tr>
<td>Δ (months)</td>
<td>8.0</td>
</tr>
<tr>
<td>HR (95% CI)*</td>
<td>0.68 (0.51–0.90)</td>
</tr>
<tr>
<td>mFU (months)</td>
<td>29.5</td>
</tr>
<tr>
<td></td>
<td>29.3</td>
</tr>
</tbody>
</table>

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

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

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

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

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

There are currently no data supporting the use of dual blockade with trastuzumab + pertuzumab and CT beyond progression (i.e. continuing dual blockade beyond progression) and therefore dual-blockade 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 the 1st line setting, for HER2+ ABC previously treated (in the adjuvant setting with DFI >12 ms) or untreated with trastuzumab, combinations of CT + trastuzumab are superior to combinations of CT + lapatinib in terms of PFS and OS.

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

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

Gelmon, K. ASCO 2012

MA.31/ EGF108919
COMPLETE TRIAL

Overall Survival
Centrally-confirmed HER2 + Analysis

HR = 1.25 (95% CI = 0.81 – 1.93), P = 0.32
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/m^2/d
PO days 1-14 q3 weeks

Capecitabine 2500 mg/m^2 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>

### Survival Analysis

#### 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>

- **Median OS**: Lapatinib + capecitabine (22.7 months) vs. Trastuzumab + capecitabine (27.3 months)
- **Hazard Ratio**: 1.34 (95% CI: 0.95, 1.90)
- **Stratified log-rank p-value**: 0.095

**Low Number of Brain Mets**: 25% of patients had low number of brain metastases (M0) at baseline.

**TRASTUZUMAB + CAPECITABINE BETTER**

---

*Note: Additional details such as subjects at risk and survival rates are provided in the graph.*
QUESTION: The optimal timing to use lapatinib?

CEREBEL trial

ALTTO Trial

MA 31 COMPLETE Trial

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

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

<table>
<thead>
<tr>
<th></th>
<th>L</th>
<th>L+T</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>

Survival, %

Patients at risk:

<table>
<thead>
<tr>
<th>Time from Randomization, months</th>
<th>L</th>
<th>L+T</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>148</td>
<td>148</td>
</tr>
<tr>
<td>6 Month OS</td>
<td>121</td>
<td>102</td>
</tr>
<tr>
<td>12 Month OS</td>
<td>88</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

HER-2 POSITIVE MBC: 2nd line and beyond

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%)

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

<table>
<thead>
<tr>
<th></th>
<th>Median (months)</th>
<th>No. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap + Lap</td>
<td>6.4</td>
<td>304</td>
</tr>
<tr>
<td>T-DM1</td>
<td>9.6</td>
<td>265</td>
</tr>
</tbody>
</table>

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

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

5 to 6 MONTHS BENEFIT IN OS
Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months.

Unstratified HR = 0.521 (P < 0.0001).

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Median (months)</th>
<th>No. of events</th>
<th>Stratified HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPC (n=198)</td>
<td>198 120 62</td>
<td>129</td>
<td>0.528 (0.422, 0.661)</td>
</tr>
<tr>
<td>T-DM1</td>
<td>404 334 241</td>
<td>219</td>
<td></td>
</tr>
</tbody>
</table>

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

Final OS Analysis

Median (months) 15.8 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)

3 ms OS BENEFIT
TOXICITIES OF T-DM1

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

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

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

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

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

• ABC: primary or metastatic HER-2 status?

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

• Overall good safety profile of anti-HER-2 therapies but cardiac surveillance & management guidelines needed
  • Important problem of brain metastases
  • Resistance - biomarkers
  • Accessibility
• Trastuzumab suppresses HER2 activity
• Flags cells for destruction by the immune system

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

DUAL BLOCKADE: TRANSTUZUMAB + PERTUZUMAB

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

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

T-DM1 binds to the HER2 protein

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

5 MONTHS BENEFIT IN OS
COST: ~ 4.000 €/cycle
New recommendations on NERATINIB, MARGETUXIMAB, TUCATINIB, TRASTUZUMAB DERUXTECAN

See talk at ESMO Africa Summit
**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
Treatment of HER2+ ABC: Progress over time

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

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

**Third / Later line**
- Physicians choice
- T-DM1

Overall survival, months

- 20.3 mos. (2001)
- 25.1 mos. (2001)
- 40.8 mos. (2015)
- 56.5 mos. (2015)
- 16.2 mos. (2010)
- 18.8 mos. (2010)
- 25.1 mos. (2012)
- 30.9 mos. (2012)
- 22.7 mos. (2015)

1 Slamon et al. NEJM 2001; 2 Swain et al. NEJM 2015; 3 Geyer et al. NEJM 2011; 4 Verma et al. NEJM 2012
5 Geyer et al. SABCS 2015. mod. from Loibl SABCS 2015
Advanced Breast Cancer

Sixth International Consensus Conference

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Lisbon, Portugal

Coordinating Chair:
F. Cardoso, PT

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