ESMO Clinical Practice Guidelines
Metastatic HER2 + Breast Cancer

Evidence to Support Clinical Case Presentation
*Updated with data from San Antonio Breast Cancer Symposium, 2015*

December 20\textsuperscript{th}, 2015
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Disclosures

Consulting or advisory role: AstraZeneca, Celgene, Novartis, Pfizer, Roche

Travel grants: Eisai, Roche, Merck
Case Summary:

- T2N2 ER - PR -, HER2 + BC
  - Treated with Anthracycline/Taxane- Herceptin x 1 year
  - Adjuvant Radiation

- Current situation
  - 1 year after completing adjuvant Herceptin - Isolated Ipsilateral supraclavicular LN recurrence

- No major comorbidities and organ dysfunctions
Should we biopsy her left supraclavicular LN? **YES!**

Proportion of negative conversion for HER2

Aurilio et al. EJC 2014; 50: 277–289
...but would this alter our treatment choice?

Table 2 Change in management based on biopsy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Therapy changed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindstrom et al. [7]</td>
<td>1,010</td>
<td>23 (HER2) 50 (ER)</td>
</tr>
<tr>
<td>Curigliano et al. [9]</td>
<td>255</td>
<td>12.1</td>
</tr>
<tr>
<td>Amir et al. [2]</td>
<td>289</td>
<td>14.2</td>
</tr>
<tr>
<td>Bogina et al. [11]</td>
<td>140</td>
<td>7.3</td>
</tr>
<tr>
<td>Amir et al. [4]</td>
<td>121</td>
<td>14</td>
</tr>
<tr>
<td>Simmons et al. [15]</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Thompson et al. [5]</td>
<td>137</td>
<td>17.5</td>
</tr>
</tbody>
</table>

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.
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: II C)

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

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)
In real practice...

• Threshold to biopsy should be lower when:
  • the radiological work-up has identified one *single lesion*,
  • when the patient has a *history of more than one cancer*,
  • when the *suspicion of an alternative diagnosis* is high
    • *Clinical course is not in keeping with natural history of disease* (ie ER + breast cancer with extensive visceral relapse within 6 months of adjuvant therapy)
What is the optimal 1st line therapy HER2 directed therapy?

PFS, progression-free survival
OS, overall survival

Gelmon et al. JCO 2015; 33:1574-83; Pivot et al. JCO 2015; 33:1564-73
Pivotal 1\textsuperscript{st} line Phase 3 Trials
Trastuzumab

<table>
<thead>
<tr>
<th>Study</th>
<th>Median Survival, Mos</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chemotherapy Alone</td>
<td>Chemotherapy + Trastuzumab</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel (Slamon)[1]</td>
<td>20.3</td>
<td>25.1</td>
<td>0.80 (0.64-1.00)</td>
</tr>
<tr>
<td>Docetaxel (Marty)[2]</td>
<td>22.7</td>
<td>31.2</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

A randomized, multicenter, phase III trial conducted at institutions in Denmark, Sweden, and Norway

Endpoints
- Primary: TTP
- Secondary: OS, 1-year survival rate of response, time to treatment failure (TTF), toxicity and tolerability

*Treatment duration to PD or unacceptable toxicity

**Vinorelbine dose per institutional preference

LABC, locally advanced breast cancer; MBC, metastatic breast cancer; OS, overall survival; PD, progressive disease; TTF, time to failure; TTP, time to progression
Doce + Trastuzumab (D+T) vs Vino + Trastuzumab (V+T)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>D+T (n = 143)</th>
<th>V+T (n = 141)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TTP, months</td>
<td>12.4</td>
<td>15.3</td>
<td>.67</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>35.7</td>
<td>38.8</td>
<td>.98</td>
</tr>
<tr>
<td>Median TTF, months</td>
<td>5.6</td>
<td>7.7</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicity Grade 3/4</th>
<th>D+T (n = 139)</th>
<th>V+T (n = 138)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>37.4</td>
<td>10.8</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>40.3</td>
<td>21.0</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Infection</td>
<td>23.7</td>
<td>13.0</td>
<td>.006</td>
</tr>
<tr>
<td>Fever</td>
<td>4.3</td>
<td>0</td>
<td>.03</td>
</tr>
<tr>
<td>Neuropathy (sensory)</td>
<td>30.9</td>
<td>3.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Edema</td>
<td>5.8</td>
<td>0</td>
<td>.003</td>
</tr>
<tr>
<td>Nail changes</td>
<td>7.9</td>
<td>0.7</td>
<td>.005</td>
</tr>
</tbody>
</table>

* Only statistically significant toxicity included in the table

In the 1st line setting, for HER-2+ MBC previously treated (in the adjuvant setting) or untreated with trastuzumab, combinations of ChT + trastuzumab are superior to combinations of ChT + lapatinib in terms of PFS and OS (LoE: I A)
**1\textsuperscript{st} line Taxane + Lapatinib vs. Taxane + Trastuzumab (NCIC CTG MA.31)**

**Progression-free survival**

- **Lapatinib + Taxane**
  - ORR: 54%
  - PFS: 9.0 months
- **Trastuzumab + Taxane**
  - ORR: 55%
  - PFS: 11.3 months

**Overall survival**

- **Lapatinib + Taxane**
  - OS: NR
- **Trastuzumab + Taxane**
  - OS: NR

- Hazard ratio: 1.37, P-value: 0.001

**Notes:**

- At the interim analysis, Lapatinib arm had inferior PFS – NCIC DSMC recommended disclosure and notification of patients. Final analysis with 395 PFS events presented here.

- **Gelmon et al. JCO 2015;1574-1583**
In 1st line therapy, the combination of CT + trastuzumab and pertuzumab is superior to CT + trastuzumab, primarily for previously untreated HER-2+ MBC, making it the preferred treatment option since it is associated with OS benefit. (LoE: 1 A) (90%)

It is currently unknown how this treatment compares to other anti-HER-2 options such as T-DM1 (Trastuzumab Emtansine).
**1st-line Pertuzumab + Trastuzumab**

**Progression-free survival**

- Pertuzumab+trastuzumab+docetaxel
- Placebo+trastuzumab+docetaxel

**Overall survival**

- Pertuzumab+trastuzumab+docetaxel
- Placebo+trastuzumab+docetaxel

<table>
<thead>
<tr>
<th></th>
<th>Pertuzumab+trastuzumab+docetaxel</th>
<th>Placebo+trastuzumab+docetaxel</th>
<th>Hazard ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>80.2%</td>
<td>69.3%</td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>PFS</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>18.7 months</td>
<td>12.4 months</td>
<td>0.69</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>OS</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>56.5 months</td>
<td>40.8 months</td>
<td>0.66</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Most common adverse events ≥Grade 3 in the pertuzumab+trastuzumab+docetaxel group:<sup>1</sup>
- Neutropenia (48.9%), febrile neutropenia (13.8%), leukopenia (12.3%) and diarrhoea (7.9%)
Docetaxel dose reductions below 75 mg/m² occurred in 47% of patients from Asia compared with 13% of patients from other regions.

But did not adversely affect efficacy in patients from Asia, with PFS and overall survival being comparable with that of patients from other regions.

A reduction in the docetaxel starting dose should therefore be considered in patients from Asia...
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
Safety of pertuzumab plus trastuzumab plus vinorelbine

Edith A. Perez et al. 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></th>
<th>VELVET</th>
<th>CLEOPATRA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>HERNATA&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) number of chemotherapy cycles</td>
<td>9 (0-21)</td>
<td>8 (1-35)</td>
<td>10.5 (2-42)</td>
</tr>
<tr>
<td>Median chemotherapy dose intensity, mg/m²/week</td>
<td>14.98&lt;sup&gt;c&lt;/sup&gt;</td>
<td>24.6</td>
<td>NR</td>
</tr>
<tr>
<td>Incidence of selected AEs, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>40.1</td>
<td>66.8</td>
<td>11.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alopecia</td>
<td>23.6</td>
<td>60.9</td>
<td>NR</td>
</tr>
<tr>
<td>Grade ≥3 neutropenia</td>
<td>23.6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>48.9</td>
<td>41.5</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5.7</td>
<td>13.8</td>
<td>10.8</td>
</tr>
<tr>
<td>Grade ≥3 leukopenia</td>
<td>8.5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>12.3</td>
<td>21</td>
</tr>
</tbody>
</table>

AC, adverse event; NR, not reported.

* Pertuzumab, trastuzumab, and docetaxel arm; ** Trastuzumab and vinorelbine arm; <sup>a</sup>Past six cycles only; <sup>b</sup>Grade ≥4 only, grade 1 activities NR; <sup>c</sup>Pooled neutropenia and febrile neutropenia count decreased preferred terms.
<sup>d</sup>Pooled leukopenia and white blood cell count decreased preferred terms.

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<sup>f</sup> or with pertuzumab plus trastuzumab plus docetaxel.<sup>g</sup>
- 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.
**MARIANNE:** Phase III study of T-DM1 with or without Pertuzumab vs Taxane and Trastuzumab (no Pertuzumab)

**HER2-positive progressive or recurrent locally advanced BC or previously untreated MBC (n=1092)**

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab + Taxane</th>
<th>T-DM1 + Placebo</th>
<th>T-DM1 + Pertuzumab</th>
<th>Hazard ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>67.9%</td>
<td>59.7%</td>
<td>64.2%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td>13.7 m</td>
<td>14.1 m</td>
<td>15.2 m</td>
<td>HR 0.91</td>
<td>p=0.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 0.87</td>
<td>p=0.14</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>HR 0.86</td>
<td>p NR</td>
</tr>
</tbody>
</table>

*Ellis et al. ASCO 2015, Breast Cancer Oral Session Monday June 1°, 2015*
## 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 (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*
## Prior Trastuzumab Efficacy Data

**Adjuvant Trastuzumab DFI > 1 year**

<table>
<thead>
<tr>
<th></th>
<th>MARIANNE (ASCO 2015)</th>
<th>CLEOPATRA (NEJM 2015)(^1)</th>
<th>BOLERO1 (SABCS 2014)</th>
<th>MA-31 (ASCO 2012)</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>

1 Swain et al NEJM Correspondence 2015
Patients whose tumours progress on an anti-HER-2 therapy combined with a cytotoxic or endocrine agent should be offered additional anti-HER-2 therapy with subsequent treatment since it is beneficial to continue suppression of the HER-2 pathway (LoE: I B)

EGF100151

GBG-26

PFS

PFS

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, since it provides an OS benefit (LoE: I A)

**Figure 3. Final overall survival in the intent-to-treat population**

Cap+Lap  | T-DM1  
---|---
25.9  | 29.9  
Median Time (months)
Hazard Ratio  | 0.75 (95% CI: 0.64-0.88)
Log-rank P-value  | 0.0003

EMILIA OS Update

SABCS 2015 V. Dieras

**TH3RESA Study Schema – 3rd line or greater**

- **Stratification factors:** World region, number of prior regimens for advanced BC,\(^d\) presence of visceral disease

- **Co-primary endpoints:** PFS by investigator and OS

- **Key secondary endpoints:** ORR by investigator and safety

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\(^a\)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**

<table>
<thead>
<tr>
<th></th>
<th>TPC (n=198)</th>
<th>T-DM1 (n=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months)</td>
<td>3.3</td>
<td>6.2</td>
</tr>
<tr>
<td>No. of events</td>
<td>129</td>
<td>219</td>
</tr>
</tbody>
</table>

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

**First Interim OS Analysis**

44 patients in the TPC arm received crossover T-DM1 treatment after documented progression.

Unstratified HR=0.57 (P=0.004).

Stratified HR=0.552 (95% CI, 0.369, 0.826); P=0.0034

**Efficacy stopping boundary**

HR<0.363 or P<0.0000013

**SUPERIOR PFS**

**Final OS Analysis**

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

**SABCS 2015**
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><strong>Single-agent chemotherapy</strong>*</td>
<td>16.8</td>
</tr>
</tbody>
</table>

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

Remember the Goals of Treatment!

• Balancing treatment efficacy and toxicity is the main objective

• Goals of treatment:
  • Improve survival (*very few agents achieve it!*)
  • Delay disease progression
  • Prolong duration of response
  • Palliate symptoms
  • Improve or maintain quality of life
  • Transform into a chronic disease

Courtesy Fatima Cardoso
HER2-targeted therapies are recommended across international treatment guidelines (ASCO, ESMO, NCCN, AGO)\(^1^–^4\)*

**First line**
- Pertuzumab + trastuzumab + docetaxel\(^2^–^4\)
- Pertuzumab + trastuzumab + paclitaxel\(^2,3\)#
- Anti-HER2 therapy (trastuzumab or lapatinib) + chemotherapy\(^1^–^3\)
- T-DM1 (relapse within 6 months after taxane and trastuzumab pre-treatment)\(^3\)
- Trastuzumab monotherapy\(^1^–^3\)
- AI + trastuzumab or lapatinib (ER-positive BC)\(^1^–^3\)

**Second line**
- T-DM1\(^2^–^4\)
- Lapatinib + capecitabine\(^1^–^3\)
- Trastuzumab + capecitabine\(^2\)#
- Trastuzumab ± chemotherapy\(^1^–^3\)#
- Trastuzumab + lapatinib\(^1^–^3\)#
- Pertuzumab + trastuzumab plus either taxane or any other second-line chemotherapy\(^3\)#
- AI + anti-HER2 therapy (ER-positive BC)\(^3\)

**Third line**
- T-DM1\(^3,4\)
- Lapatinib + capecitabine\(^1,3\)
- Trastuzumab + lapatinib\(^1,3\)#
- Trastuzumab + chemotherapy (treatment beyond progression)\(^1,3\)#
- Trastuzumab + pertuzumab\(^3\)#

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AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; AI, aromatase inhibitor; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; TGA, Therapeutic Goods Administration.

* Please refer to product-specific labels in your country for indications approved in your market. International guidelines may not be in line with current national guidelines.
# Denotes recommendations that are outside of the TGA-approved indication in Australia
Acknowledgements

- Fatima Cardoso
- Elżbieta Senkus
- Sunil Verma
- ESMO
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: IC)

**NCCTG N0574**