HER2 positive breast cancer

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SVH/TKCC
18 March 2016
Matching breast cancer types to treatment

- **Triple negative “Basal” Stem cell**
  - Chemotherapy
  - PARP inhibitors

- **Her 2 pos ER pos or neg**
  - Chemotherapy
  - *Trastuzumab/Lapatinib/Pertuzumab/T-DM1*
  - *AI or tamoxifen if ER+*

- **ER pos Luminal B**
  - Chemotherapy
  - *AI or combined hormonal therapy*

- **ER pos Luminal A**
  - *AI or Tamoxifen (longer)*
Biology of the HER2 receptor

- HER2 is a member of the EGFR family which includes HER1 (EGFR-1), HER2, HER3, HER4
- HER2 gene activation (chromosome 17q21) causes synthesis of transmembrane glycoprotein
  - intracellular domain has tyrosine kinase activity
- Heterodimerization of the different EGFR transmembrane glycoproteins with HER2 causes activation of tyrosine pathways with subsequent phosphorylation of cell signalling proteins that cause tumour cell proliferation
**HER2 Signaling Pathways**

EGFR = epidermal growth factor; HER(2-4) = human epidermal growth factor (2-4); PTEN = phosphatase and tensin homolog; VEGF = vascular endothelial growth factor

Image courtesy of Karen Gelmon, MD
Characteristics of HER2 positive BC

- Higher tumour grade
- Lack of ER
- Higher levels of tumour proliferation eg high Ki-67
- Poorer prognosis

- Up to 30% risk of recurrence for HER2 pos T1N0M0
- T1ab (<=1cm) node negative tumours have recurrence rates up to 12%

Burnstein JCO 2009;27:5671-73
Fehrenbacher JCO 2014
The HER2 gene is on chromosome 17
HER2 gene amplification is responsible for protein overexpression
HER2 overexpression detected by immunohistochemistry
HER2 gene assessment by Fluorescence in situ hybridization (FISH)

Key Features:
- Probes
  - Direct labeled
  - HER2 sequence
  - Chromosome 17 centromere
- Interpretation
  - Signal enumeration
  - Ratio of HER2:Chr 17 signals
FISH ratio = \( \frac{\text{HER2 gene copies}}{\text{chromosome 17 centromere copies}} \)
Algorithm for testing for HER2 gene amplification by ISH using a dual-signal HER2 gene assay (dual-probe ISH)

1. HER2 testing (invasive component) by validated dual-probe ISH assay
2. Batch controls and on-slide controls show appropriate hybridization

   - HER2/CEP17 ratio ≥ 2.0*
     - Average HER2 copy number ≥ 4.0 signals/cell*
       - ISH positive
     - Average HER2 copy number < 4.0 signals/cell*
       - ISH positive
   - HER2/CEP17 ratio < 2.0
     - Average HER2 copy number ≥ 4.0 and < 6.0 signals/cell*
       - ISH positive
     - Average HER2 copy number < 4.0 signals/cell
       - ISH negative

*Must order a reflex test (same specimen using IHC), test with alternative ISH chromosome 17 probe, or order a new test (new specimen if available, ISH or IHC)

Antonio C. Wolff et al. JCO 2013;31:3997-4013
HER2 targeted agents

- **Small molecules**
  - Chemical agents
  - Varying degrees of specificity
  - Penetrate plasma membrane
  - Can’t flag cells for destruction by immune system
  - Lapatinib, neratinib

- **Large molecules**
  - Large proteins
  - Highly specific
  - Cannot penetrate plasma membrane
  - Flag cells for destruction by immune system
  - Monoclonal antibodies trastuzumab, pertuzumab, T-DM1

Under investigation: PI3K inhibitors, mTOR inhibitors, HsP inhibitors
Trastuzumab

- Trastuzumab is a humanized monoclonal antibody directed against the extracellular domain of HER2 on breast cancer cells
- 4 mechanisms of action
  1. Activates antibody-dependent cellular cytotoxicity
  2. Prevents formation of p95\textsuperscript{HER2}, a truncated and very active form of HER2
  3. Inhibits cell proliferation by preventing HER2 activated intracellular signalling
  4. Inhibits HER2 regulated angiogenesis
## Pivotal phase III trastuzumab studies in metastatic breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy + trastuzumab</th>
<th>Chemotherapy</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slamon¹</td>
<td></td>
<td></td>
<td>0.80 (0.64 to 1.00)</td>
<td>0.046</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>25.1</td>
<td>20.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>50%</td>
<td>32%</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Marty²</td>
<td></td>
<td></td>
<td>Not reported</td>
<td>0.033</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>31.2</td>
<td>22.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pivotal phase III trastuzumab studies in early breast cancer
B31 (n=2,102) and N9831 (n=1944)

Women HER2 pos, Operable breast cancer N=4046

AC (dox 60, cyclo 600) X4
T (paclitaxel 80) X 12

AC (dox 60, cyclo 600) X4
T (paclitaxel 80) X 12 PLUS
Trastuzumab with first dose of paclitaxel for 1 year
NSABP B-31/NCCTG N9831

HR 0.63, 95% CI 0.54 to 0.73, P<0.001

HR 0.60, 95% CI 0.53 to 0.68, P<0.001
Adjuvant trastuzumab for HER2-positive breast cancer (HERA)

**Diagnosis**
Local determination of HER2-positive invasive breast cancer

**Primary treatment**
Surgery and adjuvant or neoadjuvant chemotherapy, or both, with or without radiation therapy

**Confirmation of HER2-positive breast cancer** (IHC 3+ or FISH+ by central review laboratory) and LVEF ≥55% after primary treatment

**5102 patients randomly assigned**

- **1701 patients randomly assigned to 2 years trastuzumab. Initial dose 8 mg/kg, maintenance dose 6 mg/kg every 3 weeks for 2 years**
- **1703 patients assigned to 1 year trastuzumab. Initial dose 8 mg/kg, maintenance dose 6 mg/kg every 3 weeks for 1 year**
- **1698 patients randomly assigned to observation**

Goldhirsch A Lancet 2013;382:1021-28
Kaplan-Meier plot of overall survival landmark analysis, n=3105

Years from randomization

Overall Survival (%)

<table>
<thead>
<tr>
<th>Years</th>
<th>Pts</th>
<th>Deaths</th>
<th>HR (2 vs 1)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 years</td>
<td>1553</td>
<td>196</td>
<td>1.05</td>
<td>(0.86-1.28)</td>
<td>0.63</td>
</tr>
<tr>
<td>1 year</td>
<td>1552</td>
<td>186</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. at risk

Trastuzumab 2 years: 1553 1553 1525 1485 1438 1382 1317 1193 708 208
Trastuzumab 1 year: 1552 1552 1513 1461 1413 1364 1329 1218 732 225
Kaplan-Meier plots for DFS (n=5099, ITT)

Goldhirsch A Lancet 2013;382:1021-28
## Adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Observation N= 1744</th>
<th>1 year of trastuzumab N= 1682</th>
<th>2 years of trastuzumab N= 1673</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one grade 3 or 4 adverse event</td>
<td>8%</td>
<td>16%</td>
<td>20%</td>
</tr>
<tr>
<td>Fatal adverse event</td>
<td>0.4%</td>
<td>1.1%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Primary cardiac endpoint</td>
<td>0.1%</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Secondary cardiac endpoint</td>
<td>0.9%</td>
<td>4%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Primary cardiac endpoint – NYHA class III or IV and LVEF drops at least 10% to below 50%, or cardiac death
Secondary cardiac endpoint – NYHA Class I or II, and LVEF drops at least 10% to below 50%
BCIRG

N=3222 women HER2 pos, high risk node negative or node positive

AC (dox 60, cyclo 600) X4
T (docetaxel 100) X 4

AC (dox 60, cyclo 600) X4
T (docetaxel 100) X 4
PLUS
Trastuzumab with first dose of docetaxel for 1 year

Docetaxel 75 X 6
Carboplatin AUC 6 X 6
PLUS
Trastuzumab with first dose of docetaxel for 1 year
### BCIRG 006: Final efficacy analysis  
10 year follow up (SABCS 2015)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AC – T N=1073</th>
<th>AC-TH N=1074</th>
<th>TCH N=1075</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DFS %</strong></td>
<td>68</td>
<td>75</td>
<td>73</td>
</tr>
<tr>
<td>HR P value vs AC-T</td>
<td>1</td>
<td>0.72 (0.61 – 0.85)</td>
<td>0.77 (0.65 -0.90)</td>
</tr>
<tr>
<td><strong>OS %</strong></td>
<td>79</td>
<td>86</td>
<td>83</td>
</tr>
<tr>
<td>HR P value vs AC-T</td>
<td>1</td>
<td>0.63 (0.51 – 0.79)</td>
<td>0.76 (0.62 – 0.93)</td>
</tr>
<tr>
<td>Acute leukaemia, n</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>&gt;10% relative LVEF decline, n</td>
<td>120</td>
<td>200</td>
<td>97</td>
</tr>
</tbody>
</table>

**Outcome Analysis:**

- **DFS (%):**
  - AC-T: 68%
  - AC-TH: 75%
  - TCH: 73%
  
  HR: 0.72 (0.61 – 0.85) vs AC-T, P <0.0001

- **OS (%):**
  - AC-T: 79%
  - AC-TH: 86%
  - TCH: 83%
  
  HR: 0.63 (0.51 – 0.79) vs AC-T, P <0.0001

**Other Observations:**

- **Acute leukaemia, n:**
  - AC-T: 6
  - AC-TH: 2
  - TCH: 1

- **>10% relative LVEF decline, n:**
  - AC-T: 120
  - AC-TH: 200
  - TCH: 97
### Critical clinical events

<table>
<thead>
<tr>
<th>Clinical event</th>
<th>AC-T</th>
<th>AC-T plus trastuzumab</th>
<th>TCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total events</td>
<td>201</td>
<td>146</td>
<td>149</td>
</tr>
<tr>
<td>Distant breast cancer recurrence</td>
<td>188</td>
<td>124</td>
<td>144</td>
</tr>
<tr>
<td>Grade 3 or 4 congestive cardiac failure</td>
<td>7</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Acute leukaemia</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*patient had received anthracycline for diffuse large B-cell lymphoma after receiving TCH for early breast cancer*

Slamon NEJM 2011
Trastuzumab toxicity

- **Cardiac**
  - About 4% (symptomatic CHF)
  - Mostly reversible decline in LVEF
- **Diarrhoea** - rare
- **Initial infusion reaction** - rare
Trastuzumab cardiotoxicity

- Not associated with cumulative dose
- Often reversible if stop treatment, rechallenge usually tolerated after recovery
- Risk factors
  - Age > 60 years
  - Prior or current use of antihypertensives
  - LVEF near LLN
- Type 1- anthracyclines, myocyte damage, clinical heart failure
- Type 2- trastuzumab, loss of contractility, more likely to be reversible
Trastuzumab cardiotoxicity in metastatic breast cancer

- Trastuzumab alone 3-7%
- Trastuzumab and paclitaxel 13%
- Trastuzumab and anthracycline 27% (>300mg/m2 anthracycline)
- AC 8%
- Paclitaxel 1%
# Trastuzumab cardiotoxicity in early breast cancer

**Symptomatic CHF/cardiac death**

<table>
<thead>
<tr>
<th>Study</th>
<th>No trastuzumab</th>
<th>Trastuzumab for 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>N9831</td>
<td>0.3%</td>
<td>3.3%</td>
</tr>
<tr>
<td>3 year follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-31</td>
<td>0.9%</td>
<td>3.8%</td>
</tr>
<tr>
<td>5 year follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCIRG006</td>
<td>0.4% (TCH)</td>
<td>2% (AC-TH)</td>
</tr>
<tr>
<td>5 year follow-up</td>
<td></td>
<td>No cardiac deaths</td>
</tr>
<tr>
<td>HERA</td>
<td>1%</td>
<td>4.9%</td>
</tr>
<tr>
<td>8 year follow-up</td>
<td></td>
<td>2 years of trastuzumab 8.2%</td>
</tr>
</tbody>
</table>
LAPATINIB
Lapatinib

- HER1 and 2 inhibitor
- Intracellular tyrosine kinase blocker
- Oral agent once daily without food
- Used in trastuzumab resistant disease
- Combined with oral capecitabine
- Potential for treatment of brain metastases
- Side effects
  - Rash, diarrhoea, fatigue, nausea
- PBS May 2008
- Early breast cancer trial ALTTO 2009
Phase III trial of capecitabine ± lapatinib in advanced or metastatic breast cancer

Eligibility criteria:
- Stage IIIB, stage IIIC with T4 lesion, or stage IV breast cancer that has progressed
- ErbB-2 overexpression (IHC3+ or 2+ or FISH)
- Unlimited previous therapies, but no previous capecitabine
- Previous therapies must include
  - Trastuzumab in metastatic setting
  - Anthracycline and taxane in either metastatic or adjuvant setting

Primary endpoint: TTP
Secondary endpoint: OS, PFS, ORR

Time to progression: ITT population independent assessment

HR 0.49 (0.34 to 0.71)

![Graph showing time to progression for two treatment groups: Lapatinib plus capecitabine and Capecitabine alone. The graph illustrates that patients treated with Lapatinib plus capecitabine had a longer time to disease progression compared to those treated with Capecitabine alone.](image-url)
Toxicity

- Most patients receiving lapatinib and capecitabine experience side effects
- Diarrhoea
- Dermatological
- Nausea and vomiting
- Patient education is crucial
MA.31 - taxane with trastuzumab or lapatinib as 1st-line therapy for HER2+ MBC

ITT PFS 11.3m vs 9.0m

Gelmon K JCO 2015
PERTUZUMAB
Pertuzumab: dimerization inhibitor

- HER2-specific monoclonal antibody
  - Binds HER2 at the extracellular dimerization subdomain II
  - Inhibits dimerisation of HER2 with other HER proteins
  - Prevents activation of cell proliferation and survival pathways

- Preclinical activity in non-HER2 overexpressing tumors
- Activity in trastuzumab-refractory cell lines
- In vitro synergy with trastuzumab
Pertuzumab and Trastuzumab: Mechanisms of Action

Trastuzumab binds to subdomain IV and inhibits downstream signaling

Pertuzumab binds to a specific domain II and inhibits ligand-activated dimerization

The combined regimen of pertuzumab and trastuzumab offers the potential for a more comprehensive HER blockade
CLEOPATRA: Study Design

- Randomization stratified by geographic region and previous treatment status (neo/adjuvant chemotherapy received or not)
- Study dosing q3w:
  - Pertuzumab/placebo  840-mg loading dose, 420-mg maintenance
  - Trastuzumab 8-mg/kg loading dose, 6-mg/kg maintenance
  - Docetaxel 75 mg/m², escalating to 100 mg/m² if tolerated

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

# Prior Therapy for Breast Cancer

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Placebo + T + D (n = 406)</th>
<th>Pertuzumab + T + D (n = 402)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior neo/adjuvant chemotherapy, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>192 (47.3)</td>
<td>184 (45.8)</td>
</tr>
<tr>
<td>No</td>
<td>214 (52.7)</td>
<td>218 (54.2)</td>
</tr>
<tr>
<td><em><em>Components of neo/adjuvant therapy</em>, n (%)</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>164 (40.4)</td>
<td>150 (37.3)</td>
</tr>
<tr>
<td>Taxanes</td>
<td>94 (23.2)</td>
<td>91 (22.6)</td>
</tr>
<tr>
<td>Hormonal treatments</td>
<td>97 (23.9)</td>
<td>106 (26.4)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>41 (10.1)</td>
<td>47 (11.7)</td>
</tr>
</tbody>
</table>

* Patients could have received more than one therapy.

CLEOPATRA: Progression free survival (median follow-up 50 months)

Median PFS 18.7m vs 12.4m
A difference of 6.3 months
CLEOPATRA: Overall survival (median follow-up 50 months)

A difference of 15.7 months

Median OS 56.5m vs 40.8m

Hazard ratio, 0.68 (95% CI, 0.56–0.84)

P<0.001
CLEOPATRA: adverse events after discontinuation of docetaxel

<table>
<thead>
<tr>
<th>Adverse events differing &gt; 5% Any grade</th>
<th>Pertuzumab group N=306</th>
<th>Control group N=261</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>28%</td>
<td>14%</td>
</tr>
<tr>
<td>Rash</td>
<td>18%</td>
<td>8%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14%</td>
<td>6%</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>8%</td>
<td>2%</td>
</tr>
</tbody>
</table>
CLEOPATRA: cardiac toxicity

<table>
<thead>
<tr>
<th></th>
<th>Pertuzumab group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= 394</td>
<td>N= 378</td>
</tr>
<tr>
<td>Fall in LVEF to &lt;50% and by 10% or more from baseline</td>
<td>6.1% (24/394)</td>
<td>7.4% (28/378)</td>
</tr>
<tr>
<td>Of these declines, the percent that were reversible</td>
<td>87.5% (21/24)</td>
<td>78.6% (22/28)</td>
</tr>
</tbody>
</table>

Ewer M 2012 ASCO abstract
CLEOPATRA: health-related QOL

- No deterioration in QOL when pertuzumab was combined with trastuzumab/docetaxel
- Pertuzumab-containing arm associated with substantial delay in breast-cancer specific symptoms
  - Probably due to significant improvement in PFS with pertuzumab-containing regimen
Cleopatra Conclusions

- The addition of pertuzumab to standard 1L therapy significantly improved median OS by 15.7 months.
  - Benefit consistent across subgroups.
- Investigator-assessed PFS benefit maintained.
- No new safety concerns.
  - Long-term cardiac safety maintained.

The 56.5-month median OS is unprecedented in this indication and confirms the pertuzumab regimen as first-line standard of care for patients with HER2-positive MBC.
NEOADJUVANT AND ADJUVANT

DUAL HER2 BLOCKADE
DUAL HER2 BLOCKADE

**STRATEGY A**
- Trastuzumab
- Lapatinib

**STRATEGY B**
- Trastuzumab
- Pertuzumab

**Metastatic disease**
- \( \uparrow \) PFS and OS
  - (2 trials)
  - EGF104900 (N=296)
  - Cleopatra (N=808)
  - NeoALTTO (N=455)
  - NeoSPHERE (N=417)
  - Cherlob (N=119)
  - LPT 109096 (N=78)
  - NSABP B-41 (N=529)
  - ALTTO (N=8381)

**Neoadjuvant**
- \( \uparrow \uparrow \) pCR
  - (4 trials)
  - ALTTO (N=8381)
  - APHINITY (N=4805)

**Non-significant**
- \( \uparrow \) pCR
  - (1 trial)
  - Adjuvant setting

- 2014 negative
- 2016 Await
pCR correlates with better EFS in subsets of breast cancer including HER2+ BC

A FDA led Meta-analysis (N=11,955 patients / 1,989 HER2+)

pCR rates (%)

<table>
<thead>
<tr>
<th></th>
<th>HER2+HR+</th>
<th>HER2+HR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Trastuzumab</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>30</td>
<td>50</td>
</tr>
</tbody>
</table>

HR=0.39, P* < 0.001

HR=0.58, P* = 0.001

HR=0.25, P* < 0.001

Cortazar Lancet 2013
Neosphere Phase II study, n=417

Trastuzumab approved for neoadjuvant use in the US and Europe based on the improved pCR

Primary endpoint:
Pathologic complete response (pCR)*

Secondary endpoints:
- Clinical response rate
- Time to clinical response
- Breast conserving surgery rate
- DFS
- PFS

pCR 29%
pCR 46%
pCR 17%
pCR 24%

Trastuzumab approved for neoadjuvant use in the US and Europe based on the improved pCR

Gianni L Lancet Oncol 2012;13: 25-32
### Tryphaena Phase II study, n=225

<table>
<thead>
<tr>
<th>Neoadjuvant regimen</th>
<th>Adjuvant regimen</th>
<th>Incidence of LVD</th>
<th>Incidence of symptomatic LVSD (CHF)</th>
<th>pCR (breast and nodes, % of patients [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cycles 1-3</strong></td>
<td>PERJETA + TCH</td>
<td>2.6</td>
<td>0.0</td>
<td>63.6 [51.9-74.3]</td>
</tr>
<tr>
<td></td>
<td>PERJETA + Herceptin (trastuzumab) + docetaxel</td>
<td>4.0</td>
<td>2.7</td>
<td>54.7 [42.7-66.2]</td>
</tr>
<tr>
<td><strong>Cycles 4-6</strong></td>
<td>HERCEPTIN</td>
<td>5.6</td>
<td>0.0</td>
<td>56.2 [44.1-67.8]</td>
</tr>
</tbody>
</table>

*Primary endpoint cardiac safety, secondary endpoint pCR*
Await APHINITY

- The role of pertuzumab in adjuvant breast cancer therapy is being further evaluated in the randomized, phase III APHINITY trial, which is evaluating the addition of pertuzumab to the current standard of care chemotherapy and trastuzumab in patients with centrally-confirmed HER2-positive early-stage breast cancer.

T-DM1
Ado-trastuzumab emtansine (T-DM1)

- Antibody–drug conjugate combining trastuzumab with cytotoxic agent, DM1 (derivative of maytansine)
  - DM1 is a microtubule inhibitor
  - The antibody and the cytotoxic agent are conjugated by a stable linker

- T-DM1 allows intracellular drug delivery to HER2 overexpressing cells
  - Improves therapeutic index of DM1, minimises exposure to normal tissue
  - Maintain biologic effect of trastuzumab

- T-DM1 indicated for use as a single agent in HER2-positive MBC previously treated with trastuzumab and a taxane, or with disease recurrence within 6 months of completing adjuvant therapy.
**EMILIA study design**

- **HER2-positive (centrally confirmed) locally advanced or metastatic breast cancer (N = 991)**

- **Key inclusion criteria**
  - Previous treatment to include a taxane and trastuzumab in adjuvant, locally advanced or metastatic setting
  - Documented progression of disease during or after treatment for advanced/metastatic disease, or within 6 mos of completing adjuvant therapy

- **Primary endpoints:** PFS by IRF, OS, safety
- **Secondary endpoints:** OS, QOL: FACT-B

- **Treatment continues until disease progression or unmanageable toxicity**
- **No provision for cross-over**

EMILIA: progression free survival
EMILIA: overall survival

- **Overall Survival (%)**
  - Lapatinib–Capecitabine: 85.2% (95% CI, 82.0–88.5)
  - Lapatinib–Capecitabine: 78.4% (95% CI, 74.6–82.3)
  - T-DM1: 64.7% (95% CI, 59.3–70.2)
  - T-DM1: 51.8% (95% CI, 45.9–57.7)

- **Median No. of Months**
  - Lapatinib–Capecitabine: 25.1
  - T-DM1: 30.9

- **No. of Events**
  - Lapatinib–Capecitabine: 182
  - T-DM1: 149

- **Stratified hazard ratio, 0.68 (95% CI, 0.55–0.85)**
P<0.001

- **Efficacy stopping boundary, P=0.0037 or hazard ratio, 0.73**
## Adverse events: grade ≥ 3 AEs with incidence ≥ 2%

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cap + lap, % (n = 488)</th>
<th>T-DM1, % (n = 490)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade ≥ 3</td>
</tr>
<tr>
<td>Total</td>
<td>97.7</td>
<td>57.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>79.7</td>
<td>20.7</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>58.0</td>
<td>16.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8.6</td>
<td>4.3</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>8.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>44.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>19.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Increased AST</td>
<td>9.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>8.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Anemia</td>
<td>8.0</td>
<td>1.6</td>
</tr>
</tbody>
</table>

There was no increase in cardiotoxicity (LVEF <50% and ≥ 15-point decrease from baseline): Cap + lap, 1.6% (445 evaluable patients); T-DM1, 1.7% (481 evaluable patients).
TH3RESA phase 3: T-DM1 vs treatment of physician’s choice
Prior trastuzumab, lapatinib and a taxane

Krop I Lancet Oncol 2014; 15: 689-99
MARIANNE: a phase III study of T-DM1 + pertuzumab vs trastuzumab + taxane in patients with MBC: study design

Patients with HER2+ progressive or recurrent locally-advanced breast cancer or previously untreated MBC (N = 1092)

Stratified by:
- World region
- Neo/adjuvant therapy (Y/N)
- Trastuzumab and/or lapatinib based therapy (Y/N)
- Visceral disease (Y/N)

- Primary endpoints: PFS as assessed by IRF, safety
- Secondary endpoints: OS, PFS by investigator, PRO analyses, biomarkers

ClinicalTrials.gov. NCT01120184.
METASTATIC HER2 POS AND ER POS
## First line - Phase III trial results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OS</th>
<th>PFS</th>
<th>% ER+</th>
<th>% Prior endocrine treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo +/- trastuzumab¹</td>
<td>+</td>
<td>+</td>
<td>NR</td>
<td>58</td>
</tr>
<tr>
<td>Anastrozole +/- trastuzumab²</td>
<td>-</td>
<td>+</td>
<td>100</td>
<td>63</td>
</tr>
<tr>
<td>Letrozole +/- trastuzumab³</td>
<td>-</td>
<td>+</td>
<td>84</td>
<td>56</td>
</tr>
<tr>
<td>Docet/trastuzumab +/- pertuzumab⁴</td>
<td>+</td>
<td>+</td>
<td>48</td>
<td>25</td>
</tr>
</tbody>
</table>

### Conclusions
- PFS and OS is longer still with chemo & anti-HER2 agents
- No OS benefit when compared to AI alone
- QOL not studied consistently
- Ongoing study (PERTAIN) trastuzumab/taxane vs trastuzumab AI +/- pertuzumab in 1<sup>st</sup> line

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4. Swain NEJM 2015;372:724-34
Summary

- **HER2+ MBC**
  - First-line: docetaxel (or paclitaxel) + trastuzumab + pertuzumab
  - Second-line: T-DM1
  - Agents for trastuzumab-exposed HER2-positive disease
    - Lapatinib and capecitabine
    - Trastuzumab and capecitabine or vinorelbine
    - Trastuzumab and lapatinib

- **HER2+ adjuvant**
  - Anthracycline – taxane and trastuzumab
  - Docetaxel, carboplatin and trastuzumab
  - Await APHINITY

- **HER2+ neoadjuvant**
  - In Australia – use same regimens as adjuvant
  - In the US and Europe – add pertuzumab

Summary

- HER2-positive patients now have an expanding menu of options for their treatment
- Continued HER2 inhibition beyond progression seems important
- Dual blockade appears better than single blockade
- Continued exploration of mechanisms of resistance is necessary to be able to individualize therapy
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