Current Status of the Treatment of Her-2/neu Positive Breast Cancer
(C. Zielinski)

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Ramon y Cajal University Hospital, Madrid, Spain
Disclosures

- **Advisor**
  - Roche, Novartis, Celgene

- **Honoraria**
  - Roche, Novartis, Celgene, Eisai

- **Partner**
  - MedSIR ARO
Trastuzumab with chemotherapy in HER2 positive MBC

Eligible patients (n=469)

- Metastatic breast cancer
- HER2 overexpression 2/3+
- No prior CT for MBC
- Measurable disease
- KPS ≥60%

Study Design

No prior anthracyclines

- Trastuzumab + AC (n=143)
- AC (n=138)

Prior anthracyclines

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

Overall survival

Probability of survival

HR=0.80
p=0.046

25.1 ms 20.3 ms

Time (months)

Slamon DJ et al. NEJM 2001
## Efficacy: Capecitabine ± Lapatinib

<table>
<thead>
<tr>
<th>End point</th>
<th>Lapatinib plus capecitabine (N = 163)</th>
<th>Capecitabine alone (N = 161)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to progression - mo</td>
<td>8.4</td>
<td>4.4</td>
<td>0.49 (0.34 - 0.71)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Median progression-free survival - mo</td>
<td>8.4</td>
<td>4.1</td>
<td>0.47 (0.33 - 0.67)</td>
<td>&lt;0.001 †</td>
</tr>
<tr>
<td>Overall response % (95% CI)</td>
<td>22 (16 - 29)</td>
<td>14 (9 - 21)</td>
<td>0.09 ‡</td>
<td></td>
</tr>
<tr>
<td>Clinical benefit - no (%)</td>
<td>44 (27)</td>
<td>29 (18)</td>
<td>0.09 ‡</td>
<td></td>
</tr>
<tr>
<td>Death - no (%)</td>
<td>36 (22)</td>
<td>35 (22)</td>
<td>0.09 ‡</td>
<td></td>
</tr>
</tbody>
</table>

*End points are based on evaluation by the independent review committee under blinded conditions
†The p value was calculated with the log-rank test
‡The p value was calculated with Fisher’s exact test

Continuation of trastuzumab prolongs median TTP in the GBG-26 study

HR=0.69
(two-sided p=0.034; one-sided p=0.015)

*Median TTP in months

von Minckwitz, et al. JCO 2009
Lapatinib or trastuzumab-based therapy as first-line?

MA 31 Trial

Gelmon K, et al. JCO 2015
Pertuzumab: A HER dimerisation inhibitor

- A mechanism of action designed to bind to the HER dimerisation domain
- By targeting HER2, the preferred pairing partner for HER1, HER3 and HER4, pertuzumab may inhibit multiple HER signaling pathways
HER2 is activated in two different ways

- **Overexpression:**
  - Arising from gene amplification which results in constitutive activation of HER2 (ligand independent)
  - Antagonized by trastuzumab

- **Co-receptor:**
  - For other HER family members especially HER3 (ligand dependent)
  - Antagonized by pertuzumab
HER2 is activated in two different ways

- **Overexpression:**
  - Arising from gene amplification which results in constitutive activation of HER2 (ligand independent)
  - Antagonized by trastuzumab

- **Co-receptor:**
  - For other HER family members especially HER3 (ligand dependent)
  - Antagonized by pertuzumab
In contrast to trastuzumab, pertuzumab inhibits HRG-mediated HER2 signaling.
Patients with HER2-positive MBC centrally confirmed (N = 808)

- Randomization was stratified by geographic region and prior 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

MBC, metastatic breast cancer; PD, progressive disease
Independently assessed PFS

*Median follow-up: 19.3 months, n = 433 PFS events*

Progression-free survival (%)

- Ptz + T + D: median 18.5 months
- Pla + T + D: median 12.4 months

\( \Delta = 6.1 \) months

HR = 0.62
95% CI 0.51–0.75
p<0.0001

n at risk
- Ptz + T + D 402
  - 345
  - 267
  - 139
  - 83
  - 32
  - 10
  - 0
  - 0
- Pla + T + D 406
  - 311
  - 209
  - 93
  - 42
  - 17
  - 7
  - 0
  - 0

Stratified by prior treatment status and region

D, docetaxel; PFS, progression-free survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Baselga J, et al. NEJM 2012
Final OS Analysis

Median follow-up 50 months (range 0–70 months)

HR 0.68
95% CI = 0.56, 0.84
p = 0.0002

40.8 months
Δ 15.7 months
56.5 months

n at risk
Ptz + T + D 402 371 318 268 226 104 28 1
Pla + T + D 406 350 289 230 179 91 23 0

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Swain S, et al. NEJM 2015
Cardiac Safety

- One new sLVD event in the pertuzumab group after 40 months (resolved)
- LVEF declines reversed in 88% of pertuzumab patients

<table>
<thead>
<tr>
<th>Safety population</th>
<th>Placebo + T + D (n = 396), %</th>
<th>Pertuzumab + T + D (n = 408), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>sLVD</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td>LVEF decline to &lt; 50% and by ≥ 10% points from baseline*</td>
<td>7.4</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Swain S, et al. NEJM 2015
Trastuzumab Emtansine (T-DM1): Mechanism of Action

Adapted from LoRusso PM, et al. Clin Cancer Res 2011

- Emtansine release
- Inhibition of microtubule polymerization
- Internalization
- Antibody: Trastuzumab
- Antibody–drug conjugate: T-DM1
- Stable linker: MCC
- Cytotoxic: DM1
- Lysosome
- Nucleus

Antibody–drug conjugate: T-DM1

Emtansine

Adapted from LoRusso PM, et al. Clin Cancer Res 2011
EMILIA Trial

HER2-positive LABC or MBC (N=980)
- Prior taxane and trastuzumab
- Progression on metastatic treatment or within 6 months of adjuvant treatment

T-DM1
3.6 mg/kg q3w IV

Capecitabine
1000 mg/m² PO bid, days 1–14, q3w +
Lapatinib
1250 mg/day PO qd

• Primary endpoints: PFS by independent review, OS, and safety
• Key secondary endpoints: PFS by investigator, ORR, DOR
• Statistical considerations: Hierarchical statistical analysis was performed in pre-specified sequential order: PFS by independent review → OS → secondary endpoints

Verma, et al. NEJM 2012
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 (\( P<0.0001 \)).

Verma, et al. NEJM 2012
**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 (\( P=0.0012 \)).

Verma, et al. NEJM 2012
Updated / post hoc / Exploratory new data from the EMILIA Trial

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

<table>
<thead>
<tr>
<th></th>
<th>Cap+Lap</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time (months)</td>
<td>25.9</td>
<td>29.9</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.64–0.88)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P-value</td>
<td>0.0003</td>
<td></td>
</tr>
</tbody>
</table>

Number at Risk:
- **Cap+Lap**: 496, 418, 326, 258, 195, 153, 82, 48, 19, 3, 0
- **T-DM1**: 495, 451, 374, 302, 231, 194, 127, 68, 23, 5, 0

Cap+Lap, capecitabine plus lapatinib; CI, confidence interval; T-DM1, trastuzumab emtansine.

Dieras V, et al. SABCS 2015
**TH3RESA Study Schema**

- **Stratification factors:** World region, number of prior regimens for advanced BC, presence of visceral disease
- **Co-primary endpoints:** PFS by investigator and OS
- **Key secondary endpoints:** ORR by investigator and safety

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

≥2 prior HER2-directed therapies for advanced BC

Prior treatment with trastuzumab, lapatinib, and a taxane

- 1
  - Treatment of physician’s choice (TPC)\(^b\)
    (n=200)
    - PD

- 2
  - T-DM1\(^c\)
    3.6 mg/kg q3w IV
    (n=400)
    - PD

\(^a\) 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.

ORR in Patients With Measurable Disease
By Investigator Assessment

Difference: 22.7% (95% CI, 16.2, 29.2)
P<0.0001

Patients, %

<table>
<thead>
<tr>
<th></th>
<th>TPC</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>8.6%</td>
<td>31.3%</td>
</tr>
<tr>
<td>N</td>
<td>14/163</td>
<td>108/345</td>
</tr>
</tbody>
</table>

Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months.

Unstratified HR=0.521 (P<0.0001).

<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>
<tr>
<td>Stratified HR</td>
<td>0.528 (95% CI, 0.422, 0.661)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

PFS by Investigator Assessment

Final OS Results

Second Interim OS Analysis
(cut-off date February 13, 2015)

- Planned: 330 (67%) of 492 targeted events
- Actual: 338 (69%) events; median follow-up 30.5 months
- Pre-specified stopping boundary \( HR < 0.748 \) or \( P < 0.012 \)
- If stopping boundary is crossed, this will be the final OS analysis

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>TPC (n=198)</th>
<th>T-DM1 (n=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (months)</td>
<td>Median (months)</td>
<td>15.8</td>
</tr>
<tr>
<td>Proportion surviving</td>
<td>Stratified HR=0.68 (95% CI: 0.54–0.85)</td>
<td></td>
</tr>
<tr>
<td>( P = 0.0007 )</td>
<td>(Pre-specified crossing boundary: ( HR &lt; 0.748; P &lt; 0.012 ))</td>
<td></td>
</tr>
</tbody>
</table>
MARIANNE Study Design

• HER2-positive (central) LABC or MBC
• No prior chemotherapy for LABC/MBC
• >6 months from prior neo-/adjuvant vinca alkaloid or taxane chemotherapy

N = 1095

- **Trastuzumab + docetaxel**
  - (8 mg/kg LD then 6 mg/kg + 100 or 75 mg/m² q3w) OR
  - **Trastuzumab + paclitaxel**
    - (4 mg/kg LD then 2 mg/kg + 80 mg/m² qw)

- **T-DM1 + placebo**
  - (3.6 mg/kg + 840 mg LD then 420 mg q3w)

- **T-DM1 + pertuzumab**
  - (3.6 mg/kg + 840 mg LD then 420 mg q3w)

**Stratification factors:** World region, Prior neo-/adjuvant therapy (if Yes: prior trastuzumab/lapatinib), Visceral disease

**Primary end point:** PFS by independent review facility (IRF), non-inferiority and superiority assessed

**Key secondary end points:** OS, PFS by investigator, ORR, Safety, Patient-reported outcomes

LD, Loading dose. aLocally progressive or recurrent and not amenable to resection with curative intent; bPertuzumab placebo.

Ellis P, et al. ASCO 2015
Statistical Considerations

- Statistical analyses were conducted independently for T-DM1 vs HT and for T-DM1+P vs HT
- Hierarchical statistical testing was performed in pre-specified sequential order

<table>
<thead>
<tr>
<th>Two-sided alpha = 2.5%</th>
</tr>
</thead>
</table>

**T-DM1 vs HT**
1. PFS non-inferiority
2. PFS superiority
3. OS superiority
4. Other secondary end points

**T-DM1+P vs HT**
1. PFS non-inferiority
2. PFS superiority

**T-DM1+P vs T-DM1**
3. PFS superiority
4. OS superiority
5. Other secondary end points

% power for target HR=0.75 (T-DM1/T-DM1+P vs. HT) and target HR=0.73 (T-DM1+P vs. T-DM1)

**Primary end point of PFS by IRF:**
- Trial was powered at 80% for both non-inferiority and superiority analyses of PFS
- Non-inferiority: Established if the upper limit of the 97.5% CI for the HR is below 1.1765 (non-inferiority margin)
- Superiority: Target HR = 0.75  (T-DM1/T-DM1+P vs HT) and target HR = 0.73 (T-DM1+P vs T-DM1). Established if $P \leq 0.025$
Progression-Free Survival by IRF

Progression-Free Survival (%) vs Time (mo.)

<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>0</td>
<td>365</td>
<td>367</td>
<td>363</td>
</tr>
<tr>
<td>6</td>
<td>265</td>
<td>257</td>
<td>261</td>
</tr>
<tr>
<td>12</td>
<td>163</td>
<td>176</td>
<td>177</td>
</tr>
<tr>
<td>18</td>
<td>107</td>
<td>133</td>
<td>135</td>
</tr>
<tr>
<td>24</td>
<td>75</td>
<td>104</td>
<td>109</td>
</tr>
<tr>
<td>30</td>
<td>50</td>
<td>67</td>
<td>75</td>
</tr>
<tr>
<td>36</td>
<td>21</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>42</td>
<td>5</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>54</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Median PFS (mo) | HT  | T-DM1 | T-DM1+P |
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13.7</td>
<td>14.1</td>
<td>15.2</td>
</tr>
</tbody>
</table>

Events (no)    | HT  | T-DM1 | T-DM1+P |
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>231</td>
<td>236</td>
<td>217</td>
</tr>
</tbody>
</table>

Stratified HR (97.5% CI) vs HT

- HT
- T-DM1: 0.91 (0.73–1.13) P=0.31
- T-DM1+P: 0.87 (0.69–1.08) P=0.14

Stratified HR (97.5% CI) vs T-DM1

- T-DM1: 0.91 (0.73–1.13)
Overall Survival (First Interim Analysis)

<table>
<thead>
<tr>
<th>Time (mo.)</th>
<th>HT</th>
<th>T-DM1</th>
<th>T-DM1+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>365</td>
<td>335</td>
<td>303</td>
</tr>
<tr>
<td>12</td>
<td>303</td>
<td>273</td>
<td>250</td>
</tr>
<tr>
<td>18</td>
<td>273</td>
<td>250</td>
<td>218</td>
</tr>
<tr>
<td>24</td>
<td>250</td>
<td>218</td>
<td>98</td>
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<td>30</td>
<td>218</td>
<td>98</td>
<td>25</td>
</tr>
<tr>
<td>36</td>
<td>98</td>
<td>25</td>
<td>1</td>
</tr>
</tbody>
</table>

**Median OS (mo.):**
- HT: NR
- T-DM1: NR
- T-DM1+P: NR

**Events (no.):**
- HT: 123
- T-DM1: 116
- T-DM1+P: 115

**Stratified HR (97.5% CI) vs HT:**
- T-DM1: 0.86 (0.64–1.16)
- T-DM1+P: 0.82 (0.61–1.11)

NR, not reached.
Objective Response Rate

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>T-DM1</th>
<th>T-DM1+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, %</td>
<td>67.9%</td>
<td>59.7%</td>
<td>64.2%</td>
</tr>
<tr>
<td>No. at Risk</td>
<td>195/287</td>
<td>181/303</td>
<td>192/299</td>
</tr>
</tbody>
</table>

Duration of Response

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>T-DM1</th>
<th>T-DM1+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, mo. (95% CI)</td>
<td>12.5 (10.5–16.6)</td>
<td>20.7 (14.8–25.0)</td>
<td>21.2 (15.8–29.3)</td>
</tr>
</tbody>
</table>

Patients without progression, %

Error bars depict 95% confidence intervals.

Ellis P, et al. ASCO 2015
Conclusion

Pertuzumab + Trastuzumab-based Therapy

HR - Pos

HR - Neg

Trastuzumab and/or Lapatinib-based

TDM1

TDM1

Previous Rx*

<6 mo

MBC1

MBC2

MBC3

MBC4

De novo

Rx

<12 mo; >12 mo

TH3RESA
Perspectives on Current Strategies in the Management of Her2+ Breast Cancer – Early Breast Cancer
DFS and OS benefits demonstrated during long-term follow-up in the four pivotal clinical trials of trastuzumab for 1 year

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up (years)</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>HR</td>
<td>p value</td>
</tr>
</tbody>
</table>
| HERA\(^{1-4}\)  
CT+/–RT→H vs. CT+/–RT | 1 | 3387 | 0.54 | < 0.0001 | 0.76 | 0.26 |
|       | 2 | 3401 | 0.64 | < 0.0001 | 0.66 | 0.0115 |
|       | 4 | 3401 | 0.76 | < 0.0001 | 0.85 | 0.1087 |
|       | 8 | 3401 | 0.76 | < 0.0001 | 0.76 | 0.0005 |
| NCCTG N9831/NSABP B-31\(^{5-7}\)  
AC→TH→H vs. AC→T | 2 | 3351 | 0.48 | < 0.0001 | – | – |
|       | 4 | 4045 | 0.52 | < 0.001 | 0.61 | < 0.001 |
|       | 8.4 | 4046 | 0.60 | < 0.0001 | 0.63 | < 0.0001 |
| BCIRG 006\(^8\)  
AC→TH→H vs. AC→T | 5.5 | 3222 | 0.64 | < 0.001 | 0.63 | < 0.001 |
| TCH vs. AC→T | | | 0.75 | 0.04 | 0.77 | 0.04 |

CT, chemotherapy; DFS, disease-free survival; H, trastuzumab; HR, hazard ratio; OS, overall survival; RT, radiotherapy; T, taxane.

7. Romond EH, et al. SABCS 2012 (abstract S5-5; oral presentation);
Several ongoing trials are investigating the optimal duration of trastuzumab in EBC. Several ongoing trials are investigating the optimal duration of trastuzumab in EBC. Trastuzumab for <1 year vs. trastuzumab for 1 year

- **PHARE**: 6 months vs. 1 year
- **HORG**: 6 months vs. 1 year
- **PERSEPHONE**: 6 months vs. 1 year

Trastuzumab for 2 years vs. trastuzumab for 1 year

- **SOLD**: 9 weeks vs. 1 year
- **SHORT-HER**: 9 weeks vs. 1 year
- **FinHer**: 9 weeks vs. chemo
- **HERA**: 2 years vs. 1 year

**Trastuzumab for 1 year remains the standard of care in EBC, as recommended by international guidelines**

FinHer: No statistically significant improvement in DDFS or OS with 9 weeks of trastuzumab vs. chemotherapy alone

Cl, confidence interval; DDFs, distant disease-free survival.

HERA: Trastuzumab for 2 years was as efficacious as the standard 1 year of treatment, with no additional benefit


**DFS**

<table>
<thead>
<tr>
<th>Years from randomisation</th>
<th>Trastuzumab 1 year</th>
<th>Trastuzumab 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>97.4%</td>
<td>97.4%</td>
</tr>
<tr>
<td>2</td>
<td>96.5%</td>
<td>96.5%</td>
</tr>
<tr>
<td>3</td>
<td>92.6%</td>
<td>92.6%</td>
</tr>
<tr>
<td>4</td>
<td>87.6%</td>
<td>87.6%</td>
</tr>
<tr>
<td>5</td>
<td>86.4%</td>
<td>86.4%</td>
</tr>
</tbody>
</table>

**OS**

<table>
<thead>
<tr>
<th>Years from randomisation</th>
<th>Trastuzumab 1 year</th>
<th>Trastuzumab 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>97.4%</td>
<td>97.4%</td>
</tr>
<tr>
<td>2</td>
<td>96.5%</td>
<td>96.5%</td>
</tr>
<tr>
<td>3</td>
<td>92.6%</td>
<td>92.6%</td>
</tr>
<tr>
<td>4</td>
<td>87.6%</td>
<td>87.6%</td>
</tr>
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</tr>
</tbody>
</table>

**DFS**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>HR (2 vs. 1 year)</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 years</td>
<td>1553</td>
<td>367</td>
<td>0.99</td>
<td>(0.84, 1.14)</td>
</tr>
<tr>
<td>1 year</td>
<td>1552</td>
<td>367</td>
<td>1.05</td>
<td>(0.86, 1.28)</td>
</tr>
</tbody>
</table>

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<th>Events</th>
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<th>p value</th>
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</thead>
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<tr>
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<td>1553</td>
<td>196</td>
<td>1.05</td>
<td>(0.86, 1.28)</td>
</tr>
<tr>
<td>1 year</td>
<td>1552</td>
<td>186</td>
<td>1.05</td>
<td>(0.86, 1.28)</td>
</tr>
</tbody>
</table>
PHARE: Non-inferiority of 6 months vs. 1 year of trastuzumab was not demonstrated

**DFS**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>HR (6 months vs. 1 year)</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>1690</td>
<td>1.46</td>
<td>(1.06, 2.01)</td>
<td>0.03</td>
</tr>
<tr>
<td>1 year</td>
<td>1690</td>
<td>1.28*</td>
<td>(1.05, 1.56)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

**OS**

<table>
<thead>
<tr>
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<th>Events</th>
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<td>0.29</td>
</tr>
</tbody>
</table>

HR (95% CI): 1.46 (1.06, 2.01)
(above the prespecified non-inferiority CI of 1.15)
## Neoadjuvant Studies I

<table>
<thead>
<tr>
<th>Scheme</th>
<th>NOAH</th>
<th>GeparQuinto</th>
<th>NeoAltto</th>
<th>CHER-LOB</th>
<th>NSABP B-41</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ch</td>
<td>Ch</td>
<td>Ch</td>
<td>Ch</td>
<td>Ch</td>
</tr>
<tr>
<td></td>
<td>+ T</td>
<td>+ T</td>
<td>+ T</td>
<td>+ T</td>
<td>+ T</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>L</td>
<td>L</td>
<td>TL</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>EFS</td>
<td>pCR breast &amp; axilla*</td>
<td>pCR breast</td>
<td>pCR breast &amp; axilla</td>
<td>pCR breast</td>
</tr>
<tr>
<td>n</td>
<td>115</td>
<td>307 308</td>
<td>154 149 152</td>
<td>36 39 46</td>
<td>177 171 171</td>
</tr>
<tr>
<td>pCR (%) breast</td>
<td>43</td>
<td>50 35</td>
<td>29 25 51</td>
<td>NR NR NR</td>
<td>52 53 62</td>
</tr>
<tr>
<td>pCR (%) breast &amp; axila</td>
<td>38</td>
<td>31 22</td>
<td>28 20 47</td>
<td>26 29 43</td>
<td>49 47 60</td>
</tr>
</tbody>
</table>

*pCR excludes ductal in situ carcinoma

Ch, chemotherapy; EFS, event free-survival; L, lapatinib; n, sample; pCR, pathological complete response; T, trastuzumab
# Neoadjuvant Studies II

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Neosphere</th>
<th>Tryphaena</th>
<th>TBCRC-006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ch + T</td>
<td>Ch + P</td>
<td>Ch + TP</td>
<td>Ch + TP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>pCR breast</th>
<th>Cardiotoxicity</th>
<th>pCR breast</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>107</td>
<td>107</td>
<td>225</td>
</tr>
<tr>
<td>pCR (%) breast</td>
<td>29</td>
<td>46</td>
<td>62</td>
</tr>
<tr>
<td>pCR (%) breast &amp; axila</td>
<td>21</td>
<td>39</td>
<td>48</td>
</tr>
</tbody>
</table>

Ch, chemotherapy; L, lapatinib; n, sample; P, pertuzumab; pCR, pathological complete response; T, trastuzumab
NeoSphere: study design and pCR results

Patients with operable or locally advanced/inflammatory HER2-positive BC

Chemo-naive & primary tumors >2 cm (N=417)

Study dosing: q3w x 4

TD (n=107)
trastuzumab (8→6 mg/kg)
docetaxel (75→100 mg/m²)

PTD (n=107)
pertuzumab (840→420 mg)
trastuzumab (8→6 mg/kg)
docetaxel (75→100 mg/m²)

PT (n=107)
pertuzumab (840→420 mg)
trastuzumab (8→6 mg/kg)

PD (n=96)
pertuzumab (840→420 mg)
docetaxel (75→100 mg/m²)

HR, hormone receptor;
HR-positive = estrogen and/or progesterone receptor-positive;
HR-negative = estrogen and progesterone receptor-negative

Kaplan–Meier curves are truncated at 60 months (the end of scheduled follow-up). However, summary statistics shown here take into account all follow-up.

Three late events occurred with PTD: two cases of PD at 63 and 71 months, and one death due to an unrelated cerebrovascular accident without PD at 76 months.
Invasive operable HER2+ BC
T > 2 cm
(inflammatory BC excluded)
LVEF ≥ 50%
N=450

Stratification:
• T ≤ 5 cm vs. T > 5 cm
• ER or PgR + vs. ER & PgR –
• N 0-1 vs. N ≥ 2
• Conservative surgery or not

52 weeks of anti-HER2 therapy
Efficacy – pCR and tpCR

Pathological Complete Response

L: lapatinib; T: trastuzumab; L+T: lapatinib plus trastuzumab
pCR pathologic complete response

Locoregional (total) pCR
* Excludes 15 patients with non-evaluable nodal status
NeoALTTO: DFS

ITT

<table>
<thead>
<tr>
<th>Number of events</th>
<th>3-year EFS (95% CI)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib plus trastuzumab</td>
<td>30</td>
<td>84% (77–89)</td>
<td>0.78 (0.47–1.28)</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>38</td>
<td>78% (70–84)</td>
<td>1.06 (0.66–1.69)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>37</td>
<td>76% (68–82)</td>
<td></td>
</tr>
</tbody>
</table>

Number at risk

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib plus trastuzumab</td>
<td>152</td>
<td>139</td>
<td>127</td>
<td>113</td>
<td>54</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>154</td>
<td>132</td>
<td>114</td>
<td>98</td>
<td>45</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>149</td>
<td>136</td>
<td>116</td>
<td>99</td>
<td>51</td>
</tr>
</tbody>
</table>

De Azambuja E, et al. Lancet Oncol 2014
ALTTO Study Design

Anti-HER2 therapy: 4 groups assigned by randomization

- Trastuzumab \((T) \times 52 \text{ wk}\)
- Lapatinib \((L) \times 52 \text{ wk}\)
- \(T \times 12 \text{ wk}^{†}\) \(\xrightarrow{6 \text{ wk}}\) \(L \times 34 \text{ wk}\)
- Trastuzumab and Lapatinib \(\times 52 \text{ wk}\)

3 modalities of chemotherapy administration per physician’s choice

- Design 1 (\(N = 4,163; \text{ mFU 4.9 y}\))
  - Chemotherapy
  - Anti-HER2 therapy
  - 12 to 18 wk \rightarrow 52 wk

- Design 2 (\(N = 3,337; \text{ mFU 4.0 y}\))
  - Anthracycline
  - Taxane
  - 9 to 12 wk \rightarrow 12 wk
  - Anti-HER2 therapy
  - 52 wk

- Design 2B (\(N = 431; \text{ mFU 2.6 y}\))
  - Docetaxel + Carboplatin
  - 18 wk
  - Anti-HER2 therapy
  - 52 wk

CURRENT ANALYSIS PLAN

Statistical procedures for the two remaining pairwise comparisons are:

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>L + T vs. T</td>
<td>Test superiority in ITT population at alpha = 0.025</td>
</tr>
<tr>
<td>T → L vs. T</td>
<td>Test non-inferiority in per protocol population (PPP) at alpha = 0.025</td>
</tr>
</tbody>
</table>

DFS ANALYSIS


**p-value ≤ 0.025 required for statistical significance**
OS ANALYSIS

DFS NON-INFERIORITY ANALYSIS

Note: Null hypothesis hazard ratio is 1.11

**p-value ≤ 0.025 required for statistical significance**
**Objective:**

Show non-inferiority of SC vs. IV based on co-primary endpoints

**PK:** observed trastuzumab $C_{\text{trough}}$ pre-dose Cycle 8 (pre-surgery)

**Efficacy:** pathological complete response (pCR) in the breast

- HER2-positive EBC (N=596)
- Clinical stage Ic to IIIc including IBC
- R 1:1
- SC trastuzumab
- IV trastuzumab

**Neoadjuvant**
- Docetaxel 75 mg/m$^2$
- FEC 500/75/500

**Adjuvant**
- Trastuzumab IV 6 mg/kg q3w (8 mg/kg loading dose)
- Trastuzumab SC 600 mg/5 mL q3w (fixed dose)

Follow-up: 24 mo

Jackisch C, et al. EBCC 2012

IBC, inflammatory breast cancer. FEC, 5-fluorouracil, epirubicin and cyclophosphamide
HannaH: Both co-primary endpoints met

Trastuzumab SC demonstrated a comparable efficacy and PK profile to the IV formulation

**Efficacy**

Difference in pCR rate: 4.7%†
(95% CI: –4.0, 13.4)

**PK**

Geometric mean ratio: 1.33*
(90% CI: 1.24, 1.44)

<table>
<thead>
<tr>
<th>Serum $C_{\text{trough}}$ levels</th>
<th>Geometric mean ratio</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab SC (n = 234)</td>
<td>69.0 µg/mL</td>
<td>pCR in the breast</td>
</tr>
<tr>
<td>Trastuzumab IV (n = 235)</td>
<td>51.8 µg/mL</td>
<td>45.4%</td>
</tr>
</tbody>
</table>

| Trastuzumab SC (n = 260)         | 45.4%                |
| Trastuzumab IV (n = 263)         | 40.7%                |

* Non-inferiority margin for the ratio between groups of 0.80
† Non-inferiority margin for the difference between groups of –12.5%
CI, confidence interval

CONCLUSIONS

1. 1-year Trastuzumab is the standard of care in patients treated
   a. In adjuvant
   b. In neoadjuvant

2. Pertuzumab in combination with Trastuzumab is a new approved approach in the neoadjuvant setting

3. SC Trastuzumab might be a more convenient strategy to administer trastuzumab