Carcinoma mammario: quando la donna è giovane

IL TRATTAMENTO ADIUVANTE E NEOADIUVANTE NEL CARCINOMA MAMMARIO HER2-POSITIVO

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UO Oncologia «Ospedale Sacro Cuore-Don Calabria» Negrar

24 giugno 2015
# Treatment recommendations for HER2-positive breast cancer

## Neoadjuvant–adjuvant therapy for HER2-positive early breast cancer

<table>
<thead>
<tr>
<th>Neoadjuvant</th>
<th>Adjuvant</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESMO 2013</strong></td>
<td>• Herceptin should be added to neoadjuvant chemotherapy in patients with HER2-positive tumours</td>
<td>• Tumours ≥1</td>
</tr>
<tr>
<td></td>
<td>• Use of Herceptin should be discussed with patients with small node-negative breast cancers</td>
<td>• pN positive</td>
</tr>
<tr>
<td><strong>NCCN 2015</strong></td>
<td>• Patients who are HER2-positive and receiving pre-operative chemotherapy should also receive Herceptin</td>
<td>• patients with tumours 0.6–1.0</td>
</tr>
<tr>
<td></td>
<td>• Tumours ≤ 0.5 or microinvasive and pN0 or pN1mic</td>
<td>• Tumours &gt; 1.0</td>
</tr>
<tr>
<td></td>
<td>• Tumours &gt; 1.0</td>
<td>• All pN positive (metastases &gt; 2mm)</td>
</tr>
<tr>
<td><strong>St. Gallen 2015</strong></td>
<td>• Herceptin should be incorporated into neoadjuvant therapy in patients with HER2-positive disease</td>
<td>• Tumours ≥1</td>
</tr>
<tr>
<td></td>
<td>• Node-negative tumours 0.5–1.0 (TH w/o Anthra-regimen)</td>
<td>• Excludes: Node-negative tumours 0.1–0.5 cm (pT1a)</td>
</tr>
</tbody>
</table>
Observational study on adjuvant trastuzumab in HER2-positive early breast cancer patients

G Mustacchi*, F Puglisi2, AM Molino3, D Crivellari4, C Ghiotto5, A Ferro6, A Brunello7, S Saracchini8, M Turazza9, E Cretella10, A Iop11, M Malagoli12 & M Stefani13

13 Oncology Centres in the NorthEast of Italy for a total of 1245 patients investigated

To investigate the use of adjuvant trastuzumab in HER2+ breast cancer in a REAL-LIFE setting OUT OF CLINICAL TRIAL
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AT yes (n = 949)</th>
<th>AT no (n = 296)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;76 years and stage I, II and III</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mean age years (range)</td>
<td>53.7 (23.9–75.8)</td>
<td>57.7 (30–75.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean follow-up, months (95% CI)</td>
<td>37.4 (36.6–38.7)</td>
<td>62.1 (58.5–65.2)</td>
<td>0.000002</td>
</tr>
<tr>
<td>Stage (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Stage I</td>
<td>353 (37.2)</td>
<td>155 (52.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>– Stage II</td>
<td>373 (39.3)</td>
<td>90 (30.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>– Stage III</td>
<td>223 (23.5)</td>
<td>51 (17.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Adjuvant/neoadjuvant chemo regimens (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– None</td>
<td>9 (0.9)</td>
<td>125 (42.2)</td>
<td>0.000001</td>
</tr>
<tr>
<td>– CMF-like</td>
<td>16 (1.7)</td>
<td>17 (5.7)</td>
<td>NS</td>
</tr>
<tr>
<td>– Anthra combo</td>
<td>316 (33.3)</td>
<td>87 (29.4)</td>
<td>NS</td>
</tr>
<tr>
<td>– Anthra mono</td>
<td>5 (0.5)</td>
<td>2 (0.7)</td>
<td>NS</td>
</tr>
<tr>
<td>– Taxane</td>
<td>70 (7.4)</td>
<td>1 (0.3)</td>
<td>NS</td>
</tr>
<tr>
<td>– Anthra/taxane</td>
<td>518 (54.6)</td>
<td>55 (18.6)</td>
<td>0.000001</td>
</tr>
</tbody>
</table>

AT: Adjuvant trastuzumab; CMF: Cyclophosphamide methotrexate fluorouracil. NS: Not significant.

* (148/296 diagnosed before adjuvant trastuzumab approval in Italy)
“Trattamento adiuvante delle neoplasie mammarie pT1a-b pN0 HER2-positive: lo studio PROMHER”

303 pazienti investigate provenienti da 28 centri italiani pT≤10mm e pNs-HER2+

Identificare quante sono state trattate con terapia adiuvante sistemica contenente trastuzumab e quali caratteristiche clinico-patologiche ne hanno influenzato la scelta
RISULTATI

34 (11%) NESSUNA TERAPIA SISTEMICA

65 (23%) TERAPIA SISTEMICA ADIUVANTE SENZA TRASTUZUMAB

204 (66%) TERAPIA SISTEMICA ADIUVANTE CON TRASTUZUMAB (CT 36%, OT 6%, CT+OT 57%)

Follow up mediano: 38.6 mesi
Local e Distant Disease Free Survival

<table>
<thead>
<tr>
<th></th>
<th>No TSA (34)</th>
<th>TSA senza T (65)</th>
<th>TSA con T (204)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 (15%)</td>
<td>2 (3%)</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

Tasso di sopravvivenza libera da malattia stimata a 5 anni:

<table>
<thead>
<tr>
<th></th>
<th>No TSA</th>
<th>TSA senza T</th>
<th>TSA con T</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>69.6</td>
<td>94.3%</td>
<td>95% p&lt;0.001</td>
</tr>
</tbody>
</table>

pT, età, Ki67, recettori ormonali
78.7% Trastuzumab with Taxanes after A-CT
12.5% Trastuzumab sequential after A-CT
7.3% TCH
1.5% Trastuzumab NOT AVAILABLE

Her2 positivity: **18-20% of breast cancers**

**Breast Cancer Cell**

*HER2* gene amplification is the underlying biological change that results in *HER2* overexpression.

- Proliferation
- Motility
- Invasiveness
- Resistance to apoptosis
- Angiogenesis

**Techniques:**
- FISH
- SISH
- IHC

**Annotations:**
- DNA
- mRNA Transcript
HER2/Neu (ErbB2) oncogene is associated with poor prognosis in breast cancer

HER2 gene amplification (Southern)

Median Survival
HER2 overexpression
HER2 normal

3 yrs
6-7 yrs

HER2 protein overexpression (IHC)

Slamon et al. Science 237:177, 1987
### Outcomes for T1a/bN0 HER2+ Tumors

#### MD Anderson series

<table>
<thead>
<tr>
<th>HER2 status</th>
<th>n</th>
<th>5 yr RFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+</td>
<td>98</td>
<td>77.1%</td>
</tr>
<tr>
<td>HER2-</td>
<td>867</td>
<td>93.7%</td>
</tr>
</tbody>
</table>

#### NCCN series

<table>
<thead>
<tr>
<th>HER2 status</th>
<th>n</th>
<th>5 yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+</td>
<td>255</td>
<td>83.3%</td>
</tr>
<tr>
<td>HER2-</td>
<td>3127</td>
<td>89.0%</td>
</tr>
</tbody>
</table>

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HER2 overexpression associated with more aggressive phenotype

1984
HER2/neu gene identified

1985
HER2 overexpression

1987
Anti-HER2 monoclonal mouse antibody humanised: trastuzumab

1989
clinical trials begin

1992

1993–1995

US approval: HER2-positive MBC

1998

EU/US approval: HER2-positive EBC

2000

EMA approval: Concurrent Herceptin + chemotherapy in EBC

2006

EU approval: HER2-positive MBC

2010

EMA approval: Neoadjuvant-adjuvant therapy with Herceptin
USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2
### Table 1. Base-Line Characteristics of the Patients.

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>AN ANTHRACYCLINE, CYCLOPHOSPHAMIDE, AND TRASTUZUMAB (N=143)*</th>
<th>AN ANTHRACYCLINE AND CYCLOPHOSPHAMIDE ALONE (N=138)+</th>
<th>PACITAXEL AND TRASTUZUMAB (N=92)</th>
<th>PACITAXEL ALONE (N=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr Mean ±SD</td>
<td>54±10.3</td>
<td>54±10.1</td>
<td>51±11.5</td>
<td>51±11.0</td>
</tr>
<tr>
<td>Range</td>
<td>27–76</td>
<td>25–75</td>
<td>25–77</td>
<td>26–73</td>
</tr>
<tr>
<td>Karnofsky score — no./no. analyzed (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90–100</td>
<td>91/138 (66)</td>
<td>89/135 (66)</td>
<td>68/90 (76)</td>
<td>61/94 (65)</td>
</tr>
<tr>
<td>60–80</td>
<td>47/138 (34)</td>
<td>46/135 (34)</td>
<td>22/90 (24)</td>
<td>33/94 (35)</td>
</tr>
<tr>
<td>Median no. of positive lymph nodes at diagnosis</td>
<td>1.0</td>
<td>0.5</td>
<td>5.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Prior therapy — no./no. analyzed (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>81/142 (57)</td>
<td>50/136 (37)</td>
<td>88/91 (97)</td>
<td>95/95 (100)</td>
</tr>
<tr>
<td>Hormonal therapy (as adjuvant, for metastasis, or both)</td>
<td>88/142 (62)</td>
<td>76/134 (57)</td>
<td>49/89 (55)</td>
<td>53/95 (56)</td>
</tr>
<tr>
<td>Radiotherapy (as adjuvant, for metastasis, or both)</td>
<td>69/143 (48)</td>
<td>76/136 (56)</td>
<td>60/89 (67)</td>
<td>72/95 (76)</td>
</tr>
<tr>
<td>Median disease-free interval — mo</td>
<td>24.5</td>
<td>22.8</td>
<td>22.4</td>
<td>18.9</td>
</tr>
<tr>
<td>Degree of overexpression of HER2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— no./no. analyzed (%)</td>
<td>35/143 (24)</td>
<td>42/138 (30)</td>
<td>24/92 (26)</td>
<td>19/96 (20)</td>
</tr>
<tr>
<td>2+</td>
<td>108/143 (76)</td>
<td>96/138 (70)</td>
<td>68/92 (74)</td>
<td>77/96 (80)</td>
</tr>
<tr>
<td>No. of metastatic sites at enrollment — no./no. analyzed (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>48/143 (34)</td>
<td>49/136 (36)</td>
<td>31/91 (34)</td>
<td>27/95 (28)</td>
</tr>
<tr>
<td>2</td>
<td>38/143 (27)</td>
<td>48/136 (35)</td>
<td>32/91 (35)</td>
<td>35/95 (37)</td>
</tr>
<tr>
<td>≥3</td>
<td>57/143 (40)</td>
<td>39/136 (29)</td>
<td>28/91 (31)</td>
<td>33/95 (35)</td>
</tr>
</tbody>
</table>
Rate of overall response was 50% for trastuzumab-group vs 32% w/o trastuzumab (p < 0.001)

Median duration of response was 9.1 months for trastuzumab-group vs 6.1 months w/o trastuzumab
Overall survival

Reduced risk of death of 18-20%.
### CARDIAC EVENTS IDENTIFIED IN METASTATIC BREAST CANCER trials

<table>
<thead>
<tr>
<th></th>
<th>H + P</th>
<th>P</th>
<th>H + AC</th>
<th>AC</th>
<th>H + D</th>
<th>D</th>
<th>ANA+H</th>
<th>ANA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic heart failure</td>
<td>8.8</td>
<td>4.2</td>
<td>28</td>
<td>9.6</td>
<td>1.1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>NYHA III-IV</td>
<td>4</td>
<td>1</td>
<td>19</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

(New York Heart Association)
Consistent disease-free survival benefit with adjuvant Herceptin for 1 year

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up (years)</th>
<th>N</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA1-3 CT+/-RT→H vs.</td>
<td>1</td>
<td>3387</td>
<td>0.54</td>
</tr>
<tr>
<td>CT+/-RT</td>
<td>2</td>
<td>3401</td>
<td>0.64</td>
</tr>
<tr>
<td>CT+/-RT</td>
<td>4</td>
<td>3401</td>
<td>0.76</td>
</tr>
<tr>
<td>BCIRG 0064 AC→TH→H vs.</td>
<td>1</td>
<td>3222</td>
<td>0.64</td>
</tr>
<tr>
<td>AC→T</td>
<td>2</td>
<td>3351</td>
<td>0.48</td>
</tr>
<tr>
<td>TCH vs. AC→T</td>
<td>5</td>
<td>4045</td>
<td>0.52</td>
</tr>
</tbody>
</table>

HR, hazard ratio

Consistent overall survival benefit with adjuvant Herceptin for 1 year

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up (years)</th>
<th>N</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA¹,²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT+/−RT→H vs.</td>
<td>2</td>
<td>3401</td>
<td>0.66</td>
</tr>
<tr>
<td>CT+/−RT</td>
<td>4</td>
<td>3401</td>
<td>0.85</td>
</tr>
<tr>
<td>BCIRG 006³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC→TH→H vs. AC→T</td>
<td>5</td>
<td>3222</td>
<td>0.63</td>
</tr>
<tr>
<td>TCH vs. AC→T</td>
<td></td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>Combined analysis⁴</td>
<td></td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>(NCCTG N9831/</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP B-31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC→TH→H vs. AC→T</td>
<td>4</td>
<td>4045</td>
<td></td>
</tr>
</tbody>
</table>

HR, hazard ratio

SUMMARY OF DFS ITT ANALYSES FOR 1 YEAR TRASTUZUMAB VS. OBSERVATION ACROSS ANALYSIS TIME POINTS

Median follow-up (% follow-up time after selective crossover) | DFS benefit | No. of DFS events 1 year trastuzumab vs observation
--- | --- | ---
2005 (0%) 1 yr MFU | 0.54 | 127 vs 220 P<0.0001
2006 (4.3%) 2 yrs MFU | 0.64 | 218 vs 321 P<0.0001
2008 (33.8%) 4 yrs MFU | 0.76 | 369 vs 458 P<0.0001
2012 (48.5%) 8 yrs MFU | 0.76 | 471 vs 570 P<0.0001

HR (95% CI)

Favours 1 year trastuzumab | Favours observation
--- | ---
0 | 1
1 | 2

SUMMARY OF OS ITT ANALYSES FOR 1 YEAR TRASTUZUMAB VS. OBSERVATION ACROSS ANALYSIS TIME POINTS

Median follow-up (% follow-up time after selective crossover)

- 2005 (0%) 1 yr MFU
- 2006 (4.1%) 2 yrs MFU
- 2008 (30.9%) 4 yrs MFU
- 2012 (45.5%) 8 yrs MFU

OS benefit

No. of deaths 1 year trastuzumab vs observation

- 2005: 29 vs 37, P=0.26
- 2006: 59 vs 90, P=0.0115
- 2008: 182 vs 213, P=0.1087
- 2012: 278 vs 350, P=0.0005

HR (95% CI)

Favours 1 year trastuzumab

Favours observation

Herceptin has a consistent safety profile based on experience in ~1,000,000 patients

- Herceptin is well tolerated with a consistent safety and tolerability profile
- Low cumulative incidence of cardiac events after long-term follow-up

Cardiac events: NYHA class III/IV or severe symptomatic CHF or cardiac death

### Adjuvant studies:
- B-31 AC→TH (n=947)
- N9831 AC→TH (n=570)
- N9831 AC→T→H (n=710)
- BCIRG 006 AC→TH (n=1068)
- HERA CT→H (n=1682)
- BCIRG 006 TCH (n=1056)

<table>
<thead>
<tr>
<th>Study</th>
<th>N9831 AC→TH</th>
<th>N9831 AC→T→H</th>
<th>HERA CT→H</th>
<th>BCIRG 006 TCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (years)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cumulative incidence (%)</td>
<td>0.4%</td>
<td>2.0%</td>
<td>3.3%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

- CHF, congestive heart failure
- NYHA, New York Heart Association

# CARDIAC EVENTS IN «EARLY BREAST CANCER TRIALS»

<table>
<thead>
<tr>
<th>EBC trials (1-yr trastuzumab)</th>
<th>Therapy</th>
<th>Number of patients</th>
<th>% Asymptomatic LVEF decline</th>
<th>% Severe CHF</th>
<th>Cardiac death</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA</td>
<td>H (1 year)</td>
<td>1678</td>
<td>3</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>NSABP B-31</td>
<td>AC--PH</td>
<td>947</td>
<td>NR</td>
<td>3.8</td>
<td>0</td>
</tr>
<tr>
<td>NCCTG N9831</td>
<td>AP--PH</td>
<td>570</td>
<td>NR</td>
<td>3.3</td>
<td>0</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>AC--DH</td>
<td>1068</td>
<td>18</td>
<td>1.9</td>
<td>0</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>DCarboH</td>
<td>1056</td>
<td>8.6</td>
<td>0.4</td>
<td>0</td>
</tr>
</tbody>
</table>

**Slamon 2006; Rastogy 2007; Smith 2007; Perez 2008**

<table>
<thead>
<tr>
<th>Recovery (% of patients)</th>
<th>Median Time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>-</td>
</tr>
<tr>
<td>Severe CHF</td>
<td>80</td>
</tr>
<tr>
<td>Symptomatic CHF</td>
<td>67</td>
</tr>
<tr>
<td>Confirmed significant LVEF drop</td>
<td>69</td>
</tr>
</tbody>
</table>
NOAH: Inclusion criteria

- Histologically proven locally advanced breast cancer (T3N1/T4) or any T plus N2/N3, or any T plus involvement of ipsilateral supraclavicular nodes
- HER2-positive disease was defined as IHC 3+ overexpression or HER2 amplification by FISH according to a central laboratory
  - For the observational arm, HER2-negative disease was defined as IHC 0 or 1+ on the basis of local laboratory testing
- Mandatory hormone receptor assessment
- LVEF $\geq$55%

NOAH (MO16432): Study design

An international, open-label, Phase III study of neoadjuvant–adjuvant trastuzumab in patients with locally advanced or inflammatory HER2-positive breast cancer

HER2-positive LABC (IHC 3+ or FISH-positive)

(n = 117)

H + AT q3w x 3 cycles

H + T q3w x 4 cycles

H q3w or q4w x 4 cycles + CMF q4w x 3 cycles

H continued q3w to week 52

(n = 118)

AT q3w x 3 cycles

T q3w x 4 cycles

CMF q4w x 3 cycles

Surgery followed by radiotherapy †

19 (16%) patients crossed to H after November 2005

(n = 99)

AT q3w x 3 cycles

T q3w x 4 cycles

CMF q4w x 3 cycles

HER2-negative LABC (IHC 0/1+)*

H, trastuzumab (8 mg/kg loading dose then 6 mg/kg);
AT, doxorubicin (60 mg/m²), paclitaxel (150 mg/m²); T, paclitaxel (175 mg/m²);
CMF, cyclophosphamide, methotrexate and fluorouracil 5-FU

* A separate treatment group of HER2-negative patients received chemotherapy only;
† Hormone receptor-positive patients received adjuvant tamoxifen.

• Gianni et al. ASCO 2013 – abs 504
NOAH neoadjuvant–adjuvant study: Significant improvement in pCR rates with Herceptin

Significant improvement in pCR with addition of Herceptin to chemotherapy in HER2-positive treatment groups

pCR, pathological complete response
bpCR, pathological complete response in breast tissue;
 tpCR, total pathological complete response (in breast and axillary nodes)
*Absence of invasive tumour cells

Gianni L, et al. 2010
NOAH: EFS (primary endpoint) in HER2-positive ITT population (follow-up data)

Significant EFS benefit with the addition of trastuzumab to chemotherapy in HER2-positive patients

- Gianni et al. ASCO 2013 – abs 504
NOAH: Overall survival in the HER2-positive ITT population (follow-up data)

Trend towards overall survival benefit with the addition of trastuzumab to chemotherapy in HER2-positive patients

- **Patients**
  - With H: 117
  - Without H: 118

- **Events**
  - With H: 36 (30.8%)
  - Without H: 47 (39.8%)

- **HR (95% CI)**
  - With H: 0.66 (0.43 - 1.01)

- **P-value**
  - 0.055

• Gianni et al. ASCO 2013 – abs 504
2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial


Lancet 2013; 382: 1021-28
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

1 patient excluded (no documentation of informed consent)

1700 patients in ITT population

1553 patients in landmark analysis population alive and disease-free at least 366 days after randomisation

1703 patients assigned to 1 year trastuzumab. Initial dose 8 mg/kg, maintenance dose 6 mg/kg every 3 weeks for 1 year

1 patient excluded (no documentation of informed consent)

1702 patients in ITT population

1552 patients in landmark analysis population alive and disease-free at least 366 days after randomisation

1698 patients randomly assigned to observation

1 patient excluded (no documentation of informed consent)

1697 patients in ITT population
884 (52.1%) crossed over to trastuzumab after release of interim analysis results in 2005; median time from randomisation to selective crossover was 22.7 months (range 4.5-52.7)
HERA-results: 1yr vs 2yrs

**HR+**

**HR-**

**Total**
FinHER study
- Adjuvant setting
- Docetaxel/vinorelbina + trastuzumab for 9 weeks --> FEC

| Table 4. FinHer: Adjuvant chemotherapy plus short trastuzumab; updated (5-year) results in HER-2+ patients |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Chemo                                           | Chemo + trastuzumab                              | HR (95% CI)                                      | p-value                                           |
| Distant disease-free survival, %                | 73.0                                             | 83.3                                            | 0.65 (0.38, 1.12)                                 | 0.12                                             |
| Overall survival, %                             | 82.3                                             | 91.3                                            | 0.55 (0.27, 1.11)                                 | 0.094                                            |


(only 200 patients treated: underpowered trial)
PHARE* Trial results comparing 6 to 12 months of trastuzumab in adjuvant early breast cancer

Xavier Pivot, Gilles Romieu, Hervé Bonnefoi, Jean-Yves Pierga, Pierre Kerbrat, Thomas Bachelot, Alain Lortholary, Marc Espié, Pierre Fumoleau, Daniel Serin, Jean-Philippe Jacquin, Christelle Jouannaud, Maria Rios, Sophie Abadie-Lacourtoisie, Nicole Tubiana-Mathieu, Laurent Cany, Stéphanie Catala, David Khayat, Iris Pauporté, Andrew Kramar.

*Lighthouse in French
www.esmo2012.org

Study design

- trastuzumab up to 12 months
- trastuzumab 6 months
- stop trastuzumab

Stratification:
1. ER pos / neg
2. Chemo: conco/ seq

Clinical exam
- LVEF
  0 3 6 9 12 15 18 21 24 30 mos

Mammography
Up to 60 mos...

R: Randomization after informed consent
www.esmo2012.org
DFS Forest plot

Age yrs
- <35 (129) 1.78 (0.70 - 4.53)
- 35-49 (1065) 1.32 (0.95 - 1.84)
- 50-59 (1059) 1.38 (0.95 - 2.01)
- >60 (1128) 1.08 (0.75 - 1.54)

Nodal status
- Negative (1842) 1.31 (0.93 - 1.84)
- 1-3 pos. nodes (1008) 1.27 (0.90 - 1.78)
- >3 pos. nodes (497) 1.22 (0.85 - 1.75)

Tumour size (cm)
- 0-2 (1771) 1.00 (0.71 - 1.42)
- 2-5 (1294) 1.46 (1.09 - 1.95)
- >5 (242) 1.23 (0.75 - 2.00)

Estrogene Receptor
- Negative (1412) 1.32 (1.01 - 1.74)
- Positive (1968) 1.23 (0.92 - 1.65)

Chemotherapy
- Sequential (1428) 1.39 (1.05 - 1.85)
- Concomitant (1952) 1.17 (0.89 - 1.54)

All patients (3380) 1.28 (1.05 - 1.56)
Overall Survival
42.5mos. median FU

<table>
<thead>
<tr>
<th>Months</th>
<th>Events</th>
<th>HR</th>
<th>95%CI</th>
<th>p-value</th>
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<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>66</td>
<td>1.47</td>
<td>1.07 – 2.02</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>93</td>
<td></td>
<td></td>
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</tr>
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<td>36</td>
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<td>48</td>
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</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

At risk
H-12m 1690
H 6m 1690

* Cox model stratified by ER status and concomitant chemotherapy
Study information

Activated: 30/05/2006

Randomization
3384 patients

4 patients excluded from analysis
1 Informed consent not signed
1 Randomized twice
2 HER2 negative after FISH testing

Trastuzumab 12 months
1690 patients

Trastuzumab 6 months
1690 patients

~20% of French HER2+ treated patients enrolled

• May 28th 2010 – IDMC meeting

"After careful thought and lengthy debate we recommend that entry to the trial be suspended. We do not recommend, at this time, a crossover to a longer duration of intervention for the 6 month group but would reserve the option of such a recommendation for the future, dependent on how the data develop"

Closed: 09/07/2010
Database locked: 31/07/2012

www.esmo2012.org
Six versus 12 months of adjuvant trastuzumab in combination with dose-dense chemotherapy for women with HER2-positive breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG)

D. Mavroudis¹*, E. Saloustros², N. Malamos³, S. Kakolyris⁴, I. Boukovinas⁵, P. Papakotoulas⁶, N. Kentepozidis⁷, N. Ziras⁸ & V. Georgoulas⁹, on behalf of the Breast Cancer Investigators of the Hellenic Oncology Research Group (HORG), Athens, Greece

¹Department of Medical Oncology, University General Hospital of Heraklion, Heraklion; ²Oncology Unit, General Hospital of Heraklion ‘Venanella’; ³Department of Medical Oncology, Elena Venizelou Hospital, Athens; ⁴Department of Medical Oncology, University General Hospital of Alexandroupolis, Alexandroupolis; ⁵Department of Medical Oncology, Bioklinic of Thessaloniki, Thessaloniki; ⁶Department of Medical Oncology, Thessaloukio Hospital, Thessaloniki; ⁷Department of Medical Oncology, 251 Airforce General Hospital, Athens; ⁸Department of Medical Oncology, Metaxa Hospital, Athens; ⁹Department of Medical Oncology, University of Crete, School of Medicine, Heraklion, Greece

Received 19 January 2015; revised 13 April 2015; accepted 23 April 2015
TREATMENT SCHEDULE
Epirubicine 75mg/mq/iv/q 2wk; Cyclophosphamide 700mg/mq/iv/q 2wks; 5-fluorouracil 700 mg/mq/iv/q 2wks
Docetaxel 75 mg/mq/iv/q 2wks; Trastuzumab 8mg/kg→6mg/Kg/iv/q2wks, maintenance 6mg/Kg/iv/q3wk
Filgrastim 5ug/Kg days 3-10
Radiation and hormonal therapy following standard care.
**RESULTS**

**Panel A**
- Proportion of patients disease-free
- DFS (months)
- P = 0.137
- HR: 1.58, 95% CI: 0.86–2.10

**Panel B**
- Proportion of alive patients
- OS (months)
- P = 0.438
- HR: 1.45, 95% CI: 0.57–3.67
Conclusions: Our study failed to show noninferiority for the 6-month arm. The results further support the current standard of care that is administration of adjuvant trastuzumab for 12 months.
Four pivotal trials have established adjuvant Herceptin for 1 year as the standard of care in HER2-positive EBC.

**HERA (ex-USA)**—Gianni L, et al. 2011
- IHC / FISH
- N = 5102
- Observation
- 1 year
- 2 years*

**BCIRG 006 (global)**—Slamon D, et al. 2011
- FISH
- N = 3222
- 1 year
- 1 year

**NCCTG N9831 (USA)**—Perez EA, et al. 2011
- IHC / FISH
- N = 2614
- 1 year

**NSABP B-31 (USA)**—Perez EA, et al. 2011
- IHC / FISH
- N = 2043
- 1 year

**Chemotherapy +/- RT**
- Doxorubicin + cyclophosphamide
- Docetaxel
- Docetaxel + carboplatin
- Herceptin
- Paclitaxel

EBC, early breast cancer; IHC, immunohistochemistry; FISH, fluorescence in situ hybridisation
*HERA 2-year data are pending*
Cosa comporta per la paziente

- Prelievi più volte/mese
- Accessi ambulatoriali più volte/mese
- Permanenza in ambulatorio da 30 minuti ad alcune ore
- Posizionamento di accessi venosi centrali (chemioterapie per via ev)
Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-II breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial

Gustavo Imael, Roberto Heg, Susanne Muehlaber, Dominik Heinze, Bert Lui, Sung-Bae Kim, Tadeusz Piek, Mikhail Lichitse, Vladimir Semiglazov, Bohuslav Melcha, Christian Jackisch

Panel: Research in context

Systematic review
The standard route of administration of trastuzumab is by intravenous injection. When recombinant human hyaluronidase (rHuPH-20) became available, development of a subcutaneous formulation of trastuzumab was possible allowing for administration of larger volumes. At the time of study design, results from a phase 1 study were available, which showed that subcutaneous trastuzumab could be given in about 5 min, and could lead to similar systemic exposure and was well tolerated. On the basis of pharmacokinetic data from this study, the fixed dose of 600 mg subcutaneous trastuzumab was developed.
Patients with HER2-positive early breast cancer

Randomisation 1:1

Subcutaneous trastuzumab

Intravenous trastuzumab

Neoadjuvant treatment

Surgery

Adjuvant treatment

18 cycles/1 year

Follow-up: 2 years

Coprimary endpoints: $C_{t_{\text{tug}}}$ and pCR

- Trastuzumab subcutaneous 600 mg (5 mL) given every 3 weeks
- Trastuzumab intravenous 8 mg/kg loading dose, 6 mg/kg given every 3 weeks
- Docetaxel 75 mg/m²
- Fluorouracil (500 mg/m²), epirubicin (75 mg/m²), and cyclophosphamide (500 mg/m²) given every 3 weeks

Figure 1: Study design
Hannah-results: efficacy

Figure 3: Proportion of patients who achieved a pathological complete response
Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer): an open-label randomised study

Xavier Pivot, Joseph Gligorov, Volkmar Müller, Peter Barrett-Lee, Sunil Verma, Ann Knoop, Giuseppe Curigliano, Vladimir Semiglazov, Guillermo López-Vivanco, Valerie Jenkins, Nana Scotto, Stuart Osborne, Lesley Fallowfield, for the PrefHer Study Group

Summary

Background Subcutaneous trastuzumab has shown non-inferior efficacy and a similar pharmacokinetic and safety profile compared to intravenous administration. The PrefHer study aimed to assess patient preference for subcutaneous versus intravenous administration.
Panel: Research In context

Systematic review
Trastuzumab is currently administered intravenously according to bodyweight. Addition of recombinant human hyaluronidase (rHuPH20) allowed development of a fixed-dose subcutaneous formulation. The phase 3 HannaH study showed non-inferior efficacy and a similar pharmacokinetic and safety profile between the subcutaneous and intravenous formulations of trastuzumab. A subcutaneous single-use injection device is under development and shows bioequivalence to subcutaneous administration via hand-held syringe. Patient preference for subcutaneous or intravenous administration of trastuzumab has not been taken into account to date.

Interpretation
Patient preference and safety results from PrefHer, combined with efficacy, pharmacokinetic, and safety results from HannaH, suggest that a fixed dose of 600 mg subcutaneous trastuzumab every 3 weeks is a validated, well tolerated treatment option for HER2-positive breast cancer and is preferred by patients.

<table>
<thead>
<tr>
<th>Subcutaneous preferred, n=216</th>
<th>n*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time saving</td>
<td>195</td>
</tr>
<tr>
<td>Less pain/discomfort</td>
<td>88</td>
</tr>
<tr>
<td>Convenience to patient</td>
<td>35</td>
</tr>
<tr>
<td>Ease of administration</td>
<td>33</td>
</tr>
<tr>
<td>Problems with Intravenous</td>
<td>25</td>
</tr>
<tr>
<td>Less stress/anxiety</td>
<td>15</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intravenous preferred, n=16</th>
<th>n*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fewer reactions (less pain, bruising, irritation, etc)</td>
<td>11</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
</tr>
<tr>
<td>Environment/staff</td>
<td>2</td>
</tr>
<tr>
<td>Perceived efficacy</td>
<td>1</td>
</tr>
<tr>
<td>Ecological considerations</td>
<td>1</td>
</tr>
</tbody>
</table>

Responses to the question “What are the two main reasons for your preference?” were recorded verbatim by the interviewer. Four experienced researchers independently scrutinised the dataset and provided overarching themes or core categories for coding. When broad consensus about these had been reached each researcher independently coded every patient’s response; the researchers then reconciled codings with each other and determined if any thematic categories could reasonably be collapsed together or if a new category was required. Some patients gave more than one reason for preference.

Table 2: Primary reasons for patients’ preferences (evaluable Intention-to-treat population)
Anti-HER2 therapy and HER family

- Trastuzumab
- Pertuzumab
- T-DM1
- Lapatinib
- Neratinib

- EGFR HER1
- HER2
- HER3
- HER4
GeparQuinto: Phase III comparison of trastuzumab vs lapatinib with chemotherapy as neoadjuvant therapy

Cohort of HER2-positive (IHC 3+ or central FISH) operable or locally advanced breast cancer n = 620 randomised 1:1

- Epirubicin + cyclophosphamide + trastuzumab q3w x 4
- Docetaxel + trastuzumab q3w x 4
- Trastuzumab q3w to 1 year total

- Epirubicin + cyclophosphamide q3w x 4 + lapatinib 1000–1250 mg qd
- Docetaxel q3w x 4 + lapatinib 1000–1250 mg qd
- Trastuzumab q3w to 1 year total

Primary endpoint: pCR defined as no microscopic evidence of residual tumour (invasive or non-invasive) in any resected specimens of the breast and axillary lymph nodes

Epirubicin 100 mg/m² + cyclophosphamide 600 mg/m² q3w x 4;
docetaxel 100 mg/m² q3w x 4;
trastuzumab 8 mg/kg loading dose followed by 6 mg/kg q3w for 12 months;

GeparQuinto: pCR for trastuzumab vs lapatinib

Trastuzumab-treated patients had a significantly higher pCR rate than those treated with lapatinib

Graphical elaboration from text data

pCR definition: No residual disease in breast and nodes

EC, epirubicin + cyclophosphamide; T, docetaxel; H, trastuzumab; L, lapatinib

GeparQuinto

The overall benefit-risk was substantially better for trastuzumab compared with lapatinib

- 33.1% (n=102) of patients receiving lapatinib did not complete treatment as planned
  - Compared with only 14% (n=43) of trastuzumab-treated patients
- 39.3% (n=120) of patients receiving lapatinib had their dose reduced to manage adverse events
  - Most common Grade 3/4 adverse event was diarrhoea
    - 11.7% in the lapatinib arm
    - 2.6% in the trastuzumab arm

Anti-HER2 therapy and HER family

- Trastuzumab
- Pertuzumab
- T-DM1
- Lapatinib
- Neratinib

Dual-vertical blockade

EGFR HER1
HER2
HER3
HER4
NeoALTTO; Study design

N=455

Invasive breast cancer
T>2 cm
HER2 positive

Before Surgery
- lapatinib
- paclitaxel

After Surgery
- lapatinib

trastuzumab
paclitaxel

SURGERY

FEC

3

6 weeks
12 weeks
9 weeks
34 weeks

Efficacy; pCR (no invasive cancer in the breast), tpCR (no invasive cancer in the breast and no Ax) rates

Dual inhibition of HER2 might be a valid approach to treatment of HER2-positive breast cancer in the neoadjuvant setting.

Event-Free Survival Analysis

All patients

Tests for interaction according to HR status
Lap + Tras vs Tras $P = .48$
Lap vs Tras $P = .56$

Overall Survival Analysis

All patients

<table>
<thead>
<tr>
<th>Arm</th>
<th>No. patients</th>
<th>No. deaths</th>
<th>3yr OS rate</th>
<th>Hazard ratio c.f. Tras</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lap+Tras</td>
<td>152</td>
<td>13</td>
<td>95%</td>
<td>0.62 (0.30,1.25)</td>
<td>0.19</td>
</tr>
<tr>
<td>Lap</td>
<td>154</td>
<td>18</td>
<td>93%</td>
<td>0.86 (0.45,1.63)</td>
<td>0.65</td>
</tr>
<tr>
<td>Tras</td>
<td>149</td>
<td>23</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tests for interaction according to HR status
Lap + Tras vs Tras $P = .54$
Lap vs Tras $P = .90$

Cardiac Safety

Note: No major cardiac dysfunction was observed in the neoadjuvant phase. One patient in each group presented a LVEF <50% and a decrease of >10% from baseline (Baselga, et al).


Main Differences in AEs by Treatment Arm

<table>
<thead>
<tr>
<th></th>
<th>Diarrhea</th>
<th>Hepatobiliary AES</th>
<th>Rash</th>
</tr>
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<tbody>
<tr>
<td>% of AEs by Treatment Arm</td>
<td>83</td>
<td>87</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>(25)</td>
<td>(22)</td>
<td>(5)</td>
</tr>
<tr>
<td></td>
<td>(26)</td>
<td>(11)</td>
<td>(&lt;1)</td>
</tr>
<tr>
<td></td>
<td>(3)</td>
<td>(7)</td>
<td>(5)</td>
</tr>
<tr>
<td></td>
<td>P&lt;.0001</td>
<td>P&lt;.0006</td>
<td>P&lt;.0001</td>
</tr>
</tbody>
</table>

AEs
- Lapatinib (L)
- Trastuzumab (T)
- L + T

Severe AEs

NeoALTTO Lapatinib-Containing Arms: Lapatinib Completion

Randomized: N = 154
- Started: N = 151
- Discontinued: N = 49
- Completed neo adj phase: N = 102

Lapatinib alone
- 100% completed
- 98% started
- Discontinued: Adv event 32, Progression 3, Other 14
- Completed adj phase: 66%

Lapatinib + Trastuzumab
- 100% started
- 98% completed
- Advances event 34, Progression 1, Other 22
- Completed adj phase: 61%

Started adj therapy: N = 115
- Discontinued: Adv event 5, Recurrence 4, Other 7
- Completed adj phase: 75%

Completed adj phase: N = 99

NeoALTTO Trastuzumab Containing Arms: Trastuzumab Completion

Trastuzumab alone
- Randomized: N = 149
- Started: N = 148
- Discontinued: N = 10
- Completed neo adj phase: N = 138

Adv event: 2
Progression: 4
Other: 4

Trastuzumab + lapatinib
- N = 152
- N = 149
- N = 12
- N = 137

Adv event: 7
Progression: 1
Other: 4

Trastuzumab + lapatinib
- N = 141
- N = 21
- N = 120

Adv event: 9
Recurrence: 2
Other: 10

USE OF ANTI-HER 2 «VERTICAL BLOCKAGE» in adjuvant setting (ALTTO study)

(Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation)

Design 1: after completion of CT
Design 2: a) concomitant “Paclitaxel” or “Docetaxel”; b) concomitant “Docetaxel” + “Carboplatin”

ALTTO (EGF106708) study design outline
EFFICACY RESULTS
(on 6281 randomized patients - excluded patients in «L» alone arm)

DISEASE-FREE SURVIVAL (DFS) ANALYSIS

<table>
<thead>
<tr>
<th>Arm</th>
<th>No. patients</th>
<th>No. events</th>
<th>4yr DFS rate</th>
<th>Hazard ratio c.f. Tras*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lap+Tras</td>
<td>2093</td>
<td>254</td>
<td>88%</td>
<td>0.84 (0.70,1.02)</td>
<td>0.048**</td>
</tr>
<tr>
<td>Tras-&gt;Lap</td>
<td>2091</td>
<td>284</td>
<td>87%</td>
<td>0.96 (0.80,1.15)</td>
<td>0.610</td>
</tr>
<tr>
<td>Tras</td>
<td>2097</td>
<td>301</td>
<td>86%</td>
<td>* 97.5% Cl</td>
<td></td>
</tr>
</tbody>
</table>

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

Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting
DFS BY HORMONE RECEPTOR STATUS

**HR positive**

- Lap+Tras: 1203 pts, 133 events, DFS rate: 90%, 4yr: 0.87 (0.69, 1.10), p-value: 0.233
- Tras->Lap: 1205 pts, 141 events, DFS rate: 89%, 4yr: 0.92 (0.73, 1.16), p-value: 0.477
- Tras: 1200 pts, 150 events, DFS rate: 88%, 4yr: *(95% CI)*

**HR negative**

- Lap+Tras: 890 pts, 121 events, DFS rate: 86%, 4yr: 0.82 (0.65, 1.04), p-value: 0.107
- Tras->Lap: 886 pts, 143 events, DFS rate: 84%, 4yr: 1.00 (0.79, 1.26), p-value: 0.990
- Tras: 897 pts, 151 events, DFS rate: 83%, 4yr: *(95% CI)*

Interaction tests: p = 0.70 T + L
p = 0.60 T → L

Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting
DFS BY CHEMOTHERAPY TIMING

Sequential (Design 1)

Concurrent (Designs 2 & 2B)

Interaction tests $p = 0.41$ L + T
$p = 0.31$ T → L

Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting
OVERALL SURVIVAL (OS) ANALYSIS

Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting
PROPORTION OF PATIENTS RECEIVING ≥ 85% OF THE PLANNED DOSE OF ANTI-HER2 DRUGS

Presented By Martine Piccart-Gebhart at 2014 ASCO Annual Meeting
Anti-HER2 therapy and HER family

- **Dual-orizontal blockade**
- Trastuzumab
- Pertuzumab
- Lapatinib
- Neratinib
- EGFR
- HER1
- HER2
- HER3
- HER4
- T-DM1
NeoSphere: Randomised, open-label study of pertuzumab and/or trastuzumab with a taxane in the neoadjuvant setting

(NEOadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation)

Gianni, Lancet Oncol 2012; 13
Patient population
- Women aged $\geq 18$ years with locally advanced, inflammatory or early HER2-positive breast cancer (N = 417)

Study design
- Phase II study of neoadjuvant trastuzumab and pertuzumab in the treatment of patients with HER2-positive breast cancer

Primary endpoint
- pCR rate at time of surgery

Key secondary endpoints
- Clinical response rate, time to response
- Rate of breast-conserving surgery
- Safety

NeoSphere: Pertuzumab and trastuzumab plus docetaxel significantly increased the pCR rate vs other arms

H, trastuzumab; P, pertuzumab; pCR, pathological complete response; T, docetaxel

TRYPHAENA: A Phase II study of pertuzumab and trastuzumab in the neoadjuvant setting

(Tolerance of Pertuzumab, Herceptin, and Anthracyclines in Neo-Adjuvant breast cancer)
TRYPHAENA: Summary

• Results from TRYPHAENA indicate a low incidence of symptomatic and asymptomatic LVSD across all arms
  – Concurrent administration of pertuzumab plus trastuzumab with epirubicin resulted in similar cardiac tolerability compared with sequential administration or the anthracycline-free regimen
• Neutropenia, febrile neutropenia, leukopenia and diarrhoea were the most frequently reported adverse events (grade ≥3) across all arms
• Regardless of chemotherapy chosen, the combination of pertuzumab with trastuzumab in the neoadjuvant setting resulted in high pCR rates (57–66%)

TRYPHAENA supports the ongoing APHINITY study, a Phase III trial to evaluate pertuzumab and trastuzumab plus standard chemotherapy in the adjuvant setting

LVSD, left ventricular systolic dysfunction; pCR, pathological complete response

DUAL ORIZONTAL BLOCKADE BETTER IN ADIUVANT SETTING?

.....WAITING FOR «APHINITY TRIAL results»

Surgery

Central confirmed HER2 status

R

Trastuzumab + Pertuzumab

Trastuzumab + Placebo
ESCALATION ATTEMPTS WITH ANTI-HER2 THERAPIES...
RANDOMIZED PHASE III TRIAL OF ADJUVANT BEVACIZUMAB IN HER2-POSITIVE BREAST CANCER: BETH STUDY

Node positive or high-risk node-negative HER2+

Cohort 1 (N=3231)
Non-Anthracycline
TCH→H

Arm 1 A: TCH→H
Arm 1 B: TCH Bev→H Bev

Cohort 2 (N=278)
Anthracycline
TH→FEC→H

Arm 2 A: TH→FEC→H
Arm 2 B: TH→FEC→Bev→H Bev

Slamon D et al, SABCS 2013
RANDOMIZED PHASE III TRIAL OF ADJUVANT BEVACIZUMAB IN HER2-POSITIVE BREAST CANCER: BETH

Median Follow up 38 months

<table>
<thead>
<tr>
<th></th>
<th>IDFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without Bevacizumab</td>
<td>92%</td>
<td>96%</td>
</tr>
<tr>
<td>With Bevacizumab</td>
<td>92%</td>
<td>97%</td>
</tr>
</tbody>
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Slamon D et al, SABCS 2013
SMALL HER2+ BREAST CANCER: THE DANA FARBER PROSPECTIVE PHASE II STUDY

N=406
Median age 55
T1a 20%
T1b 35%
T1c 42%
T2 9%
N0 98.5%
HR+ 67%

Paclitaxel weekly x12
Trastuzumab weekly x52

3y DFS= 98.7%
(95% CI: 97.6-99.8%)

Tolaney SM et al, NEJM 2015
EXTENDED ADJUVANT NERATINIB EXTENDED PHASE III TRIAL

N= 2821
HER2+ Stage II-IIIC node positive breast cancer following CT+12 months of trastuzumab adjuvant

Neratinib 240mg/po/d for 1 year

Placebo/po/d for 1 year

Extended DFS by 33% compared with placebo (HR=0.67; P=0.0046)
(Side effect: diarrhea)

At 2 years of Follow up:
absolute benefit for all patients 2.3
absolute benefit for HR positive 4.2

ASC, 2015
(On going) KATHERINE: POST NEOADJUVANT T-DM1 IN PATIENTS WITH RESIDUAL TUMOR FOLLOWING NEOADJUVANT CT + TRASTUZUMAB

Neoadjuvant CT + Trastuzumab → RESIDUAL INVASIVE CANCER

R

T-DM1

Trastuzumab

Primary endpoint: IDFS

(about 900/1400 patients recruited as today – march 2015, by M. Piccart)
THE KAITLIN ADJUVANT TRIAL: T-DM1 INSTEAD OF TAXANE

HER2 + Node + or Node -, ER- And T>20mm

R

AC x4 or FEC x3

TAXANE TRASTUZUMAB PERTUZUMAB

AC x4 or FEC x3

T-DM1 PERTUZUMAB

(1300/2500 patients recruited as today - march 2015, by M. Piccart)
(future) Is Chemotherapy Always Mandatory in HER2+ Disease?

**Identification** of **This** HER2+ and HR+ disease

<table>
<thead>
<tr>
<th>pCR Rates</th>
<th>29%</th>
<th>62%</th>
<th>73-80%</th>
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</thead>
<tbody>
<tr>
<td>Dual HER2 blockade alone</td>
<td>Dual HER2 blockade + taxane</td>
<td>Dual HER2 blockade + Taxane + Other agent (anthra, carbo)</td>
<td></td>
</tr>
</tbody>
</table>

Based on Neosphere, NeoAltto, Tryphaena
IS PIK3CA MUTATION AS MEDIATOR OF (DUAL) HER2 BLOCKADE RESISTANCE?
Pertuzumab and T-DM1 Biomarker Program

PIK3CA mutations (32% incidence): A strong candidate prognostic marker but weak predictive marker!

CLEOPATRA

EMILIA

<table>
<thead>
<tr>
<th>PIK3CA status</th>
<th>Single blockade median PFS</th>
<th>Dual blockade median PFS</th>
<th>HR</th>
<th>Lapatinib + CAP median PFS</th>
<th>T-DM1 median PFS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutant</td>
<td>8.6 months</td>
<td>12.5 months</td>
<td>0.64</td>
<td>4.3 months</td>
<td>10.9 months</td>
<td>0.45</td>
</tr>
<tr>
<td>Wild type</td>
<td>13.8 months</td>
<td>21.8 months</td>
<td>0.67</td>
<td>6.4 months</td>
<td>9.8 months</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Dual blockade works in both cohorts... but larger magnitude of benefit in wild type cohort

T-DM1 works in both cohorts... but larger magnitude of benefit in mutated cohort

Intrinsic Subtypes, PIK3CA Mutation, and the Degree of Benefit From Adjuvant Trastuzumab in the NSABP B-31 Trial

Katherine L. Pogue-Geile, Nan Song, Jong-Hyeon Jeong, Patrick G. Gavin, Seong-Rim Kim, Nicole L. Blackmon, Melanie Finnigan, Priya Rastogi, Louis Fehrenbacher, Eleftherios P. Manoukas, Sandra M. Swain, D. Lawrence Wickerham, Charles E. Geyer Jr, Joseph P. Costantino, Norman Wolmark, and Soonmyung Paik

1578 patients → 671 randomly selected for PIK3CA hotspots mutation → 24.7% mutated

Failure of PIK3CA mutation to define subset of patient with differential benefit for trastuzumab in adjuvant setting. Hypothesis: different behaviour of predictive marker in the different settings (adjuvant, neoadjuvant, metastatic due to tumor burden)
355 patients recruited in «neoALTTO trial»

In this study, we find that mutations in PIK3CA downstream of HER2 correlate with a lower response to HER2-targeted neoadjuvant therapy in breast cancer as measured by pCR. There is no significant difference for PIK3CA mutation status in survival follow-up (EFS and OS).
A PIK3CA inhibitor might have an impossible task in the presence of chemotherapy.

ON GOING DESIGN NEOADJUVANT TRIAL

ENDOCRINE THERAPY + DUAL HER2 BLOCKADE +/- PIK3CA INHIBITORS
PIK3CA Genotype and Treatment Decisions in Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer

David W. Cescon, Princess Margaret Cancer Centre, University Health Network, University of Toronto, and Campbell Family Institute for Breast Cancer Research, Toronto, Ontario, Canada
Philippe L. Bedard, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Ontario,

we will learn whether knowledge of PIK3CA mutations can improve the precision with which we apply HER2-targeted therapies; for the present, we will continue to rely on the first (and still only) actionable genomic alteration in breast cancer: amplification of HER2.
grazie dell'attenzione