Essais de supériorité / d’équivalence / de non-infériorité

Prof. X Pivot
Superiority

Confidence interval 95%

P=0.002  HR 0.75 (95%CI: 0.90 – 0.50)
P=0.05   HR 0.80 (95%CI: 1 – 0.65)

Ratio of events over the time between arm A and B and its 95%CI

Hypothesis

Null:
No different between A and B

Alternative:
B different from A (bi sided): B ≠ A
B better than A (one sided): B > A
First CMF Program

Relapse-free Survival

HR: 0.71
p = 0.0054

Total Survival

HR: 0.79
p = 0.039

Surgery

CMF

Years

5 10 15 20 25 30

Milan Cancer Institute
Breast cancer mortality

Taxanes > Anthra. > CMF > No Chemo.

RELATIVE and ABSOLUTE RISK

without adj  N = 100  DCD = 40
With adj  N = 100  DCD = 30

relatif benefit = 25%
absolute benefit = 10%

Without adj  N = 100  DCD = 12
With adj  N = 100  DCD = 9

relatif benefit = 25%
absolute benefit = 3%
Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years


<table>
<thead>
<tr>
<th>DFS Outcomes</th>
<th>Letrozole</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall 5-yr DFS, %</td>
<td>95</td>
<td>91</td>
<td>0.66 (0.48-0.91)</td>
<td>.01</td>
</tr>
<tr>
<td>Events, n (%)(%)</td>
<td>67 (7.0)</td>
<td>98 (10.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New contralateral breast cancers, n (%)</td>
<td>13 (1.4)</td>
<td>31 (3.2)</td>
<td></td>
<td>.007</td>
</tr>
<tr>
<td>Locoregional recurrences, n</td>
<td>19</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distant recurrences, n</td>
<td>42</td>
<td>53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone recurrences, n</td>
<td>28</td>
<td>37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trastuzumab in the Treatment of Breast Cancer
Gabriel N. Hortobagyi, M.D.
October 25th 2005

"Clearly, the results reported in this issue of the Journal are not evolutionary… but revolutionary."

G Hortobagyi
DFS and OS benefits were 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></th>
<th>OS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>HR</td>
<td>p value</td>
<td>HR</td>
</tr>
<tr>
<td>HERA1–4</td>
<td>1</td>
<td>3387</td>
<td>0.54</td>
<td>&lt; 0.0001</td>
<td>0.76</td>
</tr>
<tr>
<td>CT±RT→T vs. CT±RT</td>
<td>2</td>
<td>3401</td>
<td>0.64</td>
<td>&lt; 0.0001</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>3401</td>
<td>0.76</td>
<td>&lt; 0.0001</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>3399</td>
<td>0.76</td>
<td>&lt; 0.0001</td>
<td>0.76</td>
</tr>
<tr>
<td>NCCTG N9831/NSABP B-315–7</td>
<td>2</td>
<td>3351</td>
<td>0.48</td>
<td>&lt; 0.0001</td>
<td>–</td>
</tr>
<tr>
<td>AC→Tax+T→T vs. AC→Tax</td>
<td>4</td>
<td>4045</td>
<td>0.52</td>
<td>&lt; 0.001</td>
<td>0.61</td>
</tr>
<tr>
<td>BCIRG 0068</td>
<td>8.4</td>
<td>4046</td>
<td>0.60</td>
<td>&lt; 0.0001</td>
<td>0.63</td>
</tr>
<tr>
<td>AC→Tax + T vs. AC→Tax</td>
<td>5.4</td>
<td>3222</td>
<td>0.64</td>
<td>&lt; 0.001</td>
<td>0.63</td>
</tr>
<tr>
<td>Tax+Cb→T vs. AC→Tax</td>
<td></td>
<td></td>
<td>0.75</td>
<td>0.04</td>
<td>0.77</td>
</tr>
</tbody>
</table>

AC, doxorubicin and cyclophosphamide; Cb, carboplatin; CT, chemotherapy; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; RT, radiotherapy; T, trastuzumab; Tax, taxane.

In low risk cases: Paclitaxel + Trastuzumab seemed to be enough

- Phase II trial
- 406 patients,
- T < 3 cm
- Median follow up 4 years
- Occurrence of only 2 metastatic events

Update ASCO 2017
7 years Follow-up
4 metastatic events

Confidence interval 95%

Ratio of events over the time between arm A and B and its 95% CI

Hypothesis

Null:
Difference between A and B

Alternative:
No different between A and B

HR 0.95 (95%CI: 0.9 – 1.05)

HR 1 (95%CI: 0.9 – 1.1)
CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial


In this randomised, double-blind, active-controlled, phase 3 equivalence trial, we recruited women aged 18 years or older with stage I–IIIa operable HER2-positive breast cancer from 112 centres in 23 countries. Inclusion criteria were an Eastern Cooperative Oncology Group performance status score of 0 or 1; a normal left ventricular ejection fraction (LVEF); a normal serum creatinine; a serum alanine transaminase or aspartate aminotransferase level of less than 3 times the upper limit of normal (ULN); and known oestrogen and progesterone receptor status. Exclusion criteria included bilateral breast cancer, previous cancer treatment, and known human immunodeficiency virus infection. We randomly allocated 549 patients (271 [49%] to CT-P6 [eptucumab, an anti-HER2 monoclonal antibody] and 278 [51%] to reference trastuzumab intravenously [eight cycles, each lasting 3 weeks, followed by an adjuvant treatment period of up to 1 year]). Participants and investigators were masked to treatment until study completion. The primary endpoint was pathological complete response (pCR) after the last patient was enrolled. The equivalence margin of 0·04% for the relative difference (RD) in pCR between CT-P6 and reference trastuzumab was demonstrated. The 95% CI for the RD for pCR was –0·12 to 0·05 (equivalence). A similar proportion of patients achieved pathological complete response with CT-P6 compared with reference trastuzumab. The estimated treatment outcome difference (95% CI) was –0·04% [–0·12 to 0·05]. Availability of CT-P6 was similar to that of reference trastuzumab (95% CI for RD –0·15 to 0·15). Adverse events were similar. Docetaxel 75 mg/m², followed by an adjuvant chemotherapy regimen with cyclophosphamide 500 mg/m² and epirubicin 75 mg/m², was administered on day 1 of cycles 1–4. Follow-up was to week 30 (after surgery), week 24 (after the completion of neoadjuvant chemotherapy), and up to 3 years after the last patient was enrolled.

For the full study results, see the paper in Lancet Oncology.

Primary endpoint
- tpCR** after neoadjuvant therapy and surgery (up to 30 weeks); per-protocol population
- Pre-defined equivalence margins: 95% CI for RR 0.74–1.35; 95% CI for RD +/− 15%

Secondary endpoints
- Efficacy: pCR (breast only), tpCR (without DCIS), ORR, breast conservation rate, DFS, PFS, OS
- Other: PK, PD, biomarkers and safety

Abbreviations: **pCR in breast and axillary lymph nodes. †From the date of last patient enrolment. DCIS, ductal carcinoma in situ.
**CT-P6 vs trastuzumab reference product in eBC: primary endpoint tpCR in per protocol set**

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>CT-P6 + (n=271)</th>
<th>Herceptin (n=278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tpCR</td>
<td>46.8%</td>
<td>50.4%</td>
</tr>
<tr>
<td>Risk difference, (95% CI)</td>
<td>-3.62% (-12.38, 5.16)</td>
<td>0.93 (0.78-1.11)</td>
</tr>
<tr>
<td>Ratio (95%CI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours Herceptin

Phase III, Randomized, Double-Blind Study Comparing the Efficacy, Safety, and Immunogenicity of SB3 (Trastuzumab Biosimilar) and Reference Trastuzumab in Patients Treated With Neoadjuvant Therapy for Human Epidermal Growth Factor Receptor 2–Positive Early Breast Cancer

**Purpose**

This phase III study compared SB3, a trastuzumab (TRZ) biosimilar, with reference TRZ in patients with HER2-positive breast cancer. 

**Patients and Methods**

Patients were randomly assigned to receive neoadjuvant SB3 or TRZ for eight cycles concurrently with chemotherapy (four cycles of docetaxel followed by surgery, and then 10 cycles of FEC [fluorouracil, epirubicin, and cyclophosphamide] followed by surgery). 

**Results**

Overall response rate, event-free survival, overall survival, safety, and immunogenicity were comparable. Safety and immunogenicity were comparable. 

**Conclusion**

The introduction of trastuzumab (TRZ; Herceptin; biosimilar) and reference TRZ in patients treated with neoadjuvant therapy for HER2-expressing human epidermal growth factor receptor 2–positive early breast cancer has dramatically changed the natural history of this disease.

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**Primary endpoint**

- pCR (breast only) after neoadjuvant therapy and surgery; per-protocol population
- Pre-defined equivalence margins: 90% CI for RR 0.785–1.546; 95% CI for RD +/-13%

**Secondary endpoints**

- Efficacy: tpCR, ORR, EFS
- Other: PK, immunogenicity and safety
SB3 vs trastuzumab reference product in eBC: primary endpoint tpCR in ITT set

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>SB3 (n=402)</th>
<th>Herceptin (n=398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>bpCR</td>
<td>51.7%</td>
<td>42%</td>
</tr>
<tr>
<td>Risk difference, (95% CI)</td>
<td></td>
<td>10.7% (4.13, 17.26)</td>
</tr>
<tr>
<td>Ratio (95%CI)</td>
<td></td>
<td>1.259 (1.112-1.426)</td>
</tr>
</tbody>
</table>

Favours Herceptin

![Diagram showing difference in bpCR (%)](image)

X Pivot et al, JCO 2018
Non - Inferiority

Confidence interval 95%

Ratio of events over the time between arm A and B and its 95%CI

Hypothesis

Null:
Difference between A and B

Alternative:
No superiority between A and B

P = 0.02 HR 0.95 (95%CI: 0.9 – 1.05)

P = 0.04 HR 1 (95%CI: 0.9 – 1.1)
Short-HER: Disease Free Survival

Presented by: PierFranco Conte
PHARE: Non-inferiority of 6 months vs. 1 year of trastuzumab was not demonstrated

Primary endpoint: DFS

- **HR (6 months vs. 1 year)**: 1.28* (1.05, 1.56)
- **95% CI**: (1.05, 1.56)
- **p value**: 0.29

1 year

- **Patients**: 1690
- **Events**: 175

HR (95% CI): 1.46 (1.06, 2.01) (above the pre-specified non-inferiority CI of 1.15)

OS

- **HR (6 months vs. 1 year)**: 1.46 (1.06, 2.01)
- **95% CI**: (1.06, 2.01)
- **p value**: 0.03

1 year

- **Patients**: 1690
- **Events**: 66

HannaH: A pivotal Phase III trial to demonstrate the non-inferiority of trastuzumab SC vs. IV in terms of PK and efficacy

Primary endpoints
Non-inferiority of SC vs. IV based on co-primary endpoints:
- PK: observed trastuzumab $C_{\text{trough}}$ pre-dose Cycle 8 (pre-surgery)
- Efficacy: pCR in the breast

EFS, event-free survival; FEC, 5-fluorouracil, epirubicin and cyclophosphamide; OS, overall survival; R, randomisation;

HannaH: Non-inferiority margins for co-primary endpoints

Pharmacokinetic co-primary endpoint:
- Observed $C_{\text{trough}}$ at pre-dose Cycle 8
- Prespecified non-inferiority margin for geometric mean ratio SC vs. IV: 0.8

Efficacy co-primary endpoint:
- pCR in the breast
- Pre-specified non-inferiority margin for pCR rate difference SC-IV: −12.5%

$C_{\text{trough}}$: serum trough concentration; IV, intravenous; pCR, pathological complete response; SC, subcutaneous

HannaH: both co-primary endpoints were met

**PK**

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

Serum C<sub>trough</sub> levels

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab SC (n=234)</th>
<th>Trastuzumab IV (n=235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum C&lt;sub&gt;trough&lt;/sub&gt; levels</td>
<td>69.0 µg/mL</td>
<td>51.8 µg/mL</td>
</tr>
</tbody>
</table>

**Efficacy**

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

pCR in the breast

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab SC (n=260)</th>
<th>Trastuzumab IV (n=263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR in the breast</td>
<td>45.4%</td>
<td>40.7%</td>
</tr>
</tbody>
</table>

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

*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. 