Does Time Really Matter?

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Professor of Medicine
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Disclosure

• Research and Uncompensated Advisory Board with Genentech/Roche
Milestones for Trastuzumab Adjuvant Therapy for Early Breast Cancer

- Sept 1998: NSABP B31 Begins
- Feb 2000: EMA approves Trastuzumab for metastatic Breast Cancer
- May 2000: N9831 Begins
- Aug 2000: FDA approves Trastuzumab for metastatic Breast Cancer
- April 2001: BCIRG 006 Begins
- Dec 2001: HERA Begins
- May 2005: NSABP B31/NCCTG 9831/HERA ASCO
- May 2006: B31/N9831 HERA Pub NEJM
- Nov 2006: EMA approves Trastuzumab for Early Breast Cancer
- May 2008: FDA approves TCH and ACTH (006)

SMSwain
Adjuvant Trastuzumab Trial Designs

### NSABP B-31
- **H**: Doxorubicin
- **x 52**: Cyclophosphamide
- **H**: Paclitaxel
- **x 52**: Epirubicin
- **H**: Carboplatin
- **x 52**: Vinorelbine
- **H**: Fluorouracil

### BCIRG 006
- **H**: Doxorubicin
- **x 52**: Cyclophosphamide
- **H**: Paclitaxel
- **x 52**: Epirubicin
- **H**: Carboplatin
- **x 52**: Vinorelbine
- **H**: Fluorouracil

### NCCTG 9831
- **H**: Doxorubicin
- **x 52**: Cyclophosphamide
- **H**: Paclitaxel
- **x 52**: Epirubicin
- **H**: Carboplatin
- **x 52**: Vinorelbine
- **H**: Fluorouracil

### HERA
- **Standard ChemoRx**: Doxorubicin
- **H**: Cyclophosphamide
- **x 52**: Paclitaxel
- **H**: Epirubicin
- **x 52**: Carboplatin
- **H**: Vinorelbine
- **H**: Fluorouracil
- **No therapy**: Trastuzumab
- **H**: Trastuzumab

### FinHer
- **H**: Doxorubicin
- **x 9**: Cyclophosphamide
- **H**: Paclitaxel
- **x 9**: Epirubicin
- **H**: Carboplatin
- **x 9**: Vinorelbine
- **H**: Fluorouracil

### PACS 04
- **H**: Doxorubicin
- **x 52**: Cyclophosphamide
- **H**: Paclitaxel
- **x 52**: Epirubicin
- **H**: Carboplatin
- **x 52**: Vinorelbine
- **H**: Fluorouracil
- **No therapy**: Trastuzumab

Tripathy, 2011.
<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up yr</th>
<th>Hazard Ratio DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA (0 vs 1 yr)</td>
<td>4</td>
<td>.76</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>.76</td>
</tr>
<tr>
<td>NSABP B31/NCTTG 9831</td>
<td>4</td>
<td>.52</td>
</tr>
<tr>
<td>BCIRG 006 ACTH TCH</td>
<td>5</td>
<td>.64</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>.75</td>
</tr>
<tr>
<td>Fin HER</td>
<td>3 (RFS)</td>
<td>.42</td>
</tr>
<tr>
<td></td>
<td>5 (DDFS)</td>
<td>.65</td>
</tr>
<tr>
<td>PACS 04</td>
<td>4</td>
<td>.86</td>
</tr>
</tbody>
</table>
6 Months versus 12 Months Trastuzumab

PHARE
CHEMOTHERAPY → TRAS

12 Months versus 24 Months

HERA
CHEMOTHERAPY

adapted from V. Harvey
6 Months versus 12 Months Trastuzumab

PERSEPHONE-Sequential
CHEMOTHERAPY → TRAS

PERSEPHONE-Concurrent
DOC + TRAS → FEC → TRAS

HELLENIC
FEC → DOC + TRAS → TRAS

Adapted from V. Harvey
9 Weeks versus 12 Months Trastuzumab

**SOLD**
DOC + TRAS $\rightarrow$ FEC

DOC + TRAS $\rightarrow$ FEC $\rightarrow$ TRAS

**SHORT-HER**
DOC + TRAS $\rightarrow$ FEC

EC/AC $\rightarrow$ DOC + TRAS $\rightarrow$ TRAS

Adapted from V. Harvey
## Duration Trastuzumab Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Endpoint</th>
<th>Start</th>
<th>Enroll</th>
<th>Accrual</th>
<th>Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHARE</td>
<td>TTR</td>
<td>5/2006</td>
<td>3400</td>
<td>3382</td>
<td>+</td>
</tr>
<tr>
<td>HERA</td>
<td>DFS</td>
<td>12/2001</td>
<td>5043</td>
<td>5102</td>
<td>+</td>
</tr>
<tr>
<td>PERSEPHONE</td>
<td>DFS</td>
<td>10/2007</td>
<td>4000</td>
<td>2334</td>
<td>+</td>
</tr>
<tr>
<td>HELLENIC</td>
<td>3 yr DFS</td>
<td>10/2004</td>
<td>500</td>
<td>478</td>
<td>+</td>
</tr>
<tr>
<td>SOLD</td>
<td>DFS</td>
<td>1/2008</td>
<td>3000</td>
<td>1538</td>
<td>+</td>
</tr>
<tr>
<td>SHORT HER</td>
<td>DFS</td>
<td>12/2007</td>
<td>2500/1250</td>
<td>1070</td>
<td>+</td>
</tr>
</tbody>
</table>
PHARE study
6 mo vs 12 mo Trastuzumab
Disease Free Survival

![Graph showing Disease Free Survival](image)

**H 12m**
- At risk: 1690
- Events: 176
- HR: 1.28 (1.05 – 1.56)
- 95% CI: 0.29

**H 6m**
- At risk: 1690
- Events: 219
- HR: 1.28 (1.05 – 1.56)
- 95% CI: 0.29

* Cox model stratified by ER status and concomitant chemotherapy
Noninferiority Trials

• Null Hypothesis: Treatments differ by more than an acceptable level, $\Delta$
• Alternate Hypothesis: Treatments do not differ more than $\Delta$
• PHARE: $\Delta$ is 15% increase in DFS HR or HR of 1.15
• Hoping to reject the null and show the new treatment (6 mo) is noninferior or not worse than standard treatment (12 mo) by more than 15% increase in the DFS HR
• This would be accomplished if the CI does not include 1.15 and the upper limit is less than 1.15.
Primary endpoint scenarii

A: Equivalent
B: Superior
C: Non Inferior
D: PHARE trial
E: Inferior
PHARE CONCLUSIONS

• Observed HR 1.28 (CI: 1.05-1.56) so inconclusive in terms of noninferiority
• Since Lower CI > 1.0, conclude that 12 mo is better than 6 mo and increase in HR for 6 mo is at least 5%, not sure if less than 15%
• 395 events much less than planned 1040 events, so if trial had continued may have been able to statistically show HR with 6 mo greater than 15% with tighter point estimates
## DFS Forest plot

### Age yrs

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>129</td>
<td>1.78 (0.70 - 4.53)</td>
</tr>
<tr>
<td>35-49</td>
<td>1065</td>
<td>1.32 (0.95 - 1.84)</td>
</tr>
<tr>
<td>50-59</td>
<td>1059</td>
<td>1.38 (0.95 - 2.01)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>1128</td>
<td>1.08 (0.75 - 1.54)</td>
</tr>
</tbody>
</table>

### Nodal status

<table>
<thead>
<tr>
<th>Nodal Status</th>
<th>Number</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1842</td>
<td>1.31 (0.93 - 1.84)</td>
</tr>
<tr>
<td>1-3 pos. nodes</td>
<td>1008</td>
<td>1.27 (0.90 - 1.78)</td>
</tr>
<tr>
<td>&gt;3 pos. nodes</td>
<td>497</td>
<td>1.22 (0.85 - 1.75)</td>
</tr>
</tbody>
</table>

### Tumour size (cm)

<table>
<thead>
<tr>
<th>Tumour Size</th>
<th>Number</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>1771</td>
<td>1.00 (0.71 - 1.42)</td>
</tr>
<tr>
<td>2-5</td>
<td>1294</td>
<td>1.46 (1.09 - 1.95)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>242</td>
<td>1.23 (0.75 - 2.00)</td>
</tr>
</tbody>
</table>

### Estrogene Receptor

<table>
<thead>
<tr>
<th>Estrogen Status</th>
<th>Number</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1412</td>
<td>1.32 (1.01 - 1.74)</td>
</tr>
<tr>
<td>Positive</td>
<td>1968</td>
<td>1.23 (0.92 - 1.65)</td>
</tr>
</tbody>
</table>

### Chemotherapy

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Number</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential</td>
<td>1428</td>
<td>1.39 (1.05 - 1.85)</td>
</tr>
<tr>
<td>Concomitant</td>
<td>1952</td>
<td>1.17 (0.89 - 1.54)</td>
</tr>
</tbody>
</table>

### All patients (3380)

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
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<td>1.28 (1.05 - 1.56)</td>
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**Favors 6mo** vs **Favors 12mo**
Why is 6 months less effective than 12 months in the PHARE study?

- 58% of patients received sequential therapy
- HR 1.17 for concurrent treatment – closer to noninferior: but multiple testing
- Really need 12 months of therapy
HERA
1 year vs 2 years Trastuzumab
DFS FOR 2 YEARS VS. 1 YEAR TRASTUZUMAB AT 8 YRS MFU

No. at risk
Trastuzumab 2 years 1553 1553 1442 1361 1292 1223 1153 1051 633 194
Trastuzumab 1 year 1552 1552 1413 1319 1265 1214 1180 1071 649 205

Disease-free survival (%)

Years from randomization

Pts Events HR (2 vs 1) 95% CI p-value
2 years 1553 367 0.99 (0.85-1.14) 0.86
1 year 1552 367

Trastuzumab 2 years --
Trastuzumab 1 year --
DFS CUMULATIVE INCIDENCE OF BC AND NON-BC COMPETING RISKS
By HORMONE RECEPTOR STATUS

Hormone receptor positive
92.6% received endocrine therapy

Hormone receptor negative
2.8% received endocrine therapy

Trastuzumab 2 years BC event
Trastuzumab 2 years non-BC event
Trastuzumab 1 year BC event
Trastuzumab 1 year non-BC event
Considerations

- Sequential therapy in several studies has higher HR than concurrent studies.
- Only adjuvant study of single agent anti-HER2 TKI, most likely not noninferior.
- ADCC may be more important with lower burden of disease since receptors saturated.
## Sequential Studies of Adjuvant Trastuzumab

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<td>.76</td>
</tr>
<tr>
<td>0 vs 1</td>
<td>8</td>
<td>.76</td>
</tr>
<tr>
<td>2 vs 1</td>
<td>8</td>
<td>.99</td>
</tr>
<tr>
<td>PHARE 6 vs 12</td>
<td>4</td>
<td>1.28</td>
</tr>
<tr>
<td>N9831 Sequential (B) vs none</td>
<td>5</td>
<td>.67</td>
</tr>
<tr>
<td>N9831 Sequential (B) vs Concurrent (C)</td>
<td>5</td>
<td>.77</td>
</tr>
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<td>.86</td>
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</table>
How Does Trastuzumab Work?

**Signaling Disruption**

Trastuzumab binds to HER2, disrupting the signaling pathway.

**Activation of Immune Effector Mechanisms**

Antibody Dependent Cell Mediated Cytotoxicity (ADCC)

NK Cell binds to HER2+ Tumor Cell and activates cytotoxicity.

Adapted from LOUIS M. WEINER, MD
Serum Trough levels of Trastuzumab
Q 3 weeks versus weekly

Leyland-Jones et al, 2003 JCO; 21:3968
Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization trial (ALTTO)

Surgery

 +/- Anthracycline containing CT

1 year

Lapatinib

Trastuzumab

Trastuzumab

“lapatinib alone arm is unlikely to meet the pre-specified criteria to demonstrate non-inferiority to trastuzumab alone with respect to disease-free survival “ September 9, 2011

PIs: E Perez, M Piccart
There is complete inhibition of tumors in FcγRIIB (inhibitory signals)-deficient mice

TAXHER01: Preoperative Trastuzumab and Docetaxel X 6

Natural Killer Cells after 6 cycles

Control: No Trastuzumab

Arnould et al, 2006 BJC; 94: 262
Cardiotoxicity
Cumulative incidence of PRIMARY CARDIAC ENDPOINTS* (NYHA class III or IV, confirmed by a cardiologist, and LVEF < 50% and ≥ 10% below baseline OR cardiac death)

* Competing risk analysis with disease-free survival events considered as competing risks

<table>
<thead>
<tr>
<th>Years from randomization</th>
<th>Trastuzumab 1 year</th>
<th>Trastuzumab 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>2</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>3</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>4</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>5</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>6</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>7</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>8</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>9</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

No. at risk
- Trastuzumab 2 years: 1673, 1533, 1423, 1345, 1276, 1207, 1137, 1038, 637, 186
- Trastuzumab 1 year: 1682, 1536, 1399, 1306, 1254, 1203, 1169, 1063, 659, 203
NSABP B-31: 7 yr FU

Cumulative Incidence of Cardiac Events
(Cardiac death or CHF with ↓ in EF – different from HERA)

HR=3.30; P-value = 0.00038

ACP arm; 4.0 %

ACP arm; 1.3 %

Romond et al. JCO 9-2012 e pub
CUMULATIVE INCIDENCE OF PRIMARY OR SECONDARY CARDIAC ENDPOINTS*
(↓ LVEF < 50% and ≥ 10% below baseline confirmed by repeat assessment)

<table>
<thead>
<tr>
<th>Years from randomization</th>
<th>No. at risk</th>
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</thead>
<tbody>
<tr>
<td>Trastuzumab 2 years</td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td>1673</td>
</tr>
<tr>
<td>1 year</td>
<td>1682</td>
</tr>
<tr>
<td>1 year</td>
<td>1466</td>
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<td>2 years</td>
<td>1323</td>
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<td>1 year</td>
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<td>629</td>
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<tr>
<td>2 years</td>
<td>589</td>
</tr>
<tr>
<td>1 year</td>
<td>171</td>
</tr>
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</table>

* Competing risk analysis with disease-free survival events considered as competing risks
ADJUVANT TRASTUZUMAB

< 1 Year =

6 Months 2 Years

ONE YEAR ADJUVANT TRASTUZUMAB REMAINS STANDARD
Remaining Investigations

- PEER review of presented studies and longer follow up of PHARE
- Trastuzumab Overview Group (TOG)
- Lapatinib + Trastuzumab (ALTTO)
- Bevacizumab + Trastuzumab (BETH)
- Pertuzumab + Trastuzumab (APHINITY)
- TDM1 ± Pertuzumab
- Who should not receive chemo? Pertuzumab + Trastuzumab (NeoSPHERE) or Lapatinib + Trastuzumab (TBCRC 006)
Acknowledgements

• All investigators and patients on the trials
• Drs. Pivot and Gelber 😊
• Drs. Conte, Joensuu, Mavrudis, Earl
• Dr. Joe Costantino, NSABP

“Coming together is a beginning; keeping together is progress; working together is success.”

Henry Ford