Phase III Trial Comparing AC-T with AC-TH and with TCH in the Adjuvant Treatment of HER2 positive Early Breast Cancer Patients: Second Interim Efficacy Analysis


Study sponsored by Sanofi-Aventis
Support from Genentech
After the presentation these slides will be available at:

www.sabcs.org
www.cirg.org
The HER2 Alteration

Global Project Coordinator

Valerie Bee
BCIRG 006

4 x AC
60/600 mg/m²
4 x Docetaxel
100 mg/m²

AC→T

4 x AC
60/600 mg/m²
4 x Docetaxel
100 mg/m²

AC→TH

6 x Docetaxel and Carboplatin
75 mg/m²
AUC 6

TCH

1 Year Trastuzumab

Her 2+
(Central FISH)

N+
or high
risk N-

N=3,222

Stratified by Nodes and Hormonal Receptor Status

Slamon D., SABCS 2006
Endpoints

Primary
→ Disease-free Survival

Secondary
→ Overall Survival
→ Toxicity
→ Pathologic & Molecular Markers
## Patient characteristics

<table>
<thead>
<tr>
<th>Randomized (n=3,222)</th>
<th>AC-T n=1,073</th>
<th>AC-TH n=1,074</th>
<th>TCH n=1,075</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 50 years</td>
<td>52</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>KPS = 100</td>
<td>80</td>
<td>79</td>
<td>80</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>60</td>
<td>63</td>
<td>60</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>63</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td>Hormonotherapy</td>
<td>50</td>
<td>51</td>
<td>51</td>
</tr>
</tbody>
</table>

Enrollment: April 2001 to March 2004
# Tumor Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Randomized (n=3,222)</th>
<th>AC-T n=1,073</th>
<th>AC-TH n=1,074</th>
<th>TCH n=1,075</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of nodes +</strong></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>1 – 3</td>
<td>38%</td>
<td>38%</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>4 – 10</td>
<td>22%</td>
<td>24%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>&gt; 10</td>
<td>11%</td>
<td>9%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor Size (cm)</strong></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>( \leq 2 )</td>
<td>41%</td>
<td>38%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>&gt; 2 and ( \leq 5 )</td>
<td>53%</td>
<td>55%</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>&gt; 5</td>
<td>6%</td>
<td>7%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td><strong>ER and/or PR +</strong></td>
<td>54%</td>
<td>54%</td>
<td>54%</td>
<td></td>
</tr>
</tbody>
</table>
Crossover

After the trastuzumab efficacy results were announced in April ’05, to date:

- A total of 17 patients (1.6%) of 1,073 randomized to the ITT control arm (AC-T) crossed-over to receive trastuzumab
- Leaving 98.4% of the control arm enrollment intact for subsequent DFS, OS and safety comparison analyses
First/Second Interim Efficacy Analysis
(cutoff date June 30, 2005/November 01, 2006)

→ Median follow-up time = 23/36 months
→ 322/462 DFS Events
   ✓ Breast Cancer Relapse
   ✓ Second Primary Malignancy
   ✓ Death
→ 84/185 Deaths
Disease Free Survival – 1st interim analysis

Patients Events
- 1073 147 AC->T
- 1074 77 AC->TH
- 1075 98 TCH

HR (AC->TH vs AC->T) = 0.49 [0.37;0.65] P<0.0001
HR (TCH vs AC->T) = 0.61 [0.47;0.79] P=0.0002
Disease Free Survival - 2nd Interim Analysis

Absolute DFS benefits (from years 2 to 4):
AC→TH vs AC→T: 6%
TCH vs AC→T: 5%

HR (AC→TH vs AC→T) = 0.61 [0.48;0.76] P<0.0001
HR (TCH vs AC→T) = 0.67 [0.54;0.83] P=0.0003

AC® TH vs AC® T: 6%
TCH vs AC→T: 5%
### p-values at Interim Efficacy Analyses

<table>
<thead>
<tr>
<th></th>
<th>AC-T n=1,073</th>
<th>AC-TH n=1,074</th>
<th>TCH n=1,075</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with event</td>
<td>147 / 192</td>
<td>77 / 128</td>
<td>98 / 142</td>
</tr>
<tr>
<td>at 1&lt;sup&gt;st&lt;/sup&gt; interim analysis</td>
<td>p=0.0000001 / 0.000011</td>
<td>p=0.00015 / 0.00028</td>
<td>p=0.16 / 0.42</td>
</tr>
<tr>
<td>at 2&lt;sup&gt;nd&lt;/sup&gt; interim analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic events</td>
<td>113 / 143</td>
<td>52 / 93</td>
<td>67 / 98</td>
</tr>
</tbody>
</table>

**HR at 1<sup>st</sup> interim analysis**
- TCH: 0.61
- AC-TH: 0.49

**HR at 2<sup>nd</sup> interim analysis**
- TCH: 0.67
- AC-TH: 0.61

BCIRG 006
Slamon D., SABCS 2006
Overall Survival – 2nd Interim Analysis

HR (AC->TH vs AC->T) = 0.59 [0.42;0.85]  P=0.004

HR (TCH vs AC->T) = 0.66 [0.47;0.93]  P=0.017
# Deaths at Interim Efficacy Analyses

<table>
<thead>
<tr>
<th></th>
<th>AC-T</th>
<th>AC-TH</th>
<th>TCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1,073</td>
<td>36 / 80</td>
<td>20 / 49</td>
<td>28 / 56</td>
</tr>
<tr>
<td>Total number of deaths from any cause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 1\textsuperscript{st} interim analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 2\textsuperscript{nd} interim analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p=0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p=0.017</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p=0.58</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Breast Cancer Deaths

<table>
<thead>
<tr>
<th></th>
<th>AC-T</th>
<th>AC-TH</th>
<th>TCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1,073</td>
<td>33 / 69</td>
<td>19 / 44</td>
<td>21 / 47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DFS Lymph Node Negative

2nd Interim Analysis

% Disease Free

Patients Events

309 35 AC->T
310 12 AC->TH
309 17 TCH

HR (AC->TH vs AC->T) = 0.32 [0.17;0.62] P=0.0007
HR (TCH vs AC->T) = 0.47 [0.26;0.83] P=0.0096
Overall Survival Lymph Node Negative

2nd Interim Analysis

Patients Events

- 307 12 AC->T
- 309 2 AC->TH
- 307 5 TCH

HR (AC->TH vs AC->T) = 0.16 [0.04;0.73]  P=0.018
HR (TCH vs AC->T) = 0.42 [0.15;1.2]  P=0.106

Year from randomization

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Slamon D., SABCS 2006
DFS Subpopulations

AC-TH vs AC-T

Subgroup
- Node neg
- Node pos
- HR -
- HR +
- Tsize<2cm
- Tsize=2cm

AC-TH better
AC-T better

TCH vs AC-T

Subgroup
- Node neg
- Node pos
- HR -
- HR +
- Tsize<2cm
- Tsize=2cm

TCH better
AC-T better
Overall Survival Subpopulations

**AC-TH vs AC-T**

- **Subgroup**
  - Node neg
  - Node pos
  - HR -
  - HR +
  - Tsize<2cm
  - Tsize=2cm

**TCH vs AC-T**

- **Subgroup**
  - Node neg
  - Node pos
  - HR -
  - HR +
  - Tsize<2cm
  - Tsize=2cm
Safety Results
### Grade 3/4 Non-Hematological toxicity

<table>
<thead>
<tr>
<th>Condition</th>
<th>AC-T n=1,050</th>
<th>AC-TH n=1,068</th>
<th>TCH n=1,056</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>3.2%</td>
<td>3.3%</td>
<td>1.4%*</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5.2%</td>
<td>5.2%</td>
<td>1.8%*</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7.0%</td>
<td>7.3%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>1.9%</td>
<td>1.4%</td>
<td>0.0%*</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3.6%</td>
<td>3.1%</td>
<td>1.4%*</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.0%</td>
<td>5.7%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.0%</td>
<td>5.7%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.1%</td>
<td>6.8%</td>
<td>3.4%*</td>
</tr>
<tr>
<td>Irregular menses</td>
<td>27.1%</td>
<td>24.2%</td>
<td>26.4%</td>
</tr>
</tbody>
</table>

*Yellow = numerically less events AC-TH or TCH

*Statistically significant AC-TH or TCH
Specific non-hematological toxicity (all grades)

<table>
<thead>
<tr>
<th></th>
<th>AC-T n=1,050 %</th>
<th>AC-TH n=1,068 %</th>
<th>TCH n=1,056 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy-sensory</td>
<td>48.3</td>
<td>49.7</td>
<td>36.1*</td>
</tr>
<tr>
<td>Neuropathy-motor</td>
<td>5.2</td>
<td>6.3</td>
<td>4.2*</td>
</tr>
<tr>
<td>Nail changes</td>
<td>49.2</td>
<td>43.6</td>
<td>28.7*</td>
</tr>
<tr>
<td>Myalgia</td>
<td>52.8</td>
<td>55.5</td>
<td>38.6*</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.0</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Creatinine Grade 3/4</td>
<td>0.6</td>
<td>0.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Yellow = numerically less events AC-TH or TCH
*Statistically significant AC-TH or TCH
### Grade 3/4 Hematological Toxicity

<table>
<thead>
<tr>
<th>Condition</th>
<th>AC-T n=1,050</th>
<th>AC-TH n=1,068</th>
<th>TCH n=1,056</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>63.3%</td>
<td>71.3%</td>
<td>66.2%*</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>51.5%</td>
<td>60.2%</td>
<td>48.2%*</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>9.1%</td>
<td>11.0%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Neutropenic infection</td>
<td>11.3%</td>
<td>12.0%</td>
<td>11.0%</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.5%</td>
<td>3.1%*</td>
<td>5.8%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.0%</td>
<td>1.2%*</td>
<td>5.4%</td>
</tr>
<tr>
<td><strong>Leukemia (%)</strong></td>
<td>3 pts (0.3)</td>
<td>1 pt (0.1)</td>
<td>0 pts</td>
</tr>
</tbody>
</table>

Yellow = numerically less events AC-TH or TCH

*Statistically significant AC-TH or TCH
CARDIAC TOXICITY
### Cardiovascular risk factors

<table>
<thead>
<tr>
<th>Risk factors (# of Pts)</th>
<th>AC-T n=1,073</th>
<th>AC-TH n=1,074</th>
<th>TCH n=1,075</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>38</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>54</td>
<td>47</td>
<td>43</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>20</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Obesity (BMI $\geq 30$)</td>
<td>214</td>
<td>242</td>
<td>234</td>
</tr>
<tr>
<td>Hypertension</td>
<td>177</td>
<td>177</td>
<td>190</td>
</tr>
<tr>
<td>Radiotherapy (# of Pts)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After chemotherapy</td>
<td>662</td>
<td>656</td>
<td>671</td>
</tr>
<tr>
<td>To left chest</td>
<td>346</td>
<td>320</td>
<td>333</td>
</tr>
<tr>
<td><strong>Randomized</strong> (n=3,222)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>49 yrs</td>
<td>49 yrs</td>
<td>49 yrs</td>
</tr>
<tr>
<td>Range</td>
<td>(23 - 74 yrs)</td>
<td>(22 - 74 yrs)</td>
<td>(23 - 73 yrs)</td>
</tr>
</tbody>
</table>
# Cardiac Deaths and CHF
as per Independent Review Panel

<table>
<thead>
<tr>
<th></th>
<th>AC-T n=1,050</th>
<th>AC-TH n=1,068</th>
<th>TCH n=1,056</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac related death</td>
<td>0 / 0</td>
<td>0 / 0</td>
<td>0 / 0</td>
</tr>
<tr>
<td>Cardiac left ventricular function (CHF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 / 4</td>
<td>3 / 4</td>
<td>17 / 20</td>
<td>4 / 4</td>
</tr>
</tbody>
</table>

P = 0.0015

**first interim analysis**

**second interim analysis**

BCIRG 006
Slamon D., SABCS 2006
Patients with >10% relative LVEF decline

<table>
<thead>
<tr>
<th></th>
<th>AC-T</th>
<th>AC-TH</th>
<th>TCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>91/102</td>
<td>180/189</td>
<td>82/89</td>
</tr>
<tr>
<td>n</td>
<td>1012/1014</td>
<td>1040/1042</td>
<td>1029/1030</td>
</tr>
<tr>
<td>%</td>
<td>9/10</td>
<td>17.3/18</td>
<td>8/8.6</td>
</tr>
</tbody>
</table>

**First interim analysis**

\[ P = 0.002 \quad P < 0.0001 \quad P < 0.0001 \quad P < 0.0001 \]

**Second interim analysis**

\[ P = 0.5 \quad P = 0.5 \]
Mean LVEF - All Observations
1st Interim Analysis

Days

LVEF

AC->T (N=1012)
AC->TH (N=1040)
TCH (N=1029)

BCIRG 006
Slamon D., SABCS 2006
Mean LVEF - All Observations

2nd Interim Analysis

LVEF points %

Time since randomization (days)

AC→T (N=1014)
AC→TH (N=1042)
TCH (N=1030)

BCIRG 006
Slamon D., SABCS 2006
**HER2 and TOPO II in BCIRG 006**

2120 of 3222 patients analyzed

**2990 of 3222 patients analyzed**

<table>
<thead>
<tr>
<th>Region</th>
<th>Analysis 1</th>
<th>Analysis 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 q 12</td>
<td>N=2120</td>
<td>N=2990</td>
</tr>
<tr>
<td>HER2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Core region</td>
<td>1285 pts (60%)</td>
<td>1788 pts (60%)</td>
</tr>
<tr>
<td></td>
<td>91 pts (4%)</td>
<td>145 pts (5%)</td>
</tr>
<tr>
<td>TOPO II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>region</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>744 pts (35%)</td>
<td>1057 pts (35%)</td>
</tr>
</tbody>
</table>

Topo II

- Non
- Co-Amplified

First interim analysis

Second interim analysis

**Normal**  **Amplified**  **Deletion**
TOPO IIa (not HER2) Amplification as a Predictor of Anthracycline Response in Breast Cancer

Since 2002, at least 6 studies have been published demonstrating the association between topo II alpha amplification and improved anthracycline response.

<table>
<thead>
<tr>
<th>Study</th>
<th>Yr</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park et al.</td>
<td>2006</td>
<td>284</td>
</tr>
<tr>
<td>Tanner et al.</td>
<td>2006</td>
<td>525</td>
</tr>
<tr>
<td>Knoop et al.</td>
<td>2005</td>
<td>805</td>
</tr>
<tr>
<td>Park et al.</td>
<td>2003</td>
<td>188</td>
</tr>
<tr>
<td>Coon et al.</td>
<td>2002</td>
<td>35</td>
</tr>
<tr>
<td>Di Leo et al.</td>
<td>2002</td>
<td>354</td>
</tr>
</tbody>
</table>
DFS Topo II Co-Amplified vs Non Co-Amplified All Patients (1st interim analysis)

Patients | Events | Topo II | Logrank P<0.001
---|---|---|---
744 | 57 | Co-Amplified |
1376 | 191 | Non Co-amplified |

Year from randomization
DFS Topo II Co-Amplified vs Non Co-Amplified
All Patients (2\textsuperscript{nd} interim analysis)

- Co-Amplified:
  - 1044 patients
  - 119 events
  - 94% at year 1
  - 88% at year 2
  - 82% at year 3
  - 78% at year 4

- Non Co-amplified:
  - 1904 patients
  - 325 events
  - 88% at year 1
  - 84% at year 2
  - 88% at year 3
  - 84% at year 4

HR (Co-Amp vs Non Co-Amp) = 1.44 [1.16;1.78] P<0.001
DFS Co-Amplified Topo II by Arm
(1\textsuperscript{st} Interim Analysis)

% Disease Free

Year from randomization

Patients Events

<table>
<thead>
<tr>
<th>Arm</th>
<th>Patients</th>
<th>Events</th>
<th>Logrank P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC-&gt;T</td>
<td>227</td>
<td>23</td>
<td>0.24</td>
</tr>
<tr>
<td>AC-&gt;TH</td>
<td>265</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>TCH</td>
<td>252</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

Logrank P = 0.24
DFS Co-Amplified Topo II by Arm
(2nd Interim Analysis)

Year from randomization

Patients: 328
Events: 42
AC->T

Patients: 357
Events: 35
AC->TH
P=0.336

Patients: 359
Events: 42
TCH
P=0.648

P=0.336
P=0.648
DFS Non Co-Amplified Topo II by Arm
(1st Interim Analysis)

% Disease Free

Year from randomization

Patients

Events

AC->T

458

92

AC->TH

472

45

TCH

446

54

Logrank P= <0.001

BCIRG 006
Slamon D., SABCS 2006
DFS Non Co-Amplified Topo II by Arm
(2nd Interim Analysis)

% Disease Free

Year from randomization

Patients Events

- 643 146 AC->T
- 643 87 AC->TH  P<0.001
- 618 92 TCH  P<0.001

BCIRG 006
Slamon D., SABCS 2006
Therapeutic Index – Most Recent Data

→ Difference in DFS, OS and BC death events (ITT) between the 2 Herceptin-containing arms
  ✓ DFS       AC-TH - 128       TCH – 142
  ✓ OS        AC-TH - 49        TCH – 56
  ✓ Br Ca Deaths AC-TH - 44     TCH – 47

→ Difference in critical adverse events between anthracycline and non-anthracycline containing arms
  ✓ Grade 3/4 CHF
    • AC-T - 5       AC-TH - 20       TCH - 4
  ✓ Leukemia
    • Anthracycline-Based Arms - 4       TCH – 0

→ Global safety TCH > AC-TH

→ In addition, 23 pts with bona fide HER2 amplification who were randomized to the AC-TH arm never got trastuzumab due to unacceptable declines in LVEF before receiving the antibody
Critical Question

✓ Considering:

✓ The recently published data from US Oncology showing a highly statistically significant superiority of docetaxel-cyclophosphamide (TC) over adriamycin-cyclophosphamide (AC) in terms of breast cancer efficacy (Jones, S. JCO 24:5381, 2006).

✓ The 006 update for HER2 positive malignancies shows the difference in number of DFS events and breast cancer deaths in favor of AC-TH, neither of which are statistically significant, is now exceeded by the number of critical adverse events. These include grade III/IV CHF and AC-related leukemia as well as a small AND sustained loss of LVEF for 18% (189 pts) both of which are highly statistically significant...

What is the role of anthracyclines in the adjuvant treatment of breast cancer?
Acknowledgements

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- BCIRG Central Team:
  - V Bee, D Cabaribere, T Kiskartalyi, T Smith, L Lallaoui, H Taupin, K Afenjar, P Drevot, L Andersen, H Fung, J Mortimer, A Riva, MA Lindsay
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Klimo  
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**CROATIA**  
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Saghir  

*Highest recruiters*  
BCIRG 006  
Slamon D., SABCS 2006
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