BCIRG 006 Phase III Trial Comparing AC → T with AC → H and with TCH in the Adjuvant Treatment of HER2-Amplified Early Breast Cancer Patients: Third Planned Efficacy Analysis

• Dr. Buyse has no relevant financial relationships to disclose.
• Dr. Chan has no relevant financial relationships to disclose.
• Dr. Crown has disclosed that he is the recipient of research grants from sanofi-aventis, GSK and Roche. He has also disclosed that he is on the speaker’s bureau for sanofi-aventis, GSK, BMS and Roche.
• Dr. Eiermann has disclosed that he is on the speaker’s bureau for Novartis, Roche, AZ and Sanofi-Aventis. He has also disclosed that he is a consultant for AZ and Sanofi.
• Dr. Falkson has no relevant financial relationships to disclose.
• Dr. Fornander has no relevant financial relationships to disclose.
• Dr. Kiskartalyi has no relevant financial relationships to disclose.
• Dr. Landreau has no relevant financial relationships to disclose.
• Dr. Liu has no relevant financial relationships to disclose.
• Dr. Mackey has disclosed that he is on the speaker’s bureau for Amgen and Roche.
• Dr. Martin has disclosed that he is on the speaker’s bureau for BMS, Sanofi-Aventis, Roche, Pharmamar, Pfizer and Novartis. He has also disclosed that he is a consultant for Sanofi, Lilly, Glaxo and Pfizer.
BCIRG 006 Phase III Trial Comparing AC ➔ T with AC ➔ TH and with TCH in the Adjuvant Treatment of HER2-Amplified Early Breast Cancer Patients: Third Planned Efficacy Analysis

• Dr. Olsen has disclosed that he is an employee of sanofi-aventis.
• Dr. on Behalf of BCIRG006 Investigators has no relevant financial relationships to disclose.
• Dr. Pienkowski has disclosed that he is the recipient of a research grant from Roche. He has also disclosed that he is on the speaker’s bureau for Roche and Sanofi. He has also disclosed that he is a consultant for Roche.
• Dr. Pinter has no relevant financial relationships to disclose.
• Dr. Press has no relevant financial relationships to disclose.
• Dr. Robert has no relevant financial relationships to disclose.
• Dr. Rolski has no relevant financial relationships to disclose.
• Dr. Shiftan has no relevant financial relationships to disclose.
• Dr. Slamon has disclosed that he is the recipient of a research grant from Amgen. He has also disclosed that he is on the speaker’s bureau for Genentech and Sanofi-Aventis. He has also disclosed that he is a consultant for Pfizer.
• Dr. Valero has no relevant financial relationships to disclose.
• Dr. Wilson has no relevant financial relationships to disclose.
BCIRG 006
Phase III Trial Comparing
AC⇒T with AC⇒TH and with TCH
in the Adjuvant Treatment of
HER2-Amplified Early Breast Cancer Patients:

Third Planned 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

Southern
Northern
Western
IHC


BCIRG 006
Slamon D., SABCS 2009
BCIRG 006 Trial Design

Her 2+ (Central FISH)

N+ or high risk N-

N=3,222

Stratified by Nodes and Hormonal Receptor Status

AC→T
- 4 x AC 60/600 mg/m²
- 4 x Docetaxel 100 mg/m²

AC→TH
- 4 x AC 60/600 mg/m²
- 4 x Docetaxel 100 mg/m²
- 1 Year Trastuzumab

TCH
- 6 x Docetaxel and Carboplatin
  - 75 mg/m² AUC 6
- 1 Year Trastuzumab
Global Project Coordinator

Valerie Bee
BCIRG 006 Endpoints

Primary
  • Disease-free Survival

Secondary
  • Overall Survival
  • Safety
  • Pathologic & Molecular Markers
### BCIRG 006 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>68</td>
<td>67</td>
<td>69</td>
</tr>
<tr>
<td>Hormonotherapy</td>
<td>51</td>
<td>51</td>
<td>51</td>
</tr>
</tbody>
</table>

Enrollment: April 2001 to March 2004
# BCIRG 006 Tumor Characteristics

<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><strong>Number of nodes +</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>1 – 3</td>
<td>38%</td>
<td>38%</td>
<td>39%</td>
</tr>
<tr>
<td>4 – 10</td>
<td>22%</td>
<td>24%</td>
<td>23%</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>11%</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Tumor Size (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2</td>
<td>41%</td>
<td>38%</td>
<td>40%</td>
</tr>
<tr>
<td>&gt; 2 and ≤ 5</td>
<td>53%</td>
<td>55%</td>
<td>54%</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>6%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>ER and/or PR +</strong></td>
<td>54%</td>
<td>54%</td>
<td>54%</td>
</tr>
</tbody>
</table>
After the trastuzumab efficacy results were announced in April 2005, to date:

- 23 patients (2.1%) of 1,073 randomized to the control arm (AC→T) crossed-over to receive trastuzumab
- leaving 97.9% of the control arm enrollment intact for subsequent DFS, OS and safety comparisons
Efficacy
BCIRG 006 DFS Events

First/Second/Third Planned Efficacy Analyses
(cutoff dates 30Jun2005 / 01Nov2006 / 16Oct2009)

- Median follow-up time = 23/36/65 mths
- 322/462/656 DFS Events
  (42% additional events)
  - Breast Cancer Relapse
  - Second Primary Malignancy
  - Death
- 84/185/348 Deaths
  (88% additional deaths)
Initial Disease Free Survival from 1st Analysis – June 2005

Patients  Events
1073  147  AC->T
1074  77  AC->TH  HR (AC->TH vs AC->T) = 0.49 [0.37;0.65]  P<0.0001
1075  98  TCH  HR (TCH vs AC->T) = 0.61 [0.47;0.79]  P=0.0002
Current BCIRG 006
Disease Free Survival – 3rd Planned Analysis

% alive and disease-free

0 0.4 0.6 0.8 1

Time (months)

Patients 1073 1074 1075
Events 257 185 214

HR (95% C.I.) 1 (reference) 0.64 (0.53 - 0.78) 0.75 (0.63 - 0.90)

P < 0.001 0.04

AC-T
AC-TH
TCH

BCIRG 006
Slamon D., SABCS 2009
## BCIRG 006 Events by Arm

<table>
<thead>
<tr>
<th>Arm</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>Total number of DFS events</td>
<td>147/192/257</td>
<td>77/128/185</td>
<td>98/142/214</td>
</tr>
<tr>
<td>Metastatic events</td>
<td>113/143/188</td>
<td>52/93/124</td>
<td>67/98/144</td>
</tr>
</tbody>
</table>

- at 1st planned analysis: $P < 0.001$
- at 2nd analysis: $P = 0.002$
- at 3rd analysis: $P = 0.21$

BCIRG 006
Slamon D., SABCS 2009
BCIRG 006
Overall Survival – 3rd Planned Analysis

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>HR (95% C.I.)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>1073</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>1074</td>
<td>0.63 (0.48 - 0.81)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TCH</td>
<td>1075</td>
<td>0.77 (0.60 - 0.99)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Time (months)
## BCIRG 006 Deaths

<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>Total number of deaths from any cause</td>
<td>36/80/141</td>
<td>20/49/94</td>
<td>28/56/113</td>
</tr>
<tr>
<td>at 1st planned analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 2nd analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 3rd analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer deaths</td>
<td>33/69/122</td>
<td>19/44/83</td>
<td>21/47/97</td>
</tr>
</tbody>
</table>

*P* < 0.001

*P* = 0.038

*P* = 0.14

*BCIRG 006*

Slamon D., SABCS 2009
<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Events</th>
<th>HR (95% C.I.)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>309</td>
<td>46</td>
<td>1 (reference)</td>
<td>0.003</td>
</tr>
<tr>
<td>ACTH</td>
<td>310</td>
<td>23</td>
<td>0.47 (0.28 - 0.77)</td>
<td>0.057</td>
</tr>
<tr>
<td>TCH</td>
<td>309</td>
<td>32</td>
<td>0.64 (0.41 - 1.01)</td>
<td>0.057</td>
</tr>
</tbody>
</table>

**BCIRG 006**
**DFS Lymph Node Negative**

% alive and disease-free

Time (months)
BCIRG 006
OS Lymph Node Negative

Patients

AC-T 309
AC-TH 310
TCH 309

Events

22
8
12

HR (95% C.I.)

1 (reference)
0.38 (0.17 - 0.87)
0.56 (0.27 - 1.13)

P

0.02
0.11

Time (months)

0
12
24
36
48
60
72

0.4
0.5
0.6
0.7
0.8
0.9
1

% alive

BCIRG 006
Slamon D., SABCS 2009
Do Higher Risk HER2-positive Breast Cancers Require Anthracycline-based Rx
### BCIRG 006

**DFS Lymph Node Positive**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>±</th>
<th>AC-T</th>
<th>AC-TH</th>
<th>TCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>764</td>
<td>764</td>
<td>766</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>211</td>
<td>162</td>
<td>182</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Patients:**
- AC-T: 764
- AC-TH: 764
- TCH: 766

**Events:**
- AC-T: 211
- AC-TH: 162
- TCH: 182

**HR (95% C.I.):**
- AC-T: 1 (reference)
- AC-TH: 0.68 (0.56 - 0.84)
- TCH: 0.78 (0.64 - 0.95)

**P:**
- AC-T: 0.0003
- AC-TH: 0.013
- TCH: 0.013

*BCIRG 006*  
Slamon D., SABCS 2009
BCIRG 006
DFS Lymph Node ≥4

Patients | Events | HR (95% C.I.) | P
---------|--------|--------------|---
AC-T 350 | 133 | 1 (reference) | 
AC-TH 350 | 99 | 0.66 (0.51 - 0.86) | 0.002
TCH 352 | 101 | 0.66 (0.51 - 0.86) | 0.002

% alive and disease-free vs Time (months)
General Safety
## BCIRG 006

Grade 3/4 Non-Hematological toxicity

<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><strong>Arthralgia</strong></td>
<td>3.2%</td>
<td>3.3%</td>
<td>1.4%*</td>
</tr>
<tr>
<td><strong>Myalgia</strong></td>
<td>5.2%</td>
<td>5.2%</td>
<td>1.8%*</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>7%</td>
<td>7.2%</td>
<td>7.2%</td>
</tr>
<tr>
<td><strong>Hand-foot syndrome</strong></td>
<td>1.9%</td>
<td>1.4%</td>
<td>0.0%*</td>
</tr>
<tr>
<td><strong>Stomatitis</strong></td>
<td>3.5%</td>
<td>2.9%</td>
<td>1.4%*</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>3.0%</td>
<td>5.6%</td>
<td>5.4%</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>5.9%</td>
<td>5.7%</td>
<td>4.8%</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>6.1%</td>
<td>6.7%</td>
<td>3.5%*</td>
</tr>
<tr>
<td><strong>Irregular menses</strong></td>
<td>27%</td>
<td>24.3%</td>
<td>26.5%</td>
</tr>
</tbody>
</table>

Yellow=*Statistically significant less events
### BCIRG 006
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></td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Neuropathy-sensory</td>
<td>48.6</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>49.3</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>0.1</td>
</tr>
</tbody>
</table>

Yellow=*Statistically significant less events
### BCIRG 006

**Grade 3/4 Hematological Toxicity**

<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>Neutropenia</td>
<td>63.5</td>
<td>71.6</td>
<td>66.2*</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>51.9</td>
<td>60.4</td>
<td>48.4*</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>9.3</td>
<td>10.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Neutropenic infection</td>
<td>11.5</td>
<td>12.1</td>
<td>11.2</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.4</td>
<td>3.1*</td>
<td>5.8</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.6</td>
<td>2.1*</td>
<td>6.1</td>
</tr>
</tbody>
</table>

**Acute Leukemias: #(%):**

<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></td>
<td>6 (0.6)</td>
<td>1 (0.1)</td>
<td>1 (0.1**)</td>
</tr>
</tbody>
</table>

*Statistically significant less events

**Yellow =** Statistically significant less events

**B-cell lymphoma developed 24 months after TCH in this pt and represented her ITT DFS event. This acute leukemia occurred 20 months after rx with CHOP for the B cell lymphoma.**

*BCIRG 006
Slamon D., SABCS 2009*
Cardiac Safety
## Cardiovascular risk factors

<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><strong>Age</strong></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>
<tr>
<td><strong>Risk factors (# of patients)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<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 ≥ 30)</td>
<td>214</td>
<td>242</td>
<td>234</td>
</tr>
<tr>
<td>Hypertension</td>
<td>178</td>
<td>178</td>
<td>190</td>
</tr>
<tr>
<td><strong>Radiotherapy (# of patients)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After chemotherapy</td>
<td>718</td>
<td>723</td>
<td>729</td>
</tr>
<tr>
<td>To left chest</td>
<td>378</td>
<td>349</td>
<td>364</td>
</tr>
</tbody>
</table>

Slamon D., SABCS 2009BCIRG 006
### 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><strong>Cardiac related death</strong></td>
<td>0 / 0 / 0</td>
<td>0 / 0 / 0</td>
<td>0 / 0 / 0</td>
</tr>
<tr>
<td><strong>Cardiac left ventricular function (CHF)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 / 4</td>
<td>3 / 4 / 7</td>
<td>17 / 20 / 21</td>
<td>4 / 4 / 4</td>
</tr>
</tbody>
</table>

- **First planned analysis**
  - P = 0.0121
- **Second analysis**
  - P < 0.001
- **Third analysis**
  - P = 0.3852

*BCIRG 006, Slamon D., SABCS 2009*
BCIRG 006
Mean LVEF - All Observations
3rd Planned Analysis

AC->T (N=1014)
AC->TH (N=1042)
TCH (N=1030)

Slamon D., SABCS 2009
Patients with >10% relative LVEF decline

\[
\begin{array}{ccc}
\text{AC→T} & \text{AC→TH} & \text{TCH} \\
n = 1,018 & n = 1,042 & n = 1,031 \\
\text{Patients} & 91/102/\textbf{114} & 180/189/\textbf{194} & 82/89/\textbf{97} \\
\text{% of Pts} & 9/10/\textbf{11} & 17/18/\textbf{19} & 8/9/\textbf{9} \\
\end{array}
\]

First interim analysis
Second analysis
Third analysis

\[P < 0.001\]  \[P < 0.001\]  \[P = 0.19\]
Topo IIa Amplification
HER2 and TOPO IIa in BCIRG 006
2990 of 3222 patients tested

Topo II

N=2948

Non Co-Amplified

1761 (60%)
143 (5%)

Co-Amplified

1044 (35%)

TOPO II region

HER2 Core region

Normal Amplified Deletion

BCIRG 006
Slamon D., SABCS 2009
BCIRG 006
Disease Free Survival – 3rd Planned Analysis

Patients | Events | HR (95% C.I.) | P
--- | --- | --- | ---
AC-T | 1073 | 257 | 1 (reference) < 0.001
AC-TH | 1074 | 185 | 0.64 (0.53 - 0.78) 0.04
TCH | 1075 | 214 | 0.75 (0.63 - 0.90)
DFS by Arm: Topo IIa Non Co-Amplified

Patients | Events | HR (95% C.I.) | P
---|---|---|---
AC-T | 643 | 191 | 1 (reference)
AC-TH | 643 | 119 | 0.53 (0.42 - 0.67) | < 0.001
TCH | 618 | 130 | 0.61 (0.49 - 0.77) | < 0.001

BCIRG 006
Slamon D., SABCS 2009
DFS by Arm: Co-Amplified for Topo IIa

BCIRG 006
Slamon D., SABCS 2009
## Therapeutic Index – Most Recent 006 Data

<table>
<thead>
<tr>
<th></th>
<th>AC-TH</th>
<th>TCH</th>
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<tbody>
<tr>
<td>DFS Events</td>
<td>185</td>
<td>214</td>
</tr>
<tr>
<td>Grade 3 / 4 CHF</td>
<td>21</td>
<td>4</td>
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<tr>
<td><strong>Totals</strong></td>
<td>206</td>
<td>218</td>
</tr>
<tr>
<td>Rx-Related Leukemias</td>
<td>7(8)*</td>
<td>0(1)**</td>
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<tr>
<td>*Only in AC-Rx patients</td>
<td></td>
<td>**Leukemia developed after CHOP Rx</td>
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<tr>
<td>Sustained LVEF Loss &gt;10%</td>
<td>194</td>
<td>97</td>
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*BCIRG 006*
Slamon D., SABCS 2009
Conclusions: BCIRG-006

→ Trastuzumab provides a similar and significant advantage for both DFS and OS when used with either anthracycline-based (ACTH) or non-anthracycline (TCH) chemotherapy. This advantage is seen in both low and high-risk patients.

→ The acute and chronic toxicity profiles of TCH are better than those seen with the ACTH regimen in almost all parameters measured.

→ There is no statistical advantage of ACTH over TCH but there is a 29 event numerical advantage in DFS events in the ACTH treatment arm.

→ This numeric advantage comes at the cost of 21 CHFs (5X more than in TCH) and to date, there are 8 acute leukemias in BCIRG-006.....all occurring in patients receiving AC as part of their treatment.

→ BCIRG-006 demonstrates that the incremental benefit conferred by AC that is known for HER2-positive breast cancers is restricted to TOP2A co-amplified malignancies which constitute a subset (35%) of these cancers.

→ This same incremental benefit (found in the TOP2A subset) can also be achieved by trastuzumab used in a non-anthracycline regimen, avoiding the long-term and life-altering toxicities (CHF or acute leukemia) seen with the anthracycline-based regimens.
Acknowledgements

- All participating Patients and Investigators
- IDMC (Chair, S Swain) and Independent Cardiac Panel
- Central laboratories: M Press (USC), G Sauter (Basel)
- IDDI: M Buyse, F Piette
- NBCC: Fran Visco and Carolina Hinestrosa
- CIRG Central Team: L Andersen, V Bee, D Cabaribere, P Drevot, H Fung, T Kiskartalyi, V Landreau, M Lindsay, T Manella, E Mekercke, T Smith, V Wilson

**The Group of 20**
### Principal Investigators involved in the study (I)

<table>
<thead>
<tr>
<th>Argentina</th>
<th>France</th>
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<tr>
<td>Fein</td>
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<tr>
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<td>Martinez /</td>
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<td>Korbenfeld</td>
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Austria

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Belgium

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Czech Republic

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</table>

The table above lists principal investigators involved in the study, categorized by country. This list includes investigators from Argentina, France, Austria, Belgium, Czech Republic, Colombia, Croatia, Germany, Egypt, Greece, Hong Kong, Hungary, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Egypt, France, and Greece. Each investigator's name is presented in their respective country's section.
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Mosciatti / Pollera
Nardi
Panetta / Geminiani
Ravaioni
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Chahine
Ghosn
Saghir
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Chan
Silva
Valle
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Karnicka-Mlodowska
Pienkowski
Rolski / Pawlicki
Wojtukiewicz
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Roman / Tudose
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Koza
Spanik
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Beltchev
De Bruyne
Maart / Jacobs
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Rapoport
Slabber
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Bang
Choi / Lim
Im
Ro
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Alvarez
Angel Garcia-Saenz /
Martin
Aranda
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Chao
Liu
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Frikha
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Aydiner
Ozisik / Baltali
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Armstrong / Wardley
Chan / Hornbuckle
Sherwin / Levay
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Krygier / Viola
Rodriguez
USA
Abukabr
Adler
Ansari
Arena
Beall
Beattie
Berdeaux
Brufski
Burris
Bury / Yost / Marianne
Carroll
Chakrabarti
Chitneni
Chowhan
Cobb
Diaz-Lacayo / Hotchner
Dreisbach
Fain
Falkson
Fesen
Gluck / Tang
Gonzales / Wood
Goodman
Greenwald
Hajdenberg / Chiu
Hoffman
Holmes
Jhangiani
Jones
Justice
Juturi
Kalman
Kennedy
Kincaid
Kliein
Koneru
Lad / Zaren
Laufman
Lemon
Limentani
Lower
Malamud
McAndrew
McCroskey
McKeen
Mena
Mills
Modiano
Moore
Morose
Moss
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Perez / Lewis
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Petruska
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Polikoff
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Rangieni
Reich
Reiling
Rinaldi
Robert
Robertson / Osborn
Rodriguez
Rubin
Russel
Saleh / Flakson
Savin
Schleider
Schwartzberg
Shaffer
Shiftan
Silverman / Baar
Slamon
Smith
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Sparano
Sylvester
Tansino
Tchekmedyian
Teczan
Ulrich
Valero
Vargas-Cuba / Dasgupta-Cambell
Vaughn
Vogel
Waintraub
Wallmark
Wierman
Witek
Yunus
VENEZUELA
De Joghn
Vera

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Slamon D., SABCS 2009