Treatment of Early Stage HER2-positive Breast Cancer

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Molecular Portrait of Breast Cancers

Sorlie T et al, PNAS 2001
Defining HER2 Positivity in Breast Cancer

- Overexpression: marked increase in number of HER2 receptors on the cell surface
- Amplification: increase in number of HER2/neu gene copies in the nucleus

HER2-normal (HER2-) breast epithelium cell (~20,000 receptors)  
HER2-positive breast cancer cell (up to 1-2 million receptors)
Fig 2. Algorithm for fluorescent in situ hybridization (FISH)

Breast cancer specimen (invasive component)

- HER2 testing by validated FISH assay for HER2 gene amplification
  - Positive for HER2 gene amplification (FISH ratio > 2.2 or HER2 gene copy > 6.0)
  - Equivocal for HER2 gene amplification (FISH ratio 1.8-2.2 or HER2 gene copy 4.0-6.0*)
  - Negative for HER2 gene amplification (FISH ratio < 1.8 or HER2 gene copy < 4.0)

- Count additional cells for FISH or retest, or test with HER2 IHC

- Equivocal HER2 gene amplification result (Patients with HER2/CEP17 ratio ≥ 2.0 were eligible for the adjuvant trastuzumab trials)

Fig 1. Algorithm for immunohistochemistry (IHC)

Large Phase III Adjuvant Trastuzumab Trials

- B31/N9831
  - AC → T
  - AC → TH
  - (AC → T → H)

- CIRG 006
  - AC → T*
  - AC → T*H
  - T*C*H

- HERA:
  - Chemo ± XRT
  - Observation
    - H x 1 year
    - H x 2 years

A = doxorubicin
C = cyclophosphamide
T = paclitaxel
H = trastuzumab
T* = docetaxel
C* = carboplatin
NSABP B-31
Control: AC→T

Arm 1
Arm 2

NCCTG N9831
Investigational: AC→T+H

Arm A
Arm B
Arm C

= doxorubicin/cyclophosphamide (AC) 60/600 mg/m² q 3 wk x 4
= paclitaxel (T) 175 mg/m² q 3 wk x 4
= paclitaxel (T) 80 mg/m²/wk x 12
= trastuzumab (H) 4mg/kg LD + 2 mg/kg/wk x 51
4-year N9831/B31 Analysis: Disease-Free Survival

Event-free (%) vs. Years from Randomization

AC → T+H
AC → T

HR 0.52 (95% CI 0.45-0.60)
P < .001

Number at risk

1,952 1,756 1,300 891 495
1,881 1,652 1,132 702 395

4-year B31/N9831 Analysis: Overall Survival


HR 0.61 (95%CI 0.50-0.75)
P < .0001
Does the degree of HER2 amplification correlate with the degree of benefit from trastuzumab?
Hazard Ratio of Benefit to Trastuzumab by HER2 FISH Ratio in NCCTG N9831

<table>
<thead>
<tr>
<th>Ratio</th>
<th>(N)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.0</td>
<td>156</td>
<td>0.12</td>
</tr>
<tr>
<td>2.0-5.0</td>
<td>253</td>
<td>0.05</td>
</tr>
<tr>
<td>5.0-8.0</td>
<td>515</td>
<td>0.03</td>
</tr>
<tr>
<td>8.0-11.0</td>
<td>473</td>
<td>0.04</td>
</tr>
<tr>
<td>11.0-15.0</td>
<td>328</td>
<td>0.004</td>
</tr>
<tr>
<td>≥ 15.0</td>
<td>70</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Reinholz M, SABCS 2007, abstr 36
What is the significance of focally HER2-positive breast cancer?
Focal HER2 Amplified Clones
## Benefit of Adjuvant Trastuzumab in Focally Amplified HER2 Positive Breast Cancer in N9831

<table>
<thead>
<tr>
<th></th>
<th>Focally Amplified</th>
<th>Diffusely Amplified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>91* (5%)</td>
<td>1571 (95%)</td>
</tr>
<tr>
<td>DFS: HR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab vs.</td>
<td>0.50</td>
<td>0.59</td>
</tr>
<tr>
<td>No Trastuzumab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*85 of 91 amplified ≥ 2.0

What is the benefit of using trastuzumab with a non-anthracycline containing regimen?
BCIRG 006

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

AC→T

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

N=3,222

Stratified by Nodes and Hormonal Receptor Status

- Her2+
  (Central FISH)
- N+
  or high risk N-

Slamon D., SABCS 2005
### BCIRG 006 Disease Free Survival

(median follow-up 65 months)

#### Patients, Events, HR, P

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
<th>Events</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC-TH</td>
<td>1074</td>
<td>185</td>
<td>.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TCH</td>
<td>1075</td>
<td>214</td>
<td>.75</td>
<td>0.04</td>
</tr>
<tr>
<td>AC-T</td>
<td>1073</td>
<td>257</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Disease-free Survival

![Graph showing disease-free survival over time for different treatment groups](image)

#### No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC-T</td>
<td>0, 12</td>
</tr>
<tr>
<td>AC-T plus trastuzumab</td>
<td>24</td>
</tr>
<tr>
<td>TCH</td>
<td>48</td>
</tr>
<tr>
<td>AC-T</td>
<td>60</td>
</tr>
<tr>
<td>AC-T plus trastuzumab</td>
<td>72</td>
</tr>
<tr>
<td>TCH</td>
<td>84</td>
</tr>
</tbody>
</table>

What is the benefit of using trastuzumab after chemotherapy is finished?
HERA: 4 year DFS (ITT)

![Graph showing DFS over time with event numbers and HR values](image)

### HERA: 4 year DFS (ITT) Table

<table>
<thead>
<tr>
<th>Events</th>
<th>4yr DFS</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>369</td>
<td>78.6</td>
<td>0.76</td>
<td>0.66, 0.87</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>458</td>
<td>72.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Survival Analysis**

- **1-year trastuzumab**
- **Observation**

**Event Numbers**

<table>
<thead>
<tr>
<th>Time from randomization (months)</th>
<th>Alive and disease free (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>36</td>
<td>70</td>
</tr>
<tr>
<td>48</td>
<td>60</td>
</tr>
</tbody>
</table>

**Number at risk**

<table>
<thead>
<tr>
<th>Time from randomization (months)</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year trastuzumab</td>
<td>1703 1619 1552 1485 1414 1352 1280 1020 854</td>
</tr>
<tr>
<td>Observation</td>
<td>1698 1564 1440 1363 1297 1240 1180 992 712</td>
</tr>
</tbody>
</table>

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

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

HERA: Exploratory DFS subgroup analysis (ITT)
1 year trastuzumab vs observation (2)

Subgroup (no. patients) | HR (95% CI) | No. events
---|---|---
Pathological tumour size
Any (neo)adjuvant CT (372) | 0.66 (0.43, 1.00) | 39 vs 50
0-2 cm (1351) | 0.65 (0.47, 0.90) | 61 vs 95
>2-5 cm (1482) | 0.55 (0.43, 0.71) | 97 vs 150
>5 cm (171) | 1.14 (0.63, 2.06) | 20 vs 25
Hormone receptor status
ER-negative + PgR-negative (1627) | 0.63 (0.50, 0.78) | 126 vs 190
ER-negative + PgR-positive (172) | 0.77 (0.34, 1.74) | 12 vs 12
ER-positive + PgR-negative (460) | 0.82 (0.50, 1.34) | 26 vs 39
ER-positive + PgR-positive (984) | 0.63 (0.43, 0.93) | 46 vs 61
Histologic grade
3 - poorly differentiated (2047) | 0.73 (0.59, 0.90) | 157 vs 201
2 - moderately differentiated (1111) | 0.46 (0.33, 0.65) | 47 vs 97
Surgery for primary tumour
Breast-conserving procedure (1432) | 0.59 (0.44, 0.79) | 77 vs 121
Mastectomy (1968) | 0.68 (0.55, 0.84) | 141 vs 200
Previous radiotherapy
Yes (2606) | 0.64 (0.53, 0.77) | 183 vs 265
No (795) | 0.64 (0.42, 0.98) | 35 vs 56
Type of (neo)adjuvant CT
No anthracyclines (202) | 0.76 (0.35, 1.62) | 12 vs 15
Anthracyclines, no taxanes (2310) | 0.57 (0.46, 0.71) | 132 vs 221
Anthracyclines + taxanes (889) | 0.80 (0.59, 1.10) | 74 vs 85
All patients (3401) | 0.64 (0.54, 0.76) | 218 vs 321

Overall Result

Smith I, Lancet 2007
So is it better to start trastuzumab sequentially after completion of chemotherapy or concurrently with taxane chemotherapy?
NCCTG N9831 Trial Incorporating Trastuzumab in Adjuvant Therapy

HER2 positive (FISH ratio ≥2 or IHC 3+ >10%)

ARM A
- AC
- T

ARM B
- AC
- T
- H

ARM C
- AC
- T
- H

n=3,505

Perez EA. Protocol NCCTG-N9831

= AC (doxorubicin/cyclophosphamide 60/600 mg/m² q3w × 4)
= T (paclitaxel 80 mg/m²/wk × 12)
= H (trastuzumab 4 mg/kg loading + 2 mg/kg/wk × 51)
N9831: Sequential (B) vs. Concurrent (C) Disease Free Survival


AC → T+H → H (138 events)
89.1%
85.7%
84.2%

AC → T → H (174 events)
79.8%

Alive and disease free (%)

Logrank p=0.0190

Years from randomization

No. at risk

How long should trastuzumab be given in the adjuvant setting?
The Duration Question: FinHER

<table>
<thead>
<tr>
<th></th>
<th>*Chemo</th>
<th>*Chemo + H</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Pts</td>
<td>116</td>
<td>115</td>
</tr>
<tr>
<td>No. Events</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>3 yr DFS</td>
<td>78%</td>
<td>89%</td>
</tr>
<tr>
<td>P value</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Confidence Interval</td>
<td>(0.21—0.83)</td>
<td></td>
</tr>
</tbody>
</table>

* Vinorelbine or docetaxel ± trastuzumab X 9 weeks followed by 3 cycles FEC

## Current Trials Assessing Duration of Trastuzumab

<table>
<thead>
<tr>
<th>Trial</th>
<th>Protocol</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOLD</strong></td>
<td>Docetaxel + Trast (nine weeks) → FEC X 3</td>
<td>Chemotherapy + Trast X 12 months + Trast (total 1 year)</td>
</tr>
<tr>
<td>(Finland)</td>
<td>Docetaxel + Trast (nine weeks) → FEC X 3 → Trast (total 1 year)</td>
<td>Chemotherapy + Trast X 6 months</td>
</tr>
<tr>
<td><strong>PHARE</strong></td>
<td>Chemotherapy + Trast X 12 months</td>
<td>Chemotherapy + Trast X 6 months</td>
</tr>
<tr>
<td>(France)</td>
<td>Chemotherapy + Trast X 6 months</td>
<td></td>
</tr>
<tr>
<td><strong>Short-HER</strong></td>
<td>Docetaxel + Trast (nine weeks) → FEC X 3</td>
<td>AC/FEC X 4 → Taxane + Trast X 4 → Trast (18 weeks)</td>
</tr>
<tr>
<td>(Italy)</td>
<td>AC/FEC X 4 → Taxane + Trast X 4 → Trast (18 weeks)</td>
<td></td>
</tr>
<tr>
<td><strong>Hellenic</strong></td>
<td>FEC X 4 → Docetaxel + Trast → Trast (total 12 months)</td>
<td>FEC X 4 → Docetaxel + Trast → Trast (total 6 months)</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Greece)</td>
<td>FEC X 4 → Docetaxel + Trast → Trast (total 12 months)</td>
<td></td>
</tr>
<tr>
<td><strong>Persephone</strong></td>
<td>Chemotherapy + Trast X 12 months</td>
<td>Chemotherapy + Trast X 6 months</td>
</tr>
<tr>
<td>(Great Britain)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HERA</strong></td>
<td>Chemotherapy → Trast X 1 year</td>
<td>Chemotherapy → Trast X 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HERA: 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

**PHARE** Study design

- **Trastuzumab 6 months**
- **Trastuzumab up to 12 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.

* Protocol of Herceptin Adjuvant with Reduced Exposure

PHARE: Disease Free Survival

At risk
- H-12m 1690
- H 6m 1690

At risk
- H-12m 1613
- H 6m 1586

Events HR 95%CI p-value
- H 12m 176 1.28 (1.05 – 1.56) 0.29
- H 6m 219

Cox model stratified by ER status and concomitant chemotherapy

Primary endpoint scenarii

A: Equivalent
B: 6 month Superior
C: 6 month Non Inferior
D: 6 month Non Inferior
E: 6 month Inferior

Primary endpoint scenarios

A  Equivalent
B  6 month Superior
C  PHARE trial
D  6 month Non Inferior
E  6 month Inferior

HR

.85 1 1.15 1.3 1.45 1.6

## Efficacy Summary of Adjuvant Trastuzumab Trials

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Pts</th>
<th>TREATMENT</th>
<th>DFS (%)</th>
<th>HR</th>
<th>P</th>
<th>OS (%)</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>B31/N9831</td>
<td>1989</td>
<td>AC→TH</td>
<td>86*</td>
<td>0.52</td>
<td>&lt;0.001</td>
<td>93*</td>
<td>0.61</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>1979</td>
<td>AC→T</td>
<td>74</td>
<td></td>
<td></td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIRG 006</td>
<td>1074</td>
<td>AC→TH</td>
<td>84**</td>
<td>0.64</td>
<td>&lt;0.001</td>
<td>92**</td>
<td>0.63</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>1075</td>
<td>TCH</td>
<td>81</td>
<td>0.75</td>
<td>0.04</td>
<td>91</td>
<td>0.77</td>
<td>0.038</td>
</tr>
<tr>
<td></td>
<td>1073</td>
<td>AC→T</td>
<td>75</td>
<td></td>
<td></td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HERA</td>
<td>1703</td>
<td>chemo→H</td>
<td>79*</td>
<td>0.76</td>
<td>&lt;0.0001</td>
<td>89*</td>
<td>0.85</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>1698</td>
<td>chemo→obs</td>
<td>72</td>
<td></td>
<td></td>
<td>88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FinHER</td>
<td>115</td>
<td>V/T+H→FEC</td>
<td>89†</td>
<td>0.42</td>
<td>0.01</td>
<td>96†</td>
<td>0.41</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>116</td>
<td>V/T→FEC</td>
<td>78</td>
<td></td>
<td></td>
<td>90</td>
<td></td>
<td></td>
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<tr>
<td>PACS04</td>
<td>260</td>
<td>FEC/ET→H</td>
<td>73*</td>
<td>0.86</td>
<td>0.42</td>
<td>92*</td>
<td>1.27</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>268</td>
<td>FEC/ET</td>
<td>73</td>
<td></td>
<td></td>
<td>93</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† - at 3 years  * - at 4 years  ** - at 5.5 years
Cardiac Risk Assessment with Anthracycline based regimens
B-31/N9831 LVEF Evaluation Schedule

Control

\[
\text{AC x 4} \quad \rightarrow \quad \text{Paclitaxel}
\]

<table>
<thead>
<tr>
<th>Heart</th>
<th>0 mo.</th>
<th>3 mos.</th>
<th>6 mos.</th>
<th>9 mos.</th>
<th>18 mos.</th>
</tr>
</thead>
</table>

Investigational

\[
\text{AC x 4} \quad \rightarrow \quad \text{Trastuzumab + Paclitaxel}
\]

<table>
<thead>
<tr>
<th>Heart</th>
<th>0 mo.</th>
<th>3 mos.</th>
<th>6 mos.</th>
<th>9 mos.</th>
<th>18 mos.</th>
</tr>
</thead>
</table>
## Asymptomatic Patients

**Rules for Trastuzumab Continuation Based on Serial LVEF**

<table>
<thead>
<tr>
<th>Relationship of LVEF to LLN</th>
<th>Absolute decrease of &lt; 10%</th>
<th>Absolute decrease of 10%–15%</th>
<th>Absolute decrease of 15%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within normal limits</td>
<td>Cont.</td>
<td>Cont.</td>
<td>Hold*</td>
</tr>
<tr>
<td>1%–5% below LLN</td>
<td>Cont.</td>
<td>Hold*</td>
<td>Hold*</td>
</tr>
<tr>
<td>≥ 6% below LLN</td>
<td>Cont.*</td>
<td>Hold*</td>
<td>Hold*</td>
</tr>
</tbody>
</table>

*Repeat LVEF assessment after 4 weeks
  - If criteria for continuation is met then resume trastuzumab
    * If 2 consecutive holds (or a total of 3 holds occur) then discontinue trastuzumab

LLN = lower limit of normal.
N9831 Cardiac Events

Perez EA, et al. JCO 2008

Cumulative incidence of cardiac events

<table>
<thead>
<tr>
<th>Time since start of post-AC treatment (years)</th>
<th>Arm A (n = 664)</th>
<th>Arm B (n = 710)</th>
<th>Arm C (n = 570)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0%</td>
<td>0.8%</td>
<td>2.5%</td>
</tr>
<tr>
<td>1</td>
<td>0%</td>
<td>1.6%</td>
<td>3.3%</td>
</tr>
<tr>
<td>2</td>
<td>0.2%</td>
<td>2.7%</td>
<td>3.3%</td>
</tr>
<tr>
<td>3</td>
<td>0.3%</td>
<td>2.8%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

Cumulative incidence of cardiac events
NSABP B-31: 7 year cumulative incidence of cardiac events

HR=3.30; P-value = 0.00038

ACPH arm; 4.0%

ACP arm; 1.3%

Romond et al. JCO, 2012
<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>No. of Pts</th>
<th>No. with CHF (%)</th>
<th>P value</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>486</td>
<td>11 (2.3%)</td>
<td>0.03</td>
<td>Ref. group</td>
</tr>
<tr>
<td>50-59</td>
<td>313</td>
<td>16 (5.1%)</td>
<td></td>
<td>2.3 (1.1-4.9)</td>
</tr>
<tr>
<td>60+</td>
<td>148</td>
<td>8 (5.4%)</td>
<td></td>
<td>2.4 (1.0-6.0)</td>
</tr>
<tr>
<td><strong>Hypertension medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>732</td>
<td>22 (3.0%)</td>
<td>0.02</td>
<td>2.3 (1.2 - 4.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>192</td>
<td>13 (6.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline LVEF</strong></td>
<td></td>
<td></td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>&lt;54</td>
<td>70</td>
<td>9 (12.9%)</td>
<td></td>
<td>Ref. group</td>
</tr>
<tr>
<td>55-64</td>
<td>452</td>
<td>17 (3.8%)</td>
<td></td>
<td>0.3 (0.1 – 0.6)</td>
</tr>
<tr>
<td>65+</td>
<td>425</td>
<td>9 (2.1%)</td>
<td></td>
<td>0.2 (0.1 – 0.4)</td>
</tr>
<tr>
<td><strong>Left-sided tumor &amp; radiation</strong></td>
<td></td>
<td></td>
<td>0.71</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>587</td>
<td>23 (3.9%)</td>
<td></td>
<td>0.9 (0.4-1.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>351</td>
<td>12 (3.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cardiac Risk Score
(based on evaluable cohort in NSABP B-31)

\[
[7.0 + (0.04 \times \text{Age in years}) - (0.1 \times \text{Baseline percent LVEF})] \times 100
\]

4.76

Romond et al. JCO 30:3792-3799, 2012
Examples:

(a) age 45, LVEF=65%, CRS=48.3

(b) age 65, LVEF=55, CRS=86.1
NSABP B-31: Examples of Cardiac Risk Assessment
## Summary of Cardiac Dysfunction in the Large Adjuvant Trastuzumab Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median Follow-up (years)</th>
<th>Treatment Arms</th>
<th>Class III/IV CHF (%)</th>
<th>Cardiac Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-31</td>
<td>7</td>
<td>AC→P + Trast AC→P</td>
<td>4.0</td>
<td>1</td>
</tr>
<tr>
<td>NCCTG N9831</td>
<td>5</td>
<td>AC→P+Trast AC→P</td>
<td>3.3</td>
<td>1</td>
</tr>
<tr>
<td>HERA</td>
<td>4</td>
<td>Chemo→Trast Chemo→Observation</td>
<td>0.8</td>
<td>0</td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>5</td>
<td>AC→D+Trast D+Carboplatin+Trast AC→D</td>
<td>2.0</td>
<td>0</td>
</tr>
</tbody>
</table>

A: doxorubicin; C: cyclophosphamide; P: paclitaxel; D: docetaxel
Node Negative Cancers
### BCIRG 006 Node Negative Patients

<table>
<thead>
<tr>
<th></th>
<th>Randomization Group</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AC-&gt;T N=309</td>
<td>AC-&gt;TH N=306</td>
</tr>
</tbody>
</table>

#### Tumor Size
- **pT1**
  - AC->T: 157 (50.8%)
  - AC->TH: 148 (48.4%)
  - TCH: 154 (50.2%)
  - All: 459 (49.8%)
- **pT2**
  - AC->T: 145 (46.9%)
  - AC->TH: 149 (48.7%)
  - TCH: 147 (47.9%)
  - All: 441 (47.8%)
- **pT3**
  - AC->T: 7 (2.3%)
  - AC->TH: 9 (2.9%)
  - TCH: 6 (2.0%)
  - All: 22 (2.4%)

#### ER Status
- **Negative**
  - AC->T: 168 (54.4%)
  - AC->TH: 150 (49.0%)
  - TCH: 172 (56.0%)
  - All: 490 (53.1%)
- **Positive**
  - AC->T: 141 (45.6%)
  - AC->TH: 156 (51.0%)
  - TCH: 135 (44.0%)
  - All: 432 (46.9%)

#### PR Status
- **Negative**
  - AC->T: 183 (59.2%)
  - AC->TH: 176 (57.5%)
  - TCH: 201 (65.5%)
  - All: 560 (60.7%)
- **Positive**
  - AC->T: 121 (39.2%)
  - AC->TH: 122 (39.9%)
  - TCH: 100 (32.6%)
  - All: 343 (37.2%)
- **Unknown**
  - AC->T: 5 (1.6%)
  - AC->TH: 8 (2.6%)
  - TCH: 6 (2.0%)
  - All: 19 (2.1%)

#### Nuclear Grade
- **G1**
  - AC->T: 5 (1.6%)
  - AC->TH: 2 (0.7%)
  - TCH: 2 (0.7%)
  - All: 9 (1.0%)
- **G2**
  - AC->T: 76 (24.6%)
  - AC->TH: 89 (29.1%)
  - TCH: 92 (30.0%)
  - All: 257 (27.9%)
- **G3**
  - AC->T: 220 (71.2%)
  - AC->TH: 207 (67.6%)
  - TCH: 202 (65.8%)
  - All: 629 (68.2%)
- **GX**
  - AC->T: 8 (2.6%)
  - AC->TH: 8 (2.6%)
  - TCH: 11 (3.6%)
  - All: 27 (2.9%)

Valero et al, ASCO 2011, Abstr 553
BCIRG 006 Disease Free Survival

Lymph Node Negative

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Events</th>
<th>HR (95% C.I.)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC-&gt;T</td>
<td>309</td>
<td>46</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>AC-&gt;TH</td>
<td>310</td>
<td>23</td>
<td>0.47 (0.28-0.77)</td>
<td>0.003</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>

Valero et al, ASCO 2011, Abstr 553
## B31/N9831

### 4 yr DFS by Regimen

<table>
<thead>
<tr>
<th>Factor</th>
<th>AC → T+H (%)</th>
<th>AC → T (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=2,028</strong></td>
<td></td>
<td><strong>n=2.017</strong></td>
</tr>
<tr>
<td>Age: &lt; 40 yrs</td>
<td>84.2</td>
<td>69.2</td>
</tr>
<tr>
<td>40-49 yrs</td>
<td>87.4</td>
<td>75.7</td>
</tr>
<tr>
<td>50-59 yrs</td>
<td>84.6</td>
<td>75.8</td>
</tr>
<tr>
<td>60+ yrs</td>
<td>86.1</td>
<td>70.0</td>
</tr>
<tr>
<td>Positive nodes (no.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>1-3</td>
<td>89.7</td>
<td>80.6</td>
</tr>
<tr>
<td>4-9</td>
<td>83.5</td>
<td>71.1</td>
</tr>
<tr>
<td>≥10</td>
<td>73.7</td>
<td>46.5</td>
</tr>
<tr>
<td>Hormone receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+ and/or PR+</td>
<td>89.4</td>
<td>77.2</td>
</tr>
<tr>
<td>ER- and PR-</td>
<td>81.6</td>
<td>69.4</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>90.9</td>
<td>81.6</td>
</tr>
<tr>
<td>2.1-5.0</td>
<td>83.2</td>
<td>70.3</td>
</tr>
<tr>
<td>&gt;5.0</td>
<td>78.2</td>
<td>52.0</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/immediate</td>
<td>88.5</td>
<td>77.0</td>
</tr>
<tr>
<td>High</td>
<td>84.4</td>
<td>72.0</td>
</tr>
</tbody>
</table>

Perez EA. et al., J Clin Oncol 29:3366-3373, 2011
## B31/N9831

### 4 yr Event Rate by Regimen

<table>
<thead>
<tr>
<th>Factor</th>
<th>AC → T+H (%)</th>
<th>AC → T (%)</th>
<th>Absolute Event Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: &lt; 40 yrs</td>
<td>15.8</td>
<td>30.8</td>
<td>15.0</td>
</tr>
<tr>
<td>40-49 yrs</td>
<td>12.6</td>
<td>24.3</td>
<td>11.7</td>
</tr>
<tr>
<td>50-59 yrs</td>
<td>15.4</td>
<td>24.2</td>
<td>8.8</td>
</tr>
<tr>
<td>60+ yrs</td>
<td>13.9</td>
<td>30.0</td>
<td>16.1</td>
</tr>
<tr>
<td>Positive nodes (no.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1-3</td>
<td>10.3</td>
<td>19.4</td>
<td>9.1</td>
</tr>
<tr>
<td>4-9</td>
<td>16.5</td>
<td>28.9</td>
<td>12.4</td>
</tr>
<tr>
<td>≥10</td>
<td>26.3</td>
<td>53.5</td>
<td>27.2</td>
</tr>
<tr>
<td>Hormone receptors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+ and/or PR+</td>
<td>10.6</td>
<td>22.8</td>
<td>12.2</td>
</tr>
<tr>
<td>ER- and PR-</td>
<td>18.4</td>
<td>30.6</td>
<td>12.2</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>9.1</td>
<td>18.4</td>
<td>9.3</td>
</tr>
<tr>
<td>2.1-5.0</td>
<td>16.8</td>
<td>29.7</td>
<td>13.9</td>
</tr>
<tr>
<td>&gt;5.0</td>
<td>21.8</td>
<td>48.0</td>
<td>26.2</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/immediate</td>
<td>11.5</td>
<td>23.0</td>
<td>11.5</td>
</tr>
<tr>
<td>High</td>
<td>15.6</td>
<td>28.0</td>
<td>12.4</td>
</tr>
</tbody>
</table>
## B31/N9831

### 4 yr Event Rate by Regimen

<table>
<thead>
<tr>
<th>Factor</th>
<th>AC → T+H (%)</th>
<th>AC → T (%)</th>
<th>Absolute Event Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age:</strong> &lt; 40 yrs</td>
<td>15.8</td>
<td>30.8</td>
<td>15.0</td>
</tr>
<tr>
<td>40-49 yrs</td>
<td>12.6</td>
<td>24.3</td>
<td>11.7</td>
</tr>
<tr>
<td>50-59 yrs</td>
<td>15.4</td>
<td>24.2</td>
<td>8.8</td>
</tr>
<tr>
<td>60+ yrs</td>
<td>13.9</td>
<td>30.0</td>
<td>16.1</td>
</tr>
<tr>
<td><strong>Positive nodes (no.)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (CIRG 006)</td>
<td>6</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>1-3</td>
<td>10.3</td>
<td>19.4</td>
<td>9.1</td>
</tr>
<tr>
<td>4-9</td>
<td>16.5</td>
<td>28.9</td>
<td>12.4</td>
</tr>
<tr>
<td>≥10</td>
<td>26.3</td>
<td>53.5</td>
<td>27.2</td>
</tr>
<tr>
<td><strong>Hormone receptors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+ and/or PR+</td>
<td>10.6</td>
<td>22.8</td>
<td>12.2</td>
</tr>
<tr>
<td>ER- and PR-</td>
<td>18.4</td>
<td>30.6</td>
<td>12.2</td>
</tr>
<tr>
<td><strong>Tumor size (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>9.1</td>
<td>18.4</td>
<td>9.3</td>
</tr>
<tr>
<td>2.1-5.0</td>
<td>16.8</td>
<td>29.7</td>
<td>13.9</td>
</tr>
<tr>
<td>&gt;5.0</td>
<td>21.8</td>
<td>48.0</td>
<td>26.2</td>
</tr>
<tr>
<td><strong>Tumor grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/immediate</td>
<td>11.5</td>
<td>23.0</td>
<td>11.5</td>
</tr>
<tr>
<td>High</td>
<td>15.6</td>
<td>28.0</td>
<td>12.4</td>
</tr>
</tbody>
</table>
What about really small node negative breast cancers ≤ 1.0 cm (T1a/b)?
AERIO / REMAGUS Study

Node Negative, Infra-centimetric, HER2+ Invasive Br Ca

- 97 Node Negative, T1a/b Breast Cancers
  - 22 T1a, 75 T1b
- 42 received chemotherapy
  - 40 anthracycline ± taxane
  - 2 taxane alone
  - 5 received chemotherapy only
  - 37 received trastuzumab + chemotherapy
- 3 received trastuzumab alone

Results: Invasive Recurrences

Without Trastuzumab: 8/56 (14%) – [3 deaths]
With trastuzumab: 0/40

Wasserman J, et al. ASCO 2011, abstr 557
T1abN0M0 HER2+ Breast Cancers
Kaiser Permanente Northern California

- 3.3 million members
- 16,975 new Breast Cancers diagnosed from 1/1/2000 to 12/31/2006
- HER2, ER, PR IHC mandatory on all cases
- 2,168 HER2+ (IHC 3+ or FISH ratio >2.0)
- 237 T1a or T1b

Fehrenbacher L, et al. ASCO 2011, abstr 551
Recurrences: T1a+bN0 HER2+

<table>
<thead>
<tr>
<th>Median F/U 5.8 yrs</th>
<th>T1aN0 116</th>
<th>T1bN0 121</th>
<th>T1abN0 237</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive Cancer Recurrence (%)</td>
<td>(4) 3.5%</td>
<td>(11) 9.1%</td>
<td>(15) 6.3%</td>
</tr>
<tr>
<td>Invasive Cancer Local Recurrence Only (%)</td>
<td>(3) 2.6%</td>
<td>(4) 3.3%</td>
<td>(7) 2.9%</td>
</tr>
<tr>
<td>Invasive Cancer Distant Recurrence (%)</td>
<td>(1) 0.9%</td>
<td>(7) 5.8%</td>
<td>(8) 3.4%</td>
</tr>
<tr>
<td>5 year Relapse Free Interval (K-M)</td>
<td>97.4% (95% CI, 92.1, 99.1)</td>
<td>91.1% (95% CI, 83.2, 95.3)</td>
<td>94.2% (95% CI, 89.9, 96.7)</td>
</tr>
<tr>
<td>5 year Distant Relapse Free Interval (K-M)</td>
<td>99.1% (95% CI, 93.9, 99.9)</td>
<td>94.0% (95% CI, 87.1, 97.3)</td>
<td>96.5% (95% CI, 92.8, 98.3)</td>
</tr>
</tbody>
</table>

Fehrenbacher L, et al. ASCO 2011, abstr 551
## Treatments Received by T1abN0M0

<table>
<thead>
<tr>
<th></th>
<th>Received Chemo</th>
<th>Received Trastuzumab</th>
<th>Distant Recur No Chemo</th>
<th>Distant Recur with Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All T1abN0</td>
<td>59/237 (24.9%)</td>
<td>20/237 (8.4%)</td>
<td>5/178 (2.8%)</td>
<td>3/59 (5.1%)</td>
</tr>
<tr>
<td>Pre 2005</td>
<td></td>
<td>4/153 (2.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005-2006</td>
<td></td>
<td>16/84 (19.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1aN0*</td>
<td>15/116 (12.9%)</td>
<td>8/116 (6.8%)</td>
<td>1/101 (1.0%)</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>T1bN0</td>
<td>44/121 (36.3%)</td>
<td>12/121 (9.9%)</td>
<td>4/77 (5.2%)</td>
<td>3/44 (6.8%)</td>
</tr>
</tbody>
</table>

*Note: 48% ER negative

Fehrenbacher L, et al. ASCO 2011, abstr 551
<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 cm</td>
<td>Chemotherapy + trastuzumab*</td>
</tr>
<tr>
<td>0.6-1.0 cm</td>
<td>Consider chemotherapy +</td>
</tr>
<tr>
<td></td>
<td>trastuzumab*</td>
</tr>
<tr>
<td>≤ 0.5 cm</td>
<td>No adjuvant therapy*</td>
</tr>
</tbody>
</table>

* endocrine therapy if HR +
Current Adjuvant Trials
ALTTO Study Design

**HER2+ invasive breast cancer**

**Centrally-determined HER2+**

Surgery, complete (neo)adjuvant **anthracycline-based chemotherapy** (approved list)

LVEF ≥ 50

1:1 RANDOMIZATION (N=8000)

* = weekly paclitaxel x 12w; per investigator’s discretion

- Trastuzumab for 1 yr
- Lapatinib for 1 yr
- Trastuzumab for 3 mo
- Trastuzumab 3-weekly + lapatinib for 1 yr

6 wk break

Lapatinib x 7.5 mo

Pls. M Piccart, EA Perez
BETH TRIAL

Node-Positive or High Risk Node-Negative Breast Cancer HER2 Positive by Central Testing

STRATIFICATION
- Number of positive Nodes (0, 1-3 4+)
- Hormone Receptor Status

NSABP/CIRG

TCH ± B

Closed to accrual 3509 patients

CONTACT

FEC → TH ± B
Tykerb Evaluation After CHemotherapy Trial

- HER2: IHC 3+ or FISH +
- Stage I-IIlc
- Completed surgery + (neo)adjuvant chemo
- No distant mets
- Trastuzumab declined or not available

R

Lapatinib
1500 mg daily X 12 months

Placebo
daily X 12 months

Closed to accrual
3000 Patients
413 Centers
Pre-operative Therapy
**Phase III Trial of Neoadjuvant Trastuzumab + Chemotherapy for Operable Breast Cancer**

**ARM 1**
Paclitaxel $\times$ 4
+ $T \times 12$

**ARM 2**
Paclitaxel $\times$ 4

**FEC $\times$ 4**
+ $T \times 12$

$N=23$

$N=19$

*Paclitaxel 225 mg/m² q3w.
FEC = 5-fluorouracil 500 mg/m² d1, 4 + epirubicin 75 mg/m² d1 + cyclophosphamide 500 mg/m² d1, all q3w.

$T = $ trastuzumab 4 mg/kg d1, then 2 mg/kg qw x 24 weeks

Pathological Complete Response Rates

<table>
<thead>
<tr>
<th>Methodology</th>
<th>PCR (%)</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy Alone (N=19)</td>
<td>26.3</td>
<td>9 - 51</td>
</tr>
<tr>
<td>Chemo + Trastuzumab (N=23) (randomized)</td>
<td>65.2</td>
<td>43 - 84</td>
</tr>
<tr>
<td>Chemo + Trastuzumab (N=22) (assigned)</td>
<td>54.5</td>
<td>32.2 – 75.6</td>
</tr>
</tbody>
</table>

Disease-Free Survival of Randomized Study Population

Median Follow UP = 47.6 Months
P = 0.04

Patients with histologically confirmed T2-T3 invasive breast carcinoma pos for HER-2/neu

Randomize

Group 1: Paclitaxel plus Trastuzumab x 12 weeks, followed by FEC x 4 cycles plus concurrent Trastuzumab x 12 weeks

Group 2: FEC x 4 cycles, followed by Paclitaxel plus Trastuzumab x 12 weeks

BCT/Mastectomy and SLND/ALND Path evaluation for response

After completion of local therapy, patients will receive Trastuzumab to complete one year of therapy

Met target accrual of 275 patients. Closed 12/15/2011
Therapeutic Modification of Different Signaling Pathways

(A-B) Changes in apoptosis as measured by cleaved caspase-3 (CC3).
(C-D) Changes in proliferation as measured by Ki67.
Growth of BT-474 xenograft tumors in athymic mice treated with estrogen supplementation (E2) or estrogen deprivation (ED) alone or with HER blocking agents.

E2: estradiol  
ED: estrogen deprivation  
L: lapatinib  
T: trastuzumab  

TBCRC 006: Phase II Study of Neoadjuvant Lapatinib and Trastuzumab

- **Regimen:** Trastuzumab weekly X12
  - Lapatinib 1000 mg p.o. daily
  - Letrozole 2.5 mg p.o. daily (± goserelin)
- **66 patients (64 evaluable)**
  - Median T = 6 cm
  - 36 premenopausal
  - 21 HR negative
- **Results:**
  - pCR in breast 18/64 (28%)
    - ER pos: 8/39 (21%)
    - ER neg: 10/25 (40%)
  - pCR + near pCR (<1 cm in breast): 34/64 (53%)
    - ER pos: 22/39 (56%)
    - ER neg: 12/25 (48%)

Chang J, et al. ASCO 2011, abstr 505
Phase III NeoALTTO Trial

Eligibility criteria:
• Operable HER2+ breast cancer
• T > 2 cm
• LVEF ≥ 50%

Stratify by:
• Tumor size (≤ 5 cm vs. > 5 cm)
• HR status (positive vs. negative)
• N status (0/1 vs. ≥ 2)

Randomize (n = 455)

Primary endpoint: pCR (breast)
Secondary endpoints including: total pCR (breast + nodes), OR at week 6, safety

Lapatinib 1000 mg/day
Trastuzumab 2 mg/kg/week (4-mg/kg loading dose) × 18 cycles
Paclitaxel 80 mg/m²/week × 12 cycles starting at week 7

Lapatinib 1500 mg/day
Paclitaxel 80 mg/m²/week × 12 cycles starting at week 7

Trastuzumab 2 mg/kg/week (4-mg/kg loading dose) × 18 cycles
Paclitaxel 80 mg/m²/week × 12 cycles starting at week 7

*750 mg/day with paclitaxel

Baselga et al. SABCS 2010; abstract S3-3.
**NeoALTTO: Efficacy**

<table>
<thead>
<tr>
<th></th>
<th>Lapatinib/Trastuzumab (n = 152)</th>
<th>Lapatinib (n = 154)</th>
<th>Trastuzumab (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathologic CR, Breast</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By hormone receptor status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>42%</td>
<td>16%</td>
<td>23%</td>
</tr>
<tr>
<td>Negative</td>
<td>61%</td>
<td>34%</td>
<td>36.5%</td>
</tr>
<tr>
<td></td>
<td>(n = 145)</td>
<td>(n = 150)</td>
<td>(n = 145)</td>
</tr>
<tr>
<td><strong>Total Pathologic CR, Breast + Nodes</strong></td>
<td>47%</td>
<td>20%</td>
<td>28%</td>
</tr>
<tr>
<td><strong>Objective Response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At week 6</td>
<td>67%</td>
<td>53%</td>
<td>30%</td>
</tr>
<tr>
<td>At surgery</td>
<td>80%</td>
<td>74%</td>
<td>70.5%</td>
</tr>
</tbody>
</table>

All differences between lapatinib/trastuzumab and trastuzumab alone are significant ($P < .05$).

Baselga et al. SABCS 2010; abstract S3-3.
Lapatinib or Trastuzumab Combined With Neoadjuvant Chemotherapy: The GeparQuinto Study (GBG 44)

Eligibility criteria:
- Untreated primary breast cancer
- HER2+ by local pathology

Primary endpoint: pCR rate
Secondary endpoints including: compliance, toxicity

(n = 620)

EC × 4 cycles → D × 4 cycles
Lapatinib

EC × 4 cycles → D × 4 cycles
Trastuzumab

Trastuzumab × 1 year
Trastuzumab × 6 months

Epirubicin (E) 90 mg/m²
Cyclophosphamide (C) 600 mg/m²
Docetaxel (D) 100 mg/m²
Lapatinib 1000-1250 mg/day p.o.
Trastuzumab 6 mg/kg (8-mg/kg loading)
All 3-week cycles
Surgery day 21-day 35 after final D infusion

Untch et al. SABCS 2010; abstract S3-1.
Neoadjuvant Chemotherapy Plus Lapatinib or Trastuzumab: Efficacy

<table>
<thead>
<tr>
<th>Pathologic Complete Response</th>
<th>EC → D/ Lapatinib</th>
<th>EC → D/ Trastuzumab</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ypT0, ypN0</td>
<td>22%</td>
<td>31%</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>ypT0/is, ypN0</td>
<td>30%</td>
<td>45%</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>ypT0/is, ypNX</td>
<td>35%</td>
<td>50%</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Breast Conservation Rate</td>
<td>56%</td>
<td>66%</td>
<td>NR</td>
</tr>
</tbody>
</table>

pCR odds ratio favored EC → D/trastuzumab in these subgroups:
- ER⁻/PgR⁻
- ER⁺/PgR⁺
- T1-3 and N0-2

Untch et al. SABCS 2010; abstract S3-1.
NSABP B-41
Schema

Operable Breast Cancer HER-2 neu Positive

R 529 patients

Tissue for Biomarkers

AC → WP+T
AC → WP+L
AC → WP+T+L

Tissue for Biomarkers

S U R G E R Y

Trastuzumab for a total of 1 year

WP=Weekly Paclitaxel

Endpoints: pCR, cardiac events, DFS, OS

529 patients
## NSABP B-41

### Patient Characteristics

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>18%</td>
</tr>
<tr>
<td>40-49</td>
<td>34%</td>
</tr>
<tr>
<td>50–59</td>
<td>33%</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>85%</td>
</tr>
<tr>
<td>Black</td>
<td>8%</td>
</tr>
<tr>
<td>Other/Unk</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Tumor size</strong></td>
<td></td>
</tr>
<tr>
<td>2-4 cm</td>
<td>43%</td>
</tr>
<tr>
<td>&gt; 4 cm</td>
<td>57%</td>
</tr>
<tr>
<td><strong>Clinical Nodal Status</strong></td>
<td></td>
</tr>
<tr>
<td>Pos.</td>
<td>51%</td>
</tr>
<tr>
<td>Neg.</td>
<td>49%</td>
</tr>
<tr>
<td><strong>Hormone receptor status</strong></td>
<td></td>
</tr>
<tr>
<td>Pos.</td>
<td>63%</td>
</tr>
<tr>
<td>Neg.</td>
<td>37%</td>
</tr>
</tbody>
</table>
NSABP B-41
pCR Breast and Negative Nodes

Robidoux A, et al., ASCO 2012, abstr 506
NSABP B-41
pCR in Breast by Hormone Receptor Status

Robidoux A, et al., ASCO 2012, abstr 506
Trastuzumab
Pertuzumab
TDM1

HER1/HER1

HER2/HER2

HER3/HER3

HER4/HER4

Lapatinib
Neratinib
Afatinib

Neratinib
Afatinib

Cell growth
Differentiation
Cell survival
Angiogenesis

from Gradishar W, NEJM 366:176-178, 2012
Randomized Phase II Study of Neoadjuvant Pertuzumab Plus Trastuzumab: NeoSphere

Eligibility criteria:
- Operable or locally advanced/inflammatory HER2+ breast cancer
- Chemonaive
- Primary tumors > 2 cm

Primary endpoint: pCR rates
Secondary endpoints including: clinical response

Docetaxel (D) Trastuzumab (H)
(n = 107)

Docetaxel (D) Trastuzumab (H) Pertuzumab (P)
(n = 107)

Trastuzumab (H) Pertuzumab (P)
(n = 107)

Docetaxel (D) Pertuzumab (P)
(n = 96)

All q 3 weeks × 4

FEC q 3 weeks × 3
H q 3 weeks, cycles 5-17

FEC q 3 weeks × 3
H q 3 weeks, cycles 5-17

T q 3 weeks × 4 →
FEC q 3 weeks × 3
H q 3 weeks, cycles 5-17

FEC q 3 weeks × 3
H q 3 weeks, cycles 5-21

FEC: 5-fluorouracil/epirubicin/cyclophosphamide

Gianni et al. SABCS 2010; abstract S3-2.
# NeoSphere: Efficacy of Neoadjuvant Pertuzumab Plus Trastuzumab

By Hormone Receptor Status

<table>
<thead>
<tr>
<th></th>
<th>DH (n = 107)</th>
<th>DHP (n = 107)</th>
<th>HP (n = 107)</th>
<th>DP (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+/PgR+</td>
<td>20%</td>
<td>26%</td>
<td>6%</td>
<td>17%</td>
</tr>
<tr>
<td>ER-/PgR−</td>
<td>37%</td>
<td>63%</td>
<td>29%</td>
<td>30%</td>
</tr>
</tbody>
</table>

By Nodal Status

<table>
<thead>
<tr>
<th></th>
<th>DH (n = 107)</th>
<th>DHP (n = 107)</th>
<th>HP (n = 107)</th>
<th>DP (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node negative</td>
<td>21.5%</td>
<td>39%</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Node positive</td>
<td>7.5%</td>
<td>6.5%</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>

CR + PR + SD<sup>a</sup>

<table>
<thead>
<tr>
<th></th>
<th>DH (n = 107)</th>
<th>DHP (n = 107)</th>
<th>HP (n = 107)</th>
<th>DP (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>107 (100%)</td>
<td>106 (99%)</td>
<td>99 (92.5%)</td>
<td>94 (98%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Investigator assessed

D = docetaxel  
H = trastuzumab  
P = pertuzumab

Gianni et al. SABCS 2010; abstract S3-2.
TRYPHAENA

Cycles 1–3

A

FEC

Pertuzumab + trastuzumab

B

FEC

Pertuzumab + trastuzumab

C

Docetaxel

Pertuzumab + trastuzumab

Surgery

Trastuzumab to complete 1 year

• All 3 arms were experimental

• Study dosing q3w:
  – FEC: 500 mg/m², 100 mg/m², 600 mg/m²
  – Carboplatin: AUC 6
  – Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  – Pertuzumab: 840 mg loading dose, 420 mg maintenance
  – Docetaxel: 75 mg/m² (escalating to 100 mg/m² if tolerated, in Arms A and B only)

Schneeweiss, et al. SABCS 2011, Abstr S5-6
TRYPHAENA: Pathologic complete response

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ypT0/is (%)</th>
<th>ypT0 ypN0 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEC+H+P x3 T+H+P x3 (n = 73)</td>
<td>61.6</td>
<td>66.2</td>
</tr>
<tr>
<td>FEC x3 T+H+P x3 (n = 75)</td>
<td>50.7</td>
<td>51.9</td>
</tr>
<tr>
<td>TCH+P x6 (n = 77)</td>
<td>57.3</td>
<td>45.3</td>
</tr>
</tbody>
</table>

FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

Schneeweiss, et al. SABCS 2011, Abstr S5-6
<table>
<thead>
<tr>
<th></th>
<th>FEC+H+P x3 (\rightarrow) T+H+P x3 (n = 72)</th>
<th>FEC x3 (\rightarrow) T+H+P x3 (n = 75)</th>
<th>TCH+P x6 (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic LVSD (grade (\geq 3)), n (%)</strong></td>
<td>0 (0.0)</td>
<td>2 (2.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>LVSD (all grades), n (%)</strong></td>
<td>4 (5.6)</td>
<td>3 (4.0)</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td><strong>LVEF decline (\geq 10%) points and below 50%, n (%)</strong></td>
<td>3 (4.2)</td>
<td>4 (5.3)</td>
<td>3 (3.9)</td>
</tr>
</tbody>
</table>

FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; P, pertuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

Schneeweiss, et al. SABCS 2011, Abstr S5-6
Where do we go from here?

• New agents in the pipeline
• A final question
Agents Currently in Trials for Pts with HER2+ MBC

- Trastuzumab-DM1 (delivers maytansine to the tumor cell)
- Neratinib (oral pan ErbB inhibitor binds irreversibly to HER1, HER2 and HER4)
- Akt/PI3kinase inhibitors
- IGF-R1 inhibitors
- mTOR inhibitors
- HSP90 inhibitors
A Final Question: Does the standard definition of HER2 positivity mean the same thing as a predictor of response to trastuzumab + chemotherapy in the adjuvant setting as it does for metastatic breast cancer?

- B-31 is the only adjuvant trial that throughout the trial did not use a central HER2 assay for eligibility determination
- Both IHC and FISH allowed
- Central assay performed after primary end point of the joint analysis was presented
- False positive cases were expected
**B-31, distribution of cases according to central HER2 assay**

<table>
<thead>
<tr>
<th></th>
<th>IHC=0</th>
<th>IHC=1</th>
<th>IHC=2</th>
<th>IHC=3</th>
<th>unk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FISH- (&lt;2.0)</strong></td>
<td>25</td>
<td>87</td>
<td>62</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FISH+ (≥2.0)</strong></td>
<td>9</td>
<td>32</td>
<td>84</td>
<td>1457</td>
<td>6</td>
</tr>
</tbody>
</table>

“Central assay negative”

Paik, ASCO 2007, abstr 511
NSABP B-31 Updated 2009 Disease Free Survival
FISH Negative, IHC 0, 1+, 2+ Breast Cancer Pts.

HR = 0.64, p = 0.16
DFS for IHC 0-2 and FISH ratio < 2.0 in NCCTG 9831

![Graph showing disease-free survival](image)

- AC→T: doxorubicin, cyclophosphamide and paclitaxel
- AC→T+H: doxorubicin, cyclophosphamide, paclitaxel and trastuzumab

HR = 0.51

HER2 expression is a continuous variable

Hard to imagine that these two tumors respond differently to trastuzumab

Cut-off Based on IHC/FISH

Slide courtesy of S Paik
NSABP B-47 SCHEMA

Women with Resected Node-Positive or High-Risk Node-Negative Invasive Breast Cancer Determined to be HER2-Low

STRATIFICATION

- IHC score (1+, 2+)
- Number of positive nodes (0-3, 4-9, 10+)
- Hormone receptor status (ER-positive and/or PgR-positive, ER- and PgR-negative)
- Intended chemotherapy regimen (TC [docetaxel + cyclophosphamide], AC→WP [doxorubicin + cyclophosphamide followed by weekly paclitaxel])*

RANDOMIZATION

**Arm 1**
(Groups 1A and 1B)*
Chemotherapy*
(TC or AC→WP)

**Arm 2**
(Groups 2A and 2B)*
Chemotherapy*
+ Trastuzumab x 1 year**
(TC + trastuzumab or
AC→WP + trastuzumab→trastuzumab)
Summary of take-home messages

- Virtually all invasive breast cancers should be tested for HER2. HER2 testing must be done in laboratories with rigorous quality controls.
- Addition of one year of trastuzumab to adjuvant chemotherapy decreased the rate of breast cancer events by 25-48% in the large adjuvant trials. Focally positive cancers also derive similar benefit.
- Chemotherapy plus trastuzumab provides the same relative risk reduction for node negative cancers as for node positive cancers but the absolute benefit is less and also varies with tumor size and hormone receptor status.
- Cardiac monitoring must be done in all patients treated with adjuvant trastuzumab with appropriate holds when indicated. Most patients recover normal ejection fractions if holding rules are followed.
Summary of take-home messages

• In B-31 the combination of age and baseline LVEF correlates with risk of CHF when trastuzumab/paclitaxel is used following AC.
• Radiation and hormone therapy may be given after chemotherapy concurrently with trastuzumab.
• Neo-adjuvant trials are defining a framework for incorporating new targeted agents for specific patients.
• The lower limit of HER2 positivity for discerning adjuvant trastuzumab benefit is being studied further in a prospective trial (NSABP B=47).
Trastuzumab Following Adjuvant Chemotherapy in Patients With Node-Positive, HER2-Positive Breast Cancer: Four-Year Follow-Up Results of the PACS-04 Trial

- Second randomization: Central testing for HER2 status
  - Eligibility criteria for trastuzumab: ≥ 4 cycles of previous chemotherapy, adequate cardiac function, no metastases
  - Primary endpoint: 3-year DFS

## Efficacy of Trastuzumab in the PACS-04 Trial

<table>
<thead>
<tr>
<th></th>
<th>Observation (n = 268)</th>
<th>Trastuzumab (n = 260)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4-year DFS Rate</strong></td>
<td>73.2%</td>
<td>72.7%</td>
</tr>
<tr>
<td></td>
<td>HR 0.86; P = .41</td>
<td></td>
</tr>
<tr>
<td><strong>4-year OS Rate</strong></td>
<td>93.0%</td>
<td>91.5%</td>
</tr>
<tr>
<td></td>
<td>HR 1.27</td>
<td></td>
</tr>
</tbody>
</table>

### Conclusions:
- Severe symptomatic cardiac toxicity remained low
- At 4 years, no significant difference in DFS between trastuzumab and observation arms was observed in the PACS-04 trial (ITT)
- Trend toward better efficacy of trastuzumab during first 18 months

Neo-adjuvant Trastuzumab (NOAH) study design

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

<table>
<thead>
<tr>
<th>(n=115)</th>
<th></th>
<th>(n=113)</th>
<th></th>
<th>(n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H + AT</td>
<td>AT</td>
<td>AT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>q3w x 3 cycles</td>
<td>q3w x 3 cycles</td>
<td>q3w x 3 cycles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H + T</td>
<td>T</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>q3w x 4 cycles</td>
<td>q3w x 4 cycles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H q3w x 4 cycles + CMF q4w x 3 cycles</td>
<td>CMF</td>
<td></td>
<td>CMF</td>
<td></td>
</tr>
<tr>
<td>Surgery followed by radiotherapy(a)</td>
<td>Surgery followed by radiotherapy(a)</td>
<td></td>
<td>Surgery followed by radiotherapy(a)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H continued q3w to week 52</td>
<td></td>
<td></td>
<td></td>
<td>19 crossed over to H</td>
</tr>
</tbody>
</table>

HER2-negative LABC (IHC 0/1+)

Surgery followed by radiotherapy

IHC, immunohistochemistry; FISH, fluorescence in situ hybridisation;
H, trastuzumab (8 mg/kg loading dose then 6 mg/kg); AT, doxorubicin (60 mg/m²), paclitaxel (150 mg/m²);
q3w, every 3 weeks; T, paclitaxel (175 mg/m²); q4w, every 4 weeks
\(a\)Hormone receptor-positive patients will receive adjuvant tamoxifen
### NOAH: Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>HER2 positive</th>
<th>HER2 negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With H (n=115)</td>
<td>Without H (n=112\textsuperscript{a})</td>
</tr>
<tr>
<td><strong>Stage group, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4, non-inflammatory</td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td>Inflammatory disease</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>N2 or ipsilateral nodes</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td><strong>Hormone receptor status, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER and / or PgR positive</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Both negative</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td><strong>Age group, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>46</td>
<td>41</td>
</tr>
<tr>
<td>≥50 years</td>
<td>54</td>
<td>59</td>
</tr>
</tbody>
</table>

ER, oestrogen receptor; PgR, progesterone receptor

NOAH: pCR of primary tumour: intent-to-treat population

![Graph showing the percentage of patients with HER2-positive tumours with and without Herceptin (H), and HER2-negative tumours, comparing outcomes with and without Herceptin.](image)

- **With H:**
  - HER2-positive: 43%
  - HER2-negative: 17%

- **Without H:**
  - HER2-positive: 22%

*P-values: p=0.0007 for With H vs Without H in HER2-positive, p=0.37 for HER2-negative.*

NOAH: Event-free Survival
HER2-positive population

Probability, EFS

Noah: Event-free Survival
HER2-positive population

Median follow-up is 3 years

*Unadjusted for stratification variables: adjusted HR=0.58, p=0.0126
HR, hazard ratio; CI, confidence interval; CT, chemotherapy