Considerations in Adjuvant Chemotherapy

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Texas Oncology
US Oncology
EBCTCG 2005/6 Overview
Control Arms with No Systemic Treatment at 15 Years

Recurrence Mortality
N+ER+
N+ER-
N-ER+
N-ER-

72 69
45 48
65 62
33 33

Percent (%)
0 10 20 30 40 50 60 70 80

Recurrence Mortality
N+ER+
N+ER-
N-ER+
N-ER-

Albain, KS. SABCS 2012
Dilemmas in Adjuvant Chemotherapy

• Is adjuvant chemotherapy effective in ER+ disease?

• In T1a/b disease?

• Locally recurrent disease?

If adjuvant chemotherapy will be administered……

• Clinical utility of various treatment options

• Duration/sequence of adjuvant chemotherapy
Advances in Chemotherapy Have Dramatically Improved Outcomes in ER-Negative Breast Cancer

Corresponds to an absolute improvement in 5-year DFS of 23%, and to an absolute improvement in 5-year OS of 17% in ER-negative subset

Tam vs CMF/Tam: NSABP 20

1546

Node neg, ER+ pre 46%: post 53%
≤ 49 years: 45%
50-59 years: 27%
≥ 60 years: 28%

Fisher et al Lancet 364:858, 2004
NSABP B20: 12 yr Overall Survival

- 87% survival
- 83% survival
- P = 0.063

DFS, DDFS, RFS, OS benefits with CMF in ages ≤ 49 and 50-59, but not in ≥ 60
Tam vs CMF/Tam: IBCSG VIII

Node neg, premenopausal ER+ 68%; ER neg 30%

IBCSG JNCI;24:1833, 2003
IBCSG Trial VIII
STEPP Analysis

IBCSG, J Natl Cancer Inst 2003;95:1833
IBCSG Trial VIII
STEPP Analysis

IBCSG, J Natl Cancer Inst 2003;95:1833
Most Important Paradigm Shift: Breast Cancer is not one disease

- ER+ 65-75%
- HER2+ 15-20%
- Triple Negative 15%

Breast Cancer

“A”

“B”
NSABP B-20  Distant RFS by Recurrence Score

CAF Benefit Greatest in Higher RS for Both Nodal Subsets, with No Benefit in Lower RS

Five-Year Probability of Death or Disease Recurrence

Linear model for Recurrence Score and interactions with treatment

Tam, 4+ nodes (n=54)
CAF-T, 4+ nodes (n=86)
Tam, 1-3 nodes (n=94)
CAF-T, 1-3 nodes (n=133)

Chemo benefit 4+ nodes
Chemo benefit 1-3 nodes

TransATAC: 21-gene recurrence score to predict risk of distant recurrence in postmenopausal pts treated with AI

<table>
<thead>
<tr>
<th>Results</th>
<th>Node- (N=872)</th>
<th>Node+ (N=306)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% pts</td>
<td>9-year DR rate</td>
</tr>
<tr>
<td>Low RS &lt;18</td>
<td>59%</td>
<td>4%</td>
</tr>
<tr>
<td>Int RS 18-30</td>
<td>26%</td>
<td>12%</td>
</tr>
<tr>
<td>High RS ≥ 30</td>
<td>15%</td>
<td>25%</td>
</tr>
<tr>
<td>High vs. Low RS: HR 5.2</td>
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<td></td>
</tr>
<tr>
<td>Int vs. Low RS: HR 2.5</td>
<td></td>
<td></td>
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</table>

P<.001 for RS in predicting time to distant recurrence (DR) in N+ and N- patients

TAILORRx

Pre-REGISTER

n = 7047

Results expected in 2015

21 Gene RS Assay

REGISTER
Specimen Banking

Secondary Study Group 1
RS < 11
~29% of Population

ARM A
Hormonal Therapy
Alone

Primary Study Group
RS 11-25
~44% of Population

RANDOMIZE
n = 4390

Secondary Study Group 2
RS > 25
~27% of Population

ARM D
Chemotherapy Plus
Hormonal Therapy

ARM B
Hormonal Therapy

ARM C
Chemotherapy Plus
Hormonal Therapy

REGISTER
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Albain, KS. St. Gallen 2013
Node-positive (1-3 nodes) HR-positive and HER2-negative breast cancer

(N= 8,800)
Patients consent to study-sponsored RS testing, discussion of potential trials, tumor tissue submission and linkage to cancer registry data

STEP 1 REGISTRATION
Tumor tissue submission for RS

(RECURRENCE SCORE)

RS > 25
(N= 3,800)
Discuss alternative trials for high risk patients

RS ≤ 25
N= 5,800
Physician and patients discuss randomization knowing the RS

Accept

N= 1,600
Record chosen therapy and followed for vital status through cancer registry

Refuse

(N= 600)
RS already Available
Physician and patients discuss randomization knowing the RS

STEP 2 RANDOMIZATION
N= 4,000
Randomization stratified by
1. RS 0-13 vs. 14-25
2. Menopausal status
3. Axillary node dissection vs. Sentinel node biopsy

N= 2,000
Chemotherapy; appropriate endocrine therapy

N= 2,000
No Chemotherapy; appropriate endocrine therapy
Theoretical Spectrum of Sensitivity to Adjuvant Systemic Therapy by Intrinsic Subtypes
N=51246 $T_{1ab}N_0M_0$ breast cancers from SEER Program 1988-2001

Breast cancer-specific & non BC-related mortality – Unselected by Biology

**T1A,B,N0M0**: 21-gene Recurrence Score and 70-gene Assays

### 21 Gene RS Assay
2 NSABP trials, one population-based study
(N= 461 pts with ER+ disease ± tamoxifen)

### 70 Gene Assay
(N= 139 pts; about half untreated; most HER2-, ER+)

<table>
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<tr>
<th>Tumor size</th>
<th>70 gene (Good prognosis)</th>
<th>70 gene (Poor prognosis)</th>
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<tr>
<td>-pT1ab</td>
<td>84 (60%)</td>
<td>55 (40%)</td>
</tr>
<tr>
<td>-pT1c</td>
<td>441 (53%)</td>
<td>384 (47%)</td>
</tr>
</tbody>
</table>

**Similar proportion as 21 gene RS assay**

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Mook S et al; Ann Surg Oncol 2010*
Outcomes T1a/bN0 Breast Cancers
NCCN Breast Cancer Outcomes Database

Fig 2. Distant relapse-free survival of T1a/bN0 patients with breast cancer, National Comprehensive Cancer Network, 2000 to 2009. (A) HR-positive/HER2-negative group; (B) HR-negative/HER2-positive group; (C) HR-negative/HER2-negative group; (D) HR-negative/HER2-positive group. HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

Outcomes T1a/bN0 Breast Cancers
NCCN Breast Cancer Outcomes Database

NCCN Guidelines T1a,b N0 –
Give Chemotherapy?

- No for T1a  
  (Consider for high grade TNBC or HER2+)
- Yes for TN or HER2+ T1b
- Only if intermediate/high RS luminal T1b

For T1a,b we need consensus on
- SYSTEMIC THERAPY threshold
- NON-ENDOCRINE THERAPY threshold
- Robust follow-up time
Adjuvant CMF or AC vs Capecitabine in women ≥65
Give Effective Chemotherapy for Virulent BC

Muss et al, NEJM 360:2055-65, 2009
CALOR: Chemotherapy as Adjuvant for Locally Recurrent Breast Cancer

- First, isolated, ipsilateral, resectable recurrence
  - IBTR or CW recurrence
  - Axillary or SC LN
- Fully excised and radiation planned

NSABP, BIG, IBCSG, GEICAM

Aebi et al., SABCS 2012; abstract S3-2
CALOR: Challenges

– INADEQUATE POWER
  • Sample size (optimal 977) = 162

– PROTOCOL DEVIATIONS
  • Polychemotherapy recommended – 31% monotherapy

– CHEMOTHERAPY BENEFIT UNCERTAIN
  • ~65% hormone receptor-positive
  • > 50% IBTR
  • Average disease-free interval = 5-6 years
  • 42% pts chemotherapy arm and 32% pts no chemotherapy arm had had no prior chemotherapy
CALOR: Disease-Free Survival

5-yr OS 0.41 (0.19-0.89)

Aebi S et al, SABCS 2012
Dilemmas in Adjuvant Chemotherapy

- Is adjuvant chemotherapy effective in ER+ disease?
- In T1a/b disease?
- Locally recurrent disease?

If adjuvant chemotherapy will be administered……

- Clinical utility of various treatment options
- Duration/sequence of adjuvant chemotherapy
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<th>ER+ and ER poor</th>
<th>RR</th>
<th>SE</th>
<th>2p</th>
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<td>CMF vs no chemo</td>
<td></td>
<td>0.76</td>
<td>0.05</td>
<td>&lt;0.0001</td>
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<td>CAF vs no chemo</td>
<td></td>
<td>0.64</td>
<td>0.09</td>
<td>&lt;0.0001</td>
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<td>4AC/EC vs no chemo</td>
<td></td>
<td>0.78</td>
<td>0.09</td>
<td>0.01</td>
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<tr>
<td>4AC vs CMF</td>
<td></td>
<td>0.98</td>
<td>0.05</td>
<td>0.67</td>
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<tr>
<td>CAF/CEF vs 4AC</td>
<td></td>
<td>0.78</td>
<td>0.06</td>
<td>0.0004</td>
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<tr>
<td>CAF/CEF vs CMF</td>
<td></td>
<td>0.89</td>
<td>0.03</td>
<td>0.003</td>
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<tr>
<td>Anthra then T vs shorter anthra</td>
<td></td>
<td>0.86</td>
<td>0.04</td>
<td>0.0005</td>
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<tr>
<td>Anthra + taxane vs expanded</td>
<td></td>
<td>0.94</td>
<td>0.06</td>
<td>0.33</td>
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<tr>
<td>anthracycline alone</td>
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<td>4AC = 4AT E2197</td>
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<td>4AT = 4TAC NSABP B30</td>
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</table>

Duration of therapy >> specific regimen

ER+ Anthra/CMF plus ET vs ET Control

Age < 55

Age 55-69

## Anthracyclines vs No Chemotherapy by Subsets of ER+

<table>
<thead>
<tr>
<th>Category</th>
<th>Deaths/Women</th>
<th>Logrank Variance</th>
<th>Ratio of annual death rates Anth. : Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated anth.</td>
<td>O-E</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allocated control</td>
<td></td>
<td></td>
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<tr>
<td></td>
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</tr>
<tr>
<td><strong>Subsets of ER+</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+, chemo+end. vs end. only †</td>
<td>659/2622 (25 1%)</td>
<td>853/2675 (31 9%)</td>
<td>-56.2</td>
</tr>
<tr>
<td>ER10–99 fmol/mg</td>
<td>416/1371 (30 3%)</td>
<td>544/1442 (37 7%)</td>
<td>-35.3</td>
</tr>
<tr>
<td>ER100+ fmol/mg</td>
<td>274/1146 (23 9%)</td>
<td>337/1160 (29 1%)</td>
<td>-20.6</td>
</tr>
<tr>
<td>ER+, age &lt; 55</td>
<td>250/845 (29 6%)</td>
<td>316/943 (33 5%)</td>
<td>-19.4</td>
</tr>
<tr>
<td>ER+, 55–69</td>
<td>542/2071 (26 2%)</td>
<td>677/2055 (32 9%)</td>
<td>-53.9</td>
</tr>
<tr>
<td>ER+, poorly differentiated</td>
<td>100/461 (21 7%)</td>
<td>120/477 (25 2%)</td>
<td>-12.2</td>
</tr>
<tr>
<td>ER+, moderately/well differentiated</td>
<td>228/985 (23 1%)</td>
<td>286/1026 (27 9%)</td>
<td>-27.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1416/4754 (29.8%)</td>
<td>1701/4733 (35.9%)</td>
<td>-139.9</td>
</tr>
</tbody>
</table>

- 99% or 95% confidence intervals

Global heterogeneity: $\chi^2 = 5.8; p = 0.4$

Treatment effect: $2p < 0.00001$

Adjuvant Chemotherapy Regimens

CMF = AC

CAF/FAC  CEF/FEC

DAC_{(Tac)}  FEC \rightarrow P/D

AC \rightarrow P/D

AC \rightarrow \text{wkly P}

ddAC \rightarrow P
Individual Patient Meta-analysis with central HER2 FISH
CMF vs Anthracycline

Di Leo A. Lancet Oncology 12:1134, 2011
Individual Patient Meta-Analysis

CMF vs A by Breast Cancer Subtype

ER/PR+ grade 1/2

ER+/PR- or grade 3 or ER+ HER2+

ER- PR- HER2+

Di Leo A. Lancet Oncology 12:1134, 2011
### USON 9735  TC vs AC: DFS and OS

**AC x 4 q3w**
- Doxorubicin  (60 mg/m²)
- Cyclophosphamide  (600 mg/m²)

**TC x 4 q3w**
- Docetaxel  (75 mg/m²)
- Cyclophosphamide  (600 mg/m²)

- **N=1016**
- **71% ER+**
- **48% N−**

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HER-2 Negative Operable Early-Stage Breast Cancer (N=5900)

TC X 6

TAC or AC then T

Enrollment completed 2013
Meta-analysis: Adjuvant taxane vs no taxane: DFS

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<th>Control N</th>
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<tr>
<td>MD ANDERSON</td>
<td>265</td>
<td>259</td>
<td>1.55</td>
<td>0.70</td>
<td>0.47 to 1.06</td>
<td>2002</td>
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<tr>
<td>CALG B 9344</td>
<td>1,570</td>
<td>1,551</td>
<td>16.44</td>
<td>0.83</td>
<td>0.73 to 0.94</td>
<td>2003</td>
</tr>
<tr>
<td>ECTO</td>
<td>902</td>
<td>453</td>
<td>4.07</td>
<td>0.72</td>
<td>0.56 to 0.93</td>
<td>2005</td>
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<tr>
<td>GEICAM 9906</td>
<td>614</td>
<td>634</td>
<td>3.59</td>
<td>0.63</td>
<td>0.48 to 0.83</td>
<td>2005</td>
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<tr>
<td>HeCOG</td>
<td>298</td>
<td>297</td>
<td>3.22</td>
<td>0.86</td>
<td>0.65 to 1.14</td>
<td>2005</td>
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<tr>
<td>NSABP B28</td>
<td>1,531</td>
<td>1,528</td>
<td>13.64</td>
<td>0.83</td>
<td>0.72 to 0.95</td>
<td>2005</td>
</tr>
<tr>
<td><strong>Subtotal (fixed effect)</strong></td>
<td>5,180</td>
<td>4,722</td>
<td>42.52</td>
<td>0.80</td>
<td>0.74 to 0.86</td>
<td>P &lt; .00001</td>
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<tr>
<td><strong>Subtotal (random effect)</strong></td>
<td>0.80</td>
<td>0.74 to 0.86</td>
<td>P &lt; .00001</td>
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<tr>
<td>Test for heterogeneity: $\chi^2_1$ = 4.91 ($P = .03$), $I^2$ = 0%</td>
<td></td>
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<tr>
<td><strong>02 Docetaxel</strong></td>
<td></td>
<td></td>
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<tr>
<td>Anglo-Celtic</td>
<td>183</td>
<td>180</td>
<td>1.70</td>
<td>0.86</td>
<td>0.58 to 1.27</td>
<td>2005</td>
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<td>745</td>
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<td>6.55</td>
<td>0.72</td>
<td>0.59 to 0.88</td>
<td>2005</td>
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<tr>
<td>ECOG E 2197</td>
<td>1,444</td>
<td>1,441</td>
<td>7.59</td>
<td>0.97</td>
<td>0.81 to 1.17</td>
<td>2005</td>
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<td>BIG 2-98</td>
<td>1,919</td>
<td>968</td>
<td>11.56</td>
<td>0.86</td>
<td>0.74 to 1.00</td>
<td>2006</td>
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<tr>
<td>NSABP B27</td>
<td>1,602</td>
<td>802</td>
<td>17.74</td>
<td>0.90</td>
<td>0.80 to 1.02</td>
<td>2006</td>
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<tr>
<td>PACS 01</td>
<td>1,003</td>
<td>996</td>
<td>8.04</td>
<td>0.82</td>
<td>0.68 to 0.98</td>
<td>2006</td>
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<td>TAXIT-216</td>
<td>486</td>
<td>486</td>
<td>4.29</td>
<td>0.79</td>
<td>0.62 to 1.01</td>
<td>2006</td>
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<td><strong>Subtotal (fixed effect)</strong></td>
<td>7,382</td>
<td>5,619</td>
<td>57.48</td>
<td>0.86</td>
<td>0.80 to 0.92</td>
<td>P &lt; .00001</td>
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<td><strong>Total (fixed effect)</strong></td>
<td>12,562</td>
<td>10,341</td>
<td>100.00</td>
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<tr>
<td>Test for heterogeneity: $\chi^2_1$ = 12.68 ($P = .39$), $I^2$ = 5.4%</td>
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## Meta-analysis: Adjuvant taxane vs no taxane: OS

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<td><strong>4,915</strong></td>
<td><strong>4,463</strong></td>
<td><strong>45.42</strong></td>
<td><strong>0.83</strong></td>
<td><strong>0.75 to 0.92</strong></td>
<td><strong>P = .0004</strong></td>
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<td><strong>0.70 to 0.94</strong></td>
<td><strong>P = .005</strong></td>
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<td>0.92</td>
<td>0.71 to 1.19</td>
<td>2005</td>
</tr>
<tr>
<td>BIG 2-98</td>
<td>1,919</td>
<td>968</td>
<td>11.57</td>
<td>0.92</td>
<td>0.75 to 1.13</td>
<td>2006</td>
</tr>
<tr>
<td>NSABP B27</td>
<td>1,602</td>
<td>802</td>
<td>16.24</td>
<td>1.03</td>
<td>0.87 to 1.22</td>
<td>2006</td>
</tr>
<tr>
<td>PACS 01</td>
<td>1,003</td>
<td>996</td>
<td>7.26</td>
<td>0.73</td>
<td>0.56 to 0.95</td>
<td>2006</td>
</tr>
<tr>
<td>TAXIT-216</td>
<td>486</td>
<td>486</td>
<td>3.63</td>
<td>0.72</td>
<td>0.50 to 1.04</td>
<td>2006</td>
</tr>
<tr>
<td><strong>Subtotal (fixed effect)</strong></td>
<td><strong>7,382</strong></td>
<td><strong>5,619</strong></td>
<td><strong>54.58</strong></td>
<td><strong>0.87</strong></td>
<td><strong>0.79 to 0.95</strong></td>
<td><strong>P = .003</strong></td>
</tr>
<tr>
<td><strong>Subtotal (random effect)</strong></td>
<td><strong>0.84</strong></td>
<td><strong>0.73 to 0.96</strong></td>
<td><strong>P = .010</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for heterogeneity:</strong></td>
<td>$\chi^2 = 10.97 (P = .09), I^2 = 45.3%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (fixed effect)</strong></td>
<td><strong>12,297</strong></td>
<td><strong>10,082</strong></td>
<td><strong>100.00</strong></td>
<td><strong>0.85</strong></td>
<td><strong>0.79 to 0.91</strong></td>
<td><strong>P &lt; .00001</strong></td>
</tr>
<tr>
<td><strong>Total (random effect)</strong></td>
<td><strong>0.83</strong></td>
<td><strong>0.76 to 0.91</strong></td>
<td><strong>P = .0001</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 17.23 (P = .10), I^2 = 30.2\%$
BCIRG 001  FAC vs. TAC by biologic subtype

PACS 01  DFS  FEC vs FEC-Doc by Ki67

Arm A: FEC
Arm B: FEC - DOC

ER+ and Ki67−
- Arm A  n = 266
- Arm B  n = 283

ER+ and Ki67+
- Arm A  n = 63
- Arm B  n = 86

Luminal A
Luminal B

PACS-01 Distant RFS by Recurrence Score


FEC Arm

FEC-D Arm

Proportion Distant Recurrence Free

Log-rank P < .001

Risk Group | N | Events | Estimate (CI)
--- | --- | --- | ---
Low | 94 | 8 | 97.9 (91.7, 99.5)
Intermediate | 81 | 17 | 82.6 (72.5, 91.3)
High | 87 | 33 | 66.6 (57.7, 77.3)

Risk Group | N | Events | Estimate (CI)
--- | --- | --- | ---
Low | 115 | 18 | 90.4 (83.3, 94.5)
Intermediate | 78 | 11 | 92.2 (83.5, 96.4)
High | 75 | 28 | 70.1 (58.2, 79.2)
NSABP B28 Outcome by Recurrence Score

BCSS

AC

Proportion of Alive w/o Disease

- RS Low
- RS Intermediate
- RS High

P<0.001

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low RS</td>
<td>186</td>
<td>15</td>
</tr>
<tr>
<td>Intermediate RS</td>
<td>180</td>
<td>47</td>
</tr>
<tr>
<td>High RS</td>
<td>153</td>
<td>49</td>
</tr>
</tbody>
</table>

Time in years

AC → P

Proportion of Alive w/o Disease

- RS Low
- RS Intermediate
- RS High

P<0.001

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low RS</td>
<td>200</td>
<td>13</td>
</tr>
<tr>
<td>Intermediate RS</td>
<td>184</td>
<td>40</td>
</tr>
<tr>
<td>High RS</td>
<td>162</td>
<td>53</td>
</tr>
</tbody>
</table>

Time in years
Adjuvant weekly vs q3 weekly paclitaxel E1199

Figure 4. Exploratory Analysis of Disease-free and Overall Survival According to Expression of Hormone Receptors (HR).

The figure shows the hazard ratios for disease-free and overall survival the group receiving weekly paclitaxel in as compared with the group receiving paclitaxel every 3 weeks among patients with HER2-negative disease according to whether the disease was positive or negative for hormone receptors.

Sparano et al. NEJM, 2008; 358:1663
SWOG S0221: Comparison of two schedules of paclitaxel as adjuvant therapy for breast cancer: Revised Schema

- Stage I-III Breast Cancer
- Randomize

1. Doxorubicin 60 mg/m²
   - Cyclophosphamide 600 mg/m²
   - Peg-filgrastim q 2 weeks x 4

2. Paclitaxel 175 mg/m²
   - Peg-filgrastim q 2 wks x 6

3. Doxorubicin 60 mg/m²
   - Cyclophosphamide 600 mg/m²
   - Peg-filgrastim q 2 weeks x 6

4. Paclitaxel 175 mg/m²
   - Peg-filgrastim q 2 wks x 6

5. Doxorubicin 24 mg/m²
   - Cyclophosphamide 60 mg/m² po
   - GCSF d2-7 Weekly x 15 weeks

6. Paclitaxel 80 mg/m² Weekly x 12

7. Doxorubicin 60 mg/m²
   - Cyclophosphamide 600 mg/m²
   - Peg-filgrastim q 2 weeks x 6

8. Paclitaxel 80 mg/m² Weekly x 12

9. Doxorubicin 24 mg/m²
   - Cyclophosphamide 60 mg/m² po
   - GCSF d2-7 Weekly x 15 weeks

10. Paclitaxel 80 mg/m² Weekly x 12

Budd, GT, et al 2013 ASCO
April 2013
Updated Analysis

## S0221: Toxicity (Grade 3-4)

<table>
<thead>
<tr>
<th>Grade 3-4 Toxicity</th>
<th>q 2 week Paclitaxel</th>
<th>Weekly Paclitaxel</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>36%</td>
<td>35%</td>
<td>0.75</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>2.7%</td>
<td>1.9%</td>
<td>0.16</td>
</tr>
<tr>
<td>Hematologic</td>
<td>6%</td>
<td>17%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1%</td>
<td>6%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>2%</td>
<td>11%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Neutropenic Fever</td>
<td>0.1%</td>
<td>0.4%</td>
<td>0.29</td>
</tr>
<tr>
<td>Allergy</td>
<td>1.4%</td>
<td>0.6%</td>
<td>0.035</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>11%</td>
<td>3%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Neurologic</td>
<td>17%</td>
<td>10%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Duration of Adjuvant Chemotherapy
CALGB 40101: 4 Versus 6 Cycles of AC Versus Paclitaxel as Adjuvant Therapy

**Stratification factors:**
- Pre-postmenopausal
- ER/PgR
- HER2

**Protocol Changes**

<table>
<thead>
<tr>
<th>Years</th>
<th>Trial design</th>
<th>Pts enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002-2003</td>
<td>AC q3w × 4 or 6 cycles T wkly for 12 or 18 wks</td>
<td>570</td>
</tr>
<tr>
<td>2003-2008</td>
<td>AC q2w × 4 or 6 cycles Tq2w × 4 or 6 cycles</td>
<td>3173</td>
</tr>
<tr>
<td>2008-2010</td>
<td>AC q3w × 4 Tq2w × 4</td>
<td>3873</td>
</tr>
</tbody>
</table>

Tam or AI if HR+; Trastuzumab is HER2+ after 2005

- 6% 1-3 Node+
- 94% Node Negative

4 vs 6 Cycles of Therapy – Previously Reported

Relapse-Free Survival

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>4-yr RFS</th>
<th>HR of 6:4 (95% CI)</th>
<th>P</th>
<th>4-yr OS</th>
<th>HR of 6:4 (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 cycles</td>
<td>90.9%</td>
<td>1.03 (0.84-1.28)</td>
<td>0.77</td>
<td>95.3%</td>
<td>1.12 (0.84-1.49)</td>
<td>0.44</td>
</tr>
<tr>
<td>4 cycles</td>
<td>91.8%</td>
<td></td>
<td></td>
<td>96.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Shulman, JCO 2012
Relapse-Free Survival

Median f/u 6.1 years
- RFS – 437 events
  - HR = 1.26 (95% CI: 1.05-1.53); p=0.02
  - Cannot conclude equivalence
- OS – 266 deaths
  - HR = 1.27 (95% CI: 1.00-1.62); p=0.05
  - Cannot conclude equivalence

Proportion Alive & Relapse-Free

Years From Study Entry

AC 5-yr RFS: 91%
T 5-yr RFS: 88%
NSABP B-30: Combinations of doxorubicin, cyclophosphamide and docetaxel for early-stage node-positive breast cancer

Stage II or IIIA BC
Node Positive
HR+ or HR-
No metastatic disease

Stratification:
# Nodes
Radiotherapy
Surgery
Tamoxifen

Randomized:

**AC→T:** A (60 mg/m2) + C (600 mg/m2) q3w x 4 → T (100 mg/m2) q3w x 4

**AT:** A (50 mg/m2) + T (75 mg/m2) q3w x 4

**TAC:** A (50 mg/m2) + C (500 mg/m2) + T (75 mg/m2) q3w x 4

N=5351

Primary aims:
- Concurrent vs. sequential: effect on DFS, OS
- Utility of cyclophosphamide

Swain S, et al. NEJM 363:2268, 2010
NSABP B-30

Disease-Free Survival (Intention-To-Treat)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th># Events</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC→T</td>
<td>1,753</td>
<td>388</td>
<td>0.83 vs. TAC</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.80 vs. AT</td>
<td>0.001</td>
</tr>
<tr>
<td>AT</td>
<td>1,753</td>
<td>468</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAC</td>
<td>1,758</td>
<td>457</td>
<td>0.96 vs. AT</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Swain S, et al. NEJM 363:2268, 2010
BCIRG 005 6 TAC vs 4 AC then 4 Docetaxel

Disease-free Survival

Conclusions

• Does indolent ER+ EBC benefit from adjuvant chemoRx beyond OFS? TailoRx, MINDACT, RxPonder ongoing

• CMF benefits ER-poor and high RS ER+ node negative

• Anthracyclines improve survival in ER+ and ER-poor disease (advantage over non-A confined to HER2+?)

• Taxanes are effective regardless of ER and HER2 status and improve OS

• Dose dense and weekly paclitaxel are superior to q 3w paclitaxel.

• Pts with locally recurrent ER- disease benefit from adjuvant chemoRx (probably virulent ER+ disease, too)
Conclusions

• 6 cycles = 4 cycles AC or paclitaxel in node negative pts – and 6 is more toxic

• 6TAC and AC/T superior to 4-cycle regimens in node positive pts (duration matters in node +)

• Is 4 cycles TC enough in chemotherapy-sensitive node + breast cancer? (B49 6 TC vs 6TAC)

• Single agent capecitabine or paclitaxel inferior to AC/CMF

• Consider adjuvant chemoRx for virulent ≥ T1bN0

• Give most effective chemotherapy for biologically aggressive disease regardless of age – AC/T is standard of care