Non-anthracycline Adjuvant regimens in Early Breast Cancer

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Role of Anthracyclines in adjuvant treatment
  • EBCTCG2012

Non-anthracycline regimen: current evidence
  • TC for low-risk EBC
  • TCH for HER2+EBC

How to omit anthracycline
  • Define group with low risk of recurrence
    ▪ Small sized, N-EBC
  • Adding new agents instead of anthracyclines
  • Predictive markers for anthracyclines
    ▪ HER2 IHC or amplification
    ▪ TOP2 expression or alteration
    ▪ CEP17
Anthracycline-based CTx

- **EBCTCG(2012):**
  - AC4 = classic CMF
  - 3 drug-A regimen > AC4 or CMF
  - T+A > A-based regimen

High A > AC4 = CMF

A+T > same A or high A
Anthracycline-based CTx

- T+A became a standard based on
  - Proven efficacy in RCTs and EBCTCG meta-analysis
  - Relatively low risk of toxic effects of A in contemporary regimens
  - Lack of evidence that Non-A > T+A regimens
    - Until introduction of TC or TCH

Anthracyclines

- Cardiac toxicity in particular with trastuzumab
- High risk of emesis with cyclophosphamide
  - More common in younger women
- Extravasation necrosis
- Infertility
- Leukemia/MDS: −1%
Increasing evidences of role of ACT for N-EBC

- Stage I breast cancer has increased dramatically
- Unfavorable outcome without CT based on intrinsic subtype

<table>
<thead>
<tr>
<th></th>
<th>T1a</th>
<th></th>
<th></th>
<th>T1b</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ER+/HER2+</td>
<td>ER-/HER2+</td>
<td>ER+/HER2+</td>
<td>ER-/HER2+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT+/H</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>DRFS</td>
<td>96</td>
<td>100</td>
<td>93</td>
<td>100</td>
<td>94</td>
<td>96</td>
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<tr>
<td>OS</td>
<td>95</td>
<td>100</td>
<td>93</td>
<td>100</td>
<td>95</td>
<td>99</td>
</tr>
</tbody>
</table>

- Increasing % of ACT for small tumor
  (NCCN Prospective cohort study:4,113 with T1a,bN0M0 among 24,931 EBC Pts)

Ines Vaz-Luis et al. JCO 2014 &ASCO2014 abstract #522
Is T+A still beneficial for N-EBC?

- **GEICAM9805**
  - Martin M et al, NEJM 2010

- **GEICAM/2003-02**
  - Martin M et al, JCO 2013

**EBC, R0 resected N0, high risk* (N=1060)**
- **1:1**
  - TAC#6
  - FAC#6

**EBC, R0 resected N0, high risk* (N=1925)**
- **1:1**
  - FAC#4 \(\rightarrow\) wP#8
  - FAC#6

*Tumor size >2 cm, ER/PR -/-, tumor histologic grade 2 or 3, or age <35 ys
Is T+A still beneficial for N-EBC?

- **GEICAM9805**
  - Martin M et al, NEJM 2010
  
  DFS: HR=0.68 (0.49-0.93); p=0.01
  
  OS: HR=0.76 (0.45-1.26); p=0.29

- **GEICAM/2003-02**
  - Martin M et al, JCO 2013
  
  DFS: HR=0.73 (0.54-0.99); p=0.04
  
  OS: HR=0.76 (0.45-1.26); p=0.29
Is T+A still beneficial for N-EBC?

- **GEICAM9805**
  - *Martin M et al, NEJM 2010*
  - [Bar chart showing local, regional, and distant metastases for TAC and FAC treatments.]

- **GEICAM/2003-02**
  - *Martin M et al, JCO 2013*
  - [Bar chart showing locoregional and distant metastases for FAC-wP and FAC treatments.]

<table>
<thead>
<tr>
<th></th>
<th>TAC6</th>
<th>FAC6</th>
<th>P</th>
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<tbody>
<tr>
<td>G3,4</td>
<td>28.2%</td>
<td>17.0%</td>
<td>&lt;0.001</td>
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<tr>
<td>SAE</td>
<td>22.4%</td>
<td>4.2%</td>
<td></td>
</tr>
<tr>
<td>Discontinue</td>
<td>4.7%</td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>TRM</td>
<td>0</td>
<td>0</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>FAC4-wP</th>
<th>FAC6</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>G3,4</td>
<td>25.4%</td>
<td>21.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2`malignancy</td>
<td>2%</td>
<td>2%</td>
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</tr>
<tr>
<td>Discontinue</td>
<td>9.1%</td>
<td>2.0%</td>
<td></td>
</tr>
<tr>
<td>TRM</td>
<td>0.2</td>
<td>0.7</td>
<td></td>
</tr>
</tbody>
</table>
Is T+A still beneficial for N-EBC?

- RCTs for Adding Taxane: meta-analysis of RCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Node</th>
<th>N</th>
<th>HER2</th>
<th>T</th>
<th>Non-T</th>
<th>F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEICAM 9805, Martin</td>
<td>N-/+</td>
<td>1060</td>
<td>64%</td>
<td>TAC</td>
<td>FAC</td>
<td>5</td>
</tr>
<tr>
<td>ECOG 2197, Goldstein</td>
<td>N-/+</td>
<td>1893/989</td>
<td>No</td>
<td>AT</td>
<td>AC</td>
<td>5</td>
</tr>
<tr>
<td>USO 9735, Jones</td>
<td>N-/+</td>
<td>487/529</td>
<td>17%</td>
<td>TC</td>
<td>AC</td>
<td>7</td>
</tr>
<tr>
<td>UK TACT, Ellis</td>
<td>N-/+</td>
<td>835/3327</td>
<td>86%</td>
<td>FEC-T</td>
<td>FEC or E-CMF</td>
<td>5</td>
</tr>
<tr>
<td>RAPP-01, Brain</td>
<td>N-/+</td>
<td>627</td>
<td>No</td>
<td>AT</td>
<td>AC</td>
<td>5</td>
</tr>
<tr>
<td>FinHer, Joensuu</td>
<td>N-/+</td>
<td>1010</td>
<td>89%</td>
<td>T-FEC</td>
<td>V-FEC</td>
<td>5</td>
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<tr>
<td>BCIRG001, Martin</td>
<td>N+</td>
<td>1491</td>
<td>85%</td>
<td>TAC</td>
<td>FAC</td>
<td>4.5</td>
</tr>
<tr>
<td>TAXIT 216, Cognetti</td>
<td>N+</td>
<td>972</td>
<td>No</td>
<td>E-T-CMF</td>
<td>E-CMF</td>
<td>5</td>
</tr>
<tr>
<td>PACS01, Roché</td>
<td>N+</td>
<td>1999</td>
<td>No</td>
<td>FEC-T</td>
<td>FEC</td>
<td>5</td>
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<tr>
<td>BIG2-98, TAX315,</td>
<td>N+</td>
<td>2887</td>
<td>No</td>
<td>A-T-CMF or AT-CMF</td>
<td>A-CMF or AC-CMF</td>
<td>5</td>
</tr>
<tr>
<td>WSG/AGO, Nitz</td>
<td>N+ ≤ 3</td>
<td>1837</td>
<td>Yes</td>
<td>EC-T</td>
<td>FEC</td>
<td>5</td>
</tr>
<tr>
<td>HORG, Polyzos</td>
<td>N+</td>
<td>756</td>
<td>39%</td>
<td>T-EC</td>
<td>FEC</td>
<td>5</td>
</tr>
<tr>
<td>PACS-04, Roché</td>
<td>N+</td>
<td>3010</td>
<td>Yes</td>
<td>ET</td>
<td>FEC</td>
<td>5</td>
</tr>
<tr>
<td>ADEBAR, Janni</td>
<td>N+ ≥ 3</td>
<td>1502</td>
<td>Yes</td>
<td>EC-T</td>
<td>FEC</td>
<td>4</td>
</tr>
</tbody>
</table>

| 14 P-III RCTs (N=25,067) | N0 (N=4,274) |
Is T+A still beneficial for N-EBC?

- RCTs for Adding Taxane: meta-analysis of RCT

<table>
<thead>
<tr>
<th>Node negative</th>
<th>HR [95% CI]</th>
<th>P value</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS, 4 trials, 4274 pts</td>
<td>0.86 [0.73; 1.00]</td>
<td>p=0.05</td>
<td>P Het. 0.41</td>
</tr>
<tr>
<td>OS, 3 trials, 2381 pts</td>
<td>1.00 [0.75; 1.34]</td>
<td>p=0.99</td>
<td>P Het. 0.34</td>
</tr>
</tbody>
</table>

| Node positive | DFS, 12 trials, 20166 pts | 0.83 [0.77; 0.90] | p<0.001 | Random |
|---------------| OS, 11 trials, 19177 pts | 0.83 [0.74; 0.93] | p<0.001 | Random |

- Consistent with EBCTCG2012

Jacquin et al. BCRT 2012
T+A for N-EBC?

- Small efficacy but considerable toxicity
  - 2 RCTs for N- EBC showed better PFS but not OS
    - **Minimal efficacy**: Only 5% for PFS and <3% for OS
    - **Higher toxicity** rate with A+T
  - Meta-analysis of 14 RCT including N- EBC patients
    - Adding taxane seems better
    - Efficacy of T+A was limited to N+EBC

- Need to identify who benefit from T+ A regimen
  - No proven predictive marker for adding taxane
Cardiotoxicity by Anthracycline, more than expected

- More frequent in the non-trial population
  - Observation study
- Late onset is not rare
  - the 10-y follow-up of the BCIRG001 trial

![Graph showing cumulative frequency of congestive heart failure](image)

**Proportion Free of CHF**

- No adjuvant chemotherapy
- Adjuvant anthracycline
- Adjuvant other

**Time (months)**

19 vs. 14% Δ5%

47 vs. 33% Δ14%

**Cumulative frequency of congestive heart failure**

- **Giordano et al JCO 2006**
- **Martin et al, Lancet 2013**

Need Non-A regimen without compromising survival benefit
Non-A regimen for N-/+ EBC

- US9735: R-P-III (n=1016)
  - 94% S-I,II
  - 48% N0
  - 41% N1
  - 11% N2

- TC4 > AC4 superior in terms of OS as well as DFS

TC regimen for low risk EBC: US9735

- TC4 > AC4 regardless of Age, ER expression, Node

- Better safety profile
  - N/V
  - stomatitis

• (control arm) Is AC x 4 the best comparator?
  • EBCTCG 2011
• A+T as current or sequential

• (active arm) Is duration of treatment important:
  • NSABP B30:
  • TC#6 should be active arm

Graph showing recurrence and breast cancer mortality rates:
- SAME anth: 34.7%
- 8-y gain 4.4% (SE 1.0)
  5-y gain 1.3% (SE 0.4)
  Logrank 2p = 0.003

Graph showing 8-yr survival rates:
- AC4T4
- AT4
- TAC4
- 8YSR, %
  *
PlanB Trial by West German Study Group (N=2,448)

TC6 vs. EC4 → T4:

TC regimen: ongoing trials

USO 06090/NSABP B46-I/07132 (N=3,500) and B-49: TC6 vs. TAC6
Taxane single for small sized/low risk EBC

- CALGB 40101: Comparison of Doxorubicin and Cyclophosphamide Versus Single-Agent Paclitaxel As Adjuvant Therapy for Breast Cancer in Women With 0 to 3 Positive Axillary Nodes: CALGB 40101 (Alliance)

**Accrual: 3,873**

<table>
<thead>
<tr>
<th>EBC, N0-1</th>
<th>T</th>
<th>AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>T ≤ 2 cm, 65%</td>
<td>4 cycles</td>
<td>4 cycles</td>
</tr>
<tr>
<td>N0, 90%</td>
<td>6 cycles</td>
<td>6 cycles</td>
</tr>
<tr>
<td>ER+, 68%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2+, 16%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Shulman. JCO 2014
CALGB40101: P single vs. AC4 or AC6

- Similar efficacy
  - Median F/U 6.1 yr
  - non-inferiority of T over AC regardless of HR status: not conclusive

- (Weekly) P single could be optional for
  - low risk tumor
  - Patients with comorbidity
  - Elderly

<table>
<thead>
<tr>
<th></th>
<th>COD (n = 1,931)</th>
<th>T (n = 1,940)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>60</td>
<td>87</td>
</tr>
<tr>
<td>TRM</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>AML/MDS</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Shulman. JCO 2014
A+T as a standard for high risk EBC

- Toxicity is a great issue
- Predictive markers for anthracyclines
  - Some promising biomarkers introduced post-hoc analysis from RCTs
    - HER2 status by IHC or ISH
    - TOP2A alteration or expression
    - CEP17 duplication

Hanna et al Modern Pathol 2014
HER2+ : A Pooled Analysis of Randomized Trials

- 8 RCT (N=6564): HER2+ 1536/5354
- **No** trastuzumab therapy

**HER2 status as predictive for Anthracycline benefit**
- Anthracycline is only effective for HER2+ breast cancer
- Regardless of HER2 IHC or FISH, age, type of Anthracyclines
HER2 and TOP2A in Chr 17

- Important genes at Chromosome 17
### TOP2A for anthracyclines

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Topo IIα score (mean $\pm$ SD)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All tumors</td>
<td>230</td>
<td>10.6 $\pm$ 7.9%</td>
<td></td>
</tr>
<tr>
<td>Age (&lt;50 years)</td>
<td>55</td>
<td>12.1 $\pm$ 8.1%</td>
<td></td>
</tr>
<tr>
<td>Age (&gt;50 years)</td>
<td>175</td>
<td>10.1 $\pm$ 7.8%</td>
<td></td>
</tr>
<tr>
<td>Histological grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>71</td>
<td>6.3 $\pm$ 5.1%</td>
<td>NS</td>
</tr>
<tr>
<td>II</td>
<td>106</td>
<td>11.3 $\pm$ 7.6%</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>47</td>
<td>15.3 $\pm$ 8.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tumor size (&lt;2 cm)</td>
<td>127</td>
<td>9.7 $\pm$ 7.5%</td>
<td></td>
</tr>
<tr>
<td>Tumor size (&gt;2 cm)</td>
<td>85</td>
<td>11.8 $\pm$ 8.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Axillary nodal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>117</td>
<td>9.8 $\pm$ 7.6%</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>75</td>
<td>11.5 $\pm$ 7.7%</td>
<td>NS</td>
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<tr>
<td>DNA ploidy</td>
<td></td>
<td></td>
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<tr>
<td>Diploid</td>
<td>94</td>
<td>8.1 $\pm$ 6.4%</td>
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<tr>
<td>Aneuploid</td>
<td>101</td>
<td>12.0 $\pm$ 8.1%</td>
<td>0.0003</td>
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<tr>
<td>ER*</td>
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<tr>
<td>Negative</td>
<td>59</td>
<td>16.8 $\pm$ 9.4%</td>
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</tr>
<tr>
<td>Positive</td>
<td>171</td>
<td>8.5 $\pm$ 6.0%</td>
<td>&lt;0.0001</td>
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<tr>
<td>PR*</td>
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<td></td>
<td></td>
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<tr>
<td>Negative</td>
<td>102</td>
<td>13.4 $\pm$ 8.9%</td>
<td>&lt;0.0001</td>
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<tr>
<td>Positive</td>
<td>128</td>
<td>8.3 $\pm$ 6.2%</td>
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<td>c-erbB-2 overexpression</td>
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<tr>
<td>Negative</td>
<td>172</td>
<td>9.0 $\pm$ 6.7%</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>41</td>
<td>15.8 $\pm$ 8.7%</td>
<td>&lt;0.0001</td>
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<table>
<thead>
<tr>
<th>HER2 + (%)</th>
<th>HER2 - (%)</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>354</td>
<td>23/61 (38)</td>
<td>Di Leo, 2002 (27)</td>
</tr>
<tr>
<td>120</td>
<td>10/30 (33)</td>
<td>Olsen, 2004 (28)</td>
</tr>
<tr>
<td>805</td>
<td>79/263 (30)</td>
<td>Knoop, 2005 (29)</td>
</tr>
<tr>
<td>391</td>
<td>48/128 (37.5)</td>
<td>Tannier, 2006 (30)</td>
</tr>
<tr>
<td>284</td>
<td>18/74 (24.3)</td>
<td>Park, 2006 (31)</td>
</tr>
<tr>
<td>351</td>
<td>40/94 (42.6)</td>
<td>Konecny, 2006 (32)</td>
</tr>
<tr>
<td>245</td>
<td>20/37 (54)</td>
<td>Arriola, 2007 (33)</td>
</tr>
<tr>
<td>303</td>
<td>17/63 (27)</td>
<td>Bartlett, 2008 (34)</td>
</tr>
<tr>
<td>2853</td>
<td>255/750 (34)</td>
<td>26/1535 (1.6)</td>
</tr>
<tr>
<td>438</td>
<td>33/116 (28.4)</td>
<td>20/314 (6.4)</td>
</tr>
</tbody>
</table>

Rody A et al. BCRT 2009

Martin M, et al BCRT 2011
TOP-2A: preclinical study and prognostic impact

### TOP2A expression

- **Martin M, et al BCRT 2011**

### TOP2A RNA levels

- **782 pts with Node-BC, No Adjuvant Therapy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>P</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOP2A expression</td>
<td>High vs. low</td>
<td>275 vs. 266</td>
<td>&lt;0.0001</td>
<td>2.40 1.68-3.43</td>
</tr>
<tr>
<td>Node</td>
<td>Pos. vs. Neg</td>
<td>199 vs. 342</td>
<td>0.705</td>
<td>1.07 0.76-1.49</td>
</tr>
<tr>
<td>Age (years)</td>
<td>≤50 vs. &gt;50</td>
<td>173 vs. 368</td>
<td>0.962</td>
<td>1.01 0.71-1.43</td>
</tr>
<tr>
<td>Grade</td>
<td>3 vs. 1,2</td>
<td>117 vs. 424</td>
<td>0.550</td>
<td>1.12 0.77-1.62</td>
</tr>
<tr>
<td>Size (cm)</td>
<td>≤2 vs. &gt;2</td>
<td>241 vs. 300</td>
<td>0.0001</td>
<td>0.48 0.34-0.69</td>
</tr>
<tr>
<td>HER2 expression</td>
<td>High vs. low</td>
<td>45 vs. 496</td>
<td>0.007</td>
<td>1.90 1.19-3.02</td>
</tr>
</tbody>
</table>

**Rody A et al. BCRT 2009**

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**Brase JC et al. CCR 2010**
Biomarker study: MA.5 & NEAT/BR9601

MA.5
N=710

CEF (351)
CMF (359)

NEAT
N=2027

E→cCMF (1011)
cCMF (1016)
E→mCMF (183)

BR9601
N=374

E→cCMF (1094)
cCMF (1207)

CEF (351) + CMF (359) + E→cCMF (1011) + cCMF (1016) + E→mCMF (183) + mCMF (191) = cCMF (1207)
Biomarker study: MA.5 & NEAT/BR9601

MA.5
N=710

NEAT
N=2027

BR9601
N=374

HER2+

TOP2A Amplified or Deleted


O’Malley FP, et al. *JNCI* 2009
Biomarker study: MA.5 & NEAT/BR9601

ChCEP17 normal

HR 0.92, 95% CI 0.76–1.11

ChCEP17 duplication

HR 0.51, 95% CI 0.36–0.73

<table>
<thead>
<tr>
<th></th>
<th>RFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≤50 years</td>
<td>1.12 (0.94–1.33) 0.22</td>
<td>0.98 (0.81–1.19) 0.86</td>
</tr>
<tr>
<td>BCS</td>
<td>0.83 (0.69–0.99) 0.04</td>
<td>0.82 (0.67–1.00) 0.05</td>
</tr>
<tr>
<td>N+</td>
<td>1.83 (1.61–2.07) &lt;0.0001</td>
<td>1.73 (1.51–1.98) &lt;0.0001</td>
</tr>
<tr>
<td>ER -</td>
<td>0.93 (0.73–1.18) 0.53</td>
<td>0.88 (0.69–1.14) 0.34</td>
</tr>
<tr>
<td>ER+</td>
<td>0.75 (0.60–0.94) 0.01</td>
<td>0.66 (0.52–0.84) 0.0008</td>
</tr>
<tr>
<td>grade</td>
<td>1.29 (1.10–1.52) 0.002</td>
<td>1.34 (1.11–1.60) 0.002</td>
</tr>
<tr>
<td>T size</td>
<td>1.01 (1.00–1.01) 0.002</td>
<td>1.01 (1.00–1.01) 0.005</td>
</tr>
<tr>
<td>ECMF</td>
<td>0.89 (0.72–1.10) 0.27</td>
<td>0.92 (0.72–1.16) 0.47</td>
</tr>
<tr>
<td>HER2 amp</td>
<td>1.61 (1.17–2.21) 0.003</td>
<td>1.84 (1.31–2.58) 0.0005</td>
</tr>
<tr>
<td>TOP2A alteration</td>
<td>1.40 (0.99–2.00) 0.06</td>
<td>1.36 (0.93–2.00) 0.12</td>
</tr>
<tr>
<td>Ch17CEP duplication</td>
<td>1.43 (1.09–1.87) 0.01</td>
<td>1.37 (1.01–1.84) 0.04</td>
</tr>
<tr>
<td>HER2*ECMF</td>
<td>1.03 (0.66–1.61) 0.89</td>
<td>0.91 (0.56–1.47) 0.70</td>
</tr>
<tr>
<td>TOP2A*ECMF</td>
<td>0.90 (0.55–1.49) 0.69</td>
<td>0.85 (0.50–1.45) 0.54</td>
</tr>
<tr>
<td>Ch17CEP*ECMF</td>
<td>0.54 (0.35–0.83) 0.005</td>
<td>0.60 (0.38–0.95) 0.03</td>
</tr>
</tbody>
</table>

Bartlett et al, Lancet Oncol 2010
TOP2A and CEP17 as co-predictive factor for anthracycline

- Individual patients level pooled analysis from 5 RCTs

<table>
<thead>
<tr>
<th>Study arms</th>
<th>inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEAT</td>
<td>E→cCMF vs cCMF N- (31%) or N+ (69%)</td>
</tr>
<tr>
<td>BR9601</td>
<td>E→mCMF vs mCMF N+</td>
</tr>
<tr>
<td>Belgium</td>
<td>CMF vs HEC/EC N+</td>
</tr>
<tr>
<td>DBCG 89D</td>
<td>CMF vs FEC N+ or N- with risk</td>
</tr>
<tr>
<td>NCIC MA5</td>
<td>CMF vs CEF N+, premenopausal</td>
</tr>
</tbody>
</table>

- Tissue 79.1% (3846/4864) for HER2, TOP2A, CEP17
A+T as a standard for high risk EBC

- Predictive markers for anthracyclines
  - Some promising biomarkers introduced
    - HER2 status by IHC or ISH
    - TOP2A alteration or expression
    - CEP17 duplication
  - Weak evidence for predictive markers until yet
    - Inconsistent among studies
    - Need further validation
Trastuzumab may overcome the benefit of A?

- Trastuzumab into CT, mostly A+T
  - Persistent effect on RFS and OS
  - Mostly, stage II or III were rerolled in RCTs
    - 5.7% N-/HER2+
  - Cardiac toxicity, leukemia
  - Emesis

- Less toxic regimen without affecting survival advantage?
  - In particular, earlier stage HER2+EBC
    - Incidence of small/N- EBC has increased dramatically
Adjuvant Trastuzumab in HER2-Positive Breast Cancer

- Primary: DFS
- Secondary: OS, Safety

AC: doxorubicin, ab: cyclophosphamide, T: docetaxel, H: trastuzumab

BCIRG006: Results for 5YSR

- Similar efficacy in N- subset.: Δ3% for DFS; Δ1% for OS

**BCIRG 006: Results for 10YSR**

- **Final Analysis (SABCS2015, S05-04)**
  - Median follow-up time = 10.3 years
  - DFS (10.3 yrs)
  - Equally effective for high risk group (LN ≥ 4)

---

**DFS: LN ≥ 4**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>HR (95% C.I.)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC-T</td>
<td>1073</td>
<td>328</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>AC-TH</td>
<td>1074</td>
<td>269</td>
<td>0.72 (0.61 - 0.85)</td>
</tr>
<tr>
<td>TCH</td>
<td>1075</td>
<td>279</td>
<td>0.77 (0.65 - 0.90)</td>
</tr>
</tbody>
</table>

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**DFS (10.3 yrs)**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Events</th>
<th>HR (95% C.I.)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC-T</td>
<td>350</td>
<td>155</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>AC-TH</td>
<td>350</td>
<td>123</td>
<td>0.71 (0.56 - 0.89)</td>
</tr>
<tr>
<td>TCH</td>
<td>352</td>
<td>123</td>
<td>0.69 (0.54 - 0.87)</td>
</tr>
</tbody>
</table>

---

*Slamon D et al. SABCS 2015*
### BCIRG 006: Conclusion

- Trastuzumab can overcome anthracycline benefit for both low and high risk EBCs
  - Safely omit A from ACT with Trastuzumab

- TOP2A alteration as predictive marker?
  - Need final report including sub-analysis based on TOP2A
Small sized/N- HER2+ EBC

- **T1abN0 HER2+ EBC**
  - Risk of relapse
  - proven evidence of Trastuzumab regardless of T size
  - Increasing % of ACT +/- H

<table>
<thead>
<tr>
<th></th>
<th>T1a</th>
<th>T1b</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT+/-H</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>DRFS</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>OS</td>
<td>95</td>
<td>100</td>
</tr>
</tbody>
</table>

- Less toxic regimen than AC→TH or TCH for
  - Small, N- HER2+ EBC
TC4 + Trastuzumab for low risk EBC

- US Oncology; P-II, single arm study (n=493); NCT00493649
  - Low risk
    - 99% S-I, II
    - 79% N0
    - 20% N1
    - T1 67%
  - 4 x TC q3w + Trastuzumab 1 year

- Need F/U for more events
- Planned analysis by TOP2A and cMYC

Jones et al, Lancet Oncol 2013
wP + Trastuzumab for small/N- EBC

- APT trial: Phase II for N-/HER2+ EBC (NCT00542451)
  - 2007.10~2010.9

- Comparable to T+A+ H regimens
  - Similar outcome regardless of tumor size and HR

T≤3cm, N0 HER2+ BC N=406

P80 + Trastuzumab weekly x 12

Trastuzumab every 3 weeks x 13

Tolaney et al., NEJM 2015; SABCS 2013
T-DM1 vs. paclitaxel+ trastuzumab for Stage I EBC

- Phase II ATEMPT Trial (NCT01853748)
  - Dana-Faber Cancer Institute
  - Stage I HER2+ EBC (T1N0M0)
  - Recruiting since 2013

Randomize 3:1

- T-DM1 q 3 weeks x 17
  - N=375

- Paclitaxel + Trastuzumab weekly x 12
  - Trastuzumab every 3 weeks x 13
  - N=125

Stage I BC
- HER2+
- N=500

www.Clinicaltrials.gov
Non-A regimen for HER2+ EBC with low-risk

NCCN

- Regimen for HER2+
  - **Preferred regimens**
    - AC→T + Trastuzumab
    - TCH
  - **Other regimens**
    - TC + trastuzumab
    - wP + Trastuzumab
    - ...

Cancer Care Ontario guideline

- Non-anthracycline regimens
  - Low risk
  - Cardiotoxicity
    - TCH
    - TC + trastuzumab
    - wP + trastuzumab

Denduluri et al, JCO 2016; www.NCCN.org
Non-A Adjuvant chemotherapy for EBC: Summary 1

- **Low risk breast cancer**
  - Luminal A: can omit ACT for N- or possibly N1 with low RS
  - **TC 4 or 6 as a standard regimen**, especially luminal B
  - Small sized/N-: Taxane single may be considered

- **For HER2+ EBC**
  - TCH as one of standard for N+ as well as N- EBC
  - Small sized/N-:
    - wP + Trastuzumab
    - TC4 + Trastuzumab
Non-A Adjuvant chemotherapy for EBC: Summary2

- **T+A is still main ACT regimen** for
  - HR+: N+ with unfavorable features
  - TNBC: Larger or node +

- **Predictive biomarkers for Anthracyclines as personalized medicine**
  - TOP2A, CEP17 alteration as strong candidates
  - But, validation studies are still warranted
  - No proven efficacy of Gene signature
Anthracycline vs. personalized medicine

Thank you for your attention!!