Non-anthracycline Adjuvant regimens in N(-) Early Breast Cancer

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Case: Clinical history

- F/45, Premenopause
- C/C: Rt. Palpable breast mass
- P/I
  - Rt. Palpable breast mass
  - cT1cN0M0 (2cm)
- Medical History: No underlying disease
- In Hospital course (I)
  - 2008.11.27 Rt. PM with SLND
  - IDC, pT1cN0miM0, G3, LVI(-), ER/PgR/HER2/Ki67 8/6/1/24%
F/45, Premenopause

C/C: Rt. Palpable breast mass

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- cT1cN0M0 (2cm)

Medical History: No underlying disease

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1. None (tamoxifen only)
2. AC#4
3. FAC/FECG6
4. TAC#6
5. AC followed by T
6. Other
What should we consider for adjuvant treatment?

- **Clinico-pathologic factors:**
  - Node, Size, Grade, LVI
  - ER/PgR
  - HER2
  - Ki67

- **Gene Signature**
  - OncotypeDX
  - MammaPrint
  - PAM50...

- **Age & comorbidity**

- **Side effects:** acute and late

50% of all newly diagnosed
Stage I breast cancer has increased dramatically

• Only 15% in 1990’s → Up to 50% of all EBC
• New guidelines suggest active chemotherapy for small tumor based on subtype

<table>
<thead>
<tr>
<th>St Gallen 2013</th>
<th>Luminal A</th>
<th>Luminal B /HER2 -</th>
<th>Luminal B /HER2 +</th>
<th>HER2 enrich</th>
<th>TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>T1b (≥5mm)</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>T1c</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>T2</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Node +</td>
<td>1–3 +/-</td>
<td>&gt;3 +</td>
<td>+</td>
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</table>

<table>
<thead>
<tr>
<th>NCCN guidelines</th>
<th>ER +/HER2 -</th>
<th>ER +/HER2 +</th>
<th>HER2 enrich</th>
<th>TNBC</th>
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<tr>
<td>T1a</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>T1b (≥5mm)</td>
<td>RS</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
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<tr>
<td>T1c</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>T2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Node +</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

• patients with small tumor have NOT been included for adjuvant CTx trials
Adjuvant Chemotherapy for T1N0 tumor: NCCN Prospective cohort study:

- 4,113 with T1a,bN0M0 among 24,931 EBC Pts
- during 2000-2009
  - Median F/U of 5.5yr

Ines Vaz-Luis et al. JCO 2014 &ASCO2014 abstract #522
RCTs for Adjuvant chemotherapy: T+A>A based ≥ CMF

CMF6 = AC4

CEF/FEC → T or P

CAF/FAC → wP

TAC6 = AC4 → T

AC4 → P

TACT

AC6

CALGB40101

"NSABP B-15
NSABP B-23

FACS05

MA5

NSABP B-28

GEICAM9805
BCIRG001

NCIC MA.21

ECOG1199

CALGB 9741

ddAC4 → ddP

AC4 → wP12

NSABP B-30

E2197

NSABP B-30

ECOG1199
Adjuvant chemotherapy with taxane

▼ EBCTCG Lancet 2012: Taxane-containing regimens as standard for N+

<table>
<thead>
<tr>
<th>Nodal status before chemotherapy</th>
<th>(E) Nodal status before chemotherapy (trend x²=0.3; 2p=0.6; NS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO/N-</td>
<td>120/2104 (5.7%)</td>
</tr>
<tr>
<td>N1-3</td>
<td>520/6971 (7.4%)</td>
</tr>
<tr>
<td>N4+</td>
<td>783/5012 (15.6%)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>1218/8031 (15.2%)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>ER status (x²=0.1; 2p=0.7; NS)</th>
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</thead>
<tbody>
<tr>
<td>ER-poor</td>
</tr>
<tr>
<td>ER+</td>
</tr>
<tr>
<td>ER unknown</td>
</tr>
</tbody>
</table>

▼ De Laurentiis et al, JCO2008: adding taxane improves DFS & OS

- absolute 5-yr benefit: 5% for DFS and 3% of OS
- Similar efficacy regardless of type of taxane, ER status, N1-3
Adjuvant chemotherapy with taxane for N(-) EBC

\[ \text{EBCTCG Lancet 2012: Taxane-containing regimens as standard for N+} \]

<table>
<thead>
<tr>
<th>Nodal status before chemotherapy</th>
<th>(trend } \chi^2 = 0.3; \text{2p} = 0.6; \text{N5})</th>
<th>120/2104 (5.7%)</th>
<th>132/2070 (6.4%)</th>
<th>-6.0</th>
<th>61.0</th>
<th>0.91 (SE 0.12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0/N-</td>
<td></td>
<td>520/6981 (7.4%)</td>
<td>599/6977 (8.6%)</td>
<td>-41.9</td>
<td>262.1</td>
<td>0.85 (SE 0.06)</td>
</tr>
<tr>
<td>N1-3</td>
<td></td>
<td>783/5012 (15.6%)</td>
<td>849/5062 (16.8%)</td>
<td>-29.9</td>
<td>338.8</td>
<td>0.92 (SE 0.05)</td>
</tr>
<tr>
<td>N4+</td>
<td></td>
<td>1218/8031 (15.2%)</td>
<td>1388/8014 (17.3%)</td>
<td>-83.1</td>
<td>514.6</td>
<td>0.85 (SE 0.04)</td>
</tr>
</tbody>
</table>
## Clinical trials for N- EBC

<table>
<thead>
<tr>
<th>Trial</th>
<th>period</th>
<th>N</th>
<th>N −%</th>
<th>mF/U</th>
<th>regimens</th>
<th>Trial</th>
<th>period</th>
<th>N</th>
<th>N −%</th>
<th>mF/U</th>
<th>regimens</th>
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<tbody>
<tr>
<td>Anglo-Celtic</td>
<td>1999–2001</td>
<td>363</td>
<td>34</td>
<td>80</td>
<td>AD→S v AC→S</td>
<td>ECOG 1199</td>
<td>1999–2002</td>
<td>4,950</td>
<td>12</td>
<td>64</td>
<td>AC→P3 v P1 AC→P3 v D3 AC→P3 v D1</td>
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<tr>
<td>FinHER</td>
<td>2000–2003</td>
<td>1,010</td>
<td>11</td>
<td>36</td>
<td>D→FEC v V→FEC</td>
<td>USO Loesch</td>
<td>2000–2002</td>
<td>1,830</td>
<td>73</td>
<td>60</td>
<td>AP→P1 v AC→P3</td>
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<tr>
<td>USO 9735</td>
<td>1997–2000</td>
<td>1,016</td>
<td>48</td>
<td>83</td>
<td>DC v AC</td>
<td>GEICAM 9805</td>
<td>1999–2003</td>
<td>1,059</td>
<td>100</td>
<td>72</td>
<td>DAC v FAC</td>
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<tr>
<td>TACT</td>
<td>2001–2003</td>
<td>4,162</td>
<td>20</td>
<td>52</td>
<td>FEC→D v FEC or E→CMF</td>
<td>GEICAM 2003</td>
<td>2003–2008</td>
<td>1,925</td>
<td>100</td>
<td>63.3</td>
<td>FAC→wP v FAC</td>
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<tr>
<td>NCIC MA.21</td>
<td>2000–2005</td>
<td>2,104</td>
<td>22</td>
<td>30</td>
<td>AC→P v CEF AC→P v ddEC6→P</td>
<td></td>
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</tbody>
</table>
Adjuvant chemotherapy: T+A for N-EBC

- 2 RCTs only for N-EBC
  - GEICAM9805
  - GEICAM2003-02

- 1 meta-analysis
  - Jacquin et al. BCRT 2012
RCT1: TAC vs. FAC for node-negative

GEICAM9805

- Primary end points: DFS
- Key secondary end points: OS

*Tumor size >2 cm, ER/PR -/-, tumor histologic grade 2 or 3, or age <35 yrs
**amended d/t high incidence of NF

Martin M et al, NEJM 2010
GEICAM9805: TAC vs. FAC

Median F/U 77 months

- Disease-free Survival (DFS):
  - TAC (N=539): 90.1% ± 85.3%
  - FAC (N=521): 87.8% ± 81.8%
  - HR=0.68 (0.49-0.93); p=0.01

- Overall Survival (OS):
  - TAC (N=539): 95.2% ± 93.5%
  - FAC (N=521): 90.1% ± 85.3%
  - HR=0.76 (0.45-1.26); p=0.29

Martin M et al, NEJM 2010
High % of premenopause and younger aged
Higher toxicity related with TAC
Efficacy related with locoregional control than distant

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

Martin M et al, NEJM 2010
RCT2: GEICAM/2003-02: FAC-wP v. FAC

Fluorouracil, doxorubicin, and cyclophosphamide (FAC) versus FAC followed by weekly paclitaxel as adjuvant therapy for high-risk, node-negative breast cancer: results from the GEICAM/2003-02 study.

- EBC, R0 resected T1-3, N0, high risk* (N=1925)
- FAC#4→wP#8
- FAC#6

1:1

- Primary end points: DFS
- Key secondary end points: OS

* Tumor size >2 cm, ER/PR -/-, tumor histologic grade 2 or 3, or age <35 ys

Martin M et al, JCO 2013
GEICAM/2003-02: FAC-wP v. FAC

Median F/U 63.3 months

**A**

Disease-Free Survival (%)

- 93%
- 90.3%

Δ2.7%

DFS: HR=0.73 (0.54-0.99); p=0.04

**B**

Overall Survival (%)

- 97.4%
- 95.8%

Δ1.6%

OS: HR=0.76 (0.45-1.26); p=0.29

Martin M et al, JCO 2013
## Metaanalysis: T+A or T for N-EBC

<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>
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<tbody>
<tr>
<td>GEICAM 9805, Martin</td>
<td>N-/+</td>
<td>1060</td>
<td>64%</td>
<td>TAC</td>
<td>FAC</td>
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<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>
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<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>
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<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>
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<td>RAPP-01, Brain</td>
<td>N-/+</td>
<td>627</td>
<td>No</td>
<td>AT</td>
<td>AC</td>
<td>5</td>
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<tr>
<td>FinHer, Joensuu</td>
<td>N-/+</td>
<td>1010</td>
<td>89%</td>
<td>T-FEC</td>
<td>V-FEC</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>
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<td>TAXIT 216, Cognetti</td>
<td>N+</td>
<td>972</td>
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<td>E-T-CMF</td>
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<td>PACS01, Roché</td>
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<td>1999</td>
<td>No</td>
<td>FEC-T</td>
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<td>BIG2-98, TAX315,</td>
<td>N+</td>
<td>2887</td>
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<td>A-CMF or AC-CMF</td>
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<td>WSG/AGO, Nitz</td>
<td>N+ ≤ 3</td>
<td>1837</td>
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<td>HORG, Polyzos</td>
<td>N+</td>
<td>756</td>
<td>39%</td>
<td>T-EC</td>
<td>FEC</td>
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<td>PACS-04, Roché</td>
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<td>3010</td>
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<td>ET</td>
<td>FEC</td>
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<td>ADEBAR, Janni</td>
<td>N+ ≥ 3</td>
<td>1502</td>
<td>Yes</td>
<td>EC-T</td>
<td>FEC</td>
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</tr>
</tbody>
</table>

14 P-III RCTs (N=25,067)      N0 (N=4,274)

*Jacquin et al. BCRT 2012*
Metaanalysis: T+A or T for N-EBC

Jacquin et al. BCRT 2012
Which regimen for N-EBC?

▼ Taxane + Anthracycline

- 2 RCTs for N-EBC showed better PFS, but
  - **No OS benefit**
  - **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 in DFS
Anthracycline vs. CHF

- Cardiotoxicity associated with anthracyclines
  - Cumulative dose of Anthracycline: 400-450 mg/m²

A-induced cardiotoxicity

- 300mg/m² of Anthracycline (FAC) seemed safe
- A–related cardiotoxicity can occur less than 300mg/m²

- Late onset was **NOT** rare
  - the 10-y follow-up of the BCIRG001 trial
    - FAC is associated with an unexpectedly high cardiac toxicity.
      - 17 (2.3%) CHF and four (0.5%) deaths
      - LVEF drop > 20% in 41 (15%)

*Martin M et al, SabCS2010; Shulman LN et al JCO2012; Ryberg et al, JNCI 2008*
A-related Cardiotoxicity in non-trial population

- true toxicity in the non-trial population.

- Observatory study by Giordano et al JCO 2006

![Graph showing the proportion of CHF over time, with 19 vs. 14% and 47 vs. 33% differences, and Δ5% and Δ14% changes.](Giordano et al JCO 2006)
Toxicities of Anthracyclines

- Risk of cardiotoxicity: 6-26%
- High emetogenic agent
  - High proportion of young female in Korea
    - Much more intolerant to Anthracyclines d/t Nausea
- Vesicant
- Infertility
- Risk of leukemia ~0.5%
Adjuvant chemotherapy for N- EBC

- **Usually good outcome with standard treatment**
  - 5y-DFS of 85-90% or more
  - 5y-OS of 95% or more

- **Adding taxane into A-based regimen:**
  - Yes, but small efficacy (3-6% gain in DFS; 2% gain in OS)
  - Higher rate of toxicity: G3-4 hematologic toxicity, neuropathy, edema,

- **Taxane without A in low-risk group?**
  - TC
  - TCH for HER2+
USO 9735 study: TC vs. AC

Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide:

Stage I, II, or III
71% ER
48% LN negative

Stratification factors:
Age, Nodal status

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

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

Tamoxifen was given to all ER+ patients
Median follow up: 5.5 ys

✓ Primary Objective: Disease-free survival (DFS)
✓ Secondary Objective: Overall survival (OS), Safety

### USO 9735 study: TC vs. AC in “low risk group”

<table>
<thead>
<tr>
<th></th>
<th>TC (n=506)</th>
<th>AC (n=510)</th>
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<tbody>
<tr>
<td><strong>Median Age, ys (range)</strong></td>
<td>52 (27-77)</td>
<td>51 (27-77)</td>
</tr>
<tr>
<td><strong>Stage (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>104 (20)</td>
<td>112 (22)</td>
</tr>
<tr>
<td>II</td>
<td>373 (74)</td>
<td>364 (71)</td>
</tr>
<tr>
<td>III</td>
<td>27 (5)</td>
<td>34 (7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>HR status (%)</strong></td>
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<td></td>
</tr>
<tr>
<td>ER /PR(+/-,-/+,-/+,-)</td>
<td>367 (72)</td>
<td>352 (69)</td>
</tr>
<tr>
<td>ER- /PR-</td>
<td>136 (27)</td>
<td>157 (31)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td><strong>Positive nodes (%)</strong></td>
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<tr>
<td>0</td>
<td>239 (47)</td>
<td>248 (49)</td>
</tr>
<tr>
<td>1-3</td>
<td>209 (41)</td>
<td>212 (42)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>58 (12)</td>
<td>50 (9)</td>
</tr>
</tbody>
</table>

*Jones SE et al. J Clin. Oncol 2009*
USO 9735 study: TC is superior regardless of N or Age

USO 9735: Toxicity

All grade

G3,4: N/V, stomatitis

3 fatal events (CHF, MDS, MF) were found in AC arm

At 7 ys, 4 cycles of TC compared to AC was associated with

- Superior DFS (P = 0.033) and Overall Survival (P = 0.032)
- TC was effective in older as well as younger patients
- TC may have same efficacy in N(-) EBC
- TC was equally effective in ER+ disease as well as HR-disease
- Less side effects and long term sequelae

TC regimen is optimal treatment for low-risk breast cancer patients as alternative to anthracycline based adjuvant therapy
**PlanB:** P-III Anthracycline-free Taxane Based Chemotherapy in Patients With HER2/Neu Negative EBC NCT01049425

- HER2 Negative Breast Cancer (n=2,448)
- 2010.1~2014.8

- **1º End point: DFS**
- **tumor size ≥ 2 cm, grade ≥ 2, ER and PR negative, high uPA//PAI-1 levels**
**HER2+/N- EBC for small N-/HER2 EBC**

- Trastuzumab into CT, mostly A+T
  - Persistent effect on RFS and OS
  - Mostly stage II or III were rerolled in RCTs
  
  ✓ 6% N-/HER2+ in N9831+NSABP B31

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>N</th>
<th>ER+, %</th>
<th>N-, %</th>
<th>pT1, %</th>
<th>HR for DFS (95% CI)</th>
<th>HR for OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA</td>
<td>N+</td>
<td></td>
<td>45</td>
<td>32</td>
<td>40</td>
<td>0.54 (0.43–0.67)</td>
<td>0.76 (0.47–1.23)</td>
</tr>
<tr>
<td></td>
<td>N−, &gt;pT1b</td>
<td>3387</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intergroup N9831, NSABP-B31</td>
<td>N+</td>
<td></td>
<td>52</td>
<td>6</td>
<td>39</td>
<td>0.49 (0.41–0.58)</td>
<td>0.62 (0.49–0.81)</td>
</tr>
<tr>
<td></td>
<td>N−, ≥pT1c ER+</td>
<td>3969</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N−, ≥pT1b ER−</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCIRG 006</td>
<td>N+</td>
<td></td>
<td>54</td>
<td>29</td>
<td>40</td>
<td>0.49 (ACTH), 0.61 (TCH)</td>
<td>ACTH:0.63 (0.48–0.81)</td>
</tr>
<tr>
<td></td>
<td>N− &amp; risk factorsc</td>
<td>3222</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TCH:0.77 (0.60–0.99)</td>
</tr>
<tr>
<td>PACS-04</td>
<td>N+</td>
<td></td>
<td>18</td>
<td>None</td>
<td>32</td>
<td>0.86 (0.61–1.22)</td>
<td>1.27 (0.68–2.38)</td>
</tr>
</tbody>
</table>
HER2+/N- EBC for small N-/HER2 EBC

▶ Trastuzumab into CT, mostly A+T
  • Persistent effect on RFS and OS
  • Mostly stage II or III were enrolled in RCTs
    ✓ 6% N-/HER2+ in N9831+NSABP B31

▶ T1N0 HER2+: Unfavorable outcome **without CT**
  • 7% of cumulative incidence of relapse at 5 years

MDACC JCO, 2009 (N=98/965)  
NCCN JCO, 2014 (N=520/4113)
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  • CT+trastuzumab can decrease relapse in P-II or cohort studies

<table>
<thead>
<tr>
<th></th>
<th>T1a ER+/HER2+</th>
<th>T1a ER-/HER2+</th>
<th>T1b ER+/HER2+</th>
<th>T1b ER-/HER2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRFS</td>
<td>96</td>
<td>93</td>
<td>94</td>
<td>94</td>
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<tr>
<td>OS</td>
<td>95</td>
<td>93</td>
<td>95</td>
<td>95</td>
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- **T1N0 HER2+: Unfavorable outcome without CT**
  - CT+trastuzumab can decrease relapse in P-II or cohort studies
  - St. Gallen & NCCN recommend adjuvant CTx+trastuzumab

<table>
<thead>
<tr>
<th>St Gallen 2013</th>
<th>Luminal A</th>
<th>Luminal B/H ER2 -</th>
<th>Luminal B/H ER2 + HER2 enrich</th>
<th>TNBC</th>
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</thead>
<tbody>
<tr>
<td>T1a</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>T1b (≥5mm)</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>T1c</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NCCN guidelines</th>
<th>ER +/HER2 -</th>
<th>ER +/HER2 + HER2 enrich</th>
<th>TNBC</th>
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</thead>
<tbody>
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<td>T1a</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T1b (≥5mm)</td>
<td>RS</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>T1c</td>
<td>+</td>
<td>+</td>
<td>+</td>
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▼ Trastuzumab + Anthracycline as adjuvant therapy
  • Increase the incidence of Cardiac toxicity
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- Trastuzumab + Anthracycline as adjuvant therapy
  - Increase the incidence of Cardiac toxicity
  - Emesis
  - Less toxic regimen without affecting survival advantage?
    - TCH? In BCIRG006
BCIRG 006: TCH vs. AC→TH

Adjuvant Trastuzumab in HER2-Positive Breast Cancer

- HER2 Positive (Central FISH)
  - Node Positive or high risk node negative
  - N=3,222

- Stratified by Nodes & Hormonal Receptor Status

- Primary: DFS
- Secondary: OS, Safety

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

BCIRG06: TCH vs. AC→TH for N- (subanalysis)

Unplanned analysis: TCH vs. AC→TH

% alive and disease-free

0 12 24 36 48 60 72

Time (months)

Patients Events HR (95% CI) P

AC→T 1073 257 1 (reference)

AC→TH 1074 185 0.64 (0.53-0.78) <0.001

TCH 1075 214 0.75 (0.63-0.90) 0.04

% alive

0 12 24 36 48 60 72

Time (months)

Patients Events HR (95% CI) P

AC→T 1073 141 1 (reference)

AC→TH 1074 94 0.63 (0.48-0.81) <0.001

TCH 1075 113 0.77 (0.60-0.99) 0.038

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

BCIRG006: Cardiac safety

<table>
<thead>
<tr>
<th>Cardiac Adverse Event</th>
<th>AC → T (n = 1073)</th>
<th>AC → TH (n = 1074)</th>
<th>TCH (n = 1075)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac-related death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3/4 CHF</td>
<td>7 (0.7)</td>
<td>21 (2.0)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>&gt; 10% relative LVEF decline</td>
<td>114 (11.2)</td>
<td>194 (18.6)</td>
<td>97 (9.4)</td>
</tr>
</tbody>
</table>

P < 0.001

BCIRG006: QoL

- TCH as a more tolerable alternative to anthracycline-trastuzumab based adjuvant therapies

Proportion of patients whose HRQL worsened by at least 10 units

Au HJ et al. The Oncologist 2013; 18:812-818
HER2+ EBC: Non-anthracycline regimen

▼ Chemotherapy + Trastuzumab
  • significant improvements in OS and PFS

▼ Trastuzumab + Anthracycline as adjuvant therapy
  • Significant benefit of Trastuzumab
  • but, remained cardiac problems

▼ Stage I breast cancer has increased dramatically
  • Less toxic regimen without affecting survival advantage?

▼ TCH as adjuvant
  • P-II 2 & 3 trials of TCH in patients with advanced disease
  • Similar in PFS and OS
  • Better in Safety
Adjuvant chemotherapy for N- EBC

Adding taxane into A-based regimen:
- TAC
- FAC → wP
  - Yes, but small efficacy (3-6% gain in DFS; 2% gain in OS)
  - Higher rate of toxicity: G3-4 hematologic toxicity, neuropathy, edema,

Taxane without A
- TC
- TCH for HER2+

NCCN guideline v.2 2015
Preferred regimens:
- HER2 negative
  - ddAC → ddP
  - ddAC → wP
  - TC
- HER2 positive
  - AC → TH
  - TCH
Adjuvant chemotherapy for N- EBC

Adding taxane into A-based regimen:
• TAC
• FAC → wP
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  ✓ Higher rate of toxicity: G3-4 hematologic toxicity, neuropathy, edema,

Taxane without A
• TC
• TCH for HER2+
• ?Taxane only
  ✓ to avoid unexpected treatment related morbidity and mortality.
**CALGB40101: AC vs. Paclitaxel**

**AC vs. P**
- Primary Endpoint: PFS, non-inferiority
- 2002-2010
- 90% N(-), 84% HER2-
- Median F/U 6.1 yr

- **non-inferiority of T over AC regardless of HR status**

---

Shulman. JCO 2014
CALGB40101: AC vs. Paclitaxel

- AC4 vs T4 or T6
  - But small: $\Delta 3\%$ and $\Delta 1\%$

- AC: Higher hematologic toxicity and..

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>AC (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>
<tr>
<td>Other</td>
<td>47</td>
<td>63</td>
</tr>
<tr>
<td>Total</td>
<td>116</td>
<td>150</td>
</tr>
</tbody>
</table>

Taxane without A might be an option in low-risk EBC.

Shulman. JCO 2014
Small HER2+ : paclitaxel+ trastuzumab

- Phase II Adjuvant Paclitaxel and Trastuzumab for **Node-Negative** HER2-Positive Breast Cancer (NCT00542451)
  - 2007.10~2010.9
  - DFS = 98.7% at Median F/U at 4.0y

<table>
<thead>
<tr>
<th>T1a</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>77</td>
<td>19</td>
</tr>
<tr>
<td>T1b</td>
<td>124</td>
<td>31</td>
</tr>
<tr>
<td>T1c</td>
<td>169</td>
<td>42</td>
</tr>
<tr>
<td>T2 (2-3cm)</td>
<td>36</td>
<td>9</td>
</tr>
<tr>
<td>ER+</td>
<td>272</td>
<td>67</td>
</tr>
<tr>
<td>ER-</td>
<td>134</td>
<td>33</td>
</tr>
</tbody>
</table>

91%

*Tolaney et al., NEJM 2015; SABCS 2013*
Small HER2+ : paclitaxel+ trastuzumab

- Comparable to T+A+ H regimens
  - 4Y DFS = 98.7%

- Similar outcome regardless of tumor size and HR

Tolaney et al., NEJM 2015; SABCS 2013
Small HER2+ : T-DM1 vs. paclitaxel+ trastuzumab

Adjuvant for small tumors: Phase II ATEMPT Trial (NCT01853748)
- Dana-Faber Cancer Institute
- Stage I HER2+ EBC (T1N0M0)
- 2013.5 ~

Stage I BC
HER2+
N=500

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

www.Clinicaltrials.gov
How did these studies change our practice?
NCCN cohort for Adjuvant Chemotherapy for T1N0M0

A) HER2+
B) HER2- HR+
C) HER2- HR-

Ines Vaz-Luis et al. ASCO2014 abstract #522
Adjuvant chemotherapy for N- EBC

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**Taxane without A**

<table>
<thead>
<tr>
<th>HER2-</th>
<th>HER2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>• TC</td>
<td>• TCH</td>
</tr>
<tr>
<td>• T?</td>
<td>• T +/- Herceptin?</td>
</tr>
<tr>
<td></td>
<td>• T-DM1?</td>
</tr>
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</table>

**Non T, Non A**
- **CMF?**
CMF vs. Anthracyclines

- No evidence of AC4 > CMF6

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Pts</th>
<th>Population</th>
<th>regimen</th>
<th>DFS(%)</th>
<th>OS(%)</th>
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<tr>
<td>NSABP B-15</td>
<td>1557</td>
<td>node (+)</td>
<td>AC x 4</td>
<td>62 NS</td>
<td>83 NS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CMF x 6</td>
<td>63</td>
<td>82</td>
</tr>
<tr>
<td>NSABP B-23</td>
<td>2008</td>
<td>node (-)</td>
<td>AC x 4</td>
<td>87 NS</td>
<td>90 NS</td>
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<tr>
<td></td>
<td></td>
<td>,ER(-)</td>
<td>AC x 4 + Tam</td>
<td>87</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CMF x 6</td>
<td>88</td>
<td>89</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CMF x 6 +Tam</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td>Belgian</td>
<td>777</td>
<td>node (+)</td>
<td>E60Cx 8</td>
<td>64</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>E100Cx 8</td>
<td>74 NS</td>
<td>86 NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CMF x 6</td>
<td>71</td>
<td>65</td>
</tr>
</tbody>
</table>

Piccart MJ et al. JCO 2001;19(12): 3103-3110
Classic **CMF** is more effective TNBC: IBCSG VIII+IX

- IBCSG VIII+IX
- N=2257 N-EBC
- CMF6 vs. none

HR, 0.46; 95% CI, 0.29 to 0.73; \( P = .009 \)

*Colleoni et al, JCO 2010*
ELDA trial: Weekly docetaxel versus CMF as adjuvant chemotherapy for older women with early breast cancer: final results of the randomized phase III

- 302 Elderly (aged 65 – 79)
- Stage I-III
- 37% N-
**CMF: Old but still active**

- Similar outcome with AC4, CAF, w-Docetaxel
- Better than capecitabine (CALGB trial)
- **Better safety profile** than TC or AC
- Still can be an option for
  - N-EBC
  - Elderly or Cardiac concern (+)
  - ? Modified or dose-dense

<table>
<thead>
<tr>
<th>Title</th>
<th>Phase</th>
<th>N</th>
<th>Endpoint</th>
<th>No</th>
<th>Study arms</th>
<th>Inclusion</th>
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<tbody>
<tr>
<td><strong>ELDA</strong></td>
<td>3</td>
<td>300</td>
<td>DFS</td>
<td>NCT00331097</td>
<td>CMF6 v. w-docetaxel</td>
<td>60-80</td>
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<tr>
<td><strong>ICE II</strong></td>
<td>III</td>
<td>400</td>
<td>DFS</td>
<td>NCT01204437</td>
<td>CMF6 v. EC4 v X-Nab-P</td>
<td>&gt;65</td>
</tr>
<tr>
<td><strong>Sarah canon research</strong></td>
<td>3</td>
<td>150</td>
<td>DFS</td>
<td>NCT00193011</td>
<td>D v CMF</td>
<td>&gt;65</td>
</tr>
<tr>
<td><strong>UK</strong></td>
<td>3</td>
<td>2000</td>
<td>DFS</td>
<td>NCT00003577</td>
<td>CMF6 v E4 → CMF4</td>
<td>I,II</td>
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<tr>
<td><strong>CALGB</strong></td>
<td>3</td>
<td>633</td>
<td>DFS</td>
<td>NCT00024102</td>
<td>X vs AC or CMF</td>
<td>&gt;65</td>
</tr>
</tbody>
</table>
Case: In hospital course (II)

- **Plan:** Adjuvant AC#4 cycles followed by RT + Hormone (Tam)

- After 4 cycles of AC, Mild DOE with Anemia (Hb=8.2g/dl)
- Continued DOE after correction of Anemia

![Images showing C/T measurements: C/T=45.9% (pre-op) and C/T=65.4% (post-CTx)]
Case: In hospital course (II)

2D-Echocardiogram

imp: severe CHF d/t r/o Anthracycline-induced

Cardiac transplantation was done..
Summary: Adjuvant chemotherapy for N- EBC

- Node negative breast cancer is usually expected for good outcome with standard treatment,

- **T+A as concurrent or sequential**
  - **TAC**
  - **FAC → wP**
    - Yes, but small efficacy (3-6% gain in DFS; 2% gain in OS)
    - Higher rate of toxicity: G3-4 hematologic toxicity, neuropathy, edema,

- **T without A**

- **Non T, Non A**
  - **CMF**

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“Thirty-one years ago, the original AC regimen was reported. Now, there is a superior non-anthracycline regimen, TC”

Jones et al, J Clin Oncol