Fine tuning endocrine therapy in premenopausal women

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International Breast Cancer Study Group
Before June 2014

ADJUVANT ENDOCRINE THERAPY

Tamoxifen for at least 5 years with or without an GnRH analogue.

If contraindications or severe side effects to Tam: GnRH analogue alone (LoE IA) or oophorectomy

The optimal duration currently unknown (ATLAS-aTToM)

AIs alone are contra-indicated in pre-menopausal women.

AIs + GnRH analogue: NOT outside clinical trials.
ADJUVANT ENDOCRINE THERAPY

Neoadjuvant ENDOCRINE THERAPY: NOT outside clinical trials

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AIs + GnRH analogue: NOT outside clinical trials.
SOFT
**SOFT: SUPPRESSION of OVARIAN FUNCTION TRIAL**
Premenopausal ER+ve and/or PR+ve Breast Cancer

3047 Patients Randomized in ITT, Dec 2003 - Jan 2011

Primary Analysis (n= 2033)
Median follow-up 5.6 years

**Two Patient Cohorts (stratified)**

- Premenopausal, within 12 weeks of surgery
  (Median time since surgery = **1.8 months**)

- Prior Chemotherapy
  Premenopausal* after completing chemotherapy;
  Randomization within 8 months of completion
  (Median time since surgery = **8.0 months**)

Randomize

- Tamoxifen x 5y  (n=1018)
- Tamoxifen+OFS x 5y  (n=1015)
- Exemestane+OFS x 5y  (n=1014)

OFS=ovarian function suppression
(GnRH triptorelin, oophorectomy or irradiation)

*According to locally-determined E₂ level in premenopausal range

# Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No chemo 47% (n=949)</th>
<th>Prior Chemo 53% (n=1084)</th>
<th>Overall (n=2033)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age</strong></td>
<td>46 y</td>
<td>40 y</td>
<td>43 y</td>
</tr>
<tr>
<td><strong>Lymph Node +ve</strong></td>
<td>9%</td>
<td>57%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Tumor &gt; 2 cm</strong></td>
<td>14%</td>
<td>47%</td>
<td>32%</td>
</tr>
<tr>
<td><strong>Grade 1</strong></td>
<td>41%</td>
<td>14%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>7%</td>
<td>35%</td>
<td>22%</td>
</tr>
<tr>
<td><strong>HER2+ve</strong></td>
<td>4%</td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Median time since surgery</strong></td>
<td><strong>1.8 mo</strong></td>
<td><strong>8.0 mo</strong></td>
<td>3.2 mo</td>
</tr>
</tbody>
</table>
Primary analysis in overall population not significant \( (p=0.10) \)
Multivariable Cox model \( \text{HR}=0.78 \) \( (95\% \text{ CI } 0.62-0.98) \ p=0.03 \)
Cohort selected for low risk clinicopathologic features
90% ≥ age 40yr, 91% node negative, 85% tumor ≤ 2cm, 41% grade 1
Premenopausal after Prior Chemotherapy

T+OFS v T: Absolute improvement in 5-yr BCFI of 4.5%
E+OFS v T: Absolute improvement in 5-yr BCFI of 7.7% and 5-yr DRFI of 4.2%
350 patients (11.5%) under age 35
94% received chemotherapy in this age group
## Selected Adverse Events

| CTCAE v3.0                                      | T+OFS (N=1005) | | T (N=1006) | | |
|--------------------------------------------------|----------------|---------|------------|---------|
|                                                  | Grade 1-4      | Grade 3-4 | Grade 1-4  | Grade 3-4 |
| Hot flushes/flashes                              | 93%            | 13%      | 80%        | 8%       |
| Sweating                                         | 62%            | --       | 48%        | --       |
| Libido decrease                                  | 47%            | --       | 42%        | --       |
| Vaginal dryness                                  | 50%            | --       | 42%        | --       |
| Depression                                       | 52%            | 4%       | 47%        | 4%       |
| Insomnia                                         | 57%            | 5%       | 46%        | 3%       |
| Musculoskeletal symptoms                         | 75%            | 5%       | 69%        | 6%       |
| Osteoporosis (% T< -2.5)                         | 20% (6%)       | 0.3%     | 12% (3%)   | 0.1%     |
| Hypertension                                     | 23%            | 7%       | 17%        | 5%       |
| Glucose intolerance (diabetes)*                  | 3%             | 1%       | 2%         | 0.3%     |
| Hyperglycaemia*                                  | 5%             | 1%       | 2%         | 0.1%     |
| Any Gr 3- 4 targeted AE                          | --             | 31%      | --         | 24%      |

*Added during trial conduct, may be under-reported
TEXT and SOFT combined analysis

**TAMOXIFEN AND EXEMESTANE TRIAL (N=2672)**
- Enrolled: Nov03-Apr11
  - Premenopausal
  - ≤12 wks after surgery
  - Planned OFS
  - No planned chemo

  **RANDOMIZE**

  **SUPPRESSION OF OVARIAN FUNCTION TRIAL (N=3066)**
  - Premenopausal
  - ≤12 wks after surgery
  - No chemo

  **RANDOMIZE**

  - Remain premenopausal ≤ 8 mos after chemo

  **RANDOMIZE**

**Joint Analysis (N=4690)**
- Median follow-up 5.7 years

**TAMOXIFEN AND EXEMESTANE TRIAL (N=2672)**
- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

**SUPPRESSION OF OVARIAN FUNCTION TRIAL (N=3066)**
- Tamoxifen x 5y
- Exemestane+OFS x 5y

- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

- Enrolled: Nov03-Apr11
  - Premenopausal
  - ≤12 wks after surgery
  - Planned OFS
  - No planned chemo

  OR

- Premenopausal
  - ≤12 wks after surgery
  - No chemo

  OR

- Remain premenopausal ≤ 8 mos after chemo

**Average age 43 years**

57% chemotherapy

### Patients’ characteristics

<table>
<thead>
<tr>
<th></th>
<th>No chemo (N=1053)</th>
<th>No chemo SOFT (N=943)</th>
<th>Chemo TEXT (N=1607)</th>
<th>Prior chemo SOFT (N=1087)</th>
<th>Overall (N=4690)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age &lt;40 yr</strong></td>
<td>16%</td>
<td>9%</td>
<td>30%</td>
<td>49%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>LN +</strong></td>
<td>21%</td>
<td>8%</td>
<td>66%</td>
<td>57%</td>
<td>42%</td>
</tr>
<tr>
<td><strong>T-size &gt;2cm</strong></td>
<td>19%</td>
<td>15%</td>
<td>53%</td>
<td>47%</td>
<td>36%</td>
</tr>
<tr>
<td><strong>HER2 +</strong></td>
<td>5%</td>
<td>3%</td>
<td>17%</td>
<td>19%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Surgery to random. (median)</strong></td>
<td>1.5 mo</td>
<td>1.8 mo</td>
<td>1.2 mo</td>
<td>8.0 mo</td>
<td>1.6 mo</td>
</tr>
</tbody>
</table>

- **Age <40 yr**: The percentage of patients under 40 years old.
- **LN +**: Lymph node positive.
- **T-size >2cm**: Tumor size greater than 2 cm.
- **HER2 +**: HER2 positive.
- **Surgery to random. (median)**: Median time to surgery.
Exemestane + OFS Improved DFS

Difference 3.8% at 5 years

5.7 years median follow-up

No. Patients | HR (95% CI) | 5-yr DFS %
--- | --- | ---
**All Patients** | | |
E+OFS 2346 | T+OFS 2344 | 91.1 | 87.3

**Cohort**

- No chemotherapy, TEXT: 526 E+OFS, 527 T+OFS, HR = 0.96 (95% CI: 0.72-1.28), 96.1% E+OFS, 93.0% T+OFS
- No chemotherapy, SOFT: 470 E+OFS, 473 T+OFS, HR = 0.96 (95% CI: 0.75-1.23), 95.8% E+OFS, 93.1% T+OFS
- Chemotherapy, TEXT: 806 E+OFS, 801 T+OFS, HR = 0.92 (95% CI: 0.74-1.14), 89.8% E+OFS, 84.6% T+OFS
- Prior chemotherapy, SOFT: 544 E+OFS, 543 T+OFS, HR = 0.94 (95% CI: 0.76-1.18), 84.3% E+OFS, 80.6% T+OFS

**Lymph Node Status**

- Negative: 1362 E+OFS, 1350 T+OFS, HR = 0.93 (95% CI: 0.72-1.21), 95.1% E+OFS, 91.6% T+OFS
- Positive: 984 E+OFS, 994 T+OFS, HR = 0.89 (95% CI: 0.70-1.13), 85.6% E+OFS, 81.4% T+OFS
Exemestane+OFS Reduced Recurrence

- 4% absolute improvement in 5-yr freedom from breast cancer for Exe+OFS
- No significant difference in overall survival
Some women have excellent prognosis with highly-effective endocrine therapy alone >97% breast cancer-free at 5 years when treated with exemestane+OFS.
Women Who Received Chemotherapy

Absolute improvement with exemestane+OFS

5-yr freedom from breast cancer: 5.5% in TEXT and 3.9% in SOFT
5-yr freedom from distant recurrence: 2.6% in TEXT and 3.4% in SOFT
### Predictable Adverse Events Profile

<table>
<thead>
<tr>
<th>CTCAE V3.0 Grade 3-4</th>
<th>E + OFS</th>
<th>T + OFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal</td>
<td>11%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Fracture</td>
<td>1.3%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.3%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Thrombosis/embolism</td>
<td>0.8%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>2.3%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Premature discontinuation</td>
<td>16%</td>
<td>11%</td>
</tr>
</tbody>
</table>
Trial Design ABCSG-12

- 1,803 patients
- Endocrine-responsive (ER and/or PR positive)
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years
- Accrual 1999-2006
- <10 positive nodes

Gnant et al, NEJM 2009

Surgery (+ RT) → Goserelin 3.6 mg q28d 3 years → Randomization

- Tamoxifen 20 mg daily
- Tamoxifen 20 mg daily, Zoledronic acid 4 mg q6mo
- Anastrozole 1 mg daily
- Anastrozole 1 mg daily, Zoledronic acid 4 mg q6mo
Similar Outcomes with OFS+Anastrozole or OFS+Tamoxifen

Median age 45 yrs
T1 tumor 75%
N0 66%
Grade 1/2 75%
Preop CT 5%

Median FU 94.4 months

Gnant et al Ann Oncol 2014 Nov 17
Reconciling Results of ABCSG 12, TEXT/SOFT

- Different Ais  Unlikely
- Different LHRH agonists  Unlikely
- Duration of endocrine therapy  Possibly
- Different patient characteristics  Possibly
- Use of and timing of CT  Likely
- Size and statistical power  Most likely
2014: New Algorithm for Premenopausal Hormone Receptor Positive Disease?

Premenopausal Hormone receptor positive early stage breast cancer

- **Low risk**
  - Smaller tumors
  - Node negative
  - Grade 1
  - Older

  - T x at least 5 years
  - Duration?

- **Intermediate risk**
  - Low grade but larger tumor
  - Low grade but node positive

  - Chemo + OS/T or E?
  - OS + endocrine rx?

- **High risk**
  - Larger tumors
  - Node positive
  - Grade 3
  - Younger

  - OS + T or E > T
    (particularly in < 35 yo)
  - OS + E > OS + T

Duration?

OS + T or E > T

OS + E > OS + T

Courtesy Rugo H, SABCS 2014
Take home messages

• Overall, premenopausal patients did not benefit from the addition of OFS to Tam
  Some do very well with Tam alone

• For women at sufficient risk of recurrence to warrant adjuvant chemotherapy and who retain premenopausal estradiol, addition of OFS to tamoxifen reduced recurrence
  Benefit from OFS is most striking in women under age 35

• OFS enables treatment with an aromatase inhibitor which further reduced recurrence in the higher-risk cohort

• Some premenopausal women with HR+ breast cancer have an excellent prognosis with highly-effective endocrine therapy alone
Take home messages

- Addition of OFS increases menopausal symptoms, depression, hypertension, diabetes and osteoporosis.
- No significant difference in overall survival, conclusions premature at this early point in FU of HR+ BC
- Long-term follow-up is crucial to assess late toxicities -- future analyses planned (i.e. BMI)
- Translational studies are vital (e.g. multigene assays to further tailor recommendations)
ATLAS Trial Design

Eligibility (n = 12,894)*
Early breast cancer (BC)
Completed 5 y of TAM

*Of the study’s entire population
ER+ 53%; ER- 10%; unknown ER status 37%
Recurrence was defined as first recurrence of any form of BC after ATLAS entry.

R

Continue TAM therapy to 10 years (n = 6,454)

Stop TAM therapy at 5 years (n = 6,440)

Davies C et al. *Lancet* 2012
Recurrence

BC mortality

5-9 years: RR 0.90 (0.79-1.02)
≥10 years: RR 0.75 (0.62-0.90)
All years: log-rank p=0.002

5-9 years: RR 0.97 (0.79-1.18)
≥10 years: RR 0.71 (0.58-0.85)
All years: log-rank p=0.01

10% premenopausal

25% N+
Pilot Phase II Study of Ovarian Suppression + Letrozole in Premenopausal Breast Cancer Survivors

All Premenopausal Patients and Disease-free

No restrictions on duration off therapy

Tamoxifen

Lupron + Letrozole

n = 50

+Zoledronic acid q 6mos

≥ 4.5 years initial adjuvant

2 years extended adjuvant

Closed due to insufficient accrual

16 enrolled in 3.5 years

Ruddy Kj Clin Breast Cancer. 2014
Pregnancy after BC: still a taboo?
1st endpoint – DFS in ER+

Median follow-up **from date of conception**: 4.7 years (IQR: 3.1 – 6.9)

Total number of patients: 686
Total number of events: 199 (29%)

**HR**: 0.91; 95% CI (0.67 – 1.24); p=0.55

Data of conception

Azim HA Jr et al JCO 2013 Jan 1;31(1):73-9
2nd endpoint – Overall survival

Median follow-up from date of conception: 4.7 years (IQR: 3.1 – 6.9)

**Whole population (n=1,207)**

- Pregnancy after breast cancer (n=333)
- Matched breast cancer controls (n=874)

HR: 0.72; 95% CI (0.54 – 0.97); p=0.03

Interaction according to ER status: p=0.11

Azim HA Jr et al JCO 2013 Jan 1;31(1):73-9
Early pregnancy apparently not detrimental

Azim HA Jr et al JCO 2013 Jan 1;31(1):73-9
Screening/eligibility:

Patients with ER+ early breast cancer

≥ 18 and ≤42 years at enrollment

Completing 18-30 months of ET (SERMs alone, GnRH analogue + SERM or AIs) \(^1\)

Pregnancy desire

\(^1\) ± CT

\(^2\) No more than 1 month prior enroll.

Translational research

- Ovarian function evaluation
- Uterine evaluation
- Circulating tumor DNA (ctDNA)
- Genomic evaluation of primary breast tumor

Contact: monica.ruggeri@ibcsg.org
Thank you