Adjuvant Endocrine Therapy For Postmenopausal Women

SOBO 2014

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Robert H. Lurie Comprehensive Cancer Center
The Long Tail of ER-Positive Breast Cancer

Recurrence hazard rate

Initial Peak

ER/PgR+ (n=2257)
ER/PgR− (n=1305)

Long Tail

PgR = progesterone receptor.
Risk of Breast Cancer Recurrence: Two Cell Populations

1) Proliferating Micromets (CT-sensitive)
   - ER/PgR+
   - ER/PgR−

2) Relapsing Dormant Cells

PgR = progesterone receptor.
Dormancy Implications

• Therapies targeting proliferating cells may not affect dormant cells
• As therapies targeting proliferating cells improve, dormant cells will become the major cause of breast cancer death
• Targeting dormant cells will become a major challenge for some (not all) of breast cancer
Cumulative incidence curves of first distant metastasis by breast cancer subtype
British Columbia Data Registry 1986-1992

Kennecke H et al. JCO 2010;28:3271-3277
Adjuvant Therapy in ER-Negative and ER-Positive Patients

Time from Surgery in ~11 month increments

- tamoxifen, ER-positive
- CMF/AC, ER-negative
- tamoxifen + CMF, ER-positive

Dignam, NSABP ASCO ‘07
Time Dependence of Breast Cancer Recurrence in Subsets Defined by Genomic Assays

Intrinsic/PAM50

70 Gene Signature

21 Gene RS

Jatoi I et al. JCO 2011;29:2301-2304
Early Stage Breast Cancer
Tamoxifen: 5 Years Vs. Not

• More than half of recurrences and deaths occur post-treatment

EBCTCG, Lancet 2005, 365: 1687
5y in ER+ disease

Reduces
- Recurrence by 38%,
- BC death by 30%
- All deaths by 22%
- Contralateral BC by 40%

Benefits all women with ER+ disease

Unclear benefits in ER-PgR+ disease

Benefits women with ER very rich tumors more

Increases endometrial cancer by 2.3 fold
Tamoxifen

Why did we stop at 5 years anyway?
Duration of Tamoxifen: NSABP B-14
Fisher, et al. JNCI 2001

NSABP B-14
ER+, LN neg

Placebo
Tamoxifen x 5 yrs

Disease Free at 5 yrs
n=1172

Placebo
n=579
Tamoxifen x 5 years
n=593
Duration of Tamoxifen: NSABP B-14

Fisher, et al. JNCI 2001;
median f/u 7 years post-rerandomization

---

Disease-Free Survival

Relapse-Free Survival

Survival

P = 0.03

P = 0.13

P = 0.07

# Pts. # Events
Plac 569 106
Tam 583 137

# Events
34
47

# Deaths
39
57

# at risk
569
583

Year
0 1 2 3 4 5 6 7

% 100
90
80
70
60
50

% 100
90
80
70
60
50

% 100
90
80
70
60
50
Duration of Tamoxifen Therapy

- Scottish Adjuvant Trial
- N=1323
- Randomized ± tam
- Tam group: if NED at 5 yrs, randomized to stopping tam vs. indefinite tam (n=342)
- DFS (includes contralateral breast tumors)
Can the patient destined for a late recurrence be identified?
Use of molecular profiling to predict patients at risk for later recurrences

- Intrinsic subtyping (PAM50®): luminal A versus luminal B
- Breast Cancer Index (BCI)
- EndoPredict
- Estrogen-related genes from 21-gene RS

Data to date only applies up to 10 years
Background

Breast Cancer Index (BCI)

- The BCI biomarker consists of two independently developed biomarkers:
  - HOXB13:IL17BR (H/I) gene expression ratio
    - is both prognostic\(^1,2\) and predictive for extended adjuvant hormonal therapy benefit\(^3\).
  - Molecular Grade Index (MGI)
    - a set of cell cycle-related genes that predicts for distant recurrence beyond tumor grade\(^4\).


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BCI Identifies Two Late (5-10 yr) Recurrence Risk Groups

<table>
<thead>
<tr>
<th>Patients Disease Free At 5 years</th>
<th>5-yr Rate of Distant recurrence</th>
<th>HR (95% CI) (adjusted for CTS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCI Low (N=366, 61%)</td>
<td>3.5%</td>
<td>Reference</td>
</tr>
<tr>
<td>BCI Inter (N=146, 25%)</td>
<td>13.4%</td>
<td>2.93 (1.37-6.29)</td>
</tr>
<tr>
<td>BCI High (N=84, 14%)</td>
<td>13.3%</td>
<td>2.97 (1.23-7.13)</td>
</tr>
</tbody>
</table>

p=0.0001

Follow-up time [years]

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H/I is associated with benefit from extended adjuvant therapy in MA-17

- High H/I was significantly associated with patient benefit from extended endocrine therapy with letrozole (OR 0.33; 95%CI 0.15 to 0.73; p=0.0061), which represented a 67% reduction in the risk of recurrence with extended letrozole treatment as compared to placebo.
- Significant interaction between treatment and H/I: p=0.03

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, post- vs premenopausal</td>
<td>0.25 (0.02 to 2.76)</td>
<td>.26</td>
<td>0.13 (0.01 to 1.60)</td>
<td>.11</td>
</tr>
<tr>
<td>Tumor size, T2 + T3 vs T1</td>
<td>1.00 (0.23 to 4.35)</td>
<td>1.00</td>
<td>1.13 (0.21 to 6.00)</td>
<td>.88</td>
</tr>
<tr>
<td>Grade, 3 vs 1-2</td>
<td>1.56 (0.82 to 2.98)</td>
<td>.18</td>
<td>1.23 (0.58 to 2.60)</td>
<td>.59</td>
</tr>
<tr>
<td>ER status, positive vs negative</td>
<td>0.67 (0.15 to 2.98)</td>
<td>.60</td>
<td>0.83 (0.15 to 4.72)</td>
<td>.83</td>
</tr>
<tr>
<td>PR status, positive vs negative</td>
<td>1.05 (0.53 to 2.09)</td>
<td>.88</td>
<td>1.33 (0.62 to 2.86)</td>
<td>.46</td>
</tr>
<tr>
<td>HER2 status, positive vs negative</td>
<td>1.32 (0.55 to 3.18)</td>
<td>.54</td>
<td>0.99 (0.35 to 2.78)</td>
<td>.98</td>
</tr>
<tr>
<td>Node status, positive vs negative</td>
<td>1.00 (0.06 to 15.99)</td>
<td>1.00</td>
<td>1.93 (0.11 to 33.77)</td>
<td>.65</td>
</tr>
<tr>
<td>Treatment effect, letrozole vs placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H/I-low</td>
<td>0.68 (0.31 to 1.52)</td>
<td>.35</td>
<td>0.58 (0.25 to 1.36)</td>
<td>.21</td>
</tr>
<tr>
<td>H/I-high</td>
<td>0.35 (0.16 to 0.75)</td>
<td>.007</td>
<td>0.33 (0.15 to 0.73)</td>
<td>.006</td>
</tr>
</tbody>
</table>

Patients with High H/I had a 5yr absolute benefit of 16.5% from extended endocrine therapy with letrozole (p=0.007)

Patients with Low H/I had no significant benefit from extended endocrine therapy with letrozole (p = 0.35)

21 Gene Recurrence Score and recurrence risk over 10 years with endocrine therapy
21 Gene Recurrence Score and recurrence risk over 10 years with endocrine therapy

Paik et al. NEJM 2004;351:2817
Late recurrence in endocrine-treated cancers.

Cuzick et al. SABCS 2013

ATAC
N=9366

Excluded:
- Combination arm
- Chemotherapy
- No blocks received
- Insufficient tumour material

transATAC*
N=1125

PAM50
N=1007

Excluded:
- Insufficient residual RNA
- Failed PAM50 QC

N=862

Excluded:
- Not recurrence free at 5 years (N=145)

Combined dataset
N=2137

*RNA extracted by GHI

ABCSG-8
N=3714

Excluded:
- No tissue specimen
- No consent

Tissue database
N=1620

Excluded:
- Insufficient residual RNA
- Failed PAM50 QC

N=1275

Excluded:
- Not recurrence free at 5 years (N=203)

*RNA extracted by GHI
Background

• **PAM50**
  - 50-gene test developed to identify the intrinsic breast cancer subtypes (luminal A/B, HER2-enriched, Basal-like)
  (Parker et al, JCO, 2009, 27, 1160; Nielsen et al, CCR, 2010, 16, 5222)

  ➔ ROR score using 46 gene signature including tumour size (excluded BIRC5, MYBL2, GRB7, CCNB1)

• **Clinical Treatment Score (CTS)**
  - Nodal status, grade, tumour size, age, treatment
  - Developed on transATAC data set

\[ \text{ROR} = aR_{\text{LumA}} + bR_{\text{LumB}} + cR_{\text{Her2e}} + dR_{\text{Basal}} + eP + fT \]

- Pearson’s correlation to centroids
- Proliferation score (19 genes)
- Tumor size
Risk groups – ROR score

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>HR (95% CI)</th>
<th>Distant recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (N=1183 (55.4%))</td>
<td>-</td>
<td>2.4%</td>
</tr>
<tr>
<td>Intermediate (N=538 (25.2%))</td>
<td>3.26 (2.07-5.13)</td>
<td>8.3%</td>
</tr>
<tr>
<td>High (N=416 (19.5%))</td>
<td>6.90 (4.54-10.47)</td>
<td>16.6%</td>
</tr>
</tbody>
</table>

Follow-up time [years]
### Luminal A vs Luminal B

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A (N=1530 (71.6%))</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Luminal B (N=542 (25.4%))</td>
<td>2.89 (2.07 - 4.02)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

#### Graph

- **Y-axis:** Distant recurrence (%)
- **X-axis:** Follow-up time [years]

- **Luminal B:** 12.9%
- **Luminal A:** 4.1%
Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial

Christina Davies, Hongchao Pan, Jon Godwin, Richard Gray, Rodrigo Arriagada, Vinod Raina, Mirta Abraham, Victor Hugo Medeiros Alencar, Atef Badran, Xavier Bonfill, Joan Bradbury, Michael Clarke, Rory Collins, Susan R Davis, Antonella Delmestri, John F Forbes, Peiman Haddad, Ming-Feng Hou, Moshe Inbar, Hussein Khaled, Joanna Kielanowska, Wing-Hong Kwan, Beela S Mathew, Bettina Müller, Antonio Nicolucci, Octavio Peralta, Fany Pernas, Lubos Petruzelka, Tadeusz Pienkowski, Balakrishnan Rajan, Maryna T Rubach, Sera Tort, Gerard Urrútia, Miriam Valentini, Yaochen Wang, Richard Peto, for the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group*

Summary

Background For women with oestrogen receptor (ER)-positive early breast cancer, treatment with tamoxifen for 5 years substantially reduces the breast cancer mortality rate throughout the first 15 years after diagnosis. We aimed to assess the further effects of continuing tamoxifen to 10 years instead of stopping at 5 years.
15,244 women randomly allocated
- 7,629 to continue tamoxifen for another 5 years
- 7,615 to stop tamoxifen immediately

2,350 excluded completely, as tamoxifen duration before random allocation was <4 years

12,894 included in analyses of side-effects, among whom median tamoxifen duration was 5 years (IQR 4.8-5.2)
- 6,454 allocated to continue tamoxifen to 10 years
- 6,440 allocated to stop tamoxifen at 5 years

6,048 excluded from analyses of main effects, as ER status was unknown or negative

6,846 with ER-positive disease included in analyses of main effects on recurrence and breast cancer mortality
- 3,428 allocated to continue tamoxifen to 10 years
- 3,418 allocated to stop tamoxifen at 5 years
**Disease-free Survival**

- Continue tamoxifen to 10 years:
  - 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

- Stop tamoxifen at 5 years:
  - 5–9 years: RR 0.97 (0.79–1.18)
  - ≥10 years: RR 0.71 (0.58–0.88)
  - All years: log-rank p = 0.01

**Overall Survival**

- Continue tamoxifen to 10 years:
  - 5–9 years: Rate ratio 1.17 (SE 0.09)
  - 10–14 years: 1.38 (SE 0.12)
  - ≥15 years: 1.64 (SE 0.39)

- Stop tamoxifen at 5 years:
  - 5–9 years: Rate ratio 1.21 (SE 0.09)
  - 10–14 years: 2.01 (SE 0.15)
  - ≥15 years: 2.29 (SE 0.47)

Log-rank O-E and variance V:

- Continue tamoxifen to 10 years:
  - 5–9 years: -24.8/224.7
  - 10–14 years: -29.1/94.7
  - ≥15 years: -2.1/12.5

- Stop tamoxifen at 5 years:
  - 5–9 years: 0.97 (SE 0.10)
  - 10–14 years: 0.70 (SE 0.10)
  - ≥15 years: 0.79 (SE 0.27)
aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer

Richard Gray, Daniel Rea, Kelly Handley & 17 others on behalf of the aTTom Collaborators
Recruitment by ER status

- **ER-positive (40%)**
- **ER-unknown (60%)**

![Graph showing recruitment by ER status from 1991 to 2005](image.png)
10 vs 5 years of tamoxifen:
Recurrence by treatment ASCO 2013

580 vs 672 recurrences
RR=0.85 (95%CI 0.76-0.95)
p=0.003

An additional 143 vs 216 recurrences since 2008
### 10 vs 5 years of tamoxifen: Recurrence by year of follow-up

<table>
<thead>
<tr>
<th>Years from Start of Tamoxifen Treatment</th>
<th>Events/Patients (continue: stop)</th>
<th>Statistics (O-E)</th>
<th>Var.</th>
<th>O.R. &amp; 95% CI (continue: stop)</th>
</tr>
</thead>
<tbody>
<tr>
<td>years 5–6</td>
<td>168/3468 (4.8%): 154/3485 (4.4%)</td>
<td>7.4</td>
<td>76.8</td>
<td>1.10 (0.88, 1.38)</td>
</tr>
<tr>
<td>years 7–9</td>
<td>197/3113 (6.3%): 248/3139 (7.9%)</td>
<td>-24.6</td>
<td>103.3</td>
<td>0.79 (0.65, 0.96)</td>
</tr>
<tr>
<td>years 10–14</td>
<td>179/2513 (7.1%): 221/2453 (9.0%)</td>
<td>-23.4</td>
<td>92.0</td>
<td>0.78 (0.63, 0.95)</td>
</tr>
<tr>
<td>years 15+</td>
<td>36/924 (3.9%): 49/843 (5.8%)</td>
<td>-8.4</td>
<td>20.2</td>
<td>0.66 (0.43, 1.02)</td>
</tr>
</tbody>
</table>

Test for heterogeneity between subgroups: $\chi^2_3 = 7.8$; $P = 0.05$
Test for trend between subgroups: $\chi^2_1 = 6.2$; $P = 0.01$

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/Patients (continue: stop)</th>
<th>Statistics (O-E)</th>
<th>Var.</th>
<th>O.R. &amp; 95% CI (continue: stop)</th>
</tr>
</thead>
<tbody>
<tr>
<td>all years</td>
<td>580/3468 (5.8%): 672/3485 (6.7%)</td>
<td>-52.2</td>
<td>312.9</td>
<td>0.85 (0.76, 0.95)</td>
</tr>
</tbody>
</table>

Effect $2P = 0.003$
10 vs 5 years of Tamoxifen: Breast Cancer Death by Treatment Allocation

404 vs 452 breast cancer deaths

RR=0.88 (95%CI 0.77-1.01; p=0.05)  
  p=0.06
Can we select who will not benefit from tamoxifen?
Tamoxifen (TAM) is metabolized by CYP2C9 and CYP3A to form N-desmethyl-TAM. Further metabolism by CYP3A leads to 4-hydroxy-TAM. Reduced concentrations of Endoxifen, 4-hydroxy-TAM, are observed in the presence of Genetic Variants, Inhibitors, which can affect CYP2D6 activity. This results in insufficient Active and Abundant Antiestrogen.

Stearns et al. *JNCI* 2003;95:1758-64
CYP2D6 Genotypes

• Highly polymorphic
• Normal activity: *1 (wt), *2, *33, *35
• Increased activity via multiple copies: *1, *2, *35, *41
• Substantial ethnic variability:
  e.g., *4: whites, *10: Asians, *17: blacks
• Inhibitors, e.g., SSRIs
CYP2D6 Genotype and Endoxifen

P<0.001, $r^2=0.24$

Plasma Endoxifen (nM)

CYP2D6*4 (most common genetic variant associated with the CYP2D6 poor metabolizer state)

Time to Recurrence According to CYP2D6 Metabolizer Status in Women Receiving Adjuvant Tamoxifen


Goetz et al., Updated NCCTG 89-30-52, SABCS 2008
There was no statistically significant association between CYP2D6 inhibition and breast cancer recurrence in tamoxifen-treated women. The near-null association persisted regardless of whether CYP2D6 inhibition was assessed by genotype, by intake of medications that inhibit CYP2D6 function, or by a combination of genotype and medication history.

Lash, TL et al. JNCI 2011
“There were no consistent associations between CYP2D6 polymorphisms and outcomes in tamoxifen treated women with breast cancer across 16 studies included in this systemic review.”
The Update Committee recommends against using CYP2D6 genotype to select adjuvant endocrine therapy. The Committee encouraged caution with concurrent use of CYP2D6 inhibitors (such as bupropion, paroxetine, fluoxetine) and tamoxifen because of the known drug-drug interactions.

www.asco.org/guidelines/endocrinebreast ©American Society of Clinical Oncology 2010. All rights reserved
ADJUVANT ENDOCRINE THERAPY

Premenopausal¹ at diagnosis

<table>
<thead>
<tr>
<th>Tamoxifen² for 5 y (category 1) ± ovarian suppression or ablation (category 2B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider tamoxifen² for an additional 5 y to complete 10 y</td>
</tr>
<tr>
<td>Aromatase inhibitor for 5 y³ (category 1)</td>
</tr>
<tr>
<td>Premenopausal¹</td>
</tr>
<tr>
<td>Consider tamoxifen² for an additional 5 y to complete 10 y</td>
</tr>
<tr>
<td>No further endocrine therapy</td>
</tr>
</tbody>
</table>

Postmenopausal¹ at diagnosis

<table>
<thead>
<tr>
<th>Tamoxifen² for 4.5-6 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with a contraindication to aromatase inhibitors, who decline aromatase inhibitors, or who are intolerant of the aromatase inhibitors</td>
</tr>
<tr>
<td>Aromatase inhibitor³ for 5 y (category 1)</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>Tamoxifen² for 2-3 y</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>Aromatase inhibitor³ for 2-3 y (category 1)</td>
</tr>
</tbody>
</table>

Aromatase inhibitor to complete 5 y³ of endocrine therapy (category 1)

<table>
<thead>
<tr>
<th>Tamoxifen² to complete 5 y of endocrine therapy (category 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatase inhibitor for 5 y³ (category 1)</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>Up to 5 y of an aromatase inhibitor³ (category 2B)</td>
</tr>
</tbody>
</table>

¹See Definition of menopause (BINV-J).

Some SSRIs like fluoxetine and paroxetine decrease the formation of endoxifen, 4-OH tamoxifen, and active metabolites of tamoxifen, and may impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. At this time, based on current data the panel recommends against CYP2D6 testing for women being considered for tamoxifen therapy. Coadministration of strong inhibitors of CYP2D6 should be used with caution.

³The panel believes the three selective aromatase inhibitors (ie, anastrozole, letrozole, exemestane) have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and neoadjuvant settings. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Is there anything better than tamoxifen?
Years After Diagnosis

**Upfront**
- ATAC
- BIG 1-98
- ABCSG 12
- TEAM

**Sequential**
- BIG 1-98
- IES
- ITA
- NSAS BC-03
- ARNO 95
- ABCSG 8*

**Extended**
- MA.17
- ABCSG 6a
- NSABP B-33
Aromatase Inhibitors vs Tamoxifen as Adjuvant Therapy for Postmenopausal Women with Estrogen Receptor Positive Breast Cancer

Meta-Analyses of Randomized Trials of Monotherapy and Switching Strategies

J. Ingle, M. Dowsett, J. Cuzick, C. Davies for the Aromatase Inhibitors Overview Group (AIOG)
MA.27 Study Design

Eligibility:
- Postmenopausal
- ER-positive
- Early breast cancer

Stratification
- Lymph node status
- Adjuvant chemotherapy
- Trastuzumab use
- Celecoxib use
- Aspirin use

Open-label

Anastrozole
1 mg/day x 5 years

Exemestane
25 mg/day x 5 years

Study Objectives:
- **Primary**: Event-free survival (EFS)
- **Secondary**: Overall survival (OS), distant disease-free survival (DDFS), time to distant recurrence, incidence of contralateral breast cancer, incidence of clinical fractures, evaluation of breast density, cardiovascular events, toxicities, quality of life

### MA.27: Secondary Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exemestane</th>
<th>Anastrozole</th>
<th>Stratified HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>208 (5.5)</td>
<td>224 (5.9)</td>
<td>0.93 (0.77-1.13)</td>
<td>.64</td>
</tr>
<tr>
<td>DDFS</td>
<td>157 (4.1)</td>
<td>164 (4.3)</td>
<td>0.95 (0.76-1.18)</td>
<td>.46</td>
</tr>
<tr>
<td>DSS</td>
<td>89 (2.4)</td>
<td>98 (2.6)</td>
<td>0.93 (0.70-1.24)</td>
<td>.62</td>
</tr>
</tbody>
</table>

CI = confidence interval; DDFS = distant recurrence; DSS = disease-specific survival; HR = hazard ratio; OS = overall survival

FACE: Letrozole vs Anastrozole
Clinical Evaluation
Phase IIIb Head-to-Head Comparison—Study Design

EBC
- ER+
- Postmenopausal
- Node+
- Postmenopausal FSH/LH/E2 levels
- De novo adjuvant ET

Randomize

Letrozole 2.5 mg/qd
N=4000

Anastrozole 1 mg/qd

- Primary end point
  - DFS
- Secondary end points
  - Safety
  - OS
  - Time to distant metastasis
  - Time to contralateral disease
  - Breast cancer–specific survival

FSH = follicle-stimulating hormone; LH = luteinizing hormone; ET = endocrine therapy.
BIG 1-98 Overall Design

2-Arm Option
- Arm A: Tamoxifen, N=911
- Arm B: Letrozole, N=917

4-Arm Option
- Arm A: Tamoxifen, N=1548
- Arm B: Letrozole, N=1546
- Arm C: Tamoxifen, Letrozole, N=1548
- Arm D: Letrozole, Tamoxifen, N=1540

N=1,828 Enrolled 1998-2000
N=8,010* Enrolled 1999-2003

*ITT: excludes 18 patients who withdrew consent and did not receive study treatment

Previous Analyses:
Is 5 years Let superior to 5 years Tam as initial therapy?
- Primary Core Analysis (PCA), Median follow-up 26 months
- Monotherapy Arm Analysis, Median follow-up 51 months
Breast Cancer Events
Tam→Let vs. Let

Overall

By Nodal Status*

*42% of the population is node positive; 58% node negative
Breast Cancer Events
Let → Tam vs. Let

Overall

By Nodal Status*

*42% of the population is node positive; 58% node negative
<table>
<thead>
<tr>
<th>Strategy</th>
<th>RCTs</th>
<th>Pts</th>
<th>Update</th>
<th>Median FU (mo.)</th>
<th>AI</th>
<th>Efficacy [HR, p]</th>
<th>DFS/EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up-Front</td>
<td>ATAC</td>
<td>6186</td>
<td>Lancet Oncol 2008</td>
<td>100</td>
<td>ANA</td>
<td>0.90 (0.025)</td>
<td>1.00 (0.99)</td>
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</tr>
<tr>
<td></td>
<td>BIG-1-98</td>
<td>4922</td>
<td>JCO 2007</td>
<td>51</td>
<td>LET</td>
<td>0.82 (0.007)</td>
<td></td>
<td></td>
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<tr>
<td>“Early” Switch</td>
<td>ITA-1</td>
<td>380</td>
<td>JCO 2001</td>
<td>61</td>
<td>AGT</td>
<td>NR (0.6)</td>
<td>NR (0.005)</td>
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</tr>
<tr>
<td></td>
<td>ITA-2</td>
<td>448</td>
<td>Ann Oncol 2006</td>
<td>64</td>
<td>ANA</td>
<td>0.57 (0.005)</td>
<td>0.56 (0.1)</td>
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</tr>
<tr>
<td></td>
<td>IES</td>
<td>4742</td>
<td>Lancet 2007</td>
<td>56</td>
<td>EXE</td>
<td>0.76 (0.0001)</td>
<td>0.85 (0.08)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARNO 95</td>
<td>979</td>
<td>JCO 2007</td>
<td>30</td>
<td>ANA</td>
<td>0.66 (0.049)</td>
<td>0.53 (0.045)</td>
<td></td>
</tr>
<tr>
<td>Sequencing</td>
<td>ABCSG 8</td>
<td>2926</td>
<td>SABCS 2005</td>
<td>28</td>
<td>ANA</td>
<td>0.76 (0.07)</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

**Absolute DFS Reductions at 3-6 years**

<table>
<thead>
<tr>
<th></th>
<th>Up-Front</th>
<th>Early Switch</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-4 %</td>
<td>3-5%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>
## Adjuvant Endocrine Trials: Efficacy Aromatase Inhibitor Versus Placebo or No Treatment

<table>
<thead>
<tr>
<th>Strategy</th>
<th>RCTs</th>
<th>Pts</th>
<th>Update</th>
<th>Median FU (mo.)</th>
<th>Efficacy</th>
<th>[HR, p]</th>
<th>DFS/EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended Switch</td>
<td>MA.17</td>
<td>5157</td>
<td>JNCI 2005</td>
<td>30</td>
<td>LET</td>
<td>0.58</td>
<td>(0.001)</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>ABCSG 6a</td>
<td>856</td>
<td>ASCO 2005</td>
<td>60</td>
<td>ANA</td>
<td>0.64</td>
<td>(0.047)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>NSABP B-33</td>
<td>1598</td>
<td>JCO 2008</td>
<td>30</td>
<td>EXE</td>
<td>0.68</td>
<td>(0.07)</td>
<td>1.20</td>
</tr>
</tbody>
</table>

**Absolute DFS reductions at 3-6 years**

Extended Switch

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute DFS reductions at 3-6 years</td>
<td>Extended Switch</td>
</tr>
<tr>
<td></td>
<td>6%</td>
</tr>
</tbody>
</table>
The panel believes the three selective aromatase inhibitors (anastrozole, letrozole, exemestane) have similar antitumor efficacy and similar toxicity profiles. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.
Ongoing trials of extended AI therapy

MA17R
- N=1800
- Tamoxifen 3-5 years
- Any Extended AI 0-2 years
- Letrozole 5 years
- Placebo 5 years

SALSA
- N=3486
- Any Endocrine Rx 5 years
- Anastrozole 2 years

LEAD
- N=4050
- Tamoxifen 2-3 years
- Letrozole 2-3 years

DATA
- N=1900
- Tamoxifen 2-3 years
- Anastrozole 3 years

NSABP-B42
- N=3966
- Al or Tam-Al 5 years
- Letrozole 5 years
- Placebo 5 years

SOLE
- N=4800
- Any Endocrine Rx 5 years
- Letrozole 9m 9m 9m 9m 12m
- L L L L L

LEAD: Letrozole Adjuvant Therapy Duration trial; SALSA: Secondary Adjuvant Long-term Study with Arimidex trial; DATA: Different Durations of Anastrozole after Tamoxifen trial; SOLE: Study of Letrozole Extension trial Al: aromatase inhibitor; Tam: tamoxifen; L: letrozole; R: randomized; Rx: therapy; m: month

IMPAKT Breast Cancer Conference 2013

Presented By Rebecca Alexandra Dent, MD at 2013 ASCO Annual Meeting
WHY NOT JUST TREAT EVERYONE FOREVER, ANYWAY?
No Benefit If Not Taking The Drug!
Discontinuation by Treatment Year

Cumulative Discontinuation by Number of Treatment Years

- Tam Only
- AI Only
- Tam to AI

Within 1 Year
Within 2 Years
Within 3 Years
Within 4 Years
Within 5 Years

Quinn, ASCO 2011
Factors Associated With Non-Persistence

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less prescription medication coverage</td>
<td>1.8 (1.0 to 3.2)</td>
<td>0.040</td>
</tr>
<tr>
<td>Other specialty doctor (vs. medical oncologist)</td>
<td>2.7 (1.4 to 4.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Negative attitude towards taking medications</td>
<td>1.7 (0.9 to 3.0)</td>
<td>0.080</td>
</tr>
</tbody>
</table>

Controlling for clinical factors, race/ethnicity, marital status, education, site, and time from diagnosis to follow-up survey. Including 417 patients with complete data.
Patient-reported Reasons for Stopping Endocrine Therapy (N = 77)

<table>
<thead>
<tr>
<th></th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient-related</strong></td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>27</td>
</tr>
<tr>
<td>Concern about adverse effects</td>
<td>16</td>
</tr>
<tr>
<td>from therapy</td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>18</td>
</tr>
<tr>
<td>Dislike of having to be on</td>
<td>17</td>
</tr>
<tr>
<td>medications</td>
<td></td>
</tr>
<tr>
<td>Wanted to move on from the</td>
<td>11</td>
</tr>
<tr>
<td>cancer</td>
<td></td>
</tr>
<tr>
<td><strong>Doctor-related</strong></td>
<td></td>
</tr>
<tr>
<td>Told to stop by doctor</td>
<td>16</td>
</tr>
<tr>
<td>Completion of recommended</td>
<td>9</td>
</tr>
<tr>
<td>course of treatment</td>
<td></td>
</tr>
</tbody>
</table>

(Not mutually exclusive)

Pini, ASCO 2011
ATAC: annual bone fracture rates

ATAC Trialists, Lancet Oncology 2008;9:45
Persistent Risks of Therapy

- Tamoxifen
- Uterine cancer
- Thromboembolism
- Aromatase Inhibitors
- Osteoporosis
- Myalgias/arthralgias

QOL Issues: vasomotor symptoms, mood alterations, sexual dysfx, aches and pains
ADJUVANT ENDOCRINE THERAPY

Premenopausal\(^1\) at diagnosis
- Tamoxifen\(^2\) for 5 y (category 1)
  ± ovarian suppression or ablation (category 2B)
  
  _Postmenopausal\(^1\)_
  - Aromatase inhibitor for 5 y\(^3\) (category 1)
    _or_
    Consider tamoxifen\(^2\) for an additional 5 y to complete 10 y

Premenopausal\(^1\)

Postmenopausal\(^1\) at diagnosis
- Tamoxifen\(^2\) for 4.5-6 y
  
  Women with a contraindication to aromatase inhibitors, who decline aromatase inhibitors, or who are intolerant of the aromatase inhibitors
  - Aromatase inhibitor\(^3\) for 5 y\(^3\) (category 1)
    _or_
    Consider tamoxifen\(^2\) for an additional 5 y to complete 10 y

Aromatase inhibitor\(^3\) to complete 5 y\(^3\) of endocrine therapy (category 1)
  _or_
  Up to 5 y of an aromatase inhibitor\(^3\) (category 2B)
  - Tamoxifen\(^2\) to complete 5 y of endocrine therapy (category 1)

\(^1\)See Definition of Menopause (Binv-J).

\(^2\)Some SSRIs like fluoxetine and paroxetine decrease the formation of endoxifen, 4-OH tamoxifen, and active metabolites of tamoxifen, and may impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. At this time, based on current data the panel recommends against CYP2D6 testing for women being considered for tamoxifen therapy. Coadministration of strong inhibitors of CYP2D6 should be used with caution.

\(^3\)The panel believes the three selective aromatase inhibitors (ie, anastrozole, letrozole, exemestane) have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and neoadjuvant settings. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update


ABSTRACT

Purpose
To update the ASCO clinical practice guideline on adjuvant endocrine therapy on the basis of emerging data on the optimal duration of treatment, particularly adjuvant tamoxifen.

Methods
ASCO convened the Update Committee and conducted a systematic review of randomized clinical trials from January 2009 to June 2013 and analyzed three historical trials. Guideline recommendations were based on the Update Committee’s review of the evidence. Outcomes of interest included survival, disease recurrence, and adverse events.

Results
This guideline update reflects emerging data on duration of tamoxifen treatment. There have been five studies of tamoxifen treatment beyond 5 years of therapy. The two largest studies with longest reported follow-up show a breast cancer survival advantage with 10-year durations of tamoxifen use. In addition to modest gains in survival, extended therapy with tamoxifen for 10 years compared with 5 years was associated with lower risks of breast cancer recurrence and contralateral breast cancer.

Recommendations
Previous ASCO guidelines recommended treatment of women who have hormone receptor–positive breast cancer and are premenopausal with 5 years of tamoxifen, and those who are postmenopausal a minimum of 5 years of adjuvant therapy with an aromatase inhibitor or tamoxifen followed by an aromatase inhibitor (in sequence). If women are pre- or perimenopausal and have received 5 years of adjuvant tamoxifen, they should be offered 10 years total duration of tamoxifen. If women are postmenopausal and have received 5 years of adjuvant tamoxifen, they should be offered the choice of continuing tamoxifen or switching to an aromatase inhibitor for 10 years total adjuvant endocrine therapy.