Is Longer Better?

Optimal Duration of Adjuvant Anti-Hormone Therapy

2016 SABCS Patient Review

February 21st, 2017

Jay Andersen, MD
“One in Eight”

Diana Young, TBCF ‘96
Let’s Decode This!

Extended adjuvant endocrine therapy in HR-positive eBC

The updated picture

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Legend:
- Tam: Tamoxifen
- Al: Aromatase Inhibitors
- Let: Letrozole
- Ana: Anastrozole
- Exe: Exemestane
- Placebo: Placebo
Estrogen Sources

premenopausal

ovary

estragons

postmenopausal

adrenal

androgens

“aromatase”
Estrogen Receptor
Early Stage Anti-Hormone Therapy Approaches

• **Block estrogen receptor**
  – **Tamoxifen** (pre and postmenopausal)

• **Reduce estrogen production**
  – **Aromatase Inhibitors** (postmenopausal)
    • Arimidex/Anastrozole
    • Femara/Letrozole
    • Aromasin/Exemestane
Risk of Early Breast Cancer Recurrence

Annual hazard of recurrence by estrogen receptor status

Patients received CT, ET, or both (10 ECOG trials)

Abbreviations: CT, chemotherapy; ET, endocrine therapy; ECOG, Eastern Cooperative Oncology Group.
<table>
<thead>
<tr>
<th></th>
<th>2 yrs</th>
<th>5 yrs</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>local recur</td>
<td>4.3%</td>
<td>3.6%</td>
<td>-0.7%</td>
</tr>
<tr>
<td>distant recur</td>
<td>12.5%</td>
<td>9.9%</td>
<td>-2.6%</td>
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*other studies confirmed similar findings*
EBCTG Overview Analysis
5 yrs of Tamoxifen vs Placebo

5 yrs of Tamoxifen:
- reduces the odds of recurrence by **47%**
- reduces the risk of breast cancer mortality by **29%**

Lancet, 2005
Davies et al, Lancet 2011
Significant risk of recurrence remains even with tamoxifen therapy

Adapted with permission. Early Breast Cancer Trialists’ Collaborative Group Meeting, 2000
If 5 years of Tamoxifen offers benefit, would extended hormone therapy offer additional benefit?

Is $10 > 5$?
NSABP B-14: Trial Design

ER+ operable breast cancer, node-negative (initial randomization to tamoxifen vs placebo)

Second randomization (disease-free after 5 y tamoxifen) Double-blinded

Tamoxifen
n=593

Placebo
n=579

Median f/u 7 y

5 years adjuvant therapy

5 years additional therapy

NSABP B-14:
No Benefit of Extending Tamoxifen Beyond 5 Years

Tamoxifen arm had higher rates of endometrial cancer, and more deaths from ischemic heart disease and cerebrovascular disease.

Subsequent studies to re-evaluate extended Tamoxifen therapy...
Duration of Adjuvant Tamoxifen

- **ATLAS**: Adjuvant Tamoxifen Longer Against Shorter (International)
- **aTTOM**: Adjuvant Tamoxifen Treatment Offers More? (United Kingdom)

**Eligibility Criteria**
- Completely resected early-stage breast cancer or DCIS
- At least 2 years of prior tamoxifen therapy
- Relapse-free at time of randomization

**Randomization Outcome**
- Stop Tamoxifen
- Continue tamoxifen for another 5 years
### ATLAS Trial
**Tamoxifen: 5 vs 10 yrs; N = 6846**
Davies et al, Lancet 2013

<table>
<thead>
<tr>
<th></th>
<th>5 yrs</th>
<th>10 yrs</th>
<th>Difference</th>
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<tbody>
<tr>
<td>recurrence</td>
<td>21.4%</td>
<td>25.1%</td>
<td>-3.7%</td>
</tr>
<tr>
<td>BC mortality</td>
<td>15%</td>
<td>12.2%</td>
<td>-2.8%</td>
</tr>
<tr>
<td>uterine cancer</td>
<td>1.6%</td>
<td>3.1%</td>
<td>+1.5%</td>
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</tbody>
</table>

- 25% reduction in risk of recurrence and 29% reduction in breast cancer mortality

[attOM showed ~ 24% relative reduction in mortality]  
* significant “delayed effect”
So………

- TAM x 5 > TAM x 2
- TAM x 10 ~ TAM x 5……initially
- Subsequently: TAM x 10 > TAM x 5

---

- How to optimally incorporate Aromatase Inhibitors?
  - Sequence with TAM?
  - Duration?
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)
Comparison of Tamoxifen and an Aromatase Inhibitor

Designs of **Cohort 1** and **Cohort 2**

- **Tamoxifen**
- **Aromatase inhibitor**

**Cohort 1**: direct comparison as monotherapy

 Trials
ATAC
BIG 1-98/IBCSG 18-98

**Cohort 2**: comparison after 2-3 years of tamoxifen

 Trials
GABG/ARNO
IES/BIG 2-97
ITA
ABCSG VIII

5 yr
2-3 yr
2-3 yr
5 yr
Cohort 1: Direct Comparison of Tamoxifen and an Aromatase Inhibitor (9,856 Patients)
Cohort 1

≈5 Years of AI vs Tamoxifen

ER+

Recurrence rates (%/year) and logrank analyses

<table>
<thead>
<tr>
<th></th>
<th>Years 0-1</th>
<th>Years 2-4</th>
<th>Years 5+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al</td>
<td>1.69 (163/9637)</td>
<td>2.31 (261/11297)</td>
<td>2.33 (160/6879)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>2.46 (234/9510)</td>
<td>2.81 (307/10938)</td>
<td>2.78 (180/6478)</td>
</tr>
<tr>
<td>Rate ratio, from (O-E)/V</td>
<td>0.67 SE 0.08</td>
<td>0.81 SE 0.08</td>
<td>0.83 SE 0.10</td>
</tr>
</tbody>
</table>

5-yr gain 2.9% (SE 0.7)
8-yr gain 3.9% (SE 1.0)
Logrank 2P < 0.00001

Tamoxifen 19.2%
AI 15.3%

9.6%
12.6%
Cohort 2: Comparison of Tamoxifen and an Aromatase Inhibitor after 2-3 Years of Tamoxifen (9,015 Patients)
Cohort 2

2-3 Yr Tamoxifen then 2-3 Yr (Al vs Tam)

ER+

Recurrence

Time since Treatments differ

3-yr gain 3.1% (SE 0.6)
6-yr gain 3.5% (SE 1.1)
Logrank 2P<0.00001

Recurrence rates (%/year) and logrank analyses

<table>
<thead>
<tr>
<th></th>
<th>Years 0-2 (≤2-4)</th>
<th>Years 3-5 (≤5-7)</th>
<th>Years 6+ (≥8+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al</td>
<td>1.68 (187/11134)</td>
<td>2.81 (149/5298)</td>
<td>3.21 (237/716)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>2.76 (303/10962)</td>
<td>3.00 (150/5007)</td>
<td>3.87 (273/797)</td>
</tr>
<tr>
<td>Rate ratio</td>
<td>0.60 SE 0.07</td>
<td>0.93 SE 0.11</td>
<td>0.85 SE 0.27</td>
</tr>
<tr>
<td>from (O-E)/V</td>
<td>-51.0/118.4</td>
<td>-5.5/72.6</td>
<td>-2.0/12.1</td>
</tr>
</tbody>
</table>
Conclusions

- **Recurrence**: Alz produced significantly lower recurrence rates compared with TAM in both Cohorts
  - **Cohort 1**: 23% proportional reduction (absolute gains: 5 y, 2.9%; 8 y, 3.9%)
  - **Cohort 2**: 29% proportional reduction (absolute gains: 3 y, 3.1%; 6 y, 3.5%)
- In both cohorts, isolated local recurrence and contralateral disease had greater reductions than distant disease but this was not significant
Extended Schema Strategies
<more than 5 yrs>

- TAM x 10 [ATLAS, aTTOM]
- TAM x 5 → AI x 5 [MA.17]
- TAM x 2-3 → AI 6-7 [DATA, B-42, IDEAL]
- AI x 10 [B-42, IDEAL]
A Phase III Randomized, Double-Blind Study of Adjuvant Letrozole (Femara®) vs Placebo in Postmenopausal Women With Primary Breast Cancer Completing 5 Years of Tamoxifen

Results of the Femara® Extended Adjuvant Trial MA.17
MA.17: Trial Design

Randomization (Disease-free)

5 years early adjuvant

5 years extended adjuvant

Primary end point: DFS
Secondary end points: OS/safety/QOL

Tamoxifen

Letrozole 2.5 mg qd*

Placebo qd†

*n=2575 (efficacy); 2154 (safety) in the letrozole arm.
†n=2582 (efficacy); 2145 (safety) in the placebo arm.

Goss et al., 2003.
### MA.17 Results: Disease-Free Survival

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<tr>
<th></th>
<th>Letrozole (n=2575)</th>
<th>Placebo (n=2582)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
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<tr>
<td>4-y DFS rate</td>
<td>93%</td>
<td>87%</td>
<td>0.57 (0.43 - 0.75)</td>
<td>0.00008</td>
</tr>
<tr>
<td>Events</td>
<td>75</td>
<td>132</td>
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</tbody>
</table>

- Letrozole decreased the risk of recurrence by **43%** versus placebo

Goss et al., 2003.
MA.17 Results

- Increasing benefit in estimated DFS with treatment duration

Goss et al., 2003.
### MA.17 Results: Overall Survival

<table>
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<tr>
<th></th>
<th>Letrozole (n=2575)</th>
<th>Placebo (n=2582)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>4-y OS rate</td>
<td>96%</td>
<td>94%</td>
<td>0.76 (0.48 – 1.21)</td>
<td>0.25</td>
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<td>Events</td>
<td>31</td>
<td>42</td>
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Letrozole improved survival by 2% yet is **NOT** statistically significant

Goss et al., 2003.
MA.17 Results:
Safety

• Small difference in reported diagnoses of new-onset osteoporosis (5.8% letrozole vs. 4.5% placebo, p=0.07)
  – The difference in clinical fracture rate between the two groups was not significant.

Goss et al., 2003.
MA.17: Summary of Efficacy Results
Letrozole vs placebo:

- Lowers the risk of recurrence by 43%
- Improves the 4-year DFS rate by 6%
- Improves 4-year OS rate by 2% (not significant)
- Decreases incidence of contralateral breast cancer by 46%.

Similar results in:
NSABP B-33 [exemestane]. Mamounas et al, JCO 2008
ABCSG-6a [anastrozole]. Jakesz et al, JCO 2005

Goss et al., 2003.
S1-03: First results from the multicenter phase III DATA study comparing 3 versus 6 years of anastrozole after 2-3 years of tamoxifen in postmenopausal women with hormone receptor-positive early breast cancer

Vivianne Tjan-Heijnen,1 Irene van Hellemond,1 Petronella Peer,2 Astrid Swinkels,3 Carolien Smorenborg,4 Maurice van der Sangen,5 Judith Kroep,6 Hiltje De Graaf,7 Aafke Honkoop,8 Frans Erdkamp,9 Franchette van den Berkmortel,10 Jos Kitzen,11 Maaikje de Boer,1 Wilfred de Roos,12 Sabine Linn,13 Alexander Imholz,14 Caroline Seynaeve,15 on behalf of the Dutch Breast Cancer Research Group (BOOG) for the DATA Investigators

1Maastricht University Medical Center, Maastricht; 2Radboud University Medical Center, Nijmegen; 3Netherlands Comprehensive Cancer Organization IKNL, Utrecht; 4Medical Center Alkmaar, Alkmaar; 5Catharina Hospital, Eindhoven; 6Leiden University Medical Center, Leiden; 7Medical Center Leeuwarden, Leeuwarden; 8Isala Clinics, Zwolle; 9Zuyderland Medical Center, Sittard; 10Zuyderland Medical Center, Heerlen; 11Albert Schweitzer Hospital, Dordrecht; 12Gelderse Vallei Hospital, Ede; 13Netherlands Cancer Institute, Amsterdam; 14Deventer Hospital, Deventer; 15Erasmus MC Cancer Institute, Rotterdam; all in The Netherlands

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DATA Study Design

- Postmenopausal at randomization
- ER+ and/or PR+
- No sign of disease recurrence
- M0 breast cancer
- After 2-3 years adjuvant tamoxifen

6 years anastrozole
1 mg daily

3 years anastrozole
1 mg daily

Stratification
- Nodal status
- ER/PR status
- HER2 status
- Tamoxifen duration

- 80% power to detect an increase in 3-year adapted Disease-Free Survival (aDFS) from 90% to 94%, i.e., a hazard ratio (HR) of 0.60 and a significance level of 0.05
- Accounting for 10% drop-out: 950 patients per group to be included (n=1912 patients actually included)
- Minimum follow-up: ≥6 years after randomization, i.e., ≥3 years of adapted follow-up (last patient included in August 2009)
while 3 yr DFS numerically improved from 88.9% → 90.7%, favoring 6 yrs vs 3 yrs of anastrozole, this difference was **NOT** statistically significant.
Interestingly, in an unplanned subset analysis, 5 yr DFS improved by 10%, favoring 6 yrs vs 3 yrs of anastrozole in pts with ER & PR (+), LN (+) and with prior chemo
NO difference in 5 yr overall survival ~ 90%
### Predefined Adverse Events

<table>
<thead>
<tr>
<th>Grade, years 0-6</th>
<th>6-year Anastrozole (N=827)</th>
<th>3-year Anastrozole (N=833)</th>
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<tbody>
<tr>
<td></td>
<td>Any</td>
<td>Grade ≥ 3</td>
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<tr>
<td>Arthralgia / myalgia</td>
<td>57.6%</td>
<td>8.0%</td>
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<tr>
<td>Bone fractures</td>
<td>9.8%</td>
<td>2.1%</td>
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<tr>
<td>Osteopenia / osteoporosis</td>
<td>20.9%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Cardiovascular incl. arrhythmia</td>
<td>13.4%</td>
<td>3.5%</td>
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Conclusions

- The findings of the DATA study do not support extended adjuvant AI use after 5 years of sequential endocrine therapy for all postmenopausal hormone receptor-positive breast cancer patients.
- It suggests benefit for a selected group of patients, i.e., those with both ER and PR positive disease, HER2-negative disease, large tumor load, and prior chemotherapy.
- Extended AI use is associated with an increased number of bone and muscle adverse events.
- We will perform a follow-up analysis when all patients have reached a minimum adapted follow-up of 9 years.
A Randomized, Double-blinded, Placebo-controlled Clinical Trial of Extended Adjuvant Endocrine Therapy with Letrozole in Postmenopausal Women with Hormone-receptor (+) Breast Cancer who have Completed Previous Adjuvant Tx with an Aromatase Inhibitor: Results from NRG Oncology/NSABP B-42

Eleftherios P. Mamounas, MD,1,2 Hanna Bandos, PhD1,3 Barry C. Lemersky, MD,1,4 Charles E. Geyer, Jr., MD,1,5 Louis Fehrenbacher, MD,1,6 Mark L. Graham, MD,1,7 Stephen L. Chia, MD, FRCPC1,8 Adam M. Bruфsky, MD, PhD,1,4 Bryan T. Hennessy, MD,1,9 Gamini S. Soori, MD,1,10 Shaker R. Dakhil, MD,1,11 Thomas E. Seay, MD,1,12 James L. Wade, III, MD,1,13 Edward C. McCarron, MD,1,14 Soonmyung Paik, MD,1,15 Sandra M. Swain, MD,1,16 D. Lawrence Wickerham, MD,1,17 Norman Wolmark, MD1,17

1NRG Oncology/NSABP (NSABP Legacy trials are now part of the NRG Oncology portfolio), Pittsburgh, PA; 2UF Cancer Center at Orlando Health, Orlando, FL; 3University of Pittsburgh, Pittsburgh, PA; 4University of Pittsburgh Cancer Institute, Pittsburgh, PA; 5Massey Cancer Center, Virginia Commonwealth University, Richmond, VA; 6Kaiser Permanente Oncology Clinical Trials Northern California, Vallejo, CA; 7Southeast Cancer Control Consortium, Goldsboro, NC; 8British Columbia Cancer Agency (BCCA), Vancouver, British Columbia, Canada; 9Cancer Trials Ireland (Formerly known as Irish Clinical Oncology Research Group - ICORG), Dublin, Ireland; 10Missouri Valley Cancer Consortium, Omaha, NE; 11CCOP, Wichita Cancer Center of Kansas, Wichita, KS; 12Georgia NCI Community Oncology Research Program, Atlanta, GA; 13CCOP, Central Illinois, Decatur, IL; 14MedStar Franklin Square Medical Center/Weinberg Cancer Institute, Baltimore, MD; 15Severance Biomedical Science Institute and Department of Medical Oncology, Yonsei University College of Medicine, Seoul, Korea; 16Washington Cancer Institute, MedStar Washington Hospital Center, Washington, DC; 17Allegheny Health Network Cancer Institute, Pittsburgh, PA

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NSABP B-42: Schema

- Postmenopausal Pts with ER+ or PR+ Breast Cancer
- Stage I, II, or IIIa invasive BC at diagnosis
- Disease-free After 5 Years of Endocrine Therapy

Al X 5 yrs or TAM X ≤ 3 yrs → Al to Complete 5 yrs

Stratification:
- Pathological nodal status (Negative, Positive)
- Prior adjuvant TAM (Yes, No)
- Lowest BMD T score: spine, hip, femur (>-2.0, ≤ -2.0 SD)

Letrozole X 5 yrs  
R  
Placebo X 5 yrs
15% improvement in 7 yr DFS* favoring letrozole vs placebo (81.3% → 84.7%)
yet NOT statistically significant

*includes recurrence, new breast event, new cancers, death from any cause
yet, with outcome limited to 7 yr “Breast Cancer Free Interval” (BCFI)* there is a 29% improvement favoring letrozole vs placebo (10% → 6.7%) which IS statistically significant

*removes other cancers and death from other cause
reduction in the incidence of distant recurrence by 28%, favoring letrozole vs placebo (5.8% → 3.9%), which is statistically significant.
NO difference in 7 yr overall survival ~ 92%
NO difference in DFS
NO difference in overall survival
What we already knew.......... 

Tam x 10 > Tam x 5
AI x 5 > Tam x 5
[Tam x 2-3 → AI x 2-3] > TAM x 5
Yet, what about “MORE AI” after “SOME AI”?  

a) TAM x 2-3 → AI x 2-3 → MORE AI??  
b) AI x 5 → MORE AI??

Results of extended AI following “some” AI in the 1st 5 years are less impressive/negative when compared to TAM x 5 → AI x 5

- has the differential benefit already been “realized”?

Slight potential benefit must at balanced with baseline risk and tolerance to treatment

This complex decision-making process must be individualized

Evolving genomic classifier testing may offer insight
Side Effects of Hormone Therapy

**Aromatase Inhibitors**
- Osteoporosis
- Fractures
- Hypercholesterolemia
- Hypertension
- Joint pain/stiffness
- Hot flashes
- Vaginal dryness/sexual side effects

**Tamoxifen**
- Endometrial Cancer
- Blood clots
- Stroke
- Cataracts
- Hot flashes
- Vaginal dryness/sexual side effects
Balance of Risk: Benefit
Spectrum of Tolerance: Motivation

“I am glad to be finished with my cancer treatment. I don’t want to be reminded any more about my cancer. I want to be done with taking a pill everyday.”

“I want to do anything and everything to ensure this cancer never comes back. Bring it on!”
Genomic Biomarkers

- Each of these biomarkers provides prognostic information
- **BCI, Prosigna and EndoPredict** provide prognostic information specifically regarding late recurrence
- **BCI** provides predictive information re: extended endocrine therapy benefit

<table>
<thead>
<tr>
<th></th>
<th>Oncotype Dx (Genomic Health)</th>
<th>MammaPrint (Agendia)</th>
<th>Breast Cancer Index (BCI) (Biotheranostics)</th>
<th>Prosigna (Nanostring)</th>
<th>EndoPredict (Myriad)</th>
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<tbody>
<tr>
<td># of genes</td>
<td>21 (16 biomarkers + 5 normalization)</td>
<td>70</td>
<td>11 (7 biomarkers + 4 normalization)</td>
<td>50 + tumor size (+5 normalization)</td>
<td>8 + tumor size &amp; nodal status (+4 normalization)</td>
</tr>
<tr>
<td>Platform</td>
<td>RT-qPCR</td>
<td>Microarray</td>
<td>RT-qPCR</td>
<td>NanoString nCounter</td>
<td>RT-qPCR</td>
</tr>
<tr>
<td>Score</td>
<td>Low / Inter / High Risk</td>
<td>Low / High Risk</td>
<td>Prognostic: Low / Inter / High Risk</td>
<td>Low / Inter / High Risk</td>
<td>Low / High Risk</td>
</tr>
<tr>
<td>Prognostic 0-10 yr</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prognostic 5-10 yr</td>
<td>No</td>
<td>No</td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Predictive of adjuvant chemotherapy benefit</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Predictive of extended endocrine therapy benefit</td>
<td>No</td>
<td>No</td>
<td><strong>Yes</strong></td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
BCI Predictive Validation in MA.17 Prospective Randomized Controlled Trial Cohort

- **High BCI Predictive** was associated with a statistically significant **16.5%** absolute benefit ($P=0.007$)

- **Low BCI Predictive** had **NO** statistically significant benefit ($P=0.35$)

<Thank You>

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Gnant, M
Goss, P
Mamanous, EP
Tjan-Heijnen, VC