Emerging Approaches for (Neo)Adjuvant Therapy for ER+ Breast Cancer

Cynthia X. Ma, M.D., Ph.D.
Associate Professor of Medicine
Washington University in St. Louis
Outline

• Current status of adjuvant endocrine therapy for postmenopausal women with ER+ breast cancer

• Ongoing trials of multi-gene profiling to avoid adjuvant chemotherapy

• Emerging concept of neoadjuvant endocrine therapy
Outline

• Current status of adjuvant endocrine therapy for postmenopausal women with ER+ breast cancer

• Ongoing trials of Multi-gene profiling to avoid adjuvant chemotherapy

• Emerging concept with neoadjuvant endocrine therapy
Benefit of Adjuvant Tamoxifen x 5 years for ER+ Breast Cancer (EBCTCG Overview 2011)

N=10,645, node+ 44%, Chemo 51%

<table>
<thead>
<tr>
<th>Event</th>
<th>Recurrence (%)</th>
<th>Breast Cancer Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>0-4</td>
<td>5-9</td>
</tr>
<tr>
<td>Control (%) per year</td>
<td>6.71</td>
<td>3.46</td>
</tr>
<tr>
<td>Tamoxifen (%) per year</td>
<td>3.74</td>
<td>2.62</td>
</tr>
<tr>
<td>Rate ratio (Log rank analysis)</td>
<td>0.53</td>
<td>0.68</td>
</tr>
</tbody>
</table>

RR 0.61 (95% CI 0.57-0.65)
Log-rank 2p<0.00001
15-year gain 13.2% (SE 1.1)

RR 0.70 (95% CI 0.64-0.75)
Log-rank 2p<0.00001
15-year gain 9.2% (SE 1.0)
Benefit of Adjuvant Tamoxifen x 5 years for ER+ Breast Cancer (EBCTCG Overview 2011)

Benefit of tamoxifen was independent of:

• Progesterone receptor status (or level)
• Age
• Nodal status
• Use of chemotherapy
Phase III Trials of Aromatase Inhibitors for Postmenopausal Women in the Adjuvant Setting

- Upfront
- Sequential
- Extended

* Randomize

Lin N U, Winer E P. JCO 2008;26:798-805
5 yrs Adjuvant AI vs Tamoxifen
Meta-analysis of ATAC (anastrozole) and BIG 1-98 (letrozole) trials

Recurrence

5-year gain, 2.9% (SE, 0.7%)
8-year gain, 3.9% (SE, 1.0%)
Log-rank 2P < .00001

Mortality

Breast Cancer Mortality (% ± SE)

n = 9,856; mean FU 5.8 yrs

Dowsett et al. JCO 2010
5 yrs Tamoxifen vs Sequential Tamoxifen and AI
Meta-analysis of 4 trials

A. Recurrence
- 3-year gain, 3.1% (SE, 0.6%)
- 6-year gain, 3.6% (SE, 1.1%)
- Log-rank 2P < .00001

B. Mortality
- 3-year gain, 0.7% (SE, 0.3%)
- 6-year gain, 1.7% (SE, 0.8%)
- Log-rank 2P = .02

n > 9,000

Dowsett et al. JCO 2010
10-year Analysis of the ATAC Trial

![Graph showing time to recurrence and annual hazard rates for Tamoxifen and Anastrozole.]

- **Time to Recurrence**
- **Annual Hazard rates**

Cuzick, J. et al Lancet Oncol. 2010
BIG 1-98 Trial Design

A: Tamoxifen (2-arm option 3/98 - 3/00, 1835 patients)
B: Letrozole (2-arm option 3/98 - 3/00, 1835 patients)
C: Tamoxifen, Letrozole (4-arm option 9/99 - 5/03, 6193 patients)
D: Letrozole, Tamoxifen (4-arm option 9/99 - 5/03, 6193 patients)

YEARS
Survival Advantage of Letrozole 5 Years Over Tamoxifen 5 Years
BIG 1-98 at 8.1 years median follow-up

<table>
<thead>
<tr>
<th></th>
<th>5-y DFS</th>
<th>8-y DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole</td>
<td>85.5%</td>
<td>76.4%</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>82.0%</td>
<td>72.0%</td>
</tr>
</tbody>
</table>

HR 0.82 (95% CI 0.72-0.92) p=0.0002

DFS

<table>
<thead>
<tr>
<th></th>
<th>5-y OS</th>
<th>8-y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole</td>
<td>91.8%</td>
<td>85.4%</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>90.3%</td>
<td>81.4%</td>
</tr>
</tbody>
</table>

HR 0.79 (95% CI 0.69-0.90) p=0.0006

OS

Regan, M et al Lancet Oncology 2011
Equivalent Outcome of Sequential vs Letrozole Monotherapy
BIG 1-98 at 8.1 years median follow-up

Regan, M et al Lancet Oncology 2011
TEAM trial: Tamoxifen Exemestane Adjuvant Multinational phase III Trial

Van de Velde Lancet 2011
Extended Adjuvant Letrozole followed 5 years of tamoxifen (MA.17)
MA27 Trial

N=7576

postmenopausal receptor-positive women

RANDOMIZATION

Exemestane
Once daily x 5 Yrs

Anastrozole
Once daily x 5 Yrs

Equivalent in DFS for both agents
Current status of adjuvant endocrine therapy for postmenopausal women

- An AI is indicated in the adjuvant setting for postmenopausal women with ER+ breast cancer
  - Upfront for 5 years
  - Tamoxifen then AI for a total of 5 years
  - AI then tamoxifen for a total of 5 years
  - Tamoxifen for 5 years then AI for 5 years

- The three AIs are likely equivalent in efficacy
Outline

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• Emerging concept with neoadjuvant endocrine therapy
ECOG/Int TAILORx
PI: Sparano

N=7,047
ER+ Node -

21 GENE RECURRENCE SCORE ASSAY

Pre-REGISTER
REGISTER Specimen Banking

Secondary Study Group 1
RS < 11
~29% of Population

Primary Study Group
RS 11-25
~44% of Population

Secondary Study Group 2
RS > 25
~27% of Population

ARM A
Hormonal Therapy Alone

RANDOMIZE

ARM B
Hormonal Therapy

ARM D
Chemotherapy Plus Hormonal Therapy

ARM C
Chemotherapy Plus Hormonal Therapy
Prospective Trial of 70-Gene Assay: MINDACT

Evaluate clinical pathologic risk and 70-gene signature risk in 6000 patients with node-negative disease

(n = 3300)

Clinical/pathologic and 70-gene scores both HIGH risk

Discordant cases
- Clinical/pathologic score HIGH and 70-gene score LOW
- Clinical/pathologic score LOW and 70-gene score HIGH

(n = 1920)

R-T

Use clinical/pathologic risk to decide chemotherapy or not
Use 70-gene risk to decide chemotherapy or not

R-CT

Anthracycline-based Chemotherapy vs. Docetaxel/capecitabine

Whole genome arrays

Potential CT sparing in 10%-15% patients

(n = 780)

Clinical/pathologic and 70-gene scores both LOW risk

R-ET

Endocrine therapy
- Tamoxifen for 2 years
- Letrozole for 5 years vs. Letrozole for 7 years

**S1007**

**REGISTRATION**

**RECURRENCE SCORE**

- RS > 25
  - N= 5,600
    - (N= 3,800) Discuss alternative trials for high risk patients
    - Refuse
      - N= 1,600
        - Record chosen therapy

- RS ≤ 25
  - Accept
    - Randomize
      - N= 2,000
        - Chemotherapy; appropriate endocrine therapy

- Randomization stratified by:
  1. RS 0-13 vs. 14-25
  2. Menopausal status
  3. Axillary node dissection vs. Sentinel node biopsy

**ER+ Node + (1-3)**

N= 2,000
No Chemotherapy; appropriate endocrine therapy
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Neoadjuvant Endocrine Therapy to Improve Breast Conserving Surgery Rate

**P024**
- ER+ Stage 2/3
  - Letrozole
  - Tamoxifen

**IMPACT**
- 2-week Biopsy
  - Anastrozole
  - Tamoxifen
  - Combination

**Letrozole (P024)**
- Improvement rate (%)
- L: 48%
- T: 36%
- LvT: p=0.03

**Anastrozole (IMPACT)**
- Improvement rate (%)
- A: 46%
- T: 22%
- C: 26%
- AvT: p=0.03
Neoadjuvant Endocrine Therapy For Outcome Prediction

Preoperative Endocrine Prognostic Index (PEPI: T, N, ER, Ki67)

Ki67

2-4 wks

3-4 mons
Preoperative Endocrine Prognostic Index (PEPI)

Multivariable analysis of post-neoadjuvant surgical specimens on RFS and BCSS in P024 trial

<table>
<thead>
<tr>
<th>Post-therapy factors</th>
<th>RFS</th>
<th></th>
<th>Breast Cancer Specific Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Tumor stage (T1/2 vs T3/4)</td>
<td>2.8 (1.4 to 5.4)</td>
<td>.003</td>
<td>4.4 (1.7 to 11.2)</td>
</tr>
<tr>
<td>Node status (pos vs neg)</td>
<td>3.2 (1.5 to 6.9)</td>
<td>.004</td>
<td>3.9 (1.1 to 13.7)</td>
</tr>
<tr>
<td>Ki67 level per 2.7-fold increase</td>
<td>1.3 (1.1 to 1.6)</td>
<td>.003</td>
<td>1.4 (1.07 to 1.9)</td>
</tr>
<tr>
<td>ER, Allred score (0,2 vs 3-8)</td>
<td>2.8 (1.2 to 6.4)</td>
<td>.02</td>
<td>7.0 (2.4 to 20.9)</td>
</tr>
</tbody>
</table>

# Preoperative Endocrine Prognostic Index (PEPI)

<table>
<thead>
<tr>
<th>Pathology, Biomarkers Factors</th>
<th>RFS</th>
<th>BCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>Points</td>
</tr>
<tr>
<td>Tumor size</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>T1/2</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>T3/4</td>
<td>2.8</td>
<td>3</td>
</tr>
<tr>
<td>Node status</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>3.2</td>
<td>3</td>
</tr>
<tr>
<td>Ln Ki67 level</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>1+</td>
<td>1.3</td>
<td>1</td>
</tr>
<tr>
<td>2+</td>
<td>1.7</td>
<td>1</td>
</tr>
<tr>
<td>3+</td>
<td>2.2</td>
<td>2</td>
</tr>
<tr>
<td>4+</td>
<td>2.9</td>
<td>3</td>
</tr>
<tr>
<td>ER Allred</td>
<td>0-2</td>
<td>3</td>
</tr>
<tr>
<td>3-8</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

Ellis et al JNCI 2008: 100, 1380-8
Preoperative Endocrine Prognostic Index (PEPI)
Data from P024 and POL and trial

PEPI 0
- pT1/2
- pN0
- Ki67 ≤ 2.7%
- ER Allred 3-8

Data from Matthew Ellis

P024
- ER+
- Stage 2/3

4-week Biopsy

POL
- ER+
- Stage 2/3

Surgery
Neoadjuvant Endocrine Therapy For Outcome Prediction

Preoperative Endocrine Prognostic Index (PEPI: T, N, ER, Ki67)

Ki67

2-4 wks

3-4 mons

↑
RFS by Ki67 in IMPACT: Pre vs 2 Week

2 weeks endocrine therapy

Relapse Free Survival by baseline LnKi67

Not significant ← Multivariate analysis → HR 2.01 p 0.002

Dowsett, Smith et al JNCI 2007
Tumor Ki67 After 4 weeks of Neoadjuvant Endocrine Therapy for Early Identification of Non-responders

If High Ki67 after 4 weeks stop endocrine therapy and switch to chemotherapy

Ellis et al SABCC 2009
Ki67 Suppression from Baseline During Treatment (IMPACT Trial)

**Ki67**

<table>
<thead>
<tr>
<th>2 Weeks</th>
<th>12 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole (A)</td>
<td>Anastrozole (A)</td>
</tr>
<tr>
<td>Tamoxifen (T)</td>
<td>Tamoxifen (T)</td>
</tr>
<tr>
<td>Combo (C)</td>
<td>Combo (C)</td>
</tr>
</tbody>
</table>

- **A v T p=0.004**
- **A v T p<0.001**

**ATAC**
Ki67 Suppression from Baseline During Treatment (Z1031 Trial)

Ki67

E  A  L

Z1031

E v A $p = 0.56$

E v L $p = 0.32$

A v L $p = 0.16$

Biopsy

BL  16-w

Exemestane

Anastrozole

Letrozole

Surgery

ER+ Stage 2/3

E=A MA27
<table>
<thead>
<tr>
<th>Adjuvant Trial (Relapse Rate)</th>
<th>Neoadjuvant Trial (Ki67 Suppression)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIG 1-98</strong>&lt;br&gt;N=8010</td>
<td><strong>PO24</strong>&lt;br&gt;N=185</td>
</tr>
<tr>
<td>Letrozole &gt; Tamoxifen</td>
<td>Letrozole &gt; Tamoxifen</td>
</tr>
<tr>
<td><strong>ATAC</strong>&lt;br&gt;N=9366</td>
<td><strong>IMPACT</strong>&lt;br&gt;N=259</td>
</tr>
<tr>
<td>Anastrozole &gt; Tamoxifen</td>
<td>Anastrozole &gt; Tamoxifen</td>
</tr>
<tr>
<td>= Combination</td>
<td>= Combination</td>
</tr>
<tr>
<td><strong>MA27</strong>&lt;br&gt;N=7576</td>
<td><strong>Z1031</strong>&lt;br&gt;N=266</td>
</tr>
<tr>
<td>Anastrozole = Exemestane</td>
<td>Anastrozole = Exemestane</td>
</tr>
</tbody>
</table>

> better = equal
ACOSOG Z1031 Cohort B

Eligibility:
- Postmenopausal
- Clinical Stage II or III
- ER+ (Allred 6-8)
- HER2-

Path CR rate?

PEPI score 0
stage 1/0
No Chemo

PEPI > 0
Stage > 1
MD decision

Adherence with recommendation for no chemotherapy on PEPI score 0 Stage 1?

http://www.ctsu.org/
ALTERNATE Study Schema

Arm A
Anastrozole (A) x 6 mos

Arm F
Fulvestrant (F) x 6 mos

Arm A/F
(A + F) x 6 mos

Arm A
A x 4.5 years

Arm F
F x 1.5 yrs → A x 3 yrs

PEPI 0
Adjuvant Chemo not recommended

PEPI >0
Adjuvant Chemotherapy
Physician’s Choice

Endocrine therapy per physician choice

Sample size:
Maximum N=2820
- 1st phase (n=400 in each arm)
- 2nd phase (an additional 540 in each arm)

Eligibility:
- Postmenopausal
- Clinical Stage II or III
- ER+ (Allred 6-8)
- HER2-

*Weekly paclitaxel x 12 (optional d2 biopsy) or standard NCCN neochemo
# required biopsy

* Neoadjuvant Chemotherapy

SURGERY

4-week or 12-week Ki67 > 10%
Conclusion

- Adjuvant endocrine therapy reduces breast cancer recurrence
- Multi-gene assays are being tested to avoid chemotherapy in low to intermediate risk ER+ breast cancer
- Neoadjuvant endocrine therapy provides a new platform assessing endocrine responsiveness and drug development
Adjuvant Approach

AI therapy alone

Low risk

Molecular profiling
Clinical & pathological features

High risk

Alternative therapy in addition to AI
Evolving Approach

Endocrine resistant (Ki67 High)

2-4 wks AI

3-6 mos AI

Endocrine resistant PEPI > 0

AI therapy alone?

PEPI 0