National Surgical Adjuvant Breast and Bowel Project
P-2 STAR Sites in U.S., Canada & Puerto Rico

- P1 & P2 site
- New P2 site
2006 Breast Cancer Estimates

212,290 New Cases
- 4% Melanoma of skin
- 3% Thyroid
- 31% Breast
- 12% Lung and bronchus
- 2% Pancreas
- 11% Colon and rectum
- 3% Ovary
- 6% Uterus
- 2% Urinary
- 4% Non-Hodgkin lymphoma
- 22% All other sites

40,970 Deaths
- 2% Brain
- 15% Breast
- 26% Lung and bronchus
- 6% Pancreas
- 10% Colon and rectum
- 6% Ovary
- 3% Uterus
- 3% Non-Hodgkin lymphoma
- 4% Leukemia
- 2% Multiple myeloma
- 23% All other sites

Chemical Structure of Tamoxifen

\[
(CH_3)_2 N (CH_2)_2 O
\]

\[
C_2 H_5
\]
NSABP B-14

- Tumors With ER ≥ 10 fmol/mg
- Histologically Neg. Axillary Nodes
- TM or Lump. + Ax. Diss. +XRT

**Stratification**
- Age
- Clinical Tumor Size
- Quantitative ER
- Type of Operation

- Placebo
- TAM
B-14
Second Cancers
Opposite Breast

<table>
<thead>
<tr>
<th></th>
<th>PLAC 1424 pts.</th>
<th>TAM 1419 pts.</th>
<th>P = 0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td># Cancers</td>
<td>55</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

NSABP
Eligible Participants

Stratification
- Age
- Relative Risk
- Race

TAMOXIFEN
x 5 YRS.

PLACEBO
x 5 YRS.
Gail Model Variables Used to Provide Composite Risk Assessment

- No. 1st degree relatives with breast cancer
- Nulliparity or age at 1st live birth
- No. of benign breast biopsies
- Atypical hyperplasia
- Age at menarche
- Race
Participant Characteristics

Age (yrs)
- 35-49: 39%
- 50-59: 31%
- 60+: 30%

Family History
- 1 Relative: 57%
- 2 Relatives: 16%
- 3+ Relatives: 3%
- No Relatives: 24%

Gail Risk
- < 2.01: 25%
- 2.01-3.00: 31%
- 3.01-3.00: 27%
- > 5.01: 17%

Benign Disease
- LCIS: 6%
- Atypical Hyperplasia: 9%
- 85%
<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>175</td>
<td>89</td>
</tr>
<tr>
<td><strong>P</strong> &lt; 0.00001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>49% reduction</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
P-1 Invasive Breast Cancer

Rate/1000

LCIS

18*

Placebo

Tamoxifen

8

23

Atypical Hyperplasia

* # of events

* # of events

NSABP BCPT
BCPT-P1

Noninvasive Breast Cancers

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td>35</td>
</tr>
</tbody>
</table>

P = 0.002

50% reduction

NSABP
### BCPT-P1

#### Invasive Breast Cancer

- **# Events**
  - Placebo: 250
  - Tamoxifen: 145

#### Noninvasive Breast Cancer

- **# Events**
  - Placebo: 93
  - Tamoxifen: 60

- **P-value**
  - P < 0.0001
  - P = 0.008
BCPT-P1
Detrimental Events

Rate per 1000

- **Endometrial Cancer**
  - Placebo: 17
  - Tamoxifen: 53

- **Pulmonary Emboli**
  - Placebo: 13
  - Tamoxifen: 28

- **Deep Vein Thrombosis**
  - Placebo: 34
  - Tamoxifen: 49

- **Stroke**
  - Placebo: 50
  - Tamoxifen: 71

* Number of Events
Chemical Structure

Tamoxifen

Raloxifene
MORE Study

Postmenopausal women with osteoporosis

- Placebo
- Raloxifene 60 mg/d
- Raloxifene 120 mg/d
Four-Year Incidence Rates of Breast Cancer In the MORE Study

Newly Diagnosed Invasive Breast Cancer
- Placebo: 1.51%
- Raloxifene: 0.43%
- 72% Risk Reduction

Estrogen-Receptor-Positive Invasive Breast Cancer
- Placebo: 1.20%
- Raloxifene: 0.20%
- 84% Risk Reduction
NSABP STAR Schema

Risk-Eligible Postmenopausal Women

STRATIFICATION
• Age
• Relative Risk
• Race
• History of LCIS

TAMOXIFEN
20 mg/day x 5 years

RALOXIFENE
60 mg/day x 5 years
STAR Trial Objectives

Primary objective:

Evaluate the effect of raloxifene vs. tamoxifen in reducing the incidence of:

• Invasive breast cancer
STAR Trial Objectives

Secondary objectives:

- Noninvasive breast cancer
- Endometrial cancer
- Ischemic Heart Disease
- Fractures of the:
  - Hip
  - Spine
  - Wrist (Colles’)
## STAR Summary of Screening, Accrual and Follow-Up Information

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women screened for breast cancer risk</td>
<td>184,460</td>
</tr>
<tr>
<td>Women who were breast cancer risk eligible</td>
<td>96,368</td>
</tr>
<tr>
<td>Women randomly assigned treatment</td>
<td>19,747</td>
</tr>
<tr>
<td>Total person-years of follow-up</td>
<td>76,828</td>
</tr>
<tr>
<td>Average follow-up (months)</td>
<td>47.3</td>
</tr>
</tbody>
</table>
P-2 STAR
Age Distribution

- <49: 9%
- 50-59: 50%
- 60-69: 32%
- 70+: 9%
- 90+: 9%
## P-2 STAR
### Racial/Ethnic Distribution (%)

<table>
<thead>
<tr>
<th></th>
<th>TAM</th>
<th>RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>93.5</td>
<td>93.5</td>
</tr>
<tr>
<td>African-American</td>
<td>2.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Other</td>
<td>2.1</td>
<td>2.1</td>
</tr>
</tbody>
</table>
P-2 STAR
5-year Predicted Risk of Breast Cancer among Participants at Entry

Gail model risk score
P-2 STAR
First-Degree Relatives with Breast Cancer

- None: 29%
- 1: 52%
- 2: 16%
- 3+: 3%
P-2 STAR

Prior Hysterectomy 51.5% (10,027)
<table>
<thead>
<tr>
<th></th>
<th>LCIS</th>
<th>Atypical Hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number</td>
<td>1,789</td>
<td>4,426</td>
</tr>
<tr>
<td>% of Randomized</td>
<td>9.2</td>
<td>22.7</td>
</tr>
</tbody>
</table>
RESULTS
P-2 STAR
Average Annual Rate and Number of Invasive Breast Cancers

RR = 1.02, 95% CI: 0.82 to 1.28

Av Ann Rate per 1000

<table>
<thead>
<tr>
<th></th>
<th>Gail Model Projection</th>
<th>TAM</th>
<th>Raloxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td># of events</td>
<td>312*</td>
<td>163</td>
<td>168</td>
</tr>
</tbody>
</table>

* # of events
P-2 STAR
Cumulative Incidence of Invasive Breast Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At Risk by Year</th>
<th># of Events</th>
<th>Rate/1000 at 6 yrs.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>9726 6653 809</td>
<td>163</td>
<td>25.1</td>
<td>0.83</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>9745 6703 833</td>
<td>168</td>
<td>24.8</td>
<td></td>
</tr>
</tbody>
</table>

Cumulative Incidence (per 1000)
P-2 STAR
Average Annual Rate and Number of Invasive Breast Cancers by 5-year Gail Model Risk

Percent in 5 Years

<table>
<thead>
<tr>
<th>Percent in 5 Years</th>
<th>Tamoxifen</th>
<th>Raloxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>32</td>
<td>44</td>
</tr>
<tr>
<td>3 to 5</td>
<td>61</td>
<td>47</td>
</tr>
<tr>
<td>5+</td>
<td>70</td>
<td>77</td>
</tr>
</tbody>
</table>
P-2 STAR
Tumor Size (cm) of Invasive Cancers

- <1 cm: 30% Tamoxifen, 37% Raloxifene
- 1.1 to 3 cm: 61% Tamoxifen, 55% Raloxifene
- >3 cm: 9% Tamoxifen, 8% Raloxifene
P-2 STAR
Nodal Status of Invasive Cancers

Tamoxifen
Raloxifene

Percent

76
80

24
20

Negative
Positive
P-2 STAR
Average Annual Rate And Number Of Non-invasive (In Situ) Cancers

Relative risk = 1.40
95% Confidence Interval: 0.98 to 2.00

Av Ann Rate per 1000

TAM

Raloxifene

57*

80

* # of events
P-2 STAR
Cumulative Incidence of Non-Invasive Breast Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At Risk by Year</th>
<th># of Events</th>
<th>Rate/1000 at 6 yrs.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 3 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>9726 6633 805</td>
<td>57</td>
<td>8.1</td>
<td>0.052</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>9745 6667 828</td>
<td>80</td>
<td>11.6</td>
<td></td>
</tr>
</tbody>
</table>
Normal Duct

Atypical Hyperplasia

In Situ Cancer

Invasive Cancer
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th># of Events</th>
<th>Rate per 1000</th>
<th>Risk Ratio</th>
<th>RR 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAM  RAL</td>
<td>TAM  RAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCIS</td>
<td>30  44</td>
<td>0.79  1.16</td>
<td>1.46</td>
<td>0.90-2.41</td>
</tr>
<tr>
<td>LCIS</td>
<td>21  29</td>
<td>0.56  0.76</td>
<td>1.37</td>
<td>0.76-2.54</td>
</tr>
<tr>
<td>Mixed</td>
<td>6  7</td>
<td>0.16  0.18</td>
<td>1.16</td>
<td>0.33-4.18</td>
</tr>
<tr>
<td>Total</td>
<td>57  80</td>
<td>1.51  2.11</td>
<td>1.40</td>
<td>0.98-2.00</td>
</tr>
</tbody>
</table>
P-2 STAR
Average Annual Rate and Number of Invasive Breast Cancers by History of Atypical Hyperplasia and Lobular Carcinoma \textit{in Situ}
P-2 STAR

Average Annual Rate and Number of Uterine Cancers

Av Ann Rate per 1000

RR = 0.62, 95% CI: 0.35 to 1.08

* # of events
# P-2 STAR: Hysterectomy* and Endometrial Hyperplasia

<table>
<thead>
<tr>
<th></th>
<th>Tam #</th>
<th>Ral #</th>
<th>Risk Ratio (RR)</th>
<th>RR 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy*</td>
<td>244</td>
<td>111</td>
<td>0.44</td>
<td>0.35-0.56</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>84</td>
<td>14</td>
<td>0.16</td>
<td>0.09-0.29</td>
</tr>
<tr>
<td>with atypia</td>
<td>12</td>
<td>1</td>
<td>0.08</td>
<td>0.00-0.55</td>
</tr>
<tr>
<td>without atypia</td>
<td>72</td>
<td>13</td>
<td>0.18</td>
<td>0.09-0.32</td>
</tr>
</tbody>
</table>

* Among women not diagnosed with uterine cancer
P-2 STAR
Cumulative Incidence of Uterine Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At Risk by Year</th>
<th># of Events</th>
<th>Rate/1000 at 6 yrs.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>4732</td>
<td>3106</td>
<td>367</td>
<td>14.7</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>4712</td>
<td>3219</td>
<td>408</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Cumulative Incidence (per 1000)

Time Since Randomization (months)
P-2 STAR
Cumulative Incidence of Thromboembolic Events

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At Risk by Year</th>
<th># of Events</th>
<th>Rate/1000 at 6 yrs.</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>9726 6682 814</td>
<td>141 21.0</td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>9745 6764 836</td>
<td>100 16.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P-value= 0.01
P-2 STAR
Average Annual Rate and Number of Strokes

<table>
<thead>
<tr>
<th></th>
<th>TAM</th>
<th>Raloxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Av Ann Rate per 1000</td>
<td>53*</td>
<td>51</td>
</tr>
</tbody>
</table>

* # of events
P-2 STAR

Average Annual Rates of Cataracts

RR = 0.79; 95% CI 0.68 – 0.92

- TAM: 394*
- Raloxifene: 313

* # of events
### P-2 STAR
**Number of Osteoporotic Fractures by Site and Treatment Group**

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Tamoxifen #</th>
<th>Raloxifene #</th>
<th>Risk Ratio (RR)</th>
<th>RR 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>26</td>
<td>23</td>
<td>0.88</td>
<td>0.48-1.60</td>
</tr>
<tr>
<td>Spine</td>
<td>53</td>
<td>52</td>
<td>0.98</td>
<td>0.65-1.46</td>
</tr>
<tr>
<td>Radius (Colles’)</td>
<td>27</td>
<td>23</td>
<td>0.85</td>
<td>0.46-1.53</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>98</td>
<td>0.92</td>
<td>0.69-1.22</td>
</tr>
</tbody>
</table>
P-2 STAR

QOL Summary

- No significant difference in primary QOL endpoints; minimal symptom severity
- Symptom profile: small differences slightly favoring raloxifene
- Sexual function slightly favors tamoxifen
- Decision to take one or the other can be assisted by patient-reported outcomes
P-2 STAR
Summary

• Raloxifene is as effective as tamoxifen in the prevention of primary invasive breast cancer

• Raloxifene is less effective than tamoxifen in the prevention of non-invasive breast cancer (LCIS & DCIS)

• Compared to tamoxifen, raloxifene use results in:
  – Fewer thromboembolic events
  – Fewer endometrial cancers and
  – Fewer cataracts
STAR
Study of Tamoxifhen And Raloxifene
Risk-Eligible Postmenopausal Women

STRATIFICATION
- Age
- Relative Risk
- Race
- History of LCIS

Raloxifene
60 mg / day
x 5 years
+
Letrozole Placebo
x 5 years

Letrozole
2.5 mg / day
x 5 years
+
Raloxifene Placebo
x 5 years
Risk-Eligible Postmenopausal Women

STRATIFICATION
- Age
- Relative Risk
- Race
- History of LCIS

Raloxifene
60 mg / day
x 5 years
+
Letrozole Placebo
x 5 years

Letrozole
2.5 mg / day
x 5 years
+
Raloxifene Placebo
x 5 years