Endocrine Therapy in Premenopausal Breast Cancer

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US Oncology
Ovarian Ablation or Suppression vs. Not in ER+ or ER UK Breast Cancer

**Recurrence**
- Control: 31.1%
- Ovarian ablation or suppression: 44.7%

15-year gain: 3.3% (SE 1.9)
Logrank 2p = 0.00001

**Breast Cancer Mortality**
- Control: 34.9%
- Ovarian ablation or suppression: 32.2%

15-year gain: 3.3% (SE 2.0)
Logrank 2p = 0.004

Lancet. 2005;365:1687
International Breast Cancer Study Group
Trial VIII Node Neg 5yr DFS

IBCSG. J Natl Cancer Inst 2003;95:1833
# Tamoxifen Efficacy Does Not Differ Significantly According to Patient Age

**Table 1.** Five Years of Tamoxifen in ER-Positive or ER-Unknown Breast Cancer by Age: Early Breast Cancer Trialists’ Collaborative Group Overview Analysis

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Breast Cancer Recurrence Rate</th>
<th></th>
<th>Breast Cancer Death Rate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Annual Risk Ratio ± SE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For all age groups</td>
<td>0.59 ± 0.03</td>
<td></td>
<td>0.66 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>0.56 ± 0.10</td>
<td></td>
<td>0.61 ± 0.12</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>0.71 ± 0.07</td>
<td></td>
<td>0.76 ± 0.09</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>0.66 ± 0.05</td>
<td></td>
<td>0.76 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>0.55 ± 0.05</td>
<td></td>
<td>0.65 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>≥ 70</td>
<td>0.49 ± 0.12</td>
<td></td>
<td>0.63 ± 0.15</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Reproduced with permission.7
Abbreviation: ER, estrogen receptor.

OA/OS in Premenopausal ESBC Patients

• Does OA/OS add to standard tamoxifen in premenopausal ER+ ESBC pts?
Chemoendocrine Therapy for Premenopausal Women
E5188 INT 0101

CAF

PREMENOPAUSAL
Receptor-positive
Node-positive
n=1503

< 35 10%
35-39 19%
>39 71%

CAF -- Goserelin (Z) X 5 y
CAF -- Goserelin (Z) + Tamoxifen (T) X 5 y

Disease-Free Survival for Women Under 40 Years
E5188 INT 0101

9 yr DFS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAF</td>
<td>48%</td>
</tr>
<tr>
<td>CAFZ</td>
<td>55%</td>
</tr>
<tr>
<td>CAFZT</td>
<td>64%</td>
</tr>
</tbody>
</table>
Meta-analysis of LHRH agonists as adjuvant treatment in premenopausal patients with ER+ breast cancer: Recurrence risk by age

- \( \leq 35 \) years: HR 0.66
- 35-39 years: HR 0.77
- 40-44 years: HR 0.96
- 45-49 years: HR 1.03
- \( \geq 50 \) years: HR 0.85

N=9022

Significant interaction for recurrence of age for addition of LHRH agonist to chemotherapy with or without tamoxifen (p=0.046)

Lancet. 2007;369:1714
Amenorrhea and Prognosis

- Evaluation of 10 trials to assess benefit of drug-induced amenorrhea

- 9/10 trials had increased relapse free survival when amenorrhea achieved, hazard ratio 0.56

- Drug-induced amenorrhea associated with a 44% reduction in relapse.

del Mastro et al., NEJM 1995;333:596-597
NSABP B-30: Adjuvant TAC, AC/T, AT
OS and DFS According to Amenorrhea

HR in ER+: 0.52 (p=0.002)  
HR in ER+: 0.51 (p <0.001)

Cancer Care Ontario
Evidence-based recommendation

Adjuvant Ovarian Ablation in the Treatment of Premenopausal Women with Early Stage Breast Cancer

July 6, 2010

ASCO has endorsed recommendations
For premenopausal women with early stage invasive breast cancer: OA should not be routinely added to systemic therapy with chemotherapy, tamoxifen, or the combination of tamoxifen and chemotherapy.
SOFT Trial (BIG 2-02, IBCSG 24-02)

Premenopausal patients

ER $\geq 10\%$ and/or PgR $\geq 10\%$

Oestradiol in the premenopausal range either after CT or without CT

Randomise

$T \times 5$ years

OF$S + T \times 5$ years

OF$S + E \times 5$ years

Target sample size: 3,000 patients

Randomisation within a 6-month evaluation period after end of CT, or within 12 weeks after definitive surgery for patients with no CT

Stratified by CT/no CT

$T =$ tamoxifen; $E =$ exemestane; OF$S =$ ovarian function suppression; CT = chemotherapy
Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer

## Characteristics of Patients in TEXT and SOFT, Overall and According to Trial and Chemotherapy Stratum*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No-Chemotherapy Cohorts</th>
<th>Chemotherapy Cohorts†</th>
<th>Overall (N = 4690)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEXT (N = 1053)</td>
<td>SOFT (N = 943)</td>
<td>TEXT (N = 1607)</td>
</tr>
<tr>
<td>Age at randomization — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35 yr</td>
<td>41 (3.9)</td>
<td>14 (1.5)</td>
<td>191 (11.9)</td>
</tr>
<tr>
<td>35–39 yr</td>
<td>123 (11.7)</td>
<td>68 (7.2)</td>
<td>289 (18.0)</td>
</tr>
<tr>
<td>40–49 yr</td>
<td>768 (72.9)</td>
<td>690 (73.2)</td>
<td>1048 (65.2)</td>
</tr>
<tr>
<td>≥50 yr</td>
<td>121 (11.5)</td>
<td>171 (18.1)</td>
<td>79 (4.9)</td>
</tr>
<tr>
<td>Lymph-node status — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>835 (79.3)</td>
<td>865 (91.7)</td>
<td>542 (33.7)</td>
</tr>
<tr>
<td>Positive</td>
<td>218 (20.7)</td>
<td>78 (8.3)</td>
<td>1065 (66.3)</td>
</tr>
<tr>
<td>Tumor size — no. (%)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2 cm</td>
<td>847 (80.4)</td>
<td>800 (84.8)</td>
<td>738 (45.9)</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>203 (19.3)</td>
<td>139 (14.7)</td>
<td>844 (52.5)</td>
</tr>
<tr>
<td>HER2 positive — no. (%)</td>
<td>54 (5.1)</td>
<td>30 (3.2)</td>
<td>272 (16.9)</td>
</tr>
</tbody>
</table>

Study Schemas (Total N=4690)

Combined analysis planned because of low event rate
Improved DFS with Exemestane + OFS vs Tamoxifen + OFS

Difference 3.8% at 5 years

5-yr DFS
Exemestane+OFS (N=2346) 91.1%
Tamoxifen+OFS (N=2344) 87.3%

Percent Alive and Disease-Free

Years since Randomization

Events HR 95% CI P
E+OFS 216 0.72 0.60-0.85 0.0002
T+OFS 298

No. Patients
E+OFS T+OFS
All Patients 2346 2344 91.1 87.3

Cohort
No chemotherapy, TEXT 526 527 96.1 93.0
No chemotherapy, SOFT 470 473 95.8 93.1
Chemotherapy, TEXT 806 801 89.8 84.6
Prior chemotherapy, SOFT 544 543 84.3 80.6

Lymph Node Status
Negative 1362 1350 95.1 91.6
Positive 984 994 85.5 81.4

5.7 years median follow-up
Some women may have excellent prognosis with highly-effective endocrine therapy alone: >97% breast-cancer free at 5 years when treated with exemestane + OFS.
# Selected Adverse Events

<table>
<thead>
<tr>
<th>CTCAE v3.0</th>
<th>Exemestane+OFS (N=2318)</th>
<th>Tamoxifen+OFS (N=2325)</th>
</tr>
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<tbody>
<tr>
<td>Depression</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Depression</td>
<td>50%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Depression</td>
<td>50%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>89%</td>
<td>11%</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>76%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>39%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>25%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Fracture</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Fracture</td>
<td>6.8%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Fracture</td>
<td>5.2%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Cardiac ischemia/infarction</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Cardiac ischemia/infarction</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Cardiac ischemia/infarction</td>
<td>0.3%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Thrombosis/embolism</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Thrombosis/embolism</td>
<td>1.0%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Thrombosis/embolism</td>
<td>2.2%</td>
<td>1.9%</td>
</tr>
<tr>
<td>CNS ischemia</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>CNS ischemia</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>CNS ischemia</td>
<td>0.3%</td>
<td>0.1%</td>
</tr>
<tr>
<td>CNS bleeding</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>CNS bleeding</td>
<td>0.6%</td>
<td>N=1</td>
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<tr>
<td>CNS bleeding</td>
<td>0.9%</td>
<td>0.1%</td>
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<tr>
<td>Hot flushes/flushes</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Hot flushes/flushes</td>
<td>92%</td>
<td>10%</td>
</tr>
<tr>
<td>Hot flushes/flushes</td>
<td>93%</td>
<td>12%</td>
</tr>
<tr>
<td>Sweating</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
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<tr>
<td>Sweating</td>
<td>55%</td>
<td>--</td>
</tr>
<tr>
<td>Sweating</td>
<td>59%</td>
<td>--</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>52%</td>
<td>--</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>47%</td>
<td>--</td>
</tr>
<tr>
<td>Libido decrease</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Libido decrease</td>
<td>45%</td>
<td>--</td>
</tr>
<tr>
<td>Libido decrease</td>
<td>41%</td>
<td>--</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>31%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>26%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>13%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>18%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>
Is OFS + AI The New Standard of Care?

- Statistically significant difference in DFS, but not OS
- Absolute improvement in risk of distant recurrence = 2%
- Toxicity was modestly more severe with AI than tamoxifen, even when both added to OFS
- BUT, not clear if tamoxifen + OFS is superior to tamoxifen, and there are major differences in toxicity between tamoxifen alone and OFS + AI

Eric Winer, MD, ASCO, 2014
What To Consider When You Go Home (1)

- Given the greater toxicity of OFS + AI, and the fact that this toxicity extends for 5 years, caution is needed.

- We need results of OFS + tamoxifen vs tamoxifen alone from SOFT.

- Inconsistency with ABCSG 12 is puzzling and should make us more cautious.
Primary End Point: Disease-Free
No Significant Difference Between TAM and ANA

A statistically significant improvement in survival for OS + tam over OS + AI in this study has been reported.

HR 1.75  p=0.02  Lancet, 2011  62 mos f/u

<table>
<thead>
<tr>
<th></th>
<th>No. of events</th>
<th>Hazard ratio (95% CI) vs TAM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>72/903</td>
<td>1.096 (0.78 to 1.53)</td>
<td>.593</td>
</tr>
<tr>
<td>TAM</td>
<td>65/900</td>
<td></td>
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</tr>
</tbody>
</table>

Patients at risk

<table>
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<tr>
<th></th>
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<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
<th>72</th>
<th>84</th>
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<tbody>
<tr>
<td>TAM</td>
<td>900</td>
<td>840</td>
<td>736</td>
<td>580</td>
<td>439</td>
<td>264</td>
<td>141</td>
<td>60</td>
</tr>
<tr>
<td>ANA</td>
<td>903</td>
<td>849</td>
<td>743</td>
<td>558</td>
<td>436</td>
<td>271</td>
<td>151</td>
<td>59</td>
</tr>
</tbody>
</table>

Eric Winer, MD, ASCO, 2014
What To Consider When You Go Home (2)

- Hold off on routine use of OFS + Al as standard approach in **all** patients
- Acknowledge that you may recommend switch in the future, as we learn more
- **Consider** use of OFS + Al in high risk patients (e.g. stage IIB/III and grade 3/high Ki-67)
- IF OFS + Al is started and side effects are intolerable, switch to tamoxifen
- Watch for more data

Eric Winer, MD, ASCO, 2014
Goserelin Plus Anastrozole in Premenopausal, Receptor Positive, Metastatic Breast Cancer

Within 6 months, 3 of 32 women had premenopausal estradiol levels

1 Carlson RW, Schurman CM, Rivera E. Proc ASCO:Abst 1030,2006
Substantial Recurrences after 5 years of Tamoxifen Pre/Peri, ER+ vs Postmenopausal

18% @ 5 y
35% @ 15 yr

≈ 5 years tamoxifen vs. Not RECURRENT
Pre/Peri, ER+
15–y gain 9.5% (SE 1.8)
Logrank 2p < 0.00001

Control 45.0%

≈ 5 years tamoxifen
35.5%

15–y gain 14.8% (SE 1.5)
Logrank 2p < 0.00001

Control 47.6%

≈ 5 years tamoxifen
32.8%

Adj Tamoxifen To Offer More (aTTOM)

Women with invasive tumors who received ≥ 4 years of tamoxifen
N = 6934

RANDOMIZE

Discontinue Tamoxifen 20 mg PO qd
Tamoxifen 20 mg PO qd × 5 additional years

Adj Tamoxifen Longer Ag Shorter (ATLAS)

Pre and Postmenopausal women with invasive tumors
N= 10,543

RANDOMIZE

Tamoxifen 20 mg PO qd × 5 years
Tamoxifen 20 mg PO qd × 10 years
ATLAS: 10 vs. 5 Years of Tamoxifen
N=6,846

Recurrence
- Continue tamoxifen to 10 years
- Stop tamoxifen at 5 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

Breast Cancer Mortality

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

Davies et al. Lancet 2012
### 10 yrs vs 5 yrs BREAST CANCER MORTALITY IN ER+ rate ratio* by period in aTTom and ATLAS

|                  | 10 yrs tam. vs 5: aTTom trial  
|------------------|---------------------------------|
|                  | (n=6934 ER+/UK)                 | 10 yrs tam. vs 5: ATLAS trial*  
|                  |                                 | (n=10,543 ER+/UK)               |
|                  | 10 yrs tam. vs 5: aTTom & ATLAS combined  
|                  |                                 | (n=17,477 ER+/UK)               |
| years 5-9        | 1.08 (0.85-1.38)                | 0.92 (0.77-1.09)                |
|                  | 0.97 (0.84-1.15)                | 0.97 (0.84-1.15)                |
| years 10+        | 0.75† (0.63-0.90)               | 0.75 § (0.63-0.90)              |
|                  | 0.75† (0.65-0.86)               | 0.75† (0.65-0.86)               |
| All years        | 0.88‡ (0.74-1.03)               | 0.83‡ (0.73-0.94)               |
|                  | 0.85‡ (0.77-0.94)               | 0.85‡ (0.77-0.94)               |

*Inverse-variance-weighted estimate of the effect in ER+.

†p=0.007
‡p=0.1
§p=0.002
†p=0.004
†p=0.00004
†p=0.001

MA.17: Trial Design

- Eligibility criteria: PM, HR+/?, recurrence-free, 4.5-6 years’ prior TAM, ECOG PS 0-2
- Primary end point: DFS (ipsilateral, chest wall, local, metastatic, contralateral new)
- Secondary end points: OS, rate of CBC, safety, QOL
- Substudies: BMD/bone markers, lipid profile

Hazard of Recurrence in Women on Letrozole vs. Placebo (MA17)

- Benefit of letrozole seen throughout study period (up to 4 years)
- Curves continue to diverge over time
- Risk of recurrence on placebo increased over time – 3% in year 9

Letrozole 42% reduction recurrence
40% reduction distant recurrence

*Figure 1. Hazard rates for events in disease-free survival for patients randomized on trial MA.17 to either letrozole or placebo.*
Kaplan–Meier curves for DFS by treatment and menopausal status.

Pre-menopausal
Abs Diff in 4 year
DFS=10.1%
HR=0.25
P<0.0001

Post-menopausal
Abs Diff in 4 year
DFS=3.3%
HR=0.69
P=0.0008

STEPP Ki-67 LI by Treatment
BIG 1-98
Preoperative AI vs tamoxifen + Goserelin in Premenopausal BC Pts: STAGE Study

Medical Oncologists: Methods to Assess Menopause

• Prior bilateral oophorectomy
• Age $\geq$ 60 years

• Age < 60 and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene (or raloxifene), OFS, AND FSH and estradiol in the postmenopausal range

• If taking tamoxifen or toremifene and age < 60, then FSH and estradiol in the postmenopausal range (Be careful!!)

NCCN guidelines v.1.2012
Recommendations

Women who are pre- or perimenopausal

Options:

IA. Tamoxifen for an initial duration of 5 years.

IB. After 5 years, women should receive additional therapy based on menopausal status.

IB1. If women are pre- or perimenopausal, or if menopausal status is unknown or cannot be determined, they should be offered continued tamoxifen for a total duration of 10 years. (Type: Evidence-Based, Evidence Quality: High, Strength of Recommendation: Strong)

Recommendations

pre- or perimenopausal, continued

IB2. If women have become definitively postmenopausal, they should be offered continued tamoxifen for a total duration of 10 years or switching to up to 5 years of an aromatase inhibitor (AI) for a total duration of up to 10 years of adjuvant endocrine therapy. (*Type:* Evidence-Based, *Evidence Quality for tamoxifen:* High, *Evidence Quality for AI:* High; *Strength of Recommendation:* Strong)

Endocrine Therapy for Premenopausal HR+ EBC Patients: Summary

• Endocrine therapy of utmost importance in HR+ premenopausal EBC

• Premenopausal HR+ pts benefit from amenorrhea in addition to tamoxifen - US/Canada guidelines do not recommend addition of LHRH agonist or BSO – SOFT Trial SABCS 2014

• LHRH agonist plus AI for premenopausal high risk pts

• Prolonged endocrine therapy with 10 years of tamoxifen in pre- or perimenopausal pts or with AI following tamoxifen of benefit in postmenopausal pts (N- and N+)
Prevention of Early Menopause Study (POEMS)-S0230

Phase III trial (Prevention of Early Menopause Study [POEMS]-SWOG S0230) of LHRH analog during chemotherapy (CT) to reduce ovarian failure in early-stage, hormone receptor-negative breast cancer: An international Intergroup trial of SWOG, IBCSG, ECOG, and CALGB (Alliance)


ASCO 2014
POEMS/S0230 Schema

Premenopausal Stage I, II, IIIA ER-/PR- Breast Cancer Under Age 50

Stratified by age and chemotherapy regimen

RANDOMIZATION

Standard cyclophosphamide containing (neo)adjuvant chemotherapy

Primary endpoint:
Ovarian failure at 2 yrs, ie,
No menses and
Postmenopausal FSH
n=135
22% vs 8% with goserelin
HR=0.30, p=0.04

Standard cyclophosphamide containing (neo)adjuvant chemotherapy + goserelin

Goserelin 3.6mg SC every 4 weeks starting 1 week before chemoRx

Moore, H et al, ASCO 2014

257 Patients Randomized
POEMS Disease-free Survival

**Gosereclin vs Standard**

- **4-yr OS**: 92% gosereclin vs 82%
  - **HR = 0.43, p = 0.05**

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**Regression Covariates**

<table>
<thead>
<tr>
<th>Covariates</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for age and regimen</td>
<td>0.47 (0.24-0.95)</td>
<td>.04</td>
</tr>
<tr>
<td>Adjusted for age, regimen, &amp; stage</td>
<td>0.49 (0.24-0.97)</td>
<td>.04</td>
</tr>
</tbody>
</table>

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Moore, H et al, ASCO 2014