Breast Cancer Abstracts: Prevention & Adjuvant Therapy

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Disclosure

- Potential Conflicts of Interest:
  - Principal Investigator:
    - Novartis
    - ImClone
    - Exelesis
  - Sub-Investigator:
    - GHSU MB-CCOP

- Speaker’s Bureau:
  - Novartis
  - GlaxoSmithKline

“We do not know what we mean by cure because there is a great difference between cure and long-term survival. “

Dr. Arthur Holleb
American Cancer Society
Breast Cancer ASCO Abstracts: Prevention & Adjuvant Therapy

**Prevention:**
- Abs # LBA-504- Goss, PE et al. (NCIC MAP.3)

**Adjuvant Therapy:**
- Abs# 1004- Budd, GT et al. (SWOG S0221)
- Abs# LBA-1003- Whelan, TJ et al. (NCIC MA.20)
- ACOSOG Z11- Giuliano, AE et al. *(JAMA 2011)*
- Abs# 1000- Schneider, BP et al. *(ECOG E5103)*
Exemestane for Breast-Cancer Prevention in Postmenopausal Women

Paul E. Goss, M.D., Ph.D., James N. Ingle, M.D., José E. Alés-Martínez, M.D., Ph.D., Angela M. Cheung, M.D., Ph.D., Rowan T. Chlebowski, M.D., Ph.D., Jean Wactawski-Wende, Ph.D., Anne McTiernan, M.D., John Robbins, M.D., Karen C. Johnson, M.D., M.P.H., Lisa W. Martin, M.D., Eric Winquist, M.D., Gloria E. Sarto, M.D., Judy E. Garber, M.D., Carol J. Fabian, M.D., Pascal Pujol, M.D., Elizabeth Maunsell, Ph.D., Patricia Farmer, M.D., Karen A. Gelmon, M.D., Dongsheng Tu, Ph.D., Harriet Richardson, Ph.D., for the NCIC CTG MAP.3 Study Investigators

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MAP.3 Study Overview

• In postmenopausal women at increased risk for breast cancer, exemestane reduced the annual incidence of invasive breast cancer by 65% after a median follow-up of only 3 years.

• Exemestane caused no serious toxic effects and only minimal changes in quality of life.
Cumulative Incidence of Invasive Breast Cancer.


Hazard Ratios for the Development of Invasive Breast Cancer, According to Planned Subgroup Analysis.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.35 (0.18–0.70)</td>
<td>0.24</td>
</tr>
<tr>
<td>Current estrogen use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.12 (0.09–0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>No</td>
<td>0.45 (0.21–0.91)</td>
<td></td>
</tr>
<tr>
<td>Gill risk score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2%</td>
<td>0.34 (0.09–1.17)</td>
<td>0.27</td>
</tr>
<tr>
<td>≥2%</td>
<td>0.36 (0.16–0.80)</td>
<td>0.28</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60 yr</td>
<td>0.29 (0.12–0.73)</td>
<td>0.03</td>
</tr>
<tr>
<td>&lt;60 yr</td>
<td>0.44 (0.13–1.27)</td>
<td>0.16</td>
</tr>
<tr>
<td>Body-mass index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>0.35 (0.09–1.29)</td>
<td>0.09</td>
</tr>
<tr>
<td>25–30</td>
<td>0.31 (0.10–0.94)</td>
<td>0.04</td>
</tr>
<tr>
<td>≥30</td>
<td>0.41 (0.13–1.30)</td>
<td>0.10</td>
</tr>
<tr>
<td>Prior ADH, ALH, or LCIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.61 (0.20–1.82)</td>
<td>0.50</td>
</tr>
<tr>
<td>No</td>
<td>0.26 (0.11–0.64)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### Incidence of Invasive and Preinvasive Breast Events by Treatment Group

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Exemestane (N=220)</th>
<th>Aromatase (N=220)</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>Incidence (%)</td>
<td>No. of Cases</td>
<td>Incidence (%)</td>
<td></td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>22</td>
<td>0.19</td>
<td>32</td>
<td>0.25</td>
</tr>
<tr>
<td>ER-positive</td>
<td>7</td>
<td>0.12</td>
<td>27</td>
<td>0.46</td>
</tr>
<tr>
<td>ER-negative</td>
<td>4</td>
<td>0.07</td>
<td>5</td>
<td>0.00</td>
</tr>
<tr>
<td>PR-positive</td>
<td>5</td>
<td>0.02</td>
<td>20</td>
<td>0.24</td>
</tr>
<tr>
<td>PR-negative</td>
<td>6</td>
<td>0.10</td>
<td>12</td>
<td>0.20</td>
</tr>
<tr>
<td>HER2/neu-positive</td>
<td>6</td>
<td>0.03</td>
<td>6</td>
<td>0.13</td>
</tr>
<tr>
<td>HER2/neu-negative</td>
<td>10</td>
<td>0.17</td>
<td>26</td>
<td>0.44</td>
</tr>
<tr>
<td>HER2/neu unknown</td>
<td>1</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>T stage 1</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>T stage 2</td>
<td>0</td>
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<td>1</td>
<td>NA</td>
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<td>T stage 3</td>
<td>0</td>
<td>NA</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>T stage 4</td>
<td>0</td>
<td>NA</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>N stage 0</td>
<td>22</td>
<td>0.19</td>
<td>10</td>
<td>0.11</td>
</tr>
<tr>
<td>N stage I</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>N stage II</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>N stage III</td>
<td>0</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>OCUS</td>
<td>9</td>
<td>0.05</td>
<td>24</td>
<td>0.24</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>30</td>
<td>0.15</td>
<td>44</td>
<td>0.17</td>
</tr>
<tr>
<td>APH, ALH, and LCIS</td>
<td>4</td>
<td>0.07</td>
<td>12</td>
<td>0.20</td>
</tr>
</tbody>
</table>


*This table has been adapted from the original data with permission from the authors. Women with prior OCIS at baseline were excluded.

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### Side Effects during Treatment, According to Severity

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Exemestane (N=220)</th>
<th>Aromatase (N=220)</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>Incidence (%)</td>
<td>No. of Cases</td>
<td>Incidence (%)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>104</td>
<td>31</td>
<td>115</td>
<td>36</td>
</tr>
<tr>
<td>Fatigue</td>
<td>87</td>
<td>18</td>
<td>95</td>
<td>19</td>
</tr>
<tr>
<td>Nausea</td>
<td>147</td>
<td>16</td>
<td>159</td>
<td>16</td>
</tr>
<tr>
<td>Musculoskeletal arthritis</td>
<td>102</td>
<td>30</td>
<td>109</td>
<td>29</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>77</td>
<td>32</td>
<td>115</td>
<td>36</td>
</tr>
<tr>
<td>Headache</td>
<td>223</td>
<td>63</td>
<td>225</td>
<td>51</td>
</tr>
<tr>
<td>Dysintension</td>
<td>145</td>
<td>35</td>
<td>116</td>
<td>31</td>
</tr>
<tr>
<td>Nausea</td>
<td>127</td>
<td>10</td>
<td>128</td>
<td>10</td>
</tr>
<tr>
<td>Pain</td>
<td>126</td>
<td>27</td>
<td>139</td>
<td>31</td>
</tr>
<tr>
<td>Fatigue</td>
<td>67</td>
<td>12</td>
<td>71</td>
<td>14</td>
</tr>
<tr>
<td>Nausea</td>
<td>147</td>
<td>14</td>
<td>159</td>
<td>15</td>
</tr>
<tr>
<td>Musculoskeletal arthritis</td>
<td>102</td>
<td>29</td>
<td>109</td>
<td>29</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>77</td>
<td>32</td>
<td>115</td>
<td>36</td>
</tr>
</tbody>
</table>

* The grades of severity are based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0, as follows: 1: mild, 2: moderate, 3: severe, 4: life-threatening or disabling, 5: death. * indicates statistically significant difference. (c): calculated because of small number of events. PE: progesterone receptor.

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Conclusions

• Exemestane significantly reduced invasive breast cancers in postmenopausal women who were at moderately increased risk for breast cancer.

• During a median follow-up period of 3 years, exemestane was associated with no serious toxic effects and only minimal changes in health-related quality of life.

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• **Prevention:**
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• **Adjuvant Therapy:**
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  – Abs# 1000- Schneider, BP et al. (ECOG E5103)
First analysis of SWOG S0221: A phase III trial comparing chemotherapy schedules in high-risk early breast cancer.


Abs# 1004

AC+G Regimen: Background (1)

- U. Washington Adjuvant Experience
  - Dox 24 mg/m2/wk + Cyclo 60 mg/m2/d po + GCSF days 2-7
  - 85% 5 year disease-free survival in node+ breast cancer when followed by weekly paclitaxel

- S9625: Locally Advanced SWOG Phase II
  - 26% pCR rate to neo-adjuvant AC+G (without taxane)

- S0012: Locally Advanced SWOG Phase III
  - AC+G vs AC q 3 wk x 5, followed by weekly paclitaxel
  - 24% pCR vs 21% overall (p=0.45)
  - 27% pCR vs 12% in inflammatory cancer (p=0.06)
AC+G Regimen: Background

- Some features of “Metronomic Chemotherapy”
  - Possible anti-angiogenic as well as cytotoxic effects
  - Frequent, modest doses of cytotoxic chemotherapy
  - But, hematopoietic growth factors required

S0221: Eligibility

- Female or Male (19 males actually enrolled)
- Histologically Proven Stage I-III Invasive Breast Cancer
- “High Risk,” defined as
  - Node+ (N1-3)
  - Any Primary Tumor ≥2 cm
  - Tumor ≥1 cm if
    - ER- and PR-
    - ER+ or PR+ if Recurrence Score ≥26
- HER2+ tumors allowed
  - Trastuzumab given with paclitaxel after 11/15/2006
Stage I-III Breast Cancer

S0221: Schema
2 x 2 Factorial Design

- Doxorubicin 60 mg/m²
  Cyclophosphamide 600 mg/m²
  Peg-filgrastim q 2 weeks x 6
- Paclitaxel 175 mg/m²
  Peg-filgrastim q 2 wks x 6

- Doxorubicin 24 mg/m²
  Cyclophosphamide 60 mg/m² po
  GCSF d2-7 Weekly x 15 weeks
- Paclitaxel 175 mg/m²
  Peg-filgrastim q 2 wks x 6

- Doxorubicin 60 mg/m²
  Cyclophosphamide 600 mg/m²
  Peg-filgrastim q 2 weeks x 6
- Paclitaxel 80 mg/m²
  Weekly x 12

- Doxorubicin 24 mg/m²
  Cyclophosphamide 60 mg/m² po
  GCSF d2-7 Weekly x 15 weeks
- Paclitaxel 80 mg/m²
  Weekly x 12

S0221: Statistical Design

- 3250 pts to be randomized equally to the 4 arms of a 2x2 factorial design
- Primary Endpoint: Disease-free survival (DFS)
  - Power to detect HR 0.82 when comparing each weekly factor to q2 week arms
- First interim analysis (of 6 planned) after 30% of anticipated events
  - Test of efficacy: one-sided p-value ≤ 0.0001
  - Test of “futility”: Lower bound of 99.5% CI for the hazard ratio > 0.82 suggesting a benefit to weekly therapy would not be found
S0221: 1st Interim Analysis

• At the first interim analysis, the prescribed 99.5% confidence interval boundary for futility for the AC+G arm was crossed, excluding the hypothesis that the hazard ratio was 0.82 or better in favor of the AC+G arm.

• No boundary was crossed for the paclitaxel comparison and there was no significant interaction of the two factors.

• DSMC recommended suspending randomization to the AC factor – recommendation accepted by SWOG and NCI

Current Results for AC (ddAC vs. wAC+G)

• Results collapsed over paclitaxel arms
• The arms are balanced for standard prognostic factors
• Results presented:
  – Population characteristics
    • 2716 randomized patients
  – Disease-free survival to date by AC arm
    • 2662 eligible patients with follow-up
  – Major subset analyses
  – Overall survival to date by AC arm
  – Toxicity
    • 2480 patients with complete Toxicity Evaluation
Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Continuous AC+G</th>
<th>AC q 2 weeks x 6</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>1341</td>
<td>1375</td>
<td>2716</td>
</tr>
<tr>
<td>Known ineligible or withdrew consent</td>
<td>21 (1.6%)</td>
<td>33 (2.4%)</td>
<td>54 (2.0%)</td>
</tr>
<tr>
<td>Analyzed</td>
<td>1320</td>
<td>1342</td>
<td>2662</td>
</tr>
<tr>
<td>Black race</td>
<td>155 (11.7%)</td>
<td>147 (11.0%)</td>
<td>302 (11.3%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (years)</td>
<td>50</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Range (years)</td>
<td>21-79</td>
<td>23-86</td>
<td>21-86</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>620 (47.5%)</td>
<td>627 (47.6%)</td>
<td>1247 (47.6%)</td>
</tr>
<tr>
<td>Post</td>
<td>685 (52.5%)</td>
<td>689 (52.4%)</td>
<td>1374 (52.4%)</td>
</tr>
<tr>
<td>Unknown/NA(males)</td>
<td>15</td>
<td>26</td>
<td>41</td>
</tr>
<tr>
<td>Node +</td>
<td>1016 (77.3%)</td>
<td>1016 (76.2%)</td>
<td>2032 (76.7%)</td>
</tr>
<tr>
<td>Node -</td>
<td>298 (22.7%)</td>
<td>318 (23.8%)</td>
<td>616 (23.3%)</td>
</tr>
<tr>
<td>ER-/PR-</td>
<td>431 (32.8%)</td>
<td>442 (33.1%)</td>
<td>873 (33.0%)</td>
</tr>
<tr>
<td>ER+ or PR+</td>
<td>883 (67.2%)</td>
<td>892 (66.9%)</td>
<td>1775 (67%)</td>
</tr>
<tr>
<td>HER2+</td>
<td>231 (17.7%)</td>
<td>243 (18.4%)</td>
<td>474 (18.0%)</td>
</tr>
</tbody>
</table>

S0221: Updated Interim Analysis

Disease-Free Survival by Delivery of AC

- 5-year DFS: AC weekly 79% vs. AC q 2 wk 82%
- HR = 1.15 (95% CI 0.95 - 1.41) AC weekly vs. AC q 2 wk
- p=0.16

AC q 2 weeks x 6 (n=1,342; 183 events)
AC Weekly (n=1,320; 202 events)
DFS Subset Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (Weekly vs. Q 2 week)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.15</td>
<td>0.95 – 1.41</td>
</tr>
<tr>
<td>Receptor Positive</td>
<td>1.14</td>
<td>0.87 – 1.50</td>
</tr>
<tr>
<td>Receptor Negative</td>
<td>1.21</td>
<td>0.89 – 1.63</td>
</tr>
<tr>
<td>Node Negative</td>
<td>1.44</td>
<td>0.85 – 2.42</td>
</tr>
<tr>
<td>Node Positive</td>
<td>1.09</td>
<td>0.88 – 1.36</td>
</tr>
<tr>
<td>HER2 Positive</td>
<td>1.19</td>
<td>0.73 – 1.93</td>
</tr>
</tbody>
</table>

Adjusted for paclitaxel administration

S0221: First Interim Analysis

S0221: Updated Interim Analysis

Overall Survival by Delivery of AC

5-year OS: AC weekly 85% vs. AC q 2 wk 87%
HR = 1.14 (95% CI 0.90 - 1.46)
<table>
<thead>
<tr>
<th></th>
<th>Hemoglobin: AC Segments</th>
<th>WBC: AC Segments</th>
<th>Neutrophils: AC Segments</th>
<th>Platelets: AC Segments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q 2 Week</td>
<td>3 4</td>
<td>3 4</td>
<td>3 4</td>
<td>3 4</td>
</tr>
<tr>
<td>Weekly</td>
<td>9% 0.6%</td>
<td>5% 0.25%</td>
<td>8% 12%</td>
<td>2% 0.8%</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.09</td>
<td>0.6</td>
</tr>
</tbody>
</table>

S0221 Toxicity: First Interim Analysis - 2480 patients

<table>
<thead>
<tr>
<th></th>
<th>Infection – Febrile Neutropenia: AC Segments</th>
<th>Infection – Non-Neutropenic: AC Segments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q 2 Week</td>
<td>3 4</td>
<td>3 4</td>
</tr>
<tr>
<td>Weekly</td>
<td>5% 1%</td>
<td>1.7% 0.25%</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 5: 0.08%</td>
<td>Grade 5: 0.16%</td>
</tr>
</tbody>
</table>
### Mucositis: AC Segments

<table>
<thead>
<tr>
<th></th>
<th>Q 2 Week</th>
<th>Weekly</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Dermatologic/Hand-Foot Syndrome: AC Segments

<table>
<thead>
<tr>
<th></th>
<th>Q 2 Week</th>
<th>Weekly</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15%</td>
<td>2%</td>
</tr>
</tbody>
</table>

### Cardiac: AC Segments

<table>
<thead>
<tr>
<th></th>
<th>Q 2 Week</th>
<th>Weekly</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.9%</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>Grade 5:</td>
<td></td>
<td>0.08%</td>
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</table>

### Cardiac: Both AC and Paclitaxel Segments

<table>
<thead>
<tr>
<th></th>
<th>Q 2 Week</th>
<th>Weekly</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.7%</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>Grade 5:</td>
<td></td>
<td>0.3%</td>
<td></td>
</tr>
</tbody>
</table>
S0221 Toxicty: First Interim Analysis - 2480 patients

• Treatment-Related Deaths: 13/2480
  – Infection: 4
  – Cardiac: 3
  – Pulmonary: 1
  – Multi-organ Failure: 2
  – Sudden Death: 2
  – Liver Failure: 1

• Secondary Leukemia/MDS
  – AC q 2 wk: 11
  – AC+G: 10

S0221 Conclusions

• The toxicities of continuous AC+G and q 2 week AC differ
  – Weekly produces more stomatitis, dermatologic toxicity
  – Q 2 weeks produces more myelosuppression, cardiac toxicity

• Continuous AC+G is not superior to q 2 week AC and is not recommended for routine use

• The optimal dose and schedule of paclitaxel administration warrants determination
  – Changes in dose and schedule can significantly affect the toxicity and efficacy of chemotherapy
S0221: Revised Schema for remaining 534 patients

Stage I-III Breast Cancer

RANDOMIZE

Doxorubicin 60 mg/m2
Cyclophosphamide 600 mg/m2
Peg-filgrastim q 2 weeks x 4

→ Paclitaxel 175 mg/m2
Peg-filgrastim q 2 wks x 6

Doxorubicin 60 mg/m2
Cyclophosphamide 600 mg/m2
Peg-filgrastim q 2 weeks x 4

→ Paclitaxel 80 mg/m2
Weekly x 12

Breast Cancer ASCO Abstracts: Prevention & Adjuvant Therapy

• Prevention:
  – Abs # LBA-504- Goss, PE et al. (NCIC MAP.3)

• Adjuvant Therapy:
  – Abs# 1004- Budd, GT et al. (SWOG S0221)
  – Abs# LBA-1003- Whelan, TJ et al. (NCIC MA.20)
  – ACOSOG Z11- Giuliano, AE et al. (JAMA 2011)
  – Abs# 1000- Schneider, BP et al. (ECOG E5103)
NCIC CTG MA.20:
An intergroup trial of regional nodal irradiation in early breast cancer.


Abs# LBA-1003

NCIC MA.20

• Designed to ask question:
  – Does more regional radiation reduce systemic failure and reduce BC-related mortality?
• Prior trials have shown more axillary surgery does not improve survival outcomes


NCIC MA.20:

MA20 Study Schema: A Phase III Study of Regional Radiation Therapy in Early-Stage Breast Cancer

**Stratify**
- Number of positive nodes (0, 1-3, >3)
- Number of nodes removed (<10, ≥10)
- Type of chemotherapy (i.e., anthracycline, other, none)
- Hormonal therapy (yes, no)
- Treatment center

**Randomize**
- Breast Alone Radiation Therapy
- Breast and Nodal Radiation Therapy

**Inclusion Criteria**
- Invasive, female breast cancer
- Breast conserving surgery plus Level I, II axillary dissection (or SLN only if node negative)
- Systemic therapy with chemotherapy, hormones, or both
- Moderate to high risk of regional recurrence on the basis of:
  - Involved axillary nodes
  - Or if node-negative, patients must have tumors ≥2.0 cm in diameter, have <10 nodes dissected, and have either grade 3 histology, estrogen receptor-negative disease, or the disease present in lymphovascular spaces in the breast

**Planned accrual=1822**
- WBI= 916
- WBI + RNI= 916

**Powered to detect 5% improvement in survival at 5 years**

**Based upon interim results, DSMC advised results to be released**

*Whelan et al. ASCO 2011 LBA1003*
NCIC MA.20 Results

<table>
<thead>
<tr>
<th></th>
<th>WBI only (%)</th>
<th>WBI + RNI (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated LR DFS*</td>
<td>94.5</td>
<td>96.8</td>
<td>.02</td>
</tr>
<tr>
<td>DDFS</td>
<td>87</td>
<td>92.4</td>
<td>.002</td>
</tr>
<tr>
<td>DFS</td>
<td>84</td>
<td>89.7</td>
<td>.003</td>
</tr>
<tr>
<td>OS</td>
<td>90.7</td>
<td>92.3</td>
<td>.07</td>
</tr>
</tbody>
</table>

*identical IBR in each group
67% of recurrences were in the axilla

NCIC MA.20 Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>WBI only (%)</th>
<th>WBI + RNI (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>XRT Dermatitis</td>
<td>40</td>
<td>50</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pneumonitis &gt; grade 2</td>
<td>0.2</td>
<td>1.3</td>
<td>.01</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>4.1</td>
<td>7.3</td>
<td>.004</td>
</tr>
</tbody>
</table>

Whelan et al. ASCO 2011 LBA1003
NCIC MA.20 Conclusions

**Trial Conclusions:**

- RNI, added to WBI increased DFS at 5 yrs with a reduction in both locoregional and distant recurrence
- Trend toward OS benefit
- RNI associated with increased pneumonitis & lympeledema

**Clinical Implications:**

- Pts with 1-3 LN+:
  - RNI needed
  - Not candidates for partial breast XRT
  - Not candidates for hypofractionation
  - May need PMRT
    - Complicates reconstruction
    - More pts treated

**EORTC 22922/10925 asks similar question: (n=4004)**
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- ACOSOG Z11 - Giuliano, AE et al. (*JAMA* 2011)
- Abs# 1000 - Schneider, BP et al. (ECOG E5103)

ACOSOG Z0011

*Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis* 
A Randomized Clinical Trial

Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall L, Morrow M

*JAMA*, 2011 Feb 9;305(6):569-75.
ACOSOG Z0011

• Hypothesis:

SLND alone achieves similar locoregional control and survival as Level I and II ALND for H&E SN node-positive women.

ACOSOG Z0011

• Eligibility: (n=891)
  • Clinical T1 T2 N0 breast cancer
  • H&E-detected metastases in SN (AJCC 5th edition)
  • Lumpectomy with whole breast irradiation
  • Adjuvant systemic therapy by choice

• Ineligibility
  • Third field (nodal irradiation) or APBI
  • Metastases in SN detected by IHC
  • Matted nodes
  • 3 or more involved SN
ACOSOG Z0011

- Target accrual=1900
- Primary endpoint was overall survival as a measure of noninferiority of the experimental arm (i.e. SLND alone)
  - 500 deaths needed for 90% power
- Accrual closed early at DMSC recommendation (n=891)
  - Lower than expected mortality (94 deaths at 6.3 yrs median follow-up)
  - Would take 20+ years to complete at target accrual
- Adjuvant systemic therapy (ctx or endo) given to most women
  - 96% in ALND group
  - 97% in SLND group
- WBI given to most women
  - 88.9% in ALND group
  - 89.6% in SLND group
  - No data on RNI
- Adjusted HR:
  - OS= 0.87 (p= .03)
  - DFS= 0.88 (p= .47)

ACOSOG Z0011 Results

- No significant difference in DFS between patients treated with SLND (83.9%) or ALND (82.2%)
- No significant difference in OS between patients treated with SLND (92.5%) or ALND (91.8%)
- Only older age, ER-, and lack of adjuvant systemic therapy - not operation - were associated with worse OS by multivariable analysis.
ACOSOG Z0011 Conclusions

“In this prospective randomized study SLND alone provided excellent locoregional control and survival comparable to completion ALND.”

“This study does not support the routine use of ALND in early nodal metastatic breast cancer. The role of this operation should be reconsidered.”

Is this practice changing?

<table>
<thead>
<tr>
<th>Z-11</th>
<th>MA-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients randomized</td>
<td>n=891</td>
</tr>
<tr>
<td>cl T1-2 N0</td>
<td>BCT</td>
</tr>
<tr>
<td>SLND only</td>
<td>n=446</td>
</tr>
<tr>
<td>ALND</td>
<td>n=445</td>
</tr>
<tr>
<td>No difference in regional control, DFS, OS</td>
<td>Significant benefit in regional control, DDFS, DFS</td>
</tr>
</tbody>
</table>

* 85% patients with 1-3 positive nodes
Z11 v. MA.20

- MA.20 completed accrual, Z11 did not
  - Z11 still subject Type I error that SLND is inferior to ALND though not likely
  - Not adequately powered to prove hypothesis
- Greater tumor burden in MA.20
- No comment on XRT fields in Z11

- Need more info:
  - MA.20 outcomes data by #LN+ & micromets
  - Z11 outcomes data by extent of nodal disease
  - Z11 XRT fields
  - Both trials- need longer follow-up

Is Z11 or MA.20 practice changing?
Maybe…
- Less surgery ok with cN0 disease
- Regional axillary XRT improves outcomes

Breast Cancer ASCO Abstracts: Prevention & Adjuvant Therapy

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  - Abs# 1000- Schneider, BP et al. (ECOG E5103)
Genetic associations with taxane-induced neuropathy by a genome-wide association study (GWAS) in E5103.


Abs# 1000

ECOG 5103 GWAS Rationale

• Taxane-induced peripheral neuropathy
  – Most common non hematological toxicity
  – Can be severe, irreversible, and function limiting

• Weekly paclitaxel (e.g. E1199) causes highest incidence of neuropathy

• No known predictive biomarkers to predict at-risk populations for neuropathy
ECOG 5103 Schema

Will the addition of bevicizumab to a standard adjuvant chemotherapy regimen of AC-T improve survival outcomes?

ECOG 5103 GWAS study

• Biomarker assessment:
  – N=2204 evaluable
  – Peripheral blood germline DNA analysis
  – Data presented related to
      • CTC v3: grade 2-4 peripheral neuropathy phenotypic data
      • Event: Time to first neuropathy  n=613
  – Median follow-up= 15 months.
ECOG 5103 GWAS study

• Comparison of time to neuropathy to genotypic analysis using standard Cox regression models and corrected for various co-variates
  – ER status, grade, age, tumor laterality, & race

• No statistical difference in time to neuropathy between three arms

ECOG 5103 GWAS study

• Clinical predictors of neuropathy:
  – Advanced age-
    • 12.9% increase with each 10yrs (p=.004)
  – African-American race-
    • HR=2.1 (p=2.3X10^-11)
ECOG 5103 GWAS study

- Missence SNP in RWDD3 increases risk of neuropathy
- RWDD3 involved in sumoylation of cellular factors important in stress response system (e.g. HIF1-a, I-kappa-b)

ECOG 5103 GWAS study

- Other SNPs also noted to have associations with increased risk of neuropathy-
  - **TECTA SNP variant:**
    - wt/wt - 28% risk at 15 mos
    - wt/v - 30% risk at 15 mos
    - v/v - 55% risk at 15 mos
    - HR=2.07; p = 3.15 X10⁻⁷
  - 15 total SNPs in 12 genes found with p<10⁻⁷
ECOG 5103 GWAS study

- **Clinical implications:**
  - Need replication/validation of these studies *(ongoing)*
  - Need some kind of interventional, prospective study
    - ? in African-Americans or other at-risk populations for neuropathy

*Not ready for prime-time but thought provoking…stay tuned…*
GHSU Multidisciplinary Breast Cancer Program

GHSU Cancer Center
Phase I Trials Unit:
Pam Bourbo

Nicole Aenchbacher,
RN, BSN

GHSU Breast Cancer Risk Assessment Program

To all our patients & families

GHSU Cancer Center
MB-CCOP Unit:
Melanie Kumrow