Challenging Cases in the Contemporary Management of Breast Cancer

Cordoba, Argentina
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Chair – British Columbia Breast Tumour Group
University of British Columbia
Challenging Cases in 2010

- Management of HER-2 positive advanced breast cancer. Prolonging survival by continuing to target HER-2.
- Management of HER-2 positive $T_{1a-b}N_0$ breast cancer. Biology matters – not size.
DNA MICROARRAY GENE EXPRESSION PROFILING REVEALS SIGNATURES OF BREAST CANCER SUBTYPES WITH PROGNOSTIC VALUE

A van't Veer data set

B Norway/Stanford data set
Anita’s Story

Permission granted to utilize photo and story
Anita’s Story

• 30 year old pre-menopausal female cycling across Canada to raise awareness/money for cancer research
• Diagnosed with locally advanced Stage IIIc (cT$_2$N$_3$) ER+/HER 2+ right breast cancer
• Anita underwent neoadjuvant chemotherapy:
  AC x 4 → D x 4     Apr - Sept 2002
• Post modified radical mastectomy Nov 2002:
  2.8 cm residual in breast
  9/11 nodes involved
• Locoregional RT completed Jan 2003
• Adjuvant tamoxifen beginning Feb 2003
Anita’s Story

- Anita diagnosed with metastatic breast cancer to bone in Sept 2005
- Treated with TCH and maintenance trastuzumab
- Pamidronate
- Ovarian ablation and AI
- Vinorelbine + trastuzumab
- Oral HER2 TKI (phase I study ARRY380)
- Lapatinib and capecitabine
- Cisplatin and gemcitabine
- Abraxane and trastuzumab

- Died in Oct 2010
The Last Big Leap: HER-2/neu

HER2 Oncogene

Amplification

Slamon DJ et al. Science 1987;235:177–82

Shortened Median Survival

HER2 over-expressing  3 yrs
HER2 normal  6-7 yrs

Slamon DJ et al. Science 1987;235:177–82
Pivotal 1\textsuperscript{st} line Trastuzumab Study in MBC

Overall Survival

- Probability Alive
- Months

- Trastuzumab + CT
- CT

RR = 0.80
p = 0.046

20.3 mo
25.1 mo

65\% of CT group crossed over to Trastuzumab

Overall Survival Analysis: BCIRG 007

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>TH</td>
<td>131</td>
<td>67</td>
</tr>
<tr>
<td>TCH</td>
<td>132</td>
<td>71</td>
</tr>
<tr>
<td>Total</td>
<td>263</td>
<td>138</td>
</tr>
</tbody>
</table>

Log rank, $P = 0.65$

Number at risk:

- TH: 131, 127, 116, 106, 94, 71, 44, 25, 10, 3, 0
- TCH: 132, 128, 120, 102, 86, 70, 45, 22, 14, 3, 0

TH = 36.40 months
TCH = 36.57 months

Median follow-up duration:

- TH: 39.1 m vs TCH: 39.2 m
BC Population Based Outcomes Research

- BCOU queried for 4 time cohorts prior to and when new systemic agents were introduced as guidelines for MBC
  - Jan 1991 - Dec 1992
  - Jan 1994 - Dec 1995 (paclitaxel, vinorelbine)
  - Jan 1997 - Dec 1998 (docetaxel, non-steroidal AIs)
  - July 1999 - June 2001 (capecitabine, trastuzumab)
- Survival calculated from date of MBC diagnosis
- Treatments received were linked with the BCCA Pharmacy Database

Survival Rates of MBC with Current Agents

Overall Survival

4 Cohorts

Distant Mets to Oct. 31/02 or Death (yrs.)

Modest Improvements in Overall Survival Rate

<table>
<thead>
<tr>
<th>Cohort</th>
<th>n</th>
<th>median</th>
<th>1 year</th>
<th>2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>91-92</td>
<td>424</td>
<td>435 days</td>
<td>56%</td>
<td>34%</td>
</tr>
<tr>
<td>94-95</td>
<td>561</td>
<td>449 days</td>
<td>55%</td>
<td>33%</td>
</tr>
<tr>
<td>97-98</td>
<td>641</td>
<td>562 days</td>
<td>64%</td>
<td>44%</td>
</tr>
<tr>
<td>99-01</td>
<td>525</td>
<td>661 days</td>
<td>71%</td>
<td>45%</td>
</tr>
</tbody>
</table>


220 days (9 months)
Study Design: First Randomized Phase III Study to Investigate Continuation of Trastuzumab

(n=78)  
Capecitabine 2,500 mg/m² d 1–14 q3w  
(n=78)  
Capecitabine 2,500 mg/m² d 1–14 q3w + Continuation of trastuzumab 6 mg/kg q3w

Progression under trastuzumab-based first-line therapy (TFI<6 weeks) with taxane (n=114) or monotherapy or non-taxane (n=42); R = randomization


Planned accrual=450
Trastuzumab Beyond Progression Increases the Response Rate (RECIST)

OR = overall response (CR plus PR); CB = clinical benefit (CR plus PR plus NC>24 weeks);
CR = complete response; PR = partial response; NC = no change

Continuation of Trastuzumab Prolongs Time to Progression

Median follow up = 15.6 months

Continuation of Trastuzumab Shows a Trend for Improvement in Overall Survival (p=NS)

Study design: EGF 100151

- Progressive, HER2+ MBC or LABC
- Previously treated with anthracycline, taxane and trastuzumab*
- No prior capecitabine

Stratification:
- Disease sites
- Stage of disease

Lapatinib 1250 mg po qd continuously + Capecitabine 2000 mg/m²/d po days 1-14 every 3 wk

Capecitabine 2500 mg/m²/d po days 1-14 every 3 wk

Patients on treatment until progression or unacceptable toxicity, then followed for survival

*N=528

*Trastuzumab must have been administered for metastatic disease

Study EGF100151

TTP assessed by IRC 03-Apr-06

<table>
<thead>
<tr>
<th></th>
<th>L+C</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>198</td>
<td>201</td>
</tr>
<tr>
<td>Progressed/died</td>
<td>82 (41%)</td>
<td>102 (51%)</td>
</tr>
<tr>
<td>Median TTP wks</td>
<td>27.1</td>
<td>18.6</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.57 (0.43, 0.77)</td>
<td></td>
</tr>
<tr>
<td>p-value (2-sided)</td>
<td>0.00013</td>
<td></td>
</tr>
</tbody>
</table>

Note: 5 subjects who died due to causes other than breast cancer are censored.
EGF104900: Phase III Study Evaluated Dual HER2 Blockade

- HER2 (FISH+/IHC3+) metastatic breast cancer
- Progression on
  - Anthracycline
  - Taxane
  - Trastuzumab
- Progression on most recent trastuzumab regimen

Lapatinib 1500 mg/d PO (n=148)

Crossover allowed to lapatinib + trastuzumab if progression after 4 weeks on therapy (n=77)

Lapatinib 1000 mg/d PO + trastuzumab 4–2 mg/kg IV weekly (n=148)

Primary endpoint:
- Progression-free survival

Secondary endpoints:
- Overall survival
- Overall response rate
- Clinical benefit rate

Staging occurred at 4, 8, 12, 16 weeks, and then every 8 weeks

Steady state of single-agent lapatinib occurs at approximately 7 days


FISH = fluorescence in situ hybridization; IHC = immunohistochemistry.
# Patient and Tumor Characteristics

<table>
<thead>
<tr>
<th>Study Arms</th>
<th>L ( N = 148 )</th>
<th>L+T ( N = 148 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>51 (29-78)</td>
<td>52 (26-81)</td>
</tr>
<tr>
<td>ECOG performance status 0/1/2, %</td>
<td>47/49/4</td>
<td>54/41/5</td>
</tr>
<tr>
<td>Median prior chemotherapy regimens</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>- Patients ≥ 6 prior regimens, %</td>
<td>28</td>
<td>34</td>
</tr>
<tr>
<td>Median prior trastuzumab regimens for MBC</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Median time from last trastuzumab, days</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>ER- and PgR-negative, %</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td>Visceral disease, %</td>
<td>74</td>
<td>71</td>
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</tbody>
</table>
Progression-Free Survival in ITT

<table>
<thead>
<tr>
<th></th>
<th>L</th>
<th>L+T</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>145</td>
<td>146</td>
</tr>
<tr>
<td>Progressed or Died, N</td>
<td>128</td>
<td>127</td>
</tr>
<tr>
<td>Median, weeks</td>
<td>8.1</td>
<td>12.0</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.73 (0.57, 0.93)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>.008</td>
<td></td>
</tr>
</tbody>
</table>

Updated Overall Survival in ITT

<table>
<thead>
<tr>
<th></th>
<th>L</th>
<th>L+T</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>145</td>
<td>146</td>
</tr>
<tr>
<td>Died, N (%)</td>
<td>113 (78)</td>
<td>105 (72)</td>
</tr>
<tr>
<td>Median, months</td>
<td>9.5</td>
<td>14</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.74 (0.57, 0.97)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value</td>
<td>.026</td>
<td></td>
</tr>
</tbody>
</table>

6 Month OS

L+T: 80%
L: 70%
6 Month OS

12 Month OS

L+T: 56%
L: 41%
12 Month OS

 Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>L+T</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td>148</td>
<td>121</td>
<td>162</td>
</tr>
<tr>
<td>121</td>
<td>88</td>
<td>121</td>
</tr>
<tr>
<td>88</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>84</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>64</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>47</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>43</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>28</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>25</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Blackwell et al. SABCS 2009
Trastuzumab-DM1 (T-DM1) is a novel HER2 directed antibody drug–conjugate in development for the treatment of HER2+ breast cancer.¹,²

- T-DM1 combines the HER2-targeting properties of trastuzumabª with targeted delivery of a highly potent anti-microtubule derivative, DM1.³⁻⁵

- It is hypothesized that after binding to HER2, T-DM1 undergoes receptor-mediated internalization,⁶ resulting in intracellular release of DM1.
A Phase II Study of Trastuzumab-DM1 (T-DM1), a Novel HER2 Antibody–Drug Conjugate, in Patients with HER2+ Metastatic Breast Cancer who Were Previously Treated with an Anthracycline, a Taxane, Capecitabine, Lapatinib, and Trastuzumab

Ian Krop, 1 Patricia LoRusso, 2 Kathy D. Miller, 3 Shanu Modi, 4 Denise Yardley, 5 Gladys Rodriguez, 6 Sam Agresta, 7 Michael Lu, 7 Maoxia Zheng, 7 Lukas Amler, 7 Eric Winer, 1 Hope Rugo 8

1 Dana Farber Cancer Institute, Boston, MA; 2 Karmanos Cancer Institute, Detroit, MI; 3 Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN; 4 Memorial Sloan-Kettering Cancer Center, New York, NY; 5 Sarah Cannon Research Institute, Nashville, TN; 6 South Texas Oncology/Hematology, San Antonio, TX; 7 Genentech, South San Francisco, California; 8 University of California–San Francisco Comprehensive Cancer Center, San Francisco, CA
## Baseline Characteristics (N=110)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>52.5 (34–77)</td>
</tr>
<tr>
<td>Median time since metastatic diagnosis, months (range)</td>
<td>42.1 (1–149)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>54 (49.1)</td>
</tr>
<tr>
<td>1</td>
<td>53 (48.2)</td>
</tr>
<tr>
<td>2</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>ER+ or PR+,* n (%)</td>
<td>55 (50.0)</td>
</tr>
<tr>
<td>ER- and PR-,* n (%)</td>
<td>51 (46.4)</td>
</tr>
<tr>
<td>Number of distinct metastatic sites, n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>29 (26.4)</td>
</tr>
<tr>
<td>≥3</td>
<td>81 (73.6)</td>
</tr>
<tr>
<td>Sites of metastasis (in ≥40% patients), n (%)</td>
<td></td>
</tr>
<tr>
<td>Local-regional</td>
<td>70 (63.6)</td>
</tr>
<tr>
<td>Lung</td>
<td>69 (62.7)</td>
</tr>
<tr>
<td>Bone</td>
<td>57 (51.8)</td>
</tr>
<tr>
<td>Liver</td>
<td>49 (44.5)</td>
</tr>
</tbody>
</table>

*ER = estrogen receptor, PR = estrogen receptor. Information on ER/PR status was unknown for 4 patients.

Krop et al. ESMO 2010
### Prior Chemotherapy and Anti-HER2 Therapy

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number of agents for metastatic disease (range)*</td>
<td>7.0 (3–17)</td>
</tr>
<tr>
<td>Median number of agents in all therapy setting (range)*</td>
<td>8.5 (5–19)</td>
</tr>
<tr>
<td>Number of patients who received all 5 prior agents, n (%)**</td>
<td>109 (99.1)</td>
</tr>
<tr>
<td>Prior trastuzumab</td>
<td></td>
</tr>
<tr>
<td>Median duration of prior trastuzumab in metastatic setting, months (range)</td>
<td>19.7 (1.8–115.8)</td>
</tr>
<tr>
<td>Prior lapatinib</td>
<td></td>
</tr>
<tr>
<td>Median duration of prior lapatinib in metastatic setting, months (range)</td>
<td>6.8 (0.2–23.3)</td>
</tr>
</tbody>
</table>

* Includes all non-hormonal agents intended for the treatment of metastatic breast cancer
* * One patient did not receive a taxane.
### Antitumor Activity in Treated Patients

<table>
<thead>
<tr>
<th>Tumor Response</th>
<th>IRF (N=110)</th>
<th>Investigator (N=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective Response Rate, % (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>34.5</td>
<td>32.7</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>4.5</td>
</tr>
<tr>
<td>SD</td>
<td>34.5</td>
<td>28.2</td>
</tr>
<tr>
<td>PD</td>
<td>44.5</td>
<td>50.9</td>
</tr>
<tr>
<td>UE</td>
<td>18.2</td>
<td>14.5</td>
</tr>
<tr>
<td>Missing</td>
<td>1.8</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Clinical Benefit Rate, % (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>48.2</td>
<td>46.4</td>
</tr>
<tr>
<td></td>
<td>(38.8–57.9)</td>
<td>(37.1–56.1)</td>
</tr>
</tbody>
</table>

IRF - Independent Review Facility  
Objective Response - CR or PR determined by two consecutive tumor assessments at least 28 days apart.  
Clinical Benefit - objective response or SD maintained for at least 6 months.  
*Including unconfirmed PRs.
K-M Plot of Progression-Free Survival Treated Patients, IRF Assessment

T-DM1 (N=110)

Median PFS: 6.9
95% CI: (4.2 - 8.4)
25–75 percentile: 2.6 –
Range: 0.0 -19.2+

Krop et al. ESMO 2010

N                                  110
Number progressed         63 (57.3%)
Number censored         47 (42.7%)

N                                  109
No. at risk
T-DM1  109  83  59  41  33  22  19  14  8  3  0

Time on Study (Months)
## AEs that Occurred in >10% Patients (All Grades)

<table>
<thead>
<tr>
<th>AEs (%</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>All Grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>30.0</td>
<td>27.3</td>
<td>4.5</td>
<td>0</td>
<td>0</td>
<td>61.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>26.4</td>
<td>10.0</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
<td>37.3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11.8</td>
<td>13.6</td>
<td>5.5</td>
<td>1.8</td>
<td>0</td>
<td>32.7</td>
</tr>
<tr>
<td>AST Increased</td>
<td>11.8</td>
<td>11.8</td>
<td>2.7</td>
<td>0</td>
<td>0</td>
<td>26.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>20.0</td>
<td>2.7</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
<td>23.6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13.6</td>
<td>8.2</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
<td>22.7</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>19.1</td>
<td>2.7</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
<td>22.7</td>
</tr>
<tr>
<td>Headache</td>
<td>18.2</td>
<td>3.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>21.8</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>19.1</td>
<td>0.9</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
<td>20.9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12.7</td>
<td>7.3</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
<td>20.9</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>17.3</td>
<td>2.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>20.0</td>
</tr>
<tr>
<td>Anemia</td>
<td>7.3</td>
<td>10.9</td>
<td>1.8</td>
<td>0</td>
<td>0</td>
<td>20.0</td>
</tr>
</tbody>
</table>
### AEs that Occurred in >10% Patients (Cont.)

<table>
<thead>
<tr>
<th>AEs (%)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>All Grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>12.7</td>
<td>5.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>18.2</td>
</tr>
<tr>
<td>Back pain</td>
<td>11.8</td>
<td>3.6</td>
<td>2.7</td>
<td>0</td>
<td>0</td>
<td>18.2</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>12.7</td>
<td>5.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>18.2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10.0</td>
<td>3.6</td>
<td>2.7</td>
<td>0</td>
<td>0</td>
<td>16.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10.9</td>
<td>5.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16.4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10.0</td>
<td>2.7</td>
<td>1.8</td>
<td>0</td>
<td>0</td>
<td>14.5</td>
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<tr>
<td>Myalgia</td>
<td>12.7</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13.6</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>8.2</td>
<td>5.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13.6</td>
</tr>
<tr>
<td>ALT Increased</td>
<td>8.2</td>
<td>2.7</td>
<td>2.7</td>
<td>0</td>
<td>0</td>
<td>13.6</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>10.0</td>
<td>1.8</td>
<td>1.8</td>
<td>0</td>
<td>0</td>
<td>13.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9.1</td>
<td>3.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12.7</td>
</tr>
<tr>
<td>ALP Increased</td>
<td>8.2</td>
<td>2.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10.9</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>8.2</td>
<td>2.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10.9</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>7.3</td>
<td>2.7</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
<td>10.9</td>
</tr>
</tbody>
</table>

*Krop et al. ESMO 2010*
Betty’s Story

Permission granted to utilize photo and story
Betty’s Story

- 69-year-old post-menopausal woman (mother of MD) originally presented with
  - ER/PR/HER 2 negative breast cancer
  - 3 cm grade III tumour
  - negative lymph nodes (0/6)
  - history of inflammatory bowel disease and osteoarthritis

- Adjuvant AC x 4 followed by Paclitaxel x 4 (June-Nov 2007)
Betty’s Story

- 2 years later diagnosed with metastatic disease to lung
- PS 1 with mild hemoptysis
- Wanted therapy that would retain functional state but prolong time to next line of chemotherapy
- Following long discussion with patient and son – opted for 1st line therapy with capecitabine and bevacuzimab Nov 2009
remains on capecitabine (75%) and bevacizumab (15 mg/kg) x 10 months with PS 0-1 and stable disease
### Three Randomised Trials of First-Line Bevacizumab-Based Therapy in LR/mBC: Similar Trial Designs

<table>
<thead>
<tr>
<th></th>
<th>E2100&lt;sup&gt;1&lt;/sup&gt; (n=722)</th>
<th>AVADO&lt;sup&gt;2&lt;/sup&gt; (n=736)</th>
<th>RIBBON-1&lt;sup&gt;3&lt;/sup&gt; (n=1,237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo controlled</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Weekly paclitaxel</td>
<td>3-weekly docetaxel</td>
<td>Capecitabine</td>
</tr>
<tr>
<td>Bevacizumab dose</td>
<td>10mg/kg q2w</td>
<td>7.5 or 15mg/kg q3w</td>
<td>15mg/kg q3w</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>PFS</td>
<td>PFS</td>
<td>PFS</td>
</tr>
<tr>
<td>Independent review</td>
<td>Retrospective</td>
<td>No</td>
<td>Prospective</td>
</tr>
</tbody>
</table>

LR = locally recurrent; mBC = metastatic breast cancer
q2w = every 2 weeks; q3w = every 3 weeks; PFS = progression-free survival

Consistent Benefit with Bevacizumab-Based Therapy: Significant Improvement in PFS

**E2100 (IRF assessment)**
- **Paclitaxel (n=354)**
- **Bevacizumab + paclitaxel (n=368)**

HR = 0.64* (0.52–0.80) p<0.0001

**RIBBON-1: taxane/anthracycline cohort**
- **Placebo + docetaxel (n=207)**
- **Bevacizumab + taxane/anthracycline (n=415)**

HR = 0.64* (0.52–0.80) p<0.0001

**AVADO**
- **Placebo + docetaxel (n=241)**
- **Bevacizumab 15mg/kg q3w + docetaxel (n=247)**

HR = 0.67* (0.54–0.83) p=0.0002

**RIBBON-1: capecitabine cohort**
- **Placebo + capecitabine (n=206)**
- **Bevacizumab + capecitabine (n=409)**

HR = 0.69* (0.56–0.84) p=0.0002

*Stratified and censored for non-protocol therapy before disease progression

†p value is exploratory; HR = hazard ratio; IRF = independent review facility

Progression-Free Survival, Pooled Population

<table>
<thead>
<tr>
<th></th>
<th>Non-BV</th>
<th>BV</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=1008)</td>
<td></td>
<td>(n=1439)</td>
</tr>
<tr>
<td>Median, mo</td>
<td>6.7</td>
<td>9.2</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.64 (0.57–0.71)</td>
<td></td>
</tr>
</tbody>
</table>

O'Shaughnessy et al, ASCO 2010
# Consistent PFS Benefit Across Relevant Subgroups

## Baseline Risk Factor

<table>
<thead>
<tr>
<th>Baseline Risk Factor</th>
<th>E2100: Bev + Paclitaxel</th>
<th>AVADO: Bev + Docetaxel</th>
<th>RIBBON-1: Bev + Capcitabine</th>
<th>RIBBON-1: Bev + T/Anthr</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>FAVOURS BEV + P</td>
<td>FAVOURS BEV + D</td>
<td>FAVOURS BEV + CAP</td>
<td>FAVOURS BEV + T/ANTHR</td>
</tr>
<tr>
<td>Triple negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elderly (age ≥65y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior adjuvant taxane</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Median follow-up 25 months
†15mg/kg q3w; §Stratified analysis; ¶Unstratified analysis

### Secondary Endpoint: Overall Survival (OS)

<table>
<thead>
<tr>
<th></th>
<th>E2100(^1)</th>
<th>AVADO(^2)</th>
<th>RIBBON-1(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bev Pac</td>
<td>Bev* + doc</td>
<td>Bev + cap</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>24.8</td>
<td>31.9</td>
<td>21.2</td>
</tr>
<tr>
<td>HR</td>
<td>0.87</td>
<td>1.03</td>
<td>0.85</td>
</tr>
<tr>
<td>p</td>
<td>0.14</td>
<td>0.85</td>
<td>0.27</td>
</tr>
<tr>
<td>1-year OS rate, %</td>
<td>74</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>p</td>
<td>0.017</td>
<td>0.02</td>
<td>0.076</td>
</tr>
</tbody>
</table>


*15mg/kg q3w; \(^1\)Exploratory p values
Overall Survival, Pooled Population

- **Median, mo**: Non-BV: 26.4, BV: 26.7
- **HR (95% CI)**: Non-BV: 0.97 (0.86–1.08)
- **1-yr survival rate (%)**: Non-BV: 77, BV: 82

Number at Risk:
- Non-BV: 1008, 892, 748, 621, 426, 178, 51, 19
- BV: 1439, 1333, 1127, 916, 591, 204, 55, 23

O’Shaughnessy et al, ASCO 2010
## Use of Subsequent Systemic Therapies in AVADO and RIBBON-1 Studies*

*Data not available from E2100.

O'Shaughnessy et al, ASCO 2010

<table>
<thead>
<tr>
<th>%</th>
<th>Non-BV (n • 654)</th>
<th>BV (n • 1071)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any chemotherapy</td>
<td>71</td>
<td>65</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>51</td>
<td>40</td>
</tr>
<tr>
<td>Any hormonal therapy</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td># of subsequent anti-cancer agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>
Survival Post Progression Alters Overall Survival End-Point

Safety Profile Consistent Across First-Line Bevacizumab Trials in mBC

Grade ≥3 events
- E2100: bevacizumab + weekly paclitaxel
- AVADO: bevacizumab + docetaxel
- RIBBON-1: bevacizumab + capecitabine
- RIBBON-1: bevacizumab + taxane
- RIBBON-1: bevacizumab + anthracycline-based therapy

NR = data for ATEs not reported for RIBBON-1 study; GI = gastrointestinal; LVEF = left ventricular ejection fraction; ATE = arterial thromboembolic events; VTE = venous thromboembolic events

Miles. EJC Suppl 2008
ATHENA: Subpopulation Analysis of Grade ≥3 Adverse Events of Special Interest

- Hypertension: <70 years (n=1870) 4.0%, ≥70 years (n=171) 7.0%
- Proteinuria: <70 years (n=1870) 1.5%, ≥70 years (n=171) 2.9%
- Pulmonary embolism: <70 years (n=1870) 1.1%, ≥70 years (n=171) 2.1%
- ATE/VTE: <70 years (n=1870) 0.6%, ≥70 years (n=171) 0%
- Wound-healing complication: <70 years (n=1870) 0.5%, ≥70 years (n=171) 0%
- Epistaxis: <70 years (n=1870) 0.5%, ≥70 years (n=171) 0.6%
- GI perforation: <70 years (n=1870) 0%, ≥70 years (n=171) 0.3%
- CNS bleeding: <70 years (n=1870) 0.1%, ≥70 years (n=171) 0%

CNS = central nervous system

Biganzoli, et al. ASCO 2009
VEGF TKIs ineffective in metastatic breast cancer (ASCO 2010)
Final Efficacy and Safety Results of a Randomized Phase II Study of the PARP Inhibitor Iniparib (BSI-201) in Combination with Gemcitabine/Carboplatin (G/C) in Metastatic Triple Negative Breast Cancer (TNBC)

J O’Shaughnessy,¹,²,³ C Osborne,¹,²,³ J Pippen,¹,²,³ M Yoffe,³,⁴ D Patt,²,³,⁵ G Monaghan,³,⁶ C Rocha,⁷ BM Sherman,⁷ C Bradley⁷

¹Baylor Sammons Cancer Center, ²Texas Oncology, Dallas, TX; ³US Oncology, Dallas, TX; ⁴Cancer Centers of North Carolina, Raleigh, North Carolina; ⁵Texas Oncology Cancer Center, Austin, Texas; ⁶Kansas City Cancer Center, Kansas City, Missouri; ⁷BiPar Sciences, Inc., South San Francisco, CA
Study Design  Multi-center, open-label, randomized

- Metastatic TNBC (ie, hormone receptor and HER2 negative) with measurable disease
- 0-2 prior chemotherapy regimens for metastatic disease
- No prior treatment with gemcitabine, carboplatin, cisplatin, PARP inhibitor
- Stable brain metastases allowed
- ECOG PS 0–1

Randomization (1:1)  
N=62  N=61

**Gemcitabine (1000 mg/m², IV, d 1, 8)**  
Carboplatin (AUC 2, IV, d 1, 8)*  
Every 3 weeks

**Iniparib (5.6 mg/kg, IV, d 1, 4, 8, 11)**  
Gemcitabine (1000 mg/m², IV, d 1, 8)  
Carboplatin (AUC 2, IV, d 1, 8)  
Every 3 weeks

RESTAGING  
Every 2 Cycles

* Patients randomized to gem/carbo alone could crossover to receive gem/carbo + Iniparib (BSI-201) at disease progression

NCT00540358
Overall Survival (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Gem-Carbo N = 62</th>
<th>Iniparib + Gem-Carbo N=61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>7.7 (6.5, 13.3)</td>
<td>12.3 (9.8, 21.5)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.57 (0.36, 0.90)</td>
<td></td>
</tr>
<tr>
<td>P-value*</td>
<td>0.014</td>
<td></td>
</tr>
</tbody>
</table>

*P-values were not adjusted for multiple interim analyses.
### Outcome in crossover patients

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crossover from gem-carbo to iniparib</td>
<td>30</td>
</tr>
<tr>
<td>Median number cycles of iniparib (range)</td>
<td>1.5 (1–8)</td>
</tr>
<tr>
<td>Discontinued treatment after 1 or 2 cycles</td>
<td>25 (83)</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td></td>
</tr>
<tr>
<td>Partial response (unconfirmed)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>7 (23)</td>
</tr>
</tbody>
</table>
Canadian Study 20 – Olaparib in BRCA and sporadic breast and ovarian cancer

TNBC with unknown BRCA status (n=15) → Screening/enrolment → Known BRCA + breast cancer (n=10) → ≥1 response + 20 patients = (n=35) → Olaparib 400 mg bid

Known BRCA + ovarian cancer (n=10) → ≥1 response + 40 patients = (n=55) → HGSC with unknown BRCA status (n=15)

TNBC, triple-negative breast cancer; HGSC, high-grade serous ovarian carcinoma

Best % change in target lesion size by tumour type and BRCA status

Breast cancer

23 treated patients with target lesions identified at baseline
22 had at least one follow-up assessment
1 patient had no follow-up tumour size assessment
1 due to missing / incomplete post-baseline assessments

No patient met the criteria for a confirmed RECIST response. Best change in target lesion size is maximum reduction from baseline or minimum increase in absence of reduction.
L.Y’s Story

• 60 year old post-menopausal Asian female
• Screening mammography > 10 years
• Developed pruritis around left nipple in March 2007
• Diagnostic mammogram demonstrated calcification in left breast (upper outer quadrant) and retro-areolar region
• Clinical Paget’s disease
• Healthy otherwise (except for osteopenia on BMD)
L.Y’s Story

• Biopsy of both lesions demonstrated high grade DCIS
• Proceeded to simple mastectomy with sentinel node procedure July 2007
L.Y’s Story

- Pathology (Luo quadrant):
  - 5 mm high grade DCIS
  - ER/PR (-)
- Pathology (retro-areolar region):
  - 2.5 mm high focus DCIS
  - 7 mm focus high grade invasive ductal CA
  - ER/PR (-) and HER2(+) no LVI
  - 0/3 sentinel nodes (negative by IHC)
L.Y’s Story

- Treated with AC x 4 completed Dec 2007
- Adjuvant trastuzumab x 1 year completed Jan 2009
- Well with no evidence of recurrent disease
HER-2 as Prognostic Factor in Node (-)

- 4,444 cases in a TMA – 2,026 were node negative
- 70% had no adjuvant systemic therapy delivered
- IHC for HER-2 (SP3 antibody) and FISH for all IHC 2+ (and proportion of 3+ for concordance study)
- FISH positive if ratio ≥ 2.0
- Median F/U 12.4 years

HER-2+ in T1b Tumors (n=13)

T1b pN0, no systemic therapy (n = 225)

Relapse-Free Survival

Her2 positive

Her2 negative

\[ p = 0.312 \]
Risk Stratification based on ER and HER-2 in T₁ Tumors

![Graph showing the relationship between ER and HER-2 status and relapse-free survival. The graph indicates that there is no significant difference in relapse-free survival between different ER and HER-2 status groups, with a p-value of 0.32.]
Finnish Study: No Adjuvant Therapy
T1bN0 HER2+ EBC

DDFS by erbB2 Expression

DDFS by erbB2 Amplification

HER-2 as Prognostic Factor in Tumors $\leq 1$ cm

High Risk of Recurrence for Patients With Breast Cancer Who Have Human Epidermal Growth Factor Receptor 2–Positive, Node-Negative Tumors 1 cm or Smaller

Ana M. Gonzalez-Angulo, Jennifer K. Litton, Kristine R. Broglio, Funda Meric-Bernstam, Ronjay Rakhit, Fatima Cardoso, Florentia Peintinger, Emer O. Hanrahan, Aysegul Sahin, Merih Guray, Denis Larsimont, Francesco Feoli, Heidi Stranzl, Thomas A. Buchholz, Vicente Valero, Richard Theriault, Martine Piccart-Gebhart, Peter M. Ravdin, Donald A. Berry, and Gabriel N. Horribagyi
Adjuvant Trastuzumab Trials: >13,000 Patients Treated

HERA (ex-USA)

IHC/FISH (n=5,090)

Observation

1 year

2 years

BCIRG 006 (global)

FISH (n=3,222)

1 year

NCCTG N9831 (USA)

IHC/FISH (n=3,505)

1 year

NCCTG N9831 (USA)

IHC/FISH (n=2,030)

1 year

NCCTG N9831 (USA)

IHC/FISH (n=2,030)

1 year

Standard chemotherapy

Doxorubicin + cyclophosphamide

Docetaxel

Docetaxel + carboplatin

Trastuzumab

Paclitaxel

FISH = Fluorescence in situ hybridization

Slamon et al. SABCS 2006
Trastuzumab Provides Consistent DFS Benefits by 40-50%
Trastuzumab Consistently Reduces the Risk of Death by 33%

- HERA CT→H 1 year
- B-31/N9831 AC→PH
- BCIRG 006 AC→DH
- BCIRG 006 DCarboH

Overall Survival Benefit

Median Follow-up (Years)

2
3
3
3

Hazard Ratio

Favours Trastuzumab

Favours No Trastuzumab

0 1 2

Size of square represents sample size; horizontal bars indicate 95% confidence intervals

CT = chemotherapy; H = trastuzumab; AC = doxorubicin, cyclophosphamide; P = paclitaxel; D = docetaxel; Carbo = carboplatin

Perez et al. ASCO 2007, Abstract #512; Slamon et al. SABCS 2006; Smith et al. Lancet 2007
Node-Negative Patients in HERA

- The node-negative cohort of 1,099 patients includes:
  - 12 with unknown tumour size
  - 60 with tumour size <1 cm
  - 33 with tumour size = 1.0 cm
  - 510 with tumour size between 1.1 and 2.0 cm
  - 484 with tumour size >2.1 cm

Exploratory Disease-free Survival Subgroup Analysis in HERA

Subgroup (no. patients)  
Nodal status  
- Not assessed (neoadjuvant CT) (372)  
- Negative (1099)  
- 1-3 positive nodes (976)  
- ≥4 positive nodes (953)  
Hormone receptor status  
- ER negative + PgR negative (1627)  
- ER negative + PgR positive (172)  
- ER positive + PgR negative (460)  
- ER positive + PgR positive (984)  
- All patients (3401)  

No. events  
T vs obs  
0.66 (0.43, 1.00)  
0.59 (0.39, 0.91)  
0.61 (0.43, 0.87)  
0.64 (0.49, 0.83)  
0.63 (0.50, 0.78)  
0.77 (0.34, 1.74)  
0.82 (0.50, 1.34)  
0.63 (0.43, 0.93)  
0.64 (0.54, 0.76)  

T = trastuzumab; obs = observation; HR = hazard ratio; CI = confidence interval;  
CT = chemotherapy; ER = estrogen receptor; PgR = progesterone receptor

Outcomes of Women with Early Stage HER-2 Over-Expressing Breast Cancer Receiving Adjuvant Trastuzumab: A Population Based Analysis

M. Seal¹, C. Speers², S. O’Reilly¹, K. Gelmon¹-², S. Ellard²-³, and S. Chia¹-²

¹Div. Medical Oncology, ²Breast Cancer Outcomes Unit, British Columbia Cancer Agency (BCCA), Vancouver, ³BCCA, Kelowna, British Columbia, Canada

SABCS 2009
BCCA has the mandate for cancer control and provides publicly funded health care program for entire province.

- 2,700 newly diagnosed breast cancers in 2009 (>80% referred to BCCA).
- The BCCA BCOU is a prospective comprehensive database of newly diagnosed breast CA since 1989 referred to BCCA.
Objectives

- To describe the proportion of women with HER-2 over-expression early stage breast cancer receiving adjuvant Trastuzumab in British Columbia from July 2004 - Dec 2006
- To determine the outcomes of patients receiving Trastuzumab
Results

• Total cohort: 704 patients
• 68% (n=480) received adjuvant Trastuzumab (T)
• Median follow-up: 2.1 years

• 100% patients in T cohort received chemotherapy versus 28% in non-T group
2 year Outcomes

RFS: 95.9% (95% CI; 93.4-97.5)  
BCSS: 99.3% (95% CI; 97.9-99.8)
2 year RFS in Patients Receiving Adjuvant Trastuzumab (n=480)
2 year RFS in Patients Not Receiving Trastuzumab (n=224)

Relapse-Free Survival

Time (years)

Relapse-Free Survival

Node negative

Node positive

p = 0.007

90.7%

75.5%
Site of First Metastasis in Patients who had Distant Relapse

17.8%*

* 35% of distant mets in adjuvant T cohort
Assessing Cost Effectiveness from Adjuvant Trastuzumab in BC

- Used 20 health state Markov model
- Modelling scenario: 50 year old female with HER2+ breast cancer post-resection (1,000 cases run)
- Clinical data and outcome from NSABP B31/NCCTG 98-31 trials (stable at year 5)
  - 5 year DFS: 47% → 56%
  - 5 year OS: 45% → 54%
- Data for metastatic outcome from published data
- Real costs from the BCCA Pharmacy repository and the BCCA Breast Outcomes database

Hedden L, et al. Manuscript submitted
Assessing Cost Effectiveness from Adjuvant Trastuzumab in BC

- Assumed could received trastuzumab again for locoregional or distant relapse if > 12 month from last trastuzumab
- Assumed 5% of population screened ineligible based on low baseline LVEF or other co-morbidities
- Included all costs of radiotherapy, hormonal agents, and costs for palliative care (all based on published BC data)

Hedden L, et al. Manuscript submitted
Assessing Cost Effectiveness from Adjuvant Trastuzumab in BC

- 1 year of adjuvant trastuzumab with chemotherapy resulted in gain of 1.38 QALY
- Cost per QALY gained = $13,095
- Acceptability curve showed 90% probability of cost effectiveness of < $30,000
- Likely to be even more CE – for we did not consider trastuzumab beyond progression, lapatinib, TDM1 in treatment of 2nd line or greater HER 2+ MBC

Hedden L, et al. Manuscript submitted
Conclusions

• HER-2 positive breast cancer is a relatively homogenous disease. Continued targeting of HER-2 throughout disease course appears to prolong survival.

• Triple negative breast cancer is a heterogeneous disease. PARP inhibition appears efficacious only with chemotherapy (except in BRCA 1/2 tumours)

• 1\textsuperscript{st} line chemotherapy with bevacuzimab does provide clinical benefit. But we need to better define who really benefits.

• In small node negative HER-2 positive breast cancers – biology overrides size and should be treated as such.