Finding the Positives in Triple-Negative Breast Cancer: A Three-Part Live CME Webcast Series

Seminar III:  Tuesday, March 16, 2010, 8:00 PM - 9:00 PM EST

Neil Love, MD  
Editor, Breast Cancer Update Audio Series  
Research To Practice  
Miami, Florida

Kathy D Miller, MD  
Sheila D Ward Scholar of Medicine  
Associate Professor of Medicine  
The Indiana University Melvin and Bren Simon Cancer Center  
Indianapolis, Indiana

Hope S Rugo, MD  
Clinical Professor of Medicine  
Director, Breast Oncology and Clinical Trials Education  
University of California, San Francisco  
Helen Diller Family Comprehensive Cancer Center  
San Francisco, California
Disclosures for Moderator Neil Love, MD

Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience, Amgen Inc Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Centocor Ortho Biotech Services LLC, Cephalon Inc, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Genzyme Corporation, GlaxoSmithKline, ImClone Systems Incorporated, Lilly USA LLC, Millennium Pharmaceuticals Inc, Monogram BioSciences Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Roche Laboratories Inc, Sanofi-Aventis and Spectrum Pharmaceuticals Inc.

Agenda

Module 5 — Dr Miller
• New pathways and novel agents in TNBC
• Met activation and amplification: Trials evaluating Met inhibitors
• Nm23-H1 metastases suppressor gene; trials of medroxyprogesterone acetate (MPA) to stimulate production

Module 6 — Dr Rugo
• Neoadjuvant and adjuvant therapy
• Systemic therapy for metastatic disease
  – Ixabepilone
  – Bevacizumab and other anti-angiogenic strategies
  – Platinum agents
Submit a Challenging Case or Question

- Use the text box at the bottom-left of the screen to type in a case or question. You may also submit a case or question by phone at (866) 447-3623.
- You may include your full name, city and state of practice or you may choose to remain anonymous.
- Select entries will be discussed and reviewed by our esteemed faculty during the hour-long segment.

Seminar Overview

- This is the third of three unique online, integrated educational courses.
- An archive of these webcasts will also be available on www.ResearchToPractice.com within three days of the broadcast.
- Please remember to complete your CME evaluation. A link will be provided at the conclusion of each seminar.
Outside of a clinical trial, what is your treatment regimen for triple negative breast cancer (TNBC) in the:
  a. Neoadjuvant setting
  b. Adjuvant setting

— Atif Hussein, MD

A 44-year-old woman presenting with a 4.5-cm triple-negative right breast invasive ductal carcinoma, palpable nodes. No inflammatory component. PET-CT showed no metastases. She wishes for neoadjuvant chemotherapy in hopes of better post-surgical cosmesis. What is your take on using neoadjuvant single-agent cisplatin in such a situation?

— Jess F Armor, MD, Oklahoma City, Oklahoma

Is adjuvant therapy recommended for an 83-year-old woman (without any major medical problems x HBP) with 2-cm, LN-neg TNBC?

— Anonymous

A 52-year-old woman with TNBC...three treatments of AC and then five treatments of paclitaxel. Surgery: Bilateral mastectomy, 37 nodes removed, 35 positive...now what?

— Anonymous
De novo metastatic TNBC, off trial, community setting, suggested first-line therapy and sequencing?

— Anonymous

A 38-year-old with BRCA-negative TNBC with axillary metastases received neoadjuvant chemotherapy and at surgery did not have a complete response. Within six months she has metastatic disease to the bone only. Would you consider a PARP inhibitor for first-line therapy?

— AKC, Portland, Oregon

When a patient with ER-positive/HER2-negative disease converts to triple negativity in her metastatic lesion, is this phenotype to be treated like an original triple-negative?

— Michael Messer, MD
What is the status of the development of PARP inhibitors aside from BSI-201 and olaparib, such as ABT-888, AG 014699, MK4827 and INO-1001?

— Karen Tedesco, MD

BSI-201: Any use in hormone receptor-positive or HER2-positive? Any use in other cancer types?

— Helmy Guidis, MD

Please respond to whether we can obtain a PARP inhibitor through compassionate use.

— New Mexico

CASE PRESENTATION #1
Dr Miller

• 56-year-old presented with large (15 cm) mass in left breast with associated inflammatory changes and palpable axillary adenopathy
  – Biopsy Grade III IDC, ER-/PR-/HER2- (confirmed by FISH and IHC)
  – Staging negative for metastatic disease
CASE PRESENTATION #1
Dr Miller

- Enrolled in phase II clinical trial of docetaxel + capecitabine + bevacizumab
  - Resolution of inflammatory changes with modest decrease in mass after cycle 1 but with profound diarrhea (>10/day) and GCP fever
  - Admit to hospital with GCP fever and bilateral peri-rectal abscess after cycle 2
- During recovery, deleterious mutation of BRCA1 identified

CASE PRESENTATION #1
Dr Miller

- Began cisplatin 75 mg/m² q3 weeks x 4
  - All palpable disease resolved after cycle 2
  - Imaging negative after cycle 4
- Bilateral mastectomy – pCR
- Proceeding to RT
New Pathways and Novel Agents in TNBC

Kathy D Miller, MD
Sheila D Ward Scholar of Medicine
Associate Professor of Medicine
The Indiana University Melvin and Bren Simon Cancer Center
Indianapolis, Indiana

Disclosures for Kathy D Miller, MD

<table>
<thead>
<tr>
<th>Research Support/PI</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employee</td>
<td>N/A</td>
</tr>
<tr>
<td>Consultant</td>
<td>Bristol-Myers Squibb Company</td>
</tr>
<tr>
<td>Major Stockholder</td>
<td>N/A</td>
</tr>
<tr>
<td>Speakers’ Bureau</td>
<td>Genentech BioOncology, Roche Laboratories Inc</td>
</tr>
<tr>
<td>Scientific Advisory Board</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A = Not Applicable
Introduction

• Identifying novel pathways
• C-MET activation
• Metastasis suppressor genes

Finding the Positive

• Goal – identify genes that are consistently overexpressed when amplified
  – 56 by CGH, 24 by genome-wide expression
• 78% with at least one amplification
  – 40 genes identified
  – No individual amplification at high frequency
Finding the Positive (continued)

- Known oncogenes identified
  - FGFR2, BUB3, RAB20, PKN1, NOTCH3
- FGFR2 activation in 2 TBC cell lines
  - Sensitive to FGFR2 inhibition
- Independent series – relevance?
  - FGFR2 amplification in 4% (6/165) of TNBC and none (0/214) in other subtypes

Tyrosine Kinase Receptor Pathways Activated

- Gain of function common in TNBC
  - Angiopoietin
  - HGF (ligand for c-MET)
  - FAK
  - FGF
  - VEGF
  - IGF-1
- Specific genes identified varied
Gene Expression Meta-analysis

- High expression in TNBC
  - GGI (proliferation), IGF1, MYC, RAS/MAPK, PI3K/AKT/mTOR gene sets
- High expression of immune-related genes is consistently associated with better prognosis in TNBC
  - Strategies to enhance immune response?


MET in Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>Overexpression</th>
<th>Mutation or Amplification</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (NOS)</td>
<td>LN neg – 15-20%</td>
<td>Not reported</td>
<td>Decreased OS with MET: 8 mos vs. 53 mos.</td>
</tr>
<tr>
<td></td>
<td>LN pos – 30-80%</td>
<td></td>
<td>Resistance to EGFR inhibition and trastuzumab</td>
</tr>
<tr>
<td></td>
<td>Increased HGF - 65%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>65-95%</td>
<td>Not reported</td>
<td></td>
</tr>
</tbody>
</table>

Learning from Mice

- Transgenic mouse models with activating MET mutations
  - Develop breast cancers with a variety of histologies with basal characteristics by gene expression and IHC
  - Correlates with EGFR, keratin-5, markers of EMT (vimentin, snail)
  - Inversely correlated with ER and PR
**Metastasis Suppressor Genes**

- Unique from classical tumor suppressors
  - Inhibit development and growth at distant sites
  - Little or no impact on primary tumor growth
- Expression frequently lost in aggressive tumors
- Hypothesis – increased expression of MSGs may decrease growth of mets
Medroxyprogesterone Acetate

- Low doses: Birth control, HRT
- High doses: Used for advanced breast cancer until Tam
- Increases Nm23-H1 expression \textit{in vitro}
- In hormone receptor-negative BC, Nm23-H1 acts via glucocorticoid receptor
- Inhibits angiogenesis
  - Upregulates thrombospondin and PAI-1

Inhibition of Vascular Tube Formation by MPA
Preclinical Data

- MDA-MB-231T in vivo model
  - Mets in 100% of control mice vs 64-73% of MPA-treated mice
  - Mean number of mets:
    |          | Mean number of mets | Percent change |
    |----------|---------------------|---------------|
    | Control  | 32-33               | -             |
    | MPA 2.0 mg | 14.5               | 57% decrease  |
    | MPA 1.0 mg | 12.6               | 62% decrease  |
    | MPA 0.5 mg | 23.8               | 34% decrease  |
- Nm23 increased in lung mets and skin biopsies
- Trough PK clinically achievable but bioavailability highly variable

TBCRC 007: MPA Alone or with Metronomic Chemotherapy

- Post-menopausal, ER-/PR-
- Primary objective – identify clinical benefit rate ≥ 20%
  - Requires 2 CBR in first 15 patients
- MPA 1000-1500 mg daily
  - Intra-patient dose escalation based on PK data
  - Goal ≥ 50 ng/ml
TBCRC 007: Cohort 1, MPA Monotherapy

• N = 15, heavily pre-treated
• Median PFS = 55 days
  – 3 patients with SD for 63, 111, 504 days
• PAI-1 antigen increased at 4 wks
  – 16.74 ng/ml vs 21.78 ng/ml, \( P=0.0467 \)
  – No changes in PAI-1 activity or TSP

Conclusions

• Genomic profiling has identified many potential therapeutic targets in TNBC
  – Heterogeneity greater than expected
  – Expression alone may not be sufficient
  – Transgenic models may be more compelling
CASE PRESENTATION #1
Dr Rugo

29-year-old Hispanic woman

- 4.5-cm right high grade, node-neg TNBC + DCIS
- AC → T

8/2008 (seven months after adjuvant chemo completed)
- Chest wall & arm pain, pleuritic-like sternal pain, SOB
- Biopsy-confirmed TNBC lower right lung
- Stains: TTF, chromogranin, synaptophysin, CK 7 & 20, BRST2
- Paclitaxel/anti-angiogenic: excellent response
- Seizures, brain mets

9/2009
- RT → phase III BSI-201 clinical trial
Emerging Treatment Strategies for Triple-Negative Breast Cancer

Hope S Rugo, MD
Clinical Professor of Medicine
Director, Breast Oncology and Clinical Trials Education, University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center
San Francisco, California

Disclosures for Hope S Rugo, MD

<table>
<thead>
<tr>
<th>Disclosures</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support/PI</td>
<td>N/A</td>
</tr>
<tr>
<td>Employee</td>
<td>N/A</td>
</tr>
<tr>
<td>Consultant</td>
<td>N/A</td>
</tr>
<tr>
<td>Major Stockholder</td>
<td>N/A</td>
</tr>
<tr>
<td>Speakers’ Bureau</td>
<td>AstraZeneca Pharmaceuticals LP</td>
</tr>
<tr>
<td>Scientific Advisory Board</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A = Not Applicable
Response to Neoadjuvant Therapy and Long-Term Survival in Patients with Triple-Negative Breast Cancer

Liedtke C et al.


Method

Cases selected from Breast Medical Oncology Database of MD Anderson Cancer Center from patients diagnosed with nonmetastatic breast cancer between 1985-2004 who had received neoadjuvant chemotherapy.

Patients included: 1,118
TNBC patients: 255 (23%)
Non-TNBC patients: 863 (77%)
## Results: pCR Rates as a Function of Triple-Negative Status and Chemotherapy Regimens

<table>
<thead>
<tr>
<th>Regimens</th>
<th>pCR Rates</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients</td>
<td>TNBC</td>
<td>Non-TNBC</td>
<td></td>
<td>p-value</td>
</tr>
<tr>
<td>FAC/FEC/AC (n=308)</td>
<td>8%</td>
<td>20%</td>
<td>5%</td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>TFAC/TFEC (n=588)</td>
<td>19%</td>
<td>28%</td>
<td>17%</td>
<td></td>
<td>0.0072</td>
</tr>
<tr>
<td>Single-agent taxane (n=58)</td>
<td>5%</td>
<td>12%</td>
<td>2%</td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>Other (n=164)</td>
<td>9%</td>
<td>14%</td>
<td>7%</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Total (n=1,118)</td>
<td>15%</td>
<td>22%</td>
<td>11%</td>
<td></td>
<td>0.034</td>
</tr>
</tbody>
</table>

## Conclusions

- Patients with TNBC have increased pCR rates compared to patients with non-TNBC.
  - pCR rates: 22% vs 11% (p=0.034)
- Patients who achieved pCR had excellent survival regardless of receptor status (data not shown).
Breast Cancer Molecular Profiles Predict Tumor Response of Neoadjuvant Doxorubicin and Paclitaxel, the I-SPY TRIAL (CALGB 150007/150012, ACRIN 6657)

Esserman LJ et al.
ASCO 2009; Abstract LBA515.

I-SPY TRIAL: pCR in Context of IHC and Select Molecular Subtypes

<table>
<thead>
<tr>
<th>IHC</th>
<th>pCR (n=190)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR-positive, HER2-negative</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>(n=91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR-positive, HER2-positive</td>
<td>32%</td>
<td>NR</td>
</tr>
<tr>
<td>(n=23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR-negative, HER2-positive</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>(n=23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR-negative, HER2-negative</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>(n=53)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gene Profile Intrinsic Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>pCR (n=144)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A or B (n=72)</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>HER2-enriched (n=22)</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>Basal (n=48)</td>
<td>34%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Conclusions

• In low-risk subsets, low pCR rates are observed, but patients have good outcomes (<5 yrs).
• In high-risk subsets, high pCR rates are highly predictive of improved early outcome.

Esserman LJ et al. ASCO 2009; Abstract LBAS15.

Comparison of Subgroup Analyses of PFS from Three Phase III Studies of Bevacizumab in Combination with Chemotherapy in Patients with HER2-Negative Metastatic Breast Cancer

O’Shaughnessy et al.
SABCS 2009; Abstract 207. (Poster)
Method

- Assess activity of bevacizumab (B) in patients with triple negative breast cancer (ER-, PR-, HER2-) by comparing progression-free survival (PFS) in clinically important subgroups across three studies:
  - E2100: paclitaxel + B 15 mg/kg
  - AVADO: docetaxel + B 7.5 or 15 mg/kg or placebo (P)
  - RIBBON-1: capecitabine, taxane or anthracycline + B or P

Results: Improvement in PFS with Addition of B in E2100, AVADO and RIBBON-1

<table>
<thead>
<tr>
<th>Improvement in PFS (mos)</th>
<th>E2100 (n=722)</th>
<th>AVADO* (n = 736)</th>
<th>RIBBON-1** (n=1,237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (Hazard Ratio, HR)</td>
<td>5.5 (0.48)</td>
<td>0.8 (0.70); 0.9 (0.81)</td>
<td>2.9 (0.69); 1.2 (0.64)</td>
</tr>
<tr>
<td>Triple-negative (HR)</td>
<td>5.3 (0.49)</td>
<td>0.8 (0.69); 2.8 (0.53)</td>
<td>1.9 (0.72); 0.3 (0.78)</td>
</tr>
<tr>
<td>Neoadjuvant/adjuvant taxane (HR)</td>
<td>7.3 (0.33)</td>
<td>4.2 (0.62); 1.9 (0.43)</td>
<td>4.5 (0.62); 2.4 (0.65)</td>
</tr>
<tr>
<td>Age ≥ 65 (HR)</td>
<td>4.3 (0.67)</td>
<td>0.8 (0.76); 0.8 (0.68)</td>
<td>2.9 (0.69); 1.6 (0.83)</td>
</tr>
</tbody>
</table>

*B 7.5 mg/kg; 15 mg/kg; ** Capecitabine/B; Taxane/anthracycline/B
Conclusions

• The addition of B led to an increase in median PFS for patients with triple-negative tumors, patients > 65 yr and patients who had received prior adjuvant taxane chemotherapy
• The addition of B consistently improved PFS across a number of clinically relevant subsets, regardless of the chemotherapy backbone used

First-Line Bevacizumab Combination Therapy in Triple-Negative Locally Recurrent (LR)/Metastatic Breast Cancer (mBC): Subpopulation Analysis of Study MO19391 (ATHENA) in >2000 Patients
Thomssen C et al.
SABCS 2009; Abstract 6093. (Poster)
MO19391 (ATHENA) Trial Design (n = 2,251)

Eligibility
HER2-negative
No prior chemotherapy, or concomitant endocrine therapy

Bevacizumab + chemotherapy

• **Bevacizumab** = 10 mg/kg q2wks or 15 mg/kg q3wks
• **Chemotherapy** = taxane alone or in combination (clinician’s choice) or standard chemotherapy if taxane not considered standard of care

Results: Efficacy (median follow-up 12.7 months)

<table>
<thead>
<tr>
<th></th>
<th>TNBC (n = 577)</th>
<th>Non-TNBC (n = 1,593)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to progression (TTP)*</td>
<td>7.2 mos</td>
<td>10.4 mos</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>47%</td>
<td>53%</td>
</tr>
<tr>
<td>Overall Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>216 (37%)</td>
<td>398 (25%)</td>
</tr>
<tr>
<td>BC deaths, n (%)</td>
<td>199 (34%)</td>
<td>339 (21%)</td>
</tr>
</tbody>
</table>

* One patient in whom TTP was recorded before treatment start is not included in the TTP analysis.
Conclusions

The median TTP reported in this analysis for patients with TNBC is within the range reported for median progression free survival in subpopulations of patients with TNBC treated with bev in randomized trials (SABCS 2009; Abstract 207).

Pathologic Complete Response Rates in Young Women With BRCA1-Positive Breast Cancers After Neoadjuvant Chemotherapy

Byrski T et al.
Method

- Cases selected from patients diagnosed with early-onset incident breast cancer at 18 hospitals in Poland between 1996 and 2008 that received neoadjuvant chemotherapy.
- Patients screened for the three founding BRCA1 mutations occurring in Polish families.
- 102 patients identified with a BRCA1 mutation, the majority of which had triple negative breast cancer.

Results: Treatment and Response to Different Chemotherapy Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. Patients Treated</th>
<th>No. of pCRs</th>
<th>% pCRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMF</td>
<td>14</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>AC</td>
<td>23</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>FAC</td>
<td>28</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>AT</td>
<td>25</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>12</td>
<td>10</td>
<td>83</td>
</tr>
</tbody>
</table>

CMF = cyclophosphamide/methotrexate/fluorouracil
AC = doxorubicin/cyclophosphamide
FAC = fluorouracil/doxorubicin/cyclophosphamide
AT = doxorubicin/docetaxel
Conclusions

- Early data suggest that chemotherapy containing doxorubicin and cyclophosphamide or platinum may have the most potential to be beneficial to patients with breast cancer that carry BRCA1 mutations.
- Study limited by small sample size, lack of random assignment or standardization of treatment protocols and its observational nature.

**Trial Design (n = 28): Neoadjuvant Cisplatin**

**Eligibility**
Newly diagnosed, confirmed TNBC pT1,N1-3,M0 or pT2-4,N0-3, M0 (> 1.5 cm), No prior chemotherapy

- **Cisplatin** = 75 mg/m² q3wk × 4

**Results: Response to Cisplatin Neoadjuvant Treatment**

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>95% Conditional CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical response</td>
<td>18 (64)</td>
<td>44% - 81%</td>
</tr>
<tr>
<td>Complete response</td>
<td>4* (14)</td>
<td>—</td>
</tr>
<tr>
<td>Partial response</td>
<td>14 (50)</td>
<td>—</td>
</tr>
<tr>
<td>Good pathologic response</td>
<td>14 (50)</td>
<td>31% - 70%</td>
</tr>
<tr>
<td>(Miller-Payne 3, 4, and 5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathologic complete response</td>
<td>6* (21)</td>
<td>9% - 43%</td>
</tr>
<tr>
<td>Pathologic partial response</td>
<td>8 (29)</td>
<td>—</td>
</tr>
<tr>
<td>Disease progression</td>
<td>4 (14)</td>
<td>—</td>
</tr>
</tbody>
</table>

* Includes 2 patients with BRCA1 germine mutations.
Conclusions

- Neoadjuvant cisplatin demonstrated activity in a subset of patients with TNBC:
  - Miller-Payne grade 3, 4 or 5 pathologic response achieved by 50% of patients.
- Multivariate analysis demonstrated several biomarkers, including low BRCA1 mRNA expression, may predict cisplatin response (data not shown).


Neoadjuvant Cisplatin and Bevacizumab in Triple Negative Breast Cancer (TNBC): Safety and Efficacy

Ryan PD et al.
ASCO 2009; Abstract 551. (Poster)
Trial Design (n = 51): Neoadjuvant Cisplatin Plus Bevacizumab

- Eligibility Confirmed TNBC
- Cisplatin + Bevacizumab
- MRI
- Surgery

• Cisplatin = 75 mg/m2 q3wk x 4
• Bevacizumab = 15 mg/kg q3wk x 3

Results: Response to Neoadjuvant Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic Response (n=45)</td>
<td></td>
</tr>
<tr>
<td>Miller-Payne grade 5 (no tumor left)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Miller-Payne grade 4 (&gt; 90% decrease)</td>
<td>11 (21)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Clinical Response (n=51)</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>14 (27)</td>
</tr>
<tr>
<td>Partial response</td>
<td>27 (53)</td>
</tr>
</tbody>
</table>
Conclusions

• Neoadjuvant cisplatin plus bevacizumab demonstrated activity in patients with TNBC:
  – Miller-Payne grade 4 or 5 pathologic response achieved by 37% of patients.
  – Proportion of evaluable patients that achieved a clinical response was 80%.

Ryan PD et al. ASCO 2009; Abstract 551.

Ixabepilone plus Capecitabine vs. Capecitabine in Patients with Triple Negative Tumors: A Pooled Analysis of Patients from Two Large Phase III Clinical Studies

Rugo HS et al.
SABCS 2008; Abstract 3057 (Poster).
Study Design for CA 163-046 and CA 163-048*

Eligibility
Locally advanced or metastatic breast cancer (MBC)
Pretreated or resistant to taxanes and anthracyclines

Ixabepilone (Ixa)
40mg/m² IV over 3 hr d1 q3wk + Capecitabine 1,000 mg/m² BID 14 days q3wk

Capecitabine (Cape)
1,250 mg/m² BID 14 days q3wk

*Phase III trials with similar design. Data pooled (n=443)

Results: Pooled Analysis of Patients with Triple Negative MBC

<table>
<thead>
<tr>
<th></th>
<th>Ixa + Cape</th>
<th>Cape</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.62</td>
<td>0.67</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>0.52 to 0.77</td>
<td>0.71 to 1.07</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.0001</td>
<td>0.1802</td>
</tr>
</tbody>
</table>

Median PFS

- Ixa + Cape: 4.2 months (95% CI: 3.6-4.4) vs 1.7 months (95% CI: 1.5-2.4)
- Cape: 9.9 months (95% CI: 6.7 to 10.6)

ORR

- Ixa + Cape: 31%
- Cape: 15%
Conclusions

• In the largest clinical data set recorded, Ixa plus Cape in patients with triple negative MBC (TN MBC) resulted in:
  – Prolonged PFS by 2.5 months
  – Doubling of ORR
• Ixa plus Cape did not increase OS compared to Cape alone.
• Cape alone offers little benefit for patients with TN MBC previously treated with an anthracycline and taxane.

Rugo HS et al. SABCS 2008; Abstract 3057.

Eligibility
Primary invasive breast cancer
Centrally confirmed as triple negative
No clinically significant cardiovascular disease

BEATRICE Trial: Estimated enrollment = 2,530 (closed)

Standard chemotherapy
Standard chemotherapy + Bevacizumab

• Bevacizumab = 5 mg/kg/week x 1 year
• Standard chemotherapy = anthracycline with or without taxane or taxane only

NCI Physician Data Query, February 2010
**CALGB 40603 Neoadjuvant Trial Design:**
Target accrual = 362

**Eligibility**
- Stage II-IIIA resectable breast cancer > 1 cm
- HER-2 negative (IHC 0-1+ or FISH <2.0); ER-/PR-negative
- Registered on CALGB-150709

1. Paclitaxel q wk x 12 → Dose Dense (dd) AC, wks 13, 15, 17, 19
2. Paclitaxel + dd AC as in arm 1; Bevacizumab wks 1, 3, 5, 7, 9, 11, 13, 15, 17
3. Paclitaxel + dd AC as in arm 1; Carboplatin wks 1, 4, 7, 10
4. Paclitaxel + dd AC as in arm 1 + Bevacizumab as in arm 2 + Carboplatin as in arm 3

**TITAN Trial Design: Estimated enrollment = 1,800 (open)**

**Eligibility**
- Histologically confirmed invasive unilateral breast cancer
- Completion of loco-regional surgery
- HER2-, PR- and ER-negative

- Doxorubicin + Cyclophosphamide → Ixabepilone
- Doxorubicin + Cyclophosphamide → Paclitaxel

- Doxorubicin = 60 mg/m² q21days x 4
- Cyclophosphamide = 600 mg/m² q21days x 4
- Ixabepilone = 40 mg/m² q21days x 4
- Paclitaxel = 80 mg/m² weekly x 12
Finding the Positives in Triple-Negative Breast Cancer: A Three-Part Live CME Webcast Series

Seminar III: Tuesday, March 16, 2010, 8:00 PM - 9:00 PM EST

Thank you for participating. To complete your course evaluation for CME credit, please use the link below.

www.ResearchToPractice.com/CME/CME.ResearchToPractice.com