Optimizing the treatment of Triple Negative Breast Cancer: What Does the Future Hold?

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Breast Medical Oncology
Systems Biology

Sao Paulo, Brazil, 3/2012
A 50 year old woman is diagnosed with intermediate grade, 3.5 cm infiltrating ductal carcinoma, 3 involved axillary lymph nodes, no evidence of distant metastasis (stage II) 
Baseline risk of recurrence ~ 60%

If ER or PR+
Chemotherapy + Endocrine therapy

Residual risk < 25%

If HER2+
Chemotherapy + AntiHER2 therapy

Residual risk < 25%

If triple negative
Chemotherapy...

Residual risk 30%–40%

Adapted from Carey L. Oncologist 2010
Definitions

Triple negative but not basal
~25% others *(any)*

Basal but not triple negative
~25% others *(most are HER2+)*

Clinical (IHC) and Basal-like
~75% concordance

Adapted from Carey L. Oncologist 2010
Triple negative is biologically heterogeneous.

Triple negative eligibility enriches for subtype of biologic interest (basal-like) but will misclassify some.

Prat et al, Mol Oncol 2011
Basil-like Breast Cancer

- 10-20% of tumors
- Low HER2 expression
- Low ER (and related genes)
- Common in BRCA1 carriers
- 50% are p53 mutant
- Very proliferative
The Other Triple Negative?

The Claudin-Low Subtype

- 5-10% of tumors
- Typically triple negative
- Poor prognosis
- Stem cell features
- Low expression of cell-cell proteins
- Lymphocyte infiltrate
- Enriched in residual disease?

Perou et al. SABCS 2009
Basal-like Breast Cancer

Frequent, early relapses

Perou et al. SABCS 2009
Basal-like Breast Cancer: From the Beginning to the End

245 DCIS in population-based study:

<table>
<thead>
<tr>
<th>Subtype</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-like</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>Luminal A</td>
<td>149 (61%)</td>
</tr>
<tr>
<td>Luminal B</td>
<td>23 (9%)</td>
</tr>
<tr>
<td>HER2+/ER-</td>
<td>38 (16%)</td>
</tr>
<tr>
<td>Unclass.</td>
<td>16 (6%)</td>
</tr>
</tbody>
</table>

Molecular subtype persists before and after therapy and in metastases:

Livasy et al, Human Pathol 2007
Basal-like Breast Cancer and Genomic Instability

Array CGH in 89 LABC:

% DNA copy number alterations

Red=gain
Green=loss

Genome-wide aberrations

Bergamaschi. Genes Chromosomes Cancer 2006
Basal-like Breast Cancer Risk Factors

**N=1424 Population-based sample**

We need to reevaluate “breast cancer” risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Luminal A N=796</th>
<th>Basal-like N=225</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menarche &lt; 13</td>
<td>1.1 (0.9-1.3)</td>
<td>1.4 (1.1-1.9)</td>
</tr>
<tr>
<td>&gt; 3 children</td>
<td>0.7 (0.5-0.9)</td>
<td>1.9 (1.1-3.3)</td>
</tr>
<tr>
<td>First birth &lt; 26</td>
<td>0.7 (0.5-0.9)</td>
<td>1.9 (1.2-3.2)</td>
</tr>
<tr>
<td>Breastfeeding &gt; 4m</td>
<td>0.9 (0.7-1.1)</td>
<td>0.7 (0.4-0.9)</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>0.8 (0.6-1.0)</td>
<td>0.8 (0.6-1.2)</td>
</tr>
<tr>
<td>Waist:hip &gt; 0.84</td>
<td>1.5 (1.1-1.9)</td>
<td>2.3 (1.4-3.6)</td>
</tr>
</tbody>
</table>

## Characteristics of Basal-like Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>Basal-like (n=100)</th>
<th>HER2+/ER- (n=33)</th>
<th>Luminal A (n=255)</th>
<th>Luminal B (n=77)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>24%</td>
<td>28%</td>
<td>44%</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td><strong>62%</strong></td>
<td>53%</td>
<td>47%</td>
<td>54%</td>
<td>0.06</td>
</tr>
<tr>
<td>III-IV</td>
<td>13%</td>
<td>19%</td>
<td>9%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td><strong>Lymph node +</strong></td>
<td>41%</td>
<td>56%</td>
<td>34%</td>
<td>47%</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Invasive ductal</strong></td>
<td>84%</td>
<td>94%</td>
<td>70%</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td><strong>Invasive lobular</strong></td>
<td>0</td>
<td>0</td>
<td>12%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td><strong>Mixed</strong></td>
<td>6%</td>
<td>6%</td>
<td>9%</td>
<td>12%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Grade III</strong></td>
<td><strong>84%</strong></td>
<td>75%</td>
<td>31%</td>
<td>31%</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Carey LA et al, JAMA 2006
## Breast Cancer Subtypes, Race and Age

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Basal-like</th>
<th>HER2+ (ER-)</th>
<th>Luminal A</th>
<th>Luminal B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premenopausal African-American</strong></td>
<td>97</td>
<td><strong>39%</strong></td>
<td>9%</td>
<td><strong>36%</strong></td>
<td>9%</td>
</tr>
<tr>
<td><strong>Postmenopausal African-American</strong></td>
<td>99</td>
<td><strong>14%</strong></td>
<td>7%</td>
<td><strong>59%</strong></td>
<td>16%</td>
</tr>
<tr>
<td><strong>Premenopausal non African-American</strong></td>
<td>164</td>
<td><strong>16%</strong></td>
<td>6%</td>
<td><strong>51%</strong></td>
<td>18%</td>
</tr>
<tr>
<td><strong>Postmenopausal non African-American</strong></td>
<td>136</td>
<td><strong>16%</strong></td>
<td>6%</td>
<td><strong>58%</strong></td>
<td>16%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>496</td>
<td><strong>20%</strong></td>
<td>7%</td>
<td><strong>51%</strong></td>
<td>16%</td>
</tr>
</tbody>
</table>

P=0.0001

*Carey LA et al, JAMA 2006*
**Triple Receptor-Negative Breast Cancer: The Effect of Race on Response to Primary Systemic Treatment and Survival Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Black (n=100)</th>
<th>White/Other (n=371)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median follow-up (months)</strong></td>
<td>24.5 (0.3-117.0)</td>
<td>25.0 (0.3-102.6)</td>
<td></td>
</tr>
<tr>
<td><strong>pCR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17 (17%)</td>
<td>93 (25.1%)</td>
<td>0.091</td>
</tr>
<tr>
<td>No</td>
<td>83 (83%)</td>
<td>278 (74.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>3-year RFS</strong></td>
<td>68% (56%-76%)</td>
<td>62% (57%-67%)</td>
<td>0.302</td>
</tr>
<tr>
<td><strong>3-year OS</strong></td>
<td>71% (60%-80%)</td>
<td>71% (65%-76%)</td>
<td>0.919</td>
</tr>
</tbody>
</table>

Dawood S et al, J Clin Oncol 2008
Triple Receptor-Negative Breast Cancer: The Effect of Race on Response to Primary Systemic Treatment and Survival Outcomes

No pCR

p=0.214

Dawood S et al, J Clin Oncol 2008
Basal-like Breast Cancer: Pathologic Response to Anthracycline/Taxane

<table>
<thead>
<tr>
<th></th>
<th>T-FAC (N=82)*</th>
<th>AC-T (n=107)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A/B</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Normal-like</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>HER2+/ER-</td>
<td>45%</td>
<td>36%</td>
</tr>
<tr>
<td>Basal-like</td>
<td>45%</td>
<td>26%</td>
</tr>
</tbody>
</table>

* P<0.01

- Sensitive to chemotherapy
- Good outcome in pCR
- Residual disease = poor prognosis
- Additional therapy needed - what?

Pathologic Response to Anthracycline/Taxane by Subtype

369 patients from 3 neoadjuvant datasets

Modified PAM50

Overall pCR rate = 22% (82/369)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Residual dz</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-like</td>
<td>47 (58%)</td>
<td>34 (42%)</td>
</tr>
<tr>
<td>Claudin-low</td>
<td>29 (67%)</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>HER2-enriched</td>
<td>31 (63%)</td>
<td>18 (37%)</td>
</tr>
<tr>
<td>LumA</td>
<td>110 (98%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>LumB</td>
<td>56 (85%)</td>
<td>10 (15%)</td>
</tr>
<tr>
<td>Normal-like</td>
<td>13 (76%)</td>
<td>4 (24%)</td>
</tr>
</tbody>
</table>

Majority of TNBC

Courtesy C. Perou 2010
C9344 Disease-free Survival by ER and HER2

Response to Neoadjuvant Therapy and Long-Term Survival in Patients With Triple-Negative Breast Cancer

Targeted Therapeutics in Triple Negative Breast Cancer

• None known as yet, but they are coming....

• Other approaches?
  • Antiangiogenics
  • EGFR inhibitors
  • BRCA1-driven hypotheses
  • PI3K pathway
  • Src inhibition
  • C-kit
  • AR
  • TRAIL

• Virtually all being tested in conjunction with chemotherapy
  – Chemotherapy is not going away for this subtype

Courtesy of L. Carey
Treatment Choices in Basal-like Breast Cancer

Known: (DNA)
- Chemotherapy
- Chemotherapy
- Chemotherapy

Hypothesized:
- Different chemotherapy
- Antiangiogenics
- EGFR inhibitors
- BRCA1-driven hypotheses
- PI3K pathway
- Src inhibition
- C-kit
- AR
- TRAIL

"You made that diagnosis just to be mean."

Courtesy of L. Carey
Neoadjuvant Ixabepilone in Breast Cancer

St II or III breast cancer, ≥ 3 cm tumor → Ixabepilone 40 mg/m² q3 wks x 4 cycles IV → Surgery

Demographics
No. pts 161
Median age 56 (27-79)
Stage T2/T3/T4 57%/23%/16%

Response in TNBC
n = 42
pCR breast 11 (26%)

Response in all pts
n = 119
pCR breast 18 (15%)

Roche H et al. Ann Oncol 2006 Abst 256P
Phase III Adjuvant Trial: PACS-08

Operable breast cancer
Node-positive: ER-neg, PR-neg, HER2-neg or PR-neg, HER2-neg
Node-negative: ER-neg, PR-neg, HER2-neg
N = 2500

Primary endpoint: DFS at 5 yrs

FEC100 x 3
5-FU 500 mg/m², Epirubicin 100 mg/m², Cyclophosphamide 500 mg/m²
↓ Docetaxel x 3
100 mg/m²

FEC100 x 3
5-FU 500 mg/m², Epirubicin 100 mg/m², Cyclophosphamide 500 mg/m²
↓ Ixabepilone x 3
40 mg/m²

www.clinicaltrials.gov
Randomized Phase II Biomarker Neoadjuvant Study of Sequential AC Followed by Ixabepilone Compared to Sequential AC Followed by Paclitaxel

Population
- ER- / HER2-
- PR + or -
- T2-3, N0-3, M0
- tumor ≥ 2.0 cm

Endpoints
- **Primary**
  - pCR
    - Whole population
    - Biomarker predefined

- **Secondary**
  - Estimate sensitivity/specificity of predictive models
  - Explore gene / protein expression predictive of pCR
  - Clinical ORR
  - Rate of breast conserving surgery
  - Safety

N = 150

Ixabepilone
40 mg/m² IV x 4 cycles

Paclitaxel
80 mg/m² IV weekly x 12

N = 150

Status
- Accrual Goal: 330
- Sites: Global

www.clinicaltrials.gov
Paclitaxel +/- Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer (E2100)

28-day cycle:
- Paclitaxel 90 mg/m^2 D1, 8, and 15.
- Bevacizumab 10 mg/kg D1 and 15.

**Progression-free survival**

- **bevacizumab + paclitaxel (n=368)**
- **Paclitaxel (n=354)**

HR = 0.48; p < 0.0001

99% increase in median PFS

- Median PFS (months):
  - Paclitaxel: 6.7
  - bevacizumab + paclitaxel: 13.3

HR = hazard ratio; bevacizumab Summary of Product Characteristics (SmPC)

Paclitaxel +/- Bevacizumab as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer (E2100)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Progression-free Survival (mo)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone-receptor status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER-, PR-</td>
<td>233</td>
<td>4.6</td>
<td>0.53 (0.40–0.70)</td>
</tr>
<tr>
<td>ER+, PR-</td>
<td>109</td>
<td>9.3</td>
<td>0.45 (0.38–1.14)</td>
</tr>
<tr>
<td>ER+, PR+</td>
<td>789</td>
<td>8.0</td>
<td>0.44 (0.44–0.70)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>237</td>
<td>6.5</td>
<td>0.67 (0.51–0.87)</td>
</tr>
<tr>
<td>Nontaxane</td>
<td>328</td>
<td>7.7</td>
<td>0.69 (0.47–0.87)</td>
</tr>
<tr>
<td>Taxane</td>
<td>108</td>
<td>7.0</td>
<td>0.46 (0.30–0.71)</td>
</tr>
<tr>
<td>Anthracycline therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>259</td>
<td>5.6</td>
<td>1.04 (0.42–0.70)</td>
</tr>
<tr>
<td>No</td>
<td>167</td>
<td>8.0</td>
<td>0.42 (0.42–0.81)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27–49 yr</td>
<td>220</td>
<td>5.5</td>
<td>0.50 (0.38–0.67)</td>
</tr>
<tr>
<td>50–64 yr</td>
<td>305</td>
<td>4.7</td>
<td>0.44 (0.44–0.72)</td>
</tr>
<tr>
<td>65–85 yr</td>
<td>148</td>
<td>7.9</td>
<td>0.77 (0.54–1.09)</td>
</tr>
<tr>
<td>Disease-free interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–24 mo</td>
<td>277</td>
<td>4.9</td>
<td>0.69 (0.47–0.77)</td>
</tr>
<tr>
<td>&gt;24 mo</td>
<td>396</td>
<td>8.2</td>
<td>0.59 (0.48–0.73)</td>
</tr>
<tr>
<td>No. of sites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>373</td>
<td>7.1</td>
<td>0.45 (0.45–0.70)</td>
</tr>
<tr>
<td>=3</td>
<td>300</td>
<td>5.6</td>
<td>0.65 (0.51–0.82)</td>
</tr>
<tr>
<td>Visceral disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>113</td>
<td>7.2</td>
<td>0.65 (0.40–0.97)</td>
</tr>
<tr>
<td>Yes</td>
<td>560</td>
<td>5.8</td>
<td>0.59 (0.49–0.70)</td>
</tr>
<tr>
<td>Bone disease only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>612</td>
<td>5.7</td>
<td>0.57 (0.48–0.68)</td>
</tr>
<tr>
<td>Yes</td>
<td>61</td>
<td>13.0</td>
<td>0.61 (0.33–1.11)</td>
</tr>
<tr>
<td>Measurable disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>492</td>
<td>5.6</td>
<td>0.53 (0.46–0.67)</td>
</tr>
<tr>
<td>No</td>
<td>181</td>
<td>11.4</td>
<td>0.58 (0.49–0.81)</td>
</tr>
<tr>
<td>Overall</td>
<td>673</td>
<td>5.9</td>
<td>0.60 (0.47–0.79)</td>
</tr>
</tbody>
</table>

GEPARquinto

HER2-negative Part

if NC: went to non-responder part

Core biopsy

EC

Doc

Surgery
(d28-335 after last Bev infusion)

ECBev

Sonography

DocBev

E: Epirubicin 90 mg/m²
C: Cyclophosphamide 600 mg/m²
(all 3 week cycles)

Doc: Docetaxel 100 mg/m²
Bev: Bevacizumab 15 mg/kg

Von Minckwitz et al. SABCS 2010.
GEPARquinto: pCR by Subtype

Odds ratio of benefit of Bevacizumab added to EC-

Overall: OR 1.21
ER/PgR negative: OR 1.42
ER/PgR positive: OR 1.05
T1-3 and N0-2: OR 1.17
T4 or N3: OR 1.70

Von Minckwitz et al. SABCS 2010.
Phase III adjuvant study (E5103): schema

- **Primary endpoint:** DFS
- **Treatment:**
  - Doxorubicin: 60mg/m² q3wk
  - Cyclophosphamide: 600mg/m² q3wk
  - Bevacizumab: 15mg/kg q3wk
  - Paclitaxel: 80mg/m² weekly

www.clinicatrials.gov
BEATRICE: Phase III Trial of Adjuvant Bevacizumab Therapy in TNBC

Operable breast cancer
ER-neg, PR-neg, HER2-neg
N = 2530

Standard adjuvant chemotherapy* only

Standard adjuvant chemotherapy* + Bevacizumab x 1 year
15 mg/kg q 3 wk

Primary endpoint: Invasive DFS
*anthracycline / taxane or taxane only

http://clinicaltrials.gov
Hypoxia-related Features and Basal-like Tumors

- Antiangiogenic approaches work in TNBC at least as well as other subtype, possibly more.

Hu, BMC Medicine 2009
Guilt by Association: Basal-like Breast Cancer and BRCA1

Intrinsic gene list applied to Van’t Veer dataset (Nature 2002)

Sorlie T et al. PNAS 03
BRCA1 and Sporadic BBC

• Most breast cancers in BRCA1 mutation carriers are basal-like...

but

• Most basal-like breast cancers are not in BRCA1 mutation carriers

Courtesy of L. Carey
Principles of Cancer Biology: DNA Repair

Chemo, XRT and Other Insults

DNA DAMAGE

Normal cell

BRCA loss

PARP deficient

BRCA loss + PARP deficient

HR: Homologous Recombination
BER: Base Excision Repair

VIABLE VIABLE VIABLE DEAD

“Synthetic Lethality”

That which does not kill you... sets you up so that the next blow will be lethal

Adapted from Carey L. Oncologist 2010 (In Press)
Therapy Choices and BRCA Function?

But if you lose (or inactivate) BRCA1...

Modified form Kennedy et al. J Natl Cancer Inst 2004
Randomized Phase II Trial of BSI-201 plus Gemcitabine/Carboplatin in Metastatic “Triple Negative” Breast Cancer

Metastatic TNBC (n = 123)

BSI-201 5.6 mg/kg d 1, 4, 8, 11 + Gemcitabine 1000 mg/m² + Carboplatin AUC 2 d 1, 8 q3w

Gemcitabine 1000 mg/m² + Carboplatin AUC 2 d 1, 8 q3w

Restage every 2 cycles

Key inclusion criteria
• ≤ 2 prior chemotherapies for MBC
• No prior gemcitabine, platinum agent, or PARP inhibitor

Primary endpoints: CBR (CR + PR + SD ≥ 6 months), safety
Secondary endpoints: ORR, PFS, OS

Crossover to experimental arm allowed at progression

O’Shaughnessy et al. J Clin Oncol 2009 Abst 3
# Randomized Phase II Trial of BSI-201 in Triple Negative MBC: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>BSI-201 + Gem/Carbo (n = 42)</th>
<th>Gem/Carbo (n = 44)</th>
<th>( P ) Value (HR [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor Response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>20 (48%)</td>
<td>7 (16%)</td>
<td>.002</td>
</tr>
<tr>
<td>CBR</td>
<td>26 (62%)</td>
<td>9 (21%)</td>
<td>.0002</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>(n = 57)</td>
<td>(n = 59)</td>
<td></td>
</tr>
<tr>
<td>mPFS</td>
<td>6.9 months</td>
<td>3.3 months</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>mOS</td>
<td>9.2 months</td>
<td>5.7 months</td>
<td>0.342 [0.200-0.584]</td>
</tr>
</tbody>
</table>

O’Shaughnessy et al. J Clin Oncol 2009 Abst 3
**Progression-Free Survival**

- **BSI-201 + Gem/CARBO (n = 57)**
  - Median PFS = 6.9 months

- **Gem/CARBO (n = 59)**
  - Median PFS = 3.3 months

- \( P < 0.0001 \)
- \( HR = 0.342 \) (95% CI, 0.200-0.584)

O’Shaughnessy et al. J Clin Oncol 2009 Abst 3
Overall Survival

- BSI-201 + Gem/Carbo (n = 57)
  Median OS = 9.2 months
- Gem/Carbo (n = 59)
  Median OS = 5.7 months

P = 0.0005
HR = 0.348 (95% CI, 0.189-0.649)

O’Shaughnessy et al. J Clin Oncol 2009 Abst 3
Sanofi-aventis Press Release

Sanofi-aventis Reports Top-line Results from Phase III Study with BSI-201 in Metastatic Triple-Negative Breast Cancer

Paris, France - January 27, 2011 - Sanofi-aventis (EURONEXT: SAN and NYSE: SNY) and its subsidiary, BiPar Sciences, today announced that a randomized Phase III trial evaluating BSI-201 (iniparib*) in patients with metastatic triple-negative breast cancer (mTNBC) did not meet the pre-specified criteria for significance for co-primary endpoints of overall survival and progression-free survival.

Importantly, the results of a pre-specified analysis in patients treated in the second- and third-line setting demonstrate an improvement in overall survival and progression-free survival, consistent with what was seen in the Phase II study. The overall safety analysis indicates that the addition of BSI-201 did not significantly add to the toxicity profile of gemcitabine and carboplatin.

"While this trial did not meet its primary goal, we believe that the improvement in overall survival and progression-free survival in patients in the second- and third-line setting are important findings," said Dr. Debasish Roychowdhury, M.D. Senior Vice President and Head of sanofi-aventis Oncology. "We are conducting in-depth analysis to gain further insight into these Phase III results. Sanofi-aventis remains committed to improving outcomes for patients with triple negative breast cancer where there is high unmet medical need."

Sanofi-aventis plans to discuss these data with United States and European health authorities in the near future. Full study results will be presented at an upcoming major oncology conference. Patients with questions are encouraged to consult with their treating physicians. The current clinical development program for BSI-201 continues in breast, lung and other cancers.

* Iniparib is the United States Adopted Name (USAN) for the investigational agent BSI-201.
Randomized Phase III Trial in Context

Similar eligibility (< 3 prior Rx, triple negative, stage IV)
Drugs and schedule essentially the same

<table>
<thead>
<tr>
<th></th>
<th>Phase III</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple negative BC</td>
<td>519 (100%)</td>
<td>123 (100%)</td>
</tr>
<tr>
<td>Age</td>
<td>~53</td>
<td>~53</td>
</tr>
<tr>
<td>&gt; 2 involved sites</td>
<td>~60%</td>
<td>~65%</td>
</tr>
<tr>
<td>First-line</td>
<td>~57%</td>
<td>~59%</td>
</tr>
<tr>
<td>DFI</td>
<td>12-15m</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Phase III:**
- Far larger (519 vs 123)
- Co-primary endpoints of OS (p=0.04) and PFS (0.01)

O’Shaughnessy et al, ASCO 2011
Phase III: Results

- Primary statistical endpoints not met
- Numerical signal in favor of iniparib, but effect size small
  - If real, is 1 month advantage in PFS and < 1 month in OS clinically meaningful?

O’Shaughnessy et al, ASCO 2011
Exploratory Analyses

1st line, N=297 (57%)

- GC: 12.6 mos (11.9, NE)
- GCI: 12.4 mos (10.6, NE)

HR=0.65 (0.46, 0.91)

2nd/3rd line, N=222 (43%)

- GC: 8.1 mos (6.6, 10)
- GCI: 10.8 mos (9.7, 3.1)

HR=1.1 (0.78, 1.56)

Interesting, hypothesis-generating

- Adjustment for baseline differences in DFI marginally improved p-value.

O’Shaughnessy et al, ASCO 2011
Phase II Study of Olaparib in BRCA-deficient Advanced Breast Cancer

- **Patient population**
  - Stage IIIB/IIIC/IV
  - Failure of ≥ 1 prior chemotherapy for advanced disease
  - BRCA1 or BRCA2 mutation

- **Single arm, sequential cohort trial design**
  - **Cohort 1** (n = 27): olaparib 400 mg po bid 28 day cycle
  - **Cohort 2** (n = 27): olaparib 100 mg po bid 28 day cycle

- **Primary endpoint**: ORR by RECIST

- **Secondary endpoints included**: PFS and safety
# Phase II Study of Olaparib in BRCA-deficient Breast Cancer: Efficacy and Safety

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Olaparib 400 mg bid (n = 27)</th>
<th>Olaparib 100 mg bid (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>11 (41%)*</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>10 (37%)</td>
<td>6 (22%)</td>
</tr>
<tr>
<td>PFS</td>
<td>5.7 months</td>
<td>3.8 months</td>
</tr>
</tbody>
</table>

*Includes 5 patients that received prior anthracycline, taxane, and capecitabine

<table>
<thead>
<tr>
<th>Grade 3 AE</th>
<th>Olaparib 400 mg bid (n = 27)</th>
<th>Olaparib 100 mg bid (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>4 (15%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (19%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (11%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Tutt et al. J Clin Oncol 2009 CRA501
Questioning “BRCAness”

Single agent olaparib activity essentially limited to BRCA mutation carriers

Gelmon K, ASCO 2010
Phase II Study Veliparib (ABT-888) + Temozololamide

- **Response rate 7% but ONLY in BRCA1/2+ (in them, 38% RR)**
- **Side effects:**
  - Bone marrow, nausea, chemistry, fatigue
  - Required dose reduction

Isakoff S ASCO 2010
# Neoadjuvant Cisplatin in BRCA1-deficient and Triple Negative Breast Cancer

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Stage</th>
<th>Regimen</th>
<th>Pathological Complete Response, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 mutation (n = 25)</td>
<td>I - III*</td>
<td>Cisplatin 75 mg/m² q3w X4</td>
<td>18 (72%)</td>
</tr>
<tr>
<td>Triple negative (n = 28)</td>
<td>II - III</td>
<td>Cisplatin 75 mg/m² q3w X4</td>
<td>6 (22%)**</td>
</tr>
<tr>
<td>Triple negative (n = 51)</td>
<td>II - III</td>
<td>Cisplatin 75 mg/m² q3w X4 + bevacizumab 15 mg/kg q3w X3</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Triple negative (n = 78)</td>
<td>II - III</td>
<td>Multiple cisplatin-based***</td>
<td>NA (32%)</td>
</tr>
</tbody>
</table>

*Includes T1 (n = 10) and N0 (n = 18)

**Including both patients with identified BRCA1 mutations

***Retrospective study subgroup analysis

---

Ryan et al. J Clin Oncol 2009
Leone et al. J Clin Oncol 2009
CALGB Triple Negative Neoadjuvant Trial Schema

N=600 ER/PR/HER2- Stage II-IIIB

Paclitaxel → Caroboplatin → No Carboplatin

Dose-dense AC

RT prn

Bevacizumab

Breast imaging
Blood
MUGA
Tumor Biopsy*

Breast imaging
Blood
MUGA

www.clinicatrials.gov
DFCI Neoadjuvant Pilot Study

- **Primary Stage**
  - II-III
  - TNBC

- **Randomize**
  - Cisplatin 75mg/m²
  - ABT888 TBD
  - x 4 cycles

- **Adjuvant**
  - Therapy with anthracycline and taxane regimen

**Courtesy of J. Garber DFCI**
Predictive Models Suggest Subtype Target: Dasatinib

Adapted from Science 2002
Dasatinib in Breast Cancer

11 of 35 breast cancer cell lines were sensitive (IC$_{50}$ < 1μM)

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>IC$_{50}$(μM)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU-565</td>
<td>5.240</td>
<td>3.263</td>
</tr>
<tr>
<td>BT-20</td>
<td>0.165</td>
<td>0.104</td>
</tr>
<tr>
<td>BT-474</td>
<td>6.738</td>
<td>4.152</td>
</tr>
<tr>
<td>BT-549</td>
<td>9.058</td>
<td>1.142</td>
</tr>
<tr>
<td>H3396</td>
<td>8.195</td>
<td>3.255</td>
</tr>
<tr>
<td>HCC1419</td>
<td>2.509</td>
<td>0.228</td>
</tr>
<tr>
<td>HCC1428</td>
<td>7.293</td>
<td>4.144</td>
</tr>
<tr>
<td>HCC1806</td>
<td>0.219</td>
<td>0.151</td>
</tr>
<tr>
<td>HCC1954</td>
<td>0.024</td>
<td>0.017</td>
</tr>
<tr>
<td>HCC38</td>
<td>6.633</td>
<td>3.167</td>
</tr>
<tr>
<td>HCC70</td>
<td>0.034</td>
<td>0.016</td>
</tr>
<tr>
<td>HSS78T</td>
<td>0.647</td>
<td>0.589</td>
</tr>
<tr>
<td>MCF7</td>
<td>&gt;9.524</td>
<td>0.000</td>
</tr>
<tr>
<td>MCF7/Her2</td>
<td>&gt;9.524</td>
<td>0.000</td>
</tr>
<tr>
<td>MDA-MB-157</td>
<td>0.006</td>
<td>0.003</td>
</tr>
<tr>
<td>MDA-MB-231</td>
<td>0.009</td>
<td>0.006</td>
</tr>
<tr>
<td>MDA-MB-435S</td>
<td>7.780</td>
<td>2.364</td>
</tr>
<tr>
<td>MDA-MB-436</td>
<td>&gt;9.524</td>
<td>0.000</td>
</tr>
<tr>
<td>MDA-MB-453</td>
<td>&gt;9.524</td>
<td>--</td>
</tr>
<tr>
<td>MDA-MB-468</td>
<td>7.126</td>
<td>4.096</td>
</tr>
<tr>
<td>SK-BR-3</td>
<td>2.753</td>
<td>0.841</td>
</tr>
<tr>
<td>ZR-75-1</td>
<td>&gt;9.524</td>
<td>0.000</td>
</tr>
<tr>
<td>ZR-75-30</td>
<td>9.263</td>
<td>0.583</td>
</tr>
</tbody>
</table>

Mean IC$_{50}$: 1.576
Median IC$_{50}$: 6.738
Min IC$_{50}$: 0.006
Max IC$_{50}$: 9.524
Range (Log conc): 3.238

Antitumor activity of BMS-354825 in a xenograft model of HER-dependent human breast cancer (KPL4). Animals were dosed at 15 or 30 mg/kg PO, on a BID X 14, 5 days on, 2 days off schedule. Triangles adjacent to X-axis indicate dosing of BMS-354825.

Adapted from Clark, BMS 2006
Gene Expression Predictor of Dasatinib Response

- **Cell line model of dasatinib response:**
  - EphA2
  - Caveolin 1
  - Caveolin 2
  - Pol I and transcript release factor
  - Annexin A2
  - IGFBP-2

- **Human breast cancer "responders":**
  - CK 5/17 +
  - ER/PR/HER2-

Adapted from Clark, BMS 2006
Dasatinib and HR- Breast Cancer

Dasatinib is a potent broad spectrum ATP competitor of 5 critical oncogenic tyrosine kinases/kinases families: BCR-ABL, SRC, c-kit, PDGFRβ, EPH. Activity in TNBC

Gene Expression Patterns In Human ER-negative Breast Cancers

Courtesy of J. Chang
A biologic correlative study of dasatinib, a multi-targeted tyrosine kinase, in “triple-negative” breast cancer patients (PI: Chang)

TNBC Stages II or III → Dasatinib 100mg PO Daily → Standard of Care
Surgery
Adjuvant Chemotherapy
Radiotherapy

www.clinicaltrials.gov
Identification of Targets from "Intrinsic" List

- EGFR/HER1
- CRYAB
- TCF4
- Frizzled 7
- LY6D
- c-KIT
- Keratin 5
- Keratin 17
- P-Cadherin

Sections:
- Basal
- Luminal
- Proliferation
EGFR Inhibition in Basal-Like Cell Lines

SUM102 INHIBITOR GROWTH CURVES

- control
- GSK
- OSI
- Iressa

cells x 10^6

day 1  day 3  day 5  day 7

Cetuximab and Carboplatin

- Cetux->Carbo
- Carbo->Cetux
- Cetux+Carbo 6d
- Cetux+Carbo 3d

% Growth of Control

courtesy C.I. Sartor

courtesy C. Perou
**EGFR-Targeting Trials in Stage IV Triple Negatives**

**US Oncology**
- Weekly Irinotecan Carboplatin
- Weekly Irinotecan Carboplatin + Cetuximab
- PD

**TBCRC 001**
- Cetuximab
- Carboplatin + Cetuximab
- PD

*UNC, UCSF, DFCI, UAB, IU, Mayo, JHU, GT, Baylor, Duke, MDACC, Wash U*
Trials with Cetuximab in Pre-treated Triple-Negative Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Regimen</th>
<th>TBCRC Trial 001</th>
<th>US Oncology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cetuximab</td>
<td>Carboplatin/ Cetuximab</td>
</tr>
<tr>
<td>N</td>
<td>31</td>
<td>71</td>
</tr>
<tr>
<td>ORR</td>
<td>2 (6%)</td>
<td>13 (18%)</td>
</tr>
</tbody>
</table>

Carey L et al. J Clin Oncol 2008 abstr 1009
Insight into Treatment Effect from Serial Biopsies

Pre-therapy:
- EGFR expressed
- Long-term clinical response

Post-therapy:
- One week EGFR pathway
- Inspect into Treatment Effect from Serial Biopsies
- EGFR pathway
- EGFR inactivated by therapy

Confirmed by L. Carey and C. Perou
“One Dumb Tumor is Still Smarter than 10 Smart Oncologists”

16 tumors with great serial RNA:
- 4 EGFR not expressed or pathway not activated - No chance of effect
- 12 EGFR expressed and “activated”
  - Inhibited: 4 (2CB, 2PD)
  - NOT inhibited: 8 (ALL PD) ←Alternate mechanisms keeping activated

Courtesy of L. Carey and C. Perou
**BALI-1 Trial**

- **Cisplatin (n=58)**
  - Time to metastases: median 15 months
  - Liver metastases: ~ 30%
  - Lung metastases: ~ 50%

- **Cisplatin + Cetuximab (n=115)**

  - To reject null hypothesis, combination RR had to be >20% and more than 2x RR of single agent cisplatin

**NOTE:** Open label and response assessed by investigator

Baselga J, ESMO 2010
### BALI-1 Results

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>Cisplatinum + Cetuximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1.7%</td>
<td>1.7%</td>
</tr>
<tr>
<td>PR</td>
<td>8.6%</td>
<td>18.3%</td>
</tr>
<tr>
<td>ORR</td>
<td>10.3% [3.9-21.2%]</td>
<td>20.0% [13.1-28.0%]</td>
</tr>
<tr>
<td>PFS (clinical)</td>
<td>1.5 mos</td>
<td>3.1 mos</td>
</tr>
<tr>
<td>PFS (radiographic)</td>
<td>1.5 mos</td>
<td>3.7 mos</td>
</tr>
</tbody>
</table>

Modest improvement but not enough. Needs selection strategy to pursue further.

Baselga J, ESMO 2010
Targeting the death pathway

Cytotoxicity of TRA-8 vs. TN Cell Lines
An Open Label, Randomized, Phase II Trial of Abraxane, with or without Tigatuzumab in Patients with Metastatic, Triple Negative Breast Cancer

Primary endpoint: ORR in patients with metastatic TNBC
No restriction as to number of prior regimens for metastatic disease as long as patients have adequate PS.

www.clinicaltrials.gov
Androgen Receptor as a Target

- Expression reported in 45-50% of ER-negative tumors

- Adrenal steroids, DHEA and DHEA sulfate, inhibit growth of ER-negative breast cancer cell lines that strongly express AR

- Gene expression profiling has identified a subset of ER-neg and PR-neg tumors
  - Molecular signature suggests an active hormonally regulated transcription program
  - Genes known to be either direct targets of ER or responsive to estrogen

- Evidence that androgen enhanced the growth of MDA-MB-453 breast cancer cells

Doane AS et al. Oncogene 2006;25:3994-4008
Androgen Receptor as Therapeutic Target?

Supervised analysis of 497 androgen-regulated genes in 2 cohorts of ER/PR-negative breast cancer

No clear interaction with HER2 (minority+)
Androgen dependence confirmed in cell line studies

PIK3CA activating mutation associated with Class A

Doane AS, Oncogene 2006

?PI3K/mTOR inhibitors
Phase II Feasibility Study of Bicalutamide for ER(-)PR(-)AR(+) MBC

N = 28 patients
ER(-)PR(-)AR(+)
Metastatic breast cancer
≤ 2 prior chemotherapies
Measurable disease

Bicalutamide 150 mg orally
Continuous daily dosing

Toxicity assessed monthly
Response assessed q3 mo

Objectives:
Primary:
• RR = CR, PR, SD at 6 months

Secondary:
• PFS
• Correlatives

Statistics:
• If > 4 patients have response, AR-blockade is worthy of further study

www.clinicaltrials.gov
Beta-Blocker Use Is Associated With Improved RFS in Patients With TNBC

Melhem-Bertrandt et al. J Clin Oncol 2011
Beta-Blocker Use Is Associated With Improved RFS in Patients With TNBC

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relapse-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Beta-blocker use, yes v no</td>
<td>0.52</td>
<td>0.31 to 0.88</td>
</tr>
<tr>
<td>Age, ≥ 50 v &lt; 50 years</td>
<td>0.81</td>
<td>0.66 to 1.00</td>
</tr>
<tr>
<td>Race, black v non-black</td>
<td>1.37</td>
<td>1.06 to 1.77</td>
</tr>
<tr>
<td>Stage, III v II</td>
<td>1.70</td>
<td>1.38 to 2.08</td>
</tr>
<tr>
<td>Grade, III v II</td>
<td>1.18</td>
<td>0.92 to 1.53</td>
</tr>
<tr>
<td>Hormone receptor status, positive v negative</td>
<td>0.74</td>
<td>0.48 to 1.13</td>
</tr>
<tr>
<td>HER2 status, positive v negative</td>
<td>1.31</td>
<td>0.92 to 1.87</td>
</tr>
<tr>
<td>Triple-negative tumor, no v yes</td>
<td>0.71</td>
<td>0.44 to 1.14</td>
</tr>
<tr>
<td>LVI, positive v negative</td>
<td>1.89</td>
<td>1.54 to 2.32</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-29 v &lt; 25</td>
<td>0.99</td>
<td>0.77 to 1.27</td>
</tr>
<tr>
<td>30+ v &lt; 25</td>
<td>1.16</td>
<td>0.9 to 1.50</td>
</tr>
<tr>
<td>Diabetes, yes v no</td>
<td>1.20</td>
<td>0.77 to 1.88</td>
</tr>
<tr>
<td>Hypertension, yes v no</td>
<td>1.08</td>
<td>0.8 to 1.45</td>
</tr>
<tr>
<td>ACE/ARB use, yes v no</td>
<td>0.82</td>
<td>0.54 to 1.26</td>
</tr>
</tbody>
</table>

Abbreviations: LVI, lymphovascular invasion; BMI, body mass index; HER2, human epidermal growth factor receptor 2; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
Role of PTEN in PI3K Pathway Signaling

- Loss of PTEN and INPp4B in TNBC
- Inactivating mutations or deletions of PTEN/INPP4B lead to AKT activation and increased mTOR activation
- Preclinical evidence aberrations in PI3K/PTEN/AKT are susceptible to mTOR inhibitors

MDACC 2006-0790A phase II, open label randomized clinical trial of standard neoadjuvant chemotherapy (paclitaxel followed by FEC) versus the combination of paclitaxel and RAD001 followed by FEC in women with triple receptor-negative breast cancer.

Gonzalez-Angulo et al. ASCO 2011
## Response Rates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients per Treatment Arm</th>
<th>T-FEC (n=27)</th>
<th>TR-FEC (n=23)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td><strong>Response (12 week)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>3</td>
<td>11.11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>5</td>
<td>18.82</td>
<td>11</td>
<td>47.83</td>
</tr>
<tr>
<td>SD</td>
<td>16</td>
<td>59.26</td>
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<td>47.83</td>
</tr>
<tr>
<td>PD</td>
<td>3</td>
<td>11.11</td>
<td>1</td>
<td>4.35</td>
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<tr>
<td><strong>Response (24 week)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>4</td>
<td>14.81</td>
<td>2</td>
<td>8.7</td>
</tr>
<tr>
<td>PR</td>
<td>16</td>
<td>59.26</td>
<td>11</td>
<td>47.83</td>
</tr>
<tr>
<td>SD</td>
<td>7</td>
<td>25.93</td>
<td>7</td>
<td>30.43</td>
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<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>13.04</td>
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<tr>
<td><strong>pCR</strong></td>
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<tr>
<td>Yes</td>
<td>7</td>
<td>25.93</td>
<td>7</td>
<td>30.43</td>
</tr>
<tr>
<td>No</td>
<td>20</td>
<td>74.07</td>
<td>16</td>
<td>69.57</td>
</tr>
</tbody>
</table>

Gonzalez-Angulo et al. ASCO 2011
PI3K and Ras/MEK/Erk activation in basal-like (triple negative) breast cancer

Modified from. Arteaga at SABCS 2009
Basal-like breast cancer cells are sensitive to MEK inhibitors and basal-like breast tumors exhibit a Ras activation signature.

Modified from Arteaga at SABCS 2009
Inhibition of MEK results in compensatory increase in PI3K/Akt, particularly in cells with loss of PTEN


Modified from Arteaga at SABCS 2009
Combined inhibition of PI3K and MEK is effective in all basal-like preclinical breast cancer models.

Modified from Arteaga at SABCS 2009
Next Generation Sequencing Reveals Co-Activating Events in the MAPK and PI3K/AKT Pathways in Metastatic TNBC

- Multiple subtypes of mTNBC with heterogeneous biology
- Growth and Survival Pathways of Interest in mTNBC include:
  - DNA repair defects
  - IL-6/jak-2/stat-3
  - PI3K
  - VEGF
  - Androgen receptor
  - Src
  - EGFR
  - FGFR
  - ERK

Informed Consent on USON IRB-approved protocol

O’Shaughnessy, et al. SABCS 2011
## Gains and losses in TNBC

<table>
<thead>
<tr>
<th>Gene/Locus</th>
<th>Patient Tumor Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TP53</strong></td>
<td>TNBC-002, TNBC-004, TNBC-007, TNBC-009, TNBC-013</td>
</tr>
<tr>
<td><strong>RB1</strong></td>
<td>TNBC-001, TNBC-009</td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>TNBC-001, TNBC-009</td>
</tr>
<tr>
<td><strong>CTNNA1</strong></td>
<td>TNBC-001, TNBC-006</td>
</tr>
<tr>
<td><strong>ERBB4</strong></td>
<td>TNBC-001, TNBC-002, TNBC-007</td>
</tr>
<tr>
<td><strong>NF1</strong></td>
<td>TNBC-001, TNBC-009</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene/Locus</th>
<th>Patient Tumor Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF</strong></td>
<td>TNBC-002</td>
</tr>
<tr>
<td><strong>WT1</strong></td>
<td>TNBC-004</td>
</tr>
<tr>
<td><strong>WHSC1L1 and FGFR1</strong></td>
<td>TNBC-006</td>
</tr>
<tr>
<td><strong>KRAS</strong></td>
<td>TNBC-010</td>
</tr>
<tr>
<td><strong>MYB and ARAF</strong></td>
<td>TNBC-012</td>
</tr>
</tbody>
</table>

O’Shaughnessy, et al. SABCS 2011
SUMMARY
PI3K and MAPK Pathways

Arrows indicate activation or inhibition:
- Red arrows: activation
- Blue arrows: inhibition

Key to symbols:
- = mutation
- ↑: mRNA up
- ↓: mRNA down
- ▲: AMP
- ▼: DEL

Cell Proliferation
- S6K

Cell Survival
- PI3K
- PTEN
- FBXW7
Summary / Conclusions

- Triple-negative disease has aggressive behavior
  - High proliferation may make it chemosensitive
  - Duration of response typically short
- Much of the biology of TNBC is now being defined
- Chemotherapy is effective in TNBC
- Several promising “targeted” options are being tested
- Validity of approach awaits clinical trials
Thank you !!!!

agonzalez@mdanderson.org