EFFICACY AND TOLERABILITY OF VELIPARIB IN COMBINATION WITH CARBOPLATIN AND PACLITAXEL VS PLACEBO PLUS CARBOPLATIN AND PACLITAXEL IN PATIENTS WITH BRCA1 OR BRCA2 MUTATIONS AND LOCALLY RECURRENT OR METASTATIC BREAST CANCER: A RANDOMIZED, PHASE 2 STUDY

Hyo Sook Han, Véronique Diéras, Mark Robson, Markéta Palácová, P. Kelly Marcom, Agnes Jager, Igor Bondarenko, Dennis Citrin, Mario Campone, Melinda L. Telli, Susan M. Domchek, Michael Friedlander, Bella Kaufman, Christine Ratajczak, Caroline Nickner, Patrick Bonnet, Qin Qin, Jane Qian, Vincent L. Giranda, Stacie P. Shepherd, Steven J. Isakoff, Shannon Puhalla
S2-05 Efficacy and tolerability of veliparib in combination with carboplatin and paclitaxel vs. placebo in patients with BRCA1 or BRCA2 mutations and metastatic breast cancer: a randomized phase 2 study

**Background**

- Approximately half of women who inherit a BRCA1/2 mutation will develop breast cancer before the age of 70 years\(^1\).
- Existing homologous recombination DNA damage repair defects in tumors with BRCA1/2 mutations make them particularly sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors, which interfere with DNA damage repair\(^2\)-\(^3\).
- Emerging clinical data indicate that patients with BRCA mutations may also be particularly sensitive to platinum-containing therapies\(^4\)-\(^6\).
## PARP Inhibitors in Development

<table>
<thead>
<tr>
<th>PARP inhibitor</th>
<th>Pharmaceutical company</th>
<th>Investigational phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veliparib (ABT-888)</td>
<td>AbbVie</td>
<td>Phase III:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Neoadjuvant setting in combination with carboplatin/paclitaxel in triple-negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>\textit{BRCA}1/2-mutated metastatic breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase II/III:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Combination therapy in germline \textit{BRCA}1/2-mutated metastatic breast cancer</td>
</tr>
<tr>
<td>Olaparib (AZD2281)</td>
<td>AstraZeneca</td>
<td>Phase III:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Adjuvant treatment in germline \textit{BRCA}1/2-mutated high-risk, \textit{HER}2-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>primary breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Advanced setting monotherapy in germline \textit{BRCA}1/2-mutated breast cancer</td>
</tr>
<tr>
<td>Niraparib (formerly MK-4827)</td>
<td>Tesaro</td>
<td>Phase III:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Advanced setting in germline \textit{HER}-, \textit{BRCA}1/2-mutated breast cancer</td>
</tr>
<tr>
<td>Talazoparib (BMN 673)</td>
<td>Medivation</td>
<td>Phase III:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Advanced setting monotherapy in germline \textit{BRCA}1/2-mutated breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase II:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Advanced setting \textit{BRCA}1/2 wild-type, triple-negative breast cancer and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>homologous recombination deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Advanced setting \textit{BRCA}1/2-mutated breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Advanced setting in germline \textit{BRCA}-intact breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Neoadjuvant setting in \textit{BRCA}1/2-mutated breast cancer</td>
</tr>
<tr>
<td>Rucarparib (formerly AG 14699)</td>
<td>Clovis Oncology</td>
<td>Phase II:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Advanced setting in patients with known germline \textit{BRCA}1/2-mutated solid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tumors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Adjuvant setting in triple-negative breast cancer or germline \textit{BRCA}1/2-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mutated breast cancer</td>
</tr>
<tr>
<td>CEP-9722</td>
<td>Teva Pharmaceuticals Industries</td>
<td>Phase II:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Advanced setting in solid tumors</td>
</tr>
</tbody>
</table>

**PARP**: Poly(ADP-ribose) polymerase.

Adapted with permission from Livraghi et al. *BMC Med.* (2015) [12].
## PARP inhibitor Breast Trials in Georgia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Georgia Location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Veliparib</strong></td>
<td>A Phase 3 Randomized, Placebo-controlled Trial of Carboplatin and Paclitaxel With or Without Veliparib (ABT-888) in HER2-negative Metastatic or Locally Advanced Unresectable BRCA-associated Breast Cancer</td>
<td>Winship Cancer Institute at Emory University</td>
</tr>
<tr>
<td></td>
<td>Cisplatin With or Without Veliparib in Treating Patients With Stage IV Triple-Negative and/or BRCA Mutation-Associated Breast Cancer</td>
<td>Pearlman Cancer Center in Valdosta</td>
</tr>
<tr>
<td><strong>Olaparib</strong></td>
<td>NSABP B55 Olaparib as Adjuvant Treatment in Patients With Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer (OlympiA)</td>
<td>John B Amos in Columbus, St. Joseph’s/Candler in Savannah, Northside Hospital Cancer Institute, Dekalb Medical, Winship Cancer Institute</td>
</tr>
<tr>
<td></td>
<td>Assessment of the Efficacy and Safety of Olaparib Monotherapy Versus Physicians Choice Chemotherapy in the Treatment of Metastatic Breast Cancer Patients With Germline BRCA1/2 Mutations. (OlympiAD)</td>
<td>NW Georgia Oncology, Marietta (closed to accrual)</td>
</tr>
<tr>
<td><strong>Talazoparib</strong></td>
<td>A Study Evaluating Talazoparib (BMN 673), a PARP Inhibitor, in Advanced and/or Metastatic Breast Cancer Patients With BRCA Mutation vs. TPC (EMBRACA)</td>
<td>University Cancer and Blood Center in Athens, Navicent Health in Macon</td>
</tr>
</tbody>
</table>
Background

- Veliparib is a potent orally bioavailable, selective inhibitor of PARP-1 and PARP-2\(^1\).
- Antitumor activity of veliparib monotherapy in patients with BRCA-positive breast cancer has been observed in phase 1/2 trials\(^2,3\).
- Phase 1 studies suggest promising antitumor activity and acceptable toxicity of veliparib + carboplatin/paclitaxel (C/P) in breast cancer\(^4,5\).
- Veliparib/carboplatin increased pathologic complete response (CR) rate when added to standard neoadjuvant therapy (51% vs 26%) in the I-SPY 2 phase 2 study of patients with triple-negative breast cancer (TNBC)\(^6\).
- Here, safety and efficacy results for the first randomized phase 2 trial of placebo or veliparib with C/P in patients with locally recurrent/metastatic breast cancer and a BRCA1/2 mutation are reported.
BROCADE: Study Design

Locally recurrent or metastatic breast cancer with deleterious BRCA1/2 mutation
N = 290
(86 sites, 20 countries)

Stratification factors for randomization
- ER and PgR status (positive or negative)
- Prior cytotoxic therapy (yes or no)
- ECOG status (0–1 or 2)

Veliparib 120 mg D1–7 BID
+ Carboplatin AUC 6/Paclitaxel 175 mg/m²
Q3W*
N = 97

Placebo
Carboplatin AUC 6/Paclitaxel 175 mg/m²
Q3W*
N = 99

Veliparib 40 mg D1–7 BID
+ TMZ 150 to 200 mg/m² QD, D1–5†
N = 94

*Carboplatin/Paclitaxel administered on D3, 21-day cycle.
†28-day cycle.
Patients were treated until progression or unmanageable toxicity.
If both carboplatin and paclitaxel or if TMZ was discontinued, placebo/veliparib was discontinued.

Veliparib + TMZ results will be presented separately: December 9, 2016, 7.30 am – 9.30 am
SABCS program number: P4-22-02

- ≤ 2 prior lines of chemotherapy
- No prior platinum or PARP inhibitor
- No CNS metastases

- Primary Endpoint: PFS
- Secondary Endpoints: OS, CBR (week 18 progression-free rate), ORR
### Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>Placebo + C/P N = 99</th>
<th>Veliparib + C/P N = 97</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>46 (24–66)</td>
<td>44 (25–65)</td>
</tr>
<tr>
<td><strong>ER/PgR status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER negative and PgR negative</td>
<td>43 (43.4)</td>
<td>40 (41.2)</td>
</tr>
<tr>
<td>ER positive and/or PgR positive</td>
<td>56 (56.6)</td>
<td>57 (58.8)</td>
</tr>
<tr>
<td><strong>HER2 overall status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>92 (92.9)</td>
<td>94 (96.9)</td>
</tr>
<tr>
<td>Positive</td>
<td>7 (7.1)</td>
<td>3 (3.1)</td>
</tr>
<tr>
<td><strong>TNBC</strong></td>
<td>42 (42.4)</td>
<td>40 (41.2)</td>
</tr>
<tr>
<td><strong>Non-TNBC</strong></td>
<td>57 (57.6)</td>
<td>57 (58.8)</td>
</tr>
<tr>
<td><strong>BRCA1 mutation positive</strong></td>
<td>53 (53.5)</td>
<td>51 (52.6)</td>
</tr>
<tr>
<td><strong>BRCA2 mutation positive</strong></td>
<td>46 (46.5)</td>
<td>44 (45.4)</td>
</tr>
<tr>
<td><strong>ECOG status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>93 (93.9)</td>
<td>92 (94.8)</td>
</tr>
<tr>
<td>2</td>
<td>6 (6.1)</td>
<td>5 (5.2)</td>
</tr>
</tbody>
</table>

**Number of prior regimens of cytotoxic therapy (any setting)**

<table>
<thead>
<tr>
<th>Number of regimens</th>
<th>Placebo + C/P N = 99</th>
<th>Veliparib + C/P N = 97</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>23 (23.2)</td>
<td>19 (19.6)</td>
</tr>
<tr>
<td>1</td>
<td>42 (42.4)</td>
<td>47 (48.5)</td>
</tr>
<tr>
<td>2</td>
<td>25 (25.3)</td>
<td>24 (24.7)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>9 (9.1)</td>
<td>7 (7.2)</td>
</tr>
</tbody>
</table>

**Measurable disease at baseline**

<table>
<thead>
<tr>
<th>Measurable disease</th>
<th>Placebo + C/P N = 99</th>
<th>Veliparib + C/P N = 97</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>81 (83.5)</td>
<td>73 (77.7)</td>
</tr>
<tr>
<td>No</td>
<td>16 (16.5)</td>
<td>21 (22.3)</td>
</tr>
</tbody>
</table>

**Number of metastatic sites**

<table>
<thead>
<tr>
<th>Number of metastases</th>
<th>Placebo + C/P N = 99</th>
<th>Veliparib + C/P N = 97</th>
</tr>
</thead>
<tbody>
<tr>
<td>No metastases</td>
<td>5 (5.1)</td>
<td>4 (4.1)</td>
</tr>
<tr>
<td>1</td>
<td>38 (38.4)</td>
<td>39 (40.2)</td>
</tr>
<tr>
<td>2</td>
<td>28 (28.3)</td>
<td>30 (30.9)</td>
</tr>
<tr>
<td>3</td>
<td>18 (18.2)</td>
<td>13 (13.4)</td>
</tr>
<tr>
<td>≥4</td>
<td>10 (10.1)</td>
<td>11 (11.3)</td>
</tr>
</tbody>
</table>

*Positive in either primary site or metastases.

*Status missing for 2 patients in the placebo + C/P and 3 patients in the veliparib + C/P arm.

HER2, human epidermal growth factor receptor 2.
### Treatment-Emergent Grade 3/4 Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo + C/P N = 96</th>
<th>Veliparib + C/P N = 93</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 3/4 AE, n (%)</strong></td>
<td>80 (83.3)</td>
<td>73 (78.5)</td>
</tr>
<tr>
<td><strong>Common hematologic grade 3/4 AEs, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>17 (17.7)</td>
<td>16 (17.2)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3 (3.1)</td>
<td>8 (8.6)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>11 (11.5)</td>
<td>15 (16.1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>53 (55.2)</td>
<td>52 (55.9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>25 (26.0)</td>
<td>29 (31.2)</td>
</tr>
<tr>
<td><strong>Common non-hematologic grade 3/4 AEs, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (7.3)</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
<td>0</td>
<td>5 (5.4) *</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (8.3)</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>Peripheral neuropathy*</td>
<td>5 (5.2)</td>
<td>7 (7.5)</td>
</tr>
</tbody>
</table>
## Treatment-Emergent Adverse Events Leading to Study Drug Interruption, Reduction, or Discontinuation

<table>
<thead>
<tr>
<th>Any adverse event leading to:</th>
<th>Placebo + C/P N = 96</th>
<th>Veliparib + C/P N = 93</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Veliparib/Placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interruption, n (%)</td>
<td>69 (71.9)</td>
<td>70 (75.3)</td>
</tr>
<tr>
<td>Reduction, n (%)</td>
<td>10 (10.4)</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>Discontinuation, n (%)</td>
<td>20 (20.8)</td>
<td>26 (28.0)</td>
</tr>
<tr>
<td><strong>Carboplatin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interruption, n (%)</td>
<td>71 (74.0)</td>
<td>70 (75.3)</td>
</tr>
<tr>
<td>Reduction, n (%)</td>
<td>65 (67.7)</td>
<td>56 (60.2)</td>
</tr>
<tr>
<td>Discontinuation, n (%)</td>
<td>38 (39.6)</td>
<td>42 (45.2)</td>
</tr>
<tr>
<td><strong>Paclitaxel</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interruption, n (%)</td>
<td>69 (71.9)</td>
<td>72 (77.4)</td>
</tr>
<tr>
<td>Reduction, n (%)</td>
<td>51 (53.1)</td>
<td>35 (37.6)*</td>
</tr>
<tr>
<td>Discontinuation, n (%)</td>
<td>33 (34.4)</td>
<td>31 (33.3)</td>
</tr>
</tbody>
</table>
**BROCADE**

**Progression-Free Survival**

<table>
<thead>
<tr>
<th></th>
<th>Placebo + C/P</th>
<th>Veliparib + C/P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>98</td>
<td>95</td>
</tr>
<tr>
<td><strong>Median PFS, months (95% CI)</strong></td>
<td>12.3 (9.3–14.5)</td>
<td>14.1 (11.5–16.2)</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>0.789</td>
<td>(0.536–1.162)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.231</td>
<td></td>
</tr>
</tbody>
</table>

- **Number at risk**:
  - Placebo + C/P: 98, 82, 61, 35, 20, 8, 4, 0, 0
  - Veliparib + C/P: 95, 80, 60, 38, 22, 13, 4, 2, 1

Median (95% CI) PFS, Veliparib + TMZ: 7.4 (5.9–8.5) months; HR = 1.858 (1.278–2.702), P = 0.001. (SABCS program number: P4-22-02)
## PFS by Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Placebo + C/P Event/N</th>
<th>Veliparib + C/P Event/N</th>
<th>HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 mutation</td>
<td>36/53</td>
<td>29/51</td>
<td>0.745 (0.454–1.224)</td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>27/46</td>
<td>20/44</td>
<td>0.783 (0.433–1.417)</td>
</tr>
<tr>
<td>Measurable disease</td>
<td>56/80</td>
<td>43/72</td>
<td>0.809 (0.542–1.209)</td>
</tr>
<tr>
<td>Non-measurable disease</td>
<td>6/16</td>
<td>6/20</td>
<td>0.624 (0.189–2.056)</td>
</tr>
<tr>
<td>No prior cytotoxic therapy</td>
<td>16/23</td>
<td>11/18</td>
<td>1.111 (0.513–2.403)</td>
</tr>
<tr>
<td>Prior cytotoxic therapy</td>
<td>47/75</td>
<td>38/77</td>
<td>0.674 (0.437–1.039)</td>
</tr>
<tr>
<td>ECOG 0</td>
<td>30/49</td>
<td>29/60</td>
<td>0.730 (0.434–1.227)</td>
</tr>
<tr>
<td>ECOG 1–2</td>
<td>33/49</td>
<td>20/35</td>
<td>0.844 (0.482–1.477)</td>
</tr>
<tr>
<td>Age &lt;45 yr</td>
<td>29/47</td>
<td>24/48</td>
<td>0.518 (0.297–0.903)</td>
</tr>
<tr>
<td>Age ≥45 yr</td>
<td>34/51</td>
<td>25/47</td>
<td>1.067 (0.635–1.792)</td>
</tr>
<tr>
<td>TNBC</td>
<td>29/41</td>
<td>24/40</td>
<td>0.815 (0.474–1.401)</td>
</tr>
<tr>
<td>Non-TNBC</td>
<td>34/57</td>
<td>25/55</td>
<td>0.681 (0.403–1.152)</td>
</tr>
</tbody>
</table>

**HR (95% CI)**

- **Favors Veliparib + C/P**
- **Favors Placebo + C/P**
BROCADE: Overall Survival

- Placebo + C/P
  - N = 98
  - Median OS: 25.9 months (95% CI: 20.4–31.8)
- Veliparib + C/P
  - N = 95
  - Median OS: 28.3 months (95% CI: 24.9–NR)

- HR: 0.750
- P value: 0.157
## Tumor Response

<table>
<thead>
<tr>
<th></th>
<th>Placebo + C/P</th>
<th>Veliparib + C/P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N = 98</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ORR (CR + PR), n/N, % (95% CI)</strong></td>
<td>49/80 (61.3%)</td>
<td>56/72 (77.8%)*</td>
</tr>
<tr>
<td></td>
<td>(49.7–71.9)</td>
<td>(66.4–86.7)</td>
</tr>
<tr>
<td><strong>CR, n/N, (%)</strong></td>
<td>3/80 (3.8%)</td>
<td>4/72 (5.6%)</td>
</tr>
<tr>
<td><strong>PR, n/N, (%)</strong></td>
<td>46/80 (57.5%)</td>
<td>52/72 (72.2%)</td>
</tr>
<tr>
<td><strong>CBR</strong></td>
<td>87.0%</td>
<td>90.7%</td>
</tr>
<tr>
<td><strong>(week 18 progression-free rate), % (95% CI)</strong></td>
<td>(78.3–92.4)</td>
<td>(82.2–95.2)</td>
</tr>
<tr>
<td><strong>DOR, median months, (95% CI)</strong></td>
<td>11.1 (9.5–15.7)</td>
<td>11.7 (8.5–14.1)</td>
</tr>
</tbody>
</table>

**Proportion of Patients with ORR, % (95% CI)**

- **Placebo + C/P**: 49/80 (61.3%)  
  P = 0.027
**Conclusions**

- The addition of veliparib to carboplatin/paclitaxel resulted in trends toward improved PFS and OS, and a significant increase in ORR.
  - Final OS analysis will occur when the prespecified number of events is reached.
- The safety profile of veliparib + carboplatin/paclitaxel was comparable to that of carboplatin/paclitaxel alone.
- Addition of veliparib did not increase the frequency of interruption, dose reduction, or discontinuation of veliparib/placebo, carboplatin, or paclitaxel due to adverse events.
- Further evaluation of the efficacy and safety of veliparib with weekly paclitaxel and carboplatin in patients with BRCA-mutated advanced breast cancer is ongoing in the phase 3 randomized trial BROCADE3 (NCT02163694).
DNA repair deficiency biomarkers and MammaPrint High1/(ultra)High2 risk as predictors of veliparib/carboplatin response: results from the neoadjuvant I-SPY 2 TRIAL for high risk breast cancer

Denise Wolf* & Christina Yau*

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*equal contribution
S2-06 DNA repair deficiency biomarker and MammaPrint high1/(ultra)high2 risk as predictors of veliparib/carboplatin response: Results from the neoadjuvant I-SPY2 trial for high risk breast cancer

The I-SPY2 TRIAL Standing Platform

- Phase II, adaptively-randomized neoadjuvant trial
- Shared control arm
  - Standard neoadjuvant chemotherapy
- Simultaneous investigational arms
  - Up to four

* HER2 positive participants will also receive Trastuzumab. An investigational agent may be used instead of Trastuzumab.
The I-SPY2 TRIAL Standing Platform

- **Primary endpoint:** pathologic complete response (pCR)
  - Defined as **no residual invasive cancer in the breast or lymph nodes** (ypT0/is and ypN0)

- **Match therapies with most responsive breast cancer subtypes**
  - Defined by **HR, HER2**, and 70-gene signature (Mammaprint) High1/(ultra)High2 risk (**MP1/2**) status
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- **Primary endpoint**: pathologic complete response (pCR)
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- Agents/combinations **“graduate”** for efficacy = reaching >85% predictive probability of success in a subsequent phase III trial in the most responsive patient subset

- **Biomarker component**: evaluate biomarkers associated with mechanism of action of each investigational treatment, along with the pre-defined subsets
veliparib/carboplatin (VC) combination therapy graduated in the triple negative (TN) subset

- VC was open to Her2- patients

carboplatin

**Damages DNA**

Breast cancer cells

veliparib

**Inhibits DNA repair**

PARP1,2

DNA repair deficient => sensitive to VC
Biomarker proposals for specific predictors of veliparib/carboplatin response

- **BRCA1/2 germline** mutation (Myriad Genetics)

- **PARP1 protein** and cleaved protein levels (RPPA)

- 3 gene expression signatures relating to DNA damage repair deficiency
  - **PARPi-7**
    - 7 gene DNA-repair deficiency signature: BRCA1, CHEK2, MAPKAPK2, MRE11A, NBN, TDG, XPA. Predicts olaparib-sensitivity in cell lines (PMID:22875744)
  - **BRCAness**
    - 77-gene BRCA1/2 deficiency signature. Distinguishes BRCA1 from wildtype (based on PMID:22032731)
  - **CIN70**
    - 70-gene chromosomal instability (PMID:16921376)
  - **MP1/2 class**
Our Pre-specified Biomarker Evaluation Methodology is a 3-Step Process

116 patients available for analysis in V/C & concurrent control arms; 72 VC + 44 controls.

Step 1: Assess relative performance in VC and control arms
- 1) Is the biomarker associated with response in VC arm?
- 2) Is the biomarker associated with response in the control arm?
- 3) Is there a treatment x biomarker interaction of p < 0.05?

PASS – STEP 1

Step 2: Evaluate biomarker in context of graduating signature
- Is there a treatment x biomarker interaction of p < 0.05 adjusting for subtype?

PASS – STEP 2

Step 3: Bayesian modeling of estimated pCR rates
- Within each biomarker-defined subset of interest:
  1) What is the estimated pCR rates in the VC and control arms?
  2) What is the predictive probability of success in a 300-patient Phase 3 trial?
BRCA 1/2 Germline Mutation

- 13% (15/114) of patients were found to carry a deleterious or suspected deleterious BRCA1/2 mutation.
  - Most (73%: 11/15) TN.

BRCA1/2 germline mutation

- 29% (16/56) of wildtype patients have pCR
- 75% (9/12) of BRCA1/2+ patients have pCR

BRCA1/2 germline mutation status associates with response in the VC arm (OR=7.25; p=0.006) but its low prevalence in the control arm (n=3) precluded further evaluation.
PARPi-7 Signature Example

There is a significant biomarker x treatment interaction (p=0.03), which remains upon adjusting for HR status (p=0.025).

PARPi-7 is a specific predictor of VC response.
Specific Predictors of VC Response

- **BRCA1/2 germline mutation** - not evaluable
- **PARP1 protein** and cleaved protein levels (RPPA) - NO
- 3 gene expression signatures relating to DNA damage repair deficiency
  - **PARPi-7** - YES
    - 7-gene DNA-repair deficiency signature: BRCA1, CHEK2, MAPKAPK2, MRE11A, NBN, TDG, XPA. Distinguishes between olaparib-sensitive and resistant cell lines (PMID:22875744)
  - **BRCAAness** - YES
    - 77-gene BRCA1/2 deficiency signature. Distinguishes between BRCA1 and wildtype within TN (based on PMID:22032731)
  - **CIN70** - NO
    - 70-gene chromosomal instability (PMID:16921376)
  - **MP1/2 class** - YES
Concordance between PARP-i7, BRCAness, MP1/2

Concordance between pairs of VC sensitivity biomarkers in TN is just 50-67% (moderate).

(Not identifying exactly the same patients)
### Voting Scheme to Combine Biomarkers

<table>
<thead>
<tr>
<th>Biomarker 1</th>
<th>Biomarker 2</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>Resistant</td>
<td>Sensitive</td>
<td>Resistant</td>
</tr>
<tr>
<td>Sensitive</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>Sensitive</td>
<td>Sensitive</td>
<td><strong>SENSITIVE</strong></td>
</tr>
</tbody>
</table>

Patients positive for both sensitivity markers called ‘sensitive’ (need 2 YES votes!)
Combining Biomarkers Improves Predictive Performance

**Triple Negative**

Nearly all of the specific sensitivity to veliparib/carboplatin is in the 40% of TN patients positive for **BOTH** sensitivity markers.

(Bayesian models using all data – N=116)
Combining Biomarkers Improves Predictive Performance

HR+HER2-

Nearly all of the specific sensitivity to veliparib/carboplatin is in the 9% of HR+HER2- patients positive for BOTH sensitivity markers.

(Bayesian models using all data – N=116)
**BRCA1** methylation status, silencing and treatment effect in the TNT trial: A randomized phase III trial of carboplatin compared with docetaxel for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer

Andrew Tutt, Maggie Chon U Cheang, Lucy Kilburn, Holly Tovey, Cheryl Gillett, Sarah Pinder, Jerry Lanchbury, Jacinta Abraham, Sophie Barrett, Peter Barrett-Lee, Stephen Chan, Patrycja Gazinska, Anita Grigoriadis, Sarah Kernaghan, Katherine Hoadley, Alexander Gutin, Catherine Harper-Wynne, Matthew Hatton, Julie Owen, Peter Parker, Rebecca Roylance, Adam Shaw, Ian Smith, Rose Thompson, Kirsten Timms, Andrew Wardley, Gregory Wilson, Mark Harries, Paul Ellis, Alan Ashworth, James Flanagan, Charles Perou, Judith Bliss, Nazneen Rahman, Robert Brown on behalf of the TNT Trial Management Group and Investigators
S6-01 BRCA1 methylation status, silencing and treatment effect in the TNT trial

TNT Trial design

ER-, PgR-unknown & HER2- or known gBRCA1/2 mut
Metastatic or recurrent locally advanced

BRCAness A Priori subgroup analyses:
• Germline BRCA1/2 mutation
• Mutational Signatures of Homologous Recombination Deficiency (HRD)
• BRCA1 methylation in tumour DNA
• BRCA1 mRNA silencing in tumour RNA

376 patients Randomised (1:1)

Carboplatin (C)
AUC 6 q3w, 6 cycles
On progression, crossover if appropriate
Docetaxel (D)
100mg/m² q3w, 6 cycles

Docetaxel (D)
100mg/m² q3w, 6 cycles
On progression, crossover if appropriate
Carboplatin (C)
AUC 6 q3w, 6 cycles
TNT trial

Biological samples
- 376 patients recruited

Blood
- 288 patients

Negative LN
- 112 patients

Primary tumour
- 309 patients

Positive LN
- 143 patients

Recurrent tumour
- 102 patients

ICR Genetics

TNT tissue bank (Guy’s Hospital / KCL)

- gBRCA (43 inc. 6 not retested)
  BRCA1=31, BRCA2=12

- Myriad (gBRCA, HRD test n=195)

- Myriad / Imperial College
  BRCA1 Methylation (n=224)

Total RNA sequencing - UNC (n=218)

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TNT Trial

Primary Endpoint: Objective response

Randomised treatment - all patients (N=376)

- Carboplatin: 59/188 (31.4%) with OR at cycle 3 or 6
- Docetaxel: 64/188 (34.0%)

Absolute difference (C-D): -2.6% (95% CI -12.1 to 6.9)
Exact p = 0.66

Crossover treatment - all patients (N=183)

- Carboplatin: 23/94 (24.5%) with OR at cycle 3 or 6
  (Crossover = Docetaxel)
- Docetaxel: 21/89 (23.6%)
  (Crossover = Carboplatin)

Absolute difference (D-C): -0.9% (95% CI -11.9 to 12.9)
Exact p = 1

*Denominator excludes those with no first progression and those not starting crossover treatment
TNT Trial

Objective response – gBRCA 1/2 mutation status

Germline BRCA 1/2
Mutation (n=43)
Carboplatin
17/25 (68.0%)

Docetaxel
6/18 (33.3%)

No Germline BRCA 1/2
Mutation (n=273)
Carboplatin
36/128 (28.1%)

Docetaxel
50/145 (34.5%)

Absolute difference (C-D)
34.7% (95% CI 6.3 to 63.1)
Exact p = 0.03

Interaction: randomised treatment & BRCA 1/2 status: p = 0.01
Epigenetic BRCAness: CpG methylation of regulatory regions of BRCA gene

In cancer aberrant methylation of cytosines frequently occurs in the context of CpG dinucleotides in the regulatory regions of genes.

This is associated with transcriptional epigenetic silencing.

The regulatory region of BRCA1 known to be subject to such epigenetic silencing.


The regulatory region of BRCA1 has multiple CpGs

Methylation of these is found to occur in 10-40% of TNBCs (Xu et al Annals of Oncology 24: 1498–1505, 2013)

CpG Methylation associated with silencing of BRCA1 mRNA (Data from TCGA, 2016)
**TNT Trial**

**BRCA1 methylation status**

- 224 primary tumours tested
- Results met QC for 212 patients
  - 33 methylated (18%)
  - 179 non methylated
- 2 cases had both gBRCA1mut and methylation

<table>
<thead>
<tr>
<th></th>
<th>gBRCA mutated</th>
<th>gBRCA Wildtype</th>
<th>gBRCA Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA Methylated</td>
<td>2</td>
<td>27</td>
<td>4</td>
<td>33</td>
</tr>
<tr>
<td>Non BRCA</td>
<td>20</td>
<td>137</td>
<td>22</td>
<td>179</td>
</tr>
<tr>
<td>Methylated</td>
<td>21</td>
<td>109</td>
<td>34</td>
<td>164</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>273</td>
<td>60</td>
<td>376</td>
</tr>
</tbody>
</table>
TNT Trial

Objective response – BRCA1 methylation

<table>
<thead>
<tr>
<th></th>
<th>BRCA1 methylated (n=33)</th>
<th>BRCA1 non-methylated (n = 179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>3/14 (21.4%)</td>
<td>32/93 (34.4%)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8/19 (42.1%)</td>
<td>33/86 (38.4%)</td>
</tr>
</tbody>
</table>

% with OR at cycle 3 or 6 (95% CI)

Absolute difference (C-D)
-20.7% (95% CI -51.6-10.2) Exact p = 0.28

Absolute difference (C-D)
-4.0% (95% CI -18.1 to 10.1) Exact p = 0.64

Interaction: randomised treatment & BRCA methylation status: p = 0.35
# BRCA1 mRNA testing

- 218 primary tumours tested
  - 24 samples failed RNAseq QC
  - 3 duplicates
- Results available for 191 patients
  - 31 silenced (16%)
  - 160 non-silenced
- 184 patients had both mRNA and methylation status available
- 19/29 (66%) methylated samples were silenced

<table>
<thead>
<tr>
<th></th>
<th>Methylated</th>
<th>Non-Methylated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silenced</td>
<td>19</td>
<td>12</td>
<td>31</td>
</tr>
<tr>
<td>Non-Silenced</td>
<td>10</td>
<td>143</td>
<td>153</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>155</td>
<td>184</td>
</tr>
</tbody>
</table>

San Antonio Breast Cancer Symposium December 6-10, 2016
Objective response – BRCA1 mRNA silenced

<table>
<thead>
<tr>
<th>BRCA1 silencing (n=31)</th>
<th>% with OR at cycle 3 or 6 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>4/14 (28.6%)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>11/17 (64.7%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BRCA1 non-silencing (n = 160)</th>
<th>Absolute difference (C-D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>-36.1% (95% CI -68.9 to -3.3)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>0.9% (95% CI -13.5 to 15.3)</td>
</tr>
</tbody>
</table>

Interaction: randomised treatment & BRCA1 silencing status: p = 0.066
TNT Trial

PFS by germline BRCA1/2 mutation status

Progression Free Survival

Median PFS:
- D + BRCA 1/2 mutated: 4.4 (95% CI = 1.9 to 7.0)
- D + BRCA1/2 not mutated: 4.6 (95% CI = 4.2 to 5.5)

Interaction: randomised treatment & BRCA 1/2 status (restricted mean survival): p = 0.002
TNT Trial Conclusions

- BRCA1/2 mutations associated with response to carboplatin in metastatic setting
  - Consider early testing of metastatic patients

- Epigenetic silencing of BRCA in primary tumor was not associated with response to carboplatin in metastatic setting
  - Unknown if methylation status of primary tumor corresponds to metastatic disease
Can we predict response to Platinum and PARP inhibitors?

• Germline BRCA1/2 status not evaluable in ISPY2 but associated with response to carbo in metastatic setting
  – In GeparSixto trial (Doxil/Taxol ± carbo) higher pCR with carboplatin was independent of BRCA status

• Gene expression signatures in ISPY2 not currently available in clinic but promising

• Epigenetic silencing in primary tumors in TNT not associated with response
A randomized phase III trial comparing six cycles of docetaxel and cyclophosphamide (DC) to three cycles of epirubicin and cyclophosphamide followed by three cycles of docetaxel (EC-D) in patients with early breast cancer


for the Danish Breast Cancer Cooperative Group (DBCG)
**DBCG 07–READ Trial Design**

- Anthracycline-based chemotherapy associated with 3% absolute benefit in survival at 10 years compared to CMF (EBCTCG *Lancet* 2012)
- Could overall benefit be due to small number of patients (HER2+, TOP2 alteration, CEP17 duplication) having larger benefit
READ Trial Profile

7687 eligible patients between 2008 and 2012

N = 5160 (67%) TOP2A tested

0.8 < TOP2A/Cen17 ratio < 2.0

N = 4325 Normal TOP2A

N = 835 (16%) Altered TOP2A

N = 2012 (47%) Randomized
## DBCG 07–READ Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>EC-D (N=1001)</th>
<th>DC (N=1011)</th>
</tr>
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<tbody>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 45</td>
<td>205</td>
<td>199</td>
</tr>
<tr>
<td>45–49</td>
<td>199</td>
<td>204</td>
</tr>
<tr>
<td>50–54</td>
<td>230</td>
<td>277</td>
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<tr>
<td>55–59</td>
<td>265</td>
<td>237</td>
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<tr>
<td>60–74</td>
<td>102</td>
<td>94</td>
</tr>
<tr>
<td>Menopausal status</td>
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<td></td>
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<tr>
<td>Premenopausal</td>
<td>508</td>
<td>544</td>
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<tr>
<td>Postmenopausal</td>
<td>493</td>
<td>467</td>
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<tr>
<td>Co-morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent (0)</td>
<td>900</td>
<td>926</td>
</tr>
<tr>
<td>Present (1-2)</td>
<td>101</td>
<td>85</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - 10</td>
<td>131</td>
<td>127</td>
</tr>
<tr>
<td>11 - 20</td>
<td>487</td>
<td>452</td>
</tr>
<tr>
<td>&gt;20</td>
<td>383</td>
<td>432</td>
</tr>
<tr>
<td>Node negative</td>
<td>448</td>
<td>467</td>
</tr>
<tr>
<td>Malignancy grade (only ductal/lobular)</td>
<td></td>
<td></td>
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<tr>
<td>Grade 1</td>
<td>159</td>
<td>176</td>
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<tr>
<td>Grade 2</td>
<td>453</td>
<td>459</td>
</tr>
<tr>
<td>Grade 3</td>
<td>328</td>
<td>311</td>
</tr>
<tr>
<td>Other types</td>
<td>56</td>
<td>53</td>
</tr>
<tr>
<td>ER positive (≥10%)</td>
<td>702</td>
<td>738</td>
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<tr>
<td>HER2 positive (IHC 3+/FISH ≥ 2.0)</td>
<td>113</td>
<td>109</td>
</tr>
<tr>
<td>Ki67 high (&gt; 14%, N=1788)</td>
<td>588</td>
<td>568</td>
</tr>
</tbody>
</table>
DBCG 07–READ Results

Disease Free Survival (%)

HR = 1.00, 95% CI (0.78; 1.28), P = 1.00

Overall Survival (%)

HR = 1.15, 95% CI (0.83; 1.59), P = 0.41
DBCG 07–READ Subgroup Analysis

Lymph node status not included in subgroup analysis
### Timeline and Accrual of ABC Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms</th>
<th>Accrual</th>
<th>Dates of Accrual</th>
<th>Median F/U, yrs</th>
<th>Funding</th>
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<tr>
<td>USOR 06-090</td>
<td>TC TaxAC</td>
<td>1295</td>
<td>MAY 2007 to JUN 2009</td>
<td>6.3</td>
<td>Sanofi</td>
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<tr>
<td>NSABP B-461</td>
<td>TC TaxAC</td>
<td>1077</td>
<td>MAY 2009 to JAN 2012</td>
<td>4.8</td>
<td>Genentech</td>
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<tr>
<td>USOR 07132</td>
<td>*TC-BV</td>
<td>556</td>
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<tr>
<td>NSABP B-49</td>
<td>TC TaxAC</td>
<td>1870</td>
<td>APR 2012 to NOV 2013</td>
<td>2.2</td>
<td>CTEP</td>
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</tbody>
</table>

*not included in ABC Trials analysis*
ABC Trials: Invasive Disease Free Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>4 yr IDFS</th>
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<tbody>
<tr>
<td>TC</td>
<td>2094</td>
<td>220</td>
<td>88.2%</td>
</tr>
<tr>
<td>TaxAC</td>
<td>2062</td>
<td>179</td>
<td>90.7%</td>
</tr>
</tbody>
</table>

Δ=2.5%

HR=1.23, 95% CI (1.01-1.50) P=0.04

Alive and Inv. Disease-free (%)

Years from Randomization
Forest Plot of IDFS By Hormone and Nodal Status

<table>
<thead>
<tr>
<th>Nodes(+), ER/PgR Neg</th>
<th>HR</th>
<th>95% CI</th>
<th>Int.P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.31</td>
<td>0.86-1.99</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>1.58</td>
<td>0.90-2.79</td>
<td>0.71</td>
</tr>
<tr>
<td>4+</td>
<td>1.34</td>
<td>0.62-2.91</td>
<td></td>
</tr>
</tbody>
</table>

Nodes(+), ER or PgR (+)

<table>
<thead>
<tr>
<th>HR</th>
<th>95% CI</th>
<th>Int.P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.69</td>
<td>0.39-1.19</td>
<td></td>
</tr>
<tr>
<td>1.14</td>
<td>0.77-1.69</td>
<td>0.026</td>
</tr>
<tr>
<td>1.46</td>
<td>0.95-2.26</td>
<td></td>
</tr>
</tbody>
</table>

Overall 1.23 1.01-1.50

HR = Hazard Ratio

HR Favors TC       HR Favors TaxAC
0.5 0.6 1.0 1.5 2.0 2.5 3.0

Presented by: Joanne L. Blum, MD, PhD.

Presented By Joanne Blum at 2016 ASCO Annual Meeting
In the Clinic ...

- EC→T equivalent to T in READ trial among TOP2A normal patients
- But TOP2A testing is not routinely performed — 16% of patients had alterations
- No data presented on nonrandomized cohort with TOP2A alterations with EC→T
- ABC Meta-analysis (ASCO 2016) showed benefit for anthracyclines among HR- and HR+/node+ patients
The PI3K inhibitor, taselisib, has enhanced potency in PIK3CA mutant models through a unique mechanism of action

Lori Friedman, Kyle Edgar, Kyung Song, Stephen Schmidt, Donald Kirkpatrick, Lilian Phu, Michelle Nannini, Rebecca Hong, Eric Cheng, Lisa Crocker, Amy Young, Deepak Sampath

Genentech, Inc.
SABCS, December 9, 2016
S6-04 The PI3K inhibitor, taselisib, has enhanced potency in PIK3CA mutant models through a unique mechanism of action.
PIK3CA Pathway in Breast Cancer

• Prognostic value of PIK3CA mutation status is controversial in HER2-negative patients
• PIK3CA mutations associated with resistance to HER2-directed therapies
  – CLEOPATRA: PIK3CA mutation status associated with shorter PFS in both arms
    • wild-type versus mutated PIK3CA in both the control (13.8 v 8.6 months) and pertuzumab groups (21.8 v 12.5 months).
  – NeoALTTO: PIK3CA single gene and pathway mutations associated with lower pCR rate
    • Adding lapatinib to trastuzumab increased pCR
• PIK3CA mutations may be associated with endocrine resistance
• PI3K inhibitors may be best in combination with other targeted therapies due to activation of compensatory feedback loops
Can a PI3K inhibitor with the right balance of activity and tolerability be created?

### Anticipated Safety Profile

#### Number of PI3K Targets Inhibited

- **Pan-PI3K**
  - BKM120 buparlisib, GDC-0941 pictilisib

- **PI3K β-sparing**
  - GDC-0032 taselisib
  - Increased potency on PI3Kα mutant

- **PI3K α-specific**
  - G-102, G-326, BYL-719 alpelisib

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- Therapeutic index is a balance of safety and activity
- PI3K inhibitors have a narrow therapeutic index
What is the role of feedback? PI3K pathway inhibitors relieve negative feedback, leading to attenuation of anti-tumor activity and priming the pathway for reactivation.
Taselisib (GDC-0032) protects against RTK-driven pathway reactivation

- Most PI3K inhibitors are effective at 1 hr and lose potency at 24 hrs
- Taselisib (GDC-0032) is better at suppressing signaling at 24 hrs
Knock-in of mutant PI3Kα increases cellular potency for taselisib, but not other PI3K inhibitors

SW48 isogenic cell lines (PI3Ka WT, mutants); 4 day assay

- Taselisib gains 3-4 fold shift in potency in PI3Kα mutant knock-ins

- PI3K inhibitors that do not shift include: GDC-0941, BYL719, BKM120

This unexpected result implies a unique mechanism of action for taselisib in mutant cells
Taselisib (GDC-0032) leads to degradation of mutant PI3Kα protein, uniquely among clinical compounds.

**HDQP1 breast cancer cells (wildtype)**
- 0 µM GDC-0032: 0.02 units
- 0.16 units
- 0.32 units
- 0.48 units
- 0.64 units
- 0.8 units
- 1.6 units
- 0.16 units
- 0.32 units
- 0.48 units
- 0.64 units
- 0.8 units
- 1.6 units

**HCC1954 breast cancer cells (PIK3CA H1047R)**
- 0 µM GDC-0032: 0.02 units
- 0.16 units
- 0.32 units
- 0.48 units
- 0.64 units
- 0.8 units
- 1.6 units
- 0.16 units
- 0.32 units
- 0.48 units
- 0.64 units
- 0.8 units
- 1.6 units

**p110α protein degradation is:**
- dose-dependent
- time-dependent
- specific to PI3K mutants

**HCC1954 cells (PIK3CA H1047R)**
- 0.16 units
- 0.32 units
- 0.48 units
- 0.64 units
- 0.8 units
- 1.6 units

**GDC-0032**
- 0 µM GDC-0941: 0.18 units
- 0.36 units
- 0.54 units
- 0.72 units
- 0.9 units
- 1.08 units

**GDC-0941**
- 0 µM BYL719: 0.18 units
- 0.36 units
- 0.54 units
- 0.72 units
- 0.9 units
- 1.08 units

**BYL719**
- 0 µM GAPDH: 0.18 units
- 0.36 units
- 0.54 units
- 0.72 units
- 0.9 units
- 1.08 units

Other clinical compounds do not induce degradation of mutant protein.

**Hypothesis**
- PI3K inhibitors which induce degradation of the mutant protein will have greater efficacy which may widen the therapeutic index.
Taselisib induces apoptotic cell death in PIK3CA mutant cells

- 3 day cell death assay
- Taselisib (GDC-0032) compared to PI3Kalpha inhibitors G-326 and BYL719

Taselisib (GDC-0032) shows strongest induction of apoptosis

- Stronger apoptosis is likely the impact of maintaining pathway suppression after feedback has occurred
Taselisib has greater maximal efficacy than other PI3K inhibitors, in PIK3CA mutant xenografts.

HCC-1954 breast cancer xenograft PIK3CA H1047R mutant

Drugs dosed daily in mice at the Maximum Tolerated Dose
- Taselisib (GDC-0032) induces regressions
  - Stasis observed for GDC-0941 and BYL719
PI3K Inhibitor Clinical Trials

• FERGI: Fulvestrant ± Pictilisib N=168
  – No difference in PFS (6.6 vs 5.1 months)

• BELLE3: Fulvestrant ± Buparlisib N=432
  – PFS 3.9 vs 1.8 months (HR 0.67) BUT side effects

• Multiple ongoing clinical trials
  – SANDPIPER: Fulvestrant ± Taselisib
  – Ph1b/2: Enzalutamide + Taselisib for AR+ TNBC
  – BYL719 in combination with letrozole, paclitaxel
Double-blind Concordance Study of Breast Cancer Treatment Recommendations Between Manipal Multidisciplinary Tumor Board and an Artificial Intelligence Advisor for Oncology

IBM’s Watson For Oncology

Somashekar, Rohit, Arun K, Martin S, Andrew N, Amit R

San Antonio Breast Cancer Symposium
San Antonio, Texas, USA
December 6, 2016

Prof. Dr. Somashekar S.P.
MS, MCh (Oncosurgery), FRCS, Ed
Chairman Oncology Manipal Health Enterprise MHEPL
Head Of Department
Department of Surgical & Gynec. Oncology, Robotics & HIPEC
Manipal Comprehensive Cancer Centre
Manipal Hospital, Bangalore, India
S6-07 Double blinded validation study to assess performance of IBM artificial intelligence platform Watson for oncology in comparison to Manipal multidisciplinary tumour board – First study of 638 breast cancer cases

Manipal Hospital, Bangalore

- 600-bed quaternary care facility
- 52 specialties & 60 sub-specialties
- Comprehensive Cancer Center
- Ranked in top 10 multi-specialty hospitals in India
- Best hospital in Bangalore, 10 consecutive years
- 1st hospital in Karnataka, India to introduce robotic surgery
- NABH and NABL accredited
- ISO 9001:2000
How do we stay up to date with ongoing research and treatment options?
Watson for Oncology: Evidence-based, personalized treatment plans

**Dedicated**
- Dedicated Cloud
- Triple redundancy
- Speed

**Corpus**
The Corpus contains Healthline Medical Taxonomy to varied sources from:
- ASCO, EBSCO information services
- 250 textbooks
- 200 medical journals
- 15 million pages of Oncology text
- >10,000 oncology cases

**Expansion**
- Second and Third line treatment options
- New cancers

**Training**
Continuous training by MSKCC oncologists
- Refresh and Maintenance of corpus
- New cases
WFO Output

- Analyzes >100 patient attributes for breast cancer
- Some user attribute abstraction and WFO entry
- RX recommendations ranked in 3 color categories:
  - Green: Recommended Rx (REC)
  - Amber: For Consideration (FC)
  - Red: Not RECommended (N-REC)
- Provides supporting evidence

40 seconds to analyze chart
60 seconds to generate recommendation report
Breast Cancer Concordance Study at Manipal Hospital

Evaluate concordance of treatment recommendations between WFO and local expertise (Manipal Multidisciplinary Tumour Board), MMDT

N = 638 cancer cases, last 3 years

T1*: Joint MMDT Best Decision

T2**: WFO Recommendation

T2*: Joint MMDT Best Decision

T1-T2 Blinded Concordance

T2-T2 Blinded Concordance

* T1 Time of original treatment decision by MMDT in the past (last 1-3 years)
** T2 Time (2016) of WFO's treatment advice and of MMDT's treatment decision upon blinded re-review of non-concordant cases
Overall Concordance: MMDT (@ T1) and WFO (@ T2)

Breast Cancer, N=638

Concordance: FC + REC = 73%
Concordance by Stage: MMDT (@T1) and WFO (@ T2)

Concordance: FC + REC = 79%

Non-Metastatic
n=514

Metastatic
n=124
Comments:

- Study was not designed to assess why recommendations differed or inferiority/superiority.
- Goal was to reduce “cognitive burden” on oncologists by providing clinically actionable insights to assist in treating patients.
- Interesting concept but unclear how this impacts practice.
Scalp Cooling Alopecia Prevention Trial (SCALP)

Julie Nangia, Tao Wang, Polly Niravath, Kristen Otte, Cynthia Osborne, Steven Papish, Frankie Holmes, Jame Abraham, Shari Goldfarb, Jay Courtright, Richard Paxman, Mari Rude, Susan Hilsenbeck, Kent Osborne, Mothaffar Rimawi
S5-02 Scalp Cooling Alopecia Prevention trial (SCALP) for patients with early stage breast cancer

- 229 women from 12/2013 – 9/2016
- 7 US sites (3 academic, 4 community)
- Inclusion: Stage 1 or 2, neo/adjuvant
- Exclusion: migraines, anemia, hypothyroidism, uncontrolled medical condition
SCALP

229 Participants Consented

182 Randomized

Why ineligible?
- Anemia
- Migraines
- Hypothyroidism
- Stage 3 Breast Cancer

119 Device
- 95 Modified ITT

63 Control
- 47 Modified ITT

Why withdrew consent?
- Changed Mind
- Randomized to Control
  - 6 in pre-cooling phase
    - 4 Device (cold/discomfort)
    - 1 Anxiety
    - 1 Claustrophobia
    - 1 during chemo (device cold)

60 additional participants not in this analysis
Results: Primary Outcome

Hair Preservation

Fisher's exact test p<0.0001

- Cooling: 50.5% (40.7%, 60.4%)
- Non-cooling: 0% (0%, 7.6%)
Discussion

Hair Preservation in the cooling group

- **Taxane**
  - Success: 65.1% (52.8%, 75.7%)
  - Failure

- **Anthraclycline**
  - Success: 21.9% (11%, 38.8%)
  - Failure
# Results: Adverse Events

## Adverse Device Effects

<table>
<thead>
<tr>
<th>AADEs (CTCAE V4.0)</th>
<th>Cooling N = 101</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle 1</td>
</tr>
<tr>
<td>Headache</td>
<td>11.9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3%</td>
</tr>
<tr>
<td>Chills</td>
<td>1%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1%</td>
</tr>
<tr>
<td>Sinus pain</td>
<td></td>
</tr>
<tr>
<td>Skin &amp; SQ tissue disorders</td>
<td>1%</td>
</tr>
<tr>
<td>Skin ulceration</td>
<td>1%</td>
</tr>
</tbody>
</table>
## Results: Quality of Life

### Patient Reported Comfort Scale

<table>
<thead>
<tr>
<th>Comfort Scale</th>
<th>Cooling (N = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle 1</td>
</tr>
<tr>
<td>n=101</td>
<td>n=84</td>
</tr>
<tr>
<td>Very Comfortable</td>
<td>11.9%</td>
</tr>
<tr>
<td>Reasonable Comfortable</td>
<td>51.5%</td>
</tr>
<tr>
<td>Comfortable</td>
<td>28.7%</td>
</tr>
<tr>
<td>Uncomfortable</td>
<td>5.9%</td>
</tr>
<tr>
<td>Very Uncomfortable</td>
<td>-</td>
</tr>
<tr>
<td>Not Assessed</td>
<td>2%</td>
</tr>
</tbody>
</table>

Quality of Life Assessments showed no difference
Thank you