Systemic therapy for TN advanced breast cancer

Javier Cortes,
Ramon y Cajal University Hospital,
Madrid
Vall d’Hebron Institute of Oncology (VHIO) &
Medica Scientia Innovation Research (MedSIR),
Barcelona, Spain
“Triple Negative” Breast Cancer

Immunohistochemistry

- ER and PR <1% nuclear
- HER2 “negative”: IHC 0 or 1+ staining or 2+ IHC staining with negative FISH

Histology

- High grade ductal
Poor Outcome of Metastatic TNBC (N=112)

Initial therapy

First distant relapse

Median D.F.I.

First line chemo

Second line chemo

Third line chemo

“Time on Treatment”

12 weeks

9 weeks

4 weeks

What is ‘Standard Therapy’ For TNBC?

- No specific systemic regimen guidelines exist
- Little data on which to base decisions
- Few historical controls making it challenging to design clinical trials for this subgroup
TNBC: Current Treatment Strategies

- Anthracyclines
- Taxanes
- Capecitabine
- Platinum agents
- Biologic agents

- TNBC paradox: chemosensitive…but relapse more aggressive with worse OS
- Cannot treat with existing targeted therapies (hormonal therapy or trastuzumab)
- Manage same as other BCs with same grade & stage
- Limited data available from prospective trials in this population
  - Best available data mostly subpopulation analyses
CMTN: Antraciclinas vs. Docetaxel

<table>
<thead>
<tr>
<th></th>
<th>CMTN</th>
<th>HER2</th>
<th>Luminal B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel 100 mg/m² x 4 ciclos</td>
<td>29</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>Doxorubicin 75 mg/m² x 4 ciclos</td>
<td>10</td>
<td>55</td>
<td>16</td>
</tr>
</tbody>
</table>

Single agent Neoadjuvant Chemotherapy study with Doxorubicin or Docetaxel for 4 cycles in Stage II-IIIa (> 3 cm)

pCR rate by phenotype

Martin et al, ASCO 2009
# Taxanes For Metastatic TNBC?

## Retrospective subgroup analyses

## Placebo arm data

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>N</th>
<th>Setting</th>
<th>Taxane</th>
<th>Outcome in TNBC</th>
</tr>
</thead>
</table>
| CALGB 9342¹ | III   | 44  | First- or second-line metastatic | Paclitaxel weekly and q3w     | ORR = 26%  
TTF = 2.8 months  
OS = 8.6 months |
| ECOG 2100²  | III   | 110 | First-line metastatic       | Paclitaxel weekly             | ORR = 11.7%⁴  
PFS = 5.3 months |
| AVADO³      | III   | 52  | First-line metastatic       | Docetaxel q3w                 | ORR = 23.1%  
PFS = 6.1 months |

2. O'Shaughnessy, et al. SABCS 2009  
# Capecitabine For Metastatic TNBC?

## Retrospective subgroup analyses

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>N</th>
<th>Setting</th>
<th>Treatment</th>
<th>Outcome in TNBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled analysis(^1)</td>
<td>III</td>
<td>208</td>
<td>Third-line or greater metastatic</td>
<td>Capecitabine</td>
<td>ORR = 15% PFS = 1.7 months</td>
</tr>
<tr>
<td>RIBBON-1(^2)</td>
<td>III</td>
<td>50</td>
<td>First-line metastatic</td>
<td>Capecitabine + placebo</td>
<td>ORR = 24% PFS = 4.2 months</td>
</tr>
</tbody>
</table>

2. Glaspy, et al. EBCC 2010
TNT: Carboplatin vs Docetaxel in Advanced TNBC or BRCA1/2+ BC

Patients with ER-, PgR-/unknown, and HER2- or BRCA1/2+ metastatic or recurrent LA BC (N = 376)

- Primary endpoint: ORR in ITT population
- Secondary endpoints: PFS, OS, ORR (crossover), toxicity
- Subgroup analyses: BRCA1/2 mutation, basal-like subgroups, HRD biomarkers

Carboplatin AUC6 q3w x 6 cycles (n = 188)

Docetaxel 100 mg/m² q3w x 6 cycles (n = 188)

For both arms, crossover upon progression allowed

Tutt A, et al. SABCS 2014
Carboplatin vs Docetaxel in Advanced TNBC or BRCA1/2+ BC (TNT): ORR

**Response at Cycle 3 or 6 (%)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Carboplatin</th>
<th>Docetaxel</th>
<th>Crossover*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Pts (n = 376)</td>
<td>31.4%</td>
<td>35.6%</td>
<td></td>
</tr>
<tr>
<td>C→D D→C Crossover* (All pts; n = 182)</td>
<td>22.8%</td>
<td>25.6%</td>
<td></td>
</tr>
<tr>
<td>BRCA1/2 Mutation (n = 43)</td>
<td>68.0%</td>
<td></td>
<td>33.3%</td>
</tr>
<tr>
<td>No BRCA1/2 Mutation (n = 273)</td>
<td>28.1%</td>
<td></td>
<td>36.6%</td>
</tr>
</tbody>
</table>

*p = .44

*p = .73

*p = .03

*p = .16

Tutt A, et al. SABCS 2014
Carboplatin vs Docetaxel in Advanced TNBC or BRCA1/2+ BC (TNT): Survival

<table>
<thead>
<tr>
<th>Survival, Mos</th>
<th>Carboplatin</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>3.1</td>
<td>4.5</td>
</tr>
<tr>
<td>BRCA 1/2 mutated</td>
<td>6.8</td>
<td>4.8</td>
</tr>
<tr>
<td>BRCA 1/2 not mutated</td>
<td>3.1</td>
<td>4.6</td>
</tr>
<tr>
<td>Median OS</td>
<td>12.4</td>
<td>12.3</td>
</tr>
</tbody>
</table>

Tutt A, et al. SABCS 2014
Bevacizumab-based Therapy: Significant Improvement in PFS

E2100 (IRF assessment)\(^1\)

- Bevacizumab + paclitaxel (n=368)
- Paclitaxel (n=354)

HR=0.48\(^*\) (0.39–0.61)  
p<0.0001

AVADO\(^2\)

- Bevacizumab\(^+\) + docetaxel (n=247)
- Placebo + docetaxel (n=241)

HR=0.67\(^*\) (0.54–0.83)  
p<0.001\(^§\)

RIBBON-1: taxane/anthracycline cohort\(^3\)

- Bevacizumab + taxane/anthracycline (n=415)
- Placebo + taxane/anthracycline (n=207)

HR=0.64\(^*\) (0.52–0.80)  
p<0.0001

RIBBON-1: capecitabine cohort\(^3\)

- Bevacizumab + capecitabine (n=409)
- Placebo + capecitabine (n=206)

HR=0.69\(^*\) (0.56–0.84)  
p=0.0002

* Censored for non-protocol therapy before disease progression  
\(^+\)15mg/kg q3w; \(^§\)Exploratory p-value

## Meta-analysis: Analysis of PFS by Subgroups

<table>
<thead>
<tr>
<th>Baseline risk factor</th>
<th>n</th>
<th>Hazard ratio</th>
<th>(95% CI)</th>
<th>BV better</th>
<th>Non-BV better</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>2447</td>
<td>0.64</td>
<td>(0.58–0.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>1917</td>
<td>0.62</td>
<td>(0.56–0.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>530</td>
<td>0.70</td>
<td>(0.56–0.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple negative (ER- and PgR- and HER2-)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>621</td>
<td>0.63</td>
<td>(0.52–0.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1762</td>
<td>0.64</td>
<td>(0.57–0.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1707</td>
<td>0.66</td>
<td>(0.59–0.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>740</td>
<td>0.60</td>
<td>(0.49–0.74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of metastatic sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>1463</td>
<td>0.62</td>
<td>(0.54–0.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>980</td>
<td>0.64</td>
<td>(0.55–0.75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-free interval</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤24 months</td>
<td>924</td>
<td>0.65</td>
<td>(0.55–0.77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;24 months</td>
<td>1519</td>
<td>0.63</td>
<td>(0.56–0.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior adjuvant/neo-adjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1525</td>
<td>0.60</td>
<td>(0.53–0.68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>922</td>
<td>0.71</td>
<td>(0.60–0.84)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

O’Shaughnessy et al. ASCO 2010
Meta-analysis of First-line Bevacizumab Plus Chemotherapy in taxanes-pretreated Triple-Negative Breast Cancer

Hazard ratio stratified only by study = 0.61 (95% CI 0.40–0.94) p=0.0247*

*Exploratory p-value.
How could TNBCs be stratified?

TNBC

Luminal (A+B)  HER2-enriched

20-30%

CLAR non-Basal-like

70-80%

Basal-like

Claudin-low

Basal-like

BL1, BL2
IM
M, MSL
• Triple negative breast cancer is comprised of 6 molecularly distinct subtypes

  • 10% are “Luminal AR” (LAR)
  • LAR express higher levels of AR mRNA vs other TNBC subtypes
  • LAR breast cancers are heavily enriched in hormonally-regulated pathways
  • Luminal AR is more closely related to hormone receptor positive breast cancer (Luminal A and B) than to other subtypes

BL= Basal Like, IM = Immunomodulatory, ML= Mesenchymal-Like, MSL= Mesenchymal Stem-like, LAR = Luminal AR
# Phase II Trial of Bicalutamide in Patients with Androgen Receptor Positive, Hormone Receptor Negative Metastatic Breast Cancer

Ayca Gucalp, Sara Tolaney, Steven J. Isakoff, et al.

*Clin Cancer Res* Published OnlineFirst August 21, 2013.

Table 2.

<table>
<thead>
<tr>
<th>Pts with clinical benefit on bicalutamide</th>
<th>AR%</th>
<th>ER%</th>
<th>PgR%</th>
<th>HER2</th>
<th>Site of Testing</th>
<th>Site of Mets</th>
<th>Prior Therapy LABC/MBC</th>
<th>DOR on Prior Therapy (weeks)</th>
<th>DOR on bicalutamide (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10-20</td>
<td>1</td>
<td>0</td>
<td>Neg</td>
<td>1^0</td>
<td>LN</td>
<td>0</td>
<td>NA</td>
<td>231+</td>
</tr>
<tr>
<td>#2</td>
<td>&gt;80</td>
<td>3</td>
<td>0</td>
<td>Neg</td>
<td>Met</td>
<td>Gl</td>
<td>0</td>
<td>NA</td>
<td>54</td>
</tr>
<tr>
<td>#3</td>
<td>&gt;80</td>
<td>0</td>
<td>0</td>
<td>-/+</td>
<td>1^0</td>
<td>Breast LN</td>
<td>1</td>
<td>NR</td>
<td>25</td>
</tr>
<tr>
<td>#4</td>
<td>&gt;90</td>
<td>0</td>
<td>0</td>
<td>Neg</td>
<td>1^0</td>
<td>LN Bone</td>
<td>1</td>
<td>158</td>
<td>35</td>
</tr>
<tr>
<td>#5</td>
<td>&gt;50</td>
<td>0</td>
<td>0</td>
<td>Neg</td>
<td>1^0</td>
<td>LN Bone</td>
<td>1</td>
<td>15</td>
<td>43+</td>
</tr>
</tbody>
</table>
Stage 1 Results from a 2-Stage Study of Enzalutamide, an Androgen Receptor (AR) Inhibitor, in Advanced AR+ Triple-Negative Breast Cancer (TNBC)

Figure 4. Clinical Benefit Rate at 16 and 24 Weeks in Stage 1 Evaluable Patients

Length of the horizontal bars indicate duration of PFS.

Tiffany A. Traina, Joyce D’Shaughnessy, Rita Nanda, Andrea Schott, Vardana Abramson, Janvier Currie, Amy Peterson, Julia Cristina Tudor, Martha Blaney, Hirdesh Uppal, Joyce L. Schinberg, Catherine M. Kelly, Maureen Trockman, Ahmad Awada, Eric Winer, Clifford A. Hudis, Peter Schmid, Danna A. Yardeny.

Train TA, et al, SABC 2014
Progression-Free Survival by PREDICT AR Status

ITT Population

0–1 Prior Regimens

ITT = Intent to Treat; mPFS = median progression-free survival; CI = confidence interval

Cortes J, et al, ECCO 2015
Overall Survival by PREDICT AR Status

Data cutoff 1 Jul 2015
ITT = intent to treat; mOS = median survival; CI = confidence interval.

Patients at risk

<table>
<thead>
<tr>
<th>Weeks</th>
<th>PREDICT AR+</th>
<th>PREDICT AR−</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>56</td>
<td>62</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>55</td>
</tr>
<tr>
<td>16</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>24</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td>33</td>
<td>42</td>
<td>27</td>
</tr>
<tr>
<td>41</td>
<td>40</td>
<td>24</td>
</tr>
<tr>
<td>49</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>61</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>64</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>64</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>85</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

PREDICT AR+ mOS 18.0 months
PREDICT AR− mOS 7.5 months

Cortes J, et al, ECCO 2015
Drug versus Biology

PredictAR and prognosis in TNBC treated with chemo

508 TNBC
T-FAC Neoadj Rx

Log Rank p=0.965
Mutational load: somatic mutations act as tumor antigens

Lawrence et al, Nature 2013
Breast cancer has fewer mutations

Missense Mutations by Clinical Subtype. Medians displayed. TCGA Breast cancer.

p<0.0001
Early clinical trial data

- **Phase I KEYNOTE 012**
  - TNBC cohort
  - Pembrolizumab **anti-PD-1**

- **Phase I MPDL3280A**
  - TNBC
  - Atezolizumab **anti-PD-L1**

- **Phase II Atezolizumab + Nab-Pac**
  - TNBC
  - Atezolizumab **anti-PD-L1** + nab-paclitaxel

- **Phase I JAVELIN**
  - TNBC and ER+
  - Avelumab **anti-PD-L1**

- **Phase I KEYNOTE 028**
  - ER+ cohort
  - Pembrolizumab **anti-PD-1**

- **Phase I Tremelimumumab + exemestane**
  - ER+
  - Tremelimumumab **anti-CTLA-4** + exemestane
Atezolizumab in TNBC

Ongoing Phase Ia Study

- Patients with advanced solid or hematologic cancers
- Non-resectable disease or progression on previous anti-cancer therapy\(^a\) (with no current standard therapy)

Target Population:
- TNBC in a Phase Ia study expansion cohort
  - Measurable disease per RECIST v1.1
  - The TNBC cohort initially enrolled PD-L1-selected patients and was later expanded to include all-comers\(^b\)

Treatment:
- Atezolizumab IV q3w at 15 or 20 mg/kg or 1200-mg flat dose

Duration:
- Initially, patients received up to 16 cycles (or ≤ 1 year)
- Later, protocol amendments allowed for:
  - Newly enrolled patients to be treated past PD until loss of clinical benefit per investigator

Objectives:
- Primary endpoint: safety
- Key secondary endpoints: ORR, DOR and PFS (per RECIST v1.1 and irRC)
- Key exploratory endpoints: OS and biomarkers of clinical activity

Schmid P, et al. AACR 2017
Baseline Characteristics

<table>
<thead>
<tr>
<th>Patients (N = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range)</strong></td>
</tr>
<tr>
<td>**ECOG PS, 0</td>
</tr>
<tr>
<td><strong>Visceral metastatic sites</strong></td>
</tr>
<tr>
<td><strong>Bone metastatic sites</strong></td>
</tr>
<tr>
<td><strong>PD-L1 status on IC</strong></td>
</tr>
<tr>
<td><strong>IC2/3 (≥ 5%)</strong></td>
</tr>
<tr>
<td><strong>Median prior systemic therapies (range)</strong></td>
</tr>
<tr>
<td>**Anthracycline</td>
</tr>
<tr>
<td>**Platinum</td>
</tr>
<tr>
<td>**Current line of therapy, 1L</td>
</tr>
</tbody>
</table>

Prior to receiving atezolizumab, most patients were heavily pretreated.

Schmid P, et al. AACR 2017
Objective Response and Stable Disease Rate (by Subgroups)

Schmid P, et al. AACR 2017

- Numerically higher ORRs were observed in IC2/3 and 1L subgroups
- irRC criteria captured non-classical responses to atezolizumab
- Best response of SD were also observed
  - DCR per RECIST v1.1 was 23% in all patients
    - 27% in IC2/3 patients
    - 16% in IC0/1 patients

DCR, disease control rate. * Objective response—evaluable patients. Four patients had unknown PD-L1 status. † Defined as CR + PR + SD = 3 months. Confirmed, investigator-assessed responses are plotted. Patients with missing or unevaluable responses are included (16 per RECIST v1.1 and 23 per irRC). Data cutoff: March 31, 2016.
Change in Tumor Burden On Study

All Response-Evaluable Patients

RECIST v1.1 Response

Clinical benefit was observed in some patients with RECIST v1.1 SD or PD status

Overall TNBC cohort

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Median DOR (range)</th>
<th>Median PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST v1.1</td>
<td>21.1 mo (2.8 to 26.5+)</td>
<td>1.4 mo (1.3, 1.6)</td>
</tr>
<tr>
<td>irRC</td>
<td>21.1 mo (2.8 to 33.9+)</td>
<td>1.9 mo (1.4, 2.6)</td>
</tr>
</tbody>
</table>

irPR, PR per irRC; SLD, sum of target lesion longest diameter. * Re-treatment period not plotted.
Confirmed, investigator-assessed RECIST responses are included for patients with post-baseline tumor measurements. Data cutoff: March 31, 2016.

Schmid P, et al. AACR 2017
Overall Survival by Response Status (RECIST v1.1 and irRC)

- Median OS was 9.3 mo (95% CI: 7.0, 12.6) in all patients (median follow-up, 15.2 mo)
  - Landmark OS rates (95% CI) were: 41% (31, 51) at 1 year, and 22% (12, 32) at both 2 and 3 years

**RECIST v1.1 Criteria**

- 1-y OS: 100%
- 2-y OS: 100%
- 3-y OS: 100%

**irRC Criteria**

- 1-y OS: 100%
- 2-y OS: 100%
- 3-y OS: 100%

**RECIST Response**

- CR/PR (n = 11)
- SD (n = 15)
- PD (n = 70)

**irRC Response**

- CR/PR (n = 15)
- SD (n = 19)
- PD (n = 55)

Pseudo-progression was observed in patients with RECIST PD and long-term OS

- Median survival follow-up (range) was 15.2 mo (0.4+ to 36.7) in all patients, 17.0 mo (0.43+ to 36.7) in IC2/3 patients and 12.8 mo (0.8+ to 16.9) in IC0/1 patients.

- Patients included in the Kaplan-Meier plots were alive for ≥ 6 weeks. Data cutoff: March 31, 2016.
Atezolizumab: WO29522 phase III study TNBC

- **Atezolizumab**: 840mg flat dose given IV on Day 1 and Day 8 q4w
- **Placebo**: given IV on Day 1 and Day 8 q4w
- **Nab-paclitaxel**: 100mg/m² given IV on Days 1, 8 and 15 q4w

- **Primary endpoint**: PFS
- **Secondary endpoints**: OS (ITT and PD-L1-positive populations)
  ORR (ITT and PD-L1-positive populations)
  Duration of response (RECIST v1.1)
  Time to deterioration
  Safety and tolerability

- **Metastatic TNBC**
  - No prior therapy
  - ECOG PS 0–1
- **(n=350)**

- **R 1:1**
  - Atezolizumab + nab-paclitaxel
  - Placebo + nab-paclitaxel
Atezolizumab: NeoTrip – phase III study* neoadjuvant TNBC

- Locally advanced EBC (T3N1; T4a,b,c; any T and N2-3) and inflammatory BC (T4d any N) (n=272)
- Carboplatin: AUC 2 given IV on day 1 and day 8 q3w
- Nab-paclitaxel: 125mg/m² given IV on day 1 and day 8 q3w
- Atezolizumab: 1,200mg IV infusion on day 1 q3w

Primary endpoint: 3 and 5 year EFS
- 5-year EFS in control arm is assumed to be 57%. Clinically meaningful improvement to increase the 5-year EFS to 72% (HR=0.584)

*Sponsored by Fondazione Michelangelo
Phase III: randomised study of atezolizumab in 1L mTNBC in fast progressing patients (MO39193)

Key inclusion criteria:
- Previously untreated inoperable locally advanced or metastatic TNBC
- Relapse during, or <12 months from end of, eBC treatment
- Previous (neo)-adjuvant treatment with both taxane and anthracycline
- Measurable disease

Primary endpoint:
- PFS

Secondary endpoints:
- ORR
- DoR
- CBR
- PFS2
- 12m survival rate
- 18m survival rate
- QoL / PROs
- Safety

1L metastatic TNBC
N=392

R 1:1

Carboplatin/gemcitabine or capecitabine*

Carboplatin/gemcitabine or capecitabine* + atezolizumab

Physician’s choice of chemotherapy + atezolizumab

* 50%/50% split between chemotherapies

PD

PD2

18 months minimum survival follow-up after enrolment
Combination of Immune-and Chemotherapy in TNBC

Eribulin + anti-PD-1 (pembrolizumab)

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>1st line (n=17)</th>
<th>2nd/3rd L (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>34.4%</td>
<td>41.2%</td>
<td>27.3%</td>
</tr>
<tr>
<td>CBR</td>
<td>40.6%</td>
<td>47.1%</td>
<td>36.4%</td>
</tr>
</tbody>
</table>

Tolaney, et al. SABCS 2016
Pembrolizumab single agent in TNBC
Study Design – KEYNOTE-086 Cohort A

Patients
- Age ≥18 y
- Centrally confirmed mTNBC
- ≥1 prior systemic treatment for mTNBC with documented PD on/after most recent therapy
- ECOG PS 0-1
- LDH <2.5 x ULN
- Tumor biopsy sample for TNBC status and PD-L1 evaluation
- No radiographic evidence of CNS metastases
- Measurable disease per RECIST v1.1 by central review

Pembrolizumab 200 mg IV Q3W for 2 years or until PD, intolerable toxicity, patient withdrawal, or investigator decision

N = 170

Protocol-specified follow-up

- Primary end points: ORR and safety
- Secondary end points: DOR, DCR, PFS, OS

\[ ^a <1\% \text{ tumor cells positive for ER and PR by IHC, irrespective of intensity, and HER2 IHC 0 or 1+ or FISH negative.} \]
\[ ^b \text{Assessed in the total population and in the PD-L1-positive population.} \]
\[ ^c \text{DCR = disease control rate = SD ≥24 wk + CR + PR.} \]
<table>
<thead>
<tr>
<th></th>
<th>Total Population&lt;sup&gt;a&lt;/sup&gt; (N = 170)</th>
<th>PD-L1 Positive (n = 105)</th>
<th>PD-L1 Negative (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%) [95% CI]</td>
<td>8 (4.7) [2.3-9.2]</td>
<td>5 (4.8) [1.8-10.9]</td>
<td>3 (4.7) [1.1-13.4]</td>
</tr>
<tr>
<td>DCR&lt;sup&gt;b&lt;/sup&gt;, n (%) [95% CI]</td>
<td>13 (7.6) [4.4-12.7]</td>
<td>10 (9.5) [5.1-16.8]</td>
<td>3 (4.7) [1.1-13.4]</td>
</tr>
<tr>
<td>Best Overall Response, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (0.6)</td>
<td>1 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>7 (4.1)</td>
<td>4 (3.8)</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>35 (20.6)</td>
<td>22 (21.0)</td>
<td>12 (18.8)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>103 (60.6)</td>
<td>66 (62.9)</td>
<td>37 (57.8)</td>
</tr>
<tr>
<td>Not evaluable&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5 (2.9)</td>
<td>2 (1.9)</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>Not able to be assessed&lt;sup&gt;d&lt;/sup&gt;, n (%)</td>
<td>19 (11.2)</td>
<td>10 (9.5)</td>
<td>9 (14.1)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Includes the patient with unknown PD-L1 status. <sup>b</sup>DCR = disease control rate = SD ≥24 wk + CR + PR. <sup>c</sup>Patients who had ≥1 postbaseline tumor assessment, none of which were evaluable. <sup>d</sup>Patients who had no postbaseline tumor assessment because of death, withdrawal of consent, loss to follow-up, or start of new anticancer therapy. Data cutoff date: Nov 10, 2016.
Best Change From Baseline in Target Lesion Size, All Patients

Change From Baseline in Target Lesion Size, Patients With CR, PR, or SD at Any Time Point

Left panel includes patients with ≥1 evaluable postbaseline assessment (n = 143). Right panel includes patients with CR, PR, and SD at any time point (n = 46).

Response assessed per RECIST v1.1 by central review. Increases >100% truncated at 100%.

---

At the time of data cutoff (ie, Nov 20, 2016).

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASC017

Slides are the property of the author. Permission required for reuse.
Overall Survival by Best Overall Response

Events/Pts, n | Median (95% CI)
--- | ---
CR or PR | 0/8 | Not reached (NR-NR)
SD | 6/35 | Not reached (12.7-NR)
PD | 66/103 | 7.1 mo (6.3-8.8)

Patients with response that was nonevaluable (n = 5) or not assessed (n = 19) per RECIST v1.1 by central review are not included. Data cutoff date: Nov 10, 2016.
Pembrolizumab Antitumor Activity in Previously Treated and Previously Untreated mTNBC

Cohort A (N = 170): Previously Treated, Regardless of PD-L1 Expression

- Complete response: 7.6%
- Partial response: 9.5%
- Stable disease ≥24 wk: 4.7%

Cohort B (N = 52): Previously Untreated, PD-L1 Positive

- Complete response: 23.1%

1. Adams S et al. ASCO Annual Meeting; Jun 2-6, 2017; Chicago, IL; abstr 1088; presented Sunday, Jun 4, from 8:00-11:30 am on poster board #80.
Pembrolizumab (pembro) + chemotherapy (chemo) as neoadjuvant treatment for triple negative breast cancer (TNBC): Preliminary results from KEYNOTE-173

- Screening ~28 days
- Biopsy
- Breast MRI
- Cycle
  - Cohort A: Nab-paclitaxel 125 mg/m² IV days 1, 8, and 15 Q3W, Pembrolizumab 200 mg IV day 1 Q3W
  - Cohort B: Nab-paclitaxel 100 mg/m² IV days 1, 8, and 15 Q3W, Carboplatin starting dose of AUC 6 day 1 Q3W, Pembrolizumab 200 mg IV day 1 Q3W
  - Doxorubicin 60 mg/m² IV day 1 Q3W, Cyclophosphamide 600 mg/m² day 1 Q3W
- Breast MRI
- Definitive surgery
  - Tissue collection for pCR assessment

AUC, area under the concentration-time curve; MRI, magnetic resonance imaging; pCR, pathologic complete response; Q3W, every 3 weeks.

An optional biopsy was performed between days 15 and 21 of cycle 3.
Pembrolizumab (pembro) + chemotherapy (chemo) as neoadjuvant treatment for triple negative breast cancer (TNBC): Preliminary results from KEYNOTE-173

Figure 3. Pathologic Complete Response Rates in Cohorts A and B

pCR, pathologic complete response. Point estimates of pCR rates are shown with the corresponding exact 90% confidence intervals (CIs) based on the Clopper-Pearson method.

1 patient had no residual tumor in the breast but declined to undergo axillary lymph node dissection and was therefore not evaluable for ypN status and was counted as a non-pCR.
**KN-119: Randomized Phase III Study of pembrolizumab vs TPC as 2-3L for mTNBC**

- ~600 patients
  - mTNBC
  - One or two prior lines of treatment for metastatic disease
  - Previously treated with an anthracycline and/or taxane in the (neo)adjuvant or metastatic setting
  - LDH < 2.5xULN
  - ECOG PS 0-1
  - No systemic steroids
  - No autoimmune disease (active or history of)
  - No active brain metastases

**Stratification factors**
1. PD-L1 tumor status (positive vs negative)
2. Prior (neo)adjuvant therapy vs de novo metastatic disease

**Primary Endpoints**
- PFS in subjects with PD-L1 positive tumors
- PFS in all subjects
- OS in subjects with PD-L1 positive tumors
- OS in all subjects

**Pembrolizumab**
- 200 mg IV Q3W

**TPC from any one of the following (60% max cap for each drug option):**
- Capecitabine
- Eribulin
- Gemcitabine
- Vinorelbine

**Progressive Disease*/Cessation of Study Therapy**

**Protocol-Specified Follow-Up**

*Treatment may be continued beyond verified 1st radiologic evidence of disease progression according to irRECIST*
KN-355: Randomized Phase III of pembrolizumab + Chemo vs Placebo + Chemo in 1st line mTNBC

828 patients
- Recently or newly obtained tumor biopsy
- Central determination of TNBC and PD-L1
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of surgery or adjuvant treatment, whichever occurred last, ≥6 months prior to randomization
- ECOG PS 0-1
- No systemic steroids >physiologic dose
- No active autoimmune disease that required systemic treatment in past 2 years
- No active CNS metastases

Stratification factors
1. Chemotherapy treatment on study (taxane vs gemcitabine/carboplatin)
2. PD-L1 tumor status (positive vs negative)
3. Prior treatment with same class chemotherapy in the (neo)adjuvant setting (yes vs no)

Primary Endpoints
- PFS in all subjects and PD-L1-positive
- OS in all subjects and PD-L1-positive

Secondary Endpoints
- ORR, DCR, DOR in all subjects and PD-L1-positive
- Safety

Exploratory Endpoints
- irORR, irPFS, irDCR, irDOR
- ePROs
- Correlative studies

Protocol-Specified Follow-Up

Progressive Disease# / Cessation of Study Therapy

2:1

Pembrolizumab + Chemotherapy*

Placebo** + Chemotherapy*

*Paclitaxel, nab-paclitaxel or gemcitabine/carboplatin
**Normal saline

#Treatment may be continued until confirmation of PD
Registration Trial Designs for advanced BRCA mutated breast cancer patients

- gBRCA1 / BRCA2 Carriers with advanced cancer
  - Anthracycline and/or taxane pre-treated

R

Potent PARP inhibitor at MTD as continuous exposure

Primary endpoint PFS

- Physician Choice within SOC options
  - Capecitabine
  - Vinorelbine
  - Eribulin (Gemcitabine)

Niraparib – BRAVO Trial TESARO/EORTC/BIG NCT01905592

BMN 673 – EMBRACA Trial - NCT01945775

Olaparib – OlympiAD – NCT0200622
Olaparib vs Physicians' Choice: Phase 3 OLYMPIAD Study

- HER2-negative metastatic breast cancer
  - ER- and/or PR-positive (HR+) or
  - TNBC
- Deleterious or suspected deleterious gBRCAm
- \( \leq 2 \) prior chemotherapy lines in metastatic setting
- Prior anthracycline and taxane
- HR+ disease progressed on \( \geq 1 \) endocrine therapy, or not suitable
- If prior platinum use:
  - No evidence of progression adjuvant treatment
  - \( \geq 12 \) months since (neo)adjuvant treatment

Olaparib 300 mg tablets bid

Treat until progression

Primary endpoint
- Progression-free survival (RECIST 1.1, BICR)

Secondary endpoints
- Overall survival
- Time to second progression or death
- Objective response rate
- Global HRQoL (EORTC-QLQ-C30)
- Safety and tolerability

Olaparib vs Physicians' Choice:  
*Phase 3 OLYMPIAD Study*

Primary endpoint: centrally evaluated PFS

<table>
<thead>
<tr>
<th></th>
<th>Olaparib 300 mg bid</th>
<th>Chemotherapy TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (%)</td>
<td>163 (79.5)</td>
<td>71 (73.2)</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td>7.0</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Olaparib vs Physicians' Choice:

Phase 3 OLYMPIAD Study: OS

Overall Survival (%)

Months since Randomization

Hazard ratio, 0.90 (95% CI, 0.63–1.29)
P = 0.57

Olaparib (N = 205)

Standard therapy (N = 97)

OLYMPIAD: PFS in Relevant Subgroups
HR+ vs TNBC


Response rate ↑ 21% to 55%
OLYMPIAD: PFS in Relevant Subgroups

Previous platinum; yes vs no

Among patients with metastatic HER2-negative BC and a germline BRCA1/2 mutation in the OLYMPIAD study, the objective response rate with olaparib tablet monotherapy was double that seen with standard chemotherapy TPC.

Median response onset
- Olaparib: 47 days
- Chemotherapy TPC: 45 days

Delaloge S, et al. ESMO 2017. Poster-discussion#243 PD.
QoL in the OLYMPIAD Trial

Adjusted mean (± standard error) change from baseline in global health status/QoL score across all visits of 3.9 (±1.2) vs -3.6 (±2.2; difference 7.5; 95% CI: 2.48, 12.44; P = .0035)

Veliparib in a Randomized Phase 2 Study: BROCADE2

BROCADE: Study Design

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

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

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

*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

Veliparib in a Randomized Phase 2 Study: BROCADE2

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

RR ↑ 61% to 78%

Phase III BROCADE 3 pending…

Neoadjuvant Veliparib in Unselected TNBC: I-SPY2

Talazoparib in BRCA1/2 Mutation Carriers: ABRAZO Trial

Prior Platinum (sensitive) vs 3+ Prior Lines, no Platinum

Maximal Percent Change in Target Lesions by BRCA Mutation Status

Cohort 1

Cohort 2

Overall ORR for BRCA 1 = 23% and BRCA 2 = 33%

*Ongoing subjects as of data cutoff of September 1, 2016.

Talazoparib in BRCA1/2 Mutation Carriers: ABRAZO Trial (cont)

Platinum-Free Interval in Cohort 1

Median time from last platinum dose to progression was 4.0 months (range, 0.03-49.15)

ORR, %
47

ORR, %

0

7

20

Platinum-Free Interval

0-2 months
2-4 months
4-6 months
> 6 months

n = 7
n = 15
n = 10
n = 15

PFS, months

3.7

3.0

2.6

0-2 months
2-4 months
4-6 months
> 6 months

n = 7
n = 15
n = 10
n = 16

Conclusions

• Emerging data continue to support the use of PARP inhibitors in breast cancer

• Olaparib has been the first to demonstrate a superior efficacy compared with standard chemotherapy for advanced breast cancer therapy in gBRCA carriers

• Tolerability of PARP inhibitors as monotherapy appears interesting compared with standard of care
Eribulin Mesylate (E7389): A Novel Tubulin Targeted Agent

1. Eribulin suppresses microtubule polymerization

2. Eribulin has no significant effect on microtubule depolymerization

3. Eribulin sequesters tubulin into non-functional aggregates

103 Jordan MA et al. Mol Cancer Ther 2005;4:1086–95
Eribulin Mesylate (E7389): EMT to MET phenotype

Eribulin Mesylate (E7389): EMT to MET phenotype

### EMBRACE Trial: Eribulin vs TPC

**Overall results (n=762)**

<table>
<thead>
<tr>
<th>Age</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>51</td>
</tr>
<tr>
<td>≥40 - &lt;65</td>
<td>560</td>
</tr>
<tr>
<td>≥65</td>
<td>151</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>703</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>59</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Receptor status</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER/PR +</td>
<td>528</td>
</tr>
<tr>
<td>ER/PR -</td>
<td>187</td>
</tr>
<tr>
<td>Unknown</td>
<td>47</td>
</tr>
</tbody>
</table>

**ER/PR/HER2-negative (n=144)**

<table>
<thead>
<tr>
<th>No. of organs involved</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2</td>
<td>537</td>
</tr>
<tr>
<td>&gt;2</td>
<td>217</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sites of disease</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral</td>
<td>624</td>
</tr>
<tr>
<td>Non-Visceral</td>
<td>130</td>
</tr>
</tbody>
</table>

Based upon a stratified Cox analysis including geographic region, HER2 status, and prior capecitabine therapy as strata.

TPC: Treatment of Physician's Choice

Cortes et al. Lancet 2011
Eribulin vs Capecitabine (Study 301)  
TN population

- Eribulin (n=150, [events=124])  
  Median survival (95% CI): 14.4 (11.6, 15.9) months

- Capecitabine (n=134, [events=121])  
  Median survival (95% CI): 9.4 (7.9, 12.0) months

Hazard ratio (95% CI): 0.70 (0.55, 0.91)  
Stratified log-rank test: P=0.01

No. of subjects at risk:

<table>
<thead>
<tr>
<th></th>
<th>Eribulin</th>
<th>Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>150</td>
<td>134</td>
</tr>
<tr>
<td>0-3</td>
<td>129</td>
<td>113</td>
</tr>
<tr>
<td>4-6</td>
<td>107</td>
<td>88</td>
</tr>
<tr>
<td>7-9</td>
<td>93</td>
<td>63</td>
</tr>
<tr>
<td>10-12</td>
<td>78</td>
<td>47</td>
</tr>
<tr>
<td>13-15</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>16-18</td>
<td>45</td>
<td>19</td>
</tr>
<tr>
<td>19-21</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>22-24</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>25-27</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>28-30</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>31-33</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>34-36</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>37-39</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>40-42</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>43-45</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>46-48</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>49-51</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>52-54</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>55-57</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>58-60</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

LOTUS trial design
AKT inh-based trial

Stratification factors
- (Neo)adjuvant chemotherapy (yes vs no)
- Chemotherapy-free interval (≤12 vs >12 months vs no prior chemotherapy)
- Tumor PTEN status (H-score 0 vs 1−150 vs >150, by Targos IHC)

LOTUS trial design
AKT inh-based trial

- Measurable locally advanced/metastatic TNBC\(^a\) not amenable to curative resection
- No prior systemic therapy for advanced/metastatic disease
- ECOG performance status 0/1
- Archival or newly obtained tumor tissue for central PTEN assessment
- Chemotherapy-free interval ≥6 months (n≈120)

Paclitaxel 80 mg/m\(^2\) days 1, 8, & 15 + ipatasertib 400 mg qd days 1–21 q28d

R 1:1

Treatment until disease progression, intolerable toxicity\(^b\), or withdrawal of consent

Paclitaxel 80 mg/m\(^2\) days 1, 8, & 15 + placebo days 1–21 q28d

ECOG = Eastern Cooperative Oncology Group; FISH/CISH = fluorescence/chromogenic in situ hybridization; IHC = immuno-histochemistry; q28d = every 28 days; qd = once daily; R = randomization.

\(^{a}\)Defined as <1% tumor cell expression of estrogen and progesterone receptors and negative HER2 status (FISH/CISH HER2/CEP17 ratio <2.0, or locally assessed IHC 0 or 1+ [or 2+ but negative by FISH/CISH]).

\(^{b}\)Patients discontinuing paclitaxel or ipatasertib/placebo due to toxicity could continue on single-agent treatment. The protocol did not specify primary prophylactic antidiarrheal use.

Dent R, et al. ASCO 2017
Overview of PFS

ITT population (n=124)
Stratified HR 0.60
(90% CI 0.40–0.91)

PTEN-low population (IHC) (n=48)
Stratified HR 0.59
(90% CI 0.30–1.16)

PIK3CA/AKT1/PTEN-altered tumor population (NGS) (n=42)
Unstratified HR 0.44
(90% CI 0.20–0.87)

ITT population (n=124)
Stratified HR 0.60
(90% CI 0.40–0.91)

PTEN-low population (IHC) (n=48)
Stratified HR 0.59
(90% CI 0.30–1.16)

PIK3CA/AKT1/PTEN-altered tumor population (NGS) (n=42)
Unstratified HR 0.44
(90% CI 0.20–0.87)
ADCs

TNBC is negative for ER, PR, and HER2 \textit{BUT} positive for other cell surface antigens \textbf{→ targets for new ADCs?}

**IMMU-132** (Sacituzumab Govitecan, Immunomedics)
- Trop2 (>80%) – SN-38
- Phase I and II (N=100) in TNBC
- Phase III planned in Q1-2 2017 (EU)
- Breakthrough designation from the FDA for TNBC who have failed prior therapies for MBC

**SAR566658** (Sanofi)
- Phase II in TNBC (N=63)
- No other studies in [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

**SYD985** (SYD)
- HER2 – duocarmicine
- Phase I in HER2 1-3+

**BAY 94-9343** (Anetumab Raptansine, Bayer)
- Mesotelin (20%?) – DM4
- Phase I

**CDX-11** (Glembatumumab vedotin, Celldex)
- gpNMB (40%) – vcMMAE
- Ongoing randomized Phase II (vs. capecitabine)
<table>
<thead>
<tr>
<th>TNBC Subtypes: (Some) Research Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal-like 1:</strong> Cell cycle, DNA repair and proliferation genes</td>
</tr>
<tr>
<td><strong>Basal-like 2:</strong> Growth factor signaling (EGFR, MET, Wnt, IGF1R)</td>
</tr>
<tr>
<td><strong>IM:</strong> Immune cell processes (medullary breast cancer)</td>
</tr>
<tr>
<td><strong>M:</strong> Cell motility and differentiation, EMT processes</td>
</tr>
<tr>
<td><strong>MSL:</strong> Similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)</td>
</tr>
<tr>
<td><strong>LAR:</strong> Androgen receptor and downstream genes, luminal features</td>
</tr>
<tr>
<td><strong>PARPi, ± DNA damaging agents homologous recombination deficiency assay (BRCA-1 ness)</strong></td>
</tr>
<tr>
<td><strong>EGFR (cetuximab, lapatinib)</strong></td>
</tr>
<tr>
<td><strong>Self-renewal pathways (stem cell)</strong></td>
</tr>
<tr>
<td><strong>Wnt</strong></td>
</tr>
<tr>
<td><strong>Notch (PF03084014, AACR 2012)</strong></td>
</tr>
<tr>
<td><strong>Immune check point</strong></td>
</tr>
<tr>
<td><strong>PD1/PDL1, CTLA4</strong></td>
</tr>
<tr>
<td><strong>Vaccines: MUC1, NYO-ESO1</strong></td>
</tr>
<tr>
<td><strong>(eribulin?) Plus</strong></td>
</tr>
<tr>
<td><strong>PI3Ki, RAS/MEK/Erk, MET, PTEN etc, etc</strong></td>
</tr>
<tr>
<td><strong>Agents targeting androgen receptor (enzalutamide, bicalutamide, etc)</strong></td>
</tr>
</tbody>
</table>