Triple-negative breast cancer: A medical update

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Stanford University School of Medicine

November 4, 2016
Outline

- Clinical features of TNBC
- Medical update on therapeutics in TNBC
  - Platinums
  - Lurbinectedin
  - PARP inhibitors
  - Capecitabine after neoadjuvant chemotherapy
  - Immunotherapy
- Current & upcoming studies in TNBC

Will leave time for discussion, Q & A
Important subsets of breast cancers defined by molecular markers

Take away:

• Breast cancer is not one disease
Breast Cancer Prognostic Markers

The breast cancer markers ER, PR and HER2 are *prognostic* (various combinations may be favorable or unfavorable); they also are *predictive* (tell us which types of therapies are likely to be of benefit or not)
Triple-Negative Breast Cancer

- 13% of all breast cancer in California
  - California Cancer Registry 1999-2005; n=87,604

- Varies by ethnicity/race
  - White: 11%
  - Japanese: 11%
  - Chinese: 11%
  - Black: 26%
  - Hispanic: 17%

- Disproportionately affects the young (<40)

Current Status

- Standard treatment for early-stage TNBC in 2016 consists of combination chemotherapy
  - Anthracycline and taxane-based
  - Has not changed significantly in 15+ years
- No targeted therapies yet approved
TNBC patients with no residual cancer after standard neoadjuvant chemotherapy have excellent prognosis

Neoadjuvant treatment allows opportunities for post-neoadjuvant studies with novel agents in patients with residual disease

Recurrence when it happens is early

Hereditary Breast and Ovarian Cancer

- Most hereditary breast and ovarian cancers are due to germline BRCA1 and BRCA2 mutations.
- BRCA1/2-associated cancers are compromised in DNA repair.
Association between TNBC & inherited mutations in BRCA1/2

- Approximately **75-80%** of BRCA1 mutation-associated breast cancers are triple-negative\(^1,2\)

- In unselected TNBC, frequency of BRCA1/2 mutations reported to be up **11 - 19.5%**\(^3-5\)

4. Sharma BCRT, 2015
Many other genes implicated in familial breast cancer

Many in DNA repair pathways

Among 1800 patients with TNBC, in addition to BRCA1 and BRCA2, ~4% of patients had mutations in these genes:

- PALB2, BARD1, BRIP1, Rad51c, Rad51D, Rad50

DNA repair-targeted therapy is hypothesized to have a role in these patients

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Update on DNA damaging therapies:

Platinum, lurbinectedin & PARP inhibitors
Platinum

- Cisplatin first approved by the FDA in 1978
  - Noted to have activity in metastatic breast cancer

- Family of platinum salts bind directly to DNA
  - Results in formation of DNA-platinum adducts and consequently intra- and inter-strand DNA crosslinks that impede cell division

- Recent renewed interest in investigating the role of platinum chemotherapy in breast cancer
  - Hypothesis of greater susceptibility of TN and BRCA1/2 mutant BC to DNA damaging chemotherapeutic agents

Neoadjuvant platinum in BRCA1/2 mutant breast cancer

- **Proof-of-concept neoadjuvant study of 25 BRCA1 mutation carriers (80% TNBC)**
  - **pCR rate of 72%** with single agent cisplatin 75 mg/m$^2$ every 21 days x 4

- **Rate of pCR to standard anthracycline/taxane-based therapy in BRCA1/2 carriers not well known**
  - Retrospective data from USA: **pCR of 37% versus 31%** in BRCA1/2 positive vs. negative TNBC pts treated with AC +/-T
  - Retrospective data from Israel: **pCR of 67% vs. 37%** in BRCA1/2 positive vs. negative TNBC treated with AC-T dose dense

Randomized phase II neoadjuvant “add-on” carboplatin studies in TNBC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Regimen</th>
<th>pCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alba GEICAM 2006-03</td>
<td>94</td>
<td><strong>Epirubicin</strong> 90 mg/m2 + <strong>cyclophosphamide</strong> 600 mg/m2 q21 days x 4 cycles followed by <strong>docetaxel</strong> 100mg/m2 q21 days x 4 or <strong>docetaxel</strong> 75 mg/m2 + <strong>carboplatin</strong> AUC 6 every 21 days x 4 cycles</td>
<td>30% with Cp 30% no Cp</td>
</tr>
<tr>
<td>von Minckwitz GeparSixto</td>
<td>315</td>
<td><strong>Paclitaxel</strong> 80 mg/m2 every 7 days + <strong>non-pegylated liposomal doxorubicin</strong> 20 mg/m2 every 7 days + <strong>bevacizumab</strong> 15 mg/kg IV every 21 days +/- <strong>carboplatin</strong> AUC 1.5 every 7 days x 18 cycles</td>
<td>53% with Cp 37% no Cp</td>
</tr>
<tr>
<td>Sikov CALGB 40603</td>
<td>443</td>
<td><strong>Paclitaxel</strong> 80 mg/m2 every 7 days x 12 cycles followed by <strong>doxorubicin</strong> 60 mg/m2 + <strong>cyclophosphamide</strong> 600 mg/m2 every 2 weeks x 4 cycles +/- <strong>carboplatin</strong> AUC 6 every 21 days x 4 cycles (with paclitaxel) +/- <strong>bevacizumab</strong> 10 mg/ kg every 2 weeks x 9 cycles (with paclitaxel and doxorubicin/cyclophosphamide)</td>
<td>54% with Cp 41% no Cp 52% with Bev 44% no Bev</td>
</tr>
</tbody>
</table>
GeparSixto
Therapy in TNBC subgroup

N=315 centrally confirmed TNBC

PM

PMCb

Surgery

Paclitaxel 80 mg/m² q1w
Non-pegylated liposomal doxorubicin 20 mg/m² q1w
Carboplatin AUC 1.5-2* q1w

TNBC: Bevacizumab 15 mg/kg q3w

von Minckwitz et al. Lancet Oncology, May 2014
pCR Rates in TNBC Subgroup

OR 1.94 (1.24 – 3.04)
P=0.005

von Minckwitz et al. Lancet Oncology, May 2014
Disease-free Survival: Effect of Carboplatin in TNBC

Logrank $p=0.0325$

HR PMCb to PM = 0.56, 95% CI (0.33, 0.96), $p=0.0350$

von Minckwitz et al. SABCS 2015
CALGB 40603: Schema – Randomized Phase II

2 X 2 Randomization

Paclitaxel 80 mg/m² wkly x 12  ddAC x 4

Paclitaxel 80 mg/m² wkly x 12  ddAC x 4
  Bevacizumab 10 mg/kg q2wks x 9

Paclitaxel 80 mg/m² wkly x 12  ddAC x 4
  Carboplatin AUC 6 q3wks x 4

Paclitaxel 80 mg/m² wkly x 12  ddAC x 4
  Carboplatin AUC 6 q3wks x 4
  Bevacizumab 10 mg/kg q2wks x 9
CALGB 40603: pCR Breast/Axilla

+/- Carboplatin

<table>
<thead>
<tr>
<th>No Carboplatin</th>
<th>Carboplatin</th>
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<tbody>
<tr>
<td>41% (35-48%)</td>
<td>54% (48-61%)</td>
</tr>
</tbody>
</table>

Odds ratio: 1.71
p = 0.0029

N=212
N=221

CALGB 40603 – Event–free survival for carboplatin vs. not

**Graph: Event–free survival for carboplatin vs. not**

- **Y-axis:** Proportion Event-Free
- **X-axis:** Years from Study Entry

Legend:
- **Carbo**
- **No Carbo**

- No Cb 3-yr=71%
- Cb 3-yr=76%

**Table: Number at Risk**

<table>
<thead>
<tr>
<th>Years from Study Entry</th>
<th>No Cb</th>
<th>Cb</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>218</td>
<td>225</td>
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<tr>
<td>1</td>
<td>185</td>
<td>202</td>
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<td>2</td>
<td>145</td>
<td>162</td>
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<tr>
<td>3</td>
<td>94</td>
<td>101</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
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**Statistical Analysis:**

- HR=0.84 (0.58-1.22), p=0.36

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Neoadjuvant TNBC platinum data in context

- At this time, the routine addition of platinum to standard anthracycline and taxane-based therapy is not recommended
  - Inconsistent results regarding longer term outcomes in GeparSixto and CALGB 40603
  - Both GeparSixto and CALGB 40603 studies were underpowered for long-term survival endpoints and both incorporated bevacizumab

- Ultimate survival benefits need to be assessed in definitive phase III carboplatin TNBC trials

- NRG BR003 now enrolling patients
Platinum in metastatic TNBC

- Randomized data comparing platinum to other standard chemotherapies limited
  - Recently reported phase III TNT trial extremely important

- Cross-study comparisons difficult
  - Few TNBC specific trials -> mostly subsets
  - Various “triple-negative” definitions
  - BRCA1/2 genotype largely unassessed
TNT: 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, Paul Ellis, Lucy Kilburn, Cheryl Gillett, Sarah Pinder, Jacinta Abraham, Sophie Barrett, Peter Barrett-Lee, Stephen Chan, Maggie Cheang, Mitch Dowsett, Lisa Fox, Patrycja Gazinska, Anita Grigoriadis, Alexander Gutin, Catherine Harper-Wynne, Matthew Hatton, Sarah Kernaghan, Jerry Lanchbury, James Morden, Julie Owen, Jyoti Parikh, Peter Parker, Nazneen Rahman, Rebecca Roylance, Adam Shaw, Ian Smith, Rose Thompson, Kirsten Timms, Holly Tovey, Andrew Wardley, Gregory Wilson, Mark Harries, Judith Bliss on behalf of the TNT trial management group and investigators

CRUK/07/012

Making the discoveries that defeat cancer

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Trial design

ER-, PgR-/unknown & HER2- or known BRCA1/2
Metastatic or recurrent locally advanced

Exclusions include:
• Adjuvant taxane in ≤12 months
• Previous platinum treatment
• Non-anthracyclines for MBC

A Priori subgroup analyses:
• BRCA1/2 mutation
• Basal-like subgroups (PAM50 and IHC)
• Biomarkers of HRD

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

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Objective response

Randomised treatment - all patients (N=376)

- Carboplatin: 59/188 (31.4%)
- Docetaxel: 67/188 (35.6%)

Absolute difference (C-D) -4.2% (95% CI -13.7 to 5.3)
Exact p = 0.44

Crossover treatment - all patients (N=182)

- Carboplatin (Crossover=Docetaxel): 21/92* (22.8%)
- Docetaxel (Crossover=Carboplatin): 23/90* (25.6%)

Absolute difference (D-C) -2.8% (95% CI -15.2 to 9.6)
Exact p = 0.73

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

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**Objective response – BRCA 1/2 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**
  - 53/145 (36.6%)

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

Absolute difference (C-D) -8.5% (95% CI -19.6 to 2.6) Exact p = 0.16

Interaction: randomised treatment & BRCA 1/2 status: p = 0.01

This presentation is the intellectual property of the author/presenter. Contact them at trt-icrctsu@icr.ac.uk for permission to reprint and/or distribute.
Anti-tumor activity of PM01183 (lurbinectededin) in BRCA 1/2-associated metastatic breast cancer patients: Results of a single-agent phase II trial

J. Balmaña1, C. Cruz1, B. Arun2, M. Telli3, J. Garber4, S. Domchek5, C. Fernandez6, C. Kahatt6, S. Szylnergmaj6, A. Soto Matos6, A. Perez de la Haza6, J. Pérez Fidalgo7, A. Lluch7, S. Antolin8, N. Tung9, L. Vahdat10, R. Lopez11, S. Isakoff12

1Hospital Vall d’Hebron and Vall d’Hebron Institute of Oncology, Barcelona, Spain; 2MD Anderson Cancer Center, Houston, USA; 3Stanford University Medical Center, Stanford, USA; 4Dana Farber Cancer Institute, Boston, USA; 5University of Pennsylvania, Philadelphia, USA; 6Pharma Mar, S.A., Colmenar Viejo, Madrid, Spain; 7Hospital Clínico de Valencia, Valencia, Spain; 8Complejo Universitario Hospitalario La Coruña, La Coruña, Spain; 9Beth Israel Deaconess Medical Center, Boston, USA; 10Weill Cornell Medicine, New York, USA; 11Complejo Hospitalario Universitario Santiago de Compostela, Santiago de Compostela, Spain; 12Massachusetts General Hospital, Boston, USA.
**Background**

**Lurbinectedin (PM01183)** is a trabectedin analog with an unique mechanisms of action (1):

- *Inhibits active transcription* (RNA Pol II blockade and degradation)
- Binds to CG-rich motifs
- Generates double strand DNA breaks
- Affects tumor microenvironment

Deficient homologous recombination system favors PM01183-induced apoptosis (2)

Antitumor activity observed in patients resistant to platinum compounds (3)

Two Phase III trials are currently ongoing, one as a single agent in platinum resistant ovarian cancer, and one in combination with doxorubicin in 2nd line SCLC

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3. Poveda A. et al. ASCO 2014, oral presentation
Objective Response Rate = 40.7%
# Best ORR in specific subpopulations

<table>
<thead>
<tr>
<th></th>
<th>Prior Platinum</th>
<th>BRCA</th>
<th>Hormone Status</th>
<th>Prior advanced CT lines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n: 27)</td>
<td>Yes (n: 27)</td>
<td>1 (n: 31)</td>
<td>2 (n: 23)</td>
</tr>
<tr>
<td><strong>ORR</strong> (95% CI)</td>
<td>56% (35.3-55.6)</td>
<td>26% (11.1-25.9)</td>
<td>26% (11.9-25.8)</td>
<td>61% (38.5-60.9)</td>
</tr>
<tr>
<td><strong>Duration of Response</strong> (95% CI)</td>
<td>10.2 m (3.0-13.5)</td>
<td>5.9 m (2.8-12.8)</td>
<td>6.6 m (2.8-12.8)</td>
<td>6.7 m (3.4-13.5)</td>
</tr>
<tr>
<td><strong>Disease control rate</strong></td>
<td>25 (93%)</td>
<td>19 (70%)</td>
<td>23 (74%)</td>
<td>22 (96%)</td>
</tr>
<tr>
<td><strong>Clinical benefit (CR+PR+SD ≥ 3 mo)</strong></td>
<td>19 (70%)</td>
<td>14 (52%)</td>
<td>14 (45%)</td>
<td>19 (83%)</td>
</tr>
</tbody>
</table>

* Including 2 patients also HER-2 +
PARP1/2 Function

- Key enzymes involved in repair of single strand DNA breaks

- PARP is required for the repair of oxidative DNA damage-associated DNA breaks via base excision repair (BER)
PARP inhibitors in advanced BRCA positive breast cancer: *Initial proof-of-concept*

Olaparib: Superior activity at higher dose

<table>
<thead>
<tr>
<th></th>
<th>Olaparib 400 mg twice daily (n=27)</th>
<th>Olaparib 100 mg twice daily (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response</td>
<td>11 (41%; 25-59)</td>
<td>6 (22%; 11-41)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (4%; 1-18)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>10 (37%; 22-56)</td>
<td>6 (22%; 11-41)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12 (44%; 28-63)</td>
<td>12 (44%; 28-63)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4 (15%; 6-32)</td>
<td>9 (33%; 19-53)</td>
</tr>
</tbody>
</table>

Data are number (%; 95% CI).

Tutt A. Lancet. Published online July 6, 2010
I-SPY 2: Carboplatin + Veliparib
Arm in TNBC

Taxol – AC pCR = 26%

Taxol/Carbo/Veliparib – AC pCR = 51%

Phase 3 Brightness trial testing this combination just concluded enrollment

Rugo H et al. NEJM 2016
Patient Population

- Men and women ≥ 18 years of age
- Recurrent or metastatic breast cancer
- BRCA1 or BRCA2 mutation
- No prior therapy with carboplatin or cisplatin or with a PARP inhibitor
- No history of CNS metastases

Randomization 1:1:1

Veliparib BID + Temozolomide
N = 85

Placebo BID + Carboplatin/Paclitaxel
N = 85

Veliparib BID + Carboplatin/Paclitaxel
N = 85

Primary Endpoint
Progression Free Survival

Secondary Endpoints
Overall Survival
Clinical Benefit Rate
Objective Response Rate
Peripheral Neuropathy
Safety and Tolerability

Outcomes Measured

Phase 2 trial completed accrual in March 2015

Results at SABCS 2016 in December
Phase III OLympiAD Trial
(OLaparib in Advanced Disease)

Metastatic germline BRCA+ breast cancer
Prior anthracycline + taxane
0-2 prior tx for mBC
No prior platinum

Physician’s choice (capecitabine, vinorelbine, eribulin)

Olaparib

Primary endpoint: PFS (no cross-over)
Secondary: OS, PFS2
Planned sample size: 310 patients
Role of additional chemotherapy after standard neoadjuvant chemotherapy?
Can standard capecitabine chemotherapy improve outcomes in patients with residual cancer after neoadjuvant treatment?

**CREATE-X: Trial Design**

**HER2-negative**
- NAC
- Surgery
- Pathology: Non-pCR or node +

(n=900)

**Control:**
- Standard therapy

**Standard therapy + Capecitabine**

Stratification factors:
- ER, Age, NAC, ypN, 5FU and institution

Standard therapy:
- HR+: Hormone therapy
- HR-: No further systemic treatment
Among patients with residual cancer after standard preoperative chemotherapy:

- 6 months of oral capecitabine (Xeloda) decreased recurrences & improved survival
- Biggest effect in TNBC subgroup
Update on immunotherapy
Tumor mutational burden and immunogenicity

- Tumors are immunologically unique due to tumor-specific mutations
  - Tumor-specific mutations represent only a fraction of the total number of mutations in the tumor

- These tumor specific mutations produce ‘neoantigens’
  - Capable of recognition by the immune system
Figure 1 | The prevalence of somatic mutations across human cancer types. Every dot represents a sample whereas the red horizontal lines are the median numbers of mutations in the respective cancer types. The vertical axis (log scaled) shows the number of mutations per megabase whereas the different cancer types are ordered on the horizontal axis based on their median numbers of somatic mutations. We thank G. Getz and colleagues for the design of this figure. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.
Tumor-infiltrating lymphocytes (TILs)

- In early stage TNBC, increased TILs
  - Associate with good prognosis\(^1,2,3\)
  - Predict for response to neoadjuvant chemotherapy\(^4-8\)

6. Issa-Nummer et al. PLOSone 2013
8. Vinayak S, Telli ML ASCO 2014
Immune Checkpoint Blockade

- A paradigm shift in cancer therapy
- Doesn’t target tumor cells specifically
- Works by blocking inhibitory pathways to unleash the body’s anti-tumor immune response
- Drugs targeting CTLA-4, PD-1, PD-L1 approved in melanoma, lung, kidney, bladder, head and neck cancers
- Proof-of-concept in advanced TNBC recently demonstrated
Programmed death 1 (PD-1) is a receptor expressed on T cells

- Inhibits killing by T cells when binds to PD-L1
- PD-L1 expressed on tumors or in the tumor microenvironment

Many antibody drugs now targeting PD-1 and PD-L1

- Impressive activity in melanoma, kidney cancer, lung cancer, others

Phase Ib KEYNOTE-012: Pembrolizumab in Advanced TNBC

Patients with recurrent or metastatic ER-/PR-/HER2-PD-L1+ BC (N = 32)

Pembrolizumab 10 mg/kg q2w

- CR → Discontinuation permitted
- PR or SD → Treat for 24 mos or until PD or intolerable toxicity
- PD → Discontinue

- Pembrolizumab: anti–PD-1 antibody with high affinity for receptor
  - Provides dual ligand blockage of PD-L1 and PD-L2
  - Clinical activity in multiple tumor types, recent approval in melanoma
- 58% of screened patients were PD-L1 positive

Pembrolizumab in Advanced TNBC (KEYNOTE-012): Tumor Regression

- Objective response rate = 18.5%

23% of TNBC patients screened were PD-L1 positive

Objective response rate = 4/21 (19%)
  - Additional 3 patients with ‘pseudoprogression’

11% experienced grade 3 or higher toxicity
Ongoing & Upcoming Clinical Trials of Interest for TNBC
Patients with:

- stage II/III TNBC
- Neoadjuvant chemotherapy
- found to have = 1 cm in diameter of residual cancer in the breast at the time of definitive surgery

**Stratification factors:**

1. Clinical stage at diagnosis (II or III)
2. Residual cancer burden after NAC (1–3 cm or > 3 cm)
3. Planned platinum agent choice (cisplatin or carboplatin)
4. Anthracycline exposure (yes or no)
5. Administration of radiotherapy (yes or no)
6. Basal-like subtype (yes no)

Accrual = 750
1 cycle = 3 weeks

Rev. 5/16
1. TNBC: ER/PR less than 10% positive staining with weak intensity score, or less than 1% positive staining with weak or intermediate intensity score; HER2 negative per ASCO guidelines.
2. Taxane ± anthracycline based; platinum agents or capecitabine not allowed.
3. Choice of platinum agent will be per treating physician discretion.
4. Primary Endpoint: IDFS in patients with basal-like TNBC.
5. Secondary Endpoints: IDFS in patient with non-basal-like TNBC, OS and RFS.
6. Patients must have completed adjuvant radiotherapy (if applicable) prior to randomization.
7. Tumor tissue from the residual disease on the definitive surgical specimen must be submitted within 21 weeks post surgery for PAM50 analysis for stratification as outlined in Section 10.2. Patients cannot be randomized to treatment until confirmation of PAM50 analysis from the Molecular Diagnostics Laboratory performing the assessments.
8. Females of child-bearing potential must have a blood test or urine study within 2 weeks prior to treatment initiation to rule out pregnancy.

**Arm A**
Observation

**Arm B**

- Cisplatin 75 mg/m2
- Day 1 every Q3W x 4 cycles
- OR
- Carboplatin AUC 6
- Day 1 Q3W x 4 cycles

**Arm C**

- Capecitabine 1000 mg/m2
- twice daily
- D1-14 every Q3wx6 cycles

**CLOSED TO NEW ACCRUAL**

**Arm A closed to new accrual in Addendum #3. New patients are randomized to Arm B or C.**
SWOG/NRG S1418: Post-neoadjuvant immunotherapy study

A Randomized, Phase III Trial to Evaluate the Efficacy and Safety of Pembrolizumab (MK-3475) as Adjuvant Therapy for TNBC with > 1 cm Residual Invasive Cancer or Positive Lymph Nodes (pN1) After Neoadjuvant Chemotherapy

SOON TO ACTIVATE

Additional large studies of standard chemotherapy + immunotherapy being planned at this time
Adjuvant PARP inhibitor study in BRCA+
ONGOING

OlympiA
Design and Eligibility

- HER2 negative with BRCA 1 or 2 mutation
  Post adjuvant chemotherapy
    - TNBC
      - Node positive disease (any tumour size) OR
      - Node negative, primary > 2 cm
    - ER+ ≥ 4 positive nodes

Randomize 1:1
Double blind
N=1500

- HER2 negative with BRCA 1 or 2 mutation
  - Post NAC with residual disease
    - TNBC - any residual invasive disease in breast or nodes
    - ER+ - CPS+EG score ≥ 3

Olaparib
300 mg bid
12 month duration

IDFS

Placebo
12 month duration

Distant DFS, OS
TBB Trial: Talazoparib Beyond BRCA
Joshua Gruber, M.D., Ph.D. & Melinda Telli, M.D.  ONGOING

A Phase II clinical trial of talazoparib in BRCA1 and BRCA2 negative patients with:

A. advanced triple-negative breast cancer and homologous recombination deficiency as assessed by the HRD assay

B. advanced HER2-negative breast cancer with either a germline or somatic mutation in homologous recombination pathway genes:

PTEN, PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD50, RAD51C, RAD51D, MRE11, ATR, Fanconi anemia complementation group of genes (FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL)
## Ongoing immunotherapy studies in advanced TNBC

<table>
<thead>
<tr>
<th>Compound</th>
<th>Target</th>
<th>Trial</th>
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</thead>
<tbody>
<tr>
<td><strong>Atezolizumab (MPDL3280A)</strong></td>
<td>PD-L1</td>
<td>Phase III study of nab-paclitaxel +/- MPDL3280A in first line metastatic TNBC Open to enrollment</td>
</tr>
<tr>
<td><strong>Pembrolizumab</strong></td>
<td>PD-L1</td>
<td>Phase I/II study of the PARP inhibitor niraparib + pembrolizumab Open to enrollment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase III study of chemotherapy +/- pembrolizumab in firstline metastatic TNBC Open to enrollment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase III study of pembrolizumab versus chemotherapy of physician’s choice in pretreated metastatic TNBC Open to enrollment</td>
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**Early stage studies coming soon!**
Summary

- Growing evidence that therapies targeting DNA repair defects are active in TNBC
  - Results of large phase 3 studies testing platinums and PARP inhibitors are eagerly awaited

- Beyond BRCA1 and BRCA2, other inherited gene mutations have been recently associated with TNBC

- Capecitabine recently shown to improve survival in a phase 3 trial in patients with residual cancer after standard neoadjuvant therapy

- Multiple studies underway to assess additional therapies following standard chemotherapy in early TNBC and novel agents in advanced TNBC
  - Platinums, PARP inhibitors, immunotherapy
Thank you!