Hereditary metastatic breast cancer

Shaveta Vinayak, M.D., M.S.
Assistant Professor
University of Washington
Fred Hutchinson Cancer Research Center
Disclosures

- Tesaro- Advisory Board for Niraparib

- Oncosec- Advisory Board

- I will discuss investigational agents in the context of clinical trials
Outline

• Definitions (somatic versus germline testing, others)
• Clinical trials introduction
• Focus on PARP inhibitors and triple-negative breast cancer
• Updates on relevant clinical trial results (TNT, OlympiAD, EMBRACA, TOPACIO, MEDIOLA)
• Relevant future therapies
“Hereditary” breast cancer

- Breast cancer associated with a predisposition gene
- What % of all breast cancers are “hereditary”?

![Pie chart showing percentage of breast cancer types]

- Sporadic: 70-80%
- Hereditary: 5-10%
- Family clusters: 15-20%
“Metastatic” breast cancer

• Spread from breast (where it originated) or lymph nodes to other places in the body

• Pattern of spread may be different depending on breast cancer subtype
Breast Cancer: ER, PR, HER2 markers

**ER/PR-Positive (Hormone receptors)**

**Hormone-blocking pills**
- E.g. Tamoxifen, Aromatase inhibitors

**HER2-Positive**

**HER2-targeted medicines**
- E.g. Trastuzumab, Pertuzumab

**Triple-Negative**

**Ongoing Research**
- (Current standard: Chemotherapy)

**ER, PR, HER2 markers**
General treatment principles for metastatic breast cancer

• Breast cancer subtype matters!
• Goal to control and treat breast cancer
• Quality of life is important when choosing treatments
• Endocrine therapy and combinations with other agents can be used for ER/PR+ breast cancer
• Single-agent chemotherapy usually recommended
• Clinical trials- more to come!
Somatic versus Hereditary Germline mutations:

**Somatic mutations:**
- Non-germline tissues
- Cannot be inherited

**Germline mutations:**
- Germline (all) tissues
- Can be inherited
- Cause family cancer syndromes

Courtesy- Allison Kurian, MD
**BRCA1/2 Breast Cancer Subtypes:**
Intersection of tumor and germline

- **ER/PR-Positive (Hormone receptors)**
  - BRCA2

- **Triple-Negative**
  - BRCA1
What are oncologists trying to learn from tumor vs. blood/saliva testing?

- **Tumor testing (“genomic” testing)**
  - What is the next best precise treatment (whether standard or clinical trial)?
  - Germline or blood results can also show up in tumor testing!

- **Blood/saliva testing (“genetic” testing)**
  - Are there hereditary gene changes (mutations) that predispose you to breast cancer? (focus on prevention)
  - If yes, what is your personal risk of other cancers or cancer risks for your family members?
  - This can also help guide your treatment now if you have metastatic breast cancer (2 PARP inhibitors approved)
Germline Mutations in Triple-Negative Breast Cancer (TNBC)

• A large international study examining germline mutations in 17 different breast cancer predisposition genes in patients with TNBC showed:
  
  – 14.6% (267/1824) of patients had a deleterious germline mutation
  – 8.5% were BRCA1 mutations, 2.7% BRCA2 mutations and 3.7% in other genes

• NCCN criteria for BRCA1/2 genetic testing
  
  – Age 60 or below with triple-negative breast cancer
  – Age<35, if no BRCA1/2 mutation detected, then additional testing recommended
What are clinical trials?

• Our best standard treatments of today were clinical trials in the past!
• Research studies in patients to test new ways of treating cancer
• Takes many years to design and activate clinical trials (many regulatory processes for patient protection and safety)
Clinical trials are conducted to collect data regarding the safety and efficacy of new drug and device development. Generally, there are four phases of development.

**Phase I**
- Assesses the safety and effects of a drug
- Small study group of 20-100 healthy volunteers
- Studies typically last several months

**Phase II**
- Tests the efficacy and effectiveness of the drug
- A placebo is often introduced for comparative results
- Study group may include several hundred patients
- Studies may last several months to a couple of years

70% of drugs move to Phase II

33% of drugs move to Phase III

**Phase III**
- Randomized and blind testing occurs
- Study group may include several hundred to several thousand patients
- Once completed, FDA approval can be requested to sell to the public
- Allows for a more detailed understanding of the drug’s effectiveness, benefits and risks

70% of drugs move to Phase IV

90% of drugs move to Phase IV

**Phase IV**
- The drug is approved for consumer sale
- Monitors long-term effectiveness
- Compares drugs with others on the market
- Determines cost-effectiveness of new drug treatment compared to other traditional therapies

https://www.centerwatch.com/clinical-trials/overview.aspx
I just heard there's a drug in trials that might stop my cancer!!

Of course not...why would I do that?

Great! Are you going to volunteer to participate for the trial?

I wouldn't either. Sure hope they get some results soon...
How do you find clinical trials?

• Talk to your oncologist
• Referral for local trials at your institution and other academic centers (travel may be a barrier)
• Second opinions at academic centers to learn about trials that may be of potential benefit
• Resources- Clinicaltrials.gov, NCI, ASCO
Log on, google cancer clinical trials, click on the URL, scroll to the NCI link, right click, enter your user code, left click... can you find the RSS feed? Are you keeping up Grandpa? Should I text these directions? Tweet?

I just want to find the start button.
What are the potential benefits of trials?

• Potential of treatment benefit to you with a novel investigational treatment
• Potential benefit to future patients and helping improve upon our standard treatments
• You can increase your number of treatment options
• High-quality clinical care on trials with medical teams and close monitoring
When is an appropriate time to consider clinical trials?

• My perspective- clinical trials are “windows of opportunity” that open and close (standard treatment options always remain available)

• Prevalent patient perspective- “wait for clinical trials when I run out of standard options”

• Consider at every step when there is a change in treatment

• After identifying a clinical trial that you may be eligible for, screening process and several rigorous steps take place before you can begin treatment

• Steps in clinical trials help protect the rights and safety of patients who participate

• Trials are voluntary

• Lots to consider- https://www.cancer.gov/about-cancer/treatment/clinical-trials
TNT trial: Question

• In metastatic triple-negative breast cancer patients, including *BRCA1/2* mutation carriers, how does a standard chemotherapy (docetaxel) compare to platinum chemotherapy?

• Can we identify a subset of patients who highly benefit from one chemotherapy compared to the other?

Tutt et al, Nature Medicine 2018
TNT trial: Design

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

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

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**Carboplatin (C)**
AUC 6 q3w, 6 cycles

On progression, crossover if appropriate

**Docetaxel (D)**
100mg/m² q3w, 6 cycles

On progression, crossover if appropriate

**Carboplatin (C)**
AUC 6 q3w, 6 cycles

**Docetaxel (D)**
100mg/m² q3w, 6 cycles

---

Tutt et al, Nature Medicine 2018
TNT trial: Key Results

Response rates: All patients

- Carboplatin: 59 of 188 (31.4%)
- Docetaxel: 64 of 188 (34.0%)

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

Response rates: BRCA1/2 mutation carriers

- Mutated BRCA:
  - 17 of 25 (68.0%)
  - Absolute difference: 34.7% (95% CI: 6.3 to 63.1)
  - Exact P = 0.03

- Wild-type BRCA:
  - 36 of 128 (28.1%)
  - Absolute difference: -6.4% (95% CI: -17.4 to 4.6)
  - Exact P = 0.30

Interaction test: P = 0.01

Tutt et al, Nature Medicine 2018
For **BRCA1/2** mutation carriers with metastatic breast cancer, much better responses with platinum versus docetaxel.

- Only 6 cycles of chemotherapy- outcomes may be better with longer use of platinum (we typically treat until progression of cancer).

- How does platinum compare to PARP inhibitors in **BRCA1/2** mutation carriers with metastatic breast cancer?
Multiple DNA repair pathways

- Damaging agent/event:
  - Free radicals
  - Alkylating agents
  - UV light
  - X-rays
  - Replication error

- Types of damage:
  - Single-strand break
  - Bulky adduct
  - Interstrand cross-link
  - Double-strand break
  - Mismatch Insertion Deletion

- Repair pathways:
  - BER
  - NER
  - HR, NHEJ, SSA
  - MMR

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PARP (Poly(ADP Ribose) Polymerase) Inhibitors

Takes advantage of existing defect in BRCA-associated breast cancers

A great example of precision therapy!
OlympiAD trial: Question

- In germline *BRCA* mutation associated HER2-negative breast cancer, how does standard chemotherapy (single-agent) compare to olaparib (PARP inhibitor)?
OlympiAD trial: Who was included?

Table 1. Baseline Characteristics of the Patients.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Olaparib Group (N = 205)</th>
<th>Standard-Therapy Group (N = 97)</th>
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<tbody>
<tr>
<td>Age — yr</td>
<td></td>
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<tr>
<td>Median</td>
<td>44</td>
<td>45</td>
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<tr>
<td>Range</td>
<td>22–76</td>
<td>24–68</td>
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<tr>
<td>Male sex — no. (%)</td>
<td>5 (2.4)</td>
<td>2 (2.1)</td>
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<tr>
<td>Race or ethnic group — no. (%)†</td>
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<tr>
<td>White</td>
<td>134 (65.4)</td>
<td>63 (64.9)</td>
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<td>Asian</td>
<td>66 (32.2)</td>
<td>28 (28.9)</td>
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<tr>
<td>Other</td>
<td>5 (2.4)</td>
<td>6 (6.2)</td>
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<tr>
<td>ECOG performance status — no. (%)‡</td>
<td></td>
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<tr>
<td>0</td>
<td>148 (72.2)</td>
<td>62 (63.9)</td>
</tr>
<tr>
<td>1</td>
<td>57 (27.8)</td>
<td>35 (36.1)</td>
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<tr>
<td>BRCA mutation type — no. (%)§</td>
<td></td>
<td></td>
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<tr>
<td>BRCA1</td>
<td>117 (57.1)</td>
<td>51 (52.6)</td>
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<tr>
<td>BRCA2</td>
<td>84 (41.0)</td>
<td>46 (47.4)</td>
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<td>BRCA1 and BRCA2</td>
<td>4 (2.0)</td>
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<td>Hormone-receptor status — no. (%)¶</td>
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<tr>
<td>Hormone-receptor positive</td>
<td>103 (50.2)</td>
<td>49 (50.5)</td>
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<tr>
<td>Triple negative</td>
<td>102 (49.8)</td>
<td>48 (49.5)</td>
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<tr>
<td>New metastatic breast cancer — no. (%)</td>
<td>26 (12.7)</td>
<td>12 (12.4)</td>
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<tr>
<td>Previous chemotherapy for metastatic breast cancer — no. (%)</td>
<td>146 (71.2)</td>
<td>69 (71.1)</td>
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<tr>
<td>Previous platinum-based therapy for breast cancer — no. (%)</td>
<td>60 (29.3)</td>
<td>26 (26.8)</td>
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<tr>
<td>≥2 Metastatic sites — no. (%)</td>
<td>159 (77.6)</td>
<td>72 (74.2)</td>
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<tr>
<td>Location of the metastasis — no. (%)</td>
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<tr>
<td>Bone only</td>
<td>16 (7.8)</td>
<td>6 (6.2)</td>
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<tr>
<td>Other</td>
<td>189 (92.2)</td>
<td>91 (93.8)</td>
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<tr>
<td>Measurable disease — no. (%)</td>
<td>167 (81.5)</td>
<td>66 (68.0)</td>
</tr>
</tbody>
</table>

Robson et al, NEJM 2017
OlympiAD trial: Key Results

Olaparib was the winner by about 3 months

Robson et al, NEJM 2017
FDA approves olaparib for germline BRCA-mutated metastatic breast cancer

Listen to the FDA D.I.S.C.O. podcast about this approval.

On January 12, 2018, the Food and Drug Administration granted regular approval to olaparib tablets (Lynparza, AstraZeneca Pharmaceuticals LP), a poly (ADP-ribose) polymerase (PARP) inhibitor, for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative metastatic breast cancer who have been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting.
EMBRACA trial: Question

- In germline BRCA mutation associated HER2-negative breast cancer, how does standard chemotherapy (single-agent) compare to talazoparib (PARP inhibitor)?

Litton et al, NEJM 2018
EMBRACA trial: Who was included?

Table 1. Baseline Characteristics of the Patients (Intent-to-Treat Population).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Talazoparin Group (N=287)</th>
<th>Standard-Therapy Group (N=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr — Median</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>Age — yr — Range</td>
<td>27.0–84.0</td>
<td>24.0–88.0</td>
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<tr>
<td>Age &lt;50 yr — no. (%)</td>
<td>182 (63.4)</td>
<td>67 (46.5)</td>
</tr>
<tr>
<td>Female sex — %</td>
<td>98.6</td>
<td>97.9</td>
</tr>
<tr>
<td>ECOG performance status score — %†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>53.3</td>
<td>58.3</td>
</tr>
<tr>
<td>1</td>
<td>44.3</td>
<td>39.6</td>
</tr>
<tr>
<td>2</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Breast cancer stage — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>15 (5.2)</td>
<td>9 (6.2)</td>
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<tr>
<td>Metastatic</td>
<td>271 (94.4)</td>
<td>135 (93.8)</td>
</tr>
<tr>
<td>Measurable disease assessed by investigator — no. (%)</td>
<td>219 (76.3)</td>
<td>114 (79.2)</td>
</tr>
<tr>
<td>History of CNS metastases — no. (%)‡</td>
<td>43 (15.0)</td>
<td>20 (13.9)</td>
</tr>
<tr>
<td>Visceral disease — no. (%)</td>
<td>200 (69.7)</td>
<td>103 (71.5)</td>
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<tr>
<td>Hormone receptor status — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple-negative</td>
<td>130 (45.3)</td>
<td>60 (41.7)</td>
</tr>
<tr>
<td>Hormone receptor-positive</td>
<td>157 (54.7)</td>
<td>84 (58.3)</td>
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<tr>
<td>BRCA status — no. (%)</td>
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<td></td>
</tr>
<tr>
<td>BRCA 1-positive</td>
<td>133 (46.5)</td>
<td>63 (43.8)</td>
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<tr>
<td>BRCA 2-positive</td>
<td>154 (53.7)</td>
<td>81 (56.2)</td>
</tr>
<tr>
<td>&lt;12-mo disease-free interval from initial diagnosis to advanced breast cancer — no. (%)</td>
<td>108 (37.6)</td>
<td>42 (29.2)</td>
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<tr>
<td>Previous adjuvant or neoadjuvant therapy — no. (%)</td>
<td>238 (82.9)</td>
<td>121 (84.0)</td>
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<tr>
<td>No. of previous hormone-therapy—based regimens for hormone-receptor—positive breast cancer in the talazoparin group (157 patients) and the standard-therapy group (84 patients)</td>
<td></td>
<td></td>
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<tr>
<td>Median</td>
<td>2.0</td>
<td>2.0</td>
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<tr>
<td>Range</td>
<td>0–6</td>
<td>0–6</td>
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<tr>
<td>Previous platinum therapy — no. (%)</td>
<td>46 (16.0)</td>
<td>30 (20.8)</td>
</tr>
<tr>
<td>Previous cytotoxic regimens for advanced breast cancer — no. (%)</td>
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</tr>
<tr>
<td>0</td>
<td>111 (38.7)</td>
<td>54 (37.5)</td>
</tr>
<tr>
<td>1</td>
<td>107 (37.3)</td>
<td>54 (37.5)</td>
</tr>
<tr>
<td>2</td>
<td>57 (19.9)</td>
<td>28 (19.4)</td>
</tr>
<tr>
<td>3</td>
<td>12 (4.2)</td>
<td>8 (5.6)</td>
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</tbody>
</table>
EMBRACA trial: Key Results

Talazoparib was the winner by 3 months
EMBRACA trial: CNS metastases subgroup

Talazoparib better but small numbers

FDA approves talazoparib for gBRCAm HER2-negative locally advanced or metastatic breast cancer

On October 16, 2018, the Food and Drug Administration approved talazoparib (TALZENNA, Pfizer Inc.), a poly (ADP-ribose) polymerase (PARP) inhibitor, for patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative locally advanced or metastatic breast cancer. Patients must be selected for therapy based on an FDA-approved companion diagnostic for talazoparib.
# Invasive Breast Cancer

## CHEMOTHERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE

### HER2-Negative

**Single agent**
- Anthracyclines
- Doxorubicin
- Liposomal doxorubicin
- Taxanes
- Paclitaxel
- Anti-metabolites
- Capecitabine
- Gemcitabine
- Microtubule inhibitors
- Vinorelbine
- Eribulin

**Preferred regimens:**
- Nebula (option for patients with HER2-negative tumors and germline BRCA1/2 mutation)

### HER2-Negative

**Combination regimens**
- Preferred regimens:
  - None

**Useful in certain circumstances:**
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacuzumab

### HER2-Positive

**Preferred regimens:**
- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

**Other recommended regimens:**
- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel + carboplatin
- Trastuzumab + docetaxel
- Trastuzumab + vinorelbine
- Trastuzumab + capecitabine
- Lapatinib + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents

### Other recommended regimens:
- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

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1 Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (e.g., hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m².

2 Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis.

3 Patients with HER2-negative disease eligible for single-agent therapy, strongly consider for germline BRCA 1/2 testing.

4 Randomized clinical trials in metastatic breast cancer document that the addition of bevacuzumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacuzumab in combination with weekly paclitaxel.

5 Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

6 Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

7 Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents listed above for recurrent or metastatic breast cancer.
Companion diagnostics for PARP inhibitor approvals

- Olaparib and Talazoparib
  - Myriad’s comprehensive BRACAnalysis CDx test
Are there differences in side effects among PARP inhibitors?

### Olaparib

<table>
<thead>
<tr>
<th>Variable</th>
<th>Olaparib Group (N=205)</th>
<th>Standard-Therapy Group (N=91)</th>
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</thead>
<tbody>
<tr>
<td>Adverse event</td>
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<tr>
<td>Any</td>
<td>199 (97.1)</td>
<td>88 (96.7)</td>
</tr>
<tr>
<td>Anemia†</td>
<td>82 (40.0)</td>
<td>24 (26.4)</td>
</tr>
<tr>
<td>Neutropenia‡</td>
<td>56 (27.3)</td>
<td>45 (49.5)</td>
</tr>
<tr>
<td>Decreased white-cell count</td>
<td>33 (16.1)</td>
<td>19 (20.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>119 (58.0)</td>
<td>32 (35.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>61 (29.8)</td>
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<tr>
<td>Diarrhea</td>
<td>42 (20.5)</td>
<td>20 (22.0)</td>
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<tr>
<td>Decreased appetite</td>
<td>33 (16.1)</td>
<td>11 (12.1)</td>
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<tr>
<td>Fatigue</td>
<td>59 (28.8)</td>
<td>21 (23.1)</td>
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<tr>
<td>Headache</td>
<td>41 (20.0)</td>
<td>14 (15.4)</td>
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<tr>
<td>Pyrexia</td>
<td>29 (14.1)</td>
<td>16 (17.6)</td>
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<tr>
<td>Cough</td>
<td>35 (17.1)</td>
<td>6 (6.6)</td>
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<tr>
<td>Increased alanine aminotransferase level</td>
<td>23 (11.2)</td>
<td>16 (17.6)</td>
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<tr>
<td>Increased aspartate aminotransferase level</td>
<td>19 (9.3)</td>
<td>15 (16.5)</td>
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<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>1 (0.5)</td>
<td>19 (20.9)</td>
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<tr>
<td>Dose reduction owing to adverse event</td>
<td>52 (25.4)</td>
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<tr>
<td>Treatment interruption or delay owing to adverse event</td>
<td>72 (35.1)</td>
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</tr>
<tr>
<td>Treatment discontinuation owing to adverse event</td>
<td>10 (4.9)</td>
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### Talazoparib

<table>
<thead>
<tr>
<th>Variable</th>
<th>Talazoparib Group (N=286)</th>
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<tr>
<td>Adverse event</td>
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<td>Any</td>
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<tr>
<td>Anemia†</td>
<td>151 (52.8)</td>
</tr>
<tr>
<td>Neutropenia‡</td>
<td>99 (34.6)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>77 (26.9)</td>
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<tr>
<td>Leukopenia</td>
<td>49 (17.1)</td>
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<td>Lymphopenia</td>
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<td>Febrile neutropenia</td>
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<tr>
<td>Headache</td>
<td>93 (32.5)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>72 (25.2)</td>
</tr>
<tr>
<td>Cough</td>
<td>71 (24.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>63 (22.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>63 (22.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>61 (21.3)</td>
</tr>
<tr>
<td>Back pain</td>
<td>60 (21.0)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>50 (17.5)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>6 (2.1)</td>
</tr>
</tbody>
</table>

Number of patients with ≥1 hematologic adverse event, No. (%):

<table>
<thead>
<tr>
<th>Event</th>
<th>Olaparib Group (N=205)</th>
<th>Standard-Therapy Group (N=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>10 (4.4)</td>
<td>4 (4.4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51 (17.8)</td>
<td>32 (11.2)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>34 (11.9)</td>
<td>21 (7.3)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>24 (8.4)</td>
<td>18 (6.3)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>4 (2.1)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Number of patients with ≥1 nonhematologic adverse event, No. (%):

<table>
<thead>
<tr>
<th>Event</th>
<th>Talazoparib Group (N=286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>10 (3.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (3.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7 (2.4)</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (2.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (2.4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (2.4)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8 (2.8)</td>
</tr>
<tr>
<td>Back pain</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>5 (1.7)</td>
</tr>
</tbody>
</table>
Are there differences in how PARP inhibitors work?

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Inhibition</th>
<th>Trapping PARP-DNA Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veliparib</td>
<td>PARP 1/2</td>
<td>No</td>
</tr>
<tr>
<td>Olaparib</td>
<td>PARP 1/2/3</td>
<td>Yes</td>
</tr>
<tr>
<td>Rucaparib*a</td>
<td>PARP 1/2/3</td>
<td>Yes</td>
</tr>
<tr>
<td>Niraparib</td>
<td>PARP 1/2</td>
<td>Yes</td>
</tr>
<tr>
<td>Talazoparib</td>
<td>PARP 1/2</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*TABLE 1. Poly(Adenosine Diphosphate-Ribose) Polymerase Inhibitors Developed in BRCA-Positive Breast Cancer in Order of Potency (Lowest to Highest)*

Turk et al, Cancer 2018
How do we improve upon single-agent PARP inhibitors?

• Combinations with:

  o Other DNA repair targeted therapies (ATR inhibitor, etc.)
  o Chemotherapy
  o Immunotherapy
TOPACIO/Keynote-162: Niraparib + Pembrolizumab in Patients with Metastatic Triple-negative Breast Cancer (TNBC), a Phase 2 Trial

Shaveta Vinayak,1 Sara Tolaney,2 Lee Schwartzberg,3 Monica Mita,4 Georgia McCann,5 Antoinette R. Tan,6 Andrea Wahner Hendrickson,7 Andres Forero,8 Carey Anders,9 Gerburg Wulf,10 Patrick Dillon,11 Filipa Lynece,12 Corrine Zarwan,13 John Erban,14 Bruce Dezube,15 Yinghui Zhou,15 Nathan Buerstatte,15 Sujata Arora,15 Melinda L. Telli16

1Case Comprehensive Cancer Center, University Hospitals, Case Western Reserve University, Cleveland, OH, USA; 2Dana-Farber Cancer Institute, Boston, MA, USA; 3The West Clinic, Memphis, TN, USA; 4Cedars-Sinai Medical Center, Los Angeles, CA, USA; 5Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA; 6Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; 7Department of Medical Oncology, Mayo Clinic Rochester, Rochester, MN, USA 8University of Alabama at Birmingham, Birmingham, AL, USA; 9University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA and Department of Medicine, University of North Carolina, Chapel Hill, Chapel Hill, NC, USA; 10Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA; 11University of Virginia, Charlottesville, VA, USA; 12Lombardi Comprehensive Cancer Center, MedStar Georgetown University Hospital, Washington, DC, USA; 13Department of Hematology and Oncology, Lahey Hospital and Medical Center, Burlington, MA, USA; 14Tufts Medical Center, Boston, MA, USA; 15TESARO, Inc., Waltham, MA, USA; 16Stanford University School of Medicine, Stanford, CA, USA
TOPACIO trial: Why combine with immunotherapy?

**Rationale for Niraparib (PARPi) + anti-PD-1 Combination**

- Potential Mechanism of Action
  - Unrepaired DNA damage resulting from niraparib treatment leads to the abnormal presence of DNA in the cytoplasm, activating Stimulator of Interferon Genes (STING) pathway.
  - Activation of the STING pathway leads to increased expression and release of type 1 interferons, subsequent induction of γ-interferon, and intratumoral infiltration of effector T-cells.

**TOPACIO trial: Design**

**TOPACIO Phase 2 Design**

**Objective:** Evaluate niraparib and anti-PD-1 combination therapy in metastatic TNBC patients

**Key Inclusion Criteria**
- TNBC (ER-negative, PR-negative, and HER-2 negative)*
- Disease recurrence or progression following neoadjuvant/adjuvant therapy
- ≤2 prior lines of cytotoxic treatment for advanced disease (not including neoadjuvant/adjuvant therapies or targeted small molecules)⁴
- Prior platinum allowed in metastatic setting if no progression documented while on or within 8 weeks of last platinum**

**Key Exclusion Criteria**
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or PARP inhibitor

**Response Assessments**
- Scans every 9 weeks

---

*ER and PR < 3% per ASCO/CAP guidelines
⁴Prior amendment allowed up to 3 prior lines of cytotoxic therapy for advanced disease
**Prior amendment had no restriction on platinum for inclusion or exclusion criteria
TOPACIO trial: Biomarkers

Biomarker Status for Efficacy Evaluable Patients (N=46)

<table>
<thead>
<tr>
<th>Biomarker Status</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tBRCAmut</td>
<td>15 (33%)</td>
</tr>
<tr>
<td>HRRmut (excluding tBRCAmut)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Both HRRwt and tBRCAwt</td>
<td>20 (43%)</td>
</tr>
<tr>
<td>PD-L1 Positive</td>
<td>25 (54%)</td>
</tr>
<tr>
<td>PD-L1 Negative</td>
<td>13 (28%)</td>
</tr>
</tbody>
</table>

tBRCA: tumor BRCA (Myriad assay)
HRR: Mutational status of 16 Homologous Recombination Repair pathway genes excluding BRCA1/2 (Myriad assay)
PD-L1 positive: ≥1% combined proportionality score (Dako 22C3 Clinical Trial Assay)
Excludes patients whose biomarker status is unknown
TOPACIO trial: Response Rates

Best Overall Response and Objective Response Rate (ORR)

<table>
<thead>
<tr>
<th>Response</th>
<th>Response Rate, n (%) Efficacy Evaluable (N=46)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Partial Response (PR)**</td>
<td>10 (22%)</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>10 (22%)</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>23 (50%)</td>
</tr>
<tr>
<td>ORR (CR+PR)</td>
<td>13 (28%)</td>
</tr>
<tr>
<td>DCR (CR+PR+SD)</td>
<td>23 (50%)</td>
</tr>
</tbody>
</table>

*9 pts did not have evaluable post-baseline tumor assessments and were not included in the evaluable population (6 pts discontinued due to AE; 1 due to clinical progression and 2 for other reasons).

**Responses include both confirmed and unconfirmed; DCR: Disease Control Rate; Data as of April 02, 2018

9 Patients still on treatment
- 2 CR
- 6 PR
- 1 SD

Presented At: 2018 ASCO Annual Meeting
Presented By: Shaveta Vinayak, MD, MS
TOPACIO trial: Response by Biomarkers

### Biomarker-Selected Populations

<table>
<thead>
<tr>
<th>Efficacy Evaluable Patients</th>
<th>ORR (CR+PR)</th>
<th>DCR (CR+PR+SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tBRCAmut patients (n=15)</td>
<td>9 (60%)</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>HRRmut + tBRCAmut (n=20)</td>
<td>11 (55%)</td>
<td>16 (80%)</td>
</tr>
<tr>
<td>PD-L1 positive patients (n=25)</td>
<td>9 (36%)</td>
<td>13 (52%)</td>
</tr>
</tbody>
</table>

- Overall Response Rate in all evaluable (biomarker-unselected) patients (N=46): ORR 28%, DCR=50%
TOPACIO trial: Responses

**Observed Best Responses**

- **tBRCAmut**
- **HRRmut**
- **HRRwt/Unknown**
- **Ongoing**

- **Percent Change**
  - PD
  - SD
  - CR

- **30% decrease**
TOPACIO trial: Responses

Durable Clinical Benefit Extends Beyond tBRCAmut

Overall Response RECIST 1.1
- Complete response
- Partial response
- Progressive disease
- Stable disease
- Ongoing
  - tBRCAmut
  - HRRmut
  - HRRwt/Unknown

Duration on Niraparib/Pembrolizumab Treatment (Months)

Plot contains patients with CR, PR, and SD; Dacut April 2, 2018; * PD-L1 positive patients; # Patient with both tBRCAmut and HRRmut

Presented at: 2018 ASCO Annual Meeting

Presented by: Shaveta Vinayak, MD, MS
Open-label, multi-tumor, Phase II basket study of olaparib and durvalumab (MEDIOLA): Germline BRCA-mutated HER2-MBC

MEDIOLA trial: Design

Olaparib monotherapy
300 mg BID

Olaparib + durvalumab
300 mg BID olaparib
1.5 g q4w durvalumab

Week

0

4

8

12

Cycle 1:
Olaparib + durvalumab
Cycle 2:
Olaparib + durvalumab
Cycle 3:
Olaparib + durvalumab

Tumor assessments every 8 weeks
25 of 34 enrolled pts
36% first-line; 28% 2+ lines
36% prior platinum
48% HR+/52% TN
44% BRCA1; 56% BRCA2

Domcheck et al, SABCS 2017
MEDIOLA trial: Responses

MEDIOLA: Olaparib + Durvalumab (n=25)

- 12/25 (48%) had disease control at 7 months
- Median DOR/PFS/OS not yet reached
- Response independent of HR status and BRCA-mutation type

**Best Response by Line of Chemotherapy**

<table>
<thead>
<tr>
<th>Response</th>
<th>1L</th>
<th>2L</th>
<th>3L</th>
<th>4L</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>PD</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total #</td>
<td>9</td>
<td>9</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>ORR</td>
<td>6/9=67%</td>
<td>6/9=67%</td>
<td>1/5=20%</td>
<td>0/2=0%</td>
</tr>
</tbody>
</table>

Domcheck et al, SABCS 2017
Why do tumors stop responding to PARP inhibitors?

Resistance to therapy caused by intragenic deletion in BRCA2
Why do tumors stop responding to PARP inhibitors?

53BP1 loss rescues BRCA1 deficiency and is associated with triple-negative and BRCA-mutated breast cancers.
How do we capture why PARP inhibitor stopped working?

- Tumor biopsy (somatic)
- "Liquid" biopsy (cell free DNA)
- Blood testing (germline)
What’s next after PARP inhibitors?

• Can you consider platinum chemotherapy?
  – No data to guide us yet

• Clinical trials evaluating ATR inhibitors in combination with PARP inhibitors for PARP inhibitor resistant tumors

• Biomarkers that help us understand resistant mechanisms to PARP inhibitors will guide future therapies. This will also help us figure out optimal sequence

• We have to be mindful of side effects of the combinations
Effectiveness of PARP inhibitors beyond germline BRCA1/2 mutation: Ongoing clinical trials

TBCRC trial: Olaparib for metastatic breast cancer with somatic and germline DNA repair mutations (NCT0334965)

Talazoparib in advanced non-BRCA HER2-negative breast cancer (somatic and germline DNA repair mutations; tumors with a DNA repair defect) (NCT02401347)
CDK4/6 inhibitors

- Relevance for patients with ER/PR+ metastatic breast cancer
- Approved CDK4/6 inhibitors
  - Palbociclib
  - Abemaciclib
  - Ribociclib
- Need to understand how best to sequence these drugs and what agents to give after progression
Approach to treatment of hereditary metastatic breast cancer

• Self advocacy important! (you are an empowered group)
• Clinical trials
  – Treatment
  – Biomarker (Which patients respond best to a treatment? Why does the tumor stop responding to the treatment?)
  – Exciting work being done with liquid biopsies to understand these treatment related questions
• Second opinions
• Treatment based on tumor subtype
• If BRCA1/2 mutation, option of platinum-based chemotherapy or PARP inhibitor
Future

Research and clinical trials are key!
Thank you