2017 Chabner Colloquium
PARP inhibitors in breast cancer:
Clinical development and future directions

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Center for Breast Cancer
October 30, 2017
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Disclosures

- I have served as a consultant to Abbvie
- I have received research funding from Abbvie and AstraZeneca
Inhibition of poly (ADP-ribose) polymerase (PARP) kills tumor cells with mutant BRCA

Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy

Hannah Farmer, Nuala McCabe, Christopher J. Lord, Andrew N. J. Tutt, Damian A. Johnson, Tobias B. Richardson, Manuela Santarosa, Krystyna J. Dillon, Ian Hickson, Charlotte Knights, Niall M. B. Martin, Stephen P. Jackson, Graeme C. M. Smith & Alan Ashworth

Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase

Helen E. Bryant, Niklas Schultz, Huw D. Thomas, Kayan M. Parker, Dan Flower, Elena Lopez, Suzanne Kyle, Mark Meuth, Nicola J. Curtin & Thomas Helleday
**PARP Inhibitors Mechanism of Action**

1. **Single Strand Breaks in DNA Recognized by PARP**
   - SSB → PARP
   - PARP flags DNA for repair and recruits help, and adds PAR to itself
   - DNA Pol β, XRCC1, PARP, DNA Ligase III

2. **After DNA is fixed, the help is released**
   - DNA Pol β, XRCC1, DNA Ligase III

3. **PALB2 and other mutations may have similar sensitivity**

**Cancer Cell able to repair single strand break**

**Cancer Cell treated with PARP inhibitor**

**BRCA Cancer Cell treated with PARP inhibitor**

**Cancer Cell Death**
### PARP Inhibitors Mechanism of Action

1. **Single Strand Breaks in DNA** Recognized by PARP
2. PARP flags DNA for repair and recruits help, and adds PAR to itself
3. After DNA is fixed, the help is released

**Inhibit Catalytic Activity**

**PARP trapping**

**Block POLθ mediated alternative end joining**

**PALB2 and other mutations may have similar sensitivity**

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**Cancer Cell able to repair single strand break**

1. PARP

2. PARP

3. PARP

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**Cancer Cell treated with PARP inhibitor**

1. PARP

2. BRCA1/2

---

**BRCA Cancer Cell treated with PARP inhibitor**

1. PARP

2. BRCA1/2

---

**Cancer Cell Death**

1. Blocking PARP function in BRCA cancer cells leads to cell death.
# PARP Inhibitors in development for Breast Cancer

<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib (AZD2281)</td>
<td>AstraZeneca</td>
<td>Ph3 breast done, FDA Approved OvCa</td>
</tr>
<tr>
<td>Veliparib (ABT-888)</td>
<td>AbbVie</td>
<td>Ph3 in breast</td>
</tr>
<tr>
<td>Niraparib (MK-4827)</td>
<td>Tesaro</td>
<td>Ph3 in breast halted, FDA approved OvCa</td>
</tr>
<tr>
<td>Talazoparib (BMN-673)</td>
<td>Pfizer</td>
<td>Ph3 in breast</td>
</tr>
<tr>
<td>Rucaparib (AG-14699)</td>
<td>Clovis</td>
<td>Ph2 in breast, FDA Approved OvCa</td>
</tr>
<tr>
<td>BGB-290</td>
<td>BeiGene</td>
<td>Phase 1/2 (disclosed 2017)</td>
</tr>
</tbody>
</table>
Clinical Opportunities to Use PARP inhibitors in BRCA1/2 Patients

Prevention

Neoadjuvant

Monotherapy

Adjuvant

Combination

Metastatic
Metastatic Breast Cancer
• Germline BRCA1/2 carriers
• Monotherapy
• Combination with chemotherapy
ICEBERG: Proof of Principle Phase II trial with Olaparib in BRCA-deficient advanced breast cancer:

<table>
<thead>
<tr>
<th>ITT cohort</th>
<th>Olaparib 400 mg bid (n=27)</th>
<th>Olaparib 100 mg bid (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate, n (%)</td>
<td>11 (41)</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Complete Response, n (%)</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response, n (%)</td>
<td>10 (37)</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Stable Disease n (%)</td>
<td>12 (44)</td>
<td>12 (44)</td>
</tr>
</tbody>
</table>

Adverse Events:

- Fatigue: grade 1 or 2, 56%; grade 3, 15%
- Nausea: grade 1 or 2, 26%; grade 3, 11%

- Median of 3 prior lines of chemotherapy.

*Tutt, Lancet 2010*
Single Agent PARP inhibition: FDA Registration Studies for BRCA1/2+ Advanced Breast Cancer

- **gBRCA1/BRCA2 Carriers**
  - Advanced anthracycline+taxane resistant breast cancer
  - No Prior Platinum*

- **Physician Choice within Standard of Care options:**
  - Capecitabine
  - Vinorelbine
  - Eribulin
  - Gemcitabine

- **PARP inhibitor as continuous exposure**

- **Primary endpoint:**
  - Progression free survival

### Study Details:

- **Olaparib – OLYMPIAD – NCT02000622**
  - (Accrual is complete, results reported ASCO 2017 Plenary, NEJM)

- **Niraparib – BRAVO – NCT01905592**
  - (Study halted)

- **Talazoparib – EMBRACA – NCT01945775**
  - (BMN673)

**Note:** Platinum is not included in comparator arm
OlympiAD: Phase III trial of olaparib monotherapy versus chemotherapy for patients with HER2-negative metastatic breast cancer and a germline BRCA mutation

Mark Robson, Seock-Ah Im, Elżbieta Senkus, Binghe Xu, Susan M Domchek, Norikazu Masuda, Suzette Delalogue, Wei Li, Nadine Tung, Anne Armstrong, Wenting Wu, Carsten Goessl, Sarah Runswick, Pierfranco Conte

Robson, 2017 ASCO Annual Meeting Plenary Session, NEJM 2017
OlympiAD: Study Design

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious gBRCAm
- Prior anthracycline and taxane
- ≤2 prior chemotherapy lines in metastatic setting
- HR+ disease progressed on ≥1 endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression during treatment in the advanced setting
  - ≥12 months since (neo)adjuvant treatment

Primary endpoint:
- Progression-free survival (RECIST 1.1, BlCR)

Secondary endpoints:
- Time to second progression or death
- Overall survival
- Objective response rate
- Safety and tolerability

Global HRQoL (EORTC-QLQ-C30)

2:1 randomization

Olaparib
300 mg tablets bd

Chemotherapy treatment of physician’s choice (TPC)
- Capecitabine
- Eribulin
- Vinorelbine

BlCR, blinded independent central review; ER, estrogen receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, response evaluation criteria in solid tumors; TNBC, triple negative breast cancer

Robson, 2017 ASCO Annual Meeting Plenary Session
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Olaparib 300 mg bd (N=205)</th>
<th>Chemotherapy TPC (N=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median, range)</td>
<td>44 (22–76)</td>
<td>45 (24–68)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>5 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>134 (65)</td>
<td>63 (65)</td>
</tr>
<tr>
<td><strong>BRCA mutation status, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>117 (57)</td>
<td>51 (53)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>84 (41)</td>
<td>46 (47)</td>
</tr>
<tr>
<td>Both</td>
<td>4 (2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hormonal receptor status, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+ and/or PR+</td>
<td>103 (50)</td>
<td>49 (51)</td>
</tr>
<tr>
<td>TNBC</td>
<td>102 (50)</td>
<td>48 (49)</td>
</tr>
<tr>
<td><strong>Prior chemotherapy for metastasis, n (%)</strong></td>
<td>146 (71)</td>
<td>69 (71)</td>
</tr>
<tr>
<td><strong>Prior platinum treatment, n (%)</strong></td>
<td>60 (29)</td>
<td>26 (27)</td>
</tr>
</tbody>
</table>

Robson, 2017 ASCO Annual Meeting Plenary Session
Primary endpoint: progression-free survival by BICR

- Olaparib 300 mg bd
  - Progression/deaths, n (%): 163 (79.5)
  - Median PFS, months: 7.0
- Chemotherapy TPC
  - Progression/deaths, n (%): 71 (73.2)
  - Median PFS, months: 4.2

HR 0.58
95% CI 0.43 to 0.80; P=0.0009
PFS2 is potentially better surrogate for Overall Survival than PFS, recommended by EMA
Overall survival (interim analysis; 46% data maturity)

Deaths (%)
Median OS, months

<table>
<thead>
<tr>
<th></th>
<th>Olaparib 300 mg bd</th>
<th>Chemotherapy TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>0.90</td>
<td>1.00</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.63 to 1.29</td>
<td>0.83 to 1.37</td>
</tr>
<tr>
<td>P</td>
<td>0.5665</td>
<td>0.54</td>
</tr>
<tr>
<td>At risk, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 2 4 6 8 10 12 14 16 18 20 22 24 26 28</td>
<td>205 205 199 189 178 159 146 109 78 69 62 50 34 24 13 9 7 4 2 0</td>
<td></td>
</tr>
</tbody>
</table>
Objective Response by Blinded Independent Central Review

- Overall response: 60%, 29%
- Complete response: 9%, 2%

Median time to response, days:
- Olaparib 300 mg bd: 167
- Chemotherapy TPC: 66
- Olaparib: 47
- Chemotherapy TPC: 45

Median duration of response, months:
- Olaparib 300 mg bd: 6.2 (4.6–7.2)
- Chemotherapy TPC: 7.1 (2.8–12.2)
Olympiad limitation: no platinum in comparator:
Comparing the Olympiad and TNT trials

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (OlympiAD) N= 302 BRCA+</th>
<th>Carboplatin (TNT trial) N= 43 BRCA+</th>
</tr>
</thead>
<tbody>
<tr>
<td># chemo in met setting</td>
<td>0-2</td>
<td>0</td>
</tr>
<tr>
<td>subtypes</td>
<td>TNBC, ER+ HER2-</td>
<td>TNBC&gt; ER+ (12)</td>
</tr>
<tr>
<td>PFS</td>
<td>7.0 mos</td>
<td>6.8 mos</td>
</tr>
<tr>
<td>ORR</td>
<td>60% (64% 1st line)</td>
<td>68%</td>
</tr>
<tr>
<td>toxicity</td>
<td>? Likely lower</td>
<td></td>
</tr>
</tbody>
</table>
OlympiAD: Additional findings

- Compared to standard chemotherapy:
  - Similar activity regardless of prior chemotherapy exposure
  - More effective in Triple Negative than ER+
    - ER+ 65.4% olaparib vs 38.7% chemo
    - TNBC: 54.7% olaparib vs 21.2% chemo
  - Similar activity with or without prior platinum chemotherapy
  - Side effects generally similar:
    - Olaparib had more nausea
    - Chemotherapy had more leukopenia
  - Olaparib had improved Quality of Life
US FDA Accepts Regulatory Submission for LYNPARZA® (olaparib) in Metastatic Breast Cancer and Grants Priority Review

Published: October 18, 2017

*LYNPARZA has the potential to offer a new treatment option for patients with germline BRCA-mutated, HER2-negative metastatic breast cancer*

*Regulatory submission acceptance is first for a PARP inhibitor beyond ovarian cancer*

WILMINGTON, Del.--(BUSINESS WIRE)--Oct. 18, 2017-- AstraZeneca and Merck & Co., Inc., (Merck: known as MSD outside the US and Canada) today announced that the US Food and Drug Administration (FDA) has accepted and granted priority review for a supplemental New Drug Application (sNDA) for the use of LYNPARZA® (olaparib) tablets in patients with germline BRCA-mutated (gBRCAm), HER2-negative metastatic breast cancer who have been previously treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic settings. A Prescription Drug User Fee Act (PDUFA) date is set for the first quarter of 2018.
Olaparib

- Based on OlympiAD study, we anticipate Olaparib will get FDA approval for metastatic BRCA1/2 associated breast cancer in 2018.
- This will be the *FIRST* drug FDA approved specifically for BRCA1/2 breast cancer
Challenges to the Development of New Agents for Molecularly Defined Patient Subsets: Lessons From BRCA1/2-Associated Breast Cancer

Susan M. Domchek, University of Pennsylvania School of Medicine, Philadelphia, PA
Gillian Mitchell, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
Geoffrey J. Lindeman, Walter and Eliza Hall Institute of Medical Research and Royal Melbourne Hospital, Melbourne, Victoria, Australia
Nadine M. Tung, Beth Israel Deaconess Medical Center, Boston, MA
Judith Balmaña, Vall d’Hebron University Hospital, Barcelona, Spain
Steven J. Isakoff, Massachusetts General Hospital, Boston, MA
Rita Schmutzler, University of Cologne, Cologne, Germany
M. William Audeh, Cedars Sinai Medical Center, Los Angeles, CA
Niklas Loman, Skåne University Hospital, Malmö, Sweden
Clare Scott, Walter and Eliza Hall Institute of Medical Research and Royal Melbourne Hospital, Melbourne, Victoria, Australia
Michael Friedlander, Prince of Wales Cancer Centre, Sydney, New South Wales, Australia
Bella Kaufman, The Chaim Sheba Medical Center, Tel Aviv, Israel
Judy E. Garber, Dana-Farber Cancer Institute, Boston, MA
Andrew Tutt, Guy’s Hospital, King’s Health Partners Academic Health Sciences Centre, London, United Kingdom
Mark E. Robson, Memorial Sloan-Kettering Cancer Center, New York, NY
PARP in BRCA1/2 Mutant Breast Cancer: A long time coming (2009->2018?)

- In other cancers with small populations, targeted therapies have seen rapid approval
- PARP inhibitors have been slow to become available

**Table 1** | Timing of clinical trials and FDA approval for selected targeted therapies

<table>
<thead>
<tr>
<th>Mutation and drug</th>
<th>Publication date of phase I–II trial</th>
<th>Publication date of phase III trial</th>
<th>Date of FDA approval</th>
<th>FDA approved companion diagnostic test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRCA1/2 and PARP inhibitors</strong></td>
<td>24 June 2009(^{26})</td>
<td>None (June 2017)</td>
<td>None</td>
<td>Not available</td>
</tr>
<tr>
<td><strong>RET and vandetanib</strong></td>
<td>11 January 2010(^{71})</td>
<td>10 January 2012(^{73})</td>
<td>6 April 2011</td>
<td>Not needed as approval granted for medullary thyroid cancer</td>
</tr>
<tr>
<td><strong>EML4–ALK and crizotinib</strong></td>
<td>28 October 2010(^{89})</td>
<td>Ongoing(^{82})</td>
<td>26 August 2011</td>
<td>Vysis ALK Break Apart FISH ProbeTest</td>
</tr>
<tr>
<td><strong>BRAF and vemurafenib</strong></td>
<td>26 August 2010(^{76})</td>
<td>30 June 2011(^{73})</td>
<td>17 August 2011</td>
<td>Cobas 4800 V600 mutation assay</td>
</tr>
<tr>
<td><strong>EGFR and erlotinib</strong></td>
<td>15 August 2004(^{103})</td>
<td>14 July 2005(^{85})</td>
<td>18 November 2004</td>
<td>Not needed as approved for second-line therapy in non-small-cell lung cancer</td>
</tr>
</tbody>
</table>
ABRAZO: Phase 2 study of Talazoparib monotherapy in gBRCA1/2 patients

- 2 Cohorts
  - 1) PR/CR to prior platinum with no progression
    - 48 patients
  - 2) >3 lines prior therapy and no prior platinum
    - 35 patients

- Primary objective:
  - Response Rate

Talazoparib is a highly potent inhibitor of PARP


*Turner, ASCO 2017*
Primary results from ABRAZO

Maximal Percent Change in Target Lesions by BRCA Mutation Status

Cohort 1
- $RR=21\%$ (10-35)
- Overall ORR for BRCA 1 = 23% and BRCA 2 = 33%

Cohort 2
- $RR=37\%$ (22-55)

Platinum free interval:
- $< 2 \text{ mo} = 0\%$ (n=7)
- $> 6 \text{ mo} = 47\%$ (n=15)

Turner, ASCO 2017

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

- Preclinical studies demonstrate synergy with multiple combinations
  - Chemotherapy may induce DNA damage, sensitize to PARPi
- Phase 1/2 studies evaluating PARPi with:
  - Platinum (cisplatin and carboplatin)
  - Carboplatin + paclitaxel
  - Temozolomide
  - Cyclophosphamide
  - Topotecan/irinotecan
  - paclitaxel
Platinum combination therapy

- Phase 1 study
- Cisplatin 75mg/m2
- Olaparib continuous
  - Not tolerable
- Olaparib intermittent
  - 50mg BID D1-5 Tolerable
  - Cisplatin 60mg/m2
- ORR in BRCA1/2 breast ca = 71%
- Continuous monotherapy after 6 cycles had durable responses
- Dose limiting toxicity included
  - Neutropenia, lipase
Phase 2 Veliparib + temozolomide

- Preclinical data showed strong synergy
- TMZ not used in breast cancer – may offer new chemo option
- All oral regimen

Eligibility
- BRCA1/2 carrier
- Stage 4 breast cancer
- Archived tumor
- Measurable disease

Veliparib 30mg BID D1-7 + TMZ 150mg/m2 D1-5
Every 28 days

Isakoff, SABCS 2011
Phase 2 Veliparib + temozolomide: 
Prior Platinum correlated with lower response rate

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>N = 29</td>
<td></td>
</tr>
<tr>
<td>PR/CR</td>
<td>7</td>
<td>24.1%</td>
</tr>
<tr>
<td>SD</td>
<td>7</td>
<td>24.1%</td>
</tr>
<tr>
<td>CBR</td>
<td>14</td>
<td>48.3%</td>
</tr>
<tr>
<td><strong>Prior Platinum</strong></td>
<td>N = 13</td>
<td></td>
</tr>
<tr>
<td>PR/CR</td>
<td>1</td>
<td>7.7%</td>
</tr>
<tr>
<td>SD</td>
<td>1</td>
<td>7.7%</td>
</tr>
<tr>
<td>CBR</td>
<td>2</td>
<td>15.4%</td>
</tr>
<tr>
<td><strong>No Prior Platinum</strong></td>
<td>N = 16</td>
<td>(6 BRCA1, 10 BRCA2)</td>
</tr>
<tr>
<td>PR/CR</td>
<td>6</td>
<td>37.5%</td>
</tr>
<tr>
<td>SD</td>
<td>6</td>
<td>37.5%</td>
</tr>
<tr>
<td>CBR</td>
<td>12</td>
<td>75.0%</td>
</tr>
</tbody>
</table>

**Toxicity**
- PLT
- Neutropenia
- Anemia
- Nausea/Vomiting
BROCADE: Study Design
Randomized Phase 2 Study

**Metastatic breast cancer with BRCA1/2 mutation**
- ≤ 2 lines of chemo
- No prior platinum
- N = 290
  (86 sites, 20 countries)

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

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

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

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

*Carboplatin/Paclitaxel administered on D3, 21-day cycle.
†28-day cycle.

Patients were treated until progression or unmanageable toxicity. If both carboplatin and paclitaxel or if TMZ was discontinued, placebo/veliparib was discontinued.
Progression-Free Survival

Median PFS, months (95% CI)
Placebo + C/P
N = 98
12.3 (9.3–14.5)
Veliparib + C/P
N = 95
14.1 (11.5–16.2)

HR
0.789 (0.536–1.162)
P value *
0.231

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

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

*P <0.05 for placebo +C/P vs veliparib + C/P.

Tumor assessments were per independent radiology reviewer. ORR, CR, and PR shown represent confirmed responses; these analyses included all patients with measurable disease at baseline. DOR analysis included all patients with an objective response. CBR analysis included all randomized patients who had a deleterious BRCA1/2 mutation per the core lab.

DOR, duration of response; PR, partial response.
Conclusions

• The addition of veliparib to carboplatin/paclitaxel resulted in trends toward improved PFS and OS, and a significant increase in ORR
  
  – Final OS analysis will occur when the prespecified number of events is reached

• Further evaluation of the efficacy and safety of veliparib with weekly paclitaxel and carboplatin in patients with BRCA-mutated advanced breast cancer is ongoing in the phase 3 randomized trial BROCADE3 (NCT02163694)

Han, Ann. Onc, 2017
Eribulin + olaparib

- Phase 1/2 study in metastatic triple negative breast cancer
- Olaparib 300mg bid olaparib and 1.4 mg/m2 IV eribulin day 1 and 8 in 21-day cycle.
- Phase 2 primary endpoint RR
- 24 patients enrolled, median prior tx = 3
- RR 29.2% (80%CI: 17.0-44.2)
- Median PFS 4.2 months
- Median overall survival was 14.5 months

Aogi, ESMO 2017
PARP inhibitors: Adjuvant Therapy
PARP inhibitors for Early Stage Breast Cancer

• OLYMPIA study:
  – Adjuvant Olaparib
  – Assess for improvement in disease free survival (10 yr f/u)

• BRCA1/2 mutation
• Triple negative or high risk ER positive
• Complete at least 6 cycles of chemotherapy

12 months of **olaparib**
12 months of **placebo**
Neoadjuvant therapy with PARP inhibitors
I-SPY 2: Carboplatin + Veliparib in TNBC

- Adding carboplatin/veliparib to paclitaxel significantly increased pCR
- However, missing proper control arm of carbo/paclitaxel alone

Rugo et al, NEJM 2016
BrighTNess study: TNBC

TNBC N=634

- Taxol weekly
- Taxol weekly + Carboplatin
- Taxol weekly + Carboplatin + Veliparib

AC x 4 → SURGERY

- 15% pts gBRCA+ (93 BRCA carriers)
- pCR higher with carbo (not veliparib)
  - No difference due to gBRCA status
  - pCR 57.5% (+ carbo) vs 53.5 (+carbp/vel) vs 31% (no carbo)

Geyer et al; ASCO 2017; abstract 520
Neoadjuvant Talozoparib monotherapy study in germline BRCA1/2 patients

13 patients enrolled
All had shrinkage of tumor
Median volume decrease of 88%

Litton, ESMO 2016
Resistance to PARP inhibitors
Mechanisms of Resistance to PARP inhibitors

- Reversion of BRCA1/2 Truncated mutations
  - Observed in Ovarian cancer
  - Recently reported in Prostate cancer
  - Previously thought uncommon in breast cancer…
BRCA1/2 Functional Restoration

- Reversion mutations
- Intragenic deletions
  - 2/5 (40%) of BRCA1/2 pts by ctDNA

Weigelt et al, Clinical Cancer Research 2017
Mechanisms of Resistance to PARP inhibitors

- Reversion of BRCA1/2 Truncated mutations
- P glycoprotein efflux pumps
- Stabilization of BRCA1/2 mutant protein
- Loss of 53BP1
  - Results in restoration of HR in BRCA1/2 cells
- Presence of hypomorphic BRCA1/2
  - Low level expression of BRCA1/2 can be stimulated
    - ATR upregulation
Immunotherapy and PARP inhibitors

• Biologic rationale:
  - PARPi can increase cell death and inflammation → improved CD8+ T cell infiltration and activation concurrent with immune checkpoint modulators
  - PARPi can increase tumor somatic mutations → neo-antigens that prime anti-tumor CD8+ T cells in the presence of immune checkpoint modulation
  - BRCA1 tumors may have high frequency of PDL1
  - Veliparib has demonstrated synergy with anti-CTLA-4 in BRCA deficient pre-clinical models (Higuchi et al, 22nd CRI Symposium, 2014)
TOPACIO Study (KEYNOTE 162)

Phase 1/2 Clinical Study of Niraparib in Combination with Pembrolizumab in Patients with Advanced or Metastatic Triple-Negative Breast Cancer and in Patients with Recurrent Ovarian Cancer

- Phase 2 will enroll 48 Triple negative breast cancer patients
- No prior progression on platinum allowed
- Nearly complete
- In phase 1, 1/5 TNBC (BRCA wt) had SD > 10 cycles (Konstantinopoulos, ESMO 2017)
Immunotherapy and PARP inhibitors – Clinical Studies

- MTD durvalumab 1500 mg q 4 weeks and olaparib 300 mg BID
- Only 2 of 11 patients had breast ca
  - Both were BRCA wt triple negative breast ca
  - 1/11 (8% response)
  - 9/11 (83%) disease control > 4 months
- Expansion cohort now open in TNBC
- Combination with durvalumab/olaparib/cediranib complete

Lee, ASCO 2016, Zimmer, ESMO2017
Combinations of PARP inhibitor and PI3K inhibitors

- PI3K activity is important for Double Strand Break repair
- Preclinical evidence demonstrated strong synergy with PARP inhibitor/ PI3K inhibitor combinations
- Preclinical activity seen in BRCA deficient and proficient cells

Ibrahim, Cancer Discovery 2012, Juvekar, Cancer Discovery 2012
Combinations of PARP inhibitor and PI3K inhibitors

- **Ph1 study of BKM120 + olaparib**
  - 69 patients treated, 24 with breast ca, 63% breast with gBRCA mutation
  - MTD BKM120 50 mg daily, Olaparib 300mg BID
  - Toxicity: nausea, fatigue, hyperglycemia, depression, transaminitis, rash, anemia
  - RR in Breast ca = 28%, 1 with TNBC and normal BRCA1/2

- **Ph1 cohort with BYL719 + Olaparib completed**
Olaparib + AZD5363 (AKT inhibitor)

- Phase I expansion of olaparib and AZD5363 in recurrent ovarian, endometrial and triple negative breast cancer
- Olaparib orally 300 mg BID + AZD5363 400mg orally on a 4 day on/3 day off schedule.
- Pre- and on-treatment biopsies
- 38 patients enrolled.
- Dose level 1 confirmed for phase 2 dosing
- Most common adverse events:
  - anemia (89%, G3/4 16%), nausea (76%, G3/4 5%), diarrhea (74%, G3/4 5%), leukopenia (61%, G3/4 11%), elevated creatinine (58%, G3/4 3%), hyperglycemia (42%, G3/4 0%),
- Response rate 24% including 2 triple negative breast.

Westin, ESMO 2017
PARP Inhibitors Beyond BRCA1/2 Germline Mutations

- Somatic BRCA1/2 mutations: ~ 3%
  - Met prostate ca (CRPC)- respond to olaparib

- Homologous Recombination Deficiency (HRD) tools
  - Myriad HRD: LOH, TAI, LST
    - TNT- not predictive for platinum (but assessed primary tumor)
  - HRDetect :WGS; mutational signatures

- Mutations (germline & somatic) in other HR genes

Davies et al. Nature Genetics 2017
Olaparib in Prostate Cancer with Germline and Somatic Mutations in DNA repair genes

- ORR = 33% (16/49)
- ORR in DNA repair mutation = 88% (14/16)

 Mateo, NEJM 2015
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)

Similar Study with Olaparib underway: “Olaparib Expanded” (Nadine Tung, PI)
FDA Approved PARP inhibitors in Ovarian Cancer - None in Breast Cancer (yet)

- **Olaparib (Lynparza)**
  - FDA Approved 2014 for metastatic germline BRCA-mutated ovarian cancer after 3+ lines of therapy
  - FDA approved August 17, 2017 for maintenance treatment of metastatic ovarian cancer incomplete or partial response to platinum based chemotherapy

- **Niraparib (Zejula)**
  - Approved March 2017 for ovarian cancer maintenance after platinum based chemotherapy

- **Rucaparib (Rubraca)**
  - Approved December 2016 for previously treated BRCA-mutant(germline or somatic using Foundation Medicine) ovarian cancer after 2+ lines of therapy
Summary and Conclusions

• It’s been a long and winding road, but we are close…
  – Positive Phase 3 data now reported, FDA approval soon 2018
• PARP inhibitors are clearly active in BRCA1/2 breast cancer
• Therapeutic opportunities exist in metastatic, adjuvant, neoadjuvant and prevention space
• Activity and safety seen in monotherapy and combinations with chemotherapy and targeted therapy
  – But not all PARP inhibitors are equal and combinations may differ
• Additional therapeutic strategies are under development for BRCA1/2 carriers
• Resistance remains a problem
• The utility of PARP inhibitors in non-BRCA breast cancer remains unclear
Thank you

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