Targeting DNA repair pathways in women’s cancers

March 21, 2017

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COI

• I have no conflicts of interest.
Genetic sources of genomic instability

Mutually exclusive events

- Serous 82%
- Carcinosarcoma 6%
- Endometrioid 3%
- Clear cell 6%
- Mixed 3%

2016

- BRCA1 germline 6%
- BRCA2 somatic 4%
- BRCA2 somatic 3%
- other HRD 10%
- NF1 loss 17%
- CCNE1 Amplification
- RB1 loss 15%
- PTEN loss 6%
- BRCA1 methylation 6%

Patch and Bowtell et al, Nature 2015
Molecular drivers and clinical association

Extended Data Figure 7

a, Percentage (∑n) of primary tumours (total n = 80) affected by homologous recombination pathway mutations and CCNE1 copy number gains. One driver mutation counted for samples with more than one change, ranking mutations in BRCA1/2, followed by other germline, somatic, amplification, deletion and methylation events respectively.

b, Association of driver mutation subgroup with overall survival in AOCS and TCGA cohorts (Kaplan–Meier analysis, P value calculated by Mantel–Cox log-rank test).

c, d, Whole genome (c) and coding mutations (d) per megabase for samples stratified by primary clinical response group (lines indicate mean). Kruskal–Wallis test P value reported (*P, 0.05, **P, 0.01, Kolmogorov–Smirnov test).

e, Boxplots summarize CCNE1 expression in different driver mutation subgroups (****P, 0.0001, unpaired two-tailed t-test). Middle bar, median; whiskers, data range.

f, Proportions of gene expression molecular subtypes between driver mutation subgroups. HR/CCNE12 subgroup has no detected homologous recombination pathway mutations or CCNE1 copy number changes.

AOCS cohort

TCGA cohort

Survival probability

Overall survival (months)

Survival probability

Overall survival (months)

P = 0.0002

P = 0.0043

AOCS, Clin Ca Res, 2013
Patch et al, Nature 2015
PARP inhibition, synthetic lethality in the clinic

A

DNA DSB

Unrepaired SSB at replication

DNA SSB

Damaged base

APE-1

PARP

DNA polβ

XRCC1

Ligase III

Base Excision Repair

Signaling
G1 arrest
to allow repair

CHK2

BRCA1

ATM

H2A

ATR

CHK1

KU 70/80

DNA-PK

XRCC4

Ligase IV

Error prone
NHEJ in G1

Rad51

RPA

BRCA2

Error free H2
Active in dividing cells

ERCC1

XRCC3

© 2010 American Association for Cancer Research

Plummer R Clin Ca Res 2010  Lord et al, Science 2017
Olaparib maintenance: maintains clinical benefit after treatment in first or second response (EUROPEAN APPROVAL)

<table>
<thead>
<tr>
<th></th>
<th>BRCAm (n=136)</th>
<th>BRCAwt (n=118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>11.2</td>
<td>5.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.3</td>
<td>5.5</td>
</tr>
<tr>
<td>Median PFS, mo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Events: total pts (%) 26:74 (35.1) 46:62 (74.2) 32:57 (56.1) 44:61 (72.1)

\[
\text{Hazard ratio } 0.35 \\
(95\% \text{ CI, 0.25–0.49}) \\
P<0.00001
\]

\[
\text{HR}=0.18 \\
95\% \text{ CI (0.11, 0.31); } P<0.00001
\]

\[
\text{HR}=0.53 \\
95\% \text{ CI (0.33, 0.84); } P=0.007
\]
Activity in gBRCA mutation and BRCA-like OvCa

basis for FDA approval ≥3 line

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Ovarian (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR in Planned Cohorts</td>
<td></td>
</tr>
<tr>
<td>BRCA</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td>Unknown BRCA</td>
<td>14/53 (26%)</td>
</tr>
<tr>
<td>ORR by Actual BRCA Status</td>
<td></td>
</tr>
<tr>
<td>Mutant BRCA</td>
<td>7/17 (41%)</td>
</tr>
<tr>
<td>Non-BRCA</td>
<td>11/46 (24%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>219 days</td>
</tr>
</tbody>
</table>

Gelmon et al., Lancet Oncol, 2011
Rucaparib: activity in BRCA mutated OvCa

basis for FDA approval ≥2 line

Rucaparib 600mg bid
BRCA mutation
BRCAwt LOH high
BRCAwt LOH low

Efficacy

<table>
<thead>
<tr>
<th>Ovarian (n=192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, median (months)</td>
</tr>
<tr>
<td><strong>BRCA mutation</strong></td>
</tr>
<tr>
<td><strong>BRCAwt LOH high</strong></td>
</tr>
<tr>
<td><strong>BRCAwt LOH low</strong></td>
</tr>
</tbody>
</table>

Swisher et al., Lancet Oncol, 2017
Olaparib+carboplatin: active in gBRCAm and BRCAwt HGSOC

<table>
<thead>
<tr>
<th>Response</th>
<th>OvCa gBRCAm N (%)</th>
<th>Duration</th>
<th>HGSOC N (%)</th>
<th>Duration</th>
<th>Total (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>15/34 (44%)</td>
<td>12 mo [3-28+mo]</td>
<td>4/15 (27%)</td>
<td>6 mo [3-8mo]</td>
<td>19/49 (39%)</td>
</tr>
<tr>
<td>SD&gt;4mo</td>
<td>13/34 (38%)</td>
<td>12 mo [4-25+mo]</td>
<td>7/15 (47%)</td>
<td>8 mo [4-10.5mo]</td>
<td>20/49 (41%)</td>
</tr>
</tbody>
</table>

Lee et al, JNCI, 2014
Lee et al, Clin Ca Res 2016
Olaparib+carboplatin: active in gBRCAm and BRCA wt HGSOC

<table>
<thead>
<tr>
<th>Response</th>
<th>OvCa gBRCAm N (%), Duration</th>
<th>HGSOC N (%), Duration</th>
<th>Total (N=49)</th>
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</thead>
<tbody>
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<td>0</td>
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</tr>
<tr>
<td>SD≥4mo</td>
<td>13/34 (38%) 12 mo [4-25+mo]</td>
<td>7/15 (47%) 8 mo [4-10.5mo]</td>
<td>20/49 (41%)</td>
</tr>
</tbody>
</table>

pretx FOXO3a correlates with PFS

Reduction in FOXO3a+ tumor nuclei with treatment

Lee et al, JNCI, 2014
Olaparib adds benefit to carbo and paclitaxel in platinum-sensitive recurrent ovarian cancer

Events: Total patients (%)

<table>
<thead>
<tr>
<th>O/P/C</th>
<th>P/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>47:81 (58.0)</td>
<td>55:81 (67.9)</td>
</tr>
</tbody>
</table>

Median (mos)

<table>
<thead>
<tr>
<th>O/P/C</th>
<th>P/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.2</td>
<td>9.6</td>
</tr>
</tbody>
</table>

Hazard ratio = 0.51

95% CI (0.34, 0.77)

P=0.0012

Oza et al, Lancet Oncology, 2015
Lessons from PARPi in BRCA mutated OvCa

HRD appears to be a reliable target in ovarian cancer, though validated predictive biomarker(s) beyond BRCA mutation are needed.

DNA-Repair inhibition: New opportunities are arising through the new classes of agents targeting drugs in the DNA repair/cell cycle pathways.

Expanding beyond the nucleus: leveraging the cellular and tumor microenvironment targeting agents
An alternative DNA repair pathway target in HGSOC

[Diagram showing DNA damage response pathways with nodes for DSBs, ATM, ATR, CHK1, CDC25A, CDC25C, CyclinA/E, CDK1, p53, p21, and regulatory connections such as Oncogenic stress, ATRi, CHK1i, and p21 inhibition.]
Prexasertib (LY2606368): a second generation Chk1/2 inhibitor

- Potent ATP-competitive inhibitor of both Chk1/2
- Single agent activity in ovarian cancer mouse model
- Safety and activity in FIH study

McNeely et al. ACR-NCI-EORTC 2011
Hong et al. JCO 2016
14-C-0156 Study Design

A phase II single arm study of prexasertib (LY2606368)

**Cohort 1**
*Germline BRCA mutation Ov ca*

**Cohort 2**
*HGSOC BRCA wild type Negative FHx*

C1D1  C1D15  C2D1

LY2606368 105 mg/m² IV q 2 weeks…

PBMCs, CTCs for translational correlative studies

Optional 2nd and at progression bx

tumor and uninvolved skin

**Study objectives**

**Primary:** ORR (CR+PR) by RECISTv1.1

**Secondary:** Safety and tolerability, Progression-free interval

**Exploratory correlatives:** Potential predictive and PD biomarkers
## Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>BRCA mutant OvCa (n=7)</th>
<th>HGSOC (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age; median (range)</strong></td>
<td>58.5 (36-67)</td>
<td>62.6 (46.6-83)</td>
</tr>
<tr>
<td><strong>ECOG PS (0/1/2)</strong></td>
<td>1/6/0</td>
<td>4/19/2</td>
</tr>
<tr>
<td><strong>Recurrent OvCa Platinum-</strong></td>
<td>Sensitive</td>
<td>Resistant/refractory</td>
</tr>
<tr>
<td><strong># of patients</strong></td>
<td>1</td>
<td>5/1</td>
</tr>
<tr>
<td><strong># of prior lines of therapy; median (range)</strong></td>
<td>3</td>
<td>7 (3-12)</td>
</tr>
<tr>
<td><strong>Prior PARPi</strong></td>
<td>1Yes/0No</td>
<td>6Yes/0No</td>
</tr>
<tr>
<td><strong>Prior Bevacizumab</strong></td>
<td>1Yes/0No</td>
<td>5Yes/1No</td>
</tr>
</tbody>
</table>

Lee et al. ESMO 2016
**Prexasertib:**
**single agent activity in BRCAwt HGSOC**

<table>
<thead>
<tr>
<th></th>
<th>gBRCAm OvCa (n=6 evaluable)</th>
<th>HGSOC (n=20 evaluable)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>0</td>
<td>7/20 (35%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6mo (2+–13)</td>
</tr>
<tr>
<td><strong>SD≥4mo</strong></td>
<td>4/6 (67%)</td>
<td>5/20 (25%)</td>
</tr>
<tr>
<td></td>
<td>4mo (4-5)</td>
<td>5mo (4-7+)</td>
</tr>
<tr>
<td><strong>Response rate</strong></td>
<td>0%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Disease control rate</strong></td>
<td>4/6 (67%)</td>
<td>12/20 (60%)</td>
</tr>
<tr>
<td>(CR+PR+SD≥4mo)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lee et al. ESMO 2016
The diagram illustrates the best response for target lesions by patient for gBRCAm OvCa (n=6) and HGSOC (n=20) using Prexasertib activity in platinum-resistant recurrent HGSOC. The x-axis represents the change from baseline in sum of longest diameters (%), and the y-axis indicates the percentage. The data is categorized into two groups: white for platinum-sensitive disease and grey for platinum-resistant or refractory disease. The graph shows the efficacy of Prexasertib in different disease statuses, with markers indicating the response levels. Lee et al. ESMO 2016
68 yo F with platinum-resistant recurrent BRCAwt HGSOC with 13 prior tx regimens (PR, 6+mo)
Augmented cytotoxicity by combining PARPi with prexasertib in HGSOC cell lines

Brill and Lee et al, manuscript in preparation
Chk inhibition reduces RAD51 foci formation

**Figure 1:** Immunofluorescence images showing the effect of Chk inhibition on RAD51 foci formation in CAOV3 cells. The expression of Rad51 and DAPI staining are shown for control (DMSO), LY2606368, Olaparib, and LY + O treatments. The graph on the right illustrates the percentage of cells with ≥5 RAD51 foci for each treatment group. The data shows a significant reduction in RAD51 foci in the LY2606368 and Olaparib treatment groups compared to DMSO and LY + O conditions.

**Table:**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CAOV3</th>
<th>PEO1</th>
<th>PEO4</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY2606368</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Olaparib</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LY + O</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Chk inhibition reduces RAD51 foci formation* (Brill and Lee et al, manuscript in preparation)
Leveraging DNA repair pathways optimizing therapeutic targets

- Exploiting DNA-repair or cell-cycle defects
- Targeting oncogenic drivers
- Achieving synthetic lethality in cancer cells
- Targeting the altered proteome
- Exploiting nononcogene “addiction”
- Exploiting the altered metabolome
- Targeting the stroma
- Exploiting the tumor-cell environment
- Using altered drug timing and sequencing
- Using new drug combinations derived from screens

McLornan, et al. NEJM 2014
Leveraging DNA repair pathways expanding beyond the nucleus

Achieving synthetic lethality in cancer cells

- Using new drug combinations derived from screens
- Using altered drug timing and sequencing
- Exploiting DNA-repair or cell-cycle defects
- Targeting oncogenic drivers
- Exploiting the tumor-cell environment
- Targeting the stroma
- Exploiting the altered metabolome
- Exploiting nononcogene "addiction"
- Targeting the altered proteome

McLornan, et al  NEJM 2014
Olaparib and cediranib: Synergy between hypoxia and inhibition of DNA repair

Loss of H2AX diminishes proliferative drive in endothelial cells, only in hypoxic background, suggesting interaction between DNA repair and angiogenesis.

Economopoulou et al, Nat Med, 2009

Unpublished data, courtesy of AZ
Olaparib and cediranib

Clinical synergy between hypoxia and DNA repair inhibition

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Ced/Olap</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>Median PFS</td>
<td>9.0 mo</td>
<td>17.7 mo</td>
</tr>
</tbody>
</table>

p=0.005, HR 0.42 (95% CI: 0.23-0.76)

Liu et al, Lancet Oncol, 2015; Lee et al, Front Oncol 2015
Marked activity in non-BRCA mutation carriers

**gBRCAm**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>BRCA Mutation Carrier</th>
<th>BRCA Mutation Non-Carrier/Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Olaparib</td>
<td>Ced/Olap</td>
</tr>
<tr>
<td>PFS events</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Median PFS</td>
<td>16.5 mo</td>
<td>20.2 mo</td>
</tr>
<tr>
<td>P-Value</td>
<td>p=0.07</td>
<td>p=0.003</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>HR 2.24 (95% CI: 0.94-5.73)</td>
<td>HR 3.89 (95% CI: 1.55-11.05)</td>
</tr>
</tbody>
</table>

Olaparib and Cediranib:
Registration trials now open

Platinum-sensitive OvCa
NRG GY-004 (PI: J Liu)

PlatS
HGSOC
Stratify by gBRCAm

Platinum-based SoC
Olaparib
Olaparib + Cediranib

PlatR
HGSOC

Platinum-refr/resistant OvCa
NRG GY-005 (PI: J Lee)

SoC
Olaparib
Olaparib + Cediranib
Cediranib
Taking DNA repair inhibitors and VEGFR inhibitors to the next level: augmenting immunotherapy?

HYPOXIA

Increasing neoantigens through high DNA damage
VEGF suppresses lymphocyte trafficking into tumor and increases Treg proliferation
PD-L1 upregulation in hypoxic condition
Rationale for DNA repair inhibition + immune checkpoint blockade

**Survival in Discovery Set**

- **Mutation**
  - Mutation ↑ OS in ipi-tx pts
  - >100 mutations (N=17) with >0.01 by log-rank test
  - ≤100 mutations (N=8)

- **Peptide Signature**
  - Peptide signature ↑ OS in ipi-tx pts
  - With signature (N=20)
  - Without signature (N=19)
Neoantigens and potential response to immune checkpoint inhibition in human cancer

Schumacher et al. Science 2015
Higher mutational loads correlate with clinical benefit in colon cancer with DNA repair deficiency

Progression-Free Survival

Le et al, NEJM 2015
Pilot results: MSI endometrial cancer benefits from pembrolizumab

Progression-Free Survival

Endometrial cancer from this cohort

ORR: 56% (5/9)
DCR (CR+PR+SD): 88.9% (8/9)

Le et al, NEJM 2015
Nichols Fader et al, SGO 2016
Some monotherapy activity of PD-1/PD-L1 blockade in recurrent ovarian cancer

*Nivolumab single agent activity in recurrent platinum-resistant ovarian cancer*

No correlation with tumor PD-L1 labeling

Hamanishi et al  JCO 2015
Disis et al ASCO 2016
Hypothesis

Increased DNA damage by PARP inhibition and/or reduced angiogenesis by VEGFR1-3 inhibition will result in greater neoantigen expression, creating a more antigenic environment in which to stimulate the immune microenvironment.
Phase I study:
Primary Objective:
To determine the RP2D of durvalumab+olaparib (D+O) and durvalumab+cediranib (D+C) in women’s cancer.
Secondary Objectives:
• Doublet safety
• RECIST response rate
• Doublet PK and correlation with safety
• PD-L1 expression

Phase II study:
Primary Objective:
To determine the response rate (CR+PR) of the doublets in recurrent OvCa.
Secondary Objectives:
• Toxicity between two doublets
• PFS
• Correlative studies for potential predictive biomarkers
## Phase I safety evaluation

<table>
<thead>
<tr>
<th>Dose Level (DL)</th>
<th>D+O (N=12)</th>
<th>D+C (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O tablets</td>
<td>C tablets</td>
</tr>
<tr>
<td></td>
<td>q12h</td>
<td>q24h</td>
</tr>
<tr>
<td>DL 1</td>
<td>200mg</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>10mg/kg q2wk</td>
<td></td>
</tr>
<tr>
<td>DL 2</td>
<td>300mg</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>10mg/kg q2wk</td>
<td></td>
</tr>
<tr>
<td>DL 3</td>
<td>300mg</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>1500mg q4wk</td>
<td></td>
</tr>
</tbody>
</table>

1 pt (DL1) withdrew consent on cycle 1, 1 pt (DL2) took C 20mg instead of 30mg for a week during cycle 1.
D+O: durable response in non-BRCA carriers

Lee et al. JCO 2017
D+O: durable response in non-BRCA carriers
Durvalumab + Olaparib: Recurrent HGSOC patient with BRCA wild type

Before Treatment

On Treatment – 15+ months
D+C: early clinical activity in women’s cancer

Data cut-off Oct 13, 2016
D+C: early clinical activity in women’s cancer

Percent Change in Sum of Longest Diameters of Target Lesions

D+C: early clinical activity in women’s cancer

PR 3/7 OvCa, 2/2 CxCa, 1/3 En Ca
Conclusions and future direction

How can we build on this progress?

- We now have a critical mass of information and DNA repair inhibitor(s) to address actionable ideas to improve quality and quantity of life for women with ovarian cancer.
- Predictive biomarkers are necessary to optimize treatment benefits and treatment outcome interpretation.
- Unanswered questions in mechanisms of clinical resistance in both BRCA mutated and BRCA-like ovarian cancer.
- Optimal uses of DNA repair inhibitors in combination therapies.
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Mireya Gomez, PCC

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Dana-Adriana Botesteanu, BS

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University of Washington
Elizabeth Swisher, MD
The Johns Hopkins Medical Institution
Ashley Cimino-Mathews, MD
Janis Taube, MD

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