Targeting the DNA Damage Response

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Disclosures

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Overview

- Targeting PARP in the Clinic
  - \textit{BRCA1/2} mutant cancers are sensitive to PARP inhibitors

- Which patient to pick?
  - Patient selection strategies

- Path forward for PARP inhibitors
  - Combinations approaches
    - Molecularly Targeted Agents combos
    - Immunotherapry combos
**Nobel prize for DNA repair**

**Tomas Lindahl**
- Swedish citizen
- Born 1967
- Emeritus group leader at Francis Crick Institute and Emeritus director of Cancer Research UK

**Base excision repair**
- Constantly counteracts the collapse of our DNA

**Paul Modrich**
- U.S. citizen
- Born 1946
- Howard Hughes Medical Institute and Duke University School of Medicine

**Mismatch repair**
- How the cell corrects errors that occur when DNA is replicated during cell division

**Aziz Sancar**
- U.S. and Turkish citizen
- Born 1946
- University of North Carolina School of Medicine

**Nucleotide excision repair**
- The mechanism that cells use to repair UV damage to DNA
Targeting the DNA damage response in the Clinic

**DDR pathway targets**

- **Type of damage:**
  - Single-strand breaks (SSBs)
  - Double-strand breaks (DSBs)
  - Bulky adducts e.g., from platinum and UV

- **Repair targets:**
  - Base Excision Repair
  - Homologous Recombination Repair
  - Non-Homologous End Joining

- **Repair pathway:**
  - DNA-PK
  - ERCC1
  - MLH, MSH, MTH1*, etc.

**DDR cell-cycle targets**

- **G2/M checkpoint**
  - Allows time to repair any remaining DNA DSBs before reaching S phase

- **S-phase checkpoint**
  - Delays replication process to allow time to deal with unrepaired DNA damage or DNA damage resulting from replication fork collapse

**DDR Inhibitors**

- **Phase I:** ATM, DNA-PK
- **Phase II:** ATR, WEE1, CHK1
- **FDA Approved:** PARP

O’Connor, Molecular Cell 2015
Targeting PARP in the Clinic

Going back to the beginning
Increased sensitivity of BRCA1/2^-/- cells to PARP inhibition vs BRCA1/2^+/+ and BRCA1/2^+-/

No difference in sensitivity between heterozygous and wild-type BRCA cells

PARP inhibition → effective and well tolerated therapy in BRCA1/2 mutant tumors
1st responding patients to KU-0059436

Yap et al, ASCO 2007
Activity is not tumor-type specific

Phase I trial:
19 BRCA1/2 mutant cancers (15 ovarian, 3 breast, 1 prostate cancers)
- 8 PR ovarian; 1 CR breast; 1 PR prostate; 2 SD
Phase II trial
Olaparib monotherapy tested in germline BRCA1/2 mutation patients with advanced cancers:

- Breast cancer with ≥ 3 prior chemos for metastatic disease (62 patients)
- Pancreatic cancer with prior gemcitabine (23 patients)
- Prostate cancer progressed on hormone and one prior systemic treatment (8 pts)
- Platinum-resistant ovarian cancer (193 pts)

Activity is not tumor-type specific

Kaufman et al, J Clin Oncol 2015
Olaparib (AstraZeneca)
- Capsules (2014) and tablets (2017): FDA approved for advanced BRCA1/2 mutant ovarian cancer patients ≥ 3 lines of chemotherapy
- Tablets approved for maintenance therapy in ovarian cancer (2017)
- Germline BRCA mutant metastatic breast cancer who previously received chemo (Jan 2018)

Niraparib (Tesaro)
- FDA approved as maintenance treatment in recurrent ovarian, fallopian tube, or primary peritoneal cancer for patients who are in complete or partial response to platinum-based chemotherapy (2017)

Rucaparib (Clovis)
- FDA approved as monotherapy for advanced BRCA1/2 mutant ovarian cancer patients who have received ≥ 2 lines of chemotherapy (2016)
- Positive ARIEL 3 Phase III trial in maintenance 2nd/3rd line ovarian cancer setting

Talazoparib (Pfizer)
- Phase 3 EMBRACA advanced gBRCA1/2 mutant breast trial (Litton et al, NEJM 2018)

Other PARP inhibitors in clinical trials: pamiparib; veliparib
Targeting PARP

Which patient to pick?
Do we need a predictive biomarker?
Randomized Phase 3 NOVA Trial of niraparib maintenance

Among patients with platinum-sensitive, recurrent ovarian cancer, PFS was significantly longer vs placebo, regardless of presence or absence of gBRCA mutations or HRD status

March 2017: FDA approved niraparib for maintenance treatment ovarian cancer patients who are in complete or partial response to platinum-based chemotherapy
Platinum sensitivity is an important biomarker
Platinum To PARPi Interval (PTPI) is also an independent biomarker

Baseline clinical predictors of antitumor response to the PARP inhibitor olaparib in germline BRCA1/2 mutated patients with advanced ovarian cancer

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ABSTRACT

Background: The PARP inhibitor olaparib was recently granted Food and Drug Administration (FDA) accelerated approval in patients with advanced BRCA1/2 mutation ovarian cancer. However, antitumor responses are observed in only approximately 40% of patients and the impact of baseline clinical factors on response to treatment remains unclear. Although platinum sensitivity has been suggested as a marker of response to PARP inhibitors, patients with platinum-resistant disease still respond to olaparib.
Going beyond BRCA mutations
DDR deficiencies >50% of HGSOC

Gelmon et al, Lancet Oncol 2011
Monotherapy activity beyond *BRCA1/2* mutant cancers

Other aberrations result in HR deficiency – ‘BRCAness’

- Responses to olaparib in CRPC appear to be enriched in patients with DDR mutations
- Still patients with deleterious DDR variants that did not respond

Mateo et al, NEJM 2015
Table 2. Confirmed Investigator-Assessed ORR in Evaluable Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BRCA1/2</th>
<th>ATM</th>
<th>CDK12</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=25)</td>
<td>(n=5)</td>
<td>(n=8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRR, n (%) [95% CI]</td>
<td>11 (44.0%)</td>
<td>0</td>
<td>0</td>
<td>2 (25.6%)</td>
</tr>
<tr>
<td>[24.4-85.1]</td>
<td>[0.0-52.2]</td>
<td>[0.0-36.9]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>11 (44.0%)</td>
<td>0</td>
<td>0</td>
<td>2 (25.6%)</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>6 (26.0%)</td>
<td>4 (50.0%)</td>
<td>5 (62.5%)</td>
<td>5 (62.5%)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>4 (16.0%)</td>
<td>1 (20.0%)</td>
<td>2 (25.0%)</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Not evaluable, n (%)</td>
<td>1 (4.0%)</td>
<td>0</td>
<td>0</td>
<td>1 (12.5%)</td>
</tr>
</tbody>
</table>

Table 3. Confirmed PSA Response Rates

<table>
<thead>
<tr>
<th>PSA response rate</th>
<th>By HRR gene with alteration, n/N (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All evaluable patients</td>
<td>BRCA1/2</td>
</tr>
<tr>
<td>23/45 (51.1%)</td>
<td>[36.6-68.3]</td>
</tr>
<tr>
<td>With measurable disease</td>
<td>17/27 (63.0%)</td>
</tr>
</tbody>
</table>
| [42.4-80.1] | [0.0-52.2] | [0.0-52.7] | [
| With no measurable disease | 6/18 (33.3%) | 0/13 (0%) | 0/1 (0%) |
| [13.3-58.3] | [0.0-24.7] | [0.0-52.2] | [

Figure 3. Best Change from Baseline in Sum of Target Lesions (n=46)

Figure 5. Best Change from Baseline in PSA (n=84)
BRCA1/2 mutations versus ATM mutations in CRPC

Marshall et al, GU ASCO 2019
Homologous recombination deficiency (HRD) assay - Do we have one? E.g. Genomic Scarring LOH assay

- HRD causes genome wide loss of heterozygosity (LOH) or ‘genomic scarring’, which can be measured by genome profiling using NGS
- Algorithm developed to identify BRCA WT pts who are BRCA-like (high LOH) or biomarker-neg (low LOH)
- Assay clinically qualified in ARIEL2 Phase II trial with rucaparib (n=204)
The path forward for PARP inhibitors

Want more non-responders to respond
Want more responders to become super-responders
Learning from the Clinic

Why do some patients (up to 20%) stay in remission long-term?

Study 19

How do we raise the tail on the survival curve akin to IO agents?
The path forward for PARP inhibitors

- Better HRD biomarker
- Better understanding of resistance
- **Novel combination strategies**
  - Molecularly Targeted Agents
  - Immunotherapy, e.g. PD-1/PD-L1 inhibitors
  - Other DDR agents, e.g. ATR inhibitors

Pilie et al, CCR 2019
Upcoming evolution of PARP inhibitor combinations

Done to scale (www.clinicaltrials.gov)

My prediction

Pilie et al, Nature Reviews Clinical Oncology 2018
Combining PARP and Molecularly Targeted Agents
Enhance sensitivity to PARPi by inducing HRD phenotype in HR proficient tumors with molecularly targeted agents

“Chemical BRCAness”
Strategies to create a “chemical BRCAness”
A few examples (there are many more…)

Aim: Enhance sensitivity to PARPi by inducing HRD phenotype in HR proficient tumors

Preclinical +/- clinical data with:

- **Antiangiogenic agents** e.g. cediranib + olaparib
  - Hypoxia leads to impaired HR by down-regulating HR genes (Bindra et al, Mol Cell Bio 2004)
  - PFS 5.7m olaparib vs 23.7m combo (HR 0.32, p=0.002) in non-BRCA pts (Liu et al, ASCO 2017)

- **MEK inhibitors** (Sun et al, STM 2017)
  - Phase I trial of selumetinib + olaparib in cancers with RAS pathway aberrations

- **BET inhibitors** (Yang et al, STM 2017)

- **PI3K/AKT pathway inhibitors** e.g. AZD5363 + olaparib (Michelarea et al, AACR 2016)
Combining DDR and immune checkpoint inhibition
PD-1/PD-L1 inhibitor drug development
20 Agents, 803 Trials, and 166,736 patient slots

PD-1 inhibitors are like the chocolate of oncology
Chocolate makes everything better

Need to stop serendipitous development of PD-1 combos
Biology should be driving development

Yap et al, ASCO 2016
Increasing evidence linking DDR and IO

Initial hypothesis: PARPi → DNA damage → Increased neoantigen expression → more antigenic immune microenvironment (Higuchi et al, Cancer Immunol Res 2016)

- S phase-specific DNA damage leads to accumulation of cytosolic DNA, which activates STING-dependent innate immune response, priming of antitumor T-cells, and associated upregulation of PD-L1 expression (Parkes et al, PNAS 2017)
- PARP inhibition inactivates GSK3β, leading to PD-L1 upregulation; *in vivo* synergy (Jiao et al, CCR 2017)

Combining DDR and PD-1/PD-L1 inhibitors is a rational antitumor strategy
TOPACIO: Phase 1/2 Niraparib + Pembrolizumab in Platinum-Resistant Ovarian Cancer

- Addition of pembrolizumab to niraparib in tBRCAwt and HRD-neg led to ORR similar to PARPi monotherapy efficacy in tBRCAmut population
- HRD status does not correlate with response to this combo in platinum resistant/ refractory disease

<table>
<thead>
<tr>
<th>Platinum status</th>
<th>Response</th>
<th>All (%)</th>
<th>tBRCA mut (%)</th>
<th>HRD-pos (%)</th>
<th>tBRCA wt (%)</th>
<th>HRD-neg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable platinum-resistant and -refractory patients</td>
<td>ORR</td>
<td>11/46 (24)</td>
<td>2/7 (29)</td>
<td>4/15 (27)</td>
<td>9/34 (26)</td>
<td>7/24 (29)</td>
</tr>
<tr>
<td></td>
<td>DCR</td>
<td>31/46 (67)</td>
<td>4/7 (57)</td>
<td>10/15 (67)</td>
<td>23/34 (68)</td>
<td>15/24 (63)</td>
</tr>
</tbody>
</table>

*HRD-pos includes BRCA mutation or HRD score ≥42 per Myriad assay. Patients with inconclusive biomarker results were not included in the biomarker subpopulations.

Monotherapy activity cheat sheet
- Olaparib in BRCAmut platinum-resistant patients: ORR 25-30%
- Olaparib in BRCAwt platinum-resistant patients: ORR ~5%
- Olaparib in BRCAmut platinum-refractory patients: ORR 0-14%
- Nivolumab: ORR 15%
- Pembrolizumab: ORR 11%

Konstantinopoulos et al, SGO 2018
Castration-Resistant Prostate Cancer
Phase 2 trial of olaparib + durvalumab

Maximum Decline in PSA (n=17)

Karzai et al, GU ASCO 2018
Castration-Resistant Prostate Cancer
Phase 2 trial of olaparib + durvalumab

Median Radiographic PFS

- **DDR mutated**: 16.1 months (95% CI: 7.8-18.1 months)
- **Non-DDR mutated/unknown**: 4.8 months (95% CI: 1.8 months – cannot be calculated)

Karzai et al, GU ASCO 2018
Radiographic PFS of TOPARP-A and Durvalumab plus Olaparib

- Durvalumab plus Olaparib
- Olaparib (TOPARP-A*)

Proportion of patients

Months since trial entry

- Mutated/biomarker positive
- Non mutated/unknown/biomarker negative

Biomarker-positive, median: 9.8 mo

Biomarker-negative, median: 2.7 mo

16.1 mo

4.8 mo


Presented by: Fatima Karzai, M.D.
Extending the patient journey despite PARPi resistance

- 52yr Advanced gBRCA2 mutant HGSOC
- Multiple lines of chemotherapy
- RECIST CR after 3 months of olaparib
- After 81 months: CT new solitary liver metastasis; otherwise CR.
- Liver metastasectomy: BRCA2 reversion
- Restarted on olaparib
- After another 15 months: CT new liver lesion and enlarged retrocaval lymph note; otherwise CR.
- Chemoembolization and radiotherapy
- Restarted on olaparib
- Remains on treatment for 9yrs+

Lopez et al, Oncotarget 2017
Take home points

• Ovarian cancer has served as poster child for PARP inhibitors; clear opportunities in other tumor and molecular subtypes

• Need to better understand mechanisms of tumor response and resistance involved in targeting DDR

• Combinatorial strategies will widen breadth of application of DDR inhibitors
Thank you

Department of Investigational Cancer Therapeutics (A Phase I Program)

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