PARP AS A NOVEL THERAPEUTIC TARGET IN CANCER

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I have no financial disclosures.
DNA Damage and Mechanisms of Repair

Damaging agent/event

Free radicals
Alkylating agents

UV light

X-rays

Replication error

Single-strand break

Bulky adduct

Interstrand cross-link
Double-strand break

Mismatch Insertion Deletion

BER

NER

HR, NHEJ, SSA

MMR

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CCR Focus
Mechanisms of DNA Double Strand Break Repair

Double-strand break
- ATM
- TP53
- CHEK2
- BRIP1
- ZNF350

Non-homologous end joining

Homologous recombination
- PALB2
- BRCA1
- NBS1

BRCA1 pathway
- Rad50
- MRE11A
- XRCC6
- XRCC5
- DNA-PK
- LIG4
- XRCC4

DNA repair pathways
- XRCC3
- XRCC2
- Rad51
- Rad54L
- Rad52
- H2AX
- Rad21

Repaired DNA

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CCR Focus
Inherited Defects in Homologous Recombination

<table>
<thead>
<tr>
<th>Gene mutated</th>
<th>Function(s) affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>Cell-cycle arrest; recruitment of HR repair complex</td>
</tr>
<tr>
<td>BRCA2</td>
<td>HR repair complex assembly</td>
</tr>
<tr>
<td>PALB2</td>
<td>HR repair complex assembly</td>
</tr>
<tr>
<td>BRIP1</td>
<td>DNA helicase activity</td>
</tr>
<tr>
<td>MRE11</td>
<td>Assembly and activation of HR and NHEJ repair complexes</td>
</tr>
<tr>
<td>RAD50</td>
<td>Assembly and activation of HR and NHEJ repair complexes</td>
</tr>
<tr>
<td>NBS1</td>
<td>Assembly and activation of HR and NHEJ repair complexes</td>
</tr>
<tr>
<td>ATM</td>
<td>Activation of HR repair complex</td>
</tr>
</tbody>
</table>

PARP mechanism of action

• Identifies damaged DNA

• Repairs single-strand DNA breaks

• Involved in NHEJ

• Hyperactive in HR-deficient cells
PARP inhibitors in BRCA-mutant cancers

- PARP is required for repair of single-strand DNA breaks
- SSB are converted to double-strand breaks at replication forks
- Loss of BRCA function impairs repair of DNA double-strand breaks
- Accumulation of DSB overwhelms backup repair mechanisms in BRCA (HR) – deficient cells
- This should result in cell lethality
PARP inhibitors in BRCA-mutant cancers

• Non-cancer cells in carriers retain 1 normal copy of the BRCA gene
  • Non-carriers have 2 normal copies
• Some BRCA may result in less susceptibility PARP inhibition death
• A validated molecular target in a unique patient population
  • Testable in clinical trials
  • Side effects may be different in mutation carriers
PARP inhibitors in BRCA-mutant cancers

SSB: cellular metabolism, environmental exposures

Replicating cells

Normal cell
Repair by Homologous Recombination
Survival

Cancer cell with BRCA deficiency
No effective repair (No HR pathway)
CELL DEATH
Phase 1 “proof-of-concept” in BRCA-mutant cancers

Loss of PAR in tumors

DNA damage in hair follicles

Fong et al, NEJM 361:123, 2009
Phase II - BRCA-Mutated Breast Cancer

400 mg

100 mg

Tutt, et al. Lancet 2010
Phase II - BRCA-Mutated Ovarian Cancer

Phase II - BRCA-Mutated Ovarian Cancer

![Graph showing progression-free survival for BRCA-mutated ovarian cancer patients treated with Olaparib 400 mg twice daily (red line) and Olaparib 100 mg twice daily (blue line). The graph illustrates the freedom from progression as a percentage over time. The number of patients at each time point is provided in the legend.]

Number of patients:
- Olaparib 400 mg: 33, 31, 20, 17, 15, 13, 11, 8, 6, 4, 4, 3, 0
- Olaparib 100 mg: 24, 19, 8, 5, 4, 3, 2, 1, 1, 0, 0, 0, 0

Single agent activity, but not curative

- PARPi as single agents have not resulted in the expected CR and survival outcome
  
  - Can we improve efficacy and duration with combination therapy?
  
  - Which combinations?
Combinations?

- **Hypothesis:** Augmenting DNA damage stress may increase response and outcome
  - Radiation-therapy for localized cancer with PARP-i sensitization
  - Chemotherapy – systemic therapy, interactive damage
Survival
Normal cell
Repair by Homologous Recombination
Survival
Cancer cell with BRCA deficiency
No effective repair (No HR pathway)
CELL DEATH

PARP inhibitors in combination with chemotherapy target replicating cells. PARP inhibitors are used to inhibit PARP, preventing the repair of DNA damage. In normal cells, DNA damage is repaired by Homologous Recombination, allowing survival. In cancer cells with BRCA deficiency, there is no effective repair path (No HR pathway), leading to cell death.
Cytotoxic agents damage DNA

Inhibition of de novo nucleotide synthesis

Inter-strand crosslink

Inter-strand crosslink

DNA strand break

Uracil misincorporation

Purine analog misincorporation

Pt

Inter-strand Platinum adduct

GCGATCAGCCGCAAGCGGAAATTGCGCCGAC

CCGUAGTCGGCGTTCG

GAUAGTCGGCGTTCG

GGATCGAGCCGCAAGCGGAAATTGCGCCGAC

Annunziata and Dennis, 2011
<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Route of administration</th>
<th>Clinical trials</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iniparib (BSI-201)</td>
<td>BiPar</td>
<td>Intravenous</td>
<td>Non–small cell lung cancer (with gemcitabine-carboplatin)</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ovarian cancer, uterine cancer, and glioblastoma (various combinations)</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA1- or BRCA2-mutant tumors</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TNBC (with gemcitabine-carboplatin)</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Squamous cell lung cancer (with gemcitabine-carboplatin)</td>
<td>III</td>
</tr>
<tr>
<td>Veliparib (ABT-888)</td>
<td>Abbott</td>
<td>Oral</td>
<td>Leukemia and lymphoma (with topotecan or irinotecan)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other solid tumors (various combination)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA1- or BRCA2-mutant tumors</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glioblastoma, melanoma, breast, and colorectal cancers (with temozolomide)</td>
<td>II</td>
</tr>
<tr>
<td>Olaparib (AZD2281)</td>
<td>AstraZeneca</td>
<td>Oral</td>
<td>Platinum-sensitive ovarian cancer</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA-positive tumors</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA1- or BRCA2-mutant tumors</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TNBC (single-agent or with carboplatin)</td>
<td>II</td>
</tr>
<tr>
<td>AG014699</td>
<td>Pfizer</td>
<td>Intravenous</td>
<td>Advanced solid tumors</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BRCA1- or BRCA2-mutant tumors</td>
<td>II</td>
</tr>
<tr>
<td>MK-4827</td>
<td>Merck</td>
<td>Oral</td>
<td>Solid tumors, ovarian cancer, and prostate cancer</td>
<td>I</td>
</tr>
<tr>
<td>CEP-8933/CEP-9722</td>
<td>Cephalon</td>
<td>Oral</td>
<td>Solid tumors (with temozolomide)</td>
<td>I</td>
</tr>
<tr>
<td>INO-1001</td>
<td>Inotek/Genetech</td>
<td>Intravenous</td>
<td>Melanoma (with temozolomide)</td>
<td>I</td>
</tr>
<tr>
<td>GPI 21016</td>
<td>MGI Pharma</td>
<td>Oral</td>
<td>Solid tumors (with temozolomide)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**NOTE.** Data were obtained from the registry of federally and privately supported clinical trials; http://clinicaltrials.gov.

**Abbreviations.** N/A, no information available.
Phase II Study of Veliparib Plus Temozolomide in Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>Total  (n = 41)</th>
<th>BRCA1/2 Mutant  (n = 8)</th>
<th>BRCA1/2 Normal/Unknown  (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response Rate</strong></td>
<td>7%</td>
<td>37.5%</td>
<td>0</td>
</tr>
<tr>
<td><strong>Clinical Benefit Rate(a)</strong></td>
<td>17%</td>
<td>62.5%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Median Progression-Free Survival</strong></td>
<td>1.9 months</td>
<td>5.5 months</td>
<td>1.8 months</td>
</tr>
</tbody>
</table>

\(a\) ORR + stable disease

- **Efficacy appears to be restricted to** BRCA1/2 mutation carriers and further evaluation is ongoing.

Phase I/II Study of Olaparib Plus Weekly Paclitaxel for Triple-Negative Breast Cancer

- **Dose modifications:**
  - Cohort 1: paclitaxel modified in 89%; olaparib modified in 44%
  - Cohort 2: paclitaxel modified in 60%; olaparib modified in 30%

- **Conclusions:**
  - Olaparib/paclitaxel is active in triple-negative MBC.
  - Associated neutropenia reduced paclitaxel dose intensity and should be carefully monitored.

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 (No G-CSF) (n = 9)</th>
<th>Cohort 2 (G-CSF ) (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>33%</td>
<td>40%</td>
</tr>
<tr>
<td>Stable Disease ≥ 7 Weeks</td>
<td>33%</td>
<td>40%</td>
</tr>
<tr>
<td>Median Progression-Free Survival (95% CI)</td>
<td>6.3 (3.5-8.9) months</td>
<td>5.2 (3.5-NC) months</td>
</tr>
</tbody>
</table>

Abbreviation: NC = not calculable

Phase II Gemcitabine/Carboplatin +/- Iniparib in Triple Negative Breast cancer

Hazard ratio for death with iniparib, 0.57 (95% CI, 0.36–0.90) P=0.01

No. at Risk
G/C + Iniparib  61  60  54  50  46  35  24  17  12  11  6  3  0
G/C + alone  62  59  47  38  29  22  16  12  9  4  1  0  0

O’Shaughnessy, NEJM, 2011
PARP inhibition potentiates cisplatin efficacy in a BRCA1 null background.

Phase 1 Olaparib + carboplatin at NCI

Cohort 1
Br/Ov cancers
BRCA mutant
BRCApro ≥ 30%

Cohort 2
TNBC
BRCA normal
BRCApro ≤ 10%

Cohort 3
Serous Ovarian
BRCA normal
BRCApro ≤ 20%

- Olaparib 200mg twice daily (days 1-21)
- Carboplatin AUC 3 (every 21 days)
- PBMCs for PAR incorporation pre, d3, d21
- Expansion cohorts to examine endpoints in tumor tissue
- Biopsy at disease progression for BRCA sequencing
Phase 1 Olaparib + carboplatin at NCI

- **Initial escalation:**
  - Olaparib twice daily continuously
  - Carboplatin at day 8 (cycle 1) and every 3 weeks
- **N=12 pts, 2 dose levels**
  - Olaparib 100mg + carboplatin AUC 3
  - Olaparib 200mg + carboplatin AUC 3
  - Dose limiting = delayed platelet recovery
- **Clinical benefit:**
  - Ovarian: Stable disease, partial responses 2-18mos
  - Breast: Partial responses, 6-7mos
Phase 1 Olaparib + carboplatin at NCI

- Optimize “synthetic lethality” with DNA damage
- Interactive toxicity when olaparib used daily
- Biological benefits with disease regression
- Test BRCAness concept with non-mutation cohorts
- Incorporate biochemical and genetic endpoints to examine mechanisms
Phase 1 Olaparib + carboplatin at NCI

Cohort 1
Br/Ov cancers
BRCA mutant
BRCApro ≥ 30%

- Olaparib 400mg twice daily (days 1-7)
- Carboplatin AUC 5 (every 21 days)

Cohort 2
TNBC
BRCA normal
BRCApro ≤ 10%

- Olaparib 400mg twice daily (days 1-7)
- Carboplatin AUC 5 (every 21 days)

Cohort 3
Serous Ovarian
BRCA normal
BRCApro ≤ 20%

- Olaparib 400mg twice daily (days 1-7)
- Carboplatin AUC 4 (every 21 days)
Biomarker of PARP inhibition in PBMCs

08-C-0092 phase I dose levels 1/2: continuous olaparib with carboplatin AUC 3

(Preliminary data, Doroshow Lab)
PARP inhibitors in BRCA cancers

- PARP inhibitors are promising inhibitors of HR-deficient cancers carrying BRCA mutations.
- Combination with different chemotherapies has shown benefit in preclinical and clinical settings.
- Will sequence specificity matter differentially in BRCA-mutant, “BRCA-like”, and non-HR dependent cancers?
- Will tolerance be different in patients carrying BRCA mutation compared to non-hereditary cancers?
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