PARP Inhibitors in Lung Cancer

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Poly (ADP-ribose) Polymerase (PARP): Mechanism of Action

- PARPs: family of enzymes that repair base excisions in DNA single and double strand breaks
- PARPs are upregulated in cancer
- Activated in response to DNA damage
- PARP-1 localizes to sites of DNA damage and recruits proteins that mediate repair
PARP inhibition causes death by synthetic lethality only in tumor cells where DNA repair by homologous recombination (HR) is hampered (e.g., BRCA-negative cells). BER: Base excision repair.
PARP inhibitors as radiosensitizers

- Single-strand breaks (SSB) in DNA resulting from damage by ionizing radiation are sensed by PARP which recruits DNA repair proteins.

- PARP inhibitors prevent the auto-modification of PARP thereby preventing its release from damaged DNA and denying access of the SSB to the DNA repair proteins.

- PARP inhibition also prevents recruitment of some DNA repair proteins such as XRCC1.

- Collision of unrepaired SSB with replication forks in S phase result in lethal double-strand breaks enhancing the radiation effect.
## Selected PARP Inhibitors in Development

<table>
<thead>
<tr>
<th>PARP inhibitor</th>
<th>Company</th>
<th>Clinical development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rucaparib</td>
<td>Clovis</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Veliparib</td>
<td>Abbott</td>
<td>Phase II</td>
</tr>
<tr>
<td>(ABT 888)</td>
<td></td>
<td></td>
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<tr>
<td>Olaparib</td>
<td>Astra Zeneca</td>
<td>Phase II</td>
</tr>
<tr>
<td>Iniparib***</td>
<td>Sanofi Aventis/BiPar</td>
<td>Phase III</td>
</tr>
<tr>
<td>MK4827</td>
<td>Merck</td>
<td>Phase I</td>
</tr>
<tr>
<td>CEP 9722</td>
<td>Cephalon</td>
<td>Phase I</td>
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<tr>
<td>INO1001</td>
<td>Inotek</td>
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<tr>
<td>GPI 21016</td>
<td>MGI Pharma</td>
<td>Phase I</td>
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</table>
Failure of Iniparib to Inhibit Poly(ADP-Ribose) Polymerase
*In Vitro*

Anand G. Patel¹, Silvana B. De Lorenzo¹, Karen S. Flatten¹, Guy G. Poirier³, and Scott H. Kaufmann¹,²

Iniparib Nonselectively Modifies Cysteine-Containing
Proteins in Tumor Cells and Is Not a *Bona Fide* PARP Inhibitor

Xuesong Liu¹, Yan Shi¹, David X. Maag¹, Joann P. Palma¹, Melanie J. Patterson², Paul A. Ellis¹, Bruce W. Surber², Damien B. Ready², Niru B. Soni¹, Uri S. Ladror², Allison J. Xu², Ramesh Iyer², John E. Harlan², Larry R. Solomon¹, Cherrie K. Donawho¹, Thomas D. Penning¹, Eric F. Johnson¹, and Alexander R. Shoemaker¹
Phase 0 Clinical Trial of the Poly (ADP-Ribose) Polymerase Inhibitor ABT-888 in Patients With Advanced Malignancies


Treatment Groups: Dose escalation in cohorts of 3 patients each
Single oral dose of 10 mg (n=3), 25mg (n=3), 50mg (n=7)

Subjects: 13 of which 9 underwent paired tumor biopsies

Objective: Determine dose range for PARP inhibition (not MTD);
PK/PD to inform optimal design of Ph1 studies

Endpoints: Safety and Pharmacokinetics
Biomarker endpoints
- PARP activity in Tumors (8 paired biopsies)
- PARP inhibition in PBMCs
- Statistically significant inhibition of poly (ADP-ribose) levels was observed in tumor biopsies and peripheral blood mononuclear cells at the 25-mg and 50-mg dose levels.
PAR levels in (A) peripheral blood mononuclear cells (PBMCs) and (B, C) tumor samples after administration of a single dose of ABT-888
ABT 888 potentiates Platinums-Alkylating Agents and Radiation

ABT-888 potentiates radiation at well-tolerated doses

Selected PARPi trials relevant to NSCLC: Clinicaltrials.gov

- Phase I/II Olaparib Dose Escalating Trial + Concurrent RT With or Without Cisplatin in Locally Advanced NSCLC (Netherlands Cancer Institute)
- Phase Ib/II Study of Gefitinib in Combination With Olaparib (AZD2281) Versus Gefitinib Alone (GOAL) in Patients with EGFR mutated NSCLC (Spanish Lung Cancer Group)
- A Phase I Study Of Poly (ADP-Ribose) Polymerase Inhibitor Rucaparib (PF-01367338) In Combination With Several Chemotherapeutic Regimens (Clovis)
- Study of CEP-9722 in Combination With Gemcitabine and Cisplatin in Patients With Advanced Solid Tumors or Mantle Cell Lymphoma (Cephalon)

Accessed 6/23/2012
### Phase I Study of ABT-888 (Veliparib) in Combination with Carboplatin and Paclitaxel (NCI # 7967)

<table>
<thead>
<tr>
<th></th>
<th>ABT-888</th>
<th>Carbo</th>
<th>Paclitaxel</th>
<th>PK</th>
<th>PBMC</th>
<th>Bx</th>
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<tr>
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<td>Cy # 2</td>
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Determination of DLT in cycle 2
Paired Tumor Bx at the Phase II Dose

ABT-888 given on days 1-7 of each cycle
Carbo/Pac given on day 3 of each cycle

Appleman, ASCO 2012
Phase I Study of ABT-888 (Veliparib) in Combination with Carboplatin and Paclitaxel (NCI # 7967)

- N = 68 patients
- Tumor types included lung (15), breast (14), melanoma (10), squamous cell of head/neck (7), and urothelial (5).
  - Veliparib 120 mg BID, Paclitaxel 200 mg/m$^2$, Carboplatin AUC 6
    - DLTs (febrile neutropenia, hyponatremia) in 2 out of 7 patients at the MTD:
      - Veliparib 80 mg, P 200 mg/m$^2$, C AUC 6
        - DLTS in 1 out of 9 (febrile neutropenia).
  - Median number of cycles was 5 (1-17).
- Partial response was seen in 11 (lung-2, breast-2, melanoma-2, urothelial-2, head and neck, gastric, unknown primary) and complete response in 1 patient with breast cancer and 1 patient with urothelial cancer.
- Stable disease was observed in 35 patients.
- Veliparib did not affect the PK disposition of P or C.

Appleman, ASCO 2012
SWOG 1206: ABT-888 plus chemoRT for stage III NSCLC (NCI 8811)

Stage IIIA/B NSCLC
Unresectable
ECOG PS 0/1
No prior therapy

Stratification:
• PS (0 vs 1)
• Histology (SCCA vs Non-SCCA)
• Weight loss (<5% vs >5%)

Schema
Dose Finding Phase

Chest RT (63 Gy) weeks 1 – 7
Paclitaxel 45 mg/m² Qw, weeks 1-7
Carboplatin AUC2 Qw, weeks 1-7
ABT-888 twice daily po, weeks 1-7

Dose Escalation Schedule

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>ABT-888 Dose</th>
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<tr>
<td>-1</td>
<td>20 mg</td>
</tr>
<tr>
<td>1</td>
<td>40 mg</td>
</tr>
<tr>
<td>2</td>
<td>80 mg</td>
</tr>
<tr>
<td>3</td>
<td>120 mg</td>
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</table>

Carboplatin AUC 6 day 1
Paclitaxel 200 mg/m² day 1
ABT-888 80 mg BID po days 1-7 **
Q 3 weeks x 2 cycles

PI: Argiris, UT San Antonio
SWOG 1206: ABT-888 plus ChemoRT for Stage III NSCLC (NCI 8811)

Schema
Randomized Phase II

Stage IIIA/B NSCLC
Unresectable
ECOG PS 0/1
No prior therapy

Stratification:
• PS (0 vs 1)
• Histology (SCCA vs Non-SCCA)
• Weight loss (<5% vs >5%)

Chest RT (63 Gy) weeks 1 – 7
Paclitaxel 45 mg/m² Qw, weeks 1-7
Carboplatin AUC2 Qw, weeks 1-7
ABT-888 twice daily po, weeks 1-7*

4–6 wks

Chest RT (63 Gy) weeks 1 – 7
Paclitaxel 45 mg/m² Qw, weeks 1-7
Carboplatin AUC2 Qw, weeks 1-7
Placebo twice daily po, weeks 1-7*

Carboplatin AUC 6 day 1
Paclitaxel 200 mg/m² day 1
ABT-888 80 mg BID po days 1-7 *
Q 3 weeks x 2 cycles

Carboplatin AUC 6 day 1
Paclitaxel 200 mg/m² day 1
Placebo BID po days 1-7

* Biopsy by bronchoscopy at 2 weeks

N=188 (94 per arm)
S1206 Translational Science Component

<table>
<thead>
<tr>
<th>Assay</th>
<th>Measure</th>
<th>Specimen</th>
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<tbody>
<tr>
<td>PAR inhibition</td>
<td>PARP activity</td>
<td>Tumor CTCs</td>
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<tr>
<td>PARP mRNA</td>
<td>Expression levels</td>
<td>Tumor CTCs</td>
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<tr>
<td>BRCA</td>
<td>DNA repair pathways</td>
<td>Tumor CTCs</td>
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<td>ERCC1 XRCC1</td>
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<tr>
<td>γ-H2AX</td>
<td>DNA DSBs</td>
<td>PBMCs</td>
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<tr>
<td>RAD51</td>
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<td>Tumor CTCs</td>
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Jay Ji: NCI Clinical Target Validation Laboratory
DTP, DCTD
Phil Mack: UC Davis Molecular Pharmacology

PAR inhibition in tumor (from Kummar et al)
Some Unanswered Questions

• What is the degree and duration of PARP inhibition required for patient benefit?

• Do PARP inhibitors have a role in combination with chemo or RT in patients without known defects in DNA damage repair?

• Are there assays that can assess for occult defects in DNA damage repair pathways (to select patients likely to benefit)?