Targeting DNA repair in BRCA 1/2 and Triple Negative Breast Cancer

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London, United Kingdom
<table>
<thead>
<tr>
<th>Disclosures for Andrew Tutt, MB ChB, PhD</th>
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<tr>
<th>Advisory Committee</th>
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<tbody>
<tr>
<td>AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi-Aventis</td>
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<th>Honoraria</th>
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<tr>
<td>AstraZeneca Pharmaceuticals LP, Sanofi-Aventis</td>
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DNA repair mechanisms in cells

- Base-excision repair (PARP)
- Nucleotide-excision repair
- Recombinational repair (BRCA1/BRCA2)
- Mismatch repair
Double Strand Break Repair Pathways

Ionizing radiation, chemicals → Double-strand break (DSB)

NHEJ
1. End alignment
   - DNA-PK-cs
   - Ku 70/80
2. Ligation by DNA Ligase IV

HR
1. Reunion through Rad51 homology-directed repair
2. Loading of Rad51 onto ssDNA by BRCA2
3. Strand invasion
4. Ligation

Cold Spring Harb Symp Quant Biol 2005;70:139–148
How to target loss of BRCA1 or BRCA2 function?

• Lesions that arrest DNA replication forks
• Loss of homologous recombination
• How could we exploit defect?
  • Platinum cross-links?
  • Topo-1 inhibitors?
  • Alkylating agents?
  • PARP inhibitors?

BRCA1 mutation basal-like breast cancer mouse model

Poly (ADP-ribose) polymerase (PARP)

- A key regulator of DNA damage repair processes
- Involved in DNA base-excision repair (BER)
- Binds directly to DNA damage
- Produces large branched chains of poly (ADP-ribose)
- Attracts and assists BER repair effectors
PARP inhibition and tumor selective synthetic lethality

Targeting BRCA for tumor selective killing

BRCA1 or BRCA2 Carrier
Normal tissue

DNA DAMAGE

BRCA1 or BRCA2 Carrier
Tumor tissue

DNA DAMAGE

HR NHEJ SSA BER NER etc

Tumor-specific lethality

Olaparib: A novel, orally active PARP inhibitor

- A phase I trial identified olaparib (AZD2281; KU-0059436) 400 mg bid as the maximum tolerated dose\(^1\) with a 28% (13/46 pts) response rate (RECIST) in BRCA-mutated ovarian cancer\(^2\)

- Most common toxicities: CTCAE Grade 1 and 2 nausea and fatigue

- Significant PARP inhibition and tumor response at olaparib doses 100–400 mg bid

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Phase II Trial of the Oral PARP Inhibitor Olaparib in BRCA-Deficient Advanced Breast Cancer

Andrew Tutt, Mark Robson, Judy E Garber, Susan Domchek, M William Audeh, Jeffrey N Weitzel, Michael Friedlander, James Carmichael

1Breakthrough Breast Cancer Research Unit, Guy's Hospital, King's Health Partners, London, UK
2Memorial Sloan-Kettering Cancer Center, New York, NY, USA
3Dana-Farber Cancer Institute, Boston, MA, USA
4University of Pennsylvania, Philadelphia, PA, USA
5Cedars-Sinai Cancer Center, Los Angeles, CA, USA
6City of Hope Comprehensive Cancer Center, Duarte, CA, USA
7Prince of Wales Cancer Centre, Randwick, Sydney, New South Wales, Australia
8AstraZeneca, Macclesfield, UK
Study design and eligibility

- To assess the efficacy and tolerability of oral olaparib in BRCA1/BRCA2 mutation carriers with breast cancer
- Proof-of-concept phase II study, single-arm sequential cohort design

Confirmed BRCA1 or BRCA2 mutation
Advanced refractory breast cancer
(stage IIIB/IIIC/IV) after failure of ≥1 prior chemotherapy for advanced disease

<table>
<thead>
<tr>
<th>Cohort 1 (enrolled first)</th>
<th>Cohort 2</th>
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<tr>
<td>Olaparib 400 mg po bid (MTD) 28-day cycles; n = 27</td>
<td>Olaparib 100 mg po bid 28-day cycles; n = 27</td>
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## Efficacy

<table>
<thead>
<tr>
<th>ITT cohort</th>
<th>Olaparib 400 mg bid (n = 27)</th>
<th>Olaparib 100 mg bid (n = 27)</th>
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<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>
</tbody>
</table>

*An additional 1 patient in the 400 mg cohort and 3 patients in the 100 mg cohort had unconfirmed responses*
Best percent change from baseline in target lesions by genotype

Olaparib 400 mg bid cohort

BRCA 1
BRCA 2

Increasing tumor shrinkage

Best % change from baseline

One patient was excluded as only 1 of their 2 target lesions was measured at each assessment.

Tutt A on behalf of ICEBERG investigators.
ASCO 2009;Abstract CRA501
BRCA1 downregulation

- High histological grade
- Medullary histological type
- Metaplastic histological type
- Basal-like IHC phenotype

With permission from Hanneman J. EBCC-6 2008;Abstract 308; Turner et al. Oncogene 2007; Rakha, Reis-Filho, Ellis; J Clin Oncol 2008
Triple Negative Neoadjuvant Trial

Phase II Single Arm Trial

- N = 28
- median age: 50 yrs
- median tumor size = 3.0 cm (1.5 - 6.3 cm)
- 2 BRCA1 mutation carriers

- pCR – 22% - incl 2 BRCA1 carriers
- Good MP Score 3-5 – 50%
- Minor response MP 1-2 – 36%
- Progression 14%

CISPLATIN 75mg/m² q 3wks IV x 12 wks

Impaired BRCA1 and neoadjuvant cisplatin response in TNBC

<table>
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<tr>
<th>Response score</th>
<th>Progress</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>BRCA mutation</td>
<td></td>
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<tr>
<td>Low BRCA1 mRNA</td>
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<tr>
<td>BRCA1 methylation</td>
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<td>ΔNp63/TAp73 &gt; 2</td>
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</table>
PTEN pathway loss and loss of HR repair and PARPi sensitivity

- Essential role for nuclear PTEN in maintaining chromosomal integrity

- PTEN pathway loss common in TN/basal-like

- Loss of PTEN causes a reduction in HR repair and induces sensitivity to PARP inhibition
  (Mendes-Pereira A, EMBO Mol Med 1(6-7) 2009)
Efficacy of BSI-201, a PARP Inhibitor, in Combination with Gemcitabine/Carboplatin in Triple Negative Metastatic Breast Cancer: Results of a Phase II Study

Joyce O’Shaughnessy 1,2,4, Cynthia Osborne 1,2,4, John Pippen 1,2,4, Debra Patt 3,4, Christine Rocha 5, Valeria Ossovskaya 5, Barry M. Sherman 5, Charles Bradley 5

1Baylor Sammons Cancer Center
2Texas Oncology, Dallas, TX
3Texas Oncology Cancer Center, Austin, TX
4US Oncology, Dallas, TX
5BiPar Sciences, Inc., Brisbane, CA
**Gem/Carbo +/- BSI-201 in unselected TNBC**

- **Metastatic TNBC**
  - **N = 120**

- **RANDOMIZE**

- **Gemcitabine**
  - (1,000 mg/m², IV, d 1, 8)

- **Carboplatin**
  - (AUC 2, IV, d 1, 8)

- **21-Day Cycle**

- **BSI-201**
  - (5.6 mg/kg, IV, d 1, 4, 8, 11)

- **Gemcitabine**
  - (1,000 mg/m², IV, d 1, 8)

- **Carboplatin**
  - (AUC 2, IV, d 1, 8)

- **RESTAGING**
  - Every 2 Cycles

*Patients randomized to gem/carbo alone could crossover to receive gem/carbo + BSI-201 at disease progression*

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O'Shaughnessy et al. ASCO 2009
### Preliminary Efficacy Results*

<table>
<thead>
<tr>
<th></th>
<th>Gem/Carbo (n = 44)</th>
<th>BSI-201 + Gem/Carbo (n = 42)</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>Objective Response Rate n (%)</strong></td>
<td>7 (16%)</td>
<td>20 (48%)</td>
<td>0.002</td>
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<tr>
<td><strong>Clinical Benefit Rate n (%)</strong></td>
<td>9 (21%)</td>
<td>26 (62%)</td>
<td>0.0002</td>
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*Includes patients enrolled before September 30, 2008 and patients who had a confirmed response or disease progression

**Clinical Benefit Rate = CR + PR + SD ≥ 6 months
Updated BSI-201 SABCS 2009

Overall Survival (%)

OS Months

0 2 4 6 8 10 12 13 16 18 20 22 24

BSI-201/Gem/Carbo; median = 12.2 months

Gem/Carbo: median = 7.7 months

Hazard Ratio = 0.50
95% CI = (0.30, 0.82)
\( p \)-value = 0.005

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<tr>
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<td>3</td>
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Conclusions

• Single agent synthetic lethality concept shown for olaparib in BRCA1 and BRCA2 mutation carriers with advanced breast and advanced ovarian cancer

• Randomised phase II data for BSI-201 very promising for PARPi combined with gemcitabine/ carboplatin in sporadic TNBC

• Phase III RCT of BSI-201 gemcitabine/carboplatin completed and results awaited

• Consideration of investigation of novel PARPi/ chemotherapy combinations in advanced disease and in early breast cancer trials in TNBC and BRCA1 and BRCA2 carriers
Acknowledgements

• Our patients and their families
• ICEBERG Investigators
• BRCA carrier advocacy community
  – FORCE
  – Susan G Komen
• ICR Breakthrough Centre
  – Alan Ashworth, Chris Lord, Hannah Farmer, Nuala McCabe
  – Nick Turner, Jorge Reis-Filho
• KCL Breakthrough Unit
• Cancer Research UK
• KuDOS/AstraZeneca
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