Antitumour activity of the PARP inhibitor olaparib in unselected sporadic castration-resistant prostate cancer (CRPC) in the TOPARP trial.

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Disclosures

- A.O. and J.d.B. have served as advisors to Astra-Zeneca.

- The Institute of Cancer Research is a joint applicant for the patent entitled ‘DNA damage repair inhibitors for treatment of cancer’ which includes the granted application US8143241.
Background

1. Synthetic lethality between PARP inhibition and DNA repair aberrations including BRCA1 and BRCA2 loss.
2. Clinical trials reported antitumour activity with PARPi in BRCA mutation carriers including CRPC.
3. PARPi have antitumour activity in BRCAness cancers.
4. Sporadic CRPC can have DNA repair defects with preliminary evidence for antitumor activity with PARPi

Trial design

- **Investigator-initiated phase II trial.**
  - NCT-01682772; CR-UK/11/029.

- **Adaptive design** for biomarker-driven selection based on response rate, multi-stage.
  - Test set (all comers) and validation set (biomarker driven)

- Open label, Olaparib (tabs) 400mg BID.

**STUDY OBJECTIVES**

- To evaluate antitumour activity of olaparib in mCRPC.
- To identify molecular signatures for PARP inhibitor antitumour activity.
Trial design

• **Primary endpoint:** RESPONSE RATE
  - Response as per RECIST 1.1
  - PSA decline $\geq 50\%$ (PCWG-2)
  - CTC conversion ($\geq 5$ to $<5/7.5$ml)
    Confirmed by a second assessment $\geq 4$ weeks later

• **Secondary endpoints:** PFS, rPFS, OS, time to PSA progression (PCWG-2), time to radiological progression, rate of CTC conversion, duration of responses, safety-tolerability.

• **Exploratory endpoints:**
  - Study of **diffusion-weighted MRI** as response biomarker
  - QOL studies (pain improvement)
Trial design

- **PART A Stage 1:** 30 unselected patients
  - ≥ 15 respond
  - ≤ 2 respond
  - 3-14 respond
    - Recruit a further 15 patients (stage 2)
  - 15-24 respond
    - Recruit another 15 patients

- **PART A Stage 2:** 45 unselected patients
  - ≤ 5 responders
  - ≥ 23 responders
  - 6-22 responders
    - Investigate if potential biomarkers of response can be identified
      - Potential biomarker not found
        - ≥ 19/45 respond
          - Randomized clinical trial
        - ≤ 18/45 respond
          - End of trial
      - Potential biomarker found
        - Part B: 44 biomarker selected patients
          - ≤ 18 respond
            - End of trial
          - ≥ 19 respond
            - Randomized clinical trial

- **α = 0.02; β = 0.10**
- **po = RR 5%; p1 = RR 20%**
Biomarker studies

• Mandated pre- and post-treatment tumour biopsies.

• Including studies of DNA repair aberrations:
  – Whole exome and transcriptome in pre-dose samples.
  – Study of circulating tumour DNA in plasma.

• PD studies (markers of DNA damage) in tumour tissues.
Trial population

• Metastatic CRPC after 1-2 lines of taxane chemotherapy.
• Documented progressive disease by RECIST or PSA (PCWG2).
• ECOG Performance Status 0-2.
• Appropriate organ-function:  Hb >10g/l, Neut>1.5x10^9/l, Plt>100x10^9/l, Bilir<1.5x ULN, AST/ALT<2.5x uLN (x5 liver mets), Creatinine<1.5x ULN.
• No prior PARPi, platinum, cyclophosphamide or mitoxantrone.
• CTC count of ≥5 cells/7.5mls blood at screening.
Baseline characteristics

<table>
<thead>
<tr>
<th>Patients screened</th>
<th>51</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients dosed</td>
<td>31</td>
</tr>
<tr>
<td>Evaluable for response</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior lines of treatment</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>30 (100%)</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>17 (56.7%)</td>
</tr>
<tr>
<td>Abiraterone</td>
<td>29 (96.7%)</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>5 (16.7%)</td>
</tr>
<tr>
<td>Palliative radiotherapy</td>
<td>16 (53.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median age (range)</th>
<th>67.5 y (40-79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG-PS 0-1</td>
<td>24 (80%)</td>
</tr>
<tr>
<td>ECOG-PS 2</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Bone M1</td>
<td>29 (96.6%)</td>
</tr>
<tr>
<td>Visceral M1</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>Lung: 1 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Liver: 8 (26.6%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline blood test results</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/L)</td>
<td>106 (102-113)</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>235 (178-484)</td>
</tr>
<tr>
<td>Alkaline Phosphatase (U/L)</td>
<td>168 (84-374)</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td>405.5 (141-1095)</td>
</tr>
<tr>
<td>CTC count/7.5ml blood</td>
<td>42.5 (16-110)</td>
</tr>
</tbody>
</table>
**Treatment emerging AEs**

<table>
<thead>
<tr>
<th>Event</th>
<th>All grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>25 (83.3%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (66.7%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Pain</td>
<td>11 (36.7%)</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (36.7%)</td>
<td>-</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>8 (26.7%)</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>7 (23.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (23.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Leg oedemas</td>
<td>7 (23.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>7 (23.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (20%)</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (16.7%)</td>
<td>-</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5 (16.7%)</td>
<td>2 (6.7%)</td>
</tr>
</tbody>
</table>

7 pts (23%) required a dose reduction (300mg BID, tablet) mainly due to anaemia (5).
Primary endpoint assessment

- 10 responses among the first 30 patients.
- RR 33% (95% C.I. 17.3%-52.8%)

<table>
<thead>
<tr>
<th></th>
<th>Median time on treatment</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPONDERS</td>
<td>7.8 months</td>
<td>2.8*-14.4</td>
</tr>
<tr>
<td>NON RESPONDERS</td>
<td>2.7 months</td>
<td>0.2- 5.6</td>
</tr>
</tbody>
</table>


**PSA at week 12**

**CTC at week 12**
## Results: primary endpoint RR

<table>
<thead>
<tr>
<th>Responder</th>
<th>Max PSA decline</th>
<th>Measurable disease CT?</th>
<th>Best RECIST response (if measurable)</th>
<th>CTC conversion</th>
<th>Baseline CTC count (x/7.5ml)</th>
<th>Max CTC decline</th>
<th>Time on treatment (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No decline</td>
<td>YES</td>
<td>PD</td>
<td>YES</td>
<td>6</td>
<td>83%</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>47%</td>
<td>NO</td>
<td>YES</td>
<td>38</td>
<td>95%</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>95%</td>
<td>YES</td>
<td>PR</td>
<td>YES</td>
<td>8</td>
<td>100%</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>59%</td>
<td>YES</td>
<td>SD</td>
<td>YES</td>
<td>22</td>
<td>100%</td>
<td>36+</td>
</tr>
<tr>
<td>5</td>
<td>80%</td>
<td>NO</td>
<td>UNCONF</td>
<td>87</td>
<td>100%</td>
<td>42+</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>80%</td>
<td>YES</td>
<td>PR</td>
<td>YES</td>
<td>18</td>
<td>100%</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>29%</td>
<td>YES</td>
<td>SD</td>
<td>YES</td>
<td>105</td>
<td>97%</td>
<td>17</td>
</tr>
<tr>
<td>8</td>
<td>83%</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>102</td>
<td>100%</td>
<td>39</td>
</tr>
<tr>
<td>9</td>
<td>51%</td>
<td>NO</td>
<td>YES</td>
<td>24</td>
<td>100%</td>
<td>32+</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>No decline</td>
<td>YES</td>
<td>SD</td>
<td>YES</td>
<td>38</td>
<td>100%</td>
<td>12+</td>
</tr>
</tbody>
</table>
Olaparib induces responses in mCRPC

Example case 1

- Durable radiological PR, with progression after 9 months.

- Previously unreported germline BRCA2 mutation + loss of 2nd copy in tumor (no family history of cancer)
Patient with somatic DNA repair defects respond to Olaparib

Example case 2

**BASELINE**

**WEEK 12**

- Somatic DNA analysis:
  - One copy loss BRCA2
  - Fs substitution in the other BRCA2 allele.

- Germline DNA: conserved both copies of BRCA2.
Patient with somatic DNA repair defects respond to Olaparib

- Prolonged response in a patient post docetaxel, cabazitaxel, abiraterone and enzalutamide.

- The patient is still responding after 10+ months. Has stopped opioids and his mobility has improved.

- Germline FS del ATM + LOH in tumor.

- Transcriptome analysis: very low ATM expression in tumor.
Radiological assessment of response in patients with bone-only disease

Example case 4

Baseline vs Week 24

CTC count and PSA over weeks of treatment.
Radiological assessment of response in patients with bone-only disease

Example case 4

BASELINE

WEEK 24
Example case 5

- Maintained response in a patient dose-reduced to 300mg BID (tablet).

**Baseline**

**Week 12**

26-30 September 2014, Madrid, Spain
Baseline | After 3 months | After 11 months

Vol: 1.31 L | Vol: 0.54 L | Vol: 0.39 L

Number of pixels

ADC values (μm²/sec)
Conclusions

• PARP inhibition with olaparib has antitumour activity in heavily pretreated, sporadic, unselected, CRPC.

• Olaparib is well tolerated. Toxicities, mainly anaemia, was managed with dose interruptions and reductions.

• Loss of function of DNA repair genes, such as BRCA2 and ATM was identified in responding patients.
Acknowledgements

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• Cancer Biomarkers (ICR): P. Flohr, I. Figueiredo, G. Seed, R. Riisnaes, G. Boysen, L. Matthews,...
• University of Michigan: D. Robinson, K. Giles,..... and many others!!!

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