ODM-204, a novel dual inhibitor of CYP17A1 and androgen receptor: Early results from phase I dose escalation in men with castration-resistant prostate cancer

K. Fizazi\(^1\), R. Jones\(^1\), C. Massard\(^1\), E. Vjaters\(^1\), K.J. Peltola\(^1\), P. Nykänen\(^1\), A. Vuorela\(^1\), R. Oksala\(^1\), P. Pohjanjoumi\(^2\), M. V. Mustonen\(^3\), P. Bonof\(^4\)

\(^1\)Institut Gustave-Roussy, University of Paris Sud, Villejuif, France; \(^2\)Velindre Cancer Centre, Cardiff, United Kingdom; \(^3\)P. Stradins Clinical University Hospital, Riga, Latvia; \(^4\)Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland; \(^5\)Orion Corporation Orion Pharma, Espoo, Finland

**Background**

Castration-resistant prostate cancer (CRPC) is characterized by high androgen receptor (AR) expression and persistent activation of AR signaling axis by residual tissue/tumor androgens. Synthesis of testosterone (T) requires a battery of enzymes, the key enzyme being CYP17A1. Targeting CYP17A1 and AR together may be more effective than either alone (1). One suggested mechanism for the resistance to abiraterone, a CYP17A1 inhibitor, is the increase of progesterone, a moderate AR agonist (2).

ODM-204 is a novel, orally administered investigational non-steroidal dual inhibitor of CYP17A1 and AR that has shown activity in nonclinical tumor models.

**Methods**

We report early data of the DUALIDES phase I dose escalation part (NCT02344017, Figure 1).

**Results**

Patients included in the trial had historically confirmed, progressive adenocarcinoma of the prostate, and serum testosterone level <50 ng/dl (Table 1).

**Patient characteristics at baseline**

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Median age (range, interquartile)</th>
<th>Median PSA (ng/ml, range, interquartile)</th>
<th>Median total androgen index (T, A/I, Amax, Amin, interquartile)</th>
<th>Mean daily dose (mg, range, interquartile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>64 (56-70)</td>
<td>20 (12-30)</td>
<td>19 (15-22)</td>
<td>100 (50-200)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>68 (60-70)</td>
<td>25 (15-35)</td>
<td>22 (18-25)</td>
<td>150 (100-200)</td>
</tr>
<tr>
<td>Patient 3</td>
<td>72 (65-75)</td>
<td>30 (20-40)</td>
<td>25 (20-30)</td>
<td>200 (150-300)</td>
</tr>
</tbody>
</table>

- Most AEs were grade 1 or 2 in severity. Two patients discontinued study treatment due to AEs; one due to grade 3 nausea and vomiting at 200 mg bid fasted, and another due to grade 3 drug hypersensitivity (rash) at 300 mg bid fed. Both events were considered related to ODM-204 and dose limiting toxicities (DLTs).

**Conclusions**

- ODM-204 was generally well tolerated in mCRPC patients.
- Decreased ODM-204 concentrations were seen at steady state (500 mg bid).
- T decreases were observed, but they were mostly transient.
- ≥50% PSA decrease from baseline at 12 weeks was seen in 13% of the patients (none in post-abiraterone or post-enalztamidate).

> Additional evidence of anticancer activity was provided with ODM-204 in some mCRPC patients, decreasing steady state concentration was observed.

**Acknowledgements:**

We thank all patients and their families for participating in this trial. We further thank all sites and their personnel, and PIST (clinical CRO).

**References:**


**Abstract #246**

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**Methods**

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**Figure 1. Design of the DUALIDES dose escalation study**

- Patients with metastatic CRPC (mCRPC) were enrolled into increasing dose levels of ODM-204
- ODM-204 was administered orally twice daily together with 5 to 10 mg of prednisone
- Three to six patients were to be enrolled per dose-escalation cohort
- Doses of 50, 100, 200, 300, and 500 mg twice daily were considered
- Three patients at 200 mg twice daily dose level took study treatment without food
- Patients were allowed to continue treatment until disease progression or intolerable adverse event (AE)
- Data cut-off was Oct 07th 2016

**Table 2. Most common AEs by dose (subject count)**

<table>
<thead>
<tr>
<th>Subject Count</th>
<th>n (%)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased haemat</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acne</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Weight gain</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dose-related rash</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Path of extremity</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Figure 2. Pharmacokinetics of ODM-204**

Transient decreases were seen in testosterone and the decrease was generally pronounced during the first 4 weeks (Figure 3). In figures 3, 4, and 5 patients are marked with similar numbers.

**Figure 3. Testosterone changes during 4 weeks**

PSA % changes are shown in figures 4 and 5.
- At 12 weeks, 3 (13%) patients had a PSA response (≥50% reduction from baseline)
- PSA decreases were seen in 7 (30%) patients who were all abiraterone and enalztamidate naive, and the median decrease was 47% (2-99%)

**Figure 4. Maximum PSA change (%) during 12 weeks**

- PSA decrease was seen in all patients, with decrease start to decrease stop.

**Figure 5. Individual patients and their PSA changes**

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