O'DM-204, a novel dual inhibitor of androgen receptor and CYP17A1 for the treatment of castration-resistant prostate cancer: Preclinical data

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Abstract # 221

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 progestosterone, a moderate AR agonist (2). O'DM-204 is a novel, non-steroidal dual inhibitor of both CYP17A1 and AR, which has shown promising results in preclinical studies.

Methods
Inhibition of CYP17A1 in vitro: Conversion of 17α-labeled 17α-hydroxyprogrenolone into 17α-hydroxyprogrenolone (DHEA) was studied with a human adrenal cortex cell line (NCI-H295R). Formation of 17α-hydroxyprogrenolone from progesterone was tested using human, monkey and rat testicular microsomes. AR binding affinity: The binding affinity to wild type (wt) AR was determined in cytosolic lysates obtained from ventral prostates of castrated rats using a competition binding assay. Antagonism to wtAR: HEK293 cells stably transfected with wtAR and androgen-responsive luciferase reporter gene constructs were treated with T (0.45 nM) and O'DM-204, and luciferase activity was measured. Transactivation assays with mutant AR(T877A), AR(W741L) and AR(F876L): Human U2-OS cells transiently transfected with an androgen-responsive reporter gene construct and expression vectors encoding mutant ARs were treated with O'DM-204 (1 µM) and TDOHT, and luciferase activity was measured. AR antagonism in AR overexpressing cells: HEK293 cells stably overexpressing hAR and androgen-responsive luciferase reporter gene construct were treated with T (0.6 nM) and test compounds (1 µM), and luciferase activity was measured. AR nuclear translocation: AR overexpressing HEK293 cells were treated with T (0.3 nM) and test compounds (1 µM); AR was immunolabeled with polyclonal antibody (Santa Cruz; N-20). Cells were imaged with Cellomics Arrayscan VTI and analyzed with NucTrans V3 Assay Algorithm (Thermo).

VCAP and LNCAP proliferation assays: Androgen-responsive VCAP (AR overexpression) and LNCAP (AR mutation T877A) PC cells were treated with test compounds (1 µM) and a submaximal concentration of mitomycin. Cell growth was measured with WST-1 cell proliferation assay (Roche).

Inhibition of CYP17A1 in vivo: Male rats were administered with luteinizing hormone releasing hormone (LHRH) agonist leuprolide acetate and ODM-204 for 14 days, after which serum T levels and weights of androgen-sensitive tissues were measured.

VCAP xenograft: Tumors were established by subcutaneous injection of VCAP cells into male nude mice. Oral treatment of ODM-204 (50 mg/kg/day) was started when the average tumor volume reached 200 mm³ and was continued for 21 days.

Results
1. ODM-204 inhibits CYP17A1 in vitro

<table>
<thead>
<tr>
<th>Cells</th>
<th>Testicular microsomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI-H295R</td>
<td>Human</td>
</tr>
<tr>
<td>ODM-204 IC₅₀ (nM)</td>
<td>51</td>
</tr>
<tr>
<td>Galetore IC₅₀ (nM)</td>
<td>135</td>
</tr>
</tbody>
</table>

2. ODM-204 inhibits AR in vitro

a) Binding affinity to hAR (47 nM)

b) Potent antagonism to wtAR and mutated ARs

ODM-204 IC₅₀ (nM) | 62 | 95 | 277 | 6* |

*Agonism at high (> 3 µM) concentrations

3. ODM-204 inhibits CYP17A1 in vivo

Inhibitory effects of leuprolide acetate on a) T production, and b) seminal vesicle and c) dorsolateral prostate weights were potentiated by ODM-204.

a) Serum testosterone (nmol/l, mean±SD)

b) Seminal vesicles (relative weight, mean±SD)

c) Dorsolateral prostate (relative weight, mean ±SD)

Conclusions
ODM-204 is a novel dual inhibitor of CYP17A1 and AR with
• Potent inhibition of both CYP17A1 and AR, including mutant ARs
• Serum T decrease to undetectable levels in rats treated with a combination of ODM-204 and LHRH agonist. Further, an additional decrease in weights of androgen-sensitive organs was observed with ODM-204.
• Promising antitumor activity in a VCAp xenograft model overexpressing AR

Based on these nonclinical results, a phase 1/2 clinical trial (NCT 02344017) has been initiated in Europe.

References: