ODM-201, a new generation androgen receptor inhibitor for castration resistant prostate cancer: preclinical and phase I data

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Background
Castration resistant prostate cancer (CRPC) is characterized by persistent, high level androgen receptor (AR) expression and resistance to conventional AR inhibitors. ODM-201 is a novel AR inhibitor with unique pharmacologic properties that has shown promising results in preclinical and clinical studies.

Methods
Preclinical experiments
AR binding affinity of ODM-201 to wild type AR was determined in cytosolic lysates obtained from ventral prostates of castrated rats using a competition binding assay. Activity of ODM-201 on the growth of castration-resistant VCaP tumors was evaluated. Tumors were established by subcutaneous injection of VCaP cancer cells into male nude mice. After initial tumor growth, mice were castrated. ODM-201 (50 mg/kg OD or BID orally) or enzalutamide (20 mg/kg OD orally) was administered upon tumor regrowth. To assess the potential risk of seizures (which have been reported with some second generation AR inhibitors), ODM-201 concentrations were studied in mouse brain homogenates after repeated oral administration.

Phase I/II trial
The clinical effects of ODM-201 (100, 200, 300, 500, 700, 900 mg BID) were examined in dose escalation component of Phase I/II trial in patients (N=24) with progressive metastatic CRPC. ODM-201 was administered orally, twice daily with food.

Results
Preclinical experiments
ODM-201 binds to wild type AR with superior affinity compared to enzalutamide (Ki of 9 and 79 nM, respectively) (Table 1).

<table>
<thead>
<tr>
<th>Bicalutamide</th>
<th>Enzalutamide</th>
<th>ARN-509</th>
<th>ODM-201</th>
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<tr>
<td>12</td>
<td>79</td>
<td>51</td>
<td>6</td>
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In the VCaP CRPC model, ODM-201 significantly inhibited tumor growth compared to castrated control (p<0.001) and enzalutamide (p=0.005) (Figure 1).

No dose-limiting toxicities were observed. ODM-201 was well tolerated, and most commonly reported adverse events were asthenia, diarrhea and nausea (grades 1-2) (Table 2).

A PSA response (defined as ≥50% PSA decrease) was obtained in 17 (81%) of 21 patients evaluable during 12 weeks (Figure 3).

Conclusions
Preclinical studies:
- ODM-201 is a new generation AR inhibitor with superior preclinical activity compared to enzalutamide and bicalutamide.
- It does not enter the brain in preclinical studies.

Phase I/II trial:
- ODM-201 showed impressive activity and no dose-limiting toxicity in patients with metastatic CRPC, including docetaxel-pretreated patients.
- A 50% PSA decrease from baseline was seen in 92% in pre-chemotherapy and in 67% in post-chemotherapy patients.
- ODM-201 was well tolerated, and the most commonly reported grades 1-2 adverse events were asthenia, diarrhea and nausea.
- The phase II part is currently completing its planned accrual of 105 patients.

Acknowledgments
The trial is funded by Orion Corporation Orion Pharma, Turku, Finland, and the authors declare no conflict of interest.

Figure 1. Design of the Phase I/II trial.

Figure 2. Efficacy of ODM-201 in CRPC VCaP model.

Figure 3. Maximum change (% in PSA during 12 weeks by dose.

A >50% PSA decrease from baseline was seen in 92% of pre-chemo and 67% of post-chemo patients. For post-chemo pre-abiraterone patients this decrease was seen in 86% of patients (Figure 4).