CYP11A1 inhibition as a therapeutic approach for the treatment of castration resistant prostate cancer

M. Karimaa, R. Riikonen, K. Räsänen, M. Ramela, P. Vehmaan-Kreula, P. Rummakko, G. Wohlfahrt and **R. Oksala**

Orion Corporation Orion Pharma, Finland

Background:

Prostate cancer is a major global challenge due to the increasing number of aging population and frequency of diagnosis. During the past decade new treatments have been targeted to the androgen signaling axis either by inhibiting the binding of androgens to androgen receptor (AR) and AR nuclear translocation, or by inhibiting androgen production via CYP17A1 enzyme. Despite the significant progress on the research and new therapies, CRPC is still incurable and there is urgent need for better, more effective treatments. ODM-208 is an oral, non-steroidal and selective inhibitor of CYP11A1 enzyme, suppressing the synthesis of all steroid hormones that could be potential AR ligands.

Methods:

The inhibition of CYP11A1 was measured in vitro by the formation of radiolabelled isocapronic acid in a human adrenal cortex cell line (H295R). The tumor growth inhibition of ODM-208 was studied in VCaP castration-resistant prostate cancer (CRPC) xenograft model. At the end of the xenograft study, plasma ACTH and LH, and key steroid hormone concentrations were analysed from plasma and target tissues. In addition, full length AR (AR-FL) and AR-V7 were analysed from the tumors by western blot and key enzymes of androgen biosynthesis, CYP17A1, AKR1C3, SRD5A1 were quantified by qPCR. In dogs an ACTH stimulation test was done

Results:

ODM-208 potently inhibits CYP11A1 enzyme in vitro. In addition, in vivo in the VCaP CRPC xenograft model ODM-208 significantly inhibited tumor growth. Importantly, the amount of AR-FL and AR-V7 levels remained unchanged in the tumors after ODM-208 treatment. Slight increase of CYP17A1 and SRD5A1 enzyme levels was observed, indicating the activation of steroidogenesis in VCaP tumors in vivo. Treatment had no effect on plasma LH, whereas ACTH was significantly increased demonstrating reduction in glucocorticoid levels by negative feedback. In line with ACTH, all measured steroid hormones were significantly reduced both in plasma and target tissues. In dogs ACTH-stimulated cortisol production was significantly inhibited after single oral dose of ODM-208.

Conclusions:

ODM-208 shows promising antitumor activity in preclinical CRPC models and has favorable toxicological profile. Thus, ODM-208 might have potential for treating patients with CRPC. A phase 1/2 clinical trial (NTC03436485) is ongoing.

Conflict of Interest:

MK, RR, KR, MR, PVK, PR, GW and RO are employees of Orion Corporation, Orion Pharma

Funding:

Orion Corporation, Orion Pharma, Finland