ODM-208, a novel CYP11A1-inhibitor as a therapeutic approach for the treatment of castration-resistant prostate cancer

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Background

Worldwide prostate cancer (PCa) is the most common cancer in men and the prognosis for those patients, who develop castration-resistant prostate cancer (CRPC), is poor. The androgen receptor (AR) signaling axis is critical and drives all stages of prostate cancer, including CRPC. Approximately half of the men with CRPC respond initially to abiraterone or enzalutamide, but most the patients develop a disease that is refractory to all current therapies when one to two years. Majority of the abiraterone and enzalutamide-resistant tumors have still high AR expression and persistent AR activity (1).

Increased progestosterone (P) levels in CYP17A1-inhibitors treated patients have been speculated to be one of the resistance mechanisms in CRPC especially via mutated androgen receptor (2, 3). Further, also the expression of steroidogenic gene transcripts is changed in patients with CRPC, indicating altered steroid synthesis profile.

Several precursor steroids, like progestrone (P) testosterone (T) and dihydrotestosterone (DHT) and their derivatives, which bind and activate AR, can be synthesized in adrenal glands and de novo in tumors. The key enzyme of steroidogenesis is CYP11A1 (cytochrome p450sc), catalyzing the conversion of cholesterol to pregnenolone (Preg), being the first and rate-limiting step in the whole steroid hormone biosynthesis.

ODM-208 is a novel, oral, non-steroidal and selective inhibitor of CYP11A1 enzyme, which suppresses the synthesis of all steroid hormones and precursors and thus expected to be effective agent in CRPC.

Methods

Effects of castration (ORX), adrenalectomy (ADX) or combination in VCaP CRPC xenograft tumor growth: The tumor growth inhibition was studied by using androgen dependent VCaP cells, which were subcutaneously grafted to intact male nude mice. When tumor volumes reached on average 200 mm³ (study days 36-38), mice were either castrated or adrenalectomised, or both. Tumor growth was followed 31 days.

Inhibition of CYP11A1 in vivo: The inhibition of CYP11A1 was studied in vivo by measuring the conversion of 3H-labeled substrate, [24,25-3H]-cholesterol, into its 3H-labeled product, isocaproic aldehyde (IARA) in NCI-H295R cells, that originate from a hormonally active adenocarcinoma, and further analyzing Preg and T formation by ELISA in the same cell line.

Inhibition of adrenal and testicular hormone production (CYP11A1) in vivo: Inhibition of the adrenal and testicular hormone production in vivo was tested in the intact male rat assay by analyzing plasma concentrations of progestrone (P), corticosterone (C) and T (with LS-MS/MS) after single and multiple oral doses of ODM-208.

Results

1. ORX+ADX more effective than ORX only in a CRPC VCaP model

2. ODM-208 inhibits CYP11A1 in vitro

Conclusions

ODM-208 is a novel nonsteroidal inhibitor of CYP11A1

• Shows clear and dose-dependent decrease in T, P and C hormones in intact rats.

• It closely mimics the effects of ORX+ADX in CRPC VCaP model, and thus blocks all steroid hormone formation in target tissues.

• Shows promising antitumor activity in preclinical CRPC model.

Therefore ODM-208 may have the potential to be effective option for the treatment of CRPC.

Clinical trial with metastatic CRPC in major European cancer centers is under preparation.

References