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Poster Presentations - Phosphatases and Kinases as Targets for Therapy

Abstract 2848: Preclinical activity of OM-RCA-01, a humanized anti-FGFR1 antibody, in renal cell carcinoma (RCC)

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Background: Fibroblast growth factor (FGF) receptor 1 (FGFR1) is a potential therapeutic target for treatment of metastatic RCC. Early we reported that anti-FGFR1 monoclonal antibody inhibited ligand-induced phosphorylation of FGFR1, activation of MAP kinase and Akt downstream signaling pathways in FGFR1 expressing endothelial (bovine adrenal cortex capillary endothelial cells) and human RCC (Caki-1) lines (Tsimafeyeu et al. AACR/JCA joint conference 2010). Today we investigated the preclinical activity of OM-RCA-01, a novel therapeutic humanized anti-FGFR1 antibody with high affinity (Kd of 1.59 nM), in RCC. Methods: To assess the effect of anti-FGFR1 antibody on FGF-mediated signaling, the human renal carcinoma Caki-1 FGFR1-expressing cells were incubated (0.5% FBS) and were dosed with OM-RCA-01 at 100, 10, and 1 mcg/ml. Control wells were left untreated. Three hours after dosing, basic FGF was added at a concentration of 50 ng/ml. Additional control wells were treated with OM-RCA-01 without FGF-stimulation. Cell growth inhibition was determined using Promega's Cell Titer-Glo® assay. Charles River female NCr nu/nu mice (6-12 weeks of age) were set up with 1 mm3 Caki-1 tumor fragments sc in flank. Tumor sizes were measured in a blind fashion twice a week with a vernier caliper. Mice with established tumors (an average size of 80 - 120 mg) were randomly divided into vehicle, non-specific IgG or OM-RCA-01 groups per 10 animals in group. Animals were treated with antibody using different doses (1 or 10 mg/kg). Endpoint was significant differences in tumor growth delay. Results: In vitro study showed that basic FGF significantly increased proliferation of the human FGFR1-expressing renal carcinoma cells (P=0.011). No effect of basic FGF on cell line proliferation was observed when the cells were incubated with OM-RCA-01 antibody at any concentrations up to 100 mcg/kg in comparison with FGF-untreated control (P=0.855). In vivo, the tumors in untreated mice or mice treated with non-specific IgG continued their aggressive growth to reach the size of 2000 cm3, at which point the mice were killed. In contrast, treatment with OM-RCA-01 not only significant arrested further growth of the tumors (P=0.006) but also demonstrated differences in tumor volume compared with vehicle already on Day 13. A similar anti-tumor activity of OM-RCA-01 was observed when the antibody was given in low (1 mg/kg) or high (10 mg/kg) doses (P=0.917). Conclusions: High-affinity humanized anti-FGFR1 antibody OM-RCA-01 suppressed ligand-induced proliferation of human RCC cells in vitro. OM-RCA-01 has significant early anti-tumor efficacy in Caki-1 xenograft model.

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