Evexomostat/SDX-7320 demonstrates potent anti-tumor effects across stages of prostate cancer progression, including treatment refractory and neuroendocrine (AVPC) phenotypes

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Background: Androgen receptor signaling inhibitors (ARSIs) have provided significant improvements in survival for patients with mCRPC. However, the development of resistance to ARSIs remains a significant clinical issue, promoting the emergence of aggressive variant prostate cancer (AVPC), highlighting an urgent need for novel, AR pathway-independent therapies. A recent report correlated elevated expression of methionine aminopeptidase 2 (MetAP2) in prostate cancer to increased aggressiveness, with high expression in dedifferentiated phenotypes, including NEPC and other forms of AVPC. MetAP2 regulates protein translation and post-translational modifications and has a clinically validated role in angiogenesis. MetAP2 also has tumor-specific functions coordinating plasticity, vascular mimicry, and hypoxia response. Evexomostat/SDX-7320 is a polymer-drug conjugate of a novel fumagillin-derived MetAP2 inhibitor which has completed a phase I safety trial in late-stage cancer patients. Two phase 1b/2 trials are currently enrolling in metastatic breast cancer, testing the ability of evexomostat/SDX-7320 to improve clinical outcomes in combination with standard of care therapies (NCT05570253, NCT05455619). We hypothesized that evexomostat/SDX-7320 would show anti-tumor efficacy in preclinical prostate cancer xenograft models of CRPC and AVPC.
Methods: SDX-7320 (evexomostat) was tested in NSG mice harboring LNCaP xenografts (randomized to 12 or 6 mg/kg, SC, Q4D or vehicle 5% mannitol/water) in intact, castrated, and CRPC models. SDX-7320 treatment was also evaluated in LuCaP35.CR patient-derived xenograft (PDX) in castrate mice as well as in combination with enzalutamide following development of resistance to 10mg/kg daily enzalutamide treatment. SDX-7320 was further evaluated in the LTL545 (AR-negative, NE-positive) model of AVPC. Tumor growth was assessed and following dissection, subsequently analyzed for transcriptomic (RNAseq) or histological differences (H&E staining, CD34 IHC).
Results: We observed significantly reduced tumor volume with SDX-7320 treatment across all models, both as single agent and in combination with AR-targeted therapies (in AR-resistant tumors), as well as in the AR-negative LTL545 model, suggesting MetAP2 regulates important tumor growth pathways in AR-positive and AR-negative prostate tumors. Reduced CD34 staining was observed in all tumors from SDX-7320-treated mice. Gene and gene-set variation analysis of RNA-sequenced xenograft tumor tissues identified significantly decreased expression of cell cycle-associated genes and upregulation of genes associated with hypoxia, apoptosis and inflammation. In AR-positive models, evexomostat/SDX-7320 treatment increased expression of AR target genes, suggesting a potentially pro-differentiation reprogramming of the tumors. Treatment also resulted in the down regulation of MYC targets in both AR-positive and AR-negative models and down regulated neuroendocrine gene signatures in the LTL545 model.
Conclusions: These results indicate the importance of MetAP2 regulation throughout multiple stages of prostate cancer development and that its inhibition via evexomostat/SDX-7320 is a novel approach to treat prostate cancer warranting immediate clinical translation.

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