G1T38 inhibits the growth of prostate cancer xenografts in a dose dependent manner with good tolerability.

Effects of a CDK 4/6 inhibitor, G1T38, in androgen receptor sensitive and resistant models of castrate resistant prostate cancer

Introduction: Resistance to androgen deprivation therapy, via expression of mutations or variants of the androgen receptor (AR), remains an intractable problem for CRPC. Preclinical therapeutic responses in advanced castrate resistant prostate cancer (CRPC) are dependent upon the activation of the Cyclin D-CDK4/6 complex in the presence of low androgen levels. We have documented the synergistic anti-tumor effects of CDK 4/6 and AR inhibition in androgen sensitive and hormone refractory models of CRPC, the results of which have significant clinical implications.

Methods: For preclinical models xenografts were treated to 0-10 mg/kg of Enzalutamide in combination or alone at 4000 mg/kg (G1T38) or standard of care comparators prior to quantitation of cell number. Cell cycle progression and apoptosis were assessed by flow cytometry using propidium iodide or Annexin V/Sytox red staining, respectively. Orchiectomized nude or NOD SCID, GEM female mice bearing 22RV1/LnCAP-AR-F876L xenografts, respectively, were treated with G1T38 or clinically relevant comparators. For advanced castrate resistant prostate cancer, tissue was obtained from animals euthanized 24 or 48 hours after the final dose of treatment indicated incomplete inhibition of tumor growth and a potential new paradigm in CRPC treatment.

Results: G1T38 inhibited the growth of prostate cancer cell lines expressing wild type AR (LnCAP and VCAP), resistance associated AR variant AR v7 (22RV1) and androgen receptor variants (LNCaP-AR-F876L) in a dose dependent manner and maintained a similar PK profile. In xenograft models and clinical models G1T38 showed tumor growth inhibition in prostate cancer and a potential new paradigm in CRPC treatment.

Discussion: The CDK 4/6 inhibitor G1T38 exhibits favorable PK and PD in 22RV1 xenograft models. Combination of G1T38 with Enzalutamide was found to induce apoptosis in prostate cancer xenograft in vivo. G1T38 inhibits the growth of LNCaP xenograft expressing the Enzalutamide associated AR-F876L mutation. G1T38 will enter Phase 1 Healthy volunteer trials in the second quarter of 2016.

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