

Clinical Characterization of the Adenovirus Death Protein-potentiated Oncolytic Adenovirus VRX007

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Clinical trials with the oncolytic adenovirus ONYX-015 have demonstrated safety and modest evidence of clinical effectiveness with locoregional administration. Our proposed study will address clinical safety of the novel adenovirus construct VRX007 and preliminary response in cancer patients. VRX007 incorporates an amplified expression of the “Adenovirus Death Protein” (ADP; E3 11.6K), a wild type adenovirus gene that enhances tumor lysis efficiency and intratumoral spread. We have demonstrated VRX007’s capacity to suppress the growth of multiple types of human tumor xenografts in nude mice. VRX007 was superior to ONYX-015 in destroying cancer cells in vitro and in vivo. wt ADP is synthesized abundantly at very late stages of ADV infection after virions have begun to assemble in the cell nucleus. Findings with VRX007 indicated that ADP overexpression maximized viral oncolytic efficiency in vitro and in vivo by promoting efficient release of mature virions at the end of viral proliferation and enhanced cell to cell spread through the tumor. Extensive toxicology and biodistribution evaluations in adenovirus-permissive Syrian hamsters confirmed the safety of VRX007, justifying clinical IND development. GMP manufacturing has been completed and BB-IND 13304 has been approved by FDA for single intratumoral injection of VRX007 in advanced cancer patients with accessible disease. To examine the hypothesis that VRX007 is clinically safe for advanced cancers, five patient cohorts are slated to receive a single intratumoral injection of dose escalating VRX007 (2×10^8 – 2×10^{12} vp). To date, one cohort 1 patient with recurrent squamous carcinoma of the tongue has been treated (2×10^8 vp IT x 1 administration). This patient failed prior chemotherapy (taxol, carboplatin), radiation and centuximab. No VRX007 treatment related toxicity (NCI Common Toxicity Criteria Version 3.0) was observed at 15 weeks post-treatment. CT measurement of the tongue lesion indicated disease stabilization, and physical examination at day 8 confirmed subjective decrease of the hard nodular mass. Systemically, there were no remarkable alterations in immune lymphocyte subset distribution for up to day 22 post-treatment according to flow cytometric immunophenotype analyses. Evidence for VRX007 biological activity for this and subsequent patients will be based on indications of viral replication of VRX007 in the injected tumor and distal sites, and measurement of tumor mass at various time points after treatment. Additionally, immune response to VRX007 will be measured through comparison of peripheral blood neutralizing antibody and cytokines at pretreatment baseline to levels measured at various time points after treatment.