NONCLINICAL CHARACTERIZATION OF ICVB-1042, A NOVEL E2F-TUMOR SELECTIVE ONCOLYTIC VIRUS WITH THE POTENTIAL TO TREAT SOLID TUMORS

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Background A major challenge in oncolytic virotherapy is to engineer potent tumor-killing viruses that can be delivered systemically for treatment of metastatic disease while leaving normal cells unharmed. Here we report the nonclinical characterization of ICVB-1042, an optimized E2F-dependent oncolytic adenovirus rationally engineered with specific genomic modifications to confer tumor selective replication and enhanced tumor cell killing. ICVB-1042 has been further engineered with a chimeric fiber to enhance its tumor tropism and a modified capsid hexon protein to allow intravenous (IV) delivery. This combination of rationally designed modifications enables ICVB-1042 to be used for the treatment of a wide range of solid tumor types.

Methods Using a proprietary iterative adenovirus design and screening platform, IcoOVir has engineered ICVB-1042, a potent, tumor selective oncolytic adenovirus. A multi-faceted nonclinical strategy was designed to characterize key therapeutic properties of ICVB-1042 through in vitro and in vivo studies. Tumor cell selectivity was assessed by testing the replication of ICVB-1042 in a comprehensive panel of primary normal human cells compared to tumor cells. Anti-tumor efficacy was evaluated in multiple human xenograft immunocompromised mouse models. Tolerability, biodistribution and PK were assessed in human CD46 transgenic mice where particle-mediated toxicity and effects on host immune response could be assessed. Biodistribution and pharmacokinetics were evaluated in human tumor xenograft models and in CD46 transgenic mice.

Results ICVB-1042 displayed replication and cell killing against a broad range of human tumor cell lines including breast, prostate, bladder, lung, and glioblastoma. However, replication was tumor selective, and the multiplicity of infection required to kill primary normal cells was 100 to >10,000-fold greater than the concentration of virus required to kill tumor cells. The anti-tumor activity of IV-dosed ICVB-1042 was demonstrated in several subcutaneous and orthotopic models. ICVB-1042 virus particles increased in both tumors and plasma over time suggesting virus replication in tumors, which correlated with efficacy. IV dosing of ICVB-1042 was well tolerated in CD46 transgenic mice. ICVB-1042 distributed throughout CD46 transgenic mice and cleared to less than 0.1% of the administered dose by Day 15 post first dose. There was no preferential distribution into the liver over other organs.

Conclusions ICVB-1042 is a novel, potent, tumor selective, systemically administrable oncolytic virus with the potential to treat a broad range of solid tumors. The in vitro and in vivo results presented demonstrate ICVB-1042’s selective replication in tumor cells compared to quiescent primary normal cells, broad tumor tropism, and safety and anti-tumor efficacy with IV dosing.

Ethics Approval All procedures carried out were conducted in compliance with the applicable laws, regulations and guidelines of the National Institutes of Health (NIH) and with the approval of Labcorp Drug Development PCO’s Animal Care and Use Committee. Labcorp Drug Development (Greenfield) is an AAALAC accredited facility.