EVALUATION OF THE ANTI-TUMOR ACTIVITY OF ICVB-1042, A NOVEL E2F-TUMOR SELECTIVE ONCOLYTIC VIRUS, SELECTIVELY TARGETING TUMOR CELLS IN AN ESTABLISHED HUMAN GliOBLASTOMA MOUSE MODEL

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Background A major challenge in oncolytic virotherapy is to engineer potent tumor-killing viruses that can be delivered systemically for the selective treatment of metastatic disease while leaving normal cells unharmed. ICVB-1042 is a novel E2 transcription factor (E2F)-dependent oncolytic adenovirus rationally designed with genomic modifications to confer tumor selective replication, allow intravenous delivery, enhance potency and tumor tropism, and aid in screening clinical samples. The goal of this study was to compare anti-tumor activity and tumor selectivity of ICVB-1042 to that of ICVB-940, an Ad5-based oncolytic virus (OV) engineered with a 24 base pair deletion in E1A and an RGD-4C motif in HI loop of the fiber knob (D24RGD). ICVB-940 is similar to another D24RGD Ad5 OV that has been evaluated in clinical trials in glioblastoma patients.1,2 This analysis, performed in vitro on a panel of glioblastoma tumor cell lines and in vivo in an established nonobese diabetic/severe combined immunodeficiency gamma mouse-based human glioblastoma model, showed overall enhanced activity of ICVB-1042.

Methods The replication and cell killing of ICVB-1042 and ICVB-940 were compared in primary astrocytes and in glioblastoma tumor cell lines to evaluate baseline killing in primary brain cells versus tumor cells in vitro. Both viruses were compared in vivo at doses of 1.00E+08 or 2.00E+08 plaque forming units administered intratumorally in the human glioblastoma model with time to progression (TTP) and mean tumor volume for the treated versus control groups (median ΔT/ΔC) as endpoints.

Results ICVB-1042 demonstrated enhanced tumor cell killing over ICVB-940 in 11 of 13 human glioma tumor lines in vitro. ICVB-1042 showed significant decreases in tumor volume and significant increases in TTP between treated and control animals at both doses. ICVB-940 showed significant decreases in tumor volume but nonsignificant increases in TTP at the high dose; no significant differences in tumor volume or TTP at the low dose were observed. Comparison between ICVB-1042 and ICVB-940 at the low dose resulted in significant decreases in Day 38 tumor volume and significant increases in TTP for ICVB-1042 over ICVB-940. All treatments were well-tolerated, resulting in no deaths or group mean body weight loss in the treatment window.

Conclusions ICVB-1042, a novel E2F-tumor selective rationally designed OV engineered with enhanced tropism and tumor killing potency, produced higher anti-tumor activity in vitro and in vivo in GBM tumors compared to the D24RGD virus ICVB-940.

REFERENCES