1363 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

Michael Lyman*, Jessica Field, Jinkil Jeong, Valentino Gantz, Nathaniel Rice, Heba Nowyhed. *IcoOVir Bio, San Diego, CA, USA*

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 $\Delta T/\Delta C$) 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

1. Lang FF, Conrad C, Gomez-Manzano C, Yung WKA, Sawaya R, Weinberg JS, *et al*. Phase I study of DNX-2401 (Delta-24-RGD) oncolytic adenovirus: Replication and immunotherapeutic effects in recurrent malignant glioma. *J Clin Oncol* 2018;**36**:1419–1427.
2. van Putten EHP, Kleijn A, van Beusechem VW, Noske D, Lamers CHJ, de Goede AL, *et al*. Convection enhanced delivery of the oncolytic adenovirus delta24-RGD in patients with recurrent GBM: A Phase I clinical trial including correlative studies. *Clin Cancer Res*. 2022;**28**:1572–1585.

Ethics Approval All procedures 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.

http://dx.doi.org/10.1136/jitc-2022-SITC2022.1363