AUTOLOGOUS GLIOBLASTOMA TUMOR CELLS AND AN ANTISENSE OLIGONUCLEOTIDE AGAINST INSULIN-LIKE GROWTH FACTOR TYPE 1 RECEPTOR PROTECT AGAINST TUMOR CHALLENGE AND GENERATE T CELL ANTI-TUMOR RESPONSES

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Background IGV-001 is a novel immunotherapy that combines irradiated, patient-derived glioblastoma tumor cells and an antisense oligonucleotide against insulin-like growth factor type 1 receptor (IMV-001) in biodiffusion chambers (0.1-micron pore size). We recently evaluated IGV-001 in patients with newly diagnosed glioblastoma.¹ In a subgroup of IGV-001-treated, Stupp-eligible patients² with methylated O6-methylguanine–DNA methyl-transferase (MGMT) promoter, median progression free survival was 38.4 months¹ compared with 8.3 months in historical standard-of-care-treated patients (p=0.0008).² We utilized the GL261-Luciferase (-Luc) glioblastoma orthotopic murine model and conducted in vitro immunological assays using patient-derived GBM tumor cells and matched peripheral blood mononuclear cells (PBMC) to unravel the potential mechanisms associated with the activity of IGV-001.

Methods Biodiffusion chambers containing phosphate-buffered saline (PBS) alone or IGV-001 prepared with 1x10⁶ GL261-Luc cells were implanted in the flanks of C57BL/6 albino mice and explanted 48 hours later, as per the clinical protocol. GL261-Luc intracranial tumor challenge was conducted 28 days after chamber implantation. Mice were monitored for survival and tumor growth, as determined by bioluminescence intensity (BLI). For in vitro experiments, IGV-001 prepared with patient tumor cells were co-cultured with patient-derived PBMC to evaluate activated and memory T cell subsets and responses. To elucidate the immunostimulatory underpinnings of IGV-001, ATP release assay was conducted as a surrogate measure of immunogenic cell death.

Results 59% of IGV-001 treated mice were alive and continued to gain weight at the termination of the study, 58 days post-intracranial tumor challenge. In comparison, there were no survivors in the PBS group by day 24 (p<0.001). Fluorospot assays demonstrated enhanced T cell IFN-gamma responses to tumor cell antigens. In IGV-001 treated mice, serum IL-6 was positively correlated with BLI, meaning that treated mice with lower BLI signal had less circulating IL-6 (p<0.01). Fluorospot assays demonstrated enhanced T cell IFN-gamma responses to tumor cell antigens. Tumor co-culture studies showed elevated percentage of activated CD4 and CD8 T cells as well as increased central and effector memory phenotypes in both T cell subsets compared to IMV-001-treated PBMC controls. Lastly, tumor cells treated with IMV-001 released significantly more (p<0.01) ATP than untreated or sense oligonucleotide-treated controls.

Conclusions These data support the antitumor activity of IGV-001 in newly diagnosed glioblastoma, as evidenced in the phase 1 study. Th1 anti-tumor T cell activity was demonstrated. The ATP results suggest a possible immunogenic conversion by which IGV-001 stimulates the immune system and suppresses tumor growth, which can be quantified via circulating IL-6.

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Ethics Approval Ethical consent was obtained for all human biospecimens with the appropriate IRB approval.

Consent Informed consent was obtained for all human biospecimens with the appropriate IRB approval.

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