218 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 patients[2] with methylated O6-methylguanine–DNA methyl-transferase (MGMT) promoter, median progression free survival was 38.4 months[1] 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 determine 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.

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