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Clinical Trial Protocol

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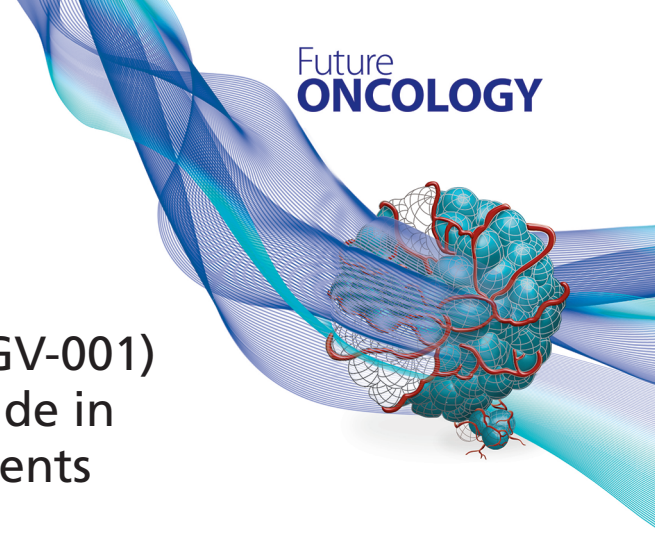

Autologous cell immunotherapy (IGV-001) with IGF-1R antisense oligonucleotide in newly diagnosed glioblastoma patients

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Standard-of-care first-line therapy for patients with newly diagnosed glioblastoma (ndGBM) is maximal safe surgical resection, then concurrent radiotherapy and temozolomide, followed by maintenance temozolomide. IGV-001, the first product of the Goldspire™ platform, is a first-in-class autologous immunotherapeutic product that combines personalized whole tumor–derived cells with an antisense oligonucleotide (IMV-001) in implantable biodiffusion chambers, with the intent to induce a tumor-specific immune response in patients with ndGBM. Here, we describe the design and rationale of a randomized, double-blind, phase IIb trial evaluating IGV-001 compared with placebo, both followed by standard-of-care treatment in patients with ndGBM. The primary end point is progression-free survival, and key secondary end points include overall survival and safety.

Plain language summary – IGV-001 in newly diagnosed glioblastoma: Glioblastoma (GBM) is a fast-growing brain tumor that happens in about half of all gliomas. Surgery is the first treatment for patients with newly diagnosed GBM, followed by the usual radiation and chemotherapy pills named temozolomide. Temozolomide pills are then given as a long-term treatment. The outcome for the patient with newly diagnosed GBM remains poor. IGV-001 is specially made for each patient. The tumor cells are removed during surgery and mixed in the laboratory with a small DNA, IMV-001. This mix is the IGV-001 therapy that is designed to give antitumor immunity against GBM. IGV-001 is put into small biodiffusion chambers that are irradiated to stop the growth of any tumor cells in the chambers. In the phase IIb study, patients with newly diagnosed GBM are chosen and assigned to either the IGV-001 or the placebo group. A placebo does not contain any active ingredients. The small biodiffusion chambers containing either IGV-001 or placebo are surgically placed into the belly for 48 to 52 h and then removed. Patients then

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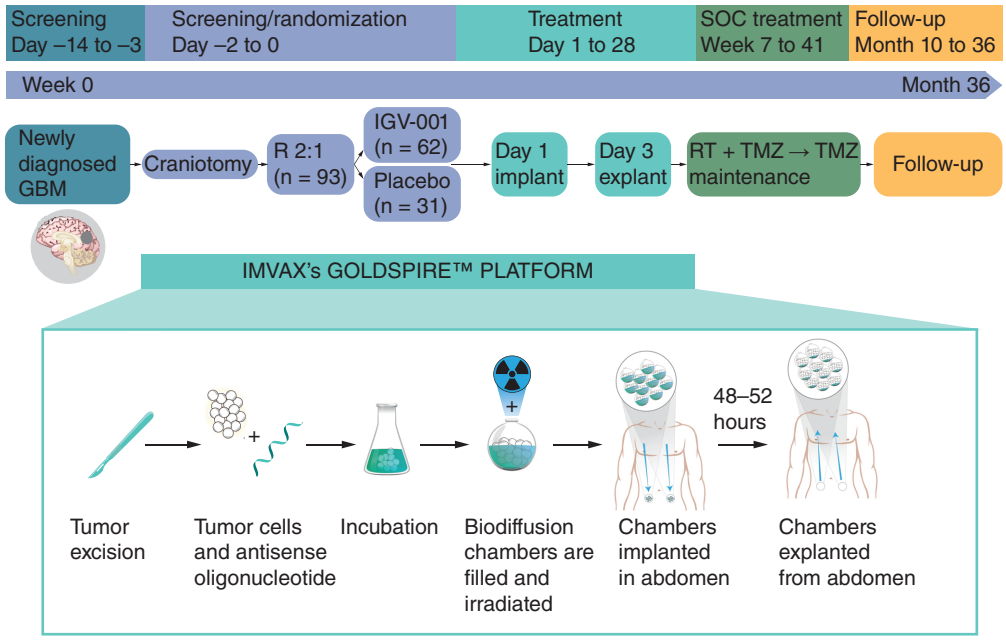
receive the usual radiation and chemotherapy treatment. Patients must be adults aged between 18 and 70 years. Patients also should be able to care for themselves overall, but may be unable to work or have lower ability to function. Patients with tumors on both sides of the brain are not eligible. The main point of this study is to see if IGV-001 helps patients live longer without making the illness worse compared with placebo.

Clinical Trial Registration: NCT04485949 (ClinicalTrials.gov)

Graphical abstract:



Tweetable abstract: IGV-001, an autologous cell biologic-device product, is being tested versus placebo, each followed by standard of care, in a randomized phase IIb trial in newly diagnosed glioblastoma. IGV-001, designed to induce antitumor immunity, is delivered via implantable biodiffusion chambers.

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Keywords: antisense • autologous • glioblastoma • Goldspire™ • IGV-001 • immunotherapy • radiation • temozolomide

Glioblastoma (GBM) is the most common and aggressive primary malignant brain tumor and has a poor prognosis with a 5-year survival rate of less than 5% [1]. About 3 in 100,000 people per year are affected by GBM in USA [1]. Patients' average age at time of diagnosis is 64 years [2]. Standard of care (SOC) typically involves maximal safe surgical resection of the tumor and adjuvant radiotherapy (RT) of 54–60 Gy over 6 weeks plus concomitant adjuvant temozolomide (TMZ; 75 mg/m^2 daily during RT), followed by TMZ maintenance for 6 cycles at a dose of 150–200 mg/m^2 given on days 1–5 of each 28-day cycle [3]. Almost inevitably, patients with GBM suffer tumor progression even with SOC. With SOC, the Stupp trial showed overall survival (OS) of 14.6 months and progression-free survival (PFS) of 6.9 months [3].

The RT component of postsurgical SOC in newly diagnosed GBM has been extensively examined [3–6]. First, although RT to 54–60 Gy over 6 weeks is standard [3], there have been investigations into shortening the duration of RT in order to minimize adverse events (AEs). A retrospective analysis of concurrent RT + TMZ versus short-course RT + TMZ lasting only 4 weeks in patients of 65 years or more, showed no difference in OS, with reduced neurologic toxicity and improved Karnofsky Performance Status (KPS) score [4]. For elderly patients 65 years or older, the addition of TMZ to a short-course RT resulted in longer survival than short-course RT alone and with equivalent toxicities [7]. Second, the timing of RT after surgery has been examined. A study demonstrated that delaying RT beyond 4 weeks after surgery was beneficial, with a 36% improvement in median OS [6]. Updated

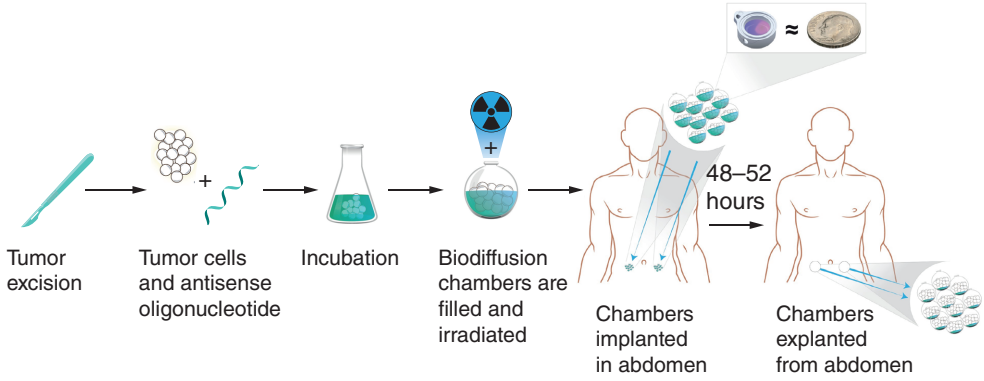

Figure 1. The Goldspire™ platform. Imvax's proprietary platform, used to produce IGV-001.

results in clinical trials using RT and concurrent TMZ suggested that delaying RT for up to 6 weeks did not change the outcome for patients and had no effect on OS [8]. Another study found that delays in RT plus chemotherapy of up to 8 weeks did not influence OS or PFS [5]. Lastly, administering more than 6 cycles of adjuvant TMZ after RT has been shown not to increase OS of patients [9,10]. Therefore, starting RT 6–8 weeks after surgery has not been shown to be detrimental.

Various molecular markers have been identified in GBM, including the isocitrate dehydrogenase (*IDH*) wild-type or mutant, and the DNA repair gene methylguanine-DNA methyltransferase (*MGMT*) [2]. IDH wild-type tumors are more common and have worse clinical outcomes than IDH-mutant tumors [11]. MGMT is another important marker measuring *MGMT* methylation in the promoter region, which is described as either methylated (MGMT+) or unmethylated (MGMT-) [11,12]. Silencing the *MGMT* gene via methylation of the promoter (MGMT+) has been associated with longer survival in GBM, and these tumors may be more sensitive to alkylating drugs such as TMZ [11,13]. Insulin-like growth factor type 1 receptor (*IGF-1R*) is overexpressed in malignant cells, including GBM [14], where it promotes cell growth, cell survival and tumor progression, and is implicated in the pathophysiology of several human cancers [15–18]. IGF-1R leads to activation of the PI3K/Akt and the Ras/Raf/MEK/MAPK signaling pathways [15,16]. IGF-1R signaling protects cancer cells from apoptosis induced by radiation [19,20] and a variety of anticancer drugs [21]. Downregulation of the IGF-1R function provides a selective target for anticancer therapies and antitumor efficacy of IGF-1R inhibition has been demonstrated in preclinical studies [15,22–25].

IGV-001

IGV-001 is the first product developed using Goldspire™, Imvax's proprietary platform (Figure 1). IGV-001 is a cellular immunotherapy combination drug product candidate consisting of a heterogeneous mixture of autologous cells that have been isolated from resected GBM tumor tissue incubated with IMV-001, a single-stranded 18-mer antisense oligonucleotide corresponding to the six codons downstream from the initiating methionine codon of the IGF-1R coding sequence. Through its effects on IGF-1R, which is highly expressed by GBM cells, treatment with IMV-001 may cause stresses on the tumor cells believed to enhance cell death, which is followed by antigen release [26,27]. In addition, IMV-001 has immunostimulatory properties that are expected to activate antigen presentation [28–30]. Dissociated GBM cancer cells treated with IMV-001 are encapsulated in biodiffusion chambers (BDC) of 0.1 µm pore size, and irradiated, to produce IGV-001. The manufactured product is implanted into two abdominal sites of patients (Figure 1), between the rectus sheet and the rectus abdominis muscle, where subcellular tumor antigens and immunostimulatory molecules diffuse out of the BDCs [26,27]. Treatment with IGV-001 occurs within 48 to 52 h of the patient's tumor surgical resection and consists of implantation of the BDCs for 48 to 52 h, when the BDCs are explanted and treatment with IGV-001 is completed [26,27].

IGV-001 leverages a type of regulated death of the autologous cancer cells within the product known as immunogenic cell death. IGV-001 elicits a potent adaptive antitumor immune response against antigens of dying/dead tumor cells in the context of damage-associated molecular pattern (DAMP) immune stimulators

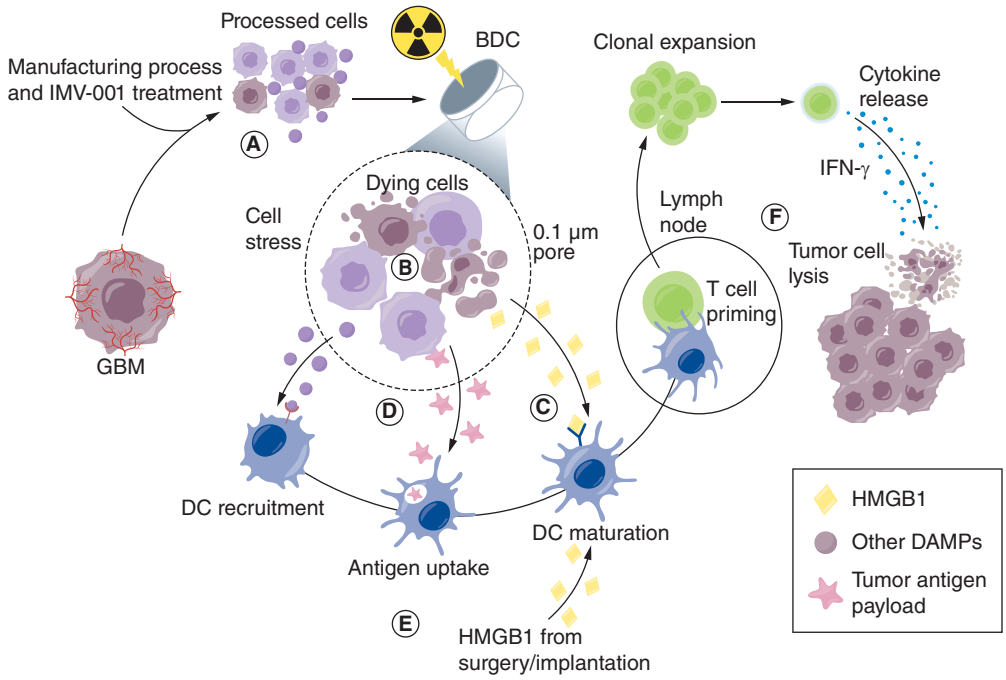

Figure 2. The IGV-001 manufacturing assembly and six-stage mechanism of action. (A) After manufacturing process, combination drug product (IMV-001-treated autologous tumor cells + IMV-001) is placed in BDCs, which are then irradiated and sent to the clinical site for implantation into the abdomen of the patient; **(B)** due to the irradiation, isolated IMV-001 treatment, low-nutrient environment, and inability to adhere inside the BDC, tumor cells are exposed to cellular stresses that ultimately result in cell death; **(C)** HMGB1, and DAMPs produced during ICD, are released from stressed/dying cells inside the BDCs and from the surrounding damaged tissue at the implantation site; **(D)** also released from the BDCs is a tumor antigen payload (<0.1 µm in size); **(E)** DCs are recruited by DAMPs adjuvanticity and mature upon tumor antigen uptake; **(F)** DC-primed T-cells undergo clonal expansion and tumor-antigen specific T-cells kill tumor cells. This figure was created with BioRender.com and then further modified. BDC: Biodiffusion chambers; DAMP: Damage-associated molecular patterns; DC: Dendritic cells; HMGB1: High mobility group box 1; ICD: Immunogenic cell death.

diffusing from the BDCs into the surrounding tissue and in combination with locally generated DAMPs at the implantation site (Figure 2). Specifically, IGV-001 administration is expected to result in the stimulation of an antitumor antigen–specific T cell–dependent immune response and immunologic memory against the autologous antigens on tumor cells (Figure 2). Evidence of immune activation has been observed in preclinical experiments [31,32] and correlative clinical studies [31–34]. Dendritic cell maturation and $CD4^+$ and $CD8^+$ T cell activation and increase in central and effector memory T cells were observed in response to IGV-001 *in vitro*. Together, these data suggest that IGV-001 contributes to the induction of tumor immunity through multiple mechanisms, including the enhancement of antigen production by autologous tumor cells within the product stimulation of antigen presentation, and induction of T cell activation and memory [33–35].

Prior clinical trial experience

An initial phase Ia pilot study of safety and feasibility from a single center (NCT01550523) in patients with malignant astrocytoma demonstrated that IGV-001 is safe and resulted in objective clinical responses in 8 of 12 patients implanted with BDCs [27]. In another single-center phase Ib study, safety and preliminary clinical activity of IGV-001 in patients with newly diagnosed GBM were evaluated (NCT02507583) [26]. Overall, 33 patients were included in the intention-to-treat (ITT) analysis. In this trial, a typical phase I study, 3 + 3 dose-escalation design was not possible as the true active pharmaceutical ingredient was the full antigen payload diffusing out of the BDCs during implantation. Instead, we designed a dose escalation based on four randomized cohorts that were assigned to receive different BDC numbers (i.e., 10 or 20) and the combination product was implanted in the abdominal wall for either 24 or 48 h as follows: cohort 1 (n = 6), 10 BDCs/24 h; cohort 2 (n = 5), 10 BDCs/48 h; cohort 3 (n = 5), 20 BDCs/24 h and cohort 4 (n = 17), 20 BDCs/48 h. Only four AEs (all grade ≤3) were reported as

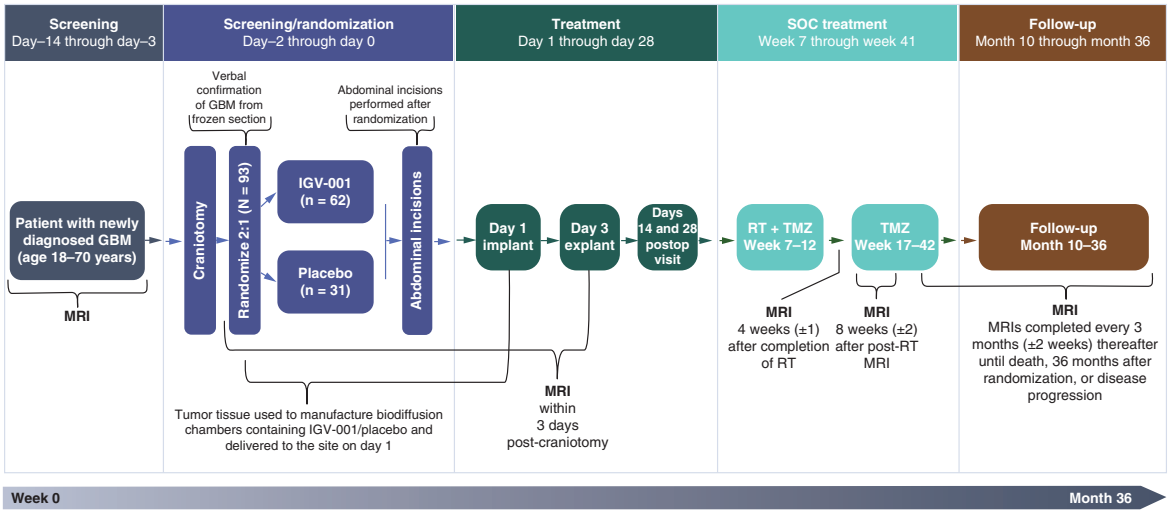

Figure 3. Study design. Schematic of Imvax's phase IIb study (NCT04485949) investigating IGV-001 plus standard of care in patients with newly diagnosed glioblastoma.
GBM: Glioblastoma; RT: Radiotherapy; SOC: Standard of care; TMZ: Temozolomide.

related to IGV-001 as follows: elevated alanine aminotransferase (grade 3) and aspartate aminotransferase (grade 3) in the same patient in cohort 4; fever (grade 1) in one patient in cohort 3; and incontinence (grade 1) in one patient in cohort 4. There were five AEs (all grade ≤3) related to the surgical procedure for IGV-001 placement: 4 hematomas and one wound complication. These complications were managed conservatively with observation or initiation of standard medical management. There were no documented abdominal wound infections. There were 26 deaths during the study; no death was attributed to IGV-001 or to the surgical procedure. IGV-001 appeared to be generally well tolerated; none of the patients had events of autoimmunity or morbidities associated with cytokine release syndrome. In this phase Ib study, median PFS across all four dose cohorts in 33 evaluable patients receiving IGV-001 was 9.8 months, and median OS was 17.3 months. The median PFS of 9.8 months compared favorably with SOC arms of published studies (median PFS of 6.5 months; p = 0.0003) [36–38]. For the high-dose cohort (20 chambers for 48 h, n = 17), median PFS was 10.4 months and for the Stupp-eligible subgroup of the high-dose cohort (n = 10), median PFS was 17.1 months [26]. OS was longest in patients who received the highest exposure of IGV-001 (cohort 4; median OS of 21.9 months; 2-year OS rate of 44%). Some patients have responded with long-term regression of tumors after TMZ/RT with associated high KPS scores. Tumor antigens in primary newly diagnosed and resected GBM include a modest number of mutations, tumor-specific proteins, and posttranslationally modified antigens, indicating that GBM is a low mutational burden tumor. Additional mutations emerging after treatment with radiotherapy and chemotherapy are unlikely to be required for tumor growth. Anecdotally, in the earlier phase Ib study, preparation of a second fresh product from resected recurrent disease, after treatment with radiotherapy and chemotherapy, did not appear to be as effective as primary product.

Collectively, these data indicate an exposure-response relationship and support the use of 20 BDCs for 48 h for IGV-001 treatment. In the phase Ib study, ten patients eligible for RT and TMZ were treated with the highest dose of IGV-001 had a PFS 10.6 months longer and an OS 22.0 months longer compared with historical controls [36–38]. IGV-001 was granted its Orphan Drug Designation by US FDA in October 2017 and designated an orphan medicinal product by the European Medicines Agency in August 2018.

Study design & treatment

The trial (NCT04485949; Imvax protocol number 14379-201 [version 6.0], 13 February 2023) is a multicenter, randomized, double-blind, placebo-controlled phase IIb study investigating the safety and efficacy of IGV-001 plus SOC (RT and TMZ treatments) versus placebo plus SOC in patients with newly diagnosed GBM (Figure 3). Patients will be randomized 2:1 to either receive IGV-001 at the highest exposure evaluated in the phase Ib study (16–20 BDCs) or placebo for 48 to 52 h and will be stratified by age groups (≤50 years vs >50 years at randomization). Patients should have a diagnosis of malignant glioma based on the treating neurosurgeon's best clinical judgment, defined using the patient's symptomology, MRI scan results, and confirmation of malignant

Table 1. Primary and secondary study end points.

Primary end points	Secondary end point	Tertiary end points	Exploratory end points	Safety end point
Compare PFS in newly diagnosed patients with GBM treated with IGV-001 with that of patients treated with placebo	Compare OS in patients treated with IGV-001 with that of patients treated with placebo	Compare patients treated with IGV-001 with patients treated with placebo for: • Time to deterioration of KPS score • PFS • OS within subgroups of patients with methylated MGMT+ and unmethylated MGMT- • PFS, OS within the subgroup of patients with histologic confirmation of WHO Grade 3 (diffuse astrocytic glioma, IDH wild-type, with molecular features of WHO Grade 4 GBM) or WHO Grade 4 GBM	Compare patients treated with IGV-001 with patients treated with placebo for: • Change in QOL • Immune response markers • Response rate in patients who have measurable residual disease after surgery • Tumor mutational burden	Determine safety and tolerability of IGV-001 in patients with newly diagnosed GBM

GBM: Glioblastoma; IDH: Isocitrate dehydrogenase; KPS: Karnofsky Performance Status; MGMT: Methylguanine-DNA methyltransferase; OS: Overall survival; PFS: Progression-free survival; QOL: Quality of life.

glioma from intraoperative frozen section. Neurosurgeons will perform craniotomy to perform a maximally safe resection of tumor and harvest tumor tissue for processing and preparation of a BDC, epigenetic and tumor proliferation analysis, and next-generation sequencing (NGS). Methylguanine-DNA methyltransferase methylation analysis and NGS brain tumor panels take at least 2 weeks to process after craniotomy; therefore, epigenetic features and NGS mutational features cannot be used as stratification variables. Abdominal incisions can be made during craniotomy (day 2) or on the day of implantation (day 1) according to the neurosurgeon's discretion. All randomized patients will receive 16–20 BDCs, regardless of the extent of resection (gross, subtotal, or partial). For patients randomized to the IGV-001 treatment group, the BDCs will contain the active study components. For patients randomized to the placebo group, the BDCs will contain placebo (inactive solution without tumor cells or oligonucleotide). The appearance of the chambers containing placebo or active study components will match to ensure blinding. The BDCs will be implanted in the patients' abdominal wall (between the rectus abdominis muscle and fascia) on day 1 (corresponding to postoperative day 2) and will be explanted at 48 (+4) h of implantation. Patients may be discharged after study drug explantation, per investigator decision, and will return for a postsurgery visit on day 14 (±2 days) and day 28 (±2 days).

The study consists of the following five periods: (i) screening period (from the day of signing informed consent [up to 14 days before randomization] to the time of randomization); (ii) treatment period (from the time of randomization to the day before the first day of SOC therapy at week 7 [±1 week]); (iii) SOC treatment period (from the first day of starting SOC therapy until the last day of the TMZ maintenance cycle, including 6 weeks of RT and TMZ combination therapy and, 4 weeks later, 6 28-day cycles of oral TMZ maintenance therapy [totaling ~34 weeks]); (iv) follow-up period (from the day after SOC treatment or early termination [ET] to 36 months after randomization) and (v) long-term survival (all randomized patients who complete the follow-up period will be followed for long-term survival every 3 months [±2 weeks] until death). ET is defined as any patient who withdraws early from the study. An ET visit (±1 week) must be completed if a patient withdraws early except for those who withdraw consent.

Objectives

End points are summarized in Table 1. The primary efficacy objective is to compare median PFS in patients with newly diagnosed GBM treated with IGV-001 or placebo. Patients on placebo are assumed to have a median PFS of 6.5 months compared with a hypothesized median PFS of 13.0 months for patients on IGV-001. The secondary efficacy objective is a comparison of median OS (assumed 14.6 months for patients on placebo and 29.2 months for patients on IGV-001). Tertiary objectives include the following: (i) time to deterioration of KPS score, (ii) PFS and OS within subgroups of patients with MGMT+ and MGMT- and (iii) PFS and OS within the subgroup of patients with histologic confirmation of the WHO Grade 3 (diffuse astrocytic glioma, IDH wild-type, with molecular features of WHO Grade 4 GBM) or WHO Grade 4 GBM. Exploratory efficacy objectives are to compare patients treated with IGV-001 with those treated with placebo for the following variables: (i) change in quality of

Table 2. Study sites actively enrolling.

State	Site
Florida	Mayo Clinic-Jacksonville
Massachusetts	Tufts Medical Center
Michigan	Henry Ford Health System
New Hampshire	Dartmouth Hitchcock Medical Center
New Jersey	Jersey Shore University Medical Center
New York	Columbia University Medical Center
	Lenox Hill Hospital
	Memorial Sloan-Kettering Cancer Center
	Montefiore Medical Center
	Mount Sinai
	North Shore University Hospital
	Weill Cornell Medicine
	Westchester Medical Center
North Carolina	University of North Carolina
Ohio	Ohio State University
	University of Cincinnati Medical Center
Pennsylvania	Penn State Medical Center
	Thomas Jefferson University
	University of Pennsylvania
Rhode Island	Rhode Island Hospital
West Virginia	West Virginia University
Wisconsin	University of Wisconsin-Madison

life (QOL), (ii) immune response markers, (iii) response rate in patients who have measurable residual disease after surgery and (iv) tumor mutational burden. Safety objectives are to determine safety and tolerability of IGV-001 in patients with newly diagnosed GBM and summarize treatment-emergent AEs using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI CTCAE, v5.0).

Methods

This study enrolls patients with newly diagnosed GBM and is being conducted in 22 sites in USA (Table 2). Enrollment began in March/April 2023.

Key inclusion criteria

- Adult aged ≥18 and ≤70 years at screening;
- KPS score ≥70 at screening;
- Diagnosis of GBM (histologic and/or WHO Grade 4 molecular diffuse astrocytoma) based on the treating neurosurgeon's best clinical judgment defined using the patient's symptomology, MRI scan results and intraoperative frozen section verbal confirmation of malignant glioma. Verbal confirmation is defined as the pathologist's interpretation of the initial result from the flash-frozen section as malignant glioma during craniotomy and verbally shared with the neurosurgeon according to SOC at the institution;
- Diagnostic contrast-enhanced MRI scan with fluid-attenuated inversion recovery sequence of the brain and thin cuts (1–1.5 mm) at screening. Patients must have a resectable contrast-enhancing lesion preoperatively with a total biperpendicular product of 4 cm^2 in two different planes (axial, sagittal, or coronal);
- Tumor location in the supratentorial compartment;
- Acceptable laboratory parameters and adequate bone marrow and organ function.

Key exclusion criteria

- Bihemispheric disease, multicentric disease, or disease burden involving the brainstem or cerebellum based on MRI after gadolinium enhancement;
- Any previous surgical resection or any anticancer intervention for GBM;

- Recurrent glioma, a concurrent malignancy, or malignancy within 3 years of randomization, unless definitive therapy is completed, with the exception of basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma *in situ* of the cervix or breast for which curative therapy has been completed;
- Any severe immunocompromised condition (e.g., HIV with a $CD4^+$ cell count $<200 \times 10^6$/l) or any active uncontrolled autoimmune disease (e.g., Crohn's disease);
- Clinically significant cardiac disease or a history of cardiac dysfunction;
- Receipt of any other investigational agent(s) or of an investigational agent within 30 days or 5 half-lives of investigational agent use, whichever is longer, before screening.

Interventions

Patients will be implanted with BDCs containing IGV-001 or placebo on day 1 and explanted with IGV-001 or placebo on day 3 (48 h after implantation plus a window of 4 h). 20 BDCs will be the target; but if 20 BDCs are not available for implantation, as few as 16 BDCs can be implanted into the patient if the total viable cells in all the available BDCs are not less than 2×10^6 cells/dose. 6 weeks after randomization, patients will receive RT (54–60 Gy total dose delivered as 2 Gy per fraction) per institutional standards for 5 days per week along with TMZ (75 mg/m^2 orally) once daily for 6 weeks. 4 weeks after completion of RT, patients will receive TMZ maintenance (150–200 mg/m^2 orally) on days 1–5 of each 28-day cycle for 6 cycles (week 41). Corticosteroids may be administered at the treating physician's discretion.

Outcomes

The primary outcome is PFS, defined as the time from randomization to event or censoring, as determined by independent central radiology review blinded to study treatment arm. Secondary outcome is OS, defined as the time from randomization to death due to any cause. Tertiary efficacy objectives are time to deterioration of KPS score, defined as KPS score <70 over two consecutive visits at least 4 weeks apart; PFS and OS in patients with MGMT with methylation (MGMT+) and MGMT without methylation (MGMT-), in whom MGMT status will be determined per epigenetic analysis of tissue obtained during surgery and PFS and OS within the subgroup of patients with histologic confirmation of WHO Grade 3 (diffuse astrocytic glioma, IDH wild-type, with molecular features of WHO Grade 4 GBM) or WHO Grade 4 GBM. Safety and tolerability of the study procedures are graded according to NCI CTCAE, v5.0. The timeline for patient participation will be up to 48 months.

Planned sample size, study period & data collection

The study will enroll approximately 93 patients with 2:1 randomization to IGV-001 (≈62 patients) and placebo (≈31 patients). The study opened to accrual in March of 2023 and recruitment is ongoing.

Assessment of disease progression will be conducted by the blinded central radiology review group based on MRI criteria from RANO [39]. In addition, if patients show disease progression on an MRI scan within the first year after randomization, a second MRI will be obtained and compared with the index scan for confirmation of progression. Between craniotomy and initiation of SOC treatment, an MRI scan will be obtained postoperatively (within 3 days). During this period, RANO criteria will determine disease progression and physician judgment will be used to determine whether a patient may proceed to the SOC treatment period. 4 weeks after completion of RT (≈week 17), an MRI scan should be performed, followed by additional MRI scans 8 weeks and 20 weeks later. Subsequent MRI scans should then be performed every 3 months thereafter until death, 36 months after randomization, or disease progression. The first post-RT MRI scan (≈week 17) during the SOC treatment period will be used as the index measurement for comparison with future MRI scans.

Statistical methods

The ITT analysis and safety analysis sets are defined as all randomized patients. The primary efficacy end point is PFS, defined as the time from randomization to first progression as determined by central radiology review, blinded to the study treatment arm, or death. Tumor progression will be assessed by blinded central radiology review based on MRI criteria from RANO. Patients alive and without progression will be censored at the date of their last tumor assessment. PFS will be analyzed using the product-limit method. Treatment groups will be compared using a stratified log-rank test. Patients will be stratified according to the stratification factor used for the randomization. Statistical tests will use a one-sided significance level of $\alpha = 0.05$. The analysis of the primary end point PFS will be performed when at least 55 events in the ITT analysis set have been observed per blinded central radiology review.

Secondary efficacy end point is OS. At the time of final analysis of PFS, continued follow-up is expected for OS. Approximately 36 months after randomization of the last patient, the final analysis for OS will be performed using a stratified log-rank test and a one-sided 0.05 significance level. The significance level for OS will be adjusted using the Benjamini-Hochberg approach [40] to maintain the one-sided 0.05 significance level.

Tertiary efficacy objectives will have multivariate analyses performed using the Cox proportional hazards model for PFS and OS to determine independent prognostic factors. The covariates evaluated for the multivariate models will be the assigned treatment group; age group; MGMT methylation status (MGMT+ or MGMT-); histologic confirmation of either WHO Grade 3 (diffuse astrocytic glioma, IDH wild-type, with molecular features of WHO Grade 4 GBM), WHO Grade 4 GBM, or diffuse astrocytoma; IDH-mutated, with any histologic feature of GBM and/or a *CDKN2A/B* mutation; and extent of resection (gross, subtotal, or partial). Medically determined KPS scores will be analyzed over time using descriptive statistics. Time to deterioration of the KPS score will be analyzed using the product-limit method.

Exploratory efficacy objectives include change in QOL, immune response markers, response rate in patients who have measurable residual disease after surgery and tumor mutational burden. QOL will be measured using the EORTC QLQ-C30 and QLQ-BN20. These measurements will be performed at the time of PFS and OS analyses and before any study procedures on the day of visit. Overall response rate (ORR) will be assessed only in patients with measurable residual disease identified on the first postoperative MRI scan. ORR is defined as the proportion of patients with a partial or complete response by the RANO criteria and evaluated by blinded central radiology review. ORR will be evaluated at the time of PFS analysis.

Safety will be reported as the incidence of procedure-related AEs and treatment-emergent AEs from the time of randomization and will be graded according to the NCI CTCAE, v5.0. AEs and serious AEs will be reported. They will also be reported separately for the screening period, the treatment period, and the SOC treatment period until the 30-day safety visit.

Given that histologic grade 3 diffuse astrocytomas represent 10% of malignant gliomas, sensitivity analyses are planned to examine the impact of grade 3 diffuse astrocytomas on the robustness of the treatment effect.

The sample size calculation is based on the primary efficacy end point of PFS. It is assumed that the hazard ratio for PFS of the IGV-001 treatment in combination with SOC therapy over placebo in combination with SOC therapy is 0.5 (translating to an improvement in median PFS from 6.5 months in the placebo group to 13 months in the IGV-001 group). The hazard ratio is derived from the phase Ib result observed (median PFS of 17.1 months) in the high-dose cohort subset of patients who would be eligible for this phase IIb study. The study is designed to achieve 80% power at a one-sided α of 0.05 to detect a statistically significant difference in PFS between the treatment groups. A total of 55 PFS events in the ITT analysis set is required. Assuming an accrual period of $\approx$7 months, a 7% yearly rate for loss to imaging follow-up, and 2:1 randomization, approximately 93 patients will be randomized to observe the 55 PFS events in the ITT analysis set by 11–12 months after the last patient is randomized into the study.

Conclusion

In patients with GBM, targeting the patient's malignant cells with IGV-001 followed by SOC provides an opportunity to enhance antitumor response beyond the current SOC. The rationale for the IGV-001 approach is supported by *in vitro* and *in vivo* studies showing enhancement of tumor antigens diffusing from the BDC, stimulation of antigen presentation and generation of adaptive antitumor immune responses. Pro- and anti-inflammatory serum cytokines as potential predictors of PFS and OS are being evaluated. Based on encouraging results from the completed phase Ib study in newly diagnosed GBM, IGV-001 is generally well tolerated without immune-related AEs typical of other immunotherapies. IGV-001 is expected to have no off-target effects and yield minimal safety signals while delivering a meaningful antitumor response, supporting the conduct of the present phase IIb study of IGV-001 in patients with newly diagnosed GBM.

Executive summary

IGV-001
- Personalized, whole tumor–derived immunotherapy targeting a broad antigenic signature of the patient's tumor.
- Contains irradiated autologous glioblastoma tumor cells obtained from resected tumor tissue and insulin-like growth factor type 1 receptor (IGF-1R) antisense IMV-001.
- Induction of tumor immunity through multiple mechanisms that include innate and adaptive immune responses against the tumor.

IMV-001
- Treatment with antisense of IGF-1R serves as an additional stressor to the autologous tumor cells in the IGV-001 product to aid cell death.

Biodiffusion chambers
- Rapid, overnight tumor cell processing of IGV-001 manufacturing facilitates integration into the radiotherapy plus temozolomide standard of care (SOC) regimen.
- Biodiffusion chambers have a subcellular pore size that allows diffusion of tumor antigens and immunostimulatory molecules, but not intact tumor cells.

Study rationale
- IGV-001 administration stimulates tumor antigen–specific T cell–dependent immune response and immunologic memory against the autologous tumor cell antigens.
- In a phase Ib study (NCT02507583), IGV-001 was well tolerated and provided extended progression-free survival and overall survival versus historical controls.

Study design
- Randomized, double-blind, placebo-controlled phase IIb trial (NCT04485949) evaluating IGV-001 compared with placebo, both followed by SOC treatments in patients with newly diagnosed glioblastoma.

Primary study objectives/end points
- The primary end point of this phase IIb trial is progression-free survival, and key secondary end points include overall survival and safety in patients treated with IGV-001 and SOC compared with those treated with placebo and SOC.

Author contributions

The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and have approved the final version.

Financial & competing interests disclosure

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Competing interests disclosure

V Agarwal reports a leadership role in the board of Alpheus Medical and holds stock options of Alpheus Medical. DW Andrews is an employee of Imvax with a leadership role, holds stock/stock options of Imvax, and has patents at Imvax. S Aulakh reports honoraria received from Caris Life Sciences, Novocure, and Ono Pharmaceutical. JA Boockvar has nothing to disclose. C Brennan has nothing to disclose. CE Silva Correia has nothing to disclose. M Diwanji is an employee of and holds stock/stock options of Imvax. JB Elder reports consulting fees from Medtronic and participation on data safety monitoring board for the GLIOX trial; holds stock options of Johnson & Johnson. LT Evans reports grants/contracts from the National Institutes of Health and from the National Institute of Biomedical Imaging and Bioengineering, with payment from Zeiss. BJ Gill has nothing to disclose. S Hanft reports institutional support for attending national meetings of the American Association of Neurological Surgeons, the Cognitive Neuroscience Society, and the Society for Neuro-Oncology. KD Judy reports clinical trial grant support from Imvax, consulting fees from Kiyatec, honoraria from The Johns Hopkins Hospital and the Neurosurgery Grand Rounds, and reports unpaid leadership role at the Council of State Neurological Societies as chair of the Northeast Region. IY Lee reports grants/contracts from StacheStrong; consulting fees from Medtronic, Monteris, and Medexus Pharmaceuticals; honoraria from Monteris and Medtronic; travel expenses for speaking engagement from Monteris; and participation on an advisory board for Medexus Pharmaceuticals. GK Pennock is a consultant to Imvax. R Perez-Olle is an employee of and holds stock/stock options of Imvax and advisor to Cancer 101. A Quiñones-Hinojosa has nothing to disclose. R Ramakrishna is the founder of and holds stock options of the educational platform Roon.com. M Schulder reports consulting fees from Hyperfine; honoraria from Varian, Zeiss, and Medtronic; support for attending meetings from Brainlab, Radionics, and Medtronic; participation on data safety monitoring board or advisory boards

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Ethical conduct of research

The authors state that they obtained appropriate institutional review board approval and followed the principles outlined in the Declaration of Helsinki for all human experimental investigations. In addition, informed consent was obtained from the patients involved.

Open access

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Ostrom QT, Bauchet L, Davis FG *et al.* The epidemiology of glioma in adults: a "state of the science" review. *Neuro. Oncol.* 16(7), 896–913 (2014).
2. Thakkar JP, Dolecek TA, Horbinski C *et al.* Epidemiologic and molecular prognostic review of glioblastoma. *Cancer Epidemiol. Biomarkers Prev.* 23(10), 1985–1996 (2014).
3. Stupp R, Mason WP, van den Bent MJ *et al.*; for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N. Engl. J. Med.* 352(10), 987–996 (2005).

•• **Provides the treatment guidelines for the treatment of patients with glioblastoma.**

4. Minniti G, Scaringi C, Lanzetta G *et al.* Standard (60 Gy) or short-course (40 Gy) irradiation plus concomitant and adjuvant temozolomide for elderly patients with glioblastoma: a propensity-matched analysis. *Int. J. Radiat. Oncol. Biol. Phys.* 91(1), 109–115 (2015).
5. Louvel G, Metellus P, Noel G *et al.* Delaying standard combined chemoradiotherapy after surgical resection does not impact survival in newly diagnosed glioblastoma patients. *Radiother. Oncol.* 118(1), 9–15 (2016).
6. Blumenthal DT, Won M, Mehta MP *et al.* Short delay in initiation of radiotherapy may not affect outcome of patients with glioblastoma: a secondary analysis from the radiation therapy oncology group database. *J. Clin. Oncol.* 27(5), 733–739 (2009).
7. Perry JR, Laperriere N, O'Callaghan CJ *et al.* Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma. *N. Engl. J. Med.* 376(11), 1027–1037 (2017).
8. Blumenthal DT, Won M, Mehta MP *et al.* Short delay in initiation of radiotherapy for patients with glioblastoma-effect of concurrent chemotherapy: a secondary analysis from the NRG Oncology/Radiation Therapy Oncology Group database. *Neuro. Oncol.* 20(7), 966–974 (2018).
9. Blumenthal DT, Gorlia T, Gilbert MR *et al.* Is more better? The impact of extended adjuvant temozolomide in newly diagnosed glioblastoma: a secondary analysis of EORTC and NRG Oncology/RTOG. *Neuro. Oncol.* 19(8), 1119–1126 (2017).
10. Gramatzki D, Kickingereder P, Hentschel B *et al.* Limited role for extended maintenance temozolomide for newly diagnosed glioblastoma. *Neurology* 88(15), 1422–1430 (2017).
11. Sareen H, Ma Y, Becker TM, Roberts TL, de Souza P, Powter B. Molecular biomarkers in glioblastoma: a systematic review and meta-analysis. *Int. J. Mol. Sci.* 23(16), 8835 (2022).
12. Hegi ME, Genbrugge E, Gorlia T *et al. MGMT* promoter methylation cutoff with safety margin for selecting glioblastoma patients into trials omitting temozolomide: a pooled analysis of four clinical trials. *Clin. Cancer Res.* 25(6), 1809–1816 (2019).
13. Hegi ME, Diserens AC, Gorlia T *et al.* MGMT gene silencing and benefit from temozolomide in glioblastoma. *N. Engl. J. Med.* 352(10), 997–1003 (2005).

14. Maris C, D'Haene N, Trepant AL *et al.* IGF-IR: a new prognostic biomarker for human glioblastoma. *Br. J. Cancer* 113(5), 729–737 (2015).
15. Larsson O, Girnita A, Girnita L. Role of insulin-like growth factor 1 receptor signalling in cancer. *Br. J. Cancer* 92(12), 2097–2101 (2005).
16. Philippou A, Armakolas A, Koutsilieris M. Evidence for the possible biological significance of the *igf-1* gene alternative splicing in prostate cancer. *Front. Endocrinol. (Lausanne)* 4, 31 (2013).
17. Philippou A, Christopoulos PF, Koutsilieris DM. Clinical studies in humans targeting the various components of the IGF system show lack of efficacy in the treatment of cancer. *Mutat. Res. Rev. Mutat. Res.* 772, 105–122 (2017).
18. Scartozzi M, Bianconi M, Maccaroni E *et al.* State of the art and future perspectives for the use of insulin-like growth factor receptor 1 (IGF-1R) targeted treatment strategies in solid tumors. *Discov. Med.* 11(57), 144–153 (2011).
19. Nakamura S, Watanabe H, Miura M, Sasaki T. Effect of the insulin-like growth factor I receptor on ionizing radiation-induced cell death in mouse embryo fibroblasts. *Exp. Cell Res.* 235(1), 287–294 (1997).
20. Turner BC, Haffty BG, Narayanan L *et al.* Insulin-like growth factor-I receptor overexpression mediates cellular radioresistance and local breast cancer recurrence after lumpectomy and radiation. *Cancer Res.* 57(15), 3079–3083 (1997).
21. Dunn SE, Ehrlich M, Sharp NJ *et al.* A dominant negative mutant of the insulin-like growth factor-I receptor inhibits the adhesion, invasion, and metastasis of breast cancer. *Cancer Res.* 58(15), 3353–3361 (1998).
22. Exley MA, Garcia S, Zellander A, Zilberberg J, Andrews DW. Challenges and opportunities for immunotherapeutic intervention against myeloid immunosuppression in glioblastoma. *J. Clin. Med.* 11(4), 1069 (2022).
23. Hartog H, Wesseling J, Boezen HM, van der Graaf WT. The insulin-like growth factor 1 receptor in cancer: old focus, new future. *Eur. J. Cancer* 43(13), 1895–1904 (2007).
24. Ryan PD, Goss PE. The emerging role of the insulin-like growth factor pathway as a therapeutic target in cancer. *Oncologist* 13(1), 16–24 (2008).
25. Sachdev D, Yee D. Disrupting insulin-like growth factor signaling as a potential cancer therapy. *Mol. Cancer Ther.* 6(1), 1–12 (2007).
26. Andrews DW, Judy KD, Scott CB *et al.* Phase Ib clinical trial of IGV-001 for patients with newly diagnosed glioblastoma. *Clin. Cancer Res.* 27(7), 1912–1922 (2021).

•• **Describes the results of the initial single-center phase Ia pilot study (NCT01550523), evaluating safety and feasibility of IGV-001 in patients with malignant astrocytoma. The findings show that IGV-001 is well tolerated, progression-free survival compares favorably with standard of care, and evidence suggests an immune-mediated mechanism.**

27. Andrews DW, Resnicoff M, Flanders AE *et al.* Results of a pilot study involving the use of an antisense oligodeoxynucleotide directed against the insulin-like growth factor type I receptor in malignant astrocytomas. *J. Clin. Oncol.* 19(8), 2189–2200 (2001).

•• **Describes the results of another single-center phase Ib study (NCT02507583), evaluating safety and preliminary clinical activity of IGV-001 in patients with newly diagnosed glioblastoma. The findings show that treatment with IGV-001 induces apoptosis and a host response *in vivo* without unusual side effects. Subsequent transient and sustained radiographic and clinical improvements warrant further clinical investigations.**

28. Fortuna D, Hooper DC, Roberts AL, Harshyne LA, Nagurney M, Curtis MT. Potential role of CSF cytokine profiles in discriminating infectious from non-infectious CNS disorders. *PLoS One* 13(10), e0205501 (2018).
29. Harshyne LA, Hooper KM, Andrews EG *et al.* Glioblastoma exosomes and IGF-1R/AS-ODN are immunogenic stimuli in a translational research immunotherapy paradigm. *Cancer Immunol. Immunother.* 64(3), 299–309 (2015).
30. Morin-Brureau M, Hooper KM, Prosniak M *et al.* Enhancement of glioma-specific immunity in mice by "NOBEL", an insulin-like growth factor 1 receptor antisense oligodeoxynucleotide. *Cancer Immunol. Immunother.* 64(4), 447–457 (2015).
31. Zellander A, Uhl C, Cultrara C *et al.* Personalized immunotherapeutic platform with evidence of clinical activity in glioblastoma protects mice against ovarian liver and bladder cancer tumor challenges. *J. Immunother. Cancer* 10(Suppl. 2), A1113 (Abstract 1398) (2022).

• **This preclinical study shows that the durable antitumor activity of IGV-001 in multiple cancers (ovarian, liver and bladder) is associated with a systemic immunologic response resulting in generation of T helper 1 antitumor cytotoxic T cells.**

32. Zilberberg J, Zellander A, Uhl C *et al.* Personalized immunotherapeutic platform with evidence of clinical activity in glioblastoma (IGV-001) protects mice against other lethal solid tumor challenges. *Cancer Res.* 82(Suppl. 12), Abstract 626 (2022).
33. Uhl C, Zilberberg J, Exley M. Autologous tumor cell immunotherapeutic platform, with evidence of clinical activity in glioblastoma, induces *in vitro* immune responses in both glioblastoma and endometrial cancer. Presented at: *CRI-ENCI-AACR Sixth International Cancer Immunotherapy Conference (CICON).* New York, NY, USA (2022).

• **This preclinical study shows that IGV-001 induces *in vitro* immune responses in glioblastoma cancer cells, including dendritic cell maturation, $CD4^+$ and $CD8^+$ T cell activation, and increases in central effector memory T cells.**

34. Zilberberg J, Zellander A, Kirby K *et al.* 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. *J. Immunother. Cancer* 9(Suppl. 2), A231 (Abstract 218) (2021).

- **This preclinical study shows that IGV-001 generates strong antitumor responses in a glioblastoma mouse model, by stimulating the immune system and suppressing tumor growth.**

35. Cultrara C, Uhl C, Kirby K *et al.* A biologic-device combination product delivering tumor-derived antigens elicits immunogenic cell death-associated immune responses against glioblastoma. *J. Immunother. Cancer* 11(8), e006880 (2023).

- **This preclinical study demonstrates that IGV-001 elicits immunogenic cellular stress, culminating with bona fide immunogenic cell death and the activation of therapeutically relevant, T helper 1–polarized immune responses against glioblastoma.**

36. Chinot OL, Wick W, Mason W *et al.* Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N. Engl. J. Med.* 370(8), 709–722 (2014).

37. Gilbert MR, Dignam JJ, Armstrong TS *et al.* A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N. Engl. J. Med.* 370(8), 699–708 (2014).

38. Stupp R, Hegi ME, Mason WP *et al.*; on behalf of the European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups, the National Cancer Institute of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 10(5), 459–466 (2009).

39. Wen PY, Chang SM, Van den Bent MJ, Vogelbaum MA, Macdonald DR, Lee EQ. Response assessment in neuro-oncology clinical trials. *J. Clin. Oncol.* 35(21), 2439–2449 (2017).

40. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. Series B Stat. Methodol.* 57(1), 289–300 (1995).