Trial in progress: a randomized, multicenter, double-blind, placebo-controlled, phase 2b study to assess the safety and efficacy of IGV-001, an autologous cell immunotherapy with antisense oligonucleotide (IMV-001) targeting IGF-1R, in newly diagnosed patients with glioblastoma

TIPS-18

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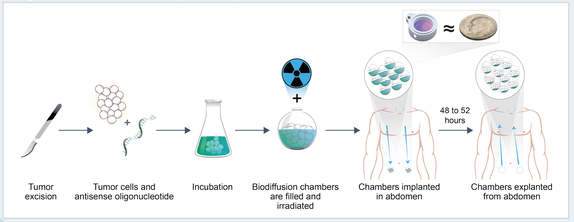
INTRODUCTION

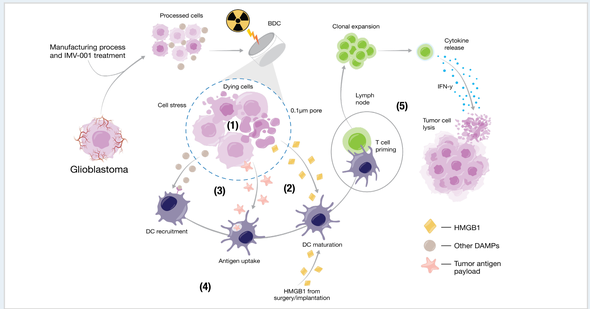
- Standard-of-care (SOC) for first-line therapy in patients with newly diagnosed glioblastoma (GBM) is surgery followed by concurrent radiotherapy (RT) and temozolomide (TMZ) followed by adjuvant TMZ alone as maintenance[1]
- With SOC, overall survival (OS) was 14.6 months and progression-free survival (PFS) was 6.9 months in the Stupp trial[1]
- Insulin-like growth factor type 1 receptor (IGF-1R) is overexpressed in malignant cells, including GBM,[2] where it promotes cell growth, cell survival, and tumor progression, and is implicated in the pathophysiology of several human cancers[3-6]
- IGF-1R leads to activation of the PI3K/Akt and the Ras/Raf/MEK/MAPK signaling pathways[3,4]
- IGF-1R signaling protects cancer cells from apoptosis induced by RT and anticancer drugs[7-9]
- Downregulation of IGF-1R function provides a selective target for anticancer therapies and antitumor activity of IGF-1R inhibition has been demonstrated in preclinical studies[3,10-12]
- IGV-001 is the first product developed using Goldspire™, Imvax's proprietary platform (**Figure 1**)

Figure 1. The Goldspire™ platform



- IGV-001 is a cellular immunotherapy combination drug product 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 6 codons downstream from the initiating methionine codon of the IGF-1R coding sequence
  - Through its effects on IGF-1R, IMV-001 is believed to enhance antigen release and expected to activate antigen presentation (**Figure 2**)[13,14]

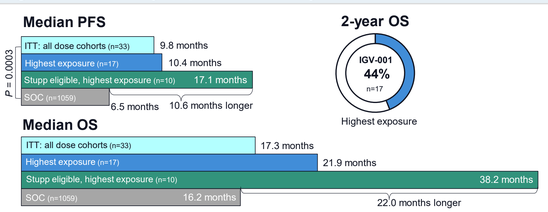
Figure 2. The IGV-001 manufacturing assembly and 5-stage mechanism of action



Processed cells removed at the time of glioblastoma resection are treated with IMV-001 (4 µg per chamber or 80 µg per dose). The combination drug product (IMV-001–treated processed autologous glioblastoma cells plus additional IMV-001) is filled into biodiffusion chambers (BDC), which are then irradiated for implantation into the abdomen of the patient. After implantation, the following stages occur: (1) processed cells undergo cellular stresses that result in cell death owing to irradiation, IMV-001 treatment, a low-nutrient environment, and an inability to adhere inside the BDC; (2) immunostimulatory factors (high mobility group box 1 [HMGB1] and damage-associated molecular patterns [DAMP] are released from stressed/dying cells inside the BDCs and mature local antigen presenting/dendritic cells (DC); (3) the antigens from the dying tumor cells diffuse out of the BDCs (<0.1 µm in size) and are taken up by the antigen presenting DC, while IMV-001 can inhibit immunosuppressive cells; (4) antigen-presenting cells migrate to lymph nodes; (5) where they activate tumor-specific T cells, which proliferate and undergo clonal expansion to promote a long-term adaptive immune response, and tumor antigen–specific T cells kill tumor cells remaining after surgery.

- Evidence of immune activation has been observed in preclinical experiments[15,16] and correlative clinical studies[13]
  - Dendritic cell maturation, CD4+ and CD8+ T-cell activation, and increase in central and effector memory T cells were observed in response to IGV-001 in vitro[13,15,16]
  - IGV-001 contributes to the induction of tumor immunity through multiple mechanisms, including the enhancement of antigen production by autologous tumor cells, inhibition of anti-inflammatory mechanisms, and the stimulation of antigen presentation in the patient (**Figure 2**)[17-19]
- In a phase 1b study (NCT02507583),[13] median PFS and OS compared favorably with SOC arms of published studies (**Figure 3**)[20-22]

Figure 3. Summary of phase 1b study data



IGV-001 was well tolerated and showed an exposure-response relationship, supporting the use, in subsequent clinical studies, of the highest exposure evaluated in the phase 1b study[13]

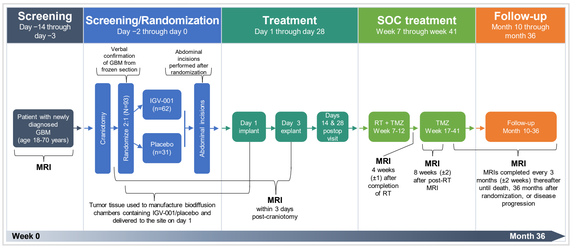
- Here, we describe the design and rationale of a randomized phase 2b study (NCT04485949) evaluating IGV-001 compared with placebo, both followed by SOC treatment in patients with newly diagnosed GBM

METHODS

Study objectives and study design

- The IGV-001 study (NCT04485949) is a multicenter, randomized, double-blind, placebo-controlled phase 2b 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 4**)
- Resected GBM cancer cells treated with IMV-001 are encapsulated in biodiffusion chambers (BDCs) of 0.1 µm pore size, which allow tumor antigens and immune-stimulating molecules but not tumor cells to diffuse, then irradiated, producing IGV-001, which is implanted into 2 abdominal sites (between the rectus abdominis muscle and fascia) of patients for 48 to 52 hours, then explanted (**Figure 1**)
- Patients will be randomized 2:1 to either receive IGV-001 at 16-20 BDCs or placebo for 48 to 52 hours and stratified by age groups (≤50 years vs >50 years at randomization)
  - The BDCs implanted in patients in the placebo group contain inactive solution without GBM tumor cells and without IMV-001
- Six weeks after randomization, patients will receive RT (54-60 Gy total dose delivered as 2 Gy per fraction) per institutional standards (hence per investigators' choice) for 5 days per week along with TMZ (75 mg/m^2 orally) once daily for 6 weeks
- Four 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)

Figure 4. Study design



GBM, glioblastoma; MRI, magnetic resonance imaging; RT, radiotherapy; SOC, standard of care; TMZ, temozolomide.

Table 1. Primary and secondary study endpoints

Primary endpoint	Secondary endpoint	Tertiary endpoints	Exploratory endpoints	Safety endpoint
PFS in patients with newly diagnosed GBM treated with IGV-001 versus patients treated with placebo	OS in patients treated with IGV-001 versus patients treated with placebo	• 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	• 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; WHO, World Health Organization.

Key inclusion criteria

- Adult aged ≥18 and ≤70 years at screening
- Karnofsky Performance Status (KPS) score ≥70 at screening
- Diagnosis of GBM (histologic and/or WHO Grade 4 molecular diffuse astrocytoma) with confirmation from intraoperative frozen section
- Diagnostic contrast-enhanced magnetic resonance imaging (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 2 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

Study endpoints

- Endpoints are summarized in **Table 1**
- The primary outcome is PFS, defined as the time from randomization to event or censoring, as determined by blinded central radiology review
- Secondary outcomes include OS, defined as the time from randomization to death due to any cause, and safety

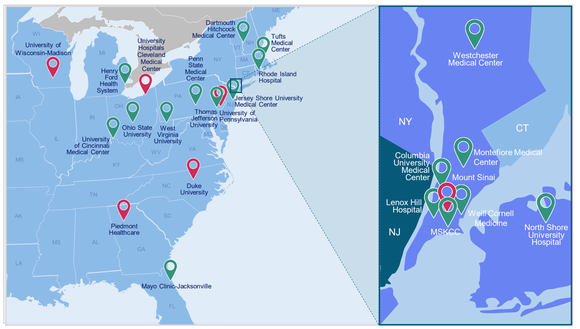
Statistical methods

- The intention-to-treat (ITT) analysis and safety analysis sets are defined as all randomized patients
- The analysis of the primary endpoint PFS will be triggered when ≥55 PFS events in the ITT analysis set have been observed per blinded central radiology review, based on Response Assessment in Neuro-Oncology (RANO) criteria,[23] and will be performed using a stratified log-rank test and a 1-sided 0.05 significance level
- The study is designed to achieve 80% power at a 1-sided α of 0.05 to detect a statistically significant difference in PFS between groups
  - Assuming an accrual period of ~7 months, a 7% yearly rate for loss to imaging follow-up, and 2:1 randomization, approximately 93 patients will be randomized to observe 55 PFS events in the ITT analysis set by 11-12 months after the last patient is randomized
- Approximately 36 months after randomization of the last patient, the final analysis of OS will be performed using a stratified log-rank test and a 1-sided 0.05 significance level, adjusted using the Benjamini-Hochberg approach[24]
- 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, 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)
- KPS score will be analyzed over time using descriptive statistics. Time to deterioration of the KPS score will be analyzed using the product-limit method
- Safety will be reported as the incidence of procedure-related adverse events and treatment-emergent adverse events from the time of randomization and will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0
  - Safety data will be reported overall as well as separately for the screening period, the treatment period, and the SOC treatment period until the 30-day safety visit

STATUS

- The study is ongoing and is planned for approximately 25 centers in the United States (**Figure 5**)
- As of July 7th , there are 18 open sites

Figure 5. Anticipated study locations



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