CTIM-11

Long-term Survivors From a Phase 1b Study of IGV-001 in Patients With Newly Diagnosed Glioblastoma

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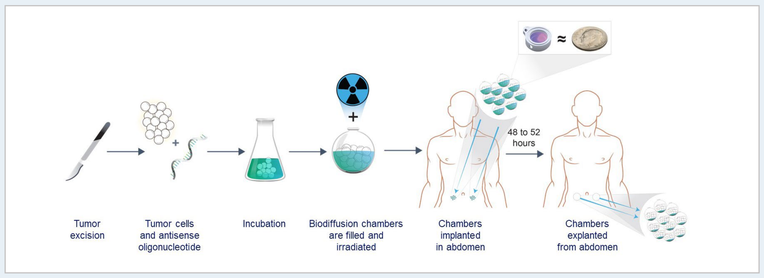
INTRODUCTION

- 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]
- In GBM, an important marker is methylation in the promoter region of the DNA repair enzyme O^6-methylguanine DNA methyltransferase (MGMT), creating either methylated (MGMT+) or unmethylated (MGMT−). MGMT+ tumors are more sensitive to some chemotherapy drugs such as TMZ[2]
- Insulin-like growth factor type 1 receptor (IGF-1R) is overexpressed in malignant cells, including GBM,[3] where it promotes cell growth, cell survival, and tumor progression, and is implicated in the pathophysiology of several human cancers[4-7]
- IGV-001 is the first product developed using Goldspire®, Imvax's proprietary platform (**Figure 1**)

Figure 1. The Goldspire® Platform

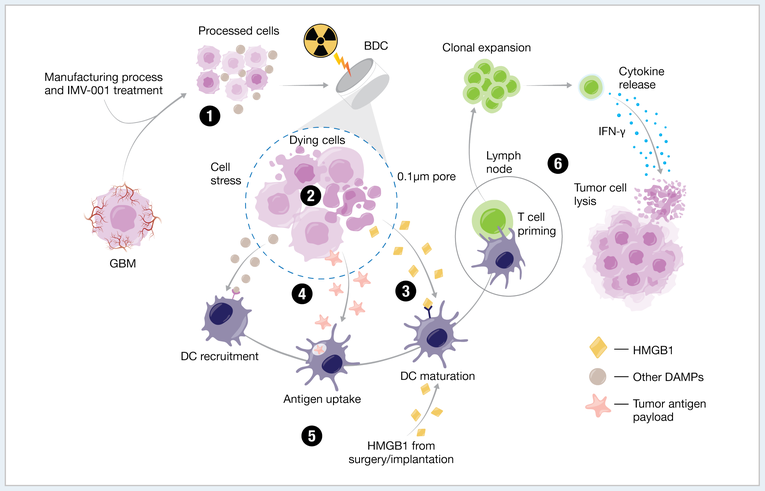
Resected glioblastoma cancer cells treated with IMV-001 are encapsulated in biodiffusion chambers (BDC) of 0.1 µm pore size, which allow tumor antigens and immune-stimulating molecules but not tumor cells to diffuse. BDCs are irradiated, producing IGV-001, which is implanted into 2 abdominal sites (between the rectus abdominis muscle and fascia) of patients for 48 to 52 hours, then explanted.



- IGV-001 can induce cellular stresses on GBM cells in the product, resulting in immunogenic cell death and consequent antitumor immunity[8]
- Antigens from dying/dead tumor cells, IMV-001, and damage-associated molecular patterns (DAMP) immune stimulators diffuse from the BDCs into the surrounding tissue and combine with locally generated DAMPs at the implantation site to train the immune system to generate tumor-specific T-cell responses that reduce/eliminate tumor burden (**Figure 2**)[8,9]

Figure 2. The IGV-001 Manufacturing Assembly and 6-Stage Mechanism of Action

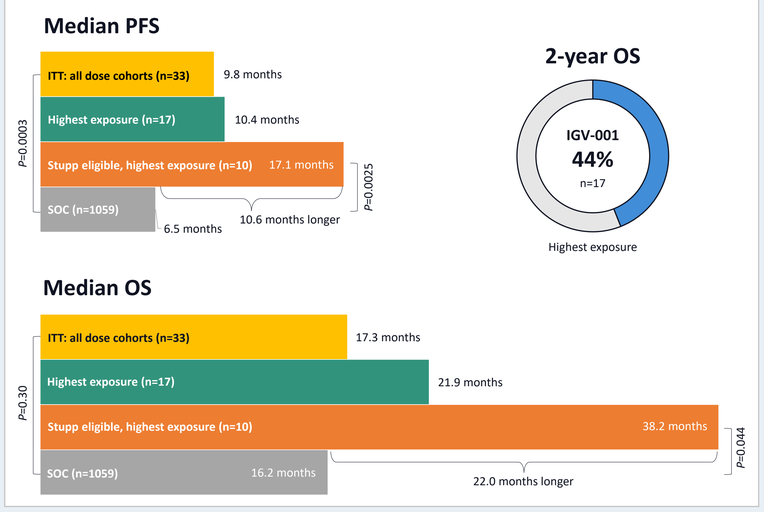
Processed cells removed at the time of GBM resection are treated with IMV-001. Specifically, the following stages occur: (1) after the manufacturing process (which takes approximately a half day), combination drug product (IMV-001–treated autologous tumor cells plus additional IMV-001) is placed in BDCs, which are then irradiated and sent to the clinical site for implantation into the abdomen of the patient; (2) 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; (3) high mobility group box 1 (HMGB1), and DAMPs produced during immunogenic cell death, are released from stressed/dying cells inside the BDCs and from the surrounding damaged tissue at the implantation site; (4) also released from the BDCs is a tumor antigen payload (<0.1 µm in size); (5) dendritic cells (DC) are recruited by DAMPs adjuvanticity and mature upon tumor antigen uptake; and (6) DC-primed T cells undergo clonal expansion and tumor antigen-specific T cells kill tumor cells.



IFN-γ, interferon gamma.

- The phase 1b study (NCT02507583) enrolled 33 patients in 4 different cohorts implanted with 10 or 20 BDCs for 24 or 48 hours[10]
- IGV-001 was well tolerated and showed an exposure-response relationship in patients with newly diagnosed GBM (ndGBM; **Figure 3**),[10] supporting the use of the highest exposure evaluated in the phase 1b study in subsequent clinical studies
- In previous studies, patients had significant changes in immune response biomarkers[11-13]

Figure 3. Summary of Phase 1b Study Data[10]



ITT, intent to treat; OS, overall survival; PFS, progression-free survival.

- Here, we report additional data from long-term survival in this phase 1b study

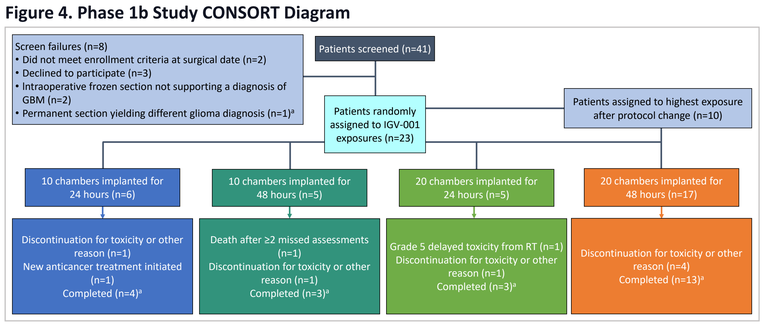
METHODS

- This phase 1b trial was a randomized, single-center, open-label study designed to assess the safety, tolerability, and preliminary efficacy of IGV-001 in patients with ndGBM. Study design, eligibility criteria, treatment plan, and statistical analyses were detailed in a prior publication[10]

Patients and Study Design

- Patients ≥18 years of age with a radiographic diagnosis of unifocal, multifocal, or bihemispheric GBM were enrolled
- A Karnofsky Performance Status (KPS) score of ≥60 or Eastern Cooperative Oncology Group performance status of 1, 2, or 3 were required
- Patients had to have a positive anergy panel (≥1 antigen)
- Exclusion criteria included an active second primary malignancy under treatment, or a major concomitant medical illness, including any autoimmune disorder
- Trial design involved randomization to 1 of 4 IGV-001 cohorts as outlined in **Figure 4**

Figure 4. Phase 1b Study CONSORT Diagram



[a]Patients with disease progression, 2 years of follow-up, or death.

Procedures and Assessments

- Magnetic resonance imaging (MRI) was performed within 14 days before surgery and at postoperative time points up to ≥24 months. KPS scores and steroid use were documented at MRI time points. Radiographic interpretations of MRI scans were performed by neuroradiologists blinded to patients' clinical status and corticosteroid dosage
- Radiographic responses were based on Response Assessment in Neuro-Oncology (RANO)[14] and immunotherapy RANO (iRANO)[15] criteria
- Time to progression was assessed from date of surgery to date of the first observation of objective disease progression measured by MRI and confirmed by an independent radiology review committee
- PFS was measured from date of surgery to progression or censoring; OS was the time between date of surgery and latest follow-up or death. Patients withdrawn from study were followed for OS
- Adverse events (AE) and serious AEs were recorded from chamber implantation until 30 days after study exit, for a minimum of 6 weeks after treatment. AEs were categorized and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

Statistical Analysis

- T-cell receptor sequencing (TCRseq) was performed on the long-term survivor subset of patients' PBMCs
  - Patient TCR clonal populations and dynamics across 3 time points were analyzed as follows: before surgery/BDC implantation, after implantation when the immune system would be highly activated, and after SOC when fewer T cells and lower IFN-γ production are seen
  - DNA was isolated from banked patient peripheral blood mononuclear cells (PBMC) and sent to Adaptive Biotechnologies (Seattle, WA) using the ImmunoSEQ platform
- The ITT population included all enrolled patients who were not screen failures and was used for evaluation of both safety and clinical outcomes
- AEs were summarized descriptively
- OS and PFS were exploratory efficacy objectives
  - OS was measured from the date of surgery until death due to any cause and patients who were alive at the end of the study were censored in the survival analysis
  - The analysis was performed by cohort, by high and low study dose, and in all patients combined using the Kaplan-Meier method
- PFS was measured from date of surgery until progression or censoring
- Progression-free analysis was performed in the same patient sets as OS
- PFS and OS were estimated using the product-limit method and graphed with points connected using a step function
- *P* values are provided for context only, and no adjustment was performed for multiple comparisons
- SAS version 9.4 (SAS Institute, Cary, NC) was used for all analyses

RESULTS

- Here, we report on 6 patients with survival beyond 4 years, including 5 patients who survived ≥5 years (15.2%; **Table 1**)
- There were 4 male and 2 female patients, with a median age of 52 years (range, 32-75). All patients were White
- At diagnosis, the MGMT promoter was methylated in 5 of 6 patients, and all had isocitrate dehydrogenase (IDH) wild-type (WT) tumors
- A second resection was performed in 5 of 6 patients, with 2 of 6 patients undergoing a third resection. One patient was resected 4 times
- After first progression, 4 of 6 patients received anticancer treatments, with 2 patients receiving additional anticancer treatment after their second progression
- None of these 6 patients were re-treated with IGV-001 upon progression

Table 1. Characteristics of Long-term Survivors in the Phase 1b Study

Case number	A	B	C	D	E	F
Age at diagnosis, y	52	67	48	52	32	75
Gender	Female	Female	Male	Male	Male	Male
Ethnicity	White	White	White	White	White	White
Sidedness	Right	Right	Right	Right	Left	Right
MGMT at diagnosis	Positive	Positive	Negative	Positive	Positive	Positive
IDH at diagnosis	WT	WT	WT	WT	WT	WT
Date of 1st resection	5/10/2016	12/7/2016	5/30/2017	2/7/2018	9/29/2015	2/5/2018
Date of 1st recurrence	11/23/2020	8/3/2023	8/13/19	1/11/2022	9/11/2018	N/A
Date of 2nd resection	12/11/2020	9/5/2023	10/23/2019	2/4/2022	12/18/2018	N/A
Date of 2nd recurrence	N/A	N/A	7/27/2021	10/7/2022	N/A	N/A
Date of 3rd resection	N/A	N/A	8/9/2021	10/24/2022	N/A	N/A
Date of 3rd recurrence	N/A	N/A	9/1/2022	N/A	N/A	N/A
Date of 4th resection	N/A	N/A	10/3/2022	N/A	N/A	N/A
Date of death	9/29/2021	12/14/2023	11/11/2023	2/28/2023	2/20/2020	N/A
Molecular abnormalities	Recurrence -IDH-WT -Ki-67 35% -PTEN -TERT -MGMT+ -CDK4 -MDM2 -KDM6A	Recurrence -IDH-WT -TERT -ATRX -EGFR -MGMT+	Initial -BRAF V600E -S-100 and vimentin – epithelioid GBM First recurrence: -BRAF V600E	Initial -TERT -p53 -EGFR Recurrence -TERT -p53 -EGFR	Initial -GFAP	-ATRX -GFAP
Anticancer treatments after first progression	-SRS -Bevacizumab	None	Boost SRS	Boost SRS	Boost SRS + TMZ	N/A
Anticancer treatments after second progression	N/A	N/A	Dabrafenib + trametinib > vemurafenib > lomustine	Clinical trial BDTX-1535	N/A	N/A
Retreatment with IGV-001 after first progression	No	No	None	No	No	N/A

SRS, stereotactic radiosurgery.

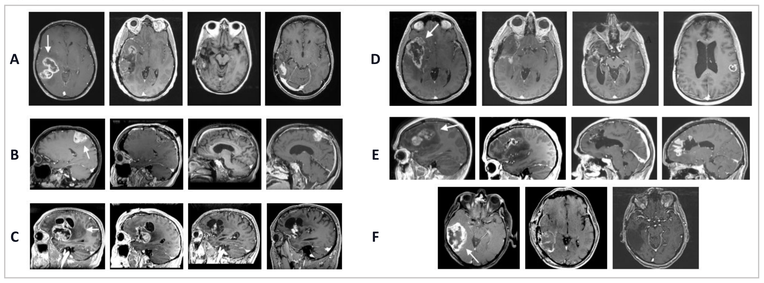
CONCLUSIONS

- Five patients in the study lived ≥5 years after treatment, and 1 patient lived >4 years after treatment. These long-term survivors, representing 15% of the study sample when using ITT analysis, lived a range of 52 to 75 months. Of the 5-year survivors, 4 had MGMT+ status, whereas 1 did not; the 4-year survivor was MGMT+
- Overall, these data support the ongoing phase 2b randomized study designed to assess the efficacy and safety of IGV-001 in patients with ndGBM (NCT04485949).[16] This phase 2b study has completed enrollment and results are expected to be available in 2025
- Immune correlates of IGV-001 suggest an association between peripheral T-cell clonal expansion and PFS/OS outcomes

- The MRIs of the 6 long-term survivors are shown in **Figure 5**

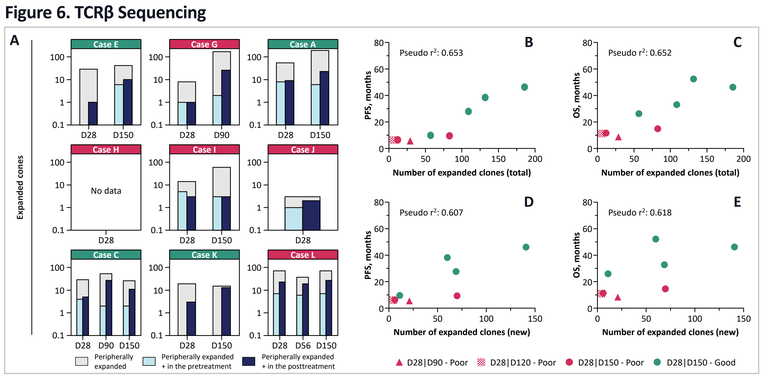
Figure 5. T1-Weighted Postcontrast MRI Scans of Long-term Survivors Treated With IGV-001

T1-weighted postcontrast MRI scans of long-term survivors treated with IGV-001 at baseline (left column), after initial resection (center left column), immediately before recurrence (center right column), and at recurrence (right column). Follow-up before recurrence was observed in case 1 (A) at 53 months, in case 2 (B) at 78 months, in case 3 (C) at 46 months, and case 5 (E) at 36 months. Scans of recurrent tumor are shown at 55 months (A), 80 months (B), 50 months (D), and 39 months (E). Images for case 4 (D) are both depicted at 59 months, demonstrating initial surgical cavity (center right) and distal recurrence in the left parietal lobe (right) at that time. Case 6 (F) did not experience recurrence; depicted is the most recent follow-up scan at 73 months (right).



- We also report on T-cell receptor Vβ CDR3 region sequencing of PBMCs and tissue-infiltrated lymphocytes that was performed in a subset of 9 patients, including 3 patients who survived beyond 4 years (**Figure 6**)
- TCRβ sequencing was conducted on 9 patients who had both peripheral blood and formalin-fixed paraffin-embedded samples from tumor tissue pretreatment and posttreatment (**Figure 6A**)
  - This analysis revealed that compared with healthy controls (n=3) (ie, gray bars in **Figure 6**), there was a higher level of clonal expansion (relative to baseline) in most patients, with case A as an outlier having 193 expanded clones at day 150
  - While overlap between pretreatment and posttreatment samples was detected across patients, cases A, C, G, J, K, and L presented with higher levels of posttreatment tumor-associated clones expanding in the periphery
- Using the TCRβ sequencing data, we conducted Cox regression analysis to evaluate the correlation between clonal expansion and patient survival
  - The results from this study showed that the total number of peripherally expanded (**Figure 6B**, **C**) and newly expanded (**Figure 6D**, **E**) TCRβ clones between day 28 and either day 90, 120, or 150 (depending on data availability) were positively correlated with PFS

Figure 6. TCRβ Sequencing



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