CTIM-17

Additional Results From a Phase 1b Study of IGV-001 in Patients With Newly Diagnosed Glioblastoma

Raul Perez-Olle, MD, PhD,[1] Greg Pennock, MD,[1] Chuck Scott, PhD,[1] D. Craig Hooper, PhD,[2,3] Kevin Judy, MD,[2] David W. Andrews, MD[1,2]

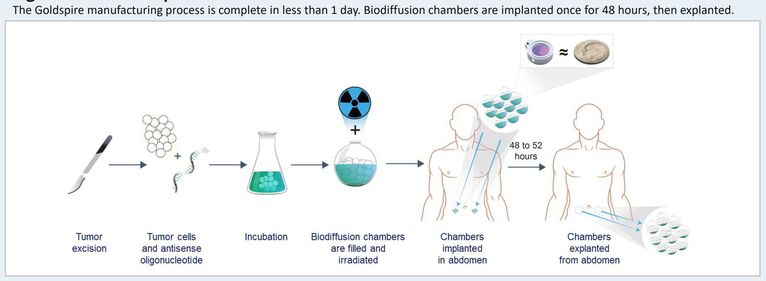
[1]Imvax, Inc., Philadelphia, PA, USA; [2]Department of Neurological Surgery, Thomas Jefferson University, Philadelphia, PA, USA;
[3]Department of Pharmacology, Physiology and Cancer Biology, Thomas Jefferson University, Philadelphia, PA, USA

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 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

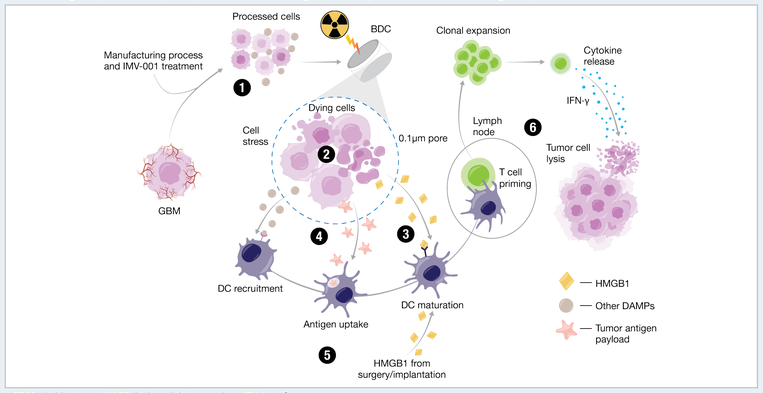
The Goldspire manufacturing process is complete in less than 1 day. Biodiffusion chambers are implanted once for 48 hours, then explanted.



- 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]
- 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]
  - With IGV-001 treatment, cancer cells are stressed by being in biodiffusion chambers (BDC), by undergoing low-level irradiation, and by the presence of IGF-1R antisense, leading to their immunogenic cell death during implantation and subsequent release of their antigens, hence stimulating an antitumor immune response

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

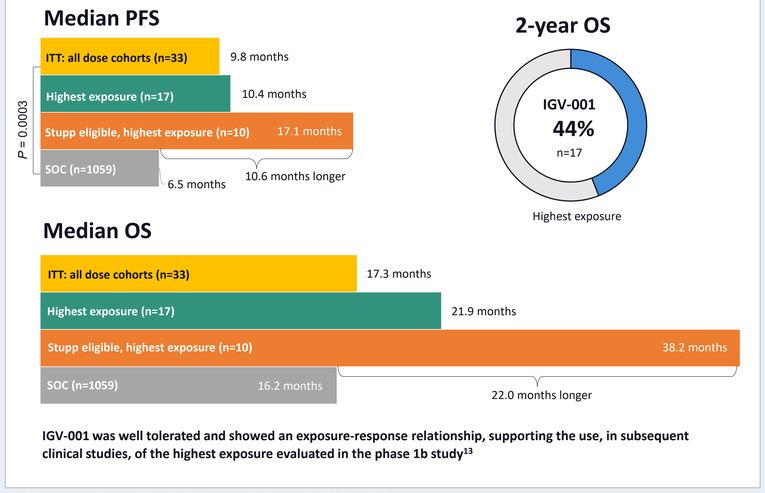
Step 1) Tumor cells treated with IMV-001 antisense are placed in biodiffusion chambers (BDC) and irradiated; 2) tumor cells in IGV-001 undergo oxidative and endoplasmic reticulum stress leading to immunogenic cell death (ICD)[17]; 3) ICD results in production of high mobility group box 1 (HMGB1) and damage-associated molecular patterns (DAMP), which are released from stressed/dying cells inside the BDCs and from the surrounding damaged tissue at the abdominal implantation site; 4) simultaneously, ICD results in a tumor antigen payload (<0.1 µm in size) being released from the BDCs; 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.



GBM, glioblastoma; HMGB, high mobility group box; IFN, interferon.

- 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]

ITT, intent to treat; OS, overall survival; PFS, progression-free survival; SOC, standard of care.

- Here, we report additional data from the phase 1b study[13]

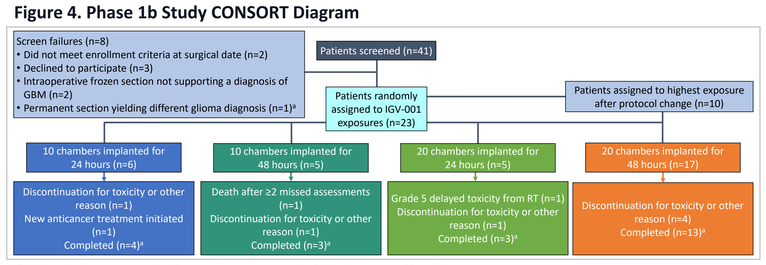
METHODS

- 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 newly diagnosed GBM. Study design, eligibility criteria, treatment plan, and statistical analyses were detailed in a prior publication[13]

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. GBM, glioblastoma; RT, radiotherapy.

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)[23] and immunotherapy RANO (iRANO)[24] criteria
- Time to progression (TTP) 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 the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03
- Four patients received retreatment with IGV-001; 2 patients received retreatment with 10 BDCs for 24 hours, and 2 patients received retreatment with 20 BDCs for 48 hours. Retreatment was conducted according to original randomization with 1 exception, a patient who initially received 10 BDCs for 24 hours but was retreated with 20 BDCs for 48 hours
- Absolute neutrophil count and absolute lymphocyte count were obtained from the Thomas Jefferson University Clinical Laboratory Improvement Amendments–certified central laboratory and recorded on case report forms as part of the phase 1b trial. The neutrophil-to-lymphocyte ratio (NLR) was calculated as the neutrophil-to-lymphocyte absolute counts

Statistical analysis

- The intent to treat (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
- 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, USA) was used for all analyses

RESULTS

Analysis of good versus poor outcomes

- Based on the median OS of 21.9 months observed in the ITT population, we identified 2 different outcome groups in the ITT population (good outcome and poor outcome). Patients were dichotomized into these 2 outcome groups with 14 (42.4%) patients in the good outcome group (OS ≥22 months) and 19 (57.6%) patients in the poor outcome group (OS <22 months)
- Baseline characteristics of the patients are summarized in **Table 1**. Younger patients (*P*=0.025) and those with methylguanine methyltransferase (MGMT) methylated promoter tumors (*P*=0.002) were more likely to be in the good outcome group when treated with IGV-001. No other groups were prognostic for OS or PFS
- Similar to the ITT population, patients with longer OS (≥22 months) typically had GBM that was isocitrate dehydrogenase 1 (IDH-1) negative and MGMT methylated

Table 1. Baseline Characteristics

Baseline characteristic	Outcome group		*P* value
	Poor outcome	Good outcome	
Sex	n (%)	n (%)	
Male	13 (68.4)	7 (50.0)	0.284
Female	6 (31.6)	7 (50.0)	
Age, years	n (%)	n (%)	
<50	1 (5.3)	5 (35.7)	0.025
≥50	18 (94.7)	9 (64.3)	
KPS	n (%)	n (%)	
60-80	3 (15.8)	3 (21.4)	0.678
90-100	16 (84.2)	11 (78.6)	
Location	n (%)	n (%)	
Frontal	1 (5.6)	4 (28.6)	0.218
Parietal	8 (44.4)	3 (21.4)	
Temporal	5 (27.8)	6 (42.9)	
Occipital	1 (5.6)	0	
Bihemispheric	3 (16.7)	1 (7.1)	
IDH-1	n (%)	n (%)	
Wild type	16 (94.1)	13 (92.9)	0.887
Mutant	1 (5.9)	1 (7.1)	
MGMT	n (%)	n (%)	
Methylated	5 (27.8)	11 (84.6)	0.002
Unmethylated	13 (72.2)	2 (15.4)	

IDH-1, isocitrate dehydrogenase 1; KPS, Karnofsky Performance Status; MGMT, methylguanine methyltransferase.

- These baseline groups were analyzed by PFS and OS (**Table 2**). Age was not statistically associated with either OS or PFS, but younger patients had a longer median OS of 37.6 months compared with older patients at 12.8 months (*P*=0.064). Tumor location and IDH-1 had too few patients in categories to meaningful statistical comparisons. Methylation status was prognostic for both OS and PFS

Table 2. Analysis of GBM Prognostic Factors in the ITT Population

Variable	Categories	Median OS (months)	*P* value	Median PFS (months)	*P* value
Sex	Male	14.9	0.436	10.4	0.54
	Female	22.6		8.0	
Age, years	<50	37.6	0.064	17.1	0.781
	≥50	12.8		9.8	
KPS	60-80	8.6	0.41	9.8	0.256
	90-100	17.3		10.4	
Location	Frontal	37.6	0.347	27.9	0.396
	Parietal	14.9		11.6	
	Temporal	22.6		10.4	
	Occipital	11.3		6.1	
	Bihemispheric	5.5		7.1	
IDH-1	Wild type	18.0	0.347	10.4	0.274
	Mutant	5.4		5.4	
MGMT	Methylated	30.9	0.014	38.4	0.001
	Unmethylated	10.1		9.3	

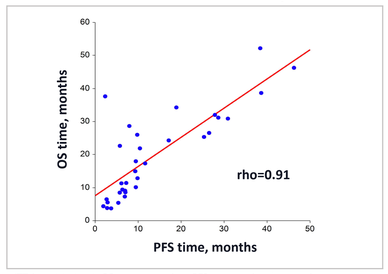
IDH-1, isocitrate dehydrogenase 1; GBM, glioblastoma; ITT, intent to treat; KPS, Karnofsky Performance Status; MGMT, methylguanine methyltransferase; OS, overall survival; PFS, progression-free survival.

- When using the estimated OS for historical SOC[13] (median OS of 16.2 months) as a cutoff, the patients in the ITT population (n=33) could be dichotomized into 17 (52%) patients with good outcome and 16 (48%) patients with poor outcome
- In the high-exposure group (n=17), there were 9 (53%) patients with good outcome and 8 (47%) patients with poor outcome
- Among the Stupp-eligible patients across all cohorts (n=22), 14 (64%) patients had good outcome and 8 (36%) patients had poor outcome

Correlation between PFS and OS

- We observed a significant correlation between PFS and OS in the ITT population. A scatter plot of OS versus PFS showing the relationship between these 2 variables is seen in **Figure 5**. The modified Spearman's rank correlation coefficient was 0.91, indicating that TTP is directly related to OS

Figure 5. Statistically Significant Correlation Between PFS and OS in the ITT Population



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

Neutrophil-to-lymphocyte ratio

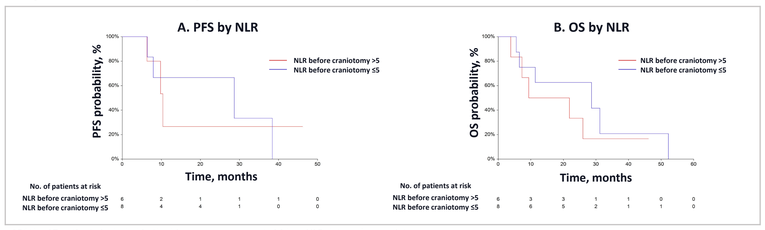
- The NLR emerged as a potential marker of good outcome that will be explored further in the ongoing phase 2b study (NCT04485949)
- Complete blood counts (if available) were taken before craniotomy, after completion of adjuvant chemotherapy and radiation, and after completion of maintenance chemotherapy, and analyzed to determine the NLR
- The average NLR decreased significantly from before craniotomy to study week 6 (before adjuvant radiotherapy). The analysis of variance indicated that the postoperative changes in NLR were statistically significant at 0.001 (**Table 3**)

Table 3. NLR Summary Statistics by Study Period

	Statistics					
Assessment	Count	Mean	Standard deviation	Median	Minimum	Maximum
Precraniotomy	27	12.43	6.89	12.10	2.54	29.39
Preradiotherapy	28	5.95	5.34	3.73	1.17	22.38
Postradiotherapy	28	7.16	5.91	6.90	0.06	28.16

- Although the data set is limited, trends towards improved PFS and OS in the setting of a lower NLR are apparent (**Figure 6**). Before radiotherapy, patients with an NLR ≤5 had a median OS of 17.3 months. When the OS analysis in patients with an NLR ≤5 was restricted to the high-exposure cohort (20 BDCs implanted for 48 hours), the median OS was 28.7 months. Patients with an NLR >5 had a median OS of 10.1 months in all patients and 9.4 months in the high-exposure cohort

Figure 6. Median PFS (A) and Median OS (B) by NLR in High-Exposure Cohort (20 BDCs Implanted for 48 Hours)[a]



[a]Of the 17 patients included in the high-exposure cohort, 14 had NLR data before radiotherapy.
BDC, biodiffusion chamber; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival.

Safety of reimplantation upon progression

- The safety of the BDC implantation and explantation procedures is further supported by data from 4 patients that were reimplanted upon progression in this phase 1b study
- Three of these 4 patients who received retreatment with IGV-001 upon progression had had unmethylated tumors as follows:
  - Two patients received retreatment with 10 BDCs for 24 hours and 2 patients received retreatment with 20 BDCs for 48 hours
  - All retreated patients received the same treatment to which they were originally randomized, except for 1 patient who was randomized to 10 BDCs for 24 hours, but received retreatment with 20 BDCs for 48 hours
- Re-resection upon progression and retreatment with IGV-001 was safe and well tolerated in these 4 patients. There were no IGV-001–related AEs in these patients

CONCLUSIONS

- Overall, these data support the ongoing phase 2b randomized study designed to assess the efficacy and safety of IGV-001 in patients with newly diagnosed GBM (NCT04485949)[25]
- The IGV-001 GBM phase 1b clinical trial, as previously reported, showed a statistically significant improvement in PFS compared with historical controls with a low AE profile[13]
- Our analysis showed a high degree of correlation between median PFS and median OS (rho=0.91) in the ITT population. These results suggest that treatments after progression had a limited impact on survival and support the use of median PFS as an end point in future clinical trials in patients with newly diagnosed GBM
- The safety profile of IGV-001 was further demonstrated by the 4 patients enrolled in this study who were retreated with IGV-001 upon progression. None of these 4 patients developed IGV-001–related AEs
- We observed a significant decrease (*P*<0.001) in NLR from before craniotomy to day 42, and this decrease was carried forward through combined therapy. The NLR emerged as a potential marker of good outcomes that will be explored further in the ongoing phase 2b study (NCT04485949)[25]
- These data provide additional support for the ongoing phase 2b randomized, multicenter, double-blind, placebo-controlled study to assess the safety and efficacy of IGV-001 in patients with newly diagnosed GBM (NCT04485949)[25]

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