Vaccine immunotherapy by homologous antigenic loading as adjuvant therapy for glioblastoma: Ongoing phase I analysis

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Abstract

Glioblastoma (GBM) is a devastating tumor of the central nervous system (CNS) for which median survival remains 14-18 months despite aggressive standard of care. Early clinical studies of dendritic cell (DC) vaccination for the adjuvant treatment of GBM previously suggested mild to moderate clinical benefit, but results were both inconsistent and inconclusive. Homologous antigenic loading is an ex vivo technique that leverages p38MAPK and mTORC1 signaling cascades to initiate powerful cDC1-like skewing in monocyte-derived DC, leading to downstream induction of CD161^{int} CD8^{+} cytolytic memory effectors. Here we report ongoing results of a completed phase I clinical trial with minimal exclusion criteria in which dendritic cell vaccines were prepared through homologous antigenic loading and administered to newly-diagnosed and relapsed patients bilaterally in the vicinity of the deep cervical lymph nodes, assisted by ultrasound sonography. Patients were additionally adjuvanted with six weeks of concurrent type I interferon. Four dose levels from 3.5 x 10^6 to 3.6 x 10^7 total vaccine cells were tested, none of which resulted in AEs > grade 2 attributable to the investigational regimen. Immunohistochemistry of tumors derived from early post-vaccination second resections displayed enhanced CD8^{+} T-cell infiltration and pathologic findings consistent with residual rather than relapsed GBM in 2/3 patients. Radiologic pseudoprogression was also routinely observed among patients of all cohorts. Analysis of post-vaccination circulating PBMC indicated expansion of both CD4^{+} and CD8^{+} central memory T-cell compartments ($p<0.05$ for each by student's two-tailed t-test) as well as expansion of CD8^{+}CD127^{+} T-cells ($p<0.05$ by student's two tailed t-test) in 9/9 patients analyzed. With an average of 12.7 months follow-up, median survival of this largely (15/16) MGMT promoter unmethylated cohort was not yet reached and was statistically greater ($p<0.05$ by log-rank[Mantle-Cox]) than that of matched historical controls. At the time of submission, 12/16 trial patients remained alive with ECOG </= 2. The results suggest that modern dendritic cell vaccines are safe, potentially efficacious, and can be effectively integrated within existing standards of care.

Introduction and Background

Homologous antigenic loading of dendritic cells (DC) is a cutting-edge manufacturing technique that leverages recent advances in dendritic cell biology. By provision of homologous class I and II peptide epitopes, a signal recognized by the high molecular weight multiaminoacyl-tRNA synthetase (mARS) complex as a critical viral PAMP, AIMp1-initiated signaling cascades that proceed through mTORC1 and p38MAPK reorganize the transcriptome, leading to the generation of a cell type with cDC1-like properties. Stimulation of monocyte-derived DC in this manner also eliminates secretion of CTLA-4^{+} microvesicles, favoring downstream development of CD161^{int} CD8^{+} T-cells. Such T-cells exhibit an enhanced capacity for serial killing, resistance to exhaustion, and a tissue homing capacity ideal for the treatment of solid tumors as demonstrated in preclinical model systems.

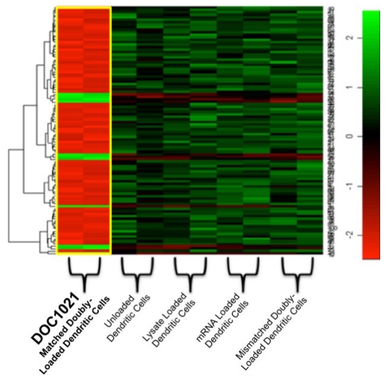


Figure 1: Heatmap of the top 100 most differentially expressed (of 1,750) genes between dendritic cells loaded with matched class I and II antigenic determinants and dendritic cells antigenically loaded by other methodologies. Adapted from Decker *et al. Blood.* 2009.

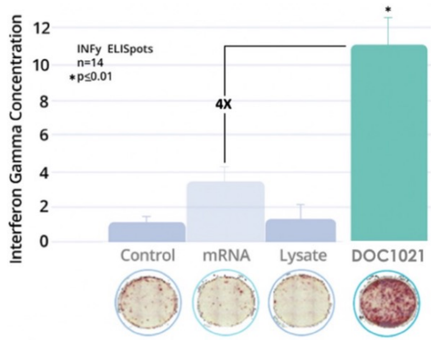
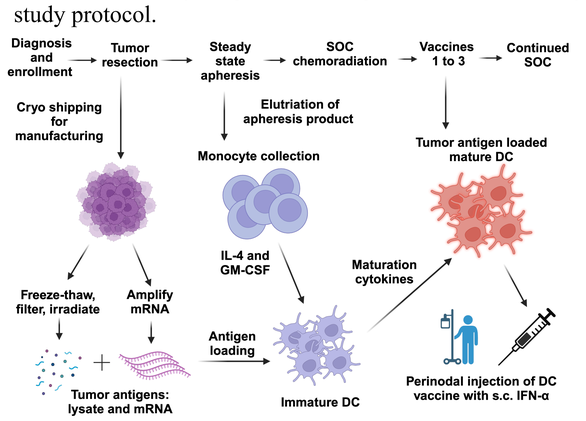


Figure 2: Dendritic Cells loaded simultaneously with matched MHC class I and II antigens stimulate co-cultured T cells to secrete substantially more IFN-γ when compared to standard loading approaches. *p<0.05 by one-way ANOVA with Tukey's post-hoc. Error bars = +/- SEM. Adapted from Decker *et al. Vaccine*. 2006.

GBM Phase I (NCT04552886) Study Design

Phase I study of Th-1 Dendritic cell immunotherapy in combination with standard chemoradiation for the adjuvant treatment of newly diagnosed adult glioblastoma :16 newly diagnosed, and 2 relapsed patients were treated under this study protocol.



Newly Diagnosed Patients Receiving DOC1021

Dose Level	Patient ID	Age & Sex at Diagnosis	MGMT Status	Survival Status	Diagnosis Date	Overall Survival (Mo.)	ECOG
DL1 (3.5M)	GBM-MDAC-001	66 / F	Unmethylated	Deceased	10/15/21	24.4	5
	GBM-MDAC-003	64 / F	Unmethylated	Deceased	5/9/22	17.5	5
	GBM-MDAC-006	73 / M	Unmethylated	Alive	8/1/22	20.1+	2
DL2 (7M)	GBM-UT-011	58 / M	Unmethylated	Alive	10/26/22	17.3+	2
	GBM-UT-012	67 / F	Unmethylated	Deceased	11/28/22	15.2	5
	GBM-MDAC-014	64 / F	Methylated	Alive	2/27/23	13.1+	0
	GBM-UT-015	58 / M	Unmethylated	Alive	3/1/23	13.1+	2
DL3 (14M)	GBM-UT-017	63 / F	Unmethylated	Deceased	4/19/23	9.8	5
	GBM-UT-018	59 / F	Unmethylated	Alive	5/1/23	11.0+	0
	GBM-UT-019	63 / M	Unmethylated	Alive	5/22/23	10.3+	1
	GBM-UT-021	51 / M	Unmethylated	Alive	6/5/23	9.9+	1
	GBM-UT-022	59 / M	Unmethylated	Alive	6/8/23	9.8+	1
DL4 (36M)	GBM-UT-023	54 / M	Unmethylated	Alive	7/14/23	8.6+	1
	GBM-UT-024	58 / F	Unmethylated	Alive	7/19/23	8.4+	1
	GBM-UT-025	73 / F	Unmethylated	Alive	7/19/23	8.4+	1
	GBM-UT-028	65 / M	Indeterminate	Alive	12/13/23	3.5+	0

Relapsed GBM Patients Receiving DOC1021

Dose Level	Patient ID	Age & Sex at Diagnosis	MGMT Status	Survival Status	Diagnosis Date	Overall Survival (Mo.)	ECOG
DL1 (3.5M)	GBM-UT-008	47 / F	Unmethylated	Deceased	9/14/22	10.4	5
DL4 (36M)	GBM-MDAC-027	66 / F	Methylated	Alive	10/30/23	5.0+	1

Results

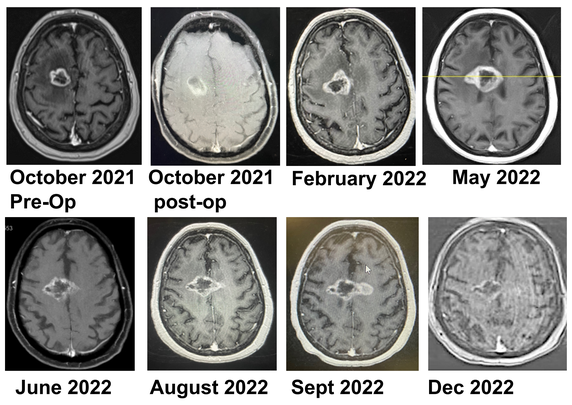


Figure 3: Pre and post operative MRI images of the patient GBM-MDAC-001 (dose cohort 1) reveal significant reduction in the tumor mass.

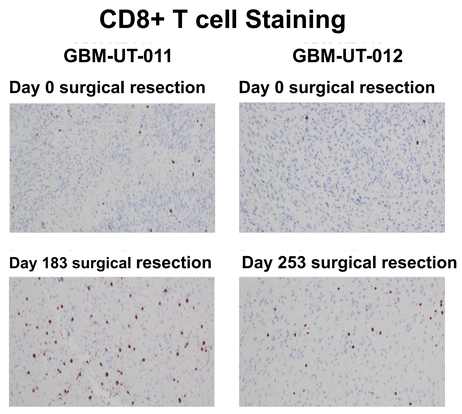


Figure 4: Representative immunohistochemistry images of tumor tissue derived from 2 GBM patients after first and second surgical resections. Both patients were treated at the University of Texas (UT) Health Science Center at Houston.

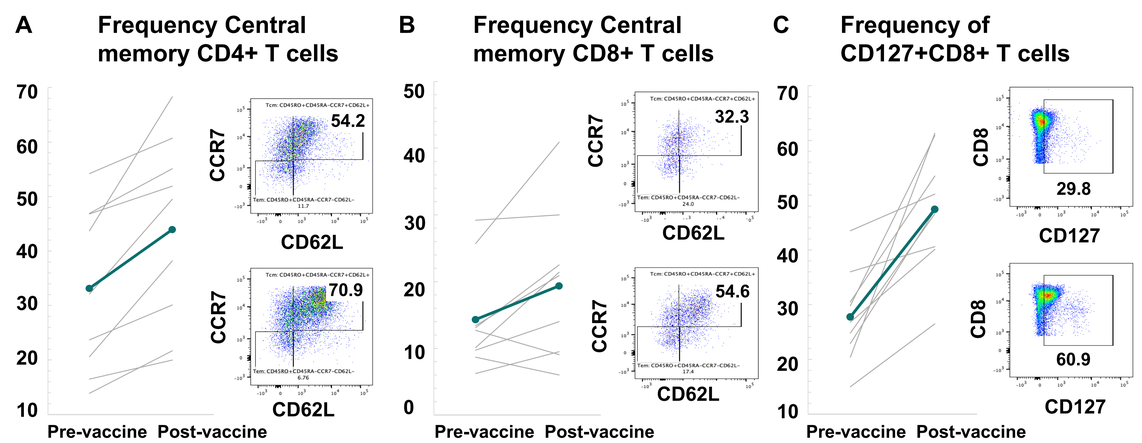


Figure 5: A statistically significant increase in the percentage of CD4^{+} (A) and CD8^{+} (B) with central memory T-cell compartments (CD45RO^{+} CD45RA^{-} CCR7^{+} CD62L^{+}) and a statistically significant increase in the percentage of CD8+ and CD127+ (C) was observed for GBM patients enrolled in DL2 and DL3, where the green line denotes the average change in cell frequency. GBM patients enrolled in other dose levels (DL1, DL4) have not been evaluated yet.

DOC1021 OS vs GBM SOC OS

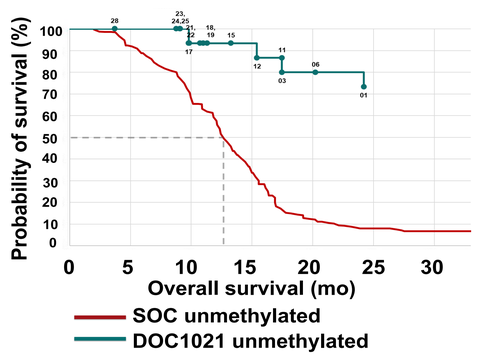


Figure 6: The overall survival (OS) of newly diagnosed unmethylated GBM patients (n = 13 of 14 shown) (green) compared to standard of care (SOC) historical data of unmethylated GBM patients (red) with a median OS of 12.7 months. With an average of 12.8 months follow-up, median survival of the unmethylated GBM patients has not been reached. Historical data derived from Fisher et, al. (2021) *Biomedicines*.

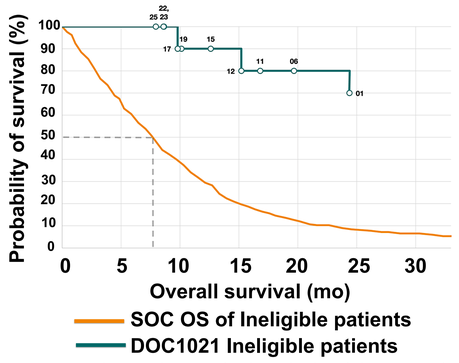


Figure 7. Kaplan Meier survival analysis of the ten patients treated with DOC1021whom would generally have been excluded from a GBM study, in comparison to the expected OS of such patients (as determined by Skaga et al., *Neurooncol Adv*; 2021), indicates a highly significant improvement (p=0.006 by log-rank [Mantle-Cox]) from 8.9 months to not yet reached with an average follow-up time of 13.2 months.

Conclusions and Future work

Dendritic cell vaccines are safe, potentially efficacious and can be effectively used in combination with standard of care against adult GBM. This cell therapy received a Fast Track designation from the FDA and is currently under consideration for a Regenerative Medicine Advanced Therapy (RMAT) designation.

Acknowledgements

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