Comprehensive Biomarker Analysis of Responders and Non-Responders in a Phase IIa Trial of a CMV Vaccine Immunotherapeutic Candidate (VBI-1901)

PY Wen[1], DA Reardon[1], D Forst[2], EQ Lee[1], T Daoud[3], T Berthoud[3], C Soare[3], F Diaz-Mitoma[3], DE Anderson[3], AB Lassman[4], FM Iwamoto[4]

[1]Dana-Farber Cancer Institute, Boston, MA USA; [2]Pappas Center for Neuro-Oncology, Massachusetts General Cancer Center, Boston, MA USA; [3]VBI Vaccines, Cambridge, MA, USA; [4]Division of Neuro-Oncology, Department of Neurology and Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center and New York-Presbyterian Hospital, New York, NY, USA

Abstract No. CTIM-14

Background

- Glioblastoma is most common malignant brain tumor in adults, accounting for 45% of all adult primary malignant brain tumors[1].
- Treatment outcomes are poor, no immunotherapy options, and a median survival rate of 12-18 months[2].
- Cytomegalovirus (CMV) antigens are reported in >90% of GBMs[3].
- **gB and pp65 antigens** are the most frequent CMV targets for CD4+ and CD8+ T-cells.
  - CD8+ T-cells are critical for killing of tumor cells.
  - CD4+ effector memory (CCR7-CD45RA-) cells preferentially migrate to the tumor microenvironment and are critical for CD8+ T-cell persistence and function.
- **VBI-1901** is a bivalent gB/pp65 enveloped virus-like particle (eVLP) adjuvanted with GM-CSF, designed to induce T-cell response against these antigens.

Phase I/IIa Trial Design

Two-part, multi-center, open-label, dose-escalation study of VBI-1901 in patients with recurrent GBM

Phase I : Dose-Escalation Phase

Population : Recurrent GBM (any #)

- *Study Arm 3:* **High Dose** (n=6) 10.0 µg + GM-CSF
- *Study Arm 2:* **Int. Dose** (n=6) 2.0 µg + GM-CSF
- *Study Arm 1:* **Low Dose** (n=6) 0.4 µg + GM-CSF

Phase IIa: Extension Phase

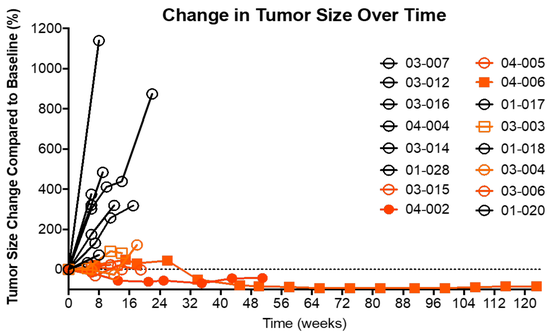
Population : Recurrent GBM (1st only)

- *Study Arm 1:* n=10 **10.0 µg + GM-CSF (i.d.)**
- *Study Arm 2:* n=10 **10.0 µg + GSK's AS01$_B$ (i.m.)**

ClinicalTrials.Gov identifier: NCT03382977

Tumor Responses – VBI-1901 + GM-CSF (High Dose Part A + Part B)

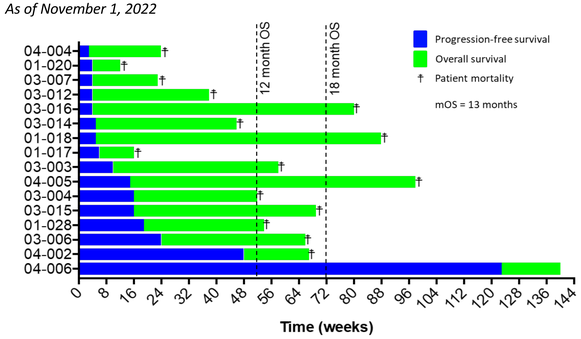
As of November 1, 2022



Legend
Orange: tumor responders
Black: tumor non-responders

Clinical Responses – VBI-1901 + GM-CSF (High Dose Part A + Part B)

As of November 1, 2022



Historical OS Controls:
(Taal et al, 2014)

- 6-month OS : ~60%
- 12-month OS : ~30%

Seven tumor responses, including two durable partial responses, were observed, which led to an 18-month OS rate of 25% and mOS of 56 weeks.

Immunomonitoring Data Results

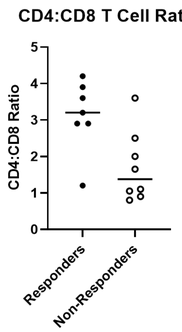
Comprehensive Biomarker Summary for the VBI-1901 + GM-CSF Cohort

- Detailed immunological testing was performed to identify potential correlations at baseline and after treatment between biomarkers and tumor responses.
- Analyses included class I and II HLA typing, modulation of plasma cytokine and chemokine responses, boosting of CMV-specific antibody and IFN-γ ELISPOT responses, and modulation of CMV-specific CD4 and CD8 Tem cells

Donor	Part A/B	Tumor Response	*CD4:CD8 Ratio	CMV gB Antibody Responder	HLA-DRB-03:01:01; HLA-DQB-02:01	**CD4+ EM+ Ki67+ pp65 Specific Proliferative Response	**CD8+ EM+ Ki67+ pp65 Specific Proliferative Response	***CMV pp65 IFN-g ELISPOT Response	***CMV gB IFN-g ELISPOT Response
01-017	A	PD	NO	NO	NO	N/A	N/A	NO	NO
01-018	A	PD	NO	NO	NO	N/A	N/A	NO	NO
01-028	B	PD	NO	YES	NO	NO	NO	NO	NO
03-007	B	PD	NO	YES	YES	YES	NO	YES	NO
03-012	B	PD	NO	NO	NO	YES	NO	NO	NO
03-014	B	PD	YES	NO	NO	NO	NO	NO	NO
04-004	B	PD	NO	YES	NO	NO	YES	YES	NO
03-016	B	PD	NO	NO	NO	NO	NO	NO	NO
03-015	B	Stable Disease	YES	YES	NO	NO	NO	NO	NO
04-005	B	Stable Disease	YES	YES	YES	YES	NO	NO	NO
03-003	A	Stable Disease	YES	YES	YES	YES	NO	YES	NO
03-004	A	Stable Disease	YES	YES	NO	YES	NO	NO	NO
03-006	A	Stable Disease	YES	YES	NO	NO	NO	NO	NO
04-002	B	Partial Response	YES	YES	YES	YES	YES	NO	NO
04-006	B	Partial Response	NO	YES	YES	YES	YES	YES	YES

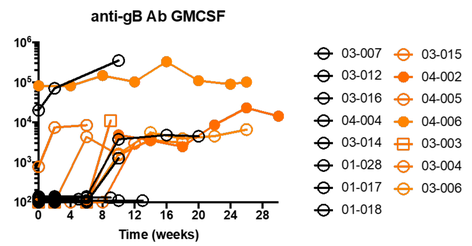
* CD4:CD8 Ratio above 4 SD below mean ratio of our healthy control donor = 2.9.
** Positive response is defined as having over 3.5% more Ki67+ CD4+ effector memory cells than the unstimulated control sample.
*** Positive response is identified if donor has 50 spot forming units (SFU) and an increase over baseline.

Influence of CD4:CD8 Ratio on Tumor Response



Significant difference between tumor responders and tumor non-responders was observed in the CD4:CD8 T-cell ratio. *(P<0.05)*

Influence of VBI-1901 Vaccination on Antibody Responses Against CMV gB



Legend
Orange: tumor responders
Black: tumor non-responders

Peak Frequencies of CMV pp65-specific CD4+ and CD8+ Tem Cells Among Patients with Tumor Responses or Progressive Disease

Donor	CD4+ EM+ Ki67+ % at Baseline	% CD4+ EM Ki67+ Peak Response	CD8+ EM+ Ki67+ % at Baseline	% CD8+ EM Ki67+ Peak Response
01-028	0.0	2.5	0.2	2.0
03-007	0.0	18.7	0.0	2.8
03-012	0.0	10.1	0.0	1.0
03-014	0.0	3.1	0.4	0.0
04-004	0.7	0.0	39.0	43.1
03-016	0.0	0.0	0.0	0.0
03-015	0.0	0.0	0.0	0.0
04-005	1.2	6.2	0.3	1.6
03-003	3.8	9.7	4.3	1.2
03-004	0.5	3.9	0.0	0.1
03-006	0.0	0.6	0.0	0.6
04-002	0.0	8.6	0.5	4.2
04-006	0.0	20.6	12.0	12.4

Responses = 3.5% or above.

Conclusions

- Normal baseline CD4+:CD8+ T cell ratio and boosting of gB antibody response were associated with tumor/clinical responses
- Higher peak frequencies of CD4+ Tem cells and particular HLA class II alleles suggest the importance of CD4+ T cell function in controlling tumor growth
- Baseline CD4/CD8 ratio and CMV seropositivity will be used as enrollment criteria in a planned extension of the on-going trial, which will include a randomized control arm, anticipated to begin enrolling in early 2023

Conflicts & Sponsorships

Dr. David E. Anderson is the Chief Scientific Officer and Dr. Francisco Diaz-Mitoma is the Chief Medical Officer at VBI Vaccines, the sponsor of the study
Dr. Andrew B. Lassman and Fabio M. Iwamoto are investigators of the study and their institution received financial support for the services performed at their study center

References

1 Ostrom et al, *Neuro Oncol*. 2013 Nov;15
2 Omuro et al, *JAMA*, 2013 Nov 6th.
3 Mitchell et al, *Neuro Oncol*. 2008 Jan 10th

Contact Information

Dr. Fabio M. Iwamoto: fi2146@cumc.columbia.edu
Dr. Andrew B. Lassman: ABL7@cumc.columbia.edu
Dr. David E. Anderson: danderson@vbivaccines.com