CMV-specific immuno-dysregulation in recurrent glioblastoma patients can be overcome with therapeutic vaccination which is associated with tumor response and overall survival benefits in a Phase I/IIa study

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AACR American Association for Cancer Research VIRTUAL ANNUAL MEETING II JUNE 22-24, 2020

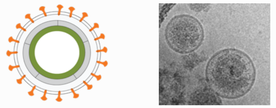
Abstract No. : 6538

Background

- Cytomegalovirus (CMV) antigens are reported in >90% of GBMs
- 'Foreign' tumor-associated viral antigens are inherently immunogenic
- 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
- Targeting CMV as a foreign viral antigen has the potential to harness, re-stimulate, and re-focus pre-existing anti-CMV immunity to clear CMV+ tumors
- VBI-1901 is a bivalent gB/pp65 enveloped virus-like particle (eVLP) formulated with GM-CSF and given as an intradermal injection
- VBI-1901 is currently in a Phase I/IIa clinical trial in recurrent GBM patients

About VBI-1901

Rationally-designed vaccine immuno-therapeutic for CMV+ solid tumors

Schematic	
Antibody Target	gB
T Cell Targets	gB ($CD4^+$), pp65 ($CD8^+$)
Target Indication	Treatment of CMV+ solid tumors, notably glioblastoma
Rationale	Targets multiple antigens, each with multiple epitopes, to promote broad immunity & avoid tumor escape
Adjuvant	Co-administered with GM-CSF via intradermal route

Phase I/IIa Trial Design

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

PART A : 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

PART B : 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

Outcome Measures : Part A & B

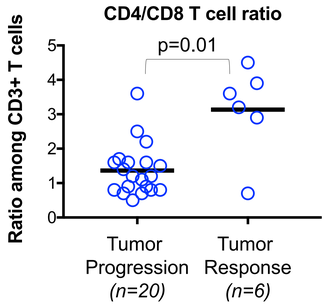
- *Safety*
- *Immunogenicity :* (1) T-cell immunity (gB, pp65), (2) serum anti-gB antibody titers, (3) other immune biomarkers
- *Tumor and clinical responses :* Based on MRIs and survival data
- *Quality of life :* Change from baseline

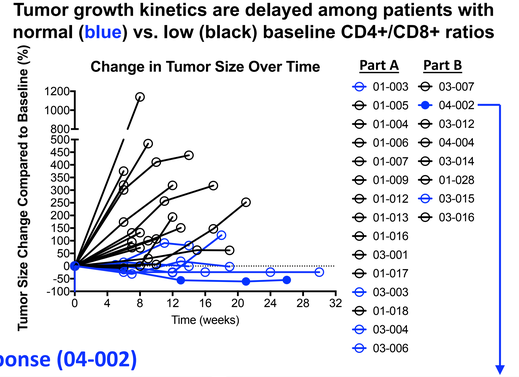
Enrollment Status and Clinical Outcomes Observed To-Date

As of June 4, 2020

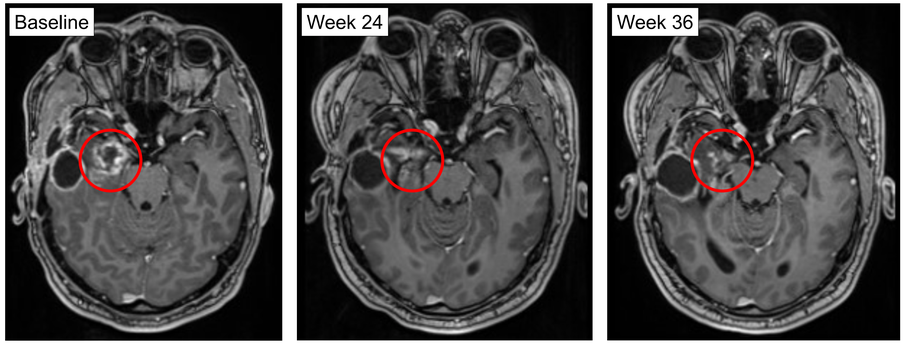
- **Part A** : enrollment complete (n=18)
  - 12-month overall survival (OS) rate of 83% in Vaccine Responders (n=6) vs. 33% in Non-Responders (n=9), based on CMV ELISPOT response
  - Vaccine Responders saw a 6.25-month improvement in median OS (14.0 mos) vs. Non-Responders (7.75 mos)
- **Part B – GM-CSF arm** : enrollment complete (n=10)
  - Tumor responses observed in 2 subjects, including one partial response
  - Results from 2 patients pending
- **Part B – $AS01_B$ arm** : enrollment ongoing

Identified Biomarker from Part A and B: Normal Baseline CD4+/CD8+ Ratio is Associated with Tumor Responses



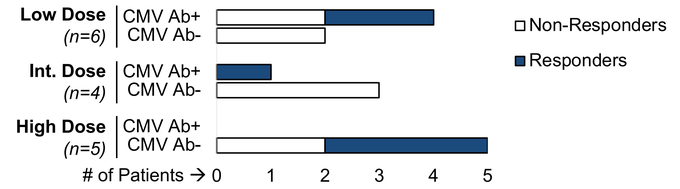


MRI of Patient with Partial Tumor Response (04-002)



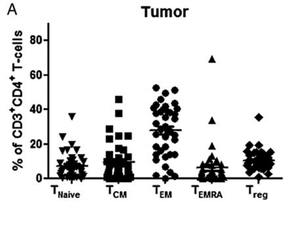
Part A : Impact of Vaccine Dose Based on CMV-Serostatus at Baseline

The high dose of VBI-1901 was able to boost CMV-specific T cells, present at baseline, in patients who were CMV antibody seronegative at baseline

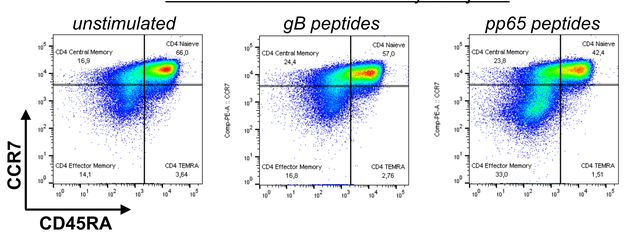


CD4+ Effector Memory Cells (T_{em}) are the Dominant T Cell Subset in the GBM Tumor Microenvironment

Dubinski D (2016)

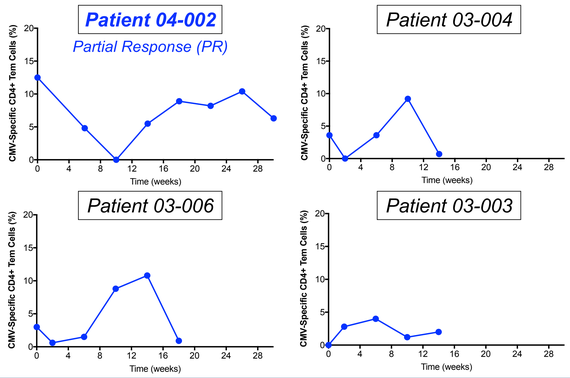


PBMCs from CMV+ Healthy Subjects

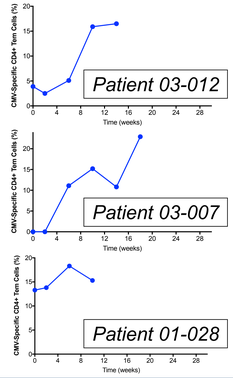


Dynamic Loss and Boosting of CMV-Specific CD4+ T_{em} Cells are Seen in Patients with Tumor Responses

Tumor Responses



Tumor Progression



Conclusions

- A biomarker present at baseline, the CD4+/CD8+ T cell ratio, captures the immunological "fitness" of CD4+ T cells in recurrent GBM patients and may be used in a follow-on trial to help enrich for and predict patients most likely to respond to, and derive clinical benefit from, treatment with VBI-1901
- In patients with tumor responses, VBI-1901 induces dynamic responses in CMV-specific CD4+ T_{em} cells, known to traffic to the GBM tumor microenvironment *(Dubinski D, 2016)*

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