Abstract No. : 4112

TCR and HLA analysis of patients in a Phase I/IIa trial of a therapeutic CMV vaccine against recurrent glioblastoma (rGBM)

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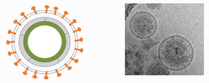
Background

- 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**, a bivalent gB/pp65 enveloped virus-like particle (eVLP), is currently in the Phase IIa portion of an ongoing Phase I/IIa clinical study
- To further assess **correlates of tumor response and clinical benefit**, human leucocyte antigen (HLA) restriction and T cell receptor (TCR) repertoires were evaluated
  - The **HLA profile** of a patient has been shown to influence the response to a variety of therapies, especially in virally-associated cancers[1] – patients with certain HLA Class I molecules have been shown to have better outcomes[2]
  - The **analysis of TCR repertoire** can be used to reflect the immune responses for patients – while the TCR repertoire is largely diverse and polyclonal under homeostatic conditions, in the context of viral infection, preferential selection of T cell clones can contribute to the narrowing of an antigen-selected TCR repertoire[3]

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

ClinicalTrials.Gov identifier: NCT03382977

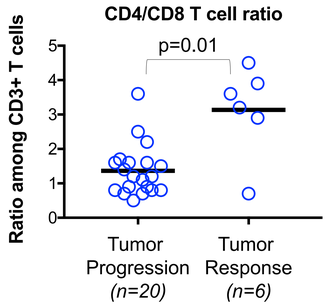
PHASE I : Dose-Escalation Phase → Recurrent GBM patients (any #), n=6/arm
- Study Arm 1 – **Low Dose** (0.4µg + GM-CSF)
- Study Arm 2 – **Intermediate Dose** (2.0µg + GM-CSF)
- Study Arm 3 – **High dose** (10.0µg + GM-CSF)

PHASE IIA : Extension Phase → Recurrent GBM patients (1^{st} only), n=10/arm
- Study Arm 1 – **High dose** (10.0µg + **GM-CSF**), i.d.
- Study Arm 2 – **High dose** (10.0µg + **GSK's $AS01_B$**),i.m.

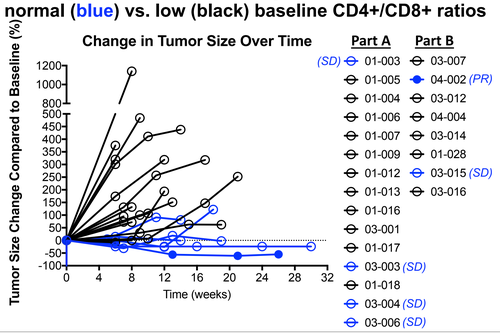
OUTCOME MEASURES :
- *Safety*
- *Immunogenicity :* (1) T-cell immunity (gB, pp65), (2) serum anti-gB antibody titers, (3) other immune biomarkers
- *Tumor and clinical responses :* Based on MRIs and survival data
- *Quality of life :* Δ from baseline

Identified Biomarker : Normal Baseline CD4+/CD8+ Ratio is Associated with Tumor Responses

- **Survival benefit observed in Phase I**
  - 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)
- **Tumor responses observed in both Phase I and Phase IIa, study arm 1**
  - As of August 31, 2020, tumor responses were observed in 6 patients – 5 stable disease (SD) and 1 partial response (PR)
- **CD4+/CD8+ ratio biomarker**
  - A normal CD4+/CD8+ T cell ratio present at baseline has been identified as a potentially predictive biomarker correlated with tumor response



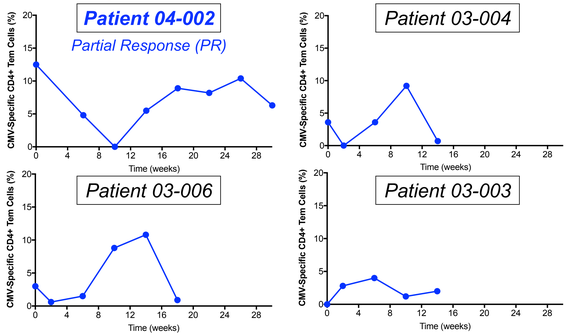
Tumor growth kinetics are delayed among patients with normal (blue) vs. low (black) baseline CD4+/CD8+ ratios



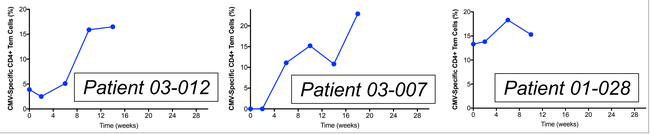
CMV-Specific Effector Memory (T_{em}) Cell Activity in Patients with Tumor Responses

Dynamic loss and boosting of CD4+ Te_m cells in patients with tumor responses

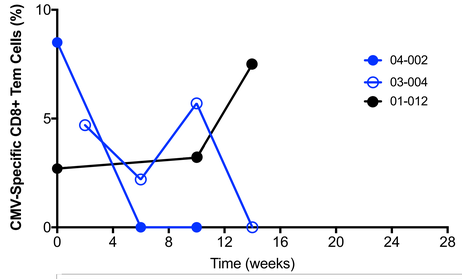
Tumor Responses



Tumor Progression



Loss of IE-1-specific CD8+ Te_m cells among patients with tumor response



Conflicts & Sponsorships

Dr. David E. Anderson is the Chief Scientific Officer at VBI Vaccines, the sponsor of the study

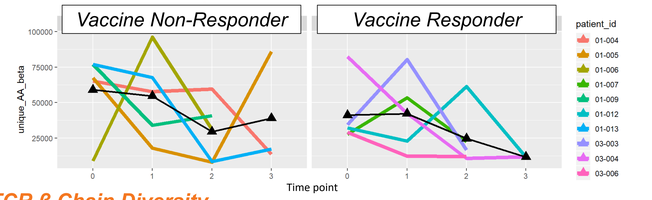
Phase I HLA Analysis : HLA Class I Haplotype

- **Vaccine Responders:** HLA-A and B alleles, reported to present CMV pp65 antigens, were present among 100% (6/6) of Vaccine Responders and 91% (10/11) of Vaccine Non-Responders
- **Tumor Response :** HLA-B*0702 allele was present among 75% (3/4) of patients with tumor responses (all of whom were vaccine responders) vs. 15% (2/13) of patients with progressive disease
- HLA-B*0702 is known to present both CMV IE-1 and pp65 peptides

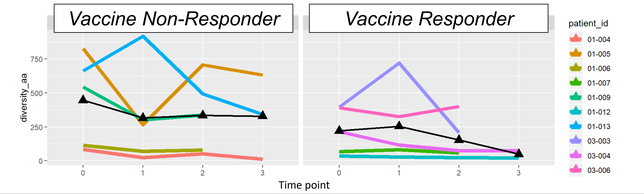
Phase I TCR Repertoire Analysis in PBMC samples

- There is a trend towards a reduced number of unique complementary determining region 3 (CDR3) sequences in the TCR β chain over time among Vaccine Responders
- This trend is consistent with a modest reduction in TCR diversity over time

# of Unique CDR3 Sequences



TCR β Chain Diversity



Conclusions

- The TCR repertoire analysis suggests that VBI-1901 potentially increased the antigen-specific immune response, resulting in a narrowing of the T cell repertoire with repeat vaccination
- The HLA analysis suggests that epitope spreading to a CMV antigen not contained in VBI-1901 (IE-1) may be associated with tumor responses in patients that responded to the vaccine
- These biomarkers and assessments will continue to be evaluated throughout the study – additional clinical data from the Phase IIa Study Arm 2 is expected in Q4 2020

References

[1]Little et al., *Trends Mol. Med.* 1999; 8:337-342
[2]Chowell et al., *Science* 2018 Feb 2;359(6375):582-587
[3]Cui J-H et al., *Front. Immunol.* 9:2729

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