Identification of a baseline biomarker associated with tumor responses in a Phase I/IIa trial of a therapeutic CMV vaccine against recurrent glioblastoma (rGBM)

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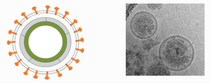
Background

- 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
- In addition to assessing safety, immunogenicity, and clinical outcomes, this study also analyzed different biomarkers which might identify those individuals most likely to respond to treatment with VBI-1901

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	GM-CSF or GSK's $AS01_B$

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 (1^{st} 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

Patients in Part B of the study received vaccination every 4 weeks until clinical progression

Outcome Measures : Phase I/IIa

- Safety
- Immunogenicity
- Tumor and clinical responses
- Quality of life

Patient Demographics : Phase IIa

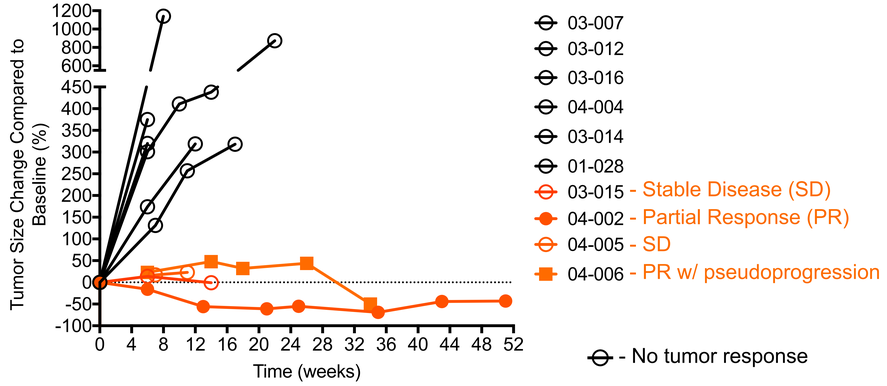
- **GM-CSF arm :** median age 58 (33-67 yrs)
  - 4 men; 6 women
- **AS01B arm :** median age 65 (40-67 yrs)
  - 7 men; 3 women

Tumor Responses : Change in Tumor Size Over Time

Disease Control Rate = Complete Response (CR) + Partial Response (PR) + Stable Disease (SD)

VBI-1901 10µg + GM-CSF

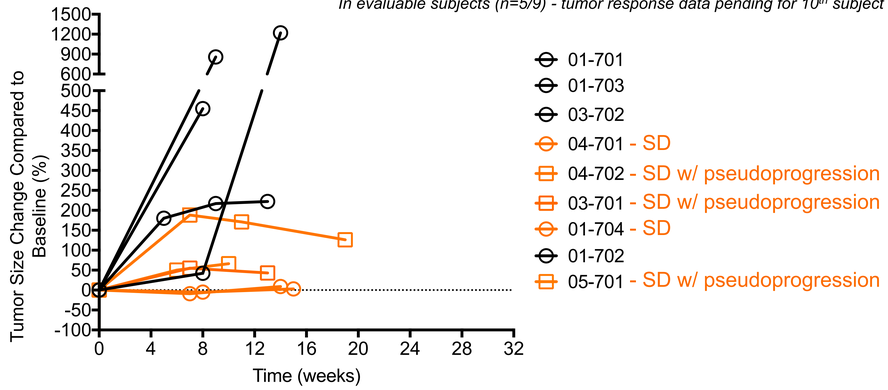
Disease Control Rate : 40% (incl. 2 PRs + 2 SDs)



VBI-1901 10µg + $AS01_B$

Disease Control Rate : 56% (incl. 5 SDs)

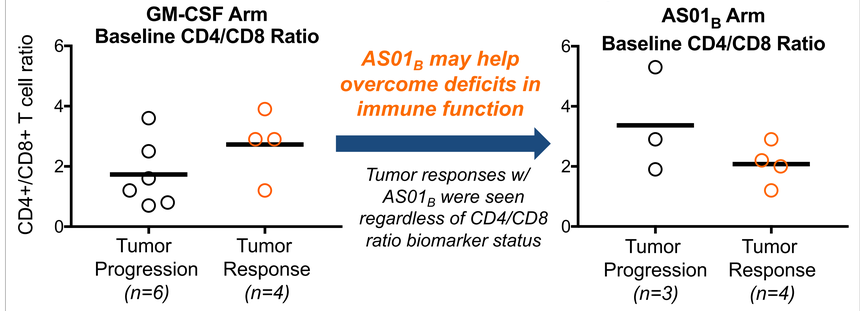
In evaluable subjects (n=5/9) - tumor response data pending for 10^{th} subject



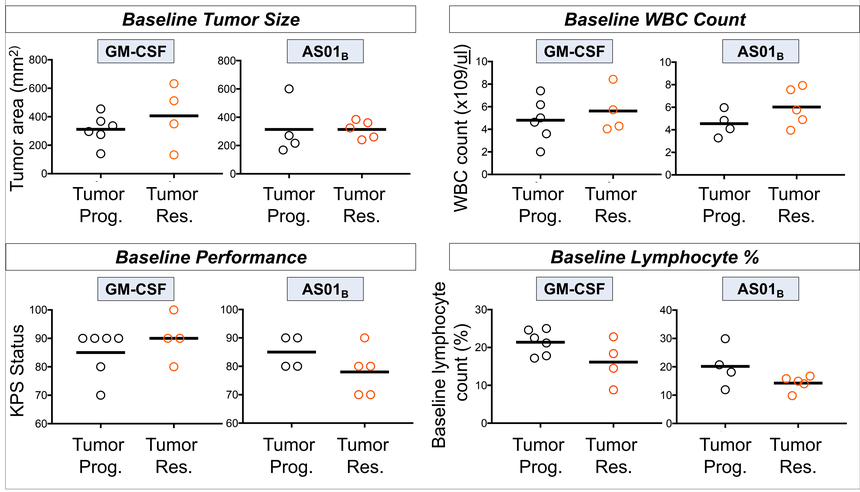
Biomarker Analyses

Identified biomarker from VBI-1901 + GM-CSF study arm:

Normal baseline CD4+/CD8+ ratio associated with tumor responses



Tumor responses achieved in subjects in both Phase IIa study arms regardless of other baseline biomarkers often predictive of immunologic fitness or baseline health



Conclusions

- 2 partial responses (PRs) observed in VBI-1901 + GM-CSF Phase IIa study arm, resulting in a disease control rate of 40%
- The VBI-1901 + $AS01_B$ Phase IIa study arm had a 56% disease control rate in subjects available for evaluation (n=5/9)
- VBI-1901 was well-tolerated with both adjuvants – no safety signals observed in either Phase IIa study arm
- Presumed pseudoprogression was observed in both arms of the Phase IIa study – defined as immune infiltration into the tumor which appears initially as tumor growth, but later subsides resulting in tumor growth stabilization and/or shrinkage
- Previously-identified biomarker to preferentially select patients most likely to benefit from VBI-1901 + GM-CSF did not correlate to tumor response in the VBI-1901 + $AS01_B$ study arm → $AS01_B$ may be sufficient to overcome deficits in baseline immunologic fitness

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 was a principal investigator of the study and his institution received financial support for the services performed at his study center

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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