On August 15th, VBI Vaccines (NasdaqCM: VBIV) reported that the FDA had accepted their Investigational New Drug (IND) application for VBI-1901, a bivalent GBM vaccine candidate based on the Company’s proprietary enveloped virus-like particle (eVLP) technology, to treat glioblastoma multiforme (GBM). GBI-1901 is designed to express two cytomegalovirus (CMV) proteins that are known to be highly immunogenic. CMV proteins are overexpressed in roughly 90% of GBM tumors but not neighboring healthy tissue, suggesting that CMV-specific epitopes could serve as localized targets for novel immunotherapies. The Company remains on track for the initiation of a Phase I/IIa study for VBI-1901 in the second half of 2017.

Launch of Phase I/IIa Trial is an Important Milestone for Company’s GBM Program. This trial will provide first-in-human data on the safety and therapeutic potential of VBI-1901. VBI’s vaccine strategy of using eVLPs has several potential advantages over other developmental programs. First, they can induce polyvalent CD4+ and CD8+ responses, and are relatively easy and cheap to manufacture as compared to autologous immunotherapies. This could provide a cost-effective strategy for targeting the immune system to primary GBM cells. CMV-targeted therapies have the potential to be an important component of the combination therapies that are expected to dominate cancer treatment in the future.

Strong Rationale for Targeting CMV Antigens in the Treatment of GBM. Although the role of CMV in the pathogenesis of GBM is not well understood, multiple Phase I studies have demonstrated the killing of primary GBM cells by autologous CMV-specific T cells. In one of these studies, 11 patients with recurrent GBM were treated with 4 infusions of autologous CMV-specific T cells. These treated patients had a median overall survival of 403 days and a median progression-free survival (PFS) of 246 days. 4 of 11 patients were free from progression during the study period with 1 patient experiencing PFS of nearly 4 years. For reference, treatment of recurrent GBM patients who have failed Anatin (bevacizumab) has been associated with a median OS 5.2 months. The survival benefit provided by this CMV-specific immunotherapy is impressive considering the difficulty of treating recurrent GBM and validates the therapeutic strategy of targeting CMV-specific antigens.

Expected Upcoming Milestones

- H2 2017 – Initiation of a Phase I/IIa trial evaluating therapeutic GBM vaccine candidate.
- H1 2018 – Completion of the Phase I study of VBI-1501A.
- H1 2019 – Results expected from Phase III trials for Sci-B-Vac.
**VBI’s GBM Vaccine Candidate is Designed Using the Company’s Proprietary eVLP Technology.** VBI’s therapeutic vaccine candidate for GBM expresses two CMV proteins in an enveloped virus-like particle (eVLP). The eVLPs closely mimic the surface of the virus in structure and protein composition and is able to induce reliable and potent immune responses without any exposure to infectious viral DNA material. One of the proteins, the gB glycoprotein, is expressed on the surface of the eVLP, and was used by VBI in an optimized conformation to develop its lead product candidate, a prophylactic CMV vaccine. VBI has demonstrated in preclinical studies that this antigen elicits a strong immune response, validating both the vaccine strategy and the eVLP platform. The pp65 CMV protein is expressed internally within the eVLPs. This dual expression pattern is designed to stimulate both CD8+ and CD4+ T cells through MHC class I and MHC class II pathways, respectively, which promotes destruction of GBM cells expressing CMV markers.

**gB/pp65 eVLPs Induced Immune Responses Consistent with Findings from Duke GBM Study.** A study by investigators at Duke University demonstrated that immune responses in GBM patients to CMV-specific dendritic cell vaccines can be augmented by priming the tumor site with a strong recall antigen. They also found that this effect was dependent of CCL3 chemokine signaling. VBI has presented data showing that the gB/pp65 eVLPs alone or mixed with granulocyte-macrophage colony-stimulating factor (GM-CSF), an adjuvant that stimulates dendritic cell function, can induce the secretion of both IFN-γ and CCL3 in freshly isolated PBMCs from 3 healthy volunteers. This result is highlighted in Figure 1. CCL3 and IFN-γ have been shown to be key markers of effective tumor immunity. The Company also showed that the eVLPs elicited CCL3 secretion from PBMCs isolated from GBM patients. In addition, VBI demonstrated that the eVLPs did not alter the release of IL-17a or IL-5, indicating that the eVLPs were capable of eliciting a specific immune response. The Duke study provided important proof-of-concept for the use of CMV-specific antigens in the targeting of GBM tumors, and VBI’s recent preclinical data is consistent with this work.

**Mouse Studies Reveal eVLP-Induced Activation of Both Th1 and CTL Immune Responses.** VBI also tested the in vivo immunogenic potential of the gB/pp65 eVLPs by immunizing mice (n=4/group) at 0 and 4 weeks. Ten days after the second dose, splenocytes were harvested from the mice and were stimulated with either gB or pp65 antigens. The investigators measured IFN-γ release as a marker of CD4+ response and perforin release as a marker of CD8+ response. Figure 2 displays the mean response frequencies in both CD4+ and CD8+ T cells with the response to empty eVLPs subtracted from the results. These data demonstrate that VBI’s eVLPs are highly immunogenic. The eVLPs are also relatively easy to manufacture compared to autologous immunotherapies, which may make VBI’s approach an ideal adjunct therapy in the treatment of GBM.
Risk to Investment

We consider an investment in VBI Vaccines to be a high-risk investment. For VBI’s clinical and preclinical vaccine programs, the Company has generated early signs of success, but these early indications of efficacy do not necessarily translate into positive clinical results. The Company may need to raise funds to support its programs, which could be dilutive to current shareholders. There are also regulatory risks associated with vaccine development, and VBI may not receive approvals for its vaccine candidates despite significant time and financial investments. Even if VBI secures regulatory approval, there is no guarantee that expectations of market penetration and sales will come to fruition.
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