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## OFRANERGENE OBADENOVEC (VB-111) IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH MICROSATELLITE STABLE COLORECTAL LIVER METASTASES: A SINGLE-CENTER, SINGLE-ARM PHASE II TRIAL

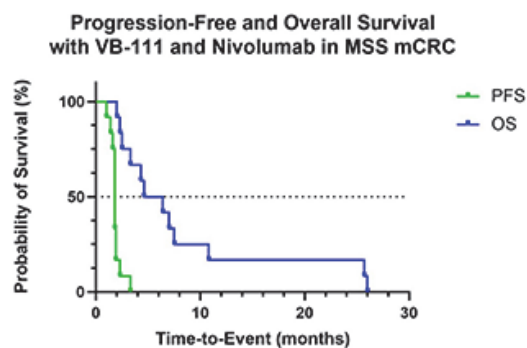
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**Background** Microsatellite stable colorectal liver metastases (MSS CLM) maintain an immunosuppressive tumor microenvironment (TME). Historically, immune-based approaches have been ineffective. VB-111 is a genetically-modified adenoviral vector targeting the TME; its unique dual mechanism induces immune response and disrupts neovascularization.<sup>1-4</sup> Checkpoint inhibition may synergize the immune response induced by viral-mediated anti-angiogenic gene therapy. We aimed to examine the safety and anti-tumor activity of VB-111 and nivolumab in patients with refractory MSS CLM and to characterize immunological treatment-response.

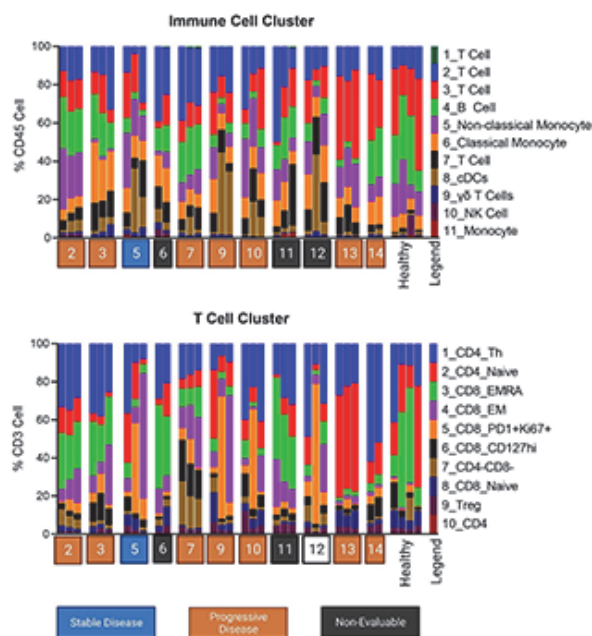
**Methods** This is a phase II study of adult patients with histologically confirmed MSS CLM who progressed on prior therapy. A priming dose of VB-111  $1 \times 10^{13}$  viral particles was given intravenously two weeks prior to starting biweekly nivolumab 240mg and continued every 6 weeks. The combination was continued until disease progression or unacceptable toxicity. Primary endpoints were ORR and safety/tolerability. Secondary endpoints included mPFS and mOS. Correlative studies were performed on paired tumor biopsies and blood.

**Results** Between August 2020 and December 2021, fourteen patients were enrolled with median age 50.5y (40–75), and 14% were female. Of the ten evaluable patients, the combination of VB-111 and nivolumab failed to demonstrate radiographic responses; at best, two patients had stable disease. After median follow-up of 5.5 months (m), mOS was 5.5m (95%CI: 2.3–10.8m), and mPFS was 1.8m (95%CI: 1.4–1.9m) (figure 1). The most common grade 3–4 treatment-related adverse events were fever/chills, flu-like symptoms, and lymphopenia. No treatment-related deaths were reported. Qualitative analysis of immunohistochemical staining of paired tumor biopsies did not demonstrate significant immune infiltration after treatment, except for one patient who had exceptional survival (25.7m). Immune analysis of PBMCs showed an increase of PD1<sup>high</sup>Ki67<sup>high</sup>CD8<sup>+</sup> T-cells and HLA-DR<sup>high</sup> T-cells after VB-111 priming dose (figure 2). Plasma cytokines IL-10 and TNF $\alpha$  increased after treatment with both drugs.

**Conclusions** In patients with MSS CLM, VB-111 and nivolumab did not improve objective response rate or survival but was tolerated with minimal toxicities. While challenging to distinguish between anti-viral or anti-tumor, correlative studies demonstrated an antigen-specific immune response with activation and proliferation of CD8<sup>+</sup> T-cells systemically; however, this was poorly sustained and immune infiltration was sparsely seen within on-treatment tumor biopsies[5]. With its transient immunogenicity and limited clinical efficacy, a single priming dose may not be the optimal strategy for viral-mediated therapies; rather, multiple sequential doses of viral vector and earlier administration of checkpoint inhibition may be required to elicit a stronger immune response to result in tumor killing.



**Abstract 585 Figure 1** Kaplan-Meier survival analyses of progression-free survival (PFS) and overall survival (OS). All patients who received at least one dose of both study drugs were included (n=12); one patient was excluded due to disease progression prior to nivolumab initiation, and one patient was taken off protocol due to malignant bowel perforation with abdominal sepsis. Time-to-event started from date of enrollment until disease progression or death, respectively. After median potential follow-up of 22.9 months, median progression-free survival was 1.8 months (95% CI 1.4–1.9), and median overall survival was 5.5 months (95% CI 2.3–10.8). MSS mCRC = microsatellite stable metastatic colorectal cancer, PFS = progression-free survival, and OS = overall survival.



**Abstract 585 Figure 2** Immune and T cell profiling of peripheral blood mononuclear cells (PBMC) after treatment with VB-111 and nivolumab. PBMCs were collected at baseline, after receiving VB-111 alone (C2D1), and after receiving both VB-111 and nivolumab (C4D1). A high-dimensional full-spectrum flow cytometry panel for immunophenotyping was performed to study different immune cell subsets and activation status. The stacked bar graphs show the frequency of distinct immune (top) and T cell (bottom) clusters across treatment by patient with their best radiographic response shown below. T cell cluster 5 represents proliferating T cells (PD1<sup>high</sup> Ki67<sup>high</sup>CD8<sup>+</sup> T-cells), which in a conventional supervised analysis (not shown) demonstrated a statistically significant increase after VB-111 that decreased at next time point, two weeks later (n=9, p<0.05, Friedman test).

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