DETECTION OF VIRAL ANTIGEN AND IMMUNE ACTIVATION AFTER INTRA-TUMOR INJECTION OF CAN-3110 (ICP-34.5 EXPRESSING HSV-1 ONCOLYTIC VIRUS) IN PATIENTS WITH RECURRENT HIGH-GRADE GLIOMA

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Background Recurrent high-grade glioma (HGG) represents a significant clinical unmet need with expected survival between 6 to 9 months. Oncolytic viruses are a new therapeutic approach for solid tumors that deploy oncolytic activity combined with local and systemic immune activation. CAN-3110 (rQNestin34.5v2) is an oncolytic herpes simplex virus (HSV), modified to encode the HSV1 ICP34.5 protein under control of the nestin promoter. Selective expression of nestin in brain tumors confers tumor-restricted replication of CAN-3110. We conducted an open-label dose-escalation phase 1 clinical trial in patients with recurrent HGG to evaluate safety, tolerability, and immunological changes after CAN-3110 treatment.

Methods Thirty patients with biopsy-confirmed recurrent HGG were enrolled from September 2017 to February 2020. CAN-3110 was injected intratumorally starting at 1x10⁶ plaque forming units (pfu) and dose-escalated by half log to 1x10¹⁰ pfu. Patients also received standard of care. Peripheral blood mononuclear cells (PBMCs), plasma and tumor samples were collected for analysis at different time-points post treatment. We evaluated HSV antigen expression in tumor tissue. RNA sequencing and T cell receptor (TCR) rearrangement analysis was performed in matched tissue and PBMCs. Cytokine profiling was completed in 29 patients at baseline, day 2, and day 28 post treatment.

Results Eighteen patients were recruited at their first recurrence and 12 at the second recurrence. Three patients presented with multifocal disease. Tumor volume ranged from 357.4 to 54,036.1mm³ (median 7,733.9mm³, SDV 15,610.2). CAN-3110 was well-tolerated with no dose-limiting toxicity. Median overall survival was 11.7 months. We demonstrated persistence of HSV antigen and CD8+ T cell infiltrates at the site of injected tumor. Preliminary analysis revealed expansion of shared TCR clonotypes and upregulation of pro-inflammatory genes in post-treatment tumors and peripheral blood samples. Longitudinal modeling of cytokine profiling demonstrated increased levels of IL-6, VEGF alpha, CCL2 and IL1-RA and a decrease in GCP-2 levels at day 2 post-treatment ($p < 0.05$). Significant correlations were observed between CXCL2 and CXCL6 ($r=0.89$ and $r=0.95$, respectively, at day 2 and day 28 post treatment; $p < 0.05$), CCL2 and CXCL6 ($r=0.73$ and $r=0.61$ at days 2 and 28 post treatment; $p < 0.05$) and between CCL2 and CXCL2 ($r=0.68$, $p < 0.05$ at day 2 post treatment) in patients surviving more than 12 months.

Conclusions Intratumoral administration of CAN-3110 appears well-tolerated in recurrent HGG. Histologic, molecular, and cytokine analyses demonstrate persistence of viral antigen as well as local and systemic immune activation after treatment.

Ethics Approval The study was approved by the Office for Human Research Studies at Dana-Farber Cancer Institute, Protocol Number 16-557.

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