1477 FIRST EFFICACY AND MULTI-OMIC ANALYSIS DATA FROM PHASE 1 CLINICAL TRIAL OF ONCOLYTIC VIRAL IMMUNOTHERAPY WITH CAN-2409 + VALACYCLOVIR IN COMBINATION WITH NIVOLUMAB AND STANDARD OF CARE IN NEWLY DIAGNOSED HIGH-GRADE GLIOMA

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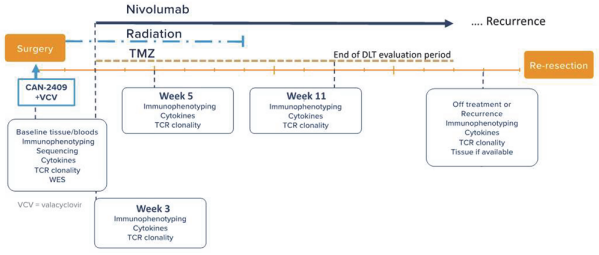
Background High-grade glioma (HGG) is characterized by a highly immunosuppressive tumor microenvironment and poor prognosis. Limited advances have been made in HGG standard of care (SoC) treatment, with immunotherapy failures reported in this indication. CAN-2409 is a replication-defective adenovirus that delivers HSV thymidine kinase to cancer cells, resulting in local conversion of oral valacyclovir into a toxic metabolite inducing immunogenic cell death. Preclinical data in a mouse model of HGG suggest CAN-2409 potential synergy with anti-PD1 agents.[1] An ongoing phase 1 clinical trial is evaluating safety, initial efficacy and immunological biomarkers associated with the combination of CAN-2409/valacyclovir with nivolumab plus SoC in patients with newly diagnosed HGG.

Methods Forty-one patients with HGG were recruited from February 2019 to March 2021. CAN-2409 was injected into the resection bed during neurosurgery, followed by valacyclovir and SoC chemoradiation. Nivolumab was initiated on day 15 and administered every 2 weeks for up to 52 weeks. Tumor and peripheral blood samples were longitudinally collected (figure 1) from 35 patients (evaluable population). Immune profiling was performed by the CIMAC network including plasma proteomics, multidimensional flow cytometry by CyTOF, whole exome sequencing (WES), TCR analysis and RNA sequencing.

Results Median OS (mOS) for patients with methylated MGMT promoter was 30.6mo for patients undergoing gross total resection (GTR) and 12.6mo for patients undergoing sub-total resection (STR). mOS for patients with unmethylated MGMT was 13.2mo (GTR) and 15.9mo (STR). Propensity score matching analysis is ongoing to evaluate mOS, controlling for known prognostic factors. Plasma proteomics at 3-week post-treatment identified increases in CXCL9, CCL11, GZMA, IFNG, CCL19, MCP1, and MCP3 concentrations (LogFC>1, FDR<0.05). Nivolumab treatment associated with significant increases in CXCL9, IL10, and PDCD1 concentrations (LogFC>1, FDR<0.05) and a trend towards elevated LAMP3, CXCL13, CXCL1, and TNFRSF9 concentrations (logFC>0.5, FDR<0.05 at week 5). Patients with methylated MGMT promoter displayed (at weeks 5 and 11) a significant increase in IL-5, IL-7, IL-10, CD4, CD27, CD40, CD38, CFS-1 and ICOSLG concentrations (FDR<0.05). Baseline concentrations of TIE2 correlated with survival (FDR<0.05). CyTOF analysis unveiled significant post-treatment changes, including increase in activated CD4 (p 0.0011; week 5), CD8 (p 0.0189; week 5), CD69+ gamma delta T cells (p0.0324; week 5), and plasmacytoid dendritic cells (p=0.0327, p=0.0020 at week 5 and 11). Additional biomarker analysis and canonical correlation analysis with clinical responses are ongoing.



Abstract 1477 Figure 1 Schema of treatment and biomarker timepoints

Conclusions Combination treatment of CAN-2409/valacyclovir plus nivolumab and SoC induces profound immunological changes and appears to associate with encouraging survival data.

Acknowledgements We would like to thank the Adult Brain Tumor Consortium for oversight on the study and the participating patients and their families, as well as site research and clinical staff.

Trial Registration NCT03576612

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Ethics Approval The protocol was reviewed by the FDA and the Institutional Review Boards at participating institutions. All study participants provided written informed consent before enrollment.

Consent All patients provided informed consent for this trial.

http://dx.doi.org/10.1136/jitc-2022-SITC2022.1477