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TMIC-15. GENETIC AND SPATIAL HETEROGENEITY OF PEDIATRIC HIGH-GRADE GLIOMAS CONFER UNIQUE INFLAMMATORY MICROENVIRONMENTS

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Significant progress has been made molecularly defining pediatric high-grade gliomas (pHGG), including diffuse midline gliomas (DMG), yet little progress has been made with respect to delineating the inflammatory microenvironment. We utilize molecularly defined human samples and immunocompetent genetic mouse models to study how tumor location and genetic driver mutations influence the tumor microenvironment (TME). We report human DMGs have a significant enrichment of Elane+ neutrophils compared to their hemispheric counterparts. We validate this utilizing the RASATv1 mouse model, which histologically and genetically recapitulates human pHGGs. Using this model we demonstrate each distinct pHGG/DMG entity confers unique transcriptional identities as made evident by NanoString RNA expression profiles and whole-tumor single-cell RNA sequencing. H3.3WT DMGs and H3.3K27M DMGs cluster together and have high expression of inflammatory genes such as Ptprc, Trem2, Lag3, and Ccl274 while H3.5WT and H3.3G34R hemispheric tumors, and H3.3K27M DMGs cluster together with low expression of these genes. Several genes were found to significantly correlate with median survival in human bulk RNA sequencing data including ITGAMRA2. Flow cytometry and immunohistochemistry demonstrate H3WT DMGs are enriched for monocytes and lymphocytes while H3.3K27M DMGs are enriched for microglia. Genetic perturbations were made to prevent TAM or neutrophil infiltration, including targeting Ccl3, Cxcl11, and Ccl8/12. Only Ccl8/12 knockout resulted in significant extension of survival in H3K27M DMGs, which was met with an increase in CD4+ and CD8+ T-cells and decreased neutrophil infiltration. CD4+ T-cell depletion and anti-PD1 therapy was performed to further study the role of lymphocyte infiltration in DMGs. Lastly, CCR1/CCR5 inhibitors were utilized to abrogate TAM infiltration in DMGs, resulting in decreased microglia infiltration and significant survival extension comparable to radiation therapy. Together, this work provides the foundation for developing or improving immunotherapies designed at specific subgroups of pHGG and DMGs, such as CAR-T-cell, oncolytic viral therapy, and checkpoint blockade.
NOW ENROLLING
Phase 2b study of IGV-001 in patients with newly diagnosed glioblastoma (NCT04485949)

OBJECTIVES

**PRIMARY OBJECTIVE**
Progression-free survival

**SECONDARY OBJECTIVE**
Overall survival

**SAFETY OBJECTIVE**
Safety and tolerability

CRITERIA

**Key Inclusion Criteria**
Patients who take part in the trial* must:
- Have newly diagnosed glioblastoma
- Be 18 to 70 years of age
- Have a KPS score ≥70 (unable to work but able to care for themselves overall)

**Key Exclusion Criteria**
Patients are not allowed to participate* in the trial if they have:
- A tumor that is on both sides of the brain
- Had previous surgery or anticancer treatment for glioblastoma
- Glioblastoma that came back
- Another cancer† while having glioblastoma or within the last 3 years that is not cured
- A weakened immune system (example: HIV, HBV, HCV) or an autoimmune disorder (example: Crohn's disease)
- Heart disease or history of heart issues

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*Additional criteria apply. Please refer to protocol 14379-201 for full inclusion and exclusion criteria. †Patients can participate if they had some skin cancers, superficial bladder cancer (cancer that was only on the surface of the lining of the bladder), or carcinoma in situ (cancer that had not spread) of the cervix or breast that had been cured.

HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; IGF-1R, insulin-like growth factor 1 receptor; KPS, Karnofsky Performance Scale; RT, radiotherapy; SOC, standard of care; TMZ, temozolomide.

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