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TIP26-314: Targeting Macrophage Migration Inhibitory Factor: A Phase 2 and Pharmacodynamic Study of Sitagliptin in Patients With Progressive Grade 4 Gliomas

Authors: Momina Qureshi, David Peereboom, Emily Zabor, Lilyana Angelov, Gene Barnett, Andrew Dhawan, Matthew Grabowski, Rachel Hufsey, Mina Lobbous, Mark Malkin, Alyssa Lucas, Alireza Mohammadi, Pranay Soni, Glen Stevens, Alejandro Torres-Trejo, and Justin Lathia

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Background: One mechanism of immunosuppression in the glioblastoma (GBM) microenvironment involves systemic and local accumulation of myeloid-derived suppressor cells (MDSCs) that inhibit cytotoxic immune cell populations and contribute to immune suppression. GBM patients have increased circulating MDSCs compared to lower grade glioma patients, and GBM patients with a better prognosis have reduced MDSCs in their tumors as well as in their peripheral circulation. A trial (NCT02669173) performed at the Cleveland Clinic demonstrated that pre-surgical anti-MDSC therapy (capecitabine) was associated with reduced circulating MDSCs and increased cytotoxic immune infiltration in tumor tissue. This proof-of-principle pilot study demonstrated that targeting MDSCs in patients can attenuate tumor-induced immunosuppression. Subsequent work at the Cleveland Clinic demonstrated that MDSCs require dipeptidyl peptidase 4 (DPP-4) for entry into the brain and overall MDSC function. Screening for a DPP-4 inhibitor identified sitagliptin as a good inhibitor with limited toxicity with efficacy in pre-clinical models. **Hypothesis:** treating GBM patients with sitagliptin will deplete circulating MDSCs and reduce their entry into the brain, reversing systemic and intratumoral immunosuppression. To test this hypothesis, we plan a “window of opportunity” clinical trial to evaluate the safety and biological impact of sitagliptin treatment in patients with recurrent grade 4 glioma undergoing clinically indicated surgical resection. For this trial, we will randomize 48 patients: 36 will receive pre- and post-operative treatment with sitagliptin and 12 will receive post-operative sitagliptin alone. All patients will receive post-operative sitagliptin and chemotherapy until disease progression. **Primary endpoint:** Difference in tumor CD8+ T cell count between the participants randomized to pre-surgical sitagliptin versus the participants randomized to no pre-surgical treatment. **Secondary endpoints:** PFS6, OS12, safety. Exploratory endpoints: peripheral and intratumoral immune profiling for assessment of TAMs, MDSCs, and CD8+ T cells; tumor radiomic features on MRI brain pre-surgery predictive of intratumoral and peripheral CD8+ T cell count and peripheral MDSC levels; peripheral blood cytokine and immune gene expression profiling for increase in immune activation signatures.

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