Background Immunotherapy is less effective against intracranial metastases compared to extracranial metastases and ineffective against primary brain tumors such as glioblastoma. Brain tumors present a unique challenge to in the context of immunotherapy, as these patients are immunosuppressed not just locally at the tumor, but also outside the CNS. Importantly, systemic immunosuppression observed in brain tumor patients limits the capacity of the immune system to respond to immunotherapy.

Methods Preclinical murine models of glioma and brain metastasis were used to uncover the immunologic mechanisms underlying success to immunotherapy in these cancers. Using the SEER Medicaid database, we retrospectively examined outcomes in patients with melanoma and lung adenocarcinoma brain metastasis who received checkpoint blockade therapy alone vs those concurrently on beta-blocker therapy.

Results Through this work we present a novel axis of immunosuppression in patients with intracranial tumors and demonstrate that overactive adrenergic signaling is a major barrier to immunotherapeutic success. Our data indicate that combining beta-adrenergic blockade with immunotherapy provides a survival benefit in the setting of brain tumors, where immunotherapy alone has proven ineffective. We demonstrate that this survival benefit is driven by a remodeling of the tumor microenvironment with an increase in cDC1s and CD8+ T cells, as well as an increase in CD40-CD40L signaling, suggesting the immune system is poised to respond. Further, we demonstrate that beta-adrenergic blockade can overcome systemic immunosuppression to restore the capacity of T cells to respond to an immune stimulus. Further, using the SEER-Medicaid database, we retrospectively examined outcomes in patients with melanoma and lung adenocarcinoma brain metastasis who received checkpoint blockade therapy alone vs those concurrently receiving beta-blocker therapy. We found that patients receiving combination therapy showed increased overall survival compared to those receiving checkpoint blockade alone. We then validated these findings in preclinical models of glioma, demonstrating that combining immunotherapy and propranolol, a widely-prescribed FDA-approved beta-blocker, extended survival.

Conclusions Beta-blockers represent a promising translational intervention that could be readily implemented to license the use of immunotherapy, particularly checkpoint blockade, in patients with primary or metastatic intracranial malignancies.

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