**ANTI-GD2 CAR T CELLS ARE POTENT IN H3-K27M+ DIFFUSE MIDLINE GLIOMAS**

Chimeric antigen receptor (CAR) T-cell therapies have exhibited efficacy against pediatric hematologic malignancies and adult glioblastoma, but it is unclear whether CAR T cells are a potential therapy for patients with pediatric central nervous system malignancies. To identify potential CAR T-cell targets, Mount, Majzner, and colleagues established patient-derived cultures of diffuse intrinsic pontine gliomas (DIPG), which are highly aggressive pediatric brain tumors. Screening of the patient-derived DIPG cultures with a cell surface antigen–targeting panel showed that the disialoganglioside GD2, which is being evaluated as an immunotherapeutic target in other cancers, was highly and specifically expressed in H3-K27M+ DIPGs compared to wild-type H3 DIPG or pediatric high-grade glioma (HGG). Anti-GD2 CAR T cells exhibited cytotoxicity against H3-K27M+ DIPGs but not GD2-negative patient-derived DIPG cells in vitro; consistent with these findings, anti-GD2 CAR T-cell therapy reduced orthotopic H3-K27M+ DIPG growth and significantly increased survival of a highly aggressive patient-derived DIPG, SU-DIPG-13P+, xenograft in vivo. Further, anti-GD2 CAR T-cell therapy resulted in eradication of SU-DIPG-13P+ xenografts and was accompanied by inflammatory infiltration of the parenchyma, meninges, and ventricles with no evidence of neuronal toxicity. Anti-GD2 CAR T-cell therapy was efficacious against orthotopic patient-derived pediatric H3-K27M+ spinal cord diffuse midline glioma (DMG) xenografts without toxicity; however, anti-GD2 CAR T cells induced tumor clearance and significant toxicity in mice harboring orthotopic patient-derived pediatric H3-K27M+ thalamic DMG xenografts potentially due to ventricular compression and herniation. Taken together, these results identify GD2 as an immunotherapeutic target for patients with pediatric H3-K27M+ DMGs, and provide evidence that the toxicity of inflammation-induced edema is significantly dependent upon neuroanatomic location.


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**CLINICAL TRIALS**

**Major finding:** Treatment with nivolumab alone or nivolumab plus ipilimumab achieves intracranial responses.

**Concept:** Nivolumab with or without ipilimumab exhibits no unexpected toxicities in patients with brain metastases.

**Impact:** Nivolumab plus ipilimumab may be effective first-line therapy in patients with untreated brain metastases.

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**IMMUNE CHECKPOINT BLOCKADE IS ACTIVE IN MELANOMA BRAIN METASTASES**

Immune checkpoint blockade with nivolumab monotherapy or combination nivolumab plus ipilimumab has improved survival in patients with melanoma. However, it is not known if these therapies are effective in active brain metastases. Long and colleagues evaluated the safety and efficacy of nivolumab alone or in combination with ipilimumab in an open-label phase II trial that treated 77 patients with melanoma brain metastases in three cohorts. In cohort A, 35 patients with asymptomatic brain metastases without previous local brain therapy were treated with nivolumab plus ipilimumab. In cohort B, 26 patients with asymptomatic brain metastases without previous local brain therapy were treated with nivolumab alone. In cohort C, 16 patients with active brain metastases or who had failed local therapy were treated with nivolumab monotherapy. The primary endpoint was intracranial response from week 12, and secondary endpoints included safety. Intracranial responses were achieved by 16 of 35 (46%) patients in cohort A, including 6 intracranial complete responses, 5 of 25 (20%) patients in cohort B, including 3 intracranial complete responses, and 1 of 16 (6%) patients in cohort C. Patients who had progressed on combined BRAF and MEK inhibitors had poorer progression-free survival, supporting first-line up-front treatment with ipilimumab plus nivolumab. No unexpected toxicities occurred. Treatment-related grade 3–4 adverse events occurred in 54% of patients in cohort A, 16% of patients in cohort B, and 13% of patients in cohort C. Taken together, the results of this phase II trial suggest that immune checkpoint blockade with nivolumab or nivolumab plus ipilimumab is effective in melanoma brain metastases. As a high proportion of patients achieved responses with combination therapy, more than that observed with nivolumab monotherapy, these findings support the use of nivolumab plus ipilimumab as first-line therapy in patients with asymptomatic untreated brain metastases.

Immune Checkpoint Blockade Is Active in Melanoma Brain Metastases

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