ABSTRACT

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GD2-CAR T cell therapy for H3K27M-mutated diffuse midline gliomas.

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Diffuse intrinsic pontine glioma (DIPG) and other H3K27M-mutated diffuse midline

gliomas (DMG) are universally lethal paediatric central nervous system tumours1. We previously discovered that the disialoganglioside GD2 is highly expressed on H3K27M-mutant glioma cells and demonstrated promising preclinical efficacy of GD2-directed chimeric antigen receptor (CAR) T cells2, providing the rationale for a first-in-human Phase 1 clinical trial (NCT04196413). Because CAR T-cell-induced brainstem inflammation can result in obstructive hydrocephalus, increased intracranial pressure, and dangerous tissue shifts, neurocritical care precautions were incorporated. Here we present the clinical experience from the first four patients with H3K27M-mutant DIPG/DMG treated with GD2-CAR T cells (GD2-CART) at dose level 1 (1e6 GD2-CAR T cells/kg administered intravenously). Patients who exhibited clinical benefit were eligible for subsequent GD2-CAR T infusions administered intracerebroventricularly3. Toxicity was largely related to tumor location and reversible with intensive supportive care. On-target, off-tumor toxicity was not observed. Three of four patients exhibited clinical and radiographic improvement. Proinflammatory cytokines were increased in plasma and cerebrospinal fluid (CSF). Transcriptomic analyses of 65,598 single cells from CAR T cell products and CSF elucidate heterogeneity in response between subjects and administration routes. These early results underscore the promise of this approach for H3K27M+ DIPG/DMG therapy.

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