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Intracranial Injection of Investigational Ex Vivo Expanded and Activated Gamma-Delta T Cells Engineered With a Methylguanine-DNA Methyltransferase–Expressing Lentivector in Patients With Primary Glioblastoma

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Abstract

Purpose

We developed a novel approach to treat newly diagnosed glioblastoma (GBM) using genetically modified gamma-delta (γδ) T cells following the forced upregulation of stress-associated targets on tumor cells. We leveraged the temozolomide (TMZ)-induced activation of the DNA damage response pathway to transiently upregulate the natural killer ligand (NKG2D-L) targets on GBM. Manufactured γδ T cells are engineered to be resistant to alkylating chemotherapies, including TMZ, through insertion of a methylguanine-DNA methyltransferase (MGMT)–expressing lentivector (DeltEx drug-resistant immunotherapy—DRI).

Methods

A total of 23 patients were enrolled, and 13 were treated (62% male; median age 66 years [range, 21-75]; 92% isocitrate dehydrogenase wild type (IDH-WT), 54% MGMT unmethylated, 46% subtotal resection). Cohorts 1, 2, and 3 received 1, 3, or up to 6 doses, respectively (1×10^7 DRI cells/dose), using a Rickham catheter, which was placed into the resection cavity. The DRI cells were dosed in combination with 150 mg/m^2 intravenous (IV) TMZ once per day on Day (D) 1 of each maintenance cycle, which was followed by 4 days of oral TMZ.

Results

No dose-limiting toxicities were seen nor were any occurrences of cytokine release syndrome (CRS) or neurotoxicity (immune effector cell–associated neurotoxicity syndrome) observed. The median follow-up of patients who received DRI γδ T cells was 15.6 months. For Cohort 1 patients who received a single dose of DRI γδ T cells, the median progression-free survival (mPFS) was 8.0 months; the median PFS was 9.9 months for all patients and 16.1 months for patients who received repeated doses in Cohorts 2 and 3. The median overall survival for all patients was 15.6 months.

Conclusion

To date, all patients had manageable toxicity with outpatient treatment and a continued encouraging trend in outcomes from repeated investigational treatments with intracranially delivered, longitudinal DRI γδ T cells.

Data Sharing Statements

- Data Sharing Statement: Clinical
- Data Sharing Statement: Correlates

Study Protocol

The following protocol information is provided solely to describe how the authors conducted the research underlying this article. The information provided may not reflect the complete protocol or any previous amendments or modifications. As described in the Information for Contributors, *JCO* requests only specific elements of the most recent version of the protocol. The protocol information is not intended to replace good clinical judgment in selecting appropriate therapy and in determining drug doses, schedules, and dose modifications. The treating physician or other health care provider is responsible for determining the best treatment for the patient. *ASCO* and *JCO* assume no responsibility for any injury or damage to persons or property arising out of the use of this protocol material or due to any errors or omissions. Readers seeking additional information about the protocol are encouraged to consult the corresponding author directly.

Please click the protocol link below to access the information.

- Protocol

Prior Presentation

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Clinical Trial Information

NCT04165941

Data Sharing Statement

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-25-02463.

Authors' Disclosures of Potential Conflicts of Interest

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Patents, Royalties, Other Intellectual Property: Development of novel inhibitors to HuR through NCI-funded peer reviewed research

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