BRIEF REPORT

Intraventricular CARv3-TEAM-E T Cells in Recurrent Glioblastoma

Bryan D. Choi, M.D., Ph.D., Elizabeth R. Gerstner, M.D., Matthew J. Frigault, M.D., Mark B. Leick, M.D., Christopher W. Mount, M.D., Ph.D., Leonora Balaj, Ph.D., Sarah Nikiforow, M.D., Ph.D., Bob S. Carter, M.D., Ph.D., William T. Curry, M.D., Kathleen Gallagher, Ph.D., and Marcela V. Maus, M.D., Ph.D.

SUMMARY

In this first-in-human, investigator-initiated, open-label study, three participants with recurrent glioblastoma were treated with CARv3-TEAM-E T cells, which are chimeric antigen receptor (CAR) T cells engineered to target the epidermal growth factor receptor (EGFR) variant III tumor-specific antigen, as well as the wild-type EGFR protein, through secretion of a T-cell–engaging antibody molecule (TEAM). Treatment with CARv3-TEAM-E T cells did not result in adverse events greater than grade 3 or dose-limiting toxic effects. Radiographic tumor regression was dramatic and rapid, occurring within days after receipt of a single intraventricular infusion, but the responses were transient in two of the three participants. (Funded by Gateway for Cancer Research and others; INCIPIENT ClinicalTrials.gov number, NCT05660369.)

From the Cellular Immunotherapy Program (B.D.C., M.J.F., M.B.L., C.W.M., K.G., M.V.M.) and Krantz Family Center for Cancer Research (M.B.L., K.G., M.V.M.), Mass General Cancer Center, and the Departments of Neurology (E.R.G.), Pathology (C.W.M., K.G.), Neurosurgery (B.D.C., L.B., B.S.C., W.T.C.), and Medicine (M.J.F., M.B.L., M.V.M.), Massachusetts General Hospital and Harvard Medical School, and Connell and O'Reilly Families Cell Manipulation Core Facility, Dana–Farber/Harvard Cancer Center (S.N.) — both in Boston. Dr. Maus can be contacted at mvmaus@mgh.harvard.edu. Any other requests related to this trial can be addressed to CARTEAMinGBM@mgb.org.

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Glioblastoma is the most aggressive primary brain tumor, and the prognosis for recurrent disease is exceedingly poor with no effective treatment options. Chimeric antigen receptor (CAR) T cells represent a promising approach to cancer because of their proven efficacy against refractory lymphoid malignant neoplasms, for which they have become the standard of care. However, the use of CAR T cells in solid tumors such as glioblastomas has been limited to date, largely owing to the challenge in targeting a single antigen in a heterogeneous disease and to immunosuppressive mechanisms associated with the tumor microenvironment.

In a previous clinical trial, we found that peripheral infusion of epidermal growth factor receptor (EGFR) variant III–specific CAR T cells (CART-EGFRvIII) safely mediated on-target effects in patients with glioblastoma. Despite this activity, no radiographic responses were observed, and recurrent tumor cells expressed wild-type EGFR protein and showed heavy intratumoral infiltration with suppressive regulatory T cells.[1] To address these barriers, we developed an engineered T-cell product (CARv3-TEAM-E) that targets EGFRvIII through a second-generation CAR while also secreting T-cell–engaging antibody molecules (TEAMs) against wild-type EGFR, which is not expressed in the normal brain but is nearly always expressed in glioblastoma. We found in preclinical models that TEAMs secreted by CAR T cells act locally at the site where cognate antigen is engaged by the CAR T cells in the treatment of heterogeneous tumors.[2] We also found in vitro that these molecules have the capacity to redirect even regulatory T cells against tumors.[3] On the basis of these data, we initiated a first-in-human, phase 1 clinical study — the Intraventricular CARv3-TEAM-E T Cells in Patients with Glioblastoma (INCIPIENT) study

— to evaluate the safety of CARv3-TEAM-E T cells in patients with recurrent or newly diagnosed glioblastoma. Here, we report the findings from a prespecified interim analysis involving the first three participants treated with this approach.

METHODS

STUDY OVERSIGHT AND DESIGN

This nonrandomized, open-label, single-site study was approved by the institutional review board at Dana–Farber/Harvard Cancer Center. The authors designed the study, gathered and analyzed the data, and made the decision to submit the manuscript for publication. An external data and safety monitoring board oversaw the conduct of the study. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol, available with the full text of this article at NEJM.org.

Enrollment in a safety run-in cohort preceded enrollment in the other study cohorts. As specified in the protocol, eligible participants were 18 years of age or older with pathologically documented, World Health Organization grade 4, recurrent, EGFRvIII-positive glioblastoma. Participants had to have measurable disease, defined as at least one lesion at least 10 mm in diameter on magnetic resonance imaging (MRI). Previous receipt of EGFRvIII-targeted therapy was an exclusion criterion.

TREATMENT AND MOLECULAR TESTING

Participants in the safety run-in cohort received 10×10^6 CAR-positive CARv3-TEAM-E T cells as a single infusion through an Ommaya reservoir. Details regarding the methods used for determining *EGFRvIII* expression and *EGFR* amplification, as well as those pertaining to extracellular-vesicle RNA isolation, and downstream analyses are provided in the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org.

MANUFACTURE OF THE T-CELL PRODUCT

Autologous T cells were obtained by means of leukapheresis and transduced with the CARv3-TEAM-E lentiviral vector containing an anti-EGFRvIII single-chain variable fragment and an intracellular 4-1BB costimulatory domain linked to CD3 zeta. An EGFR-targeted TEAM was also included in the same vector following a ribosomal skip element. A third transgene that codes for a truncated CD19 molecule was used as a surface marker for transduction (Fig. S1 in the Supplementary Appendix). Biotinylated human EGFR was used to detect T-cell–bound TEAMs. Details regarding manufacturing as well as the release criteria for the T-cell product are provided in the Supplementary Methods section and Table S1. CARv3-TEAM-E T cells were formulated at a target dose of 10×10^6 CAR-positive T cells per vial after thawing. Cells were thawed, diluted to a volume of 10 ml, and transferred to a syringe under sterile conditions before infusion.

TOXICITY ANALYSIS

Participants were monitored for toxic effects throughout the study. Adverse events were graded according to the Common Toxicity Criteria for Adverse Events, version 5.0. A dose-limiting toxic effect was defined as having to be at least possibly related to the investigational product and not attributed to disease progression. These included any related grade 4 or greater toxic effects (except grade 3 or 4 cytokine-release syndrome or immune-effector cell–associated neurotoxicity syndrome that did not resolve to grade 2 or lower within 3 weeks) or any related grade 3 toxic effect that did not resolve to grade 2 or lower within 2 weeks. Two specific investigators were deemed the arbiters of relatedness to the investigational product.

RESULTS

SAFETY AND ADVERSE EVENTS IN THE SAFETY RUN-IN COHORT

From March 2023 through July 2023, three participants with recurrent glioblastoma were enrolled in the safety run-in cohort of the INCIPIENT study at Massachusetts General Hospital (participant characteristics are listed in Table S2). No associated dose-limiting toxic effects were noted among the participants.

Grade 3 events that were at least possibly attributable to the investigational product included grade 3 encephalopathy for 3 days in Participant 1 and grade 3 fatigue for 8 days in Participant 3 (both of which were deemed by an investigator to be probably related to treatment) (Tables S3, S4, and S5). Participant 1 died from disease progression 63 days after study discontinuation; the cause of death was gastrointestinal perforation while

the participant was receiving bevacizumab and dexamethasone. This event was not attributed to CARv3-TEAM-E infusion.

In the workup of cyclic fevers in Participants 2 and 3, development of transient pulmonary nodules and ground-glass opacities was observed on chest computed tomography. These findings were otherwise asymptomatic and had spontaneously and completely resolved on repeat imaging within 4 to 6 weeks. None of the participants received glucocorticoids during the initial post-treatment phase or for any therapy-related indication.

PARTICIPANT 1

A 74-year-old right-handed man presented with a 1-week history of headache and confusion, and an enhancing mass in the left insula was found on imaging. He underwent craniotomy, which led to a diagnosis of a glioblastoma with wild-type isocitrate dehydrogenase (*IDH*) and methylated O^6-methylguanine–DNA methyltransferase (*MGMT*). The tumor was positive for *EGFRvIII* and *EGFR* copy-number gain. He received standard care consisting of radiation and temozolomide chemotherapy. At 12 months after diagnosis, findings on MRI were suggestive of disease recurrence. A repeat craniotomy was performed, and the recurrent tumor was confirmed to be *EGFRvIII*-positive (Fig. 1A). Participant 1 was subsequently enrolled in the current clinical study.

An interval MRI scan was obtained 6 days before CARv3-TEAM-E infusion (day −6) and showed active progression (Fig. 1B). Participant 1 underwent placement of an Ommaya reservoir ventriculostomy catheter on day −1. CARv3-TEAM-E T cells (10×10^6 CAR-positive T cells) were subsequently administered through the catheter device on day 0. An MRI scan obtained on day 1 after this single infusion showed rapid regression of the tumor (Fig. 1B). This radiographic improvement was confirmed on subsequent MRI scans over the next 2 weeks but was ultimately transient. On the basis of the initial response and with permission from regulatory authorities, he received a second infusion of 10×10^6 CAR-positive CARv3-TEAM-E T cells on day 37 (cycle 2).

At several time points throughout each treatment cycle, liquid biopsy was performed with the use of extracellular-vesicle RNA derived from cerebrospinal fluid (CSF) and peripheral-blood samples.[4] *EGFRvIII* and *EGFR* copy numbers were elevated during cycle 1 and decreased over time, eventually becoming undetectable in post-treatment CSF samples (Fig. 1C). Extracellular-vesicle RNA from peripheral-blood samples obtained before and after infusion also showed decreases in the copy numbers of both *EGFRvIII* and *EGFR* (Fig. 1D). Participant 1 returned to the operating room on day 72 for biopsy after interval MRI revealed progression. Consistent with the findings on liquid biopsy, both next-generation sequencing and immunohistochemical analysis (Fig. S2) of post-treatment tumor tissue were also negative for *EGFRvIII* in the context of maintained gain in *EGFR* copy number (ratio, 3.5, relative to probes for centromere 7 [normal ratio, approximately 1]) (Fig. S3).

PARTICIPANT 2

A 72-year-old right-handed man presented with difficulty reading, and a left-sided, contrast-enhancing mass in the posterior temporal lobe was detected on MRI. He underwent craniotomy and tumor resection, and pathological analysis confirmed glioblastoma, which was *EGFRvIII*-positive, *IDH* wild-type, and *MGMT*-methylated. He received standard radiation therapy and temozolomide chemotherapy, as well as tumor-treating field therapy. At 20 months after the initial diagnosis, surveillance imaging showed evidence of progression. He was then enrolled in the current study on the basis of *EGFRvIII* status at initial diagnosis, in accordance with an amended schematic workflow (Fig. 2), which had been modified to enable concomitant craniotomy, tissue sampling, and Ommaya reservoir placement during a single surgery. Molecular histopathological analysis at the time of repeat craniotomy revealed *EGFRvIII*-positive, recurrent glioblastoma.

Participant 2 was discharged and then readmitted 1 week later for infusion. He received a single infusion of 10×10^6 CAR-positive CARv3-TEAM-E T cells through an intraventricular catheter. On day 2, MRI was performed and showed a decrease in cross-sectional area of the tumor by 18.5%, which on day 69 had further decreased by 60.7% from the preinfusion baseline value. This response continued to improve and remained durable at the last assessment, more than 150 days after a single infusion, in the absence of glucocorticoid or antiangiogenic therapy (Fig. 3A). Longitudinal liquid biopsy with the use of extracellular-vesicle RNA from CSF samples showed a

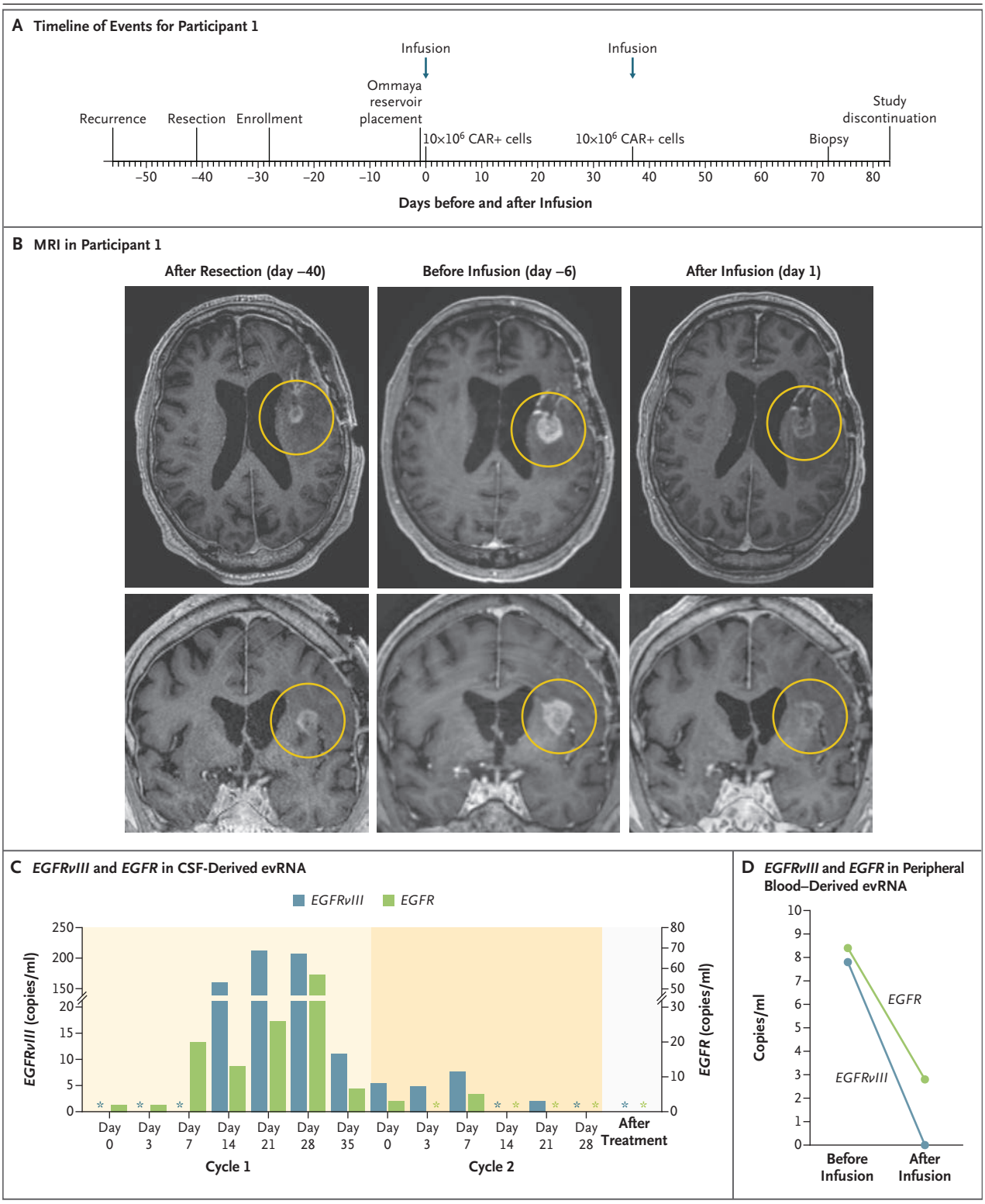

Figure 1 (facing page). Treatment Response on MRI and Liquid Biopsy in Participant 1.

Panel A summarizes the timeline of events for Participant 1. CAR+ cells denote CARv3-TEAM-E T cells, which are chimeric antigen receptor (CAR) T cells engineered to target the epidermal growth factor receptor (EGFR) variant III (EGFRvIII) tumor-specific antigen, as well as the wild-type EGFR protein, through secretion of a T-cell–engaging antibody molecule (TEAM). Panel B shows contrast-enhanced T1-weighted magnetic resonance imaging (MRI) in Participant 1 immediately after resection, before infusion, and after infusion. The day numbers specified above the images are relative to the day of infusion (day 0). The yellow circles indicate the tumor. The top row shows axial views, and the bottom row shows coronal views. Panel C shows the copy numbers of *EGFRvIII* and *EGFR* over time, as detected in extracellular-vesicle RNA (evRNA) derived from cerebrospinal fluid (CSF). Asterisks indicate that the *EGFRvIII* and *EGFR* copy numbers were below the threshold of detection. Panel D shows the copy numbers of *EGFRvIII* and *EGFR* before and after infusion, as detected in evRNA derived from peripheral-blood samples.

decrease in *EGFRvIII* and *EGFR* copy numbers over time, with the copy numbers remaining below the threshold of detection in post-treatment samples (Fig. 3B).

PARTICIPANT 3

A 57-year-old right-handed woman presented with several weeks of word-finding difficulty and concern for seizure, and a left parietal, contrast-enhancing mass was detected on MRI. She underwent craniotomy and tumor resection, and pathological analysis confirmed glioblastoma, which was *IDH* wild-type and *MGMT*-unmethylated. The tumor was positive for *EGFRvIII* expression and *EGFR* copy-number gain. She received radiation therapy and temozolomide chemotherapy, the dose of which was reduced owing to the development of thrombocytopenia. By 6 months after diagnosis, interval imaging showed evidence of recurrent disease.

Participant 3 was enrolled in the current study (Fig. 2). She underwent repeat craniotomy for open biopsy and implantation of an Ommaya reservoir. Tissue analysis at the time of surgery for recurrence revealed a loss of *EGFRvIII* expression, but wild-type *EGFR*–amplified nuclei were documented by fluorescence in situ hybridization; *EGFR* transcripts were also detected. Preinfusion MRI was performed and again showed

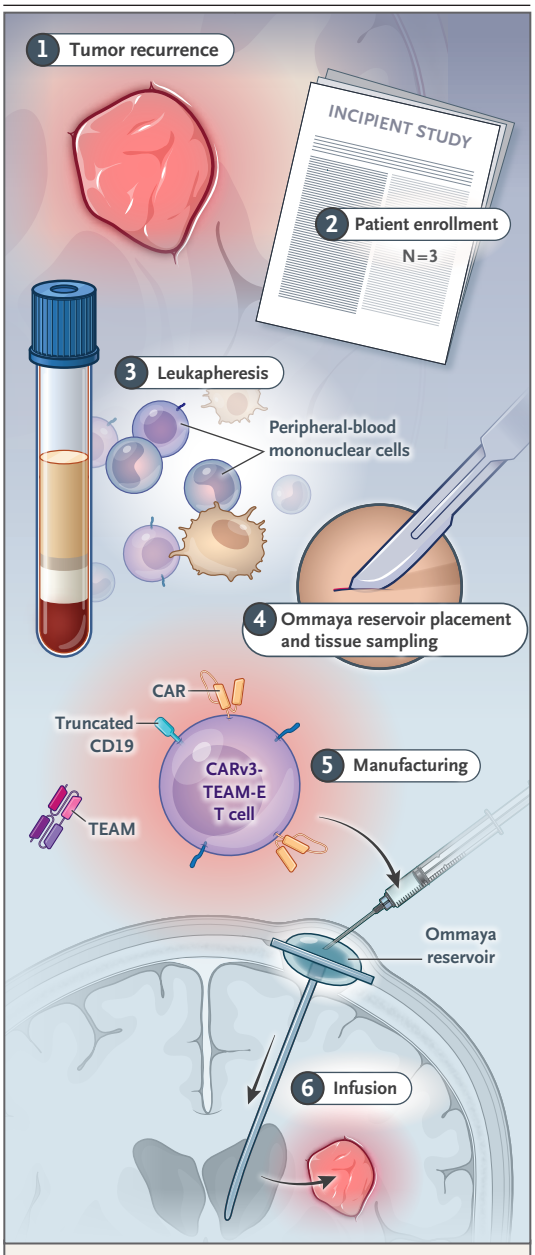

Figure 2. Amended Workflow Used in Participants 2 and 3.

Shown is the amended workflow used in Participants 2 and 3, which enabled concomitant craniotomy, tissue sampling, and Ommaya reservoir placement during a single surgery.

extensive recurrent disease burden (Fig. 3C). Participant 3 was discharged and then readmitted 2 weeks later for infusion. She received 10×10^6 CAR-positive CARv3-TEAM-E T cells through the intraventricular catheter. An MRI scan obtained on day 5 after this single infusion showed near-

complete tumor regression (Fig. 3C); however, evidence of recurrence appeared within 1 month after infusion. Extracellular-vesicle RNA derived from a post-treatment CSF sample showed low copy numbers of *EGFRvIII* and *EGFR* at isolated time points, which later became undetectable (Fig. S4).

CORRELATIVE DATA

All three participants had fevers that peaked by day 2 after infusion (Fig. 4A). Intravenous therapy with the interleukin-1–receptor antagonist anakinra (100 mg every 6 hours) was used intermittently in the management of fevers (Fig. S5). Levels of systemic inflammatory markers increased later and peaked in the second and third weeks after infusion, returning to baseline values by day 30 (Fig. S6).

Cytopathological analysis of the CSF sample revealed an elevated total nucleated cell count immediately after infusion, which decreased exponentially in the first week and then gradually over time. The cell differential in the CSF samples initially showed a neutrophilic predominance before shifting to a primarily lymphocytic population over the 30 days after infusion (Fig. S7). Quantification by vector copy-number analysis and flow cytometry (Fig. 4B) indicated that CAR-positive and TEAM-positive T cells temporarily persisted in the CSF sample that was obtained

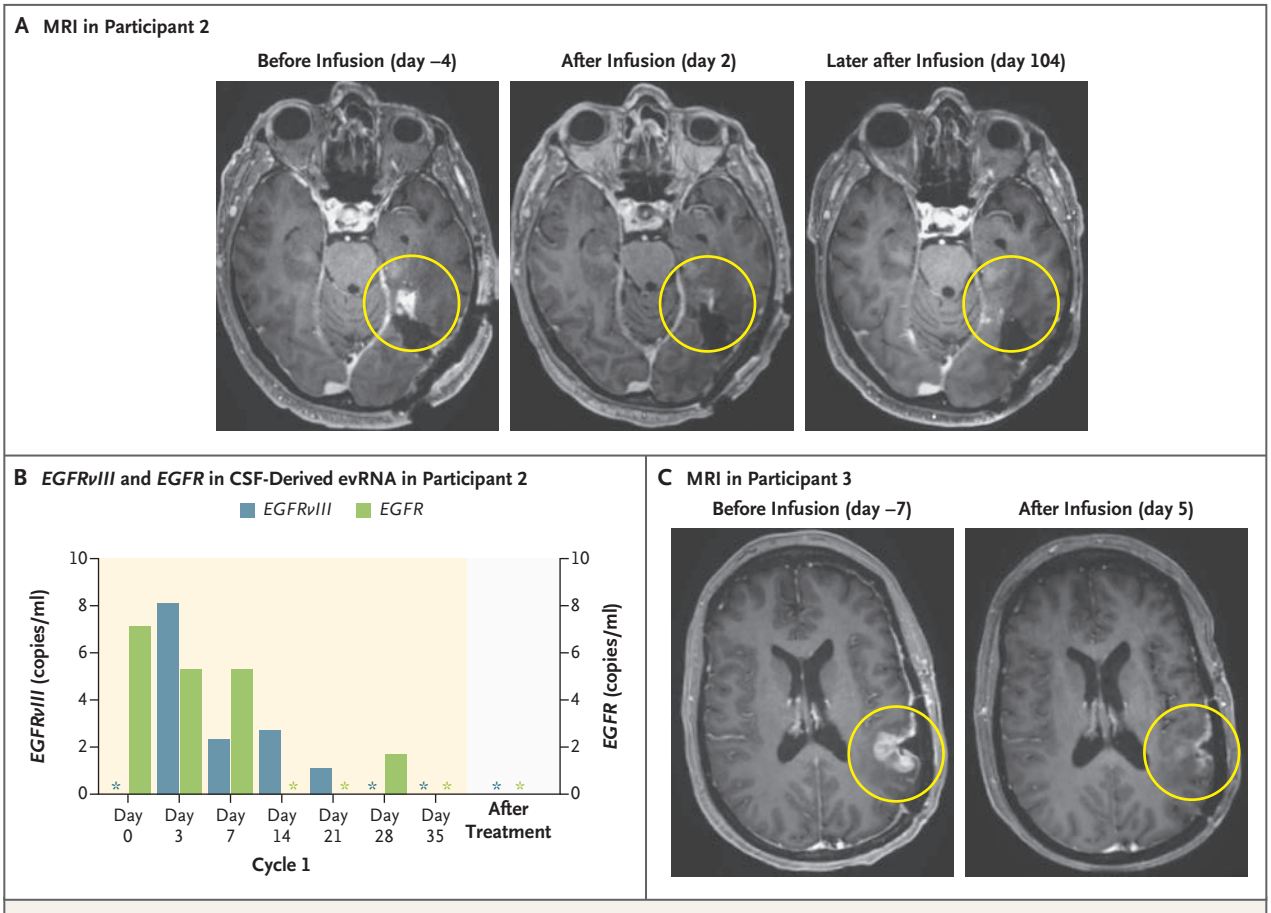

Figure 3. Treatment Response on MRI and Liquid Biopsy in Participants 2 and 3.

Panel A shows an axial, contrast-enhanced T1-weighted MRI scan in Participant 2 before and after infusion; tumor regression was observed at day 2 after infusion. The tumor continued to regress, and this regression was sustained at later time points. The number of the day above the images is relative to the day of infusion (day 0). The yellow circles indicate the tumor. Panel B shows *EGFRvIII* and *EGFR* copy number over time, as detected in evRNA derived from CSF. Panel C shows an axial, contrast-enhanced T1-weighted MRI scan in Participant 3 before and after a single infusion of CARv3-TEAM-E T cells. Asterisks indicate that the *EGFRvIII* and *EGFR* copy numbers were below the threshold of detection.

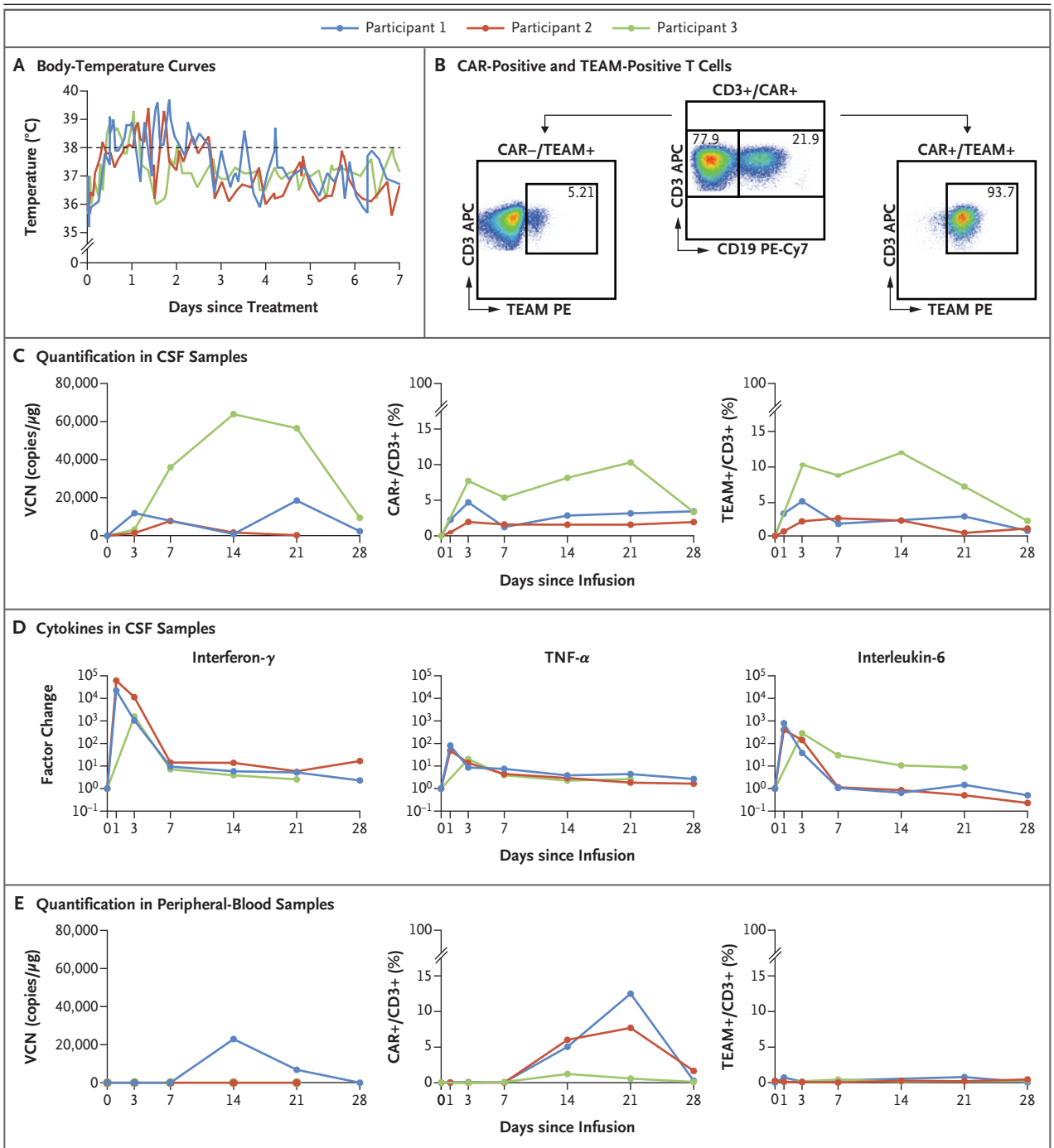

Figure 4. Correlative Data on All Three Participants.

Panel A shows the body temperature curves for all three participants over time. Panel B shows a representative flow cytometric analysis of the engineered T-cell product (CARv3-TEAM-E) in Participant 1, with gating for CAR-positive and TEAM-positive T cells among all CD3+ T cells. The numbers in the plots indicate the corresponding percentages. APC, PE, and PE-Cy7 are fluorophore labels on the indicated antibodies. Panel C shows quantification of CAR-positive and TEAM-positive T cells by means of vector copy number (VCN) analysis and flow cytometry in all three participants. Panel D shows changes in inflammatory cytokines in the CSF samples obtained from the participants in the first month after infusion. Panel E shows detection of CAR-positive and TEAM-positive T cells in the peripheral-blood samples. TNF-α denotes tumor necrosis factor α.

after infusion but declined by week 4 (Fig. 4C and Fig. S8), which corresponded with normalization of the inflammatory cytokine milieu in the CSF compartment over the same period (Fig. 4D). CARv3-TEAM-E cells were detected in the peripheral blood between 2 and 3 weeks after infusion, but their presence was transient (Fig. 4E and Fig. S9).

The absolute count of CAR T cells in the peripheral blood peaked at day 21 in all three participants (Fig. S9). At that time, the percentage of CAR-positive T cells that had surface-bound TEAM in the blood was 2.00% in Participant 1, 0.64% in Participant 2, and 0.00% in Participant 3. Conversely, the percentage of CAR-positive T cells that had surface-bound TEAM in the CSF sample was 70.3% in Participant 1, 17.6% in Participant 2, and 56.2% in Participant 3. These data provide additional support that the CARv3-TEAM-E platform may facilitate safe, local targeting of wild-type EGFR in the central nervous system.

DISCUSSION

We report the results of an early phase 1, first-in-human study of intraventricularly delivered CARv3-TEAM-E T cells in patients with recurrent glioblastoma. Previous studies have shown that CAR T cells can be safely administered to patients with glioma.[1,5-8] Here we show dramatic radiographic responses in multiple participants within days after a single intraventricular infusion of dual-targeting CARv3-TEAM-E T cells. These effects were transient in two of three participants, and one participant had a durable regression through a short-term follow-up period. Findings from liquid biopsy with the use of CSF and peripheral-blood samples are reported as a correlative study in these participants.

Despite successful translation of CAR T cells in the treatment of hematologic malignant conditions, the usefulness of this strategy in patients with solid tumors remains unproved, although it has been reported that this approach showed promise against neuroblastoma.[9] As described previously, CAR T cells and bispecific antibodies for patients with glioblastoma have been used to target only single antigens and thus have been limited by tumor heterogeneity, the emergence of antigen loss, and eventual immune escape.[1,10] Our study of CARv3-TEAM-E T cells provides proof of principle that multiple surface antigens can be targeted simultaneously with the use of CAR T cells and confirms that EGFR is a suitable immunotherapeutic target in glioblastoma. Moreover, the secreted T-cell–engaging antibody made by the CAR T cells was safe despite widespread expression of its target in systemic tissues.

This study shows that antitumor CAR-mediated responses can be rapidly obtained in patients with glioblastoma, even in those with advanced, intraparenchymal cerebral disease. This finding contrasts with a previous report of a complete response that was observed in a patient with recurrent leptomeningeal disease who received treatment with 16 intracranial infusions of monospecific interleukin-13 receptor alpha 2 CAR T cells.[8] It was hypothesized by the investigators of that study that the involvement of glioblastoma in the leptomeninges may have rendered the disease more responsive to intraventricular therapy. Our experience in the current study suggests that even a single dose of intraventricularly administered living drugs such as CAR T cells also have the capacity to access and mediate activity against infiltrative, parenchymal glioblastoma.

It is notable that CARv3-TEAM-E T cells showed signs of antitumor activity in the absence of *EGFRvIII* expression (in Participant 3). Certainly, interpretation of these data remains subject to the limitations of tissue sampling in a heterogeneous disease, the sensitivity of the assays used to measure *EGFRvIII* expression, and the evanescent nature of *EGFRvIII* expression, in which variations occur throughout the natural history of these tumors.[11] However, the potential efficacy of CARv3-TEAM-E T cells in patients with *EGFRvIII*-negative glioma recapitulates previous observations of CAR-independent, TEAM-mediated antitumor effects in our preclinical studies.[2] Moreover, several glioblastomas without *EGFR* amplification still readily express wild-type EGFR at the protein level,[12] which suggests a potential therapeutic window for the CARv3-TEAM-E platform even in the absence of overt genetic copy-number alterations. Additional work is needed to elucidate the nuances of antigen status and its relation to efficacy, as well as the nascent role of extracellular-vesicle–based liquid biopsy during therapeutic responses to cell therapy (i.e., as a marker of cell death, a proxy for tumor presence, or a predictor of clinical outcomes).

Despite the remarkable responses in this case

series, we observed eventual tumor progression in two of the three participants, which corresponded in part with limited persistence of CARv3-TEAM-E T cells over the weeks after infusion. As such, these data warrant future evaluation of CARv3-TEAM-E T cells alongside strategies specifically designed to enhance durability, perhaps through preconditioning with chemotherapy or additional scheduled infusions.[13]

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