



## ORIGINAL ARTICLE BRIEF REPORT

# Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy

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## Summary

A patient with recurrent multifocal glioblastoma received chimeric antigen receptor (CAR)–engineered T cells targeting the tumor-associated antigen interleukin-13 receptor alpha 2 (IL13R $\alpha$ 2). Multiple infusions of CAR T cells were administered over 220 days through two intracranial delivery routes — infusions into the resected tumor cavity followed by infusions into the ventricular system. Intracranial infusions of IL13R $\alpha$ 2-targeted CAR T cells were not associated with any toxic effects of grade 3 or higher. After CAR T-cell treatment, regression of all intracranial and spinal tumors was observed, along with corresponding increases in levels of cytokines and immune cells in the cerebrospinal fluid. This clinical response continued for 7.5 months after the initiation of CAR T-cell therapy. (Funded by Gateway for Cancer Research and others; ClinicalTrials.gov number, [NCT02208362](https://clinicaltrials.gov/ct2/show/study/NCT02208362).)

## Introduction

**G**LIOMASTOMA, AN AGGRESSIVE PRIMARY BRAIN TUMOR, IS AMONG THE MOST LETHAL OF HUMAN CANCERS. WE present evidence of the potential therapeutic benefit of adoptive T-cell therapy against glioblastoma with the use of CAR-engineered T cells targeting IL13R $\alpha$ 2, a glioma-associated antigen linked to a reduced rate of survival.<sup>1-3</sup> The clinical potential of CAR T-cell therapy has been most convincingly shown by the successful use of CD19-specific CAR T cells against refractory B-cell cancers.<sup>4-6</sup> However, extension of the use of CAR therapy beyond hematologic cancers and the efficacy of this therapy against solid tumors remain to be established.<sup>7,8</sup>

Our previous clinical study evaluating intracranial administration of CD8 T cells expressing a first-generation IL13R $\alpha$ 2-targeted CAR in patients with glioblastoma showed transient antiglioma responses with no high-grade therapy-related side effects.<sup>9,10</sup> Building on these initial results, we modified the IL13R $\alpha$ 2-targeted CAR T cells to improve antitumor potency and T-cell persistence by incorporating 4-1BB (CD137) costimulation and a mutated IgG4-Fc linker to reduce off-target Fc-receptor interactions<sup>11</sup> into the CAR (IL13BB $\zeta$ ) and by genetically engineering enriched central memory T cells.<sup>12,13</sup> To evaluate the safety and therapeutic potential of IL13BB $\zeta$ –CAR T-cell therapy for the treatment of high-grade glioma, we initiated a clinical trial and report here our clinical experience with one patient.

## Case Report

A 50-year-old man presented with glioblastoma in the right temporal lobe, with an unmethylated O<sup>6</sup>-methylguanine–DNA methyltransferase (MGMT) promoter, a nonmutated IDH1 R132H, and an IL13R $\alpha$ 2 H score of 100 (with no staining in 30% of cells, weak-intensity staining in

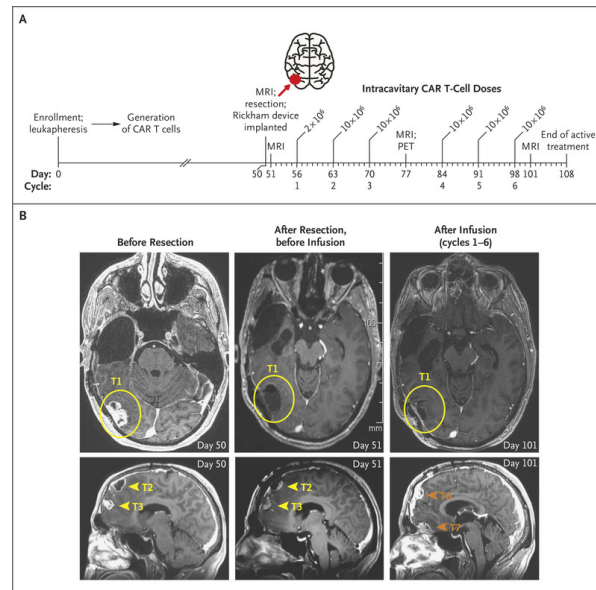
30%, moderate-intensity staining in 20%, and high-intensity staining in 10%) (Fig. S1 in the [Supplementary Appendix](#), available with the full text of this article at NEJM.org). The H score, a method of quantitating immunohistochemical results, is based on the following formula:  $(3 \times \text{the percentage of strongly staining cells}) + (2 \times \text{the percentage of moderately staining cells}) + (1 \times \text{the percentage of weakly staining cells})$ , resulting in a range of 0 to 300.

The patient received standard-of-care therapy consisting of tumor resection, radiation therapy, and temozolomide.<sup>14</sup> Six months after the diagnosis, magnetic resonance imaging (MRI) and positron-emission tomography–computed tomography (PET-CT) of the brain showed evidence of disease recurrence (Fig. S2A in the [Supplementary Appendix](#)). The patient was then enrolled in this clinical study of IL13R $\alpha$ 2-targeted CAR T cells (Fig. S2A in the [Supplementary Appendix](#)).

While the IL13BB $\zeta$ -CAR T cells were being manufactured, the patient participated in an investigational clinical trial (ClinicalTrials.gov number, [NCT01975701](#)) at a different institution (Fig. S2A in the [Supplementary Appendix](#)). However, the disease progressed rapidly during treatment, with the development of multifocal leptomeningeal glioblastoma involving both cerebral hemispheres (Figs. S3 and S4 in the [Supplementary Appendix](#)).

The patient then began to receive treatment in our clinical study and underwent resection of three of five progressing intracranial tumors (Figs. S4 and S5 in the [Supplementary Appendix](#)), including the largest tumor in the right temporal–occipital region (tumor 1) and two tumors in the right frontal lobe (tumors 2 and 3). Two smaller tumors in the left temporal lobe (tumors 4 and 5) were not surgically removed.

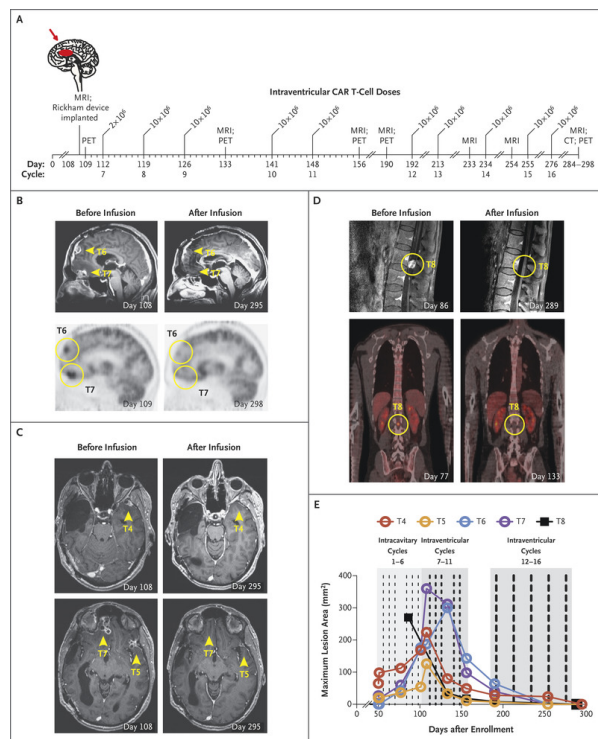
## Figure 1.



Local Tumor Control after Intracavitary Delivery of IL13BB $\zeta$ –Chimeric Antigen Receptor (CAR) T Cells.

IL13BB $\zeta$ –CAR T cells were administered according to dose schedule 1 (an initial infusion of  $2 \times 10^6$  CAR+ T cells followed by five infusions of  $10 \times 10^6$  CAR+ T cells) (Table S1 in the [Supplementary Appendix](#)), and the patient received weekly intracavitary infusions of IL13BB $\zeta$ –CAR T cells into the resected cavity of tumor 1 through a catheter device. Treatment was paused for assessment of safety and disease after the third and sixth infusions ([Figure 1](#), and Fig. S2A in the [Supplementary Appendix](#)).

**Figure 2.**



In this phase 1 study for recurrent malignant glioma, intracavitary infusions of CAR T cells targeting IL13R $\alpha$ 2 were administered as described in the Supplemental Methods section in the [Supplementary Appendix](#). Intraventricular infusions were then provided according to a compassionate-use protocol. Both protocols were approved by the institutional review board at the City of Hope, and the patient provided written informed consent. The [protocols](#) are available at NEJM.org. There was no commercial support for this study.

#### MANUFACTURE OF CELL PRODUCTS

Enriched central memory T cells were lentivirally transduced with an interleukin-13 (E13Y-mutated) ligand-based CAR<sup>2,15</sup> containing a 4-1BB costimulatory domain (IL13BB $\zeta$ ), and truncated CD19 (CD19t) was used as a marker for transduction (Fig. S6A and the Supplemental Methods section in the [Supplementary Appendix](#)). Details regarding the construction and manufacturing of the CAR T cells, product infusion, and additional procedures are included in the Supplemental Methods section in the [Supplementary Appendix](#).

To obtain sufficient material for 16 infusions, we manufactured two CAR T-cell products; the first was used for cycles 1 through 11, and the second was used for cycles 12 through 16. Both products (Fig. S6B and S6C in the [Supplementary Appendix](#)) were phenotypically similar and predominantly CD4<sup>+</sup> (74% and 90%, respectively); their CD19t expression (64% and 81%) was used to calculate CAR T-cell dosing.

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## Results



#### SAFETY AND ADVERSE-EVENT PROFILE

Intracavitary infusions (cycles 1 through 6) and intraventricular infusions (cycles 7 through 16) of IL13BB $\zeta$ -CAR T cells were delivered at a maximum dose of  $10 \times 10^6$  CAR<sup>+</sup> T cells. These infusions were not associated with any toxic effects of grade 3 or higher (Table S2 in the [Supplementary Appendix](#)).

Grade 1 or 2 events that were at least possibly attributable to therapy were observed within 72 hours after the T-cell infusions. These events included headaches, generalized fatigue, myalgia, and olfactory auras. Concomitant medications that may have influenced this safety profile included dexamethasone at a dose of 0 to 4 mg per day (Fig. S2D in the [Supplementary Appendix](#)), divalproex at a dose of 750 mg twice a day for seizure control, and acetaminophen as needed.

#### CLINICAL RESPONSE

At the time of treatment, the patient presented with a highly aggressive recurrent glioblastoma with features indicating a poor prognosis, including multifocal leptomeningeal disease (Figs. S3 and S4 in the [Supplementary Appendix](#)), histologic features of dedifferentiated glioblastoma (Fig. S5 in the [Supplementary Appendix](#)), and a proliferative rate of more than 60%. Expression of IL13R $\alpha$ 2 was heterogeneous but similar in the primary tumor and the recurrent tumors (tumors 1, 2, and 3); the mean ( $\pm$ SD) H scores in the primary tumor and in the recurrent tumors were 100 and  $88\pm 20$ , respectively (Figs. S1 and S5 in the [Supplementary Appendix](#)). Chromosomal analysis of the recurrent tumors also showed a clonal relationship with the primary tumor, albeit with some minor variations (Fig. S7 in the [Supplementary Appendix](#)).

During the six weekly intracavitary infusions (cycles 1 through 6) ([Figure 1A](#)), the treated tumor in the temporal–occipital region (tumor 1) remained stable for more than 45 days after surgery without evidence of disease progression ([Figure 1B](#)). However, MRI revealed that nonresected tumors in the left temporal lobe (tumors 4 and 5) and new tumors (tumors 6 and 7) near the resected lesions 2 and 3 were progressing ([Figure 1B](#)). In addition, new metastatic lesions in the spine causing leg numbness, including one large tumor that was 18 mm in diameter and several smaller tumors ( $\leq 4$  mm), were detected ([Figure 2C](#), and Fig. S2A in the [Supplementary Appendix](#)). These results suggested that although intracavitary administration of IL13BB $\zeta$ –CAR T cells may have prevented tumor recurrence locally (at the tumor 1 injection site), these infusions were not sufficient to effectively control tumor progression at distant sites.

Subsequently, we administered 10 intraventricular infusions of IL13BB $\zeta$ –CAR T cells into the right lateral ventricle without any other therapeutic interventions ([Figure 2A](#)). After the first three intraventricular infusions (on day 133), we observed a dramatic reduction in the size of all intracranial and spinal tumors, and after the fifth intraventricular infusion (on day 190), all tumors had decreased by 77 to 100% (Table S3 in the [Supplementary Appendix](#)).

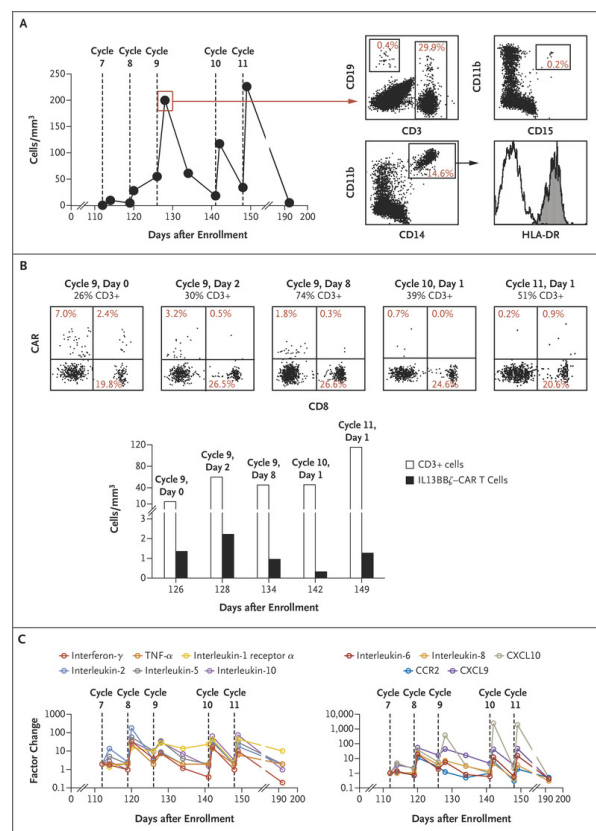
Five additional intraventricular infusions were administered (cycles 12 through 16), and during this consolidation phase, all lesions continued to resolve. The tumors were not measurable by means of MRI and remained undetectable by means of PET ([Figure 2B through 2E](#), and Table S3 in the [Supplementary Appendix](#)). Most remarkably, after intraventricular delivery of IL13BB $\zeta$ –CAR T cells, all metastatic tumors in the spine were completely eliminated ([Figure 2D and 2E](#)). During intraventricular treatment (day 108 through day 284), systemic dexamethasone was gradually eliminated (Fig. S2D in the [Supplementary Appendix](#)), and the patient returned to normal life and work activities.

This dramatic clinical response was sustained for 7.5 months after the initiation of CAR T-cell therapy, and none of these initial tumors (tumors 1 through 7 and spinal tumors) recurred. These results show that treatment with IL13BB $\zeta$ –CAR T cells mediated a complete response according to Response Assessment in Neuro-Oncology criteria (see the Supplemental Methods section in the [Supplementary Appendix](#)).<sup>16</sup> Unfortunately, this patient's disease eventually recurred after cycle 16 (228 days after the first CAR T-cell treatment) at four new locations that

were distinct and nonadjacent to tumors 1 through 7 and the spinal tumors. The cause of this tumor recurrence is currently under investigation, with preliminary results suggesting decreased expression of IL13R $\alpha$ 2 (Fig. S8 in the [Supplementary Appendix](#)).

### CAR T-CELL PERSISTENCE AND CENTRAL NERVOUS SYSTEM INFLAMMATORY RESPONSE

**Figure 3.**



Cerebrospinal Fluid (CSF) Analysis of Immune-Cell Populations, CAR T-Cell Persistence, and Inflammatory Cytokines during Intraventricular Therapy.

Immediately after each intraventricular infusion (on day 1 or 2), the total number of immune cells per cubic millimeter of cerebrospinal fluid increased by a mean ( $\pm$ SD) factor of  $7.0 \pm 3.6$ , as compared with preinfusion levels (on day 0 of each cycle), and typically decreased over the 7-day treatment cycle ([Figure 3A](#)). Evaluation on day 2 of cycle 9 showed that the immune-cell populations in the cerebrospinal fluid included both endogenous and CAR-expressing CD3<sup>+</sup> T cells, CD14<sup>+</sup>CD11b<sup>+</sup>HLA-DR<sup>+</sup> mature myeloid populations, CD19<sup>+</sup> B cells, and few



CD11b+CD15+ granulocytes (**Figure 3A**). Consistent with flow-cytometric data, cytopathological analysis of the cerebrospinal fluid on day 1 of cycle 11 confirmed the presence of reactive lymphocytes, monocytes, and macrophages (data not shown).

After the administration of intraventricular therapy (cycles 7 through 11), CAR+ T cells were detected at all time points evaluated (**Figure 3B**). CAR+ T cells persisted in the cerebrospinal fluid for at least 7 days, as indicated by their presence 7 days after cycle 8, before the cycle 9 infusion (CAR+ T cells composed 9.4% of CD3 cells on day 0 of cycle 9). We observed only small increases in levels of CAR+ T cells in the cerebrospinal fluid, with an increase by a factor of 1.6 after cycle 9 (day 2 of cycle 9 vs. day 0 of cycle 9), followed by a decrease by a factor of 2.3 over 8 days (as assessed on day 8 of cycle 9). In later cycles (e.g., on day 1 of cycle 10 and on day 1 of cycle 11), when the tumor burden was significantly lower, the numbers of CAR+ T cells in the cerebrospinal fluid after infusion decreased.

Each intraventricular infusion of IL13BB $\zeta$ -CAR T cells in cycles 7 through 11 was associated with significantly elevated levels of cytokines in the cerebrospinal fluid. The measured levels and calculated factor change for 30 cytokines are provided in Tables S4A and S4B in the **Supplementary Appendix**. Levels of 11 inflammatory cytokines increased by a factor of more than 10 from preinjection baseline levels (on day 0 of cycle 7) immediately after at least one infusion. These cytokines included interferon- $\gamma$ , tumor necrosis factor  $\alpha$ , interleukins 2, 10, 5, 6, and 8; chemokines C-X-C motif chemokine ligand 9 (CXCL9) (or monokine induced by interferon- $\gamma$  [MIG]), C-X-C motif chemokine ligand 10 (CXCL10) (or IP-10), and CCR2 (monocyte chemoattractant protein 1 [MCP-1]); and soluble receptor interleukin-1 receptor  $\alpha$  (**Figure 3C**). Increases in levels of inflammatory cytokines appeared to correspond with the incidence of grade 1 and 2 symptoms such as fever, fatigue, and myalgia (Table S2 in the **Supplementary Appendix**), and these levels returned to near baseline levels between weekly treatment cycles.

These immunologic changes were restricted to the cerebrospinal fluid, since no notable increases in levels of cytokines (Tables S5 and S6 in the **Supplementary Appendix**) and no CAR+ T cells (data not shown) were detectable in the peripheral blood. Unfortunately, we were unable to recover fluid during the intracavitary infusions for comparison, since the catheter tip, which was placed at the edge of the resection cavity, prevented aspiration of tumor cyst fluid.

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## Discussion



We report that autologous CAR T cells targeting IL13R $\alpha$ 2 mediated a transient complete response in a patient with recurrent multifocal glioblastoma, with dramatic improvements in quality of life, including the discontinuation of systemic glucocorticoids and a return to normal life activities. This clinical response was achieved despite the nonuniform tumor expression of IL13R $\alpha$ 2 and without previous chemotherapy

designed for depletion of lymphocytes. Such chemotherapy has been used to augment systemic adoptive T-cell responses,<sup>17,18</sup> but it was not incorporated in this study because of increased risks of bleeding and infection associated with surgical resection and uncertainty as to whether systemic depletion of lymphocytes would enhance responses to local delivery in the brain.

The use of CAR T cells for the treatment of solid tumors involves a unique set of challenges, including antigen validation, tumor trafficking and infiltration, tumor heterogeneity, and an immunosuppressive microenvironment.<sup>7,8</sup> This study provides proof-of-principle data that confirm IL13R $\alpha$ 2 as a useful immunotherapeutic target in glioblastoma and establish that CAR T cells can mediate profound antitumor activity against a difficult-to-treat solid tumor.

Insights from this study are derived from the comparison in one patient of two intracranial CAR T-cell delivery routes — infusion into the resected tumor cavity and infusion into the ventricular system. In this patient, both routes (intracavitary and intraventricular) had similar low toxicity profiles, but they differed in their apparent ability to abrogate tumor growth at distant sites. While intracavitary therapy appeared to control local tumor recurrence, progression of glioblastoma at distant sites, including the appearance of new lesions, was observed. By contrast, after intraventricular administration of IL13BB $\zeta$ -CAR T cells, regression of all central nervous system tumors, including spinal tumors, was achieved. It is possible that the leptomeningeal presentation of this patient's recurrent glioblastoma, which is often seen in late-stage refractory disease, may have rendered the tumors more responsive to intraventricular therapy. Nevertheless, these data provide support for further exploration of the usefulness of intraventricular administration of CAR T cells for the treatment of malignant brain tumors.

This case also highlights the potential role of the endogenous immune system in CAR T-cell-mediated antitumor responses. Immediate increases in endogenous immune cells and inflammatory cytokines after each intraventricular infusion suggest recruitment and stimulation of the host immune system. This finding may explain how a complete response was achieved even though the tumor did not uniformly express the target. Correlative studies to evaluate the potential contributions of endogenous immune responses after administration of IL13BB $\zeta$ -CAR T cells are under way.

This study showed antitumor activity against multifocal glioblastoma, with manageable therapy-related toxic effects, through targeting of the glioma-associated antigen IL13R $\alpha$ 2. The absence of systemic toxic effects is particularly noteworthy given the severe cytokine release syndrome and neurotoxicity that are often associated with antitumor responses against high disease burden in patients receiving CD19-targeted CAR T-cell therapy.<sup>19,20</sup> After each intraventricular infusion of IL13BB $\zeta$ -CAR T cells, we observed rapid and pleiotropic changes in levels of inflammatory cytokines in the cerebrospinal fluid, with significant increases in the interferon- $\gamma$ -inducible chemokines CXCL9 and CXCL10, which have antitumor potential.<sup>21,22</sup> These changes in cytokine levels did not affect neurologic function or the general well-being of

the patient and thus provide an initial framework for defining the range of achievable therapy-related changes in cytokine levels in the cerebrospinal fluid without the development of dose-limiting toxic effects.

Although this patient had a remarkable clinical response, CAR T-cell accumulation and expansion in the cerebrospinal fluid in later cycles and over the 7-day infusion cycle were limited. This might be due to less antigen drive as a consequence of decreased tumor burden or to immune rejection of the therapeutic product — although clinical symptoms indicative of a rejection response<sup>23</sup> were not observed. The use of our platform to manufacture central memory T cells<sup>12,13</sup> and the 4-1BB-containing CAR design were based on data showing improved antitumor potency and persistence in preclinical models (Brown CE, et al.: unpublished data). However, how these platform modifications translate to persistence of IL13BB $\zeta$ -CAR T cells and expansion in the cerebrospinal fluid, trafficking to tumor sites, or both in this patient remains uncertain.

The patient described here was a participant in this ongoing dose-escalation safety study to evaluate the role of intracranial CAR T-cell therapy targeting IL13R $\alpha$ 2 in patients with malignant gliomas. Among the seven patients who have received this therapy, this patient's clinical experience of receiving both intracavitary and intraventricular administration of IL13BB $\zeta$ -CAR T cells remains unique and has prompted the expansion of our phase 1 study to evaluate intraventricular administration in a larger cohort of patients. Overall, our clinical experience along with recent studies of human epidermal growth factor receptor 2-CAR T cells and epidermal growth factor receptor deletion mutant variant III (EGFRvIII)-CAR T cells against glioblastoma<sup>24,25</sup> provide initial evidence of the safety and antitumor activity of CAR T-cell immunotherapy in patients with malignant brain tumors.

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[Disclosure forms](#) provided by the authors are available with the full text of this article at NEJM.org.

Drs. Forman and Badie contributed equally to this article.

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## Supplementary Material

<a href="#">Protocol</a>	PDF	2414KB
<a href="#">Supplementary Appendix</a>	PDF	1420KB
<a href="#">Disclosure Forms</a>	PDF	366KB

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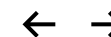
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