Cilta-cel CAR T cells as an effective and well tolerated treatment for POEMS: a case study

POEMS syndrome causes polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal plasma cells (M) and skin changes (S).[1] It is driven by vascular endothelial growth factor (VEGF) and proinflammatory cytokines such as interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α), leading to increased vascular permeability, edema, effusions, sclerotic bone lesions, papilledema, pulmonary hypertension, leukocytosis, and thrombocytosis.[2] Capillary leak syndrome is a major cause of death in POEMS, supporting a critical role of inflammatory cytokines in pathogenesis.[3]

Patients with advanced disease typically receive multiple myeloma (MM)-like therapy including autologous transplants.[2,4] However, there is no consensus on the treatment in the relapsed setting.[4] The approval of B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor T cells (CAR T), idecabtagene vicleucel (ide-cel), and ciltacabtagene autoleucel (cilta-cel),[5] transformed the outcomes of relapsed MM patients. To date, there is only one published report on the use of a non-standard CAR T in a single patient with POEMS without any translational immune data.[6] Herein, we report for the first time on the efficacy, toxicity, and immune-related consequences of cilta-cel in a patient with relapsed POEMS syndrome after multiple lines of therapy.

A 73-year-old male presented in June 2018 with a 6-month history of progressive neuropathy, lower extremity weakness, and an inability to walk. He experienced painful jerking spasms of the back and extremities, requiring high-dose opioids and muscle relaxants. On physical exam, he exhibited bilateral edema, severe upper and lower extremity weakness, absent deep tendon reflexes, diminished proprioception, foot drop, and steppage gait. Electromyography and nerve conduction studies revealed demyelinating polyneuropathy and reduced conduction velocity. He had blurred vision and papilledema on fundoscopy. Positron emission tomography/computed tomography (PET/CT) showed hepatomegaly, diffuse lymphadenopathy and sacral lytic/sclerotic lesions. He had thrombocytosis and anemia, an immunglogulin (Ig)A λ monoclonal protein of 0.8 g/dL, total IgA of 1,105 mg/dL, and serum free λ light chains of 82.9 mg/L. VEGF was 263 pg/mL (normal range, 9-80 pg/mL). Bone marrow (BM) biopsy showed 20% λ-restricted plasma cells with normal cytogenetics. He received daratumumab, lenalidomide, and dexamethasone, achieving a very good partial remission (VGPR), followed by lenalidomide maintenance. By February 2023, he relapsed with worsening painful neuropathy, spasms, and increasing edema. He received daratumumab, pomalidomide, and dexamethasone without significant improvement in markers or symptoms (Figure 1A, B). By April 2024, his neurological symptoms worsened, and he was unable to walk. Laboratory work showed evidence of biomarker progression and a PET/CT showed lymphadenopathy and paraspinal soft tissue lesions (Figure 1D) with confirmed plasma cells on a lymph node biopsy. After discussing his options, we proceeded with cilta-cel CAR T-cell therapy. He received $0.6x10^8$ cells after lymphodepletion with fludarabine and cyclophosphamide. Importantly, at baseline (pre-LD chemotherapy) only very few chemokines/cytokines showed significant levels in the patient's blood: monocyte chemoattractant protein-1 (MCP-1; 370 pg/mL), macrophage inflammatory protein-1 α (MIP-1α; 250 pg/mL), MIP-1β with 37 pg/mL, and perforin with 1,324 pg/mL.

The patient was enrolled into the Institutional Review Board-approved protocol 2043GCCC (IRB HP-00091736) for the immunomonitoring of patients following CAR T treatment. Blood and BM samples were collected and plasma was generated by centrifugation at 400g and frozen immediately at -80°C. Peripheral blood mononuclear cells (PBMC) were isolated using density gradient centrifugation and were either analyzed immediately or cryopreserved in liquid nitrogen until analysis.

On day+6 post CAR T, he developed grade 3 cytokine release syndrome (CRS), with increased serum ferritin and C-reactive protein (CRP); after two doses of tocilizumab, his symptoms resolved, and markers normalized (Figure 2A). On day+7, we found marked increases over baseline levels in his blood cytokine profile with interferon(IFN)-γ inducible protein 10 (IP-10) and MCP-1 showing the highest peak levels followed by MIP-1β, IL-6, IL-7, MIP-1β, granzyme B, IFN-γ, IL-13, and TNF-β (Figure 2B). By day+7, CAR T cells were detectable in the blood (Figure 2C). The CAR T cells were $CD4^+$ and $CD8^+$, displaying a central memory (CM) or effector memory (EM) phenotype (Figure 2D). Count recovery was achieved by day+10. He had no neurotoxicity. By day+14, most cytokines/chemokines levels had returned to baseline, except for perforin, which showed a "late" peak correlating with peak CAR T levels (Figure 2B,C).

Over the next few weeks, the patient continued to show high levels of $CD8^+$ and $CD4^+$ CAR T cells shifting to an EM and terminally differentiated effector memory (EMRA) phenotype (Figure 2C, D). By day+30, the patient had achieved a stringent complete remission with resolution of the osseous lesions and lymphadenopathy on PET/CT scans (Figure 1D). The clinical response was associated with a marked decrease in serum concentrations of VEGF and the patient's involved free light chains (Figure 1A), M-protein and total IgA levels (Figure 1B), as well as serum concentrations of soluble BCMA (Figure 1C). Over the next 6+ months, the CAR persisted in the patient's blood and continued to evolve into more differentiated effector-type

cells (Figure 2C, D). This durable CAR T response, without upregulation of exhaustion markers (e.g., Tim-3), was associated with strong CD27 expression on the CAR T; an established enhancer of CAR T activation/persistence;[7] and upregulation of CD127 (IL-7Rα), which is crucial for survival and protection from exhaustion of long-lived memory T cells (Figure 3).[8,9] Clinically, the patient reported resolution of his painful spasms, and improvement of jerking movements and edema. He had stopped all pain medications and reported a significant improvement in mobility.

Chronically elevated levels of proinflammatory cytokines are a typical POEMS feature and, accordingly, cytokine-modulating agents and even cytokine removal with plasmapheresis have been reported to be effective.[10,11] An engraftment syndrome with fever, weight gain, pulmonary infiltrates, skin rash, and diarrhea occurs in up to 50% of POEMS patients treated with an autologous stem cell transplant; possibly related to an aberrant cytokine production during hematopoietic recovery, and typically responds to steroids.[12] Importantly, cytokines involved in T-cell-mediated immune responses, such as IL-2/sIL-2R, have also been shown to be chronically elevated in POEMS patients.[11] In many cases, biomarker responses alone did not relieve POEMS symptoms if cytokine levels (e.g., VEGF) were persistently elevated.[10]

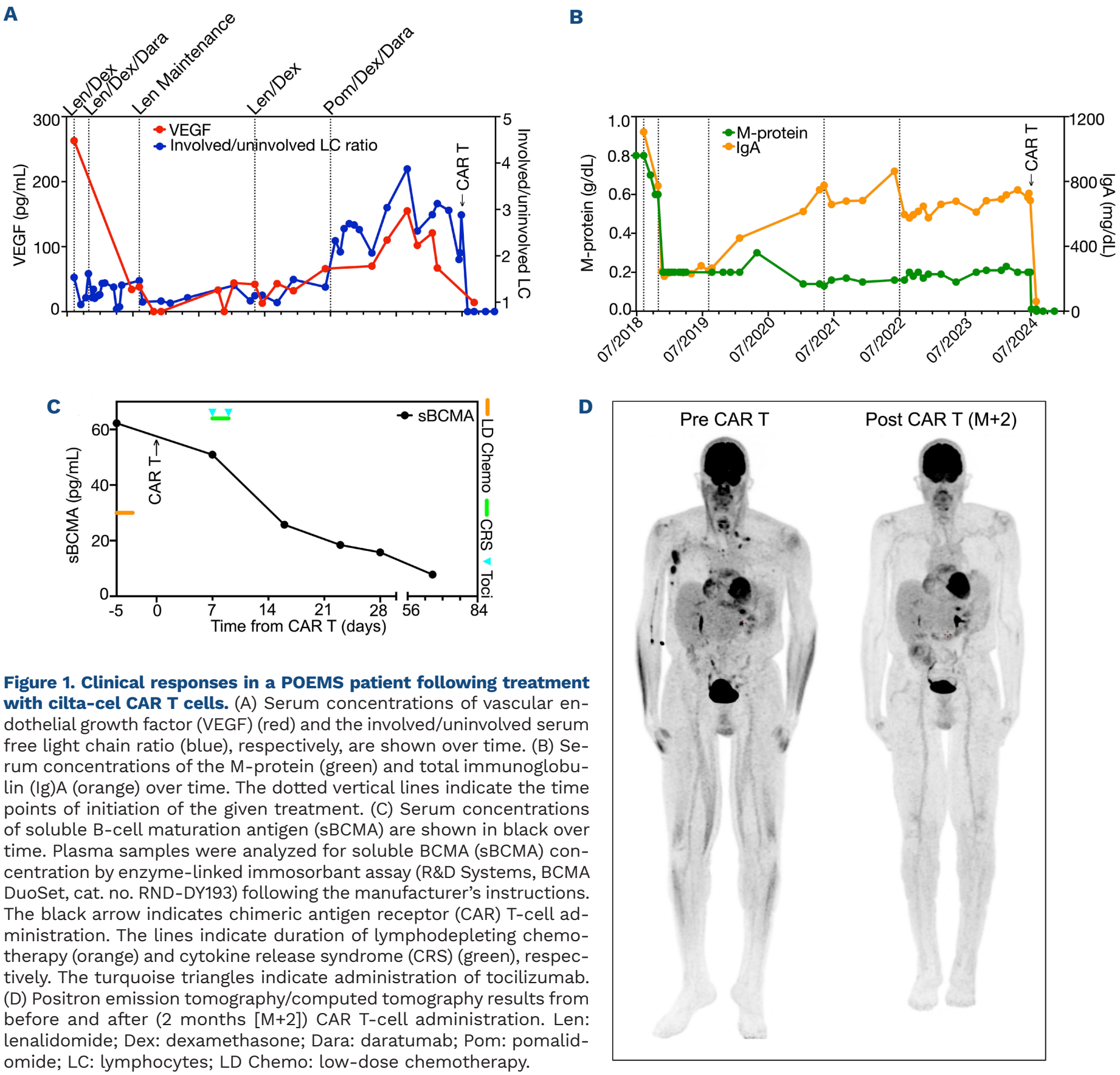

Figure 1. Clinical responses in a POEMS patient following treatment with cilta-cel CAR T cells. (A) Serum concentrations of vascular endothelial growth factor (VEGF) (red) and the involved/uninvolved serum free light chain ratio (blue), respectively, are shown over time. (B) Serum concentrations of the M-protein (green) and total immunoglobulin (Ig)A (orange) over time. The dotted vertical lines indicate the time points of initiation of the given treatment. (C) Serum concentrations of soluble B-cell maturation antigen (sBCMA) are shown in black over time. Plasma samples were analyzed for soluble BCMA (sBCMA) concentration by enzyme-linked immosorbant assay (R&D Systems, BCMA DuoSet, cat. no. RND-DY193) following the manufacturer's instructions. The black arrow indicates chimeric antigen receptor (CAR) T-cell administration. The lines indicate duration of lymphodepleting chemotherapy (orange) and cytokine release syndrome (CRS) (green), respectively. The turquoise triangles indicate administration of tocilizumab. (D) Positron emission tomography/computed tomography results from before and after (2 months [M+2]) CAR T-cell administration. Len: lenalidomide; Dex: dexamethasone; Dara: daratumab; Pom: pomalidomide; LC: lymphocytes; LD Chemo: low-dose chemotherapy.

Initially, we had several concerns about treating our patient with cilta-cel. First, the impact of CRS after CAR T-cell infusion on a patient already in a pro-inflammatory state. Interestingly, following CAR T-cell infusion, we saw a brisk, but transient increase of inflammatory cytokines and manageable CRS. Second, would a chronically activated immune system in POEMS impair the activity and/or expansion of the CAR T cells? It has been shown that patients with POEMS

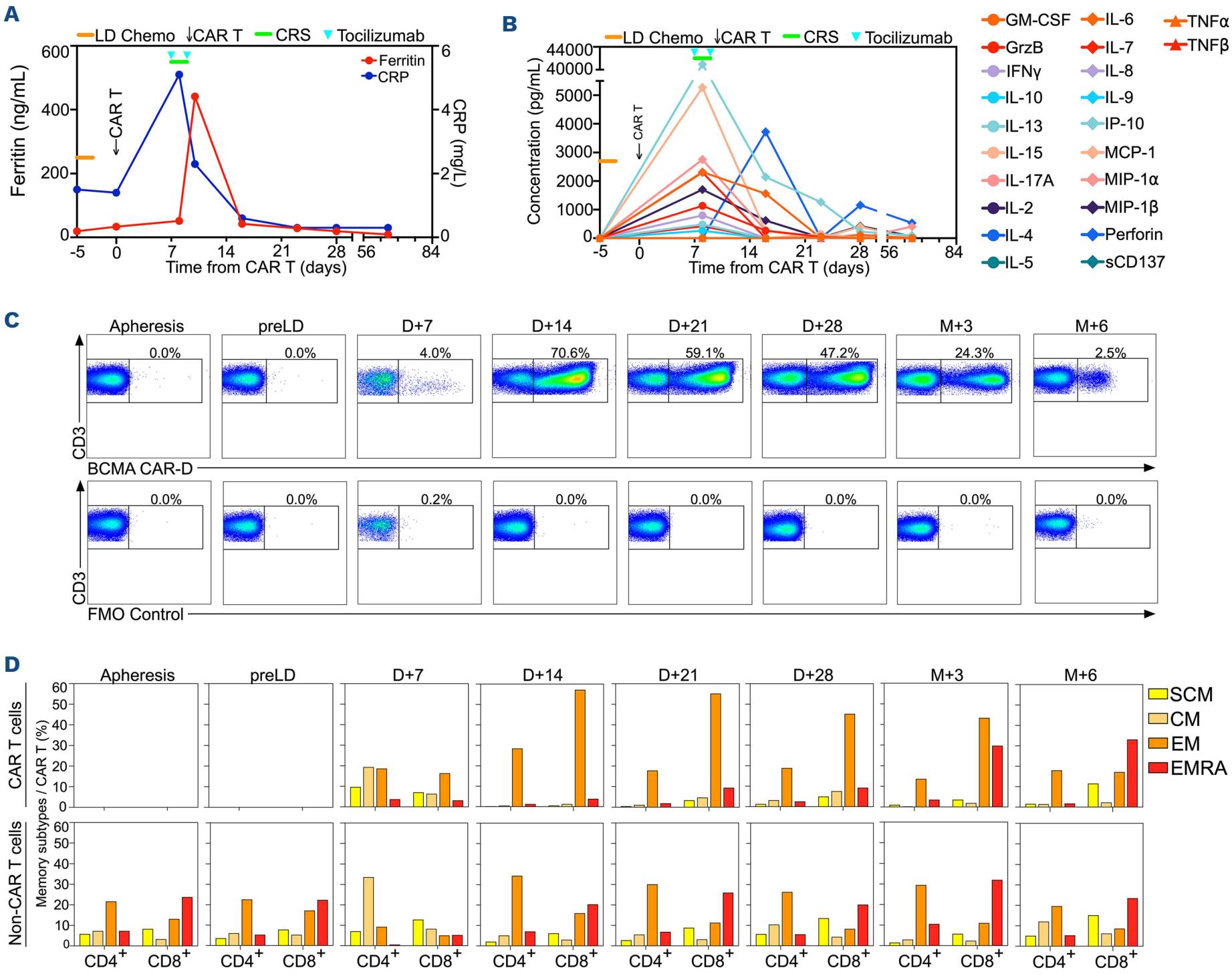

Figure 2. Cytokine and CAR T-cell responses to treatment of a POEMS patients using cilta-cel. (A) Serum concentrations of ferritin (red) and C-reactive protein (CRP) (blue) are shown over time. The black arrow indicates chimeric antigen receptor (CAR) T-cell administration. The lines indicate duration of lymphodepleting chemotherapy (orange) and cytokine release syndrome (CRS) (green), respectively. The turquoise triangles indicate administration of tocilizumab. (B) Serum concentrations of 22 cytokines/chemokines were measured over time in our POEMS patient using CodePlex Secretome technology. Cytokine/chemokine concentrations were quantified using the CodePlex Secretome Human Adaptive Immune Panel kit (IsoPlexis, cat. no. CODEPLEX-2L01). To carry out the CodePlex analysis, samples were added to a chip microchamber. The chip was then loaded into the Isolight reader (Isoplexis, Branfold, CT) and automated analysis of raw data was performed using IsoSpeak software (Isoplexis). Results are shown as absolute concentrations in pg/mL minus baseline levels from the pre-low-dose chemotherapy (LD Chemo) time point. (C) Analysis of B-cell maturation antigen (BCMA)-targeted CAR T-cell numbers in the peripheral blood (PB) over time before and after CAR T infusion. Analyses were performed by flow cytometry following co-staining with anti-CD3 and BCMA CAR detection reagent which represents a fluorescent, full-length, recombinant BCMA protein binding to the CAR expressed on the cell surface. Samples were acquired using a Miltenyi MACSQuant Analyzer 10. Background levels without CAR staining are shown below. Numbers indicate percentages of all $CD3^+$ T cells. (D) Different T-cell memory subpopulations among CAR T cells (upper panel) and non-CAR T cells (lower panel) were identified by flow cytometry using co-staining with anti-CD45RA and anti-CD62L monoclonal antibodies; cilta-cel: ciltacabtagene; INF: interferon; IL: interleukin; GrzB: granzyme B; GM-CSF: granulocyte macrophage colony-stimulating factor; d: day; M: month; SCM: stem cell-lime memory ; CM central memory, EM: effector memory; EMRA: terminally differentiated EM.

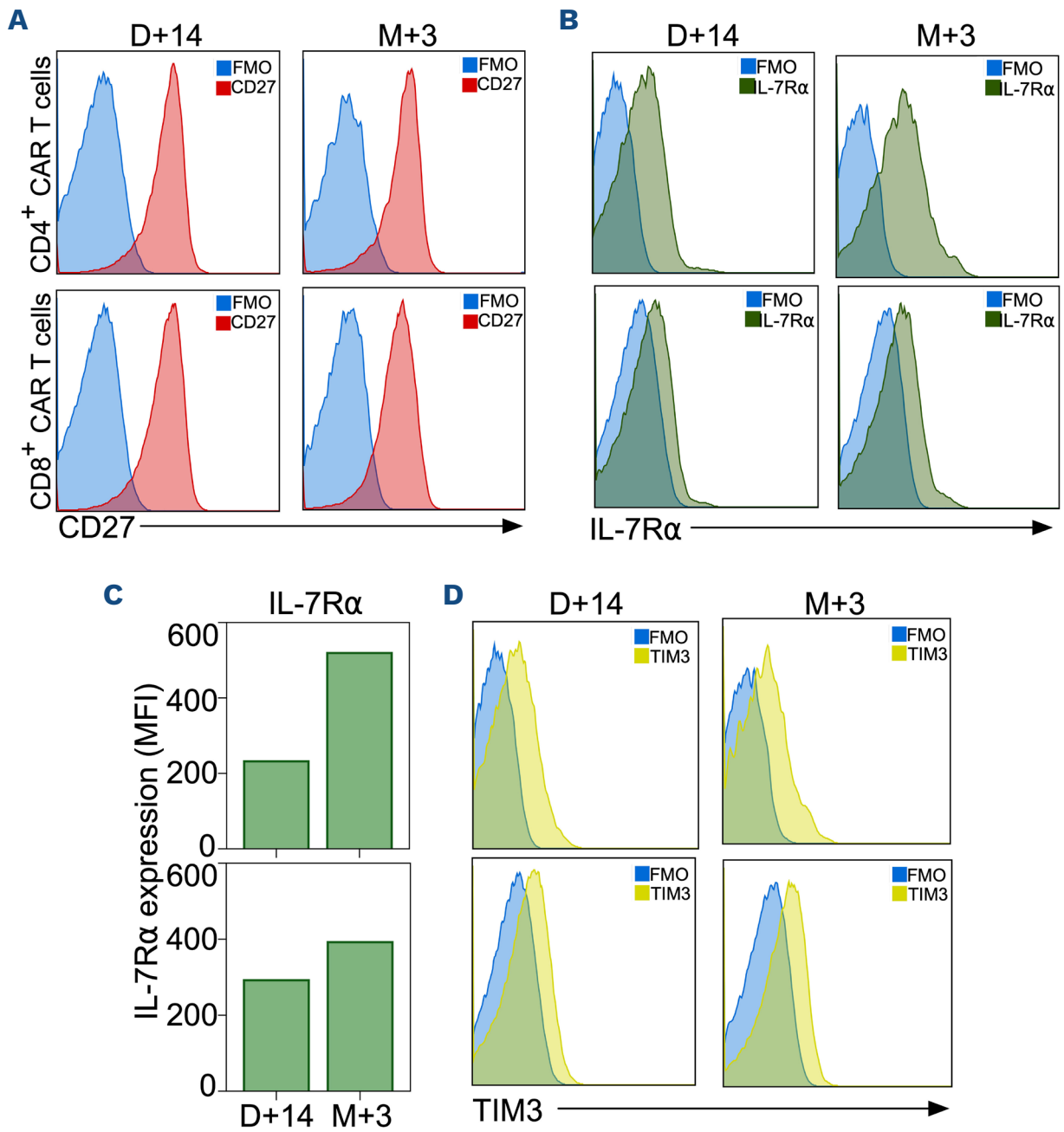

Figure 3. Factors potentially promoting long-term persistence of the CAR T in our POEMS patient. (A) Surface expression levels of CD27 on CD4+ or CD8+ chimeric antigen receptor (CAR) T cells on day+14 (D+14) and at month+3 (M+3), respectively. (B) Surface expression levels of CD127 (IL-7Rα) on CD4+ or CD8+ CAR T cells on D+14 and at M+3, respectively. (C) Green bars indicate mean fluorescence intensity (MFI) on CD4+ or CD8+ CAR T cells on D+14 and at M+3, respectively. (D) Surface expression levels of exhaustion marker TIM3 on CD4+ or CD8+ CAR T cells on D+14 and at M+3, respectively.

evidence a higher proportion of chronically antigen-stimulated and exhausted T cells in their BM.[13] However, we demonstrated, for the first time, that even in the setting of chronic inflammation and potential T-cell exhaustion, CAR T cells were effectively manufactured, expanded rapidly and persisted long-term after infusion, leading to a complete response. Last, BCMA-targeting CAR T cells and especially cilta-cel, have been associated with acute neurologic toxicity (ICANS), delayed effects on cranial nerves, and a progressive Parkinson-like syndrome.[5,14,15] However, despite pre-existing neuropathy in our patient, there was no CAR T-related neurotoxicity; on the contrary, he experienced a marked improvement in his pre-existing neurologic symptoms. Successful treatment of POEMS requires elimination of the malignant clone as well as control of cytokine levels such as VEGF - both goals were achieved in our patient.[1,4] In summary, we report on the safety and efficacy of cilta-cel in a POEMS patient relapsing after multiple lines of therapy. Cilta-cel CAR T cells showed robust expansion/persistence without inducing a toxic cytokine storm and led to a deep and durable clinical response. More cases will help define the role of CAR T-cell therapy in this devastating and rare disorder.

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Contributions

MW collected patient clinical data. DA, RM and DY processed patient samples, performed laboratory experiments, analyzed the data and made figures. AB designed the study, treated the patient, contributed patient material. All authors wrote and approved the final manuscript.

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Data-sharing statement

Study data will be made available upon request by email.

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