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Chronic inflammatory demyelinating polyneuropathy (CIDP) after cilta-cel therapy

Ciltacabtagene-autoleucel (cilta-cel) is a CAR-T cell therapy highly active in relapsed/refractory multiple myeloma but can induce severe immune-mediated toxicities. We describe two patients who developed chronic inflammatory demyelinating polyneuropathy (CIDP) after cilta-cel. Patient 1 presented with rapidly progressive gait ataxia, flaccid paraparesis, and oculomotor palsy 112 days post infusion; Patient 2 developed an analogous syndrome on day 19. In both patients, electromyography and nerve-conduction studies confirmed sensorimotor axonal-demyelinating neuropathy; brain MRI and CSF infection panels were unremarkable. CAR-T cells were detectable in blood and CSF, yet a predominance of $CD8^+$ non-CAR-Tcells was observed. TCR-β sequencing revealed a hyper-expanded clone (~30% of all reads) in patient 1 versus a polyclonal repertoire in patient 2. High-dose dexamethasone plus intravenous immunoglobulin failed to improve neurologic symptoms and prompted T-cell-depleting cyclophosphamide, which lowered CAR- and non-CAR-T cells. Patient 1 died from respiratory failure, whereas patient 2 improved and could be discharged. These observations indicate that CIDP is a severe complication of cilta-cel therapy and may arise from bystander expansion of autoreactive $CD8^+$ T-cells rather than direct CAR-T cell activity. Timely escalation to T-cell-depleting therapy may improve outcomes.

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Dear Editor,

Ciltacabtagene-autoleucel (cilta-cel), a chimeric antigen receptor T (CAR-T) cell targeting B-cell maturation antigen (BCMA), is approved for relapsed/refractory multiple myeloma (MM). Beyond hematologic malignancies, CAR-T cell therapy shows promise in autoimmune rheumatic and immune-mediated neurological disorders [1]. Despite efficacy, CAR-T cells can cause severe adverse events including cytokine release syndrome (CRS), secondary T-cell lymphomas, gastrointestinal symptoms, and Parkinsonism [2–5]. Neurological complications, usually linked to immune cell-associated neurotoxicity syndrome (ICANS), typically occur early post-infusion; delayed or atypical sequelae are poorly understood [4, 6–8]. Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare immune-mediated disorder involving T-cell and antibody-driven inflammation and demyelination of peripheral nerves, causing progressive motor and sensory deficits. Recently, BCMA/CD19 bispecific CAR-T cells have been tested in treatment-refractory CIDP, showing benefit as a novel immunomodulatory approach [9]. We report two cases of CIDP following BCMA-specific CAR-T cell therapy.

Two female patients (65 and 73 years) with relapsed MM and extramedullary lesions received cilta-cel after fludarabine/cyclophosphamide lymphodepletion. Both were in partial remission before infusion. Early toxicities were limited: neither patient developed ICANS; one experienced CRS°2, which resolved after a single tocilizumab dose. Both were discharged two weeks postcilta-cel infusion. By day 30, bone-marrow biopsy and serological markers revealed a complete response, including radiological reduction of extramedullary tumor. Patient 1 experienced insidious, progressively worsening gait ataxia and lower-limb weakness beginning on day 112 after cilta-cel infusion, whereas patient 2 developed similar symptoms on day 19 post CAR-T, characterized by bilateral abducens-nerve palsy with inward eye deviation. Electromyography and nerve conduction studies revealed mixed sensorimotor axonal demyelinating polyneuropathy (Supplementary Table 1). No abnormalities were observed in cranial MRIs and routine EEGs. Blood tests for viral infection, including CMV, were negative. Cerebrospinal fluid (CSF) analysis showed no viral infections or malignant plasma cells, and protein concentrations were within normal limits. Each patient exhibited immunoparesis at symptom onset. CAR-T cells were detected in the peripheral blood and CSF of both patients (Figs. 1A and 2A, Supplementary Table 1) and in the bone marrow of patient 2. Detection of CAR-T cells in the bone marrow of patient 1 was not performed. Both patients received high-dose dexamethasone and intravenous immunoglobulin therapy, standard treatment for CIDP, which resulted in partial symptom control in patient 1. However, due to new onset progressive neurological decline marked by ascending sensorimotor deficits and areflexia in both patients, cyclophosphamide was initiated intravenously for patient 1 and orally for patient 2 to deplete T-cell activity on day 97 and 15 after symptom onset, respectively. Additionally, patient 1 received intrathecal triple therapy 103 days after symptom onset with CSF cell counts decreasing from 7/µl to 1 /µl, while patient 2 was treated with intrathecal dexamethasone 18 and 23 days (CSF cell count 1/µl) after symptom onset (Figs. 1A and 2A, Supplementary Table 1). In patient 1, cyclophosphamide and intrathecal chemotherapy was postponed due to a previously stable neurological condition that deteriorated after a severe infection on day 87 after symptom onset. Patient 2 showed gradual neurological improvement including marked gains in gait and postural stability and a complete resolution of the abducens nerve palsy. This improvement allowed for discharge 86 days after symptom onset with continued neurological recovery observed 10 months later. Patient 1, however, succumbed to progressive neurological deterioration and treatment-refractory infections 114 post symptom onset (Figs. 1A and 2A). Serious infectious complications, including recurrent pneumonia and invasive aspergillosis due to cytopenia in patient 1 and COVID-19 pneumonia and

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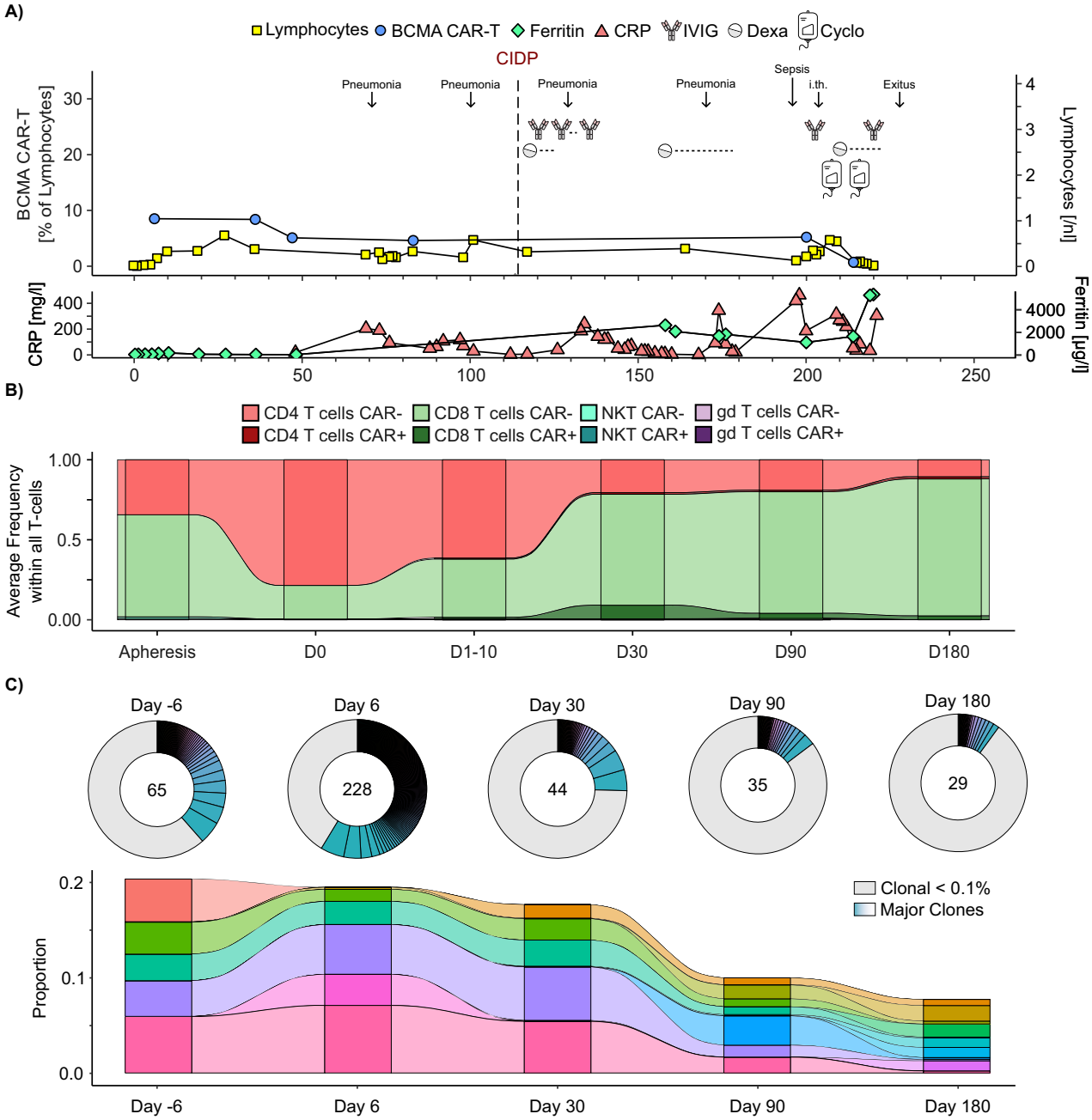

Fig. 1 Clinical course, immune cell profiling, and TCR-β sequencing in patient 1. A Clinical timeline showing CAR-T cell kinetics and inflammatory markers. The upper panel displays BCMA-CAR-T cells as a percentage of total lymphocytes (flow cytometry) and absolute lymphocyte counts (CBC), with CAR-T cells identified via spectral flow cytometry. The lower panel illustrates the course of C-reactive protein (CRP) and ferritin. IVIG was administered at 20 g on days 120 and 127–130, 10 g on days 131 and 220, and 30 g on day 202. An additional dose of IVIG was administered on day 136, although the exact dosage is not documented. Therapeutic interventions are indicated. Dexa: dexamethasone, IVIG: intravenous immunoglobulin, Cyclo: cyclophosphamide, i.th.: intrathecal chemotherapy. **B** Alluvial plot depicting the average distribution of T-cell subsets (as a proportion of all T-cells) across selected time points, based on spectral flow cytometry. **C** T-cell clonality assessed by TCR-β sequencing. Donut plots (upper panel) show the proportion of dominant clones (>0.1% of all sequences), with each colored segment representing a distinct clone; bar width corresponds to clonal size. The lower panel presents an alluvial plot illustrating the temporal dynamics the largest T-cell clones identified at each timepoint.

urosepsis in patient 2, were prominent during hospitalization. Both patients required admission to the intensive care unit. Additionally, on day 37 post symptom onset, patient 2 developed new neurological deficits, including a right upper quadrant visual loss and diplopia, prompting a cranial CT scan, revealing a subacute posterior infarction (Figs. 1A and 2A). Lymphocyte counts in patient 1 remained low throughout the disease course, with a detectable population of BCMA-directed CAR-T cells despite treatment with high-dose dexamethasone and IVIG; a decline in CAR-T cell levels was only observed following cyclophosphamide administration. In contrast, BCMA CAR-T cell levels in patient 2 decreased upon initiation of dexamethasone and declined further under cyclophosphamide therapy, correlating with gradual neurological improvement (Figs. 1A and 2A).

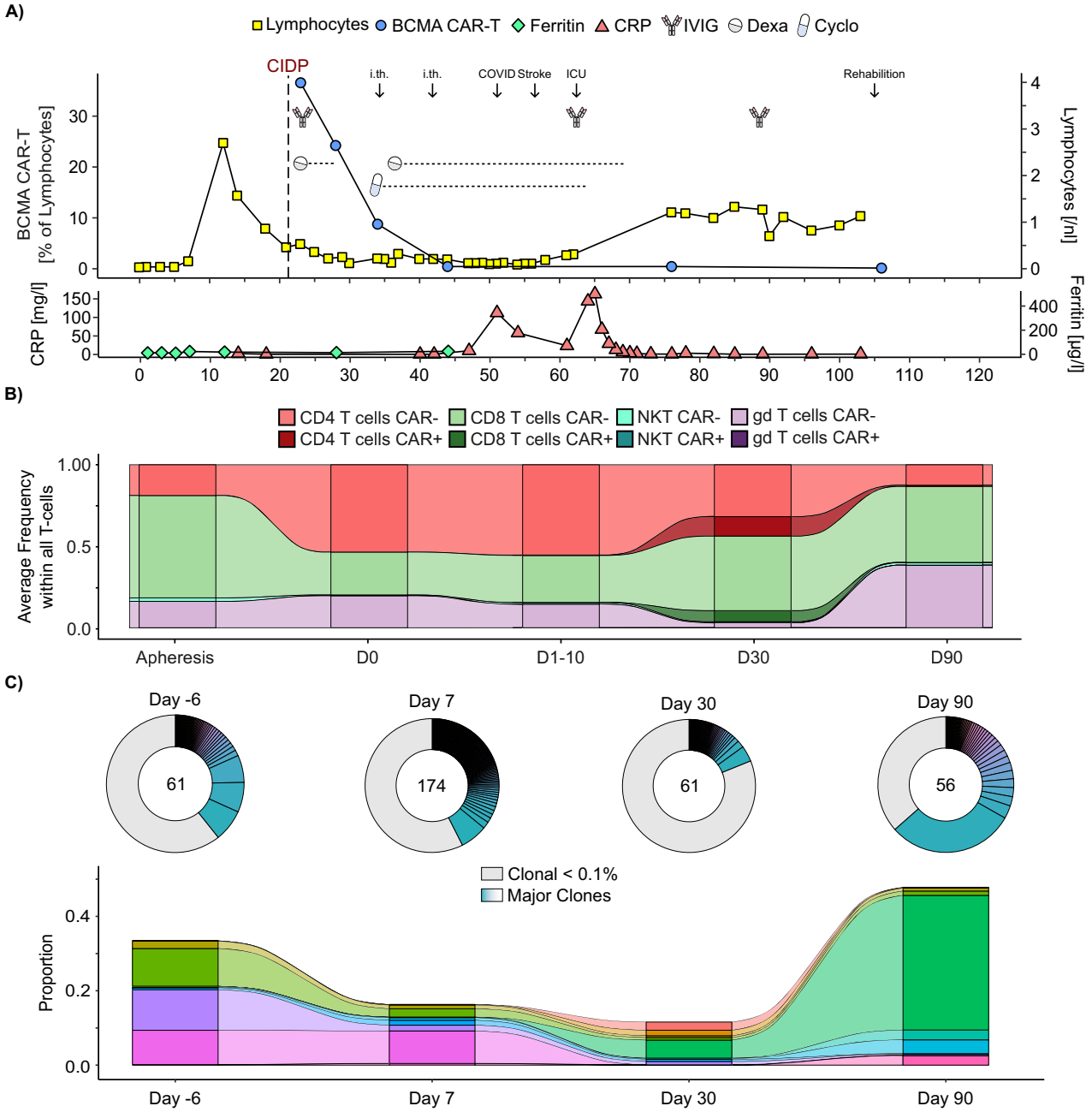

Fig. 2 Clinical course, immune cell profiling, and TCR-β sequencing in patient 2. A Clinical timeline showing CAR-T cell kinetics and inflammatory markers. The upper panel displays BCMA-CAR-T cells as a percentage of total lymphocytes (flow cytometry) and absolute lymphocyte counts (CBC), with CAR-T cells identified via spectral flow cytometry. The lower panel illustrates the course of C-reactive protein (CRP) and ferritin. IVIG was administered at 20 g on days 23 and 89, and 30 g on day 63. Therapeutic interventions are indicated. Dexa: dexamethasone, IVIG: intravenous immunoglobulin, Cyclo: cyclophosphamide, i.th.: intrathecal chemotherapy. **B** Alluvial plot depicting the average distribution of T-cell subsets (as a proportion of all T-cells) across selected time points, based on spectral flow cytometry. **C** T-cell clonality assessed by TCR-β sequencing. Donut plots (upper panel) show the proportion of dominant clones (>0.1% of all sequences), with each colored segment representing a distinct clone; bar width corresponds to clonal size. The lower panel presents an alluvial plot illustrating the temporal dynamics the largest T-cell clones identified at each timepoint.

To better understand the immunopathology of this rare complication, we performed spectral flow cytometry and T-cell receptor (TCR) repertoire sequencing. Serial spectral-flow cytometry revealed a relative expansion of CD8⁺ non-CAR-T cells with only a minimal fraction of CAR-T cells; Patient 2 also showed a pronounced γδ-T-cell expansion on day 90. CAR-T cells remained only a small subset of T-cells (Figs. 1B and 2B). In-depth phenotypic analysis showed that CD8⁺ non-CAR-T cells in both patients predominantly exhibited effector and effector memory phenotypes, with dynamic changes in the naïve subset and a constant population of central memory T-cells over time. CD4⁺ non-CAR-T cells were mainly central and effector memory type, with a variable regulatory T-cell component in patient 1 (Supplementary Figs. 1a and 2a). Cytokine profiling revealed distinct kinetics: Patient 2 showed persistently high IL-6, IL-2, IFN-γ and cytotoxic effectors from baseline to day 180, consistent with sustained cytotoxic T-cell activity possibly involving

γδ-T-cells, whereas patient 1 displayed low baseline levels but a late rise in IL-2, IL-4 and cytotoxic effectors, suggesting delayed activation (Supplementary Fig. 3). TCR-β sequencing revealed a polyclonal T-cell response in patient 1, characterized by an increase in clones immediately after CAR-T cell infusion, followed by a gradual decline. Patient 2 exhibited a prominent hyperexpanded clone, accounting for approximately 30% of the T-cell repertoire (Fig. 2C, D). Notably, the hyperexpanded T-cell clone was also detected in the bone marrow albeit at lower frequencies. At early time points clonal size in the bone marrow was comparable to that in the peripheral blood for both patients, however by day 30 post infusion it was approximately twofold higher in the bone marrow of patient 2 (Supplementary Figs. 1b, c and 2b, c). Cross-referencing a curated epitope database revealed the highest number of matches with viral epitopes and only a few with autoimmune responses. Interestingly, five exact CDR3 sequence matches were identified in patient 1 and one in patient 2 exclusively within non-expanded T-cell clones previously linked to Guillain–Barré syndrome (GBS) [10].

These two cases add to emerging evidence that CIDP — beyond classic ICANS — represents a rare yet potentially life-threatening neurotoxicity of BCMA-directed CAR-T cell therapy. While the CARTITUDE studies have already described Parkinson-like late manifestations, our description of rapidly progressive, predominantly peripheral neuropathy consistent with CIDP expands the spectrum of "non-ICANS" toxicities [4]. The recent EBMT guidelines therefore, call for a structured management beyond ICANS algorithms [11]. Systematic registry data show that delayed neurotoxicity after BCMA-CAR-T cell therapy is rare (<5%) but associated with high morbidity [12]. In addition to our CIDP cases, the literature reports GBS after BCMA- and after CD19-CAR-T cell therapy, as well as Parkinsonism, cognitive deficits, and cranial neuropathies [4, 6–8]. In the largest FAERS analysis to date, 67 serious neurotoxicity events were found under BCMA-CAR-T cell therapy, 21% of which were non-ICANS polyneuropathies [13]. Our two CIPD cases thus fit into a heterogeneous but consistent pattern of autoimmune-inflammatory complications associated with T-cell therapies. The onset of CIDP in patients after B-/plasma-cell depleting therapies seems paradoxical, especially since BCMA/CD19 bispecific CAR-T cells have been used successfully in therapy-refractory CIDP [9]. However, both cellular and humoral immune reactions likely contribute to peripheral-nerve damage in CIDP. Remarkably, polyclonal CD8⁺ non-CAR-T cells predominated in our two patients, whereas the CAR-T cell burden in blood and CSF was low. Additionally, we identified a higher proportion of γδ-T-cells in patient 2, which may have contributed to aberrant immune activation. While prior work has suggested direct neurotoxic effects of CAR-T cells, our data support a model in which secondary activation of autoreactive, polyclonal T-cells—rather than CAR-T cells themselves—mediates neurotoxicity [4, 6]. A recently published mouse model demonstrating that CAR-T cell therapy induces white matter neuroinflammation via indirect immune activation aligns with our observation [14]. This is supported by the fact that the common first-line therapy with high-dose steroids ± IVIG showed no adequate therapeutic effect in our patients. In patient 2, cyclophosphamide and intrathecal dexamethasone led to a reduction of CAR-T and CD8+ T-cells accompanied by clinical improvement. Together with previously published single cases, this argues for early escalation to T-cell-depleting strategies in patients with neurotoxicity. For example, intrathecal methotrexate + cytarabine has been used successfully for movement/cognitive toxicities after cilta-cel [15]. Further studies are needed to clarify the interplay between CAR-T cell persistence, cytokine signature, and polyclonal T-cell activation. Importantly, a normal brain or spinal MRI should not deter suspicion of an immune-mediated process. In affected patients, rapidly initiated electromyography, nerve conduction studies, and CSF cytometry, including CAR-T cell detection, are essential for diagnostic workup.

In conclusion, the cases reported here exemplify that CIDP is a rare but serious complication after CAR-T cell therapy. Beyond confirming previous observations of delayed neurotoxicity, we provide novel insights implicating polyclonal CD8⁺ non-CAR-T cell expansion as a likely driver of CIDP. These findings underscore the need for prospective monitoring strategies capturing not only ICANS but also other delayed, non-classical neurotoxicity. Our work supports early initiation of T-cell-depleting therapies in such cases and offers a rationale for mechanistic studies to further delineate the immunopathology underlying these rare but impactful events.

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DATA AVAILABILITY

All raw data not present in the manuscript are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

MK conceptualized the study, designed and performed experiments, analyzed data, and wrote the manuscript. JL and SY designed and performed experiments, analyzed data, and reviewed the manuscript. SS, UMD, JB, MO, DB, NCG, VvL, SB, ET, SH, and CF interpreted results and reviewed the manuscript. LH performed experiments. SHa, UK, JK, and AB conceptualized the study, designed experiments, interpreted data, and wrote the manuscript.

COMPETING INTERESTS

AB: Received honoraria not related to this manuscript from Novartis, Kite, MSD, AstraZeneca, and Takeda, as well as travel grants from Gilead, Takeda, and Janssen. JK: Advisory role, consulting, and travel support from Johnson & Johnson.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Clinical data were retrospectively collected from health records following institutional approval (Ethikkommission der Charité – Universitätsmedizin Berlin: EA2/142/20). Informed consent was obtained from all participants. All methods were carried out in accordance with relevant guidelines and regulations.

ADDITIONAL INFORMATION

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