BCMA x CD3 T-cell engager in a patient with penta-refractory multiple myeloma and HIV: a clinical and immunological report

T-cell-based immunotherapies aimed at redirecting cytolytic T-cell responses against tumor cells have transformed therapeutic opportunities. B-cell maturation antigen (BCMA)-targeted agents to treat relapsed or refractory multiple myeloma (RRMM) have recently been authorized in the United States and the European Union. Teclistamab is the first BCMA x CD3 bispecific T-cell engager (TCE) approved for RRMM after three previous lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.[1] In the phase I-II MajesTEC-1 study, teclistamab induced deep and durable responses with manageable toxicity,[2] and its high efficacy compared to the standard of care in RRMM highlights its clinical relevance.[3] However, data on teclistamab and other T-cell-based immunotherapies, such as chimeric antigen receptor (CAR) T cells, in people living with human immunodeficiency virus (HIV) (people with HIV [PWH]) are lacking. Currently, only a few studies have reported on anti-CD19 CAR T cells in HIV-associated lymphomas[4] and there are no data on bispecific antibody treatments in PWH. This data gap results from the *a priori* exclusion of PWH from the respective clinical trials due to safety concerns[2] despite a statement of the American Society of Clinical Oncology supporting clinical trial eligibility of PWH with well-controlled HIV.[5] Theoretically, TCE therapy might be affected by the composition and disturbance of the T-cell compartment caused by HIV.[6] Here, we report our encouraging experience with this novel option in a penta-refractory RRMM patient in the setting of HIV-associated immunodeficiency.

This 54-year-old man was diagnosed with HIV-1 infection in September 2010 at Centers for Disease Control and Prevention/World Health Organization stage A2 (268 $CD4^+$ cells/μL and 157,000 HIV-1 RNA copies/mL). Antiretroviral therapy (ART) was initiated within a randomized clinical trial (*clinicaltrials gov. Identifier: NCT01108510*) consisting of cobicistat-boosted atazanavir, tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). In August 2011, ART was modified to TDF/FTC and ritonavir-boosted darunavir due to insufficient virological response. Since then, under various ART regimens (mostly modified for non-virological reasons), a sustained viral suppression below 50 HIV-1 RNA copies/mL was observed. However, a moderate immunodeficiency with $CD4^+$ T cells constantly below 500/μL persisted. A sustained virological response for a chronic hepatitis C co-infection (genotype 3) was achieved in early 2015 with daclatasvir/sofosbuvir.

In August 2013, the patient was diagnosed with Durie-Salmon stage IIIA light-chain κ multiple myeloma after experiencing recurrent hip pain. In February 2022, a cytogenetic analysis revealed chromosome 1q-amplification, a prognostic marker associated with inferior outcome.[7] After VCD induction (bortezomib, cyclophosphamide, dexamethasone) followed by high-dose melphalan and autologous peripheral blood stem cell transplantation in January 2014, a complete response according to international consensus criteria was achieved.[8] In January 2017, a newly developed osteolysis confirmed a relapse of the disease. Second-line therapy was initiated with KRd (carfilzomib, lenalidomide, dexamethasone) followed by lenalidomide maintenance therapy, resulting in partial response.

Due to a second relapse with multiple, newly developed osteolytic lesions and a pathological rib fracture, the patient was referred to our tertiary center in September 2020. DVd therapy (daratumumab, bortezomib, dexamethasone) was initiated, inducing a partial response (Figure 1A). A third relapse in October 2021 was refractory to PCd (pomalidomide, cyclophosphamide, dexamethasone) and Isa-KCd (isatuximab, carfilzomib, cyclophosphamide, dexamethasone). Salvage therapy with VTd-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide) achieved a minor response. Case discussion in the tumor board led to the recommendation of BCMA-targeted CAR T-cell therapy. Despite previous hematological treatment without HIV-related complications and consolidation of viral suppression by switching from a rilpivirine-based to a bictegravir-based ART in January 2022, CAR T-cell therapy was unfeasible due to a positive but not quantifiable result in a highly sensitive HIV-1 RNA polymerase chain reaction (PCR) (limit of detection 13.2 copies/mL) which precluded CAR T manufacturing according to good manufacturing practice (Figure 1B).

Due to progressive disease in July 2022, therapy with the BCMA x CD3 TCE teclistamab once weekly was initiated despite the lack of treatment experience in PWH. Alternative treatment options such as selinexor-based treatment seemed inferior to teclistamab in this patient with highly refractory myeloma, and other bispecific antibodies had not been approved at that time. Acyclovir, trimethoprim/sulfamethoxazole, and intravenous immunoglobulins were administered as infection prophylaxis. Except for one grade 3 infection of unknown origin about 4 weeks after treatment initiation, the patient did not suffer from any severe adverse events. A very good partial response was

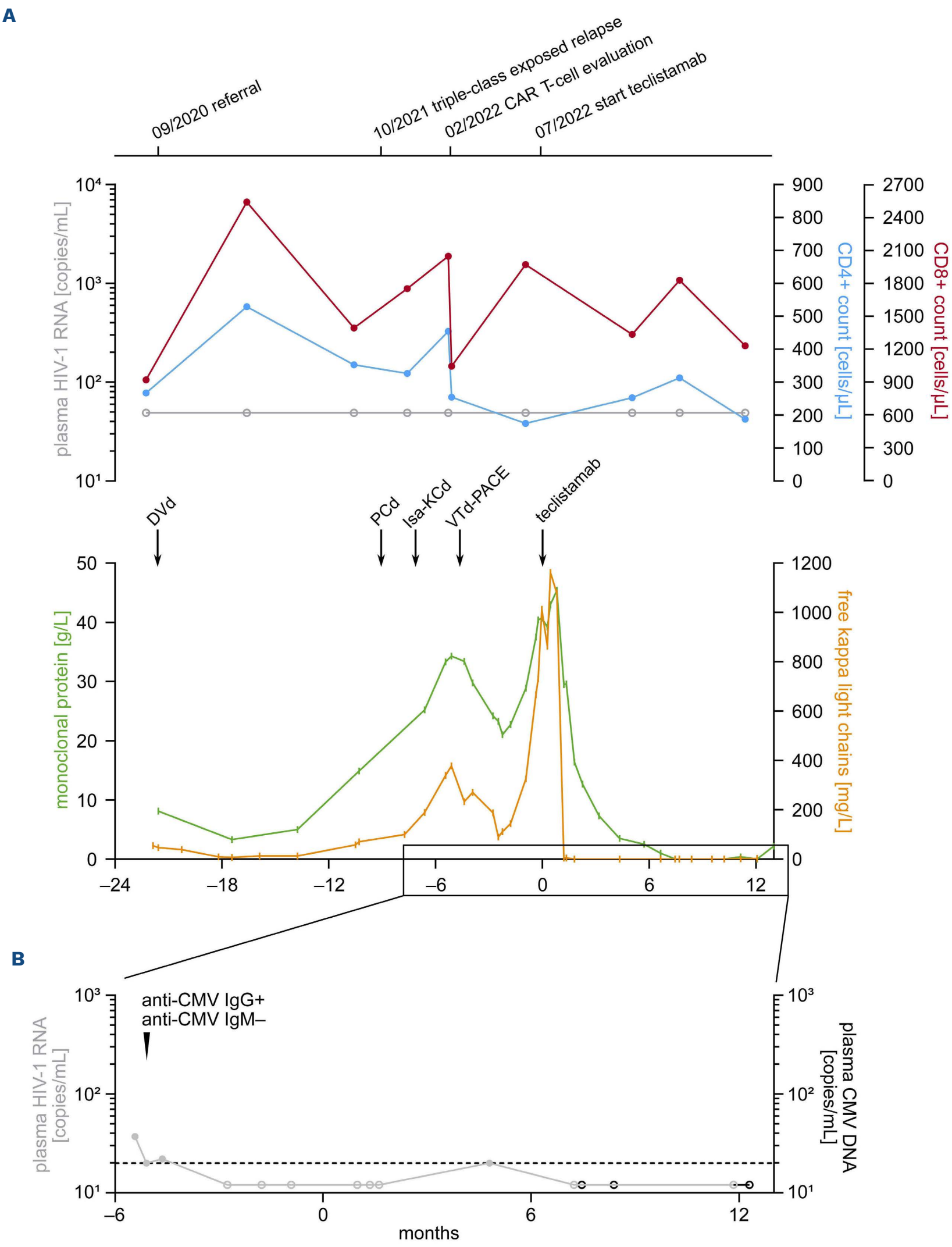

Figure 1. Clinical course before and after teclistamab initiation. (A) Clinical events and laboratory parameters before and after initiation of teclistamab therapy. (B) High-sensitive HIV-1 RNA polymerase chain reaction and cytomegalovirus (CMV) DNA polymerase chain reaction results. Open symbols indicate values below the lower limit of detection. DVd: daratumumab, bortezomib, dexamethasone; PCd: pomalidomide, cyclophosphamide, dexamethasone; Isa-KCd: isatuximab, carfilzomib, cyclophosphamide, dexamethasone; VTd-PACE: bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide; Ig: immunglobulin.

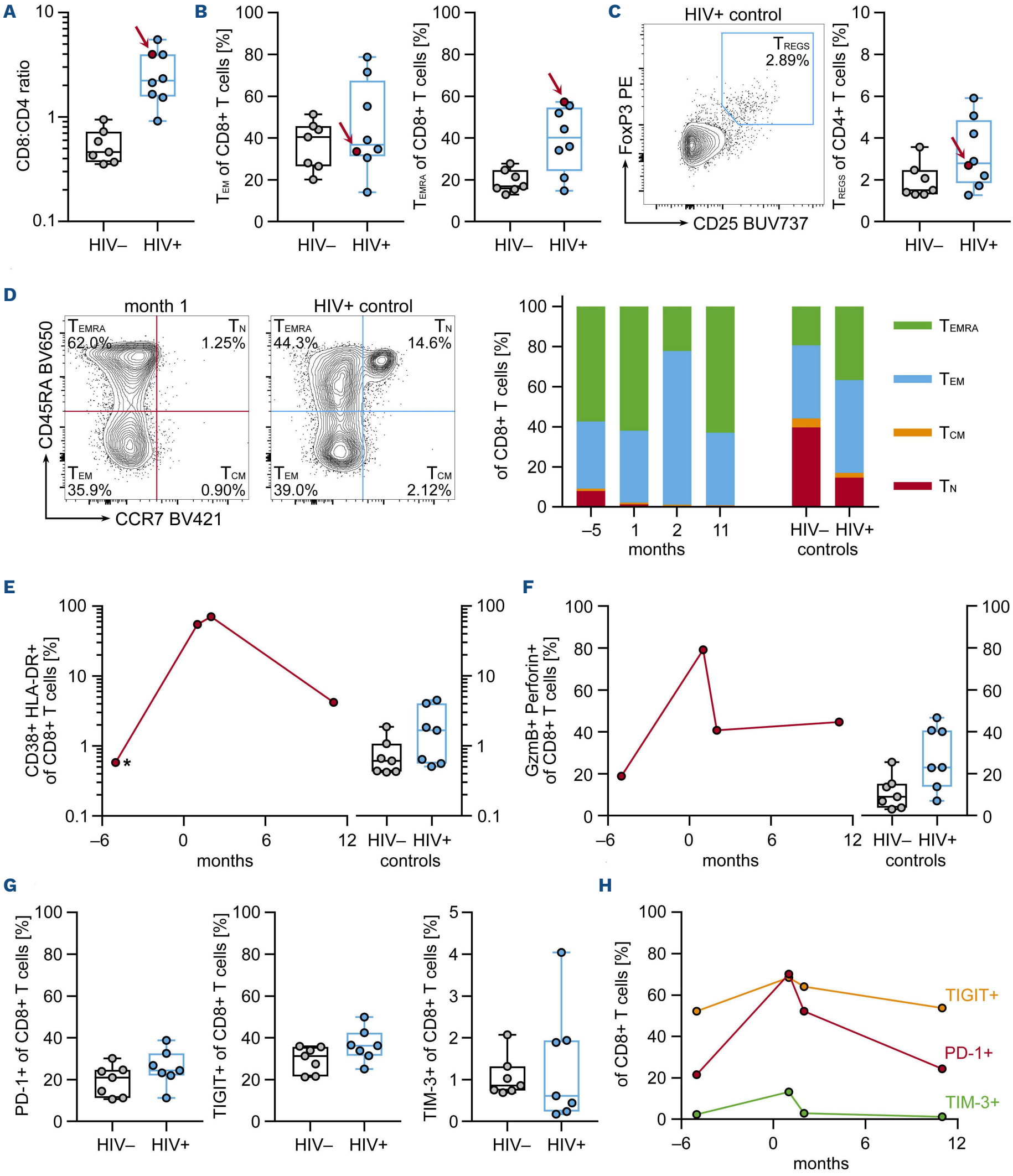

Figure 2. Characterization of peripheral blood T cells before and during teclistamab therapy. (A) Elevated CD8:CD4 ratio, (B) high frequencies of late differentiated CD8⁺ T cells and (C) regulatory CD4⁺ T cells are present in the pretreatment samples of the described patient (red arrows) as positive and negative prognostic markers for teclistamab response,[10] and correspond to immunological changes typically observed in people with human immunodeficiency virus (HIV). (D) The CD8⁺ T-cell memory phenotype is skewed towards an effector memory and a terminally differentiated phenotype and marked by loss of naïve T cells. (E) Peripheral blood CD8⁺ T cells were highly activated 1 and 2 months after treatment initiation, as indicated by CD38 and HLA-DR co-ex-

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pression. The result from 5 months before treatment initiation (*) is most likely underestimated due to anti-CD38 pretreatment. (F) Circulating CD8$^+$ T cells showed high cytolytic (granzyme B$^+$ perforin$^+$) response frequencies. (G) The expression of the immune checkpoint molecules PD-1, TIGIT, and TIM-3 is slightly elevated on CD8$^+$ T cells of patients with HIV (PWH) compared to HIV-negative controls (HIV-). (H) Expression of PD-1, TIGIT, and TIM-3 on CD8$^+$ T cells peaked 1 month after teclistamab initiation in the described patient. For the respective analyses, the results of each N=7 HIV-positive (HIV+) and HIV– controls are displayed as median with interquartile range or mean (bar charts). T_{EM}: effector memory T cells; T_{EMRA}: terminally differentiated T cells; T_{REG}: regulatory T cells; T_{CM}: central memory T cells; T_N: naïve T cells.

achieved after five cycles of teclistamab (Figure 1A), and a blood sample nearly 1 year after treatment initiation revealed complete peripheral B-cell aplasia as an indicator of effective B-cell targeting. HIV-1 plasma viral loads remained suppressed during the entire treatment except for another positive but not quantifiable HIV-1 RNA PCR (Figure 1B). A drop of CD4$^+$ T-cell counts to 175/μL 1 month before treatment initiation was most likely due to previous chemotherapy. Teclistamab was continued weekly in full dose. Peripheral blood mononuclear cells of the patient were isolated by density gradient centrifugation and analyzed by flow cytometry as described before[9] with comprehensive antibody panels for B-cell and T-cell phenotyping. Samples from N=7 PWH and N=7 HIV-negative participants were stained for comparison. All participants were recruited voluntarily at the University Medical Center Hamburg-Eppendorf and provided written informed consent, complying with the Declaration of Helsinki. The ethics board of the Ärztekammer Hamburg approved the study protocols (MC316/14, PV4780).

Recently, retrospective pretreatment analyses revealed a high CD8:CD4 ratio and elevated frequencies of effector memory (T_{EM}) and terminally differentiated effector (T_{EMRA}) CD8$^+$ T cells as correlates of teclistamab response.[10] At the same time, non-responders showed high frequencies of regulatory CD4$^+$ T cells.[10] Since HIV typically leads to all these perturbances,[6,11] both predictors for teclistamab response and non-response were detected before treatment initiation in the described patient. Particularly, an elevated CD8:CD4 ratio (Figure 2A) and higher frequencies of late differentiated CD45RA$^-$CCR7$^-$ T_{EM} und CD45RA$^+$CCR7$^-$ T_{EMRA} CD8$^+$ T cells (Figure 2B) were observed compared to HIV-negative controls but not compared to other PWH. The frequency of regulatory T cells was also comparable to other PWH (Figure 2C). Importantly, TCE therapy with teclistamab coincided with further T-cell differentiation, resulting in almost complete disappearance of naïve T cells from the peripheral blood and predominance of T_{EM} and T_{EMRA} cells (Figure 2D). High frequencies of CD38$^+$HLA-DR$^+$ activated CD8$^+$ T cells indicated effective engagement of T cells by teclistamab treatment (Figure 2E), particularly during the first 2 months of treatment. Additionally, high levels of cytolytic CD8$^+$ T cells were observed (Figure 2F). After almost 1 year of therapy, CD8$^+$ T-cell activation and cytolytic T cells returned to values comparable with other PWH, but the loss of naïve T cells persisted.

Persistent viral infections can drive T-cell exhaustion, a mechanism that potentially affects TCE efficacy. Therefore, we analyzed the expression of the co-inhibitory receptors PD-1, TIGIT, and TIM-3 on CD8$^+$ T cells. PWH on ART with suppressed viral load show slightly elevated expression of PD-1 and TIGIT but not TIM-3 compared to HIV-negative controls (Figure 2G). In the described patient, frequencies of PD-1, TIGIT, and TIM-3 on CD8$^+$ T cells were generally comparable to other PWH before teclistamab therapy. Four weeks after treatment initiation the expression peaked with 70.1%, 68.4%, and 13.2% positive CD8$^+$ T cells, respectively (Figure 2H). Upregulation of immune checkpoint expression might be beneficial to prevent serious immunologic complications such as cytokine release syndrome, but the effect on treatment efficacy remains unclear for now. Seven weeks after treatment initiation, flow cytometry failed to identify any relevant frequencies of B cells in peripheral blood (Figure 3A). Interestingly, during the initial treatment phase, a shift of the peripheral B-cell subsets towards a transitional CD24$^+$CD38^{high} phenotype was observed compared to the pretreatment sample (Figure 3B), consistent with the reported low or absent BCMA expression in this B-cell subset.[12] Of note, both CD38$^+$ T cells and CD38$^+$ B cells were depleted in the pretreatment sample coherent with prior anti-CD38 treatment (Figure 3C, D).

Considering the redirection of CD8$^+$ T cells to target myeloma cells, transient loss of immune-mediated control of persistent viral pathogens in patients receiving TCE could be of clinical significance. Accordingly, high rates of CMV reactivation have been reported.[13,14] Regarding HIV, activation of CD4$^+$ T cells shortly after treatment initiation (Figure 3E) additionally favors reservoir propagation by promoting viral transcription and facilitating target cell infection.[9,15] However, HIV-1 RNA and CMV DNA remained suppressed during teclistamab therapy (Figure 1B).

This case demonstrates that TCE can be an effective and safe treatment option in RRMM despite HIV-associated immunodeficiency. Viral suppression was maintained with standard ART despite potential impairment of immune-mediated control and high levels of T-cell activation observed with TCE. The favorable outcome should encourage physicians to consider the potential benefits - but certainly also potential complications - of TCE therapy in patients with malignancies and concomitant but well-controlled HIV infection. Furthermore, all stakeholders should explore new ways to bring CAR T-cell therapies to underserved patient populations, such as PWH, who currently might not be eligible.[4,5] Although there is insufficient data on

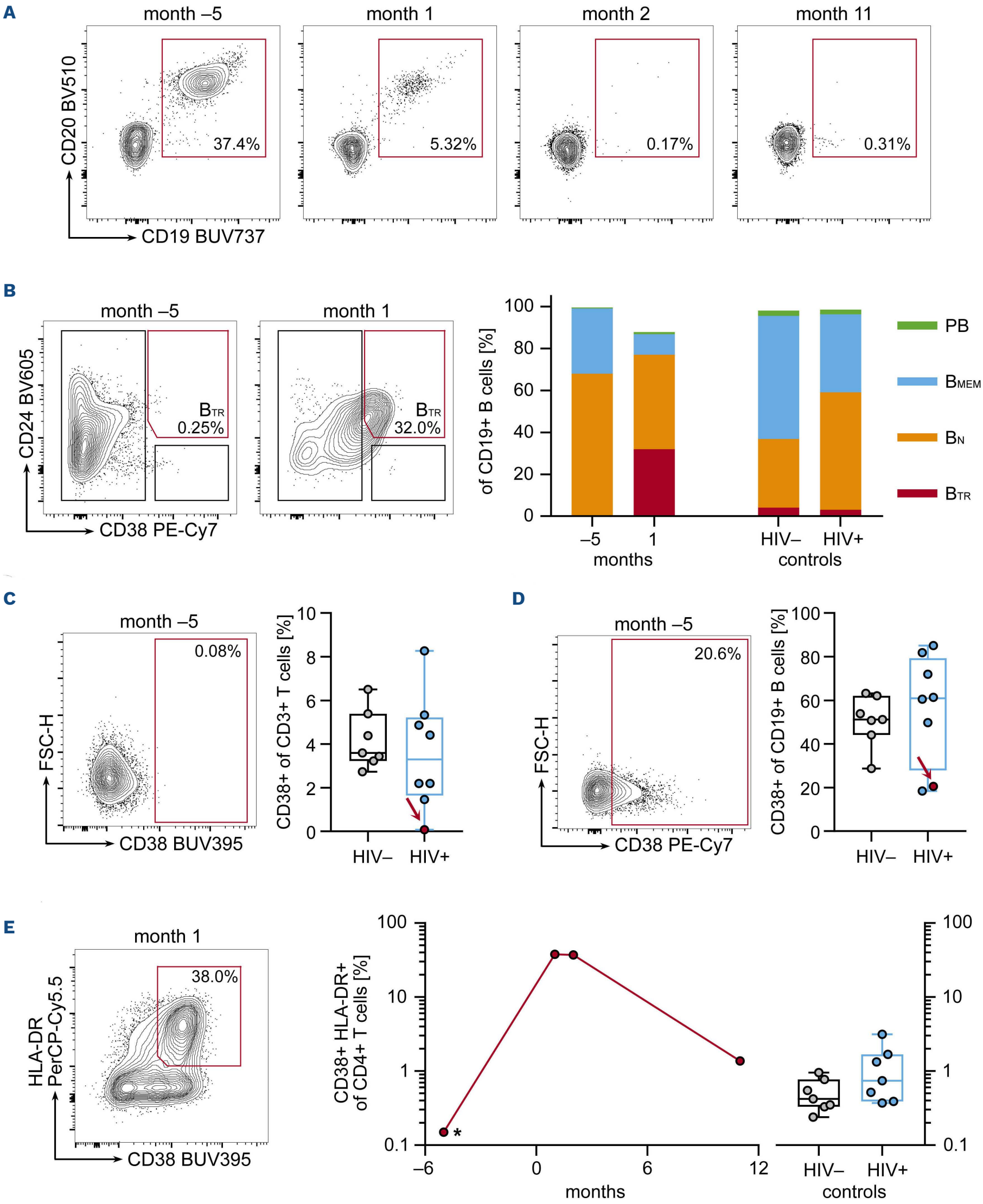

Figure 3. Teclistamab-associated changes in the B-cell compartment and CD4⁺ T-cell activation. (A) CD19⁺ B cells disappeared from peripheral blood samples during teclistamab therapy. Gated on viable, CD14⁻, CD3⁻ single lymphocytes. (B) One month after therapy initiation, the phenotype of the remaining B cells shifted towards a predominant CD24⁺ CD38^{high} transitional phenotype.

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(C) Depletion of CD38$^+$ T cells and (D) CD38$^+$ B cells due to anti-CD38 treatment before teclistamab therapy. (E) Peripheral blood CD4$^+$ T cells were highly activated 1 and 2 months after treatment initiation, as indicated by CD38 and HLA-DR co-expression. The result from 5 months before treatment initiation (*) is most likely underestimated due to anti-CD38 pretreatment. The results of each N=7 human immunodeficiency virus (HIV)-positive (HIV+) and HIV-negative (HIV–) controls are displayed as median with interquartile range or mean (bar charts).B_{MEM}: memory B cells; B_N: naïve B cells; B_{TR}: transitional B cells; PB: plasmablasts.

the impact of cellular immunodeficiencies on treatment response, these therapies should not be withheld from PWH due to the promising results from the clinical trials[2] and higher response rates compared to alternative treatment options.[3] However, prospective studies are needed to investigate whether particularly CD4$^+$ T-cell depletion and T-cell exhaustion affect the outcome of T-cell-based therapies.

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Contributions

LC, CS, JSzW, and KCW conceived and designed the study. LC and SC designed and/or performed the experiments. LC, CS, CH, JSzW, and KCW performed the analyses and/or interpreted the data. LC, CS, and CH visualized the data. CS, AK, CH, CB, LL, WA, and KCW were involved in the clinical management of the patient and/or collected and handled patient samples. FH, SP, and JSzW provided critical resources and control samples. LC, CS, JSzW, and KCW wrote the draft of the paper. All authors critically reviewed the paper and contributed important intellectual content.

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Data-sharing statement

The data supporting the findings of this study are available upon request via email to the corresponding author within the data protection constraints in the written informed consent signed by the study participants.

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