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Emapalumab and eltrombopag rescue for prolonged immune effector cell-associated hemophagocytic syndrome after CAR T-cell therapy in multiple myeloma

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Chimeric antigen receptor (CAR) T cell therapy and bispecific antibodies (BsAbs) have demonstrated efficacy in relapsed/refractory multiple myeloma (RRMM).[1] While cytokine release syndrome (CRS), immune effector cell (IEC)-associated neurotoxicity syndrome (ICANS), and prolonged cytopenias are well-recognized toxicities, IEC-hemophagocytic lymphohistiocytic syndrome (IEC-HS) is an emerging complication that lacks standardized management.[2] Treatment of hemophagocytic lymphohistiocytosis (HLH), a hyperinflammatory syndrome driven by uncontrolled macrophage and T cell activation, now includes anakinra, ruxolitinib, and emapalumab (anti-IFNγ monoclonal antibody),[3] yet the optimal approach to IEC-HS is undetermined.

We present a high-risk RRMM patient who progressed to plasma cell leukemia (PCL) with hypereosinophilic syndrome after BsAb therapy and developed prolonged IEC-HS following CAR T cell infusion. We detail three phases of management of this case: preemptive inflammatory control, early CRS mitigation, and treatment of refractory IEC-HS. We demonstrate how CXCL9-guided emapalumab combined with eltrombopag achieved transfusion independence while preserving deep anti-myeloma response. Elevated CXCL9, a biomarker of systemic IFNγ activity, identified persistent IFNγ-driven marrow inflammation, providing a rationale for IFNγ blockade.[4] This study was approved by the Mount Sinai institutional review board (IRB) (GCO#: 11-01978).

A 75-year-old male with International Staging System (ISS) stage II IgG-λ RRMM and high-risk cytogenetics (+1q21, −1p32, t(14;16)) progressed through five lines of therapy over 7 months. Three cycles of talquetamab (GPRC5D-targeting BsAb) induced complete response (CR) with measurable residual disease (MRD) at 0.0016% by next-generation sequencing (NGS), permitting stem-cell collection and leukapheresis for ciltacabtagene autoleucel (cilta-cel) manufacturing. Talquetamab was paused as ferritin exceeded 2,000 ng/mL, which predicts adverse outcomes after CAR T.[5]

After 3 months off talquetamab, his myeloma rapidly progressed to PCL, refractory to talquetamab re-initiation, with intractable diarrhea and marked hypereosinophilia. Eosinophils comprised 92.4% of peripheral leukocytes (absolute 23.5×10^3/μL) and 64% of bone marrow (BM) cells **(Figure 1A)**. Work-up excluded infections, autoimmune diseases, HLA-B*58:01, and myeloproliferative neoplasms, including those associated with *PDGFRA/PDGFRB* aberrations.

Positive findings included serum IgE 405 kU/L (normal: 0-214 kU/L) and *KRAS* p.A146V mutation. Prednisone 1 mg/kg daily for 4 days resolved both the diarrhea and eosinophilia.

Immunohistochemistry (IHC) and single-cell RNA sequencing (scRNA-seq) confirmed absence of GPRC5D protein and RNA expression **(Figure 1B–C)**. Peripheral flow cytometry revealed γδ T cell expansion (16% of lymphocytes). Given rapidly progressive PCL and hypereosinophilia, direct CAR T infusion carried unacceptable risk of fatal CRS, ICANS, and movement and neurocognitive treatment-emergent adverse events (MNTs). Therefore, the patient received carmustine 100 mg/m² and melphalan 100 mg/m² followed by stem cell boost (SCB; 3.17×10^6 CD34+ cells/kg), for rapid debulking, achieving a very good partial response.

Ferritin remained >2,000 ng/mL, prompting 2 weeks of prednisone before lymphodepletion. Subcutaneous anakinra 200 mg every 8 hours was started prophylactically on day 2 after cilta-cel infusion for 2 weeks, then continued daily for 285 days. The patient developed grade 1 CRS, with no ICANS or MNTs, and received tocilizumab. Cytokine profiling revealed IL-1β peaking at 21.5 pg/mL (normal: <1.2 pg/mL), IL-2Rα at 11,375 pg/mL (normal: 223-710 pg/mL), IL-6 at 4,747 pg/mL (normal: <5 pg/mL), IFNγ at 89.6 pg/mL (normal: <8.6 pg/mL), and TNFα at 63.4 pg/mL (normal: <2.2 pg/mL) **(Figure 1D)**. IL-1β, IL-6, and IFNγ peaked within the first 1-2 weeks and declined thereafter, consistent with early attenuation by anakinra and tocilizumab; TNFα and IL-2Rα continued to rise, peaking around day 24 and remaining elevated through day 57.

Cytopenias were observed after cilta-cel infusion, but rather than recovering with expected post-lymphodepletion kinetics, they deepened and became refractory and transfusion-dependent, coinciding with a ferritin rise to ~33,000 ng/mL around day 20 **(Figure 2)**. Cytokine measurements were more consistent with ongoing macrophage activation than resolving CRS **(Figure 1D)**. Over six months, the patient required >70 red-cell/platelet transfusions and received weekly granulocyte colony-stimulating factor (G-CSF). Serial IFNγ-pathway assessment during this prolonged cytopenic phase was unavailable. Soluble CXCL9 was first measured on day 247 for suspected IEC-HS and consideration of IFNγ-directed therapy.

The patient met HLH-2004 criteria[6]: fever >38.5°C, hypertriglyceridemia, hypofibrinogenemia, transaminitis, cytopenias, hyperferritinemia, elevated soluble CD25/IL-2Rα, and hemophagocytosis on day-100 BM **(Figure 1E)**. However, soluble CD25/IL-2Rα was not

measured prior to CAR T. He also fulfilled IEC-HS-specific criteria[2]: hyperferritinemia, refractory cytopenias, transaminitis, lactate dehydrogenase elevation, hypertriglyceridemia, and BM hemophagocytosis; fibrinogen nadir (161 mg/dL) was just above the <150 mg/dL threshold. Critically, the marrow was cellular with active but ineffective hematopoiesis amidst hemophagocytosis so additional stem cell infusion was therefore deferred. TCR β/γ gene rearrangement showed no clonal T cell population, arguing against T cell large granular lymphocytic (LGL) leukemia, so high-dose IVIg was not administered. Throughout this period of toxicity, MRD by NGS remained negative.

Prednisone and anakinra yielded modest platelet improvement after addition of eltrombopag (150 mg daily). A brief transition from anakinra to ruxolitinib showed no benefit **(Figure 2)**. Given elevated CXCL9 (2,735 pg/mL), measured by the ELLA platform (Cincinnati Children's Hospital), emapalumab was initiated on day 255 with twice-weekly step-up dosing (1, 3, 6, and 10 mg/kg), followed by a single 10 mg/kg dose one week later, then 10 mg/kg every 2 weeks for 4 additional doses (9 total doses). The response was dramatic: undetectable IFNγ within 1 week, CXCL9 normalization within 3 weeks, and transition from heavy transfusion dependence to complete independence, with decreased G-CSF requirements.

Infectious complications were modest while on emapalumab: self-limited *E. coli* enterocolitis and mild CMV viremia (peak viral load 384 IU/mL) that resolved with 30 days of valganciclovir.

At 2 years post-cilta-cel, the patient remains in stringent CR and MRD-negative. He has no circulating B cells and remains immunocompromised; however, his CD4+ T cell count normalized within 280 days, reflecting immune reconstitution. Ferritin remains chronically elevated with stable counts.

Classical HLH features a hyperactivated yet ineffective immune response in which CD8+ T cells produce high IFNγ levels, driving a self-amplifying inflammatory loop between lymphocytes and macrophages.[7] IEC-HS shares this pathophysiology, with CAR T cells inducing sustained macrophage activation via IFNγ.[2] Susceptibility is likely modulated by disease burden, CAR construct biology, host immune milieu, and antecedent inflammation.[2] Our patient had several pro-inflammatory features: high-risk myeloma, persistently elevated ferritin, antecedent PCL with hypereosinophilia, and γδ T cell expansion (24% of lymphocytes during BsAb therapy). Although

direct associations between PCL-associated hypereosinophilia or γδ expansion and IEC-HS are not established, BsAbs can promote γδ T cell expansion,[8] which may modulate eosinophil biology.[9] Notably, the manufactured CAR T product contained a sizeable CD4+CD7− population (24% of lymphocytes), a phenotype linked to chronic immune activation[10] and T cell lymphoproliferative disorders,[11] suggesting that the BsAb-exposed T cell compartment may have contributed to the pro-inflammatory trajectory.

The prolonged hyperinflammation likely reflected multiple non-mutually-exclusive factors: robust, durable cilta-cel persistence sustaining immune activation beyond the CRS window; high disease burden (high BCMA expression) driving CAR T activation; antecedent BsAb exposure skewing the T cell compartment, evidenced by γδ expansion and CD4+CD7− cells in the manufactured product; and marrow microenvironment priming by aggressive PCL with hypereosinophilia. Their relative contributions cannot be determined from a single case but may inform risk stratification.

Chemotherapy plus SCB before CAR T likely provided benefit, as direct CAR T infusion in the setting of progressive PCL and hypereosinophilia carried high risk of severe CRS, ICANS, and MNTs.[5] Persistent ferritin elevation prompted pre-emptive corticosteroids and prophylactic anakinra, which may have limited CRS to grade 1 and prevented ICANS; pre-CAR T tumor debulking with carmustine/melphalan likely also reduced inflammation. Longitudinal cytokine data highlight the transition from acute CRS to chronic IEC-HS: early IL-1β and IL-6 decline indicated effective attenuation by anakinra and tocilizumab, but persistent IL-2Rα and TNFα elevation through day 57, worsening transfusion-dependent cytopenias, and ferritin hyper-elevation suggested macrophage activation no longer responsive to IL-1/IL-6 blockade. Although IFNγ-pathway activity was not measured during the intervening period, markedly elevated day-247 CXCL9 and rapid response to emapalumab support an IFNγ-driven process. The decision to use emapalumab was guided by elevated CXCL9, a validated biomarker of systemic IFNγ activity in HLH.[4, 12] Reduction below ~300 pg/mL correlates with treatment response,[12] and levels ≥3,500 pg/mL may identify patients most likely to benefit from IFNγ-targeted therapy.[13] Rapid CXCL9 normalization correlated with clinical improvement. Importantly, day-100 BM demonstrated hemophagocytosis rather than hypocellularity, confirming that IFNγ neutralization - not additional stem cells - addressed the root cause. This distinction is clinically relevant: prolonged post-CAR

T cytopenias are common and SCBs are increasingly used as default intervention, but when cytopenias are IEC-HS-driven, additional stem cells will not resolve IFNγ-mediated marrow inflammation. Accurate IEC-HS identification, guided by BM morphology and CXCL9, is essential for therapeutic decision-making.

Real-world emapalumab experience for IEC-HS is limited, and high per-dose cost is a significant barrier, particularly where CXCL9 testing is unavailable.[2-4] However, CXCL9-guided selection provides rationale that may optimize cost-effectiveness: in our patient, the transition from >70 transfusions to transfusion independence substantially reduced healthcare utilization. Eltrombopag played a complementary role by supporting hematopoietic progenitors and bypassing thrombopoietin receptor resistance in IFNγ-rich states.[14] This case highlights the importance of integrating CXCL9-guided IFNγ-directed immunomodulation with hematopoietic support in refractory IEC-HS, an approach that reversed prolonged inflammatory marrow failure while preserving MRD-negative remission. As cellular therapies expand, early IEC-HS recognition, biomarker-guided IFNγ-directed therapy, and tailored hematopoietic support will be essential for improving outcomes.

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Figure Legends:

Figure 1. Multimodal characterization of an aggressive plasma cell leukemia trajectory and subsequent IEC-HS. (A) H&E-stained bone marrow aspirate and biopsy demonstrating marked hypereosinophilia during rapid disease progression, with eosinophils comprising the majority of nucleated cells. (B) Immunohistochemistry of the patient's bone marrow at time of progression after talquetamab showing absence of GPRC5D compared to a positive control. (C) scRNA-seq of the plasma cell compartment, showing loss of GPRC5D RNA expression compared to a positive control. (D) Longitudinal cytokine measurements after cilta-cel illustrating elevations in IL-1β, IL-2Rα, IL-6, IFNγ, and TNFα. (E) Wright Giemsa–stained bone marrow aspirate smear at 3 months post–cilta-cel with macrophages showing evidence of hemophagocytosis.

Figure 2. Longitudinal treatment course and hematologic recovery following CAR T cell therapy. This figure illustrates the complete therapeutic timeline beginning shortly before CAR T cell infusion and extending to 1.5 years post–CAR T. Shown alongside the sequence of interventions are the corresponding trajectories of ferritin, hemoglobin, platelets, absolute neutrophil count (ANC), and CXCL9. The figure highlights the period of refractory IEC-HS marked by cytopenias and hyperferritinemia and demonstrates subsequent hematologic improvement following initiation of eltrombopag and emapalumab.

FIGURE 1

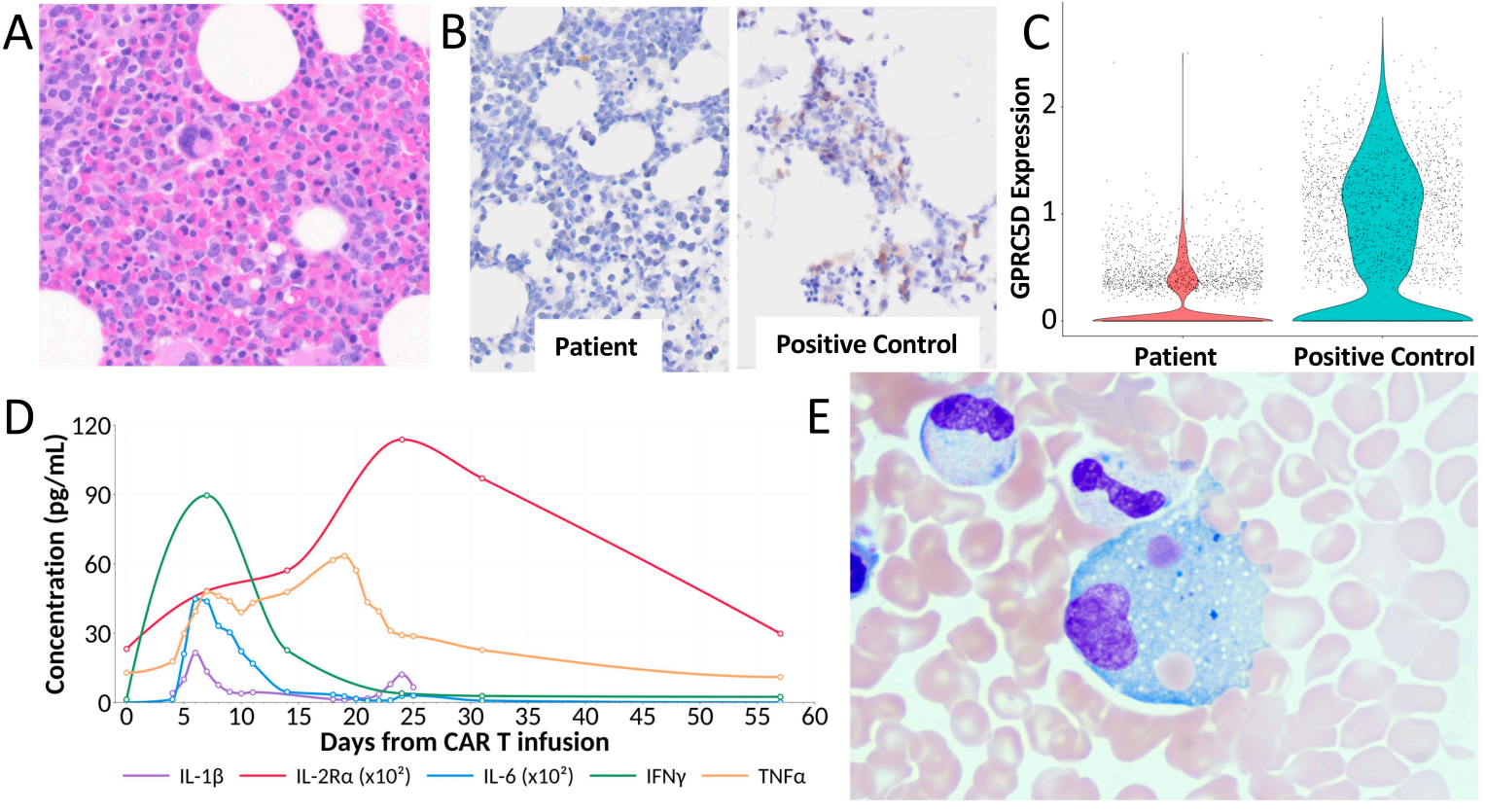
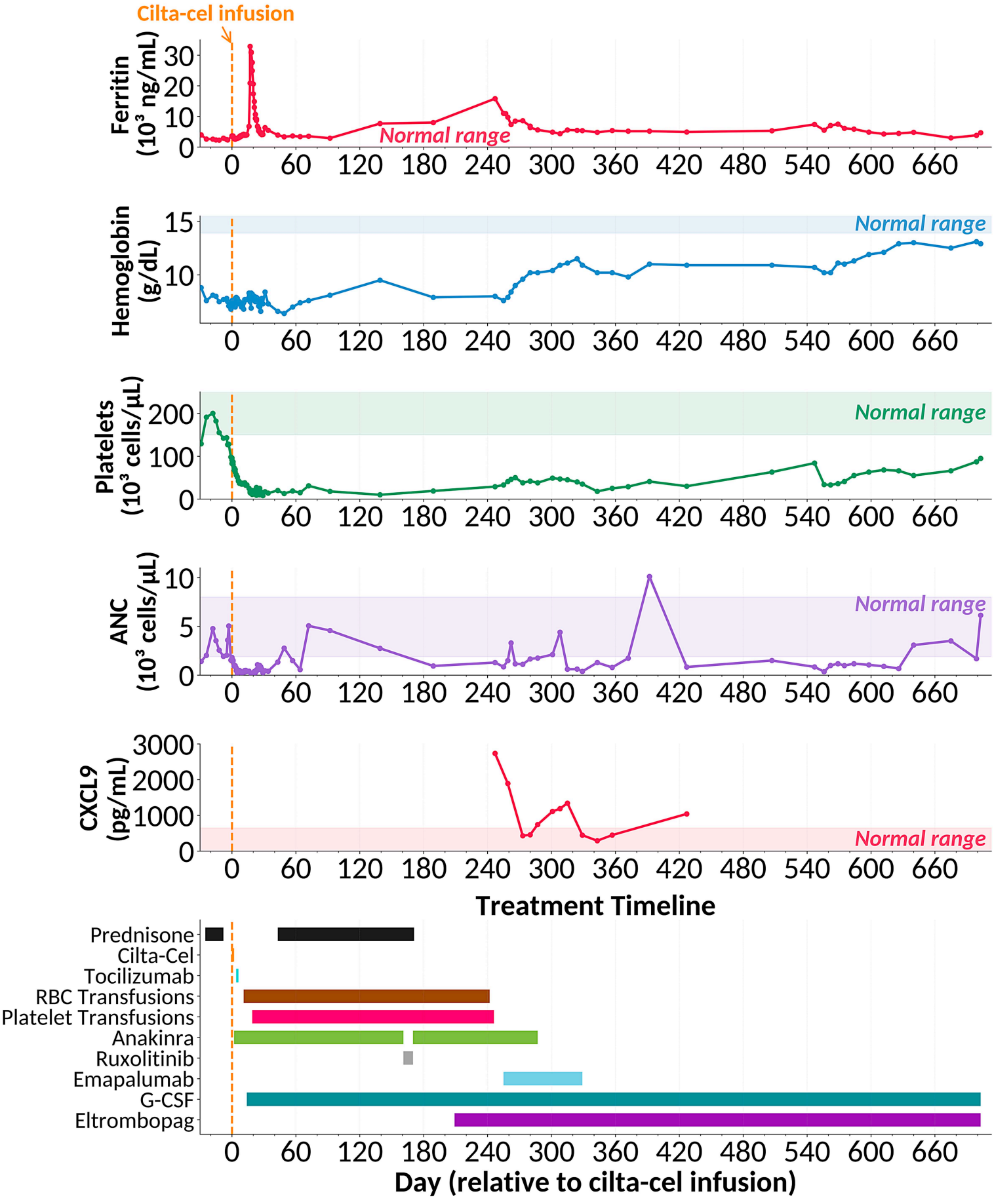

A
B
Patient
Positive Control
C
GPRC5D Expression
2
1
0
Patient
Positive Control
D
Concentration (pg/mL)
120
90
60
30
0
0
5
10
15
20
25
30
35
40
45
50
55
60
Days from CAR T infusion
IL-1β
IL-2Rα (x10²)
IL-6 (x10²)
IFNγ
TNFα
E

FIGURE 2


Cilta-cel infusion
Ferritin (10³ ng/mL)
Normal range
Hemoglobin (g/dL)
Normal range
Platelets (10³ cells/µL)
Normal range
ANC (10³ cells/µL)
Normal range
CXCL9 (pg/mL)
Normal range
Treatment Timeline
Prednisone
Cilta-Cel
Tocilizumab
RBC Transfusions
Platelet Transfusions
Anakinra
Ruxolitinib
Emapalumab
G-CSF
Eltrombopag
0 60 120 180 240 300 360 420 480 540 600 660
Day (relative to cilta-cel infusion)