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Phase 1/2 study of Trovocabtagene autoleucel, a BCMA CART, combined with ASCT in UHR MM and pPCL

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Abstract

Background This phase I/II trial evaluated the safety and efficacy of trovocabtagene autoleucel (trovo-cel, C-CAR088), a novel 2nd generation Chimeric Antigen Receptor-T cell (CAR-T) product targeting B-cell maturation antigen (BCMA), combined autologous stem cell transplantation (ASCT) in patients with ultra-high-risk multiple myeloma (UHR-MM) or primary plasma cell leukemia (pPCL) who failed or had suboptimal responses to standard first-line therapy.

Methods The study aims to assess the safety and efficacy of C-CAR088 combined ASCT in patients with UHR-MM. Eligible patients are ones having genetic ultra-high-risk, primary refractory, early relapse or pPCL, failed or had suboptimal responses to standard first-line triplet/quadruplet-based regimen. Patients underwent conditioning, ASCT (D0) and trovo-cel at 3×10^6cells/kg on Day 3.

Results Totally 16 patients received ASCT+trovo-cel. The most common treatment-emergent AE was hematological toxicity. Fifteen patients (93.8%) developed cytokine release syndrome; all cases were grade 1–2 and recovered. No ICANS or IEC-HS events were reported. All patients completed hematological reconstitution with a median time of 15.0 days to neutrophil engraftment and 14.5 days to platelet engraftment post-ASCT. The sCR rate was 100%. The MRD negativity rate (next-generation flow cytometry [NGF] 10^{-5}) at 1, 3, 6, and 12 months was 92.3%, 100%, 93.3%, and 93.3%, respectively. Median PFS and OS were not reached during a median follow-up of 26.9 months. The PFS and OS rate at 2 years were both 87.5%. When ASCT+CART was used as a frontline consolidation strategy, 2-year PFS and OS reached 100%. Remarkably, even in patients with kinetic ultra-high-risk features (primary refractory or early progression), the 2-year PFS and OS stood at 75%.

Conclusions ASCT+trovo-cel induced deep and durable responses with good tolerability for UHR-MM and pPCL, especially in the earlier-line setting. ASCT + CAR-T may represent a highly promising treatment, is worthy of further exploration.

Trial Registration ClinicalTrials.gov Identifier: NCT05632380

INTRODUCTION

With standardized systematic treatment, the median overall survival (OS) of multiple myeloma (MM) patients now exceeds 10 years.[1] However, prognosis remains poor in ultra-high-risk (UHR) patients, who generally have an expected survival under 2–3 years. Advances in understanding MM pathogenesis and novel therapeutics have refined high-risk/UHR MM definitions, yet no risk stratification system incorporates all high-risk factors.[2,3,4,5] Recently, the International Myeloma Society and International Myeloma Working Group established an HRMM genomic staging consensus identifying ~ 20% patients with dismal prognosis despite potent triplet and quadruplet combinations treatment.[6]

Another UHR entity is pPCL, defined as the presence of ≥ 5% circulating plasma cells.[7] In our center, of 130 evaluable pPCL patients with 54.7 months of follow-up, median PFS and OS were 16.9 months and

30.0 months, respectively. Stratified by best response (no response, partial response (PR), ≥very good partial response (VGPR)), median PFS was 2.4, 11.2, and 31.9 months, with corresponding median OS of 2.4, 24.9, and 62.1 months (all $P < 0.001$).[8]

Dynamic treatment response has also gained increasing prognostic importance. Patients with suboptimal induction response or early relapse are classified as functional high-risk (FHR) MM. An Australian and New Zealand Myeloma and Related Diseases Registry study[9] found that 40% of patients with a minimal response or stable disease died within 3 years, while those with early progression (within 12 months of induction) had median OS of merely 20.2 months. Soekojo et al.[10] characterized FHR-MM as early treatment failure without conventional high-risk genetics. The European Myeloma Network further defined FHR-MM as disease progression within 18 months of first-line therapy in the absence of HRCA.[11] Early progression remains a significant predictor for shorter OS in the present era.[12]

Currently, research on treatment strategies for HRMM and UHR-MM remains scare. The standard-of-care regimen combining ASCT with novel agents fails to achieve satisfactory long-term efficacy in real world UHR-MM patients.

Chimeric antigen receptor autologous T-cell (CAR-T) therapy targeting B-cell maturation antigen (BCMA) has achieved deep overall response rate (ORR) and minimal residual disease (MRD) negativity in R/R MM, representing one of the most effective treatment modalities.[13,14,15] Frontline CAR-T for high-risk newly diagnosed MM (NDMM) has also shown promising results.[16,17] Still, CAR-T has limitations in the first-line setting for UHR patients. In the FUMANBA-2 trial (81.5% UHR-MM participants),[16] the regimen led to 100% ≥VGPR with 100% MRD negativity, yet 24-month PFS and OS rate were 74.5% (95% confidence interval[CI]: 42.7–91.7) and 81.3% (95% CI: 52.5–93.5) respectively, indicating room for improvement in long-term benefits.

Based on previous work with combinational regimens in R/R non-Hodgkin lymphoma,[18] we designed a combination approach to improve the depth and durability of treatment responses in MM. This novel approach consists of ASCT combined with BCMA-CAR-T (C-CAR088 or trovocabtagene autoleucel, often shortened to trovo-cel) as earlier-line consolidation for patients with UHR-MM or pPCL. This regimen debulks tumor burden by conditioning and ASCT, followed by CAR-T infusion and subsequent maintenance therapy, with the ultimate goals of achieving sustained MRD negativity and potential clinical cure. This report presents the results of this trial (NCT05632380).

METHODS

Patients and study design

This open-label, Phase I/II, single-arm, investigator-initiated study of trovo-cel combined with ASCT was performed in patients who were diagnosed to have UHR-MM or pPCL between July 21, 2022 and May 27, 2024, and failed on or had a suboptimal response to standard first-line therapy. All participants provided

written informed consent. The study protocol and any amendments were approved by the relevant regulatory authorities and national ethics committees in the Institute of Hematology & Blood Diseases Hospital, Chinese Academic Medical Science & Peking Union Medical College. The trial adheres to the International Conference on Harmonization of Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

Trovo-cel is a second-generation anti-BCMA CAR T-cell therapy manufactured by Shanghai AbelZeta Ltd. (Shanghai, China). The single-chain variable fragment (scFv) of this agent was derived from a human IgG1 antibody and was found to have a high binding affinity for epitome cluster E3 in the BCMA extracellular domain using a surface plasmon resonance sensor. Trovo-cel demonstrated a good efficacy and safety profile in patients with R/R MM when administered as 3.0×10^6 cells/kg and 6.0×10^6 cells/kg.[19,20]

Patients were eligible for participation in the study if they were aged 18–70 years, eligible for transplantation, and had an Eastern Cooperative Oncology Group performance status score of 0–1. UHR-MM is defined as at least one of following: (1) genetic ultra-high-risk [del(17p) ≥60% or at least two HRCA, including TP53 mutation, del(17p)/P53 deletion (<60%), t(4;14), t(14;16), t(14;20), or 1q21 gain/amplification]; and CR not reached after four cycles of standard first-line therapy; (2) primary refractory disease (minimal response not reached after two cycles or a PR not reached after four cycles of standard first-line therapy); (3) early relapse (disease progression with best response duration of less than 6 months); or (4) pPCL (diagnosed as ≥5% circulating plasma cells[7]) and CR not reached after four cycles of standard first-line therapy.

Standard first-line therapy consisted of a triplet/quadruplet-based regimen including at least one proteasome inhibitor, one immunomodulatory drug, and a glucocorticoid with or without a CD38 monoclonal antibody. The HRCA markers t(4;14), t(14;16), t(14;20), 1q21 gain/amplification, and del(17p) were assessed by fluorescence in situ hybridization (FISH, with a cut-off level of 10% for fusion abnormalities and 20% for numeric abnormalities[21]). TP53 mutations were detected using next-generation sequencing with a sequencing depth of 1000× to 2000×. Patients who had previously received ASCT, CAR-T, or BCMA-targeted therapy were excluded.

Study treatment

Eligible patients underwent leukapheresis for CAR-T production followed by stem cell mobilization and collection, unless adequate cryopreserved stem cells were available. Bridging therapy (same as the induction regimen) was permitted during the trovo-cel manufacturing interval, but patients who achieved a CR after bridging were excluded from further investigation. Following successful manufacturing of trovo-cel and collection of stem cells, the patients underwent conditioning, which consisted of high-dose melphalan (HDM, 140 mg/m²) divided into two infusions on days -3 and -2, with or without fludarabine (FLU) at 25-30 mg/m² on days -6 to -4, to assess whether intensified lymphodepletion with additional

FLU-mediated immunosuppression impacts CAR-T cell expansion. ASCT was performed on day 0, followed by a single intravenous infusion of trovo-cel (3.0×10^6 cells/kg) on day 3. Based on our prior phase I trial in RRMM[19], where 3×10^6 cells/kg was established as the recommended phase II dose, all patients in this study received the same dose and achieved sCR consistently; no dose escalation was pursued. All patients receive IMids-based, at least dual-agent maintenance therapy (combining with one or two drugs from proteasome inhibitors and/or CD38 monoclonal antibodies based on the patient's financial affordability and treatment willingness) until disease progression or intolerable toxicity (**Figure 1**). After CAR-T infusion, acyclovir is routinely administered to prevent herpes zoster, and trimethoprim-sulfamethoxazole is used to prevent Pneumocystispneumonia. In the event of neutropenia, moxifloxacin tablets and posaconazole are added for prophylaxis against bacterial and fungal infections, respectively. When IgG falls below 5 g/L, intravenous immunoglobulin (IVIG) is given. Imaging (CT) was performed at screening, pre-conditioning, and when EMD suspected.

Endpoints and assessments

The primary endpoint was the incidence and severity of adverse events. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded using the 2019 American Society for Transplantation and Cellular Therapy criteria,[22] while other adverse events were evaluated as per the NCI Common Terminology Criteria for Adverse Events version 5.0. Secondary endpoints included the ORR (PR, VGPR, CR, sCR), MRD negativity rate, duration of response, time to response, PFS, and OS. The assessment of response and MRD were done at 3m, 6m, 12m, 18m, 24m after ASCT/CART. All responses were investigator-assessed using the 2016 International Myeloma Working Group criteria.[23] MRD was performed using next-generation flow cytometry (NGF) at 10^{-5} sensitivity. Bone marrow biopsies were required at baseline, for CR/sCR confirmation and routine monitoring following CR. All patients underwent imaging assessments at screening, pre-conditioning visit and whenever extramedullary disease (EMD) was suspected. For patients presenting with baseline EMD, serial imaging was routinely performed at post-ASCT efficacy evaluation. Patients are being followed closely for 24 months post-ASCT before transitioning to longer-term follow-up for survival extending to 15 years.

Statistical analysis

The safety and efficacy analyses were performed using the modified intention-to-treat population, namely, patients who received both ASCT and trovo-cel. Continuous variables are summarized using descriptive statistics (mean ± standard deviation or median and range) and categorical variables as the count/percentage. Time-to-event endpoints (duration of response, PFS, and OS) were analyzed using Kaplan–Meier curves (95% confidence intervals were calculated using the Brookmeyer–Crowley method). Patients who had not experienced events by the date of analysis were censored. The linear trapezoid method was used for calculation of areas under the curve. Pharmacokinetic analyses were

performed used the PKNCA Package in R (version 0.9.5, The R Foundation for Statistical Computing, Vienna, Austria). All other statistical analyses were performed using SAS version 9.4 and the two-sided significant level was 0.05 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patients/enrollment

A total of 16 patients with UHR-MM or pPCL received the combination of ASCT and trovo-cel 3.0×10^6 cells/kg during the study period. Eight patients received HDM as the conditioning regimen, and the other eight patients received HDM + FLU. The trovo-cel was manufactured successfully for all patients, with a median production time of 20 days (range 18–29).

The patients were predominantly male (81.3%), and the median age was 58 years (**Table 1**). The median interval between diagnosis and screening was 8.5 months (5.2-19.0). Seven patients (43.8%, 7/16) received ASCT + CAR-T in their first line of therapy (LOT1, patient did not experience disease relapse/progression before ASCT+CART, and ASCT+CART was administered as consolidation part of first-line therapy) and 56.3% (9/16) received it as their second or third line (LOT≥2, patients with primary refractory disease or early progression needed to switch to second-line or even third-line salvage chemotherapy; therefore, in these patients, ASCT+CART was given as consolidation part of second-line/third-line therapy). All patients received triplet/quadruplet-based regimen as induction; 50.0% were exposed to at least two proteasome inhibitors, 43.8% to at least two IMiDs, and 81.3% to daratumumab. Risk stratification revealed that 31.3% (5/16) were genetically UHR, 37.5% (6/16) had primary refractory disease, 12.5% (2/16) had early progression, and 31.3% (5/16) had pPCL, with 12.5% (2/16) meeting multiple UHR criteria. One patient had EMD. Thirteen patients (81.3%) received bridging therapy and all patients received maintenance therapy starting from 3 months from ASCT. Full treatment histories covering diagnosis, bridging therapy, ASCT plus CAR-T, and maintenance for individual patients are provided in **Supplemental Table 1**.

Table 1 Demographics, disease history, and pre-conditioning baseline characteristics

Characteristics	Total N=16, n (%)
Median age, yr (range)	58.0 (39-69)
Male, n (%)	13 (81.3)
Median duration, mo, (range)	8.50 (5.2-19.0)
ECOG 0, n (%)	16 (100)
UHR definitions, n (%)	
UHR-cytogenetic	5 (31.3)
primary refractory	6 (37.5)
early progression	2 (12.5)
pPCL	5 (31.3)
≥2 definitions	2 (12.5)
MM type, n (%)	
IgG κ	6 (37.5)
IgG λ	6 (37.5)
IgA κ	1 (6.3)
IgM κ	1 (6.3)
κ chain only	2 (12.5)
EMD, n (%)	1 (6.3)
R-ISS at diagnosis, n (%)	
I	1 (6.3)
II	6 (37.5)
III	4 (25.0)
UK	5 (31.3)
Cytogenetic at diagnosis, n (%)	
Any high-risk	9 (56.3)
t(4;14)	3 (18.8)
t(14;16)	0
t(14;20)	2 (12.5)

Characteristics	Total N=16, n (%)
1q21^{amp}	8 (50.0)
Del(17p)/P53^{del}	1 (6.3)
TP53 mutation	1 (6.3)
Double hit	5 (31.3)
None	7 (43.8)
Median LOT when receiving ASCT+CAR-T, (range)	2.0 (1-3)
LOT=1, n(%)	7 (43.8)
LOT≥2, n(%)	9 (56.3)
Induction therapy, n (%)	
Any PIs	16 (100)
Any IMiDs	16 (100)
Anti-CD38 mAb	13 (81.3)
≥2 PIs	8 (50.0)
≥2 IMiDs	7 (43.8)
Penta exposure	4 (25.0)
Bridging, n (%)	13 (81.3)
Maintenance after ASCT+CART, n (%)	16 (100)

Notes: penta exposure includes at least two PIs, two IMiDs, and one anti-CD38 mAb. Double hit refers to two high-risk cytogenetic features. Abbreviations: ASCT, autologous stem cell transplantation; CAR-T, chimeric antigen receptor T-cell; ECOG, Eastern Cooperative Oncology Group; EMD, extramedullary disease; IMiDs, immunomodulator drugs; LOT, lines of therapy; mAb, monoclonal antibody; MM, multiple myeloma; PI, proteasome inhibitor; pPCL, primary plasma cell leukemia; R-ISS, Revised International Staging System; UHR, ultra-high-risk; UK, unknown

Safety

Adverse events were evaluated in all 16 patients, with the most common treatment-emergent adverse event being hematologic toxicity. Grade 3 or higher treatment-related adverse events included neutropenia (100%), thrombocytopenia (100%), lymphocytopenia (100%), leukopenia (100%), anemia (12

patients [75%]), pneumonia (not specified, 3 patients [18.8%]), pneumonia (mycoplasma infection, 1 patient [6.3%]), sepsis (1 patient [6.3%]), and hypokalemia (2 patients [12.5%]) (**Table 2**).

Table 2. Adverse events related to ASCT or trovocabtagene autoleucel (trovo-cel)

	Any grade, n (%)	Grade ≥G3, n (%)
Hematological toxicities		
Neutropenia*	16 (100)	16 (100)
Thrombocytopenia*	16 (100)	16 (100)
Lymphocytopenia*	16 (100)	16 (100)
Leukopenia*	16 (100)	16 (100)
Anemia	16 (100)	12 (75.0)
Infection events		
Pneumonia, not specified	5 (31.3)	3 (18.8)
Upper respiratory tract infection	2 (12.5)	0
Conjunctivitis	1 (6.3)	0
Cytomegalovirus viraemia	1 (6.3)	0
Infection, not specified	1 (6.3)	0
Pneumonia mycoplasmal	1 (6.3)	1 (6.3)
Respiratory syncytial virus infection	1 (6.3)	0
Respiratory tract infection viral	1 (6.3)	0
Sepsis	1 (6.3)	1 (6.3)
Others		
Hypoglobulinemia	4 (25.0)	0
Hypogammaglobulinemia	15 (93.8)	0
Cytokine release syndrome	15 (93.8)	0
Hypoproteinemia	15 (93.8)	0
Hypokalemia	13 (81.3)	2 (12.5)
Hypocalcemia	12 (75.0)	0
hypophosphatemia	12 (75.0)	0
Hyponatremia	10 (62.5)	0
Hypomagnesaemia	10 (62.5)	0
Hypochloremia	3 (18.8)	0

	Any grade, n (%)	Grade ≥G3, n (%)
Hyperuricemia	3 (18.8)	0
Decreased appetite	2 (12.5)	0
Hypertriglyceridemia	2 (12.5)	0
Hypophagia	2 (12.5)	0
Hyperchloremia	1 (6.3)	0
Hypermagnesemia	1 (6.3)	0
Vomiting	8 (50.0)	0
Nausea	8 (50.0)	0
Diarrhea	4 (25.0)	0
Mouth ulceration	2 (12.5)	0
Abdominal discomfort	1 (6.3)	0
Upper abdominal pain	1 (6.3)	0
Flatulence	1 (6.3)	0
Sinus tachycardia	1 (6.3)	0
Ventricular extrasystoles	1 (6.3)	0
Conjunctival hyperemia	1 (6.3)	0
Immune-mediated scleritis	1 (6.3)	0
Asthenia	2 (12.5)	0
Chest discomfort	1 (6.3)	0
Pyrexia	1 (6.3)	0
Listless	1 (6.3)	0
Oropharyngeal pain	1 (6.3)	0
Henoch-Schoniein purpura	1 (6.3)	0
Treatment related SAE		
Pneumonia, not specified	2 (12.5)	2 (12.5)

Notes: thrombocytopenia was coded according to the preferred terms of “thrombocytopenia” and “platelet count decreased”, neutropenia was coded according to the preferred terms of “neutropenia” and “neutrophil count decreased”, lymphocytopenia was coded according to the preferred terms of “lymphocytopenia” and “lymphocyte count decreased”, and leukopenia was coded according to the

preferred terms of “leukopenia” and “white blood count decreased”. Abbreviations: ASCT, autologous stem cell transplantation; SAE, serious adverse events

CRS occurred in 15 patients (93.8%), all of whom recovered, with only one grade 2 event. No grade 3 or higher cases of CRS were observed. CRS had a median time to onset of 3.0 days (range 2–3) after CAR-T cell infusion and lasted for a median of 6.0 days (range 3–12). Due to the overlap between the occurrence of CRS and febrile neutropenia after preconditioning, CRS was also counted when the two conditions were difficult to fully differentiate. Therefore, the reported incidence of CRS in this study may be higher than the actual incidence, and the reported median duration of CRS may also be longer than the actual duration. Management of CRS consisted of glucocorticoids alone in seven patients and a combination of glucocorticoids and tocilizumab in one patient. There were no cases of tumor lysis syndrome, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), ICANS or any other types of neurological toxicities. All 82 pre-infusion and post-infusion samples from the 16 patients tested negative for replication competent lentivirus.

Infections related to the study treatment were primarily respiratory tract infections, most of which were viral. Infections were more likely to occur within 31 days after ASCT (28 days after trovo-cel infusion). There was one patient in the LOT≥2 cohort who developed grade 5 pneumonia 8 months after ASCT, which was considered to be unrelated to the study treatment. Prior to the onset of pneumonia, the patient had normal IgG levels, peripheral B- and T-cell counts and sustained a sCR at Month 6 on-study visit. Three patients developed grade 1 COVID-19 infections, one of which occurred concurrently with CRS. All patients (100%) experienced treatment-related globulin reduction, covering adverse events with preferred terms of hypogammaglobulinemia or globulin decreased. Ten patients (62.5%) received supportive IVIG during the study. Compared with historical data from ASCT alone, the combination of ASCT and trovo-cel did not increase the overall incidence, severity, or long-term infection rates. (**Figure 2**).

Treatment-emergent serious adverse events occurred in three patients, one was fatal as mentioned above, and the other two were pneumonia events assessed as related to both ASCT and trovo-cel. The latter two cases were resolved by the cutoff date.

All patients completed hematological reconstitution within 28 days post-ASCT (median 17.0 days, range 13–26), with a median time of 15 days (range 12–26) to neutrophil engraftment and 14.5 days (range 4–22) to platelet engraftment. Grade ≥3 hematological toxicities (either neutropenia, thrombocytopenia or anemia) were observed at 1, 3, 6, and 12 months post-ASCT in 25%, 18.8%, 18.8%, and 12.5% of cases, respectively (**Figure 2**). Prolonged neutropenia and thrombocytopenia that were unresolved by 30 days post trovo-cel infusion each occurred in 6.3% of patients.

Efficacy

The combination of trovo-cel and ASCT demonstrated promising efficacy in patients with UHR-MM or pPCL. Among the 13 patients who received bridging therapy, post-bridging responses were VGPR (n=7), PR (n=4), SD (n=1), and PD (n=1). All patients achieved an sCR with a median time to CR of 1 month after combination therapy. The rates of CR or better reached 56.25% at month 1, 87.5% at month 3, 93.8% at month 6. During a median follow-up of 26.9 months (data cutoff, March 31, 2026) [21.85 months (range, 19.22–38.7) in the LOT1 cohort, and 27.56 months (range, 7.79–42.02) in the LOT≥2 cohort], median PFS, OS, and duration of response were not reached in the overall population. The 2-year PFS and OS rates were both 87.5%. The median duration of response (DOR) was not reached (NR) (**Figure 3**).

The median follow-up was 26.92 months (range, 7.79–42.02) in the overall population, 21.85 months (range, 19.22–38.7) in the LOT1 cohort, and 27.56 months (range, 7.79–42.02) in the LOT≥2 cohort. (**a**) Efficacy swimming plot showing the treatment response over time when stratified by LOT. Pt 04, 07, 11, 13-16 were in the LOT1 cohort, and Pt 01-03, Pt 05-06, Pt 08-10, Pt 12 were in the LOT≥2 cohort. The horizontal axis shows the change in response for each patient from baseline (response to induction/bridging therapy before conditioning) through follow-up. Bridging therapy was administered to 13 patients, whereas Patients 03, 06, and 07 received no bridging therapy. The 'response before study treatment' in fig 3a depicts treatment responses as follows: for the 13 patients who received bridging therapy, the data reflect responses to bridging therapy; for Patients 03, 06, and 07, the data corresponds to responses to their prior therapies administered before screening. All patients underwent ASCT on day 0 and received a CAR-T infusion on day 3 (±1 day). At the investigator's discretion, maintenance therapy was administered 3 months after ASCT. The purple and yellow diamond symbol indicates MRD assessed by NGF (10^{-5}), which were included in the pooled NGF MRD analysis. The red and grey diamond symbol indicates MRD assessed by conventional flow cytometry and were excluded from the pooled NGF MRD analysis. This exclusion applied to all visits for Patient 03; baseline and 3-month visits for Patient 01; the 1-month visit for Patient 02; baseline and 12-month visits for Patient 04; the baseline visit for Patient 09; and the 3-month visit for Patient 10. (**b**) Kaplan–Meier curve for progression-free survival. Median progression-free survival was not reached in the LOT1 cohort, the LOT≥2 cohort, or the overall population. (**c**) Kaplan–Meier curve for overall survival. Median overall survival was not reached in either cohort or in the overall population. (d) Kaplan–Meier curve for duration of response. ASCT, autologous stem cell transplantation; CAR-T, chimeric antigen receptor T-cell; CI, confidence interval; CR, complete response; LOT, line of therapy; MRD, minimal residual disease; PD, progressive disease; PR, partial response; sCR, stringent disease; SD, stable disease; VGPR, very good partial response.

All evaluable patients (n=15) achieved MRD negativity by NGF at 10^{-5} sensitivity. NGF-based MRD negativity rates at 1, 3, 6, and 12 months post-ASCT were 92.3% (12/13), 100% (14/14), 93.3% (14/15), and 93.3% (14/15), respectively. (**Supplemental Table 2**)

All seven patients in the LOT1 cohort had MRD negativity (10^{-5}) on NGF. Six patients maintained an sCR, and one experienced biochemical progression (24.5 months after ASCT+CART). This patient is currently undergoing salvage therapy with a GPRC5D-CD3 bispecific antibody combined with a CD38 monoclonal antibody for two cycles and has already achieved a partial response. During a median follow-up of 21.85

months (range, 19.22–38.7), the estimated PFS rate was 100% at both 18 months and 24 months in the LOT1 cohort. MRD negativity on NGF was sustained in all evaluable patients at 3 months (7/7), 12 months (7/7), and 18 months (7/7). One patient had transient MRD reversion at M6 but regained negativity, so six patients maintaining negativity for ≥12 months. Impressively, the 2 years PFS and OS in this cohort were both 100%.

The eight evaluable patients in the LOT≥2 cohort had MRD negativity rates on NGF of 100% at 3 months (7/7), 87.5% at 9 months (7/8), 87.5% at 12 months (7/8), 85.7% at 18 months (6/7), and 75.0% at 24 months (6/8). One patient from the LOT≥2 cohort received only conventional flow cytometry (which yielded MRD-negative results) without NGF testing; this patient was thus excluded from the NGF MRD evaluable set. Total 3 patients died by cutoff date, including two patients progressed (at 9.2 and 25.1 months) and later died of disease progression; one died of non-treatment-related pneumonia 8 months post-ASCT during an sCR. (**Figure 3**) Remarkably, even in this patient cohort with kinetic ultra-high-risk features (primary refractory or early progression), the 2-year PFS and OS stood at 75%. No significant difference in PFS or OS was observed between the LOT1 and LOT≥2 cohorts, likely because of the limited cohort size.

Pharmacokinetics and pharmacodynamics

Robust CAR T-cell expansion was observed in all patients, with a median time to peak concentration of 7 days (range, 4–11). The favorable expansion profile was supported by adequate lymphodepletion following conditioning. All patients achieved an absolute lymphocyte count (ALC) $<0.2\times10^9$/L before CAR-T infusion. The median peak concentration was 785,958 copies/μg gDNA (range, 77,674–1,333,385), and the median area under the curve from time zero to 28 days ($AUC_{0-28\ days}$) was 7,833,861 copies/μg gDNA·day (range, 464,487–18,621,613). The median T_{last} was 73 days (range, 28–752+) (**Figure 4, Supplemental Table 3**). Correspondingly, the peak peripheral blood ALC was observed on Day 13 (range: 7–28) following CAR-T infusion, with a median peak ALC of 3.35×10^9/L (range: 1.12–6.72). Trovo-cel showed consistent pharmacokinetics and robust expansion across all subgroups, with no significant differences observed based on previous treatment (LOT1 vs. LOT≥2) or conditioning regimen (HDM vs. HDM + FLU) (all P>0.05) (**Figure 4**). Maintenance therapy appears to have minimal impact on Trovo-cel persistence. The majority of patients had their last detectable CAR-T level (T_{last}) within 90 days. For the 6 patients with measurable CAR-T copy numbers at the time maintenance was initiated, CAR-T cells were found to persist during subsequent monitoring (**Supplemental Table 3**). When compared with the single-agent trial in R/R MM,[19,20] trovo-cel combined with ASCT had a significantly accelerated T_{max} (7 days vs. 14 days, P<0.05) at the same dose level, while maintaining comparable exposure metrics (P>0.05 for both peak concentration and $AUC_{0-28\ days}$) (**Supplemental Table 3**).

We observed significant elevations in serum interleukin-6, interferon-gamma, and interlekuin-10 levels in all patients, with a median time to peak of 4 days post trovo-cel infusion. No significant differences were

found according to LOT (**Figure 4, Supplemental Table 4**).

Most patients had B-cell aplasia at baseline, with a median peripheral blood $CD19^+$ B-cell count of 7 cells/μL (range, 0–67). By day 31, all 14 evaluable patients (100%) had either undetectable or zero $CD19^+$ B-cell counts. At month 3, B-cell recovery (i.e., back to normal) was observed in 11 of 14 evaluable patients. A persistent decrease in immunoglobulin G (IgG) was noted in the context of preexisting hypogammaglobulinemia at baseline (10/16 patients had low IgG at baseline, including two with levels below 4 g/L). IgG was <4 g/L in three patients at month 6, three at month 9, and three at month 12. T-cell recovery occurred rapidly in most patients, with prompt reconstitution of both $CD4^+$ and $CD8^+$ T-cell subsets (**Supplemental Table 5**).

DISCUSSION

This study presents a novel therapeutic approach, sequentially application of ASCT combining with BCMA CAR-T, specifically targeting this exceptionally challenging population. In 16 patients, this strategy showed remarkable preliminary efficacy, achieving a 100% sCR rate and encouraging 2-year PFS and OS rates of both 87.5%.

In this trial, UHR was defined as either having UHR cytogenetics, or primary refractory disease, or early progression, or pPCL, encompassing either static or dynamic UHR features. To our knowledge, these criteria are more stringent than existing definitions. Early progression is commonly defined as progression within 18 months of first-line treatment (ER18), associated with median PFS 10 vs 40 months and OS 29 vs 76 months vs non-EPD ($P < 0.001$)[24]. Our center's previous data showed ER18 correlated with more aggressive biology and poorer response ($p < .001$), with a median OS of only 28.9 months[25]. In this study, early progression patients had a best response duration ≤ 6 months and primary refractory patients showed no response to intense induction. This subgroup has minimal probability of durable deep responses or survival benefit from standard-of-care regimens including triplet/quadruplet induction, ASCT, and maintenance. Thus, innovative therapeutic strategies are urgently needed for these patients, together with those with UHR cytogenetic, and pPCL.

Emerging data supports the feasibility of incorporating CAR-T into transplantation in hematological malignancies, yet the optimal ASCT-CAR-T combination modality remains undefined, especially for MM and pPCL. Sequential ciltacabtagene autoleucel (cilta-cel) ± lenalidomide (NCT04133636) achieved a ≥ CR rate of 94% and an 18-month PFS rate of 94% in 17 patients with NDMM who had suboptimal responses post-ASCT (less than CR). [26] Shi et al[27] reported a ≥ CR rate of 88% and a median PFS of 38 months for 10 patients with high-risk NDMM who were treated sequentially with ASCT, anti-CD19 CAR-T, anti-BCMA CAR-T, and lenalidomide. Both trials adopted CAR-T infusion after hematopoietic reconstitution post-ASCT. Their high-risk definitions were relatively lenient, and patients with dynamic high-risk features were not enrolled.

Wei's team at Tongji Hospital demonstrated superior 24-month PFS (77.5% vs. 48.4%) when ASCT was added to CD19/CD22 CAR-T therapy in lymphoma.[28] Our previous research confirmed that early CAR-T infusion within 2–4 days post-ASCT achieves favorable efficacy and safety in patients with R/R large B-cell lymphoma (DLBCL), along with reduced exhaustion markers (e.g., PD-1, TIM-3) and prolonged persistence,[18] supporting applying this strategy to UHR-MM. The myeloablative conditioning for ASCT optimizes the immune microenvironment to facilitate CAR-T cell engraftment and function, superior to conventional FLU/CYC schema used for CAR-T monotherapy, and post-ASCT cytokine remodeling further activates CAR-T cells.[29] Moreover, the debulking and reduction of myeloid cells and cytokines following conditioning and ASCT may alleviate CRS. CAR-T can also correct the T-cell immune reconstitution imbalance and antagonize T-cell dysfunction after ASCT,[29] although we have not yet conducted such analysis in this single-arm study. Faster expansion and earlier peak activity of trovo-cel was observed when combined with ASCT versus the trovo-cel monotherapy trial, which may be partly attributed to the aforementioned synergistic effects.

In this study, this regimen yielded profound deep and durable responses, evidenced by the universal achievement of sCR, MRD negativity by NGF (10^{-5}, 100%), with a median PFS still unreached. The estimated 18-month and 24-month PFS and OS rates in the LOT1 cohort were all 100%. These compare favorably with those reported in trials for newly diagnosed UHR-MM treated with potent induction followed by ASCT, such as the MASTER trial[30] (MRD negativity rates of 83.3% at 10^{-5} and 66.7% at 10^{-6} and a 24-month PFS of 58% in patients with ≥ 2 HRCAs) and the OPTIMUM (MUKnine) trial[31] (40% MRD < 10^{-5} negativity rate in patients with UHR-MM or pPCL). Neither of both trials enrolled patients with dynamic high-risk features, who represented most of our study population. Among our kinetic UHR cohort, the 2-year PFS was 75%, exceeding the 63.3% 2-year PFS seen in KARMMA-2 cohort 2b (ide-cel-treated FHR patients, with more permissive FHR criteria).[32,33] Compared with other frontline CAR-T therapies in NDMM which not surprisingly have set a high benchmark for a deep response, our regimen also appears to have greater long-term benefits.[16,17] Those trials still failed to avoid incomplete deep responses and early relapse, and they excluded pPCL and dynamic high-risk cases. By contrast, our trial enrolled 8 patients with functional high-risk disease (early relapse and primary refractory) and 5 patients with pPCL and yielded satisfactory efficacy (**Supplemental Table 1**). These findings support earlier-line use of CAR-T combined with ASCT in UHR-MM or pPCL to achieve deeper and more durable MRD negativity and eventually improve long-term outcomes,[34] potentially altering the natural history of these aggressive disease phenotypes.

Importantly, the safety profile of this sequential approach was manageable and did not appear to exacerbate toxicity. CRS was mild and manageable. No cases of ICANS were reported. All patients achieved complete hematological reconstitution within 28 days post-ASCT (median 17.0 days, range 13–26), consistent with the typical 2-week recovery pattern in patients receiving ASCT.[35] Prolonged neutropenia and thrombocytopenia (unresolved by day 30 after trovo-cel infusion) each occurred in 6.3% of patients, which compares favorably with the higher rates reported with idecabtagene vicleucel (ide-cel)[36] (40%/42%) and cilta-cel[37] (27%/33%). With maintenance therapy initiated at month 3, the

incidence of late grade ≥ 3 cytopenia remained favorable versus with single CART therapy[37,38] or delayed CART infusion strategies[27]. Trovo-cel was infused on day 3 after stem cell reinfusion, a timing that balances adequate melphalan-based lymphodepletion with minimized infection and myelosuppression risks. Stem-cell rescue after lymphodepletion, combined with CAR-T, likely limits CAR-T-associated long-term hematologic toxicity and reduces infection risk. Consistent with the aforementioned low rate of late-onset severe cytopenia, this finding may be attributable to the early loss of B-cell aplasia and rapid T-cell recovery (**Supplemental Fig. 1**). Three months after CAR-T, the B lymphocyte counts of most patients had recovered to normal, and T lymphocytes had recovered to above the lower limit of normal. In general, this well-tolerated safety profile supports the feasibility of this approach.

This study has limitations, primarily its small sample size and relatively short follow-up duration. The long-term durability of responses and the ultimate cure rate remain to be determined. Furthermore, the optimal timing, conditioning regimen for ASCT, and CAR-T product characteristics for this sequence need further refinement. In addition, the lack of a universally accepted definition for UHR-MM poses a challenge in terms of standardizing patient selection criteria and comparing outcomes across studies. Since this preliminary exploratory study enrolled a relatively heterogeneous patient population, we hope to conduct more targeted investigations in these four different ultra-high risk patient subgroups in the future. Distinct biological features and natural histories (e.g., pPCL vs. functional HR) may lead to differential treatment responses and toxicities. We recommend pre-planned subgroup analyses in larger trials, or dedicated phase II studies focusing on specific categories.

In conclusion, this study suggests that trovo-cel combined with ASCT is well tolerated with promising efficacy in patients with UHR genetic abnormalities, functional high-risk features or pPCL. Further research in larger and more diverse cohorts using a standardized definition of UHR disease is warranted to validate these findings and refine treatment strategies.

Declarations

Competing Interests

W.L, Y.X, L.L,C.Z and J.Z are employees of Shanghai AbelZeta Ltd..J.H and Y.Y are employees of AbelZeta Inc. The remaining authors declare no competing financial interests.

Author Contribution

Y.X, W.L, L.Q, and D.Z conceived and designed the study; Y.X, G.A, W.L, W.S, S.D, W.H, Q.W, W.X, C.D, R.L, T.W, S.Y, L.Q, and D.Z were responsible for the provision of study material or patients, Y.X, W.L, G.A, W.L, W.S, S.D, W.H, Q.W, W.X, C.D, R.L, T.W, S.Y, Y.X, L.L, C.Z, J.Z, J.H, K.Z, Y.Y, L.Q, and D.Z collected and analyzed the data, Y.X, W.L, L.Q, and D.Z wrote the manuscript, all the authors approved the final manuscript and are accountable for all aspects of the work.

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Data Availability

All relevant data are presented within the manuscript and supplementary materials. Raw patient-level data cannot be shared publicly to protect patient confidentiality.

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Figures

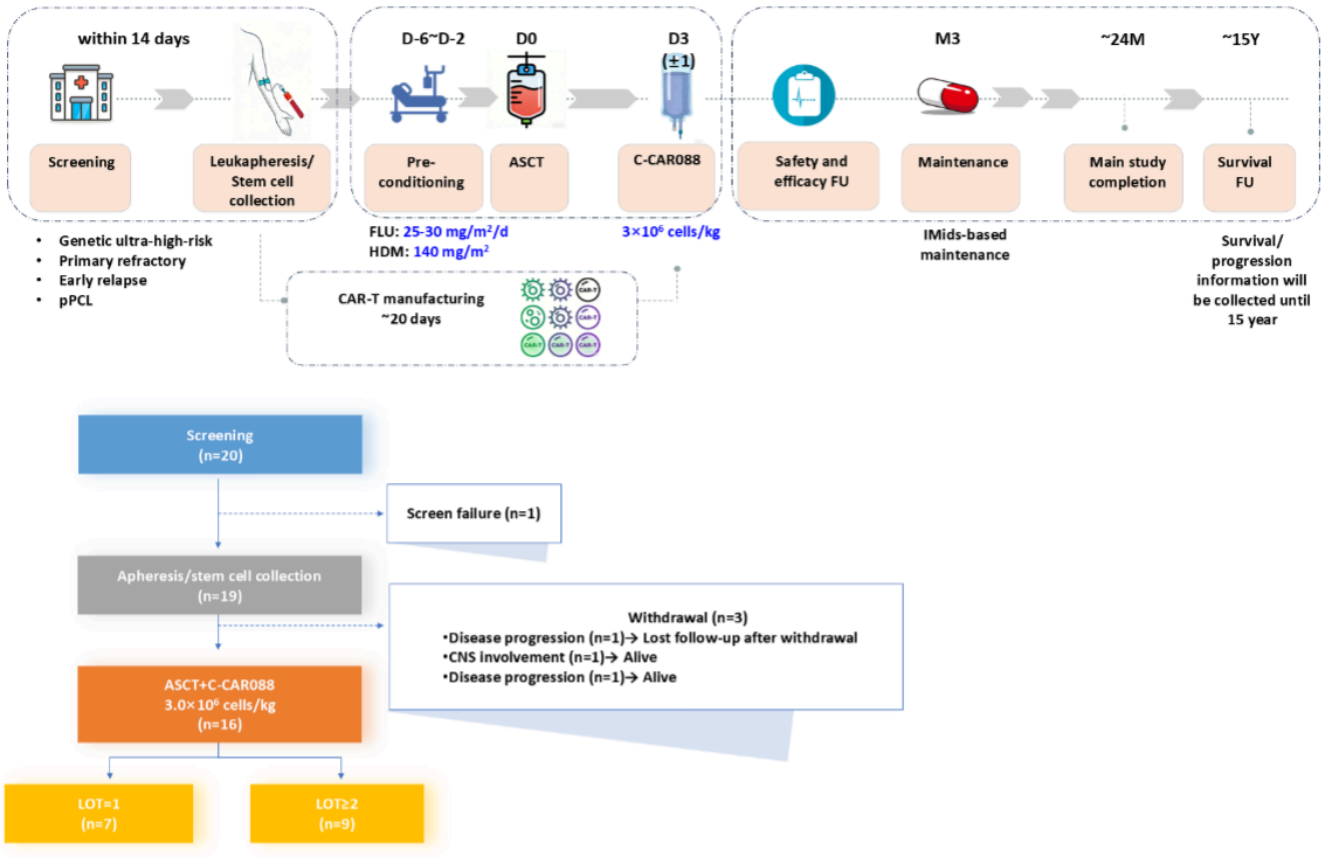


Figure 1

Study design and patient distribution.

ASCT, autologous stem cell transplantation; CAR-T, chimeric antigen receptor T-cell; FLU, fludarabine; FU, follow-up; HDM, high-dose melphalan; IMiDs, immunomodulator drugs; pPCL, primary plasma cell leukemia

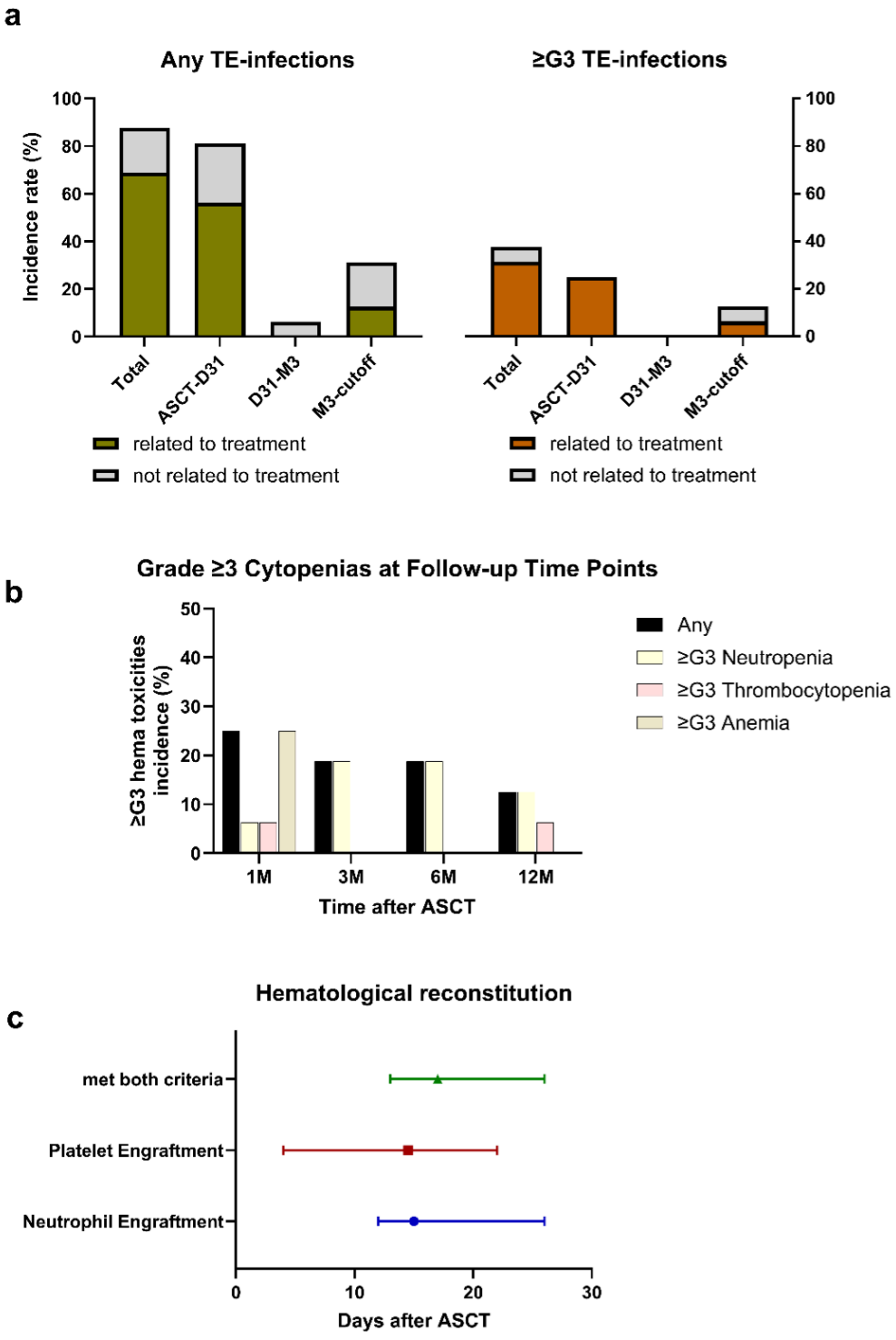


Figure 2

Infection and hematologic profiles after ASCT and CAR-T therapy in patients with ultra-high-risk multiple myeloma or primary plasma cell leukemia

(**a**) Treatment-emergent and treatment-related infectious events following ASCT. Stacked bar charts show the number of events occurring in the various post-ASCT periods. The total height of each bar

represents all treatment-emergent events, with the darker segment indicating the subse t of treatment-related events. The left panel indicates any-grade events and the right panel indicates events that are grade ≥3. (**b**) Line graphs depict the incidence (percentage) of grade ≥3 cytopenias (any, neutropenia, thrombocytopenia, and anemia) at day 30 post-CAR-T infusion (approximately day 33 post-ASCT) and at 3, 6, and 12 months after ASCT. (**c**) Point plots with error bars indicate median time (with range) to neutrophil engraftment, platelet engraftment, and full hematological reconstitution after ASCT. ASCT, autologous stem cell transplantation; CAR-T, chimeric antigen receptor T-cell; TE, treatment-emergent.

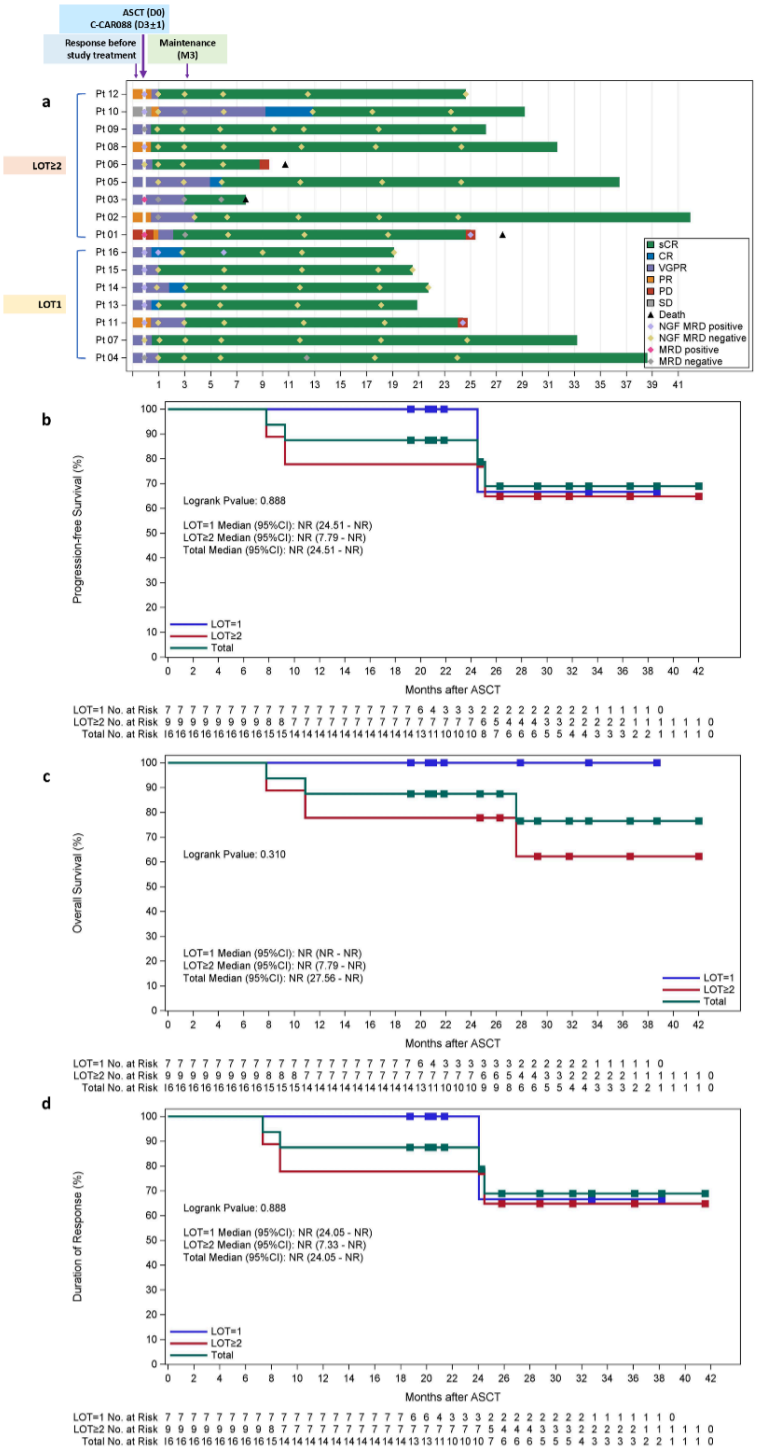


Figure 3

Efficacy outcomes in patients with ultra-high-risk multiple myeloma or receiving ASCT combined with trovocabtagene autoleucel (trovo-cel) therapy

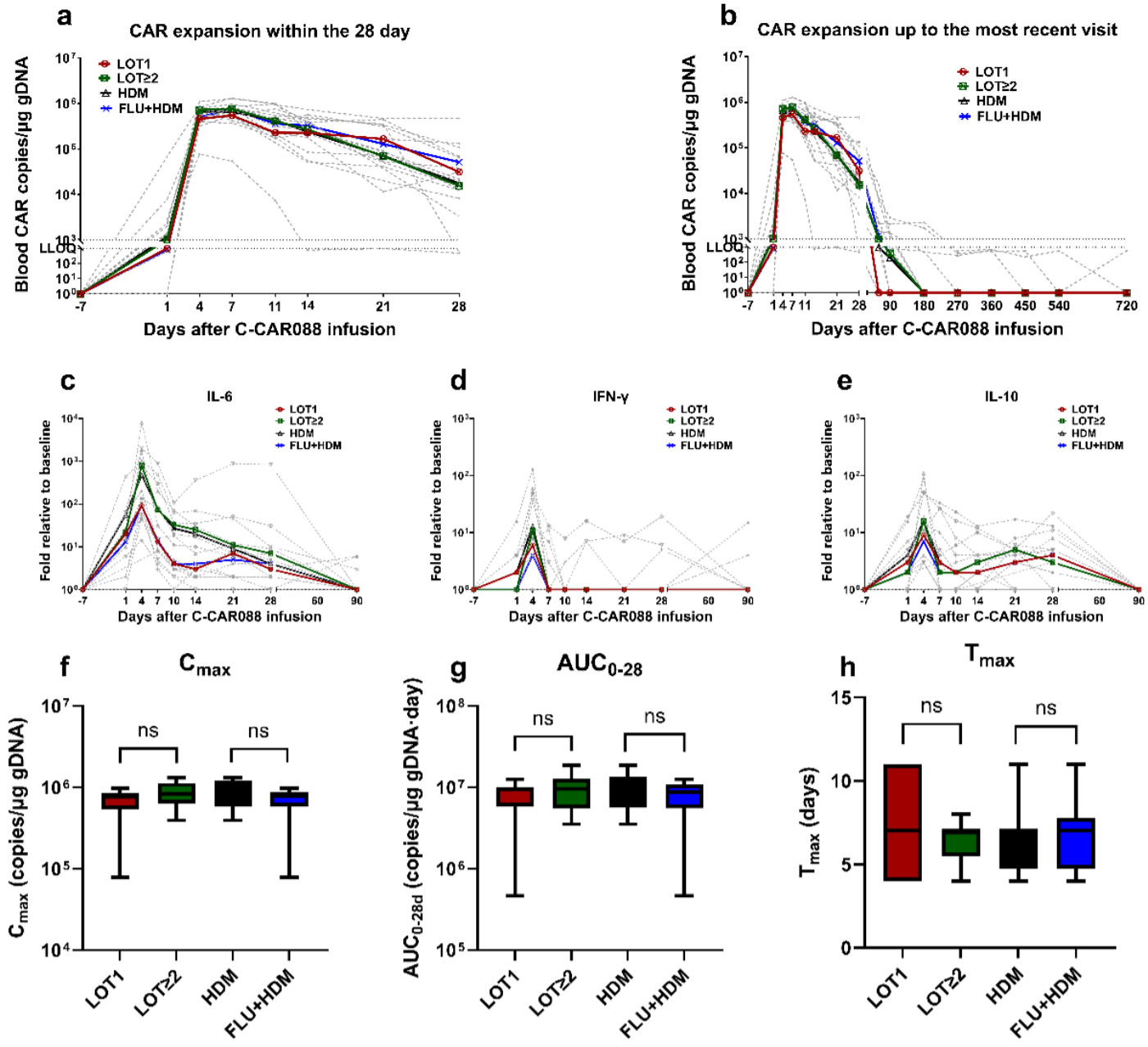


Figure 4

Peripheral blood CAR-T expansion and changes in cytokines

(**a**) Peripheral blood CAR-T cell copy number measured by quantitative polymerase chain reaction within 28 days after infusion of C-CAR088 (trovocabtagene autoleucel, trovo-cel). The dashed line represents the expansion in 16 patients, the red solid line represents the median expansion level in the LOT1 cohort, and the green line represents the median expansion level in the LOT≥2 cohort; (**b**) Peripheral blood CAR-T cell copy number changes to the most recent pharmacokinetic sampling time. (**c–e**) Comparison of changes in serum concentrations of IL-6, IFN-γ, and IL-10 over time with baseline after ASCT and C-CAR088 infusion. (**f-h**) Comparison of median C_{max}, $AUC_{0\text{-}28days}$, and T_{max} according to LOT number. Red

and green lines represent the median changes in the LOT1 and LOT≥2 cohorts, respectively. ASCT, autologous stem cell transplantation; $AUC_{0\text{-}28\ days}$, median area under the curve from time zero to 28 days; CAR-T, chimeric antigen receptor T-cell; C_{max}, peak concentration; IFN-γ, interferon gamma; IL, interleukin; LOT, line of therapy; T_{max}, time to peak concentration.

Supplementary Files

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