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Mesenchymal stromal cells as add-on therapy to anti-CD25 antibodies for treating gastrointestinal-involved steroid-refractory acute graft-versus-host disease: a multicenter, single-arm, pivotal clinical trial

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Abstract

Background Steroid-refractory acute graft-versus-host disease (SR-aGVHD) is the predominant cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT), with gastrointestinal involvement (SR-GI-aGVHD) remaining a key obstacle. We conducted a multicenter, single-arm, pivotal trial to assess the efficacy and safety of hUC-MSC PLEB001, a human umbilical cord-derived mesenchymal stromal cells (MSCs) product, plus anti-CD25 monoclonal antibody as second-line therapy for SR-GI-aGVHD.

Methods Eligible patients with grade II or higher SR-GI-aGVHD received hUC-MSC PLEB001 with protocol-defined anti-CD25 monoclonal antibody therapy. hUC-MSC PLEB001 was infused at a dose of 10^6 cell/kg twice weekly for 4 consecutive weeks, starting at day 1, and efficacy was assessed on day 28. Patients achieving complete response (CR), progressive disease (PD) or no response (NR) concluded treatment; those with partial response (PR) continued the same regimen for additional 4 weeks. The primary endpoint of the study is the overall response rate (ORR) at day 28.

Results Fifty-four patients (median age 43, range 14–68) were enrolled. The number of Grade II–IV SR-aGVHD patients was 21, 16, 17, respectively. Thirty-seven patients were GI-involved only, 15 patients were GI and skin involved, and 2 patients were GI and liver involved. The ORR at day 28 was 63.0% (95% CI 48.7%, 75.7%), with a CR rate

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of 55.6% (41.4%, 69.1%). The 28-day durable complete response rate (DCR) was 51.9% (37.8%, 65.7%). The ORR and CR rate at day 56 was 51.9% (37.8%, 65.7%) and 50.0% (36.1%, 63.9%), respectively. The overall survival (OS) for full analysis set (FAS) at day 28, 56, 100, 360 for the entire cohort were 94.4% (83.8%, 98.2%), 88.9% (76.9%, 94.9%), 79.6% (66.2%, 88.2%), 65.8% (51.1%, 77.0%) respectively. Treatment was well tolerated, and no infusion-related toxicity or treatment-related serious adverse events were observed.

Conclusions In this multicenter single-arm study, hUC-MSC PLEB001 plus anti-CD25 monoclonal antibody therapy was associated with clinically meaningful response rates and an acceptable safety profile in patients with SR-GI-aGVHD. These findings support further evaluation of MSC-based approaches within multimodal treatment algorithms for this challenging condition.

Trial registration: Registry: Chinese Clinical Trial Registry, TRN: ChiCTR2300073965, Registration date: 2023-07-26 (retrospectively registered).

Keywords Mesenchymal stromal cells, Allogeneic hematopoietic stem cell transplantation, Acute graft-versus-host disease, Steroid-refractory, Gastrointestinal aGVHD

Background

Acute graft-versus-host disease (aGVHD) is a common and potentially life-threatening complication following allogeneic hematopoietic stem cell transplantation (allo-HSCT) [1, 2]. The severity of aGVHD ranges from grade I to IV, with the clinical manifestations spanning from mild rash to severe organ dysfunction or even death [3]. The incidence of Grade II–IV aGVHD is 30–60%, and that of Grade III–IV aGVHD is 14–40% [4–6]. Despite advances in prophylaxis and treatment, aGVHD remains a formidable barrier on the path of allo-HSCT yet to be fully overcome.

First-line treatment of aGVHD is systemic glucocorticoids with a response rate of 40–60% [1, 3, 7]. Steroid-refractory (SR) disease remains a major issue associated with poor clinical outcomes, with reported 1-year survival rates of 10–38% [3, 8]. A significant advance was achieved with ruxolitinib, a JAK inhibitor approved by FDA in 2019, which improved median survival time to approximately 11 months in SR-aGVHD patients [8]. Nonetheless, ruxolitinib and other second-line therapies such as calcineurin inhibitors, basiliximab, methotrexate (MTX) and mycophenolate mofetil (MMF) are associated with substantial immunosuppressive burden, which may impair immune reconstitution and increase the risk of cytopenia and infections [1, 9].

SR-aGVHD patients with gastrointestinal involvement (SR-GI-aGVHD) exhibit poor prognosis and high non-relapse mortality (NRM), with a 2-year overall survival (OS) rate of approximately 25% [10–12]. A real-world study on SR-GI-aGVHD patients treated with ruxolitinib showed the overall and complete response at day 28 were 44.5% and 13%, respectively [13], which remain lower than responses observed in patients with other organ manifestations, highlighting the particular therapeutic challenge of gastrointestinal involvement. Therefore, although ruxolitinib has emerged as an effective second-line therapy supported by randomized clinical trial evidence, alternative immunomodulatory approaches continue to be explored in real-world clinical practice, especially in settings where treatment paradigms have evolved over time.

Mesenchymal stromal cells (MSCs) have emerged as a potential option for the treatment of SR-aGVHD since 2004 [14]. MSCs exert immunomodulatory effects in aGVHD by suppressing effector T cell activity, promoting regulatory T cell populations, and modulating monocyte function [15–17]. Concurrently, they facilitate tissue repair through trophic support and mitochondrial transfer, demonstrating a dual capacity for immune regulation and tissue recovery [18]. Clinical studies have demonstrated favorable tolerability, acceptable safety profiles, and signals of clinical activity, with response rates at day 28 ranging from 40 to 82.6% [15, 16, 19–24]. The bone marrow-derived MSC products Prochymal and TEMCELL were approved in Canada (2012) and Japan (2015) respectively for the treatment of SR-aGVHD [25]. Recently FDA approved Ryoncil (Remestemcel-L-rknd), an allogeneic bone marrow-derived MSC therapy, for pediatric patients with SR-aGVHD [26]. However, substantial variability in clinical efficacy across MSC trials has been reported, likely reflecting differences in tissue origin (e.g., bone marrow, umbilical cord), donor variability, and patient-specific characteristics [15, 25]. This heterogeneity underscores the need for further well-designed clinical trials with expanded cohorts to definitively establish the therapeutic potential of MSCs.

In a multicenter, randomized, double-blind, placebo-controlled phase II study (Chinese Clinical Trial Registry, ChiCTR2000035740), we evaluated the efficacy and safety of human umbilical cord-derived MSCs (hUC-MSC PLEB001) in combination with anti-CD25 monoclonal antibody therapy [27, 28]. Anti-CD25 therapy provides targeted inhibition of IL-2 receptor–dependent effector T-cell activation [29, 30], while MSCs exert broader immunomodulatory effects, and may contribute

to restoration of the gastrointestinal immune microenvironment [15]. These complementary biological effects provided a mechanistic rationale for their combined use at the initiation of second-line therapy rather than sequential escalation. The post-hoc analysis showed that MSCs plus anti-CD25 treatment increased the overall response rate (ORR) at day 28 in GI-SR-aGVHD patient compared with control (66.7% vs. 33.3%, odds ratio: 4.00; 95% CI 1.11 to 14.43; $p = 0.031$) [28]. Other studies have also reported the feasibility and activity of MSCs combined with basiliximab-based regimens as second-line therapy for SR-aGVHD [20, 21]. To further evaluate the efficacy and safety of hUC-MSC–based therapy for SR-GI-aGVHD, we designed this multicenter single-arm pivotal clinical trial (Chinese Clinical Trial Registry, ChiCTR2300073965). Exploratory analyses of biomarker profiles and immune cell subsets were additionally performed to generate hypotheses regarding potential immunomodulatory effects.

Methods

Study design and oversight

This multicenter, single-arm pivotal clinical trial was designed to evaluate the efficacy and safety of hUC-MSC PLEB001 for treating SR-GI-aGVHD of Grade II or above. The investigated hUC-MSC PLEB001 was manufactured and packaged as was previously described [27]. The trial was conducted in 4 hospitals in China (Chinese PLA General Hospital, Chinese Academy of Medical Sciences Blood Diseases Hospital, The Fifth Medical Center of Chinese People's Liberation Army General Hospital, and Beijing University People's Hospital) from February 2023 to June 2024. The trial was approved by the ethics committees per institution and was conducted in accordance with the Declaration of Helsinki. The trial was registered at Chinese Clinical Trial Registry (ChiCTR2300073965).

Patients

During the recruitment period, consecutive patients at each participating center who developed grade II–IV aGVHD with gastrointestinal involvement after allo-HSCT for hematological malignancies were assessed for eligibility. Eligible patients were aged 13–70 years and diagnosed with SR-GI-aGVHD of grade II or higher. The diagnostic criteria for aGVHD were based on the Mount Sinai Acute GVHD International Consortium (MAGIC) criteria [31]. Gastrointestinal involvement was diagnosed using an integrated clinical approach that considered characteristic gastrointestinal symptoms (including persistent diarrhea, abdominal pain, nausea, or vomiting) occurring after allo-HSCT, together with the temporal relationship to transplantation. Infectious causes of gastrointestinal symptoms were systematically evaluated and excluded according to local clinical practice, including microbiological stool testing and viral screening when indicated. Endoscopic biopsy was performed in a subset of patients when clinically indicated, but histological confirmation was not mandatory for study inclusion.

Standard first-line glucocorticoid therapy was defined as methylprednisolone at a dose of 1–2 mg/kg/day or an equivalent regimen, consistent with the Chinese expert consensus [32]. SR-aGVHD was defined as aGVHD progression after 3 days of first-line glucocorticoid treatment, no improvement after 7 days of treatment, failure to achieve complete remission after 14 days of treatment, or GVHD reactivation during steroid tapering.

Written informed consent was obtained from all patients or their legal guardians prior to enrolment. Once eligibility was confirmed and informed consent was obtained, study treatment was initiated within 3 days.

Patients were excluded if they had conditions that could interfere with study evaluation or patient safety, including severe pulmonary disease, active solid malignancy within five years prior to screening, uncontrolled infections, severe organ dysfunction, or ECOG performance status > 3. Patients who had received donor lymphocyte infusion (DLI) for the treatment of hematological malignancy relapse or who were receiving systemic therapy for aGVHD other than glucocorticoids at screening were also excluded. Patients who had received DLI for relapse prevention were eligible for enrolment. All screening decisions and reasons for exclusion were prospectively documented. The complete exclusion criteria were showed in Table s1. None of the patients included in this study were previously reported in our earlier phase II trial [28].

Investigational product

hUC-MSC PLEB001, developed by Platinumlife Biotechnology (Beijing) Co. Ltd., is a mesenchymal stromal cell product derived from umbilical cords from healthy donors. After removal of arteries and veins, the residual umbilical cord tissue is minced and subjected to enzymatic digestion for primary cell isolation, which are then expanded in serum-free medium. No cell enrichment, purification, or selection procedures are conducted during the manufacturing process. Cells are cryopreserved at early passages and formulated into the final clinical product [28].

Treatment protocol and concomitant therapy

All eligible patients received hUC-MSC PLEB001 at a dose of 10^6 cell/kg per infusion, administered twice weekly for consecutive 4 weeks. The day of first administration was set as day (1) In accordance with routine clinical practice and ethical considerations, one background second-line treatment was administered for every

patient. Anti-CD25 monoclonal antibody (basiliximab or daclizumab) was administered as the first choice of second-line therapy. Anti-CD25 monoclonal antibody treatment was initiated on Day 0, Day 1, or Day (2) Basiliximab was administered at a dose of 20 mg per infusion, and daclizumab at a dose of 1 mg/kg per infusion. Anti-CD25 monoclonal antibody was administered on days 1, 4, and 8, and subsequently repeated weekly until aGVHD improved to grade <II. If aGVHD significantly worsened or progressed, an additional second-line agent was introduced as salvage treatment according to standard-of-care protocols per institution. The addition of a second distinct second-line therapy for aGVHD was considered a treatment failure.

Concomitant events were defined as premature discontinuation, patient withdrawal due to unmet expectations, or administration of prohibited medications. Patients with concomitant events were defined as non-responders.

Endpoints and assessments

Patients' response was assessed by local investigators at each participating center according to prespecified criteria based on the MAGIC consensus [31]. Response categories included complete response (CR), partial response (PR), no response (NR), and progressive disease (PD). Overall response (OR) included CR and PR. If a patient achieved CR, PD or NR, the treatment was concluded. Patients achieving PR continued treatment for additional 4 weeks with the same dose and frequency.

The primary endpoint was overall response rate (ORR) at day 28. The secondary endpoints included ORR at day 56, durable CR within 100 days, overall survival (OS), non-relapse mortality (NRM), relapse-free survival (RFS), failure-free survival (FFS), cumulative incidence of recurrence (CIR), cumulative incidence of cGVHD and safety outcomes.

Failure-free survival was defined as time from enrolment to relapse or progression of aGVHD, non-relapse mortality, or addition of a second distinct systemic second-line therapy for aGVHD. OS was defined as the time from first injection to end of follow-up. The follow-up course lasted until death, withdrawal of informed consent, or 100 ± 7 days after first administration, whichever occurred first. Prolonged follow-up lasted until 365 ± 15 days after treatment initiation, death or withdrawal of informed consent, whichever occurred first. Patients achieving OR at day 28 were defined as responder and those who did not achieve OR at day 28 were defined as non-responder.

Safety analysis was assessed based on Safety Set. Frequency and instance of treatment-emergent adverse event (TEAE), which was defined as AE occurring or exacerbating during/after the injection of investigational drug until end of follow-up, was analyzed. The severity of TEAE was recorded in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Treatment-relating adverse event (TRAE) was defined as TEAE attributed to the investigational drug. Occurrence of TEAE was described in terms of case and instance. Infusion toxicity was defined as TRAE including fever, phlebitis, chest pain, shortness of breath, transient pulmonary edema, allergic reactions, rash, itching at the injection site, nausea, etc., which was evaluated from day 1 until 14 days after completion of study treatment.

Biomarkers and immune cell subpopulations were tested at day 1, 15, 28 and 56 to explore dynamic changes. Biomarkers included soluble ST2 (sST2), REG3α, soluble TNF receptor 1 (sTNFR1), IL-6 and IL-8. Baseline levels were compared between responders and non-responders.

Statistical analysis

Null hypothesis was that the expected ORR at day 28 was no higher than 37%. The primary endpoint would be achieved if the lower bound of the two-sided 95% confidence interval (CI) of 28-day ORR were above 37%. The threshold and sample size was decided as follows: Single-arm Objective Performance Criteria (OPC) was applied for sample size calculation since there was no approved counterpart in China. Several studies offered reference for the determination of threshold. In the REACH2 study of ruxolitinib, the best available treatment (BAT) achieved an ORR of 39.2% at Day 28 for SR-aGVHD, and an ORR of 33% at day 28 for lower gastrointestinal tract-involved SR-aGVHD [8]. In our previous Phase II clinical trial, the ORR at Day 28 for the placebo group was 33.3% [28]. Based on the evidence above and discussions with experts from the Stem Cell Application Study Group, Hematology Branch of Chinese Medical Association, the threshold for ORR at day 28 in this study was set at 37%. Considering the one-sided test level $\alpha = 0.025$, power $1\text{-}\beta = 0.8$, and lower 95% confidence interval for ORR being greater than 37%, the sample size would be no less than 48 subjects. Taking into account of 20% drop-out rate, a total of 60 patient would be recruited.

Three datasets were defined in this study: safety analysis set (SS) included participants with at least one administration and safety data and was used for safety analysis; full analysis set (FAS) included participants with at least one administration and was applied for evaluating primary endpoint; per protocol set (PPS) included participants who received standard treatment.

Time-to-event outcomes were estimated using the Kaplan–Meier method. Cumulative incidence functions were used for competing-risk analyses, with relapse and non-relapse mortality treated as competing events, and death treated as a competing risk for cGVHD.

Comparisons of cumulative incidence were performed using the Fine–Gray model.

To minimize guarantee-time bias when comparing overall survival by response status at day 28, a prespecified landmark analysis at day 28 was performed.

For exploratory analysis on biomarker and cell subpopulation between response group and non-response group, t test was applied if the data was normal and rank sum test was applied otherwise. No transformation or missing-data imputation was applied.

All statistical computation was performed using SAS®9.4 or above. Non-missing frequency, missing frequency, mean, standard deviation, median and quantiles were reported for continuous data. Categorical data was displayed as frequency plus percent. All statistical tests were two-sided and $P < 0.05$ was set as significant.

Results

Patient characteristics

During February 2023 and March 2024, a total of 77 patients signed informed consent for screening and 23 patients met exclusion criteria. Reasons for screening failure were summarized in Table s2. Finally, 54 candidates were included into the study. All 54 patients received at least one injection and were included in full analysis set and safety analysis set. Four patients discontinued treatment early because of meeting withdrawal criteria ($N = 1$), death due to SAE ($N = 1$), poor compliance ($N = 1$) or relapse ($N = 1$); fifty patients finished complete therapy and were included in per protocol set. The flow diagram was illustrated in Fig. 1. The baseline demographics were shown in Table 1.

Forty-nine (90.7%) patients developed aGVHD after allo-HSCT. In addition, five patients (9.3%) had received prophylactic DLI prior to the onset of aGVHD. The median time from HSCT or DLI to onset of aGVHD was 34 (15, 117) days. All patients had steroid-refractory or steroid-dependent aGVHD according to protocol definitions. The median time from aGVHD to enrollment was 4.5 [3, 34] days. At enrollment, the number of Grade II-IV aGVHD patients was 21 (38.9%), 16 (29.6%), and 17 (31.5%), respectively. GI involvement was present in all patients, which was in align with the study protocol, with upper GI involvement observed in 10 patients (18.5%) and lower GI involvement observed in 51 patients (94.4%). Thirty-seven patients (68.5%) were GI involved only, while 15 (27.8%) patients were GI and skin involved, and 2 (3.7%) patients were GI and liver involved. Other information regarding disease and therapy timeline are shown in Table s3.

Treatment exposure and concomitant systemic therapies

All 54 patients received at least one administration of hUC-MSC PLEB001 and were included in full analysis set. Among the 50 participants in per protocol set, 45 patients received the protocol-defined course of 8 injections. Five patients who achieved PR at day 28 received an extended course of 16 injections. Four patients who were in full analysis set but not in per protocol set received 1, 4, 4, 5 injections, respectively.

All 54 patients in full analysis set (100%) received anti-CD25 monoclonal antibody as background second-line therapy for aGVHD. From day 1 to day 28, twelve patients (22.2%) received two systemic second-line therapies and 3 patients (5.6%) received three or more systemic second-line therapies. Initiation of additional systemic immunosuppressive therapy prior to efficacy assessment was considered treatment failure, in accordance with protocol definitions. Detailed information on concomitant systemic medications and treatment discontinuations is shown in Table s4 and s5.

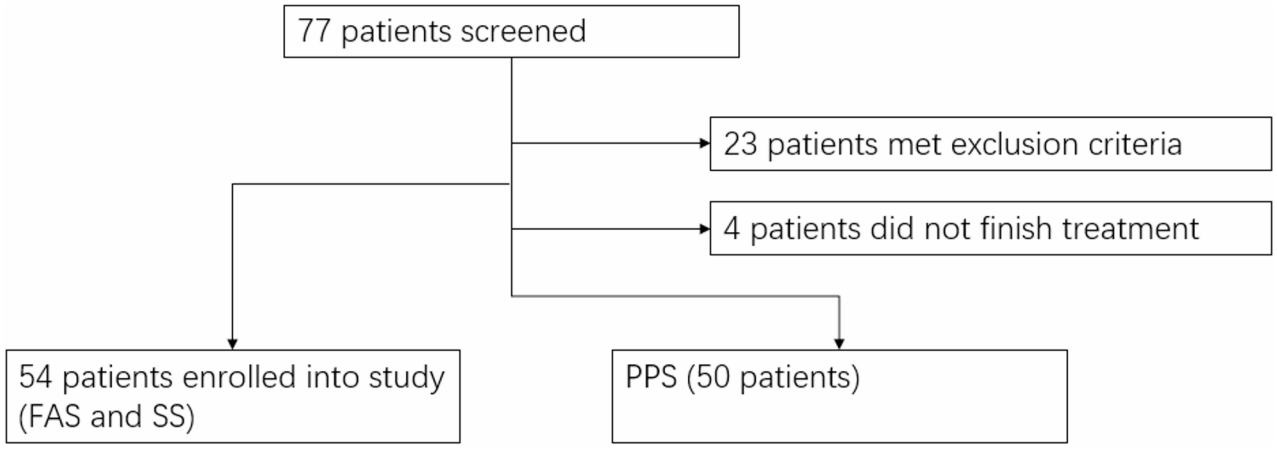

Fig. 1 Flowchart of the study

Table 1 Baseline characteristics of full analysis set (FAS) and per protocol set (PPS)

Characteristics	FAS	PPS
Number of patients	54	50
Age, median (range), years	43 (14, 68)	42 (14, 68)
Gender, n (%)		
Male	34 (63.0%)	30 (60.0%)
Female	20 (37.0%)	20 (40.0%)
Disease, n (%)		
AML	25 (46.3%)	23 (46.0%)
MDS	12 (22.2%)	10 (20.0%)
ALL	10 (18.5%)	10 (20.0%)
Others	7 (13.0%)	7 (14.0%)
HLA matching, n (%)		
MSD	12 (22.2%)	11 (22.0%)
HID	40 (74.1%)	37 (74.0%)
URD	2 (3.7%)	2 (4.0%)
Conditioning, n (%)		
BU based	44 (81.5%)	40 (80.0%)
TBI based	9 (16.7%)	9 (18.0%)
Selinexor + DAC + Thiotepa + Mel	1 (1.9%)	1 (2.0%)
Graft source, n (%)		
PB	50 (92.6%)	46 (92.0%)
PB + UCB	2 (3.7%)	2 (4.0%)
PB + BM	2 (3.7%)	2 (4.0%)
GVHD prophylaxis, n (%)		
CNI + MTX	2 (3.7%)	2 (4%)
ATG + CNI + MTX	7 (13%)	6 (12%)
ATG + CNI +MTX + MMF	35 (64.8%)	34 (68%)
ATG + CNI +MTX + MMF + basiliximab	9 (16.6%)	7 (14%)
PTCy + CNI +MTX + MMF	1 (1.9%)	1 (2%)
Initial corticosteroid dose* in aGVHD treatment		
1 mg/kg/day	27 (50%)	26 (52%)
2 mg/kg/day	27 (50%)	24 (48%)
aGVHD grade at baseline, n (%)		
II	21 (38.9%)	21 (42.0%)
III	16 (29.6%)	15 (30.0%)
IV	17 (31.5%)	14 (28.0%)
Organ involvement, n (%)		
GI only	37 (68.5%)	33 (66.0%)
GI + skin	15 (27.8%)	15 (30.0%)
GI + liver	2 (3.7%)	2 (4.0%)
DLI infusion		
Yes	5 (9.3%)	5 (10.0%)
No	49 (90.7%)	45 (90.0%)
SR aGVHD categories, n (%)		
Progression after day 3	42 (77.8%)	39 (78.0%)
No improvement after day 7	3 (5.6%)	2 (4.0%)
Failure to achieve CR after day 14	0	0
Failure during taper	9 (16.7%)	9 (18.0%)

In a small subset of patients, anti–CD25 monoclonal antibody (basiliximab) was also used as part of GVHD prophylaxis. Basiliximab was administered once on post-transplant day +3 at a dose of 20 mg. Considering its reported elimination half-life (7.2 ± 3.2 days) and the fact that aGVHD in enrolled patients typically developed approximately 30 days after transplantation, the prophylactic use of basiliximab was not expected to overlap with or confound its subsequent use for GVHD treatment

*Refers to methylprednisolone or an equivalent dose of other corticosteroids

AML acute myeloid leukemia, *MDS* myelodysplastic syndrome, *ALL* acute lymphoblastic leukemia, *TBI* total body irradiation, *CB* cord blood, *PB* peripheral blood, *BM* bone marrow, *MTX* methotrexate, *MSD* matched sibling donor, *HID* haplo-identical donor, *URD* unrelated donor, *DLI* donor lymphocyte infusion, *GI* gastrointestinal

Primary efficacy endpoint: ORR at day 28

Main endpoint was evaluated at day 28 based on full analysis set. Four patients discontinued before day 28 with premature treatment was assessed as non-response. Fifty patients received standard treatment with efficacy evaluation on day 28. Of all 54 participants, 30 (55.6%) achieved CR at day 28, 4 (7.4%) achieved PR, 17 (31.5%) remained NR and 3 (5.6%) experienced PD. Overall, the CR rate (95%CI) at day 28 was 55.6% (41.4%, 69.08%), and the ORR (95%CI) at day 28 was 63.0% (48.74%, 75.71%) (Fig. 2). The lower bound of the two-sided 95% CI exceeded the predefined efficacy threshold of 37%, which demonstrated that the efficacy of hUC-MSC PLEB001 plus anti-CD25 monoclonal antibody was significant.

In the per protocol set, 30 (60%) patients achieved CR at day 28 and the ORR at day 28 was 68% (53.3%, 80.5%) (Fig. 2). These results were consistent with those observed in the full-analysis set.

Key secondary efficacy outcomes

The ORR at day 56 for full analysis set was 51.9% (37.8%, 65.7%), and the CR rate at day 56 was 50.0% (36.1%, 63.9%) (Fig. 2). The durable CR at day 28 was 51.9% (37.8%, 65.7%). The median time to response (TTR) was 15 days with 95% CI of [8, 22]. The ECOG score at baseline, day 28, 56, 100 was 1.5 ± 0.6, 1.6 ± 0.6, 1.5 ± 0.8, 1.4 ± 0.7, respectively, which remained generally stable over time.

Exploratory subgroup analyses

Subgroup analysis was performed with per protocol set (Table 2). The ORRs at day 28 for patients with Grade II and Grade III-IV aGVHD were 85.7% (63.7%, 97.0%) and 55.2% (35.7%, 73.6%), respectively; the corresponding ORRs at day 56 were 66.7% (43.0%, 85.4%) and 48.3% (29.5%, 67.5%), respectively. In steroid-refractory patients, the ORR at day 28 was 63.4% (46.9%, 77.9%) compared to 88.9% (51.8%, 99.7%) in steroid-dependent

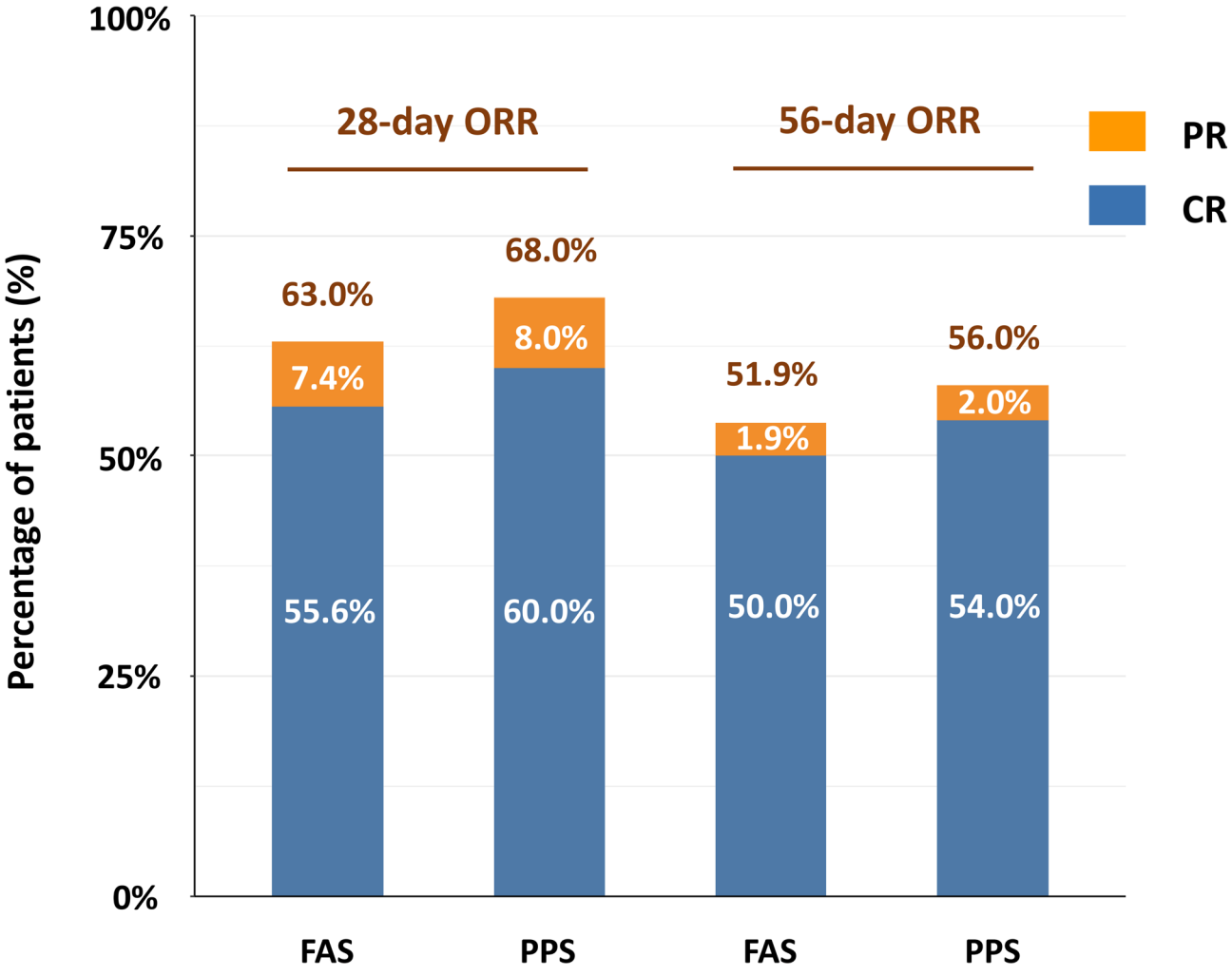

Fig. 2 Overall response rate (ORR) at day 28 and day 56. Stacked bar graphs show the proportion of complete response (CR) and partial response (PR) in the full analysis set (FAS) and per-protocol set (PPS). The primary endpoint was ORR at day 28 in the FAS

patients. No significance was tested between subgroups given the limited sample size.

Time-to-event analysis

Full Analysis Set was used for time-to-event analysis. The median OS was not reached (95% CI 361, not reached). The OS estimates at predefined timepoints are shown in Table 3. In a landmark analysis including patients alive and evaluable at day 28, responders demonstrated improved post–day 28 survival compared with non-responders (Fig. 3B). The median failure-free survival was 65.5 days (95% CI 44.0, 180.0) (Fig. 3C). Additional outcomes, including RFS, NRM, CIR, incidence of cGVHD, incidence of moderate-to-severe cGVHD are shown in Figure s1 and Table 4.

Safety analysis

Safety analyses were performed in Safety Set including all 54 patients who received at least one infusion of hUC-MSCs with safety data collected. Fifty-three (98.1%) patients experienced 1712 TEAEs including 464 TEAEs above Grade 3 in 52 (96.5%) patients. Nineteen TESAEs were reported in 18 (96.3%) patients, including 11 TESAEs leading to death in 10 patients, among which infection was predominant (7 events in 7 patients). No TRAE or intravenous toxicity was reported. A summary of key safety outcomes is provided in Table 5, and detailed adverse event listings by system organ class and preferred term are presented in Tables s6.

Explanatory analysis

Exploratory analysis of biomarker profiles and immune cell subsets were performed to assess potential immunomodulatory effects associated with hUC-MSC therapy. Higher baseline levels of sST2 and sTNFR1 were observed in non-responders compared with responders, and divergent trajectories were observed over the first 56 days (Figure s2). Considerable inter-individual variability

Table 2 Subgroup analysis: treatment response at day 28 and day 56 in full analysis set (FAS) and per protocol set (PPS)

Grouping variable	FAS (*N*=54)		PPS (*N*=50)	
	Day 28	Day 56	Day 28	Day 56
ORR by aGVHD grade				
Grade II	18/21, 85.7% (63.7%, 97.0%)	14/21, 66.7% (43.0%, 85.4%)	18/21, 85.7% (63.7%, 97.0%)	14/21, 66.7% (43.0%, 85.4%)
Grade III-IV	16/33, 48.5% (30.8%, 66.5%)	14/33, 42.4% (25.5%, 60.8%)	16/29, 55.2% (35.7%, 73.6%)	14/29, 48.3% (29.5%, 67.5%)
ORR by aGVHD grade				
Grade II	18/21, 85.7% (63.7%, 97.0%)	14/21, 66.7% (43.0%, 85.4%)	18/21, 85.7% (63.7%, 97.0%)	14/21, 66.7% (43.0%, 85.4%)
Grade III	9/16, 56.3% (29.9%, 80.3%)	8/16, 50.0% (24.7%, 75.4%)	9/15, 60.0% (32.3%, 83.7%)	8/15, 53.3% (26.6%, 78.7%)
Grade IV	7/17, 41.2% (18.4%, 67.1%)	6/17, 35.3% (14.2%, 61.7%)	7/14, 50.0% (23.0%, 77.0%)	6/14, 42.9% (17.7%, 71.2%)
ORR by age				
<40 years	14/24, 58.3% (36.6%, 77.9%)	14/24, 58.3% (36.6%, 77.9%)	14/23, 60.9% (38.5%, 80.3%)	14/23, 60.9% (38.5%, 80.3%)
≥40 years	20/30, 66.7% (47.2%, 82.7%)	14/30, 46.7% (28.4%, 65.7%)	20/27, 74.1% (53.7%, 88.9%)	14/27, 51.9% (32.0%, 71.3%)
ORR by gender				
Male	22/34, 64.7% (46.5%, 80.3%)	16/34, 47.1% (29.8%, 64.9%)	22/30, 73.3% (54.1%, 87.7%)	16/30, 53.3% (34.3%, 71.7%)
Female	12/20, 60.0% (36.1%, 80.9%)	12/20, 60.0% (36.1%, 80.9%)	12/20, 60.0% (36.1%, 80.9%)	12/20, 60.0% (36.1%, 80.9%)
ORR by organ involved				
GI only	28/37, 75.7% (58.8%, 88.2%)	21/37, 56.8% (39.5%, 72.9%)	28/33, 84.8% (68.1%, 94.9%)	21/33, 63.6% (45.1%, 79.6%)
GI with other	6/17, 35.3% (14.2%, 61.7%)	7/17, 41.2% (18.4%, 67.1%)	6/17, 35.3% (14.2%, 61.7%)	7/17, 41.2% (18.4%, 67.1%)
ORR by HLA matching				
Haplo	25/40, 62.5% (45.8%, 77.3%)	21/40, 52.5% (36.1%, 68.5%)	25/37, 67.6% (50.2%, 82.0%)	21/37, 56.8% (39.5%, 72.9%)
Others	9/14, 64.3% (35.1%, 87.2%)	7/14, 50.0% (23.0%, 77.0%)	9/13, 69.2% (38.6%, 90.9%)	7/13, 53.8% (25.1%, 80.8%)
DLI or not				
DLI	2/5, 40.0% (5.3%, 85.3%)	1/5, 20.0% (0.5%, 71.6%)	2/5, 40.0% (5.3%, 85.3%)	1/5, 20.0% (0.5%, 71.6%)
Non-DLI	32/49, 65.3% (50.4%, 78.3%)	27/49, 55.1% (40.2%, 69.3%)	32/45, 71.1% (55.7%, 83.6%)	27/45, 60.0% (44.3%, 74.3%)
ORR by graft				
PB	32/50, 64.0% (49.2%, 77.1%)	26/50, 52.0% (37.4%, 66.3%)	32/46, 69.6% (54.3%, 82.3%)	26/46, 56.5% (41.1%, 71.1%)
Others	2/4, 50.0% (6.8%, 93.2%)	2/4, 50.0% (6.8%, 93.2%)	2/4, 50.0% (6.8%, 93.2%)	2/4, 50.0% (6.8%, 93.2%)
ORR by SR type				
Steroid resistence	26/45, 57.8% (42.2%, 72.3%)	21/45, 46.7% (31.7%, 62.1%)	26/41, 63.4% (46.9%, 77.9%)	21/41, 51.2% (35.1%, 67.1%)
Steroid dependence	8/9, 88.9% (51.8%, 99.7%)	7/9, 77.8% (40.0%, 97.2%)	8/9, 88.9% (51.8%, 99.7%)	7/9, 77.8% (40.0%, 97.2%)
ORR by conditioning regimen				
Non-TBI	26/45, 57.8% (42.2%, 72.3%)	23/45, 51.1% (35.8%, 66.3%)	26/41, 63.4% (46.9%, 77.9%)	23/41, 56.1% (39.8%, 71.5%)
TBI based	8/9, 88.9% (51.8%, 99.7%)	5/9, 55.6% (21.2%, 86.3%)	8/9, 88.9% (51.8%, 99.7%)	5/9, 55.6% (21.2%, 86.3%) ,
ORR by disease				
ALL	9/11, 81.8% (48.2%, 97.7%)	5/11, 45.5% (16.8%, 76.6%)	9/11, 81.8% (48.2%, 97.7%)	5/11, 45.5% (16.8%, 76.6%)
Others	25/43, 58.1% (42.1%, 73.0%)	23/43, 53.5% (37.7%, 68.8%)	25/39, 64.1% (47.2%, 78.8%)	23/39, 59.0% (42.1%, 74.4%)

Table 3 Time-to-event analysis: OS

	Full analysis set (*N*=54)	Response group (*N*=34)	Non-response group (*N*=20)
28-day OS	94.4% (83.8%, 98.2%)	100.0% (100.0%, 100.0%)	80.0% (55.1%, 92.0%)
56-day OS	88.9% (76.9%, 94.9%)	100.0% (100.0%, 100.0%)	65.0% (40.3%, 81.5%)
100-day OS	79.6% (66.2%, 88.2%)	94.1% (78.5%, 98.5%)	50.0% (27.1%, 69.2%)
180-day OS	72.2% (58.2%, 82.2%)	85.3% (68.2%, 93.6%)	45.0% (23.1%, 64.7%)
360-day OS	65.8% (51.1%, 77.0%)	80.6% (61.0%, 91.0%)	40.0% (19.3%, 60.1%)

was observed. Given the exploratory nature of these analyses and the limited sample size, these findings are descriptive and hypothesis-generating and are presented in detail in the Supplementary Materials (Figure s2, s3 and Table s7, s8).

Discussion

In this multicenter, single-arm pivotal study, treatment with hUC-MSC PLEB001 plus protocol-mandated background second-line therapy achieved an ORR of 63.0% (48.74%, 75.71%) at day 28 and 51.9% (37.84%, 65.66%) at day 56 in patients with SR-GI-aGVHD. No TRAE or TRSAE was reported during the study. The results of this study further verified the post-hoc analysis in our previous phase II trial [28], supporting the reproducibility of clinical activity of this MSC product in a clinically

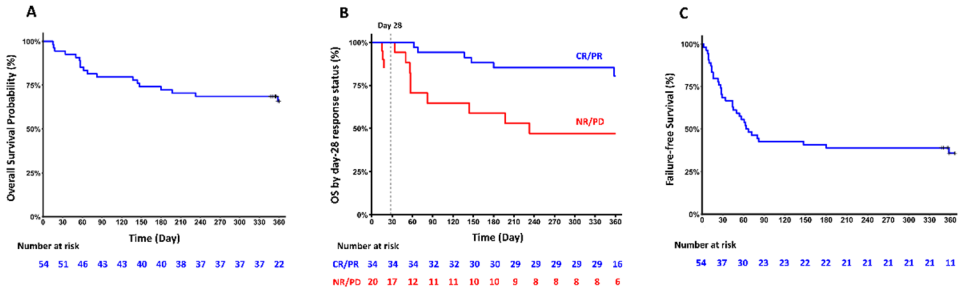

Fig. 3 One-year overall survival (OS), overall survival from the day-28 landmark and one-year failure-free survival (FFS) in full analysis set (FAS). **A** One-year OS in FAS. **B** OS by day-28 response status. Kaplan–Meier curves of OS from the day-28 landmark, stratified by response status at day 28. **C** One-year FFS in FAS.*OS* overall survival, *FAS* full analysis set, *FFS* failure-free survival

Table 4 Time-to-event analysis (RFS, FFS, NRM, CIR, incidence of cGVHD, incidence of moderate-to-severe cGVHD)

	28 day	56 day	100 day	180 day	360 day
RFS (95% CI)	94.4% (83.8%, 98.2%)	87.0% (74.7%, 93.6%)	79.6% (66.2%, 88.2%)	72.2% (58.2%, 82.2%)	65.8% (51.1%, 77.0%)
FFS (95% CI)	70.4% (56.3%, 80.7%)	57.4% (43.2%, 69.3%)	42.6% (29.3%, 55.2%)	38.9% (26.0%, 51.5%)	35.9% (23.0%, 49.0%)
NRM (95% CI)	3.7% (0.7%, 11.4%)	9.3% (3.4%, 18.8%)	16.7% (8.1%, 27.8%)	24.1% (13.6%, 36.2%)	30.5% (18.5%, 43.5%)
CIR (95% CI)	1.9% (0.2%, 8.7%)	3.7 (0.7%, 11.4%)	3.7% (0.7%, 11.4%)	3.7% (0.7%, 11.4%)	3.7% (0.7%, 11.4%)
Incidence of cGVHD	0.0% (NA, NA)	1.9% (0.2%, 8.7%)	9.3% (3.4%, 18.9%)	20.4% (10.8%, 32.1%)	33.3% (21.1%, 46.1%)
Incidence of moderate-to-severe cGVHD (95% CI)	0.0% (NA, NA)	1.9% (0.2%, 9.0%)	9.3% (3.4%, 18.9%)	20.4% (10.8%, 32.1%)	29.6% (18.0%, 42.2%)

Table 5 Summary of key safety outcomes

Safety outcome	No. of patients (%)	No. of events
TEAE	53 (98.1%)	1712
TEAE above Grade 3	52 (96.3%)	464
TESAE	18 (33.3%)	19
TESAE led to death	10 (18.5%)	11
Infection	7 (13.0%)	7
Liver dysfunction*	1 (1.9%)	1
Relapse of malignant hematological diseases	1 (1.9%)	1
Multiple organ dysfunction syndrome	1 (1.9%)	1
Thrombotic microangiopathy	1 (1.9%)	1
TESAE led to withdraw	1 (1.9%)	1
Relapse of malignant hematological diseases	1 (1.9%)	1
other TESAE	8 (14.8%)	8
Infection	4 (7.4%)	4
Thrombotic microangiopathy	1 (1.9%)	1
Anemia	1 (1.9%)	1
Diarrhea*	1 (1.9%)	1
Bronchial occlusion disease	1 (1.9%)	1
TRAE	0 (0.0%)	0
TRSAE	0 (0.0%)	0
TRAE above grade 3	0 (0.0%)	0
TEAE of intravenous toxicity	0 (0.0%)	0

* Excluded patients with aGVHD

AE: adverse event, *SAE* severe adverse event, *TEAE* treatment-emergent adverse event, *TESAE* treatment-emergent severe adverse event, *TRAE* treatment-related TEAE, *TRSAE* treatment-related TESAE

well-defined, high-risk subgroup of aGVHD with gastrointestinal involvement.

Given mandatory background anti-CD25 therapy, efficacy cannot be attributed to MSCs alone. Rather, the observed outcomes reflect responses achieved following incorporation of hUC-MSC PLEB001 into a broader immunosuppressive treatment strategy. Besides, our prior randomized phase II study showed improved responses in anti-CD25 combined with MSCs group compared to anti-CD25–based treatment alone, suggesting incremental and potentially synergistic effects rather than anti-CD25–driven activity alone. The consistency of efficacy across studies underscores the therapeutic stability of this MSC product. Based on the accumulated evidence from the present study, in January 2025, Chinese National Medical Products Administration (NMPA) conditionally approved hUC-MSC PLEB001 (Amimestrocel) for treating SR-aGVHD in patients above 14 years old, and this was the first MSC product approved by NMPA in China.

SR-aGVHD remains a major cause of transplant-related morbidity and mortality. Based on the pivotal randomized, placebo-controlled trial (REACH2) by Zeiser et al., ruxolitinib is currently recommended by the EBMT as the preferred second-line therapy for SR-aGVHD [33]. Despite of its superiority over best available therapy (BAT), a substantial proportion of patients failed to achieve durable response, particularly those with severe gastrointestinal involvement; and treatment-related complications remain a major clinical concern. In this context, there is an ongoing unmet need for additional

therapeutic strategies with distinct mechanisms of action that may complement existing standards of care.

The present study was designed to prospectively evaluate reproducibility in a clinically well-defined high-risk subgroup—patients with gastrointestinal involvement—rather than to re-establish efficacy across the full SR-aGVHD spectrum. The therapeutic strategy was also shaped by regional practice patterns and the temporal context at trial initiation. Anti-CD25 antibodies have been widely used as second-line therapy and were supported by Chinese expert consensus at the time of study initiation [20, 30, 34], whereas updated consensus documents positioning ruxolitinib as the preferred second-line option were published after enrollment had begun [32]. Consequently, the treatment approach in this trial reflected the prevailing domestic standards and ethical considerations during the study period, and the results should be interpreted as complementary rather than competitive with ruxolitinib-based strategies.

Heterogeneity in clinical responses to MSC therapy has long been a major concern. Differences in tissue source, manufacturing processes, dosing strategies, and patient characteristics likely contribute to variable efficacy across trials. In this context, our findings—together with prior studies—suggest that gastrointestinal involvement may represent a clinical phenotype more likely to derive benefit from certain MSC products, although contrasting results have been reported for other products and organ involvement patterns [35, 36]. These discrepancies highlight the need for further mechanistic and comparative studies to define phenotype–product matching and to clarify context-dependent mechanisms of action of MSC therapies.

Exploratory analyses of biomarkers and immune cell subpopulations in this study revealed substantial inter-individual variability in established aGVHD-associated markers and immune reconstitution patterns. While differences in baseline levels and early dynamic trends were observed between responders and non-responders, the wide dispersion of values and heterogeneous trajectories limit the utility of individual biomarkers as stand-alone predictors in modest-sized cohorts. These findings support the concept that meaningful treatment individualization in SR-GI-aGVHD is unlikely to be achieved using isolated biomarkers alone, and instead will require integrated models combining quantitative biomarkers with readily available clinical features and early response kinetics. Given the risk of overfitting, such approaches will require prospective validation in larger, systematically designed studies.

Several limitations should be acknowledged. First, the single-arm design without a control group limits causal inference and precludes direct comparison with other second-line therapies. Second, enrolment depended on predefined eligibility criteria, clinical stability, safety considerations, and patient or family consent; reasons for screening failure were prospectively documented, and this process may introduce selection bias and limit generalizability. Third, management of severe SR-GI-aGVHD often required multiple systemic interventions; heterogeneity in concomitant second-line therapies and time-dependent escalation (including step-up ruxolitinib use) may confound outcome interpretation. In addition, ruxolitinib was not uniformly used as second-line therapy in this cohort, which may limit applicability to settings where ruxolitinib-based treatment is standard. Fourth, gastrointestinal aGVHD diagnosis was based on integrated clinicopathological approach and histological confirmation was not mandatory or centrally reviewed. Finally, the sample size and follow-up duration limit the precision of subgroup analyses and long-term safety evaluation. Larger controlled studies with standardized treatment algorithms and biomarker-guided designs are warranted to further define the role of hUC-MSC–based strategies in the evolving treatment landscape of SR-GI-aGVHD.

Conclusions

This multicenter study showed that the addition of hUC-MSC PLEB001 to anti-CD25 antibody was associated with favorable early response rates and response durability in patients with SR-GI-aGVHD. Together with its acceptable safety profile, these results suggest that MSC-based strategies may represent a complementary therapeutic option within the evolving treatment landscape for this challenging condition.

Abbreviations

SR-aGVHD	Steroid-refractory acute graft-versus-host disease
allo-HSCT	Allogeneic hematopoietic stem cell transplantation
SR-GI-aGVHD	SR-gastrointestinal-aGVHD
MSCs	Mesenchymal stromal cells
ORR	Overall response rate
CR	Complete response
DCR	Durable complete response rate
OS	Overall survival
NRM	Non-relapse mortality
FFS	Failure-free survival
FAS	Full analysis set
cGVHD	Chronic GVHD
MTX	Methotrexate
MMF	Mycophenolate mofetil
PR	Partial remission
TTR	Time to response
DLI	Donor lymphocyte infusion
PD	Progressive disease
NR	No response
SS	Safety analysis set
PPS	Per protocol set
OR	Overall response
OPC	Objective Performance Criteria
BAT	Best available treatment
CI	Confidence interval
AE	Adverse event
SAE	Severe adverse event

ALL	Lymphoblastic lymphoma/leukemia
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent severe adverse event
TRAE	Treatment-related TEAE
TRSAE	Treatment-related TESAE
NMPA	Chinese National Medical Products Administration
MAGIC	Mount Sinai Acute GvHD International Consortium
Treg cells	T regulatory cells

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

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Author contributions
Drs. EJ, DL, XZ and DY had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Drs. YZ, LW and XM contributed to drafting the manuscript. Drs. YZ, LW and XM conducted the statistical analysis. Drs. DL and MH supervised the study. Drs. DL, DY, XM, YZ, and YL were involved in enrolling patients and performing medical interventions. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study involving human umbilical cord–derived mesenchymal stromal cells (hUC-MSCs) was conducted in accordance with the Declaration of Helsinki. The study protocol, informed consent form (ICF), and all relevant documents were reviewed and approved by the ethics committees of all participating centers. Written informed consent for participation in the study and the use of clinical data and samples was obtained from all patients or their legal guardians/legally authorised representatives. The following ethics approvals were obtained: (1) Title: To evaluate the therapeutic effect of hUC-MSC PLEB001 in Steroid-Refractory acute graft versus host disease (aGVHD): a multicenter, single arm, pivotal clinical trial. Committee: Ethics Committee of the First Medical Center of the Chinese People's Liberation Army General Hospital. Approval number: C2022-059-02. Date of approval: 17 February 2023. (2) Title: To evaluate the therapeutic effect of hUC-MSC PLEB001 in Steroid-Refractory acute graft versus host disease (aGVHD): a multicenter, single arm, pivotal clinical trial. Committee: Ethics Committee of the Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences. Approval number: XY2022083-EC-1. Date of approval: 24 February 2023. (3) Title: To evaluate the therapeutic effect of hUC-MSC PLEB001 in Steroid-Refractory acute graft versus host disease (aGVHD): a multicenter, single arm, pivotal clinical trial. Committee: Ethics Committee of the Fifth Medical Center of the Chinese People's Liberation Army General Hospital. Approval number: 2023-2-5-1. Date of approval: 1 March 2023. (4) Title: To evaluate the therapeutic effect of hUC-MSC PLEB001 in Steroid-Refractory acute graft versus host disease (aGVHD): a multicenter, single arm, pivotal clinical trial. Committee: Ethics Committee of Peking University People's Hospital. Approval number: 2023PHC039-001. Date of approval: 6 September 2023.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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