

Evaluation of Zevorcabtagene Autoleucel as a Fully Human BCMA-Targeted CAR T-Cell Therapy in a Phase II Trial for Relapsed/Refractory Multiple Myeloma

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Abstract

Zevorcabtagene autoleucel (zevor-cel) is a fully human, autologous chimeric antigen receptor (CAR) T-cell therapy targeting B-cell maturation antigen. It gained regulatory approval in China in 2024 for use in adults with relapsed/refractory multiple myeloma (RRMM). The LUMMICAR STUDY 1 trial was a phase 2, single-arm, open-label study conducted at 23 clinical sites across China. Enrolled individuals were adults between 18 and 75 years old diagnosed with RRMM, who had measurable disease after receiving three or more previous lines of therapy. They were required to have adequate organ function, sufficient bone marrow reserve, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Those with any prior exposure to CAR T-cell therapy or BCMA-targeted agents were not permitted to participate. The main endpoint was the objective response rate (ORR) evaluated by an Independent Review Committee. Additional endpoints covered investigator-determined ORR, rates of complete response (CR) and stringent complete response (sCR), duration of response (DOR), achievement of minimal residual disease negativity, safety assessments (including the occurrence and severity of adverse events), and the pharmacokinetic behavior of zevor-cel. A total of 125 patients underwent apheresis, 105 underwent lymphodepletion, and 102 ultimately received zevor-cel infusion. These participants had a median age of 59.5 years (range: 38–75), with 53.9% male and 46.1% female. The ORR was 92.2% (95% confidence interval: 85.13–96.55), including 68.6% (70 patients) who reached sCR and 2.9% (3 patients) who attained CR. With a median follow-up period of 20.3 months (interquartile range: 12.5–23.8), 44.1% (45 patients) experienced progression-free survival (PFS) events and 19.6% (20 patients) had overall survival (OS) events; however, data for DOR, PFS, and OS had not yet reached maturity. Cytokine release syndrome developed in 90.2% (92 patients), of which 6.9% (7 patients) were grade 3 or 4. Immune effector cell-associated neurotoxicity syndrome occurred in only two patients, both at grade 1, with no reports of grade 3 or higher neurotoxicity linked to zevor-cel. In heavily pretreated patients with RRMM, zevor-cel delivers profound and durable responses with an acceptable safety profile.

Keywords: Targeted immunotherapy, Chimeric antigen receptor T cell, CAR T cells, BCMA, Zevorcabtagene autoleucel, Zevor-cel

Introduction

Multiple myeloma (MM) constitutes approximately 10% to 15% of hematologic cancers [1]. In the United States,

the 5-year survival rate for this condition is 57.9% [2]. Over the past thirty years in China, the incidence and overall burden of MM have roughly doubled [3]. Patients in China generally experience poorer outcomes than those in other regions, largely due to later-stage diagnosis and reduced access to innovative therapies [4]. Even at major academic centers, the 5-year overall survival rate remained under 50%, with only about half of patients receiving bortezomib-containing regimens [5]. This is consistent with data from a single-center retrospective analysis in China, which reported a 5-year OS rate of 47.6% [6].

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Although major advancements in multiple myeloma treatment have occurred over the last twenty years, the majority of patients continue to relapse and eventually develop refractory disease [7-10]. CAR T-cell therapies have recently emerged as an important addition to the treatment landscape for MM [6]. Two BCMA-directed CAR T products, ciltacabtagene autoleucel (cilta-cel) [11] and idecabtagene vicleucel (ide-cel) [12], have secured approval from the US Food and Drug Administration (FDA) for RRMM. Clinical studies of these agents have shown overall response rates of 73%-100%, with CR or sCR rates of 33%-83% [13-17]. Given China's substantial patient population, there is a critical demand for potent, cost-effective options. However, commercial CAR T-cell therapies have had limited availability in the country. Equecabtagene autoleucel (eque-cel), a locally developed BCMA-specific CAR T-cell product, secured approval from China's National Medical Products Administration (NMPA) for RRMM patients following at least three prior treatment lines. In a research study involving 103 individuals, this therapy achieved a 96.1% response rate and a 78.8% PFS rate at 12 months. While CAR T-cell approaches demonstrate strong antitumor activity, safety considerations remain significant, encompassing cytokine release syndrome (CRS), various forms of neurotoxicity (including parkinsonism-like symptoms), infections, and the potential for secondary cancers. Non-relapse mortality rates were approximately 6% with cilta-cel (largely infection-related) and 5% with ide-cel [16, 18].

Zevorcabtagene autoleucel (zevor-cel, also known as CT053) is a BCMA-targeted CAR T-cell therapy constructed with a fully human anti-BCMA single-chain variable fragment (scFv), CD8 α hinge and spacer regions, a CD8 α transmembrane domain, a 4-1BB costimulatory domain, and a CD3 ζ activation domain connected in series [19]. Manufacturing employs a third-generation self-inactivating lentiviral vector platform, designed to enhance safety over earlier vector

generations [20]. Early results from an investigator-initiated study indicated a favorable safety profile and a 100% ORR [21]. The phase 1 segment of LUMMICAR STUDY 1 (NCT03975907) further confirmed durable responses with a 100% ORR and acceptable tolerability [22]. Zevor-cel obtained NMPA approval in China in February 2024 [22, 23]. The current report details the outcomes from the pivotal phase 2 cohort of LUMMICAR STUDY 1, which served as the basis for this approval.

Materials and Methods

Study design and patients

LUMMICAR STUDY 1 (NCT03975907) consisted of a pivotal, single-arm, open-label, multicenter phase 2 investigation focused on the efficacy, safety, and pharmacokinetic profile of zevor-cel in RRMM. The trial enrolled patients at 23 centers nationwide in China. Autologous peripheral blood mononuclear cells were harvested at each study site and forwarded to the CARsgen Therapeutics production facility for CAR T-cell manufacturing. When medically appropriate, bridging therapy was permitted following apheresis, typically involving agents the patient had already received. Lymphodepletion was achieved with fludarabine (25 mg/m²) and cyclophosphamide (300 mg/m²), administered daily for 3 days. Zevor-cel was infused once at a target dose of 150×10^6 CAR-positive T cells (increased to 180×10^6 for patients over 80 kg body weight, per investigator judgment) between 1 and 2 days after lymphodepletion concluded. Participants underwent 24 months of active monitoring for efficacy and safety outcomes, followed by extended observation for up to 15 years (**Figure 1**). Premedication to prevent infusion reactions included antihistamines (such as promethazine 12.5–50 mg or equivalent) and antipyretics (indomethacin suppositories 50–100 mg or equivalent) given within 30 minutes before infusion.

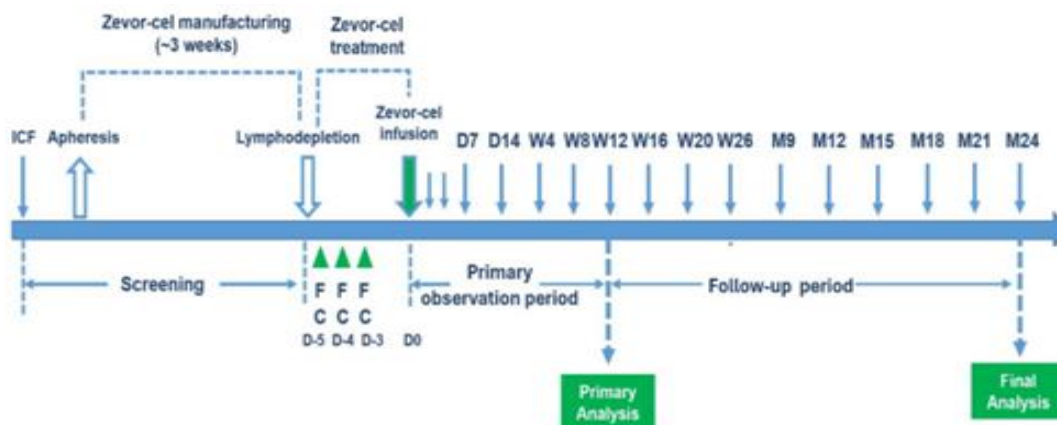


Figure 1. Study design. C = cyclophosphamide (300mg/m²); D = day; F = fludarabine (25 mg/m²); ICF = informed consent form; M = month; W = week.

Management of infections followed routine institutional or national protocols for prophylaxis and treatment. Individuals showing evidence of past hepatitis B exposure (HBcAb positive) began antiviral prophylaxis before lymphodepletion and received ongoing liver function surveillance. Immunoglobulin replacement was initiated for patients with sustained hypogammaglobulinemia (IgG $\leq$ 400 mg/dL) or those with IgG levels of 400–600 mg/dL accompanied by serious, recurrent infections, neutropenia, or grade $\geq$ 3 CRS.

Key inclusion criteria

Participants were required to be adults aged 18 to 75 years with a diagnosis of RRMM who had progressed after, or were refractory to, at least 3 prior treatment lines, including an immunomodulatory agent and a proteasome inhibitor. They needed an ECOG score of 0–1 and evidence of measurable disease, defined as serum M-protein $\geq$ 10 g/L, urine M-protein $\geq$ 200 mg per 24 hours, or an abnormal free light chain ratio with the involved FLC $\geq$ 100 mg/L when M-protein levels were not measurable.

Sufficient bone marrow function was mandated without recent growth factor support or heavy transfusion requirements (within the prior 7 days): ANC $\geq$ 1.0×10^9 /L, platelets $\geq$ 75×10^9 /L (or $\geq$ 50×10^9 /L if bone marrow plasma cell infiltration exceeded 50%), hemoglobin $\geq$ 70 g/L, and ALC $\geq$ 0.4×10^9 /L. Organ function criteria included creatinine clearance $\geq$ 40 mL/min, ALT and AST each $\leq$ 2.5 times the upper limit of normal (ULN), and total bilirubin $\leq$ $2 \times$ ULN.

Key exclusion criteria

Exclusion applied to anyone with a history of CAR T-cell treatment, prior BCMA-directed therapies, allogeneic stem cell transplant at any time, or autologous stem cell transplant within the 12 weeks preceding leukapheresis. Patients showing serious organ problems were also barred, including cases of uncontrolled heart failure, angina pectoris, recent heart attack, stroke (apart from small lacunar strokes), previous coronary bypass surgery, significant irregular heartbeats, uncontrolled blood sugar levels, pulmonary embolism, or an LVEF under 50% measured before leukapheresis. Complete information on the overall trial structure and all eligibility rules is publicly available at <http://www.chinadrugtrials.org.cn/clinicaltrials.searchlist.shtml>. This research followed the ethical principles of the Declaration of Helsinki and the International Council on Harmonization Good Clinical Practice standards. Every participant gave written informed consent before joining the study.

Endpoints and assessments

The main goal was to measure the objective response rate (ORR) according to the 2016 International Myeloma Working Group (IMWG) standards, with evaluation performed independently by an Independent Review Committee (IRC). Other key goals included ORR as judged by the study doctors, deeper response levels such as the proportion achieving CR or sCR, the Percentage reaching very good partial response or higher ($\geq$ VGPR), how long responses lasted (DOR), progression-free survival (PFS), overall survival (OS), the time until first

response (TTR), how often patients became MRD negative, and various safety aspects like the rate and seriousness of treatment-linked side effects, particular events of interest (especially CRS and brain-related toxicities), lab test changes, immune reactions to the product, and how zevor-cel moved through the body (pharmacokinetics).

All efficacy blood and bone marrow tests — such as serum protein electrophoresis (SPEP), serum immunofixation (SIFE), 24-hour urine protein electrophoresis (UPEP), urine immunofixation (UIFE), serum free light chain levels and ratio, bone marrow staining, and MRD testing — were processed at a central lab.

Doctors checked treatment responses at specific times after infusion: weeks 4, 8, 12, 16, 20, 26, and months 9, 12, 15, 18, 21, plus 24, using IMWG 2016 rules. After that point, checks happened once every six months until the disease advanced, the patient passed away, left the study, or finished the extended observation phase.

Side effects were scored with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. CRS and ICANS received special grading based on the 2019 American Society for Transplantation and Cellular Therapy (ASTCT) guidelines [24].

Minimal residual disease testing used the EuroFlow technique capable of detecting one cancer cell among 100,000. The growth and persistence of zevor-cel in the body were tracked by quantitative PCR, expressed as DNA copies per microgram. CRS onset was defined as the first day of fever or other typical symptoms identified by the doctor when no other cause was found. The ICE score was measured before starting lymphodepletion chemotherapy (as the reference point), then on days 3 and 7, and again when leaving the hospital. Any fresh brain or mental symptoms triggered repeated ICE scoring until the issues cleared or returned to the starting level.

Statistical analysis

Historical data showed about 30% response rates for non-CAR T medicines in RRMM, so researchers set a null hypothesis of 50% ORR at week 12 for zevor-cel. Early trial information suggested an actual ORR around 75%.

They calculated that 42 patients would provide 90% power to show a 25-percentage-point improvement. To gain a solid understanding of safety, they planned to treat at least 100 people.

Both the modified intention-to-treat group and the safety group included all patients who received the zevor-cel infusion; these populations were used separately for effectiveness and safety reviews. MRD results were presented as counts and percentages at set time points, along with 95% confidence intervals calculated by the Clopper-Pearson method. Survival-type outcomes (PFS, DOR, OS) were analyzed using Kaplan-Meier curves, and confidence intervals were calculated using the Brookmeyer-Crowley method. Safety summaries focused on how often treatment-emergent adverse events appeared. Pharmacokinetic findings used standard descriptive numbers. All calculations and graphs were produced with SAS software, release 9.4 or newer.

Results and Discussion

Baseline and disease characteristics

Enrollment ran from December 1, 2020, through January 15, 2022, during which 125 people from 23 hospitals provided cells via apheresis. After this step, 20 left the study: four chose to withdraw consent, 15 no longer qualified for the next chemotherapy step, and one had fast-growing disease. Of the 105 who began lymphodepletion, three more did not receive CAR T cells — two because of rapid progression and one because they did not meet final infusion standards. This left 102 patients who received zevor-cel. On average, 33 days passed between cell collection and infusion (range 20–99 days). Twenty-six individuals (25.5%) needed bridging treatment in between.

When data collection stopped, 22 patients had finished the full 24 months of close monitoring, 31 were still being followed in that period, and 49 had stopped early (five in the initial 12 weeks and 44 later). Thirty-two patients moved into the extended long-term tracking phase. This group included the 22 who completed 24 months plus others who left regular study visits but agreed to keep sharing survival information (**Figure 2**).

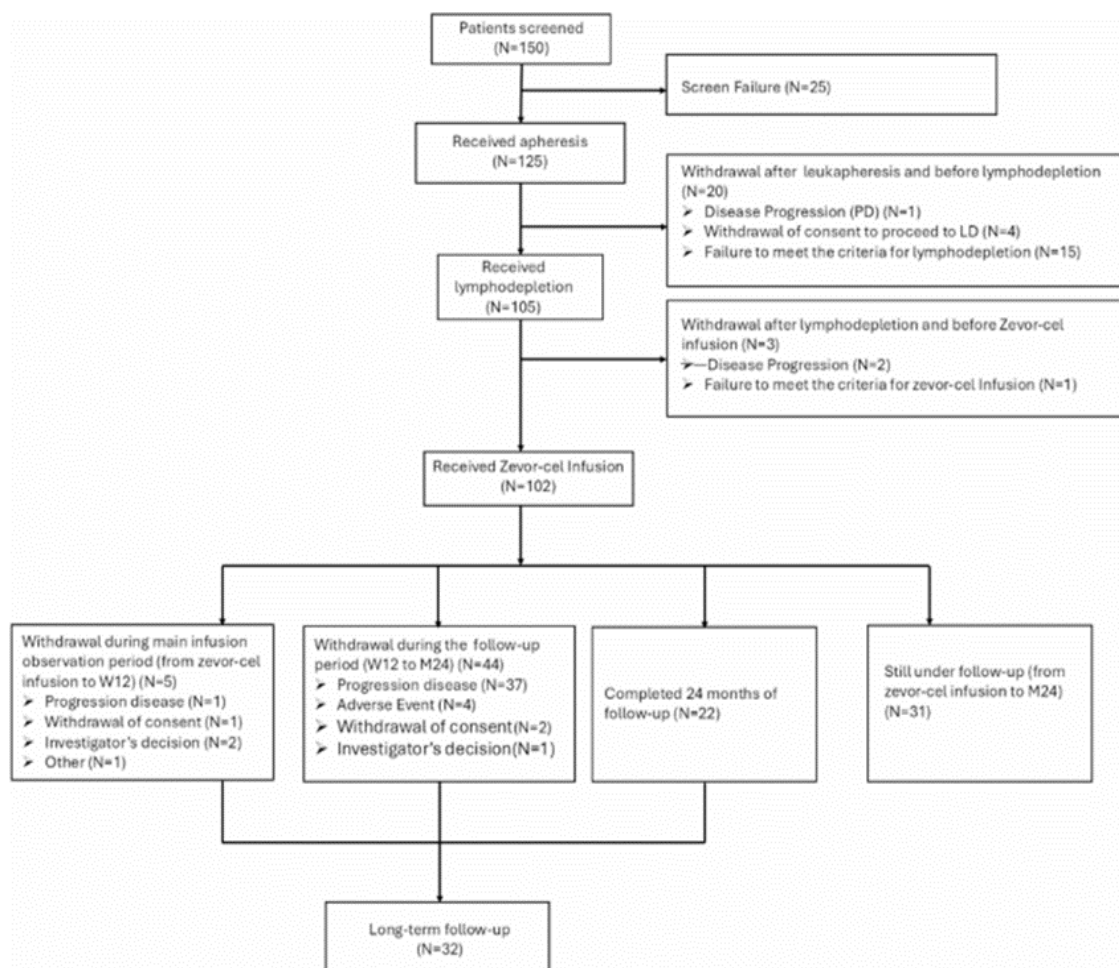


Figure 2. Patient flow. This diagram illustrates participants' progression through the trial's stages, from initial screening to the extended long-term follow-up period. Abbreviations: BCMA = B-cell maturation antigen; CAR-T = chimeric antigen receptor T-cell; N = number of patients.

The 102 treated patients had a median age of 59.5 years (IQR 53–66), 53.9% were men, and all participants were ethnically Chinese (**Table 1**). Thirty-nine (38.2%) had advanced ISS stage III disease at the start, while 46 (45.1%) carried high-risk chromosome changes. Eleven patients (10.8%) showed extramedullary disease according to IRC review.

Table 1. Baseline characteristics and prior treatments

Characteristics	Patients (n = 102)
Age, median (range), years	59.5 (38–75)
18 – < 65	71 (69.6)
65–75	31 (30.4)
> 75	0
Sex, n (%)	
Male	55 (53.9)
Female	47 (46.1)
Time since diagnosis, median (range), years	3.6 (0.7–16)

Lines of previous anti-MM treatment, median (range)	4.0 (3–15)
Type of immunoglobulin, n (%)	102 (100%)
IgG	58 (56.9)
IgA	20 (19.6)
IgM	0
IgD	4 (3.9)
IgE	1 (1.0)
Light Chain	19 (18.7)
ECOG PS, n (%)	
0	54 (52.9)
1	48 (47.1)
> 1	0
ISS Stage, n (%)	102 (100)
I	24 (23.5)
II	39 (38.2)
III	39 (38.2)
BCMA expression rate, n (%) ^b	89
< 50%	16 (15.7)
≥ 50%	73 (71.6)
Plasma cells in bone marrow, n (%)	

< 50%	83 (81.4)
≥ 50%	17 (16.7)
Disease risk classification, n (%)	
High risk ^a	46 (45.1)
Not detected	56 (54.9)
Cytogenetic Features, (%)	
Del (17p13.1)	
(-)	67 (65.7)
(+)	22 (21.6)
t (4;14)	
(-)	59 (57.8)
(+)	29 (28.4)
t (14;16)	
(-)	86 (84.3)
(+)	2 (2.0)
t (14;20)	
(-)	87 (85.3)
(+)	1 (1.0)
Presence of extramedullary disease, n (%) ^c	11 (10.8)
Proteasome inhibitors, n (%)	
Bortezomib	101 (99.0)
Carfilzomib	102 (100)
Ixazomib	101 (99.0)
IMiDs, n (%)	102 (100)
Lenalidomide	101 (99.0)
Pomalidomide	34 (33.3)
Thalidomide	55 (53.9)
Anti-CD38 monoclonal antibody, n (%)	30 (29.4)
Daratumumab	21 (20.6)
Other anti-CD38 monoclonal antibodies	9 (8.8)
Prior autologous stem-cell transplantation	24 (23.5)
Double-class exposed, n(%) ^d	102 (100)
Triple-class exposed, n(%) ^e	30 (29.4)
Penta-class exposed, n(%) ^f	6 (5.9)
Double-class refractory, n (%) ^g	91 (89.2)
Triple-class refractory, n (%) ^h	23 (22.5)
Bridging therapy, n (%)	26 (25.5)

- Baseline measurements were taken as the final set of non-missing results obtained immediately before the patient began lymphodepletion chemotherapy.
- BCMA stands for B-cell maturation antigen; CD38 stands for cluster of differentiation 38; ECOG PS refers to the Eastern Cooperative Oncology Group Performance Status Scale; IMiD means immunomodulatory drug; ISS stands for International Staging System; MM stands for multiple myeloma.
- ^a High-risk status was assigned when at least one of the following chromosomal changes was present: del(17p), t(4;14), t(14;16), or t(14;20). Detection was performed using fluorescence in situ hybridization (FISH) on bone marrow specimens. Any cytogenetic results not matching these were recorded as 'not detected'.
- ^b The level of BCMA expression was determined on the surface of abnormal plasma cells taken from bone marrow.
- ^c The presence of extramedullary disease was identified when imaging (MRI, CT scan, or the CT part of a PET/CT scan) revealed at least one measurable soft tissue lesion or paramedullary plasmacytoma.
- ^d Double-class exposed patients were those who had previously been given at least one proteasome inhibitor (examples include bortezomib, carfilzomib, or ixazomib) plus at least one

immunomodulatory agent (such as lenalidomide, pomalidomide, or thalidomide).

- ^e Triple-class exposed patients had received at least one proteasome inhibitor (e.g., bortezomib, carfilzomib, or ixazomib), at least one immunomodulatory drug (e.g., lenalidomide, pomalidomide, or thalidomide), and at least one anti-CD38 therapy (e.g., daratumumab or similar anti-CD38 monoclonal antibodies or conjugates).
- ^f Penta-drug exposed patients had been treated with at least two different proteasome inhibitors (e.g., bortezomib, carfilzomib, ixazomib), at least two immunomodulatory drugs (e.g., lenalidomide, pomalidomide, thalidomide), and at least one anti-CD38 antibody (e.g., daratumumab or other anti-CD38 agents or conjugates).
- ^g Double-class refractory patients were those whose disease no longer responded to at least one proteasome inhibitor (bortezomib, carfilzomib, or ixazomib) and at least one immunomodulatory drug (lenalidomide, pomalidomide, or thalidomide), with therapy stopped because of disease progression, insufficient effect, or related reasons.
- ^h Triple-class refractory patients were defined as those refractory to at least one proteasome inhibitor (bortezomib, carfilzomib, or ixazomib), at least one immunomodulatory drug (lenalidomide, pomalidomide, or thalidomide), and at least one anti-CD38 targeted treatment (daratumumab or other anti-CD38 monoclonal antibodies or conjugates), where treatment was discontinued due to disease progression, lack of response, or similar causes.

These individuals had undergone a median of 4 prior treatment regimens (range 3–15), and nearly one-quarter (24 patients, 23.5%) had undergone prior stem cell transplants. Most — 91 patients (89.2%) — were refractory to two drug classes, 23 (22.5%) to three classes, and 28 (27.5%) to anti-CD38 medicines.

Efficacy of zevor-cel

Response rates

By the cutoff point (17.9 months after the last infusion), the overall median observation time stood at 20.3 months (IQR 12.5–23.8) for the whole group and 24.7 months (range 23.3–31.4) for the 32 patients in long-term follow-up. Among all 102 treated and evaluable cases, 92.2% responded (94 people; 95% CI 85.1–96.6%). This broke down to 68.6% (70 patients) achieving sCR, 2.9% (3 patients) achieving CR, 19.6% (20 patients) achieving VGPR, and 1% (1 patient) achieving partial response (**Table 2**). Nearly all — 91.2% (93/102) — achieved VGPR or deeper, and 71.6% (73/102) reached CR/sCR levels. Responses often became stronger over time as patients were observed. The typical time to any response was 29 days (range 26–93), while reaching CR/sCR took a median of 146 days (range 28–609). Of 99 patients whose samples could be tested for MRD, 91.9% (91 patients; 95% CI 84.7–96.5%) tested negative for MRD

at the 10^{-5} level. This rate was 100% (73/73; 95% CI 95.1–100%) for those in CR/sCR and 95.7% (88/92; 95% CI 89.2–98.8%) for those with at least VGPR. A swimmer plot displays each patient's response journey, including when they hit CR, VGPR, stable disease, or progression (Figure 3).

Table 2. Summary of responses to zevor-cel

	Zevor-cel 1.5×10^8 (N = 102)
Best Overall Response, n (%)	
Stringent Complete Response (sCR)	70 (68.6)
Complete Response (CR)	3 (2.9)
Very Good Partial Response (VGPR)	20 (19.6)
Partial Response (PR)	1 (1.0)
Minimal Response (MR)	1 (1.0)
Stable Disease (SD)	2 (2.0)
Progressive Disease (PD)	4 (3.9)
Unknown (UNK)	1 (1.0)
Objective Response Rate (ORR), n (%)	94 (92.2)
95% CI	(85.13, 96.55)
CR/sCR rate, n (%)	73 (71.6)
95% CI	(61.78, 80.06)
sCR rate, n (%)	70 (68.6)
95% CI	(58.69, 77.45)
CR rate, n (%)	3 (2.9)
95% CI	(0.61, 8.36)
VGPR or better rate, n (%)	93 (91.2)
95% CI	(83.91, 95.89)
MRD negativity within patients with MRD results ($< 10^{-5}$), n (%) ^a	91 (91.9)

95% CI	(84.70, 96.45)
CR/sCR patients with MRD assessment, n	73
MRD negativity within CR/sCR patients with MRD results ($< 10^{-5}$), n (%) ^b	73 (100)
95% CI	(95.07, 100.00)
VGPR or better patients with MRD assessment, n	92
MRD negativity within VGPR or better patients with MRD results ($< 10^{-5}$), n (%) ^c	88 (95.7)
95% CI	(89.24, 98.80)

1. At the data cutoff, the 102 patients who received zevor-cel had been monitored for a median of 20.3 months. Meanwhile, the 32 patients who moved into the extended long-term observation phase had been followed for a minimum of 23.3 months since their zevor-cel infusion.
2. The 95% confidence intervals were computed using the Clopper-Pearson approach.
3. ORR= objective response rate; sCR= stringent complete response; CR= complete response; VGPR= very good partial response; PR= partial response; MR= minimal residual disease; SD= stable disease; PD= progressive disease; UNK= unevaluable.
4. ^a The percentages shown were calculated using only those patients who underwent MRD testing as the denominator.
5. ^b Percentages were determined using as the denominator only the patients who achieved confirmed CR or better responses (as assessed by the IRC) and who also had MRD testing performed.
6. ^c The percentages were derived using as the denominator only those patients confirmed to have achieved VGPR or deeper responses (per IRC assessment) who also had available MRD test results.

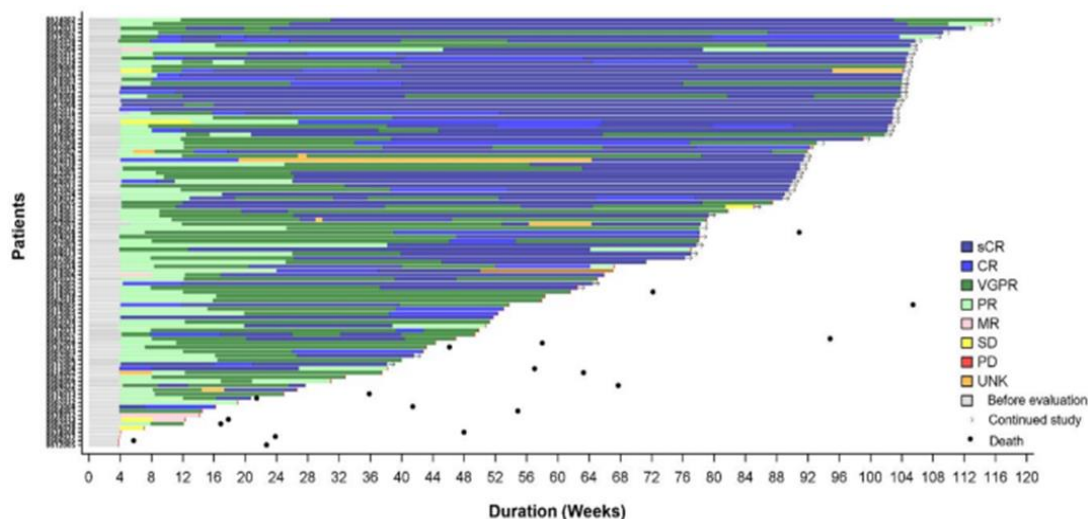


Figure 3. Swimmer plot showing individual patient outcomes following zevor-cel infusion. The vertical axis lists the 102 treated patients by their assigned numbers. The horizontal axis displays time measured in days from the date of zevor-cel administration. All response evaluations were performed by the Independent Review Committee (IRC). Bar length indicates the duration each patient remained under observation in the study. Symbols along the bars reflect tumor response assessments at different evaluation points. Patients lacking

arrows at the end of their bars discontinued study participation. Abbreviations: CR = complete response; IRC = independent review committee; MR = minimal residual disease; PD = progressive disease; PR = partial response; sCR = stringent complete response; SD = stable disease; UNK = unevaluable; VGPR = very good partial response.

Duration of response, progression-free survival, and overall survival

During the 20.3-month median follow-up (IQR 12.5–23.8), 45 patients (44.1%) had PFS events and 20 (19.6%) had OS events (**Figure 4**). PFS stood at 76.3% (95% CI 66.5–83.6%) at 12 months and 61.9% (95% CI 51.2–70.9%) at 18 months. Forty-one patients (40.2%) eventually saw their disease progress. Estimated rates for

sustained responses lasting 12 months or longer and 18 months or longer were 76.8% (95% CI 66.7–84.2%) and 62.4% (95% CI 51.2–71.6%). Overall survival percentages were 90.2% (95% CI 82.6–94.6%) at 12 months, 83.3% (95% CI 74.6–89.3%) at 18 months, and 79.4% (95% CI 69.7–86.3%) at 30 months. Full maturity for DOR, PFS, and OS had not been reached when data collection ended.

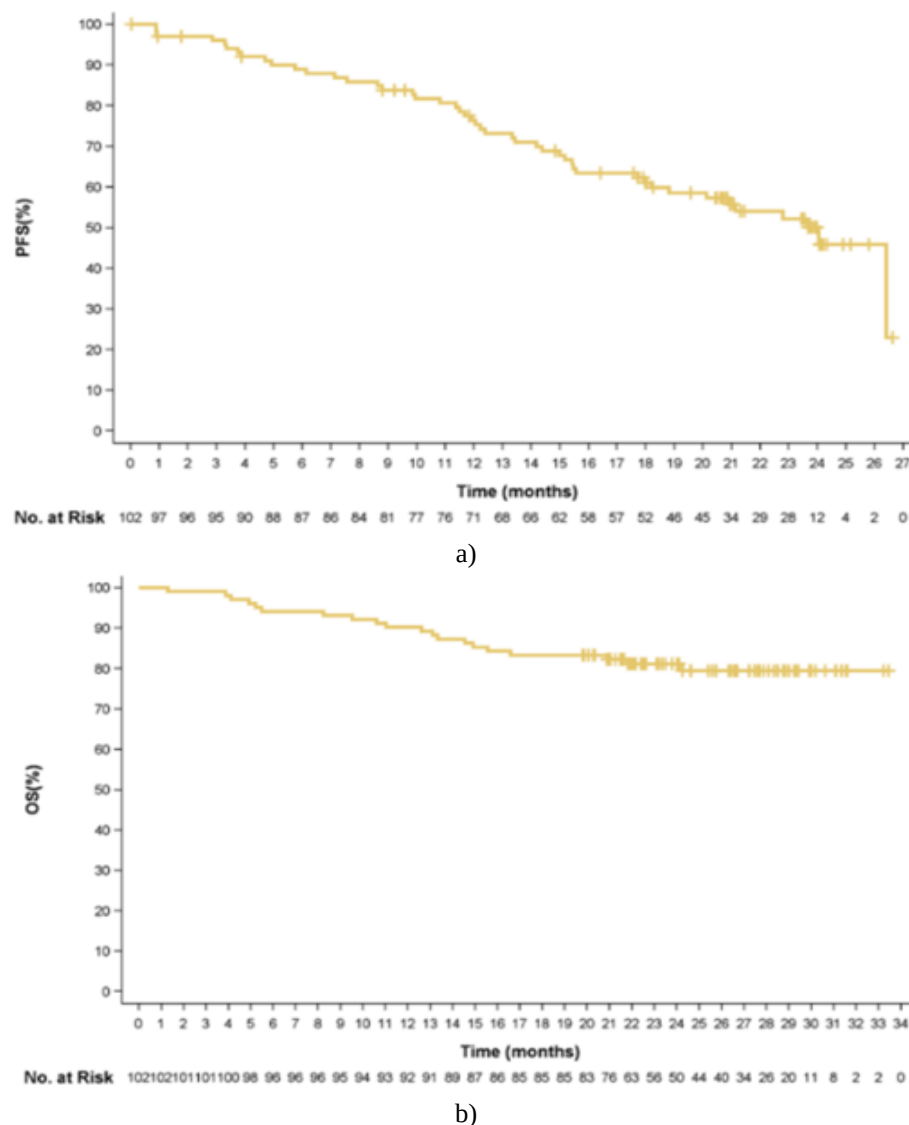


Figure 4. Kaplan-Meier curves depicting progression-free survival (PFS) and overall survival (OS). PFS= progression-free survival; OS= overall survival.

Among the 73 patients (71.6%) who attained confirmed CR or sCR, results were notably better. Their PFS event-free rates were 88.8% (95% CI 78.8–94.2%) at 12 months and 78.6% (95% CI 67.0–86.5%) at 18 months. The shares keeping responses for at least 12 and 18 months were 85.9% (95% CI 75.4–92.2%) and 76.9% (95% CI 65.0–85.2%), respectively. Survival rates in this group were 95.9% (95% CI 87.8–98.7%) at 12 months, 93.2% (95% CI 84.3–97.1%) at 18 months, and 87.7% (95% CI 76.6–93.8%) at 30 months.

Safety of zevor-cel

Treatment-emergent adverse events (TEAEs) and those linked to zevor-cel occurred in every patient. The most frequent side effects of zevor-cel were reductions in blood cell counts. Every patient experienced at least one grade 3 or higher blood-related toxicity, with 88.2% (90 patients) having grade 4 events and none reaching grade 5 (**Table 3**). Most of these severe decreases in blood counts improved within 30 days after the infusion. Laboratory results from the first 30 days post-infusion showed that 93.1% (95 patients) developed grade 3/4 neutropenia, and 91.6% (87 of them) recovered within 30 days. Grade 3/4 thrombocytopenia affected 61.8% (63 patients), and 73.0% (46 patients) recovered within the same timeframe. Grade 3/4 lymphopenia was seen in 98.0% (100 patients), and 99.0% (99 patients) recovered within 30 days. Grade 3/4 anemia occurred in 59.8% (61 patients), of whom 85.2% (52 patients) recovered within 30 days.

Table 3. Summary of zevor-cel-related adverse events by SOC, PT and grade (all grade $\geq$ 20%)

Zevor-cel 1.5×10^8 ($N = 102$)		
SOC, n(%) PT, n (%)	$\geq$ Grade 3	Total
Number of patients with at least one zevor-cel -related AE	98 (96.1)	102 (100)
Investigations	95 (93.1)	101 (99.0)
Neutrophil count decreased	91 (89.2)	95 (93.1)
White blood cell count decreased	78 (76.5)	93 (91.2)
Lymphocyte count decreased	71 (69.6)	86 (84.3)
Platelet count decreased	61 (59.8)	86 (84.3)
Serum ferritin increased	16 (15.7)	70 (68.6)
C-reactive protein increased	7 (6.9)	65 (63.7)
Aspartate aminotransferase increased	22 (21.6)	57 (55.9)
Blood lactate dehydrogenase increased	5 (4.9)	57 (55.9)
Fibrin D dimer increased	8 (7.8)	48 (47.1)
Alanine aminotransferase increased	4 (3.9)	37 (36.3)

Blood alkaline phosphatase increased	4 (3.9)	27 (26.5)
Blood creatinine increased	3 (2.9)	26 (25.5)
Lymphocyte count increased	1 (1.0)	26 (25.5)
Fibrin degradation products increased	4 (3.9)	25 (24.5)
Gamma-glutamyltransferase increased	6 (5.9)	25 (24.5)
Blood fibrinogen decreased	2 (2.0)	23 (22.5)
Alpha hydroxybutyrate dehydrogenase increased	3 (2.9)	22 (21.6)
Procalcitonin increased	1 (1.0)	21 (20.6)
Immune system disorders	10 (9.8)	98 (96.1)
Cytokine release syndrome	7 (6.9)	92 (90.2)
Hypogammaglobulinemia	5 (4.9)	27 (26.5)
General disorders and administration site conditions	13 (12.7)	96 (94.1)
Pyrexia	11 (10.8)	95 (93.1)
Blood and lymphatic system disorders	36 (35.3)	70 (68.6)
Anaemia	35 (34.3)	67 (65.7)
Metabolism and nutrition disorders	23 (22.5)	65 (63.7)
Hypokalaemia	14 (13.7)	41 (40.2)
Hypocalcaemia	9 (8.8)	39 (38.2)
Hyponatraemia	1 (1.0)	27 (26.5)
Hypoalbuminemia	0	23 (22.5)
Hyperuricaemia	1 (1.0)	21 (20.6)
Hypophosphatemia	0	21 (20.6)
Infections and infestations	28 (27.5)	54 (52.9)
Pneumonia	20 (19.6)	24 (23.5)
Gastrointestinal disorders	1 (1.0)	41 (40.2)
Diarrhoea	0	21 (20.6)
Vascular disorders	6 (5.9)	27 (26.5)
Hypotension	5 (4.9)	24 (23.5)

Adverse events were coded using MedDRA version 24.1. Abbreviations: PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

CRS of any severity was observed in 90.2% (92 patients). Most cases were mild to moderate: grade 1 in 51.0% (52 patients) and grade 2 in 32.4% (33 patients). Grade 3 CRS occurred in 4.9% (5 patients) and grade 4 in 2.0% (2 patients) (**Table 4**). The median time from infusion to the start of CRS was 4 days (range 1–14 days), and the median duration was 6 days (range 1–22 days). All CRS episodes had resolved by the data cutoff. Tocilizumab was used in 66 of the 92 affected patients, while corticosteroids were given to 25.

Table 4. Incidence, Severity, and Management of CAR T-Cell–Related CRS and ICANS Following Zevor-cel Administration

CAR T-cell–related adverse events	Zevor-cel 1.5×10^8 cells ($n = 102$)
Cytokine release syndrome (CRS)	
Patients experiencing CRS*, n (%)	92 (90.2)

CRS severity distribution, n (%)	
Grade 1	52 (56.5)
Grade 2	33 (35.9)
Grade 3	5 (5.4)
Grade 4	2 (2.2)
Grade 5	0
Median time to CRS onset, days (range)	4 (1–14)
Median CRS duration, days (range)	6 (1–22)
Patients receiving tocilizumab, n (%)	66 (71.7)
Patients receiving corticosteroids, n (%)	25 (27.2)
Immune effector cell–associated neurotoxicity syndrome (ICANS)	
Patients experiencing ICANS*, n (%)	2 (2.0)
ICANS severity distribution, n (%)	
Grade 1	2 (100)
Grade 2	0
Grade ≥ 3	0
Median time to ICANS onset, days (range)	15.5 (12–19)
Median ICANS duration, days (range)	7 (3–11)
Patients receiving tocilizumab, n (%)	0
Patients receiving corticosteroids, n (%)	0
Patients with CRS and/or ICANS, n (%)	92 (90.2)

1. Percentages for each maximum severity grade were calculated using the total number of patients who experienced CRS or ICANS as the denominator.
2. Time to onset was computed as the date of the first CRS or ICANS event minus the zevor-cel infusion start date, plus one day.
3. Duration was determined by subtracting the earliest CRS or ICANS onset date from the latest end date, plus one day. This calculation included any days without events in cases where patients had multiple episodes of CRS or ICANS.
4. AE= adverse event; CRS= cytokine release syndrome; d= day; ICANS= immune effector cell-associated neurotoxicity syndrome.

*Grading was performed according to the ASTCT Consensus Guidelines for Cytokine Release Syndrome and Neurologic Toxicity Linked to Immune Effector Cell Therapies.

ICANS occurred in just 2 patients (2.0%), both at grade 1. Both recovered completely without needing tocilizumab or steroids. Nervous system issues connected to zevor-cel were noted in 18.6% (19 patients). The most common were dizziness and headache, each affecting 7.8% (8 patients) and limited to grade 1 or 2. No cases of movement disorders, cognitive problems, parkinsonism, cranial nerve issues, or Guillain-Barré syndrome were observed. There were no grade 3 or higher neurological events related to zevor-cel.

Infections associated with zevor-cel were reported in 52.9% (54 patients). Severe (grade 3 or higher) infections occurred in 27.5% (28 patients), including one

grade 5 case of pneumonia (1.0%). Low immunoglobulin levels (hypogammaglobulinemia) were seen in 26.5% (27 patients), with 4.9% (5 patients) at grade 3 or higher. Serious adverse events (SAEs) affected 51.0% (52 patients). Of these, 36.3% (37 patients) had SAEs considered related to zevor-cel, primarily infections. Zevor-cel-related infections occurred in 19.6% (20 patients), mostly grade 3, with pneumonia being the most frequent (15.7%, 16 patients). Other common SAEs related to zevor-cel included decreased platelet counts in 14.7% (15 patients) and CRS in 2.9% (3 patients).

A total of 19.6% (20 patients) died during the study. Causes included progressive disease in 13 cases, adverse events in 4 cases, a combination of progression and an AE in 1 case, septic shock in 1 case, and COVID-19 pneumonia in 1 case (the latter not counted as an AE per study rules). Only one death (1.0%) was judged related to zevor-cel — due to pneumonia that began 149 days after infusion.

Four patients developed second primary cancers: one case each of basosquamous skin carcinoma, acute myeloid leukemia, ampulla of Vater tumor, and HPV16-positive cervical squamous cell carcinoma. All were considered unrelated to zevor-cel. No autoimmune conditions linked to zevor-cel were observed. All patients tested negative for replication-competent lentivirus (RCL).

Pharmacokinetics, immunogenicity and exposure-response relationship

All 102 patients who received the infusion were evaluated in the pharmacokinetic (PK) analysis. Detectable levels of zevor-cel appeared in 91.2% (93 patients) within the first 3 days. The median peak concentration (C_{max}) was 202543.5 copies/μg gDNA (range: 9544–1,128,461), and the median time to peak (T_{max}) was 14.0 days (range: 7–22). The median last detectable time (T_{last}) was 140.0 days (range: 26–740). Median area under the curve values were 2,193,780.7 daycopies/μg gDNA (range: 59,293.9–13,937,955.4) for AUC_{0–t} and 2,448,492.6 daycopies/μg gDNA (range: 174,872.7–13,941,661.8) for AUC_{0–inf}. Median AUC values from day 0–7 to day 0–26 steadily rose from 77,228.0 (range: 478.9–1,157,968.0) to 2,232,862.9 (range: 177,306.8–13,922,819.3) day*copies/μg gDNA (Figure 5).

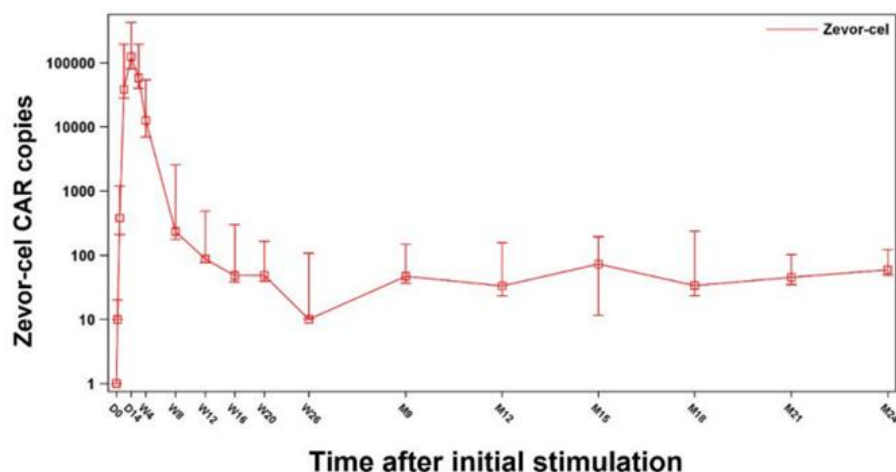


Figure 5. Zevor-cel copy numbers detected by qPCR over time. Expansion of ZEVOR-CEL in peripheral blood was assessed as the number of copies per microgram of genomic DNA by quantitative PCR. Abbreviations: D = day; CAR = chimeric antigen receptor; M = month; qPCR = quantitative PCR; W = week.

Anti-drug antibodies (ADAs) developed in 20.6% (21 patients), and neutralizing antibodies (NABs) were found in 15.7% (16 patients) by the data cutoff.

Patients who experienced CRS showed higher AUC0–28 values than those without CRS, though the difference was not statistically significant (median 2,008,586.8 vs. 1,559,700.1 copies/ μ g gDNA; $P = 0.2557$). In contrast, Cmax was significantly higher in patients whose CRS required treatment compared to those with untreated CRS (median 76,383.0 vs. 24,155 copies/ μ g gDNA; $P = 0.0095$). Cmax was also numerically higher in treated CRS patients versus those without any CRS, but this did not reach statistical significance (median 214,923.5 vs. 133,426.5 copies/ μ g gDNA; $P = 0.3137$).

Response rates were markedly different based on CRS status: 95.7% among the 92 patients with CRS versus 60.0% among the 10 without CRS ($P = 0.0028$). Similarly, MRD negativity rates (at 10^{-5}) were 94.4% in patients with CRS (90 patients) compared to 66.7% in those without (9 patients), a statistically significant difference ($P = 0.0235$). Levels of the cytokines IL-2, IL-6, IL-10, and IFN- γ were all significantly elevated in patients who developed CRS compared to those who did not (all $P < 0.05$).

Although CAR T-cell treatments have shown promising results for patients with relapsed/refractory multiple myeloma (RRMM) across various regions, their benefits for individuals in China are constrained by limited availability, variations in healthcare systems, and economic challenges. Zevor-cel offers a promising and effective treatment alternative for RRMM, supported by

the overall response rate (ORR) of 92.2% and the complete response/stringent complete response (CR/sCR) rate of 71.6% documented in this trial. For context, the pivotal phase 2 KarMMa study [12] of ide-cel showed an ORR of 72 % and a stringent CR rate of 28 %, while the phase 1b/2 CARTITUDE-1 trial of cilta-cel demonstrated an ORR of 97.9 % along with an sCR rate of 80.4 % [14]. Separately, the LEGEND-2 trial conducted in China with cilta-cel reported an ORR of 87.8% and a CR rate of 73% [17]. In the phase 1b/2 FUMANBA-1 study, also conducted in China, equecel achieved an ORR of 96.0%, with 74.3% of participants attaining CR or better [25].

The durability of responses (DOR) across BCMA-directed CAR-T approaches has differed notably. In the KarMMa trial, ide-cel had a median DOR of 11 months, compared with 33.9 months for cilta-cel in CARTITUDE-1 (median follow-up of 33.4 months). In the China-based LEGEND-2 study, cilta-cel yielded a median DOR of 23 months (median follow-up 65.4 months). Eque-cel showed a median DOR of 12.3 months in the FUMANBA-1 trial (median follow-up of 13.8 months, range 0.4–27.2) [25]. For zevor-cel, the median DOR data had not yet matured at a median follow-up of 20.3 months, at which point 62.4 % (95% CI: 51.2%–71.6%) of patients remained progression-free or event-free at 18 months. In summary, the response rates and DOR seen with zevor-cel in this analysis were numerically better than those for ide-cel and generally aligned with findings from cilta-cel and eque-cel studies

in China. Nonetheless, such cross-trial comparisons must be interpreted carefully.

Importantly, the overall survival (OS) rates for zevor-cel reached 90.2% at 12 months, 83.3% at 18 months, and 79.4% months—notably strong figures and hithat Subgroup evaluations in the pivotal Phase II portion of the LUMMICAR STUDY 1, focusing on those comprising over 20% of the 102 patients who received zevor-cel infusion—including age (< 65 vs. ≥ 65 years), International Staging System (ISS; stages I/II vs. III), and high-risk cytogenetics—revealed that baseline patient features did not meaningfully alter zevor-cel's clinical performance. This implies that individuals with RRMM and unfavorable prognostic indicators can still derive substantial benefit from the therapy [26].

Even with the high efficacy of BCMA-targeted cell therapies, safety remains a key consideration. The overall safety data for zevor-cel in LUMMICAR-1 were encouraging. Cytokine release syndrome (CRS) of any grade affected 92 patients (90.2%), mostly grades 1–2 (85 patients; 83.3%), while grade 3–4 events occurred in just 7 patients (6.9%), all of whom recovered completely. These rates align closely with cilta-cel results from the CARTITUDE-1 and CARTITUDE-4 trials (CRS in 84% overall, with 4 % experiencing grade ≥ 3) [27] and ide-cel findings from KarMMa and KarMMa-3 (CRS in 89% overall, with 7.9% grade ≥ 3, including one fatality) [28]. CAR T-cell therapies can also trigger significant neurological side effects. In CARTITUDE-1 and CARTITUDE-4, neurologic toxicities occurred in 24 % (69/285) of cilta-cel recipients, with grade ≥ 3 events in 7% (19/285). These included immune effector cell-associated neurotoxicity syndrome (ICANS) in 13%, peripheral neuropathy in 7%, cranial nerve issues in 7%, and parkinsonism in 3%. In ide-cel-treated patients in KarMMa and KarMMa-3, neurotoxicity occurred in 40% (139/349), with grade 3–4 events in 4.6% (16/349). Common issues involved encephalopathy/ICANS (21%), headache (15%), dizziness (8%), delirium (6%), and tremor (6%). By comparison, zevor-cel-related nervous system disorders were observed in 18.6% of our patients. The predominant events were dizziness and headache (each 7.8%), both limited to grades 1–2. No grade 3 or higher neurotoxicity linked to zevor-cel was recorded, and only two patients had grade 1 ICANS.

The risk of secondary cancers due to genomic integration or other factors continues to be monitored with CAR T-cell products. A recent US FDA summary identified 22 instances of T-cell malignancies following CAR T

treatment [29]. Myeloid neoplasms developed in 5% (13/285) of cilta-cel patients in CARTITUDE-1 and CARTITUDE-4 (including 9 myelodysplastic syndromes, 3 acute myeloid leukemias, and 1 case progressing from MDS to AML) [11]. In our trial, four second primary malignancies occurred (one basosquamous skin carcinoma, one acute myeloid leukemia, one ampulla of Vater tumor, and one cervical squamous cell carcinoma). Variations in follow-up length may partly explain incidence differences, but a potential safety benefit for zevor-cel cannot be excluded. Only one death in this study was deemed zevor-cel-related, resulting from pneumonia 149 days after infusion. The majority of adverse events (AEs) were grade 1–2, which often permitted outpatient care. In contrast, a phase 2 cilta-cel study (median follow-up 26.4 months) reported grade ≥3 treatment-emergent AEs in all 48 patients and 12 post-infusion deaths (8 treatment-related) [30]. A phase 1b/2 trial of CT103A (median follow-up 147 days) noted frequent grade ≥3 treatment-related AEs, primarily hematologic [31]. Research by Li *et al.* [32] highlighted that while CAR T therapy is effective against R/R MM, persistent severe hematologic toxicity remains challenging, with prolonged hematologic toxicity on day 28 post-infusion linked to worse progression-free survival (PFS) and OS. In our study, most grade ≥3 hematologic toxicities resolved within 30 days, reinforcing zevor-cel's favorable safety profile and its potential to improve OS.

Collectively, zevor-cel appears to offer a potentially better safety profile than other approved BCMA-directed CAR-T therapies, while acknowledging the limitations of indirect comparisons. The fully human design of zevor-cel may contribute to these advantages. Additionally, the lower lymphodepleting doses used (fludarabine 25 mg/m² and cyclophosphamide 300 mg/m² daily for 3 days) may have contributed to the favorable tolerability. For heavily pretreated RRMM patients—who frequently have multiple comorbidities, frailty, and reduced bone marrow function—zevor-cel represents a strong therapeutic option owing to its distinctive safety attributes.

This trial involved a relatively modest sample size and exhibited variability in disease characteristics and time since diagnosis. The absence of a control group prevented direct comparison of zevor-cel against other standard treatments. Ongoing efforts include the larger multicenter LUMMICAR STUDY 2 in the USA and Canada (NCT03915184) and a real-world evidence

study in China (NCT06659770), which will provide further insights into the long-term safety and effectiveness of zevor-cel in RRMM.

Conclusion

In heavily pretreated patients with RRMM, zevor-cel delivers strong anti-myeloma effects, producing deep and sustained clinical responses alongside a manageable safety profile.

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