Infections and Immune Reconstitution in the Phase 3 CARTITUDE-4 Trial of Ciltacabtagene Autoleucel vs Standard Care in Patients With Lenalidomide-Refractory Multiple Myeloma and 1–3 Prior Lines

Joaquín Martínez-López[1], Niels WCJ van de Donk[2], Binod Dhakal[3], Magdalena Dutka[4], Leyla Shune[5], Cyrille Touzeau[6], Xavier Leleu[7], Yaël C Cohen[8], Winfried Alsdorf[9], Roberto Mina[10], Katherine Li[11], Man Zhao[12], Quanlin Li[13], Arnab Ghosh[14], Martin Vogel[15], Nikoletta Lendvai[14], Ana Slaughter[16], Carolina Lonardi[17], Vicki Plaks[11], Mythili Koneru[18], Nitin Patel[18], Erika Florendo[18], Albert Oriol[19], Rakesh Popat[20], P Joy Ho[21]

[1]Hospital 12 de Octubre, Universidad Complutense, CNIO, MIC, Madrid, Spain; [2]Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands; [3]Medical College of Wisconsin, Milwaukee, WI, USA; [4]Medical University of Gdańsk, Gdańsk, Poland; [5]The University of Kansas Medical Center, Kansas City, KS, USA; [6]Centre Hospitalier Universitaire de Nantes, Nantes, France; [7]CHU Poitiers, Poitiers, France; [8]Tel Aviv Sourasky (Ichilov) Medical Center, Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv, Israel; [9]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [10]AOU Città della Salute e della Scienza di Torino, Turin, Italy; [11]Johnson & Johnson, Spring House, PA, USA; [12]IQVIA, Shanghai, China; [13]Johnson & Johnson, Apex, NC, USA; [14]Johnson & Johnson, Raritan, NJ, USA; [15]Johnson & Johnson, Neuss, Germany; [16]Johnson & Johnson, Zug, Switzerland; [17]Johnson & Johnson, Buenos Aires, Argentina; [18]Legend Biotech USA Inc., Somerset, NJ, USA; [19]Institut Català d'Oncologia and Institut Josep Carreras, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [20]University College London Hospitals NHS Foundation Trust, London, UK; [21]Royal Prince Alfred Hospital, Camperdown, NSW, Australia

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INTRODUCTION

- Patients with multiple myeloma (MM) have increased risk of infection[1]
- Infection risk factors include immune dysregulation due to MM, and for patients receiving chimeric antigen receptor (CAR)-T therapy, lymphodepletion (LD), toxicity management with corticosteroids, and immune suppression exerted by CAR-T cells[1,2]
- Ciltacabtagene autoleucel (cilta-cel) is approved in the US and EU for treatment of lenalidomide-refractory MM after ≥1 prior line of therapy (LOT) based on the phase 3 CARTITUDE-4 trial[3-5]
  - At 15.9-month median follow-up, cilta-cel vs standard of care (SOC) improved progression-free survival (PFS) (hazard ratio, 0.26 [protocol-specified weighted analysis], $P<0.001$)[5]
- We characterize infections and immune reconstitution in CARTITUDE-4 after 21.5-month median follow-up

METHODS

- Eligibility criteria included lenalidomide-refractory MM and 1–3 prior LOT, including a proteasome inhibitor (PI) and immunomodulatory drug (IMiD)
- Patients were randomized 1:1 to cilta-cel or SOC (daratumumab, pomalidomide, and dexamethasone [DPd] or pomalidomide, bortezomib, and dexamethasone [PVd])
- Patients in the cilta-cel arm underwent apheresis, received bridging therapy, and then a single cilta-cel infusion (target dose, 0.75 × 10^6 CAR+ viable T cells/kg) 5–7 days after LD
- Patients in the SOC arm received DPd or PVd until progression
- Infections were assessed in all patients who received any part of study treatment (SOC or apheresis, bridging therapy, LD, and cilta-cel; safety set)
- Treatment-emergent (TE) adverse events (AEs) were:
  - AEs at/after first dose of study treatment until ≤112 days after cilta-cel, ≤30 days after last PVd/DPd dose (SOC arm), or subsequent anti-MM therapy start, whichever was first
  - Any study treatment-related AE regardless of start date (ie, AEs beginning later than 112 days after infusion)
- In addition, in the cilta-cel arm, delayed AE reporting collected all grade ≥3 infections from the time of infusion and for the duration of the study regardless of causality or seriousness
- Lymphocyte counts over time were assessed by flow cytometry in patients who received cilta-cel as study treatment
- Serum antibody levels were determined by immunoturbidimetry (Labcorp)

RESULTS

Patients

- 208 patients were randomized to cilta-cel and 211 to SOC; baseline characteristics are shown in the **Table**
- At the April 2023 data cut-off, median follow-up was 21.5 months (range, 0.1–32.8)

Table: Baseline characteristics

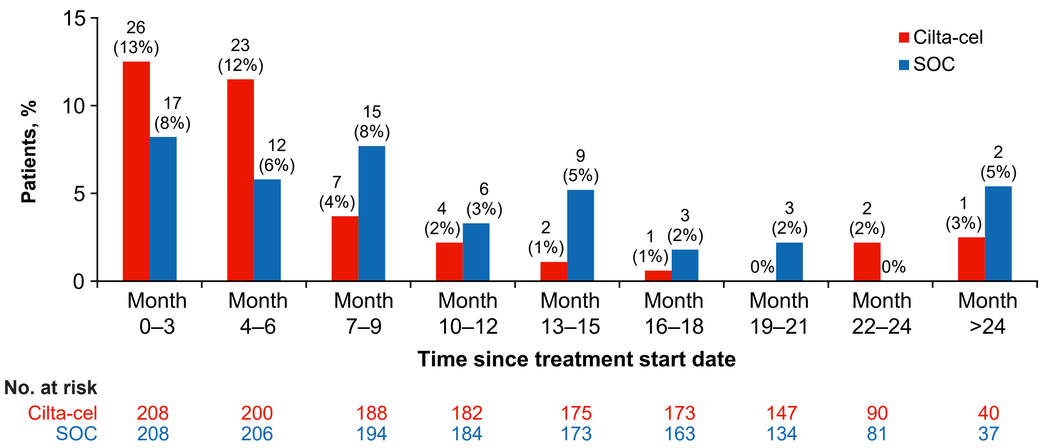
Baseline characteristic	ITT population	
	Cilta-cel (n=208)	SOC (n=211)
Age, median (range), years	61.5 (27–78)	61.0 (35–80)
ISS stage, n (%)		
I	136 (65.4)	132 (62.6)
II	60 (28.8)	65 (30.8)
III	12 (5.8)	14 (6.6)
Bone marrow plasma cells ≥60%,[a] n (%)	42 (20.4)	43 (20.7)
Presence of soft tissue plasmacytomas,[b] n (%)	44 (21.2)	35 (16.6)
Years since diagnosis, median (range)	3.0 (0.3–18.1)	3.4 (0.4–22.1)
Prior LOT, median (range)	2 (1–3)	2 (1–3)
1 prior LOT, n (%)	68 (32.7)	68 (32.2)
2 or 3 prior LOT, n (%)	140 (67.3)	143 (67.8)
Triple-class[c] exposed, n (%)	55 (26.1)	53 (25.5)
Penta-drug[d] exposed, n (%)	10 (4.7)	14 (6.7)
MM type, n (%)		
IgG	113 (54.3)	108 (51.2)
IgA/IgM	37 (17.8)	38 (18.0)
Light chain	47 (22.6)	56 (26.5)

[a]Including extramedullary and bone-based plasmacytomas with measurable soft tissue component. [b]In 206 (cilta-cel arm) and 208 (SOC arm) patients; maximum value from bone marrow biopsy and bone marrow aspirate selected if both results available. [c]At least 1 PI, 1 IMiD, and 1 anti-CD38 antibody. [d]At least 2 PIs, 2 IMiDs, and 1 anti-CD38 antibody.
Ig, immunoglobulin, ISS, International Staging System; ITT, intent-to-treat.

Safety set

- 208 patients in the cilta-cel arm and 208 in the SOC arm received study treatment
  - 176 patients received cilta-cel as study treatment
  - In the SOC arm, median duration of DPd (n=182) was 12.1 months (range, 0.5–31.3) and for PVd (n=26) was 4.8 months (range, 0.5–25.4)
- 128 (61.5%) patients in the cilta-cel arm and 157 (75.5%) in the SOC arm had TE infections of any grade
  - Viral infections occurred in a respective 29.8% and 43.3%
  - Bacterial infections occurred in 16.8% and 10.6%
  - Fungal infections occurred in 5.8% and 9.6%, and were invasive in 4 (grade 3/4, n=2) and 5 (grade 3/4, n=2) cases, respectively
- Grade ≥3 TE infections occurred in 57 (27.4%) patients in the cilta-cel arm and 56 (26.9%) in the SOC arm
  - In the cilta-cel arm, rates were highest in the first 6 months after study treatment start; in the SOC arm, rates were highest in the first 9 months (**Figure 1**)
  - Grade ≥3 events decreased substantially in the cilta-cel arm after month 6; a more gradual decrease over time was observed in the SOC arm

Figure 1: Grade ≥3 TE infections

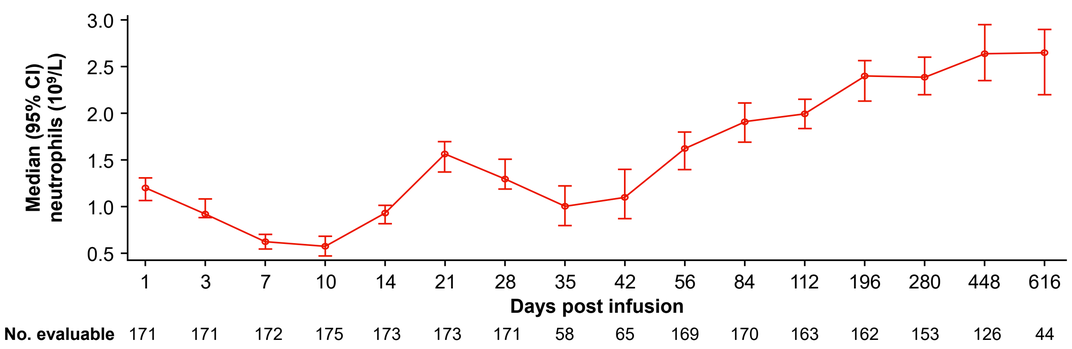


- 9 (4.3%) patients in the cilta-cel arm and 6 (2.9%) in the SOC arm had TE fatal infections, most of which occurred in the first 9 months after study treatment start
  - 7 fatal infections in the cilta-cel arm and 2 in the SOC arm were due to COVID-19 pneumonia; most of these occurred during the pandemic's omicron wave
    - None of the patients who died of COVID-19 in the cilta-cel arm were fully vaccinated; none of these deaths occurred after implementation of protocol-specified COVID-19 mitigation strategies
- 189 (90.9%) patients in the cilta-cel arm and 149 (71.6%) in the SOC arm had either TE hypogammaglobulinemia or postbaseline IgG <500 mg/dL
- A respective 142 (68.3%) and 33 (15.9%) patients received intravenous Ig (IVIg)

Postinfusion clinical course and immune recovery in patients who received cilta-cel as study treatment

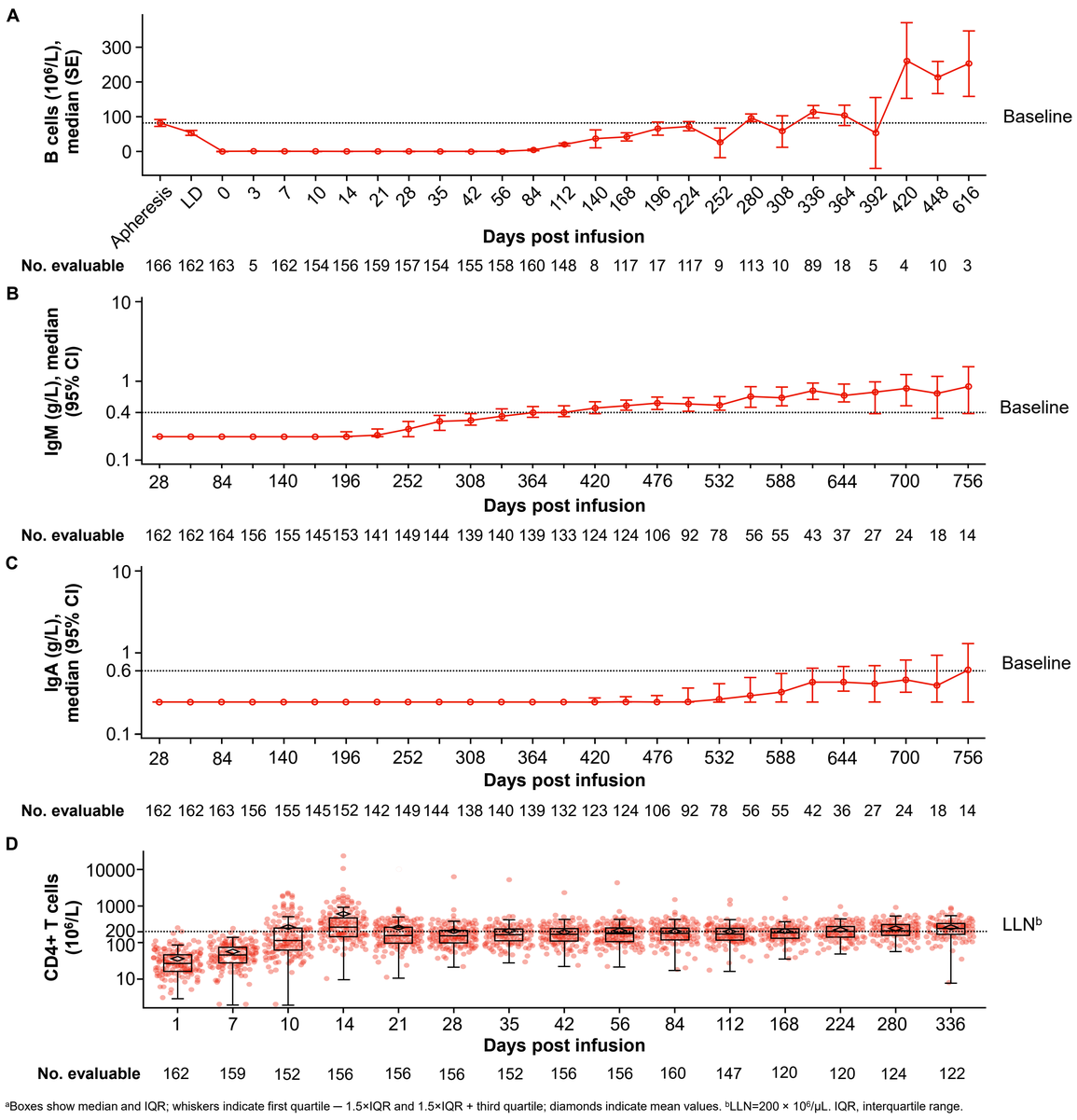
- Among 176 patients who received cilta-cel as study treatment, 54 (30.7%) had grade ≥3 infections (TE and non-TE), which occurred most often in the first 6 months after infusion
  - Fatal infections (TE and non-TE) occurred in 11 patients who received cilta-cel as study treatment, including the 7 in the safety set who died due to COVID-19
- 89.2% of patients who had grade 3/4 neutropenia recovered to grade ≤2 by day 60 (**Figure 2**)

Figure 2: Absolute neutrophil counts over time



- B-cell counts in blood began to return to baseline levels ~4 months post infusion and reached baseline at ~9 months post infusion (**Figure 3A**)
- IgM and IgA levels returned to baseline ~1 and 2 years, respectively, after treatment with cilta-cel (**Figure 3B, C**)
  - Measurement of IgG recovery is confounded by IVIg supplementation; however, it is expected to occur between 1 and 2 years, based on IgM and IgA recovery[6]
- Median CD4+ T median CD4+ T-cell counts began to rise above the lower limit of normal (LLN; 200 × 10^6/μL) starting day 168 post infusion (**Figure 3D**)

Figure 3: Blood levels of B cells (A), IgM (B), IgA (C), and CD4+ T cells[a] (D) over time



[a]Boxes show median and IQR; whiskers indicate first quartile ─ 1.5×IQR and 1.5×IQR + third quartile; diamonds indicate mean values. [b]LLN=200 × 10^6/μL. IQR, interquartile range.

KEY TAKEAWAY

- These results underscore the importance of monitoring, infection prophylaxis, and supportive care following cilta-cel infusion and for patients receiving continuous treatment

CONCLUSIONS

- Patients in both the cilta-cel and SOC arms were at risk of severe and fatal infections; infection risk is multifactorial and contributors include neutropenia, low CD4+ T-cell counts, and low antibody levels
- In both the cilta-cel and SOC arms, most severe and fatal infections occurred early after treatment start, with higher risk in the first few months
- After the first 6 months, grade ≥3 infection rates were generally higher in the SOC arm than the cilta-cel arm
- Timing of immune recovery in patients who received cilta-cel as study treatment corresponds with a reduction in infection risk; however, immune recovery may take longer in some patients, underscoring the importance of tailored infection prophylaxis

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