The 7th World Congress on CONTROVERSIES IN MULTIPLE MYELOMA (COMy)

CARTITUDE-1: PHASE 1B/2 STUDY OF CILTACABTAGENE AUTOLEUCEL (CILTA-CEL) IN RELAPSED/REFRACTORY MULTIPLE MYELOMA (RRMM)

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INTRODUCTION

- Ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) is a chimeric antigen receptor T-cell therapy
  - 2 BCMA-targeting single-domain antibodies designed to confer avidity
- In the phase 1b portion of the CARTITUDE-1 study, cilta-cel yielded deep, durable responses with a manageable safety profile in patients with relapsed/refractory MM[1]
- Here, we report initial results from the combined phase 1b/2 CARTITUDE-1 study of cilta-cel

METHODS

Primary objectives

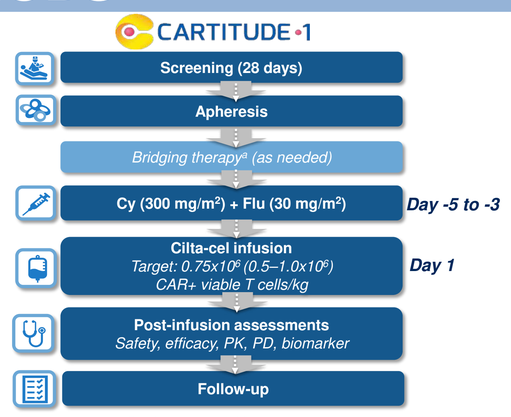
- Phase 1b: Characterize the safety of cilta-cel and confirm the recommended phase 2 dose
- Phase 2: Evaluate the efficacy of cilta-cel by ORR

Key eligibility criteria

- Progressive MM per IMWG criteria
- ECOG PS ≤1
- Measurable disease
- ≥3 prior therapies or double refractory
- Prior PI, IMiD, anti-CD38 therapy

Median administered dose

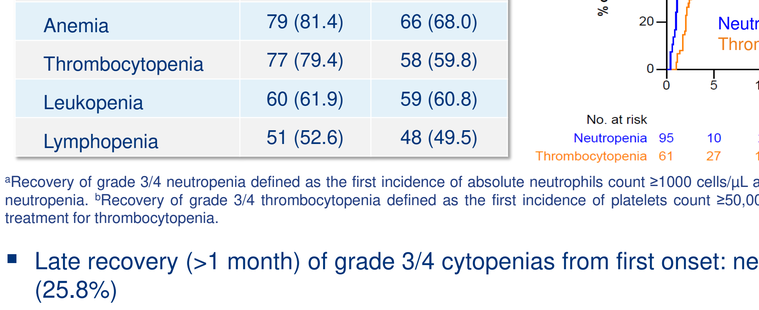
- 0.71x10^6 (0.51–0.95x10^6) CAR+ viable T cells/kg



CAR, chimeric antigen receptor; Cy, cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance status; Flu, fludarabine; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; ORR, overall response rate; PD, pharmacodynamics; PI, proteasome inhibitor; PK, pharmacokinetics. [a]Treatment with previously used agent resulting in at least stable disease. NCT03548207; Sep 1, 2020 data cut-off.

RESULTS

Figure 1. CARTITUDE-1 CONSORT Diagram



- 73 patients received bridging therapy
- Median turnaround time[b] for cilta-cel was 29 days
- No patient discontinued due to manufacturing failure

[a]Deaths due to progressive disease (5), acute cardio-respiratory arrest (1), sepsis (1), subdural hematoma (1), and acute respiratory failure (1; after lymphodepletion). [b]Turnaround time was defined as time from receipt to release of product.

Table 1. CARTITUDE-1 Baseline Characteristics

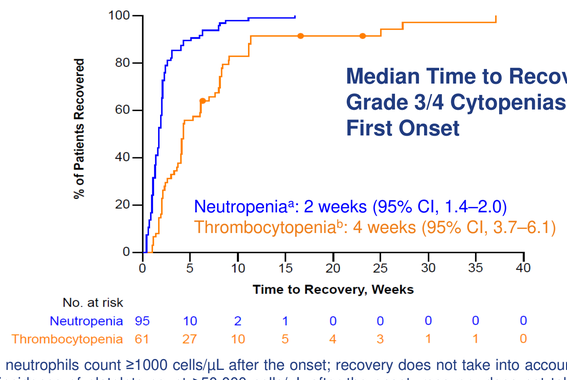
Characteristic	N=97
Age, median (range) years	61.0 (43–78)
Male, n (%)	57 (58.8)
Extramedullary plasmacytomas ≥1, n (%)	13 (13.4)[a]
Bone-marrow plasma cells ≥60%, n (%)	21 (21.9)
Years since diagnosis, median (range)	5.9 (1.6–18.2)
High-risk cytogenetic profile, n (%)	23 (23.7)
del17p	19 (19.6)
t(14;16)	2 (2.1)
t(4;14)	3 (3.1)
Tumor BCMA expression ≥50%, n (%)	57 (91.9)[b]

Characteristic	N=97
Prior lines of therapy, median (range)	6.0 (3–18)
Previous stem-cell transplantation, n (%)	
Autologous	87 (89.7)
Allogenic	8 (8.2)
Triple-class exposed,[c] n (%)	97 (100)
Penta-exposed,[d] n (%)	81 (83.5)
Triple-class refractory[c]	85 (87.6)
Penta-refractory[d]	41 (42.3)
Refractory status, n (%)	
Carfilzomib	63 (64.9)
Pomalidomide	81 (83.5)
Anti-CD38 antibody	96 (99.0)
Refractory to last line of therapy, n (%)	96 (99.0)

BCMA, B-cell maturation antigen; IMiD, immunomodulatory drug; PI, proteasome inhibitor. [a]Additional 6 patients had a soft-tissue component of a bone-based plasmacytoma (total plasmacytomas, 19.6%). [b]Denominator n=62, the number of evaluable samples; BCMA expression detected in all evaluable samples. [c]At least 1 PI, at least 1 IMiD, and 1 anti-CD38 antibody. [d]At least 2 PIs, at least 2 IMiDs, and 1 anti-CD38 antibody.

Table 1. Hematologic Adverse Events

Adverse Events ≥20%, n (%)	N=97	
	Any grade	Grade 3/4
Hematologic	97 (100)	96 (99.0)
Neutropenia	93 (95.9)	92 (94.8)
Anemia	79 (81.4)	66 (68.0)
Thrombocytopenia	77 (79.4)	58 (59.8)
Leukopenia	60 (61.9)	59 (60.8)
Lymphopenia	51 (52.6)	48 (49.5)



[a]Recovery of grade 3/4 neutropenia defined as the first incidence of absolute neutrophils count ≥1000 cells/μL after the onset; recovery does not take into account treatment for neutropenia. [b]Recovery of grade 3/4 thrombocytopenia defined as the first incidence of platelets count ≥50,000 cells/μL after the onset; recovery does not take into account treatment for thrombocytopenia.

- Late recovery (>1 month) of grade 3/4 cytopenias from first onset: neutropenia (10.3%) and thrombocytopenia (25.8%)
- Any-grade infections occurred in 57.7%; grade 3/4 infections (19.6%) and included pneumonia (8.2%) and sepsis (4.1%)

Table 3. Nonhematologic Adverse Events (N=97)

AEs ≥20%, n (%)	Any grade	Grade 3/4
Metabolism and nutrition disorders		
Hypocalcemia	31 (32.0)	3 (3.1)
Hypophosphatemia	30 (30.9)	7 (7.2)
Decreased appetite	28 (28.9)	1 (1.0)
Hypoalbuminemia	27 (27.8)	1 (1.0)
Hyponatremia	22 (22.7)	4 (4.1)
Hypokalemia	20 (20.6)	2 (2.1)
Gastrointestinal		
Diarrhea	29 (29.9)	1 (1.0)
Nausea	27 (27.8)	1 (1.0)
Constipation	21 (21.6)	0

AEs ≥20%, n (%)	Any grade	Grade 3/4
Other		
Fatigue	36 (37.1)	5 (5.2)
Cough	34 (35.1)	0
AST increased	28 (28.9)	5 (5.2)
ALT increased	24 (24.7)	3 (3.1)
Chills	20 (20.6)	0
Pyrexia	20 (20.6)	0

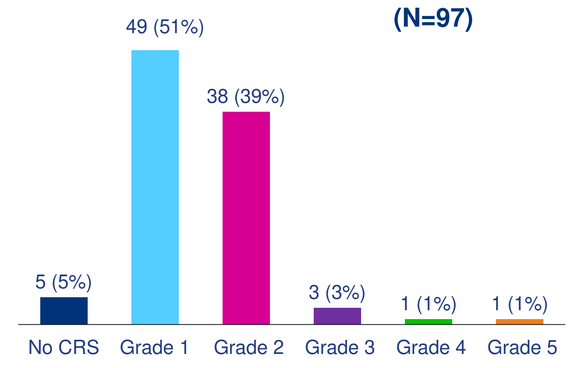
CAR-T-related AEs	Any grade	Grade 3/4
CRS	92 (94.8)	4 (4.1)
Neurotoxicity	20 (20.6)	9 (9.3)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome.

RESULTS (*CONTD.*)

Table 4. Cytokine Release Syndrome

	N=97
Patients with a CRS event,[a] n (%)	92 (94.8)
Time to onset, median (range) days	7 (1–12)
Duration, median (range) days	4 (1–97)[b]
Supportive measures, n (%)	88 (90.7)
Tocilizumab	67 (69.1)
Corticosteroids	21 (21.6)
Anakinra	18 (18.6)
Vasopressor used	4 (4.1)
Intubation/mechanical ventilation	1 (1.0)
Other	
Cyclophosphamide	1 (1.0)
Etanercept	1 (1.0)



ASTCT, American Society for Transplantation and Cellular Therapy; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis. [a]CRS was graded using Lee et al. (*Blood* 2014) in the phase 1b portion of the study and ASTCT in phase 2; in this combined analysis, Lee et al. criteria were mapped to ASTCT criteria for patients in the phase 1b portion. [b]The patient with 97-day duration died due to CRS/HLH.

- Of 92 patients with CRS, 94.6% were grades 1/2
  - CRS onset on Day 4 or later: 89.1% (n=82); Day 6 or later: 73.9% (n=68)
- CRS resolved in 91 (98.9%) patients within 14 days of onset
- 14 deaths occurred in the study: 5 from progressive disease, 3 unrelated AEs, and 6 related AEs

Neurotoxicity

Total CAR-T cell neurotoxicities
- Any grade: 20 (20.6%)
- Grade ≥3: 10 (10.3%)

ICANS
- Any grade: 16 (16.5%)
- Grade ≥3: 2 (2.1%)

Other neurotoxicities[a]
- Any grade: 12 (12.4%)
- Grade ≥3: 9 (9.3%)

	ICANS	Other neurotoxicities[a]
Time to onset, median (range) days	8 (3–12)	27 (11–108)
Time to recovery, median (range) days	4 (1–12)	75 (2–160)

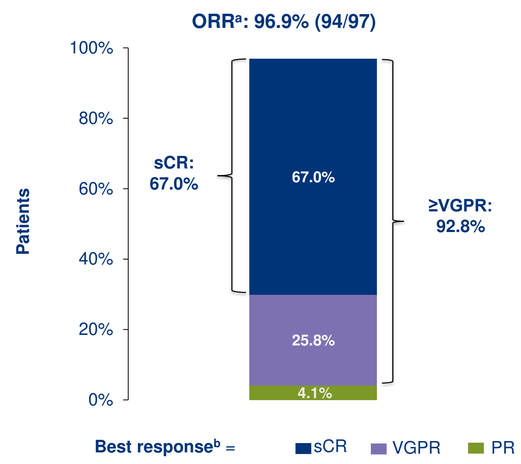
Other neurotoxicities[a]
- **Occurring after resolution of CRS and/or ICANS**
- Among 12 patients
  - 5 had AEs including movement and/or neurocognitive changes
  - 7 had AEs including nerve palsy, peripheral motor neuropathy

Outcomes for CAR-T cell neurotoxicities
- ICANS resolved in all patients
- Other neurotoxicities resolved in 6 patients, and did not resolve in 6 patients:
  - 1 patient has ongoing neurotoxicity
  - 1 patient died from complications of neurotoxicity
  - 4 patients died due to other causes
- No additional movement and neurocognitive AEs were seen in the CARTITUDE development program

AE, adverse event; CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome. [a]Events not reported as ICANS [ie, onset after a period of recovery from CRS and/or ICANS]).

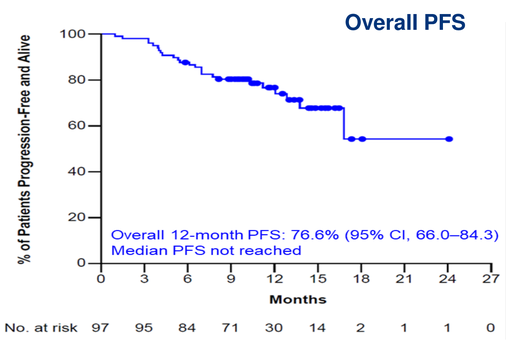
Figure 3. Overall Response Rate

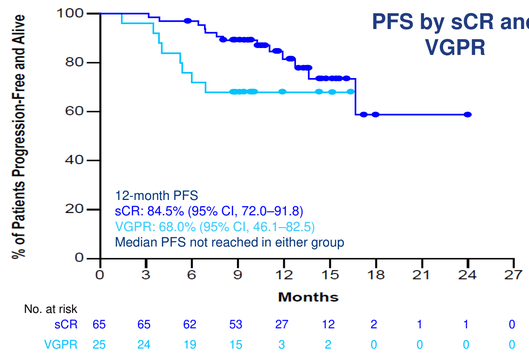
- Median time to first response: 1 month (0.9–8.5)
- Responses ongoing in 70 (72.2%) patients
- Of evaluable patients, 93.0% achieved MRD[c] 10^{-5} negativity
  - Median time to MRD 10^{-5} negativity: 1 month (0.8–7.7)
- Among patients with 6 months individual follow-up, most had cilta-cel CAR+ T cells below the level of quantification (2 cells/μL) in peripheral blood



CAR, chimeric antigen receptor; CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response. [a]PR or better, Independent Review Committee assessed. [b]No patient had CR or stable disease as best response. [c]MRD was assessed in evaluable samples at 10^{-5} threshold by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) in all treated patients at Day 28, and at 6, 12, 18, and 24 months regardless of the status of disease measured in blood or urine; patients were not evaluable primarily due to lack of an identifiable clone in the baseline bone marrow sample.

Figure 4. Progression-free Survival





OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

CONCLUSIONS

- **Cilta-cel has a manageable safety profile at the recommended phase 2 dose**
  - CRS was mostly grades 1/2; median time to onset of CRS was 7 days (range, 1–12)
  - CAR-T-related neurotoxicities occurred in 20 patients (20.6%); 10.3% had grade ≥3
- **Low dose of cilta-cel yielded early, deep, and durable responses in heavily pretreated relapsed/refractory MM**
  - 96.9% ORR, with sCR 67.0%
  - Median PFS not reached; 12-month PFS rate was 76.6%, OS rate was 88.5%
- **Cilta-cel is under further investigation in other populations of patients with MM in earlier-line settings**
  - Outpatient administration is being studied in CARTITUDE-2 (NCT04133636) and CARTITUDE-4 (NCT04181827)

REFERENCE

1. Berdeja J, et al. *J Clin Oncol* 2020;38(Suppl):8505.

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Previously presented at ASH 2020