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ORAL ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

The Phase 2 CARTITUDE-2 Trial: Updated Efficacy and Safety of Ciltacabtagene Autoleucel in Patients with Multiple Myeloma and 1-3 Prior Lines of Therapy (Cohort A) and with Early Relapse after First Line Treatment (Cohort B)

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Introduction: CARTITUDE-2 (NCT04133636) is a phase 2, multicohort study evaluating the safety and efficacy of ciltacabtagene autoleucel (cilta-cel), an anti-BCMA chimeric antigen receptor (CAR)-T cell therapy, in various populations of patients with multiple myeloma (MM). We previously reported 17-month median follow-up results from cohort A (1-3 prior lines of therapy [LOT] and lenalidomide [len]-refractory) and 18-month median follow-up results from cohort B (early relapse: ≤12 months after either autologous stem cell transplant [ASCT] or start of initial anti-myeloma treatment, if not transplanted). Cilta-cel is also under evaluation in patients with len-refractory MM after 1-3 LOT in the phase 3 CARTITUDE-4 study, which showed cilta-cel significantly prolonged progression-free survival (PFS) vs standard of care (HR, 0.26) at a median follow-up of 16 months. Here, we present updated efficacy and safety data from CARTITUDE-2 cohorts A and B, both with a median follow-up of ~29 months.

Methods: Patients in cohorts A and B, all naive to CAR-T and/or anti-BCMA therapies, received a single cilta-cel infusion (target dose 0.75×10^{6} CAR+ viable T cells/kg) 5-7 days after lymphodepletion. In both cohorts, the primary endpoint was minimal residual disease (MRD)-negativity (10^{-5} threshold, by next-generation sequencing or next-generation flow cytome-

try). Management strategies were implemented after the phase 1b/2 CARTITUDE-1 study to reduce risk of movement and neurocognitive treatment-emergent adverse events (MNTs).

Results: As of April 2023, 20 patients in cohort A had received cilta-cel (median follow-up, 29.9 months; 35% with high-risk cytogenetics; median 2 prior LOT; 95% refractory to last LOT; 40% triple-class refractory; 85% with prior ASCT). At the same data cut-off, 19 patients in cohort B hadreceived cilta-cel (median follow-up, 27.9 months; 16% with high-risk cytogenetics; 79% refractory to last LOT; 16% triple-class refractory; 79% with prior ASCT). All (100%) 17 MRD-evaluable patients in cohort A and 14 (93%) of 15 MRD-evaluable patients in cohort B achieved MRD negativity (10^{-5} threshold). Eight (40%) of 20 patients in cohort A and 10 (53%) of 19 patients in cohort B sustained MRD negativity at 10^{-5} for ≥6 months (Table 1). In the 20 patients in cohort A and 19 in cohort B, cilta-cel led to overall response rates of 95% (complete response or better [≥CR], 90%) and 100% (≥CR, 90%), respectively. Median PFS was not reached in either cohort, and 24-month PFS rates were 75% in cohort A and 73% in cohort B; respective 24-month overall survival rates were 75% and 84%. In cohort A, hematologic treatment-emergent adverse events (TEAEs) occurring between 17.1- and 29.9-month median follow-up included maximum grade (gr) 3/4 leukopenia in 1 patient (all gr,12 total; 60%), maximum gr 3/4 lymphopenia in 2 patients (all gr,16 total; 80%), and maximum gr 3/4 thrombocytopenia in 1 patient (all gr,16 total; 80%). In cohort B, no new patients reported hematologic TEAEs between 18.0- and 27.9-month median follow-up (Table 2). In cohort A, no new patients had CAR-T cell neurotoxicity, and no patients had a second primary malignancy (SPM). In cohort B, no new patients had MNTs, but other neurotoxicity (gr 2 sensory loss) occurred in 1 additional patient (all gr, 5 total; 26%) and resolved; and SPM (gr 4 choroid melanoma) occurred in 1 additional patient (all gr, 2 total; 11%). One new death (total 5) occurred in cohort A on day 666 due to progressive disease, and 1 new death (total 4) occurred in cohort B on day 749 due to cardiac arrest (not treatment related).

Conclusions: These longer-term follow-up data show that patients treated with cilta-cel in earlier LOT, both those with len-refractory MM after 1-3 LOT (cohort A) and those with early relapse (cohort B), experienced deep and durable responses. No new CAR-T-related safety signals, except for 1 additional CAR-T cell neurotoxicity in cohort B, were reported. Cohort A provides insight into potential longer-term survival outcomes that may be expected in the phase 3 CARTITUDE-4 trial, which enrolled the same patient population but has shorter follow-up thus far. The long-term cohort B data highlight the durable efficacy of cilta-cel in patients who had early relapse; this is a functionally high-risk population for whom standard risk factors, including a high-risk cytogenetic profile, may not predict risk of relapse and for whom there is significant unmet need.

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TABLE 1: CARTITUDE-2 cohorts A and B efficacy

	Cohort A (N=20)	Cohort B (N=19)
Follow-up[a] (months), median (range)	29.9 (3.3–35.6)	27.9 (5.2–32.1)
Overall MRD negativity (10^{-5}), n[b,c] (%)	17 (100)	14 (93.3)
Sustained MRD negativity ≥6 months (10^{-5}), n (%)	8 (40.0)	10 (52.6)
Sustained MRD negativity ≥12 months (10^{-5}), n (%)	7 (35.0)	7 (36.8)
ORR, % (95% CI)	95.0 (75.1–99.9)	100.0 (82.4–100)
sCR, % (95% CI)	85.0 (62.1–96.8)	73.7 (48.8–90.9)
CR, % (95% CI)	5.0 (0.1–24.9)	15.8 (3.4–39.6)
VGPR, % (95% CI)	5.0 (0.1–24.9)	10.5 (1.3–33.1)
PR, % (95% CI)	0	0
DOR (months), median (95% CI)	NE (23.4–NE)	NE (23.7–NE)
24-month DOR rate, % (95% CI)	73.3 (47.2–87.9)	70.5 (42.5–86.7)
PFS (months), median (95% CI)	NE (12.9–NE)	NE (22.6–NE)
24-month PFS rate, % (95% CI)	75.0 (50.0–88.7)	73.3 (47.2–87.9)
OS (months), median (95% CI)	NE (21.9–NE)	NE (NE–NE)
24-month OS rate, % (95% CI)	75.0 (50.0–88.7)	84.2 (58.7–94.6)
Time to first response (months), median (range)	1.0 (0.7–3.3)	1.0 (0.9–9.7)
Time to best response (months), median (range)	3.3 (0.9–13.6)	5.1 (0.9–11.8)

[a]As of April 2023 data cut-off. [b]Of 17 MRD-evaluable patients in cohort A and 15 MRD-evaluable patients in cohort B. [c]Four patients in cohort A and 5 patients in cohort B who were MRD negative subsequently became MRD positive. CR, complete response; DOR, duration of response; MRD, minimal residual disease; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

TABLE 2: CARTITUDE-2 cohorts A and B cytopenias and adverse events of special interest

	Cohort A (N=20)		Cohort B (N=19)	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Treatment-emergent cytopenias, n (%)				
Neutropenia	19 (95.0)	19 (95.0)	18 (94.7)	17 (89.5)
Lymphopenia	16 (80.0)	16 (80.0)	9 (47.4)	9 (47.4)
Thrombocytopenia	16 (80.0)	8 (40.0)	11 (57.9)	5 (26.3)
Anemia	15 (75.0)	9 (45.0)	11 (57.9)	9 (47.4)
Leukopenia	12 (60.0)	12 (60.0)	6 (31.6)	6 (31.6)
AESI, n (%)				
CRS	19 (95.0)	2 (10.0)	16 (84.2)	1 (5.3)
CAR-T cell neurotoxicity	6 (30.0)	1 (5.0)	6 (31.6)	1 (5.3)
ICANS	3 (15.0)	0	1 (5.3)	0
Other neurotoxicities	3 (15.0)	1 (5.0)	5 (26.3)	1 (5.3)
MNT	0	0	1 (5.3)	1 (5.3)
Second primary malignancy	0	0	2 (10.5)	1 (5.3)

AESI, adverse events of special interest; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; MNT, movement/neurocognitive treatment-emergent adverse event.

Figure 1

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