MM - 1119

Arlocabtagene autoleucel (arlo-cel) in patients with heavily pretreated relapsed/refractory multiple myeloma: final analysis from the phase 1 study

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Study summary: phase 1 study (NCT04674813) — cohort A

How was the study designed?

Cohort A of this phase 1 study tested different doses of arlo-cel in adults who previously received at least 3 lines of therapy for relapsed/refractory multiple myeloma (RRMM)

Who took part in this study?

- 86 people who previously received 1 to 3 lines of therapy for their RRMM joined the study and had their white blood cells collected; 84 received arlo-cel
- 5 was the median number of previous treatments people had tried for their MM
- >76% of people did not respond to at least 3 different types of myeloma drugs taken before the study began

What were the key results of the study?

Safety: side effects were similar to previous reports of arlo-cel

- Few people had severe or disabling side effects such as infections or cytokine release syndrome
- Side effects in the skin, nails, and mouth related to arlo-cel were generally short-lived; most resolved with minimal treatment
- Some people experienced effects on their brain or nervous system

Efficacy: arlo-cel showed strong and long-lasting benefits

- **Overall response rate:** 87% of people responded to arlo-cel
- **Progression-free survival:** median 18.3 months without their myeloma getting worse
- **Overall survival:** 86% of people were alive 18 months after receiving arlo-cel

What ongoing trials are currently studying arlo-cel?

- QUINTESSENTIAL (NCT06297226): Phase 2 study: arlo-cel is being studied in people who previously received at least 4 types of treatments and had at least 3 lines of therapy
- QUINTESSENTIAL-2 (NCT06615479): Phase 3 study: arlo-cel is being compared with standard treatment in people who had previously received 1-3 lines of therapy, including lenalidomide

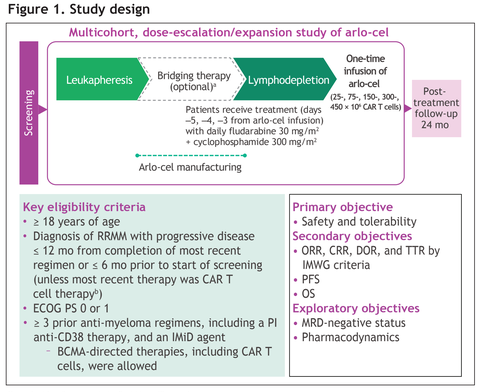
Background

- Multiple myeloma remains incurable, with frequent relapses and progressively shorter responses to subsequent therapies, including standard proteosome inhibitor (PI), immunomodulatory drug (IMID), anti-CD38, and anti-B-cell maturation antigen (BCMA)-targeting agents[1]
- Use of anti-BCMA-targeting therapies in earlier lines of treatment has expanded the BCMA-exposed patient population overall[2]
- G protein-coupled receptor class C group 5 member D (GPRC5D)-directing bispecifics are effective for BCMA-exposed patients[3]; however, gaps in duration of response, long-term outcomes, and toxicity management underscore a substantial unmet need
- Arlo-cel, a potential first-in-class chimeric antigen receptor (CAR) T cell therapy targeting GPRC5D, demonstrated deep and durable responses with well-tolerated safety in early- and late-line patients with RRMM[3-5]
- Here we report the final analysis (data cutoff date, February 17, 2026) from the first-in-human phase 1 trial of cohort A in heavily pretreated patients (≥ 3 prior lines of therapy [pLOT]) with RRMM

Methods

- This was an open-label, phase 1, multicohort, dose-escalation, dose-expansion trial of arlo-cel in patients with RRMM; cohort A included patients who had received ≥ 3 pLOT (NCT04674813; **Figure 1**)
- Safety and efficacy were assessed in all-treated patients who received arlo-cel
  - Overall response rate (ORR) and complete response rate (CRR) were assessed in the subpopulation evaluable for efficacy, which included all patients who received arlo-cel, had measurable disease at the most recent disease assessment prior to arlo-cel infusion, and had ≥ 1 post-infusion disease-response assessment

Figure 1. Study design



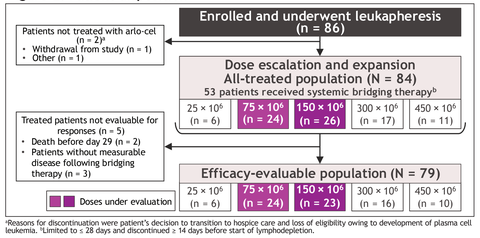
[a]If required for disease control. [b]Could be > 12 mo prior.
DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IMWG, International Myeloma Working Group; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; PS, performance status; TTR, time to response.

Results

Patients

- Of 86 enrolled patients, 53 (62%) patients received bridging therapy, and 84 (98%) received a one-time infusion of arlo-cel (**Figure 2**)
  - Arlo-cel manufacturing was successful for all patients (100%)
- For the efficacy-evaluable subpopulation (n = 79), across all dose cohorts the median (range) follow-up was 24.0 mo (3.8–38.4; **Figure 2**)
  - Median (range) follow-up was 24.2 mo (3.8–38.4) for the 75 x 10^6 dose cohort (n = 24)
  - Three patients in the 150 × 10^6 dose cohort were excluded because they lacked measurable disease at the most recent disease assessment and/or ≥ 1 post-infusion disease-response assessment; this exclusion did not affect the median (range) follow-up of 24.0 mo (4.6–36.0; n = 23)
- Among all patients who were treated with arlo-cel across all dose cohorts, the median (range) follow-up time was 24.0 mo (0.3–38.4)
  - Median (range) follow-up was 24.2 mo (3.8–38.4) for the 75 × 10^6 dose cohort (n = 24) and 24.0 mo (4.6–36.0) for the 150 × 10^6 dose cohort (n = 26)

Figure 2. Patient disposition



[a]Reasons for discontinuation were patient's decision to transition to hospice care and loss of eligibility owing to development of plasma cell leukemia. [b]Limited to ≤ 28 days and discontinued ≥ 14 days before start of lymphodepletion.

Baseline characteristics

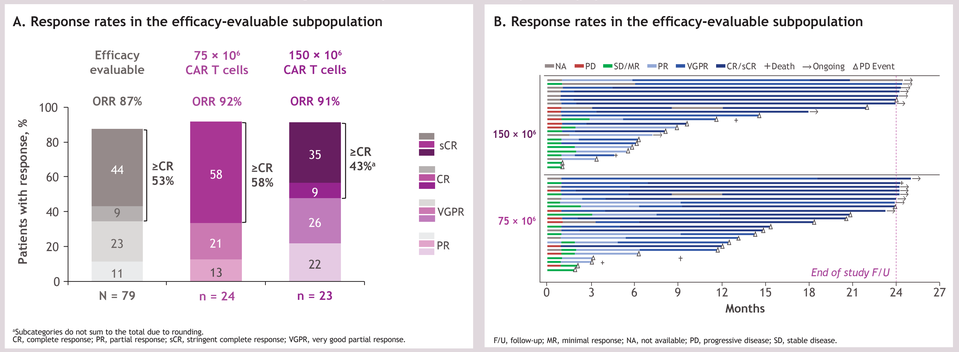
- Baseline characteristics were similar between the patients who received 75 × 10^6 and 150 × 10^6 CAR T cells (**Table 1**)

Safety

- In both dose cohorts, 100% of patients reported ≥ 1 treatment-emergent adverse event (TEAE; **Table 2**)
  - Hematological TEAEs were the most commonly reported class of adverse event in the 75 × 10^6 and 150 × 10^6 dose cohorts
- Grade 3/4 treatment-related adverse events (TRAEs) occurred in both dose cohorts (**Table 3**)
  - Cytokine release syndrome (CRS) was the most commonly reported TRAE; all events were grade 1/2 and resolved
  - Immune effector cell–associated neurotoxicity syndrome (ICANS) was infrequent, with one event in each dose cohort; both events resolved
  - Other select neurotoxicities (OSN) were rare and only occurred in the 150 × 10^6 dose cohort
- On-target, off-tumor (OTOT) TRAEs were similar between the 2 dose cohorts and most resolved with little to no intervention (**Table 4**).
  - For the 75 × 10^6 and 150 × 10^6 dose cohorts, the median (interquartile range, IQR) time to resolution was 12 (8-111) and 32 (21-93) days for skin events, respectively. 15.5 (7-36) and 167 (98–450) days for oral events, and 170 (159-227) and 96 (77–632) days for nail events
  - No weight-loss events occurred in the 75 × 10^6 dose cohort; in the 150 × 10^6 dose cohort, the median (interquartile range) time to resolution was 47 (5–164) days

Patients demonstrated deep, durable responses following a single infusion of arlo-cel

Figure 3. Response rates across patient populations



[a]Subcategories do not sum to the total due to rounding.
CR, complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
F/U, follow-up; MR, minimal response; NA, not available; PD, progressive disease; SD, stable disease.

Table 1. Patient baseline and disease characteristics

Characteristic	All treated (N = 84)	75 × 10^6 CAR T cells (n = 24)	150 × 10^6 CAR T cells (n = 26)
Age, median (range), y	63.0 (39–80)	62.5 (47–75)	63.0 (39–74)
Sex, male, n (%)	43 (51.2)	15 (62.5)	14 (53.8)
Primary race, n (%)			
White	56 (66.7)	18 (75.0)	19 (73.1)
Black or African American	14 (16.7)	1 (4.2)	3 (11.5)
Asian	4 (4.8)	0	2 (7.7)
Other[a]	10 (11.9)	5 (20.8)	2 (7.7)
High-risk cytogenetics, n (%)			
del(17p), t(4;14), and/or t(14;16)	37 (44.0)	10 (41.7)	13 (50.0)
del(17p)	27 (32.1)	6 (25.0)	12 (46.2)
1q21 amp/gain	47 (56.0)	14 (58.3)	16 (61.5)
Extramedullary plasmacytoma, n (%)	38 (45.2)	13 (54.2)	9 (34.6)
Time since diagnosis, median (range), mo	73.1 (8.5–205.0)	76.5 (25.2–205.0)	81.8 (15.6–138.2)
Prior myeloma regimens, median (range)	5 (3–15)	5 (3–15)	5 (3–14)
Prior BCMA-targeted therapy, n (%)	41 (48.8)	11 (45.8)	12 (46.2)
Refractory status to prior therapies,[b] n (%)			
Triple-class-refractory[c]	64 (76.2)	18 (75.0)	22 (84.6)
Penta-drug-refractory[d]	29 (34.5)	9 (37.5)	12 (46.2)
Most recent multiple myeloma regimen	69 (82.1)	22 (91.7)	24 (92.3)

Data cutoff: February 17, 2026. All-treated population. [a]Other included American Indian or or Alaska Native, Native Hawaiian or unknown race. [b]Refractory was defined as progression during or within 60 days of end of treatment or lack of response. [c]A PI, IMiD agent, and anti-CD38 antibody. [d]≥ 2 PIs, ≥ 2 IMiD therapies, and an anti-CD38 antibody.

Table 2. TEAEs

TEAE, n (%)	All treated (N = 84)		75 × 10^6 CAR T cells (n = 24)		150 × 10^6 CAR T cells (n = 26)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TEAE	84 (100.0)	78 (92.9)	24 (100.0)	21 (87.5)	26 (100.0)	24 (92.3)
Hematologic TEAEs[a]						
Neutropenia	67 (79.8)	62 (73.8)	16 (66.7)	15 (62.5)	22 (84.6)	19 (73.1)
Anemia	43 (51.2)	27 (32.1)	12 (50.0)	7 (29.2)	13 (50.0)	11 (42.3)
Thrombocytopenia	40 (47.6)	26 (31.0)	8 (33.3)	6 (25.0)	10 (38.5)	5 (19.2)
Non-hematologic TEAE[a]						
Hypokalemia	38 (45.2)	4 (4.8)	10 (41.7)	0	12 (46.2)	2 (7.7)
Headache	33 (39.3)	1 (1.2)	6 (25.0)	0	10 (38.5)	0
Fatigue	31 (36.9)	2 (2.4)	4 (16.7)	0	13 (50.0)	1 (3.8)
Hypocalcemia	29 (34.5)	2 (2.4)	6 (25.0)	0	7 (26.9)	0
Hypophosphatemia	28 (33.3)	2 (2.4)	6 (25.0)	0	11 (42.3)	1 (3.8)
Diarrhea	27 (32.1)	2 (2.4)	10 (41.7)	1 (4.2)	10 (38.5)	1 (3.8)
Nausea	27 (32.1)	1 (1.2)	2 (8.3)	0	8 (30.8)	1 (3.8)
Dysgeusia[b]	26 (31.0)	-	7 (29.2)	-	9 (34.6)	-
Infections and infestations	49 (58.3)	15 (17.9)	11 (45.8)	2 (8.3)	16 (61.5)	3 (11.5)

All-treated population. Medical Dictionary for Regulatory Activities (MedDRA) version: 28.1. [a]≥ 30% in all-treated population for any grade TEAEs. [b]Dysgeusia is limited to grades 1-2 per Common Terminology Criteria for Adverse Events. †Infections and infestations occurred in 45.8% and 61.5% of patients in the 75 × 10^6 and 150 × 10^6 dose cohorts, respectively; most commonly COVID-19 (12.5% and 11.5%), upper respiratory infection (8.3% and 11.5%), and pneumonia (4.2% and 11.5%).

Efficacy

- Within the overall efficacy-evaluable subpopulation (n = 79), ORR was 87% and CRR was 53%
  - ORRs were similar in the 75 × 10^6 and 150 × 10^6 dose cohorts (92% and 91%, respectively); CRRs were 58% and 43% (**Figure 3A**)
- For responders, the median (95% CI) DOR was 19.6 mo (13.3–23.0) and the median (IQR) TTR was 0.99 mo (0.95–1.0); responses were durable and deepened over time (**Figure 3B**)
- The median (95% CI) PFS was 18.3 mo (11.8–23.7) for the overall efficacy-evaluable population, and the 18-mo OS rate for the all treated population was 86.4% (**Figure 4A**)
  - In an exploratory analysis, PFS and OS appeared generally consistent between patients with and without prior BCMA-targeted therapies; no statistical comparisons were performed (**Figure 4B**)
- For the 75 × 10^6 and 150 × 10^6 dose cohorts, the sustained MRD-negativity rate (sensitivity level, 10^{-5}) in patients with ≥ CR was 35.7% (n = 14) and 45.5% (n = 22), respectively

Table 3. TRAEs of special interest

	All treated (N = 84)	75 × 10^6 CAR T cells (n = 24)	150 × 10^6 CAR T cells (n = 26)
Any TRAE, n (%)	79 (94.0)	22 (91.7)	25 (96.2)
Grade 3/4	62 (73.8)	18 (75.0)	18 (69.2)
CRS, n (%)	70 (83.3)	18 (75.0)	23 (88.5)
Grade 3/4	4 (4.8)	0	0
ICANS, n (%)	8 (9.5)	1 (4.2)	1 (3.8)
Grade 3/4	2 (2.4)	0	0
HLH, n (%)	3 (3.6)	0	0
Grade 3/4	3 (3.6)	0	0
OSN,[a] n (%)	10 (11.9)	0	3 (11.5)
Grade 3/4	6 (7.1)	0	2 (7.7)
OTOT event,[b] n (%)	41 (48.8)	11 (45.8)	14 (53.8)
Grade 3/4	0	0	0

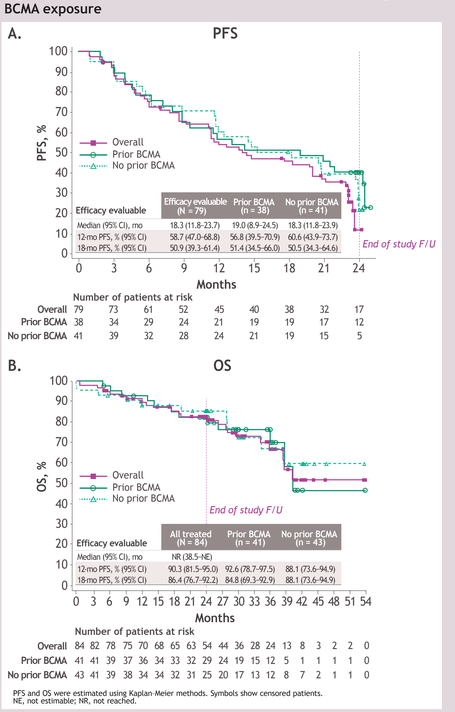
[a]Other select neruotoxicity includes ataxia, neurotoxicity, nystagmus, dysarthria, diplopia, dysmetria, and gait disturbance (excluding dizziness). There were no grade 4 events. [b]Cumulative events include selected preferred terms from skin and subcutaneous tissue disorders and tongue conditions (within gastrointestinal disorders), as well as ad hoc preferred terms lagenuia, dysphagia, dysgeusia, and taste disorder), and excluded preferred terms include night sweats, dermal cyst, hyperhidrosis, and skin mass.
All-treated population.
MedDRA version: 28.1. CTCAE version 5.0. CRS graded using Lee DW, et al.[4]
HLH, hemophagocytic lymphohistiocytosis.

Table 4. Select on-target, off tumor-events

	All treated (N = 84)	75 × 10^6 CAR T cells (n = 24)	150 × 10^6 CAR T cells (n = 26)
Skin			
With event	26 (31.0)	5 (20.8)	9 (34.6)
Grade 1	24 (28.6)	5 (20.8)	8 (30.8)
Grade 2	2 (2.4)	0	1 (3.8)
Resolved[a]	23 (88.5)	5 (100)	7 (77.8)
Oral			
With event	27 (32.1)	8 (33.3)	9 (34.6)
Grade 1	20 (23.8)	8 (33.3)	6 (23.1)
Grade 2	7 (8.3)	0	3 (11.5)
Resolved[a]	20 (74.1)	6 (75.0)	6 (66.7)
Nail			
With event	19 (22.6)	6 (25.0)	5 (19.2)
Grade 1	19 (22.6)	6 (25.0)	5 (19.2)
Grade 2	0	0	0
Resolved[a]	14 (73.7)	5 (83.3)	3 (60.0)
Weight loss			
With event	6 (7.1)	0	3 (11.5)
Grade 1	4 (4.8)	0	2 (7.7)
Grade 2	2 (2.4)	0	1 (3.8)
Resolved[a]	5 (83.3)	NA	3 (100)

[a]Percent resolved calculated based on patients with an event. Multiple events occurring within 1 day from each other are considered as 1 episode.
NA, not applicable.

Figure 4. PFS and OS in the (A) overall population and (B) by prior BCMA exposure



PFS and OS were estimated using Kaplan-Meier methods. Symbols show censored patients.
NE, not estimable; NR, not reached.

Conclusions

- In this final analysis of cohort A from the phase 1 study of arlo-cel for patients with heavily pretreated RRMM (≥3 prior pLOT), the safety profile was consistent with previous reports; no new safety signals were observed
  - The incidence of non-hematological TEAEs, high-grade infections, CRS, ICANS, and OTOT AEs was low
- Arlo-cel demonstrated deep and durable responses following a single infusion
  - Response rates were high: ORR, 87% (all efficacy-evaluable patients), 92% (75 × 10^6), and 91% (150 × 10^6)
  - Median PFS was 18.3 mo, and the 18-mo OS rate was 86.4%
- Arlo-cel elicited similar PFS and OS, regardless of prior BCMA exposure
- These results represent the longest follow-up of GPRC5D-targeted CAR T cell therapy and support arlo-cel as a potential efficacious treatment option for patients with RRMM regardless of prior BCMA exposure
- The ongoing phase 2 QUINTESSENTIAL (NCT06297226) and phase 3 QUINTESSENTIAL-2 (NCT06615479) are further exploring the use of arlo-cel in patients with RRMM

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