UNIVERSAL Updated Phase 1 Data Highlight Role of Allogeneic Anti-BCMA ALLO-715 Therapy for Relapsed/Refractory Multiple Myeloma

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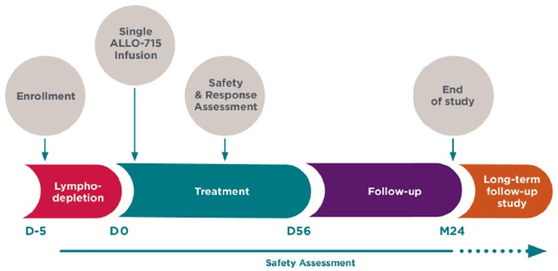
Background

- Autologous chimeric antigen receptor (CAR) T therapies have advanced the treatment of relapsed/refractory multiple myeloma (R/R MM).[1,2]
- Due to access and treatment delays, many patients may not benefit from these therapies. Allogeneic CAR T cell products may address access challenges and ensure eligible patients benefit.[1]
- ALLO-715 is a genetically modified anti–B-cell maturation antigen (BCMA) AlloCAR T™ cell therapy that uses TALEN® technology to disrupt the T-cell receptor alpha constant (TRAC) and the CD52 genes.
- The goal of intervention with ALLO-715 is to eliminate the risk of graft-versus-host disease (GvHD) and permit the use of ALLO-647, an anti-CD52 monoclonal antibody (mAb), for selective and transitory lymphodepletion (LD).
- UNIVERSAL is an open-label, multicenter (13 US centers), Phase 1 trial (NCT04093596) in adults with R/R MM. This report of UNIVERSAL Part A evaluates the safety, efficacy, cellular kinetics, immunogenicity, and pharmacodynamics of ALLO-715 with a focus on Dose Level 3 (DL3: 320 X 10^6 CAR+ T cells) following LD with two different ALLO-647-containing regimens (with ALLO-647 at 39 mg or 60 mg).

Methods

Design

Figure 1. UNIVERSAL Trial Design/Part A[a]



ALLO-715 Dose Escalation: 40, 160, 320, 480 x 10^6 CAR+ T cells	
Lymphodepletion Regimens (FCA[b], CA[c])	**Doses**
Fludarabine	30 mg/m^2/day x 3 days
Cyclophosphamide	300 mg/m^2/day x 3 days
ALLO-647	13 to 30 mg/day x 3 days

ALLO-715 dose expansion was at 320M CAR+ (DL3) using FCA39 and FCA60 LD regimens

Eligibility Criteria

• R/R MM	• ≥3 prior therapies including IMiD, proteasome inhibitor & anti-CD38
• Refractory to last prior therapy	• ECOG 0 or 1
• No donor-specific antibodies	• No prior systemic therapy within 2 weeks

Methods

Primary Endpoints

- Safety and dose-limiting toxicity (DLT)

Secondary Endpoints

- Recommended ALLO-715 Phase 2 dose and LD regimen
- Anti-tumor activity (ORR, duration of response, PFS, and MRD)
- ALLO-715 cellular kinetics (blood levels of anti-BCMA CAR T cells)
- ALLO-647 pharmacokinetics (serum ALLO-647 concentrations)

[a] Part B (combination of ALLO-715 + nirogacestat) and Part C (consolidation regimen) are not reported here; [b] FCA= conditioning with fludarabine/cyclophosphamide/ALLO-647; [c] CA=conditioning with cyclophosphamide/ALLO-647.

Study Population

- As of October 11, 2022, 59 patients were enrolled; 54 received LD and were treated with ALLO-715; 5 became ineligible due to organ failure from rapidly progressing disease
- Patients had advanced disease following prior therapies (Table 1).

Table 1. Patient Demographics, Disease Status, and Prior Therapies in DL3 Expansion

	DL3 (320 x 10^6 CAR+ T Cells)		
	N=28	**FCA39 (n=11)**	**FCA60 (n=17)**
Age, median (range), yrs	65 (49, 78)	66 (57, 77)	65 (49, 78)
Gender: Male / Female, %	64 / 36	64 / 36	65 / 35
ECOG PS: 0 / 1, %	50 / 50	55 / 46	47 / 53
ISS Stage III, %	25	0	41
High-Risk Cytogenetics*, %	25	27	29
Extramedullary Disease, %	29	36	24
High Tumor Burden at Screening†, %	25	36	18
Time Since Initial Diagnosis, median (range), yrs	7.2 (1.9, 26.4)	6.4 (2.5, 20.5)	8.1 (1.9, 26.4)
Prior Anti-Myeloma Regimens, median (range)	6 (3, 9)	8 (3, 9)	6 (3, 9)
Prior Autologous SCT, %	89	91	88
Penta-refractory, n (%)	25	36	24

* High-risk cytogenetics is defined as del 17p, t(4;14), or t(14;16)
† High tumor burden considered when more than 50% plasma cells in bone marrow

- Median time from enrollment to LD was 5 days.
- No patient required bridging therapy.
- 100% of infused product was manufactured and released as per product specifications.
- In the DL3 expansion cohorts, 24 (86%) were penta exposed.

Safety Results

- Cytokine release syndrome (CRS) occurred in 52% of patients; all were Gr 1/2 except 1 patient with Gr 3.
- The use of tocilizumab and steroids across all patients was 24% and 17%, respectively.
- Potential events of neurotoxicity were identified in 36 (67%) patients for whom all but one (2%) were Gr 1/2.
- Infections occurred in 59% of patients; Gr 3+ in 30% of patients.
- Of all infections, viral infections or low Gr viral reactivation were most common.
- No GvHD events were observed with any dose of ALLO-715 following ALLO-647-containing LD regimens (Table 2).
- A DLT event associated with ALLO-647 (CA 39) occurred and led to discontinuation of study participation in 1 (2%) patient; no DLTs were observed with ALLO-715.
- 3 Gr 5 infections were previously reported; no new Gr 5 events occurred since last report.

Safety Results

Table 2. Adverse Events of Special Interest (Safety Analysis Set)

TEAE of Interest* (N=54)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cytokine Release Syndrome	16 (30)	11 (20)	1 (2)	0 (0)	0 (0)	28 (52)
Neurotoxicity†	25 (46)	10 (19)	1 (2)	0 (0)	0 (0)	36 (67)
Graft-versus-Host Disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Infection‡	7 (13)	9 (17)	13 (24)	0 (0)	3 (6)	32 (59)
Infusion Reaction to ALLO-647	8 (15)	8 (15)	1 (2)	0 (0)	0 (0)	17 (31)

* Number of patients with AE occurring from the start of study drug up to subsequent anti-cancer therapy. For patients reporting more than one AE within a preferred term, only one AE with the maximum grade is reported
† Events of NT identified using Allogene MedDRA query, over 200 preferred terms (PT) selected to identify the medical concept of Neurologic toxicities including ICANs
‡ All infections (bacterial, fungal, and viral) included

- The absence of DLTs and data on overall safety profiles support the selection of two expanded DL3 cohorts (FCA39 and FCA60) for further study.

Efficacy Results

- Twenty-eight patients received DL3 at FCA39 or FCA60 with 23 patients included in the efficacy-evaluable population*.
- Five patients followed for less than 3 months are not included due to limited follow-up, with best responses ranging from SD to PR.

Table 3. Responses in Efficacy Evaluable Patients Followed ≥3 Months

Response Rates in Expansion Cohorts

Cell Dose	DL3 (320M CAR+ T Cells)		
LD Regimen	**FCA39 (n=11)**	**FCA60 (n=12)**	**Total (n=23)**
ORR†, n (%)	7 (64)	8 (67)	15 (65)
95% CI	31, 89	35, 90	43, 84
VGPR+‡ rate, n (%)	6 (54)	5 (42)	11 (48)
95% CI	23, 83	15, 72	27, 69
CR/sCR§ rate, n (%)	3 (27)	2 (17)	5 (22)
95% CI (%)	6, 61	2, 48	8, 44
Median DOR	8.3	9.2	8.3

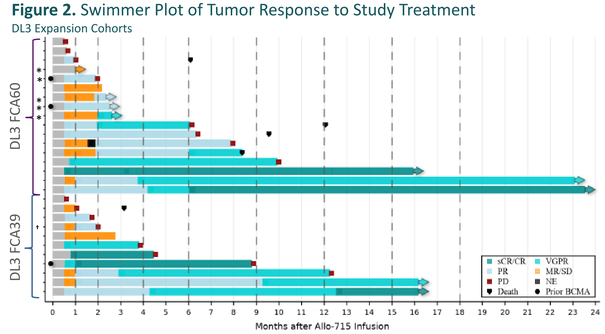
* Patients with minimum follow up of 3 months only.
† Overall response rate, confirmed; clinical response evaluation was based on International Myeloma Working Group (IMWG) response criteria.[3] An objective response is defined as a partial response or better.
‡ VGPR+ is very good partial response, complete response or stringent complete response, confirmed.
§ Complete response/stringent complete response.

- Through a median follow-up of 14.8 months in these patients, the ORR was 64% in the FCA39 cohort and 67% in the FCA60 cohort (Table 3).
- DL3 CAR+ T cell dose achieved durable responses in patients with R/R MM (Figure 2) with a median DOR of response of 8.3 and 9.2 months in DL3 FCA39 and DL3 FCA60, respectively.
- All DL3 patients that achieved a VGPR+ response achieved MRD negative status
- Responses were seen across all subgroups including patients with high-risk cytogenetics and extra medullary disease (Figure 3).

ALLO-715 (BCMA) utilizes TALEN® gene-editing technology pioneered and owned by Cellectis. Allogene has an exclusive license to the Cellectis technology for allogeneic products directed at this target and holds all global development and commercial rights for this investigational candidate.

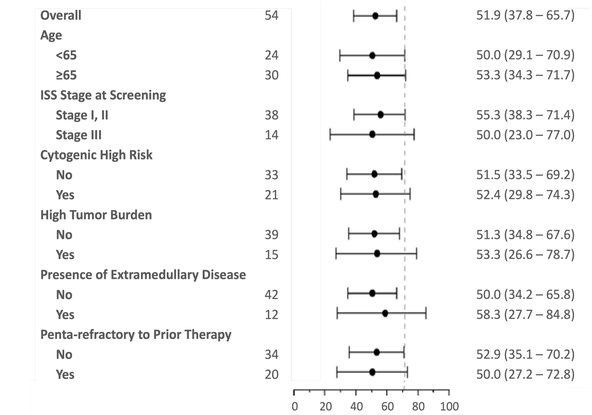
Efficacy Results

Figure 2. Swimmer Plot of Tumor Response to Study Treatment



* Followed for <3 months and not included on response analysis
† Unconfirmed response of Partial Response; Best Overall Response was stable disease

Figure 3. Forest Plot of Response by Subgroups



Conclusions

- 92% of enrolled patients received product with 100% of infused product manufactured and released as per product specifications.
- Median time of 5 days from enrollment to LD; no patients required bridging therapy.
- ALLO-715 and ALLO-647 demonstrated manageable safety profiles on par with autologous CAR T therapies.[4]
- UNIVERSAL demonstrates significant and durable responses from allogeneic CAR T therapy with ongoing responses up to 24 months.
- A dose of 320 million cells with FCA conditioning appears promising; 100% of VGPR+ patients achieved MRD negative status and this dose deserves further exploration.

References: 1. Rendo MJ, et al. *Blood Lymphat Cancer*. 2022;12:119-136. 2. Keller AL. *Front Oncol.* 2022;12:925818. 3. Kumar S, et al. *Lancet Oncol.* 2016;17: e328-e346. 4. Abecma and Carvykti USPI.

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Data Cutoff Date: October 11, 2022