Safety and PK/PD of ALLO-647, an Anti-CD52 Antibody, With Fludarabine (Flu)/Cyclophosphamide (Cy) for Lymphodepletion in Allogeneic CAR T Cell Therapy

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Background

- Allogeneic chimeric antigen receptor (CAR) T cell therapy is an off-the-shelf CAR T that holds promise in addressing the logistical and manufacturing challenges of autologous CAR T cell therapy
- Allogene's platform uses TALEN® gene editing to knocks out the TCRα constant gene which may reduce graft-versus-host disease (GvHD)*, and edits CD52 to permit the use of ALLO-647
  - ALLO-501 and ALLO-501A are anti-CD19 allogeneic CAR Ts; ALLO-501A removes rituximab recognition domain
  - ALLO-715 is an anti-BCMA allogenic CAR T
- ALLO-647 is a humanized anti-CD52 monoclonal antibody used to selectively deplete CD52 positive host lymphocytes

Methods

Study Design and Patient Population

- Three studies (ALPHA, ALPHA2, and UNIVERSAL) were included in the analyses. For complete study details, please scan the QR code
- ALPHA (NCT03939026) is a Phase 1 study evaluating ALLO-501 in adults with R/R large B cell lymphoma (LBCL) or follicular lymphoma (FL)
- ALPHA2 (NCT04416984) is a Phase 1/2 study evaluating ALLO-501A in adults with R/R LBCL
- UNIVERSAL (NCT04093596) is a Phase 1 study of ALLO-715 in adults with R/R multiple myeloma (MM)
- Most pts received ALLO-647 on Days -5, -4 and -3 in combination with Cy 300 mg/m^2/d +/- Flu 30 mg/m^2/d (FCA; n=69)
- Two other cohorts were treated with CA only (n=6) or a staggered regimen of FCA (n=13), as described via the QR code
- In the consolidation cohort, pts received FCA60 followed by the first cell infusion and ALLO-647 30 mg and a second cell infusion if D28 response was ≥SD

Objectives

- Evaluate safety and PK of ALLO-647
- Evaluate PD effects on host T cells, IL-15, CAR T cell expansion, and clinical response

Results

Table 1. Patient Flow

n	Multiple Myeloma: UNIVERSAL (N=34)		NHL: ALPHA (N=41) & ALPHA2 (N=13)	
ALLO-647 Dose	FCA	CA	FCA	FCA-staggered
39 mg	16	6	11	0
60 mg	9	0	13	1
90 mg**	3	0	17	12

Patient Characteristics

- All trials enrolled heavily pretreated pts with advanced stage disease
- 91% of the myeloma patients were penta-exposed, and 50% were penta-refractory; 64% of lymphoma pts were chemorefractory
- Additional pt characteristics are available via the QR code and in abstract 2529

*Using TALEN® gene editing is a technology pioneered and controlled by Cellectis.
**One subject in the 90 mg group was treated with 70 mg.

Results

Table 2. Adverse Events

n (%)	Multiple Myeloma: UNIVERSAL (N=34)			NHL: ALPHA (N=41) & ALPHA2 (N= 13)			
ALLO-647 Dose	39 mg (n=22)	60 mg (n=9)	90 mg (n=3)	39 mg (n=11)	60 mg (n=14) FCA60 & C (n=14)	60 mg (n=14) C† (n=9)	90 mg (n=29)
All TEAEs††	22 (100)	9 (100)	3 (100)	11 (100)	13 (93)	8 (89)	29 (100)
Grade ≥3 AEs	18 (82)	9 (100)	3 (100)	10 (91)	10 (71)	6 (67)	25 (86)
Serious AEs/ALLO-647	2 (9)	3 (33)	-	-	2 (14)	1 (11)	7 (24)
All Infection‡	12 (55)	6 (67)	1 (33)	7 (64)	4 (29)	3 (33)	21 (72)
Grade ≥3 Infection‡	5 (23)	4 (44)	-	1 (9)	2 (14)	1 (11)	8 (28)
Infusion-Related Reaction to ALLO-647 (All Grades)	6 (27)	2 (22)	1 (33)	5 (45)	6 (43)	4 (44)	20 (69)
Grade ≥3 Hematologic AEs							
Anemia	7 (32)	2 (22)	-	2 (18)	3 (21)	-	12 (41)
Thrombocytopenia	6 (27)	3 (33)	1 (33)	3 (27)	5 (36)	2 (22)	14 (48)
Neutropenia	11 (50)	6 (67)	2 (67)	9 (82)	8 (57)	4 (44)	21 (72)

Safety Results

- Myelosuppression was observed as a consequence of lymphodepletion (Table 2)
- ALPHA and ALPHA2 had no Grade 5 events associated with lymphodepletion
- UNIVERSAL had two Grade 5 events
  - Fungal pneumonia related to progressive myeloma and conditioning regimen with cyclophosphamide and ALLO-647
  - Adenoviral hepatitis in a 78-year-old male, heavily pretreated and with ongoing lymphopenia and adenovirus reactivation
- Consolidation (C) dosing was well tolerated

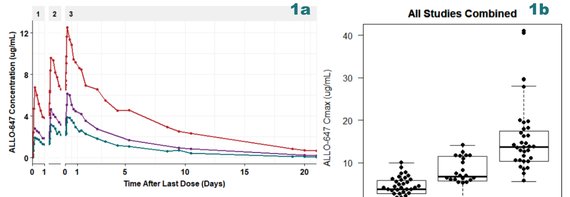
Pharmacokinetics (PK)§

- Serum ALLO-647 concentration increased with applied dose (Figure 1a,b), as did C_{max} and AUC (Figure 1b and Table 3)
- ALLO-647 was best described via a two-compartment PK model, which included a saturable (concentration-dependent) elimination pathway
- Clearance (CL) increased with increasing baseline absolute lymphocyte count (ALC) and decreased with increasing dose of ALLO-647
- Body weight, age, race, and ethnicity were not found to be significant covariates of clearance
- Trend toward lower concentration with higher baseline lymphocyte count was observed across all dose levels (Figure 2)

†C is a subset of FCA & 60 subjects that were enrolled to consolidation cohort.
††Number of patients with AEs 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.
‡All infections (bacterial, fungal, and viral) included.
§PK and PD calculations shown are based on modeled data from all three studies *Int J Clin Pharmacol Ther.* 1997 Oct;35(10):401-13.; *CPT Pharmacometrics Syst Pharmacol.* 2014 Jan;3(1):e88.

Results

Figure 1. ALLO-647 Exposure Increased with Dose



PK figures include 87 pts who received ALLO-647; one subject did not receive CAR T cells.

Table 3. ALLO-647 C_{max} and AUC¶ Increased with Dose

	39 mg	60 mg	90 mg**
N=87	33	22	32
C_{max} (ug/mL)	4 (65%)	7 (70%)	14 (42%)
AUC (ug/mL*d)	25 (121%)	50 (119%)	109 (65%)

Values in Table 3 represent geometric mean (geom CV%).

Figure 2. ALLO-647 Exhibits Target Mediated Drug Disposition

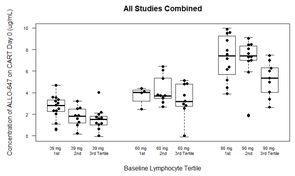


Table 4. Incidence of ALLO-647 Treatment Emergent ADAs – All Studies Combined

ALLO-647 Dose	ADA (N)	C_{max} (ug/mL)	AUC (ug/mL*d)
39 mg	No (25)	5 (2)	37 (32)
	Yes (8)	4 (1)	28 (13)
60 mg	No (22)	8 (3)	63 (36)
90 mg	No (31)	15 (7)	127 (71)
	Yes (1)	16 (NA)	145 (NA)

Values in Table 4 represent arithmetic mean (SD).

- In the ALPHA/ALPHA2 studies, no subjects developed treatment emergent anti-drug antibodies (ADA) against ALLO-647
- In the UNIVERSAL study, 26.4% of subjects developed ADAs, but they did not affect systemic exposure

Pharmacodynamics (PD)

- LD was deeper and longer with higher ALLO-647 AUC (Figure 3)
- A positive correlation was observed between ALLO-647 AUC and IL-15 C_{max}# (Figure 4)
- ALLO-647 AUC was associated with higher CAR T expansion (Figure 5)
  - Expansion is defined as any post-CAR T infusion (beyond D0) with a quantifiable concentration (>50 copies/ug)
- ALLO-647 AUC was associated with clinical response (VGPR+ or better for MM and CR for NHL^ [Figure 6])

¶ALLO-647 AUC is defined as area under the modeled concentration-time curve from the time of first infusion until 28 days post CAR T sample.
#IL-15 C_{max} calculated from time of first ALLO-647 infusion to Day 7 post CAR T infusion.
^Clinical response evaluation was based on IMWG response criteria, Kumar et al. 2016; NHL Lugano 2014.

Results

Figure 3. Higher ALLO-647 Exposure Associated with Deeper/Longer LD

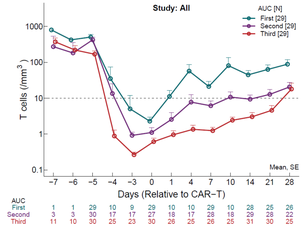
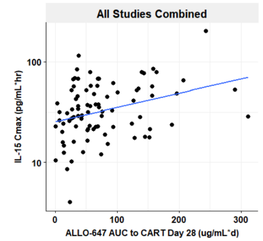


Figure 4. Higher ALLO-647 Exposure Associated with Higher IL-15 Blood levels



First, second and third represent tertiles in Figure 3.

Figure 5. ALLO-647 Associated with Probability of Expansion

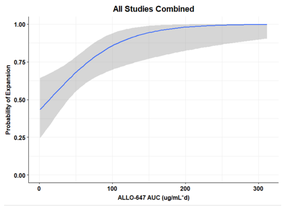
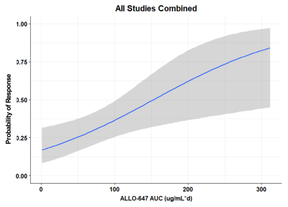


Figure 6. ALLO-647 Associated with Probability of Response



Gray shaded area in Figures 5 and 6 represent the 95% CI; Consolidation pts were excluded from these graphs.

Conclusions

- ALLO-647, when used in combination with Flu/Cy, had a manageable safety profile and produced an exposure-dependent deep and durable period of lymphodepletion, providing a window of opportunity for allogeneic CAR T tumor killing
- ALLO-647 exhibited target-mediated drug disposition; clearance increased with increasing baseline lymphocyte count, and decreased with increasing dose of ALLO-647
- Across the three studies and across cell doses, ALLO-647 exposure trended with
  - Higher IL-15 levels
  - Higher CAR T expansion
  - A greater clinical response

Acknowledgements: ALLO-501, 501A and 715 are allogeneic CAR Ts (AlloCAR T™) that use Cellectis technology. Allogene has an exclusive license to Cellectis technology for allogeneic products directed at BCMA and holds all global development and commercial rights for ALLO-715. ALLO-501/501A are anti-CD19 AlloCAR T therapies being jointly developed under a collaboration agreement between Servier and Allogene based on an exclusive license granted by Cellectis to Servier. Servier grants to Allogene exclusive rights to ALLO-501/501A in the U.S. while Servier retains exclusive rights for all other countries.

For questions or comments, please e-mail Michael.Tees@HealthONECares.com.

Data Cutoff Date: April 19, 2021.