ALPHA Study: ALLO-501 Produced Deep and Durable Responses in Patients with Relapsed/Refractory Non-Hodgkin's Lymphoma, Comparable to Autologous CAR

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Background

- Allogeneic (off-the-shelf) chimeric antigen receptor (CAR) T cell therapy is promising to bring the curative power of CAR T to more patients quickly
- ALLO-501 is a genetically modified anti-CD19 AlloCAR T cell product with rituximab recognition domains. ALLO-501 uses TALEN®* gene editing to disrupt the T-cell receptor alpha (TCRα) constant domain gene and the CD52 gene with TALEN to reduce the risk of graft-versus-host disease (GvHD) and permit the use of ALLO-647 (anti-CD52 humanized monoclonal antibody [mAb]) for host lymphodepletion (LD)
- Data from ALLO-501 support development of ALLO-501A, which excludes rituximab recognition domains

Methods

Design

- Phase 1 open-label, multicenter dose escalation study in patients (pts) with relapsed/refractory large B-cell lymphoma (R/R LBCL) or follicular lymphoma (FL) after ≥2 prior lines of therapy
- Following LD with ALLO-647 (39, 60, or 90 mg), fludarabine 30 mg/m^2/d x 3d (Flu), and cyclophosphamide 300 mg/m^2/d x 3d (Cy), escalating doses of ALLO-501 (40, 120, or 360 x 10^6 viable CAR T cells [DL1, DL2, and DL3]) were given. For pts receiving one ALLO-501 dose, retreatment was allowed
- For consolidation, following LD with ALLO-647 (60 mg), fludarabine 30 mg/m2/d x 3d (Flu), and cyclophosphamide 300 or 500 mg/m2/d x 3d (Cy), first dose of 120 x 10^6 viable CAR T+ cells was administered on day 0
  - For pts who achieved ≥stable disease (SD) at D28, 30 mg ALLO-647 was given followed by a second CAR T dose of 120 x 10^6 viable CAR T+ cells

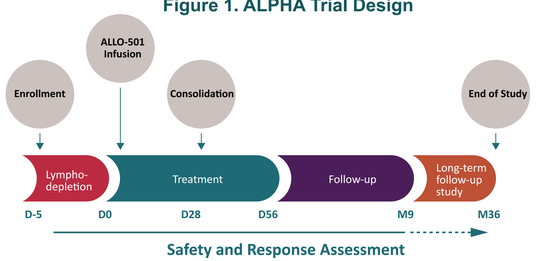
Inclusion Criteria

- R/R LBCL or FL
- Failed ≥2 prior lines of therapy, including an anti-CD20 mAb
- ECOG Performance Status of 0 or 1

Exclusion Criteria

- Prior autologous CAR T as reflected in protocol amendment
- Donor (product)-specific anti-HLA antibodies and baseline rituximab >15 ng/mL

Figure 1. ALPHA Trial Design



Primary Endpoints

- Safety and dose-limiting toxicity of ALLO-647/Flu/Cy followed by ALLO-501

Secondary Endpoints

- Objective response rate (ORR), complete response rate (CR), duration of response (DOR), progression free survival, overall survival
- ALLO-501 cell kinetics
- ALLO-647 pharmacokinetics

*TALEN® gene editing is a technology pioneered and controlled by Cellectis.

Study Population

- As of October 18, 2021, 50 pts were enrolled; 38 were in the single-dose cohort and 11 in the consolidation cohort; 1 pt was not assigned at data cut
- Pts had advanced-stage disease (Stage III: 18 [37%], Stage IV: 28 [57%]) and were heavily pretreated (median of 4 prior lines [range 2-12]) (Table 1)
- In the study, 18% of pts were R/R after prior auto CAR T therapy; 53% were chemo refractory (never achieved PR or better or relapse within a year)

Table 1. Patient Disposition, Demographics, and Disease Characteristics

	DL1 40M (N=4)	DL2 120M (N=16)	DL3 360M (N=18)	Consol (N=11)	All patients (N=49)
Mean age (yrs)	56	62	57	65	60
Stage IV disease (%)	75	56	50	64	57
ECOG baseline of 0/1 (%)	75/25	50/44	28/72	27/73	39/59
Baseline LDH > ULN (%)	50	69	67	18	55
Baseline LDH > 2x ULN	50	25	22	0	20
IPI score ≥3 (%)	25	50*	50*	27*	43*
Median # prior regimens	3	4	4	6	4
Median baseline spd mm^2	2296	1698	1348	3354	1768
Double or triple hit (%)	0	13	22	18	16
Diffuse LBCL (%)	0	38	22	18	25
Follicular lymphoma (%)	25	50	50	73	53

*3 pts missing IPI score in DL2, 1 pt missing IPI score in DL3, 3 pts missing IPI score in C1+C2.

Safety Results

- No dose-limiting toxicities (DLTs) or GvHD was observed (Table 2)
- 2 pts (4%) experienced Grade (Gr) 3+ immune effector cell-associated neurotoxicity syndrome (ICANS) and 2 pts (4%) experienced Gr 3+ CRS, all resolved
- Cytopenias were the most common adverse event (AE) and occurred in 84% of pts; 80% of pts had maximum grade AEs of Gr 3+
- Gr 3+ infections occurred in 13 pts (27%)
- As previously reported, 5 pts died after treatment not related to PD

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

%	DL1 40M (N=4)	DL2 120M (N=16)	DL3 360M (N=18)	Consol (N=11)	All patients (N=49)
IRR	50	69	61	64	63
CRS	0	31	33	27	29
Neurotoxicity*	25	25	22	36	27
GvHD	0	0	0	0	0
Infection	75	63	61	64	62
Serious TEAE (%)	25	56	28	27	37

*Neurotoxicity using SMQ search strategy.

Table 3. Gr 3+ Treatment Emergent Hematological AEs (Safety Analysis Set)

	DL1 40M (N=4)		DL2 120M (N=16)		DL3 360M (N=18)		Consol (N=11)		All patients (N=49)	
%	All	Gr3+	All	Gr3+	All	Gr3+	All	Gr3+	All	Gr3+
Pts with any TEAE	100	100	75	75	83	72	91	91	84	80
Neutropenia	100	75	75	75	83	72	82	64	82	71
Anemia	75	25	50	25	61	39	55	27	57	31
Thrombocytopenia	75	50	38	25	67	50	45	27	53	37
Lymphopenia	50	50	25	19	28	28	36	36	31	29
Pancytopenia	0	0	0	--	6	6	0	0	2	2

Efficacy Results

- Efficacy in auto CAR T naïve pts (n=40) was evaluated in the modified-intent-to-treat (mITT) population and was nearly identical to the intent-to-treat (ITT) population. The ORR and CR rates were 75% and 53%, respectively (Table 4). Breakdown by dose level for FL and LBCL are included in Tables 5 and 6, respectively
- Among the 21 FL and 11 LBCL auto CAR naïve pts who had the opportunity to be followed for 6 months, 33% of FL and 36% of LBCL pts remained in CR at month 6
- The 12-mo estimated DOR rates were 22% (FL) and 44% (LBCL) with a median follow-up of 5.8 and 11.2 months, respectively
- Longest CR remains on study at 18+ months. All consolidation pts who responded remain in response with the longest response being a CR at month 7+ (Figure 2)
- Consolidation dosing has improved ORR and CR rates compared to single dosing in FL (Table 5). The small number of consolidated patients in LBCL precludes comparison with patients treated with single dose (Table 6)

Table 4. ORR for Auto CAR Naïve Patients by Disease Subtype

n (%)*	FL (N=26)	LBCL (N=14)	All patients (N=40)
ORR	21 (81)	9 (64)	30 (75)
95% CI	61, 94	35, 87	59, 87
CR	15 (58)	6 (43)	21 (53)
95% CI	37, 77	18, 71	36, 69

*Across all 49 pts including prior CAR T treated pts, the ORR and CR rates were 63% and 45%, respectively.

Table 5. ORR for FL Auto CAR Naïve Patients by Regimen

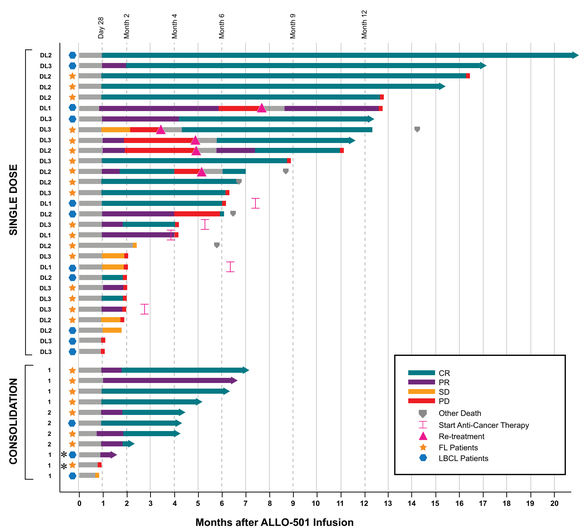
n (%)	DL1 40M (N=1)	DL2 120M (N=8)	DL3 360M (N=9)	Consol (N=8)
ORR	1 (100)	6 (75)	7 (78)	7 (88)
95% CI	3, 100	35, 97	40, 97	47, 100
CR	0	5 (63)	4 (44)	6 (75)
95% CI	0, 98	25, 92	14, 79	35, 97

Efficacy Results

Table 6. ORR for LBCL Auto CAR Naïve Patients by Dose Regimen

n (%)	DL1 40M (N=3)	DL2 120M (N=4)	DL3 360M (N=4)	Consol (N=3)
ORR	2 (67)	3 (75)	2 (50)	2 (67)
95% CI	9, 99	19, 99	7, 93	9, 99
CR	1 (33)	2 (50)	2 (50)	1 (33)
95% CI	1, 91	7, 93	7, 93	1, 91

Figure 2. Swimmer Plot of Tumor Response to Study Treatment for Auto CAR T Naïve Patients



*Did NOT receive consolidation dose

Conclusions

- This updated data continues to highlight that allogeneic anti-CD19 CAR T therapy can be safely and effectively delivered to pts with R/R NHL with encouraging durability of response
- Ninety-eight percent of pts enrolled were treated with ALLO-501 with a median of 5 days from enrollment to LD, supporting the ease and speed pts were able to be treated with AlloCAR T therapy
- No DLT or GvHD; 2 cases of Gr 3+ ICANS and CRS, all resolved. Infection rates were similar to that observed in autologous CAR T trials
- ALLO-501 responses remain on par with the response rate seen in autologous anti-CD19 CAR T with an ORR and CR rate of 75% and 53%, respectively
- Consolidation dosing demonstrated similar safety, and improved efficacy vs a single higher cell dose with an 82% ORR and 64% CR rate in 11 pts
- Longest CR remains on study at 18+ months
- In LBCL, the 6-month CR rate and 12-month duration of response was 36% and 44%, respectively. In FL it was 33% and 22%, respectively
- These results will inform the pivotal study that uses ALLO-501A, the next generation anti-CD19 CAR T that lacks the rituximab recognition domain

Acknowledgements: ALLO-501/501A are anti-CD19 allogeneic CAR T (AlloCAR T™) therapies being jointly developed under a collaboration agreement between Servier and Allogene based on an exclusive license granted by Cellectis to Servier. ALLO-501/501A uses Cellectis technologies. Servier grants to Allogene exclusive rights to ALLO-501/501A in the US while Servier retains exclusive rights for all other countries.

Data Cutoff Date: October 18, 2021.