**Allogeneic CAR T Cell Products Cemacabtagene Ansegedleucel/ALLO-501 in Relapsed/Refractory Large B-Cell Lymphoma: Phase 1 Experience From the ALPHA2/ALPHA Clinical Studies**

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**SUPPLEMENTARY APPENDIX**

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**Supplemental Methods**

*Patients*

Patients with current or history of central nervous system (CNS) lymphoma, or clinically significant CNS dysfunction were excluded from the study, as were patients receiving autologous hematopoietic stem cell transplant (HSCT) within last 6 months or allogeneic HSCT within last 6 months prior to ALLO-647 in ALPHA2 and autologous stem cell transplant within the last 6 weeks or allogeneic HSCT within the last 3 months prior to ALLO-647 in ALPHA.

Adequate organ function was defined as: bone marrow (absolute neutrophil count ≥1000 cells per µl, platelet count ≥50,000 cells per µl and absolute lymphocyte count ≥200 per for ALLO-501 and ≥300 cells per µl for cema-cel), renal function (estimated creatine clearance ≥50 mL/min in ALPHA2 and ≥60 mL/min in ALPHA) or directly measured with 24-hour urine collection), and liver function (total bilirubin ≤1.5 x the upper limit of normal (ULN); aspartate aminotransferase and alanine aminotransferase ≤3 x ULN; ≤5 x ULN if liver involvement by tumor).

Patients needed to have non-clinically significant donor-specific anti-HLA antibodies (DSA) from lots.

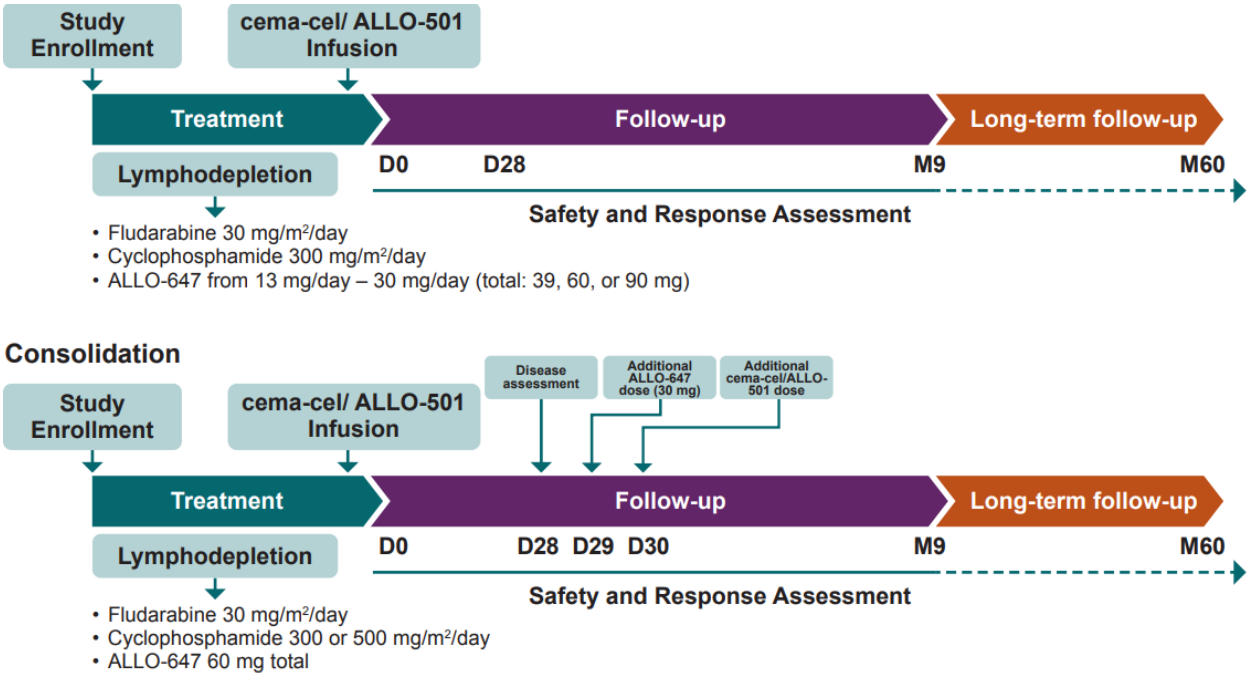
*Pharmacokinetics/Pharmacodynamics*

Pharmacokinetic/pharmacodynamic effects were examined to assess extent and effect of lymphodepletion with ALLO-647 in all treated patients with an available assessment. Allogeneic chimeric antigen receptor (CAR) T cell expansion was monitored using a whole transcriptome analysis used for comparisons for the level of lymphodepletion provided by ALLO-647; overall response was assessed by Lugano classification criteria.[1] Biospecimens were collected at various time points and examined as follows: ALLO-647 pharmacokinetic monitoring via enzyme-linked immunosorbent assay (ELISA), cellular kinetics samples were assayed via quantitative polymerase chain reaction (qPCR) measurement of transgene levels and using a validated flow cytometry assay. Blood draws for flow cytometry evaluation

were performed on Days 7, 10, 14, 21, 28, 42, 56, and at Month 4. Transgene levels were measured on Days 0, 1, 4, 7, 10, 14, 21, 28, 42, 56 and Month 4. In addition to the main sample collection, additional blood samples were collected from patients who experienced unexpected or serious adverse events to evaluate levels of CAR T cells.

Patients with available data (n=18) were retrospectively evaluated for high-resolution human leukocyte antigen-matching between CAR T cells at the allelic level.

**Supplemental Figure 1.** Study Design of ALPHA2/ALPHA




Regimens evaluated in phase 1 include: (1) LD followed by a single dose of cema-cel/ALLO-501 (120 x $10^6$ CAR+ cells) or (2) LD followed by a single dose of cema-cel/ALLO-501 and then an additional dose of ALLO-647 on D29 and ALLO-501/cema-cel on D30.

Cema-cel, cemacabtagene ansegedleucel; D, day; LD, lymphodepletion; M, month.



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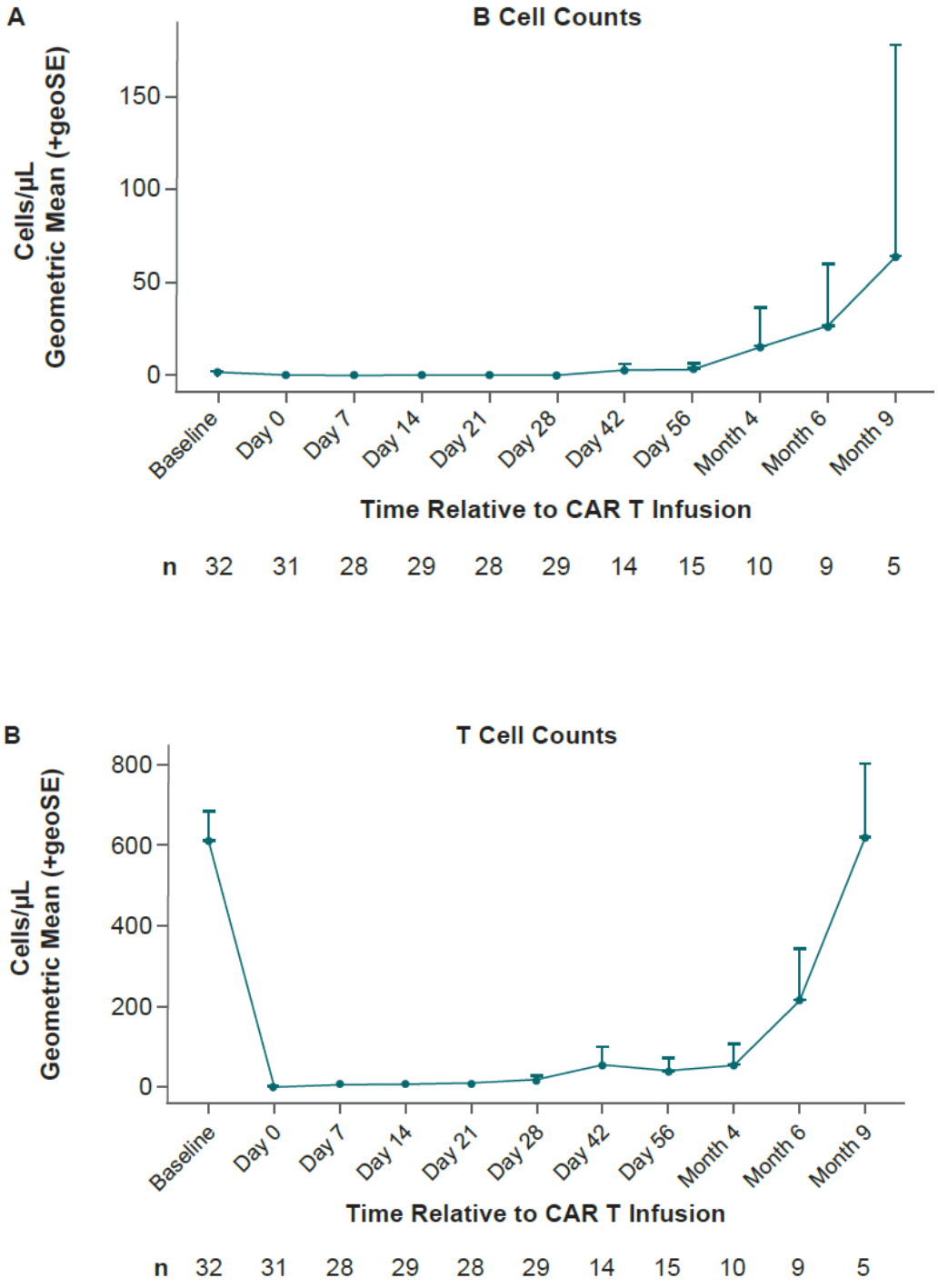
**Supplemental Figure 2.** B and T Cell Count Recoveries Over Time




CAR, chimeric antigen receptor; geoSE, geometric standard error



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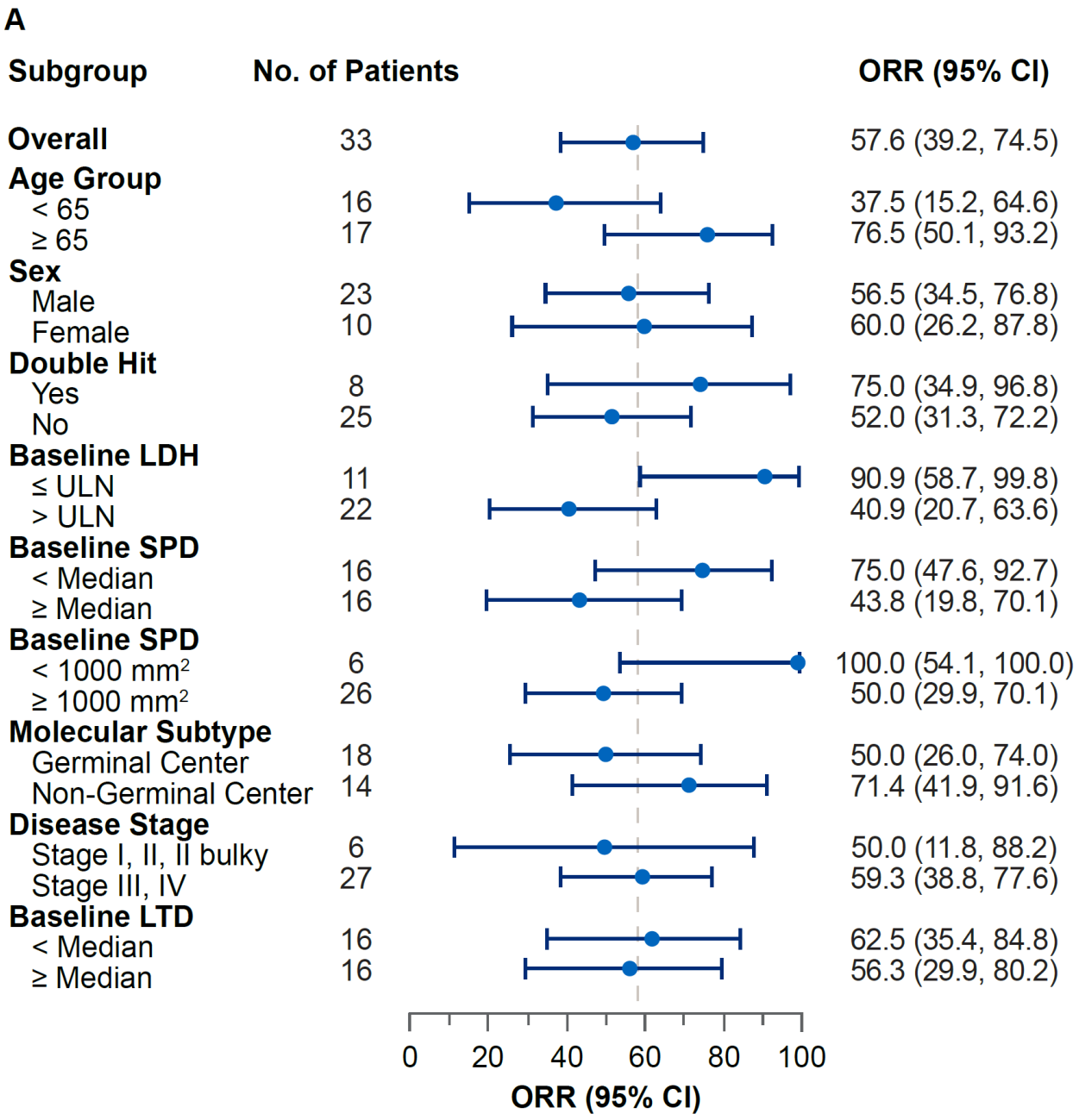
**Supplemental Figure 3.** Overall (A) and Complete Response (B) Rates by Subgroup



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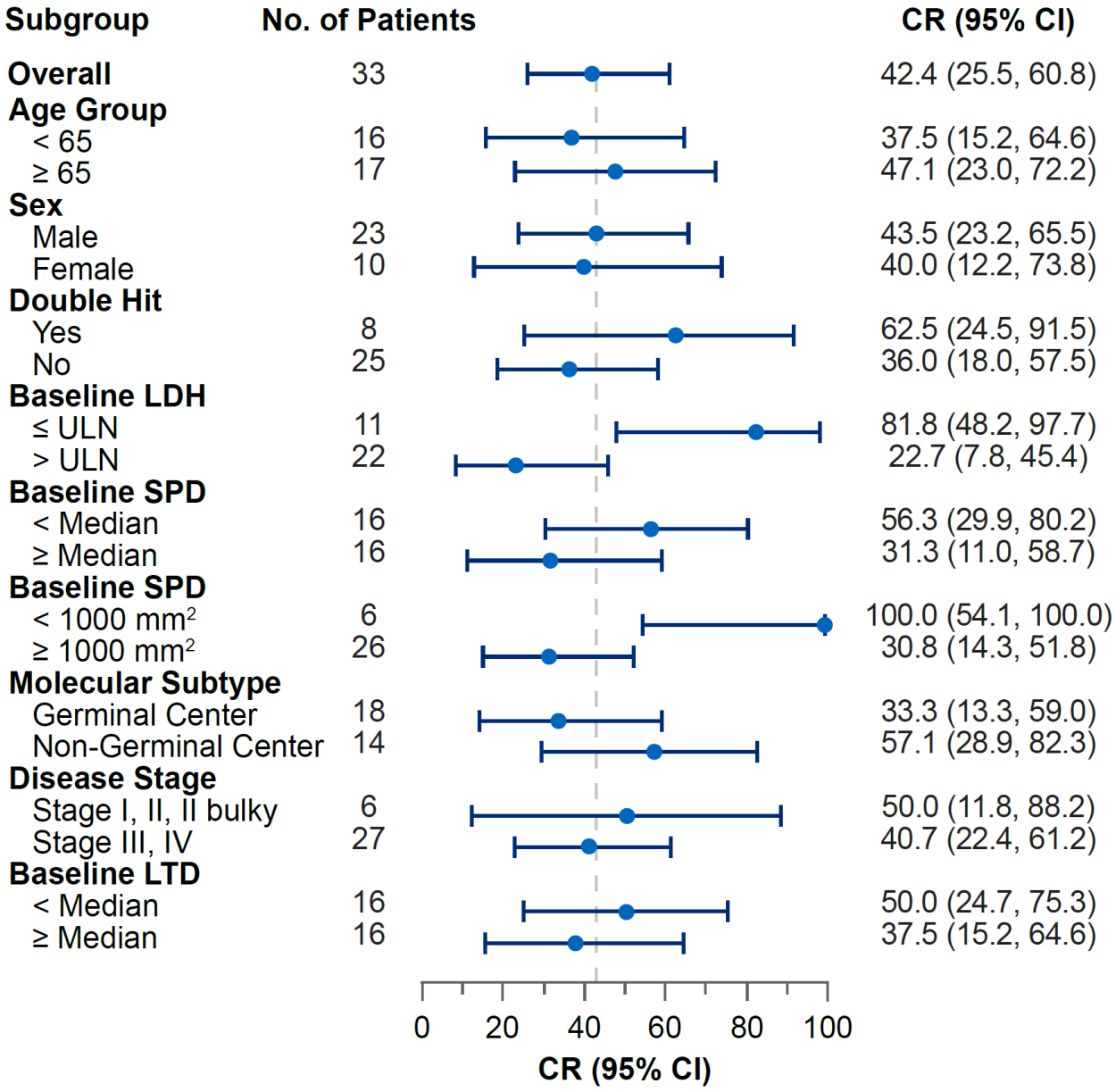
**B**




CR, complete response; LDH, lactate dehydrogenase; LTD, longest tumor diameter; ORR, overall response rate; SPD, sum of the products of longest diameters; ULN, upper limit of normal.



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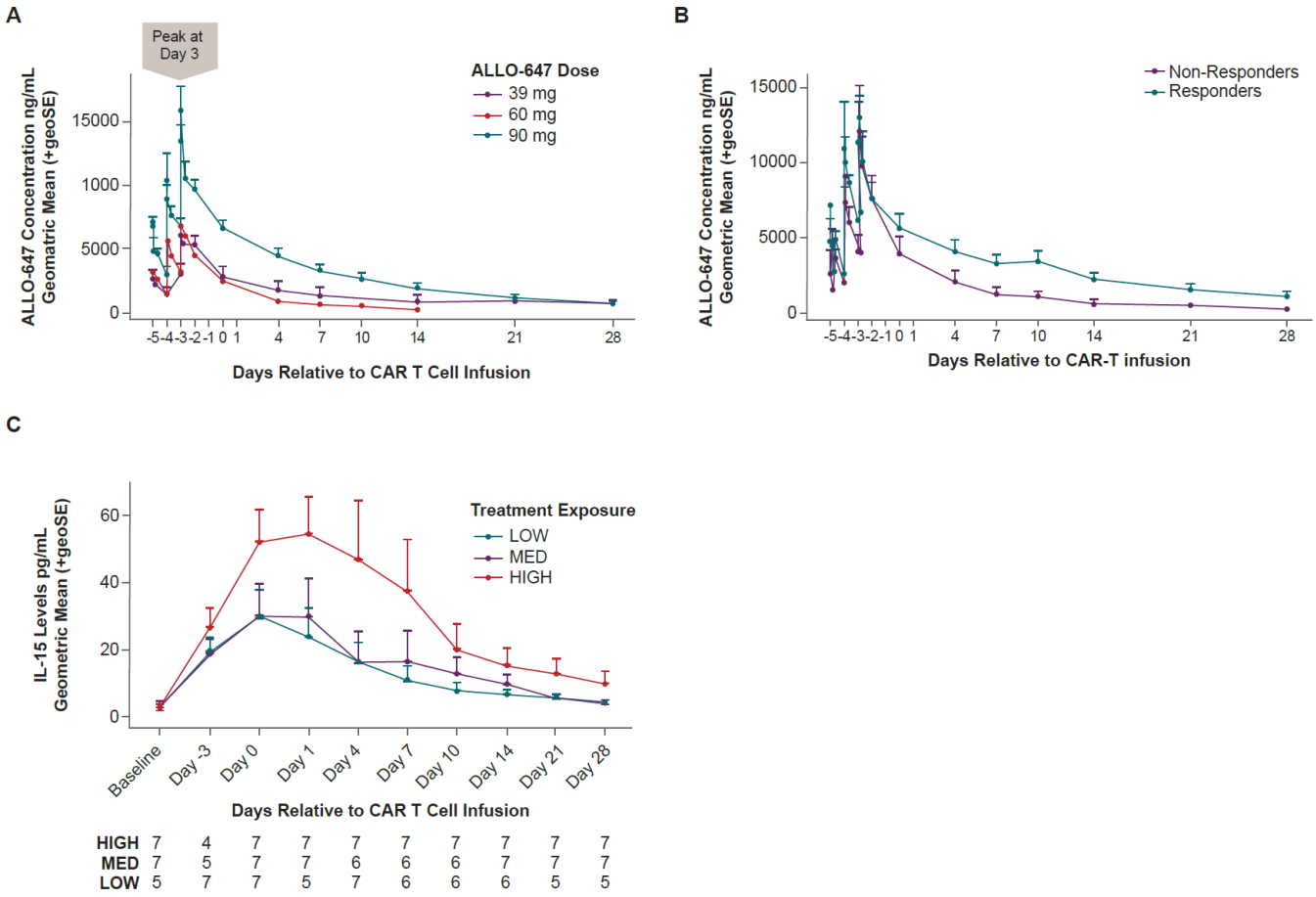
**Supplemental Figure 4. ALLO-647 Concentration Over Time By Dose and Response, and IL-15 Levels Over Time** (A) ALLO-647 concentration, by dose, versus time pre– and post–CAR T cell infusion (N=33); (B) ALLO-647 exposure in responders versus nonresponders; and (C) IL-15 levels by systemic ALLO-647 pharmacokinetic exposure




CAR, chimeric antigen receptor; geoSE, geometric standard error; IL-15, interleukin-1; MED, medium.

**Supplemental Table 1.** Most Common Infections (≥5% Any Grade)[a]

| | CAR T-Naive R/R LBCL | | | |
|---|---|---|---|---|
| n (%) | All patients (N=33) | | Patients who received selected phase 2 dose[b] (n=12) | |
| | Any Grade | Grade ≥3[c] | Any Grade | Grade ≥3[c] |
| Patients with any infection event | 19 (58) | 5 (15) | 8 (67) | 1(8) |
| Viral infections | 14 (42) | 4 (12) | 6 (50) | 1 (8) |
| Cytomegalovirus infection reactivation | 10 (30) | 4 (12) | 4 (33) | 1 (8) |
| COVID-19 | 2 (6) | 1 (3) | 1 (8) | 0 (0) |
| Metapneumovirus infection | 2 (6) | 0 (0) | 0 (0) | 0 (0) |
| Other infections | 9 (27) | 5 (15) | 3 (25) | 1 (8) |
| Pneumonia | 4 (12) | 3 (9) | 0 (0) | 0 (0) |
| Urinary tract infection | 3 (9) | 0 (0) | 3 (25) | 0 (0) |
| Bacteremia | 2 (6) | 2 (6) | 1 (8) | 1 (8) |
| Sepsis | 2 (6) | 2 (6) | 1 (8) | 1 (8) |
| Bacterial infections | 3 (9) | 2 (6) | 2 (17) | 1 (8) |
| Fungal infections | 2 (6) | 0 (0) | 2 (17) | 0 (0) |

[a] Patients receiving ALLO-647 were required to receive anti-infective prophylaxis as recommended by and dose/schedules according to international guidelines for patients receiving anti-CD52 monoclonal antibodies. These prophylactic treatments include fluoroquinolone prophylaxis during neutropenia (eg, ciprofloxacin, levofloxacin, or moxifloxacin) for bacterial infections, posaconazole or voriconazole for fungal infections, and TMP or SMX for *Pneumocystis jirovecii* prophylaxis from Day -5 until ANC of >500 cells/µL. In addition, after ALLO-647 and until CD4 count > 200 cell/µL (from Day −5 for a minimum of 2 months after ALLO-647), acyclovir, famciclovir, or valacyclovir was required for Herpes virus prophylaxis. In case of CMV reactivation, first line of preemptive therapy was to be administered (valganciclovir or ganciclovir). The infectious disease prophylaxis evolved over time.

[b] Fludarabine/cyclophosphamide lymphodepletion with 90-mg of ALLO-647 (FCA90).

[c] None of the Grade ≥3 infections were fatal.

ANC, absolute neutrophil count; CAR, chimeric antigen receptor; CMV, cytomegalovirus; LBCL, large B-cell lymphoma; R/R, relapsed/refractory.

**Supplemental Table 2**. Grade ≥3 Cytopenias Over Time[a]

| | CAR T-Naive R/R LBCL | |
|---|---|---|
| Time | **All patients (N=33)** | **Patients who received selected phase 2 dose[b] (n=12)** |
| Day 28, n (%) | 10 (30) | 3 (25) |
| Day 56, n (%) | 6 (18) | 2 (17) |
| Day 121 (Month 4), n (%) | 6 (18) | 2 (17) |

[a] Assessed in all enrolled patients who receive any study drug (safety analysis population). TEAEs include any AE occurring from the first dose of any study drug through the start of another treatment period, death, or the date prior to initiation of another anticancer agent, whichever came first. Grade ≥3 cytopenias include neutropenia, thrombocytopenia, anemia, or pancytopenia.
[b] Fludarabine/cyclophosphamide lymphodepletion with 90-mg of ALLO-647 (FCA90).
AE, adverse event; CAR, chimeric antigen receptor; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; TEAE, treatment emergent adverse event.

**Supplemental Table 3**. Most Common Serious TEAEs[a]

| | CAR T-Naive R/R LBCL | |
|---|---|---|
| n (%) | **All patients (N=33)** | **Patients who received selected phase 2 dose[b] (n=12)** |
| Pyrexia | 2 (6) | 1 (8) |
| Cytomegalovirus infection reactivation | 2 (6) | 1 (8) |
| COVID-19 | 2 (6) | 1 (8) |
| Bacteremia | 2 (6) | 1 (8) |
| Pneumonia | 2 (6) | 0 |
| Infusion-related reaction | 2 (6) | 0 |
| TEAEs leading to death<br>Treatment-related | 2 (6)[c]<br>0 | 0 (0)<br>0 |

[a] Assessed in all enrolled patients who receive any study drug (safety analysis population). TEAEs include any AE occurring from the first dose of any study drug through the start of another treatment period, death, or the date prior to initiation of another anticancer agent, whichever came first.
[b] Fludarabine/cyclophosphamide lymphodepletion with 90-mg of ALLO-647 (FCA90).
[c] Two patients (6%) had TEAEs that led to death (respiratory failure and torsade de pointes [n=1 each]). One patient had multiple organ dysfunction syndrome and one patient had pneumonia, both in the context of disease progression that led to death, but these were not TEAEs per protocol.
AE, adverse event; CAR, chimeric antigen receptor; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.



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**Reference**

1. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 32:3059-68, 2014.