ZUMA-19: A Phase 1/2 Multicenter Study of Lenzilumab Use With Axicabtagene Ciloleucel (Axi-Cel) in Patients With Relapsed or Refractory Large B Cell Lymphoma

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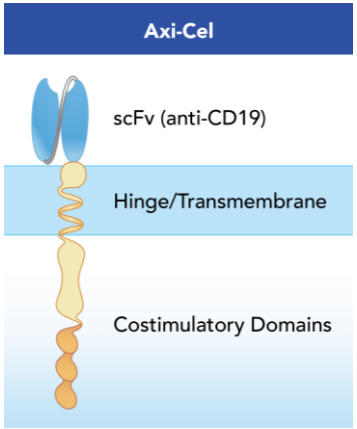
Background

- Axi-cel is an autologous anti-CD19 CAR T cell therapy approved for patients with R/R LBCL with ≥ 2 prior systemic therapies[1]
  - With a median follow-up of 27.1 months in the pivotal ZUMA-1 study, the ORR with axi-cel was 83% (58% CR rate) in patients with refractory LBCL[2]
    - Gr ≥ 3 CRS and NEs occurred in 11% and 32% of patients, respectively[2]
  - In an updated analysis with 51 months of follow-up in ZUMA-1, median OS was 25.8 months; 4-year OS rate was 44%[3]
- CRS can be ameliorated in some patients with the anti–IL-6 receptor antibody tocilizumab; however, NEs may be unaffected or worsened by tocilizumab[4-7]
- Mitigation strategies for NEs are complicated by significant associations between CAR T cell expansion and ORR as well as Gr ≥ 3 NEs[8]
  - Data from ZUMA-1 Cohort 4 suggested that earlier use of corticosteroids for immune system suppression in patients with mild NEs (Gr < 2) and low-grade CRS (Gr 1) may reduce the incidence of Gr ≥ 2 NEs without significant impact on efficacy (73% ORR; 51% CR; reactive strategy)[9]
  - The ZUMA-1 Cohort 6 primary analysis (median follow-up, 8.9 months) showed that prophylactic steroids reduced the rate of Gr ≥ 3 CRS to 0% and Gr ≥ 3 NEs to 13%, while achieving an ORR of 95% and a CR rate of 80% (proactive strategy)[10]
- Additional proactive strategies are needed to improve CAR T cell therapy safety without negatively affecting efficacy



1. YESCARTA® (axicabtagene ciloleucel) [PI]. Santa Monica, CA: Kite Pharma, Inc; 2020. 2. Locke FL, et al. *Lancet Oncol*. 2019;20:31-42. 31. 7. Locke FL, et al. *Blood.* 2017;130(suppl, abstr):1547. 8. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-2544. 9. Topp MS, et al. *Blood.* 2019;134(suppl, abstr):243. 10. Oluwole OO, et al. Manuscript in preparation.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; Gr, grade; IL, interleukin; LBCL, large B cell lymphoma; NE, neurologic event; ORR, objective response rate; PI, prescribing information. R/R, relapsed/refractory; scFv, single-chain variable fragment.

Rationale for GM-CSF Neutralization With CAR T Cell Therapy

- On tumor challenge, CAR T cells produce GM-CSF,[1] which promotes myeloid activation, expansion, and cytokine production[2]
- In ZUMA-1, GM-CSF was significantly associated with Grade ≥ 3 NEs[3]
  - GM-CSF levels peaked before most other cytokines, and no direct association was observed between GM-CSF levels and ORR[4]
  - This suggests that GM-CSF may initiate inflammatory events that cause NEs; therefore, GM-CSF inhibition has the potential to improve the safety of CAR T cells without affecting efficacy
- GM-CSF depletion with lenzilumab, a humanized mAb that neutralizes GM-CSF, prevented CRS and NEs in preclinical models of CAR T cell toxicity[5]
- The Phase 1/2 ZUMA-19 study is evaluating sequenced therapy with lenzilumab and axi-cel to abrogate risk of axi-cel–related CRS and NEs in patients with R/R LBCL (NCT04314843)

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; GM-CSF, granulocyte-macrophage colony-stimulating factor; LBCL, large B cell lymphoma; mAb, monoclonal antibody; NE, neurologic event; ORR, objective response rate; R/R, relapsed/refractory.

1. Giavridis T, et al. Nat Med. 2018;24:731-738. 2. Spath S, et al. Immunity. 2017;46:245-260. 3. Neelapu SS, et al. N Engl J Med. 2017;377:2531-2544. 4. Rossi JM, et al. EMA Workshop, 2016. 5. Sterner RM, et al. Blood. 2019;133:697-709.

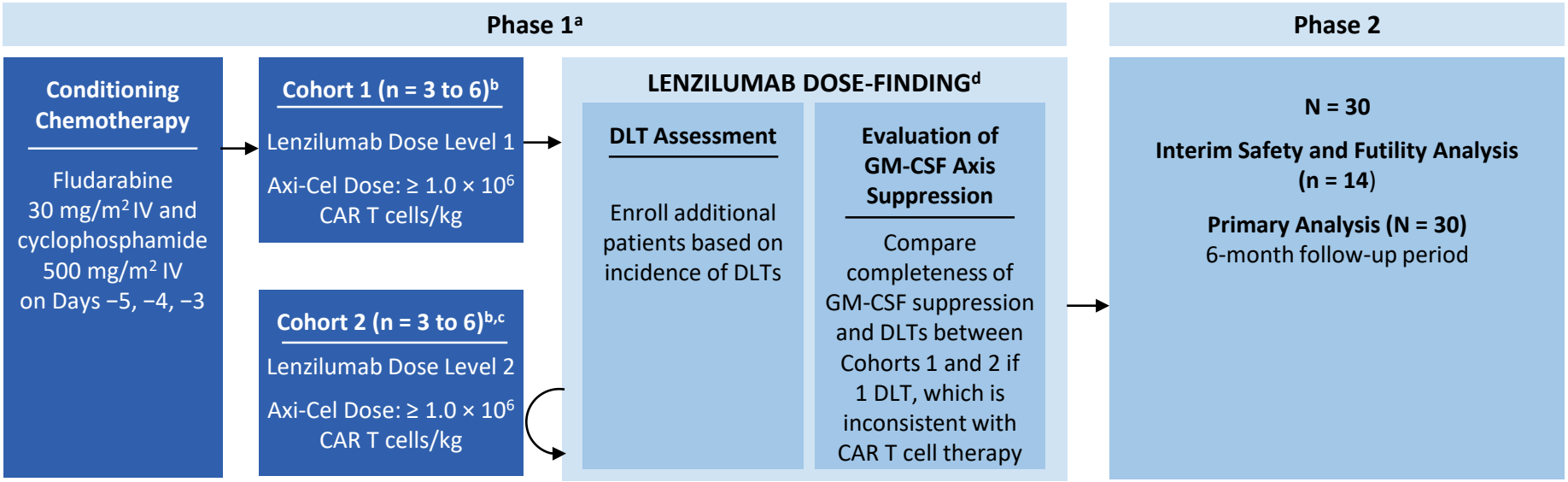
Objectives

- Primary objectives:
  - Phase 1: To evaluate the safety of sequenced therapy with lenzilumab and axi-cel in patients with R/R LBCL
  - Phase 2: To evaluate the incidence of Grade ≥ 2 NEs with sequenced therapy at the RP2D of lenzilumab in patients with R/R LBCL

- Secondary objectives:
  - To evaluate the safety and efficacy of sequenced therapy, the extent of GM-CSF axis suppression in the blood, and the levels of CAR T cells and cytokines in the blood

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor; LBCL, large B cell lymphoma; NE, neurologic event; R/R, relapsed/refractory; RP2D, recommended Phase 2 dose.

Study Schema

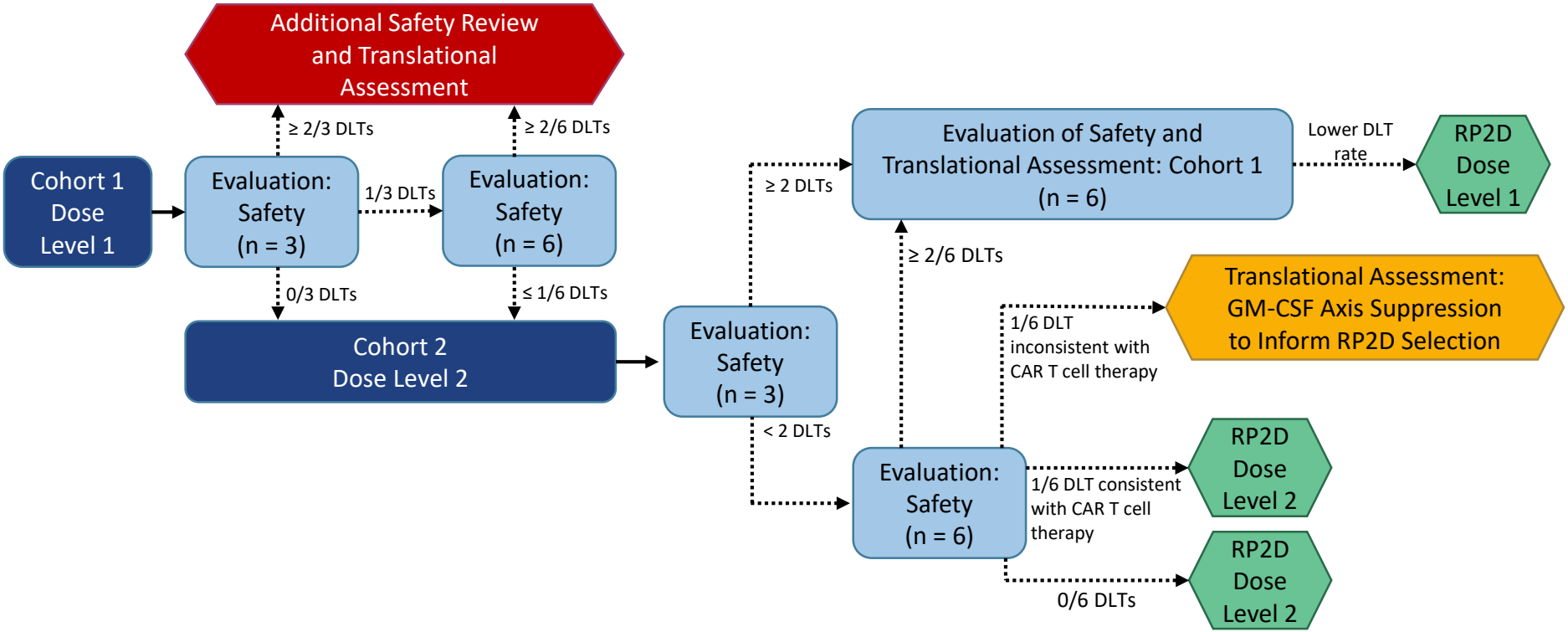


- Primary endpoints: DLTs (Phase 1) and Grade ≥ 2 NEs (Phase 2)
- Key secondary endpoints: safety, ORR, CR rate, DOR, PFS, and OS

[a] Additional details for Phase 1 study flow can be found in Figure 4. [b] Patients were hospitalized before administration of lenzilumab, at dose level 1 over 1 hour (Cohort 1) or dose level 2 IV infusion over 2 hours (Cohort 2). Axi-cel was administered 6 hours after lenzilumab infusion. [c] Cohort 2 will be enrolled if Cohort 1 passes DLT evaluation. [d] RP2D of lenzilumab will depend on the number of DLTs with each dose and the GM-CSF suppression level in each cohort.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DLT, dose-limiting toxicity; DOR, duration of response; GM-CSF, granulocyte-macrophage colony-stimulating factor; IV, intravenous; NE, neurologic event; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Phase 1 Dose Escalation Schema



CAR, chimeric antigen receptor; DLT, dose-limiting toxicity; GM-CSF, granulocyte-macrophage colony-stimulating factor; RP2D, recommended Phase 2 dose.

Study Populations

- **Full analysis set**: all enrolled patients and will be used for the summary of patient disposition
- **Primary objective analysis set**: all patients enrolled and treated with axi-cel ≥ 1.6×10^6 anti-CD19 CAR T cells/kg (≥ 1.6×10^8 anti-CD19 CAR T cells for patients who weigh > 100 kg) and target dose of lenzilumab at the RP2D prior to axi-cel infusion and will be used for the primary endpoint analysis
- **Modified intent-to-treat set**: all patients enrolled and treated with axi-cel ≥ 1.0×10^6 anti-CD19 CAR T cells/kg (≥ 1.0×10^8 anti-CD19 CAR T cells for patients who weigh > 100 kg) and target dose of lenzilumab at the RP2D prior to axi-cel infusion and will be used for all efficacy analyses
- **Safety set**: all patients treated with any dose of axi-cel and/or lenzilumab
- **DLT-evaluable set**: all patients in each Phase 1 cohort who received the target dose of lenzilumab and axi-cel and were followed for at least 28 days or received a dose of lenzilumab lower than the target for that cohort and experienced a DLT during the 28-day period

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; DLT, dose-limiting toxicity; RP2D, recommended Phase 2 dose.

Study Analyses and Statistical Outputs

Study Analyses

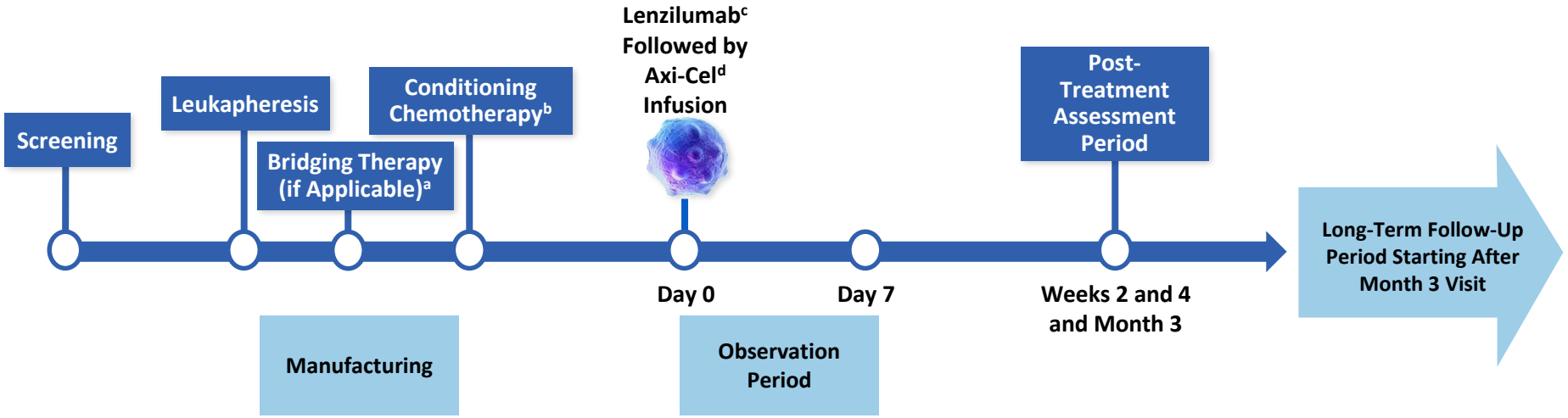
- Interim analysis: An SRT will review safety during Phase 1 after 3 and 6 (as needed) patients have been followed for 28 days after axi-cel infusion and will make recommendations on further study conduct in Phase 1 and progression to Phase 2. The SRT will meet during Phase 2 after 14 patients are treated with axi-cel ≥ 1.6×10^6 anti-CD19 CAR T cells/kg and lenzilumab at the RP2D prior to axi-cel infusion and followed for 28 days
- Primary analysis will be performed after 30 patients in the primary objective analysis set have been evaluated for response 6 months after axi-cel infusion

Statistical Outputs

- DLTs and Grade ≥ 2 NEs: incidence rates and, for Grade ≥ 2 NEs, exact 2-sided 95% CIs
- Safety: incidence rates of AEs per NCI CTCAE v4.03, including all, serious, fatal, Grade ≥ 3, and treatment-related AEs reported throughout the conduct of the study
- ORR and CR: incidence rates and exact 2-sided 95% CIs
- DOR, PFS, and OS: Kaplan-Meier estimates and 2-sided 95% CIs

AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DLT, dose-limiting toxicity; DOR, duration of response; NCI CTCAE v4.03, National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03; NE, neurologic event; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RP2D, recommended Phase 2 dose; SRT, Safety Review Team.

Treatment Schema



[a] Bridging therapy with corticosteroids will be administered at the discretion of the investigator, up until 5 days prior to administration of axi-cel. [b] Conditioning chemotherapy consists of administration of fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2 for 3 consecutive days (Day −5 through Day −3). [c] Lenzilumab will be administered on Day 0, at a dose determined by dose cohort, 6 hours prior to axi-cel infusion. [d] Axi-cel consists of a single IV infusion of a target of 2 × 10^6 anti-CD19 transduced autologous CAR T cells/kg (maximum dose 2 × 10^8 anti-CD19–transduced autologous CAR T cells) administered on Day 0.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; IV, intravenous.

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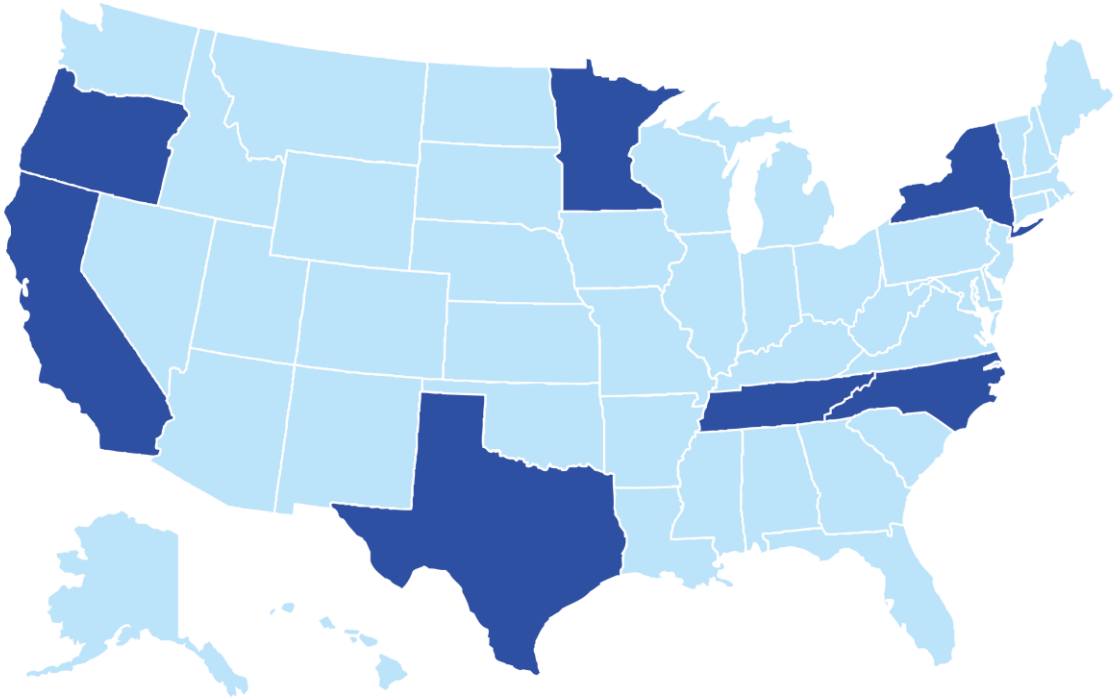
Patient Eligibility

Key Inclusion Criteria	Key Exclusion Criteria
• Patients aged ≥ 18 years with LBCL, including DLBCL not otherwise specified, PMBCL, HGBL, and DLBCL arising from FL • Patients with relapsed disease after ≥ 2 lines of systemic therapy or chemotherapy-refractory disease: – No response to first-line therapy – No response to ≥ 2 lines of therapy • ECOG PS of 0 or 1 • ≥ 1 Measurable lesion • Adequate prior therapy, at a minimum: – Anti-CD20 mAb – Anthracycline-containing chemotherapy • Adequate bone marrow, renal, hepatic, pulmonary, and cardiac function	• History of Richter transformation CLL • Autologous SCT within 6 weeks of axi-cel infusion • Prior allogeneic SCT • History of pulmonary alveolar proteinosis • Prior CD19-targeted therapy or prior CAR T cell therapy • Clinically significant infection • Detectable CSF malignant cells or brain metastases or concomitant CNS lymphoma • History of CNS disorders such as seizure, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement • Clinically significant autoimmune disease

CLL, chronic lymphocytic leukemia; CNS, central nervous system; CSF, cerebrospinal fluid; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HGBCL, high-grade BCL; LBCL, large BCL; mAb, monoclonal antibody; PAP, pulmonary alveolar proteinosis; PMBCL, primary mediastinal BCL; PS, performance status; SCT, stem cell transplantation.

Status

- ZUMA-19 is open, and as of November 10, 2020, is currently enrolling participants at 8 sites across the US



California

Minnesota

New York

North Carolina

Oregon

Tennessee

Texas

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- This study is being conducted in collaboration with Kite, a Gilead Company, and Humanigen

Disclosures

SJK: consultancy or advisory role for Humanigen and Torque; research funding from Novartis, Kite, a Gilead Company, Gilead, Juno, Bristol-Myers Squibb, Humanigen, Tolero, Sunesis, MorphoSys, and Lentigen; and patents, royalties, or other intellectual property from Novartis, Humanigen, and Mettaforge. **OOO:** honoraria from Kite, a Gilead Company; consultancy or advisory role for Pfizer, Spectrum Pharmaceuticals, Bayer, and Kite, a Gilead Company; research funding from Kite, a Gilead Company. **PM:** honoraria from Juno/Celgene/Bristol-Myers Squibb, Karyopharm, Magenta, Janssen, Takeda, AbbVie, and Genentech; consultancy or advisory role for Juno/Celgene/Bristol-Myers Squibb, Karyopharm, Magenta, Janssen, Takeda, AbbVie, and Genentech; research funding from Celgene. **RR:** honoraria from Gilead and Novartis; consultancy or advisory role for Magenta, Atara, Celgene, and Gilead; research funding from Gilead, Bristol-Myers Squibb, Takeda, Incyte, Pharmacyclics, Immatics, Shire, Bluebird, Atara, and Kiadis; expert testimony for Monsanto; travel support from Gilead Sciences. **PS:** research funding from Kite, a Gilead Company, and Orca BioSystems, Inc. **OA:** employment with Humanigen; and stock or other ownership in Humanigen. **JLG:** previous employment with Kite, a Gilead Company; stock or other ownership in Gilead Sciences. **MN:** employment with Kite, a Gilead Company; stock or other ownership with Gilead and Humanigen; research funding from Astex, Sanofi, and Bristol-Myers Squibb (prior academic research support). **SSN:** personal fees from Kite, a Gilead Company, Merck, Bristol-Myers Squibb, Novartis, Celgene, Pfizer, Allogene Therapeutics, Cell Medica/Kuur, Incyte, Precision Biosciences, Legend Biotech, Adicet Bio, Calibr, and Unum Therapeutics; research support from Kite, a Gilead Company, Bristol-Myers Squibb, Merck, Poseida, Cellectis, Celgene, Karus Therapeutics, Unum Therapeutics, Allogene Therapeutics, Precision Biosciences, and Acerta; royalties from Takeda Pharmaceuticals; intellectual property related to cell therapy.