Long-Term Survival and Gradual Recovery of B Cells in Patients With Refractory Large B Cell Lymphoma Treated With Axicabtagene Ciloleucel

Caron Jacobson, MD[1]; Fredrick L. Locke, MD[2]; Armin Ghobadi, MD[3]; David B. Miklos, MD, PhD[4]; Lazaros J. Lekakis, MD[5]; Olalekan O. Oluwole, MD, MPH, MBBS[6]; Yi Lin, MD, PhD[7]; Ira Braunschweig, MD[8]; Brian T. Hill, MD, PhD[9]; John M. Timmerman, MD[10]; Abhinav Deol, MD[11]; Patrick M. Reagan, MD[12]; Patrick Stiff, MD[13]; Ian W. Flinn, MD, PhD[14]; Umar Farooq, MD[15]; Andre H. Goy, MD[16]; Peter A. McSweeney, MD[17]; Javier Muñoz, MD[18]; Tanya Siddiqi, MD[19]; John M. Rossi, MS[20]; Adrian A. Bot, MD, PhD[20]; Lianqing Zheng, PhD[20]; Remus Vezan, MD, PhD[20]; Zahid Bashir, MBBS[20]; Jenny Kim, MD, MS[20]; Rong Chu, PhD[20]; and Sattva S. Neelapu, MD[21]

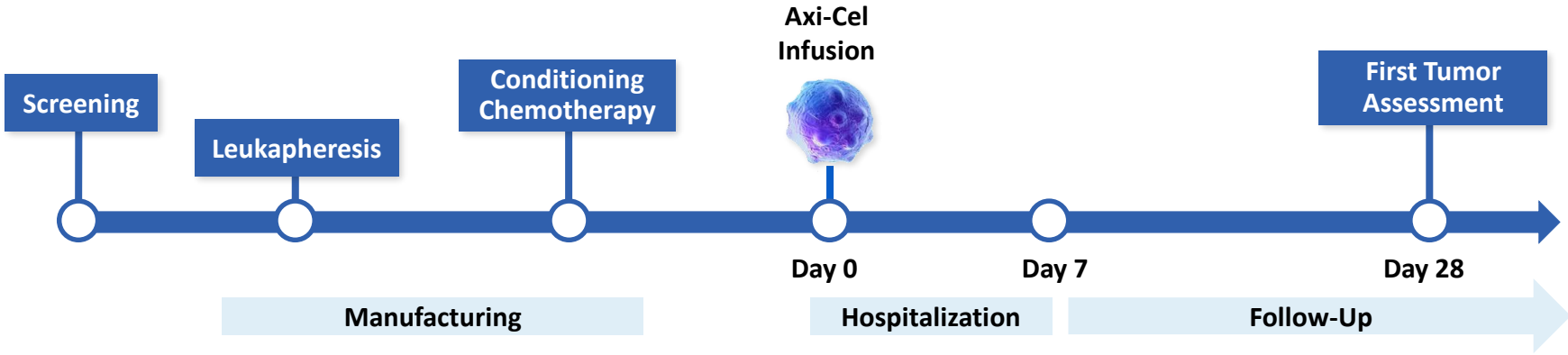
[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Moffitt Cancer Center, Tampa, FL, USA; [3]Washington University School of Medicine, St Louis, MO, USA; [4]Stanford University School of Medicine, Stanford, CA, USA; [5]Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL, USA; [6]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [7]Mayo Clinic, Rochester, MN, USA; [8]Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA; [9]Cleveland Clinic Foundation, Cleveland, OH, USA; [10]UCLA David Geffen School of Medicine, Los Angeles, CA, USA; [11]Karmanos Cancer Center, Wayne State University, Detroit, MI, USA; [12]University of Rochester School of Medicine, Rochester, NY, USA; [13]Loyola University Chicago Stritch School of Medicine, Maywood, IL, USA; [14]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; [15]University of Iowa, Iowa City, IA, USA; [16]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; [17]Colorado Blood Cancer Institute, Denver, CO, USA; [18]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [19]City of Hope National Medical Center, Duarte, CA, USA; [20]Kite, a Gilead Company, Santa Monica, CA, USA; and [21]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background

- Axi-cel is an autologous anti-CD19 CAR T cell therapy approved for the treatment of adult patients with relapsed/refractory LBCL after ≥ 2 prior lines of systemic therapy[1]
- ZUMA-1 (NCT02348216) is the multicenter, single-arm, registrational Phase 1/2 study of axi-cel in patients with refractory LBCL
- In a 2-year analysis of ZUMA-1 (median follow-up, 27.1 months; n = 101)[2]:
  - 83% ORR (58% CR rate) with 39% ongoing response rate at the data cutoff date
  - Grade ≥ 3 CRS (11%) and NEs (32%) were manageable and largely reversible
- In a 3-year follow-up analysis of ZUMA-1 (median follow-up, 39.1 months), median OS was 25.8 months, and the KM estimate of the 3-year OS rate was 47%[3]
- Data from ZUMA-1 Cohort 4 suggested that earlier use of corticosteroids for immune system suppression in patients with mild NEs (Grade < 2) and low-grade CRS (Grade 1) may reduce the incidence of Grade ≥ 2 NEs without significant impact on efficacy (73% ORR; 51% CR; reactive strategy)[4]
- The ZUMA-1 Cohort 6 primary analysis (median follow-up, 8.9 months) showed that prophylactic steroids reduced the rate of Grade ≥ 3 CRS to 0% and Grade ≥ 3 NEs to 13%, while achieving an ORR of 95% and a CR rate of 80% (proactive strategy)[5]
- Here, we present additional survival findings with ≥ 4 years of follow-up and recovery of polyclonal B cells from ongoing responders in ZUMA-1

1. YESCARTA® (axicabtagene ciloleucel) [prescribing information]. Santa Monica, CA: Kite Pharma, Inc; 2020. 2. Locke FL, et al. *Lancet Oncol.* 2019;20:31-42. 3. Neelapu SS, et al. Oral presentation at ASH 2019. #203.
4. Topp MS, et al. *Blood.* 2019;134(suppl, abstr):243. 5. Oluwole OO, et al. Manuscript in preparation.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; KM, Kaplan-Meier; LBCL, large B cell lymphoma; ORR, objective response rate; NE, neurologic event.

ZUMA-1 Treatment Schema



Key eligibility criteria for ZUMA-1

- Refractory LBCL (DLBCL, PMBCL, TFL)
- No response to last chemotherapy or relapse ≤ 12 months post ASCT
- Prior anti-CD20 monoclonal antibody and anthracycline

Conditioning regimen

- Cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 for 3 days

Axi-Cel

- 2 × 10^6 CAR+ cells/kg

Axi-cel, axicabtagene ciloleucel; ASCT, autologous stem cell transplantation; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; DLBCL, diffuse large B cell lymphoma; LBCL, large B cell lymphoma; PMBCL, primary mediastinal B cell lymphoma; TFL, transformed follicular lymphoma.

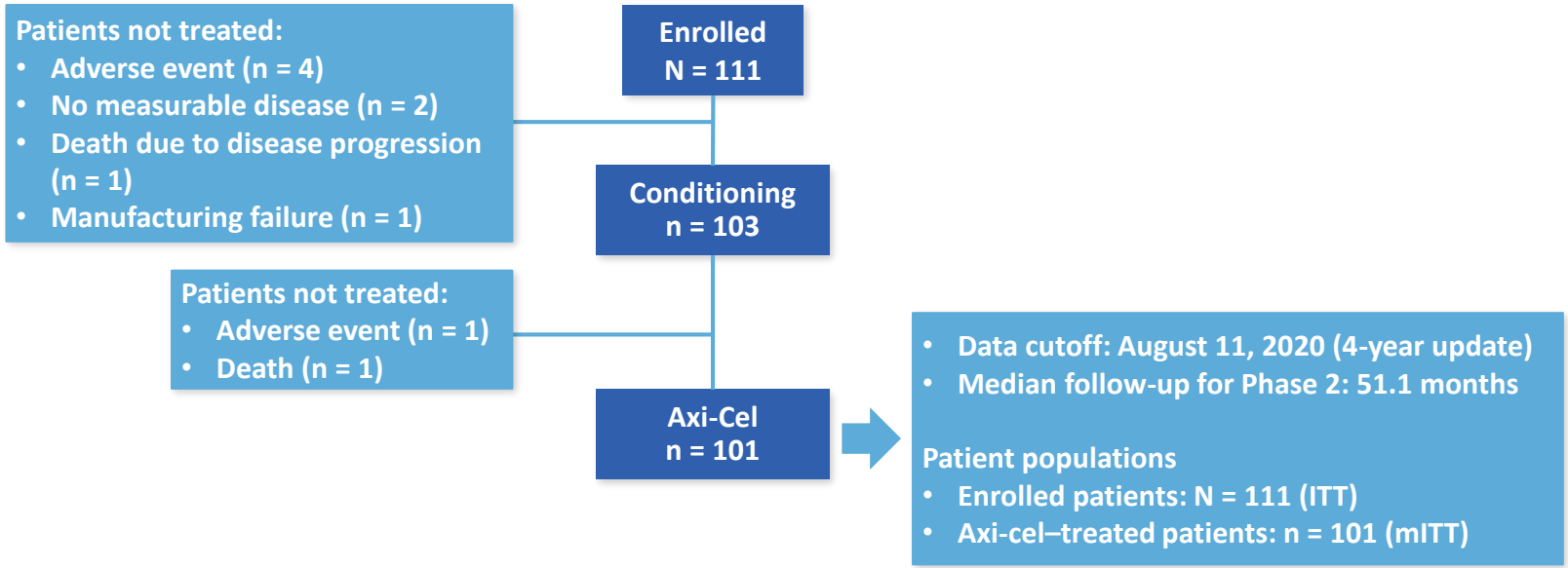
Jacobson et al ASH 2020 Abstract 1187

Methods

- The primary endpoint was ORR, and the first response assessment occurred 4 weeks after infusion
- Response assessments were performed, per protocol, up to 24 months or until disease progression, whichever occurred first
- For patients in ongoing response beyond Month 24, response assessments were performed per institutional SOC
- Time to next therapy was defined as time from axi-cel infusion to initiation of new anticancer therapy, including CAR T cell retreatment and excluding stem cell transplantation, or death from any cause
- Median OS, 4-year survival rates, and time to next therapy were estimated using Kaplan-Meier methodology
- Blood levels of CAR T cells were quantified using a validated polymerase chain reaction, and B cells were phenotyped using flow cytometry
  - Data are presented for patients with ongoing responses at ≥ 3 years of follow-up who also had evaluable samples

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; ORR, objective response rate; OS, overall survival; SOC, standard of care.

ZUMA-1 Phase 2 Patient Disposition and Axi-Cel Manufacturing



- Among the 111 patients who were enrolled (ITT population), the median manufacturing time was 17 days (range, 14 – 51; n = 110 [manufacturing was not feasible for 1 patient]), with an overall manufacturing success rate of 99%

Axi-cel, axicabtagene ciloleucel; ITT, intent-to-treat; mITT, modified intent-to-treat.

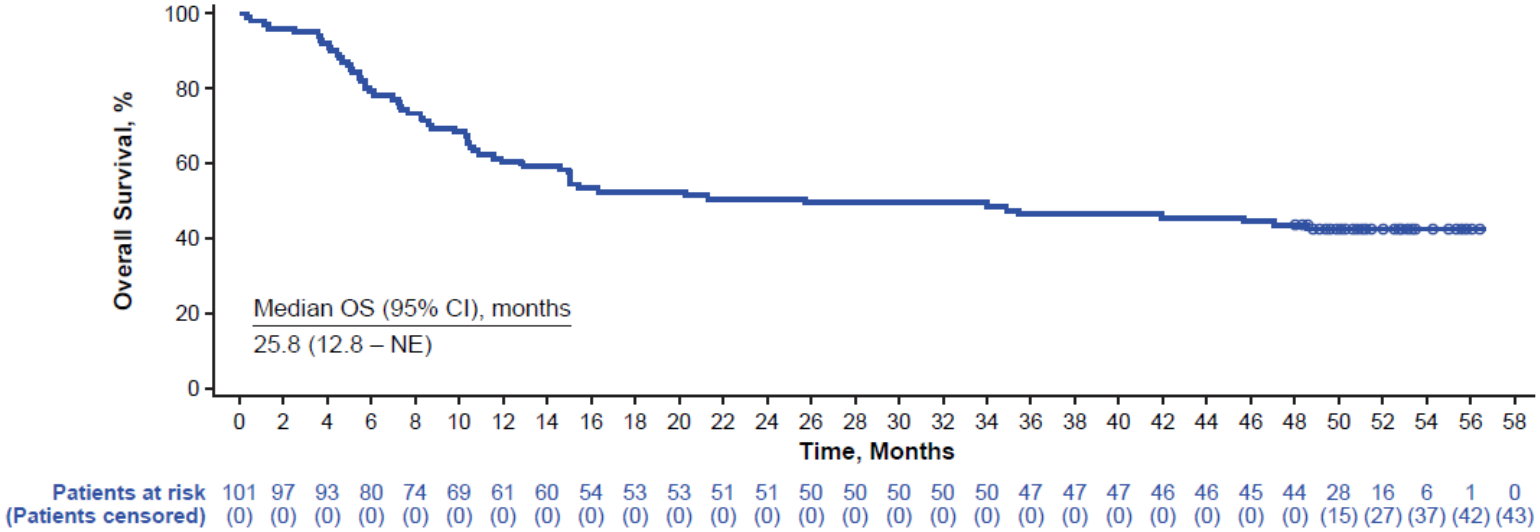
Time to Response and Next Therapy

- As previously reported in the 2-year ZUMA-1 analysis,[1] among patients who received axi-cel (mITT, n = 101), the median time from axi-cel infusion to both objective response and CR was 1.0 month (range, 1 – 12)
- Among the 111 patients who constituted the ITT population, the median time from enrollment/leukapheresis to objective response and CR was 1.7 months (range, 0.7 – 12.9) and 1.9 months (range, 0.7 – 13.3), respectively
  - 76% of enrolled patients had an objective response, and 53% had a CR[1]
- Median time to next anticancer therapy was 8.7 months (range, 0.3 – 53.8) after axi-cel infusion (mITT population)
- Two patients in axi-cel–induced remission underwent alloSCT

1. Locke FL, et al. *Lancet Oncol*. 2019;20:31-42.

Axi-cel, axicabtagene ciloleucel; alloSCT, allogeneic stem cell transplantation; CR, complete response; ITT, intent-to-treat; mITT, modified intent-to-treat.

Overall Survival At 4 Years (mITT, n = 101)



- Among axi-cel–treated patients (mITT, n = 101), with ≥ 4 years of follow-up (median, 51.1 months), median OS was 25.8 months, and the KM estimate of the 4-year OS rate was 44%
- Among the entire enrolled population (ITT, n = 111), median OS was 17.4 months, and the KM estimate of the 4-year OS rate was 41%

Axi-cel, axicabtagene ciloleucel; KM, Kaplan-Meier; mITT, modified intent-to-treat; NE, not estimable; OS, overall survival.

Safety

- Since study initiation, 59% of patients in the ITT population have died (**Table**)
- Since the 2-year data cutoff date[1]:
  - Eight patients have died (progressive disease [n = 5]; secondary malignancy [MDS, unrelated to axi-cel], cardiac arrest, and unknown [n = 1 each])
  - No new axi-cel–related SAEs have been reported
  - Four patients received IVIG therapy

n (%)	N = 111
Patients who died	66 (59)
Primary cause of death	
Progressive disease	52 (47)
Other	8[a] (7)
Adverse event	5[b] (5)
Secondary malignancy	1 (1)

- Importantly, as of this 4-year data cutoff date, and similar to previous reports[1,2]:
  - No axi-cel–related secondary malignancies have been reported
  - No confirmed cases of RCR have been reported

[a] Three events had no causal relationship (MDS [n = 1, patient was enrolled but not treated]; cardiac arrest [n = 2]), 4 events occurred post subsequent therapy (sepsis [n = 1], infection [n = 2], and pulmonary nocardiosis [n = 1]), and 1 event was unknown. [b] One event was related to conditioning chemotherapy (tumor lysis syndrome; patient was enrolled but not treated), 2 events had no causal relationship (sepsis, pulmonary embolism), and 2 events were related to axi-cel (brain injury and hemophagocytic lymphohistiocytosis [also considered to be Grade 5 cytokine release syndrome]).

1. Locke FL, et al. *Lancet Oncol*. 2019;20:31-42. 2. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-2544.

Axi-cel, axicabtagene ciloleucel; ITT, intent-to-treat; IVIG, intravenous immunoglobulin; MDS, myelodysplastic syndrome; RCR, replication-competent retrovirus; SAE, serious adverse event.

CAR T Cell and B Cell Detection in Blood

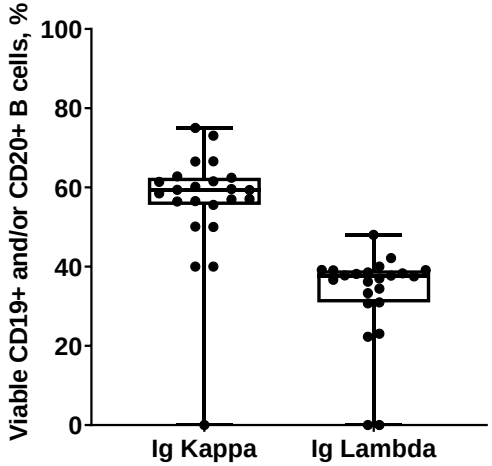
- As previously reported, patients in ongoing response after 2 years had significantly greater peak CAR T cell expansion in blood 7 – 14 days after axi-cel infusion than did patients with relapse (P = .014) or no response (P = .0003)[1]

- Blood samples from 21 patients in ongoing response (per institutional SOC) at ≥ 3 years were available for analysis of CAR T cells and evaluation of B cell presence
  - All evaluable patients had detectable B cells in blood at 3 years after axi-cel treatment
  - 67% of patients (n = 14/21) had detectable CAR gene-marked cells and polyclonal B cells in blood at 3 years

1. Locke FL, et al. *Lancet Oncol*. 2019;20:31-42.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; SOC, standard of care.

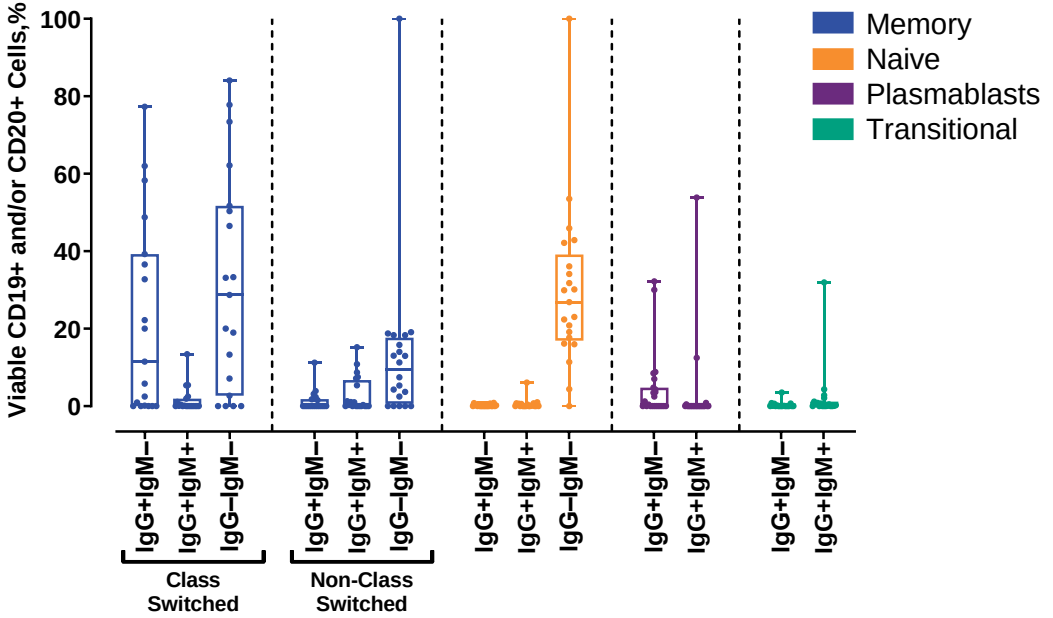
Most Patients With Evaluable B Cells in Ongoing Response at 3-Year Follow-Up Demonstrated Polyclonal B Cell Recovery and Diversity

B Cell Recovery



- 91% of patients (n = 21/23) demonstrated polyclonal B cell recovery
- The median Ig kappa-lambda ratio was 1.6[a]

B Cell Diversity



B cells were characterized in cryopreserved PBMCs using multicolor flow cytometry. Viable cells were calculated as a percentage of the total number of viable CD45+ leukocytes. B cell subsets were defined as CD45+CD3−CD14−CD16−CD56−CD19+ and/or CD20+ and further phenotyped as follows: Ig kappa, Ig lambda, class-switched memory (CD20+CD27+IgD−), non–class-switched memory (CD20+CD27+IgD+), naïve (CD20+CD27−IgD+CD24lowCD38low), plasmablasts (CD38highCD20−), and transitional (CD20+CD27−IgD+CD24+CD38mid).

[a] n = 21 patients because 2 patients had lambda value equal to 0.

Ig, immunoglobulin; PBMC, peripheral blood mononuclear cell.

Conclusions

- Axi-cel produced rapid responses, robust CAR T cell expansion, and long-term disease control in patients with refractory LBCL
  - Most responses, including CRs, occurred by the first assessment (Day 28)
  - The ORR in the mITT was 83%, with a CR rate of 58%[1]
  - With ≥ 4 years of follow-up, axi-cel treatment produced deep and durable responses, with a 4-year OS rate (KM estimate) of 44% among axi-cel–treated patients
- The brief time elapsed between enrollment/leukapheresis and objective response supports both the speed, success, and reliability of manufacturing
  - Among enrolled patients (N = 111), 53% achieved a CR[1]
- ZUMA-1 patients with ongoing responses at ≥ 3 years showed evidence of restoration of a polyclonal B cell compartment and clearance of functional CAR T cells, a key component of the long-term safety of CD19-directed CAR T cell therapies
  - The median kappa-lambda ratio and relative levels of key B cell subsets, including memory and naive B cell immunophenotypes, suggest reconstitution of the B cell repertoire, which is consistent with published data in healthy individuals[2,3]
- Altogether, these findings support the hypothesis that persistence of functional CAR T cells is not necessary for deep and durable remissions in LBCL while allowing for gradual recovery and reconstitution of the humoral immune system

1. Locke FL, et al. *Lancet Oncol*. 2019;20:31-42. 2. Deneys V, et al. *J Immunol Methods.* 2001;253:23-36. 3. Scott GD, et al. *J Clin Pathol.* 2018;71:174-179.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; KM, Kaplan-Meier; LBCL, large B cell lymphoma; mITT, modified intent-to-treat; ORR, objective response rate.

Acknowledgments and Funding

- The patients, families, friends, and caregivers
- The study investigators, coordinators, and health care staff at each study site
- Medical writing support was provided by Ashley Skorusa, PhD, of Nexus Global Group Science LLC, funded by Kite, a Gilead Company
- This study was funded by Kite, a Gilead Company

Disclosures

CJ: honoraria from Kite, a Gilead Company, Celgene, Novartis, Pfizer, Humanigen, Precision Biosciences, Nkarta, Lonza, and AbbVie; consulting or advisory role with Kite, a Gilead Company, Celgene, Novartis, Pfizer, Humanigen, Precision Biosciences, Nkarta, Lonza, and AbbVie; speakers' bureau participation with Axis and Clinical Care Options; research funding from Pfizer; and travel, accommodations, and expenses from Kite, a Gilead Company, Celgene, Novartis, Pfizer, Humanigen, Precision Biosciences, and Lonza. **FLL:** scientific advisory role for Kite, a Gilead Company, Novartis, Amgen, Celgene/Bristol Myers Squibb, GammaDelta Therapeutics, Wugen, Calibr, and Allogene; consultant with grant options for Cellular Biomedicine Group, Inc; and research support from Kite, a Gilead Company. **AG:** consulting or advisory role for Kite, a Gilead Company, Amgen, Atara, Wugen, and Celgene and honoraria from Kite, a Gilead Company. **DBM:** consultancy or advisory role for Kite-Gilead, Novartis, Juno/Celgene/Bristol Myers Squibb, Adaptive Biotech, Pharmacyclics, and Janssen; research funding from Kite-Gilead, Novartis, Juno/Celgene/Bristol Myers Squibb, Adaptive Biotech, Pharmacyclics; patents, royalties, or other intellectual property from Pharmacyclics; and travel support from Kite-Gilead, Novartis, Juno/Celgene/Bristol Myers Squibb, Adaptive Biotech, Pharmacyclics, and Janssen. **LJL, IB:** no relevant financial relationship(s) to disclose. **OOO:** honoraria from Kite, a Gilead Company; consultancy or advisory role for Kite, a Gilead Company, Pfizer, Spectrum Pharmaceuticals, and Bayer; and research funding from Kite, a Gilead Company. **YL:** consultancy or advisory role for Kite, a Gilead Company, Janssen, Novartis, Celgene, Bluebird Bio, Juno, Legend, Sorrento, Gamida Cell, and Vineti and research funding from Kite, a Gilead Company, Janssen, Celgene, Bluebird Bio, Merck, and Takeda. **BTH:** honoraria from, consultancy or advisory role for, research funding from, and travel support from Kite, a Gilead Company. **JMT:** stock or other ownership in Genmab, Corvus, Marker Therapeutics, and Bluebird Bio; consultancy or advisory role for Kite, a Gilead Company, Celgene, Immune Design, and Celldex Therapeutics; research funding from Bristol Myers Squibb, Kite, a Gilead Company, Spectrum Pharmaceuticals, and Merck; and travel support from Bristol Myers Squibb and Kite, a Gilead Company. **AD:** consultancy or advisory role for Kite, a Gilead Company, and Novartis. **PMR:** consultancy or advisory role for Kite, a Gilead Company, and Curis and research funding from Seattle Genetics. **PS:** research funding from Kite, a Gilead Company, Amgen, Gamida Cell, Atara, and Macrogenics. **IWF:** employment with Sarah Cannon Research Institute; stock or other ownership in Johnson & Johnson; consultancy or advisory role for AbbVie, AstraZeneca, BeiGene, Gilead Sciences, Great Point Partners, Iksuda Therapeutics, Janssen, Juno Therapeutics, Kite, a Gilead Company, MorphoSys, Nurix Therapeutics, Pharmacyclics, Roche, Seattle Genetics, Takeda, Unum Therapeutics, Verastem, and Yingli Pharmaceuticals; and research funding from AbbVie, Acerta Pharma, Agios, ArQule, AstraZeneca, BeiGene, Calithera Biosciences, Celgene, Constellation Pharmaceuticals, Curis, F. Hoffman-La Roche, Forma Therapeutics, Forty Seven, Genentech, Gilead Sciences, IGM Biosciences, Incyte, Infinity Pharmaceuticals, Janssen, Juno Therapeutics, Karyopharm Therapeutics, Kite, a Gilead Company, Loxo, Merck, MorphoSys, Novartis, Pfizer, Pharmacyclics, Portola Pharmaceuticals, Roche, Seattle Genetics, Takeda, Teva, TG Therapeutics, Trillium Therapeutics, Triphase Research & Development Corp., Unum Therapeutics, and Verastem. **UF:** honoraria from Kite, a Gilead Company. **AHG:** employment with Regional Cancer Care Associates/OMI; leadership role at COTA (Cancer Outcome Tracking Analysis); stock or other ownership in COTA; consultancy or advisory role for AstraZeneca, Celgene, Gilead Sciences, Kite, a Gilead Company, and Xcenda; and research funding from Acerta, AstraZenca, Celgene, Constellation, Genentech-Hoffmann La Roche, Infinity, and Infinity Verastem. **PAM:** employment with Colorado Blood Cancer Institute Medical Group; consultancy or advisory role for Kite, a Gilead Company; speakers' bureau participation for Kite, a Gilead Company; and research funding from Kite, a Gilead Company. **JM:** honoraria from Kyowa and Seattle Genetics; consultancy or advisory role for Pharmacyclics, Bayer, Kite, a Gilead Company, Pfizer, Janssen, Juno/Celgene, Bristol Myers Squibb, Kyowa, Alexion, Fosun Kite, Innovent, Seattle Genetics, and BeiGene; speakers' bureau participation for Kite, a Gilead Company, Kyowa, Bayer, Pharmacyclics/Janssen, Seattle Genetics, Acrotech/Aurobindo, BeiGene, Verastem, AstraZeneca, Celgene/Bristol Myers Squibb, Genentech/Roche, and AbbVie; and research funding from Bayer, Kite, a Gilead Company, Celgene, Merck, Portola, Incyte, Genentech, Pharmacyclics, Seattle Genetics, Janssen, and Millennium. **TS:** consulting or advisory role for AstraZeneca, Pharmacyclics, Celgene, Juno, Kite, a Gilead Company, and BeiGene; speakers' bureau with PCYC, Janssen, AstraZeneca, and Seattle Genetics; and research funding from PCYC, Juno, Kite, a Gilead Company, AstraZeneca, BeiGene, Oncternal, TG Therapeutics, and Celgene. **JMR, JK:** employment with Kite, a Gilead Company and stock or other ownership in Gilead Sciences. **AAB:** employment with Kite, a Gilead Company; stock or other ownership in Gilead Sciences; consultancy or advisory role for Gilead Sciences; and travel support from Gilead Sciences. **LZ:** former employment with Kite, a Gilead Company. **RV:** employment with Kite, a Gilead Company; stock or other ownership in Gilead Sciences, AbbVie, and Merck; honoraria from Kite, a Gilead Company; and travel support from Kite, a Gilead Company. **ZB:** employment with Kite, a Gilead Company, and OmniacPharmConsult Ltd and stock or other ownership in OmniacPharmConsult Ltd. **RC:** employment with Sarepta Therapeutics and former employment with Kite, a Gilead Company; and stock or other ownership in Gilead Sciences, Celgene, and Sarepta Therapeutics. **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; and intellectual property related to cell therapy.