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Lisocabtagene Maraleucel (liso-cel) Combined with Ibrutinib (ibr) for Patients (pts) with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): Primary Results from the Open-Label, Phase 1/2 Transcend CLL 0...

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Authors

Wierda, William G
Dorritie, Kathleen
Gauthier, Jordan
et al.

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ORAL ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Lisocabtagene Maraleucel (liso-cel) Combined with Ibrutinib (ibr) for Patients (pts) with Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): Primary Results from the Open-Label, Phase 1/2 Transcend CLL 004 Study

William G. Wierda[1], *Kathleen Dorritie, MD*[2], *Jordan Gauthier, MD MSc*[3], *Rajneesh Nath, MD*[4], *Thomas J. Kipps, MD*[5], *Peter A. Riedell, MD*[6], *Herbert A. Eradat, MD*[7], *Saad S. Kenderian, MD*[8], *Mohamed A. Kharfan-Dabaja, MD MBA*[9], *Nirav N. Shah, MD*[10], *Scott R. Solomon, MD*[11], *Daniel A. Ermann, MD*[12], *Jon E. Arnason, MD*[13], *Abhinav Deol, MD*[14], *Tatyana Feldman, MD*[15], *Charalambos Andreadis, MD MS*[16], *Monalisa Ghosh, MD*[17], *Shuo Ma, MD PhD*[18], *Stephen J. Schuster, MD*[19], *Usama Gergis, MDMBA*[20], *Julie M. Vose, MD MBA*[21], *Jacob D. Soumerai, MD*[22], *Koen van Besien, MD PhD*[23], *Sherilyn A. Tuazon, MD*[24], *Serena K. Perna, MD*[25], *San-San Ou, MS*[24], *Neha Rane, MD*[25], *Eniko Papp, PhD*[24], *Yizhe Chen, PhD*[25], *Tanya Siddiqi, MD MBBS*[26]

[1] The University of Texas MD Anderson Cancer Center, Houston, TX
[2] UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA
[3] Fred Hutchinson Cancer Center, Seattle, WA
[4] Banner MD Anderson Cancer Center, Gilbert, AZ
[5] Division of Hematology Oncology, Department of Medicine, University of California, San Diego, La Jolla, CA
[6] David and Etta Jonas Center for Cellular Therapy, University of Chicago, Chicago, IL
[7] University of California, Los Angeles, Santa Monica Cancer Center, Santa Monica, CA
[8] Mayo Clinic, Rochester, MN
[9] Mayo Clinic Comprehensive Cancer Center, Jacksonville, FL
[10] Medical College of Wisconsin, Milwaukee, WI
[11] Northside Hospital Cancer Institute, Atlanta, GA
[12] Huntsman Cancer Institute, University of Utah, Salt Lake City, UT
[13] Beth Israel Deaconess Medical Center, Boston, MA
[14] Karmanos Cancer Institute/Wayne State University, Detroit, MI
[15] John Theurer Cancer Center at Hackensack Meridian Health, HMH School of Medicine, Hackensack, NJ
[16] University of California, San Francisco, San Francisco, CA
[17] University of Michigan Health System, Ann Arbor, MI
[18] Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL
[19] Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA
[20] Thomas Jefferson University, Philadelphia, PA
[21] University of Nebraska Medical Center, Omaha, NE
[22] Center for Lymphoma, Massachusetts General Hospital Cancer Center, Boston, MA
[23] Weill Cornell Medical College, New York, NY
[24] Bristol Myers Squibb, Seattle, WA
[25] Bristol Myers Squibb, Princeton, NJ
[26] City of Hope National Medical Center, Duarte, CA

Background: In TRANSCEND CLL 004 (NCT03331198),monotherapy with liso-cel, an autologous, CD19-directed CAR T cell product (100 × 10^6 CAR^+ T cells [dose level (DL) 2]), resulted in 43% ORR and 18% CR/CR with incomplete marrow recovery (CRi) rate per IRC in pts with third-line or later R/R CLL/SLL who had PD on Bruton tyrosine kinase inhibitor (BTKi) and failed venetoclax (Siddiqi T, et al. *Lancet* 2023). Ibr + other CAR T cell therapies has shown high ORR and reduced cytokine release syndrome (CRS) severity in pts with R/R CLL/SLL. In the phase 1 dose-escalation ibr combination cohort, DL2 was the recommended dose of liso-cel for expansion (Wierda WG, et al. *Blood* 2020). Here, we report results of liso-cel + ibr in pts with R/R CLL/SLL from TRANSCEND CLL 004.

Methods: Eligible pts ≥ 18 y of age with CLL/SLL had ≥ 1 of the following: 1) receiving BTKi with PD at entry, 2) high-risk disease and < CR after ≥ 6 mo on BTKi, 3) *BTK/PLCγ2* mutation ± ibr PD, 4) prior BTKi with no contraindications to ibr, and 5) (per amendment) PD on BTKi and received prior venetoclax. At enrollment, pts started or continued ibr (420 mg daily or less for toxicity) through leukapheresis and for up to 90 d (or longer per investigator [inv]) after liso-cel (target dose of 50 × 10^6 CAR^+ T cells [DL1] or DL2). Response was per inv by 2018 iwCLL criteria. Primary endpoint was CR/CRi rate at DL2; secondary endpoints included safety, ORR, duration of response (DOR), duration of CR/CRi (DOCR), time to response, time to CR/CRi, PFS, OS, and undetectable MRD (uMRD) rate in blood. Cellular kinetics was exploratory. Efficacy analyses were at DL2 and safety at DL1 + DL2. Treatment-emergent AEs (TEAE) occurred the latter of ≤ 90 days after liso-cel or ≤ 30 days of ibr completion. Liso-cel-treated pts who completed or withdrew from study could enroll in a separate long-term follow-up (LTFU) study (NCT03435796) for safety and OS ≤ 15 y after liso-cel.

Results: A total of 65 pts underwent leukapheresis; 56 received ibr + liso-cel (DL1, n = 5; DL2, n = 51). At data cutoff (01/12/2024), 28 of 56 (50%) pts had discontinued the study, 11 (20%) completed the study, and 17 (30%) were ongoing; 5 of 28 (18%) eligible pts enrolled in LTFU. Median (IQR) on-study follow-up (including LTFU) was 24.8 mo (14.2-34.6). Median (range) age was 65 y (44-77); 55 (98%) pts had high-risk cytogenetics, such as del(17p) (n = 25), *TP53* mutation (n = 24), and unmutated IGHV (n = 39); 43% had LDH ≥ ULN; and median (range) SPD was 27 cm^2 (1-218). Pts had a median (range) of 5 (1-13) prior therapies (≤ 2, n = 13 [23%]). Median (range) time from leukapheresis to liso-cel availability was 25 d (17-79). Median (range) ibr exposure was 34 d (15-188) before and 94.5 d (6-1517) after liso-cel.

At DL2, ORR (95% CI) was 86% (73.7-94.3), median (range) time to first response was 1.0 mo (0.9-6.0), and median (95% CI) DOR was 41.4 mo (23.3-not reached [NR]). CR/CRi rate (95% CI; primary endpoint) was 45% (31.1-59.7), median (range) time to first CR/CRi was 3.1 mo (0.9-12.1), and median (95% CI) DOCR was NR (26.6-NR). Median (95% CI) PFS and OS was 31.4 mo (20.1-NR) and NR (27.5-NR), respectively. uMRD rate (95% CI) in blood and marrow was 86% (73.7-94.3) and 84% (71.4-93.0), respectively.

Grade (gr) ≥ 3 TEAEs occurred in 48 (86%) pts (most commonly neutropenia [52%] and anemia [41%]) with no gr 5 TEAEs. Liso-cel-related gr ≥ 3 TEAEs occurred in 32 (57%) pts and ibr-related gr ≥ 3 TEAEs in 24 (43%) pts including cardiovascular events of hypertension (7%) and atrial fibrillation (2%). Any-gr CRS occurred in 45 (80%) pts (gr ≥ 3, n = 2 [4%]) and any-gr neurological events (NE) in 23 (41%) pts (gr ≥ 3, n = 6 [11%]). Eight (14%) pts had gr ≥ 3 infections and 5 (9%) had second primary malignancies. Twenty-five (45%) pts had prolonged cytopenias (gr ≥ 3 at D30); most recovered to gr ≤ 2 by D90. Sixteen pts died after infusion (PD, n = 6; unknown, n = 6; COVID-19, n = 3; mixed septic/cardiogenic shock, n = 1). Liso-cel showed rapid expansion (median t_{max}, 10 d) and was detected up to 42 mo after infusion.

Conclusions: Combined liso-cel + ibr demonstrated substantial efficacy with deep remissions (86% ORR, 45% CR rate, and 86% blood uMRD rate) and manageable safety in pts with R/R CLL/SLL. Though comparisons should be made with caution and there were differences in disease characteristics between cohorts, liso-cel + ibr showed a numerically higher ORR/CR rate and lower gr ≥ 3 CRS/NE rates vs liso-cel monotherapy, supporting the combination as a promising new therapeutic strategy for pts with R/R CLL/SLL.

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Off Label Disclosure: Yes, lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed CAR T cell product approved for the treatment of several B-cell malignancies, including adult patients with R/R CLL/SLL who have received at least 2 prior lines of therapy including a Bruton tyrosine kinase inhibitor (BTKi) and a B-cell lymphoma 2 inhibitor. The current abstract describes a clinical study evaluating use of liso-cel concurrent with the BTKi ibrutinib in patients who have received at least 1 prior line of therapy.

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