

frontMIND: Phase 3 study of tafasitamab (Tafa) plus lenalidomide (Len) and R-CHOP for patients (pts) with newly diagnosed diffuse large B-cell lymphoma (DLBCL).

Georg Lenz, Marek Trněný, John M. Burke, Grzegorz S. Nowakowski, Christopher P. Fox, Annalisa Chiappella, Johannes Dull, Youngwoo Jeon, Chan Cheah, Jason Westin, Joseph Z. Ye, Priscilla Baetiong Caguioa, David Belada, Ho Jin Shin, Sung Yong Oh, Sandy Amorim, Philomena Colucci, Sonia Ioannidis, Lulu Cheng, Umberto Vitolo; University Hospital Münster, Department of Medicine A for Hematology, Oncology and Pneumology, Münster, Germany; First Faculty of Medicine, Charles University, Prague, Czech Republic; Sarah Cannon Research Institute at Rocky Mountain Cancer Centers, Aurora, CO; Division of Hematology, Mayo Clinic Rochester, Rochester, MN; School of Medicine, University of Nottingham, and Clinical Haematology, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom; Fondazione IRCCS Istituto Nazionale dei Tumori, Hematology, Milano, Italy; Department of Internal Medicine II, University Hospital Würzburg, Würzburg, Germany; Department of Hematology, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea; Hollywood Private Hospital, Nedlands, Western Australia, Australia; The University of Texas MD Anderson Cancer Center, Houston, TX; Vista Oncology, Olympia, WA; St. Luke's Medical Center, Quezon, Philippines; Department of Internal Medicine-Haematology, Charles University, Hospital and Faculty of Medicine, Hradec Králové, Czech Republic; Division of Hematology-Oncology, Department of Internal Medicine, Research Institute of Medical Science, Pusan National University Hospital, Pusan National University School of Medicine, Busan, South Korea; Division of Hematology-Oncology, Department of Internal Medicine, Dong-A University College of Medicine, Busan, South Korea; Department of Hematology and Cellular Therapy, Hôpital Saint Vincent de Paul, Lille, France; Incyte Corporation, Wilmington, DE; Incyte Biosciences International Sàrl, Morges, Switzerland; Candiolo Cancer Institute, FPO-IRCCS Candiolo, Turin, Italy

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Integrating BTK inhibition into R-da-EPOCH for HIV-related DLBCL.

Ida Wong-Sefidan, Deukwoo Kwon, Richard F. Ambinder, Ariela Noy, David H. Henry, Robert A. Baiocchi, Paul G. Rubinstein, Juan C. Ramos, Christopher Dittus, Lee Ratner, Ethel Cesarman, Joseph A. Sparano, Erin G. Reid, The Consortium for Advancing Management and Prevention of Cancer in People With HIV (AMC); University of California, San Diego, San Diego, CA; Icahn School of Medicine at Mount Sinai, New York, NY; Johns Hopkins Cancer Center, Lutherville, MD; Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; University of Pennsylvania, Pennsylvania Hospital, Philadelphia, PA; The Ohio State University, Columbus, OH; University of Illinois Hospital & Health Sciences System, Chicago, IL; Jackson Memorial Hospital, Miami, FL; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; Washington University School of Medicine in St. Louis, St. Louis, MO; Weill Cornell Medicine Graduate School of Medical Sciences, New York, NY; Icahn School of Medicine at Mount Sinai, Mount Sinai Tisch Cancer Center, New York, NY

Background: Human immunodeficiency virus (HIV)-related diffuse large B-cell lymphomas (DLBCL) are heterogeneous in nature, clinically, & molecularly. R-da-EPOCH is accepted as a standard of care in HIV+DLBCL. Classifying tumors with respect to immunophenotype & genomic features may facilitate personalized therapy to improve outcomes in this diverse disease. The Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib (ibr), also inhibits inducible T cell kinase (ITK). As HIV hijacks host ITK during replication, ibr may have additional clinical benefits in HIV+DLBCL. This trial added ibr to R-da-EPOCH in HIV+DLBCL, with an attempt to enrich for non-germinal center B-cell (non-GCB) subtype, to evaluate safety, feasibility & activity, impact on T cells, & correlate lymphoma cell of origin (COO) with response. **Methods:** This multi-center study included a 3+3 dose de-escalation cohort followed by dose-expansion at recommended phase 2 dose (RP2D). Participants (pts) age 18–64 years (y) with stage II–IV HIV-DLBCL were untreated or received 1 cycle (cy) R-da-EPOCH/CHOP off-study. CD4 <100 & asymptomatic leptomeningeal disease were allowed. Ibr was dosed daily days 1–21 & R-da-EPOCH administered as previously published (PMID 32430507) for 6 total cy. Moderate/strong CYP3A4 inhibitors were excluded, due to effects on ibr and chemotherapy. **Results:** 43 pts were evaluable for toxicity & 37 evaluable for response. 41/43 (95%) pts tolerated ≥ 2 cy; median cy of study therapy (tx) received = 5. At baseline median age was 52y (24–64) & CD4 count 204 (21–757); 9 pts had CD4 <100. 81% were male, 42% White & 49% Black. 86% were stage III/IV, 40% non-GCB, & 88% had ECOG 0–1. Ibr RP2D was 560mg daily. Noting PET was optional, overall response rate was 100% with 57% (21/37) complete (CR) & 43% (16/37) partial responses (PR). Relapse/progression occurred in 16% (6/37; 1CR, 5PR) during a median follow-up of 4.2y (95% CI = 2.3 to 4.87); median duration of response = 2.8y. 3y event-free (EFS) & overall survival (OS) were 83 & 81% respectively (GCB: 88 & 87%, non-GCB: 76 & 63%). Among 679 treatment-related adverse events (TRAE), the most frequent were (total, % grade (gr) 3+) anemia (105, 50%), thrombocytopenia (81, 41%), neutropenia (60, 88%) & lymphopenia (60, 68%). Non-hematologic AEs (total TRAE, # max gr) included diarrhea (22, 2 gr3), nausea (21, 1 gr3), hypokalemia (20, 4 gr3), fatigue (17, 17 gr1), & sepsis (1 gr4). Reasons for tx discontinuation: 1 progression, 4 withdrawal, 4 TRAE, 1 lost to follow up. **Conclusions:** Incorporating ibrutinib 560mg daily with R-da-EPOCH in HIV-related DLBCL treatment resulted in manageable toxicities typical of R-da-EPOCH. Although lower confirmed CR, 3y EFS & OS are comparable or higher than prior studies of HIV+DLBCL R-da-EPOCH. Ongoing studies to be updated at the meeting include impact on T cell subsets, & correlations of response & survival with circulating tumor DNA & lymphoma features (EBV, MYC, BCL2, BCL6 & genomic determinations of COO). Clinical trial information: NCI-2017-01240. Research Sponsor: None.

Phase 2 trial of epcoritamab in combination with rituximab-mini CVP for older unfit/frail or anthracycline-ineligible adult patients with newly diagnosed diffuse large B-cell lymphoma: Interim futility analysis.

Dai Chihara, Ayushi Chauhan, Ruitao Lin, Amanda Mason, Lauren Johnson, Karmila Murphy, Jared Henderson, Luis Malpica, Chijioke C. Nze, Mark Hamilton, Anath Christopher Lionel, Preetesh Jain, Paolo Strati, Ranjit Nair, Sattva Swarup Neelapu, Christopher Flowers, Jason Westin; Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The median age at diagnosis of diffuse large B-cell lymphoma (DLBCL) is approximately 65 years, with nearly one third of patients in the US diagnosed at age >75 years. This older unfit/frail population is particularly vulnerable to treatment-related toxicity due to comorbidities and limited cardiac reserve, frequently leading to treatment discontinuation, and outcomes with standard attenuated anthracycline-based chemoimmunotherapy remain sub-optimal. There is therefore a critical unmet need for effective, better-tolerated non-anthracycline treatments. We hypothesize that epcoritamab combined with non-anthracycline chemotherapy (R-miniCVP) can achieve high and durable CR rates. **Methods:** This is an open-label, single-arm phase 2 trial conducted at MD Anderson Cancer Center (NCT06045247). Eligible patients have histologically confirmed DLBCL and are unfit/frail per FIL simplified geriatric assessment, or not eligible for anthracycline due to reduced ejection function (<50%), or prior anthracycline exposure therapy. Patients receive one cycle of R-miniCVP for debulking, followed by epcoritamab added from cycle 2 using step-up dosing, then 48 mg on day 1 of each subsequent cycle. After 6 cycles, patients achieving CR complete treatment, while patients with PR continue epcoritamab to 12 cycles. The primary endpoint is CR rate after 6 cycles. **Results:** We plan to enroll 40 patients. At the data cutoff, 22 patients have completed six cycles of therapy. The median age of 22 patients was 80 years (range, 71–87); 27% had PS 2, and 86% had an IPI ≥ 3 . All patients completed planned treatment. The CR rate after 6 cycles was 86% (95% CI, 65–97%). Two patients achieved PR and continue on epcoritamab. One patient achieved PR after cycle 3 but progressed after cycle 6 and subsequently died of progressive lymphoma following 2 additional lines of therapy. With a median follow-up of 11 months (range: 5–23 months), the 1-year progression-free survival was 94.7% (95% CI, 68–99%). Cytokine release syndrome occurred in 12 patients (55%), all grade 1 and occurred around C2D15, which fully resolved in 1–2 days in all patients. Four of them received tocilizumab. One patient developed grade 2 neurotoxicity after C2D15, which resolved within 24 hours after switching prednisone to dexamethasone. The trial protocol was amended to change prophylactic steroid from prednisone to dexamethasone, after which no further neurotoxicity was observed. **Conclusions:** The combination of epcoritamab with R-mini-CVP demonstrated encouraging efficacy with a favorable tolerability profile in older, unfit or frail patients who may be unable to tolerate full-dose chemotherapy. Based on these promising early-phase results, the study is planned for expansion into a multicenter trial with a larger patient cohort. Clinical trial information: NCT06045247. Research Sponsor: None.

A phase 1 study of the PRMT5 inhibitor AZD3470 in patients with relapsed/refractory classic Hodgkin lymphoma (PRIMAVERA).

Enrico Derenzini, Franck Morschhauser, Vincent Ribrag, Elizabeth Phillips, Hervé Ghesquieres, Hun Ju Lee, Borchmann Peter, Paul Jan Bröckelmann, Tae Min Kim, Katharine L. Lewis, Jakub Svoboda, Antonia Rodriguez Izquierdo, Won Seog Kim, Anna Sureda, Graham P. Collins, Kaitlyn Beyfuss, Cedric Dos Santos, Richard F. Olsson, Pier Luigi Zinzani; Instituto Europeo Di Oncologia SRL, Milano, Italy; Lille University Hospital, Lille, France; Institut Gustave Roussy, Villejuif, France; The Christie NHS Foundation Trust and Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom; Hôpital Lyon Sud, Lyon, France; Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; Universitätsklinikum Köln, Cologne, Germany; Seoul National University Hospital, Seoul, South Korea; Linear Clinical Research, Sir Charles Gairdner Hospital, and University of Western Australia, Perth, Australia; Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; Hospital Universitario 12 de Octubre, Madrid, Spain; Samsung Medical Center, Seoul, South Korea; Instituto Catalán de Oncología - Hospital Duran i Reynals, Barcelona, Spain; Oxford Cancer and Haematology Centre, Oxford, United Kingdom; Hematology R&D, AstraZeneca, Mississauga, ON, Canada; Hematology R&D, AstraZeneca, South San Francisco, CA; Hematology R&D, AstraZeneca, Gothenburg, Sweden; A.O.U. di Bologna – Policlinico Sant'orsola-Malpighi, Bologna, Italy

Background: The epigenetic enzyme protein arginine methyltransferase 5 (PRMT5) plays a critical role in cell proliferation and differentiation; PRMT5 dysregulation is associated with cancer development. Methylthioadenosine (MTA) is an endogenous partial inhibitor of PRMT5 that accumulates in cancer cells deficient in MTA phosphorylase (MTAP). In classic Hodgkin lymphoma (cHL), we previously reported that >80% of primary patient (pt) tumor samples are MTAP deficient (Urosevic J, ASH 2023). The MTA-cooperative PRMT5 inhibitor AZD3470 preferentially binds to the MTA-bound state of PRMT5, increasing its target engagement to MTAP-deficient cancer cells. Here, we present safety and preliminary efficacy of AZD3470 from a first-in-human Phase 1 study in relapsed/refractory (r/r) cHL (NCT06137144). **Methods:** Eligible pts were ≥18 years with r/r cHL after ≥3 prior lines of therapy (including brentuximab vedotin (BV) and anti-PD-1). In dose escalation, pts received oral AZD3470 monotherapy QD in ascending dose levels (DLs) using an mTPI-2 design. Primary endpoints were incidence and severity of treatment-emergent adverse events (TEAEs) and dose-limiting toxicity (DLT). Secondary endpoints were overall response rate (ORR) and complete response rate (CRR) per Lugano 2014 criteria. **Results:** As of Nov 25, 2025, 39 pts had received AZD3470 at DLs ranging from 1 to 8. Most pts were male (62%) with stage IV disease (77%) and a median age of 42 (range 25–78) years. Pts had received a median of 6 prior lines of anticancer therapy (range 3–14); all had had prior BV and anti-PD1 treatments, and 20 (51%) and 5 (13%) pts had had prior autologous and allogeneic hematopoietic stem cell transplantation, respectively. All patients evaluable for MTAP protein expression were MTAP deficient. Median duration of exposure was 15 weeks (range 0.1–45.1), with treatment ongoing in 16 pts (41%). TEAEs occurred in 85% of pts, predominantly grades 1 or 2. The most common TEAEs (any grade) were anemia (28%) and nausea (15%), followed by asthenia, constipation, fatigue, and neutropenia (13% each). Grade ≥3 TEAEs occurred in 28% of pts, most commonly neutropenia (related) and hypokalemia (n=2 each). Serious TEAEs occurred in 5 (13%) pts. Two pts had dose reductions due to TEAEs (grade 4 hypertriglyceridemia and grade 3 esophagitis). No DLTs, treatment discontinuations nor deaths due to TEAEs were reported. Of the 31 pts evaluable for efficacy, 14 had an objective response, with responses at doses ≥DL4. The highest response rate was observed at doses ≥DL7 (n=10) with an ORR of 80% and CRR of 50%. **Conclusions:** AZD3470 monotherapy was well tolerated up to DL8, with no DLTs and mainly low-grade AEs. Incidences of grade ≥3 AEs and SAEs were low. Importantly, both the ORR and CRR were dose-dependent and notably high in this heavily pretreated cHL population. Dose optimization is ongoing and further safety and efficacy will be reported. Clinical trial information: NCT06137144. Research Sponsor: AstraZeneca.

Linperlisib plus CHOP for newly diagnosed peripheral T-cell lymphoma: A single-arm, phase Ib/II study (LINCH trial).

Qingqing Cai, Yi Xia, Huiqiang Huang, Ying Zhao, Hongyan Tong, Tao Wu, Xiuhua Sun, Runhui Zheng, Jianbo Liu, Rong Tao, Fan Yang, Wenning Xu, Chunmei Yang, Xiaojie Fang, Man Nie, Bing Bai, Hang Yang, Yu Fang, Yuchen Zhang, Yi Cao; State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China; Sun Yat-sen University Cancer Center, Guangdong, China; The First People's Hospital of Foshan, Foshan, China; The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, China; Guizhou Cancer Hospital, Guiyang, China; Department of Hematology, Second Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China; The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China; The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; Fudan University Shanghai Cancer Center, Shanghai, China; The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Sun Yat-sen University Cancer Center, Guangzhou, China; State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University Cancer Center, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China; Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Peripheral T-cell lymphoma (PTCL) is a heterogeneous type of aggressive non-Hodgkin lymphoma with poor prognosis. CHOP-based regimens are most widely used for PTCL yet response rates and long-term survival remain unsatisfactory. Linperlisib, a selective PI3Kα inhibitor, has shown encouraging antitumor activity with manageable safety profile in relapsed or refractory PTCL. This study aimed to evaluate the efficacy and safety of linperlisib plus CHOP (L-CHOP) as first-line treatment for newly diagnosed PTCL. **Methods:** The LINCH trial (NCT05949944), a multi-center, single-arm phase Ib/II study, enrolled patients aged ≥ 18 years with newly diagnosed PTCL. In phase Ib, 6 patients received 6 cycles of L-CHOP to determine the recommended phase II dose (RP2D). In phase II, patients received L-CHOP at the RP2D. Following 6 cycles, patients achieving complete response (CR) or partial response (PR) continued linperlisib maintenance until progression or intolerable toxicity or up to 24 months. The primary endpoints were the DLTs incidence (phase Ib) and the CR rate after 6 cycles of L-CHOP (phase II). Preliminary results were reported. **Results:** From August 15, 2023 to November 15, 2025, 44 patients were enrolled, including 6 patients in phase Ib. The median age was 57 years (range 18–77); 28 patients were males (63.6%). Most patients (n = 35, 79.5%) had stage III-IV disease, and 17 (38.6%) had an IPI score of 3–5. In phase Ib, one DLT (grade 3 febrile neutropenia) occurred in cycle 1, confirming linperlisib 80 mg once daily as RP2D. At the data cutoff on December 30, 2025, efficacy was evaluable in 34 patients (26 completed six cycles; 8 discontinued early), with 10 still receiving induction therapy. After six cycles of combination therapy, 19 patients (55.9%) achieved CR and four achieved PR, resulting in an objective response rate (ORR) of 67.6%. Treatment-emergent adverse events (TEAEs) occurred in 32 patients (94.1%); hematologic toxicity were common: neutropenia (n = 24, 70.6%), leukopenia (n = 21, 61.8%), anemia (n =14, 41.2%). Grade ≥ 3 TEAEs occurred in 19 patients (55.9%), most frequently neutropenia (n = 13, 38.2%), leukopenia (n = 10, 29.4%) and pneumonia (n = 4, 11.8%). **Conclusions:** Preliminary results from LINCH study suggest that linperlisib combined with CHOP as first-line treatment for PTCL achieved promising efficacy and manageable safety. A randomized controlled trial evaluating linperlisib plus CHOP versus CHOP in patients with newly diagnosed PTCL has been initiated (NCT06548347). Clinical trial information: NCT05949944. Research Sponsor: None.

Baseline characteristics.	
Characteristics	Patients (n=44)
Age, years (median [IQR])	57 (18-77)
Sex	
Male	28 (63.6%)
Female	16 (36.4%)
ECOG PS	
0-1	39 (88.6%)
2	5 (11.4%)
Lugano stage	
I-II	9 (20.5%)
III-IV	35 (79.5%)
Pathological types	
AITL	23 (52.3%)
PTCL-NOS	14 (31.8%)
ALCL	3 (6.8%)
TFHL-NOS	2 (4.5%)
MEITL	1 (2.3%)
SPTCL	1 (2.3%)

Impact of VT-EBV-N on disease-free survival as post-remission therapy in EBV-positive extranodal NK/T-cell lymphoma: A randomized, double-blind, placebo-controlled phase 2 study.

Youngwoo Jeon, Young Rok Do, Won-Sik Lee, Sung-Yong Kim, Ho Jin Shin, Jae-Yong Kwak, Dong Won Baek, Duck-Hwan Yang, Seok-Goo Cho; Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; Keimyung University Dongsan Hospital, Dalseo-Gu, South Korea; Department of Hematology/Oncology, Inje University Busan Paik Hospital, Busan, South Korea; Konkuk University Medical Center, Seoul, South Korea; Division of Hematology-Oncology, Department of Internal Medicine, Research Institute of Medical Science, Pusan National University Hospital, Pusan National University School of Medicine, Busan, South Korea; Chonbuk National University Medical School and Hospital, Jeonju, South Korea; Kyungpook National University Chilgok Hospital, Daegu, South Korea; Hwasun Chonnam National University Hospital, Hwasun, South Korea; Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, none, South Korea

Background: Extranodal NK/T-cell lymphoma (ENKL) is an aggressive EBV-associated malignancy. Although complete remission (CR) can be achieved with intensive therapy, patients with high-risk features remain at substantial risk of relapse, and no standard post-remission therapy exists. VT-EBV-N is an autologous EBV-specific cytotoxic T lymphocyte (EBV-CTL) therapy designed to eliminate residual EBV-infected malignant cells. This phase 2 study evaluated the efficacy and safety of VT-EBV-N as post-remission therapy in patients with EBV-positive ENKL. **Methods:** This randomized, double-blind, placebo-controlled phase 2 trial enrolled patients with EBV-positive ENKL who had achieved CR within 6 months prior to enrollment and had at least one predefined high-risk factor for relapse. Patients were randomly assigned (1:1) to receive VT-EBV-N or autologous peripheral blood mononuclear cells (PBMC) as control. Treatment was administered IV weekly for 4 weeks, followed by a 4-week rest, and then once weekly for an additional 4 weeks (total 8 doses). The primary endpoint was 2-year disease-free survival (DFS). Secondary endpoints included overall survival (OS) and safety. Efficacy was analyzed in the full analysis set (FAS), and safety was assessed in the safety set. **Results:** A total of 50 patients were randomized, and 46 patients (VT-EBV-N, n=21; control, n=25) were included in the FAS. Baseline characteristics and distributions of high-risk features were generally balanced between groups. At 2 years, VT-EBV-N demonstrated a clinically meaningful and significant improvement in DFS compared with control (95.0% vs 77.6%). DFS events occurred in 1/21 patients (4.8%) in the VT-EBV-N group and 8/25 patients (32.0%) in the control group. Stratified log-rank analysis confirmed a significant DFS benefit with VT-EBV-N ($p=0.0347$). No deaths occurred in the VT-EBV-N group, whereas 4 deaths (16.0%) were observed in the control group; the difference in OS did not reach statistical significance ($p=0.0580$). VT-EBV-N was generally well tolerated. Most adverse events (AEs) were grade 1–2. Grade ≥ 3 AEs (CTCAE) occurred in 2/21 patients (9.52%) in the VT-EBV-N group and 4/25 patients (16.00%) in the control group. No treatment-related deaths were reported. **Conclusions:** VT-EBV-N demonstrated a clinically meaningful improvement in disease-free survival with a favorable safety profile in patients with EBV-positive ENKL in complete remission and at high risk of relapse. These findings support VT-EBV-N as a promising post-remission therapeutic option for this rare and aggressive lymphoma. Clinical trial information: KCT0003592. Research Sponsor: ViGenCell Inc.

Key efficacy and safety outcomes.

Outcome	VT-EBV-N	Control (PBMC)
Patients analyzed (FAS), n	21	25
2-year DFS, %	95.0	77.6
DFS events, n (%)	1 (4.8)	8 (32.0)
Deaths, n (%)	0 (0.0)	4 (16.0)
Grade ≥ 3 AEs, n (%)	2 (9.52)	4 (16.00)

Fixed-duration glofitamab monotherapy in relapsed/refractory (R/R) mantle cell lymphoma (MCL) with/without prior Bruton's tyrosine kinase inhibitor (BTKi) exposure: Updated data after a 3.5-year follow-up.

Yasmin Karimi, Martin Hutchings, Tycel Jovelle Phillips, Marek Trněný, Michael Dickinson, Fritz C. Offner, Franck Morschhauser, Emmanuel Bachy, Nancy L. Bartlett, Joshua Brody, Jan Zaucha, Tomasz Wrobel, Lidia Gil, Vanessa Breton, Raluca Negricea, Martine Kallemijn, Aurelien Berthier, Gila Sellam, Linda Lundberg, Carmelo Carlo-Stella; Division of Hematology/Oncology, University of Michigan, Ann Arbor, MN; Rigshospitalet and University of Copenhagen, Copenhagen, Denmark; City of Hope National Medical Center, Duarte, CA; First Faculty of Medicine, Charles University and the General Hospital, Prague, Czech Republic; Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, VIC, Australia; Department of Hematology Universitair Ziekenhuis, Gent, Belgium; CHU Lille, Service des Maladies du Sang, Lille, France; Centre Hospitalier Lyon Sud, Lyon, France; Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO; Tisch Cancer Institute, New York, NY; Medical University of Gdańsk, Gdańsk, Poland; Wrocław Medical University, Wrocław, Poland; Department of Hematology and Hematopoietic Cell Transplantation, Medical University, Poznań, Poland; Hoffmann-La Roche Ltd, Mississauga, ON, Canada; Roche Products Ltd, Welwyn Garden City, United Kingdom; F. Hoffmann-La Roche Ltd, Basel, Switzerland; Humanitas University and IRCCS Humanitas Research Hospital, Milan, Italy

Background: Patients (pts) with advanced R/R MCL have poor outcomes, especially pts with high-risk features or those progressing after BTKi therapies. Glofitamab is a CD20xCD3 2:1 bispecific antibody that redirects T cells to eliminate malignant B cells. A Phase 1/2 trial (NCT03075696) evaluated glofitamab monotherapy, given with step-up dosing (SUD) after obinutuzumab pretreatment (Gpt), in pts with R/R MCL. Prior analyses showed high response rates and manageable safety, regardless of prior BTKi exposure (Phillips, et al. ASCO 2024). We report longer follow-up data from this MCL cohort. **Methods:** Pts with R/R MCL after ≥ 1 prior line of systemic therapy received Gpt (single 1000 mg dose or 2000 mg split over 2 days, as needed) on cycle (C)1 day (D)1. Glofitamab SUD was given on C1D8 (2.5 mg) and C1D15 (10 mg), then the target dose of 16 or 30 mg every 3 weeks on D1 of C2–12. Efficacy endpoints included investigator-assessed complete response (CR) rate, overall response rate (ORR), duration of CR (DoCR), duration of response (DoR), progression free survival (PFS), and overall survival (OS). **Results:** As of Sept 8, 2025, 61 pts with R/R MCL were enrolled (Gpt: 1000 mg, n=17; 2000 mg, n=44); 60 pts were treated. The median number of prior lines of therapy was 2 (range 1–5), median age was 72.0 years (range 41–86), 86.9% of pts had Ann Arbor stage III/IV, and 26.3% had a simplified MCL International Prognostic Index score of ≥ 6 . Pts had high-risk disease features such as Ki-67 proliferation index $\geq 30\%$ (62.3%), blastoid/pleomorphic variants (9.8%), and TP53 mutation (19.7%). The median number of glofitamab cycles received was 12 (range 1–13). With a median OS follow-up of 41.5 months (mo; 95% CI: 37.4–48.7), the ORR and CR rate were 82% and 77%, respectively. Median DoCR was 40.8 mo (95% CI: 14.1–NE); 48.9% of pts had ongoing CRs at the data cut-off. Estimated 33-mo DoCR and DoR rates were 50.5% and 47.4%, respectively. Median (95% CI) PFS was 18 mo (11.3–42.8) and OS was NE (26.9–NE). For pts who received prior BTKi therapy (n=34 [55.7%]), the ORR and CR rate were 73.5% and 70.6%, respectively. Median (95% CI) DoCR was 15.4 mo (8.3–NE), PFS was 11.3 mo (5.1–32.6), and OS was 29.9 mo (11.3–NE). Estimated 33-mo DoCR and DoR rates were 42.7% and 41.0%, respectively. No new safety signals were observed. Cytokine release syndrome remained the most common adverse event (n=42/60, 70%; Grade 1–2, 58.3%; Grade 3–4, 11.6%), with lower rates in the 2000 mg (n=28/44, 63.6%) vs 1000 mg (n=14/16, 87.5%) Gpt cohorts. **Conclusions:** Updated data on fixed-duration glofitamab monotherapy in heavily pretreated pts with R/R MCL show robust efficacy and manageable safety, including in BTKi-exposed pts. Glofitamab monotherapy is a suitable treatment for pts with R/R MCL in need of rapid disease control and is under investigation in the Phase 3 GLOBRYTE trial. Clinical trial information: NCT03075696. Research Sponsor: F. Hoffmann-La Roche Ltd.

Mosunetuzumab plus polatuzumab vedotin (Mosun-Pola) versus rituximab, gemcitabine and oxaliplatin (R-GemOx) in patients with relapsed/refractory large B-cell lymphoma (R/R LBCL): Updated efficacy and safety from the phase 3 SUNMO study including in second-line (2L) versus third-line plus (3L+) patient subgroups.

Wonseog Kim, Jason Westin, Dai Maruyama, Huilai Zhang, Hideki Goto, Huangming Hong, Mark Fesler, Boone Goodgame, Zhiming Li, Eduardo M. Rego, Adam J. Olszewski, Nikesh Shah, Bei Hu, Shen Yin, Hao Wu, Martin Janousek, Song Pham, Connie Batlevi, Michael C. Wei, L. Elizabeth Budde; Samsung Medical Center, Seoul, South Korea; The University of Texas MD Anderson Cancer Center, Houston, TX; Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; Tianjin Medical University Cancer Institute, Tianjin, China; Hokkaido University Hospital, Sapporo, Japan; Si Chuan Cancer Hospital, Chengdu, China; St. Luke's Hospital, Chesterfield, MO; Dell Medical School, The University of Texas at Austin, Austin, TX; Sun Yat-sen University Cancer Center, Guangzhou, China; Instituto D'Or de Pesquisa e Ensino, São Paulo, Brazil; Brown University, Providence, RI; Tampa General Hospital Cancer Institute, Tampa, FL; Atrium Health Levine Cancer Institute and Wake Forest School of Medicine, Charlotte, NC; Genentech, Inc., South San Francisco, CA; F. Hoffmann-La Roche Ltd, Basel, Switzerland; Hoffmann-La Roche Ltd, Mississauga, ON, Canada; City of Hope National Medical Center, Duarte, CA

Background: At the primary analysis, Mosun-Pola demonstrated superior efficacy versus R-GemOx, with infrequent cytokine release syndrome (CRS) events and manageable safety in patients (pts) with R/R LBCL in the Phase 3 SUNMO trial (NCT05171647; Budde et al. 2025). We report updated efficacy and safety, including in the 2L setting. **Methods:** Pts with R/R LBCL ineligible for autologous stem-cell transplant (ASCT) were randomized 2:1 to Mosun (subcutaneous)-Pola or R-GemOx. Dual primary endpoints were IRC-assessed progression-free survival (PFS) and objective response rate (ORR); secondary endpoints included complete response (CR) rate, duration of response (DOR), duration of CR (DOCR), and safety. Overall survival (OS) was not assessed as the data cut-off was prior to the pre-defined final OS analysis. **Results:** At data cut-off (August 8, 2025), 138 and 70 pts were assigned to Mosun-Pola or R-GemOx, respectively. Overall, 91 pts had 1 prior line of therapy (LOT; 2L; Mosun-Pola, n=61; R-GemOx, n=30) and 117 had ≥2 prior LOT (3L+; Mosun-Pola, n=77; R-GemOx, n=40). With a median follow-up of 28.3 months (mos), Mosun-Pola continued to demonstrate superior PFS benefits over R-GemOx (HR, 0.41; 95% CI: 0.28–0.60; Table). ORRs with Mosun-Pola were 70.3% vs 40.0% with R-GemOx. The observed PFS benefit of Mosun-Pola over R-GemOx was similar in 2L (HR, 0.38; 95% CI: 0.22–0.67) and 3L+ (HR, 0.48; 95% CI: 0.29–0.81) subgroups. With Mosun-Pola vs R-GemOx in 2L, the 2-year PFS rates were 40.3% vs 20.1%, and the 2-year DOCR estimates were 60.8% vs 37.5%, respectively. Median DOCR was not reached with Mosun-Pola in 2L and 3L+ subgroups. ORRs with Mosun-Pola vs R-GemOx were 75.4% vs 36.7% in 2L pts, and 66.2% vs 42.5% in 3L+ pts, respectively. The safety profile was unchanged since the primary analysis. Grade (Gr) ≥2 CRS occurred in 4% of Mosun-Pola-treated pts and no ICANS events occurred. The safety profile was consistent in 2L pts: Gr 2 CRS occurred in 3% of Mosun-Pola-treated pts, with no Gr ≥3 CRS events. **Conclusions:** Mosun-Pola continues to show notable efficacy with manageable safety in pts with ASCT-ineligible R/R LBCL, particularly in the 2L setting. Clinical trial information: NCT05171647. Research Sponsor: F. Hoffmann-La Roche Ltd.

Mos (95% CI), unless stated	Mosun-Pola (n=138)	R-GemOx (n=70)	2L Mosun-Pola (n=61)	2L R-GemOx (n=30)	3L+ Mosun-Pola (n=77)	3L+ R-GemOx (n=40)
Median PFS	11.6 (5.6–17.6)	3.8 (2.9–4.1)	17.6 (5.6–NE)	3.6 (2.1–5.3)	8.6 (4.0–16.2)	3.9 (2.1–5.6)
Median DOR	18.8 (11.5–NE)	6.0 (3.7–23.9)	18.8 (11.3–NE)	6.0 (3.9–NE)	21.5 (9.5–NE)	5.4 (2.3–18.3)
CR, % (95% CI)	51.4 (42.8–60.0)	24.3 (14.8–36.0)	60.7 (47.3–72.9)	20.0 (7.7–38.6)	44.2 (32.8–55.9)	27.5 (14.6–43.9)
Median DOCR	NE	18.3 (3.9–NE)	NE (15.6–NE)	21.4 (3.9–NE)	NE (21.5–NE)	7.5 (2.3–NE)

NE, not estimable.

Mediterranean CD19 genetic variations and potential influence on CAR T-cell therapy efficacy: Implications for population-tailored immunotherapy.

Osama Alsmadi, Anas Al-okaily, Maysa Al-Hussaini; King Hussein Cancer Center, Amman, Jordan; Cell Therapy and Applies Genomics Department, KHCC, Amman, Jordan

Background: CAR T-cell therapy has transformed the treatment of B-cell malignancies. However, relapse due to CD19 antigen escape remain a major challenge, often driven by genetic variants affecting CD19 structure, leading to CAR-T resistance. Mediterranean populations including Arabs, remain underrepresented in genomic studies. The Arabian prevalence and functional impact of CD19 variants is unknown. **Methods:** We analyzed and annotated CD19 NGS data from a Mediterranean cohort comprised of 1,305 Arabian individuals. The overall allele frequencies were compared to global databases. Clinically reported resistance mutations were prioritized based on published CAR T-cell studies. Hardy-Weinberg Equilibrium (HWE) was also assessed. **Results:** This study characterizes functionally significant CD19 polymorphisms in a Mediterranean population, with particular focus on the clinically relevant L174V (rs2904880) variant known to associate with CAR-T therapy resistance. 174V was seen in this cohort with a Minor Allele Frequency (MAF) of 76.3%, and a variant allele homozygosity (V/V) of 65.2%. **Conclusions:** Our cohort displayed elevated V174 homozygosity compared to other populations, including Europeans, Americans, and South Asians, potentially predisposing to diminished CAR-T efficacy. These findings indorse population-adjusted CAR-T product development, and implementation of pre-therapy CD19 genotyping protocols to identify at-risk patients. Development of CARs targeting conserved CD19-epitopes, or combinatorial antigen approaches is warranted to mitigate resistance. Research Sponsor: None.

First-line odronextamab (Odro) plus chemotherapy (CHOP) in diffuse large B-cell lymphoma (DLBCL): OLYMPIA-3 Part 1B results.

Matthew Matasar, Thomas A. Jandl, Rita Assi, Philip Kuriakose, Chait Iragavarapu, Thomas Illmer, Neta Goldschmidt, Abraham Avigdor, Youngwoo Jeon, Shin Ong, Costas K. Yannakou, Hanlon Sia, Ho Jin Shin, Lily Wong, Sonia Gonzalez de Villambrosia, Ahlam Naila Kori, Ciel De Vriendt, Alice Cao, Nazia Iqbal, Jean-Marie Michot; Rutgers Cancer Institute, New Brunswick, NJ; Stony Brook University Hospital, Stony Brook, NY; Indiana University School of Medicine, Indianapolis, IN; Henry Ford Health System, Detroit, MI; Hematology & Cellular Therapy, University of Kentucky College of Medicine, Markey Cancer Center, Lexington, KY; Berufsausbildungsgemeinschaft, Dresden, Germany; Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel; Chaim Sheba Medical Center, Ramat Gan, Israel; Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; Singapore General Hospital, Singapore, Singapore; Epworth HealthCare and The University of Melbourne, Melbourne, VIC, Australia; Pindara Private Hospital, Gold Coast, NSW, Australia; Division of Hematology-Oncology, Department of Internal Medicine, Research Institute of Medical Science, Pusan National University Hospital, Pusan National University School of Medicine, Busan, South Korea; Queen Elizabeth Hospital, Kota Kinabalu, Malaysia; Hospital Universitario Marqués de Valdecilla, Santander, Spain; Hospital Tengku Ampuan Afzan, Kuantan, Malaysia; Ghent University Hospital, Ghent, Belgium; Regeneron Pharmaceuticals, Inc., Tarrytown, NY; Gustave Roussy, Villejuif, France

Background: Approximately 25% of patients (pts) treated with rituximab + CHOP do not have a complete response (CR), and those with refractory/relapsed disease or high-risk features have poor outcomes. To address this unmet need, bispecific antibody combinations are being evaluated. In Part 1A (dose escalation) of the Phase 3 OLYMPIA-3 study (NCT06091865), odronextamab (Odro)-CHOP demonstrated generally manageable safety (most common treatment-emergent adverse events [TEAE] were neutropenia [81.8%] and cytokine release syndrome [CRS; 54.5%]) and encouraging preliminary efficacy in pts with previously untreated DLBCL, with CR rates of 100% on PET/CT (160 mg dose level, selected for Part 1B dose optimization). Here, we report Part 1B results. **Methods:** Part 1B included pts aged ≥ 18 years with untreated CD20+ DLBCL not otherwise specified or high-grade B-cell lymphoma with at least 1 high-risk feature. Odro-CHOP was administered in 6×21 -day cycles, with Odro 0.7/4/20 mg step-up dosing from Cycle 1 Day 8. Pts were randomized 1:1 to receive Odro 160 mg QW/320 mg Q2W (Regimen [R] 1) or Odro 160 mg QW/160 mg Q3W (R2) with CHOP. Primary endpoint was safety. Secondary endpoints included investigator-assessed objective response rate (ORR) and CR rate per 2014 Lugano criteria. **Results:** At data cut-off (August 19, 2025), 40 pts were enrolled in Part 1B (20 per regimen). Median age was 67.5 years, 60.0% of pts were male, and 75.0% had an IPI score of 3–5. Median duration of treatment exposure was 18.1 weeks (R1) and 16.6 weeks (R2); 67.5% of pts completed 6 treatment cycles. Median relative dose intensity ranged from 90.1 to 100% for Odro and 92.7 to 100% for CHOP. The safety profile of Odro-CHOP was similar across regimens. TEAEs led to dose interruption/delay in 70.0% vs 50.0% of pts and to CHOP dose reduction in 10.0% vs 5.0% of pts with R1 vs R2, respectively. No TEAEs led to Odro dose reduction and 1 led to treatment discontinuation (Grade 4 neutropenic sepsis, R2). The most common TEAEs were neutropenia (57.5%), CRS (55.0%), and anemia (42.5%). CRS rates were consistent with Part 1A, predominantly Grade 1 (42.5% of pts). ICANS occurred in 3 pts (all Grade 1) and resolved completely. All enrolled pts were analyzed including 3 pts who discontinued treatment prior to tumor imaging assessment. With a median follow-up of 2.3 months in both regimens, ORRs were 95.0% (R1) and 90.0% (R2), and CR rates were 85.0% (both regimens). **Conclusions:** In Part 1B of OLYMPIA-3, the safety profile of Odro-CHOP was generally manageable and preliminary efficacy was encouraging with no meaningful differences between regimens, and combination with Odro did not impact the delivery of CHOP. Given these results, the less frequent Odro dosing regimen (R2) with CHOP was selected as the recommended Phase 3 dose for Part 2 (randomized controlled trial). Biomarker data will be presented. Clinical trial information: NCT06091865. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Real-world outcomes of bispecific antibodies in relapsed/refractory (R/R) follicular lymphoma (FL).

Jessica Allen, Rahul Shah, Lei Feng, Lorenzo Falchi, Ayushi Chauhan, Sonia Godbole, Swetha Kambhampati Thiruvengadam, Ajay Major, Andrew Philip Jallouk, Reid Merryman, Amy Ayers, Jennifer Leigh Crombie, Shakthi Bhaskar, Steven Michael Bair, Alex F. Herrera, Yazeed Sawalha, Gilles A. Salles, Naren Epperla, Sairah Ahmed, Allison Marie Bock, On behalf of all investigators of the Collaborative US Bispecifics Consortium (CUBIC); University of Utah/Huntsman Cancer Institute, Salt Lake City, UT; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY; Ohio State University Wexner Medical Center, Columbus, OH; City of Hope, Duarte, CA; Division of Hematology, Department of Medicine, University of Colorado School of Medicine, Aurora, CO; Vanderbilt University Medical Center, Nashville, TN; Dana-Farber Cancer Institute, Boston, MA; University of Colorado Denver, Aurora, CO; The Ohio State University - Division of Hematology, Columbus, OH; Memorial Sloan Kettering Cancer Center, New York, NY; Huntsman Cancer Institute at The University of Utah, Salt Lake City, UT

Background: Mosunetuzumab (mosun) and epcoritamab (epco) are bispecific antibodies (BsAbs) approved for R/R FL, with pivotal trials (n=90–128) initially demonstrating 60–63% complete response rate (CRR), 80–82% overall response rate (ORR), and 1-year progression-free survival (PFS) rate of 58–66%. Real-world outcomes remain limited. We report the real-world efficacy and safety outcomes of BsAbs for patients (pts) with R/R FL treated in the Collaborative United States Bispecifics Consortium (CUBIC). **Methods:** This is a multicenter retrospective study of adult pts with R/R FL treated with standard of care mosun or epco between 2/2023 and 9/2025 at eight CUBIC centers. Efficacy outcomes included ORR, CRR, PFS, and overall survival (OS). PFS and OS were estimated using the Kaplan–Meier method. Safety outcomes included incidence and grade (G) of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). **Results:** A total of 99 pts with R/R FL were treated with BsAb, with 92% receiving mosun (n=91) and 8% (n=8) receiving epco. Median age was 68 years (range 33–101), 61% were ≥65 years (n=60), 63% were male (n=62), 8% Hispanic (n=8), 92% (n=79) had ECOG performance status (PS) of 0–1, 51% (n=42) had FLIPI ≥3, and 31% (n=30) had elevated LDH. Median prior lines of therapy were 3 (range 1–14), and 15% (n=15) had prior CAR-T. Among 96 pts with complete response data, the ORR was 87% and CRR was 72%. Median time to best response was 2.9 months (mo) (range 1.2–12.7). Response rates were not significantly associated with BsAb, ECOG PS, FLIPI, elevated LDH, or prior CAR-T. At median follow-up of 16.9 mo, the one-yr and 18 mo PFS rates were 72% (95%CI 62–83%) and 56% (95%CI 45–70%). One-yr and 18 mo OS rates were 94% (95%CI 90–99%) and 92% (95%CI 86–99%), respectively. Hispanic pts had better PFS than non-Hispanic pts (2-yr PFS 100% vs 42%, p=0.02). PFS was not significantly influenced by BsAb product, elevated LDH, ECOG PS, FLIPI, or prior CAR-T. Patients with ECOG of 2 had inferior OS than pts with ECOG of 0–1 (2-yr OS 43% vs 89%, p=0.02). Male sex was associated with inferior OS compared to female sex (2-yr OS 76% vs 100%, p=0.02). No differences in ORR, CRR, PFS, or OS were observed between pts <65 vs ≥65 yrs or <80 vs ≥80 yrs. Of 96 pts with complete safety data, CRS occurred in 34% of pts (G1 26%; G2 6%), with no ≥G3 events. ICANS occurred in 3% of pts (n=3), all G1 events. The incidence of CRS or ICANS was not significantly associated with age, LDH, ECOG, FLIPI, or prior CAR-T. **Conclusions:** In this diverse, heavily pretreated real-world cohort, 61% of patients were aged ≥65 years. Bispecific antibodies for R/R FL demonstrated high response rates, favorable survival outcomes, lower rates of cytokine release syndrome—primarily due to fewer grade ≥2 events—and ICANS rates comparable to those observed in pivotal clinical trials, supporting their use across heterogeneous populations, including very elderly patients. Research Sponsor: None.

Golcadomide (GOLCA), a potential, first-in-class, oral CELMoD, + Pola-RCHP in patients (pts) with newly diagnosed aggressive B-cell lymphoma (a-BCL): Safety and 12-month (mo) efficacy results.

Marc S. Hoffmann, Grzegorz S. Nowakowski, Michal Kwiatek, Maria Bouzani, Dagmara Zimowska-Curylo, Muhamad Alhaj Moustafa, Alejandro Martin Garcia-Sancho, Juan-Manuel Sancho, Wojciech Jurczak, Arpankumar Patel, Floriane Boucaud, Argyrios Gkasiamis, Mark Kaplan, Arnaud Amzallag, Matt Stokes, Tanvi Jindia, Serena K. Perna, Theodoros Vassilakopoulos; The University of Kansas Cancer Center, Kansas City, KS; Mayo Clinic Rochester, Rochester, MN; Poznan University of Medical Sciences, Poznan, Poland; Evangelismos General Hospital, Athens, Greece; Krakow University Hospital, Krakow, Poland; Mayo Clinic Florida, Jacksonville, FL; Hospital Universitario de Salamanca, IBSAL, CIBERONC, University of Salamanca, Salamanca, Spain; Germans Trias i Pujol University Hospital, ICO-IJC, Badalona, Spain; MSC National Research Institute of Oncology, Krakow, Poland; Late Clinical Development, Hematology/Oncology and Cell Therapy, Bristol Myers Squibb, Princeton, NJ; Late Clinical Development, Hematology/Oncology and Cell Therapy, Bristol Myers Squibb, Boudry, Switzerland; Translational Development, Bristol Myers Squibb, Madison, NJ; Informatics and Predictive Sciences, Bristol Myers Squibb, Cambridge, MA; Informatics and Predictive Sciences, Bristol Myers Squibb, Summit, NJ; Global Biometrics and Data Sciences, Bristol Myers Squibb, Hyderabad, Telangana, India; Late Clinical Development, Hematology/Oncology and Cell Therapy, Bristol Myers Squibb, Madison, NJ; National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece

Background: Up to 40% of pts with diffuse large B-cell lymphoma (DLBCL) will relapse or have refractory disease following 1L treatment (Tx) with SOC chemoimmunotherapy regimens R-CHOP or Pola-RCHP. High risk (HR) populations include those with International Prognostic Index (IPI) score 3–5 and IPI 1–2 with either ≥ 1 lesion ≥ 7 cm or baseline LDH $> 1.3 \times$ ULN. GOLCA is a potential, first-in-class, oral CELMoD designed for the Tx of lymphoma, with preferential distribution to lymphoid organs and enhanced activity in lymphoma cell lines. GOLCA induces rapid and deep degradation of Ikaros and Aiolos, leading to direct cell killing and immunomodulatory activity. GOLCA 0.4 mg + R-CHOP has shown promising safety, a $\geq 90\%$ minimal residual disease (MRD) negativity rate, and durable efficacy (24-mo PFS, 79%) in 1L a-BCL (Nowakowski et al, ASH 2025, 476) and is being evaluated in the Phase (Ph) 3 study GOLSEEK-1 (NCT06356129). We report initial Ph1b results with GOLCA + Pola-RCHP in 1L a-BCL. **Methods:** Pts aged ≥ 18 y with ECOG PS ≤ 2 , IPI 0–5 (Part 2A) or 2–5 (Part 2B), and newly diagnosed a-BCL with measurable tumorous disease were included. Pts were treated with GOLCA + Pola-RCHP for six 21-day (D) cycles or until disease progression/unacceptable toxicity/study withdrawal. In dose escalation, GOLCA was dosed at 0.2 and 0.4 mg D1–7. In dose expansion, pts were randomized 1:1 to Pola-RCHP + GOLCA 0.2 or 0.4 mg. Primary endpoint: safety; efficacy was a secondary endpoint. **Results:** At data cutoff, 57 pts were treated with GOLCA + Pola-RCHP (0.2 mg, n=28; 0.4 mg, n=29). Median age was 63 y. Most pts had HR disease (86%) and DLBCL not otherwise specified histology (84%). For known cell of origin (COO), 47% were germinal center B cell (GCB) and 39% non-GCB by Hans algorithm. Forty-seven pts (83%) completed Tx and 52 (91%) entered the follow-up (f/u) period. Grade 3/4 Tx-emergent adverse events occurred in 95% of pts, most frequently neutropenia (86%; an on-target side effect of GOLCA) and anemia (39%). Median relative dose intensity for GOLCA and Pola-RCHP components was $> 95\%$. At 15.5 mo median f/u, end of Tx (EOT) complete metabolic response (CMR) rate was 69% at 0.2 mg, 82% at 0.4 mg, and similar across COO subtypes. EOT CMR was consistent in HR pts (65% at 0.2 mg, 83% at 0.4 mg). The 12-mo DOR and PFS rates were 92% and 88% at 0.2 mg, and 96% and 96% at 0.4 mg. In pts with both pre-Tx and EOT ctDNA analysis, 65% and 83% at 0.2 and 0.4 mg achieved MRD negativity (PhasED-Seq) at EOT. **Conclusions:** GOLCA + Pola-RCHP demonstrated a predictable and manageable safety profile, and addition of GOLCA did not compromise median dose intensity of Pola-RCHP. GOLCA 0.4 mg + Pola-RCHP resulted in a high rate of durable CMRs, high rate of MRD negativity, and a promising 12-mo PFS rate. These data continue to show that GOLCA + SOC regimens R-CHOP and Pola-RCHP has potential to improve outcomes in 1L HR a-BCL. Clinical trial information: NCT04884035. Research Sponsor: Bristol Myers Squibb.

Safety and efficacy of Azer-cel, an allogeneic CD19 CAR T for the treatment of patients with relapsed/refractory non-Hodgkin lymphoma and chronic lymphocytic leukemia not previously exposed to autologous CAR T therapy.

Danielle Nicole Blunt, Matthew Ku, Houston Holmes, Nagendraprasad Sungala, Vinay Vanguru, Jean Yared, Scott Solomon, Hannah Rose, Aparna Raval, Grey A. Wilkinson, John Chong Han Byon, Supriya Gupta; Royal Adelaide Hospital, Department of Radiation Oncology, Adelaide, SA, Australia; Department of Haematology, St. Vincent's Hospital, Melbourne, VIC, Australia; Texas Oncology PA, Baylor/Sammons Cancer Center, Dallas, TX; Liverpool Hospital, Sydney, NSW, Australia; Institute of Haematology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia; University of Maryland, Baltimore, MD; Northside Hospital Cancer Institute, Atlanta, GA; Department of Haematology, Andrew Love Cancer Centre, Barwon Health, Geelong, VIC, Australia; Imugene Limited, Sydney, NSW, Australia; Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, MN

Background: Azer-cel (azercabtagene zapreleucel) is an allogeneic, off-the-shelf, CD19-directed, chimeric antigen receptor (CAR) T-cell therapy derived from healthy donor T cells. We report the outcomes of patients treated with azer-cel plus low-dose interleukin-2 (IL-2) who enrolled in a Phase 1b dose expansion cohort for patients with r/r NHL and CLL and were naive to prior autologous CAR T-cell therapy (NCT03666000). **Methods:** Eligible patients with an aggressive B-cell CD19+ disease included those with diffuse large B-cell lymphoma (DLBCL, not otherwise specified or transformed), high-grade B-cell lymphoma, follicular lymphoma (FL, Grade 1-3a), marginal zone lymphoma (MZL), Waldenstrom macroglobulinemia (WM), primary central nervous system lymphoma (PCNSL), and CLL/small lymphocytic lymphoma. Patients must have had at least 1-2 prior lines of therapy, depending on histological subtype, and no prior treatment with an autologous CAR T-cell therapy. Prior autologous stem cell transplant (ASCT) and bispecific antibodies were allowed. Patients received lymphodepletion with fludarabine (30 mg/m²/day) and cyclophosphamide (750 mg/m²/day) (Aug/Cy) for 3 days, followed by azer-cel infusion (500×10⁶ cells) on Day 0 and subcutaneous low-dose IL-2 (1 million IU daily) for 14 days. Peripheral blood was collected at multiple timepoints, and levels of azer-cel transgene were quantified using qPCR. **Results:** Nineteen patients received azer-cel with low-dose IL-2. Median age was 59 years (range: 56-73). Disease subtypes included: DLBCL (5), MZL (5), CLL (4), PCNSL (3), FL (1), and WM (1). Of these, 4 (21%) had received ≥4 prior therapies, 3 (16%) had prior bispecific antibodies, and 2 (11%) had prior ASCT. Primary refractory disease was present in 6 (32%) patients. Median tumor burden was 36 cm² (range: 5.5-125). The overall response rate was 81% (13/16), with a complete response (CR) rate of 31% (5/16). Objective response by subtype included: DLBCL, 60% (1 CR, 2 partial responses [PRs]); MZL, 100% (3 CRs, 1 PR); CLL, 100% (3 PRs); PCNSL, 50% (1 PR); FL, 100% (1 CR); and WM, 100% (1 PR). Pharmacokinetic analysis (n=16) showed a mean CAR T-cell peak expansion of 1.7×10⁵ copies/μg genomic DNA (SEM: 0.6×10⁵), AUC₀₋₂₈ of 9.5×10⁵ copies/μg genomic DNA (SEM: 3.4×10⁵), and time to peak expansion 5.9 days (SEM: 0.63). ICANS occurred in 7 patients (37%), with 3 Grade 1-2 events, 3 Grade 3 events, and 1 Grade 4 event. CRS was observed in 15 patients (79%), with no Grade ≥3 events. **Conclusions:** Azer-cel in autologous CAR T-naïve patients demonstrates promising clinical activity across a broad range of CD19+ B-cell malignancies, including MZL and CLL. Encouraging response rates, robust CAR T-cell expansion, and a manageable safety profile support further investigation. Clinical trial information: NCT03666000. Research Sponsor: None.

REVO-U: A next-generation, gene-editing–free universal CAR-T platform to enable ultra–high-yield manufacturing and identification of early clinical activity in relapsed/refractory DLBCL.

Di Wu, Sijie Zhao, Xiaoning Wang, Huaiyu Wang, Jing Zhao, Jie Wang, Busheng Xue, Wenjing Luo, Miaoqing Li, Mei Zhang, Mengchang Wang, Jieying Xi, Huasheng Liu, Chunhong Sun, Ruimin Liu, Xiaohu Frank Fan, Yi Lv, Pengcheng He; The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; The First Affiliated Hospital of Xian Jiaotong University, Xian, China; Wondercel Therapeutics, Shenzhen, Guangdong, China; Department of Hematology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Background: We previously invented autologous CAR-T product ciltacabtagene autoleucel (Carvykti) for multiple myeloma, with robust efficacy. However, its personalized nature incurs high costs and limits scalability. Conventional universal CAR-Ts rely on complex gene editing, yielding 50–100 doses/batch, yet to be commercially approved. We created REVO-U, a gene-editing-free universal CAR-T platform using proprietary technologies, initiating explorations in hematologic and solid tumors. It enables >3,000 doses/single batch from healthy donor cells, reducing costs and potentially eliminating capacity constraints in cell therapy. **Methods:** REVO-U uses protein-directed degradation to mitigate GvHD without gene editing. In a single-arm, open-label exploratory study, CD19-targeted REVO-UW19 was given post-lymphodepletion (fludarabine/cyclophosphamide) with short-term oral mycophenolate sodium (EC-MPS) in relapsed/refractory DLBCL patients. **Results:** Four subjects treated (see Table for details). Subject 1 (Flu 30/Cy 300 mg/m² + 100e6 cells; EC-MPS 1440 mg BID x5 days, MPA average AUC 22.12 mg·h/L): PK Cmax 4.3k copies/mL, Transient fever (38.5°C, grade 0 CRS); ≥PR ongoing >10 months. Subject 2 (Flu 30/Cy 400 mg/m² + 200e6 cells; EC-MPS 1440 mg BID x11 days, MPA average AUC 71.44 mg·h/L): Cmax 173.9 k copies/mL, grade 1 CRS, CMR by PET-CT (PFS 4 months). Subject 3 (73y, high burden; Flu 30/Cy 500 mg/m² + 200e6 cells; EC-MPS x14 days, MPA average AUC 71.23 mg·h/L): REVO-U CAR-T expansion was highly significant. Cmax reached 19,057.6 k copies/mL, grade 3 CRS/HLH (controlled), followed by prolonged neutropenia and a fatal infection; PR, unconfirmed CR. Subject 4 (post-DLT: Flu 30/Cy 400 mg/m² + 50e6 cells; EC-MPS x22 days, MPA average AUC 15.21 mg·h/L): Cmax 2.01 k copies/mL, No CRS, PD. No GvHD in any patient. The target effective MPA AUC is >30 mg·h/L. Only Subjects 2 and 3 achieved this threshold on average MPA exposure. **Conclusions:** REVO-U enables ultra-scalable manufacturing like biologic drugs. Early DLBCL data show no GvHD, with expansion, CRS and responses influenced by lymphodepletion, dose & MPA exposure. Timely EC-MPS adjustment per MPA AUC may be needed for efficacy assurance. Promising PK expansion, persistence post-EC-MPS withdrawal, and efficacy signals have also emerged in solid tumor target explorations. We will report updated data on this innovative universal platform across malignancies at future conferences. Clinical trial information: NCT06662227. Research Sponsor: Wondercel Therapeutics; The First Affiliated Hospital of Xi'an Jiaotong University.

Summary of lymphodepletion, cell dosing, MPA exposure, pharmacokinetic, safety, and efficacy.

Subject #	Flu/CTX (mg/m ²)	Dose (million cells)	EC-MPS (Day used)	MPA-mAUC (mg·h/L)	PK Cmax (k Copies/mL)	CRS (Grade)	DLT	Efficacy (30 days)	PFS (months)
1	30/300	100	5	22.12	4.3	0	-	PR (CR?)	>10
2	30/400	200	11	71.44	173.9	1	-	CMR	3
3	30/500	200	14	71.23	19057.6	3	+	PR (CR?)	
4	30/400	50	22	15.21	2.01	0	-	PD	

First-in-human in vivo CAR T-cell generation using a CD8-targeted lipid nanoparticle platform in relapsed/refractory B-cell lymphoma.

Xi Zhang, Li Gao, Xixi Xiang, Ruihao Huang, Jiang Qu, Yunjing Zeng, Xianlan Zhao, Weitong Xu, Yuting Chen, Jun Liao, Huang Hai, Xue Li, Chutong Ouyang, Han Zheng, Yuquan Wei, Xiangrong Song; Xinqiao Hospital of Army Medical University, Chongqing, China; Xinqiao Hospital, Army Medical University, Chongqing, China; Xinqiao Hospital of Army Medical University, Chengdu, China; Cancer Center and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China; WestGene Biopharma Co., Ltd., Chengdu, China

Background: R/R B-cell lymphomas remain challenging despite advances in ex vivo CAR T-cell therapies, which are limited by complex logistics, manufacturing delays, and cost. In vivo CAR T-cell generation using targeted delivery offers a paradigm shift. We report the first-in-human study of a CD8-targeted lipid nanoparticle (CD8-tLNP) platform to generate functional CD19 CAR T cells *in vivo*. **Methods:** The CD8-tLNP was constructed by conjugating an anti-CD8 VHH to the surface of LNP encapsulating mRNA coding a CD19-directed chimeric antigen receptor. Safety, pharmacodynamics, and tolerability were first evaluated in non-human primates following intravenous administration. Subsequently, 4 patients with R/R CD19⁺ B-cell lymphoma received four intravenous doses of CD19-CD8-tLNPs. Peripheral blood was collected at serial time points to assess CAR⁺ CD8⁺ T cells, B-cell depletion, cytokine levels, and clinical laboratory parameters. Antitumor activity was evaluated by PET-CT imaging, and adverse events were graded according to standard criteria. **Results:** The platform showed favorable safety and PD in monkeys. To date, seven patients with relapsed or refractory CD19⁺ B-cell lymphoma have been treated. Among the evaluable patients, two patients achieved PR with decreased tumor lesions, one maintained SD by day 28; four patient remains pending efficacy evaluation. Following i.v. administration, CAR gene and surface expression in peripheral blood CD8⁺ T cells peaked within 4–6 hours and declined thereafter, consistent with transient in vivo CAR T-cell generation. This was accompanied by rapid and near-complete peripheral B-cell clearance, with complete depletion (<1 B cell/ μ L) observed between 12 hours and day 3. Three booster doses administered at 3-day intervals sustained complete B-cell depletion and CAR T-cell activity. The treatment was generally well tolerated. No cytokine release syndrome of grade ≥ 2 was observed. Transient increases in CRP and ferritin were observed and were clinically manageable, without significant elevations in liver enzymes or prolonged cytopenias. Two patients showed naïve B-cell reconstitution by day 32 or 47. **Conclusions:** This first-in-human study demonstrates the feasibility and early clinical activity of in vivo CAR T-cell generation using a CD8-targeted LNP platform in patients with relapsed or refractory B-cell lymphoma. The approach enables rapid, transient CAR T-cell expression, repeatable dosing, and a favorable safety profile without lymphocyte clearance and complex manufacturing in ex vivo CAR T-cell. These findings provide clinical proof of concept for a scalable, off-the-shelf CAR T-cell therapy and support further clinical evaluation in hematologic malignancies. Clinical trial information: 2025-02-02. Research Sponsor: None.

First-in-human novel bispecific epitope anti-CD5 nanobody CAR-T cells for refractory or relapsed T-cell malignancies.

Lu Haiyang, Su Li, Yuxuan Song, Chuanhe Jiang, Jing Pan, Xiaoxia Hu; Ruijin Hospital, Shanghai, China; Department of Hematology, Shanghai Lique Hospital, Shanghai, China; State Key Laboratory of Experimental Hematology, Department of Hemato-Oncology and Immunotherapy, Beijing Gubroad Hospital, Beijing, China; Shanghai Institute of Hematology, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine, Shanghai Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Background: Refractory/relapse (r/r) aggressive T-cell lymphomas have poor prognosis with 5-year PFS of 20~30%, meanwhile CAR-T therapy brings new hope to this progressive disease. We previously reported allogeneic humanized CD5 CAR-T (huCD5 CAR) therapy achieved 100% ORR in r/r acute T lymphoblastic leukemia/lymphoma (T-ALL) patients. However, huCD5 CAR-T exhibit insufficient expansion activity, necessitating the optimization of CAR-T structure. Here, we developed a llama-derived nanobody-based bispecific epitope anti-CD5 CAR (NbCD5 CAR) construct, and evaluated its efficacy and safety in r/r T-ALL and T-cell non-Hodgkin's Lymphoma (T-NHL). **Methods:** llama-derived nanobody library was utilized to screen for CD5-specific nanobodies. The efficacy was then examined in NSG mice inoculated with Jurkat cell line. Tumor burden was assessed by flow cytometry and bioluminescent imaging. Finally, the efficacy and safety of the NbCAR vector were evaluated in the trials of r/r T-ALL (NCT07070323) and r/r T-NHL (NCT07022964). **Results:** We selected the NbCD5 CAR-T cells with superior cytotoxicity against T-cell lines compared to huCD5 CAR-T constructs. Then we determined its efficacy in NSG mice inoculated with Jurkat cell line. On day 7 post-tumor inoculation, mice received either Mock-T, huCD5 CAR-T or NbCD5 CAR-T cells. We observed that the NbCD5 CAR completely controlled tumor burden in mice and showed superior efficacy compared to huCD5 CAR. Then we proceed to the clinical trials containing 5 cases of T-ALL and 9 cases of T-NHL. In the T-ALL cohort, 3 patients have history of allo SCT, 4 patients received prior CD7 CAR-T therapy. All patients have infused 1.0×10^6 /kg NbCD5 CAR-T cells. The adverse events (AEs) included grade 1 CRS (5/5), grade 2 ICANS (1/5), and grade 1~2 GVHD (2/5). All patients achieved CR at day 30 evaluation. In the median follow-up time of 80 days, 2 patients bridged to allo SCT, 1 patient relapsed at day 45 and died shortly thereafter. In the T-NHL cohort, 9 patients aged 30 to 64 have failed of at least 2 lines of chemotherapy, and 1 patient had history of auto SCT. The patients have received 1.0×10^6 /kg NbCD5 CAR-T cells. All patients had grade 1~2 CRS, no ICANS was reported. Notably, EBV reactivation (5/9) was observed, including Grade 3~5 EBV reactivation (3/9). The ORR was 66.7% at day 30, 2 patients failed to respond for CAR-T expansion failure or weak CD5 expression. The CAR-T expansion was reached its peak at day 12 (range: 11~17), with the clearance of CD5⁺ T cells in blood. In the median follow-up time of 94 days, 5 patients bridged to allo SCT. **Conclusions:** We optimized the nanobody NbCD5 CAR construct and showed superior cytotoxicity *in vitro* and *in vivo*. We also got preliminary safety and efficacy profiles in r/r T-ALL and T-NHL. This clinical trial is still ongoing, and long-term efficacy and clinical complication of CD5 CAR-T cell therapy still require further investigation. Clinical trial information: NCT07070323, NCT07022964. Research Sponsor: None.

Genetic signatures of CNS relapse in DLBCL patients profiled with next-generation sequencing (NGS).

Jackson Thomas Bowers, Anjanaa Vijayanarayanan, Natalie Gill, Michela Traglia, Reuben Thomas, Charalambos Andreadis, Weiyun Zhuang Ai, Carrie Ho, Lawrence D. Kaplan, Mwanasha Hamuza Merrill, Madhav Rao Seshadri, Michael Paul Randall, Karthik Ganapathi, Sonam Prakash, James L. Rubenstein, Patrick Devine, Michael Alexander Spinner; Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; Department of Pathology, University of California San Francisco, San Francisco, CA; Gladstone Institutes Bioinformatics Core, San Francisco, CA

Background: CNS relapse of DLBCL is a devastating event with median survival <6 months. While the overall incidence is low (~5%), various factors impact the risk of CNS relapse including CNS-IPI, cell-of-origin (COO), and MYC rearrangement. Recent studies using NGS have defined DLBCL genetic subgroups with distinct biology. The MCD and C5 subgroups, defined by LymphGen and DLBclass, respectively, have a shared genetic signature characterized by MYD88 L265P and CD79B mutations, immune evasion, and extranodal tropism with enrichment in CNS lymphomas. We investigated the impact of MCD/C5 signature on the risk of CNS relapse in a large cohort of DLBCL patients (pts) profiled with NGS. **Methods:** We performed a retrospective analysis of 155 DLBCL pts treated with chemoimmunotherapy and profiled with the UCSF500 NGS panel, which includes 529 genes and copy number data. FISH was performed to evaluate for MYC, BCL2 and BCL6 rearrangements. Pts with CNS involvement at diagnosis were excluded. Data were extracted from medical records including demographics, WHO-HAEM5 diagnosis, COO per Hans algorithm, CNS-IPI, and treatment history. LymphGen and DLBclass subtypes were determined using online classifiers incorporating NGS and FISH data. We identified LymphGen and DLBclass subtypes enriched in pts with CNS relapse. We performed univariable and multivariable analysis (MVA) (Cox proportional hazards model) to assess the impact of COO, CNS-IPI, and genetic signature on the cumulative incidence (CI) of CNS relapse. **Results:** The median age was 61. 60% were male, 57% non-Hispanic white, 21% Asian, 16% Hispanic, and 3% Black. DLBCL subgroups included DLBCL-NOS (60%), transformed DLBCL (15%), Richter transformation (8%), high-grade B-cell lymphoma (HGBCL)-double hit (5%), primary mediastinal LBCL (4%), DLBCL, post-transplant (3%), HGBCL-NOS (3%), and T-cell histiocyte-rich LBCL (2%). 67% were stage III-IV, 51% non-GCB type, and 21% high-risk CNS-IPI. LymphGen subtypes included EZB-MYC- (26%), ST2 (12%), MCD (9%), EZB-MYC+ (7%), BN2 (7%), N1 (3%), and composite cases (3%); 34% were unclassifiable. DLBclass subtypes included C1 (13%), C2 (3%), C3 (52%), C4 (8%), and C5 (11%); 14% were not classified given <50% confidence in assignment. Median follow-up was 30 months. 18 pts experienced CNS relapse; these cases were enriched for MCD and C5 subtypes (28% each). The 2-year CI of CNS relapse in pts with MCD and/or C5 subtypes (N=21) was 20.4% vs. 6.4% in non-MCD/C5 cases (HR 3.46, p=0.007). Notably, 3 MCD/C5 pts had late CNS relapse (>3 years from diagnosis). In MVA, MCD/C5 signature was an independent risk factor for CNS relapse (HR 4.51, 95% CI 1.42-14.32, p=0.011) along with MYC rearrangement (p=0.036) and non-GCB COO (p=0.028). **Conclusions:** In this heterogeneous DLBCL cohort, MCD/C5 genetic signature was an independent risk factor for CNS relapse. Incorporation of CNS-active agents should be prioritized for this subgroup. Research Sponsor: UCSF Clinical and Translational Science Institute.

Outcomes by LymphoMAP archetypes in untreated diffuse large B-cell lymphoma from the POLARIX trial.

R. Andrew Harkins, Will Harris, Michael Green, Alex F. Herrera, Fabrice Jardin, Georg Lenz, Franck Morschhauser, Matthew Sugidono, Mark Yan, Connie Batlevi, Christopher Flowers, Yanwen Jiang; The University of Texas MD Anderson Cancer Center, Houston, TX; Genentech, Inc., South San Francisco, CA; City of Hope, Duarte, CA; University of Rouen, Rouen, France; University Hospital Münster, Münster, Germany; Lille University Hospital Center, Lille Cedex, France; Roche, Inc., Basel, Switzerland

Background: Single cell multiomics helped identify three tumor microenvironment archetypes: FMAC, high tumor-associated fibroblasts and macrophages; LN, high naive and memory T cells; TEX, high exhausted CD8⁺ T cells (Li, et al, Cancer Cell 2025) with FMAC associated with inferior outcomes with 1L R-CHOP. The POLARIX study showed sustained and significant 5-year PFS/DFS benefits favoring Pola-R-CHP (Morschhauser et al, JCO 2025) supporting use as a standard of care for pts with untreated intermediate/high-risk LBCL. In this post hoc exploratory analysis, we investigated the clinical outcomes of LymphoMAP subtypes in POLARIX. **Methods:** LymphoMAP subtypes were determined from global gene expression patterns (GEP) using the LymphoMapR classifier. Cell of origin (COO) status was determined by NanoString. Hazard ratios (HR) were adjusted for IPI score (2 vs 3–5), age (≤ 60 vs > 60 years) and COO. All statistics are descriptive. **Results:** GEP data were available for 669 pts (Pola-R-CHP, n=331; R-CHOP, n=338; baseline characteristics comparable with ITT); among which 244 (33.5%), 229 (34.2%), 196 (29.3%) were FMAC, LN, and TEX respectively (Table). Balanced baseline clinical characteristics seen across subtypes, except lower proportion of LN with high IPI (3–5) and higher proportion of TEX as ABC-DLBCL (Table). With a median follow-up 61 months, the adjusted HRs for PFS favored Pola-R-CHP compared with R-CHOP in all subtypes and were 0.66 (95% CI: 0.43–1.01) for FMAC, 0.79 (95% CI: 0.51–1.23) for LN, and 0.81 (95% CI: 0.50–1.32) for TEX. The 5-yr PFS estimates (95% CI) were 66.0 (57.1–76.2)%, 64.6 (55.4–75.4)%, 68.8 (59.7–79.4)% for FMAC, LN, and TEX respectively in the Pola-R-CHP arm, and 56.9 (47.6–68.0)%, 61.2 (52.8–70.9)%, 56.6 (45.8–69.9)% for FMAC, LN, and TEX respectively in the R-CHOP arm. A similar trend of OS improvement was observed in the FMAC subtype with 5-yr OS estimates of 82.5 (76.3–89.3)% vs 72.0 (63.8–81.2)% with Pola-R-CHP vs R-CHOP (HR 0.64; 95% CI: 0.37–1.10). Trends of PFS and OS improvements of Pola-R-CHP over R-CHOP were observed in ABC-DLBCL pts across all LymphoMAP subtypes. For GCB-DLBCL pts, no benefit was observed with Pola-R-CHP vs R-CHOP in the TEX subtype. **Conclusions:** In this exploratory analysis, Pola-R-CHP demonstrated PFS/OS improvement trends over R-CHOP in all three LymphoMAP subtypes, especially for the FMAC subtype. Future prospective validation is required. Research Sponsor: F. Hoffmann–La Roche Ltd.

	FMAC (N = 244)	LN (N = 229)	TEX (N = 196)	BEP (N = 669)
Pola-R-CHP	134 (55%)	105 (46%)	92 (47%)	331 (50%)
R-CHOP	110 (45%)	124 (54%)	104 (53%)	338 (50%)
Age Median [Min, Max]	65 [22, 80]	66 [19, 80]	64 [22, 80]	65 [19, 80]
IPI 3–5	157 (64%)	125 (55%)	133 (68%)	415 (62%)
Bulky	109 (45%)	99 (43%)	87 (44%)	295 (44%)
Extranodal	174 (71%)	146 (64%)	143 (73%)	463 (69%)
COO ABC	68 (28%)	56 (24%)	90 (46%)	214 (32%)
GCB	138 (57%)	135 (59%)	65 (33%)	338 (50%)
Unclassified	20 (8%)	34 (15%)	38 (19%)	92 (14%)
Unknown	18 (7%)	4 (2%)	3 (2%)	25 (4%)

Epigenetic profiling to identify aggressiveness markers in non-Hodgkin lymphoma via a targeted methylation-based multi-cancer early detection (MCED) blood test.

Xiang-Yu Zhao, Shuhua Yi, Yu Wu, Zhitao Ying, Wenhui Zhao, Pengcheng He, Yang Xu, Ou Bai, Yi Xia, Lihong Liu, Zhongxing Jiang, Zhiyong Zeng, Xuanhui Liu, Yang Wang, Yue An, Min Li, Ying Xin, Jing Liu, Baoliang Zhu, Xiaohui Wu; Peking University People's Hospital, Peking University Institute of Hematology, Beijing, China; National Clinical Research Center for Blood Diseases, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China; Department of Hematology and Institute of Hematology, West China Hospital, Sichuan University, Chengdu, China; Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; Department of Breast & Hematology Medical Oncology, Harbin Medical University Cancer Hospital, Harbin, China; Department of Hematology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; Department of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, China; Department of Hematology, The First Hospital of Jilin University, Changchun, China; Department of Hematology, The First Affiliated Hospital with Nanjing Medical University (Jiangsu Province Hospital), Nanjing, China; Department of Hematology, The Fourth Hospital of HeBei Medical University, Shijiazhuang, China; Department of Hematology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; Department of Hematology, The First Affiliated Hospital, Fujian Medical University, Fuzhou, China; The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; Shanghai Xiaohu Medical Laboratory Co. Ltd., Beijing, China; Shanghai Xiaohu Medical Laboratory Co. Ltd., Shanghai, China; Shanghai Xiaohu Medical Laboratory Co. Ltd., Guangzhou, China

Background: Non-Hodgkin lymphoma (NHL) encompasses a broad spectrum of malignancies, ranging from highly indolent to highly aggressive subtypes, each requiring distinct clinical management strategies. We developed a targeted methylation-based MCED test, and our prior work showed aggressive solid tumors exhibit elevated cell-free DNA (cfDNA) tumor fractions and distinct methylation signatures characterized by high methylated-to-unmethylated (M/U) ratios. This study focused on NHL subtypes to systematically compare epigenetic biomarkers (cfDNA tumor fraction and methylation signatures) for reliable differentiation of indolent and aggressive NHL. **Methods:** Pretreatment blood samples from NHL patients enrolled in a MCED study were analyzed using the targeted methylation assay. Patients were stratified into aggressive (diffuse large B-cell lymphoma [DLBCL], n=134; mantle cell lymphoma [MCL], n=18; other aggressive NHL, n=2) and indolent subgroups (follicular lymphoma [FL], n=58; marginal zone lymphoma [MZL], n=38; other indolent NHL, n=16). cfDNA tumor fraction was quantified via a zero-inflated negative binomial model, based on the distribution of methylation signal intensities. Methylation profiles were assessed by computing M/U ratios between subgroups. Intergroup comparisons of these biomarkers were conducted using the Mann-Whitney *U* test, with adjustments for multiple testing. Additional subgroup analyses were stratified by clinical stage to mitigate confounding factors. **Results:** MCED testing showed higher sensitivity in identifying aggressive NHL subtypes (78.06% vs 67.54% in indolent subtypes), even in stage I-II cases (62.50% vs 46.34% in indolent subtypes). Aggressive subtypes exhibited significantly higher cfDNA tumor fractions than indolent subtypes (Wilcoxon rank-sum test, $p=1.27e^{-06}$). A total of 31,075 methylation markers (71.66% hypomethylated) showed elevated M/U ratios in aggressive subtypes. These differences in cfDNA tumor fractions and M/U ratios persisted after clinical stage stratification. **Conclusions:** The MCED assay's superior sensitivity for aggressive NHL suggests preferential detection of aggressive NHL while minimizing indolent NHL over-diagnosis. Aggressive NHL is characterized by elevated cfDNA tumor fractions and distinct methylation profiles with high M/U ratios. These findings demonstrate cfDNA methylation patterns are promising epigenetic biomarkers, enabling aggressiveness differentiation in both solid tumors and NHL. Collectively, this study establishes a potential non-invasive strategy for NHL risk stratification and optimized clinical management. Research Sponsor: Shanghai Xiaohu Medical Laboratory Co. Ltd.

Fragmentia AI—Lymphoma: A cfDNA language model for lymphoma detection using ultra-low-pass WGS.

Rui Liu, Yang Dai, Xushu Zhong, Ke Xu, Yang Xu, Guofeng Sun, Liuqing Zhu, Qiaolin Zhou, Xu Sun, He Li, Jie Wang, Jinrong Yang, Yijun Wu, Ailin Zhao, Xiaoxi Chen, Haimeng Tang, Xue Wu, Hua Bao, Yang Shao, Ting Niu; Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing, China; Department of Hematology, West China Hospital, Sichuan University, Chengdu, China; Nanjing Geneseeq Technology Inc., Nanjing, China; Department of Hematology, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, China; Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Toronto, ON, Canada

Background: Despite the potential of cfDNA liquid biopsy for non-invasive cancer monitoring, its clinical utility is often limited by high sequencing costs and a reliance on detectable driver mutations. To address these barriers, we introduce Fragmentia AI – Lymphoma, a novel transformer-based cfDNA language model designed for lymphoma detection using cost-effective ultra-low-pass whole genome sequencing (ULP-WGS). **Methods:** Trained on a cohort of 389 samples (189 lymphoma and 200 healthy), the architecture integrates genomic language model backbone with gated attention-based multiple instance learning. Fragmentia AI – lymphoma learned to identify malignancy-associated, mutation-independent signals directly from raw cfDNA sequences. We validated performance on an independent test cohort of 190 lymphoma patients and 200 healthy controls. Additionally, to evaluate clinical scalability, we conducted a read-depth titration analysis to test the minimum input requirements for sustained model performance. **Results:** Fragmentia AI – lymphoma achieved an AUC of 0.943 in the training cohort and 0.944 in the testing cohort. At 95% specificity, the model demonstrated a sensitivity of 0.889 (F1 score: 0.913). Notably, diagnostic performance remained robust even with a threefold reduction in sequencing reads ($AUC > 0.94$), significantly lowering the required depth compared to standard somatic mutation calling. Feature attribution analysis revealed that model's decision-making was predominantly anchored in pathognomonic fragmentomic signatures, specifically GC-content biases and aberrant fragment-size distributions characteristic of malignant cfDNA. **Conclusions:** Our model effectively identified mutation-independent diagnostic signals from low coverage sequencing data, providing a scalable and cost-effective approach for lymphoma screening and monitoring. Research Sponsor: National Natural Science Foundation of China; 82370192; 1.3.5 Project of Center for High Altitude Medicine, West China Hospital, Sichuan University; GYYX24003; Natural Science Foundation of Sichuan Province; 2026NSFSC1696; Qimingxing" Research Fund for Young Talents, West China Hospital, Sichuan University; HXQMX0101; National Natural Science Foundation of China; 82500245; National Natural Science Foundation of China; 82400248; Natural Science Foundation of Sichuan Province; 2026NSFSC0677.

Early corticosteroid dosing after anti-CD19 CAR-T therapy for large B-cell lymphoma: Multicenter associations with neurotoxicity, cytokine release syndrome, and survival.

Randa Elzein, Safa Elzein; Upstate Medical University, Syracuse, NY; Upstate University Hospital, Syracuse, NY

Background: Corticosteroids are key to CAR-T toxicity management, but the impact of early dosing remains unclear. Over-treatment may blunt efficacy; under-treatment risks severe neurotoxicity. We evaluated early corticosteroid strategies after anti-CD19 CAR-T for large B-cell lymphoma (LBCL). **Methods:** Multicenter retrospective cohort across 22 U.S. programs (2019–2024). Adults receiving commercial anti-CD19 CAR-T for LBCL were included. Early steroid strategies: (1) Moderate (≤ 48 h from first fever or grade 1–2 ICANS; 0.5–1 mg/kg for ≤ 3 days, taper ≤ 5 days); (2) High-dose (≥ 1.5 mg/kg or ≥ 5 days); (3) None within 48 h. Primary endpoint: 12-month overall survival (OS). Secondary endpoints: grade ≥ 3 ICANS/CRS (Fine-Gray models), ICU admission, hospital stay (LOS), 6-month relapse, and day-30 response. Multivariable Cox/logistic models adjusted for key clinical covariates and center effects. Sensitivity analyses used inverse-probability weighting and time-dependent exposure. **Results:** N = 2,186; median age 62. Strategies: Moderate 34 %, High-dose 22 %, None 44 %. Versus None, Moderate dosing reduced grade ≥ 3 ICANS (sub-hazard ratio [sHR] 0.62, 95 % CI 0.50–0.78; $p < 0.001$) with no OS change (adjusted hazard ratio [aHR] 0.96, 0.84–1.10; $p = 0.55$). High-dose was linked to worse OS (aHR 1.22, 1.05–1.41) and more early relapse (aHR 1.28, 1.06–1.54) despite similar CRS rates. ICU admission was lower with Moderate vs None (adjusted odds ratio [aOR] 0.78, 0.64–0.95) and LOS shorter (-1.2 days, 95 % CI -2.0 to -0.4). Findings were consistent across age ≥ 65 and high-risk groups. **Conclusions:** A moderate, time-limited early steroid approach after anti-CD19 CAR-T reduced severe ICANS without loss of efficacy, whereas high-dose/prolonged use correlated with poorer survival and earlier relapse. Results support adopting standardized moderate early dosing and avoiding routine high-dose regimens. Research Sponsor: None.

Clinical outcomes by early corticosteroid strategy after anti-CD19 CAR-T.					
Outcome	None (n=963)	Moderate (n=742)	High- dose (n=481)	Adjusted effect vs None (95 % CI)	P value
12-mo OS (%)	61	62	55	aHR 0.96 (0.84–1.10); 1.22 (1.05–1.41)	0.55; 0.009
Grade ≥ 3 ICANS (%)	13.4	8.7	12.9	sHR 0.62 (0.50–0.78); 0.96 (0.75–1.23)	<0.001; 0.77
Grade ≥ 3 CRS (%)	6.1	5.4	5.8	sHR 0.89 (0.67–1.19); 0.94 (0.72–1.23)	0.43; 0.65
ICU admission (%)	18.9	15.4	19.6	aOR 0.78 (0.64–0.95); 1.03 (0.83–1.29)	0.013; 0.77
Hospital LOS (days)	10.1	8.9	10.6	$\Delta -1.2$ (-2.0 to -0.4); $\Delta +0.3$ (-0.5 to $+1.1$)	0.003; 0.48
Early relapse (6 mo %)	23.7	24.1	29.8	aHR 1.01 (0.87–1.18); 1.28 (1.06–1.54)	0.88; 0.009
Day-30 response (%)	68.2	69.5	66.9	aOR 1.05 (0.90–1.22); 0.94 (0.79–1.12)	0.54; 0.49

Abbreviations: aHR = adjusted hazard ratio; sHR = sub-hazard ratio; aOR = adjusted odds ratio; Δ = adjusted difference in medians.

Overcoming resistance to prior CAR-T therapy: Efficacy and safety of a sequential, multi-antigen targeted CAR T-cell strategy in B-cell NHL.

Guoai Su, Fangfang Cheng, Huihui Zhao, Peihao Zheng, Biping Deng, Alex H. Chang, Yajing Zhang; Beijing GoBroad Boren Hospital, Beijing, China; Engineering Research Center of Gene Technology, Ministry of Education, Institute of Genetics, School of Life Sciences, Fudan University, YaKe Center for Cell Engineering and Therapeutics, Shanghai, China

Background: Relapse following CAR T-cell therapy is a significant unmet need for patients with B-cell non-Hodgkin lymphoma (B-NHL). Strategies to effectively salvage these patients are urgently required. We report the results of a prospective study evaluating a novel approach of sequential CAR T-cell administration, often with alternative antigen targeting, in this heavily pre-treated population. **Methods:** In this single-center, Phase I/II investigator-initiated trial, we enrolled patients with R/R B-NHL who had progressed after at least one prior CAR T-cell infusion. Patients received a second autologous CAR T-cell product targeting a different (e.g., CD20, CD22, CD79b) or re-challenging the same antigen with a different construct. The primary endpoints were safety and overall response rate (ORR). The cohort included high-risk subtypes such as primary central nervous system lymphoma (PCNSL). **Results:** As of the data cut-off, 26 patients with R/R B-NHL (DLBCL, n=18; PCNSL, n=6; Burkitt, n=2) were infused. The median number of prior therapies was 5 (range 3–8). All patients had failed a prior CAR-T therapy. With a median follow-up of 10.2 months, the ORR was 88.5% (23/26), with an outstanding CR rate of 73.1% (19/26). Efficacy was profound even in the most challenging histologies; in the cohort of 6 patients with R/R PCNSL, the CR rate was an unprecedented 83.3% (5/6). The safety profile was highly encouraging. Cytokine release syndrome (CRS) occurred in 92.3% (24/26) of patients, with the majority being Grade 1 (61.5%) or Grade 2 (30.8%). No Grade ≥ 3 CRS was observed. Immune effector cell-associated neurotoxicity syndrome (ICANS) was rare and mild, with only Grade 1 events reported in 19.2% (5/26) of patients; no Grade ≥ 2 ICANS occurred. Hematologic toxicities were manageable and reversible. **Conclusions:** Sequential CAR T-cell therapy is a highly effective and safe strategy that can induce high rates of durable complete responses in B-NHL patients who have relapsed after initial CAR-T treatment. The exceptional activity observed in PCNSL suggests this approach can overcome the blood-brain barrier and address a critical unmet need. These results support the integration of sequential CAR T-cell therapy as a new standard of care for this patient population. Clinical trial information: ChiCTR1900025419. Research Sponsor: None.

Late infectious complications after CD19-directed chimeric antigen receptor T-cell (CAR-T) therapy for large B-cell lymphomas (LCBL): Real-world predictors and outcomes.

Daniel E. Goyco Vera, Omer Abdrabbuh, Fatima Massare Somers, Song Zhang, Heather Renee Wolfe, Praveen Ramakrishnan, Farrukh Tauseef Awan, Kiran Kumar, Margaret Kozak, Elif Yilmaz; UT Southwestern Medical Center, Dallas, TX

Background: CD19-directed CAR-T therapy is a curative option for patients (pts) with relapsed/refractory (R/R) LBCL. Infectious complications are a major source of morbidity and non-relapse mortality (NRM). While early infections are attributed to lymphodepleting chemotherapy and management of immune-related toxicities, real-world data defining predictors of late infections after CAR-T remain limited. **Methods:** We performed a single-center retrospective study of adult pts with R/R LBCL, including transformed indolent lymphomas, treated with anti-CD19 CAR-T. Infectious events were defined by compatible clinical features supported by laboratory, microbiologic, or radiographic evidence. Early infections were defined as ≤ 30 days post-infusion and late infections as > 30 days. Logistic regression assessed associations with late infection risk. Multivariable models included a priori selected clinically relevant covariates. Stepwise logistic regression was performed as a sensitivity analysis. **Results:** Ninety-five pts were included (median age 65 years; median follow-up 32 months). Most pts received axi-cel (88%); 10% received liso-cel and 2% tisa-cel. Salvage and/or bridging therapy prior to CAR-T was administered in 59% of pts. Early infections occurred in 16% of pts, while 63% experienced late infectious complications. Among patients with late infections, 53% were in remission post CAR-T; 43% had both viral and bacterial infections over time, 33% viral only, 22% bacterial only, and 2% fungal overall. Hypogammaglobulinemia (IgG < 400 mg/dL at day +30 and/or +90) occurred in 48%, and grade 4 neutropenia between days +30 and +90 in 31%. Five-year NRM was 12%, with infections contributing to 80% of deaths. On univariate analysis, hypogammaglobulinemia was associated with higher infection risk (OR 2.38, 95% CI 1.00–5.85; $p=0.053$). After adjustment for prespecified covariates, the association was attenuated but directionally consistent ($p=0.082$) and remained the only variable retained on stepwise regression. **Conclusions:** Infectious complications are common following anti-CD19 CAR-T therapy for R/R LBCL and occur predominantly beyond 30 days post-infusion. Hypogammaglobulinemia showed a consistent association with infection risk across multiple modeling strategies. Ongoing prospective studies will clarify the role of immunoglobulin replacement in mitigating late infectious complications in CAR-T recipients. Research Sponsor: None.

Real-world patient characteristics, outcomes, and resource utilization of chimeric antigen receptor (CAR) T cell therapy across Foundation for the Accreditation of Cellular Therapy (FACT) and non-FACT treatment centers in large B-cell lymphoma (LBCL).

Renju V. Raj, Timothy C. Beer, Fei Fei Liu, Aviral Bahuguna, Xiaoying Shi, Debasmita Roy, Christine T. Fu, Yeran Li, Lucio N. Gordon, David L. Porter; University of Tennessee Knoxville Medical Center, Knoxville, TN; Ann B. Barshinger Cancer Institute, LGH Penn Medicine, Lancaster, PA; Bristol Myers Squibb, Princeton, NJ; ZS Associates, Pune, India; ZS Associates, South San Francisco, CA; Bristol Myers Squibb, San Francisco, CA; Florida Cancer Specialists & Research Institute, Gainesville, FL; Center for Cell Therapy and Transplant, University of Pennsylvania, Philadelphia, PA

Background: CAR T cell therapy has transformed the LBCL treatment landscape and is now being offered in some non-FACT accredited centers. We evaluated clinical characteristics, AEs, time to next treatment (TTNT), and health care resource utilization (HCRU) of patients with LBCL who received CAR T cell therapy from FACT versus non-FACT centers. **Methods:** This retrospective cohort study used the Komodo Health Claims Database (01/2015–08/2025). Adults with LBCL receiving CAR T cell therapy were identified via International Classification of Diseases, Ninth/Tenth Revision, diagnosis and procedure codes. Centers were classified as FACT or non-FACT based on public records. Cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), and infections were assessed within 15 and 30 days after infusion. TTNT was estimated using KM methods. All-cause HCRU was reported as per patient per month (PPPM) to adjust for variation in follow-up duration; inpatient utilization was assessed by length of stay (LOS). Comparisons used chi-square test. **Results:** Among 6857 CAR T cell therapy–treated eligible patients with LBCL (FACT, n = 6748; non-FACT, n = 109), demographics and characteristics were comparable between cohorts; mean Charlson Comorbidity Index score was 4.6 versus 4.9, respectively. Significantly more patients treated at FACT sites traveled > 50 miles compared with those treated at non-FACT sites (43% vs 31%; $P < 0.05$); median distance traveled was 34 versus 17 miles, respectively. Rates of CRS (44% vs 40%), ICANS (21% vs 24%), and infections (39% vs 36%) within 15 days after infusion were similar between cohorts (FACT vs non-FACT, respectively); rates were also comparable within 30 days. Median (95% CI) TTNT was numerically lower in the FACT–treated (23 months [21–25]) versus non-FACT–treated cohort but not statistically significant (42 months [18–not estimable]; $P = 0.20$; estimates limited by small sample size); 12-month TTNT rates were 58% versus 67%, respectively. Excluding infusion visits, FACT–treated patients had marginally higher postinfusion HCRU (PPPM) over 1 year, including inpatient (0.93 vs 0.61; $P = 0.52$), outpatient (3.84 vs 3.16; $P < 0.05$), and ICU visits (0.13 vs 0.07; $P < 0.05$). Standardized 1-year inpatient LOS was 18.4 versus 15.9 days, respectively ($P = 0.58$). Among patients treated in an inpatient setting, HCRU including infusion visit exhibited a similar trend. **Conclusions:** In this real-world LBCL cohort, clinical characteristics, safety, TTNT, and HCRU were generally comparable between FACT- and non-FACT- accredited centers. Despite the non-FACT sample size and claims-based limitations, these findings suggest patients have similar outcomes across both types of authorized treatment centers. Research Sponsor: This study was funded by Bristol Myers Squibb.

Real-world outcomes of lisocabtagene maraleucel (liso-cel) in patients (pt) with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL): First results from CIBMTR.

Emily Tomasulo, Nitin Jain, John C. Byrd, Travis Grant Williams, Monalisa Ghosh, Iris Isufi, Matthew Alexander Lunning, David Bernasconi, Debasmita Roy, Samantha Mary Jaglowski, Tania Jain, Bradley Hunter; University of Pennsylvania, Philadelphia, PA; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Cincinnati Medical Center, Cincinnati, OH; St. Luke's Regional Medical Center, Boise, ID; University of Michigan Health System, Ann Arbor, MI; Yale University School of Medicine, New Haven, CT; University of Nebraska Medical Center, Omaha, NE; Bristol Myers Squibb, Boudry, Switzerland; Bristol Myers Squibb, Princeton, NJ; Center for International Blood and Marrow Transplant Research (CIBMTR), Medical College of Wisconsin, Milwaukee, WI; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Intermountain LDS Hospital, Salt Lake City, UT

Background: Liso-cel is an autologous, CD19-directed CAR T cell product with established efficacy and safety across B-cell malignancies. In TRANSCEND CLL 004 (NCT03331198), liso-cel demonstrated promising efficacy and manageable safety in pts with R/R CLL, including those previously exposed to Bruton tyrosine kinase inhibitor (BTKi) and B-cell lymphoma 2 inhibitor (BCL2i). Here, we report real-world effectiveness and safety of liso-cel in pts with R/R CLL. **Methods:** This observational study evaluated US pts with R/R CLL who received commercial liso-cel (05/2024–09/2025) and had ≥ 1 postinfusion assessment reported to CIBMTR. Effectiveness outcomes were ORR, CR rate, duration of response (DOR), PFS and OS; safety outcomes included AEs of special interest, nonrelapse mortality (NRM) and death. Results are descriptive. **Results:** Of 45 eligible pts, 64% were male; median age was 62 y (range, 44–83; ≥ 65 y, 44%). In pts with available data, all had ECOG PS 0–1 (43/43) and 57% (21/37) had ≥ 1 comorbidity, most commonly ($> 10\%$) cardiac (24%) or pulmonary (16%). Elevated LDH was observed in 35% (15/43) and unmutated IGHV in 91%. Pts had a median of 6 (range, 1–10) prior therapies and 71% received liso-cel as fifth-line or later treatment (tx). Most pts (84%) were previously exposed to covalent BTKi and BCL2i, and nearly half (47%) had prior pirtobrutinib tx. Bridging therapy was used in 48% (21/44) of pts. At a median (95% CI) follow-up of 6.0 mo (5.4–7.1), ORR was 84% (70–93), and CR rate was 55% (39–70); 81% (13/16) of pts in CR with available data were MRD negative. Median (95% CI) DOR, PFS, and OS were not reached. Among responders ($n = 36$), 6-mo DOR was 89% (70–96.5); 6-mo PFS and OS were 77% (60–87) and 87% (72–95), respectively. Among pts with any-grade (gr) cytokine release syndrome (80%; gr ≥ 3 , 4%) or immune effector cell-associated neurotoxicity syndrome (36%; gr ≥ 3 , 13%), no gr 5 events occurred. Clinically significant infections were reported in 40% of pts, and at 30 d after infusion, 18% had persistent gr 4 thrombocytopenia and/or neutropenia. Rates were low of HLH/MAS (7%), second primary malignancies (2%; 1 case of basal cell carcinoma 34 d postinfusion), tumor lysis syndrome (7%), and gr 3/4 organ toxicity (9%). Of the 5 deaths, 2 each were due to relapse/progression or infection, and 1 pt had multiple causes reported; 6-mo NRM was 5% (95% CI, 0.8–14). Among the 49% of pts intended for outpatient infusion, 55% (12/22) were hospitalized postinfusion, with a median (range) time to hospitalization of 5.5 d (1–20) and a stay of 5.5 d (1–26). **Conclusions:** In routine clinical practice, liso-cel demonstrated response rates higher than in clinical trials, with a consistent safety profile. These real-world data support liso-cel as an effective option for pts with R/R CLL, including heavily pretreated or high-risk pts, and the potential for outpatient administration. Research Sponsor: This study was funded by Bristol Myers Squibb.

Measurable residual disease (MRD) by circulating tumor (ct) DNA in patients (pt) with R/R follicular lymphoma (FL) treated with lisocabtagene maraleucel (liso-cel) in TRANSCEND FL.

Ariel Avilion, Sahar Ansari, Abood Okal, Ethan G. Thompson, Maria Strocchia, Merav Bar, Luciana Bueno, David M. Kurtz, Alejandro Martin Garcia-Sancho, Juan Luis Reguera, Saurabh Dahiya, Guillaume Cartron, Loretta J. Nastoupil, Maria Lia Palomba, Kirit Ardeshta, Jeremy S. Abramson, Koji Izutsu, Martin H. Dreyling, Franck Morschhauser, Leanne Peiser; Bristol Myers Squibb, Seattle, WA; Bristol Myers Squibb, Cambridge, MA; Bristol Myers Squibb, Boudry, Switzerland; Natera, Inc., Austin, TX; Hospital Universitario de Salamanca, IBSAL, CIBERONC, Universidad de Salamanca, Salamanca, Spain; Hospital Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS) / CSIC, Universidad de Sevilla, Seville, Spain; Stanford University School of Medicine, Stanford, CA; Montpellier University Hospital Center, UMR CNRS 5535, Montpellier, France; Southwest Oncology, CommonSpirit Mercy, Durango, CO; Memorial Sloan Kettering Cancer Center, New York, NY; University College London Hospitals NHS Foundation Trust, London, United Kingdom; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; National Cancer Center Hospital, Tokyo, Japan; Medizinische Klinik III Klinikum der Universität LMU München, München, Germany; Centre Hospitalier Universitaire de Lille, Groupe de Recherche sur les formes Injectables et les Technologies Associées, Lille, France

Background: ctDNA is a minimally invasive method for detecting MRD in various malignancies. MRD negativity (MRD^{neg}) has been linked to improved PFS and durable disease control, including after liso-cel treatment in R/R large B-cell lymphoma. The prognostic value of MRD after chimeric antigen receptor (CAR) T cell therapy in R/R FL has not been established. We report an exploratory MRD analysis from TRANSCEND FL (NCT04245839), in which pts had high rates of deep and durable responses after liso-cel. **Methods:** Of 103 efficacy-evaluable pts with third-line or later (3L+) FL, 89 (86%) had ctDNA samples, of whom 90% (80/89) had evaluable ctDNA and efficacy data after liso-cel infusion. Tumor-derived phased variants were primarily identified from screening (baseline) plasma or tumor tissue when plasma was insufficient, using PhasED-Seq. Post-treatment ctDNA-MRD was assessed at months (M) 1 and 3 after infusion for all pts, and at M24 for ongoing responders. MRD positivity (MRD^{pos}) was defined as ctDNA above the assay detection threshold (lower limit of detection of 0.7 parts per million, with sample-specific sensitivity dependent on DNA input). **Results:** MRD^{neg} was achieved by 89% (71/80) of evaluable pts from TRANSCEND FL. Among pts with a best overall response of CR, 93% (71/76) of them achieved MRD^{neg}. ctDNA clearance increased over time, with MRD^{neg} rates of 68% (52/76) at M1, 83% (63/67) at M3, and 97% (57/59) at M24. In contrast, pts with PR, SD, or PD (n=4) never achieved MRD^{neg}. Baseline ctDNA levels were not associated with PFS after liso-cel treatment. MRD^{neg} after infusion was associated with longer PFS compared with MRD^{pos} ($P<0.001$). In addition, MRD status at M3 (HR, 7.0 [95% CI, 3.0–16.2]) showed a stronger correlation with PFS than at M1 (HR, 3.0 [95% CI, 1.3–6.8]), with 36-M PFS rates of 80% for MRD^{neg} (n=63) versus 38% for MRD^{pos} (n=13) pts. Multivariate analysis controlling for PET findings confirmed the independent prognostic value of MRD for PFS. Importantly, PFS was longer for pts with both CR by PET and MRD^{neg} at M3 (n=62) compared to pts with CR and MRD^{pos} (n=9; HR, 5.0, [95% CI, 1.8–13.4]), with 36-M PFS rates of 81% versus 56%, respectively, suggesting that combining MRD with PET may provide additional prognostic information for long-term outcomes. **Conclusions:** Liso-cel induced deep molecular responses in pts with 3L+ FL with most pts (89%) achieving MRD^{neg} after infusion. Although baseline ctDNA levels were not associated with PFS, MRD^{neg} after infusion was significantly associated with improved PFS, highlighting the therapeutic benefit of liso-cel regardless of tumor burden before treatment. These findings support the potential of ctDNA-based MRD as a prognostic biomarker in FL and underscore that liso-cel is a key treatment option capable of inducing MRD^{neg} and durable clinical outcomes in pts with 3L+ R/R FL. Clinical trial information: NCT04245839. Research Sponsor: This study was funded by Bristol Myers Squibb.

Outcomes of lisocabtagene maraleucel (liso-cel) in patients (pt) with relapsed or refractory (R/R) mantle cell lymphoma (MCL): First real-world data from the CIBMTR.

Jennifer Jing Huang, Taylor Brooks, Jason Romancik, Michael Wang, Elise A. Chong, Uttam Rao, Lizamarie Bachier, Amitkumar Mehta, Matthew Alexander Lunning, David Bernasconi, Lin Wang, Kartik Patel, Debasmita Roy, Samantha Mary Jaglowski, Bradley Hunter, Iris Isufi; Fred Hutchinson Cancer Center, University of Washington, Seattle, WA; Cleveland Clinic, Cleveland, OH; Hackensack University Medical Center, Hackensack, NJ; The University of Texas MD Anderson Cancer Center, Houston, TX; Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; St. David's South Austin Medical Center, Austin, TX; Northside Hospital Cancer Institute, Atlanta, GA; University of Alabama at Birmingham, Birmingham, AL; University of Nebraska Medical Center, Omaha, NE; Bristol Myers Squibb, Boudry, Switzerland; Bristol Myers Squibb, Princeton, NJ; Center for International Blood and Marrow Transplant Research (CIBMTR), Medical College of Wisconsin, Milwaukee, WI; Intermountain LDS Hospital, Salt Lake City, UT; Yale University School of Medicine, New Haven, CT

Background: Liso-cel, an autologous, CD19-directed CAR T cell product, demonstrated deep, durable responses with manageable safety in pts with R/R MCL in the MCL cohort of TRANSCEND NHL 001 (NCT02631044). In this study, we present the first report of real-world outcomes for pts with R/R MCL who received liso-cel, using data from CIBMTR. **Methods:** This retrospective study included pts in the US with R/R MCL who received commercial liso-cel from 05/2024 to 09/2025 with ≥ 1 postinfusion assessment reported to CIBMTR. Effectiveness outcomes included ORR, CR rate, duration of response (DOR), PFS, and OS. Safety outcomes included AEs of special interest, nonrelapse mortality (NRM), and death. Results are descriptive. **Results:** A total of 94 pts were eligible. Median age was 73 y (range, 46–85), 74% were male, 4% (4/92) had ECOG PS ≥ 2 , and 65% (53/81) had ≥ 1 clinically significant comorbidity, with cardiac (31%), pulmonary (31%), and obesity (17%) being most common ($> 10\%$). Largest nodal mass > 10 cm, indicative of bulky disease, was observed in 15% of pts (9/60), 31% had ≥ 2 extranodal involvement, and 5% had CNS involvement. Data on TP53 mutation status and Ki-67 score were limited. Median number of prior lines of therapy (including HSCT/cell therapy) was 4 (range, 2–12); 69% of pts (62/90) had refractory disease and 72% (67/93) received bridging therapy. At a median follow-up of 6.0 mo (95% CI, 5.9–6.2), ORR was 88% (95% CI, 80–94) with CR rate of 80% (95% CI, 70–87). Median DOR, PFS, and OS were not reached; 6-month DOR, PFS, and OS rates were 79% (95% CI, 55–91), 79% (95% CI, 68–87), and 92% (95% CI, 83–96.5), respectively. Any-grade (gr) cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome were reported in 65% (gr ≥ 3 , 2%) and 37% (gr ≥ 3 , 12%) of pts, respectively, with no gr 5 events. Clinically significant infections were reported in 23% of pts, gr 4 thrombocytopenia and/or neutropenia persistent at 30 days after infusion in 18%, and second primary malignancies in 5%, with skin malignancies being the most common. Gr 3/4 organ toxicity occurred in 1 (1%) pt, and none had tumor lysis syndrome. Nine (10%) pts died, including 6 (6%) due to PD. The NRM rate at 6 mo was 1% (95% CI, 0.1–5.4). Of the 36% of pts planned for outpatient infusion, 59% (20/34) were reported as being hospitalized post-infusion with a median (range) time to hospitalization and stay of 5.5 days (1–35) and 4.5 days (2–32), respectively. **Conclusions:** These results show that liso-cel is associated with high response rates in a broad population of heavily pretreated pts with R/R MCL with early signs of durable benefit and safety profile consistent with TRANSCEND NHL 001. While longer follow-up is needed, this supports the potential of liso-cel to address critical gaps for pts with limited treatment options, providing strong effectiveness and manageable safety. Research Sponsor: This study was funded by Bristol Myers Squibb.

Efficacy of tocilizumab in resolving chimeric antigen receptor T-cell (CAR T)–induced cytokine release syndrome (CRS): A pooled clinical trial (CT) analysis of patients (pts) with B-cell lymphoma (BCL).

Soon Jye Kho, Rahul Jain, Sheila Diamond, Srishti Gupta, Jacob Aptekar, Sean Patrick Bliven, Mayur Subhash Narkhede; Medidata Solutions, a Dassault Systèmes Company, New York, NY; University of Alabama at Birmingham, Birmingham, AL; Mercy Cancer institute, Rockford, IL

Background: CAR T therapy offers significant efficacy in the treatment of relapsed/refractory hematologic malignancies but is also associated with developing immune-mediated toxicity, such as CRS. Tocilizumab, an interleukin-6 receptor antagonist, is the only FDA-approved treatment for CAR T-induced CRS, but its efficacy in large pt populations remains limited. This study aims to evaluate the efficacy of tocilizumab by assessing complete response (CR) rates and median time-to-CR in pts with BCL experiencing CAR T-induced CRS, using pooled clinical trial data. **Methods:** We pooled aggregated, anonymized data made available through Medidata Clinical Cloud across <10 multinational CTs, comprising 2,304 patients. Inclusion criteria required a BCL diagnosis, who developed CAR T-induced CRS and were treated with tocilizumab. The index date was defined as the initiation of tocilizumab. CR was defined as CRS resolution within 14 days of the index date without meeting any failure to respond criteria. Non-response was defined as requiring >2 doses of tocilizumab, rescue therapy with siltuximab, CRS grade escalation after 2 tocilizumab doses, or CRS recurrence after 2 tocilizumab doses. The CRS events were graded using Lee's Criteria 2014. CR rate was described as a proportion, and time-to-CR was estimated using the Kaplan-Meier method. **Results:** Of the 2,304 pts included in the database, 680 met the inclusion criteria (37% aged $\geq$ 65 yrs; 63% male; 80% white; 47% Diffuse Large BCL, 14% Follicular Lymphoma & 13% Mantle Cell Lymphoma; 49% Eastern Cooperative Oncology Group (ECOG) performance score=0 & 49% ECOG=1; 48% Ann Arbor Stage IV; 27% had bulky disease; 65% without bridging therapy; 73% received CD28 costimulatory domain-targeted CAR T-infusion, 27% received 41bb costimulatory domain-targeted CAR T-infusion; 72% with grade 1 CRS at the time of onset). The median time from CAR-T infusion to CRS onset was 2 days (IQR: 1 - 4), and the median time from CRS onset to the first dose of tocilizumab was 2 days (IQR: 1 - 3). The CR rate was 66% (95% CI: 62.5% - 69.6%) and the median time to CR was 4 days (95% CI: 3 - 4), with 35% achieving CR in $\leq$ 2 days and 80% in $\leq$ 7 days. **Conclusions:** This large-sample pt-level study of pooled CT data showed significant efficacy of tocilizumab in resolving CAR T-induced CRS among pts with BCL, with two-thirds of pts achieving CR. The rapid median time-to-CR (4 days) underscores the role of tocilizumab as a first-line intervention. However, the 34% of pts who did not meet the CR criteria suggest a need for further investigation into other treatment strategies. Research Sponsor: None.

Long-term real-world outcomes of axicabtagene ciloleucel (axi-cel) in relapsed/refractory (R/R) large B-cell lymphoma (LBCL).

Caron Alyce Jacobson, Tanya Siddiqi, Sairah Ahmed, Armin Ghobadi, David Bernard Miklos, Yi Lin, Miguel-Angel Perales, Matthew Alexander Lunning, Megan Herr, Brian T. Hill, Siddhartha Ganguly, Waleska Perez, Zhongyu Feng, Timothy Best, Grace Lee, Olga Nikolajeva, Brad Du, Babatunde Adedokun, Samantha Mary Jaglowski, Frederick L. Locke; Dana-Farber Cancer Institute, Boston, MA; City of Hope, National Medical Center, Duarte, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; Washington University School of Medicine, St. Louis, MO; Stanford University, Stanford, CA; Mayo Clinic Rochester, Rochester, MN; Memorial Sloan Kettering Cancer Center, New York, NY; University of Nebraska Medical Center, Omaha, NE; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Cleveland Clinic, Cleveland, OH; Houston Methodist Hospital, Houston, TX; Center for International Blood and Marrow Transplant Research (CIBMTR), Medical College of Wisconsin, Milwaukee, WI; Kite, a Gilead Company, Santa Monica, CA; Moffitt Cancer Center, Tampa, FL

Background: Axi-cel, autologous anti-CD19 CAR T-cell therapy, showed long-term survival and curative potential in R/R LBCL (ZUMA-1; Neelapu et al. *Blood*. 2023). Few studies have examined long-term outcomes beyond clinical trials. Here we report long-term real-world outcomes of axi-cel in R/R LBCL using large-sample CIBMTR data. **Methods:** A total of 1500 adults from 79 US centers receiving commercial axi-cel after ≥ 2 LOT for LBCL from Oct 2017–Aug 2020 were enrolled in a post-marketing requirement study. A protocol was developed prior to the study's implementation, reviewed by Kite and CIBMTR. This is a secondary analysis of said study. Key outcomes were progression-free survival (PFS), overall survival (OS), time to next therapy (TTNT), disease-specific mortality (competing risks were non-relapse deaths), subsequent malignancies, and non-relapse mortality (NRM). Outcomes were analyzed descriptively. Cases with missing data were excluded separately for each endpoint. **Results:** As of Aug 2025, 1446 patients (pts) were included in the analysis. Median age at infusion was 62.2 y (range, 19.6–90.8; 38% of pts ≥ 65 y); 65% were male. Five percent of pts had ECOG PS ≥ 2 and 16% had high-grade lymphoma. Pts had a median of 3 (range, 2–4) prior LOT, 28% had prior autologous hematopoietic cell transplantation, and 50% received bridging therapy. At 59.7 mo median follow-up, median PFS (95% CI) was 7.9 mo (6.3–10.9) and 5-y PFS was 30% (27–32). The median OS was 25.7 mo (21.6–30.2); 5-y OS was 38% (35–41). The 5-y cumulative incidence of disease-specific mortality was 51%. Among pts who were progression-free at 2, 3, 4, or 5 y post-infusion, the OS at 6 y (95% CI) was 73% (68–78), 81% (76–86), 90% (84–94), and 94% (89–97), respectively. The median duration of response (DOR) was 25.3 mo (95% CI, 20.7–32.8) and 5-y DOR was 38% (35–41). The median TTNT was 12.2 mo and 30% did not need additional LOT at 5 y. Of pts who received subsequent salvage therapy, 12 (2%) received cell therapy, 39 (7%) received hematopoietic cell transplant, and 475 (90%) received other therapy. The 1, 2, 3, 4, and 5-y cumulative incidence of relapse (95% CI) was 49% (46–51), 52% (50–55), 54% (52–57), 55% (53–58), and 56% (53–59), respectively. No new safety signals were observed. The primary causes of death (n=864; 60%) were primary disease (540; 63%), infection (111; 13%), and organ failure (57; 7%). The 5-y cumulative incidence of NRM was 16% (95% CI, 14–18). At 5 y, 11% (95% CI, 10–13) had subsequent malignancies, mostly therapy-related myeloid neoplasms (6%) and non-melanoma skin cancer (3%); none were directly attributed to axi-cel. **Conclusions:** This real-world study showed sustained survival at 5 y among pts with R/R LBCL treated with axi-cel after ≥ 2 LOT, consistent with ZUMA-1. Infection and organ failure were common causes of NRM. These results continue to support the use of axi-cel with curative intent in R/R LBCL. Research Sponsor: Kite, a Gilead Company.

Fixed-duration subcutaneous (SC) mosunetuzumab (Mosun) in elderly/unfit patients with previously untreated diffuse large B-cell lymphoma (DLBCL): Interim analysis and patient-reported outcomes (PROs) from the phase 2 MorningSun study.

Ian W. Flinn, John M. Burke, Aung M. Tun, Ayed Ayed, Juliana M. L. Biondo, Mei Wu, Farah Hossain, Yong Mun, Rona Farighi, Avrita Singh, Jamal Misleh, Shachar Peles, L. Elizabeth Budde, Jose C. Villasboas, Jeff P. Sharman; Tennessee Oncology and OneOncology, Nashville, TN; SCRI at Rocky Mountain Cancer Centers, Aurora, CO; The University of Kansas Cancer Center, Kansas City, KS; Cancer Specialists of North Florida, Jacksonville, FL; Genentech, Inc., South San Francisco, CA; Delaware/Christiana Care National Cancer Institute Community Oncology Research Program, Helen Graham Cancer Center, Newark, DE; Florida Cancer Specialists & Research Institute, Tampa, FL; City of Hope National Medical Center, Duarte, CA; Mayo Clinic Rochester, Rochester, MN; Willamette Valley Cancer Institute, Eugene, OR

Background: Mosun, a CD20xCD3 T-cell engaging bispecific antibody, is approved for relapsed/refractory follicular lymphoma after ≥ 2 prior lines of therapy. We report an interim analysis and PROs with Mosun SC in elderly/unfit patients with previously untreated DLBCL. **Methods:** MorningSun (NCT05207670) is a Phase 2, basket study of Mosun SC in patients with B-cell non-Hodgkin lymphoma. In the DLBCL cohort, eligible patients (aged ≥ 80 years, or 65–79 years and ineligible for chemoimmunotherapy) received outpatient Mosun SC: Day (D) 1 (5 mg), D8 (45 mg) and D15 (45 mg) of Cycle (C) 1, then 45 mg on D1 for up to 17 21-day cycles. Primary endpoint was progression-free survival (PFS) rate at 24 months. Other endpoints included overall survival (OS), objective response rate (ORR), complete response (CR) rate, change from baseline (CfB) in lymphoma symptoms as assessed by the Functional Assessment of Cancer Therapy-Lymphoma subscale (FACT-Lym LYMS; higher scores indicate improvement, a ≥ 3 -point increase is considered clinically meaningful) and safety. **Results:** Forty-nine patients were enrolled, primarily from community sites ($n=34$). Median age was 83 years (range: 71–101). International Prognostic Index was 3–5 in 53.1% patients and 18.4% of patients had bulky disease. As of February 10, 2025, the median duration of follow-up was 12.5 months (range: 1.4–30.8). PFS and OS rates at 12 months were 71.3% (95% confidence interval [CI]: 54.8–82.7) and 74.7% (95% CI: 58.5–85.4), respectively. ORR was 73.5% and CR rate was 59.2%. Completion rates for FACT-Lym LYMS were $\geq 95\%$ at baseline and remained $\geq 87\%$ at each subsequent timepoint. Patients reported improvement in health-related quality of life (HRQoL) over time, demonstrated by increased mean CfB (standard deviation [SD]) in FACT-Lym LYMS scores: C4D1, 5.1 (9.8); C9D1, 5.6 (11.8); C17D1, 9.8 (11.4). Clinically meaningful improvements in lymphoma symptoms were observed in 53.1% (95% CI: 38.3–67.5) of patients. The most common any-grade adverse event (AE) was injection site reaction (53.1%; all Grade [Gr] 1/2). Gr 3/4 AEs were reported in 65.3% of patients and 8.2% experienced a Gr 5 AE (no Gr 5 AEs were Mosun related, per investigator assessment). Serious AEs occurred in 42.9% of patients. Infection AEs occurred in 49.0% of patients (Gr 1: 4.1%; Gr 2: 28.6%; Gr 3: 16.3%) and resolved in 91.7%. Cytokine release syndrome occurred in 12.2% of patients (Gr 1: 10.2%; Gr 2: 2.0%; all resolved). Updated data with around one additional year of follow-up will be presented. **Conclusions:** Mosun SC showed promising efficacy with manageable safety in elderly/unfit patients with previously untreated DLBCL in an outpatient setting. Clinically meaningful improvements in lymphoma symptoms suggest that Mosun SC improves aspects of HRQoL in this population. Clinical trial information: NCT05207670. Research Sponsor: Genentech, Inc.

Pre-lymphodepletion CRP and ferritin risk stratification as a predictor of early immune toxicities and hematologic complications after CAR-T therapy: A propensity-matched cohort study.

Fayaz Aijaz Ahmed Khan, Muzammil Dastagir, Megan Herr, Meredith Stone, Brian Betts, Shernan G. Holtan, Marco Davila; Roswell Park Comprehensive Cancer Center, Buffalo, NY; UT Health San Antonio, San Antonio, TX; Roswell Park Cancer Center, Buffalo, NY

Background: Inflammation before CAR-T has been linked to higher rates of immune effector cell-associated toxicities and worse outcomes. A pragmatic pre-lymphodepletion risk stratification using C-reactive protein (CRP) and ferritin has been proposed to identify patients at elevated risk. We used the TriNetX Network to evaluate whether CRP/ferritin risk groups predict clinically relevant early outcomes following CAR-T in a real-world setting. **Methods:** We performed a retrospective study using TriNetX Network. Adults (≥ 18 years) treated with CAR-T (day 0) were included if CRP & ferritin were available in the pre-lymphodepletion window (day -20 to -5). Patients were classified as low risk (CRP < 4 and ferritin < 400), intermediate risk (CRP ≥ 4 with ferritin < 400 or CRP < 4 with ferritin ≥ 400), and high risk (CRP ≥ 4 and ferritin ≥ 400). Propensity score matching was performed using demographics, comorbidities, transplant status, malignancy diagnoses & lymphodepletion therapy. Outcomes were assessed from day 0 to +30. We analyzed outcomes using odds ratio (OR) with 95% confidence interval (CI) and time-to-event comparison using log-rank p-value. **Results:** After propensity matching, high vs low risk cohorts included 246 patients per group. For intermediate vs low risk, cohorts included 298 per group. High-risk patients had higher odds of cytokine release syndrome (CRS) (OR 1.56, 95% CI 1.1–2.2; $p=0.04$) and immune effector cell-associated neurotoxicity syndrome (ICANS) (OR 1.86, 95% CI 1.1–3.1; $p=0.01$) versus low risk. In intermediate vs low risk, ICANS remained increased (OR 1.69, 95% CI 1.1–2.7; $p=0.02$), while CRS showed a nonsignificant trend (OR 1.36, 95% CI 0.98–1.9; $p=0.06$). High risk cohort was associated with greater supportive care utilization, including higher odds of G-CSF use (OR 2.93, 95% CI 1.5–5.8; $p<0.01$) and blood transfusion (OR 2.65, 95% CI 1.2–5.9; $p=0.01$) versus low risk. High vs low-risk was associated with higher odds of platelets < 50 (OR 3.59, 95% CI 1.98–6.5; $p<0.01$) and hemoglobin < 8 (OR 2.81, 95% CI 1.3–5.9; $p<0.01$). Neutropenia (ANC < 500) was not significantly different. In intermediate vs low risk, cytopenia-related endpoints were not significantly different. All-cause mortality analysis was not performed due to low event rates. **Conclusions:** In a TriNetX propensity-matched real-world cohort, a simple pre-lymphodepletion CRP and ferritin stratification identified CAR-T recipients at significantly higher risk for early immune toxicities (CRS, ICANS) and clinically meaningful hematotoxicities (severe thrombocytopenia and anemia) within 30 days, along with increased need for G-CSF & transfusion support. These findings support using simple pre-infusion inflammatory biomarkers to guide counseling, risk-adapted monitoring, and proactive supportive care strategies in routine practice. Research Sponsor: None.

Longitudinal safety of lisocabtagene maraleucel (liso-cel) in patients (pt) with second-line or later (2L+) large B-cell lymphoma (LBCL).

Manali Kirtikumar Kamdar, Jeremy S. Abramson, Alison Sehgal, Scott R. Solomon, Leo I. Gordon, Matthew Alexander Lunning, Nilanjan Ghosh, Bertram Glaß, Stephan Mielke, Pim Mutsaers, Franck Morschhauser, Koji Izutsu, Robert Braun, Maria Strocchia, Muskan Mittal, Giovanna Andreola, Jon E. Arnason; University of Colorado Cancer Center, Aurora, CO; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center, Pittsburgh, PA; Northside Hospital Cancer Institute, Atlanta, GA; Northwestern University, Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL; University of Nebraska Medical Center, Omaha, NE; Atrium Health, Levine Cancer Institute, Wake Forest University School of Medicine, Charlotte, NC; Helios Klinikum Berlin-Buch, Berlin, Germany; Karolinska Institutet and University Hospital; Karolinska Comprehensive Cancer Center, Karolinska ATMP Center, Stockholm, Sweden; Erasmus University Medical Center, Rotterdam, Netherlands; Centre Hospitalier Universitaire de Lille, Groupe de Recherche sur les formes Injectables et les Technologies Associées, Lille, France; National Cancer Center Hospital, Tokyo, Japan; Bristol Myers Squibb, Boudry, Switzerland; Syneos Health, Haryana, India; Beth Israel Deaconess Medical Center, Boston, MA

Background: Liso-cel has shown favorable efficacy and a manageable, consistent safety profile across B-cell malignancies, including R/R LBCL. Here, we present pooled longitudinal safety results in pts who received liso-cel as 2L+ treatment for LBCL in 3 pivotal clinical trials.

Methods: Data from liso-cel-treated pts in the TRANSFORM (2L transplant-eligible LBCL, NCT03575351), PILOT (2L transplant-noneligible LBCL, NCT03483103), and TRANSCEND NHL 001 (third-line or later LBCL, NCT02631044) trials were pooled. Incidences of infections, laboratory parameters, and concomitant medication/procedure use were assessed from Day (D) 0–15, D16–30, Month (M) 2–3, M4–6, M7–9, M10–12, M13–18, M19–24, and M25 to end of study (EOS). Incidences were calculated as pts with ≥ 1 event divided by ongoing pts during that period. **Results:** A total of 420 pts were included. Incidence of grade (gr) ≥ 3 neutropenia was highest from D0–15 (Table), decreased sharply after M6, then remained low. Overall, 62% of pts received growth factors for neutropenia, with highest use from D0–15 and minimal use after M3. Rate of gr ≥ 3 anemia was highest from D0–15, declined by M9, then remained low. A total of 4.9% of pts received red blood cell (RBC) transfusions at any point with highest use from D0–15 and minimal use after M3. Incidence of gr ≥ 3 thrombocytopenia was highest from D0–M3, declined by M9, then remained low. Platelet transfusions were received by 31% of pts at any point with highest use from D0–M3 and minimal use after M3. Use of erythropoiesis- and thrombopoiesis-stimulating agents was rare (1% and 2% at any point, respectively). Incidence of gr ≥ 3 infections was 15% overall and remained low in all periods (Table). Hypogammaglobulinemia (serum immunoglobulin < 500 mg/dL) ranged from 43% to 63% across periods with IVIG use in 20% of pts at any point on study. B-cell aplasia declined over time from 99% from D0–15 to 73% by M12 and $< 50\%$ beyond M18. The overall incidence of second primary malignancies was 6%. **Conclusions:** In these longitudinal analyses in liso-cel-treated pts with 2L+ LBCL, gr ≥ 3 cytopenias and concomitant medication use decreased over time with minimal needs for growth factors or transfusions after M3. Gr ≥ 3 infections remained low in the short- and long-term periods despite persistent hypogammaglobulinemia and B-cell aplasia in most pts at M12. These data underscore the favorable long-term safety of liso-cel in pts with 2L+ LBCL, reinforcing the feasibility of outpatient management and the potential for low health care resource utilization in clinical practice. Clinical trial information: NCT03575351, NCT03483103, and NCT02631044. Research Sponsor: This study was funded by Bristol Myers Squibb.

Period	Gr ≥ 3 neutropenia, %	Growth factor for neutropenia, %	Gr ≥ 3 anemia, %	RBC transfusion, %	Gr ≥ 3 thrombo- cytopenia, %	Platelet transfusion, %	Gr ≥ 3 infection, %
D0–15	87	42	29	35	23	12	6
D16–30	36	18	12	19	35	22	2
M2–3	33	16	17	20	32	18	5
M4–6	26	5	12	5	16	3	2
M7–9	12	1	4	2	9	2	< 1
M10–12	15	2	2	1	1	< 1	1
M13–18	10	< 1	1	< 1	3	0	< 1
M19–24	4	1	3	< 1	3	0	2
M25–EOS	6	1	2	1	1	1	1

Long-term cognitive impairment after CAR-T therapy compared with autologous stem cell transplantation.

Andrea Yun-En Sun, Po-Huang Chen, Cho-Hao Howard Lee; College of Medicine, National Yang Ming Chiao Tung University, Taipei City, Taiwan; Tri-Service General Hospital, Taipei City, Taiwan; Division of Hematology and Oncology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical University, Taipei, Taiwan

Background: Chimeric antigen receptor T-cell (CAR-T) therapy has transformed the management of relapsed and refractory hematologic malignancies, challenging the established role of autologous stem cell transplantation (ASCT). However, the chronic neurocognitive effects of CAR-T therapy remain unclear. This study compares the long-term risk of cognitive impairment between CAR-T and ASCT therapy recipients. **Methods:** We conducted a retrospective cohort study using US hospital data from the TriNetX research network. Patients exclusively receiving either CAR-T therapy or ASCT were propensity score-matched 1:1 and adjusted for age, sex, primary cancer diagnosis, major comorbidities, neuropsychiatric comorbidities, dexamethasone use, and laboratory values (BMI, LDH if available). Participants with prior cognitive impairment diagnosis within 1 year before index or who received multiple treatment modalities during the study period were excluded. The primary endpoint was time-to-event cognitive impairment, defined by ICD-10 codes for mild cognitive impairment, memory loss, and difficulty with concentration. Secondary outcomes included time to neurological dysfunction (delirium, encephalopathy, seizures), mood and stress-related disorders (depression, anxiety, sleep disorder), fall-related injuries, mobility impairment, and secondary malignancies. **Results:** After propensity score matching, 3,067 CAR-T patients were compared with 3,067 ASCT patients. CAR-T recipients demonstrated a 58% higher risk of cognitive impairment (HR 1.583; 95% CI 1.390–1.80) and a 57% higher risk of neurological dysfunction (HR 1.567; 95% CI 1.403–1.751) compared to ASCT patients. Encephalopathy was the most prominent individual complication, with CAR-T patients showing a 2-fold higher hazard compared to ASCT patients (HR 2.035; 95% CI 1.727–2.398). To account for acute ICANS, events occurring within the first 7 days were excluded, and CAR-T patients maintained higher hazard of cognitive impairment (HR 1.695; 95% CI 1.466–1.959). The risk was highest within the first 30 days (HR 4.224; 95% CI 3.227–5.528) and remained persistently elevated throughout the follow-up period, even at 2500 days (HR 1.761; 95% CI 1.535–2.021). Among CAR-T products, ciltacabtagene autoleucel showed the highest hazard (HR 2.013; 95% CI 1.092–3.708), while tisagenlecleucel showed the lowest (HR 1.530; 95% CI 1.030–2.271). All $p < 0.001$. **Conclusions:** Compared to ASCT, CAR-T cell therapy was associated with a significantly increased risk of long-term cognitive impairment and neurological dysfunction. These findings have important implications for incorporating neurocognitive assessment into treatment discussion, informed consent, and the need for long-term monitoring. Research Sponsor: None.

Real-world toxicity of bispecific antibodies versus CAR-T cell therapy in diffuse large B-cell lymphoma and follicular lymphoma.

Nanda Krishnan Siva, Shanawar Ali Waris, Syed Abdul Mannan Shah, Shilajeet Ray, Muqtasid Aftab Khan, Salah Ud Din Safi; West Virginia University School of Medicine, Department of Internal Medicine, Morgantown, WV; West Virginia University Cancer Institute, Department of Medical Oncology, Morgantown, WV; Joan C. Edwards School of Medicine, Marshall University, Huntington, WV; University of Alabama at Birmingham Heersink School of Medicine - Huntsville, Department of Internal Medicine, Huntsville, AL

Background: CAR-T cell therapy and bispecific antibodies (BsAbs) have transformed treatment of relapsed or refractory B-cell lymphomas. While CAR-T toxicities are well characterized, real-world comparative safety data for newer BsAbs remain limited. We compared early and delayed toxicities of CAR-T versus BsAbs in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). **Methods:** Using the TriNetX Research Network, we conducted a retrospective cohort study of adults with DLBCL or FL treated with BsAbs or CAR-T therapy. 1:1 propensity score matching was performed for demographics, comorbidities, laboratory values, and prior lines of chemotherapy. Outcomes included cytokine release syndrome (CRS) at 14 and 30 days; immune effector cell-associated neurotoxicity syndrome (ICANS) at 30 and 60 days; ICU admission within 90 days; infections within 90 days; hypogammaglobulinemia within 180 days; neutropenia within 90 days; and treatment-related mortality at 90 days. Analyses used Kaplan–Meier methods, hazard ratios (HR), risk ratios (RR), and 95% confidence intervals (CI). **Results:** A total of 1,110 CAR-T-treated and 897 BsAb-treated patients met inclusion criteria. After matching, 384 patients were included per cohort. Compared with CAR-T, BsAbs were associated with lower CRS at 14 days (RR 0.45, 95% CI 0.37–0.55) and 30 days (RR 0.52, 95% CI 0.44–0.62), and lower ICANS at 30 days (RR 0.30, 95% CI 0.20–0.47) and 60 days (RR 0.36, 95% CI 0.25–0.51). ICU admission within 90 days occurred less frequently with BsAbs (RR 0.56, 95% CI 0.40–0.78). Infection rates at 90 days (RR 1.06, 95% CI 0.87–1.30) and hypogammaglobulinemia at 180 days (RR 0.81, 95% CI 0.65–1.01) were similar between groups. Neutropenia within 90 days was lower with BsAbs (RR 0.55, 95% CI 0.49–0.61). 90-day overall survival was lower with BsAbs (HR 2.99, 95% CI 1.89–4.73), likely driven by treatment selection bias, as BsAbs are frequently used in patients ineligible for CAR-T due to poor performance status, comorbidities, or aggressive disease. **Conclusions:** In this real-world cohort of DLBCL and FL, BsAbs were associated with substantially lower early immune-mediated toxicity and healthcare utilization compared with CAR-T therapy, while infectious and delayed immune complications were similar. These findings provide important safety data for newer bispecific agents. Research Sponsor: None.

Outcome	Bispecific Antibodies (n = 384)	CAR-T (n = 384)	HR/RR [95% CI]
CRS (0–14 days)	25.3%	56.3%	0.45 [0.37–0.55]
CRS (0–60 days)	31.8%	59.6%	0.53 [0.45–0.63]
ICANS (0–30 days)	8.1%	22.4%	0.30 [0.20–0.47]
ICANS (0–60 days)	9.4%	26.0%	0.36 [0.25–0.51]
ICU admission (0–90 days)	12.0%	21.4%	0.56 [0.40–0.78]
Infections (0–90 days)	34.6%	32.6%	1.06 [0.87–1.30]
Neutropenia (0–90 days)	49.2%	89.6%	0.55 [0.49–0.61]
Hypogammaglobulinemia (0–180 days)	27.1%	33.6%	0.81 [0.65–1.01]
Overall Survival (0–90 days)	81.4%	93.2%	2.99 [1.89 – 4.73]

The influence of advanced age on outcomes in patients with diffuse large B-cell lymphoma treated with CAR-T therapy.

Muqtasid Aftab Khan, Nanda Krishnan Siva, Shanawar Ali Waris, Syed Abdul Mannan Shah, Shilajeet Ray, Salah Ud Din Safi; University of Alabama at Birmingham Heersink School of Medicine - Huntsville, Department of Internal Medicine, Huntsville, AL; West Virginia University School of Medicine, Department of Internal Medicine, Morgantown, WV; West Virginia University Cancer Institute, Department of Medical Oncology, Morgantown, WV; Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Background: Chimeric antigen receptor T-Cell (CAR-T) has emerged as a potentially curative treatment for diffuse large B-Cell lymphoma (DLBCL). The median age at DLBCL diagnosis is 66 years with nearly 30% of patients diagnosed at ≥ 75 years. Studies have examined outcomes of CAR-T therapy in DLBCL, with elderly patients (≥ 65 years) included in analyses; however, clinical trial populations have underrepresented the true age distribution of the disease. This study evaluates the impact of advanced age on survival and toxicity outcomes in patients with DLBCL treated with CAR-T therapy. **Methods:** A multicenter retrospective cohort study was conducted using TriNetX, a federated database of over 159 million de-identified electronic health record and claims data. Patients aged ≥ 75 years with DLBCL treated with CD19-directed CAR-T therapy were compared with a 1:1 propensity score-matched cohort of patients aged 18–65. Propensity score matching was performed based on demographics, comorbidities, and baseline laboratory values. Primary outcomes included 1-year and 3-year overall survival (OS), as well as the development of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and infection within 100 days following CAR-T infusion. Outcomes were assessed using Kaplan–Meier survival analyses, hazard ratios (HR), risk ratios (RR), and 95% confidence intervals (CI). **Results:** Prior to PSM, there were 326 patients ≥ 75 years and 816 patients aged 18–65 years who were treated with CD-19 directed CAR-T for DLBCL. After PSM, there were 241 patients in each cohort. There was no statistically significant difference in one-year or three-year overall survival between patients ≥ 75 years vs. 18–65 years (1-year HR: 0.89, 95% CI [0.63–1.26]; 3-year HR: 1.00, 95% CI [0.74–1.36]). Interestingly, patients ≥ 75 years were at a lower risk for the development of CRS compared younger patients (RR: 0.84, 95% CI [0.72, 0.98]). There was no statistically significant difference in the risk for development of ICANS (RR: 0.98, 95% CI [0.70–1.38]). Risk of infection at 100 days post-CAR-T infusion was lower in patients ≥ 75 years (RR: 0.75, 95% CI [0.58–0.95]). **Conclusions:** In this large multicenter real-world analysis, patients aged ≥ 75 years experienced comparable overall survival and no increased toxicity following CAR-T therapy for DLBCL. These findings suggest that advanced age alone should not preclude CAR-T eligibility and support broader consideration of CAR-T therapy in appropriately selected older adults. Research Sponsor: None.

Outcome	Age ≥ 75 (n=241)	Age 18-65 (n=241)	HR/RR [95% CI]
1-year OS	71.6%	68.6%	0.89 [0.63-1.26]
3-year OS	47.3%	53.7%	1.00 [0.74-1.36]
CRS	52.3%	62.2%	0.84 [0.72–0.98]
ICANS	21.6%	22.0%	0.98 [0.70–1.38]
Infection (≤ 100 days)	30.3%	40.7%	0.75 [0.58–0.95]

Immune priming with the EZH2 inhibitor tazemetostat in B-cell lymphomas receiving CAR T-cell therapy.

Samuel Yamshon, Caitlin Gribbin, Yusuke Isshiki, Ioannis Karagiannidis, Sunjae Lee, Jizhi Yan, Gwynne Ozkan, Anna Alperovich, Barbara T. Ma, Christopher Hackett, Mateo Mejia Saldarriaga, Daniel Chimin Choi, Selina Chen-Kiang, John Paul Leonard, Ari Melnick, Nathan Hale Fowler, Juliet Naomi Barker, Giorgio Inghirami, Wendy Béguelin, Peter Martin; Weill Cornell Medicine, New York, NY; BostonGene Corporation, Waltham, MA; NYU Langone, New York, NY

Background: While chimeric antigen receptor (CAR) T cells have shown efficacy in B cell lymphomas, most patients (pts) still relapse. Preclinical studies have shown that inhibiting histone methyltransferase EZH2 prevents T cell exhaustion, promotes a T-cell memory phenotype, and sensitizes immune-based approaches. **Methods:** We administered the EZH2 inhibitor tazemetostat in pts receiving standard-of-care CART for diffuse large B cell, follicular, or mantle cell lymphoma (DLBCL, FL, MCL). Pts received tazemetostat for ≥ 7 days prior to apheresis and continued to lymphodepletion. Following CART, pts resumed tazemetostat at count recovery and continued for up to 12 mo (6 mo in pts with complete remission [CR]). Peripheral blood mononuclear cells were collected Day -24 and Day -5. To evaluate the immunomodulatory effects of priming, high parameter flow cytometry, RNA-seq with cell deconvolution, differential gene expression patterning, and functional gene signature scoring using ssGSEA were compared. **Results:** 13 pts enrolled (7 DLBCL, 5 FL, 1 MCL). Median prior lines of therapy were 2 (1-4), and 85% were refractory to the last therapy. EZH2 mutations were present in 2 pts. 4 pts had TP53 mutation or deletion, 4/7 DLBCL pts had MYC translocation and 3 had transformed disease. Five pts received axi-cel, 5 liso-cel, 2 tisa-cel, and 1 brexu-cel. All successfully completed CART manufacturing. The ORR was 100%, including 77% in CR (DLBCL 71%, FL 100%). At a median follow up of 18 months, 54% remain progression-free, and 77% remain alive. Ten pts (77%) experienced CRS, with 1 grade 3 CRS. 6 pts had transient grade 1-2 ICANS. Grade 3+ neutropenia was seen in 77%. Three pts experienced grade 3 infections. The most common AEs were gastrointestinal and almost exclusively grade 1-2. Comparing baseline and pre-CART samples, pts experienced a 14% and 20% increase in NK cells and CD16+ monocytes ($p < 0.03$) and a 14% and 53% decrease in Tregs and CD14+ monocytes ($p < 0.02$). Increases in the expression of functional gene signatures associated with MHC-I antigen presentation ($p = 0.010$), antigen-specific T cell activation ($p = 0.019$), and cellular cytotoxicity ($p = 0.043$) were also observed. Parallel reductions in signatures associated with tolerogenic dendritic cells ($p = 0.011$), myeloid suppression ($p = 0.043$), and coagulation ($p = 0.030$) were also seen. There was no observed negative impact on CART transduction efficiency, activation, or expansion. **Conclusions:** Addition of the EZH2 inhibitor tazemetostat is associated with high clinical efficacy and peripheral immune remodeling. Increases in lymphocyte activation and cytotoxicity along with decreases in myeloid tolerogenicity and immunosuppression could potentially augment CART expansion and persistence. Additional immune correlates are ongoing, and randomized studies are planned to validate this approach. Clinical trial information: NCT05934838. Research Sponsor: Ipsen.

Predictors of low- and high-grade ICANS after CAR-T: A nationwide analysis.

Ashish Nepal, Trilok Shrivastava, Sapna Kumari, Falah Abu Hassan, Joseph Kannarkatt; WellSpan York Hospital, York, PA; University of Arkansas Medical Sciences, Little Rock, AR; Wellspan Health York Hospital, York, PA; The University of Arizona College of Medicine, Phoenix, AZ; Cancer Care Associates of York, York, PA

Background: Immune effector cell-associated neurotoxicity syndrome (ICANS) is a leading cause of morbidity following chimeric antigen receptor T-cell (CAR-T) therapy. However, the real-world predictors of severity remain incompletely defined. We evaluated whether ICANS risk differs between multiple myeloma (MM) and other CAR-T indications. **Methods:** CAR-T hospitalizations were identified using ICD-10-PCS procedure codes. ICANS was identified using ICD-10-CM grade-specific codes (G92.00–G92.05) and severity was graded as none, low-grade (1–2), or high-grade (3–5). The 2022–2023 Healthcare Cost and Utilization Project National Inpatient Sample (HCUP NIS) with discharge weights was used for this analysis. Multivariable multinomial (nominal) regression (reference outcome: no ICANS) estimated adjusted odds ratios (aORs) for low- and high-grade ICANS. Cancer type was modeled with MM as a reference and compared with lymphomas, leukemias, solid/metastatic malignancies, and unspecified/other malignancies, adjusting for prespecified comorbidities including dementia, diabetes, and substance use diagnoses. **Results:** Among 10,105 weighted CAR-T hospitalizations, the risk of high-grade ICANS varied significantly by cancer type. Relative to MM, high-grade ICANS was significantly higher in leukemia (aOR 5.23 (95% CI 3.81–7.16), $p < 0.001$); lymphoma (aOR 3.91 (95% CI 3.07–5.00), $p < 0.001$); solid/metastatic malignancy (aOR 1.92 (95% CI 1.30–2.83), $p = 0.001$); and unspecified/other malignancy (aOR 6.34, 95% CI 4.98–8.07, $p < 0.001$). For low-grade ICANS, lymphoma was associated with increased odds compared with MM (aOR 1.53, 95% CI 1.31–1.78; $p < 0.001$). Comorbidity signals were dominated by baseline neurologic vulnerability and metabolic disease. Dementia was the strongest predictor of high-grade ICANS (aOR 7.54, 95% CI 4.13–13.78; $p < 0.001$). Drug abuse was associated with increased odds of low-grade ICANS (aOR 2.68, 95% CI 1.45–4.97; $p = 0.002$). Diabetes with complications was associated with both low-grade (aOR 1.49, 95% CI 1.24–1.79; $p < 0.001$) and high-grade ICANS (aOR 1.63, 95% CI 1.33–1.99; $p < 0.001$). **Conclusions:** In a nationally representative inpatient cohort, multiple myeloma (MM) was associated with significantly lower odds of high-grade ICANS compared with other CAR-T indications, especially leukemia and lymphoma. Dementia and complicated diabetes were highly predictive of high-grade ICANS across all cancer types. These findings identify a clinically actionable risk profile that may inform future risk-stratified monitoring and early intervention strategies as CAR-T use expands. Limitations include reliance on administrative ICD-10 coding, which may misclassify ICANS severity, the possibility of clinical confounding, and a lack of product-specific and other clinical granularity. Research Sponsor: None.

Real-world outcomes of epcoritamab vs glofitamab in relapsed/refractory diffuse large B-cell lymphoma: A TriNetX retrospective study.

Juhi Ardeshtna-Chovatiya, Amna Bint I Munir, Wei Ju Lin, Jasmin Chovatiya; University of California Riverside, Riverside, CA; North Alabama Medical Center, Florence, AL; Hemet Global Medical Center, Hemet, CA

Background: Glofitamab and epcoritamab are CD20-directed bispecific antibodies that engage CD3-positive T cells and are approved for relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). While trials reported high response rates, real-world comparative data on survival, safety, and treatment complications are limited. We conducted a propensity score-matched analysis to compare the effectiveness and safety of glofitamab and epcoritamab in R/R DLBCL.

Methods: We conducted a retrospective cohort study of adult relapsed/refractory diffuse large B-cell lymphoma patients treated with glofitamab or epcoritamab through January 2026 using the TriNetX network. Eligible patients had confirmed R/R DLBCL, ≥ 2 prior systemic therapies and ≥ 30 days follow-up. Data from 134 million patients across 70 US healthcare organizations were analyzed. Propensity-score matching was done for age, sex, race, comorbidities, prior CAR T, and prior therapies. Outcomes included overall survival, all-cause mortality, hematologic adverse events, CRS, ICANS, infections, and ICU admissions. **Results:** A total of 369 epcoritamab and 337 glofitamab patients met the inclusion criteria. After 1:1 propensity-score matching, 205 patients were included in each cohort. Median age was 68 years for glofitamab and 67.8 years for epcoritamab, with 62.9% vs 64.9% male. Median follow-up was 6.8 months vs 5.8 months. At 6 months, mortality was 29.3% versus 39.0% (RR 0.75, 95% CI 0.57-0.99; $p=0.037$), with estimated overall survival 68.1% versus 55.8% (HR 0.68, 95% CI 0.49-0.95; $p=0.023$). This benefit persisted at 12 and 24 months (estimated overall survival 54.0% vs 43.8% and 37.5% vs 33.3%, HR 0.73-0.75), though fixed-time risk differences were not significant. Any-grade CRS occurred in 22.4% vs 30.2% (RR 0.74, 95% CI 0.53-1.03; $p=0.073$), with grade ≥ 3 CRS not significantly different between cohorts. ICANS occurred in 7.3% vs 11.7% (RR 0.63, 95% CI 0.34-1.16; $p=0.130$), and tocilizumab use was comparable (20.0% vs 22.0%). Hematologic adverse events, including neutropenia (21.5% vs 26.8%), thrombocytopenia (34.1% vs 35.1%), anemia (35.1% vs 40.0%), and ICU admissions (19.0% vs 25.4%), were comparable and not significantly different. Infections were significantly lower with glofitamab (38.0% vs 48.8%, RR 0.78, 95% CI 0.62-0.98; $p=0.028$), supporting a favorable safety profile. **Conclusions:** In this real-world analysis, glofitamab and epcoritamab had similar safety profiles, with glofitamab showing lower early mortality and higher overall survival. Hematologic adverse events, CRS, ICANS, and ICU admissions were comparable, while infections were significantly lower with glofitamab. The selection of CD20 $\times$ CD3 bispecific antibodies should consider infection risk and early survival outcomes until longer follow-up clarifies durability and late toxicities. Research Sponsor: None.

Baseline phosphoproteomic signatures in peripheral blood and prediction of durable response to CAR T-cell therapy in B-cell malignancies.

Christian A. Gorrillo, Weronika E. Borek, Federico Pediconi, Amy E. Campbell, Edmund H. Wilkes, Arran David Dokal, Ran Reshef; Columbia University Irving Medical Center, New York, NY; Kinomica Limited, Macclesfield, United Kingdom

Background: Despite the success of Chimeric Antigen Receptor (CAR) T-cell therapy, most patients fail to achieve durable remission. T-cell "fitness" is a critical, yet undercharacterized, determinant of efficacy. Standard immune and transcriptomic profiling do not measure the dynamic signaling networks driving cellular function. We hypothesized that baseline phosphoproteomic signatures in peripheral blood mononuclear cells (PBMCs) prior to CAR T-cell could serve as functional biomarkers for T-cell fitness, predicting durable response. **Methods:** We performed unbiased LC-MS/MS-based phosphoproteomics (KScan) on baseline PBMCs from 59 patients (39 Aggressive Lymphoma [DLBCL], 20 Multiple Myeloma [MM]) treated with CD19- or BCMA-directed CAR-T. Kinase Substrate Enrichment Analysis (KSEA) inferred upstream kinase activity. The primary endpoint was Complete Response (CR) at 6 months. We also analyzed a subset of DLBCL patients (n=6) who achieved CR at Day 30 but progressed (POD) by Month 6 ("early relapse") to identify markers of transient versus durable response. **Results:** We quantified 7,602 phosphopeptides. In the DLBCL cohort (20 CR, 17 POD), distinct phosphorylation in kinase signaling networks separated durable responders from non-responders, specifically implicating dysregulated stress response and MAPK signaling in resistance. KSEA revealed dysregulation in the MAPK/ERK, Casein Kinase (e.g., CSNK1E), and Cyclin-Dependent Kinase activity, linking baseline proliferative potential to long-term efficacy. Notably, the "early relapse" group (Day 30 CR / Month 6 POD) exhibited a unique profile, characterized by differential phosphorylation of proteins involved in apoptotic regulation and chromatin remodeling (e.g., FADD, ARID1A, ACIN1, KMT2A), suggesting these intrinsic defects may limit CAR T-cell persistence. Correlation analysis further integrated these signaling features with CD3+, CD4+, and CD8+ T-cell counts, validating their biological relevance. In the MM cohort, the signaling landscape was heavily dominated by immune cell composition. KSEA revealed that kinase activity in CR patients strongly correlated with the CD4:CD8 ratio and absolute CD3+ counts, validating that the captured phosphoproteomic variance reflects the underlying T-cell phenotype required for successful expansion and cytotoxicity. **Conclusions:** Baseline PBMC phosphoproteomics is a powerful tool for predicting CAR T-cell efficacy. We identified specific signatures—distinct from broad immune cell counts—that differentiate durable responders from patients at risk of primary refractory disease or early relapse. These targets highlight avenues for pharmacological conditioning to enhance T-cell fitness. These data support integrating functional proteomic biomarkers into patient stratification strategies to optimize outcomes. Research Sponsor: None.

Clonal hematopoiesis as a predictor of immune toxicity and efficacy after chimeric antigen receptor T-cell therapy: A systematic review and meta-analysis.

Adam Bowen, Kristina Golovataya, Claire Russell, Muhammad Saleem, Sarah Gergis, Katlyn Wendel, Lakshmi Thulluri, Stephen Caucchi, Sanjay Rao Gergal Gopalkrishna Rao; McLaren Greater Lansing, Lansing, MI; Karmanos Cancer Center, Lansing, MI; Michigan State University, Lansing, MI; Division of Hematology and Oncology, Department of Medicine, SUNY Upstate Medical University, Syracuse, NY

Background: Clonal hematopoiesis of indeterminate potential (CHIP) is associated with age-related inflammation and may influence immune toxicity and efficacy after CAR T-cell therapy, although reported associations are inconsistent. We performed a systematic review and meta-analysis to quantify CHIP associations with CAR-T toxicities and response. **Methods:** We conducted a systematic review and meta-analysis of comparative studies reporting CAR-T outcomes by sequencing-defined CHIP status. PubMed, Embase, Cochrane Central, and Web of Science were searched through 2025; nine observational studies were included from 3,529 records. The evidence comprised nine retrospective cohorts (n=869) of adults receiving commercial CD19 CAR-T for B-cell malignancies (mainly aggressive lymphoma/LBCL, B-ALL) or BCMA CAR-T for multiple myeloma. CHIP was identified from pre-infusion blood-derived samples using targeted myeloid sequencing, typically at VAF $\geq 2\%$ (range $>0.3\%$ – $\geq 2\%$; one study $\geq 1\%$), with prevalence 16–56%. Primary endpoints were ASTCT grade ≥ 3 CRS and ICANS; secondary endpoints included CRS ≥ 2 , any-grade ICANS, ORR, and CR. Risk ratios were pooled using random-effects Mantel–Haenszel models with prespecified subgroup and sensitivity analyses by CAR target/disease; risk of bias was assessed with ROBINS-I. **Results:** Four cohorts (n=360; 2 CD19, 1 BCMA, 1 mixed) contributed to primary toxicity analyses. CHIP was not associated with severe CRS (ASTCT ≥ 3 ; 8/172 vs 14/188; RR 0.72, 95% CI 0.24–2.13; $I^2=31\%$) or severe ICANS (RR 1.16, 95% CI 0.48–2.81; $I^2=39\%$), with wide confidence intervals reflecting low event counts. A CD19-restricted sensitivity analysis demonstrated higher risk of severe ICANS among CHIP-positive patients (RR 1.66, 95% CI 1.03–2.65; $I^2=0\%$). For moderate-to-severe CRS (ASTCT ≥ 2), five cohorts (n=456) showed no association (RR 1.04, 95% CI 0.73–1.48; $I^2=59\%$); exclusion of a mixed cohort reduced heterogeneity and remained null (RR 1.02, 95% CI 0.79–1.32; $I^2=18\%$). Any-grade ICANS was not increased (six cohorts, n=440; RR 1.10, 95% CI 0.85–1.41; $I^2=1\%$). Efficacy was preserved: ORR was modestly higher in CHIP-positive patients in full-text cohorts (n=347; RR 1.14, 95% CI 1.02–1.27; $I^2=0\%$), with similar estimates when including abstract-only data (RR 1.10, 95% CI 1.01–1.21). CR showed a small overall increase (n=385; RR 1.24, 95% CI 1.01–1.52; $I^2=15\%$) that was not robust on sensitivity analysis (RR 1.23, 95% CI 0.90–1.67). **Conclusions:** CHIP was not consistently associated with CRS severity or overall ICANS incidence after CAR-T therapy, although severe ICANS may be higher in CD19 CAR-T lymphoma. Efficacy was preserved in CHIP-positive patients, with no evidence of impaired ORR or CR, and observed response differences should be interpreted cautiously given observational design and heterogeneous definitions. Research Sponsor: None.

The impact of COVID-19 mRNA vaccination on bispecific antibody outcomes in hematologic malignancies: A retrospective multicenter cohort study.

Mostafa Eysha, Ekrem Turk, Mohanad Elchouemi, Jowan Al-Nusair, Malak Fouani, Islam Hamza Zaki, Sharda Prakash Singh, Wanyu Zhang, Jose Conejo-Garcia, Nicholas C. DeVito, Muhammad Bilal Abid; Texas Tech University Health Sciences Center El Paso, El Paso, TX; Moffitt Cancer Center, Tampa, FL; Department of Internal Medicine, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center El Paso, EL Paso, TX; Joan C. Edwards School of Medicine, Marshall University, Huntington, WV; Duke University Medical Center, Durham, NC; Children's National Hospital, Washington, DC; Texas Tech University Health Science Center Lubbock, Lubbock, TX; Duke University, Durham, NC; Division of Hematology/Oncology, Texas Tech University Health Sciences Center, Lubbock, TX

Background: Bispecific antibody (BsAb) therapies are universally available, off-the-shelf therapies and are increasingly being used in hematologic malignancies. However, long term efficacy, durability and survival data are lacking. Furthermore, widespread expansion is limited by immune-mediated toxicities, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and infections. The real-world impact of mRNA SARS-CoV-2 vaccines on outcomes in patients receiving BsAb therapies remain unknown. **Methods:** We conducted a retrospective, propensity score-matched cohort study using the TriNetX federated electronic health record network. Adult patients with hematologic malignancies who received BsAb therapy were included and stratified by receipt of mRNA SARS-CoV-2 vaccines. Patients with documented COVID-19 infection or post-COVID-19 conditions were excluded. Cohorts were matched 1:1 on baseline demographic and clinical characteristics, yielding 238 patients per group, and followed longitudinally. Outcomes included all-cause mortality, any-grade CRS grade, and ICANS, graded per the ASTCT criteria. Associations were assessed using risk estimates and time-to-event analyses with Kaplan-Meier methods and Cox proportional hazards models. Event burden was evaluated by the number of events per patient among those experiencing CRS or ICANS. **Results:** All-cause mortality was lower in the vaccinated cohort compared with the unvaccinated cohort (21.4% vs 29.0%; $p=0.057$), with significantly improved survival on time-to-event analysis (hazard ratio [HR] 0.55; 95% CI, 0.38-0.79; log-rank $p=0.001$). The incidence of CRS grade 1/2 was similar between cohorts (25.2% vs 24.0%), with no difference in time to first CRS event (HR 0.98; 95% CI, 0.68-1.41). ICANS incidence was also comparable (10.9% vs 11.3%), with no significant difference in time-to-event (HR 0.87; 95% CI, 0.51-1.50). Among patients who developed ICANS, the vaccinated cohort experienced a higher mean number of ICANS episodes (2.58 vs 1.67; $p=0.036$) see (table1). **Conclusions:** In this propensity score-matched real-world analysis, mRNA SARS-CoV-2 vaccination was associated with significantly reduced all-cause mortality (HR, 0.55) among patients receiving BsAb therapy, without an increased risk of CRS grade 1/2 or ICANS. These findings support the safety of mRNA vaccination in this high-risk population and suggest a potential survival benefit necessitating prospective validation. Research Sponsor: None.

Outcome	Vaccinated (n=238)	Unvaccinated (n=238)	Key Effect
All-cause mortality	21.4%	29.0%	HR 0.55 (95% CI 0.38-0.79)
CRS grade 1/2	25.2%	24.0%	HR 0.98 (95% CI 0.68-1.41)
CRS grade 1/2 episodes (mean)	2.98	2.35	$P=0.16$
ICANS	10.9%	11.3%	HR 0.87 (95% CI 0.51-1.50)
ICANS episodes (mean)	2.58	1.67	$p=0.036$

Early toxicity, healthcare utilization, and survival after CAR T-cell therapy versus bispecific antibodies in DLBCL: A propensity-matched real-world analysis.

Jatin Thukral, Kanishka Uttam Chandani, Ansy Patel, Riya Kaushal Shah, Sooraj Srirangadhamu Gopu, Vida Tajiknia, Nikhil Thukral, Diana Zamora, Sarah Elizabeth Monick, Ahmed Nadeem, Talal Hilal, Vishnu Yanamaladoddi; New York Medical College, Landmark Medical Center, Woonsocket, RI; Mayo Clinic Arizona, Phoenix, AZ; SUNY Upstate Medical University, Syracuse, NY; Landmark Medical Center, Woonsocket, RI; Brown University, Legorreta Cancer Center, Providence, RI; Pt Deendayal Upadhyay National Institute for Persons with Physical Disabilities, New Delhi, India; Mayo Clinic Hospital, Phoenix, AZ; Division of Hematology/Oncology, Mayo Clinic Arizona, Phoenix, AZ; Creighton University School of Medicine-Phoenix, Phoenix, AZ

Background: CD20×CD3 bispecific antibodies and CD19-directed CAR T-cell therapies are increasingly used in relapsed/refractory DLBCL. CAR T therapy is associated with higher rates of CRS, ICANS, and cytopenias, whereas bispecific antibodies are often perceived as less toxic and more outpatient-friendly. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network. Adult patients with DLBCL treated with bispecific antibodies (glofitamab, epcoritamab) were compared with those receiving commercial CAR T-cell therapy (tisa, liso, axi). Propensity score matching was performed on demographics, comorbidities, baseline laboratory values, and corticosteroid exposure, yielding 468 patients per cohort. Outcomes included CRS, ICANS, severe neutropenia ($ANC < 500/\mu L$), and thrombocytopenia (platelets $< 50 \times 10^3/\mu L$), as well as hospitalization and ICU admission at 1, 3, 6, and 12 months. Overall survival (OS) was assessed using Kaplan–Meier analysis with log-rank testing. **Results:** After matching, CAR T therapy was associated with significantly higher immune-mediated toxicity. CRS occurred more frequently with CAR T at 1 month (37.4% vs 22.4%), 3 months (39.3% vs 27.6%), 6 months (40.6% vs 28.8%), and 12 months (41.2% vs 29.7%) (all $p < 0.001$). ICANS was also more common with CAR T across all timepoints (1 month: 10.5% vs 4.9%; 12 months: 12.6% vs 7.5%). Severe neutropenia and thrombocytopenia were markedly more frequent in the CAR T cohort, with neutropenia affecting 66.7% vs 12.8% at 1 month and 71.6% vs 32.7% at 12 months (all $p < 0.001$). Despite higher toxicity, healthcare utilization was comparable. Hospitalization rates were similar between groups at 1 and 3 months (61.8% vs 66.7% and 67.1% vs 75.9%), and ICU admission rates did not differ meaningfully at any timepoint. Importantly, overall survival consistently favored CAR T therapy. Survival differences emerged early and persisted over time, with lower mortality in the CAR T cohort at 1 month (2.1% vs 9.0%), 3 months (7.7% vs 18.6%), 6 months (15.8% vs 26.7%), and 12 months (26.5% vs 35.3%), corresponding to significantly improved OS by log-rank testing at all timepoints ($p < 0.001$). **Conclusions:** In this large, real-world, propensity-matched analysis of relapsed/refractory DLBCL, CAR T-cell therapy was associated with substantially higher rates of CRS, ICANS, and severe cytopenias compared with bispecific antibodies. However, these toxicities did not translate into higher hospitalization or ICU utilization. Despite a less favorable early toxicity profile, CAR T therapy conferred a consistent and clinically meaningful survival advantage from early to late follow-up. Early toxicity alone should not preclude CAR T referral in appropriate candidates, underscoring the need for optimized patient selection, sequencing strategies, and supportive care. Research Sponsor: None.

Real-world impact of atrial fibrillation (AFib) on cardiovascular (CV) outcomes and healthcare resource utilization (HCRU) in patients with chronic lymphocytic leukemia (CLL).

Michael Fradley, Daniel Addison, Qianhong Fu, Ayad K. Ali, Derrick van Beuge, Dong Yuan, Mei Xue, Rhys Williams, Keri Yang; University of Pennsylvania School of Medicine, Philadelphia, PA; UT Southwestern Medical Center, Dallas, TX; BeOne Medicines, Ltd., San Carlos, CA; BeOne Medicines Ltd, San Carlos, CA

Background: While the association between AFib and CLL has been reported, real-world evidence on its clinical and economic impact is limited. This study evaluated impact of AFib on CV outcomes (stroke, bleeding, heart failure) and HCRU in patients (pts) with CLL overall, by age, and by Bruton tyrosine kinase inhibitor (BTKi) therapy. **Methods:** This retrospective observational study used the US Symphony database to identify adults newly diagnosed with CLL (2014–2024). Pts were followed for 1 year after CLL diagnosis to assess incidence of AFib. Subsequent CV outcomes (stroke, bleeding, heart failure) and HCRU (inpt, outpt, other services) were compared in CLL pts with and without AFib. Multivariate regression analyses assessed associations between AFib and outcomes. Subgroup analyses were conducted in elderly pts aged ≥ 65 years. Exploratory analyses compared first-line (1L) BTKi use (ibrutinib, acalabrutinib, or zanubrutinib). **Results:** In 233,362 newly diagnosed CLL pts, 13.1% had AFib within 1 year of CLL diagnosis. A significantly greater proportion of CLL pts with AFib had ≥ 1 inpt visit within 1 year of CLL diagnosis than those without AFib (54.9% vs 23.2%, $P < .0001$), as well as a higher likelihood to incur inpt service (OR: 2.28, 95%CI [2.21, 2.35], $P < .0001$). Significantly higher proportions of CLL pts with AFib had subsequent stroke (14.3% vs 8.9%), bleeding (27.9% vs 19.1%), and heart failure (54.5% vs 18.9%) than those without AFib ($P < .0001$). Age ≥ 65 , male, non-white, and AFib were associated with subsequent stroke, bleeding, or heart failure ($P < .01$). Results were consistent in pts aged ≥ 65 years. In pts initiating 1L BTKi, AFib rate within 1 year of treatment for 1L zanubrutinib vs acalabrutinib vs ibrutinib was 11% vs 13% vs 16%, respectively; $P < .0001$. Compared to 1L ibrutinib and 1L acalabrutinib, a lower proportion of CLL pts with AFib treated with 1L zanubrutinib had subsequent stroke (12.2% vs 9.4% vs 4.8%, respectively), bleeding (27.4% vs 21.5% vs 17.4%), and heart failure (50.9% vs 45.6% vs 39.6%) ($P < .002$). CLL pts with AFib treated with 1L zanubrutinib had less inpt services than 1L ibrutinib and 1L acalabrutinib within 1 year of BTKi treatment (46.4% vs 51.5% vs 60.4%; $P < .0001$). In multivariate regression, 1L acalabrutinib pts had 29% higher odds than 1L zanubrutinib pts (OR: 1.29, 95% CI [1.12, 1.50], $P = .0005$); 1L ibrutinib pts had 69% higher odds than 1L zanubrutinib pts (OR: 1.69, 95% CI [1.48, 1.93], $P < .0001$) to incur inpt service within 1 year after initiating BTKi treatment. **Conclusions:** Findings highlight significant real-world CV and HCRU burden incurred by CLL pts with AFib. Exploratory analyses suggested 1L zanubrutinib may offer potentially favorable outcomes over other BTKi in lessening AFib and related clinical and HCRU complications. Future studies with longer follow-up are warranted to confirm these findings. Research Sponsor: BeOne Medicines, Ltd.

Effect of first-line treatment of CLL/SLL with the all-oral combination of sonrotoclax (sonro) and zanubrutinib (zanu) on minimal residual disease (uMRD) rates, including in patients with del(17p)/TP53.

Constantine Si Lun Tam, Stephen Opat, Masa Lasica, Peter Browett, Mary Ann Anderson, Emma Verner, Shuo Ma, Robert Weinkove, Marc S. Hoffmann, Jacob Drobnik Soumerai, Mazhar Shadman, Tahla Munir, Sophie Leitch, Raul Cordoba, David A. Westerman, Paolo Ghia, Yiqian Fang, Binghao Wu, Sheel Patel, Chan Cheah; Alfred Hospital and Monash University, Melbourne, VIC, Australia; Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand; Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Melbourne, Australia; Concord General Repatriation Hospital, Concord, NSW, Australia; Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL; Malaghan Institute of Medical Research, Wellington, New Zealand; The University of Kansas Cancer Center, Kansas City, KS; Mass General Brigham Cancer Institute and Harvard Medical School, Boston, MA; Fred Hutchinson Cancer Center and University of Washington, Seattle, WA; Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; Te Whatu Ora Health New Zealand, Auckland, New Zealand; Fundacion Jimenez Diaz University Hospital, Madrid, Spain; Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Australia; Università Vita-Salute San Raffaele and Comprehensive Cancer Center, IRCCS Ospedale San Raffaele, Milano, Italy; BeOne Medicines, Ltd., San Carlos, CA; Sir Charles Gairdner Hospital and the University of Western Australia, Perth, WA, Australia

Background: Oral, fixed-duration BTKi-BCL2i combinations are effective and convenient options for first-line treatment of CLL. However, all current regimens, including those using second-generation BTKi, are limited by low uMRD rates of 29–47%. We hypothesize that upgrading the BCL2i component of BTKi-BCL2i with sonro, a next generation BCL2i with ~14x pharmacological potency compared with venetoclax, may lead to improved uMRD rates. Here, we report updated safety and efficacy results in patients with treatment-naïve CLL/SLL treated with zanu+sonro (320 mg cohort) in a phase 1/1b study (NCT04277637), with a median follow-up of 30.9 months (range, 3.1–41.9 months). **Methods:** Study treatment consisted of lead-in zanu 320 mg QD for 8–12 weeks, after which sonro was added with a ramp-up to the target dose of 320 mg QD. Patients were treated until progression, unacceptable toxicity, or protocol-defined elective discontinuation after 96 weeks of combination treatment at target dose. Primary endpoint was safety per NCI-CTCAE v5.0. Secondary endpoints included overall response rate (ORR). Exploratory endpoints included uMRD₄ rates in peripheral blood per flow cytometry and next generation-sequencing (NGS). **Results:** Of the 86 patients enrolled in the sonro 320 mg cohort, 45 (52%) remained on treatment at data cut-off, and 40 (47%) discontinued sonro, most due to protocol-defined elective discontinuation (85%; n=34). The most common (≥30%) any-grade treatment-emergent adverse events (TEAEs) were neutropenia (38%), contusion (38%), COVID-19 (33%), and upper respiratory tract infection (30%). Neutropenia was the most common grade ≥3 TEAE (29%). No TLS occurred, and no AEs led to death. In 84 efficacy-evaluable patients, the ORR was 100%, with 46 (55%) achieving complete response. Median time to response was 2.6 months (range, 1.5–9.1 months). No patients in the 320 mg cohort experienced progression with an estimated 30-month PFS of 100%. The best uMRD₄ rate assessed by flow cytometry was 99% (83/84) and 100% (10/10) in patients with TP53/del(17p) mutations. Median time from reaching sonro target dose to uMRD was 3.0 months (range, 2.3–27.4 months), and the best uMRD₄ rates by weeks 24, 48 and 96 were 81% (69/85), 91% (63/69) and 98% (55/56), respectively. No patient with uMRD₄ reverted to MRD₄+. In the NGS evaluable set, best uMRD₅ (<10⁻⁵) was 86% (66/77). Updated results will be presented. **Conclusions:** Sonro+zanu was well tolerated and achieved uMRD rates of >90%, including in patients with high-risk cytogenetics. The depth and kinetics of uMRD achieved with sonro+zanu highlights the improved potency and differentiated profile of this combination vs available combination therapies in first-line CLL. Sonro+zanu is being evaluated in two phase 3 clinical trials (NCT06073821, NCT07277231). Clinical trial information: NCT04277637. Research Sponsor: BeOne Medicines, Ltd.

Pirtobrutinib in treatment-naïve patients with CLL/SLL: Pooled results from BRUIN CLL-313 and BRUIN CLL-314.

William G. Wierda, Wojciech Jurczak, Jose Antonio Garcia Vela, Marcelo Capra, Gerardo Musuraca, Michal Kwiatek, Lugui Qiu, Jianyong Li, Hiro Tatetsu, Shinsuke Iida, Kamel Laribi, Lutz Jacobasch, Catherine Callaghan Coombs, Katharine L. Lewis, Katherine Bao, Alejandro Levy, Yuanyuan Faith Bian, Weiji Su, Marisa E. Hill, Jennifer Ann Woyach; The University of Texas MD Anderson Cancer Center, Houston, TX; National Research Institute of Oncology, Kraków, Poland; Department of Haematology, Hospital Universitario Puerta de Hierro, Madrid, Spain; Centro Integrado de Hematología e Oncología, Hospital Mãe de Deus, Porto Alegre, Brazil; Hematology unit, IRCCS - Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori "Dino Amadori" I.R.S.T., Meldola, Italy; AIDPORT Clinical Trials Hospital, Skorzewo, Poland; Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences, Tianjin, China; Department of Hematology, the First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China; Department of Hematology, Rheumatology and Infectious Diseases, Kumamoto University Hospital, Kuma Moto, Japan; Department of Hematology & Oncology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; CH Le Mans, Le Mans, France; Praxis of Haematology and Oncology, Dresden, Germany; University of California, Irvine, CA; Linear Clinical Research, Sir Charles Gairdner Hospital, and University of Western Australia, Perth, Australia; Eli Lilly and Company, Indianapolis, IN; Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: Pirtobrutinib, a highly selective, non-covalent Bruton tyrosine kinase inhibitor (BTKi), is approved globally for patients (pts) with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) previously treated with a covalent BTKi. BRUIN CLL-313 and BRUIN CLL-314 are open-label, randomized phase 3 studies evaluating pirtobrutinib for therapy of pts with CLL/SLL, including in the treatment-naïve (TN) setting [versus bendamustine plus rituximab (BendaR; CLL-313, NCT05023980) and versus ibrutinib (CLL-314, NCT05254743)]. **Methods:** Pooled data from TN CLL pts randomized to receive pirtobrutinib from CLL-313 and CLL-314 were used to assess efficacy [overall response rate (ORR), progression-free survival (PFS) and overall survival (OS)] and safety. PFS and OS estimates were calculated by the Kaplan-Meier method. All pts (253) randomized within each study to receive pirtobrutinib are included in efficacy analyses and all pts (252) who received pirtobrutinib treatment are included in safety analyses. **Results:** A total of 253 TN pts, median age of 66 yrs, were assigned to receive pirtobrutinib (CLL-313 n=141; CLL-314 n=112); all but one received treatment. Among pts with evaluable samples 134/233 (58%) had unmutated IGHV, 14/253 (6%) had del(17p) and 21/220 (10%) had mutated TP53. Efficacy was consistent between the two studies (Table). Overall, ORR was 93.3%. Median PFS was not reached; the 24-month PFS rate was 93.2% (95%CI, 89.1–95.8). Median OS was also not reached; the 24-month OS rate was 97.5% (95%CI, 94.6–98.9). Median duration of therapy was 29.1 months. Treatment discontinuation due to TEAEs occurred in 4.8% of pts with 1.6% treatment related. Any-grade infection occurred in 59.9% of pts; neutropenia in 18.3% and grade ≥ 3 bleeding in 2.4%. Any-grade hypertension occurred in 10.7% of pts and atrial fibrillation/flutter was reported in 2.8%. **Conclusions:** In 253 TN pts with CLL randomized on two phase 3 studies, pirtobrutinib showed a high ORR and favorable 24-month PFS and OS rates. The safety profile was consistent with prior studies using pirtobrutinib in more heavily treated pts, with low rates of atrial fibrillation/flutter, hypertension and TEAE-related discontinuations. These findings reinforce the potential of pirtobrutinib as a meaningful and clinically relevant treatment option for pts with TN disease. Clinical trial information: NCT05023980 and NCT05254743. Research Sponsor: Eli Lilly and Company.

Efficacy of pirtobrutinib in TN patients with CLL/SLL.

Parameter		CLL-313 N = 141	CLL-314 N = 112	Pooled TN pts N=253
ORR	ORR, % (95% CI)	94.3 (89.1, 97.5)	92.0 (85.3, 96.3)	93.3 (89.5, 96.0)
	24-month PFS rates, % (95% CI)	92.7 (86.8, 96.0)	94.3 (87.8, 97.4)	93.2 (89.1–95.8)
OS	Median FU, months	28.1	22.4	27.7
	24-month OS rates, % (95% CI)	97.8 (93.3, 99.3)	97.2 (91.5, 99.1)	97.5 (94.6–98.9)
	Median FU, months	32.7	26.7	29.5

ORR includes a best response of partial response or better.

Real-world treatment and survival outcomes for zanubrutinib (zanu) and acalabrutinib (acala) monotherapy among treatment-naïve patients with chronic lymphocytic leukemia (CLL) in the United States.

Ryan Jacobs, Manasi Suryavanshi, Gregory Maglinte, Divya Nagpal, Nishit Jain, Varun Gupta, Qianhong Fu, Rhys Williams, Daniel Arthur Ermann; Atrium Health Levine Cancer Institute, Wake Forest University School of Medicine, Charlotte, NC; BeOne Medicines, Ltd., San Carlos, CA; ZS Associates, Gurugram, Haryana, India; Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT

Background: Bruton tyrosine kinase (BTK) inhibitors are central to the management of CLL/SLL (hereafter referred to as CLL). Acala was approved for CLL in the US in 2019, followed by zanu in 2023. Despite their widespread use, real-world evidence comparing therapy effectiveness is limited. This US-based study compared the real-world effectiveness of zanu and acala monotherapy as first-line treatment for patients with CLL based on overall survival (OS) and time to next treatment (TTNT). **Methods:** This retrospective analysis utilized the Komodo claims database between January 2015 and August 2025. Eligible patients were adults (aged ≥ 18 years) in the US with ≥ 2 diagnoses of CLL or SLL, who were treatment naïve for CLL and had an index claim for monotherapy with zanu (January 2023 to August 2025) or acala (November 2019 to August 2025). The index date was defined as the date of the first observed claim for the respective therapy. Patients were required to have continuous enrollment or activities within 1 year prior to and 3 months after the index date. Patients with evidence of clinical trial participation, prior CLL/SLL treatment, or two diagnoses of mantle cell lymphoma between January 2015 and the index date were excluded. Outcomes included OS (measured from index claim to all-cause mortality), and TTNT (measured from index claim to initiation of subsequent therapy or death). If death did not occur, patients were censored at the date of last activity or the enrollment end date. For OS analysis, Komodo data captured the death date, but not the cause of mortality. Survival analyses were conducted using Kaplan-Meier estimates and Cox proportional hazards models. Inverse probability of treatment weighting (IPTW) was adjusted for age, sex, US region, treatment initiation year, and Charlson Comorbidity Index (CCI). **Results:** Among 16,788 patients (zanu, $n=5819$; acala, $n=10,969$), median age was higher in zanu (73.3 years) vs acala (71.8 years) cohorts. Most patients were male (acala, 62%; zanu, 59%), non-Hispanic white (acala, 73%; zanu, 72%), and the median CCI was 2 in both cohorts. Median follow-up was 12.8 and 16.4 months for in zanu and acala cohorts, respectively. Median TTNT and OS were not reached for either cohort. With the unadjusted model, zanu had a longer TTNT (unadjusted HR, 0.88; 95% CI, 0.79–0.97; $P=.009$) and OS (HR, 0.72; 95% CI, 0.62–0.82; $P<.001$). After IPTW adjustment, zanu was associated with a significantly improved OS (IPTW-adjusted HR, 0.75; 95% CI, 0.65–0.86; $P<.001$) and TTNT (IPTW-adjusted HR, 0.89; 95% CI, 0.80–0.98; $P=.02$) compared with acala. **Conclusions:** In this real-world analysis, zanu monotherapy demonstrated significantly longer TTNT and improved OS compared with acala monotherapy. These findings suggest that zanu may offer superior outcomes in the real-world setting. Research Sponsor: BeOne Medicines, Ltd.

Subsequent therapies and time to second progression-free survival events (PFS2) in treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma (TN CLL/SLL) previously treated with zanubrutinib (zanu) or bendamustine-rituximab (BR) in SEQUOIA.

Constantine Si Lun Tam, Brad S. Kahl, Talha Munir, Tadeusz Robak, Paolo Ghia, Stephen Opat, Patricia Walker, Masa Lasica, Ian W. Flinn, Wojciech Jurczak, Jiayi Shen, Marcus Lefebure, Jamie H. Hirata, Mazyar Shadman; Alfred Hospital and Monash University, Melbourne, VIC, Australia; Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO; Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; Copernicus Memorial Hospital, Medical University of Lodz, Lodz, Poland; Università Vita-Salute San Raffaele and Comprehensive Cancer Center, IRCCS Ospedale San Raffaele, Milano, Italy; Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; Peninsula Health and Peninsula Private Hospital, Frankston, Melbourne, VIC, Australia; St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; Tennessee Oncology/OneOncology, Nashville, TN; Maria Skłodowska-Curie National Research Institute of Oncology, Kraków, Poland; BeOne Medicines, Ltd., San Carlos, CA; BeOne Medicines, Ltd., London, United Kingdom; Fred Hutchinson Cancer Center and University of Washington, Seattle, WA

Background: Cohort 1 of the phase 3 SEQUOIA trial assessed zanu, a next-generation BTKi, compared to BR in TN CLL/SLL without del(17p). Zanu previously demonstrated sustained superiority in progression free survival (PFS) and time to next treatment (TTNT) vs BR. However, evidence regarding outcomes on subsequent therapies (tx) after progressive disease (PD) on zanu remain limited. Here, we present results on follow-up (FU) tx after zanu, including PFS2. **Methods:** Pts without del(17p) were randomized to receive continuous zanu or six cycles of BR. Pts who received BR could crossover to receive zanu after PD. All pts were followed post-PD for details on any subsequent anti-CLL treatments. This analysis evaluated PFS, TTNT, TTNT or death (TTNT-D) and PFS2. *P*-values are descriptive. **Results:** In total 479 pts were randomized; 241 to zanu and 238 to BR. Baseline demographics and disease characteristics were well balanced between the arms. As of 31 October 2025, median FU was 78.7mo (range, 0.0–96.0). Sustained PFS superiority with zanu vs BR was observed (HR, 0.28; 95% CI, 0.21–0.38; *P* < .0001) with 78mo PFS estimates of 70.9% (95% CI, 64.2–76.6) for zanu and 28.6% (21.7–35.8) for BR. Overall, 211/241 (87.6%) of pts treated with zanu had not received subsequent tx and 34 pts had died without subsequent tx. TTNT and TTNT-D favored zanu over BR (HR, 0.23 [95% CI, 0.15–0.35; *P* < .0001] and 0.37 [0.27–0.50; *P* < .0001], respectively). Overall, 24/241 (10.0%) zanu pts and 82/238 (34.0%) BR pts had PD after study treatment and received subsequent tx. Of the 24 zanu pts receiving subsequent tx after PD, 13 (54.2%) received BCL2i-based regimens, 8 (33.3%) received chemoimmunotherapy (CIT) (incl. anti-CD20 antibody monotherapy), and 3 (12.5%) received BTKi. Of the 82 BR pts receiving subsequent tx after PD, 77 (93.9%) received BTKi (incl. 71 crossover pts), 3 (3.7%) received BCL2i-based regimens and 2 (2.4%) received CIT. Median time from PD following first tx to initiation of next tx was 2.1mo for zanu (range 0–25.7) and 7.4mo (0.3–48.0) for BR. Zanu pts who had PD and received subsequent BCL2i-based tx had a median FU of 33.5mo from initiation of next-line tx. Among these pts, 10 remain alive and without PD, two had died, and one had PD. Overall, PFS2 significantly favored zanu over BR (HR, 0.66; 95% CI, 0.45–0.98; *P* < .05) with 78mo PFS2 estimates of 81.3% (95% CI, 75.6–85.8) vs 73.8% (67.2–79.3), respectively. **Conclusions:** PFS2 remained superior with zanu despite broad use of novel subsequent tx (including crossover) in BR pts. Importantly, BCL2i-based salvage after initial zanu achieved high PFS rates at almost 3 years of FU. Together, these findings support that initial zanu provides durable benefit while preserving sensitivity to effective subsequent tx. Clinical trial information: NCT03336333. Research Sponsor: BeOne Medicines, Ltd.

Real-world outcomes among Medicare beneficiaries treated with first-line (1L) Bruton tyrosine kinase inhibitors (BTKis) for chronic lymphocytic leukemia (CLL).

Daniel Arthur Ermann, Deborah M. Stephens, Xiaoliang Wang, Irene Varghese, Heidi De Souza, Caitlin Sheetz, Qianhong Fu, Gregory Maglinte, Erlene Kuizon Seymour, Derrick van Beuge, Mazyar Shadman, Ryan Jacobs; Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT; The University of North Carolina School of Medicine, Chapel Hill, NC; BeOne Medicines, Ltd., San Carlos, CA; ADVI Health LLC, Washington, DC; Fred Hutchinson Cancer Center and University of Washington, Seattle, WA; Atrium Health Levine Cancer Institute, Wake Forest University School of Medicine, Charlotte, NC

Background: Covalent BTKi monotherapies are standard of care for 1L CLL in the US. However, there is a lack of head-to-head BTKi trials in the 1L setting, and previous real-world studies had limited sample size and follow-up time. We used a large US database to evaluate clinical outcomes among patients (pts) treated with BTKis for 1L CLL. **Methods:** This retrospective cohort study utilized the de-identified Medicare Fee-For-Services database. Eligible pts included those with a CLL/SLL diagnosis at age ≥ 65 y who started 1L BTKi monotherapy between 01/01/2020 and 06/30/2025 and ≥ 12 months (mos) enrollment pre-1L. Outcomes included real-world overall survival (OS), time to next treatment (tx) or death (TTNT), and time to tx discontinuation or death (TTD) from 1L start. Landmark tx and survival probabilities at 12 and 24 mos were estimated using Kaplan–Meier methods. Adjusted hazard ratios (aHRs) and 95% CIs were estimated using Cox proportional hazard models, adjusting for age, sex, race/ethnicity, Charlson Comorbidity Index (CCI) and year of 1L start. Subgroup analysis was performed by age groups (65–74, 75–84, ≥ 85 y). **Results:** A total of 10,523 pts were included (zanubrutinib [zanu]:3006; acalabrutinib [acala]:4309; ibrutinib [ibr]:3208). Median age at 1L was 77 y for zanu and acala, and 76 y for ibr. Most pts were male (58%), non-Hispanic White (91%), and resided in urban areas (78%). Median CCI score was 4 for zanu and acala, and 3 for ibr. At baseline, hypertension was 65% overall, and atrial fibrillation was 17% for zanu and acala, and 12% for ibr. Median follow-up was 16 mos (range: 0–61) for zanu, 21 mos (0–69) for acala and 35 mos (0–69) for ibr. Median OS was not reached (NR) for all groups. Median TTNT was NR for zanu (95% CI, 45–NR), 40 mos (38–42) for acala, and 30 mos (29–32) for ibr. Median TTD was NR (NR–NR) for zanu, 24 mos (22–25) for acala, and 14 mos (13–15) for ibr. Pts on zanu had higher probability of survival, not advancing to next line of therapy and not discontinuing tx at 12 and 24 mos, than those receiving acala and ibr (Table; with 95% CIs). After adjusting for baseline factors and year of 1L, pts on zanu had a statistically significantly lower risk of death, advancing to next line, or discontinuing tx, than those on ibr or acala. Similar results were observed across age subgroups. **Conclusions:** In this large cohort of pts aged ≥ 65 yrs with longest follow up to date, zanu monotherapy was associated with better survival and tx outcomes, compared to ibr and acala. Research Sponsor: BeOne Medicines, Ltd.

Tx	OS			TTNT			TTD		
	12 mos %	24 mos %	aHR	12 mos %	24 mos %	aHR	12 mos %	24 mos %	aHR
Zanu	91 (90-92)	86 (84-87)		82 (81-94)	71 (69-74)		72 (71-74)	63 (61-65)	
Ibr (ref)	85 (84-86)	75 (74-77)	0.64 (0.54-0.77)	74 (72-75)	56 (55-58)	0.63 (0.55-0.71)	53 (51-55)	35 (33-37)	0.57 (0.51-0.64)
Acala (ref)	87 (86-88)	80 (78-81)	0.77 (0.66-0.88)	78 (77-80)	67 (65-68)	0.87 (0.78-0.96)	63 (61-64)	49 (47-51)	0.86 (0.78-0.94)

Targeted combination therapies for untreated chronic lymphocytic leukemia: A network meta-analysis of randomized trials.

Owais Gul, Taimoor Hassan, Fnu Sawaira, Shariq Hayat, Abdul Rehman Azam, Nabahat Shafi, Aizaz Anwar Khalid, Sarim Hassan Shahab, Jahangir Khan Afridi, Khadija Mohib, Ayesha Ahmad, Muhammad Yasir, Ashfaq Ahmad, Obuli Srinivasan Gurunathan; United Health Services Hospitals, Johnson City, NY; King Edward Medical University, Lahore, Pakistan; Khyber Girls Medical College, Peshawar, Pakistan; Khyber Medical College, Peshawar, Pakistan; Dow University of Health Sciences, Karachi, Pakistan; Peshawar Medical College, Peshawar, Pakistan; Nishtar Medical University, Multan, Punjab, Pakistan; St. Luke's Hospital, St Louis, MO; Kirk Kerkorian School of Medicine at UNLV, Las Vegas, NV; Bacha Khan Medical College, Mardan, Pakistan; Gomal Medical College, Dera Ismail Khan, Pakistan

Background: Treatment options for previously untreated chronic lymphocytic leukemia (CLL) have expanded to include both fixed-duration venetoclax-based combinations and continuous Bruton tyrosine kinase (BTK) inhibitor therapy. While both approaches improve outcomes compared with chemoimmunotherapy, their relative benefits and risks have not been well defined. We performed a network meta-analysis to compare the efficacy and safety of these frontline targeted strategies. **Methods:** We searched MEDLINE, Embase, PubMed, the Cochrane Library, Web of Science, and major oncology conference proceedings from inception through November 2025. Phase II–III randomized trials enrolling treatment-naïve adults with CLL and evaluating venetoclax-based combinations or continuous BTK inhibitor-based regimens were included. A frequentist random-effects network meta-analysis was conducted. Treatment effects were summarized using hazard ratios (HRs) for progression-free survival (PFS) and risk ratios (RRs) for grade ≥ 3 adverse events. **Results:** Eight randomized trials including 3,056 patients and five treatment regimens were analyzed. All targeted therapy-based regimens significantly improved PFS compared with chlorambucil plus obinutuzumab. The greatest PFS benefit was observed with ibrutinib plus obinutuzumab (HR 0.41; 95% CI, 0.29–0.59), followed by venetoclax plus ibrutinib and venetoclax plus obinutuzumab. Acalabrutinib plus obinutuzumab also significantly reduced the risk of progression (HR 0.52; 95% CI, 0.41–0.67). No significant inconsistency was detected across the treatment network. Safety outcomes varied by regimen, reflecting differences in treatment duration and mechanism of action. **Conclusions:** In previously untreated CLL, fixed-duration venetoclax-based combinations achieve PFS outcomes comparable to continuous BTK inhibitor-based therapy, with distinct safety and treatment exposure profiles. These findings support personalized frontline treatment selection based on patient comorbidities, tolerability, and preference for time-limited therapy. Research Sponsor: None.

Outcome comparison of once versus twice daily dosing of zanubrutinib.

Allison Kagerer, Hannah Farnworth, Theresia Akhlaghi, Zhengming Chen, Erin Mulvey, Richard R. Furman, John N. Allan; Weill Cornell Medicine, New York, NY

Background: Zanubrutinib, a Bruton tyrosine kinase inhibitor (BTKi), approved as frontline treatment in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), can be dosed as 320mg once daily (QD) or 160mg twice daily (BID). In phase I trials 160mg BID and 320mg QD achieved comparable BTK occupancy in peripheral blood. While most clinical trials utilized BID dosing, there is limited data evaluating outcomes between regimens. Thus, we performed a retrospective study comparing outcomes of QD vs BID dosing of zanubrutinib in frontline CLL/SLL patients (pts). **Methods:** We conducted a single center retrospective study evaluating pts with CLL/SLL treated with zanubrutinib QD vs BID at Weill Cornell Medical Center (May 1, 2020 – Feb 1, 2025). Included CLL/SLL pts were treated with frontline zanubrutinib and separated into 3 groups: 320mg QD (Group 1), 160mg BID (Group 2) and dose switch (Group 3). Pearson's Chi-squared test and Fisher's exact test were used to compare baseline characteristics. Progression-free survival (PFS) and overall survival (OS) were evaluated with Kaplan-Meier (KM) method and log-rank test was used to compare KM curves; however, few events limited statistical power and prevented formal survival comparison and are presented as descriptive only. The median follow-up time was estimated by reverse KM method. **Results:** We identified 23 pts initiated on QD dosing, 43 pts initiated on BID dosing, and 33 pts who switched groups. Thirty pts switched from BID to QD and 3 pts from QD to BID. Median follow up time was 28.4 months. Median overall age was 71 with 60% male. There were no differences in age, sex, immunoglobulin heavy chain gene (IGHV) mutational status or incidence of complex karyotype, del11q, del13q, del17p, trisomy 12 and TP53 mutations. There was 1 death (Group 2) due to a second cancer. OS KM curves visually appeared similar ($p=0.62$). One pt in Group 2 and 2 pts in Group 3 progressed on zanubrutinib. PFS KM curves were visually similar ($p=0.88$). Twenty-two (22.2%) pts discontinued therapy due to intolerance. In Group 1, one pt (4.3%) discontinued for hypertension (HTN). In Group 2, 17/43 (39.5%) pts discontinued for rash (29.4%), infection (17.6%), bruising/bleeding (17.6%), HTN (11.7%), atrial fibrillation (11.7%) and diagnosis of second cancer (11.7%). In Group 3, 4/33 (12.1%) pts stopped for rash (50%) and HTN (50%). Zanubrutinib cessation was lower in QD vs BID ($p < 0.002$). **Conclusions:** We retrospectively compared QD vs BID dosing of zanubrutinib to evaluate impact on outcomes. While lack of progression and death limited our ability to make definitive statements on PFS or OS, we observed overlap of KM curves with 2 years of follow-up. We observed a lower treatment discontinuation rate with QD dosing. Our results suggest QD dosing in frontline CLL/SLL may improve tolerability while maintaining comparable efficacy. Further research is needed to confirm real-world non-inferiority of these safety and survival outcomes. Research Sponsor: None.

Hematologic and cardiovascular outcomes of SGLT2 inhibitors in patients with chronic lymphocytic leukemia and type 2 diabetes: A real-world TriNetX analysis.

Safa Saadat Afridi, Sai Sushrutha Mudupula Vemula, Ranadheer Reddy Dande, Fnu Deeksha, Haritha Gandicheruvu, Soumith Sanka, Daniel Isaac; SUNY Upstate Medical University, Syracuse, NY; University of Michigan Health Sparrow Hospital, Lansing, MI; Charleston Area Medical Center, Charleston, WV; Post Graduate Institute of Medical Education and Research, Chandigarh, India; Sinai Hospital/George Washington University, Baltimore, MD; Michigan State University, East Lansing, MI; Karmanos Cancer Institute McLaren Healthcare, Michigan State University, Lansing, MI

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) exhibit biologically plausible metabolic and immunomodulatory effects beyond glycemic control that may be relevant in chronic lymphocytic leukemia (CLL), by reducing insulin resistance, activating AMPK signaling, suppressing downstream PI3K/AKT/mTOR activity, and improving cellular metabolic homeostasis. SGLT2i also decrease systemic and adipose-derived inflammation by inhibiting the NLRP3 inflammasome, reducing IL-6 and TNF- α levels, and mitigating oxidative stress. Improved mitochondrial efficiency and modulation of HIF-1 α signaling may influence leukemic cell survival and immune exhaustion, suggesting a plausible role for SGLT2i in reducing infection risk, cardiovascular events, and survival outcomes in patients with CLL. However, real-world clinical evidence remains limited. **Methods:** We conducted a retrospective cohort study using the TriNetX Analytics Network to evaluate outcomes associated with SGLT-2i use in adults with CLL and type 2 diabetes mellitus. SGLT-2-exposed and non-exposed cohorts were compared for infectious complications, hematological outcomes like cytopenias, cardiovascular (CV), and all-cause mortality. Propensity score matching minimized confounding due to contemporary CLL therapies, baseline demographics, comorbidities, and treatment-related outcomes. Time-to-event outcomes were analyzed using Kaplan-Meier and Cox models. **Results:** After propensity score matching, with comparable mean short and long term follow durations (60–821 days), SGLT2 inhibitor use was associated with a significantly lower risk of pneumonia (5.4% vs 8.0%; HR 0.70, 95% CI 0.56–0.89) and CV mortality (13.9%, vs 21.9%) with improved survival on KM analysis ($p < 0.001$; HR–0.70, 95% CI 0.59–0.83). A modest reduction in sepsis was observed in SGLT2i users (4.7% vs 6.0%), but did not reach statistical significance (HR 0.82, 95% CI 0.65–1.05). All-cause mortality was numerically lower in the SGLT2 cohort (7.4% vs 8.5%), but no significant difference in survival was observed (HR 0.91, 95% CI 0.76–1.10). The SGLT2i group showed lower thrombocytopenia risk and a similar rare risk of AIHA between the two cohorts, with no significant difference in time-to-event analysis, suggesting that SGLT2 inhibitors may preferentially reduce selective infectious complications and CV mortality without significant improvement in overall mortality. **Conclusions:** SGLTI might have biologically plausible cardioprotective, metabolic, and immunomodulatory effects that may improve outcomes related to inflammation and infection, and reduce CV mortality in CLL, without a demonstrable short-term overall mortality benefit. Longer follow-up and prospective studies are needed to define the durability of these effects and their impact on survival. Research Sponsor: None.

Impact of SGLT2 inhibitors on clinical outcomes in diabetic patients with CLL receiving BTK inhibitors: A global propensity-matched study.

Angimar Uriepero-Palma, Dhriti Sood, Muluken Megiso, Chidiebube Ugwu, Sam Joseph King, Ariana N. Neely, Akshay Ratnani, Ana Chachua, Jude O. Ossai, Gabor Varadi; Jefferson Einstein Philadelphia Hospital, Philadelphia, PA; Albert Einstein Medical Center, Jefferson Health, Philadelphia, PA; Rutgers/Newark Beth Israel Medical Center, Newark, NJ

Background: Diabetic patients with chronic lymphocytic leukemia (CLL) receiving Bruton's tyrosine kinase inhibitors (BTKi) face intersecting challenges of metabolic dysfunction, immune dysregulation, and treatment-related toxicities, including cardiovascular complications and increased susceptibility to infections. Sodium-glucose cotransporter 2 inhibitors (SGLT2i), have emerged as a pleiotropic cardio-renal-metabolic therapeutic class with benefits extending beyond glycemic control. We hypothesize that early initiation of SGLT2i in diabetic patients with CLL may mitigate BTKi-associated toxicities and improve long-term treatment tolerability and clinical outcomes. **Methods:** We used the TriNetX Global Collaborative Network to identify patients with CLL (C91.1, C83.00) and diabetes (E08–E13) treated with BTK inhibitors (ibrutinib, acalabrutinib, or zanubrutinib), comparing those with and without SGLT2 inhibitor exposure. Propensity score matching adjusted for demographic, metabolic, cardiovascular, and renal confounders, as well as hypoglycemic and cardiovascular medications. After matching, 1,102 patients (551 per cohort) were included. Outcomes were assessed within 3 years of the index event, and hazard ratios (HRs) with 95% confidence intervals were estimated. **Results:** The 3-year all-cause mortality was significantly lower with concurrent BTKi and SGLT2i compared with BTKi alone (HR 0.50, 0.38–0.66), corresponding to a 3-year overall survival of 77% versus 62% ($p < 0.0001$). Hematologic toxicity was also significantly lower in the SGLT2i cohort, including grade 3 thrombocytopenia (HR 0.632, 0.461–0.866), grade 3 anemia (HR 0.532, 0.422–0.671), and neutropenia (HR 0.618, 0.419–0.911). Infectious complications were less frequent in the SGLT2i group, with a significant decrease in neutropenic fever (HR 0.393, 0.221–0.698), sepsis (HR 0.686, 0.504–0.934), and pneumonia (HR 0.65, 0.506–0.835). Likewise, a lower incidence of Deep vein thrombosis and pulmonary embolism was found in the SGLT2i cohort (0.555, 0.35–0.879). Surprisingly, cardiovascular outcomes were not significantly different between groups, including hypertension (HR 1.10, 0.961–1.278), atrial fibrillation (HR 1.073, 0.86–1.339), and heart failure (HR 1.128, 0.919–1.385). **Conclusions:** SGLT2i use was associated with significantly longer 3-year overall survival and lower hazards of severe cytopenias and serious infections in diabetic patients with CLL receiving BTK inhibitors, with no meaningful differences in major cardiovascular outcomes. The mechanisms underlying these associations is unclear; however, emerging evidence suggests that SGLT2i may exert immunomodulatory effects and have been shown to reduce tumor cell proliferation in breast cancer models. Further studies are warranted to confirm the role of SGLT2i in diabetic CLL patients. Research Sponsor: None.

Real-world overall survival outcomes of BTK inhibitors vs. venetoclax-based therapy as second-line treatment for chronic lymphocytic leukemia.

Mariah Black, Jourdyn Horton, Mostafa Eysha, Islam Hamza Zaki, Yasmin Youssef, Manar Hamed; Texas Tech University Health Sciences Center El Paso, El Paso, TX; Texas Tech University Health Science Center at El Paso, Paul L. Foster School of Medicine, El Paso, TX; Children's National Hospital, Washington, DC; Faculty of Medicine, Mansoura University, Mansoura, Egypt; Medical Oncology Unit, Internal Medicine Department, Faculty of Medicine and Oncology Center, Mansoura University, Mansoura, Egypt

Background: Chronic lymphocytic leukemia (CLL) is a B-cell malignancy with highly variable clinical behavior. The treatment landscape has shifted from chemoimmunotherapy to targeted agents, specifically Bruton's tyrosine kinase inhibitors (BTKi) and venetoclax (BCL-2 inhibitor). While both are established first-line options, the optimal treatment sequence to maximize long-term survival remains undefined. This real-world analysis evaluates overall survival (OS) when utilizing BTKi or venetoclax-based therapy as second-line (2L) treatment. **Methods:** This retrospective, propensity-matched cohort study utilized de-identified electronic medical record data from the TriNetX network (through Jan. 2026), covering 189 million patients. Adult patients with CLL (ICD-10: C91.1) were identified based on treatment sequencing of 1L BTKis followed by 2L Venetoclax or vice-versa. The index event was the initiation of 2L therapy with either a BTKi or venetoclax. Patients receiving traditional chemotherapy were excluded from analysis. To minimize confounding, 1:1 Propensity Score Matching (PSM) was performed using a greedy nearest-neighbor algorithm based on demographics (age, sex, race/ethnicity) and comorbidities (hypertension, ischemic heart disease, diabetes, CKD, COPD, obesity). Standardized mean differences (<0.1) confirmed covariate balance. The primary endpoint was OS through 10 years. **Results:** A total of 5,841 patients met inclusion criteria (BTKi $n=2,589$; venetoclax $n=2,892$). After PSM, 1,959 patients were included per cohort. Ten-year OS was significantly higher in patients receiving BTKi as 2L therapy compared to venetoclax (71.5% vs. 68.0%; HR 0.651, 95% CI 0.55–0.77; $p < 0.0001$). Median follow-up duration was longer for the BTKi group (1,287 days) than the venetoclax group (639 days). **Conclusions:** In this real-world analysis, treatment sequence with Venetoclax (1L) and BTKis (2L) was associated with a significant long-term survival advantage compared to venetoclax. The observed reduction in mortality risk (HR 0.651) suggests that treatment sequencing of immunotherapy with Venetoclax followed by a BTKi may offer superior clinical outcomes for treatment of CLL. While these results support preferential sequencing of BTKis after venetoclax, additional prospective studies are needed for further evaluation and confirmation. Research Sponsor: None.

Modern Hodgkin lymphoma treatments to reduce second cancer risks: Influence of risk-adapted screening.

Aislinn Macklin-Doherty, David Cunningham, Ian Chau, Andrew Tom Bates, Mark Bower, A Murray Brunt, George Follows, Christopher Fox, John A. Frew, John G. Gribben, Peter Hoskin, Clive Irwin, Lisa Lowry, John Radford, Isabel Syndikus, Emma Thomas, Anjali Zarkar, Michael Jones, Amy Berrington de González, Anthony Swerdlow, England & Wales Hodgkin Lymphoma Follow-Up Group; Institute of Cancer Research / Royal Marsden Hospital, London, United Kingdom; Gastrointestinal & Lymphoma Unit, Department of Medicine, The Royal Marsden NHS Foundation Trust, London and Surrey, United Kingdom; Gastrointestinal Unit, Department of Medicine, The Royal Marsden NHS Foundation Trust, London and Surrey, United Kingdom; University Hospital Southampton, Southampton, United Kingdom; Department of Oncology, Imperial College London, London, United Kingdom; School of Medicine, Keele University, Keele, Staffordshire, United Kingdom; Department of Haematology, Addenbrooke's Hospital NHS Trust, Cambridge, United Kingdom; Nottingham University Hospitals NHS Trust UK, Nottingham, United Kingdom; Northern Centre for Cancer Care (NCCC), Newcastle upon Tyne, United Kingdom; Department of Medical Oncology, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; Department of Clinical Oncology, Mount Vernon Cancer Centre, Rickmansworth, Middlesex, United Kingdom; Department of Oncology, University Hospital Coventry, Coventry, United Kingdom; Department of Haematology, Somerset Foundation Trust, Musgrove Park Hospital, Taunton, United Kingdom; University of Manchester and The Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom; Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, United Kingdom; Leeds Cancer Centre, St. James' Hospital, Leeds, United Kingdom; University Hospitals Birmingham NHS Trust, Birmingham, United Kingdom; The Institute of Cancer Research, Sutton, United Kingdom; Institute of Cancer Research, London, United Kingdom; The Institute of Cancer Research, London, United Kingdom

Background: Second primary malignancies (SPMs) are the leading cause of long-term treatment-related mortality in Hodgkin Lymphoma (HL). Although substantial improvements have been made to treatments over recent decades, few studies have demonstrated reduced SPM risk, particularly following modern treatments, and how risks should inform screening.

Methods: We assembled a national cohort of 7,428 women treated for HL aged <36 across England & Wales 1954–2010, with 99% complete follow-up until 2018. We analyzed SPM incidence from national cancer registry linkage. Treatment data were collated from >250 treatment centers. Standardized incidence ratios (SIRs) and Absolute Excess Risks (AERs) for SPMs were calculated, and multivariable analyses (Hazard Ratios, HR) were undertaken to assess the impact of changes in treatment and assess changing incidence trends over time.

Results: Twelve hundred women (16%) developed 1,467 SPMs with mean follow-up of 22 years (range 0–62 years). Overall SIR to develop any SPM was 3.3 (95% CI 3.1–3.5), with breast cancer contributing the greatest excess risk (AER 30.8 95% CI 27.7–34.1). Radiotherapy use halved from 1954–1980 to 2000–2010 (98% to 47%) and mean dose dropped from 48Gy to 33Gy. Conversely chemotherapy use doubled from 55% to 97%, with anthracyclines used in 94% and classic alkylators in 31% of treatments in the most recent period compared with 6% and 48% respectively pre-1980. Radiotherapy conferred the greatest treatment-specific risk factor for SPMs, (SIR 3.5 95% CI 3.3–3.7), with a strong dose-response relationship trend (HR 1.01/Gy $p < 0.001$), and highest relative risks seen in those treated with radiotherapy aged <15 years (SIR 7.4 (95% CI 5.7–9.1). There was a 25% reduction in SPM risk from the earliest treatment period (<1990) to most recent (2000–2010) and 34% reduction in solid SPM risk (Table). The decrease in risk for SPMs became smaller and non-significant after adjusting for reduced radiotherapy use and dose (HR 0.89, p_{trend} 0.11). There was no attenuation after adjustment for chemotherapy. Despite declining risks, risks remained significantly elevated beyond 40 years after treatment. **Conclusions:** Modern HL treatments are associated with a substantial reduction in SPM risks, which appears to be largely attributable to decreased radiotherapy use and dose. However large persistent excess risks, particularly for breast and lung cancers, underscore the need for targeted screening in high-risk survivors treated in more recent eras. Research Sponsor: National Institute of Health Research Biomedical Research Centre – Royal Marsden Hospital / Institute of Cancer Research; Breast Cancer Now; Cancer Research UK.

Risk of SPMs by treatment era.

SPMs & treatments	Treated <1990 HR (ref)	Treated 1990-1999 HR (95% CI)	Treated 2000-2010 HR (95% CI)	P_{trend}
All SPMs				
Any treatment	1.0	0.77 (0.65-0.90)	0.75 (0.57-0.99)	0.001
Adjusted for radiotherapy & dose	1.0	0.83 (0.69-1.00)	0.90 (0.63-1.28)	0.11
Solid SPMs				
Any treatment	1.0	0.71 (0.60-0.85)	0.66 (0.48-0.90)	<0.001
Adjusted for radiotherapy & dose	1.0	0.79 (0.65-0.96)	0.81 (0.55-1.20)	0.03

Invasive-field radiotherapy plus rituximab versus rituximab alone after response to immunochemotherapy in stage III follicular lymphoma: An open-label, multicenter, randomized clinical study.

Tongyu Lin, Huangming Hong, Zegeng Chen, He Huang, Xiaoqian Li, Liqun Zou, Liling Zhang, Hongqiang Guo, Ke Xie; Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China; Sichuan Clinical Research Center For Cancer/Sichuan Cancer Hospital & Institute, Chengdu, Sichuan, China; Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; Shandong Cancer Hospital and Institute, Jinan, Shandong, China; West China Hospital, Sichuan University, Chengdu, Sichuan, China; Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; Medical Oncology, Henan Cancer Hospital, Zhengzhou, China; Sichuan Provincial People's Hospital, Chengdu, China

Background: Stage III follicular lymphoma (FL) remains incurable with immunochemotherapy followed by rituximab maintenance. Radiotherapy plays a critical role in the curative treatment of early-stage FL; however, its role in the management of stage III disease remains undefined. **Methods:** In this open-label, multicenter, randomized clinical trial, patients with stage III FL, who demonstrated complete or partial response without bulky after induction immunochemotherapy were enrolled. Eligible patients randomly assigned (1:1) to receive invasive field consolidation radiotherapy (IFRT) combined rituximab maintenance (IFRT+R arm) or rituximab maintenance alone (R arm). The dose of IFRT was 30Gy. The primary endpoint was 5-year progression-free survival (PFS), and the secondary endpoint was 5-year overall survival (OS). This study is registered with Chinese ClinicalTrials.gov, number ChiCTR2000032550. **Results:** Between January 2015 to January 2021, 152 eligible patients were randomly assigned to receive IFRT+R (n=74) or R alone (n=78). Baseline characteristics showed no significant differences between the two arms. After a median follow-up of 82 months, the 5-year PFS was 88.9% in IFRT+R group and 66.7% in R alone group (HR, 0.32; 95% CI, 0.16–0.66, P = 0.002). The 5-year OS was 97.3% in IFRT+R group versus 84.4% in R group (HR, 0.23; 95% CI, 0.07–0.81, P = 0.02). Treatment-related adverse events were more frequent in the IFRT+R arm than in the R arm (58% vs 38%), predominantly consisting of acute hematologic toxicities, including neutropenia (33% vs 26%) and leukopenia (34% vs 28%). Grade 3–4 toxicities were more common in the IFRT+R arm (27% vs 18%), and no treatment-related deaths were observed. **Conclusions:** Involved-field radiotherapy after effective systemic therapy significantly improved PFS and OS with manageable toxicity, highlighting its potential role in the management of stage III FL. Clinical trial information: ChiCTR2000032550. Research Sponsor: National Natural Science Foundation of China; U24A20679 and 82470237.

Single-cell analysis and functional profiling of galectin-3 in the tumor immune microenvironment in transformed follicular lymphoma.

Xiaohui Wang, Huilai Zhang; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Department of Lymphoma, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Histological transformation of follicular lymphoma (tFL) represents an aggressive subtype characterized by a complex and immunosuppressive tumor immune microenvironment (TIME). Therefore, it is urgent to investigate the characteristics of TIME and develop more effective immunotherapy strategies for tFL patients. **Methods:** Using single-cell RNA sequencing, a high-resolution landscape of the entire TIME ecosystem of follicular lymphoma (FL) and tFL patients is depicted. Findings were validated by multiplex immunofluorescence (mIF) staining, in vitro assays, and a mouse model. **Results:** Compared to FL patients, tFL patients exhibited a higher proportion of exhausted CD8⁺T cells expressing checkpoint receptors such as LAG3, CTLA4, PD-1, and HAVCR2. Notably, Galectin-3 expression was acquired by tumor cells after transformation, leading to enhanced Galectin-3–LAG3 interactions with CD8⁺ T cells, as confirmed by mIF staining. In co-culture experiments, Galectin-3-overexpressing tumor cells impaired CD8⁺ T cell proliferation and cytotoxicity, inducing an exhausted phenotype. Treatment with the Galectin-3 inhibitor GB1107 rescued T cell function. Similar T cell dysfunction and GB1107 response were observed in Galectin-3-overexpressing mouse xenograft model. Additionally, we identified an accumulation of MDSC-like monocytes and M2-like macrophages in tFL patients, further contributing to immune suppression. **Conclusions:** Galectin-3 drives T cell exhaustion and reshapes the immune microenvironment in tFL patients, promoting immune evasion and disease progression. Targeting Galectin-3 may represent a promising immunotherapeutic strategy for tFL patients. Research Sponsor: None.

Diagnostic yield after pre-biopsy steroid administration in primary CNS high-grade B-cell lymphoma.

Charmi Trivedi, Ryan Snow, Chanjun Park, Sathwik Madireddy, Sovijja Pou, Kaavya Mandi, Kelly Pan, Alex Friefeld, Huang He Ding, Thomas Ollila, Ari Pelcovits; Brown University Health, Providence, RI

Background: Primary central nervous system high-grade B-cell lymphoma (PCNSL) is typically diagnosed via brain biopsy. Corticosteroids are often administered pre-biopsy to reduce vasogenic edema, but are hypothesized to decrease diagnostic yield by inducing lymphocyte apoptosis. This study aims to evaluate whether steroid administration prior to biopsy affects the likelihood of obtaining a diagnostic result in pts with PCNSL. **Methods:** A retrospective chart review of Brown University Health pts (2015–2024) with PCNSL, including primary CNS diffuse large B cell lymphoma (DLBCL), was conducted. Collected variables included demographics (age, sex, ECOG), steroid dose, biopsy type (excisional, incisional, or stereotactic needle biopsy) and outcome of biopsy (diagnostic vs. undiagnostic). Statistical analysis comparing pre-biopsy steroid (PBS) group with steroid naive group was conducted using Chi-squared, Wilcoxon rank sum and Fisher’s Exact test. **Results:** A total of 59 pts were found to have biopsy proven PCNSL and were included in statistical analysis. 53 pts had DLBCL and 6 had high grade PCNSL. Baseline demographics and biopsy types did not significantly differ between PBS group and steroid-naive pts ($p>0.05$). Among pts that received PBS, 35/35 (100%) had a diagnostic biopsy compared with 22/24 (92%) in pts who did not receive steroids. Pre-biopsy steroid use was not associated with a statistically significant difference in diagnostic yield, (Fisher’s Exact $p=0.16$). As there were no non-diagnostic biopsies in the PBS group, the odds ratio was infinite and the upper confidence bound could not be estimated. Median dose of steroids was 213mg (prednisone equivalents; Q1 93mg, Q3 307mg). As all pts in the PBS group had diagnostic biopsies no analysis based on steroid dose could be conducted. All pts who received steroids had documented concern for vasogenic edema and steroids were not used for empiric treatment. **Conclusions:** In our cohort, pre-biopsy corticosteroid administration did not appear to affect diagnostic yield. There was no difference in the rate of diagnostic first biopsies between the PBS and steroid naive group. Among pts receiving steroids, all biopsies were diagnostic regardless of timing relative to biopsy or total steroid dose. Due to the small sample size and the universal diagnostic success, statistical comparisons were limited. These findings suggest that steroids may not compromise the diagnostic yield of PCNSL biopsies. Research Sponsor: None.

Clinical characteristics and biopsy outcomes.

	Steroid Naive N = 24	Steroids before Biopsy N = 35	p-value
Age	69 (Q1 63; Q3 73)	66 (Q1 57; Q3 75)	0.3
Female	15 (63%)	19 (54%)	0.5
Normal LDH	16 (94%)	12 (67%)	0.088
ECOG 2-4	4 (16.6%)	9 (27.3%)	0.6
DLBCL	21 (88%)	32 (91%)	0.33
Total steroid dose 100-700mg (in Prednisone Equivalents)	–	23 (70%)	
Steroids within 24 hours of biopsy		14 (40%)	
Stereotactic needle biopsy	18 (75%)	17 (52%)	0.3
Diagnostic Biopsy	21 (91%)	33 (100%)	0.2

Chemotherapy use and survival by demographic and socioeconomic factors in primary central nervous system lymphoma: A population-based SEER analysis.

Kevin Cheng Liang Wu, Mary Owolabi, Omar Sadaqah, Kai Wang, Homero Ferreira da Silva Neto, Yue Faat Raymond Kwok; Zucker School of Medicine at Hofstra/Northwell, Staten Island University Hospital, Staten Island, NY; Staten Island University Hospital, Staten Island, NY

Background: Primary central nervous system lymphoma (PCNSL) is a rare non-Hodgkin lymphoma confined to the brain and spinal cord. Despite the introduction of rituximab to modern systemic therapy, previous population-based studies suggest that survival disparities by race and socioeconomic status persist. This study uses chemotherapy utilization modeling and contemporary 2000–2022 data to quantify the real-world survival impact of chemotherapy underuse across ethnic and neighborhood income strata in adults with PCNSL. **Methods:** Adults (≥ 20 years) with histologically confirmed PCNSL diagnosed from 2000–2022 were identified from SEER 21 registries. Patients with concurrent systemic lymphoma were excluded. Chemotherapy receipt was coded as yes vs no/unknown; with blank fields excluded. Binary logistic regression estimated odds of receiving chemotherapy by demographics. Multivariable Cox proportional hazards models evaluated associations of age, sex, race, neighborhood median household income (MHI), rural–urban residence, and chemotherapy with cause-specific survival. MHI was categorized into quintiles derived from the cohort distribution (approximately equal case counts per band). Kaplan–Meier methods estimated cause-specific survival and median survival times. **Results:** A total of 9,533 adults met the inclusion criteria. Compared with Whites, Black (OR 0.42, 95% CI 0.35–0.49) and Hispanic patients (OR 0.75, 95% CI 0.66–0.84) were less likely to receive chemotherapy; patients from neighborhoods with MHI $< \$65k$ also had reduced chemotherapy use versus $\geq \$100k$ (OR 0.53, 95% CI 0.45–0.62). Median survival was 64 months for patients receiving chemotherapy versus 3 months for those with no/unknown chemotherapy. Median survival by race was 17 months in Black patients, 25 months in Whites, and 38 months in Hispanics. Median survival was 14 months in the lowest MHI band ($< \$65k$) and 46 months in the highest ($\geq \$100k$). In Cox models, lack of chemotherapy was associated with more than twice the hazard of lymphoma-specific death (HR 2.29, 95% CI 2.17–2.44). After adjustment for age, sex, race, MHI, residence, and chemotherapy; Black patients had higher mortality than Whites (HR 1.22, 95% CI 1.10–1.36), female gender had improved survival than males (HR 0.88, 95% CI 0.833–0.929), and MHI $< \$65k$ was associated with worse survival versus $\geq \$100k$ (HR 1.20, 95% CI 1.09–1.32). **Conclusions:** In this cohort of adults with PCNSL, chemotherapy use, race, neighborhood income, and age were powerful independent determinants of cause-specific survival. Chemotherapy underuse was concentrated among Black, Hispanic, and lower-income patients and was associated with a dramatic survival penalty, indicating that inequities in access to systemic therapy are likely major drivers of persistent racial and socioeconomic survival gaps in PCNSL. Research Sponsor: None.

Navigating the post-covalent bruton tyrosine kinase inhibitor (cBTKi) landscape in mantle cell lymphoma (MCL): Real-world insights on treatment patterns, discontinuation, and healthcare resource utilization (HCRU).

Alvaro Jose Alencar, Swetha Challagulla, Dong Yuan, Qianhong Fu, Keri Yang, Toby Andrew Eyre; University of Miami/Sylvester Comprehensive Cancer Center, Miami, FL; BeOne Medicines, Ltd., San Carlos, CA; Oxford Cancer and Haematology Centre, Churchill Hospital, Headington, Oxford, United Kingdom

Background: cBTKis have become standard therapy for relapsed/refractory MCL and are rapidly advancing to the first-line setting. However, real-world evidence on clinical and economic outcomes following cBTKi therapy is limited. Treatment patterns, time to treatment discontinuation (TTD), and HCRU were evaluated among patients (pts) with MCL previously treated with cBTKis. **Methods:** This retrospective observational study used claims data from the Symphony Integrated Dataverse (Jan 2020-Aug 2025) to identify adults with MCL who received a cBTKi in any line of therapy (LOT) and, following discontinuation, initiated another treatment. Post-cBTKi regimens were categorized as B-cell lymphoma 2 inhibitor (BCL2i), cBTKi, noncovalent BTKi (ncBTKi), chimeric antigen receptor T-cell therapy (CAR-T), chemo-±immunotherapy (C±IT), and other. TTD and HCRU (outpatient/inpatient/other medical, reported per-patient-per-month [PPPM]), were assessed for regimens received post cBTKi. **Results:** Of 10,519 total US pts with MCL, 571 were previously treated with cBTKis and received a subsequent therapy (median age, 72.0 years; ≥65 years, 77%; male, 74%; White non-Hispanic, 67%; Medicare, 62%). Regimens received in a subsequent LOT after cBTKi included cBTKis (38%), ncBTKis (32%), C±IT (11%), BCL2is (9%; monotherapy 7%), CAR-T (2%), and other (8%). Median TTD was longest with cBTKis (365 days), followed by ncBTKis (206 days), and shortest with BCL2is (140 days). Mean HCRU PPPM was lowest with cBTKis (outpatient, 1.21; inpatient, 0.20; other medical, 1.07) and highest with CAR-T (outpatient, 10.63; inpatient, 1.89; other medical, 1.55). **Conclusions:** In this real-world analysis, pts with MCL who previously received cBTKis were most frequently re-treated with cBTKis, highlighting the need for novel treatment options in the post-cBTKi setting. TTD was greatest in pts who received cBTKis or ncBTKis and shortest in those treated with BCL2is. HCRU burden was lowest for pts who received cBTKis and highest for those treated with CAR-T. Further research, including an understanding of the reasons for re-exposure to cBTKis, is warranted to confirm these findings. Research Sponsor: BeOne Medicines, Ltd.

TTD and HCRU by MCL treatment regimens received post cBTKi.						
Outcomes	All N=571	cBTKi n=215	ncBTKi n=182	C±IT n=62	BCL2i n=53	CAR-T n=12
Follow-up, median (IQR), days	294 (118-628)	414 (206-762)	189 (89-453)	330 (116-727)	256 (70-844)	412 (216-912)
TTD, median (95% CI), days	222 (181-281)	365 (278-460)	206 (173-304)	169 (112-183)	140 (100-315)	NA
HCRU, mean (SD), PPPM						
Outpatient	1.95 (2.82)	1.21 (1.61)	1.48 (2.19)	2.19 (2.65)	2.34 (2.70)	10.63 (5.05)
Inpatient	0.34 (0.91)	0.20 (0.67)	0.33 (0.75)	0.29 (0.82)	0.43 (1.22)	1.89 (1.89)
Other medical services	1.47 (2.62)	1.07 (1.93)	1.35 (2.54)	2.54 (3.59)	1.64 (2.82)	1.55 (1.70)

Efficacy, safety, and genetic analysis of orelabrutinib combined with rituximab as first-line systemic treatment for marginal zone lymphoma.

Xian Li, Yun Liang, Wenbin Qian, Yaping Xie, Wenping Wu, Ying Lu; The Second Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China; The Second Affiliated Hospital, College of Medicine, Zhejiang University, Hang Zhou, China; Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China; People's Hospital of Quzhou, Quzhou, China; The Affiliated People's Hospital of Ningbo University, Ningbo, China

Background: Marginal zone lymphoma (MZL) is a heterogeneous B-cell malignancy that is often managed with chemoimmunotherapy in the first-line setting, but chemotherapy entails considerable toxicity. Orelabrutinib, a novel oral BTK inhibitor which offers improved target selectivity and fewer off-target effects. This study evaluates the chemo-free combination of orelabrutinib plus rituximab in untreated MZL. **Methods:** This is a prospective, single-arm, multicenter phase II clinical trial (NCT07022223). Patients with untreated MZL who met ECOG criteria of 0–2 and were in need of treatment, or who had failed local, were eligible. All participants will receive induction therapy with the orelabrutinib and rituximab regimen. The treatment cycle is 28 days, with a total of 4–6 cycles. The induction treatment period is as follows: Cycle 1: Rituximab, 375 mg/m², on day 1. Cycles 2–6: Orelabrutinib, 150 mg, once daily orally, from day 1–28, plus rituximab 375 mg/m² on day 1. Patients who achieve a partial response (PR) or better will enter a 2-year maintenance period with orelabrutinib. The primary endpoint is the overall response rate (ORR). Secondary endpoints include complete response (CR) rate, PR rate, progression-free survival (PFS), and overall survival (OS). Safety is assessed by monitoring adverse events (AEs). **Results:** From March 2025 to December 2025, a total of 40 patients with MZL (32 MALT, 6 NMZL, 2 SMZL) were enrolled. The median age at diagnosis was 68 years (range 44–84), and 82.5 % of patients were older than 60 years. 21 (52.5%) were female. Most patients had an ECOG score of 0–1 (28/40), Ann Arbor Stage III–IV disease (35/40). Twelve patients had an MZL–International Prognostic Index score of ≥2. Thirteen patients had failed prior local therapy, the majority of whom had undergone surgical resection. After three cycles, 25 patients were evaluable, with an ORR of 80 % (20/25) and a CRR of 24 %. Following six cycles, 13 patients were evaluable, achieving an ORR of 100 % (13/13) and a CRR of 62 % (8/13). The median time to response was 72 days. With a median follow-up of 5.7 months (range, 5.1–6.8), the median PFS and OS were not reached, the 1-year PFS rates were 97.2% and the 1-year OS rates were 100%. Next-generation sequencing (NGS) was performed on 16 patients, a total of 158 mutated genes were identified, with missense mutations predominating (62.7%). The most frequently mutated genes were NOTCH2, FAT4, LRP1B, PCLO, and SYNE1, all at 31.2 %. Treatment was generally well tolerated, only 13 patients experienced adverse events, the most common adverse events were anemia (15 %), infection (12.5 %) and neutropenia (10 %). Notably, BTK inhibitor–associated atrial fibrillation (0 %) and bradycardia (0 %) were absent. **Conclusions:** The combination of orelaburtinib and rituximab shows significant activity in MZL, with a manageable toxicity profile. Clinical trial information: NCT07022223. Research Sponsor: None.

Diagnostic accuracy of circulating tumor DNA for post-remission surveillance in diffuse large B-cell lymphoma: A systematic review and meta-analysis.

Mohammad Ahsen Soomro, Mohamed Ahmed, Manzar Abbas, Hala Soomro, Nausheen Ahmed, Forat Lutfi, Joseph Bennett; Internal Medicine, The Wright Center for Graduate Medical Education, Scranton, PA; Hackensack Meridian JFK Medical Center, Edison, NJ; Hospital Medicine, Brown University Health, Rhode Island, RI; University of Kansas Cancer Center, Westwood, KS; Hematologic Malignancies and Cellular Therapeutics, University of Kansas Medical Center, Westwood, KS; University of Kansas Medical Center, Department of Internal Medicine, Kansas City, KS

Background: Relapse after complete remission remains a major cause of treatment failure in Diffuse Large B-Cell Lymphoma (DLBCL). Standard surveillance using clinical assessment and imaging often detects recurrence after substantial tumor regrowth. Circulating tumor DNA (ctDNA) has emerged as a promising biomarker for minimal residual disease detection; however, its diagnostic accuracy for relapse surveillance in DLBCL has not been systematically quantified. **Methods:** A systematic review and meta-analysis was performed per a prespecified PROSPERO protocol (CRD420251179858). MEDLINE, Embase, CENTRAL, and major conference proceedings were searched through October 2025. Following systematic screening of B-cell non-Hodgkin lymphoma studies, those eligible for quantitative synthesis enrolled adults with DLBCL in complete remission undergoing post-treatment ctDNA surveillance, with clinically or radiologically confirmed relapse as the reference standard. Studies were included if sufficient data were available to construct 2×2 contingency tables. Pooled sensitivity and specificity were estimated using a bivariate random-effects logistic regression model with a logit link, accounting for between-study heterogeneity. A continuity correction of 0.5 was applied to all cells in studies with zero counts prior to model fitting. **Results:** Three studies (N=157) comprising patients in complete remission after first-line therapy were included in the quantitative synthesis. Using a bivariate random-effects model, the pooled sensitivity of ctDNA for detection of clinical relapse was 58.6% (95% CI 32.2–80.8%), while pooled specificity was 93.9% (95% CI 83.6–97.9%), indicating high specificity but moderate sensitivity during surveillance. Specificity was consistently high, supporting strong rule-in performance. Sensitivity varied across studies (range: 31%–88%), likely reflecting differences primarily in sampling density, as well as assay platforms (tumor-informed Ig-HTS vs. targeted NGS). Across included cohorts, ctDNA positivity generally preceded or coincided with clinically detected relapse, while ctDNA negativity was associated with durable remission during follow-up. **Conclusions:** In patients with DLBCL in complete remission after first-line therapy, ctDNA surveillance demonstrates very high specificity but only moderate sensitivity for detection of clinical relapse. These findings support ctDNA as a highly specific rule-in biomarker for relapse during surveillance, potentially resolving ambiguity in equivocal imaging findings. However, its moderate sensitivity limits its standalone ability to detect relapse. Prospective validation of standardized testing intervals and assay harmonization are needed to optimize sensitivity before integration with standard monitoring strategies. Research Sponsor: None.

Epcoritamab (epcor) + chemoimmunotherapy (CIT) in patients (pts) with relapsed/refractory large B-cell lymphoma (R/R LBCL) eligible for autologous stem cell transplant (ASCT): Pooled results from arms 4 and 10 of EPCORE NHL-2.

Yasmin Karimi, Pau Abrisqueta, Charalambos Andreadis, Chan Cheah, Justin Darrah, Sven de Vos, Lorenzo Falchi, Gerardo Musuraca, Marek Trněný, Anna Sureda, Charles Kearns, Kimberly G. Archer, Milan Geybels, Malene Risum, Jon Ukropec, Mohammad E. Atiya, Raul Cordoba; University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; Hospital Universitario Vall d'Hebron, Barcelona, Spain; Division of Hematology and Oncology, University of California San Francisco, San Francisco, CA; Sir Charles Gairdner Hospital and the University of Western Australia, Perth, WA, Australia; Cedars-Sinai Medical Center, Los Angeles, CA; Ronald Reagan University of California Los Angeles Medical Center, Los Angeles, CA; Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY; IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy; Charles University and General University Hospital, Prague, Czech Republic; Institut Català d'Oncologia – L'Hospitalet, IDIBELL; Universitat de Barcelona, Barcelona, Spain; AbbVie, Inc, North Chicago, IL; Genmab, Plainsboro, NJ; Genmab, Copenhagen, Denmark; Fundación Jiménez Díaz University Hospital, Madrid, Spain

Background: Pts with R/R LBCL can have inadequate response to salvage treatment (tx), precluding ASCT. While CAR T therapies are standard of care in the 2L setting for pts with early relapse (< 12 mo of 1L tx), their use is limited by eligibility, accessibility, or cost. Regimens that enhance salvage tx response rates enabling pts to proceed to ASCT are needed. In Arms 4 and 10 of the phase 1b/2 EPCORE NHL-2 trial (NCT04663347), epcor + CIT showed high response rates in ASCT-eligible R/R LBCL. A pooled analysis of these data is reported. **Methods:** ASCT-eligible pts received epcor + rituximab, dexamethasone, cytarabine, and oxaliplatin/carboplatin (R-DHAX/C) (Arm 4) or epcor + rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) (Arm 10). After salvage tx, pts could proceed to ASCT or remain on epcor mono tx. ORR per investigator, DOCR, PFS, OS, and safety are reported. **Results:** The analysis included 63 pts (Arm 4: n = 29; Arm 10: n = 34). Baseline characteristics: median age 61 y (range 28–77), 68% male, 71% stage III/IV, 13% (8/33 assessed) high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* translocations (central lab), 8% prior CAR T. 79% (n = 50) were receiving 2L tx; 57% (n = 36) were receiving 2L tx and were refractory or had early relapse to 1L tx. Median relative CIT dose intensity was $\geq 80\%$. At 18.3 mo median follow-up, ORR and CR rates were 84% and 67% (Table). 57% (n = 36) proceeded to ASCT; 16% (n = 10) remained on epcor mono tx due to pt/physician decision. Median DOCR, PFS, and OS were not reached in pts who proceeded to ASCT or who remained on epcor. Similar outcomes were seen in 2L pts and across 2L pts with early and late relapse. Overall, the most common any-grade TEAEs were anemia (68%), thrombocytopenia (68%), and neutropenia (62%). CRS occurred in 48% of pts and ICANS in 3%; all events were grade 1–2. Serious infections occurred in 17%. TEAEs led to tx discontinuation in 11%. There were no fatal TEAEs. **Conclusions:** In this pooled analysis of ASCT-eligible pts with R/R LBCL, tx with epcor + salvage CIT resulted in high CR rates, enabling a large proportion of pts to proceed to ASCT. Deep, durable responses were seen in pts who underwent ASCT and those who continued epcor mono tx. A high CR rate was also observed in 2L pts with early relapse. Safety was consistent with prior reports. Dose intensity of CIT was not impacted. These findings support epcor-based combination salvage strategies to increase response depth and facilitate higher ASCT rates and possible cure in ASCT-eligible pts with DLBCL. Clinical trial information: NCT04663347. Research Sponsor: Genmab A/S and AbbVie.

	All pts (N = 63)	2L (n = 50)	2L with early relapse ^a (n = 36)	Proceeded to ASCT (n = 36)	Remained on epcor mono (n = 10)
ORR/CR, %	84/67	84/68	81/61	100/94	100/80
DOCR, 18-mo rate, %	79	80	81	83	64
PFS, 18-mo rate, %	62	62	58	80	67
OS, 18-mo rate, %	82	82	77	93	100

^aPts receiving 2L tx who were refractory to or progressed <12 mo of 1L tx.

A real-world comparison of treatment and survival outcomes with zanubrutinib (zanu) and acalabrutinib (acala) monotherapy among patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL) in the United States.

Yucui Wang, Manasi Suryavanshi, Gregory Maglinte, Rucha Kulkarni, Divya Nagpal, Melissa Hagan, Nishit Jain, Erlene Kuizon Seymour, Rhys Williams, Javier Munoz; Mayo Clinic Rochester, Rochester, MN; BeOne Medicines, Ltd., San Carlos, CA; ZS Associates, San Francisco, CA; ZS Associates, Gurugram, Haryana, India; Mayo Clinic Arizona, Phoenix, AZ

Background: MCL is a rare and aggressive subtype of B-cell non-Hodgkin lymphoma that remains incurable. Bruton tyrosine kinase (BTK) inhibitors are an established standard of care for R/R MCL. However, comparative effectiveness data for different BTK inhibitors for R/R MCL are limited. This study evaluated the real-world effectiveness of zanu and acala in US patients with R/R MCL based on overall survival (OS) and time to next treatment (TTNT). **Methods:** A retrospective cohort study was conducted using Komodo health administrative claims data. Eligible patients were adults (aged ≥ 18 years) with ≥ 2 MCL diagnoses and continuous enrollment or activities within 1 year prior to and 3 months following the index date. Patients were required to initiate monotherapy with zanu (index period: November 2019 to August 2025) or acala (index period: October 2017 to August 2025) as a second-line or later (2L+) treatment, with index date defined as the first observed claim for zanu or acala. Patients with evidence of clinical trial participation, end stage renal disease or prior stem cell transplant were excluded. Outcomes included OS (time from index date to all-cause mortality) and TTNT (time from index date to subsequent therapy with an allowable gap of 120 days). If an outcome was not observed, patients were censored at the date of last activity or enrollment end date. Survival analyses were conducted using Kaplan-Meier estimates and Cox proportional hazards models. Inverse probability of treatment weighting (IPTW) was adjusted for age, sex, US region, treatment initiation year and Charlson Comorbidity Index (CCI). **Results:** In total, 2219 patients (zanu, $n=931$; acala, $n=1288$) were eligible and included in the study. The mean age was higher in the zanu (72.3 years; SD, 9.4) vs acala cohort (71.4 years; SD, 9.7). Most patients were male (zanu, 71%; acala, 75%), non-Hispanic white (zanu, 73%; acala, 74%), and the mean CCI was 3.5 (SD, 3.2) and 3.6 (SD, 3.1) in the zanu and acala cohorts, respectively. Median follow-up was 14.8 and 18.2 months in zanu and acala cohorts, respectively. Median TTNT was 26.7 months for zanu and 20.8 months for acala. Median OS was not reached for zanu and was 60.6 months for acala. In the unadjusted model, zanu had a longer TTNT (HR, 0.86; 95% CI, 0.76–0.97; $P=.012$) and OS (HR, 0.74; 95% CI, 0.62–0.88; $P<.001$). After IPTW adjustment, TTNT and OS favored zanu treatment (TTNT: IPTW-adjusted HR, 0.86; 95% CI, 0.76–0.98; $P=.025$; OS: IPTW-adjusted HR, 0.81; 95% CI, 0.68–0.98; $P=.03$). **Conclusions:** In this real-world analysis of US health claims data, zanu monotherapy demonstrated significantly longer TTNT and improved OS compared with acala in patients receiving 2L+ therapy for MCL. These findings support zanu as an effective BTK inhibitor for R/R MCL. Research Sponsor: BeOne Medicines, Ltd.

Signatures of biological heterogeneity associated with treatment outcome in diffuse large B-cell lymphoma.

Boya Wang, George Wright, Julius Enssle, Yandan Yang, James D. Phelan, Thomas Oellerich, Giorgio Inghirami, Louis M. Staudt; Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; National Cancer Institute, National Institutes of Health, Bethesda, MD; Goethe University Frankfurt, Frankfurt, Germany; Weill Cornell Medicine, New York, NY

Background: Genetic subtypes of diffuse large B-cell lymphoma (DLBCL) capture biological differences between tumors that influence the response to immunochemotherapy (Schmitz et al., NEJM 2018). However, nearly 40% of DLBCL cases remain unclassified. The addition of gene expression signatures can accelerate classification and inform therapeutic intervention. **Methods:** We generated single-cell RNA sequencing of 103 DLBCL patient biopsies from Weill Cornell Medicine, New York Presbyterian Hospital, and the National Institutes of Health. We also utilized bulk genomic data from a discovery cohort (n=311, Ennishi et al., J Clin Oncol 2019) and a validation cohort (n=574, Schmitz et al., NEJM 2018). **Results:** Single cell sequencing allowed us to isolate the malignant B cells and develop genetic subtype signatures. The MCD signature was associated with poor overall survival ($p < 10^{-6}$), as was the BN2 signature within ABC tumors ($p < 10^{-3}$). When applied to unclassified tumors, the subtype signatures identified characteristic genetic alterations including SLC1A5 mutations in MCD ($p < 10^{-5}$), UBE2A mutations in BN2 ($p < 10^{-13}$), C10orf12 truncations and copy number loss in EZB ($p < 10^{-6}$), and SGK1 mutations in ST2 ($p < 10^{-7}$). Moreover, we discovered that most DLBCL tumors (80%) contained two or more genetic subclones (median 2, range 1-5) based on DNA copy number differences. The genetic subclones had distinct phenotypes based on expression of six recurrent gene expression meta-signatures, herein termed themes. The germinal center (GC) B cell, memory B cell, plasma cell, and pan-B cell themes reflect B cell differentiation whereas two other themes – cell cycle and cell growth – reflect proliferative and metabolic states that are independent of the differentiation states. Surprisingly, 23% of DLBCL (24/103) harbored genetic subclones expressing B cell differentiation themes that distinguished them from other malignant cells in the same tumor. The GC B cell theme was associated with a favorable response to R-CHOP chemotherapy ($p < 0.02$), as expected, while the cell growth theme (but not the cell cycle theme) was associated with adverse survival ($p < 0.02$). **Conclusions:** Our study revealed that genetic subtypes have distinct gene expression signatures. We further demonstrated a role for tumor subclones in generating intra-tumoral biological diversity. We developed signatures of inter and intra-tumoral heterogeneity that are associated with overall survival. Research Sponsor: U.S. National Institutes of Health.

Differential clinical and economic signatures of CAR T-cell therapy in DLBCL across demographic and payer strata: A national analysis.

Karnav Modi, Himil Mahadevia, Yajur Arya, Arshi Syal, Aakriti Adhikari, Deepthi Vodnala, Taiyeb Khumri, Furha Cossor; University of Missouri Kansas City, Kansas City, MO; Mayo Clinic Florida, Jacksonville, FL; Saint Luke's Hospital of Kansas City, Kansas City, MO

Background: Chimeric antigen receptor (CAR) T cell therapy has revolutionized care for relapsed/refractory diffuse large B cell lymphoma (DLBCL), yet granular delineation of real-world immune effector toxicities, organ-specific sequelae and economic burden across demographic and socioeconomic strata requires further exploration. **Methods:** Using the National Inpatient Sample (2017–2022), we identified adult DLBCL hospitalizations receiving CAR T through ICD-10-PCS codes. Cytokine release syndrome (CRS) [all grades – 2021–2022], immune effector cell–associated neurotoxicity syndrome (ICANS) [all grades – 2022], infections, cardiac events and acute kidney injury (AKI) were identified through ICD-10 codes. Age was stratified into 21–40, 41–60, 61–80 and ≥81 years. Payer groups were Medicare, Medicaid, Private and Uninsured. Races were White, African American, Hispanic and others [Pacific Islanders, Native Indians, Asians]. Chi-square analysis was performed, and multivariate regression adjusted for demographics, comorbidities, and hospital characteristics. **Results:** Across >11,000 weighted hospitalizations, inpatient mortality, all-grade CRS and ICANS were comparable across age, race, and payer groups ($p>0.05$). Inpatient mortality was numerically higher in other minor races (6.6%) vs White (3.3%), African American (3.1%), and Hispanic (0.9%; $p=0.230$). Any grade CRS was numerically higher in other minor races (72.5%) than in White (62.3%) and African American (60.6%; $p=0.614$). Any grade ICANS dispersion included 29.5% (White), 39.1% (African American), 22.5% (Hispanic) and 11.1% (Other; $p=0.204$). A race-specific signal for ICANS grade 5 ($p=0.030$) was seen, but numbers were small. Among cardiac events, arrhythmias rose from 7.6% (age 21–40 years) to 57.1% (age ≥81 years) ($p<0.001$). By payer, arrhythmias were highest in Medicare (31.2%; $p<0.001$). Other cardiac events including myocardial infarction, stroke and cardiogenic shock were similar across groups. Pneumonia rates varied by payer, peaking in the Uninsured (23.8%; $p=0.010$). Sepsis and septic shock rates showed no differences. AKI ($p=0.007$) rates showed differences but attenuated after adjustment. Hispanic and other minor races had lower adjusted costs than White (Odds ratio [OR] 0.9, $p=0.046$; OR 0.8, $p=0.006$), while ages 61–80 had higher adjusted costs vs 21–40 (OR 1.2, $p=0.023$). **Conclusions:** In this national cohort, CRS, ICANS and mortality were similar across demographic and payer strata, indicating consistent immune effector safety. Cardiac arrhythmia rates were higher among the elderly and Medicare beneficiaries. There were lower expenditures among minor race groups and higher costs in elderly. These findings highlight discrete domains of variability and suggest intensified cardiac surveillance in elderly and equitable resource allocation to optimize outcomes with CAR-T. Research Sponsor: None.

Frontline intensified vs standard immunochemotherapy in high-risk diffuse large B-cell lymphoma: A systematic review and meta-analysis.

Lauren Scarpetti, Ricardo Sanchez-Mendez, Mohammad Alhomoud, Roni Shouval, Kai Rejeski, Cosmin Tegla, Michael L. Grossbard, Catherine S. Diefenbach, John Paul Leonard, Peter Martin, Samuel Yamshon; Department of Medicine, NYU Langone Health, New York, NY; NYU Grossman School of Medicine, New York, NY; Adult BMT Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; Perlmutter Cancer Center, NYU Langone Health, New York, NY

Background: While the phase III CALGB 50303 trial comparing frontline REPOCH vs standard RCHOP for diffuse large B-cell lymphoma (DLBCL) showed comparable outcomes overall, it suggested a potential benefit of intensified therapy in high-risk patients, including high-grade (HG) and double/triple-expressor (DE/TE) disease. Subsequent studies evaluating REPOCH in HG and DE/TE DLBCL have been small, retrospective and nonrandomized, with conflicting results. Despite limited evidence and greater toxicity, REPOCH is commonly used in these cohorts. We conducted a systematic review and meta-analysis to assess outcomes after front-line REPOCH vs RCHOP in HG and DE/TE DLBCL, comprising the largest high-risk cohort to date. **Methods:** Original research studies evaluating outcomes after frontline REPOCH or RCHOP in HG or DE/TE DLBCL from 2009 to 2025 were included. HG was defined by *MYC* translocation, including double/triple-hit (DH/TH; *MYC* and *BCL2* and/or *BCL6* translocation). DE/TE was defined by *MYC* and *BCL2* and/or *BCL6* by IHC. Studies were excluded if they had <10 subjects or used agents in addition to the RCHOP or REPOCH backbones. RCHOP-like regimens with comparative substitutions were included (e.g., RCOMP). We used random effects models to calculate pooled response rates and survival outcomes. **Results:** 69 studies were included with 3979 total patients (1818 HG; 2161 DE/TE). 2698 patients (68%) were treated with RCHOP, and 1281 (32%) with REPOCH. Limited reporting of patient characteristics in HG or DE/TE cohorts precluded multivariable analysis of prognostic factors. While overall response rate (ORR) did not differ between treatment groups (relative risk [RR] 1.04, CI 0.92–1.19), patients treated with REPOCH were more likely to achieve complete response (CRR; RR 1.12, CI 1.01–1.23). This difference was especially notable in the HG subgroup (RR 1.4, CI 1.21–1.61), but there was no difference in the DE/TE subgroup (RR 1.04, CI 0.93–1.17). Across all patients, REPOCH was associated with significantly improved progression-free survival (PFS; hazard ratio [HR] 0.5, CI 0.39–0.65) and overall survival (OS; HR 0.59, CI 0.43–0.82). Landmark 2-year PFS (65% vs 52%, $p = 0.013$) and OS (75% vs 50%, $p < 0.0001$) were significantly higher for REPOCH. Subgroup analysis showed significantly improved 2-year OS with REPOCH in both HG (72% vs 47%, $p < 0.0001$) and DE/TE (67% vs 51%, $p = 0.032$) disease. **Conclusions:** In this large cohort, REPOCH was associated with significantly improved CRR, PFS and OS relative to RCHOP in HG and DE/TE DLBCL. Reported patient characteristics were limited, and the REPOCH arm may have preferentially included younger patients with better performance status. Nevertheless, our analysis provides evidence in an area lacking randomized trial data. While not definitive, our findings support the common clinical practice of treating select high-risk patients with REPOCH. Research Sponsor: None.

Differences in outcomes for elderly patients with DLBCL treated at academic vs community programs: A 10-year survival analysis.

Carolina Velez-Mejia, Perla Colunga, Luis Villela, Qianqian Liu, Joel Michalek, Adolfo Enrique Diaz Duque; Virginia Commonwealth University - Mays Cancer Center, Richmond, VA; Universidad Autónoma de Nuevo León "Dr. José Eleuterio González" UANL, Monterrey, Mexico; Universidad Autónoma de Sinaloa, Facultad de Medicina, Hospital Fernando Ocaranza del ISSSTE & Centro Médico Dr. Ignacio Chavez ISSSTESON, Hermosillo, SO, Mexico; Mays Cancer Center, University of Texas Health Science Center at San Antonio, San Antonio, TX; Mays Cancer Center - University of Texas Health at San Antonio, San Antonio, TX

Background: Diffuse large B-cell lymphoma (DLBCL) is an aggressive B-cell malignancy that primarily affects older adults. Optimal treatment management in the geriatric population is challenging due to the high-risk disease biology and their age-specific vulnerabilities. Combination chemotherapy is effective, however, due to frailty often a dose-reduced regimen is administered. This large population real-world study compares demographic, clinical and survival characteristics of patients older than 75 years and compares Academic Cancer Programs (ACP) vs Community Cancer Programs (CCP). **Methods:** A retrospective analysis using the National Cancer Database was conducted on 103,671 patients (ACP: 51,848; CCP: 51,823) diagnosed with DLBCL between 2004 and 2022 was carried out. ACP included academic and National Cancer Institute-designated research centers; CCP included community, comprehensive community, and integrated network cancer programs. Kaplan-Meier and Cox regression models were used to compare overall survival (OS), adjusting for: age, race/ethnicity, insurance status, Charlson-Deyo comorbidity score, and distance from treating facility. **Results:** Patients in ACP and CCP were mostly females with a median age of 81 years. For both cohorts the majority were non-Hispanics and Whites; however, for ACP it was noted a higher rate of Hispanics (6% vs 5%) and Blacks (5% vs 3%) compared to CCP. Most of the patients in both groups were from the Metropolitan area, but the median distance in miles for ACP was 9.0 vs 7.4 in CCP. Treatment rates were higher for ACP vs community settings (63% vs 59%, $p < 0.001$), with more patients presenting at Stage IV (36% vs 33%, $p < 0.001$). Better OS was noted in elderly patients treated at ACP, $p < 0.001$. The median OS for ACP was of 1.79 years vs 1.50 years at CCP, which was consistent with a longer median follow up time of 17.7 months vs 14.1, $p < 0.001$. This survival advantage remained consistent throughout long-term observation, with 2-year OS rates of 49% at ACP [CI: 0.48,0.49] vs 46% at CCP [CI: 0.459,0.468], 5-year OS of 34% [CI: 0.336,0.346] vs 32% [CI: 0.317,0.327], and 10-year OS of 16% [CI: 0.154,0.164] vs 15% [CI: 0.142,0.151], respectively. **Conclusions:** Among patients aged ≥ 75 years with DLBCL, OS differed by treatment facility type, with a statistically significant but modest survival advantage observed among patients treated at ACP compared with CCP (log-rank $p < 0.001$). This difference occurred in the context of higher treatment rates and greater disease severity at presentation. Given the relatively small absolute survival differences, these findings suggest that care for older adults with DLBCL is largely standardized across practice settings; however, this highlights an opportunity to optimize treatment delivery and intensity, supportive care, and geriatric-focused management in both academic and community programs. Research Sponsor: None.

Efficacy and tolerability of duvelisib in relapsed/refractory peripheral T-cell lymphoma: A multicenter real-world analysis.

Priyanka Pullarkat, Kishan Kamlesh Patel, Alison J. Moskowitz, Omar Elghawy, Stefan K. Barta, Josie Ford, Salvia Jain, Lauren Shea, Shambhavi Singh, Jie Wang, Fatima Tuz Zahra, Yumeng Zhang, Neha Akkad, Swaminathan P. Iyer, Alexander Daniel Sanjurjo, Seda S. Tolu, Matthew Alexander Lunning, Bret Wankel, Conner Liddle, Neha Mehta-Shah; Washington University School of Medicine, St. Louis, MO; Memorial Sloan Kettering Cancer Center, New York, NY; Hospital of the University of Pennsylvania, Philadelphia, PA; University of Pennsylvania Health System, Philadelphia, PA; Massachusetts General Hospital, Boston, MA; University of Alabama at Birmingham, Birmingham, AL; Duke University Hospital, Durham, NC; Duke Cancer Institute, Durham, NC; University of South Florida/ H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; University of South Florida, Tampa, FL; The University of Texas MD Anderson Cancer Center Hematology/Oncology Fellowship, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Columbia University Medical Center, New York, NY; Columbia University, New York, NY; University of Nebraska Medical Center, Omaha, NE; University of Rochester, Rochester, NY; University of Utah Health Sciences Center, Salt Lake City, UT

Background: Relapsed/refractory (R/R) peripheral T-cell lymphomas (PTCL) are a rare group of non-Hodgkin lymphomas with median survival at relapse of 6-10 months and few treatment options. Duvelisib is a g/Δ phosphatidylinositol 3-kinase inhibitor approved in CLL and NCCN compendium listed in PTCL. In indolent lymphomas, concerns for cumulative duvelisib toxicity limit its use. In contrast, studies in R/R PTCL show duvelisib to be well-tolerated. Therefore, we sought to assess the efficacy and tolerability of duvelisib in a real world setting in R/R PTCL. **Methods:** We conducted a retrospective analysis of patients with R/R PTCL treated with duvelisib from 2012-2025 at 12 centers. **Results:** We identified 207 patients with PTCL: nodal PTCL with TFH phenotype (n=106, 51%), PTCL-NOS (n=78, 38%), ALCL (n=16, 8%), enteropathy associated T-cell lymphoma (n=4, 2%), NK/T-cell lymphoma (n=2, 1%), adult T-cell leukemia/lymphoma (n=1, 0.5%). 90 patients (43%) were female. Median age was 64; median International Prognostic Index score 3. Median prior lines of therapy was 2 (range 1-9). 26% received frontline transplant (23% auto, 3% allo). 118 patients received single agent duvelisib; 89 patients received duvelisib in combination with other agents (66 romidepsin, 12 bortezomib, 4 azacitadine, 3 ruxolitinib, 4 other). Of patients with response data, ORR was 51% (94/186; 31% CR, 17% PR) with median OS 12 months. ORR in patients with TFH-phenotype vs. non-TFH phenotype was 60% and 41% respectively. ORR in patients treated with single agent duvelisib and duvelisib combinations was 46% (46/99; 29% CR, 17% PR) and 55% (48/87; 39% CR, 16% PR), respectively with no difference in OS. Median duration of therapy was 84 days; the most common reason for discontinuation was progression (41%, 76/186). 13% (25/196) underwent allo-SCT after duvelisib therapy. Toxicity data is summarized in our table. In patients receiving single agent duvelisib therapy, rates of cytopenia were lower (7% vs. 34%, p<0.001) and rates of colitis were higher (17% vs. 7%, p= 0.03). **Conclusions:** In this real world, multicenter analysis of patients with R/R PTCL treated with duvelisib-based regimens, the ORR of 51% was consistent with published trials. Duvelisib therapy was well tolerated and a minority required hospitalization for toxicity. This suggests that duvelisib is safe in patients with R/R PTCL who have poor prognosis and limited treatment options. Research Sponsor: None.

Adverse Event	Full Cohort n (%) n=207	Single agent n (%) n=118	Combination therapy n (%) n=89	Single vs. Combination p value	Steroid Given n (% full cohort)	Hospitalization n (% full cohort)
Rash	41 (20%)	24 (20%)	17 (19%)	0.83	23 (11%)	6 (3%)
Colitis	26 (13%)	20 (17%)	6 (7%)	0.03	20 (10%)	16 (8%)
Pneumonitis	7 (3%)	4 (3%)	3 (3%)	0.99	5 (2%)	3 (1%)
Cytopenia	38(18%)	8 (7%)	30 (34%)	<0.001	*	*
Transaminitis	33 (16%)	21 (18%)	12 (13%)	0.40	*	*
Infection	66 (32%)	36 (31%)	30 (34%)	0.63	N/A	42 (20%)

*Not available.

Comparative safety and efficacy of obinutuzumab versus rituximab in combination with chemotherapy for follicular lymphoma: A systematic review and meta-analysis.

Abdul Rafae Faisal, Rana Uzair Ahmad, Muhammad Huzaifa Ahmed Khan, Syeda Emmama, Muhammad Asad, Muhammad Uzair, Rameesha Mehreen, Muhammad Atif, Mahnoor Jan, Nouman Aziz, Haseeb Tareen, Safi Ur Rehman Daim, Amro Al-Omari, Umer Javaid, Abat Khan; CMH Multan Institute of Medical Sciences, Multan, Pakistan; Trinity Health Livonia Hospital, Livonia, MI; Harlingen Medical Center, Harlingen, TX; Dow University Of Health Sciences, Karachi, Pakistan; Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan; Sheikh Zayed Medical College, Rahim Yar Khan, Pakistan; Tufts Medical Center, Boston, MA; University of Kansas Medical Center, Kansas City, KS; Shaikh Khalifa Bin Zayed Al-Nahyan Medical and Dental College, Lahore, Pakistan; Wyckoff Heights Medical Center, Brooklyn, NY; Henry Ford Jackson Hospital, Jackson, MI; Carle Foundation Hospital, Urbana, IL; Department of Medicine, Trinity Health Livonia, Livonia, MI; Memorial Cancer Institute, Pembroke Pines, FL

Background: Follicular lymphoma is one of the most common non-Hodgkin lymphoma subtypes, typically presenting with advanced-stage disease and a relapsing-remitting course. Over the past two decades, anti-CD20 monoclonal antibodies combined with chemotherapy have significantly improved outcomes. Rituximab, a first-generation anti-CD20 antibody, has been the standard of care since approval. Obinutuzumab, a type II glycoengineered anti-CD20 antibody with enhanced antibody-dependent cellular cytotoxicity and direct cell death mechanisms, is a newer option with potential efficacy advantages. While individual randomized trials have shown promising results with obinutuzumab, comparative data on safety and efficacy remain limited. **Methods:** A systematic search of PubMed, ClinicalTrials.gov, Scopus, Embase, and Cochrane CENTRAL identified relevant English-language randomized controlled trials and observational studies. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using fixed- or random-effects models based on heterogeneity. Statistical significance was set at $p < 0.05$, and heterogeneity was assessed using the I^2 statistic. Analyses were performed using Review Manager version 5.3, following PRISMA guidelines. **Results:** Three studies met inclusion criteria, including two retrospective observational studies (Claustre et al., 2023; Berger et al., 2023) and one randomized controlled trial (Marcus et al., 2017). The pooled sample included 1,482 patients, of whom 53% were female. Compared with rituximab, obinutuzumab was associated with higher partial response rates (OR=0.66; 95% CI: 0.50–0.89; $p=0.006$) and improved disease progression outcomes (OR=0.64; 95% CI: 0.49–0.86; $p=0.002$). No significant differences were observed in overall response rate (OR=1.18; 95% CI: 0.84–1.65; $p=0.34$) or complete response (OR=0.82; 95% CI: 0.63–1.06; $p=0.13$). Obinutuzumab was associated with a higher incidence of adverse events during induction (OR=1.56; 95% CI: 1.04–2.33; $p=0.03$) and maintenance (OR=1.48; 95% CI: 1.13–1.93; $p=0.004$). Treatment discontinuation, dose reduction, or interruption due to adverse events occurred more frequently with obinutuzumab (OR=1.65; 95% CI: 1.13–2.42; $p=0.01$), as did neutropenia (OR=1.38; 95% CI: 1.12–1.71; $p=0.002$). **Conclusions:** This meta-analysis demonstrates that obinutuzumab provides improved efficacy, including higher partial response rates and reduced disease progression, compared with rituximab in follicular lymphoma. However, this benefit is accompanied by increased toxicity. Treatment selection should balance efficacy gains against safety risks. Research Sponsor: None.

Survival and socioeconomic disparities in the elderly population with mycosis fungoides and Sézary syndrome: A comparative analysis of 2,690 patients by facility type.

Oscar Hinojosa, Juan Ospina, Joel Michalek, Qianqian Liu, Adolfo Enrique Diaz Duque, Adolfo Enrique Diaz Duque; Department of Hematology Oncology, The University of Texas Health Science Center, San Antonio, TX; Instituto Nacional de Cancerología, Bogota, Colombia; Mays Cancer Center, University of Texas Health Science Center at San Antonio, San Antonio, TX

Background: Mycosis fungoides (MF) and Sézary syndrome (SS) are rare T-cell malignancies (0.26 and 0.36/100,000 person-years, respectively), that predominantly affect elderly patients, a population frequently underrepresented in clinical trials and with limited access to specialized care. While population-level outcomes are known, the impact of facility type on management and survival remains poorly studied. We utilized the National Cancer Database (NCDB) to conduct the largest retrospective cohort analysis comparing patient demographics, treatment patterns, and survival (OS) between Academic Cancer Programs (ACPs) and Community Cancer Programs (CCPs). **Methods:** Patients ≥ 75 years old diagnosed with MF/SS in the US from 2000 to 2020 were identified. Facilities were categorized as ACPs (Academic/research programs) and CCPs (Comprehensive community/integrated network programs). Demographic and clinical variables were compared. Overall survival (OS) was estimated using Kaplan–Meier methods, with Cox proportional hazards models performed to assess associations between facility type and survival. **Results:** A total of 2690 patients were identified (ACPs: 2176;CCPs: 514). Both cohorts showed male predominance (ACPs: 58%;CCPs: 64%) and were primarily White (ACPs: 84%;CCPs: 92%). Socioeconomic analysis revealed that ACP patients were more likely to belong to the highest income quartiles compare to CCP patients across all periods (2000: 43% vs 32%; 2008–2012: 36% vs 26%; 2012–2016: 39% vs 29%; and 2016–2020: 40% vs 30%; all $p < 0.01$). Notably, ACP patients were more likely to receive systemic treatment (71% vs 65%; $p < 0.05$) and experienced shorter median times to treatment initiation (37 vs 48 days; $p < 0.05$). Conversely, radiotherapy was utilized more frequently at CCPs (29% vs 15.2%; $p < 0.01$). With a longer median follow-up at ACPs (37 vs 31 months; $p < 0.05$), a higher proportion of patients remained alive at the end of the study (42% vs 30%). OS was superior among patients treated at ACPs, with higher 2-, 5-, and 10-year survival rates and a longer median OS (4.9 vs 3.0 years; log-rank $p = 0.001$). **Conclusions:** In elderly patients with mycosis fungoides and Sézary syndrome, management at an Academic Cancer Program was associated with a statistically significant and clinically meaningful overall survival advantage compared with Community Cancer Programs. This survival difference occurred alongside more frequent use of systemic therapies, expedited treatment initiation, and distinct socioeconomic differences between care settings. These findings highlight important system-level disparities and underscore the critical need to strengthen referral pathways and academic–community partnerships to improve access to specialized care and optimize outcomes for this vulnerable population. Research Sponsor: None.

Exploring improved prognostication using PET/CT radiomics in relapsed/refractory, TP53-aberrant diffuse large B-cell lymphoma (DLBCL).

Vincenzo Pizzuti, Samvid Kotia, Muthiah Nachiappan, Manali Kirtikumar Kamdar; University of Colorado Department of Medicine, Aurora, CO; University of Colorado Department of Radiology, Aurora, CO; University of Colorado Cancer Center, Aurora, CO

Background: Patients (pts) with TP53-aberrant DLBCL have inferior progression-free survival (PFS) and overall survival (OS) compared to pts with wild type disease, and outcomes are worse for those with R/R disease. Improved prognostics are needed to identify those at risk for inferior outcomes to guide enhanced surveillance and early initiation of subsequent therapy. **Methods:** Retrospective data from pts with R/R, TP53-aberrant DLBCL treated at the University of Colorado system with 2 distinct PET/CT scans at time of R/R diagnosis and post-treatment between 2016 and 2025 were included in this analysis. PET/CT measurements were conducted by two nuclear medicine physicians blinded to outcomes and included SUVmax, total metabolic tumor volume (TMTV) by 41% SUVmax method, and total lesional glycolysis (TLG). Receiver operator curves (ROC) were constructed to determine the optimal cutoff points for PFS at 1 year using Youden's J statistic. Survival analysis was conducted using Kaplan-Meier and Cox analyses. **Results:** The 22 pts had a median age of 66.9 years (44-83), median follow-up of 18.7 months (mos.), and a median OS of 28.7 mos. (95% CI 19.0 – 53.8) from R/R diagnosis. 17/22 (77%) pts had primary refractory disease, 7/22 (32%) had bulky disease, 13/22 were GCB, and 8/22 (36%) had double-hit lymphoma. 17/22 pts received CAR-T therapy as next line of therapy, and OS was not associated with therapy type or line by Cox regression. ROC analysis for PET/CT interval changes from R/R diagnosis to post-treatment identified cutoffs of 86.7% for Δ SUVmax, 93.43% for Δ TMTV, and 97.98% for Δ TLG. The known prognostic Δ SUVmax >70% was associated with better OS with hazard ratio (HR) of 0.307 (p=0.025). Each radiomic metric was independently associated with superior PFS (Table 1). R-IPI >3 at progression was not associated with differences in PFS or OS (p=0.751 and p=0.655, respectively). Pts with 2 or more high-risk PET/CT radiomic features (any combination of 2+ makers less than the cutoffs) was associated with inferior PFS (Table 1), OS (HR=0.265, p=0.009), and had a median PFS of 3.5 months and OS of 19.0 months. **Conclusions:** PET/CT radiomic metrics were independently associated with PFS and OS in R/R, TP53-aberrant DLBCL pts. Pts with 2 or more high-risk PET/CT features were at high risk for progression and inferior OS compared to those with ≤ 1 , and this 2-component model significantly outperformed R-IPI for predicting PFS and OS in this exploratory analysis, which warrants validation in future study. Research Sponsor: None.

	Median PFS	Median OS	HR for PFS (95% CI, p-value)
Δ SUVmax $\geq$ 86.7%	NR	50.1 months	0.259 (0.078-0.861, p=0.0164)
Δ TMTV $\geq$ 93.43%	NR	46.3 months	0.294 (0.085-1.03, p=0.0223)
Δ TLG $\geq$ 97.98%	NR	46.4 months	0.223 (0.066-0.758, p=0.0071)
≥ 2 high-risk PET/CT features	3.5 months	19.0 months	0.181 (0.055-0.591, p=0.0012)
High-risk IPI (3 or higher)	36.7 months	28.6 months	1.207 (0.341-4.279, p=0.751)

Conditional survival by primary extranodal site in diffuse large B-cell lymphoma: A population-based landmark analysis.

Muhammad Dawood Amir Sheikh, Muhammad Areeb Ashfaq, Hussein Rizkar Akram Haidari, Daisy E. Escobar; University of South Alabama, Mobile, AL

Background: Diffuse large B-cell lymphoma (DLBCL) frequently presents with extranodal involvement. Prior population-based studies report site-specific survival differences from diagnosis, but these estimates are influenced by early mortality and may not reflect prognosis among longer-term survivors. We therefore evaluated conditional survival by primary site using landmark analyses. **Methods:** Adolescents and adults (≥ 15 years) with primary extranodal DLBCL diagnosed in the Surveillance, Epidemiology, and End Results (SEER) database (2002–2022) were identified. Overall survival was assessed using multivariable Cox models adjusted for age, sex, race/ethnicity, and era. Landmark Cox models at 12 and 24 months estimated survival among patients alive at each timepoint. Gastrointestinal (GI) tract served as the reference site. **Results:** Among 30,963 patients, survival differed significantly by primary site ($p < 0.001$). From diagnosis, CNS/brain involvement was associated with markedly worse survival compared with GI disease (HR 2.09, 95% CI 2.00–2.19), while several sites appeared favorable at diagnosis. Among 12-month survivors ($n=20,497$), excess risk for CNS persisted (HR 2.46). In contrast, early advantages for bone/bone marrow and head/neck diminished, and breast, skin/soft tissue, and testis were associated with higher subsequent hazards (HR ~1.2 each). At 24 months ($n=17,614$), increased risk remained for CNS (HR 2.47), lung/pleura (HR 1.41), breast (HR 1.35), skin/soft tissue (HR 1.23), and testis (HR 1.26), while most other differences were small or no longer significant. **Conclusions:** Prognostic differences by primary site change after conditioning on early survival. CNS involvement remains high risk, while several sites that appear favorable at diagnosis lose this advantage over time. Landmark analyses provide more meaningful risk estimates for survivors but cannot account for site-specific treatment differences in SEER. Research Sponsor: None.

Adjusted hazard ratios for overall survival by primary extranodal site among 12- and 24-month survivors.

Site (ref: GI)	12m HR (95% CI)	24m HR (95% CI)	Site (ref: GI)	12m HR (95% CI)	24m HR (95% CI)
Bone/Bone marrow	1.01 (0.93–1.11)	0.96 (0.87–1.07)	Breast	1.24 (1.09–1.42)	1.35 (1.17–1.55)
CNS/Brain	2.46 (2.29–2.65)	2.47 (2.27–2.68)	Head/Neck	1.03 (0.96–1.11)	1.08 (1.00–1.17)
Hepatobiliary/ Pancreas	1.18 (1.04–1.34)	1.12 (0.97–1.29)	Kidney/ Adrenal	1.26 (1.07–1.48)	1.07 (0.88–1.29)
Lung/Pleura	1.39 (1.26–1.54)	1.41 (1.26–1.58)	Skin/Soft tissue	1.23 (1.14–1.33)	1.23 (1.13–1.34)
Spleen	0.91 (0.80–1.04)	0.92 (0.80–1.06)	Testis	1.23 (1.11–1.37)	1.26 (1.12–1.41)

Adjusted for age, sex, race/ethnicity, and diagnosis era. Landmark Cox models among patients alive at 12 and 24 months.

Deep learning–based PET/CT radiomics-clinical model for prognostic stratification and immunotherapy exploration in natural killer/T-cell lymphoma.

Tongyu Lin, Zegeng Chen, Huangming Hong, Zi-Jian Lu, He Huang, Liqun Zou, Hongqiang Guo, Zhiming Li, Wei Fan; Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China; Sun Yat-sen University Cancer Center, Guangzhou, China; Sichuan Clinical Research Center For Cancer/Sichuan Cancer Hospital & Institute, Chengdu, Sichuan, China; Sun Yat-sen University Cancer Centre, State Key Laboratory of Oncology in South China, Collaborative Innovation Centre for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, China; Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; West China Hospital, Sichuan University, Chengdu, China; Medical Oncology, Henan Cancer Hospital, Zhengzhou, China; Department of Lymphoma Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Nuclear Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Natural killer/T-cell lymphoma (NKTCL) is a highly aggressive malignancy with substantial heterogeneity. The value of deep learning on PET/CT-based radiomics for risk stratification in NKTCL remains to be defined. **Methods:** In this retrospective multicenter study, 425 consecutive NKTCL patients from four hospitals were randomly assigned to training or validation cohorts. Radiomics features extracted from pretreatment PET/CT images were used to construct prognostic models with multiple deep learning algorithms. The best model was integrated with established clinical prognostic factors, and its performance in informing treatment decisions was tested in another independent immunochemotherapy cohort. **Results:** The XGBoost-based radiomics model achieved the highest prognostic accuracy for progression-free survival (PFS) and overall survival (OS) across cohorts. Integration with clinical factors yielded the Radiomic-Clinical Prognostic Model (RCPM), which further improved prediction (training cohort AUC: PFS 0.977, OS 0.946; validation cohort AUC: PFS 0.834, OS 0.814) and effectively stratified patients into high- and low-risk groups with distinct PFS and OS (all $P < 0.001$). In another exploratory treatment cohort, high-risk patients derived significant benefit from PD-1 inhibitor therapy (3-year PFS: 67.7% vs. 21.7%, 3-year OS: 81.7% vs. 39.6%; both $P < 0.001$), whereas low-risk patients did not. **Conclusions:** In conclusion, the RCPM demonstrated strong prognostic value and may help identify patients who could potentially benefit from immunotherapy in NKTCL. Research Sponsor: National Natural Science Foundation of China; U24A20679 and 82470237.

Efficacy and safety of mesutoclax (ICP-248) in combination with orelabrutinib in patients with B-cell malignancies: A pooled analysis.

Zhiming Li, Keshu Zhou, Fei Li, Hongmei Jing, Shuhua Yi, Wei Yang, Yanli Yang, Liqun Zou, Zunmin Zhu, Aijun Liao, Wenjuan Yu, Hongling Peng, Fang Zhou, Stephen Yang Liang, Xiaobing Huang, Xiaohan Li, Nuo Chen, Weige Wang, Renbin Zhao, Lugui Qiu; Sun Yat-sen University Cancer Center, Guangzhou, China; Henan Cancer Hospital, Zhengzhou, China; The First Affiliated Hospital of Nanchang University, Nanchang, China; Peking University Third Hospital, Beijing, China; Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences, Tianjin, China; Shengjing Hospital Affiliated to China Medical University, Shenyang, China; The First Affiliated Hospital of Bengbu Medical University, Bengbu, China; West China Hospital of Sichuan University, Chengdu, China; Henan Provincial People's Hospital, Zhengzhou, China; Department of Hematology, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China; Department of Hematology, First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; The Second Xiangya Hospital, Central South University, Changsha, China; Hunan Cancer Hospital, Changsha, China; Department of Hematologic Oncology, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, China; Sichuan Provincial People's Hospital, Sichuan, China; Beijing InnoCare Pharma Tech Co., Ltd., Beijing, China; Department of Lymphoma and Myeloma, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences, Tianjin, China

Background: Mesutoclax (ICP-248) is a next-generation BCL2 inhibitor, and orelabrutinib is a marketed BTK inhibitor for CLL/SLL, MCL, and MZL. However, the clinical activity of their combination in these malignancies remains undefined. This analysis evaluated the combination of mesutoclax and orelabrutinib across B-cell malignancies. **Methods:** Patients with relapsed and refractory (R/R) MCL, MZL were enrolled in a phase 1 study (NCT05728658), and treatment-naïve (TN) CLL/SLL were enrolled in a phase 2 study (NCT06378138). R/R MCL and MZL patients received continuous daily mesutoclax (125 mg) and orelabrutinib (150mg) from cycle 1 day 1 continuously until disease progression or unacceptable toxicity. For CLL/SLL patients, induction therapy with orelabrutinib (150 mg QD, Cycles 1-17) was administered first, followed by mesutoclax (100 mg or 125 mg QD, Cycles 3-14). The orelabrutinib treatment continued beyond cycle 17 if the uMRD ($\leq 10^{-4}$) was not achieved. Mesutoclax was implemented with a ramp-up schedule in all patients to mitigate the risk of TLS. **Results:** As of 05 Jan 2026, 60 patients were enrolled and treated in the studies: 8 R/R MCL, 10 R/R MZL, and 42 TN CLL/SLL (mesutoclax 100 mg, n=21; 125 mg, n=21). In R/R patients, the median number of prior lines of therapy was 1 (1-4). 6 (33.3%) were refractory to the last line of therapy. For TN CLL/SLL, 76.2% (32/42) of patients had moderate or high TLS risk, and 14.3% (6/42) had TP53 mutation or del (17p). Among 5 MCL and 8 MZL patients who had at least one disease evaluation, the overall response rate (ORR) was 100%, with CRR of 100% and 50%, respectively. Five patients (38.5%) achieved peripheral blood (PB) uMRD. In the 21 CLL/SLL patients receiving mesutoclax 125 mg, the ORR was 100% and the CRR was 38.1%, and the peripheral blood uMRD rate at 36-week was 65%. The median time to CR was 3.7 months in R/R group and 7.1 months in TN group. The 12-month PFS rate was 100% in CLL/SLL, while data for MCL and MZL are immature due to short follow-up. As the safety data cutoff (31 Dec 2025), the combination of mesutoclax and orelabrutinib was well tolerated with a favorable safety profile, and no new safety signals were identified compared to either agent as monotherapy. Most TEAEs were grade 1-2, with no TEAEs leading to drug discontinuation or death reported. The most common grade ≥ 3 TEAEs include neutrophil count decreased (35%), platelet count decreased (11.7%). Notably, no grade ≥ 3 anemia was reported. No clinical or laboratory TLS occurred. **Conclusions:** Mesutoclax in combination with orelabrutinib demonstrated a tolerable safety profile across B cell malignancy subtypes (MCL, MZL, CLL/SLL). Significant 100% ORR and deep response were observed in patients receiving mesutoclax 125mg combined with orelabrutinib. This all oral, chemo-free regimen has the potential to establish a novel therapeutic option for B-NHLs. Clinical trial information: NCT05728658. Research Sponsor: None.

Effect of FDG-PET-based bone marrow assessment on prognostic accuracy compared to conventional histologic evaluation in patients with follicular lymphoma: A subanalysis of the FIL FOLL12 trial.

Stefano Luminari, Giovanni Manfredi Assanto, Luca Guerra, Luigi Marcheselli, Elizabeth Katherine Anna Triumbari, Rexhep Durmo, Elisa Genuardi, Maria Elena Nizzoli, Carola Boccomini, Benedetta Puccini, Alessandro Pulsoni, Vincenzo Pavone, Annalisa Arcari, Annarita Conconi, Marco Ladetto, Sara Galimberti, Ilaria Del Giudice, Massimo Federico, Stephane Chauvie, Simone Ferrero, Fondazione Italiana Linfomi; Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy; Hematology, Department of Translational and Precision Medicine, 'Sapienza' University of Rome – AOU Policlinico Umberto I, Roma, Italy; Nuclear Medicine, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy; Uffici Studi Fondazione Italiana Linfomi, Modena, Italy; Medipass Ergéa Group, Unità di Medicina Nucleare Fondazione Campus Bio-Medico, Roma, Italy; Nuclear Medicine Unit, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy; Hematology, Department of Molecular Biotechnologies and Health Sciences, University of Torino, Turin, Italy; Hematology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy; Hematology Division, A.O.U. Città della Salute e della Scienza di Torino, Torino, Italy; Hematology Unit, Careggi University Hospital, Firenze, Italy; Department of Hematology, SM Goretti Hospital, Sapienza University Polo-Pontino, Latina (LT), Italy; Card. Panico Hospital, Tricase (LE), Italy; Hematology, Ospedale Guglielmo da Saliceto, Piacenza, Italy; Hematology Unit, Department of Internal Medicine, Ospedale degli Infermi, Ponderano (BI), Italy; Department of Translational Medicine, SCDU Ematologia AOU SS Antonio e Biagio E Cesare Arrigo, Università del Piemonte Orientale, Alessandria, Italy; Hematology Division, Pisa University Hospital, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; Chimomo Department, University of Modena and Reggio Emilia, Modena, Italy; Medical Physics Division, Santa Croce e Carle Hospital, Cuneo, Italy; Hematology, Department of Molecular Biotechnologies and Health Sciences, University of Torino, Torino, Italy

Background: Bone marrow biopsy (BMB) is an invasive staging procedure for follicular lymphoma (FL) and its results are needed to calculate FLIPI2 and PRIMA-PI scores. Beyond conventional biopsy bone marrow can also be assessed through FDG-PET bone staging (PETb). We report preliminary data on a comparison of BMB and PETb in assessing BM involvement among FL patients enrolled in the FIL-FOLL12 trial. **Methods:** Untreated stage II–IV FL patients requiring therapy were included. Patients were balanced according to treatment received and arm. BMBs were assessed by morphology and immunohistochemistry. PET/CT scans were reviewed by two expert nuclear medicine physicians. Pathological bone uptake (PETb+) was defined as mono- or multifocal, or diffuse FDG uptake in bone segments higher than liver activity (SUVmax). **Results:** This analysis included 179 patients; no significant differences in disease characteristics were observed between the revised cohort and the remaining patients enrolled in the FOLL12 trial. High-risk FLIPI2 was noted in 35.4%, and β 2-microglobulin was increased in 53% of patients. BMB involvement was present in 58.5% (median infiltration 30%, range 0.5–95%). PETb was positive in 38 cases (21%), including 14% with focal or multifocal involvement and 7% with diffuse increased uptake. Concordant results between BMB and PETb were observed in 53.6%: among 103 BMB+ patients, 30 were PETb+ (29%). PETb identified BM involvement in 8 cases missed by BMB. While BMB+ was not associated with a different risk of PFS compared to BMB-, we observed a significant impact of PETb+ on PFS: PETb+ had 41% 5-year PFS (CI 25–72, $p=0.003$), while BMB+/PETb- showed 74% (CI 62–83, $p=0.27$) and BMB-/PETb- 66% (CI 52–72, reference). We then calculated FLIPI2 and PRIMA-PI using either conventional BMB or PETb to define BM involvement. The agreement between BMB and PETb scores was 87% for FLIPI2 and 67% for PRIMA-PI and the main disagreement was due to reallocation to lower risk groups; FLIPI2 0–2 patients raised from 65% to 74.3% according to FLIPI2-PET. FLIPI2 was confirmed prognostic for PFS and its c-Harrel increased from 0.582 to 0.602 when BMB was substituted with PETb (Table 1), with a 52% (CI 39–64) 5-Year PFS for conventional high risk FLIPI2 shifting to 41% (CI 26–56) for high risk FLIPI2-PET. **Conclusions:** Although BMB detects marrow involvement in most patients, this does not uniformly translate into adverse prognosis. PETb, while less sensitive, identifies metabolically active and prognostically relevant bone disease. A FDG-PET-based assessment of bone involvement could refine risk stratification in FL and spare BMB in most patients. Research Sponsor: None.

Score	HR for High risk	CI	c-Harrell
FLIPI2	2.03	1.25-3.31	0.582
FLIPI2-PET	2.58	1.57-4.26	0.602
PRIMA-PI	1.23	0.67-2.23	0.537
PRIMA-PI-PET	1.47	0.85-2.54	0.550

Defining APOBEC-like signature in diffuse large B-cell lymphoma and demonstration of distinct transcriptomic profile.

Adam Albitar, Andrew Ip, Sally Agersborg, Ahmad Charifa, Tatyana A. Feldman, Andre Goy, Maher Albitar; Genomic Testing Cooperative LCA, Lake Forest, CA; John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; Genomic Testing Cooperative, Lake Forest, CA; John Theurer Cancer Center at Hackensack Meridian Health, Hackensack, NJ

Background: APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like) mutational signatures are uncommon in hematologic malignancies compared with solid tumors. This signature is characterized by C>T and C>G substitutions and clustered chromosomal abnormalities and is typically defined using whole-genome or whole-exome sequencing. Data on APOBEC signatures detected by targeted gene panels are limited. We interrogated a database of diffuse large B-cell lymphoma (DLBCL) cases sequenced between 2023 and 2025 using a targeted panel. Cases with >30 mutations were classified as “APOBEC-like,” and their molecular and expression features were analyzed. **Methods:** DNA and RNA were extracted from FFPE samples and sequenced by next-generation sequencing. DNA sequencing used a 302-gene panel and RNA sequencing a 1,600-gene panel. Hybrid-capture libraries were sequenced on an Illumina NovaSeq 6000. **Results:** Among 670 DLBCL cases, 39 (6%) demonstrated an APOBEC-like signature. A striking feature was the presence of multiple mutations within the same gene. One case harbored 20 distinct SOCS1 mutations, and 20 of 39 cases (51%) had at least one gene with ≥ 10 mutations. Cell of origin was germinal center B-cell in 21 cases (54%). All APOBEC-like cases showed numerous chromosomal abnormalities, most commonly 6q deletion/monosomy 6 (23 cases, 59%). Deletion of 17p was rare (2 cases). TP53 mutations were detected in 12 cases (31%), PIM1 in 23 (58%), and SOCS1 in 18 (46%). Gene expression profiling revealed significant differences between APOBEC-like and average DLBCL cases. TRAF3, TRAF5, and TRAF2 expression was significantly lower in APOBEC-like cases ($\log_{10}$ FDR < -12), while NAMPT, PRPF8, SF3A1, NFYC, LUC7L2-MCM3AP, and SMAD5 were significantly overexpressed ($\log_{10}$ FDR < -7). Despite the limited cohort size, random forest modeling demonstrated that expression profiling could distinguish APOBEC-like cases, with 20 genes achieving an AUC of 0.904 in a testing set. **Conclusions:** APOBEC-like mutational signatures can be identified in approximately 6% of DLBCL cases using targeted gene panels and are characterized by extreme intragenic hypermutation, recurrent chromosomal abnormalities, and a distinct expression profile that enables accurate classification by machine-learning approaches. Research Sponsor: None.

Aberrant somatic hypermutation in large B-cell lymphomas and its relationship to mutational signatures, including a novel haloalkane pattern.

Nicholas J. Dcunha, Menglei Zhu, Ahmet Dogan, Gilles A. Salles, Chad Vanderbilt, Maria E. Arcila; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Diffuse large B cell lymphoma (DLBCL) is a genetically complex disease, often characterized by the simultaneous occurrence of multiple mutations within single driver genes. Here, while activation-induced cytidine deaminase (AID)-driven aberrant somatic hypermutation (aSHM) is recognized as a major contributor to mutation, many genes could be heavily mutated due to other mechanisms. In this study, we evaluate clinical DLBCL samples identified as hypermutated, to assess the presence of AID driven mutation and the contribution of other defined mutational signatures which may contribute to clinicopathologic heterogeneity.

Methods: Clinical samples of DLBCL tested by a hybrid-capture next-generation sequencing (NGS) panel targeting up to 468 genes, were identified. Hypermutated cases were selected based on the qualifying criteria of having three or more co-occurring mutations in at least 1 gene. Based on the mutational position from transcriptional start site and inter-mutational distance, cases were initially classified as having aSHM or Kataegis. Mutational signature analysis was performed using all high-confidence somatic single-base substitutions (SBS) identified and interpreted according to COSMIC SBS signatures v3.5. A predominant signature was defined when >40% of the mutations were attributed to the signature. Wherever possible, correlation between the morphological type, molecular subtype, and mutational signatures was performed. **Results:** Out of the 216 samples identified as hypermutated, most (n=172, 79.6%) were classified as having aSHM, 9.3% (n=20) as Kataegis and 11.1% (n=24) were unclassifiable. The 3 most common genes targeted by aSHM were PIM1(n=66), SOCS1(n=55) and BCL2(n=35). By contrast, SGK1(n=16), MYC(n=12), GNA13(n=6) and ITPKB(n=6) were the common targets of Kataegis. The most frequent dominant molecular signatures included AID (n=82) and Clock-like aging(n=48), followed by Haloalkane (n=24), MMR deficiency (n=17) and the SBS39 (n=14) signature of unknown etiology. Based on morphology and immunophenotype, cases were primarily stratified as either Germinal Center B-cell like (GCB; n=86) or Non-GCB (n=87), with lower representation of Primary mediastinal B cell lymphomas (n=21), High grade B cell lymphomas with MYC and BCL2 translocations (n=18), and DLBCL special subtypes (n=4). The same top 3 molecular signatures were identified across all subtypes, except in GCB, where MMR deficiency constituted the 3rd most frequent signature. **Conclusions:** In DLBCL, mutational signatures are primarily driven by endogenous processes, namely AID and Aging. The identification of a haloalkane signature in a small proportion of cases is a novel finding, raising suspicion for the role of exogenous influences, either environmental or therapeutic in origin. Further studies are needed to better define this cohort. Research Sponsor: None.

An exploratory study to assess the safety, immunogenicity, and preliminary anti-tumor activity of the EBV mRNA vaccine (WGc-043 injection) combined with PD-1 antibody in patients with relapsed or refractory ENKTL.

Xingchen Peng, Ming Jiang, Chunli Yang, Huaju Yang, Xi He, Yuting Chen, Jun Liao, Hai Huang, Xue Li, Han Zheng, Xiangrong Song; Cancer Center and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China; WestGene Biopharma Co., Ltd., Chengdu, China; WestGene Biopharma Co., Ltd., Chengdu, Sichuan, China

Background: Extranodal NK/T cell lymphoma (ENKTL) is a rare and aggressive lymphoma associated with Epstein-Barr virus (EBV) infection and requires novel therapeutic strategies. WGc-043, a therapeutic mRNA vaccine, showed promise against ENKTL patients alone by targeting EBV-driven oncogenesis in our previous study. This study evaluates the safety, immunogenicity, and preliminary anti-tumor activity of WGc-043 combined with PD-1 antibody in patients with relapsed or refractory ENKTL (r/r ENKTL). **Methods:** This single-center, open-label, exploratory study enrolled 5 patients with EBER1/2 positive r/r ENKTL. The primary inclusion criteria were patients with an ECOG of 0-2 who have failed an asparaginase-based regimen. WGc-043 was administered intramuscularly, including 5 doses of base immunization followed by optional personalized treatment. The base immunization was given at week 1, 2, 3, 4 and 7. Tislelizumab (PD-1 antibody) was administered every three weeks until disease progression, for a maximum of two years. The primary endpoint is safety. Secondary endpoints include immunogenicity, ORR and DCR. The exploratory analysis focuses on immune biomarkers predictive of therapeutic response. **Results:** WGc-043 combined with PD-1 antibody (Tislelizumab) demonstrated a favorable safety and efficacy in patients with r/r ENKTL. It was well tolerated with only grade 1 adverse events. The most common adverse events were injection site reactions (100%, 4/4), hemoglobin decreased (50%, 2/4), TSH elevated (50%, 2/4), fever (25%, 1/4), weakness (25%, 1/4) and lymphopenia (25%, 1/4). Importantly, this combo showed good, durable responses, with 2 patients achieving CR in 4 evaluable patients, and both remained CR status on the Jan 11, 2026. This result indicates that the combination of WGc-043 and PD-1 antibody is promising as part of the therapeutic strategy for this challenging lymphoma. **Conclusions:** WGc-043 combined with PD-1 antibody is well tolerated with a safety profile and yields encouraging CR rate and durable responses. Further investigations are warranted to validate these findings and to explore the full potential of this regimen in larger studies. Clinical trial information: 2200065962. Research Sponsor: None.

Efficacy and safety.					
Response category	Number of subjects				
CR	2				
PR	0				
SD	0				
PD	2				
Total	4				
ORR	50%				
DCR	50%				
Adverse events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any adverse event	4/4 (100%)	0	0	0	0
Injection site reaction	4/4 (100%)	0	0	0	0
Hemoglobin decreased	2/4 (50%)	0	0	0	0
TSH elevated	2/4 (50%)	0	0	0	0
Fever	1/4 (25%)	0	0	0	0
Weakness	1/4 (25%)	0	0	0	0
Lymphopenia	1/4 (25%)	0	0	0	0

Safety and efficacy of GT719, an off-the-shelf CAR-NKT therapy, in adults with relapsed or refractory CD19-positive B-cell malignancies.

Yarong Liu, Jing Yu, Dehui Zou, Hongsheng Zhou, Liqing Ma, Bowen Li, Hang Chen, Derun Shen, Sisi Feng, Jingwei Sun, Pin Wang; Grit Biotechnology, Shanghai, China; Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences, Tianjin, China; Ganzhou City People's Hospital, Ganzhou, Jiangxi, China; Grit Biotechnology Ltd., Shanghai, China; University of Southern California, Los Angeles, CA

Background: GT719 is an off-the-shelf CAR-NKT therapy derived from umbilical cord blood hematopoietic stem cells and genetically engineered to co-express an anti-CD19 CAR, an invariant natural killer T (NKT)-specific TCR, and secreted interleukin-15 (IL-15). This design enables CD19-targeted tumor killing, avoids risk of graft-versus-host disease (GVHD), and enhanced cellular expansion, persistence, and immune function through IL-15 signaling. We report clinical data from 7 adults with relapsed or refractory (R/R) CD19-positive B-cell hematologic malignancies enrolled in two open-label, single-arm studies (NCT06948981, NCT07131254) evaluating the safety and preliminary efficacy. **Methods:** The primary endpoint was safety, including treatment-emergent adverse events (TEAEs), graded per CTCAE v5.0. Secondary endpoints included 3-month overall response rate (ORR), best overall response (BOR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Efficacy was assessed using Lugano 2014 criteria and the 2024 Chinese guidelines for adult acute lymphoblastic leukemia. **Results:** As of December 31, 2025, 7 patients were treated (median age 51 years; median two prior therapies), including 3 with B-ALL and 4 with B-NHL. Following FC lymphodepletion, all patients received a single GT719 infusion (5×10^7 to 1×10^9 viable cells). Most adverse events (AEs) were Grade 1-2. Grade ≥ 3 AEs were limited to lymphodepletion-related cytopenia and resolved or improved to Grade ≤ 2 within 14 days, excluding disease-related cytopenia. One patient experienced Grade 1 cytokine release syndrome that resolved within 1 day. No ICANS, neurotoxicity, or GVHD, severe infections, or serious TEAEs were observed. Efficacy was evaluable in all patients across B-ALL, follicular lymphoma (FL, grade 3a), and diffuse large B-cell lymphoma (DLBCL). The 3-month ORR was 50% (3/6), with all responders achieving CR; one patient was excluded due to insufficient follow-up. The disease control rate (DCR) was 71.4% (5/7). Two of 3 FL patients achieved CR, while one had a PR and remained under follow-up. One of three B-ALL patients achieved stringent complete remission, maintained through 24 weeks of relapse-free follow-up. CAR transgene analysis demonstrated robust in vivo expansion, with peak levels occurring between Days 7-10 in B-ALL and within two months in FL. GT719 persistence was observed for up to six months post-infusion. **Conclusions:** GT719 demonstrated a favorable safety profile and encouraging antitumor activity in adults with R/R CD19-positive B-cell malignancies. The absence of severe GT719-related toxicities and evidence of durable cellular persistence support further clinical investigation of this off-the-shelf CAR-NKT therapy. Clinical trial information: NCT06948981, NCT07131254. Research Sponsor: Grit Biotechnology. Research Sponsor: None.

First-in-human study of in vivo CAR-T therapy GT801 in adults with relapsed or refractory CD19-positive B-cell hematologic malignancies.

Yarong Liu, Li Wang, Xianchao Ding, Zhiyang Xu, Zhenzhen Wang, Lihua Yan, Wei Xu, Pin Wang, Jing Yu, Liqing Ma, Hang Chen, Derun Shen, Jingwei Sun; Vivacta Biotechnology, Shanghai, China; Yihe Hospital, Zhengzhou, Henan, China; University of Southern California, Los Angeles, CA; Grit Biotechnology, Shanghai, China; Grit Biotechnology Ltd., Shanghai, China

Background: Despite high initial cure rates, patients with B-cell hematologic malignancies, including B-ALL and B-NHL, experience substantial relapse, with markedly reduced disease-free and overall survival after second-line therapy. GT801 is a first-in-human, in vivo CAR-T therapy that uses antibody-displayed lipid nanoparticle (LNP) to deliver CD19 CAR mRNA directly to T cells, enabling in vivo reprogramming without ex vivo cell manufacturing or lymphodepletion. We report initial safety and efficacy data from an open-label, single-arm phase I study (NCT07205315). **Methods:** GT801 was evaluated using a modified 3+3 dose-escalation design across three dose levels (0.5, 1.5, and 3.0 mg). Patients received up to 4 treatment cycles, each consisting of a single intravenous administration of GT801 on Day 1 of a 7-day cycle. The primary endpoint was safety, including treatment-emergent adverse events (TEAEs), graded per CTCAE v5.0. Secondary endpoints included 3-month overall response rate (ORR), best overall response (BOR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS), assessed per Lugano 2014 criteria. **Results:** As of January 13, 2026, 3 patients were enrolled (median age 60 years; median three prior therapies). One patient received 3 doses at 0.5 mg, and two patients received 4 doses at 1.5 mg. All patients had B-NHL. Premedication included dexamethasone, NSAIDs, antihistamines. Most AEs were Grade 1-2. Common TEAEs included cytokine release syndrome (CRS), cytopenia, and transient liver enzyme elevations. Grade ≥ 3 events were hematologic toxicities and CRS. No neurotoxicity or organ failure was observed. At Week 4, all patients demonstrated a treatment response. Peripheral blood flow cytometry showed rapid CAR-T generation, with CD8⁺ CAR-T cells detectable within 4 hours post-infusion and peak levels on Day 1. Reprogramming efficiency reached up to 93% and was maintained with repeat dosing. Minimal off-target CAR expression was detected in monocytes. Complete peripheral B-cell depletion occurred within 4 hours after the first dose and was sustained for at least 7 days; after the third dose, B-cell depletion and CAR-T detection were observed in both peripheral blood and bone marrow. **Conclusions:** GT801 demonstrated a manageable safety profile and early signs of antitumor activity in heavily pretreated B-NHL patients. The ability to generate functional CAR-T cells in vivo without lymphodepletion supports further clinical evaluation of GT801 as a promising therapeutic approach. Clinical trial information: NCT07205315. Research sponsor: Vivacta Biotechnology (Shanghai) Co., Ltd. Research Sponsor: None.

Zanubrutinib plus rituximab as front-line treatment for mucosa-associated lymphoid tissue (MALT) lymphoma: A single-arm, phase II study (ZAMA).

Yi Xia, Qingqing Cai, Huiqiang Huang, Nan Chen, Junfeng Jiang, Zhitao Ying, Runhui Zheng, Jianbo Liu, Yirong Jiang, Liang Wang, Xiaojie Fang, Man Nie, Yan Gao, Xiaoxiao Wang, Yuchen Zhang, Jun Cai, Yi Cao; Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China; State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; Sun Yat-sen University Cancer Center, Guangdong, China; The Fifth Affiliated Hospital, Sun Yat-sen University, Zhuhai, China; Sun Yat-sen University Cancer Center Gansu Hospital, Lanzhou, China; Peking University Cancer Hospital & Institute, Beijing, China; The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China; The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; Affiliated Dongguan People's Hospital, Southern Medical University, Dongguan People's Hospital, Dongguan, China; Beijing TongRen Hospital, Capital Medical University, Beijing, China; Sun Yat-sen University Cancer Center, Guangzhou, China; State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University Cancer Center, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Mucosa-associated lymphoid tissue (MALT) lymphoma is the most common subtype of marginal zone lymphoma and follows an indolent clinical course. For patients with advanced-stage disease with an indication for treatment, rituximab-based immunochemotherapy is recommended as frontline therapy; however, toxicity and tolerability remain concerns. Zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor, has shown promising antitumor activity with a manageable safety profile in marginal zone lymphoma. This study aimed to evaluate zanubrutinib plus rituximab as frontline treatment for MALT lymphoma. **Methods:** The ZAMA study (NCT06647732), a multicenter, single-arm, phase II trial, enrolled patients aged ≥18 years with histologically confirmed CD20-positive MALT lymphoma. Eligible patients had newly diagnosed advanced-stage disease or relapsed disease after prior local therapy, had not received prior systemic treatment, and had at least one measurable lesion. Patients received rituximab (375 mg/m²) plus zanubrutinib (160 mg twice daily) in 28-day cycles. Treatment was administered for six cycles, after which patients achieving complete response (CR) entered observation, while those with partial response or stable disease received two additional cycles. The primary endpoint was the CR rate as best response. **Results:** From October 30, 2024 to December 12, 2025, 39 patients were enrolled. At the data cutoff of January 10, 2026, 23 patients had completed protocol-specified treatment, including 14 patients who received six cycles and 9 patients who received eight cycles. The median age was 58 years (range 24–75); 7 patients were males (30.4%). Most patients (n = 21, 91.3%) had an ECOG performance status of 0–1, and 21 patients (91.3%) had Ann Arbor stage III–IV disease; two patients had relapsed disease after prior local therapy. Eighteen patients (78.2%) achieved CR, and the remaining five patients achieved PR. Treatment-emergent adverse events (TEAEs) occurred in 20 patients (87.0%); hematologic toxicity were most common: neutropenia (n = 2, 8.7%), and thrombocytopenia (n = 2, 8.7%). Grade ≥ 3 TEAEs occurred in 4 patients (17.4%), most frequently neutropenia (n = 2, 8.7%), and thrombocytopenia (n = 2, 8.7%). **Conclusions:** Preliminary results from the ZAMA study show that frontline zanubrutinib plus rituximab provides encouraging efficacy with manageable safety in MALT lymphoma. The study is ongoing, and patient enrollment is continuing. Clinical trial information: NCT06647732. Research Sponsor: None.

Baseline characteristics.	
Characteristics	Patients (n=23)
Age, years (median [range])	58 (24-75)
Sex	
Male	7 (30.4%)
Female	16 (69.6%)
ECOG PS	
0-1	21 (91.3%)
2	2 (8.7%)
Ann Arbor stage	
III-IV	21 (91.3%)
Prior local therapy	2 (8.7%)
MALT-IPi score	
0	1 (4.3%)
1	21 (91.3%)
2	1 (4.3%)
Bone marrow involvement	4 (17.4%)

Brentuximab vedotin plus cyclophosphamide, doxorubicin, etoposide, and prednisone (CHEPA) in newly diagnosed CD30-positive peripheral T-cell lymphomas with integrated ctDNA analysis: Results of the phase 2 CHEPA trial.

Marek Trněný, Pavel Klener, Jozef Michalka, David Belada, Heidi Móciková, Aleš Obr, Katerina Steinerova, Juraj Duras, Katerina Benesova, Andrea Janikova, Diana Malarikova, Alice Sykrova, Vaclav Ptacnik, Jan Galko, Vit Campr, Takeshi Sugio, Jurik Mutter, Troy Noordenbos, Ash A. Alizadeh, Magdalena Klanova; Charles University, 1st Fac Medicine, General Hospital, Prague, Czech Republic; University Hospital Brno and Faculty of Medicine, Masaryk University Brno, Brno, Czech Republic; 4th Department of Internal Medicine - Haematology, Charles University, Hospital and Faculty of Medicine, Hradec Kralove, Czech Republic; Department of Hematology, University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic; Department of Hemato-Oncology, Palacký University and University Hospital, Olomouc, Czech Republic; University Hospital Pilsen, Pilsen, Czech Republic; University Hospital Ostrava, Ostrava, Czech Republic; 4th Department of Internal Medicine-Hematology, University Hospital and Faculty Medicine, Hradec Kralove, Czech Republic; Department of Pathology and Molecular Medicine, 2nd Faculty of Medicine, Charles University in Prague and Motol University Hospital, Prague, Czech Republic; Stanford Cancer Institute, Institute for Stem Cell Biology & Regenerative Medicine, Stanford, CA; Stanford Cancer Institute, Stanford University, Stanford, CA

Background: Peripheral T-cell lymphomas (PTCLs) are aggressive malignancies associated with poor outcomes. While adding brentuximab vedotin (BV) to CHP has improved results in CD30+ PTCL, relapses remain common. Given the suggested benefit of etoposide (CHOEP) in younger patients, the prospective multicenter single-arm Phase 2 CHEPA study (NCT05006664) was conducted to evaluate the efficacy and safety of CHEPA (BV-CHEP) induction combined with circulating tumor DNA (ctDNA) analysis. **Methods:** Patients with previously untreated CD30+ PTCL eligible for autologous stem cell transplantation (ASCT) were enrolled. Treatment consisted of 6 cycles of CHEPA (D1: BV 1.8 mg/kg, cyclophosphamide 750 mg/m², doxorubicin 50 mg/m²; D1–3: etoposide 100 mg/m²; D1–5: prednisone 100 mg/d) every 21 days. The primary endpoint was the complete metabolic response (CMR) rate at the end of treatment (EOT). Secondary endpoints included safety, PFS, OS, ORR, and exploratory ctDNA analysis. Plasma cfDNA was profiled using CAPP-Seq (259 genes) and clonotypic VDJ sequencing at all TCR loci via SABER. **Results:** Between 05/2022 and 09/2025, 40 patients were screened; 33 met eligibility criteria and initiated therapy. The cohort included 14 (42%) ALCL and 19 (58%) non-ALCL cases (median age 57 years, range 26–69). Baseline characteristics showed a predominance of males (67%), advanced-stage disease (79%), elevated LDH (58%), and bone marrow involvement (30%); all pts had an ECOG PS of 0–1. All 33 pts completed 6 cycles of CHEPA. At EOT, 25/33 (76%) achieved CMR, meeting the primary endpoint. The ORR was 91% for the entire cohort (CMR: 86% for ALCL, 68% for non-ALCL). ASCT was preplanned in 21/33 pts and has been performed to date in 14 pts. At a median follow-up of 19 months, the 18-month PFS and OS probabilities were 75% and 92%, resp. Specifically, PFS was 100% for ALCL vs. 59% for non-ALCL, while OS was 100% vs. 87%. Age and bone marrow involvement were the only baseline variables significantly associated with CMR. Baseline ctDNA burden was significantly correlated with total metabolic tumor volume ($r=0.68$, $p<0.001$), LDH level ($r=0.48$, $p=0.03$), and PIT ($p<0.05$). Grade 3–4 adverse events occurred in 82% of pts, primarily hematological: neutropenia (79%), thrombocytopenia (18%), febrile neutropenia (15%), and anemia (15%). No grade 3–4 peripheral neuropathy or grade 5 events were reported. **Conclusions:** The CHEPA study met its primary endpoint with a 76% CMR rate. Despite limited follow-up and high non-ALCL prevalence of our cohort, PFS and OS results are promising. Toxicity was manageable with no treatment-related deaths even though 33% of patients were >60 years old, supporting the safety of adding etoposide to the BV-CHP backbone. Further investigation of outcomes based on EOT MRD by ctDNA is ongoing. Clinical trial information: NCT05006664. Research Sponsor: AZV NW26-03-00462; Prchal Foundation; BBMRI_CZ LM2023033.

Chidamide in combination with CHOP in previously untreated peripheral T-cell lymphoma with T follicular helper phenotype: Results of the phase II SWIFT trial.

Qingqing Cai, Yi Xia, Huiqiang Huang, Rong Tao, Runhui Zheng, Jianbo Liu, Qike Zhang, Dongfeng Zeng, Xiaojun Xu, Qingsong Yin, Xiaoxiao Wang, Xiaojie Fang, Bing Bai, Man Nie, Yuchen Zhang, Shenrui Bai; Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; Fudan University Shanghai Cancer Center, Shanghai, China; The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China; The Fifth Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; Department of Hematology, Gansu Provincial Hospital, Gansu, China; Chinese People's Liberation Army, Army Medical Center, Chongqing, China; The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, China; Department of Hematology, The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China; State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; Sun Yat-sen University Cancer center, Guangzhou, China; State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Sun Yat-sen University Cancer Center, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China; State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Sun Yat-sen University, Guangzhou, China

Background: Peripheral T-Cell Lymphoma with T-follicular helper phenotype (PTCL-TFH), which mainly includes angioimmunoblastic T-cell lymphoma (AITL), is a biologically distinct subtype characterized by frequent epigenetic alterations. Chidamide is an oral, histone deacetylase (HDAC) inhibitor that targets HDAC subtypes 1, 2, 3, and 10, has shown encouraging activity in R/R PTCL-TFH. This study aimed to evaluate the efficacy and safety of chidamide in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in previously untreated PTCL-TFH patients. **Methods:** This is a multicenter, open-label, single-arm phase II study (NCT05572983). Patients with previously untreated PTCL-TFH were enrolled and received chidamide (20 mg, oral, biweekly) combined with CHOP regimen for up to six induction cycles. Patients achieving complete response (CR) after induction entered a maintenance phase with chidamide for up to two years. The primary endpoint was CR rate. Secondary endpoints included overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Between May 2023 and July 2025, a total of 47 patients were enrolled, and enrollment was completed. All patients had the AITL subtype. The median age was 62 years (IQR, 54–67), and 25.5% were female. Advanced-stage disease (stage III–IV) was present in 85.0% of patients, and 48.9% had extranodal involvement. The median number of induction cycles was 5 (range, 1–6), with 33 patients completing six cycles of induction therapy. Among 35 patients who underwent post-treatment PET/CT evaluation, the best CR rate during the induction phase was 85.2% (30/35), with an ORR of 100%. At the end of induction therapy, the CR rate was 87.9% (29/33), and the ORR remained 100%. As of October 2025, disease progression was observed in 10 patients. The most common grade 3–4 adverse events were neutropenia (42.6%), thrombocytopenia (19.1%), infections (17.0%), anemia (6.4%), and elevated transaminases (2.1%). **Conclusions:** Chidamide in combination with CHOP demonstrated promising efficacy with a manageable safety profile in previously untreated PTCL-TFH patients. A randomized controlled trial is currently ongoing to further validate these findings (NCT06947967). Clinical trial information: NCT05572983. Research Sponsor: None.

Baseline characteristics.	
Characteristics	Patients (n=47)
Age, years (median [IQR])	62 (54-67)
Sex	
Male	35 (74.4%)
Female	12 (25.5%)
IPI score	
0-2	25 (53.1%)
≥3	22 (46.9%)
Ann Arbor Stage	
I-II	7 (14.8%)
III-IV	40 (75.2%)
Extranodal involvement	
No	24 (51.1%)
Yes	23 (48.9%)

Data are shown as number (%).

Prognostic impact of comorbidity burden on overall survival in patients with Waldenström macroglobulinemia in the United States.

Gaëlle Haddad, Hong Liang, Chieh Lin Fu, Yehuda Galili, Chakra Pani Chaulagain; Cleveland Clinic, Weston, FL; Department of Clinical Research, Cleveland Clinic Florida, Weston, FL; Cleveland Clinic Florida, Weston, FL; Cleveland Clinic Weston, Weston, FL; Department of Hematology and Oncology, Myeloma and Amyloidosis Program, Cleveland Clinic Florida, Weston, FL

Background: Waldenström macroglobulinemia (WM), also known as lymphoplasmacytic lymphoma (LPL), is a rare indolent Non-Hodgkin B-cell lymphoma affecting approximately 1500 patients annually in the US. Existing prognostic models: IPSS-WM, revised IPSS-WM, and MSS-WM focus primarily on disease specific factors including age, albumin, hemoglobin, platelet count, β_2 -microglobulin, LDH, and monoclonal IgM at diagnosis, and were derived from small cohorts. However, comorbidity burden is not included in these models, despite data showing that mortality is frequently attributed to comorbidities unrelated to lymphoma. We conducted this analysis to identify prognostic factors with emphasis on the impact of comorbidity burden on overall survival in WM. **Methods:** In this IRB approved retrospective study, we analyzed 17130 patients with histologically confirmed WM (ICD-O-3 9761/3) from the NCDB (2004–2023). Univariable and multivariable Cox regression identified independent prognostic factors for overall survival. Age stratified sub-analysis assessed the prognostic impact of comorbidity within each age group. Analyses were performed using SAS 9.4. **Results:** On multivariable Cox regression with backward elimination, Charlson comorbidity score (CC) ≥ 1 emerged as a significant independent predictor of mortality (HR 1.7 95% CI 1.58–1.75 $p < 0.0001$). Age-stratified analysis confirmed CC ≥ 1 significance in all age groups (HR 1.52–2.07, $p < 0.0001$). Seven additional prognostic factors were identified: advanced age was associated with progressively worse survival ($55 \leq \text{age} < 65$: HR 1.7; $65 \leq \text{age} < 75$: HR 2.3; $\text{age} \geq 75$: HR 5.5; all $p < 0.0001$), while female sex was protective (HR 0.86; $p < 0.0001$). Lower median household income was associated with worse outcomes ($< \$40,227$: HR 1.38; $\$40,227 - \$50,353$: HR 1.26; $\$50,354 - \$63,332$: HR 1.1; all $p < 0.0001$). Private insurance was associated with better OS compared with uninsured (HR 1.7; $p < 0.0001$) and governmental insurance (HR 1.3; $p < 0.0001$). Treatment at non-academic facilities (HR 1.13; $p < 0.0001$) and multiple primary malignancies (HR 1.19; $p < 0.0001$) were associated with inferior survival. No difference was observed between multi- and single-agent chemotherapy (HR 1.0; $p = 0.96$), while patients not requiring chemotherapy had superior survival (HR 0.80; $p < 0.0001$). **Conclusions:** In the largest WM cohort to date, we identified several prognostic factors impacting survival WM patients in the US. Among these factors, CC ≥ 1 was a strong independent predictor of mortality. Given that half of deaths in WM patients are due to comorbidities, comorbidity assessment is essential for accurate prognostication and individualized treatment planning. Managing comorbidities may be as important as treating the disease itself. CC or equivalent should be integrated into future prognostic models to improve clinical decision-making in WM. Research Sponsor: None.

Age and HIV status as survival predictors in HHV8-positive diffuse large B-cell lymphoma: The largest population-based analysis to date.

Gaëlle Haddad, Claudia Villa-Celi, Hong Liang, Chieh Lin Fu, Yehuda Galili, Chakra Pani Chaulagain; Cleveland Clinic, Weston, FL; Cleveland Clinic Weston, Weston, FL; Department of Clinical Research, Cleveland Clinic Florida, Weston, FL; Cleveland Clinic Florida, Weston, FL; Department of Hematology and Oncology, Myeloma and Amyloidosis Program, Cleveland Clinic Florida, Weston, FL

Background: HHV8-positive Diffuse Large B Cell Lymphoma (HHV8+ DLBCL) is a rare and aggressive subtype of Non-Hodgkin Lymphoma that is frequently associated with HHV8-positive Multicentric Castleman Disease (MCD). Due to its rarity, population-based studies have been limited to small cohorts or have focused primarily on demographic features without survival analysis. This study explores demographic features, treatment pattern and prognostic factors affecting survival in patients diagnosed with (HHV8+ DLBCL) in the United States.

Methods: Following IRB approval, we analyzed the largest cohort of HHV8+ DLBCL to date (n=262) using the National Cancer Database (NCDB) (2010–2023). Patients with histologically confirmed HHV8+ DLBCL (ICD-O-3 9738/3) were included. Univariable Cox regression identified factors associated with survival; significant variables were included in multivariable cox regression with backward elimination ($p < 0.05$). Data was analyzed using SAS version 9.4.

Results: Among 262 patients with HHV8+ DLBCL, (mean age 52.6 years), 65.6% were <60 years, 76.7% were male, and 66.0% were white. Primary site was predominantly nodal (78.6%), with extranodal involvement in 21.4%. 19.2% were HIV-positive, and 63.3% had no comorbidities (Charlson-Deyo score 0). The majority received systemic therapy (84.6%). Among treated patients, 62.2% received chemotherapy and 43.1% received immunotherapy. Median overall survival was 133 months, with 1-, 3- and 5-year survival rates of 68.2%, 63.1%, and 59.9%, respectively. On multivariable Cox regression analysis, age ≥ 60 years (HR 2.20, $p = 0.0004$), higher Charlson-Deyo score (HR 1.67, $p = 0.0090$), HIV-positive status (HR 2.56, $p = 0.0026$), and absence of systemic treatment (HR 2.16, $p = 0.0016$) was independently associated with worse overall survival. **Conclusions:** In conclusion, HHV8+ DLBCL is a rare and aggressive lymphoma with poor long-term survival, frequently associated with multicentric Castleman disease, mainly affecting males with nodal involvement. Age ≥ 60 years, higher Charlson-Deyo score, HIV-positive status, and lack of systemic treatment independently predicted worse survival. Our study provides the largest cohort analysis of HHV8+ DLBCL to date. Nevertheless, further prospective studies with larger sample sizes are necessary to gain deeper insight into the pathogenesis and optimize treatment of this rare lymphoma. Research Sponsor: None.

Multivariable Cox regression for overall survival in patients with HHV8+ DLBCL.		
Factor	HR (95%CI)	p-value
Age		
Age <60 (ref)	1	
Age ≥ 60	2.20(1.42-3.40)	0.0004
Charlson Deyo Score		
No morbidities (ref)	1	
≥ 1 Morbidities	1.67(1.14-2.44)	0.0090
Systemic Treatment Status		
No Treatment	2.16(1.34-3.48)	0.0016
Receipt of Treatment (ref)	1	
HIV		
Negative (ref)	1	
Positive	2.56(1.39-4.71)	0.0026
Unknown	0.96(0.59-1.56)	0.8601

Genomic profiling of Burkitt lymphoma in adults: Novel molecular insights and implications for outcomes.

Manju Sengar, Epari Sridhar, Tanuja Shet, Hasmukh Jain, Alok Shetty, Lingaraj Nayak, Uma Sakhadeo, Prachi Bapat, Omshree Shetty, Girish B S, Meghana C S, Neha Sharma, Thomas Eipe, Anupa John, Bhausaheb Bagal; Tata Memorial Hospital, Mumbai, India; Tata Memorial Hospital and ACTREC, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India; Tata Memorial Hospital and Homi Bhabha National Institute, Mumbai, India; Tata Memorial Hospital, Parel, India; Tata Memorial Hospital, Mumbai, Maharashtra, India; Tata Memorial Centre, Mumbai, India; Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India; Believers Church Medical College Hospital, Thiruvalla, India

Background: The real-world treatment outcomes of Burkitt lymphoma (BL) from low-middle income countries appear to be inferior (<60%). Delays in diagnosis, treatment interruptions and toxicities are often attributed as the reasons for poor outcomes. However, biological differences could also explain the observed differences. However, there is limited information on the molecular profile of adult BL from developing countries. **Methods:** We evaluated a cohort of adult BL (histopathologically confirmed) who received treatment at our centre between 2012–2019. The data on demography, stage, HIV status, treatment type, response and survival was recorded. The formalin-fixed paraffin blocks were subjected to targeted next-generation sequencing using the hybrid capture based targeted panel – SOPHiA Lymphoma Solution which identifies single nucleotide variants (SNVs), indels from 73 genes and gene amplification events in 68 genes. **Results:** Among a total of 165 patients, the adequate quality DNA was extracted from 76 patients (83% males). Median age was 34 years; 67% patients had stage III/IV disease, 10% were HIV positive. Treatment regimen were high-dose methotrexate based – 74%, 24% – DA-EPOCH. Rituximab was given to 83% of patients. Complete response was seen in 69% of patients. 67 cases (88.2%) harboured at least one somatic variant, while no variants were detected in 9 cases (11.8%) within the genes covered by the targeted panel. A total of 712 somatic variants were identified across the cohort. Based on ACMG/AMP classification, 88 variants (12.4%) were categorized as oncogenic and 318 variants (44.7%) as likely oncogenic. This indicates a substantial mutational burden in Burkitt lymphoma, despite its classical characterization as a MYC-driven malignancy. Considering only oncogenic and likely oncogenic variants, the most recurrently mutated genes were *KMT2D*, *CREBBP*, *ARID1A*, *EP300* and *TP53*. *TP53* showed the highest number of confirmed oncogenic variants (22 variants) and also accounted for the largest number of missense mutations (16 out of 158 missense variants). Mutations in *PTPRD* and *ITPKB* were mutually exclusive ($p = 0.051$), as were mutations in *CCND3* and *KMT2D* ($p = 0.053$). These patterns suggest possible distinct molecular subsets of Burkitt lymphoma, potentially reflecting alternative oncogenic pathways driven either by aberrant cell cycle regulation (*CCND3*) or by epigenetic dysregulation (*KMT2D*). **Conclusions:** Our data suggests that histopathologically confirmed BL have complex mutational landscape characterized by frequent alterations in epigenetic regulators, tumour suppressor genes, and key signalling molecules which can lead to inferior outcomes. Research Sponsor: None.

iMARIX for primary and secondary central nervous system lymphomas.

Ekin Kırca, Selin Merih Uru, Uğur Şahin, İbrahim Tek, Güldane Cengiz Seval, Selami Kocak Toprak, Onder Arslan, Muhit Özcan; Mediana International Ankara, Ankara, Turkey; Mediana International Ankara Hospital, Hematology and Stem Cell Transplantation Unit, Ankara, Turkey; Ankara University Faculty of Medicine, Ankara, Turkey; Department of Hematology, Ankara University, Ankara, Turkey; Ankara University School of Medicine Department of Hematology, Ankara, Turkey; Department of Hematology, Faculty of Medicine, Ankara University, Ankara, Turkey

Background: The Bruton tyrosine kinase inhibitor (BTKi) ibrutinib is used in relapsed/resistant central nervous system (CNS) lymphoma because it can cross the blood-brain barrier and is effective as a single drug. Its efficacy has been demonstrated in combination with rituximab and high-dose methotrexate. CNS lymphomas are aggressive lymphomas, and responses to single-agent therapies are generally poor or insufficient. Also, even well-established agents used in lymphoma treatment may sometimes be unavailable worldwide, and drug restrictions may be experienced worldwide. Thiotepa is one of these agents. In this case series, we summarized the iMARIX treatment in which we used ibrutinib in combination with high-dose methotrexate, cytarabine and rituximab instead of thiotepa for the treatment of primary/secondary CNS lymphomas. **Methods:** The participants diagnosed with primary/secondary CNS lymphoma and treated between August 2022 and December 2025, received rituximab 375 mg/ m² (one day), 3.5 g/m² methotrexate (one day), 2x2 g/ m² cytarabine (two days), and ibrutinib 560 mg/day in each course. Ibrutinib was continued provided that platelet count is over 30.000/ mm³ and neutrophil count is over 500/ mm³. Patient data were collected retrospectively. **Results:** 17 patients were treated with iMARIX protocol during the study course. Male/ female ratio was 8 (47%)/ 9 (53%) and the median age was 53 (21- 71). 8 (47 %) of the participants had primary whereas 9 (53 %) had secondary CNS lymphoma. 4 (23.5%) participants died of either relapse or sepsis during the study period. The median overall survival was 16.3 months (4- 31.6). 13 (76,5 %) patients underwent consolidative autologous stem cell transplantation (ASCT). One patient experienced atrial fibrillation due to ibrutinib use. One patient experienced relapse after ASCT and was further treated with allogeneic stem cell transplantation. **Conclusions:** Although our patient series is small, the results suggest that the combination of ibrutinib with high-dose methotrexate, rituximab and cytarabine is a combination that may yield good clinical results with an acceptable tolerance and adverse effect profile. Research Sponsor: None.

Evaluating the incidence and predictors of chronic opioid use in early survivorship for patients with diffuse large B-cell lymphoma.

Mithunan Ravindran, Jessie Peng, Jonathan Zipursky, Jin Luo, Ning Liu, Kelvin K. Chan, Matthew C. Cheung, Lee Mozessohn; Department of Medicine, University of Toronto, Toronto, ON, Canada; Sunnybrook Health Sciences Centre, Toronto, ON, Canada; ICES, Toronto, ON, Canada; Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Background: Exposure to opioids during cancer treatment is common and may lead to new persistent opioid use (NPOU) in a subset of patients in survivorship. There are limited data on the incidence and predictors of NPOU in a diffuse large B-cell lymphoma (DLBCL) cohort. **Methods:** We conducted a population-based cohort study utilizing health administrative datasets from Ontario, Canada. We included patients ≥ 18 years old with DLBCL who received first-line rituximab-based chemoimmunotherapy from 2014 to 2021 and survived >365 days after treatment. We considered patients to be opioid exposed if they filled ≥ 1 opioid prescriptions from 90 days prior to and 180 days after first rituximab-based chemoimmunotherapy (the exposure window). The primary outcome was NPOU defined as filling ≥ 1 opioid prescriptions in each of the two half-years of follow up after the exposure window (i.e. within both 0–180 days and 181–365 days). We used a multivariable Poisson regression model with robust error variance to assess the relative risk (RR) of NPOU while controlling for covariates. **Results:** Our cohort consisted of 4,988 patients with DLBCL. The median age was 66 years and 32.3% had relapsed/refractory disease. Opioid exposure occurred in 55.0% of the entire cohort. Of the entire cohort, 6.7% fulfilled criteria for NPOU including 10.4% of exposed patients compared to 2.4% of unexposed patients. In the multivariable analysis, exposed patients were four times more likely to develop NPOU (RR 3.81, 95% CI 2.85–5.07). After adjustment, other statistically significant predictors of NPOU included palliative care use in follow-up (RR 2.77, 95% CI 2.21–3.47), relapsed/refractory disease (RR 1.63, 95% CI 1.33–1.99), comorbid disease burden (RR 1.50, 95% CI 1.01–2.23), and prior mental health diagnoses (RR 1.27, CI 1.01–1.58). **Conclusions:** Over 1 in 2 DLBCL patients were exposed to opioids during treatment and 1 in 10 exposed patients developed NPOU. Exposed patients were four times more likely to develop NPOU. Our study identified several clinically relevant predictors of NPOU in DLBCL, which may enable clinicians to identify high-risk patients who would benefit from early intervention. Research Sponsor: None.

Survival outcomes of plasmablastic lymphoma according to immune status.

Hien Lau, Shirley Ye, Zaw Win Myint; Department of Medicine, University of Southern California (USC), Los Angeles, CA; University of Southern California Keck School of Medicine, Los Angeles, CA; Division of Hematology, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA

Background: Plasmablastic lymphoma (PBL) is a rare, aggressive subtype of NHL associated with HIV, but also reported in other immunosuppressed states. Outcomes of PBL patients with non-HIV-related immunosuppression remain poorly defined. We compared clinicopathological features and survival outcomes among patients with HIV-associated immunosuppression (IS-HIV), and non-HIV-related immunosuppression (IS) and those without HIV or history of immunosuppression (IC). **Methods:** We retrospectively analyzed 35 patients with pathologically confirmed PBL, including 14 IC, 16 IS-HIV, and 5 IS patients. Associations between immune status and clinical characteristics were assessed using chi-square analysis. Progression-free survival (PFS) and overall survival (OS) were evaluated using Kaplan-Meier analysis with log-rank testing and multivariable Cox proportional hazards regression. **Results:** Median ages were 49, 45, and 56 years for IC, IS-HIV, and IS groups, with male predominance across all groups (71.4%, 93.8%, and 100%), respectively. Epstein-Barr virus positivity was significantly higher in IS-HIV (93.8%) and IS (40.0%) compared with IC patients (14.3%; $p < 0.01$). IS patients had lower rates of extranodal involvement than IC and IS-HIV patients (80.0% vs 100%; $p = 0.04$). Immune status was not associated with age, sex, ethnicity, ECOG performance status, stage, IPI score, radiation therapy, CNS prophylaxis, or autologous stem cell transplantation. Rates of primary refractory disease and relapse did not differ significantly among IC (14.3%, 21.4%), IS-HIV (31.3%, 12.5%), and IS (40.0%, 0%) groups ($p = .42$ and $p = .48$, respectively). Response rates following first-line therapy were numerically lower in IS patients but did not differ significantly ($p = 0.23$). Median follow-up was 30, 21, and 4 months for IC, IS-HIV, and IS groups, respectively. Median PFS was 60.5 months, not reached, and 4 months for IC, IS-HIV, and IS groups, respectively ($p = 0.03$). One- and two-year OS rates were 78.6% and 64.3% (IC), 74.0% and 65.8% (IS-HIV), and 0% and 0% (IS; $p = 0.02$). On multivariable analysis, IS status was associated with inferior PFS (HR 3.6, $p = 0.03$) and OS (HR 3.9, $p = 0.03$), whereas IS-HIV was not. **Conclusions:** PBL patients with non-HIV-related immunosuppression experienced significantly inferior PFS and OS compared with IC and IS-HIV patients. Although lower response rates and higher primary refractory disease were observed in IS patients, these differences did not reach statistical significance, likely due to small sample size. Consistent with prior reports, HIV-associated immunosuppression was not associated with worse survival. Larger studies are needed to better define disease biology and optimize therapeutic strategies for this high-risk population. Research Sponsor: None.

Survival of hematologic malignancy in patients with early-stage chronic kidney disease (SHIP-CKD).

Songphol Tungjitviboonkun, Kevin Shi, Brian Schult, Christopher Seaman; University of California, San Francisco, San Francisco, CA

Background: Chronic kidney disease (CKD) is a common comorbidity among cancer patients and may influence treatment options and outcomes. However, the independent effect of CKD in patients with hematologic malignancies remains unclear. **Methods:** We conducted a retrospective cohort study using electronic medical records, including 1,238 adult patients diagnosed with hematologic malignancies between 2015 and 2019. Patients with CKD stages 1–3A were compared to those without CKD. The primary outcome was 5-year all-cause mortality. We used stratified Cox proportional hazards models adjusted for age, sex, and comorbidities (HIV, diabetes, hypertension, and COPD) and performed 1:1 propensity score matching without replacement. Subgroup analyses by cancer subtypes were performed. **Results:** Among 1,238 patients, 529 (42.7%) had CKD. CKD patients were older (67 vs. 55 years), with higher rates of hypertension (66.0% vs. 48.0%). Five-year mortality was higher in the CKD group (24.4% vs. 17.8%, $p=0.006$). In adjusted Cox models, CKD was not significantly associated with mortality (HR 1.08; 95% CI: 0.82–1.43). Subgroups by stages showed no significant risk: stage 1 (HR 1.27; 95% CI: 0.76–2.13), stage 2 (HR 1.05; 95% CI: 0.77–1.43), stage 3A (HR 1.03; 95% CI: 0.60–1.78). In matched analysis ($n=758$), CKD remained non-significant (HR 1.04; 95% CI: 0.77–1.41). **Conclusions:** Early-stage CKD was common and linked to higher unadjusted mortality, but not with increased mortality after adjusting for covariates. These findings suggest that early-stage CKD may not independently impact survival among patients with hematologic malignancies. Research Sponsor: None.

Baseline characteristics by CKD status after propensity score matching.			
	No CKD	CKD	P-value
	N=379	N=379	
Age (years)	63.0 [57.0,68.0]	64.0 [56.0,69.0]	0.886
BMI (kg/m ²)	26.1 [23.5,29.9]	25.9 [23.3,29.8]	0.626
CKD			
No CKD	379 (100.0%)	0 (0.0%)	<0.00
G1	0 (0.0%)	58 (15.3%)	
G2	0 (0.0%)	267 (70.4%)	
G3a	0 (0.0%)	54 (14.2%)	
Sex			
Female	154 (40.6%)	165 (43.5%)	0.46
Male	225 (59.4%)	214 (56.5%)	
Race/Ethnicity			
White	207 (54.6%)	245 (64.6%)	
Latino	67 (17.7%)	39 (10.3%)	
Asian	52 (13.7%)	44 (11.6%)	
Black or African American	21 (5.5%)	24 (6.3%)	
Multi-Race/Ethnicity	11 (2.9%)	11 (2.9%)	
Native American or Alaska Native	0 (0.0%)	2 (0.5%)	
Native Hawaiian or Other Pacific Islander	2 (0.5%)	0 (0.0%)	
Southwest Asian and North African	3 (0.8%)	3 (0.8%)	
Other	11 (2.9%)	5 (1.3%)	
Unknown/Declined	5 (1.3%)	6 (1.6%)	
Disease			
Follicular lymphoma	3 (0.8%)	3 (0.8%)	1.00
Non-follicular lymphoma	67 (17.7%)	67 (17.7%)	
Myeloma	200 (52.8%)	200 (52.8%)	
Acute leukemia	56 (14.8%)	56 (14.8%)	
Chronic leukemia	53 (14.0%)	53 (14.0%)	
HIV status			
No HIV	372 (98.2%)	374 (98.7%)	0.77
HIV	7 (1.8%)	5 (1.3%)	
Diabetes status			
No DM	316 (83.4%)	318 (83.9%)	0.92
DM	63 (16.6%)	61 (16.1%)	
Hypertension status			
No HT	151 (39.8%)	154 (40.6%)	0.88
HT	228 (60.2%)	225 (59.4%)	
COPD status			
No COPD	369 (97.4%)	372 (98.2%)	0.63
COPD	10 (2.6%)	7 (1.8%)	

Comparative effectiveness of CAR-T and bispecific antibodies in relapsed/refractory large B-cell lymphoma: A network meta-analysis of phase III trials.

Aniqa Baloch, Sameer Bhimani, Taimoor Nasir, Ramsha Khan, Muhammad Umair Anjum, Mohamed Daoud, Waleed Iftikhar, Naman Modi, Douglas Klamp; The Wright Center for GME, Scranton, PA

Background: Second-line and later-line cellular therapies and bispecific antibodies have transformed the management of relapsed/refractory large B-cell lymphoma (LBCL), yet comparative efficacy across platforms remains uncertain due to the absence of head-to-head trials. We conducted a network meta-analysis (NMA) to compare disease control and overall survival (OS) across contemporary randomized phase III studies, representing the first synthesis of contemporary CAR-T and bispecific antibody phase III data. **Methods:** A frequentist graph-theoretical NMA was performed using trial-level hazard ratios (HRs) extracted from five randomized phase III trials (ZUMA-7, TRANSFORM, BELINDA, STARGLO, SUNMO). Treatments included axicabtagene ciloleucel, lisocabtagene maraleucel, tisagenlecleucel, glofitamab-GemOx, mosunetuzumab-polatuzumab, and chemoimmunotherapy as the reference. Outcomes were disease control (EFS/PFS) and OS. Random-effects models were applied, and P-scores were used to rank treatment hierarchy. **Results:** Five trials encompassing approximately 2,000 patients were included. For disease control, lisocabtagene maraleucel (HR 0.35, 95% CI 0.23–0.53), axicabtagene ciloleucel (HR 0.40, 95% CI 0.31–0.51), glofitamab-GemOx (HR 0.40, 95% CI 0.28–0.57), and mosunetuzumab-polatuzumab (HR 0.41, 95% CI 0.29–0.58) each significantly improved outcomes, whereas tisagenlecleucel did not (HR 1.07, 95% CI 0.82–1.40). Ranking favored lisocabtagene maraleucel (P-score 0.82), followed by axicabtagene ciloleucel (0.67), glofitamab-GemOx (0.67), and mosunetuzumab-polatuzumab (0.64). For OS, lisocabtagene maraleucel (HR 0.59, 95% CI 0.40–0.87), glofitamab-GemOx (HR 0.62, 95% CI 0.43–0.89), and axicabtagene ciloleucel (HR 0.73, 95% CI 0.55–0.97) significantly improved survival, while mosunetuzumab-polatuzumab showed a non-significant favorable trend (HR 0.80, 95% CI 0.52–1.24). Tisagenlecleucel did not improve OS (HR 1.24, 95% CI 0.83–1.85). OS rankings again favored lisocabtagene maraleucel (P-score 0.84), followed by glofitamab-GemOx (0.80) and axicabtagene ciloleucel (0.61). **Conclusions:** Across randomized phase III evidence, lisocabtagene maraleucel demonstrated the highest probability of being the most effective therapy for both disease control and overall survival in relapsed/refractory LBCL, followed closely by glofitamab-GemOx and axicabtagene ciloleucel, while tisagenlecleucel consistently ranked lowest. Although limited by cross-trial heterogeneity inherent to indirect comparisons, these findings highlight meaningful differences across platforms and may inform treatment sequencing while prospective head-to-head studies mature. Research Sponsor: None.

Utility of a modified geriatric assessment to identify impairments in adults of all ages with lymphoma: A prospective observational cohort study.

Christopher Edward Jensen, Hrishika Muthukrishnan, Kirsten A. Nyrop, Natalie Sophia Grover, Christopher Dittus, Deborah Marie Stephens, Devin McCarthy, Timothy Harper Wilkinson, Hyman Muss, Anne W. Beaven; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; School of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Performance status assessments may overlook important health vulnerabilities in adults with cancer. While geriatric assessment (GA) systematically evaluates multiple domains including physical function, cognition, psychological health, comorbidity, and nutrition, it has been predominantly studied in older adults. We evaluated the prevalence and patterns of GA-identified deficits among adults of all ages initiating systemic therapy for lymphoma. **Methods:** Adults with lymphoma enrolled in a prospective registry at an academic cancer center from 2018-2025 completed a modified Cancer and Aging Research Group (CARG) GA at treatment initiation. The assessment included validated measures across eight domains: mobility (Timed Up and Go), falls history, instrumental activities of daily living (IADLs), medication burden, comorbidities, weight loss, cognition (Blessed Orientation-Memory-Concentration test), and psychological health (Mental Health Index-13). Karnofsky Performance Status (KPS) was documented. Prevalence of deficits was compared between adults <65 and ≥65 years. **Results:** Among 97 participants (mean age 57 years, range 22-84; 39% ≥65 years), 94% had normal KPS (≥80). Despite preserved performance status, 56% had multiple (≥2) GA-identified deficits, and only 21% had zero deficits. The most common deficit was unintentional weight loss (43% overall). Among younger adults (<65 years), substantial proportions reported weight loss (34%), falls (27%), IADL impairment (27%), and anxiety or depression (45%). Most deficits did not differ significantly between age groups, though weight loss, multimorbidity (≥4 comorbidities), and severe polypharmacy (≥10 medications) were more prevalent in older adults. **Conclusions:** GA reveals high prevalence of health-related deficits across multiple domains in adults with lymphoma regardless of age, despite preserved performance status. These findings support a shift toward needs-based rather than age-based approaches to identify individuals who may benefit from supportive care interventions. Research Sponsor: None.

Functional measures among adults treated for lymphoma, stratified by age.				
Deficit Domain	Full Cohort % (95% CI)	Age < 65 % (95% CI)	Age ≥ 65 % (95% CI)	p**
Weight Loss	43 (33-53)	34 (23-47)	57 (41-71)	0.035
Mental Health	37 (28-46)	45 (33-58)	24 (13-39)	0.051
IADL Impairment	29.9 (21.7-39.6)	27.1 (17.4-39.6)	34.2 (21.2-50.1)	0.50
Falls (≥ 1 in past 6 months)	24 (16-33)	27 (17-40)	18 (9-33)	0.46
Polypharmacy (≥ 10 medications)	17 (11-25)	7 (3-16)	32 (20-49)	0.002
Cognitive Impairment (BOMC ≥ 5)	32 (23-43)	28 (18-42)	38 (24-54)	0.36
High Comorbidity (≥ 4 conditions)	10 (6-18)	5 (2-14)	18 (9-33)	0.047
TUG >14 seconds	5 (2-12)	4 (1-14)	6 (2-19)	1.0

*Reflects missing values (1 each for weight loss, MHI13, daily medications, and comorbid conditions, 10 for BOMC, and 16 for TUG).
**P-values from Fisher's exact test.

Temporal trends in ischemic heart disease mortality among lymphoma patients in the United States, 1999–2023: A 25-year nationwide analysis.

Prithvi Raghavan, Reshman Naga Kumar Jonnadula, Sai Lahari Sangaraju, Siri Sanmayi Medicherla, Sri Pranita Cherukuri, Gowrishankar Palaniswamy, Sravani Bhavanam; Sinai Hospital of Baltimore, Baltimore, MD; Mamata Medical College, Khammam, Telangana, India; Berkshire Medical Center, Inc., Pittsfield, MA; Osmania Medical College, Hyderabad, India; Columbia University, New York, NY; Medical University of South Carolina, Lancaster, SC; Brookdale University Hospital and Medical Center, New York, NY

Background: Enhanced lymphoma survival has transitioned clinical priorities toward non-malignant late effects, particularly cardiovascular morbidity. Although life-extending therapies like radiation and anthracyclines are effective, their cardiotoxic profiles significantly increase Ischemic Heart Disease (IHD) risk. Despite this, longitudinal trends and demographic disparities in lymphoma-IHD mortality remain under-investigated. This study analyzes 24 years of data to characterize mortality shifts and identify vulnerable populations, aiming to optimize integrated cardio-oncology management. **Methods:** We conducted a population-based retrospective analysis using the CDC WONDER Multiple Cause of Death database from 1999 to 2023. Deaths among individuals with lymphoma were identified using ICD-10 codes C81–C85, and IHD-related deaths were identified using ICD-10 codes I20–I25. Age-adjusted mortality rates (AAMRs) per 100,000 persons were calculated and stratified by sex, race/ethnicity, geographic region, urbanization status, and place of death. Temporal trends were analyzed using Joinpoint regression to estimate annual percent change (APC) and average annual percent change (AAPC). **Results:** Between 1999 and 2023, a total of 61,480 deaths were reported among individuals with both lymphoma and IHD in the United States. The overall AAMR declined from 0.93 in 1999 to 0.62 in 2023. Females had a lower overall AAMR compared with males (0.43 vs 1.13). By race/ethnicity, Non-Hispanic individuals had a higher AAMR than Hispanic individuals (0.74 vs 0.46). Regionally, the Midwest had the highest overall AAMR (0.84), while the South had the lowest (0.64). A higher AAMR was observed in non-metropolitan compared with metropolitan areas (0.84 vs 0.69). Most deaths occurred in inpatient medical facilities (22,633 deaths; 36.8%), followed by deaths at home (18,922 deaths; 30.8%). **Conclusions:** While mortality has declined overall, continued excess risk among males, rural residents, and Midwestern populations highlights inequities in care delivery. Expanding integrated cardio-oncology programs in non-metropolitan areas may further reduce national mortality. Research Sponsor: None.

Comparative analysis of age-adjusted mortality rates (AAMR) for comorbid lymphoma and ischemic heart disease by demographic and geographic subgroups (1999–2023).

Category	Group with Highest AAMR	Group with Lowest AAMR
Sex	Males (1.13)	Females (0.43)
Ethnicity	Non-Hispanic (0.74)	Hispanic (0.46)
Region	Midwest (0.84)	South (0.64)
Urbanicity	Non-metropolitan (0.84)	Metropolitan (0.69)

Multivariable analyses (MVAs) of overall survival (OS) in the phase 3 SUNMO, STARGLO, and POLARGO trials in relapsed/refractory large B-cell lymphoma (LBCL).

Matthew Matasar, Jason Westin, Jeremy S. Abramson, Adam J. Olszewski, Song Pham, Jue Wang, Steven P. Barrett, Iris To, Shen Yin, Connie Batlevi, Lisa Musick, Linda Lundberg, Michael C. Wei, L. Elizabeth Budde; Rutgers Cancer Institute, New Brunswick, NJ; The University of Texas MD Anderson Cancer Center, Houston, TX; Massachusetts General Hospital Cancer Center, Boston, MA; Brown University, Providence, RI; Hoffmann-La Roche Ltd, Mississauga, ON, Canada; Genentech, Inc., South San Francisco, CA; F. Hoffmann-La Roche Ltd, Basel, Switzerland; City of Hope National Medical Center, Duarte, CA

Background: Phase 3 trials, notably SUNMO (NCT05171647), STARGLO (NCT04408638) and POLARGO (NCT04182204), have shown superior efficacy of combination treatments over rituximab (R) + gemcitabine and oxaliplatin (GemOx) in second line or later LBCL. However, baseline imbalances may impact the robustness of efficacy results, even with stratified randomization. We conducted MVAs of SUNMO, STARGLO and POLARGO to assess OS. As the target number of OS events was not reached at the SUNMO interim OS analysis, to increase the sample size we also conducted a pooled analysis of mosunetuzumab (Mosun) + polatuzumab vedotin (Pola; data from SUNMO and GO40516 [Phase 2; NCT03671018]) vs R-GemOx (comparators from SUNMO, STARGLO and POLARGO). **Methods:** A multivariable Cox regression model was used to estimate treatment effect while adjusting for potential confounding factors selected by a systematic process involving: 1) univariable analysis of prespecified baseline factors; 2) multicollinearity assessment of pairwise correlation among selected factors; 3) MVA of the experimental arm (SUNMO: Mosun-Pola; STARGLO: glofitamab [Glofit]-GemOx; POLARGO: Pola-R-GemOx) vs the control arm (R-GemOx) and selected non-collinear prognostic baseline factors from steps 1 and 2. **Results:** In SUNMO, patients treated with Mosun-Pola had more high-risk features, such as a higher ECOG performance status and greater bulky disease, vs those treated with R-GemOx. The MVA-adjusted hazard ratio (HR, 0.65 [95% confidence interval [CI]: 0.41–1.02]) was more favorable than the unadjusted interim OS HR (0.80 [95% CI: 0.54–1.20]) for Mosun-Pola vs R-GemOx. The MVA-adjusted HR for POLARGO was also more favorable than the unadjusted HR; the HR for STARGLO remained largely unchanged (Table). A pooled MVA was used to increase the sample size, noting baseline differences between trials (e.g. ≥ 2 prior lines of therapy: SUNMO, 56%; STARGLO, 37%; POLARGO, 35%). In this pooled analysis, OS HRs favored Mosun-Pola vs R-GemOx in the unadjusted (HR, 0.62 [95% CI: 0.48–0.81]) and MVA-adjusted (HR, 0.59 [95% CI: 0.44–0.81]) models, with lower HRs and narrower 95% CIs vs the MVA of SUNMO alone. **Conclusions:** The MVAs support favorable OS benefits in SUNMO, STARGLO and POLARGO, all with an MVA-adjusted OS HR ≤ 0.65 vs R-GemOx. The pooled MVA further supports the OS benefit of Mosun-Pola vs R-GemOx. Overall, the MVAs show that baseline imbalances can influence OS estimates, thus multivariable adjustment is important when interpreting pooled or cross-trial comparisons. Clinical trial information: NCT05171647, NCT04408638, NCT04182204, NCT03671018. Research Sponsor: F. Hoffmann-La Roche Ltd.

	SUNMO n=208	STARGLO n=274	POLARGO n=255	Pooled Mosun-Pola vs R-GemOx n=465
Median follow-up, months (range)	23.2 (0–32)	20.7 (0–36)	24.6 (0–34)	–
MVA-adjusted OS HR (95% CI)	0.65 (0.41–1.02)	0.63 (0.44–0.90)	0.52 (0.36–0.74)	0.59 (0.44–0.81)
Unadjusted OS HR (95% CI)	0.80 (0.54–1.20)	0.62 (0.43–0.88)	0.60 (0.43–0.83)	0.62 (0.48–0.81)

Iopofosine I-131 after BTK inhibitors in Waldenström macroglobulinemia: CLOVER-WaM subgroup efficacy and safety.

Jarrold Longcor, Sikander Ailawadhi, Maria Gavriatopoulou, Jennifer Peterson, Ioannis Ntanas-Stathopoulos, Ghassan El-Haddad, Levy Moshe, Judith Trotman, Jorge Julio Castillo, Francisco J. Hernandez-Ilizaliturri, Ajay K. Nooka, Shirley D'Sa, Clark Cutrer, Sheeba K. Thomas, Katherine Oliver, Larry D. Anderson; Cellectar Biosciences, Inc, Florham Park, NJ; Division of Hematology/Oncology, Department of Medicine, Mayo Clinic Florida, Jacksonville, FL; Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece; Department of Radiation Oncology, Mayo Clinic Florida, Jacksonville, FL; Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Texas Oncology – Sammons Cancer Center, Dallas, TX; Concord Repatriation General Hospital, University of Sydney, Sydney, NSW, Australia; Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Roswell Park Comprehensive Cancer Center, Buffalo, NY; Winship Cancer Institute of Emory University, Atlanta, GA; Centre for Waldenström's Macroglobulinemia and Associated Disorders, University College London Hospital Foundation Trust, London, United Kingdom; University of Tennessee Medical Center, Knoxville, TN; The University of Texas MD Anderson Cancer Center, Houston, TX; Cellectar Biosciences, Florham Park, NJ; Myeloma, Waldenström's and Amyloidosis Program, Section of Hematologic Malignancies and Cellular Therapy, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX

Background: Waldenström Macroglobulinemia (WM) remains incurable with current available therapeutic options. Treatment options for relapsed/refractory pts are limited and often continuous, underscoring the need for new agents with novel mechanisms of action and pt-centered, fixed duration therapy. Iopofosine I 131 is a novel radiopharmaceutical compound composed of a lipid raft-targeting phospholipid ether covalently bound to ^{131}I , a beta emitting radioisotope. Here, we report preliminary sub-group results of the CLOVER-WaM study [NCT02952508] in WM pts treated with a Bruton's Tyrosine Kinase inhibitor (BTKi) immediately prior to iopofosine. **Methods:** Eligible WM pts had received >2 prior therapies and had symptomatic disease requiring therapy according to consensus recommendations for WM. Treatment consisted of 2 cycles of iopofosine I 131 administered at 15 mCi/m² on days 1 and 15 of each 57-day cycle. The primary efficacy endpoint was major response rate (MRR; partial response or better, as determined by the modified IWWM-VI). Secondary and exploratory endpoints included overall response rate (ORR), treatment-free survival (TFS), progression free survival (PFS), duration of response (DOR), and clinical benefit rate (CBR; stable disease or better). Herein, efficacy endpoints were assessed in the modified intent-to-treat (mITT) population (all pts who received ≥ 60 mCi total administered dose of iopofosine I 131), and whose treatment regimen prior to iopofosine included a BTKi. Safety was evaluated using CTCAE v4.03 in pts who received ≥ 1 dose of iopofosine. Data cut off for this analysis was Jan. 16, 2026. **Results:** As previously reported, 65 pts were dosed and 55 are included in the mITT population. Of those, 22 (40%) had received a BTKi containing regimen immediately prior to iopofosine; and 11 who previously received at least 2 regimens utilizing BTKis and 12 who were refractory to rituximab. In this subgroup, median age was 70.5 (range 55–88), 17 (77%) were male, and 5 (23%) were female. The median number of prior therapies was 3 (range 2–7), 15/22 (68%) were MYD88 mutated and 18/22 (82%) were TP53 wildtype. The MRR was 15/22 (68.2%), ORR was 19/22 (86.4%) and CBR was 100%, median PFS was 12 months (range 1.6 to 28.0) and median TFS was 19.1 months (range 2.5–34.4). Grade ≥ 3 , related treatment emergent adverse events (TEAE) occurring in > 10% of pts included anemia (41%), leukopenia (41%), neutropenia (58%), and thrombocytopenia (86%). **Conclusions:** Iopofosine I 131 demonstrated significant efficacy; 100% CBR, 86.4% ORR and 68.2% MRR with a median PFS of 12 months (range: 1.6 – 28.0 months) in a pt population with no current standard of care therapy. The treatment was well-tolerated with a manageable toxicity profile with cytopenias as the only Grade 3 or greater TEAE. Based on the results of this pivotal trial, iopofosine I 131 could be a promising novel treatment for WM pts after BTKi therapy. Clinical trial information: NCT02952508. Research Sponsor: None.

Analysis of sex-based differences in tumor microenvironments within hematopoietic and reticuloendothelial system malignancies.

Vera Vaz, Neil Arya Babu, Thomas Noonan, Karen Dong-Tran, Katharine Thomas; Renown Health/University of Nevada Reno School of Medicine, Reno, NV; UNR School of Medicine, Reno, NV; Renown Regional Medical Center, Reno, NV

Background: While sex-specific disease incidence, genomic profiles, and survival outcomes are widely recognized in hematologic malignancies, the biological mechanisms and tumor micro-environment (TME) factors driving these sex-based disparities remain largely undefined, particularly at the level of the TME, which plays a key role in immune surveillance, therapeutic response, and disease progression. This meta-analysis investigates whether significant differences exist in the abundance of various cell types between males and females within lymphoid and myeloid leukemias, plasma cell tumors, mature B-cell lymphomas, and acute lymphoblastic leukemia. Characterizing these variations is essential for developing tailored therapeutic strategies that optimize clinical outcomes for both sexes. **Methods:** Computational meta-analysis was performed on the TCGA National Database, using xCell enrichment scores across transcriptomic samples from hematopoietic and reticuloendothelial system tumors, comparing males (n= 3,829) and females (n= 2,995). Mann-Whitney U testing with Bonferroni correction identified cell populations with differential enrichment ($\text{padj} < 0.05$). Cohorts were balanced for age, race, and tumor type (primary, recurrence, metastatic) (all $p > 0.05$). **Results:** Of the 64 cell types screened, 12 exhibited a significant difference in abundance between males and females. Nine of these were female-enriched populations ($\text{padj} < 0.01$). These included erythrocytes (Mean Difference [Male-Female]: -0.5192), neutrophils (-0.4343), eosinophils (-0.4147), GMP (-0.1345), platelets (-0.1097), common myeloid progenitors (CMP) (-0.0917), mast cells (-0.0640), MPP (-0.0556), and megakaryocytes (-0.0131) indicating higher relative enrichment in females. Conversely, the male-enriched populations ($\text{padj} < 0.02$) consisted of DC (0.2210), Th2 cells (0.0761), and Th1 cells (0.0634). **Conclusions:** This study demonstrates sex-based differences in TME cellular abundance in hematopoietic and reticuloendothelial tumors. Females exhibited a higher presence of early-stage progenitor populations, such as MPP and CMP, and innate immune cells, including neutrophils and eosinophils, potentially due to hormonal influences, differences in myelopoiesis, or sex-linked immune polarization. In contrast, males had a higher presence of DC and Th cells. Among all cell types analyzed, erythrocytes exhibited the greatest magnitude of difference in abundance between sexes, showing potential distinctions in metabolic and oxygenation profiles. These findings highlight biologically meaningful sex specific variations in the TME, underscoring the need for further mechanistic studies linking sex-specific TME compositions to therapeutic responses and incorporating biological sex as a critical variable in immunotherapy trial design. Research Sponsor: None.

Real-world outcomes of mogamulizumab retreatment in cutaneous T-cell lymphoma: A single-center retrospective study.

Shahzeem Bhayani, Amy Liao, Marcus Paul Watkins, Amy Musiek, Neha Mehta-Shah; Washington University in St. Louis, St. Louis, MO; Washington University School of Medicine in St. Louis, St. Louis, MO; Washington University School of Medicine, St. Louis, MO

Background: Mogamulizumab, monoclonal antibody against CCR4, is approved for relapsed/refractory cutaneous T cell lymphoma (CTCL), with an overall response rate of 28% in CTCL. The most common toxicity is mogamulizumab-associated rash (MAR), occurring in ~24% of patients and reported in up to 88% of responders, frequently leading to treatment discontinuation. Given the limited therapeutic options in CTCL, retreatment with mogamulizumab is clinically appealing but not well described. We report a single center experience with mogamulizumab retreatment in patients with CTCL. **Methods:** We conducted a single-center retrospective study of all adult patients with CTCL treated with mogamulizumab from 2013 to 2025. Retreatment was defined as reinitiation after a >90-day treatment-free interval. Disease status, patient characteristics, response and toxicity to therapy was collected. **Results:** Among 54 CTCL patients treated with mogamulizumab, 13 (24%) (MF=7, SS=6) underwent retreatment. Median age at diagnosis was 67 years (range, 44 - 84) and mostly male (69%). Patients had a median of 5 prior systemic therapy lines (range, 3-9). The median interval from initial mogamulizumab discontinuation to retreatment was 11.4 months (range 3.1- 40.2). During initial mogamulizumab exposure, ORR 92.3% (12/13, 8 CR, 4 PR). 11 discontinued mogamulizumab due to rash, 1 due to clinical response and 1 with PD. Retreatment dosing schedules included weekly administration in 2 patients (15%), every-2-week dosing in 8 (62%), and every-4-week dosing in 3 (23%). On retreatment, ORR was 38.5% (5/13) with CR in 2 patients and PR in 3, SD in 3 and progressive disease (PD) in 5. Median number of doses on retreatment was 5 (range 1-44). Among retreatment responders (CR/PR; n=5), median DOR was 15.0 months (range, 6.2-28.0). Median PFS from retreatment initiation was 4.0 months (range, 0.0-40.7) and estimated 2 -year OS was 84.6%. Both deaths were unrelated to CTCL progression or mogamulizumab-related toxicity. MAR occurred in 10/13 (76.9%) patients on retreatment. Rechallenge strategies included temporary treatment interruption until resolution of MAR (n=7) and increasing dosing intervals (n=3). Rash was predominantly maculopapular or morbilliform, most commonly involving the trunk and extremities. All MAR events were CTCAE grade 1-2. MAR was managed with topical steroids (n=9), oral steroids (n=1), and cessation of mogamulizumab (n=9). **Conclusions:** In this real-world, heavily pretreated CTCL cohort, mogamulizumab retreatment demonstrated meaningful clinical activity with durable responses in patients despite prior exposure. Although rash was common, it was most often low to moderate grade, responsive to standard management, and retreatment or rechallenge after resolution was feasible. Research Sponsor: None.

Lisocabtagene maraleucel (liso-cel) as first-line (1L) therapy for transplant-ineligible patients (pt) with primary central nervous system lymphoma (PCNSL): The CAROLYN study.

Allison Marie Winter, Michael Scordo, Caroline Houillier, Gerald Illerhaus, Alberto Vasconcelos, Joe DeStefano, David Bernasconi, Zhi Cheng, Vincent Bize, Roch Houot; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Memorial Sloan Kettering Cancer Center, New York, NY; Hôpital Pitié-Salpêtrière, Paris, France; Klinikum Stuttgart, Stuttgart, Germany; Bristol Myers Squibb, Boudry, Switzerland; Bristol Myers Squibb, Princeton, NJ; University of Rennes, Rennes, France

Background: Treatment of PCNSL is based on high-dose methotrexate (HD-MTX) induction chemotherapy, followed by consolidative autologous stem cell transplantation (ASCT) in eligible pts. Those deemed transplant ineligible have a high risk of relapse and are a population with a significant unmet therapeutic need. Liso-cel, an autologous, CD19-directed chimeric antigen receptor (CAR) T cell product, demonstrated promising results in secondary CNS lymphoma. In a phase 2 study (NCT03484702), 4 of 5 pts with PCNSL treated with liso-cel after failure of 1L high-dose chemotherapy and ASCT achieved a CR. Here, we report the study design of the CAROLYN study (NCT07015242; currently enrolling), which is evaluating efficacy and safety of liso-cel as 1L therapy in transplant-ineligible pts with PCNSL. **Methods:** This open-label, single-arm, multicenter, phase 2 study will enroll approximately 65 pts. The primary endpoint is investigator-determined 12-month PFS rate (from infusion date). Secondary endpoints include additional efficacy assessments (PFS, event-free survival, and OS from enrollment; CR rate, ORR, and duration of response), safety (AEs, serious AEs, and AEs of special interest), and health-related quality of life. Key inclusion criteria are newly diagnosed PCNSL confirmed by local pathology, receipt of ≥ 2 cycles of standard-of-care regimens, transplant ineligibility (defined by investigator assessment and either age ≥ 65 years or hematopoietic stem cell transplantation-specific comorbidity index score ≥ 3), MTX-sensitive disease (CR or PR), and ECOG PS ≤ 2 . Key exclusion criteria include diagnosis of secondary CNS lymphoma, primary intraocular lymphoma, primary vitreoretinal lymphoma, and isolated cerebrospinal fluid involvement. Enrolled pts can receive optional holding therapy with a HD-MTX-based regimen while awaiting leukapheresis. After leukapheresis, bridging therapy with a HD-MTX-based regimen is permitted during liso-cel manufacturing. Before liso-cel infusion, pts receive lymphodepleting chemotherapy consisting of fludarabine (30 mg/m²/day for 3 days) and cyclophosphamide (300 mg/m²/day for 3 days). Pts then receive a single infusion of liso-cel at a target dose of 100×10^6 CAR⁺ T cells. After infusion, pts remain in the treatment period for 90 days and then transition to follow-up for 2 years from enrollment. The total study duration is expected to be 3 years; pts who receive liso-cel can enroll in a separate 15-year long-term follow-up (NCT03435796). Clinical trial information: NCT07015242. Research Sponsor: This study was funded by Juno Therapeutics, a Bristol-Myers Squibb Company.

KITE-753: A phase 2 study of an autologous anti-CD19/CD20 CAR T-cell therapy in CAR-naïve patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL).

Saurabh Dahiya, Timothy Voorhees, Matthew Ulrickson, Jean Yared, Patrick Michael Reagan, Marie José Kersten, Max S. Topp, Lizamarie Bachier, Michael David Jain, Andrew Philip Jallouk, Andre Goy, Ran Reshef, Cameron Turtle, Gary Simmons, Justyna Kanska, Jinghui Dong, Will Watts, Sara Beygi, Myrna Nahas, Sairah Ahmed; Stanford University, Stanford, CA; The Ohio State University, James Comprehensive Cancer Center, Columbus, OH; Banner MD Anderson Cancer Center, Gilbert, AZ; Greenebaum Comprehensive Cancer Center, Baltimore, MD; University of Rochester School of Medicine, Rochester, NY; University of Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany; The Blood and Marrow Transplant Group of Georgia and Northside Hospital, Atlanta, GA; Moffitt Cancer Center, Tampa, FL; Vanderbilt University Medical Center, Nashville, TN; John Theurer Cancer Center, Hackensack, NJ; Columbia University Irving Medical Center, New York, NY; Royal North Shore Hospital, University of Sydney, St Leonards, Australia; Virginia Oncology Associates, Norfolk, VA; Kite, a Gilead Company, Santa Monica, CA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: CD19-directed CAR T-cell therapy has become the standard of care for R/R LBCL; however, some patients are refractory to CD19 CAR T-cell therapy and a subset of responders relapse (Eyre et al. *Ann Oncol.* 2025, Westin et al. *N Engl J Med.* 2023). KITE-753 is an investigational, bicistronic, CD19/CD20 CAR T-cell therapy with a parallel CAR design to optimally engage two tumor antigens, synergistic CD28/4-1BB costimulation to enhance T-cell function, and a rapid manufacturing process that preserves naïve and stem cell memory T cells. It is designed to improve cure rates while limiting toxicity for patients with R/R LBCL. In vitro, KITE-753 demonstrated potent antitumor activity at a dose >25-fold lower than an identical product manufactured with a traditional ex vivo expansion period (Murakami et al. ASH 2024). Phase 1 assessment of KITE-753 showed very low rates of immune effector cell-associated neurotoxicity syndrome (ICANS) and no high-grade cytokine release syndrome or ICANS in patients with R/R LBCL at the intended pivotal dose level. Furthermore, high response rates were observed with 79% of patients achieving complete response (CR). CAR T-cell expansion was comparable to KITE-363 and axi-cel despite a 10-fold lower dose (Dahiya et al. ASH 2025, Dahiya et al. ASCO 2025). Based on Phase 1 outcomes, the Phase 2 dose was established as 2×10^5 CAR T cells/kg. This Phase 2 study will evaluate the safety and efficacy of KITE-753 in CAR-naïve patients with R/R LBCL. **Methods:** In this open-label, multicenter, single-arm study, patients will undergo leukapheresis and receive optional bridging therapy, followed by lymphodepleting chemotherapy (cyclophosphamide [300 mg/m²/day] and fludarabine [30 mg/m²/day]) from Day -5 to Day -3, and infusion of KITE-753 at a target dose of 2×10^5 CAR T cells/kg on Day 0. The primary endpoint is objective response rate (CR rate + partial response rate) assessed by central review per Lugano Classification (Cheson et al. *J Clin Oncol.* 2014). Secondary outcomes include CR rate, duration of response, progression-free survival, overall survival, and safety. The target enrollment is 80 patients. Eligible adults have histologically confirmed R/R LBCL (including transformation of indolent lymphomas and primary mediastinal B cell lymphoma) after ≥ 2 prior lines of systemic therapy (including anti-CD20 mAb or bispecific antibody + anthracycline). Other key inclusion criteria are adequate bone marrow and organ function and ECOG performance status ≤ 2 . Key exclusion criteria are prior CAR T-cell therapy or active central nervous system involvement from lymphoma. This study is currently open and actively accruing patients (NCT04989803). Clinical trial information: NCT04989803. Research Sponsor: Kite, a Gilead Company.

Sonrotoclax (BGB-11417) + zanubrutinib (SZ) vs venetoclax + acalabrutinib (AV) in treatment-naïve chronic lymphocytic leukemia (TN CLL): A phase 3 randomized trial design (CELESTIAL-TNCLL-2).

Mazyar Shadman, Jennifer R. Brown, Tanya Siddiqi, Loic Ysebaert, Paolo Ghia, Jianyong Li, Constantine Si Lun Tam, Alicia Palomino Mosquera, Wai Chan, Zaixing Shi, Arnon Philip Kater; Fred Hutchinson Cancer Center, University of Washington, Seattle, WA; Dana-Farber Cancer Institute, Boston, MA; City of Hope National Medical Center, Duarte, CA; University Cancer Institute of Toulouse Oncopole, Toulouse, France; Università Vita-Salute San Raffaele and Comprehensive Cancer Center, IRCCS Ospedale San Raffaele, Milano, Italy; The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China; Alfred Hospital and Monash University, Melbourne, VIC, Australia; BeOne Medicines, Ltd., San Carlos, CA; BeOne Medicines, Ltd., Shanghai, China; Lymphoma and Myeloma Research Amsterdam, Amsterdam, Netherlands

Background: Inhibition of B-cell lymphoma 2 (BCL2) and Bruton tyrosine kinase (BTK) has emerged as an effective fixed-duration treatment (tx) strategy that can induce high rates of undetectable minimal residual disease (uMRD) in patients (pts) with TN CLL. AV is approved in the EU as a first-line fixed-duration tx for TN CLL. Sonrotoclax, a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation. Zanubrutinib is a highly potent next-generation BTK inhibitor that is approved in the US/EU for CLL. In an ongoing phase 1/1b trial (NCT04277637), SZ has had promising efficacy, with a 100% ORR (n=135) and high rates of blood uMRD at 10^{-4} sensitivity (uMRD₄) in pts with TN CLL, including those with high-risk disease features. SZ is generally well tolerated, with neutropenia as the most common grade ≥ 3 TEAE and no laboratory or clinical TLS events occurred. The phase 3 trial BGB-11417-304 (NCT07277231) was designed to directly compare fixed-duration SZ vs AV in TN CLL to investigate whether SZ compared with AV, may improve efficacy in terms of achieved uMRD rate after completing treatment and PFS and potentially improve tolerability and safety. **Methods:** BGB-11417-304 is a global phase 3, open-label, randomized study. Eligible adults have a confirmed diagnosis of previously untreated CLL requiring tx per iwCLL 2018 criteria, adequate hematologic and organ function, ECOG PS 0–2, and measurable disease confirmed by CT/MRI. Exclusion criteria include prior systemic tx for CLL; diagnosis of prolymphocytic leukemia or Richter transformation; known central nervous system involvement; history of confirmed progressive multifocal leukoencephalopathy; or uncontrolled hypertension or clinically significant cardiovascular disease. Approximately 500 pts will be enrolled and randomized 1:1 to arm A (3 lead-in cycles of oral zanubrutinib monotherapy followed by 12 cycles of oral SZ) or arm B (2 lead-in cycles of oral acalabrutinib monotherapy followed by 12 cycles of oral AV). Randomization will be stratified by age (<65 y vs ≥ 65 y), IGHV mutation status, and presence of del(17p) and/or TP53 mutations. The primary endpoint is PFS in arm A vs arm B, as determined by independent review committee (IRC), with an intermediate endpoint of uMRD₄ rate in blood and bone marrow in arm A vs arm B, assessed by next-generation sequencing (clonoSEQ) at the first post-tx follow-up visit. Key secondary endpoints are PFS-IRC in high-risk subgroups and OS. Other secondary endpoints are ORR and complete response assessed by IRC and investigator (INV), uMRD₅ rate (clonoSEQ), PFS-INV, duration of response by IRC and INV, time to next tx, pt-reported outcomes, and safety/tolerability. Enrollment in BGB-11417-304 is currently ongoing. Clinical trial information: NCT04277637. Research Sponsor: BeOne Medicines, Ltd.

ROCKET-CLL: A randomized, open-label, multicenter, phase 3 study of rocbrutinib (LP-168) versus pirtobrutinib in covalent BTK inhibitor (cBTKi) in pretreated relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

Anna Chen, Jennifer Ann Woyach, John Francis Seymour, Danielle M. Brander, Deborah Marie Stephens, Neil E. Kay, Fenlai Tan, Yi Chen, Stephen Patrick Anthony, Kewei Shang, Yue Shen, Yejiang Lou, John C. Byrd; Newave Pharmaceutical Inc, Pleasanton, CA; The Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, The Ohio State University, Columbus, OH; Peter MacCallum, Melbourne, VIC, Australia; Duke University Health System, Durham, NC; Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC; Mayo Clinic Rochester, Rochester, MN; Guangzhou Lupeng Pharmaceutical, Guangzhou, China; Newave Pharmaceutical Inc., Pleasanton, CA; Newave Pharmaceuticals Inc, Pleasanton, CA; UPMC Hillman Cancer Center, Pittsburgh, PA

Background: Bruton tyrosine kinase covalent inhibitors (cBTKi) have been transformative in CLL treatment. Despite achieving extended remissions, in most patients disease still relapses despite cBTKi therapy, often associated with *BTK* C481 mutations. Non-covalent BTKi (ncBTKi), including pirtobrutinib, can overcome this resistance (Sharman et al. ASCO. 2025). Pirtobrutinib received FDA approval in Dec 2025, for R/R CLL/CLL patients pretreated with cBTKi. Rocbrutinib (LP-168) is a highly selective next-generation BTKi that can covalently bind wild-type and gatekeeper mutations (T474X, commonly seen in patients relapsed after pirtobrutinib) and non-covalently target C481-mutated *BTK*, with preclinical efficacy in treatment-naïve and BTKi-resistant CLL (Gordon et al. IWCLL. 2025). In the rocbrutinib phase 1 trial (NCT04775745), encouraging safety and efficacy have been observed in CLL patients with prior exposure to BTKi and/or BCL2 inhibitor (BCL2i) (Woyach et al. *Blood*. 2025). Presented here is the design of a phase 3 trial aiming to compare the efficacy of rocbrutinib versus pirtobrutinib in cBTKi-pretreated R/R CLL/SLL patients. **Methods:** ROCKET-CLL (NCT07342478) is a randomized, open-label, multicenter, phase 3 study comparing rocbrutinib (Arm 1) to pirtobrutinib (Arm 2) in R/R CLL/SLL subjects who previously received treatments including covalent BTKi. Eligible subjects must require treatment per 2018 iwCLL criteria, have measurable lesions by CT, an ECOG performance score of 0-2, and adequate hematologic and other organ functions. About 306 subjects will be randomized 1:1 based on stratification factors such as 17p deletion/*TP53* mutation presence, reasons for discontinuing prior cBTKi, prior BCL2i treatment, and geographic region. Participants assigned to each arm will receive rocbrutinib (200 mg QD) or pirtobrutinib (200 mg QD) tablets continuously until disease progression, unacceptable toxicity, withdrawal, or other study discontinuation criteria are met. The primary endpoint is progression-free survival (PFS), assessed by an independent review committee (IRC) per iwCLL 2018 criteria with CLL (Hallek et al. 2018) and Lugano 2014 criteria with SLL (Cheson et al. 2014). Important secondary endpoints include overall survival (OS), time to next treatment (TTNT), event-free survival (EFS), overall response rate (ORR), duration of response (DOR), PFS assessed by investigator (INV), concordance between IRC and INV PFS, safety and tolerability, and population PK. Exploratory endpoints include health-related quality of life and biomarker assessment. Recruitment is ongoing. Clinical trial information: NCT07342478. Research Sponsor: None.

A global multicenter, open-label, randomized, phase 3 registrational study of lisaftoclax (APG-2575) in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): GLORA trial in progress.

Matthew Steven Davids, Sikander Ailawadhi, Gerardo Musuraca, Wojciech Jurczak, Martin Šimkovic, Antonio Gutierrez, Sami N. Malek, Vladimir Ivanov, Eugene Nikitin, Elena Misyrina, Gulnara Nailevna Khusainova, Gayane Tumyan, Cecile Tomowiak, Katell Le Du, Andrea Visentin, Monica Tani, Ciprian Tomuleasa, Eva Mikuskova, Dajun Yang, Yifan Zhai; Dana-Farber Cancer Institute, Boston, MA; Division of Hematology/Oncology, Department of Medicine, Mayo Clinic Florida, Jacksonville, FL; IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy; Maria Skłodowska-Curie National Research Institute of Oncology, Krakow, Poland; University Hospital Hradec Kralove, Hradec Kralove, Czech Republic; Son Espases University Hospital, Palma De Mallorca, Spain; University of Michigan, Ann Arbor, MI; Almazov National Medical Research Center, St. Petersburg, Russian Federation; City Clinical Hospital named after S.P. Botkin, Moscow, Russian Federation; City Clinical Hospital No. 52, Moscow, Russian Federation; Republican Clinical Oncology Dispensary Named After Professor M.Z. Sigal, Kazan, Russian Federation; N.N. Blokhin National Medical Research Center of Oncology, Moscow, Russian Federation; Department of Hematology, University Hospital, Poitiers, France; L'Hôpital Privé du Confluent, Nantes, France; Hematology unit, Department of Medicine, University of Padova, Azienda Ospedale-Università Padova, Padova, Italy; Azienda USL di Ravenna, Ravenna, Italy; Department of Personalized Medicine and Rare Diseases, Medfuture Institute for Biomedical Research, Hematology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; Narodny Onkologicky Ustav, Bratislava, Slovakia; Ascentage Pharma (Suzhou) Co., Ltd., Suzhou, China; Ascentage Pharma Group Inc., Rockville, MD

Background: Patients with high-risk CLL/SLL not achieving a complete response (CR) after $\geq$ 12 months of BTKi inhibitor (BTKi) monotherapy remain at risk for early progression due to residual disease and BTKi resistance. A BCL-2 inhibitor (BCL-2i) introduces a complementary, BCR-independent apoptotic mechanism that may deepen responses and prolong progression-free survival (PFS). Lisaftoclax, a selective oral BCL-2i with a short half-life (4–6 h), enables once-daily dosing and is approved in China as second-line CLL therapy. Lisaftoclax monotherapy has demonstrated overall response rates (ORRs) of 67% in relapsed/refractory CLL and 62.5% in BTKi-refractory disease, including del(17p)/TP53-mutated cases. Lisaftoclax combined with acalabrutinib achieved ORRs $>97\%$ with favorable tolerability. This study evaluates whether lisaftoclax plus BTKi (acalabrutinib, zanubrutinib, or ibrutinib) improves PFS and/or overall survival (OS) (vs continued BTKi monotherapy) in patients with CLL/SLL and residual disease after prolonged BTKi treatment. **Methods:** This study will enroll approximately 440 patients randomly allocated to receive lisaftoclax plus BTKi or BTKi alone. Eligible patients have CLL/SLL and, after ≥ 12 months of BTKi monotherapy (lines 1–3), have achieved neither CR nor progressive disease (PD). Randomization is stratified by del(17p)/TP53 status. Key inclusion criteria include age ≥ 18 years, ECOG PS 0–2, and residual disease with either high-risk features (del(17p)/TP53 mutation, unmutated IGHV, or complex karyotype [≥ 5 abnormalities]), or measurable residual disease with lymph nodes ≥ 2.5 cm in the absence of high-risk features. Exclusion criteria include prior BCL-2i therapy or Richter transformation. Patients in the investigational arm will undergo a 5-day oral lisaftoclax ramp-up to 400 mg once daily plus physician's choice of BTKi in 28-day cycles until progression or toxicity. Control patients continue their current BTKi monotherapy. Safety and disease assessments (CT/MRI) will occur regularly. The primary endpoint is PFS by independent review committee (iwCLL 2018); key secondary endpoint OS; and other secondary endpoints, PFS by investigator, ORR, duration of response, MRD negativity, and safety. Enrollment is ongoing across 126 sites in 18 countries (ClinicalTrials.gov ID: NCT06104566). Clinical trial information: NCT06104566. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).

Golcadomide (GOLCA), a potential, first-in-class, oral CELMoD, plus rituximab (R) versus investigator's choice (IC) in patients (pts) with relapsed/refractory follicular lymphoma (R/R FL) who have received ≥ 1 line of systemic therapy: GOLSEEK-4, a phase (Ph) 3, randomized study.

Clémentine Sarkozy, Eliza Anne Hawkes, Yuqin Song, Muhit Ozcan, Franck Morschhauser, Charalambos Andreadis, Alev Akyol, Parth Rao, Antonia Di Micco, Adrien Petel, Serena K. Perna, Alex F. Herrera; Institut Curie, Hôpital Saint-Cloud, Université de Versailles, Saint-Quentin, France; Olivia Newton John Cancer Research at Austin Health, Heidelberg, VIC, Australia; Key Laboratory of Carcinogenesis and Translational Research, Department of Lymphoma, Peking University Cancer Hospital & Institute, Beijing, China; Ankara University School of Medicine, Ankara, Turkey; Department of Hematology, Claude Huriez Hospital, Lille University Hospital, Lille, France; UCSF Health, San Francisco, CA; Bristol Myers Squibb, Princeton, NJ; Late Clinical Development, Hematology/Oncology and Cell Therapy, Bristol Myers Squibb, Princeton, NJ; Bristol Myers Squibb, Steinhausen, Switzerland; Bristol Myers Squibb, Rueil-Malmaison, France; Late Clinical Development, Hematology/Oncology and Cell Therapy, Bristol Myers Squibb, Madison, NJ; City of Hope, Duarte, CA

Background: Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL), typically presenting as advanced-stage at diagnosis. With current SOC (chemo-immunotherapy [CIT] and maintenance), many pts can achieve remission; however, FL remains incurable, with shorter remissions and overall survival (OS) following relapses. Treatments for R/R FL, including CIT or R-lenalidomide (R^2), offer limited long-term benefit. T-cell-redirecting therapies in $\geq 3L$ provide better efficacy but are limited by tolerability and logistical challenges. An unmet need persists for effective, well-tolerated, convenient options for R/R FL pts after $\geq 1L$ of systemic therapy. GOLCA is a potential, first-in-class, oral CELMoD designed for the treatment of lymphoma, with preferential distribution to lymphoid organs and enhanced activity in lymphoma cell lines. GOLCA induces rapid and deep degradation of Ikaros and Aiolos, leading to direct cell killing and immunomodulatory activity. GOLCA 0.4 mg + R was studied in heavily pre-treated R/R FL pts (including those given lenalidomide [LEN] and T-cell redirecting therapies) in the Ph 1/2 CC-99282-NHL-001 study, resulting in objective response rate 97%, complete response rate 78% and tolerable safety, suggesting benefit vs SOC (Chavez et al., ASH 2025, #1006). As a result, the Ph 3 study, GOLSEEK-4 (NCT06911502) was initiated. **Methods:** GOLSEEK-4 is a global, randomized, Ph 3 study evaluating fixed-duration, chemo-free GOLCA + R vs IC (R^2 or R-chemo) in R/R FL after ≥ 1 prior lines of therapy. Included: adults (≥ 18 yr) with grade 1-3A R/R FL or cFL, PET-positive disease with measurable lesions (Lugano criteria), ECOG 0-2 (or 3 if due to lymphoma), require treatment based on modified GELF, and ≥ 1 prior regimen, including anti-CD20 + alkylating agent. Prior T-cell-redirecting therapy allowed. Excluded: composite DLBCL/FL, transformed NHL, CNS involvement, those who are R/R or intolerant to all options in IC arm. Approximately 400 pts will be randomized 1:1 to GOLCA (0.4 mg QD, Days 1-14 per 28-day cycle) + R for 5 cycles, then GOLCA monotherapy for 7 cycles (12 cycles total) or IC (R^2 for 5 cycles then LEN monotherapy for 7 cycles, or R-CHOP or R-Bendamustine for 6 cycles). Randomization will be stratified by disease progression within 24 months (mo) vs >24 mo from initial CIT, prior lines (2L vs 3L+), and IC regimen. Pts will be followed for at least 5 yrs. Recruitment began July 2025. Primary endpoint: progression-free survival (IRAC). Secondary endpoints: overall response rate (IRAC), OS, complete metabolic response, minimal residual disease, time to next therapy, duration of response. Safety is exploratory. Acknowledgement: BMS ChatGPT4 used to revise existing text with human author input (Jan 26). Clinical trial information: NCT06911502. Research Sponsor: Bristol Myers Squibb.

Phase 1 study of ARV-393, a PROTAC BCL6 degrader, as monotherapy in patients with advanced non-Hodgkin lymphoma (NHL) or combined with glofitamab in patients with diffuse large B-cell lymphoma (DLBCL).

Martin Hutchings, Andrew David Zelenetz, Jacob Haaber Christensen, Almudena Cascales Hernandez, Sarit E. Assouline, Luis E. Malpica Castillo, Shalin Kothari, Dipenkumar Modi, Miguel Angel Canales Albendea, Damian Cubillas, Alejandro Martin Garcia-Sancho, Catherine S. Diefenbach, John Kuruvilla, Paolo Fabrizio Caimi, Krish Patel, Sean Landrette, Xin Zhi, Yuanyuan Zhang, Roland Meier, Matthew Matasar; Rigshospitalet and University of Copenhagen, Copenhagen, Denmark; Memorial Sloan Kettering Cancer Center, New York, NY; Odense University Hospital, Odense, Denmark; Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain; Jewish General Hospital, McGill University, Montreal, QC, Canada; The University of Texas MD Anderson Cancer Center, Houston, TX; Yale School of Medicine and Yale Cancer Center, New Haven, CT; Karmanos Cancer Institute, Wayne State University, Detroit, MI; Clínica Universidad de Navarra, Pamplona, Spain; START Center for Cancer Research, Madrid, Spain; Hospital Universitario de Salamanca, IBSAL, CIBERONC, University of Salamanca, Salamanca, Spain; Perlmutter Cancer Center, NYU Langone Health, New York, NY; Princess Margaret Cancer Centre, Toronto, ON, Canada; Cleveland Clinic, Cleveland, OH; Sarah Cannon Research Institute, Nashville, TN; Arvinas Operations, Inc., New Haven, CT; Rutgers Cancer Institute of New Jersey, New Brunswick, NJ

Background: Despite recent advancements in NHL therapies, many patients experience disease progression or relapse. Agents with novel mechanisms of action and combination strategies are needed to improve clinical outcomes. B-cell lymphoma 6 (BCL6) is a master transcriptional regulator of immune cells, particularly of germinal center B cells, and an established oncogenic driver in NHL. ARV-393 is an oral PROteolysis TArgeting Chimera (PROTAC) BCL6 degrader that binds an E3 ubiquitin ligase and BCL6 to induce ubiquitination of BCL6 and its subsequent proteasomal degradation. ARV-393 monotherapy potently inhibited tumor growth and induced tumor regressions across NHL cell-derived xenograft (CDX) and patient-derived xenograft models, including models of DLBCL, transformed follicular lymphoma, and nodal T-follicular helper cell lymphoma (nTFHL). Furthermore, administration of ARV-393 with a CD20×CD3 bispecific antibody, glofitamab, demonstrated combinatorial antitumor activity in a humanized high-grade B-cell lymphoma CDX model, inducing deeper tumor growth inhibition and increased tumor regressions vs either monotherapy. These preclinical findings demonstrated single-agent ARV-393 antitumor activity across NHL subtypes and suggested mechanistic synergy with glofitamab, supporting clinical investigation of monotherapy in NHL and this chemotherapy-free combination in patients with DLBCL. **Methods:** This global, multicenter, open-label, first-in-human, phase 1 dose escalation and optimization/expansion study (NCT06393738) is evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of ARV-393 as monotherapy in relapsed or refractory (R/R) NHL or in combination with glofitamab in R/R DLBCL, with a primary objective of determining provisional doses for further exploration. Patients eligible for ARV-393 monotherapy are adults with confirmed R/R B-cell NHL who previously received ≥ 2 lines of systemic therapy (including rituximab), or nTFHL who previously received standard of care therapy. Patients eligible for ARV-393 in combination with glofitamab are adults with pathologically confirmed R/R DLBCL, DLBCL not otherwise specified, or large B-cell lymphoma arising from follicular lymphoma who were treated with ≥ 2 prior lines of systemic therapy. ARV-393 will be administered orally once daily in 28-day cycles alone or in combination with intravenous glofitamab during 21-day cycles. Approximately 255 patients will be enrolled across study cohorts. As of January 2026, enrollment is ongoing. Copyright © 2026 AACR. Originally presented at AACR 2026. Reprinted with permission. Clinical trial information: NCT06393738. Research Sponsor: Arvinas Operations Inc.

waveLINE-011: Zilovetamab vedotin plus R-CHP versus polatuzumab vedotin plus R-CHP as first-line therapy in germinal center B-cell–like (GCB) diffuse large B-cell lymphoma (DLBCL).

Max S. Topp, Guoqing Wang, Puja Patel, Rushdia Zareen Yusuf, David Lavie; University of Würzburg, Würzburg, Germany; Merck & Co., Inc., Rahway, NJ; Hadassah Medical Center, Jerusalem, Israel

Background: DLBCL is a heterogeneous malignancy broadly categorized into 3 subtypes: activated B-cell–like (ABC) DLBCL, GCB DLBCL, and unclassified DLBCL. The standard-of-care first-line treatment option for DLBCL regardless of subtype is polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP). However, while polatuzumab plus R-CHP prolongs PFS compared with R-CHOP in ABC DLBCL, it provides no benefit over R-CHOP in GCB DLBCL. Alternative first-line treatment options for GCB DLBCL are needed. Receptor tyrosine kinase–like orphan receptor 1 (ROR1) is an oncofetal transmembrane protein that is overexpressed in DLBCL, making it an attractive therapeutic target. Zilovetamab vedotin is an antibody–drug conjugate comprising an anti-ROR1 antibody with a proteolytically cleavable linker and the cytotoxic antimicrotubule agent MMAE. In the phase 1 waveLINE-001 study, zilovetamab vedotin was shown to have antitumor activity in heavily pretreated lymphoid cancers and promising efficacy and manageable safety in combination with R-CHP as first-line treatment for DLBCL. The randomized, open-label, phase 2 waveLINE-011 study (NCT06890884) has been designed to evaluate the efficacy and safety of zilovetamab vedotin plus R-CHP versus polatuzumab vedotin plus R-CHP in participants with previously untreated GCB DLBCL. **Methods:** Key eligibility criteria include age ≥ 18 years, previously untreated histologically confirmed GCB DLBCL (including but not limited to: DLBCL not otherwise specified GCB type and high-grade B-cell lymphoma [HGBL] GCB subtype), PET-positive disease at screening, an ECOG performance status score of 0 to 2, and an International Prognostic Index (IPI) score of 2 to 5. Participants with a history of transformation of indolent disease to DLBCL or with primary mediastinal B-cell lymphoma or gray zone lymphoma are excluded. All participants will be randomly assigned (1:1) to zilovetamab vedotin 1.75 mg/kg plus R-CHP or polatuzumab vedotin 1.8 mg/kg plus R-CHP on day 1 of every 3-week cycle for 6 cycles. Randomization will be stratified by geographic region (Western Europe vs US vs rest of world), IPI score (2 vs 3–5), bulky disease (< 7.5 cm vs ≥ 7.5 cm), and histopathology (HGBL vs others). The primary end point is CR rate at the end of therapy per Lugano criteria by BICR. Secondary end points include PFS, EFS, duration of CR, OS, safety, and change in PROs. Response assessments (CT/FDG-PET) will be performed after cycle 4 day 1 but on or before cycle 5 day 1, and at 12 weeks after the cycle 4 scan. Follow-up efficacy assessments will be completed every 24 weeks for 2 years from the end of treatment assessment, then every year for 3 years. Adverse events will be graded per NCI CTCAE v5.0. Approximately 594 participants will be enrolled. Recruitment is ongoing. Clinical trial information: NCT06890884. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

AQUARIUS: A longitudinal multi-center molecular biomarker discovery registry for patients with hematologic malignancies.

Michael A. Thompson, Mitchell Reed Smith, Mehrdad Mobasher, David McCullagh, Tracy Dooley, Shwetha Lakshmipathi, Andy Zhu, Simon Bignet, Amy Taraszka; Tempus AI, Inc., Chicago, IL; The Follicular Lymphoma Foundation, Washington, DC; IFLI, Diamond Bar, CA; IFLI, San Francisco, CA; Tempus AI, Chicago, IL

Background: Despite therapeutic innovations over the past decade in hematologic malignancies, there remains a significant unmet need in understanding disease progression, identifying progression and resistance biomarkers, and accurately predicting responses to various treatments. Identifying new therapeutic targets by moving deeper into the molecular and genetic architecture of the tumor is key to overcoming resistance and tailoring interventions to the unique biological profile of each individual. For example, follicular lymphoma (FL) demonstrates heterogeneous clinical behavior ranging from not requiring therapy (active observation), with not as yet well-defined high risk features for early progression, to patients who relapse early after initial therapy (POD24) and the ongoing risk of transformation to aggressive histology. Registry studies, in particular, provide insights into tumor heterogeneity, progression patterns, and clinical behaviors, which are essential for designing effective clinical trials and developing targeted therapies. The Tempus AQUARIUS hematologic biomarker discovery registry (NCT07154823) is a non-interventional, multi-center registry study aiming to create a robust dataset of molecular and clinical data from patients with hematologic malignancies to facilitate clinician-led research using whole genome sequencing (WGS) to generate hypotheses for predictive biomarkers, identify potential resistance mechanisms, and guide therapy selection. **Methods:** AQUARIUS is designed as a master protocol with multiple real world (rw) cohorts continuously added as future research questions emerge. The first cohort is on patients with FL, followed by additional cohorts in 2026. The FL cohort will encompass the following populations: newly diagnosed active observation (n: 100), newly diagnosed high risk (n: 150), relapsed/refractory high risk POD24 (n: 125), and transformed FL (n: 125), aiming to enroll 500 patients in total. Lymph node tissue or bone marrow aspirate and blood samples are collected during routine standard of care visits, with blood samples collected at all follow-up timepoints. Clinical data is collected—including demographics, medical history, treatment, and outcomes—at all timepoints, along with standard of care images. The emerging DNA WGS assay (Tempus xH) and existing RNA whole transcriptome sequencing assay (Tempus xR) will be performed at screening and progression/primary refractory disease to capture specific molecular alterations and potential genomic variants. Multimodal molecular profiling data will be generated prospectively. The following endpoints will be assessed: rw Overall Survival (OS), rw Progression Free Survival (PFS), rw Time to Next Treatment (TTNT), rw Time to Discontinuation (TTD), and changes in biomarkers over time. The study is open and actively enrolling. Clinical trial information: NCT07154823. Research Sponsor: None.

ROCK-2: An ongoing open-label, randomized, multicenter phase 2 study of rocbrutinib versus investigator's choice of therapy in patients with R/R non-GCB DLBCL.

Peng Liu, Sheng Yang, Fei Li, Xiuhua Sun, Wenyu Li, Yanyan Liu, Liang Wang, Liang Huang, Ling Qin, Wenbin Qian, Liping Su, Qingqing Cai, Xiaohong Tan, Wei Yang, Mingyu Jia, Nawei Liu, Yejiang Lou, Yue Shen, Fenlai Tan, Yuankai Shi; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; First Affiliated Hospital of Nanchang University, Nanchang, China; The Second Hospital of Dalian Medical University, Dalian, China; Guangdong Provincial People's Hospital, Guangzhou, China; Henan Provincial Cancer Hospital, Zhengzhou, China; Beijing TongRen Hospital, Capital Medical University, Beijing, China; Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences, Tianjin, China; The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China; The Second Affiliated Hospital - Zhejiang University School of Medicine, Hangzhou, China; Shanxi Cancer Hospital, Taiyuan, China; Sun Yat-sen University Cancer Center, Guangzhou, China; Guangxi Medical University Cancer Hospital, Nanning, China; Shengjing Hospital of China Medical University, Shenyang, China; Guangzhou Lupeng Pharmaceutical Company Ltd., Guangzhou, China

Background: Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma. Aberrant activation of the Bruton's tyrosine kinase (BTK)-related signaling pathway is present in the non-GCB subtype of DLBCL (Davis et al. *Nature* 2010). Multiple BTK inhibitors (BTKi) have demonstrated efficacy in relapsed or refractory (R/R) non-GCB DLBCL (Strati et al. *Haematologica*. 2021; Wilson et al. *Nat Med*. 2015; Yang et al. *Blood Adv*. 2022), however, there remains room for further improvement. Rocbrutinib is a novel, highly selective, the fourth generation covalent (irreversible) and non-covalent (reversible) BTKi. Phase 1 study showed that in 45 patients with R/R non-GCB DLBCL who had received ≥ 2 prior lines of systemic therapy, rocbrutinib monotherapy achieved an overall response rate (ORR) of 57.8% and a complete response (CR) rate of 31.3% (Song et al. *CSCO*. 2025). This article describes the design and progress of a phase 2 pivotal study aimed at comparing the efficacy and safety of rocbrutinib versus investigator's choice of therapy in patients with R/R non-GCB DLBCL. **Methods:** ROCK-2 (NCT07189065; CTR20253693) is an open-label, randomized, multicenter phase 2 study conducted in China. Eligible patients must have non-GCB DLBCL, not otherwise specified (NOS) per the 2017 WHO classification, received ≥ 2 prior lines of systemic therapy. Additionally, patients must have measurable disease, an ECOG performance status of 0-2, and adequate hematologic and organ function. Key exclusion criteria include central nervous system involvement, DLBCL transformed from indolent lymphoma, prior refractoriness to BTK-targeting agents, uncontrolled systemic diseases, active infection. Approximately 150 eligible subjects will be randomized 1:1 to receive either rocbrutinib or BR/R², stratified by the number of prior lines of therapy (2 vs ≥ 3) and International Prognostic Index (IPI) score (0-2 vs 3-5). Subjects in the experimental group will receive rocbrutinib [200 mg once daily (QD)] until disease progression or unacceptable toxicity. Subjects in the control group will receive either BR or R² according to the investigator's choice. The BR regimen consists 6 cycles of rituximab (375 mg/m² on day 1) plus bendamustine (90 mg/m²/d on days 1-2). The R² regimen consists of rituximab (375 mg/m² on day 1 of cycles 1-6) plus lenalidomide (20 mg QD on days 1-21 of each 28d-cycle until disease progression or unacceptable toxicity). The primary endpoint is ORR assessed by Independent Review Committee (IRC) according to the 2014 Lugano criteria. Secondary endpoints include ORR assessed by investigator (INV), and CR rate, progression-free survival (PFS), duration of response (DOR), time to response (TTR), overall survival (OS) assessed by IRC or INV. The first subject was enrolled on Nov 27th, 2025. Recruitment is ongoing. Clinical trial information: NCT07189065. Research Sponsor: Guangzhou Lupeng Pharmaceutical Company Ltd.

Phase 2 trial of lisocabtagene maraleucel for minimal residual disease in patients with large B-cell lymphoma.

Dai Chihara, Ruitao Lin, Alexander Boardman, Ryan C. Lynch, David M. Kurtz, Mazhar Shadman, Alex F. Herrera, Jeremy S. Abramson, Gilles A. Salles, Jason Westin; Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Memorial Sloan Kettering Cancer Center, New York, NY; Fred Hutchinson Cancer Center, University of Washington, Seattle, WA; Foresight Diagnostics, Inc., Boulder, CO; Fred Hutch Cancer Center, Seattle, WA; City of Hope, Duarte, CA; Massachusetts General Hospital Cancer Center, Boston, MA

Background: Patients with relapsed/refractory large B-cell lymphoma (LBCL) have a poor prognosis. Identifying patients at high risk of recurrence after completion of first line (1L) treatment is crucial to enable early intervention with further treatments that may improve outcomes. Recent studies have shown that detectable minimal residual disease (MRD) by circulating tumor DNA (ctDNA) assay after 1L chemoimmunotherapy is prognostic for risk of recurrence. We hypothesize that lisocabtagene maraleucel (liso-cel) will eradicate the MRD in patients with LBCL who have detectable ctDNA at the end of 1L treatment will lead to improved long-term outcomes relative to historical results with liso-cel in second line treatment for patients with radiologically-detected disease. **Methods:** This is an open-label, phase 2, single-arm, multicenter, investigator-sponsored trial designed to evaluate the efficacy and safety of lisocabtagene maraleucel (liso-cel) in patients with LBCL who have achieved a response to 1L standard-of-care therapy but have detectable MRD. The trial will enroll 50 evaluable patients. Eligible participants are adults with LBCL, including DLBCL-NOS and HGBCL, who received 1L anthracycline-based chemoimmunotherapy (R-CHOP, DA-EPOCH-R, or polatuzumab-R-CHP) for six cycles, with or without an additional two cycles of rituximab, for previously untreated disease. Patients must have achieved a CR, or a PR with a negative biopsy or biopsy not feasible, and must demonstrate detectable MRD as assessed by the Foresight CLARITY ctDNA-MRD assay following completion of 1L therapy. The primary endpoint is event-free survival rate at 12 months, and secondary endpoints include rate of undetectable MRD. Correlative studies are designed to build a holistic model for understanding the tumor-intrinsic and immune features that contribute to response, as well as treatment-associated toxicities following liso-cel in patients with LBCL and detectable MD, a population at high risk of recurrence. Enrollment to the trial is planned at five centers in the US: MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, Fred Hutchinson Cancer Center, City of Hope and Massachusetts General Hospital (NCT07316010). Clinical trial information: NCT07316010. Research Sponsor: None.