Prospective validation of end of treatment ctDNA-MRD by PhasED-Seq in DLBCL patients from a national trial.

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Background: The prognostic utility of circulating tumor DNA measurable residual disease (ctDNA-MRD) detection at end of treatment (EOT) using phased variant (PV) enrichment and detection sequencing (PhasED-Seq) has been demonstrated in patients with diffuse large B-cell lymphoma (DLBCL) receiving first-line (1L) therapy. Prior studies are limited by treatment, patient, and sample heterogeneity. Here, we independently validate the prognostic value of PhasED-Seq in a national, multi-center study of uniformly treated 1L DLBCL patients. **Methods:** ctDNA-MRD was assessed using Foresight CLARITY in LBCL patients enrolled on HOVON-902 from >50 centers in the Netherlands and Belgium. Patients were treated with curative-intent 1L therapy (R-CHOP or DA-EPOCH-R). We evaluated the prognostic significance of MRD status [positive (+), negative (-)] on progression-free survival (PFS) and overall survival (OS). PVs were identified from pretreatment biopsies or plasma with matched normal DNA. EOT plasma samples were used for ctDNA-MRD detection. **Results:** A total of 150 of 156 (96%) eligible patients had successful PV identification. Of included patients, 90%, 9%, and 1% had DLBCL, HGBL, and PBMCL, respectively. IPI distribution was 22% low, 29% low-intermediate, 27% high-intermediate, and 22% high risk; median age was 67.5. The 24-month PFS and OS in this cohort were 74% and 86%, respectively, with 31 months of median follow-up. At the EOT, 76% of patients were MRD- and 24% were MRD+. MRD+ status significantly predicted inferior PFS (2 yr PFS 88 vs 28%; HR 9.7, 95% CI 4.2-22.3, $p<0.0001$) and OS (2 yr OS 97 vs 50%; HR 10.6, 95% CI 4.1-27.7, $p<0.0001$). Moreover, in patients without complete response, MRD+ was significantly prognostic for PFS, suggesting an ability to adjudicate imaging results (HR for PFS 7.6, 95% CI 3.6-16.3, $p < 0.0001$). Among patients who were MRD- and achieved CMR at EOT, 2-year PFS and OS were 91% and 99%, respectively. All patients who failed to achieve CMR and remained MRD+ experienced relapse. ctDNA-MRD was prognostic for outcomes in all subgroups considered, including source of baseline sample (tumor versus plasma), best clinical response, IPI, sex, lactate dehydrogenase, stage, or extranodal disease. In multivariate analysis including ctDNA-MRD, IPI, and best overall response, ctDNA-MRD was significantly and independently prognostic for both PFS [HR for ctDNA: 7.1, 95% CI 3.5-14.3, $p<0.0001$] and OS [HR for ctDNA: 5.1, 95% CI 2.2-11.9, $p=0.00018$]. **Conclusions:** We validated the prognostic value of PhasED-Seq-based ctDNA-MRD in a real-world multicenter 1L DLBCL cohort. This highlights the utility of ctDNA-MRD to confirm residual disease in patients without complete response by imaging, as well as the potential to identify patients who may benefit from consolidation therapy. These results support the integration of MRD as a standard component of response evaluation in 1L DLBCL treatment. Research Sponsor: None.

7001 Oral Abstract Session

Revision of staging system for natural killer T-cell lymphoma: A multicenter study from the Chinese Southwest Oncology Group and Asia Lymphoma Study Group.

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Background: Natural killer T-cell lymphoma (NKTCL), characterized by extranodal involvement, challenges the efficacy of the Ann-Arbor staging system (AASS) in its precise prognostic stratification. A revised staging system is warranted for precise prognosis prediction in the modern chemotherapy era. **Methods:** A training cohort of patients with newly diagnosed NKTCL was assessed to revise the AASS in the context of the modern chemotherapy era. The results were validated in an independent international cohort that received asparaginase-based chemotherapy. **Results:** Our analysis of 2017 newly diagnosed NKTCL patients from 19 centers across two countries highlights the limitations of the AASS, which demonstrates an uneven patient distribution and insufficient differentiation of outcomes, particularly between stages III and IV. We proposed a revised staging system in which AASS stage I patients with nasal-type disease only were classified as stage I, whereas those with local invasion or limited non-nasal-type disease were reclassified as stage II. AASS stage II patients with regional lymph node involvement were assigned to stage III. Additionally, patients with distant lymph node involvement or extensive skin/subcutaneous soft tissue involvement were classified as stage IVA, those with extensive visceral organ invasion were classified as stage IVB, and those with bone marrow infiltration or hemophagocytic lymphohistiocytosis were classified as stage IVC. This proposal better distinguishes clinical outcomes across different stages, achieves a more equitable distribution of patients, and demonstrates multiple advancements over the AASS. **Conclusions:** The revised staging system is promising for the staging of NKTCL patients with different prognoses and could be useful for decisions regarding the treatment strategy and future clinical trial designs. Research Sponsor: National Natural Science Foundation of China; 82470237; National Natural Science Foundation of China; 82270198; Cancer Innovative Research Program of Sun Yat-sen University Cancer Center; CIRP-SYSUCC-0022.

Molecular landscape of distinct follicular lymphoma histologic grades: Insights from genomic and transcriptome analyses.

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Background: The 2022 *World Health Organization Classification of Hematologic Malignancies* classifies follicular lymphoma grades 1-2 (FL1-2) and grade 3A (FL3A) as classical follicular lymphoma (cFL) and reclassifies grade 3B (FL3B) as follicular large B-cell lymphoma (FLBL), without addressing cases of patients with concurrent FL and DLBCL. However, genetic information of FL histologic grading remains limited, and the latest classification lacks sufficient evidence to resolve whether these subgroups represent single or multiple distinct biological entities. **Methods:** This study analyzed clinical data from 831 patients, whole-exome sequencing (WES) from 149 patients, and transcriptome sequencing from 63 patients to explore differences among FL1-2, FL3A, FL3B, and FL/DLBCL. **Results:** A total of 1006 patients were initially identified. After excluding those under 18 years of age, those with histological transformation, and those with incomplete clinical information, 831 patients remained. Among them, 588 (71%) had FL1-2, 84 (10%) had FL3A, 67 (8%) had FL3B, and 92 (11%) had FL/DLBCL. Baseline clinical and tumor characteristics are summarised in table. The Kaplan-Meier survival analysis was performed on 477 FL patients who received R-CHOP treatment. Age $>$ 60, spleen involved, elevated serum LDH, elevated β2-MG and grade 3B were associated with inferior PFS and OS; while ECOG 3-4 and Ann Arbor stage III/IV disease were associated with inferior PFS. Factors that retained significance on multivariable analysis for PFS were grade 3B (HR 2.08, 95% CI 1.22-3.56, p = 0.0076) , ECOG 3-4 (HR 2.49, 95% CI 0.98-6.32, p = 0.05) and elevated serum LDH (HR 1.68, 95% CI 1.05-2.69, p = 0.03), while for OS, it was only grade 3B (HR 4.67, 95% CI 1.95-11.15, p $<$ 0.001). Genomics showed that FL3B and FL/DLBCL lack mutations in epigenetic regulators CREBBP and KMT2D but exhibit additional copy number variations, such as 1p36.32 losses and 3p21.1 gains, which are linked to poor prognosis. Transcriptomics revealed that with increasing histologic grade, immune-related pathway activity decreases, whereas metabolic pathway activity increases, which may be associated with the upregulation of MYC, IRF4, and BATF expression. **Conclusions:** In summary, these findings define FL3B and FL/DLBCL as biologically and clinically distinct B-cell lymphomas, differing from traditional FL. FL1-2 and FL3A differ in their tumor microenvironments rather than genetic profiles. Research Sponsor: None.

Clinical and genetic characteristics among four subgroups.

Clinical characteristics	FL1-2 (%)	FL3A (%)	FL3B (%)	FL/DLBCL (%)	P
No. of patients	588 (71)	84 (10)	67 (8)	92 (11)	
Age					**<0.0001**
Median years (range)	52 (24-87)	56.5 (28-82)	56 (24-78)	60 (27-87)	
< 60 years	439 (75)	48 (57)	36 (54)	43 (47)	
≥60 years	149 (25)	36 (43)	31 (46)	49 (53)	
ECOG performance status					**0.029**
< 2	549 (93)	82 (98)	60 (90)	79 (86)	
≥2	8 (1)	0 (0)	3 (4)	4 (4)	
Missing	31 (5)	2 (2)	4 (6)	9 (10)	
B symptoms					0.110
Yes	75 (13)	18 (21)	10 (15)	17 (18)	
No	482 (82)	64 (76)	52 (78)	66 (72)	
Missing	31 (5)	2 (2)	5 (7)	9 (10)	
Ann Arbor stage					**0.001**
I–II	98 (17)	19 (23)	20 (30)	25 (27)	
III–IV	445 (76)	58 (69)	39 (58)	51 (55)	
Missing	45 (8)	7 (8)	8 (12)	16 (17)	
POD24					0.078
Yes	97 (16)	8 (10)	17 (25)	18 (20)	
No	436 (74)	65 (77)	46 (69)	60 (65)	
Missing	55 (9)	11 (13)	4 (6)	14 (15)	
Lymph nodes <5					**<0.0001**
Yes	208 (35)	34 (40)	37 (55)	54 (59)	
No	371 (63)	49 (58)	25 (37)	35 (38)	
Missing	9 (2)	1 (1)	5 (7)	3 (3)	
Marrow involved					**0.003**
Yes	80 (14)	16 (19)	4 (6)	3 (3)	
No	504 (86)	63 (75)	60 (90)	88 (96)	
Missing	4 (1)	5 (6)	3 (4)	1 (1)	
Spleen involved					0.295
Yes	139 (24)	25 (30)	14 (21)	15 (16)	
No	407 (69)	54 (64)	47 (70)	65 (71)	
Missing	42 (7)	5 (6)	6 (9)	12 (13)	
FLIPI					0.269
0-1	141 (24)	18 (21)	24 (36)	24 (26)	
2	220 (37)	22 (26)	10 (15)	19 (21)	
3-5	183 (31)	37 (44)	24 (36)	31 (34)	
Missing	44 (7)	7 (8)	9 (13)	18 (20)	
FLIPI2					0.316
0-1	398 (68)	51 (61)	39 (58)	51 (55)	
2	100 (17)	16 (19)	9 (13)	19 (21)	
3-5	64 (11)	13 (15)	10 (15)	11 (12)	
Missing	26 (4)	4 (5)	9 (13)	11 (12)	
LDH(u/L)>UNL					**<0.0001**
Yes	88 (15)	26 (31)	23 (34)	44 (48)	
No	500 (85)	58 (69)	44 (66)	48 (52)	
β2-MG≤3mg/L					0.943
Yes	411 (70)	61 (73)	46 (69)	64 (70)	
No	172 (29)	23 (27)	20 (30)	28 (30)	
Missing	5 (1)	0 (0)	1 (1)	0 (0)	
Genetic alterations					
No. of patients	99	22	10	18	
KMT2D mutation	50 (51)	8(36)	2 (20)	1 (6)	**p<0.001**
CREBBP mutation	39 (39)	7 (32)	0 (0)	2 (11)	**p<0.001**
STAT6 mutation	21 (21)	2 (9)	0 (0)	0 (0)	**p=0.045**
1p36.32 alteration	21(21)	3(14)	5(50)	6(33)	p=0.096
6p22.1 alteration	27(27)	11(50)	3(30)	11(61)	**p= 0.016**
7q22.3 alteration	8(8)	3(14)	7(70)	10(56)	**p<0.0001**
3p21.1 alteration	19(19)	7(32)	4(40)	9(50)	**p<0.0001**

Note: Differences in patient/disease characteristics among groups (FL1-2, FL3A, FL3B and FL/DLBCL respectively) were analyzed using Fisher's exact test for discrete variables and the Kruskal-Wallis H test for continuous variables. DLBCL, diffuse large B cell lymphoma; ECOG, Eastern Cooperative Oncology Group; POD24, progression of disease within 2 years; FLIPI, Follicular Lymphoma International Prognostic Index; HGB, hemoglobin; LDH, lactate dehydrogenase; CRP, C-reactive protein; β2-MG, β2-macroglobulin.

A phase 1 study of KITE-363 anti-CD19/CD20 chimeric antigen receptor (CAR) T-cell therapy in patients (pts) with relapsed/refractory (R/R) B-cell lymphoma (BCL).

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Background: Approximately 30% of pts with R/R LBCL who relapse after CAR T-cell therapy experience CD19 antigen escape (Spiegel et al. *Blood.* 2021).KITE-363 is a bicistronic, autologous CAR T-cell therapy that can potentially prevent CD19 escape through upfront dual targeting of CD19 and CD20. Here we report safety and preliminary efficacy from an open-label, multicenter Phase 1 study of KITE-363 in R/R BCL. **Methods:** Eligible adults had LBCL, indolent NHL, nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), or mediastinal gray zone lymphoma R/R after ≥2 lines of therapy (LoT). Pts with LBCL may have had primary refractory disease after ≥1 LoT. Study included dose escalation (1A) and expansion (1B; LBCL only) cohorts. After lymphodepleting chemotherapy, pts received KITE-363 at dose levels (DLs) 1, 2, or 3 (0.5×10^6, 1×10^6, or 2×10^6 CAR T cells/kg, respectively). Primary endpoints were incidence of dose-limiting toxicities (DLTs; Phase 1A) and investigator-assessed objective response rate (ORR per Lugano; Phase 1B). **Results:** As of 10/14/2024, 41 pts enrolled and 37 received KITE-363 (see table). For pts with LBCL (n = 34), 50% were primary refractory and 44% had IPI 3-4. No DLTs occurred. Grade ≥3 adverse events (AEs) occurred in 76% of treated pts and serious AEs in 49%. Grade 3 cytokine release syndrome (CRS; per Lee et al. 2014) occurred in 1 pt (3%; NLPHL; DL 3); Grade 3 immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 3 pts (8%; 1 DL 2; 2 DL 3); no Grade ≥4 CRS/ICANS occurred. Median onset of ICANS was 6 d with median duration of 5 d, and median onset of CRS was 4 d with median duration of 5 d. Six pts died (5 to progression; 1 to myelodysplastic syndrome concurrent with LBCL relapse, unrelated to KITE-363). At 7.3 months median follow-up, ORR in CAR-naive pts at DL 3 was 87%; complete response (CR) rate was 78%. Among those, all 7 pts with LBCL who were CAR-naive after ≥2 LoT had a CR. Those in DL 3 who were primary refractory (n = 15) had an 80% ORR (CR rate, 67%). Median duration of response was not reached. In all pts at DL 3 (n = 26), median CAR T-cell expansion peak, area under the curve (AUC), and time to peak were 121.5 cells/μL, 711.1 cells/μL×d, and 10 d, respectively. For CAR-naive pts in DL 3, median peak and AUC were 132.2 cells/μL and 819.2 cells/μL×d; medians in those with prior CAR T-cell therapy (n = 3) were 5.7 cells/μL and 85.7 cells/μL×d, respectively. **Conclusions:** No DLTs occurred in Phase 1A. Safety profile of KITE-363 was tolerable, with no Grade ≥3 CRS in pts with LBCL and 2 cases of Grade 3 ICANS at the highest DL. KITE-363 demonstrated high responses in pts with highly refractory BCL, including those with primary refractory disease. Clinical trial information: NCT04989803. Research Sponsor: Kite, a Gilead Company.

Baseline characteristics.

	Treated Pts (N=37)[a]
Median age, y (range)	62 (25-83)
ECOG 1	59
Stage III/IV	73
≥3 prior LoT	41
Prior CAR T-cell exposure	19

[a]Percent unless otherwise specified.

Multi-virus specific T cells to enhance the activity of bispecific antibodies in lymphoma.

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Background: Although Bispecific Antibodies (BsAbs) have the advantage of an "off the shelf" immune approach, their clinical activity relies on the patients' native T-cell population that is impaired by prior chemotherapy and tumor-induced T cell exhaustion. T-cell dysfunction within the TME is one potential mechanism of BsAb resistance (Falchi, L. et. al. Blood), while continuous exposure to bispecific molecules also induces T-cell exhaustion (Phillipp, N. et. al. Blood). A higher frequency of regulatory T cells and increased markers of T cell exhaustion were seen in BsAb non-responders (Cortes-Selva, D. et. al. Blood). Banks of multi-virus specific T cells (MVSTs) have safely controlled viral infections in allogeneic hematopoietic stem-cell transplantation recipients (Tzannou, et. al JCO). Expanded MVSTs have a differentiated phenotype, exhibit immediate effector functions (cytotoxicity and cytokine secretion) and have not produced severe graft versus host disease in hundreds of recipients. We hypothesized that MVSTs would enhance the antitumor activity of BsAbs. **Methods:** To compare the anti-tumor activity of PBMCs and MVSTs, we cocultured GFP-labeled CD20+ BJAB lymphoma cells alone or with healthy donor PBMCs or MVST at a 1:1 ratio, in the presence or absence of CD3xCD20 BsAb. We evaluated T-cell activation using CD69 and CD25 antibodies using quantitative flow cytometry and tumor cell killing by assessing tumor survival at 24 and 48 hours. **Results:** While the addition of both MVSTs and PBMCs alone reduced tumor cell numbers, PBMCs + BsAbs reduced tumor cells to less than 50% of the cultures at 24 hours but the subsequent increase tumor cell numbers indicated lack of effective control. By contrast, MVSTs reduced the frequency of tumor cells from 42.5% at 24 hours and less than 2% by 48 hours. The number of T-cells in PBMCs decreased by 0.88-fold after 48-hours, while MVSTs increased by 2.16-fold in the presence of 1ng/ml BsAb. The number of T cells expressing CD25 increased 6.25-fold with PBMCs and 456.68-fold with MVST in the presence of BsAb. **Conclusions:** We have demonstrated that in combination with BsAb, MVSTs exhibit more rapid effector function and expansion than similarly cultured PBMCs, suggesting they could enhance tumor response depth. Despite using healthy donor PBMCs, which showed a 6-fold increase in activated T cells with BsAb, MVSTs induced 456-fold increase. This significant boost in T cell activation highlights MVSTs' potential to overcome endogenous T cell exhaustion and enhance BsAb therapy. Research Sponsor: National Cancer Institute; 5 P50 CA126752-12 (Heslop).

Tumor cell and T cell numbers after co-culture with PBMC or MVST +/- BsAb.

	Tumor cell numbers		CD3+ T-cell numbers	CD25+ Activated T-cells
	24 hours	48 hours	48 hours	48 hours
BJAB Alone	104,345	101,992		
+ PBMC	104,632	57,094	30,458	5,058
+ PBMC + BsAb 1ng	17,350	37,621	26,665	31,621
BJAB Alone	51,633	69,183		
+ MVST	52,815	19,858	86,545	419
+ MVST + BsAb 1ng	28,259	1,584	186,737	191,348

7005 Oral Abstract Session

WaveLINE-003: Phase 2/3 trial of zilovertamab vedotin plus standard of care in relapsed/refractory diffuse large B-cell lymphoma.

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Background: Outcomes for patients relapsed/refractory (R/R) diffuse large B cell lymphoma (DLBCL) remain poor. Zilovertamab vedotin (ZV) is a novel ROR1-targeting antibody-drug conjugate that has shown promising efficacy in patients with DLBCL. Here we present results of the dose confirmation part of the waveLINE-003 (NCT05139017) trial evaluating ZV plus rituximab and gemcitabine-oxaliplatin (R-GemOx) in pts with R/R DLBCL. **Methods:** The phase2/3 trialwaveLINE-003 enrolled adult participants (pts) with confirmed R/R DLBCL after ≥1 lines of therapy (LOT) who were ineligible for chimeric antigen receptor T-cell therapy (CAR-T), autologous stem-cell transplant (ASCT), or failed such therapies (cohort A). In the dose confirmation phase, eligible pts received ZV (1.5, 1.75, or 2.0 mg/kg) plus R-GemOx Q3W for ≥6 cycles. Primary endpoints were safety and recommended phase 2 dose (RP2D). Secondary endpoints were objective response rate (ORR) and duration of response (DOR) per Lugano 2014 response criteria by central review, and overall survival. **Results:** At data cut-off date (August 1, 2024),40 pts had been enrolled in cohort A to receive R-GemOx plus ZV 1.5 mg/kg (n=17), 1.75 mg/kg (n=16), or 2.0 mg/kg (n=7); 22 (55%) were ≥65 years old, and 8 (20%) relapsed >12 mo. Median number of prior LOTs was 2.0 with 7 (18%) pts receiving prior CAR-T, and 7 (18%) receiving prior ASCT. Median follow-up was 9.8 months (mo). Seven DLTs (1 for ZV [1.5 mg/kg], 2 for ZV [1.75 mg/kg], and 4 for ZV [2.0 mg/kg]) were reported. Treatment-related adverse events (AE) were reported in 39 (98%) pts; the most common being diarrhea (n=18 [45%]), nausea (n=15 [38%]), anemia (n=11 [28%]), and platelet count decrease (n=11 [28%]). Grade ≥3 treatment-related AEs were reported in 26 (65%) pts, the most common being neutropenia (n=9 [23%]), neutrophil count decreased (n=9 [23%]), platelet count decreased (n=9 [23%]), and anemia (n=8 [20%]). Two pts discontinued due to AE (sepsis and respiratory failure, both treatment-related), and 1 pt died due to sepsis (treatment related), all in the 2.0 mg/kg dose cohort. The RP2D was determined to be 1.75 mg/kg. ORR was 27% (3 CR, 1 PR [ZV 1.5 mg/kg]), 56% (8 CR, 1 PR [ZV 1.75 mg/kg]), and 57% (3 CR, 1 PR [ZV 2.0 mg/kg]), with median DOR of 14.4 mo, 8.7 mo and not reached (NR), respectively. Median overall survival was 11.5 mo (ZV 1.5 mg/kg), NR (ZV 1.75 mg/kg), and 7.4 mo (ZV 2.0 mg/kg), with 6-month OS rate of 70.0%, 78.8%, and 68.6%, respectively. **Conclusions:** Zilovertamab vedotin in combination with R-GemOx demonstrated promising efficacy and acceptable safety in R/R DLBCL at the RP2D of ZV of 1.75 mg/kg plus R-GemOx. The study is proceeding to the phase 3 portion randomizing patients to ZV-RGemOx versus RGemOx. Clinical trial information: NCT05139017. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; N/A.

Sintilimab (anti-PD-1 antibody) combined with chidamide (an oral subtype-selective HDACi) followed by P-GemOx regimen in patients with treatment-naïve extranodal natural killer/T cell lymphoma (TN-ENKTL): A multicenter, open-label, single-arm, phase II study (SCENT-2 trial).

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Background: ENKTL is a highly aggressive NHL with a higher incidence in Asia. P-GemOx regimen is one of standard first-line treatment with mildly toxicities. We confirmed that Sintilimab plus Chidamide (SC) is safe and efficacious in patients(pts) with relapsed or refractory (r/r) ENKTL in previous study (SCENT trial). Initiation of SC prior to r/r might further optimize pts outcomes. Therefore, we conducted a prospective study to investigate the efficacy and safety of SC followed by P-GemOx for TN-ENKTL (NCT04994210). Here we present the preliminary results of pts with early stage. **Methods:** This is an investigator-initiated study,-eligible pts were aged 18-80 years with histologically confirmed TN-ENKTL. Pts received 2 cycles of SC (SC×2) with standard doses (part A). Once pts had a CR or PR, 2 cycles of P-GemOx (P-GemOx×2) were administered (part B). If they got SD or PR, pts received P-GemOx×4. All pts accepted involved field radiotherapy (IFRT) after part B. The primary endpoint is the CR rate (CRR) of part A+B. Key secondary endpoints include CRR of part A, duration of CR (DoCR), PFS, OS and safety. According to historical data of P-GemOx, we expected a CRR of 80% and a minimum CRR of 60% after part A + B. A sample size of 47 was required. Pretreatment FFPE tumor and blood samples were analyzed by capture-based NGS targeting lymphoma relevant genes. **Results:** From Aug 2022 to Dec 2024, 47 eligible pts were enrolled from 3 centers in China. Two pts remained on treatment. All pts underwent PET/CT for efficacy evaluation. Across the 46 efficacy-evaluable pts after SC×2, 36 (78.2%) achieved response, including 29(60.3%) CR pts. Median cycles of P-GemOx were 2(1-4). After part B, among the 42 response-evaluable pts, the CRR was 95.2% (40/42), and the ORR was 97.6% (41/42). The median follow-up time was 12.4 (0.2-23.7) months. The 1-year DoCR, PFS, OS rates were 96.2% (95%CI, 75.7-99.5), 97.5% (95%CI, 83.6-99.6), 95.3% (95%CI, 82.2-98.8), respectively. The most common myelotoxicities were neutropenia (97.8%), lymphopenia (89.4%), anemia (74.5%), thrombocytopenia (58.7%), and non-myelotoxicities including appetite (38.3%), nausea (38.3%), lipase increased (31.9%). Most toxicities came from P-GemOx. Three patients died, 2 due to disease progression and 1 due to accident. Tumor DNA data in relation to efficacy will be presented at the meeting. **Conclusions:** Preliminary results from SCENT-2 trial exceeded expected efficacy. It may be a promising chemo-reduced therapeutic and manageable toxicities for this population. Further investigation is needed. Clinical trial information: NCT04994210. Research Sponsor: None.

7007 Oral Abstract Session

Sintilimab (anti-PD-1) plus ifosfamide, carboplatin, and etoposide (ICE) in second-line classical Hodgkin lymphoma (cHL): Results of a multicenter, randomized, controlled, double-blind phase 3 study (ORIENT-21).

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Background: Sintilimab monotherapy for cHL in third-line setting and beyond has been evaluated in a single-arm, phase 2 study ORIENT-1. Here, we present results of the phase 3 study ORIENT-21 evaluating sintilimab plus ICE versus placebo plus ICE as the second-line treatment for cHL. **Methods:** This study enrolled cHL pts who have failed first-line standard chemotherapy. The study has a safety run-in phase to enroll pts receiving sintilimab plus ICE, followed by a randomized phase in which pts were assigned in a 1:1 ratio to receive either sintilimab plus ICE (experimental arm) or placebo plus ICE (control arm) for 6 cycles. Patients without disease progression continued either sintilimab or placebo monotherapy. Stratification factors were age (<50 vs ≥ 50), disease status (relapsed vs refractory), and international prognostic score (IPS, <3 vs ≥ 3). Primary endpoint was complete remission rate (CRR) assessed by investigators according to Lugano 2014 criteria. Secondary endpoints included progression-free survival (PFS), duration of complete remission (DoCR) and safety. **Results:** As of Nov 21, 2024, 81 pts (ITT set: 10 in safety run-in, 34 in experimental arm, 37 in control arm) were enrolled (age≥ 50: 12.3%, IPS≥ 3: 18.5%, relapsed: 56.8%, refractory: 43.2%) with a median follow-up of 38.4 months (range: 0-58). In mITT set (randomized pts, n=71), significant higher CRR was observed in the experimental arm than the control arm (61.8% vs 32.4%, p=0.0295). Consistent results were also observed in ITT set (CRR: 61.4% vs 32.4%, p=0.0105). In mITT and ITT sets, median DoCR was not reached in sintilimab plus ICE (events in 28.6% and 22.2% pts), and was 20.7 months in placebo plus ICE. There were 16 pts in control arm switching to sintilimab monotherapy after disease progression. In ITT set, median PFS was not reached in sintilimab plus ICE (events in 34.1% pts), and was 9.0 months in placebo plus ICE (HR: 0.48, 95% CI: 0.23-1.00). Favorable PFS was observed in CR pts than non-CR pts with either sintilimab plus ICE (HR: 0.22, 95% CI: 0.08-0.63) or placebo plus ICE (HR: 0.15, 95% CI: 0.04-0.52). In safety set (n=80), all pts had treatment-emergent adverse events (TEAEs) while $\geq$grade 3 TEAEs occurred in 81.4% pts with sintilimab plus ICE (n=43) and in 97.3% pts with placebo plus ICE (n=37). Most common $\geq$grade 3 TEAEs were neutrophil count decreased (62.8% vs 70.3%), white blood cell count decreased (53.5% vs 64.9%) and platelet count decreased (51.2% vs 67.6%). TEAEs led to treatment discontinuation in both arms (18.6% vs 13.5%). No TEAE led to death. **Conclusions:** Sintilimab plus ICE significantly improved CRR and showed a trend of favorable PFS compared with placebo plus ICE. The safety profiles were manageable and no new safety signal was observed. Clinical trial information: NCT04044222. Research Sponsor: Innovent Biologics (Suzhou) Co., Ltd.

Results from the completed dose-finding part of phase 2 study of the innate cell engager acimtamig (AFM13) in combination with AlloNK (AB-101) in relapsed or refractory classical Hodgkin lymphoma (LuminICE-203).

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Background: There is an unmet need for new treatment approaches for patients (pts) with relapsed or refractory (R/R) classical Hodgkin lymphoma (HL) who progress following standard systemic therapies. Combining acimtamig (AFM13), a tetravalent bispecific CD30/CD16A innate cell engager (ICE), with AlloNK (AB-101), a cryopreserved, off-the-shelf, cord blood-derived NK cell product, induces antibody-dependent cellular cytotoxicity against CD30+ lymphoma cells. **Methods:** This Phase 2, open-label, multi-center, multi-cohort study (LuminICE-203; NCT05883449) is evaluating the efficacy and safety of acimtamig in combination with AlloNK in pts with R/R HL. An initial dose-finding part with 4 cohorts is investigating 2 doses of acimtamig (200 mg or 300 mg weekly flat dosing for 6 weeks) in combination with AlloNK (dose level 1 [DL1]: 3 doses of 2×10^9 cells on Days 1, 8 and 15; or dose level 2 [DL2]: 1 dose of 4×10^9 on Day 1, followed by 2 doses of 2×10^9 cells on Days 8 and 15), after a standard lymphodepletion up to 3 cycles, followed by a randomized part using a Simon's 2-stage design. The primary endpoint is objective response rate (ORR) assessed by an Independent Radiology Committee (IRC) based on PET-CT per Lugano classification criteria. **Results:** As of 16 December 2024, 24 pts with R/R HL were treated in the initial dose-finding part of the study and were assessed by the IRC for metabolic response. Median (range) age was 42.5 (23–80) years; 16 (67%) were male. All pts in the study were heavily pretreated with chemotherapy, brentuximab vedotin and PD-1 inhibitors; median (range) prior treatment lines was 4.5 (2–13), including previous stem cell transplant in 14 (58%) pts. An ORR of 88% was achieved with 14 (58%) complete responses (CR) (Table). The safety profile was in line with that previously reported, with mostly mild to moderate infusion related reactions as the most common reported treatment-related adverse event (TRAE) in 50% of patients; no fatal TRAEs and no stopping criteria have been observed. The study is ongoing and updated safety and efficacy results, including pharmacokinetic / pharmacodynamic analyses and preliminary results on duration of response will be presented. **Conclusions:** Acimtamig in combination with AlloNK shows promising efficacy with a well-managed safety profile with the potential to address an unmet need in pts with R/R HL who have exhausted standard-of-care treatment options. Clinical trial information: NCT05883449. Research Sponsor: Affimed GmbH and Artiva Biotherapeutics Inc.

Efficacy results of acimtamig plus AlloNK in pts with R/R HL.

Efficacy, n (%) (Best Response per Lugano Criteria)	AlloNK DL1 + 200 mg acimtamig (N=6)	AlloNK DL1 + 300 mg acimtamig (N=6)	AlloNK DL2 + 200 mg acimtamig (N=6)	AlloNK DL2 + 300 mg acimtamig (N=6)	Total dose-finding part (N=24)
CR	4 (67)	3 (50)	4 (67)	3 (50)	14 (58)
ORR	**5 (83)**	**5 (83)**	**6 (100)**	**5 (83)**	**21 (88)**

7009 Rapid Oral Abstract Session

Combination of zanubrutinib (zanu) + venetoclax (ven) for treatment-naive (TN) CLL/SLL: Results in SEQUOIA arm D.

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Background: Zanu monotherapy demonstrated superior progression-free survival (PFS) compared with bendamustine + rituximab in patients (pts) without del(17p) at 26.2-month follow-up and sustained PFS benefit at 5-year follow-up. In a single-arm cohort, zanu monotherapy was also shown to be effective in pts with del(17p). Several CLL studies have demonstrated promising efficacy with the combination of B-cell lymphoma 2 + Bruton tyrosine kinase inhibitors; however, pts with del(17p)/*TP53* mutation comprised a small percentage of or were excluded from study populations. Here, we present results in SEQUOIA (NCT03336333) arm D with zanu + ven in pts with or without del(17p) and/or *TP53* mutation. **Methods:** Arm D is a nonrandomized cohort of the SEQUOIA study in pts aged ≥65 years (or 18-64 years with comorbidities). Pts received zanu (160 mg twice daily) + ven (ramp-up to 400 mg once daily) from cycle 4 to cycle 28, followed by continuous zanu monotherapy until progressive disease (PD), unacceptable toxicity, or meeting undetectable minimal residual disease (uMRD)–guided early zanu or ven stopping rules (CR/CRi and uMRD [$<1\times10^{-4}$ by flow cytometry] in peripheral blood [PB] and bone marrow on 2 consecutive tests ≥12 weeks apart). Efficacy responses were assessed by investigator every 3 cycles until cycle 28, then every 6 cycles with PB MRD assessment. **Results:** Between Nov 2019 and Jul 2022, 114 pts were enrolled: 66 (58%) with del(17p) and/or *TP53* mutation, 47 (41%) without del(17p) and *TP53* mutation, and 1 with missing *TP53* results. In all pts, median age was 67 years (range, 26-87), 64 (56%) were male, 86 (75%) had unmutated IGHV, and 47 (41%) had complex karyotype (≥3 abnormalities). As of Sept 16, 2024, 85 (75%) remained on treatment. The most common reasons for early discontinuation were reaching the uMRD-guided early stopping rules (zanu: 7%; ven: 7%), adverse events (AEs) (zanu: 8%; ven: 6%), and PD (zanu: 5%; ven: 4%). Six pts died (5 due to non–treatment-related AEs; 1 due to PD). Pts with or without del(17p)/*TP53* mutation achieved similar efficacy responses and best PB uMRD (Table). The most common any-grade treatment-emergent AEs (TEAEs) were COVID-19 (54%), diarrhea (41%), contusion (32%), and nausea (30%). The most common grade ≥3 TEAEs were neutropenia (17%), hypertension (10%), diarrhea (6%), and neutrophil count decreased (6%). **Conclusions:** SEQUOIA arm D data demonstrate promising efficacy and tolerability of zanu + ven combination treatment in TN CLL/SLL, regardless of del(17p) and/or *TP53* mutation status. The safety profile of zanu + ven was consistent with results of prior zanu studies, and no new safety signals were identified. Clinical trial information: NCT03336333. Research Sponsor: BeiGene.

	del(17p)− and *TP53* wt n=47	del(17p)+ or *TP53* mut n=66	Total N=114
Median follow-up, mo	30	39	31
24-month PFS rate, %	89	94	92
ORR, n/N (%)	45/46 (98)	65/65 (100)	111/112 (99)
CR/CRi, n/N (%)	23/46 (50)	31/65 (48)	55/112 (49)
Best PB uMRD, %	60	59	59

Phase 1/2 studies of DZD8586 in CLL/SLL patients after covalent or non-covalent BTK inhibitors and BTK degraders.

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Background: New therapies are needed for patients with relapsed or refractory (r/r) CLL/SLL following covalent and/or non-covalent BTK inhibitors. While early clinical data showed encouraging anti-tumor activities from BTK degraders in these patients, resistance mutations to both BTK inhibitors and degraders have already been reported. In addition, concerns with emerging clinical safety signals from these degraders may limit their longer-term clinical use. DZD8586 is a rationally designed LYN/BTK dual inhibitor with high selectivity against other TEC family members. Here we report results from ongoing phase 1/2 clinical studies of DZD8586 in r/r CLL/SLL patients with prior treatment of covalent and/or non-covalent BTK inhibitors as well as BTK degraders. **Methods:** The data from two clinical studies, TAI-SHAN5 (NCT05824585) and TAI-SHAN8 (NCT06539182, CTR20240120), were pooled for the safety and efficacy analysis in patients with CLL/SLL. Modulation of PD biomarkers was evaluated at doses tested. Tumor response was assessed by investigators per iwCLL 2018 or Lugano 2014 criteria as appropriate. **Results:** As of January 3, 2025, a total of 40 patients with r/r CLL/SLL have been enrolled and received DZD8586 at doses ranging from 25 mg to 100 mg once daily (QD). The median age was 64.5 years, 62.5% were male, and 60% had ECOG score of 1 or 2. A total of 30 patients were evaluable for efficacy analysis. The median number of prior therapies was 2 (range 1-8). Most common prior CLL/SLL therapies included BTK inhibitor (76.7%), and Bcl-2 inhibitor (43.3%). Patients previously treated by non-covalent BTK inhibitor (13.3%) and BTK degrader (13.3%) were also reported. Across all dose levels, 15 out of 30 patients achieved tumor response, with objective response rate (ORR) of 50%. At the recommended phase 2 dose (RP2D) of 50 mg QD, 9 out of 14 patients achieved tumor response, with ORR of 64.3%. Efficacy was observed in patients with prior BTK inhibitor treatment (ORR 52.2%), and Bcl-2 inhibitor treatment (ORR 46.2%). Seventy five percent patients who received prior BTK degrader treatment achieved partial response. As of the data cut-off date, the longest responder was on therapy for 12.1 months. Deepening response was observed with longer treatment time. DZD8586 was well tolerated across the doses investigated. At the RP2D, the most common ≥grade 3 TEAEs were neutropenia (15%) and pneumonia (10%). No major bleeding or atrial fibrillation was reported. No grade 4/5 AEs reported. **Conclusions:** DZD8586 showed encouraging anti-tumor activity with a well tolerated and manageable safety profile in heavily pre-treated CLL/SLL patients, including patients with prior covalent BTKi, non-covalent BTKi, BTK degrader and Bcl-2 inhibitor treatment. PK/PD results confirmed dose/exposure-dependent pathway inhibition by DZD8586. The updated data will be presented at the meeting. Clinical trial information: NCT06539182, NCT05824585. Research Sponsor: None.

7011 Rapid Oral Abstract Session

SEQUOIA 5-year follow-up in arm C: Frontline zanubrutinib monotherapy in patients with del(17p) and treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

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Background: Zanubrutinib (zanu) is a next-generation Bruton tyrosine kinase inhibitor that is approved for 5 indications, including CLL/SLL. Initial results from the SEQUOIA study (NCT03336333), at a median follow-up of 26.2 mo, demonstrated superior progression-free survival (PFS) by independent review with zanu vs bendamustine + rituximab (arms A and B) in patients (pts) with treatment-naive (TN) CLL/SLL without del(17p) as well as high overall response rate (ORR) and PFS benefit in pts with del(17p) (arm C). Additionally, the 5-y follow-up in arm A demonstrated durable PFS benefit, with estimated 54- and 60-mo PFS rates of 80% and 76%, respectively. Here we report updated results in SEQUOIA arm C, in pts with del(17p), after approximately 5 y of follow-up (data cutoff: Apr 30, 2024). **Methods:** Arm C is a non-randomized cohort of SEQUOIA pts with del(17p) that received zanu monotherapy. Investigator-assessed PFS, overall survival (OS), ORR, and safety/tolerability were evaluated. Adverse events (AEs) were recorded until disease progression or start of next-line therapy. **Results:** Between Feb 2018 and Mar 2019, 111 TN ptswith del(17p) were enrolled to receive zanu. The median age was 71 y (range, 42-87 y), 79 (71%) were male, 67 (60%) were IGHV unmutated, and 47 (42%) had both del(17p) and *TP53* mutation. At a median follow-up of 65.8 mo (range, 5-75 mo), median PFS was not reached. The estimated 60-mo PFS rate was 72.2% (62.4%-79.8%), or 73.0% (63.3%-80.6%) when adjusted for COVID-19. Median OS was also not reached. The estimated 60-mo OS rate was 85.1% (76.9%-90.6%), or 87.0% (79.0%-92.1%) when adjusted for COVID-19. The ORR was 97.3%, and the complete response/complete response with incomplete hematologic recovery rate was 18.2%. Zanu treatment was ongoing in 62.2% of pts. The most common causes for treatment discontinuation were AEs and progressive disease (in 17.1% and 15.3%, respectively). Key AEs of interest (AEI) included any-grade infection (82%), bleeding (60%), neutropenia (19%), hypertension (18%), anemia (9%), thrombocytopenia (8%), and atrial fibrillation/flutter (7%). Grade ≥3 AEI included infection (33%), neutropenia (16%), hypertension (8%), bleeding (6%), atrial fibrillation/flutter (5%), and thrombocytopenia (2%). **Conclusions:** With this 5-y follow-up in SEQUOIA, the efficacy of zanu in TN higher-risk pts with del(17p) was maintained, and pts continue to demonstrate PFS benefits consistent with the randomized cohort of pts without del(17p) (arm A). Additionally, with longer-term follow-up, no new safety signals were identified. This update, in the largest cohort of uniformly treated pts with del(17p), suggests that zanu remains a valuable frontline treatment option for patients with or without del(17p) CLL/SLL. Clinical trial information: NCT03336333. Research Sponsor: BeiGene.

A phase 1/2 study to evaluate the safety and efficacy of XNW5004, a selective EZH2 inhibitor, in subjects with relapsed/refractory non-Hodgkin lymphoma.

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Background: Prognosis of relapsed/refractory (R/R) non-Hodgkin Lymphoma (NHL) which has progressed on standard therapy remains poor. EZH2 is a methyltransferase playing crucial roles in gene regulation and epigenetic modifications. Gain-of-function mutations/overexpression of EZH2 has been found in NHL and correlates with disease progression. XNW5004 is a small molecule, highly selective inhibitor of EZH2. Here, we report the safety and efficacy of XNW5004 in subjects with R/R NHL from a phase 1/2 study. **Methods:** Subjects with histologically confirmed, R/R NHL who has received ≥ 2 lines of systemic therapies were eligible to enroll in this multicenter, open label, dose escalation and dose expansion study in China. Standard 3+3 design with accelerated titration was used for dose escalation in 6 doses of XNW5004 from 100mg to 2000mg, PO, BID. 800mg BID and 1200mg BID were selected for dose expansion in subjects with follicular lymphoma (FL) and peripheral T cell lymphoma (PTCL). **Results:** As of Dec 18, 2024, 120 subjects were enrolled (escalation:19, expansion: 101) including 51 FL and 58 PTCL. Median follow-up was 17.4 months (mos). 87.4% of the subjects had an Ann Arbor Stage of III-IV at baseline. The median lines of prior systemic therapy were 3. 93.8% of the FL subjects received anti-CD20 antibody, 68.8% were POD24 (progression of disease within 24 months of diagnosis). 91.7% of the PTCL subjects received HDAC inhibitor prior to enrollment. Any grade treatment-emergent adverse events (TEAEs) in ≥10% subjects included diarrhea, anemia, WBC count decreased, platelet count decreased, vomiting, nausea, and neutrophil count decreased. No DLT was observed. In dose escalation phase, ORR and DCR of the 16 evaluable subjects across doses was 56.3% and 87.5%, respectively. Median progression-free survival (mPFS) was 9.2 mos. Median duration of response (mDOR) and median overall survival (mOS) were not reached. In dose expansion phase, 1200mg BID was selected as RP2D. At 1200 mg BID, ORR in all FL, EZH2 wild type FL, and EZH2 mutant FL was 66.7%, 63.2%, and 70%, respectively. mPFS and mDOR in all FL was 10.8 mos and 7.4 mos, respectively. mOS was not reached. ORR in FL with POD24 was 56.5%. ORR in FL previously treated with CAR-T was 66.7%. ORR in FL previously received autologous stem cell transplantation was 100%. At 1200 mg BID, ORR in all PTCL, PTCL-NOS, and PTCL-AITL was 70.3%, 72%, and 68.2%, respectively. In all PTCL, mPFS was 15.7 mos and mDOR was 13.9 mos. mOS was not reached. **Conclusions:** XNW5004 has shown a well-tolerated safety profile and promising efficacy in different types of NHL. Pivotal studies of XNW5004 monotherapy in PTCL are ongoing. Clinical trial information: NCT06558513. Research Sponsor: Evopoint Biosciences, Co. Ltd.

7013 Rapid Oral Abstract Session

CD79b-targeted antibody-drug conjugate (ADC) SHR-A1912 in combination with rituximab, gemcitabine, and oxaliplatin (R-GemOx) in relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL): Data from a phase 1b/2 study.

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Background: Patients (pts) with transplant-ineligible r/r DLBCL have an unmet need, with an objective response rate (ORR) of around 40%. CD79b, a key component of the B-cell receptor and expressed in a majority of mature malignancies of B-cell origin, is an attractive therapeutic target for DLBCL. We initiated a phase 1b/2 study to assess the safety and efficacy of SHR-A1912, a novel CD79b-targeted ADC, in combination with chemotherapy in pts with r/r or treatment-naive DLBCL. Here, we report the findings of SHR-A1912 plus R-GemOx regimen in the r/r DLBCL cohort. **Methods:** The study comprised a dose-escalation (D-ESC) and dose-expansion (D-EXP) phase 1b part and an efficacy-expansion phase 2 part. For the r/r DLBCL cohort, pts who had failed to respond to or had progressed after ≥1 prior anti-cancer therapy were enrolled to receive SHR-A1912 plus R-GemOx (Q3W, IV) for up to 8 cycles, followed by maintenance therapy with SHR-A1912 until disease progression, intolerable toxicity, or investigator decision. The primary endpoints were safety and recommended phase 2 dose (RP2D) in the phase 1b part and ORR in the phase 2 part. **Results:** As of cutoff date on Nov 19, 2024, 41 pts were enrolled (n=7, 8, and 26 in D-ESC, D-EXP, and phase 2 parts). During D-ESC, DLTs were observed in 2 of the 4 pts receiving 2.7 mg/kg of SHR-A1912 plus R-GemOx (1 with grade 4 decreased platelet count and 1 with grade 3 asthenia and grade 3 decreased appetite); subsequently, 3 pts were given 1.8 mg/kg of SHR-A1912 plus R-GemOx, and no DLTs occurred. 1.8 mg/kg was determined to be the RP2D of SHR-A1912 when combined with R-GemOx. Totally, 37 r/r DLBCL pts received 1.8 mg/kg of SHR-A1912 plus R-GemOx in the study. Grade ≥3 treatment-emergent adverse events occurred in 21 (56.8%) out of the 37 pts, with the most common being hematological toxicities (decreased platelet count, 29.7%; decreased white blood cell count, 24.3%; decreased neutrophil count, 21.6%; anemia, 13.5%; decreased lymphocyte count, 10.8%). Among the 37 pts, 19 achieved a complete response (CR), and 8 achieved a partial response. The ORR was 73.0% (95% CI, 55.9–86.2), and the CR rate was 51.4% (95% CI, 34.4–68.1). 23 (85.2%) of the 27 responders showed an objective response at their first anti-tumor assessment, with a time to response of 1.4 mo (95% CI, 1.2–3.5). All responses were ongoing as of the cutoff date. **Conclusions:** Inpts with r/r DLBCL, SHR-A1912 at 1.8 mg/kg in combination with R-GemOx was tolerable and demonstrated a safety profile consistent with its individual components. This combination exhibited potent anti-tumor activity, as well as rapid and durable responses. Clinical trial information: NCT06104553. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

Fixed duration subcutaneous (SC) mosunetuzumab (Mosun) in patients with previously untreated high-tumor burden follicular lymphoma (FL): Interim results from the phase II MorningSun study.

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Background: Mosun is a CD20xCD3 bispecific antibody that can be administered in the outpatient setting for a fixed duration. Intravenous Mosun is approved for the treatment of relapsed/refractory FL after ≥2 prior lines of therapy. Mosun SC achieved high response rates with manageable safety in patients with 3L+ FL in a pivotal Phase II study (Bartlett et al. ASH 2024). We report the efficacy and safety of Mosun SC in patients with previously untreated high-tumor burden FL in the Phase II MorningSun study (NCT05207670). **Methods:** Patients with previously untreated high-tumor burden FL, per GELF criteria, were enrolled into this cohort. Mosun SC was administered with step-up dosing in Cycle (C)1 (Day [D]1, 5mg; D8, 45mg; D15, 45mg) then 45mg on D1 for up to 17 cycles (1 year; 21-day cycles). Patients with a partial or complete metabolic response (CMR) after C17 could receive additional Mosun maintenance therapy (45mg every 8 weeks for up to 1 year). Corticosteroid prophylaxis to reduce the risk of cytokine release syndrome (CRS) was mandatory in C1–2 and optional thereafter. The primary endpoint was progression-free survival (PFS) rate at 24 months. Key secondary endpoints included objective response rate (ORR), time to response (TTR), and safety. **Results:** As of May 29, 2024, 102 patients were enrolled; 55 patients had completed initial treatment (17 cycles), 31 had discontinued (most commonly due to progressive disease [n=19] and adverse events [AEs; n=4]), and 16 were ongoing initial treatment. Forty-two patients received maintenance treatment, and this was ongoing in 38 patients. Median age was 65 years (range: 24–86); 52.0% of patients were female. Most patients had Ann Arbor stage III/IV (91.2%) and a FLIPI score ≥2 (78.4%). Median duration of follow-up was 13.9 months. The 12-month PFS rate was 82.8% (95% confidence interval [CI]: 73.0–89.3). ORR was 87.3%; 60.8% of patients had a CMR. Among the 89 patients with a response, the median TTR was 2.7 months (range: 1.2–5.8). The most common AEs (≥30%) were injection-site reaction (57.8%), fatigue (42.2%), CRS (34.3%), headache (31.4%), and nausea (30.4%). Grade ≥3 AEs and serious AEs (SAEs) were reported in 44.1% and 29.4% of patients, respectively. CRS events were all Grade 1/2 and SAE of CRS occurred in 10.8% of patients (Table); all events resolved. **Conclusions:** Mosun SC demonstrated promising efficacy in patients with previously untreated high-tumor burden FL. The manageable safety profile, including rate of CRS, supports the administration of fixed duration Mosun SC in an outpatient setting. Additional data, including cytokine profiling and T/B/NK dynamics, will be presented. Clinical trial information: NCT05207670. Research Sponsor: Genentech, Inc.

CRS events, n (%)	Patients N=102
Any grade	**35 (34.3)**
Grade	
1	30 (29.4)
2	5 (4.9)
SAE	**11 (10.8)**
Management	
Steroids	8 (7.8)
Tocilizumab	6 (5.9)
Steroids + tocilizumab	3 (2.9)
Fluids	3 (2.9)
ICU admission	2 (2.0)

7015 Rapid Oral Abstract Session

Glofitamab plus gemcitabine and oxaliplatin (Glofit-GemOx) in patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): 2-year (yr) follow-up of STARGLO.

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Background: Glofitamab, a CD20:CD3 bispecific antibody, has shown durable responses as fixed duration monotherapy in R/R DLBCL after ≥2 prior lines of therapy (LOT; Dickinson et al. NEJM 2022). When combined with GemOx, glofitamab has shown overall survival (OS) and progression-free survival (PFS) benefits in autologous stem cell transplant (ASCT)-ineligible R/R DLBCL (Abramson et al. Lancet 2024). We present updated efficacy and safety of Glofit-GemOx vs rituximab (R)-GemOx in pts with R/R DLBCL after ≥1 LOT from the Phase 3 STARGLO trial (NCT04408638), including landmark analyses of pts in complete remission (CR). **Methods:** Pts were randomized 2:1 to Glofit-GemOx (8 cycles plus 4 cycles glofitamab monotherapy) or R-GemOx (8 cycles) and stratified by no. of prior LOT (1 vs ≥2) and refractoriness to last therapy. After obinutuzumab pretreatment, glofitamab was given in Cycle (C) 1 as weekly step-up doses (2.5/10mg) then 30mg target dose every 21 days from C2 Day 1. Pts with only 1 prior LOT must have been ASCT-ineligible. Primary endpoint was OS. Secondary endpoints included independent review committee (IRC)-assessed PFS and CR rate. A landmark analysis of pts in CR at end of treatment (EOT) was performed. **Results:** Of 274 pts (Glofit-GemOx, n=183; R-GemOx, n=91), 172 (62.8%) had 1 prior LOT, 102 (37.2%) had ≥2 prior LOT, 153 (55.8%) were primary refractory, and 166 (60.6%) were refractory to last therapy. Baseline characteristics were unchanged and balanced across arms. With 2 yrs follow-up (data cut off: June 17, 2024; median follow-up: 24.7 months [mo]), Glofit-GemOx continued to confer superior OS benefits (median: not evaluable [NE] vs 13.5 mo; HR 0.60, 95% CI: 0.42–0.85), median IRC-assessed PFS (13.8 vs 3.6 mo; HR 0.41, 95% CI: 0.29–0.58), and CR rate (58.5 vs 25.3%) vs R-GemOx. For Glofit-GemOx-treated pts in CR (n=107), median duration of CR was not reached (95% CI: 27.2–NE; median CR follow-up, 18.2 mo [range: 15.2–19.3]). In pts with a CR at EOT (n=82), the OS and PFS rates 1 yr after EOT were 89.3% and 82.4%, respectively. The Glofit-GemOx safety profile was unchanged. Cytokine release syndrome (CRS) was the most common adverse event in glofitamab-exposed pts (Grade [Gr] 1, 32.0%; Gr 2, 10.5%; Gr 3, 2.3%). Events consistent with immune effector cell-associated neurotoxicity syndrome occurred in 4 pts (all concurrent with CRS; most Gr 1–2 [n=3]). Exploratory biomarker and immune recovery data will be presented. **Conclusions:** With 2 yrs follow-up, Glofit-GemOx sustained a clinically meaningful benefit in OS and PFS vs R-GemOx in ASCT-ineligible pts with R/R DLBCL, with most (82%) pts in CR at EOT still in remission. The safety profile was consistent with known risks of each drug. The updated analyses support the long-lasting remissions and maintained OS benefit in pts with R/R DLBCL treated with fixed duration Glofit-GemOx. Clinical trial information: NCT04408638. Research Sponsor: F. Hoffmann-La Roche Ltd; N/A.

7016 Rapid Oral Abstract Session

Worldwide experience of chronic active EBV infection: Retrospective cohort study.

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Background: Chronic active Epstein-Barr virus disease (CAEBV) is a rare, life-threatening disorder characterized by systemic inflammation and clonal proliferation of EBV-infected T or NK cells. The disease exhibits clinical variability, ranging from mild to rapidly progressive and fatal forms. Despite advances in understanding its features, most studies are based on small cohorts or case reports, with no standardized diagnostic or therapeutic guidelines. Regional differences in age distribution, clinical characteristics, and treatment strategies exist. This study analyzed 763 CAEBV cases to summarize global experiences and propose a new classification and risk stratification model. **Methods:** This retrospective cohort study analyzed 763 CAEBV cases from 57 centers across 9 countries, including data from a systematic review and institutional data from Tongji Hospital, Wuhan, China. A novel classification system and risk stratification model were developed based on clinical and pathological data. Treatment outcomes, including allo-HSCT, anti-PD-1 therapy, and chemotherapy, were evaluated using survival analysis and multivariate Cox regression. **Results:** Among the 763 cases, 98.1% were from East Asia (China 53%, Japan 41%, Korea 4%), with smaller contributions from America (2%) and other countries. The median age at diagnosis was 18 years, with 53.7% of cases in those under 20. EBV-infected T cells were seen in 52% of cases, NK cells in 38%, and mixed infections in 10%. A new classification system divided systemic CAEBV (sCAEBV) into four subtypes: cutaneous (10%), gastrointestinal (4.6%), vascular (3.2%), and not otherwise specified (82.2%). Gastrointestinal involvement was associated with the poorest prognosis, necessitating early intervention. Treatment data from 399 patients showed that allo-HSCT is the only curative option, significantly improving survival rates. For high-risk patients unable to undergo allo-HSCT, anti-PD-1 therapy showed potential as an adjunctive treatment. A risk stratification model categorized patients into low-risk, high-risk, and very high-risk groups. Low-risk patients were monitored and treated with anti-PD-1 therapy, high-risk patients received either anti-PD-1 therapy or allo-HSCT, and very high-risk patients were advised to undergo allo-HSCT. **Conclusions:** This study represents the largest global cohort of CAEBV cases, with 763 cases from 9 countries. A novel classification system for sCAEBV was proposed, highlighting gastrointestinal involvement as a poor prognostic factor. Based on clinical symptoms and laboratory findings, a new risk stratification model was developed, guiding personalized treatment. Allo-HSCT remains the only curative treatment, significantly improving survival, while anti-PD-1 therapy offers potential as an adjunctive treatment for high-risk patients who cannot undergo allo-HSCT. Research Sponsor: This study was supported by the National Natural Science Foundation of China, the Natural Science Foundation of Hubei Province.

Efficacy and safety of first-line ibrutinib plus venetoclax in patients with mantle cell lymphoma (MCL) who were older or had *TP53* mutations in the SYMPATICO study.

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Background: The phase 3 SYMPATICO study evaluated ibrutinib (Ibr) combined with venetoclax (Ven) in 3 cohorts of patients (pts) with MCL: an open-label safety run-in phase to evaluate concurrent initiation of Ibr+Ven in relapsed/refractory (R/R) MCL; a randomized phase to evaluate Ibr+Ven vs Ibr+placebo (Pbo) in R/R MCL; and an open-label cohort to evaluate first-line Ibr+Ven in treatment-naive (TN) MCL. Primary analysis of the randomized phase showed superior PFS with Ibr+Ven vs Ibr+Pbo in pts with R/R MCL (Wang M et al, *Lancet Oncol*, in press). Here, we report efficacy and safety of Ibr+Ven in pts with TN MCL in older pts (≥65 y) or younger pts with a *TP53* mutation (*TP53*mut) (≥18 y) who are in need of novel and better tolerated treatment options. **Methods:** Older pts (≥65 y) or pts with a *TP53*mut with TN MCL received oral Ibr 560 mg once daily and Ven (5-wk ramp-up to 400 mg once daily) for 2 y, then single-agent Ibr 560 mg until PD or unacceptable toxicity. Primary endpoint was complete response (CR) rate assessed by investigator per Lugano. Key secondary endpoints included overall response rate (ORR), duration of response (DOR), PFS, OS, and time to next treatment. Subgroup analyses were performed according to *TP53*mut status and age. **Results:** In total, 78 TN MCL pts were enrolled. At baseline, 83% of pts were ≥65 y, 97% had ECOG PS of 0–1, 45% had high-risk simplified MIPI score, 31% had bulky disease (≥5 cm), 78% had bone marrow involvement, 46% had splenomegaly, and 37% had *TP53*mut. Median time on study was 40.5 mo (range, 0.6+–46.9). CR rate was 69% (95% CI, 58–79), and ORR was 95% (95% CI, 87–99). Median DOR was 37.1 mo (95% CI, 30.3–NE). Median PFS was 40.2 mo, and 3-y OS was 79%. CR rate was 76% in pts ≥65 y without *TP53*mut, 44% in pts ≥65 y with *TP53*mut, and 73% in pts <65 y with *TP53*mut; median PFS was 40.2, 22.0, and 15.4 mo, and 3-y OS was 85%, 66%, and 73%, respectively (Table). Median duration of treatment was 24.0 mo (range, 0.3–46.9). Most common AEs were diarrhea (49%), fatigue (37%), neutropenia (35%), and COVID-19 (32%). Most common grade ≥3 AE was neutropenia (29%). **Conclusions:** First-line Ibr+Ven showed promising efficacy with high CR rates and durable remissions in pts with TN MCL with and without *TP53*mut. Safety was acceptable and trended better in younger pts. Ibr+Ven may be an option for older pts with TN MCL or pts of any age with *TP53*mut. Clinical trial information: NCT03112174. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.

Outcomes (95% CI)	Without *TP53*mut n=44	With *TP53*mut n=29	≥65 y without *TP53*mut n=42	≥65 y with *TP53*mut n=18	<65 y without *TP53*mut n=2	<65 y with *TP53*mut n=11	Total N=78
CR rate, %	77 (62–89)	55 (36–74)	76 (61–88)	44 (22–69)	100 (16–100)	73 (39–94)	69 (58–79)
ORR, %	98 (88–100)	90 (73–98)	98 (87–100)	89 (65–99)	100 (16–100)	91 (59–100)	95 (87–99)
Median PFS, mo	40.2 (37.2–NE)	22.0 (9.2–NE)	40.2 (37.2–NE)	22.0 (11.3–NE)	NR (11.1–NE)	15.4 (8.2–NE)	40.2 (29.4–NE)
3-y OS, %	86 (71–93)	68 (47–82)	85 (70–93)	66 (39–83)	100 (100–100)	73 (37–90)	79 (68–86)

Incidence of infections, cardiac events, neurological toxicity and cytokine response syndrome (CRS) in patients treated with chimeric antigen receptor (CAR) T cell therapy: A 3-year nationwide analysis.

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Background: CAR-T cell therapy represents a notable advancement in treating relapsed/refractory (R/R) hematological malignancies. Adverse events include CRS, infections, and neurological and cardiac complications. While there are reports from major academic institutions on the adverse effects of CAR-T therapy, we used data from the National Inpatient Sample (NIS) to gather national estimates of complications related to CAR-T therapy. **Methods:** A retrospective study was conducted to analyze patients who underwent CAR-T cell therapy by utilizing appropriate ICD-10-PCS procedure codes (XW033C3, XW043C3, XW23346, XW24346, XW23376, and XW24376) from NIS 2019 to 2021. Data regarding infections, toxic encephalopathy (a surrogate for neurological toxicity), and adverse cardiac events were extracted using relevant ICD-10-CM diagnostic codes. Patients experiencing various grades of CRS were identified through specific ICD-10 codes available in 2021 (Grades 1-5: D89.831-D89.835). **Results:** This study analyzed 6515 patients who underwent CAR-T cell therapy from January 2019 to December 2021. Among them, 60.7% were male. 74.6% were Caucasian, 11.7% were Asian and 6.7% were African American. 49.8% of patients had private insurance, 36.2% had Medicare, and 8.6% had Medicaid. 6.8% of patients were diagnosed with pneumonia, while sepsis occurred in 7.4% of patients and 3% experienced septic shock. 19.4% of patients experienced cardiac arrhythmias, and major cardiovascular events were recorded in 4.7% of the cohort. Acute myocardial infarction and stroke were documented in 0.6 and 1.2% of patients, respectively. Toxic encephalopathy was reported in 19.7% of patients. Among 2235 patients identified to have received CAR-T in 2021, 59.7% developed CRS. Grade 1 and grade 2 CRS were reported in 32% and 21% of patients, respectively, while grade 3 and grade 4 reactions were noted in 4.7% and 2% of patients, with no cases of grade 5 identified. The mean total cost of hospitalization was 308,364$, and the mean length of hospital stay was 19.5 days. The overall in-hospital mortality rate was 3.4%. **Conclusions:** Our study describes real-world outcomes from a large dataset of CAR-T patients. Infections pose a significant challenge with CAR-T therapy, highlighting the importance of early detection and timely antimicrobial treatment. CRS is common, with a 60% incidence, similar to previous clinical trials (55%). Immediate management is crucial for addressing CRS toxicity. Adverse neurological and cardiovascular incidents are often reported, emphasizing the need for meticulous monitoring and coordinating multidisciplinary care plans. The financial burdens also bear mentioning: CAR-T therapy costs significantly higher than autologous stem cell transplants. Further studies to address these issues are warranted. Research Sponsor: None.

Association of enrichment of CD7⁺CXCR3⁺ CAR T cells in infusion products with remission in relapsed or refractory diffuse large B-cell lymphoma.

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Background: Chimeric antigen receptor (CAR) T-cell therapy is the standard of care for relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL), yet more than half of patients do not achieve durable remission. Identifying predictive biomarkers in CAR T-cell infusion products (IPs) could guide strategies to improve outcomes. **Methods:** This was a single-centre observational study conducted at Lausanne University Hospital (CHUV), Switzerland. IPs from 13 patients with R/R DLBCL who underwent CAR T-cell therapy were analyzed using a 39-marker mass cytometry panel. We compared phenotypic and functional markers between long-term responders (R) and non-responders (NR). Both unsupervised and supervised analyses were performed. Additionally, longitudinal blood samples collected over 30 days after infusion were examined to track CAR T-cell subpopulation dynamics. **Results:** At a median follow-up of 13.5 months, median progression-free survival (PFS) was 13.3 months (95% CI 9.7–24.3) in R (n=8) versus 3.5 months (95% CI 0.5–5.4) in NR (n=5) (hazard ratio 56.67 [95% CI 7.3–439.3]; p=0.0001). A subset of CD3⁺CXCR3⁺CD7⁺ CAR T-cells—present within both CD4⁺ and CD8⁺ subsets—was significantly enriched in R. These cells showed increased expression of perforin, granzyme B, and NKG2D (restricted to CD8⁺ cells). In contrast, NR had a higher frequency of CXCR3⁺CD7⁺LAG3⁺ CAR T-cells. Surface expression levels of CD3, CD7, CXCR3, and NKG2D were higher in R, whereas LAG3, Ki67, and CD71 were elevated in NR. A predictive cut-off ratio of CD3⁺CXCR3⁺CD7⁺LAG3⁺CAR⁺ T-cells <0.83 and CD3⁺CXCR3⁺CD7⁺NKG2D⁺CAR⁺ T-cells >1.034 yielded a predictive accuracy of 0·92. Serum CXCL9 and CXCL10 concentrations did not differ between groups. **Conclusions:** The enrichment of CD7⁺CXCR3⁺ CAR T-cells and expression of NKG2D in R, as opposed to elevated LAG3 and CD71 in NR, emerged as robust correlates of therapeutic outcome. These findings could inform the development of biomarker-driven strategies to optimize CAR T-cell products and enhance the likelihood of sustained remission.
Research Sponsor: CHUV pôle prioritaire.

Clinical outcomes of cytomegalovirus infection among patients receiving chimeric antigen receptor T cell therapy.

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Background: Chimeric antigen receptor T (CAR-T) cell therapy is a transformative treatment for hematologic malignancies, including multiple myeloma (MM), non-Hodgkin lymphoma (NHL), and acute leukemia (AL). Despite its success, CAR-T therapy is associated with significant toxicities and an increased risk of infections, particularly cytomegalovirus (CMV) infection. CMV infection in CAR-T recipients has been linked to increased non-relapse mortality (NRM) and prolonged hospital stays; however, comprehensive data on its clinical impact remains limited. This study aimed to evaluate the clinical impact of CMV infection on outcomes in CAR-T therapy recipients. **Methods:** This retrospective cohort study utilized the HCUP-National Readmission Database (NRD) 2021 database to analyze adult hospitalized patients (≥18 years) who underwent CAR-T cell therapy for MM, NHL, or AL in the USA. Patients with a prior CMV diagnosis or discharged in the last three months of 2021 were excluded. Propensity score matching (PSM) was applied to balance baseline characteristics, and weighted estimates were used for outcome analysis. The primary outcome was all-cause mortality within three months post-discharge. Secondary outcomes included length of hospital stay (LOS) and CAR-T-related complications. **Results:** A total of 1806 hospitalizations met the inclusion criteria. The mean age was 61.9 years, with a male majority of 64.4%. The underlying disorders were NHL (73.7%), MM (21.6%), and AL (4.7%). The incidence of CMV infection during the index hospitalization was 2.2%, increasing to 4.2% within three months post-CAR-T therapy. Matched analysis showed higher three-month mortality in CMV-infected patients (15.8%) compared to non-CMV patients (2.5%) (risk ratio 6.32, 95% CI: 1.46-27.30, p=0.004). CMV-infected patients had a significantly longer mean LOS (41.5 vs. 15.9 days, adjusted mean difference 15.5 days, 95% CI: 6.7-24.2, p=0.001). CMV infection was significantly associated with encephalopathy (risk ratio 13.21, 95% CI: 1.66-105.2, p=0.015), while other complications such as cytokine release syndrome (CRS), AKI, and transaminitis did not show a statistically significant association. **Conclusions:** CMV infection in CAR-T cell therapy recipients is associated with increased mortality, prolonged hospitalization, and risk of encephalopathy. These findings underscore the need for vigilant CMV surveillance and targeted management strategies to improve patient outcomes. Research Sponsor: None.

Characterization of mechanisms driving CD20 loss in patients with relapsed or refractory large B-cell lymphoma treated with glofitamab.

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Background: Glofitamab is a CD20xCD3 T-cell engaging bispecific monoclonal antibody that redirects T cells to eliminate malignant B cells in patients (pts) with relapsed or refractory non-Hodgkin Lymphoma. We characterized mechanisms driving CD20 loss in pts from a Phase I/II trial (NP30179) receiving Glofitamab monotherapy for Relapsed/Refractory Large B-cell lymphoma (R/R LBCL). **Methods:** Pts with LBCL and ≥2 prior therapies received obinutuzumab pretreatment followed by fixed-duration Glofitamab at the approved dose in phase I/II trial NP30179 (NCT03075696) (Dickinson, et al. N Engl J Med 2022). Tumor biopsies were collected prior to treatment (Baseline, BL) in 128 pts, during treatment (tx) or at progression (PD) in 11 pts. The proportion of CD20+ tumor cells was determined by immunohistochemistry (IHC) using a dual CD20+ PAX5+ assay. Expression of *MS4A1*, the gene encoding CD20, was measured by RNA-sequencing (RNA-seq) in 105/139 biopsies. *MS4A1* mutation profiling was performed by next-generation sequencing on Cell-free circulating tumor DNA (ctDNA) from 133 pts. We subsequently characterized the functional consequences of identified mutations in vitro. **Results:** CD20 levels evaluated by IHC were high (>75% CD20+ tumor cells) in 110/128 BL biopsies. At BL, CD20 loss (<5% CD20+ tumor cells) was seen in 4/128 (3.1 %) biopsies. For 11 pts with BL and on-tx or at-PD biopsies, 7/11 (63.6%) pts presented CD20 loss on-tx/at-PD and 4/11 (36.4%) did not. Evaluation of gene expression profile showed a good correlation between CD20 gene and protein expression. Among the 7 pts with CD20 loss on-tx/at-PD biopsies, there were 4 biopsies with available gene expression data, and decreased CD20 expression was identified in 2/4. Evaluation of CD20 mutation revealed 11/134 (8.2%) pts harbored 16 *MS4A1* mutations at BL or on-tx/at-PD. IHC data were available for 8/11 pts at BL where 2/8 presented CD20 loss (<5% CD20+ tumor cells), and for 1 pt at-PD who presented CD20 loss. 12/16 mutations were not previously reported. We characterized 14 mutations in vitro and subsequently demonstrated that 8 frameshift or deletion mutations lead to truncation of the protein, and 4 missense mutations lead to disruption in the transmembrane domain of CD20. These 12 mutations lead to loss of intracellular and extracellular CD20 expression, and abrogation of Glofitamab-mediated cytotoxicity in vitro. **Conclusions:** In pts with R/R LBCL treated with Glofitamab, loss of tumor antigen CD20 expression is one resistance mechanism to Glofitamab. Genetic alterations (fs, del or missense mutations) and transcriptional down-regulation can contribute to loss of CD20 expression and they were both observed in pts treated with Glofitamab. Acknowledgments: The NCT03075696 study is sponsored by F. Hoffmann-La Roche Ltd. Research Sponsor: Roche.

Trends and outcomes by inpatient and outpatient infusion of axicabtagene ciloleucel (axi-cel) in the US for patients (pts) with relapsed/refractory large B-cell lymphoma (R/R LBCL).

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Background: Axi-cel is an autologous chimeric antigen receptor (CAR) T-cell therapy approved for adults with R/R LBCL after ≥ 1 prior line of therapy (LoT). Adverse events, such as cytokine release syndrome (CRS) and neurologic events (NEs), may deter centers from using axi-cel in an outpatient (OPT) setting, though individual centers have observed comparable safety and effectiveness in OPT and inpatient (IPT) care (Furqan et al. *Blood Adv*. 2024). Here, we present safety and effectiveness outcomes of axi-cel by intention to treat in OPT and IPT settings in a multicenter real-world dataset. **Methods:** Pts receiving axi-cel for R/R LBCL in the US from 01/2021-07/2023 with data in the Center for International Blood and Marrow Transplant Research (CIBMTR) registry were eligible for analysis. Pts with prior allogeneic transplant or unknown intended care setting were excluded. Of potential pts, 119 OPT pts were identified from 29 centers where an increasing trend was seen (9.6% of pts in 2021 were OPT, 13.5% in 2022, 22.8% in 2023). Pts were matched to 119 IPT pts by propensity score matching on age, sex, comorbidities, lactate dehydrogenase (LDH), bulky disease, prior LoT, chemosensitivity, and infusion year (see table). **Results:** OPT pts had median age of 63 y (25% ≥ 70), 66% were male, and 67% had ≥ 1 comorbidity. Half (50%) had elevated LDH and 73% had 1 prior LoT. Bulky disease was reported in 3%, and 60% had chemo-resistant disease. Outcomes were analyzed at median follow-up of 12 mo. Safety and effectiveness outcomes were similar between OPT and IPT pts (see table). In multivariate analyses, no differences were found between intended care setting and CRS (odds ratio [OR] 1.09 [95% CI 0.51-2.35]), CRS Gr ≥ 3 (OR 0.57 [0.12-2.60]), NEs (OR 1.14 [0.65-2.00]), or NEs Gr ≥ 3 (OR 0.98 [0.48-2.00]). Among OPT pts, 24% and 50% did not require hospital admission within 30 d and 3 d, respectively. In pts aged ≥ 70 y, only any Gr NEs were higher in the OPT group. **Conclusions:** After matching on key factors that may be used to select pts for OPT infusion, outcomes were comparable between intended care settings. These findings corroborate prior results and support the consideration of axi-cel in appropriate OPT care settings. Research Sponsor: Kite, a Gilead Company.

Outcomes between matched pts with R/R LBCL receiving axi-cel intended for OPT or IPT.

	OPT (n=119)[a]	IPT (n=119)[a]
CRS any Gr / Gr ≥ 3	83 (75−89) / 3 (<1−7)	83 (74−89) / 4 (1−10)
NE any Gr / Gr ≥ 3	47 (38−57) / 19 (12−27)	46 (37−56) / 21 (14−30)
Overall / complete response rates	78 (69−85) / 68 (59−76)	76 (67−83) / 62 (52-70)
Duration of response @ 12 mo	64 (52−74)	69 (58−78)
Progression-free survival @ 12 mo	53 (43−62)	53 (43−61)
Overall survival @ 12 mo	71 (61−78)	72 (62−79)
Non-relapse mortality @ 12 mo	6 (2−11)	4 (1−8)
Hospital admission within 30 days of infusion / median duration (range), d	76 (67−83) / 9 (2−53)	Not Applicable

[a]Percent (95% CI) unless otherwise specified.

Real-world outcomes of axicabtagene ciloleucel (axi-cel) for the treatment of relapsed/refractory (R/R) secondary central nervous system lymphoma (SCNSL).

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Background: Axi-cel is an autologous anti-CD19 CAR T-cell therapy that demonstrated durable, long-term efficacy and manageable safety in R/R LBCL. However, there is paucity of data using axi-cel in SCNSL, a subset associated with poor clinical outcomes. Here, we describe effectiveness and safety outcomes of axi-cel in R/R SCNSL. **Methods:** Patients (pts) receiving commercial axi-cel for R/R active SCNSL from 2018-2023 were selected from the CIBMTR database. Pts with primary CNS lymphoma and diseases other than LBCL were excluded. Outcomes included overall response rate (ORR), complete response (CR) rate, cumulative incidence of relapse (CIR), duration of response (DOR), progression-free and overall survival (PFS and OS), cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) per ASTCT consensus grading, other adverse events, and non-relapse mortality (NRM). Outcomes were analyzed descriptively. **Results:** At May 2024 data cutoff, 65 pts from 28 centers were identified. Median age at infusion was 63 y (range, 21-79) with 66% male and 81% white. Few pts (9/58, 16%) had ECOG PS ≥2; 52/65 (80%) had clinically significant comorbidities. Double-/triple-hit lymphoma was seen in 12/50 pts (24%), and 51/58 (88%) had Stage III/IV disease. CNS sites involved preinfusion were brain (51%), cerebrospinal fluid (12%), epidural space (15%), leptomeninges (11%), eyes (9%), and spinal cord (5%). Median number of prior lines of therapy was 4 (IQR, 3-5); 12/65 pts (18%) had prior autologous stem cell transplantation. Median time from leukapheresis to infusion was 28 days (IQR, 26-34). Bridging therapy was given to 47/65 pts (75%; systemic, 40 [63%]; intrathecal, 12 [19%]; radiation, 17 [27%]). At 48.2-mo median follow-up, ORR was 72% (95% CI, 60-83); CR rate was 51% (95% CI, 38-63). Median (95% CI) DOR, PFS, and OS were 4.0 (2.3-NE), 3.6 (2.2-4.9), and 8.4 mo (6.6-18.2), respectively. CIR was 66% (95% CI, 51-77) at 1 and 2 y. At 2 y and 3 y, PFS (95% CI) was 26% (16-38) and 23% (13-35), respectively, and OS (95% CI) was 36% (24-49) and 32% (20-44). Among pts without progression at 1 y, PFS was 100% and 90% (47-99) at 2 y and 3 y, respectively; OS was 82% (59-93) and 72% (48-86). Grade ≥3 CRS and ICANS occurred in 14% and 37% of pts, respectively (any grade, 81% and 62%). Of 56 pts with CRS and/or ICANS, tocilizumab, corticosteroids, and anakinra were used in 68%, 73%, and 7% of pts, respectively. Prolonged cytopenia (by Day 30) was reported in 25/63 pts (40%; thrombocytopenia, 37%; neutropenia, 11%), and 39/65 (60%) had clinically significant infections. Subsequent cancers were found in 3/39 pts (8%); 2 were myeloid. NRM at 3 y was 12%. **Conclusions:** With 4-y median follow-up, this real-world study highlights the potential use of axi-cel as an option to treat this challenging group of pts. Further studies are needed to improve response durability. Research Sponsor: U.S. National Institutes of Health; Kite, a Gilead Company.

Social vulnerability by neighborhood of association correlates with CAR T referrals.

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Background: Chimeric antigen receptor T (CAR T) cell therapies are effective for relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and multiple myeloma (MM). However, factors influencing referrals remain unclear, particularly among the denominator of all eligible candidates. This study examines patterns of CAR T referral in the VA health system. **Methods:** A retrospective review identified veterans with R/R DLBCL or MM eligible for CAR T per FDA label during approval periods. Multivariable logistic regression assessed associations of CAR T referral with demographics, comorbidities, and social deprivation index (SDI). SDI is a composite social determinants of health measure at the zip code level, with higher SDI (range: 0-100) indicating greater social disadvantage. **Results:** Of 1,474 eligible patients across 112 VA hospitals, 25% (153/606) of DLBCL and 7.5% (65/868) of MM patients were referred for CAR T. Multivariable analysis showed that higher SDI (OR 0.90 per 10 points, 95% CI 0.84-0.96, p = 0.001) and older age (OR 0.58 per 10 years, 95% CI 0.49-0.69, $p < 0.0001$) were associated with a lower chance of referral, while DLBCL diagnosis (OR 3.22, 95% CI 2.28-4.59, $p < 0.0001$) and Hispanic ethnicity (OR 1.964, 95% 1.09-3.45, p = 0.02) were more likely to have referrals. Marital status, sex, race, psychiatric history, substance abuse, heart disease, kidney disease, cirrhosis, and rural/urban residence were not significant. Among referred patients, older age (OR 0.98, 95% CI 0.95-0.99) and substance abuse (OR 0.42, 95% CI 0.19-0.88) were linked to lower CAR T administration. Median lines of therapy for CAR T were 4 (range: 2-6) for DLBCL and 7 (range: 5-10) for MM. Common reasons for not receiving CAR T included death (23%), age/performance status (21%), alternative therapies (18%), adequate disease control (13%), comorbidities (8%), and patient preference (5%). **Conclusions:** Social vulnerability by neighborhood of association is associated with fewer CAR T referrals. Once referred, most variables minimally impacted CAR T administration. Efforts should focus on improving referral rates and addressing access barriers across all patients. Research Sponsor: None.

Baseline characteristics of DLBCL and multiple myeloma cohorts.

	DLBCL (n = 606)	Multiple Myeloma (n = 868)
Median Age (range)	70 (30 – 96)	73 (36 – 97)
Male Sex (%)	585 (97%)	829 (96%)
Race/Ethnicity (%)		
Non-Hispanic White	402 (66%)	458 (53%)
Non-Hispanic Black	94 (16%)	320 (37%)
Hispanic	56 (9%)	53 (6%)
Other	17 (3%)	14 (2%)
Rural-Urban Residence (%)		
Urban	410 (68%)	645 (74%)
Rural	188 (31%)	219 (25%)
Marital Status (%)		
Married	361 (60%)	495 (57%)
Never Married	64 (11%)	83 (10%)
Divorced/Separated/ Widowed	178 (29%)	287 (33%)
> 3 FACT-Accredited Centers in State (%)	342 (56%)	493 (57%)
Median SDI (range)	52 (1-99)	55 (1-100)
Comorbidities (%)		
Heart Disease	226 (37%)	315 (36%)
Severe CKD	55 (9%)	171 (20%)
Hepatic Cirrhosis	36 (6%)	39 (4%)
Psychiatric Diagnosis	336 (55%)	442 (51%)
Substance Abuse	100 (17%)	135 (16%)

Optimizing post–chimeric antigen receptor (CAR) T cell monitoring: Evidence across lisocabtagene maraleucel (liso-cel) pivotal clinical trials and real-world experience.

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Background: CAR T cell therapies have shown remarkable efficacy in B-cell NHL. Here, we report CRS and ICANS timing in 1579 patients (pt) treated with liso-cel in clinical trials across indications or in the standard of care (SOC) setting to inform safety monitoring requirements. **Methods:** Data from pivotal trials (TRANSCEND NHL 001, TRANSCEND CLL 004, TRANSFORM, PILOT, TRANSCEND FL) included pts treated with liso-cel for R/R LBCL, CLL/SLL, MCL, and FL; data from the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry included pts who received commercial liso-cel for R/R LBCL and had ≥ 1 assessment after infusion. Outcomes were incidence, onset, grade (gr), and duration of CRS and ICANS from pivotal trials and the CIBMTR Registry. **Results:** Of 702 pts treated with liso-cel in 5 clinical trials, 46% had no CRS, 54% had any-gr CRS (gr ≥ 3 at onset, 1%); 98% of events had onset ≤ 2 wk after infusion and median duration was 5 d (Table). Of 7 pts with CRS onset > Day 15 (gr 1, n = 5; gr 2, n = 2), all resolved. Most (69%) pts had no ICANS, 31% had any-gr ICANS (gr ≥ 3 at onset, 5%); 88% of events had onset ≤ 2 wk after infusion and median duration was 7 d (Table). Of 27 pts with ICANS onset > Day 15 (gr 1, n = 20; gr 2, n = 6; gr 3, n = 1), all resolved except 1 pt with gr 2 leukoencephalopathy. Of 877 liso-cel–treated pts from the CIBMTR Registry, 51% had no CRS, 49% had any-gr CRS (gr ≥ 3, 3%); 97% of events had onset ≤ 2 wk after infusion and median duration was 4 d (Table). Of 15 pts with CRS onset > Day 15 (gr 1, n = 9; gr 2, n = 2; gr 3, n = 1; unknown, n = 3), 13 resolved (missing, n = 2). Most (73%) pts had no ICANS, 27% had any-gr ICANS (gr ≥ 3, 7%). Of 150 pts with reported onset date, 95% had onset ≤ 2 wk after infusion and median duration was 5.5 d. Of 8 pts with ICANS onset > Day 15 (gr 1, n = 5; gr 2, n = 1; gr 4, n = 2), 5 resolved (missing, n = 3). Further characterization/management of CRS/ICANS events will be presented. **Conclusions:** Data from the liso-cel pivotal clinical trials and SOC setting from the CIBMTR Registry demonstrated that most CRS/ICANS events occurred ≤ 2 wk after infusion and were not severe. For the few pts who experienced onset of CRS/ICANS after Day 15, most events were low grade and resolved. Clinical trial information: NCT02631044, NCT03331198, NCT03483103, NCT03575351, NCT04245839. Research Sponsor: This study was funded by Bristol Myers Squibb. Writing and editorial assistance were provided by Amy Agbonbhase, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by Bristol Myers Squibb.

CRS and ICANS in liso-cel–treated pts.

	Pivotal clinical trials (N = 702)		CIBMTR Registry (N = 877)	
	CRS	ICANS	CRS	ICANS
Any gr, n (%)	381 (54)	220 (31)	430 (49)[a]	234[a,b] (27)
Gr 3/4/5,[c] n (%)	4 (0.6)/3 (0.4)/0	29 (4)/3 (0.4)/0	4 (0.5)/13 (1)/7[d] (0.8)	43 (5)/17 (2)/5 (0.6)
Median (range) time to onset, d	5 (1–63)	8 (1–63)	4 (IQR, 3–6)	6 (IQR, 4–9)
Median (range) duration from onset, d	5 (1–37)	7 (1–119)	4 (IQR, 2–6)	5.5 (IQR, 2–11)
Onset > Day 15, n/N (%)	7/381 (2)	27/220 (12)	15/430 (3)	8/150 (5)

[a]Gr was to be determined for 3 pts; [b]A total of 150/234 had a reported onset date; [c]Gr at onset for clinical trials; maximum gr during reporting period for CIBMTR; [d]Three pts had PD and 1 had ICANS reported as primary cause of death.

7027 Poster Session

Comprehensive precise CAR-T bridging therapy for diffuse large B-cell lymphoma: A multicenter study from the Chinese Southwest Study Group.

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Background: Chimeric antigen receptor T-cell (CAR-T) therapy has showed substantial efficacy in relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). However, over 50-60% of patients fail to respond or relapse following CAR T-cell treatment, underscoring the need for strategies to enhance its efficacy. **Methods:** We prospectively evaluated the efficacy of the Chinese Southwest Oncology Group (CSWOG) regimen, a precise bridging strategy, in patients with r/r DLBCL who received commercial CAR-T therapy. All patients underwent re-biopsy to assess the expression of biomarkers including CD19, CD20, CD22, CD30, CD38, CD79b, ALK, BCL2, PD-L1, and Ki-67 to identify potential treatment targets. Only patients with positive CD19 expression were eligible for inclusion. Patients received a precise salvage therapy consisting of non-cross-resistant chemotherapy and targeted immunotherapy guided by the re-biopsy results. Only those who responded to salvage therapy proceeded to leukapheresis and received an additional cycle of salvage immunochemotherapy. Non-responders were switched to an alternative precise regimen. Based on our previous findings that low-dose radiation enhances CAR-T cell recruitment and increases antigen exposure, all patients received involved-field low-dose radiation prior to CAR-T cell infusion. Patients treated with axicabtagene ciloleucel (axi-cel) in a real-world setting served as the control group. **Results:** Seventy-one patients with r/r DLBCL received the CSWOG bridging regimen, while 101 Chinese patients treated with axi-cel in a real-world setting served as the control group. In the CSWOG group, 63 patients (88.7%) responded to salvage precise immunochemotherapy, while 8 patients (11.3%) who did not respond were switched to alternative immunochemotherapy regimen. All patients in the CSWOG group received a median dose of 24.0 Gy involved-field radiation. After CAR-T infusion, the best overall response (BOR) rate was 84.5% in CSWOG group, with 74.6% achieving complete response (CR) and 9.9% partial response (PR). The BOR rate in control group was 83.2%, with 58.4% achieving CR and 24.8% achieving PR. After a median follow-up of 15.3 months, the 2 - year overall survival (OS) and progression-free survival (PFS) rates were 84.1% and 75.2%, respectively, in the CSWOG group, compared to 70.0% and 49.8% in the control group. Grade 3 or higher cytokine release syndrome occurred in 9.8% of the CSWOG group and 15.2% of the control group. Neurologic events of any grade were observed in 12.8% of the CSWOG group and 16.2% of the control group. Among the 4 CSWOG patients with neurologic events, all were managed with steroids and resolved; however, all 4 relapsed. **Conclusions:** Our results show that combining precise immunochemotherapy with low-dose radiation optimizes CAR-T therapy, supporting its global implementation. Clinical trial information: ChiCTR2100043613. Research Sponsor: National Natural Science Foundation of China; 82470237.

Postmarketing safety profile of chimeric antigen receptor (CAR) T cell therapies in diffuse large B-cell lymphoma (DLBCL): Analysis of real-world (RW) AE reporting from the FDA Adverse Event Reporting System (FAERS).

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Background: CAR T cell therapies have emerged as effective treatment options with deep and durable responses in patients (pt) with DLBCL. Although efficacy and safety data from clinical trials are usually used for drug approval, potentially relevant AEs may not be captured due to limited study follow-up and population. Surveillance databases like FAERS can further characterize safety of therapeutic biologics by capturing RW AEs. We aimed to characterize the safety profile of CAR T cell therapies in the DLBCL population using FAERS. **Methods:** FAERS was used to identify AEs in pt with DLBCL treated with 2 commercially available CAR T cell therapies, lisocabtagene maraleucel (liso-cel) or axicabtagene ciloleucel (axi-cel). AEs of interest were cytokine release syndrome (CRS), neurological events (NE), hemophagocytic lymphohistiocytosis (HLH), cytopenia, and infections. The primary analysis examined all case reports from Q4 2017 to Q3 2024, the latest available quarterly release. Two sensitivity analyses adjusting for differences in follow-up after FDA approvals were performed: (1) AEs reported any time after liso-cel FDA approval (02/05/2021), which is later, and (2) AEs reported within 2 years of FDA approval for each CAR T cell therapy. Disproportionality analysis compared relative frequency of AEs. Reporting odds ratios (ROR) and 95% CIs were used to identify significant differences in AEs between treatments (ie, 95% CI did not cross 1). An ROR >1 indicated higher event frequency for axi-cel vs liso-cel. **Results:** From Q4 2017 to Q3 2024, 3251 AE reports in pt with DLBCL were associated with liso-cel (n = 232) or axi-cel (n = 3019). In disproportionality analysis, axi-cel had significantly higher ROR for CRS (1.48; 95% CI, 1.13–1.93), NE (1.61; 1.23–2.11), and cytopenia (2.45; 1.41–4.24) than liso-cel. Considering limitations of underreporting and incomplete information inherent in FAERS, no statistically significant difference can be inferred for infections (1.36; 95% CI, 0.75–2.48), seizures (1.36; 0.42–4.40), and HLH (1.18; 0.36–3.83). Observed trends were consistent in both sensitivity analyses, where reporting frequencies remained significantly higher with axi-cel vs liso-cel for CRS (1.60; 95% CI, 1.17–2.17 and 2.02; 1.37–2.98), NE (1.59; 1.18–2.15 and 2.04; 1.39–3.00), and cytopenia (2.00; 1.11–3.60 and 2.60; 1.24–5.46), after adjusting for differences in follow-up durations. **Conclusions:** This retrospective analysis of FAERS, using spontaneous safety reporting data after approval and broader population beyond clinical trials, demonstrated a favorable RW safety profile for liso-cel vs axi-cel for CRS, NE, and cytopenia. These findings provide valuable insights into the safety profile of CAR T cell therapies in DLBCL to inform clinical decision-making and pt management. Research Sponsor: This study was funded by Bristol Myers Squibb. Writing and editorial assistance were provided by Emily Burke, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by Bristol Myers Squibb.

Pregnancy and infant outcomes post–CD19-directed CAR-T therapy: Tisagenlecleucel (tisa-cel) and/or huCAR19 (CTL119).

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Background: Data on pregnancy post–CD19-directed CAR-T therapy for B-cell malignancies are limited (Ligon et al). There is a theoretical risk of cross-placental transmission of CAR-T cells in female patients (pts) during pregnancy. The impact of CAR-T on fertility, conception or pregnancy in pts is uncertain. High-dose chemotherapy/radiation has a high infertility risk (Lowe et al). Early use of CAR-T may increase the chance of fertility preservation. **Methods:** In this retrospective cohort analysis, a cumulative search in the Novartis Global Safety database for all CAR-T products, up to Jan 2025 was conducted using the Standard MedDRA Query: Pregnancy and neonatal topics (narrow). Transgene levels were monitored in clinical trial pts for all indications. Ongoing B-cell aplasia (BCA)/deficiency or intravenous immunoglobulin (IVIG) utilization was used as a surrogate marker for persistence of tisa-cel in pts with acute lymphoblastic leukemia (ALL). Pregnancy outcomes were collected via pregnancy and infant forms at birth and 3 and 12 month (mo), subject to reporter and/or patient consent. **Results:** Sixteen events of tisa-cel or CTL119 exposure during pregnancy were reported. Elective termination of pregnancy was noted in 2 cases. Pathology review of placental/fetal parts in one of these cases was unremarkable. One case did not have consent for follow-up (FU) and another one did not have newborn status. One pregnancy was ongoing with normal pregnancy to date and delivery expected in Q2 2025 (commercial tisa-cel). Eleven pregnancies resulted in live birth of 12 healthy infants (1 pregnancy with twins). Further details on these 11 pregnancies are provided in Table 1. Persistent CAR transgene levels in the clinical trial pts with ALL have shown concordance with the use of IVIG/ongoing BCA/deficiency (data not shown). One infant was enrolled to long-term FU and tested negative for huCAR19 transgene on day 7, though the number of B cells (80 cells/μL) and IgG levels were slightly low at birth. Among 3 commercial tisa-cel pts with reported pregnancies, 2 had ongoing IVIG during pregnancy and 1 at the time of delivery. **Conclusions:** Pregnancy and delivery of a healthy infant after CAR-T therapy is possible. The use of CAR-T therapy may improve chances of healthy pregnancy by avoiding the risks for infertility associated with high-dose chemotherapy and/or radiation. Capturing data on all pregnancies post CAR-T remains an important goal. Research Sponsor: Novartis Pharma AG.

Pregnancy and infant status post CAR-T.

Pts	1 *	2*	3	4	5	6	7	8	9	10	11
Indication	ALL					ALL				B-NHL	FL
Product	Tisa-cel*		CTL119					CTL019			
Approx. age at conception (y), sex	22F	25M	20F	30M	29F	39M	25M	35M	28F	31F	M
Approx. time from CAR-T to conception	1y	3y	3y	6.5y	8y	1.5y	7mo	2.5y	6y 9mo	1y 7mo	1y 3mo
Latest FU of healthy infant(s)	2y	4mo	22mo	18mo	Birth	1y	21mo	Birth (twins)	Birth	Birth	1y

*Commercial tisa-cel.
B-NHL, B-cell non-Hodgkin's lymphoma; FL, follicular lymphoma; y, years.

Effect of prophylactic corticosteroids on toxicities and outcomes in CAR T-cell therapy: A cohort study.

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Background: Common toxicities associated with infusion of Chimeric antigen receptor T-Cell (CAR T-cell) therapy include cytokine release syndrome (CRS) and immune-effector-cell-associated neurotoxicity syndrome (ICANS). While early steroid use has correlated with a reduced risk of high-grade CRS and ICANS, there is conflicting data regarding its impact on CAR-T efficacy. We aim to study the impact of prophylactic steroid use on toxicities and outcomes at our institution. **Methods:** We performed a single-center comparative analysis between two patient cohorts at higher risk of CRS and ICANS based on elevated inflammatory markers, (ferritin ≥400 ng/mL and CRP ≥4 mg/dL). One cohort received prophylactic dexamethasone 10 mg on days 0,1, and 2. Univariate statistics were calculated using X2, Fisher's exact tests, and ANOVAs, where appropriate. Kaplan Meier was used to estimate overall survival (OS) and progression-free survival (PFS) and compared using the log-rank test. **Results:** Out of 63 patients with high ferritin and CRP, 10 patients received prophylactic steroids (Group PS) and 53 patients did not (Group NPS). In the NPS group, 46 patients had a primary diagnosis of non-Hodgkin lymphoma and 7 had a diagnosis of multiple myeloma. In the PS group, 9 had non-Hodgkin lymphoma and 1 had multiple myeloma. The median age at CAR-T was 58 years in PS and 64 years in NPS group (p=0.48). The rate of CRS grade ≥3 was higher in the NPS group compared to the PS group, (47.2 vs 20%, p=0.26) whereas ICANS grade ≥3 was similar (32% in NPS and 30% in PS group). More patients achieved a complete response in the PS group (60%) compared to the NPS group (30.2%). The1-year PFS was higher in PS group compared to NPS (60% vs 28%,p=0.08) which was also reflected in the 1-year OS (70% vs 38%, p=0.10). At a median follow-up of 22 months, 70% patients were alive in the PS group compared to 28.3% patients in the NPS group. **Conclusions:** Our study shows lower rates of CRS and a pattern towards higher rates of complete remission and survival benefit in patients undergoing CAR T-cell therapy receiving prophylactic steroids. The data must be interpreted with caution given the small sample size, but it warrants the need for future studies. Research Sponsor: None.

Outcomes of patients by prophylactic steroid status (n=63).

Parameter	NPS (n=53)	%	PS (n=10)	%	p-value*
Best Response					0.42
Complete Response	16	30.2	6	60.0	
Partial Response	4	7.5	1	10.0	
Stable Disease	2	3.8	0	0.0	
Progressive Disease	24	45.3	3	30.0	
NE*	7	13.2	0	0.0	
Disease progression					0.30
No	25	47.2	7	70.0	
Yes	28	52.8	3	30.0	
Time to disease progression, days, median (range)	66.5	5-996	96	92-158	0.75
Median follow-up among survivors (n=22), months (range)	46.5	9-73.8	11.4	8.3-24.2	<0.01
Alive	15	28.3	7	70.0	
Dead	38	71.7	3	30.0	
2nd Cancer	1	2.6	1	33.3	
CNS failure	2	5.3	0	0.0	
COVID	1	2.6	0	0.0	
Disease	23	60.5	2	66.7	
Hemorrhage	1	2.6	0	0.0	
Infections	9	23.7	0	0.0	
Unknown	1	2.6	0	0.0	

NE*= not included in analysis.

Phase I study to evaluate the safety and efficacy of switchable CAR-T cell therapy with FY001 and CART001 in patients with refractory CD20-positive B-cell non-Hodgkin lymphoma (EPOC1803).

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Background: CD19-targeted CAR-T cell therapy has shown remarkable efficacy against relapsed/refractory B-cell non-Hodgkin lymphoma (r/r B-NHL). However, clinical challenges persist, including relapse due to CD19 antigen loss and severe immune-related adverse events such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). We developed a combination therapy using FITC-labeled rituximab (FY001) with FITC-recognizing CAR-T cells (CART001). FY001 binds to CD20 on lymphoma cells, and CART001 activation occurs exclusively through FY001, enabling fine-tuning of anti-tumor activity while minimizing adverse events. This switchable CAR-T can be applied to broader r/r B-NHL cases, including elderly or frail patients. In addition, for patients with target antigen loss, FITC-labeled antibodies targeting different antigens can activate residual CART001 to combat relapsed lymphoma cells. We conducted a phase I trial to assess the safety and efficacy of the switchable CAR-T. **Methods:** This investigator-initiated phase I trial enrolled patients with r/r B-NHL, to evaluate adverse event, including dose-limiting toxicities (DLTs), as the primary endpoint. The trial design specified evaluating DLTs in 3 initial participants; zero DLTs prompted the addition of 3 expansion cohort participants; one DLT necessitated 3 additional participants for DLT evaluation; two or more DLTs led to enrollment discontinuation. Participants underwent lymphocyte-depleting chemotherapy (LDC) until the day before FY001 administration. Following LDC, participants received intravenous FY001 administration at 2 mg/kg, and CART001 infusion at 1×10^6 cells/kg on the subsequent day. **Results:** Between March 2020 and March 2022, 6 participants received FY001 and CART001 treatment, in DLT evaluation (n=3) and expansion (n=3) cohorts. Participant ages ranged from 68-79 years, with 2-8 prior therapy lines; five had diffuse large B-cell lymphoma and one had follicular lymphoma. In all cases, no DLTs occurred. Observed adverse events, none of which were determined to be causally related to FY001 or CART001, included 1 case of Grade 4 blood creatine phosphokinase elevation (16.7%) and 1 case of Grade 3 anemia (16.7%). Notably, no CRS or ICANS cases were reported. The best overall response rate reached 100% (95% CI: 54.1%-100%), comprising 4 complete responses (CR) and 2 partial responses (PR). As of January 2025, 2 patients continue maintaining CR (57 and 47 months). **Conclusions:** The switchable CAR-T demonstrated excellent tolerability and 100% response rate with long-term remission in r/r B-NHL patients. These promising results warrant further clinical development of this therapy. Clinical trial information: jRCT1080224690. Research Sponsor: Advanced Research and Development Programs for Medical Innovation.

Impact of pre-lymphodepletion (pre LD) and day 30 (M1) immune cell counts on outcomes of CAR T therapy in patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL).

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Background: The impact of immune cell counts pre LD and during immune reconstitution on CAR T therapy outcomes is poorly understood. We investigated the association between CD4, CD8 and NK cell counts and CAR T therapy outcomes in patients with LBCL. **Methods:** Retrospective study of R/R LBCL patients who received CAR T cells between 2016-24 at Mayo Clinic, Rochester, were included in this analysis. Peripheral blood CD4, CD8 and NK counts were measured pre LD and at M1 post CAR T infusion. The receiver operating characteristic (ROC) curve was used to determine the optimal cutoff for pre LD and M1 immune cells to predict patients who were alive and in remission at 6 months (M6) post CAR T infusion. Patients who progressed or were lost to follow up prior to day 30 were excluded from M1 ROC analysis. **Results:** Of 140 patients, 81 were alive and in remission at M6 (Group A), while 59 had relapse or death (Group B). Axicabtagene ciloleucel was the CAR T product given in 81% of patients (114/140). Median pre LD CD4 counts were significantly lower in Group B compared to group A (143 vs 280 cells/μL, p = 0.001). No significant difference was observed in median pre LD CD8 counts (205 vs 221 cells/μL, p = 0.8). ROC analysis identified an optimal pre LD CD4 count of 124.5 cells/μL for M6 alive+remission. Lower pre LD CD4 counts ($<$124.5) predicted worse progression free survival (PFS) in univariate (HR = 3.02, 95% confidence interval [CI]: 1.73–5.27, p$<$ 0.01) and multivariable analysis (MVA) adjusted for IPI and the number of prior lines (aHR = 2.54, 95% CI: 1.39–4.62, p$<$ 0.01).Lower pre LD CD4 counts also predicted inferior overall survival (OS) in MVA (aHR = 2.27, 95% CI: 1.08–4.77, p = 0.03). (Table 1) On day 30 landmark analysis, ROC identified M1 optimal CD4 count of $\geq$ 99.5 cells/μL to be associated with a trend toward superior PFS (P=0.09), but not OS (p=0.90) in MVA. Median pre LD NK cell counts were significantly lower in Group B (73 vs 98 cells/μL, p = 0.04). ROC analysis identified an optimal pre LD NK count of 151 cells/μL for M6 alive + remission. Lower pre LD NK counts ($<$151) predicted worse PFS, both on univariate (HR = 4.17, 95% CI: 1.29–13.47, p = 0.02) and MVA (aHR = 4.64, p$<$ 0.01). The lower pre LD NK cell count group had worse OS in MVA (aHR = 5.69, 95% CI: 1.16–28.1, p = 0.01). (Table 1) On D30 landmark analysis, M1 NK cell count of $\geq$ 128.5 cells/μL was associated with a trend toward superior PFS (P=0.08), but not OS (p=0.30) in MVA. **Conclusions:** Pre LD CD4 and NK cell counts are significantly associated with PFS and OS post CAR T therapy in patients with R/R LBCL. Pre-treatment immune subset levels may identify patients at higher risk of relapse or death after CAR-T therapy. Research Sponsor: None.

Groups	Median PFS	2 Year PFS	Median OS	2 Year OS
CD4 ≥124.5 cells/μL (N=75)	NR	58%	3.31 years	67%
CD4 <124.5 cells/μL (N=30)	2.2 months	22%	1.59 years	45%
NK ≥151 cells/μL (N=17)	NR	77%	NR	84%
NK <151 cells/μL (N=82)	10.6 months	44%	3.31 years	62%

Influence of pre-existing autoimmune disease on outcomes in patients treated with CD-19 targeting CAR-t cell therapy for lymphoma: A retrospective propensity score matched study utilizing TriNetX.

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Background: There is a lack of studies in the literature about the impact of baseline autoimmune diseases (AD) on outcomes in patients with lymphoma treated with CD-19 targeting-chimeric antigen receptor T-cell (CAR-T) therapy. This retrospective propensity score matched study aims to provide real-world evidence to understand the impact of pre-existing AD on outcomes in this population. **Methods:** This multicenter retrospective study included 504 patients with pre-existing AD diagnoses prior to receiving treatment with CD-19 targeting CAR-T therapy for lymphoma and 504, 1:1 propensity-score matched controls, without pre-existing AD, in the TriNetX Network. The outcomes analyzed were 5-year mortality, development of cytokine release syndrome (CRS), development of immune effector cell-associated neurotoxicity syndrome (ICANS), all cause hospitalization, ICU level care, risk of infection, and steroid use. Kaplan-Meier analysis, hazard ratios (HR), risk ratios (RR), and 95% confidence intervals (CI) were used to assess the primary outcomes. **Results:** Patients with pre-existing AD diagnosis were not at a statistically significant increased risk of mortality when compared to non-AD patients (HR = 1.10 [95% CI, 0.90-1.36]; P= 0.081). Both all-cause hospitalization (RR, 1.07 [95% CI, 1.03-1.10]) and ICU level of care (RR, 1.49 [95% CI, 1.19-1.84]) were higher in the pre-existing AD group when compared to non-AD patients. There was an increased risk for development of CRS in the AD group when compared to the non-AD group (RR, 1.17 [95% CI, 1.06-1.28]). There was no significant difference in the development of ICANs between the AD and non-AD group (RR, 1.10 [95% CI, 0.88-1.37]). There was an increased risk of infection amongst the AD group when compared to the non-AD group (RR, 1.48 [95% CI, 1.32-1.66]). Steroid use was higher in the pre-existing AD group (RR, 1.22 [95% CI, 1.09-1.38]). There was no statistically significant difference in rates of subsequent bone marrow transplant in patients with the pre-existing AD compared to the non-AD group (RR, 1.17 [95% CI, 0.93 -1.47]). **Conclusions:** CD19 CAR T- therapy has emerged as a promising therapeutic option for patients with AD, given its capacity to target and eliminate B-cells, which are vital in the pathogenesis of many AD. To our knowledge, this study represents the largest examination of the real-world impact of a baseline AD on clinical outcomes in patients undergoing CD19-targeted CAR T-cell therapy for lymphoma. Our findings indicate that pre-existing AD is associated with an increased risk of hospitalization, ICU level of care, CRS, and infections, without significantly affecting survival probability. Clinical trials are ongoing to evaluate the efficacy and safety of CAR T therapy in patients with AD. Research Sponsor: None.

Comparing outcomes of lymphoma-directed CAR T-cell therapy in patients with and without HIV: A retrospective cohort study from a global health research network.

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Background: Since its introduction into the world of oncology, chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of relapsed and refractory lymphomas. However, patients with HIV (PWH) have historically been excluded from CAR T-cell studies. This is likely due to assumed decreased efficacy and increased infection-related morbidity and mortality due to their immunocompromised status. This lack of understanding contributes to healthcare disparities, resulting in fewer individuals from this vulnerable population receiving this innovative treatment. Thus, this study aims to compare the 1-year survival and safety outcomes of CAR T-cell therapy for Hodgkin and Non-Hodgkin lymphomas in adult patients with and without HIV. **Methods:** Using TriNetX global health research network, we identified 35 PWH who received lymphoma-directed CAR T-cell therapy. For the control group, we identified 2,575 patients without HIV who received lymphoma-directed CAR T-cell therapy. We then conducted a log-rank test and calculated relative risks (RR) to compare outcomes in 1-year overall survival (OS) and incidence of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), bacteremia and sepsis. **Results:** In our group of PWH, we observed a mean age of 56.1+/-12.6 years at time of CAR T-cell therapy, compared to a mean age of 63.0+/-13.0 years in our group of patients without HIV. RR analysis demonstrated significantly increased 1-year risk for development of sepsis (RR=1.75, 95%CI 1.03, 2.97) and bacteremia (RR=2.41, 95%CI 1.41, 4.12) in our group of PWH. However, it showed no statistically significant differences in risk for development of CRS (RR=1.11, 95%CI 0.788, 1.57), ICANS (RR=1.23, 95%CI 0.723, 2.08), or death from any cause (RR=1.43, 95%CI 0.873, 2.35). Log rank test revealed no significant differences in 1-year OS (p=0.208) or incidence of CRS (p=0.567), ICANS (p=0.223), bacteremia (p=0.561) or sepsis (p=0.225). Median OS was not reached in either group. **Conclusions:** This data supports that PWH may be at increased risk of infectious complications, but not increased mortality, following lymphoma-directed CAR T-cell therapy. While this study is limited by a small cohort size, its results support the need to include PWH in future clinical trials to better understand the effect of HIV infection on CAR T-cell treatment outcomes. Research Sponsor: None.

7035 Poster Session

Risk of invasive fungal infections in patients with chronic lymphocytic leukemia treated with Bruton tyrosine kinase inhibitors: A TriNetX-based retrospective cohort study from 2000-2025.

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Background: Chronic lymphocytic leukemia (CLL) is associated with immunosuppression, and Bruton tyrosine kinase inhibitors (BTKis) may further increase the risk of invasive fungal infections (IFIs). This retrospective study evaluates the trends in BTKi use and the associated risk of IFIs among CLL patients in a real-world setting. **Methods:** We conducted a retrospective cohort study using the TriNetX database, analyzing U.S. CLL patients diagnosed between January 2000 and January 2025. Propensity score matching (1:1) by age, comorbidities, and immunosuppressive therapy was performed. Outcomes included invasive fungal infections (candidiasis, aspergillosis, cryptococcosis, and pneumocystis jirovecii pneumonia), assessed using Kaplan-Meier survival analysis and risk measures. **Results:** Among 10,736 patients treated with BTK inhibitors and 80,446 controls, the median follow-up was 881 and 868 days, respectively. Patients in the BTK cohort had a mean age of 75±10 years, predominantly male (62.21%) and primarily White (76.24%). In contrast, the control cohort had a mean age of 76±12 years, with 55.87% male patients and 73.12% identified as White. On the other hand, the risk of invasive candidiasis was significantly lower in the BTK cohort (RR: 0.364, 95% CI: 0.193–0.686), as was the risk of invasive aspergillosis (RR: 0.532, 95% CI: 0.289–0.98). Pneumocystis jirovecii pneumonia (PJP) rates were comparable between the cohorts (RR: 0.961, 95% CI: 0.497–1.855). Cryptococcosis was detected in 0.001% of the BTKi group but did not occur in the control cohort; this variation, however, did not reach statistical significance (P = 0.823). **Conclusions:** This retrospective study reveals the complex infection profile associated with BTK inhibitor use in CLL patients. Treatment with BTK inhibitors was linked to a significant decrease in the occurrence of invasive candidiasis and aspergillosis in the BTK cohort, and rates of Pneumocystis jirovecii pneumonia (PJP) and Cryptococcus were similar between groups. Although the absolute rates of fungal infections remain low, these findings underscore the importance of identifying at-risk patients to guide preventive and cost-effective interventions. Further research is needed to differentiate infection risks across specific BTK inhibitors and develop tailored management strategies to optimize patient outcomes. Research Sponsor: None.

7036 Poster Session

Final analysis of fixed-duration ibrutinib + venetoclax for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) in the phase 2 CAPTIVATE study.

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Background: First-line ibrutinib (Ibr) + venetoclax (Ven) treatment for CLL/SLL was tested in the phase 2 CAPTIVATE study, including minimal residual disease (MRD)–guided randomized discontinuation (MRD cohort) and Fixed Duration (FD) cohorts. We report final analysis results for patients (pts) treated with FD Ibr+Ven in the FD cohort and MRD cohort placebo arm. **Methods:** Pts ≤70 y with previously untreated CLL/SLL received 3 cycles of Ibr, then 12 cycles of Ibr+Ven (Ibr, 420 mg/d orally; Ven, 5-wk ramp up to 400 mg/d orally), up to 13 cycles in the MRD cohort placebo arm. On-study retreatment included single-agent Ibr; FD cohort pts with progressive disease (PD) >2 y after end of treatment (EOT) could be retreated with FD Ibr+Ven. **Results:** 202 pts completed FD Ibr+Ven (FD cohort, n=159; MRD cohort placebo arm, n=43). With median follow-up of 68.9 mo (range, 0.8–83.9), 5.5-y PFS and OS rates (95% CI) were 66% (58–72) and 97% (93–99), respectively. 5.5-y PFS rates (95% CI) in pts without and with del(17p)/mutated *TP53* were 70% (62–76) and 36% (17–55), respectively. In pts with unmutated IGHV, 5.5-y PFS was 55% (45–64): 63% (49–74) in pts without, and 44% (28–60) in pts with, concomitant del(17p)/mutated *TP53*/complex karyotype. The corresponding rates for pts with mutated IGHV were 79% (68–87), 85% (71–93), and 62% (34–81). Undetectable MRD (uMRD4; $<10^{-4}$ by flow cytometry) was achieved in peripheral blood (PB) in 54% of pts at C7 and 69% at EOT, and in bone marrow in 69% of pts at EOT. 5.5-y PFS rates (95% CI) were higher in pts with uMRD4 in PB at EOT (75% [67–82]) vs those with MRD (47% [33–59]). 64 pts had PD after completion of FD Ibr+Ven. 5.5-y freedom from next-line treatment was 73% (95% CI 66–79). Of 40 pts with available samples at PD to date, 1 had an acquired subclonal mutation in *BCL2* of unclear significance (A113G, VAF 8.3%); none had acquired resistance-associated mutations in *BTK* or *PLCG2*. 36 pts initiated retreatment with Ibr (n=25) or Ibr+Ven (n=11). With 28.4 mo median follow-up on Ibr retreatment (range, 3.7–59.1), ORR was 76% (best response: 1 CR; 1 nodular PR; 17 PR; 4 SD; 1 PD [Richter transformation]; 1 no assessment); 2-y PFS and OS rates from the start of retreatment were 91% and 96%, respectively. With 15.2 mo median follow-up on Ibr+Ven retreatment (range, 7.4–29.3), ORR was 82% (best response: 1 CR; 8 PR; 2 SD); 1-y PFS and OS rates from the start of retreatment were both 100%. Second malignancies occurred in 24 pts across the entire study period, including 12 initial treatment and 4 retreatment TEAEs. **Conclusions:** Ibr+Ven is an all-oral, once-daily, chemotherapy-free FD regimen for first-line treatment of CLL/SLL that continues to provide durable PFS and OS with long-term follow-up, including in pts with high-risk genomic features. Ibr-based retreatment provided durable responses in pts needing subsequent therapy after completion of FD Ibr+Ven. Clinical trial information: NCT02910583. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.

Propensity score (PS) comparison between lisocabtagene maraleucel (liso-cel) plus ibrutinib combination therapy (combo) and liso-cel monotherapy (mono) cohorts from TRANSCEND CLL.

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Background: TRANSCEND CLL 004 (NCT03331198) is a phase 1/2, open-label, nonrandomized, multicohort study in adult patients (pt) with R/R chronic lymphocytic leukemia/small lymphocytic lymphoma with liso-cel mono and liso-cel + ibrutinib combo cohorts. Given the study design, we performed PS matching/weighting to adjust for differences in key covariates between cohorts to compare efficacy and safety. **Methods:** Here, PS is the probability of receiving combo given the covariates and estimated by logistic regression. Covariates were hemoglobin, LDH, number of prior therapies, platelets, prior BTKi + venetoclax exposure, R/R on prior BTKi, and bulky disease for efficacy; and ALC, bulky disease, CRP, ferritin, and number of prior therapies for safety. PS balancing methods were optimal 1:1 matching, average treatment effect for treated pts (ATT) full matching, and ATT inverse probability of treatment weighting (IPTW). Efficacy endpoints were response (CR rate, ORR) and time to event endpoints (DOR, PFS, OS). Safety endpoints were proportions of pts with any-grade (gr)/gr $\geq$ 3 cytokine release syndrome (CRS) and investigator-identified neurological events (NE). **Results:** Fifty-one and 88 efficacy-evaluable pts were treated at dose level 2 (100×10^6 CAR^+ T cells) in the combo and mono cohorts, respectively. Before matching/weighting on PS, odds of achieving CR and overall response were statistically significantly higher for combo (Table). DOR did not differ between cohorts. For PFS and OS, HRs were lower with combo vs mono (not statistically significant [NS]). Odds of gr $\geq$ 3 CRS/NE were lower with combo vs mono (NS). After matching/weighting, odds of CR (except IPTW ATT) and overall response remained statistically significantly higher in combo. HRs for PFS and OS and ORs for gr $\geq$ 3 CRS/NE were numerically lower with combo vs mono (NS, except IPTW ATT for PFS). HRs for DOR were less but close to HR of 1. **Conclusions:** The liso-cel + ibrutinib combo demonstrated a trend for better efficacy and safety vs liso-cel mono, with statistically significant differences for CR rate and ORR. Clinical trial information: NCT03331198. Research Sponsor: This study was funded by Bristol Myers Squibb. Writing and editorial assistance were provided by Nikola Vojtov, PhD, of The Lockwood Group (Stamford, CT, USA), funded by Bristol Myers Squibb.

Efficacy and safety outcomes: combo vs mono.

	No adjustment	ATT optimal 1:1	IPTW - ATT
CR rate, OR (95% CI)	2.07* (1.01–4.28)	2.40* (1.05–5.66)	2.00 (0.89–4.61)
ORR, OR (95% CI)	3.96* (1.68–10.51)	3.43* (1.33–9.71)	4.18* (1.63–11.78)
DOR, HR (95% CI)	0.98 (0.51–1.87)	0.88 (0.43–1.78)	0.96 (0.50–1.85)
PFS, HR (95% CI)	0.62 (0.37–1.02)	0.61 (0.35–1.05)	0.59* (0.35–0.98)
OS, HR (95% CI)	0.70 (0.38–1.28)	0.73 (0.37–1.43)	0.66 (0.36–1.22)
CRS, OR (95% CI)	0.63 (0.26–1.56)	0.67 (0.24–1.84)	0.69 (0.24–1.88)
Gr ≥ 3 CRS, OR (95% CI)	0.23 (0.01–1.35)	0.49 (0.02–5.28)	0.26 (0.01–1.94)
NE, OR (95% CI)	0.84 (0.41–1.68)	0.92 (0.40–2.08)	1.10 (0.48–2.52)
Gr ≥ 3 NE, OR (95% CI)	0.56 (0.19–1.45)	0.58 (0.16–1.89)	0.68 (0.19–2.30)

*Statistically significant difference at 5% level.

Preliminary safety and efficacy data of ICP-248, a novel BCL2 inhibitor, in patients with relapsed or refractory B-cell malignancies.

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Background: BCL2, a critical protein regulator of the apoptotic pathway, highly expressed in various malignancies, including B-cell non-Hodgkin lymphomas (B-NHLs). The only approved BCL2 inhibitor, Venetoclax, has been approved for the treatment of chronic lymphocytic leukemia/small cell lymphoma (CLL/SLL) or acute myeloid leukemia (AML). However, hematologic toxicities and tumor lysis syndrome (TLS) remain as safety challenges in clinical practice. ICP-248 was developed as a potent and highly selective BCL2 inhibitor. Preclinical studies have demonstrated favorable pharmacokinetics profile and excellent safety profile. **Methods:** ICP-CL-01201 is an ongoing phase I study (NCT05728658) including dose escalation and dose expansion parts. Safety and tolerability of ICP-248 was evaluated from target doses of 50 mg to 200 mg. Patients receive oral treatment every day until disease progression or intolerable toxicities. Eligible patients include those aged 18-80 years, diagnosed with CLL/SLL and B-NHLs who are in relapsed or refractory disease. Key exclusion criteria include CNS involvement, resistance to BCL2 inhibitors and clinically significant cardiovascular disease. Efficacy was evaluated according to the Lugano 2014 or iwCLL 2018 criteria. **Results:** As of 12 Dec 2024, 55 patients were enrolled in the study: 18 in dose escalation and 37 in dose expansion. 24 patients were CLL/SLL, 26 patients were mantle cell lymphoma (MCL), 5 patients were other B-NHLs. The median age was 65 years, and 72.7% of patients were refractory disease and 56.4% of the patients were previously treated with BTK inhibitors. The median prior therapeutic line was 2 (1-8). ICP-248 was well tolerated through all dose levels, with no dose-limiting toxicities (DLTs) observed, and maximum tolerated dose (MTD) not reached. Toxicity leading to drug discontinuation and death was not observed. Most of TEAEs were in grade 1-2. The most frequent TEAEs were hematologic AEs including neutropenia, leukopenia, and thrombocytopenia. Serious adverse events (SAEs) were reported in 16.4% patients. As cutoff date, 20 CLL/SLL and 19 MCL patients treated with ICP-248 dose $\geq$100 mg had at least one response assessment: ORR was 80% and CRR was 15% in r/r CLL/SLL patients, while those for r/r MCL patients were 78.9% and 42.1% respectively. uMRD was reported in 10% CLL/SLL and 15.8% MCL patients. In 10 patients with previous BTK inhibitor refractory MCL patients (2 blastoid or pleomorphic subtype and median 3.5 prior treatment lines), the ORR was 80% and CRR was 30%; in 11 patients with previous BTK inhibitor failure CLL/SLL, the ORR was 81.8% and CRR was 18.2%. **Conclusions:** The preliminary results of ICP-248 monotherapy suggests a well-tolerated safety profile and an exciting efficacy with dose-dependent effect in BTK failed, heavily treated, relapsed or refractory B-cell malignancies. Clinical trial information: NCT05728658. Research Sponsor: None.

Comparison of outcomes for patients (pts) with R/R chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) previously treated with Bruton tyrosine kinase inhibitor (BTKi) and venetoclax from the TRANSCEND CLL 004 study versus a matched cohort of real-world (RW) pts.

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Background: Pts with R/R CLL/SLL who failed BTKi and venetoclax have limited treatment (tx) options and poor prognoses. FDA approval of lisocabtagene maraleucel (liso-cel) for R/R CLL/SLL was based on positive results from TRANSCEND CLL 004 (NCT03331198), a single-arm trial. We assessed relative efficacy of liso-cel vs standard of care (SOC) by identifying (or assembling) an external comparator cohort of pts treated in a RW setting. **Methods:** Pts from TRANSCEND CLL 004 and a matched RW cohort were analyzed. Eligible pts were ≥ 18 y with CLL/SLL, had ≥ 2 prior lines of therapy (pLoT), including a BTKi and venetoclax, and started subsequent tx for CLL/SLL. SOC pts were selected from de-identified datasets (Flatiron [1993–2023], COTA [2000–2023], and ConcertAI [1997–2022]). TRANSCEND CLL 004 eligibility criteria were applied as applicable. Liso-cel pts were eligible trial participants treated with liso-cel and efficacy-evaluable. Endpoints were ORR, PFS, and OS. Inverse probability of tx weighting (IPTW) and regression model were used to balance pt characteristics between cohorts, including age, sex, race, time from initial diagnosis, Rai stage, bulky disease, ECOG PS, high-risk cytogenetics, pLOT, prior chemoimmunotherapy and phosphatidylinositol 3-kinase inhibitor (PI3Ki), and refractoriness to BTKi and venetoclax. **Results:** Analysis included 278 pts (SOC, n = 212; liso-cel, n = 66). SOC regimens included chemotherapy, immunotherapy (excluding CAR T cell therapy), BTKi, venetoclax, PI3Ki, and combinations. Median follow-up was 17.2 mo for SOC and 35.4 mo for liso-cel. Most pt characteristics were balanced after IPTW (Table) with imbalance adjusted by regression. After adjustment, ORR (95% CI) was 19.2% (14.1–26.1) for SOC vs 52.5% (34.8–79.2) for liso-cel. Median (95% CI) PFS was 4.4 mo (3.2–5.5) for SOC vs 12.0 mo (10.8–13.2) for liso-cel (HR, 0.40; 95% CI, 0.24–0.68). PFS probabilities at 24 and 36 mo were 11.5% and 5.1% for SOC vs 46.3% and 30.3% for liso-cel. Median (95% CI) OS was 14.8 mo (9.4–20.1) for SOC vs 33.6 mo (31.7–35.5) for liso-cel (HR, 0.47; 95% CI, 0.28–0.79). OS probabilities at 24 and 36 mo were 35.1% and 29.7% for SOC vs 73.4% and 42.6% for liso-cel. **Conclusions:** Liso-cel was associated with significantly improved response, delayed progression, and prolonged survival vs SOC in pts with R/R CLL/SLL after ≥ 2 pLOTs, including a BTKi and venetoclax. Clinical trial information: NCT03331198. Research Sponsor: This analysis was funded by Bristol Myers Squibb. Writing and editorial assistance were provided by Nikola Vojtov, PhD, of The Lockwood Group (Stamford, CT, USA), funded by Bristol Myers Squibb.

Characteristics before/after IPTW.

	SOC (before)	Liso-cel (before)	SOC (after)	Liso-cel (after)
Mean age, y	70.5	65.4	68.7	69.3
Rai stage III/IV, %	56	57	55	52
Bulky disease, %	86	62	77	69
High-risk cytogenetics, %	83	83	84	76
Mean pLOTs	3.9	6.1	4.5	4.6
Prior chemoimmunotherapy, %	58	88	67	72
Prior PI3Ki, %	18	30	22	23
BTKi refractory, %	69	88	74	77
Venetoclax refractory, %	54	92	64	84

Circulating tumor DNA assessment in patients with early-stage classical Hodgkin lymphoma treated with combination of brentuximab vedotin and nivolumab.

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Background: Recent data suggest circulating tumor DNA (ctDNA) can be detected in patients with classical Hodgkin lymphoma (cHL), with molecular response potentially complementing imaging assessments. We report on the use of an ultra-sensitive assay for ctDNA detection in patients with early-stage cHL to explore its utility in this population. **Methods:** In SGN35-027 (NCT03646123) Part C study, patients with stage I or II cHL without bulky disease (N=154) received brentuximab vedotin, nivolumab, doxorubicin, and dacarbazine (AN+AD) intravenously on days 1 and 15 of each 28-day cycle. Responses were assessed by PET/CT according to Lugano Classification with LYRIC at cycle (C) 2 day (D) 25-28 and end of treatment (EOT). 36 of 154 patients (23%) had plasma samples (collected at baseline, prior to C2D1 and C4D1, and EOT) analyzed for ctDNA using the PhasEDseq MRD assay. PET/CT results were compared with ctDNA dynamic changes in those with detectable baseline ctDNA. A genAI tool (12/19/24; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** Baseline ctDNA was detectable in 34 of 36 patients (94%) and was higher in patients with greater disease burden (indicated by baseline stage/risk status [*P*=0.015] and International Prognostic Score [*P*=0.014]). At C2D1, ctDNA was undetectable in 27 of 33 patients (82%). ctDNA levels decreased in all patients after 1 cycle of treatment. At C2 interim PET/CT, 18 of 34 patients (53%) achieved complete metabolic response (CMR); of these, 17 patients had ctDNA samples evaluable with 16 patients having undetectable ctDNA. The remaining 16 patients achieved partial metabolic response (PMR); of these, 5 patients had detectable ctDNA and 11 had undetectable ctDNA (all 11 patients with undetectable ctDNA achieved CMR at later time points). At C4D1, only 1 patient continued to have detectable ctDNA. At EOT, PET/CT showed that 26 of 34 patients (76%) achieved CMR, 5 achieved PMR, and 3 achieved indeterminate response (IR); none had detectable ctDNA at EOT. In long-term follow up (LTFU), 4 of the 5 PMRs eventually converted to CMR; 1 patient developed a second primary malignancy (mantle cell lymphoma). Follow up assessments during LTFU confirmed that 2 IRs converted to CMR and 1 converted to PMR. **Conclusions:** ctDNA was detectable in majority of patients with early-stage cHL at baseline, and higher levels are associated with increased disease burden. Treatment with AN+AD reduced ctDNA levels, with ctDNA becoming undetectable by EOT in all patients. In some patients, decline in ctDNA levels was observed earlier than responses observed through imaging, suggesting that ctDNA clearance may be an early indicator of treatment response. The potential value of ctDNA as a biomarker for early detection and monitoring of treatment response in early-stage cHL should be further investigated. Clinical trial information: NCT03646123. Research Sponsor: Pfizer Inc.

7041 Poster Session

Updated efficacy and safety results from the phase 2 study of timdarpacept in combination with tislelizumab in patients with classical Hodgkin lymphoma for whom prior anti–PD-1 therapy failed.

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Background: Timdarpacept (IMM01), a recombinant SIRPa-Fc fusion protein, can activate macrophages to enhance anti-tumor activity by blocking CD47-SIRPa interaction. Timdarpacept showed unique property of weak human erythrocyte binding in preclinical studies, and low incidence of anemia in early clinical trials with no need for a priming dose. **Methods:** Eligible patients (pts) with R/R classical Hodgkin lymphoma (cHL) who had failed prior anti-PD-1 treatment were enrolled in this study (NCT05833984). Timdarpacept (2.0mg/kg, QW) and tislelizumab (200mg, Q3W) were intravenously administered in 3-week treatment cycle until disease progression or intolerable toxicity. Objective response rate (ORR) by Lugano 2014 was the primary endpoint and secondary endpoints include tolerability, disease control rate (DCR), duration of response (DoR), progression free survival (PFS) and time to response (TTR). **Results:** As of 18 Oct 2024, 33 cHL pts were enrolled with 19 refractory to anti PD-(L) 1 therapy (best objective response was SD/PD or CR/PR and progressed within 12 weeks of last dose). The median age was 35 years with 23 (69.7%) male pts. The median prior lines of therapy were 4. In all 33 efficacy-evaluable pts with median follow up of 13.83 months, the ORR, complete response (CR) rate and DCR were 69.7%, 24.2% and 93.9%, respectively. For PD-(L) 1 refractory pts, the ORR was 68.4%, and 1 pt achieved CR. The median TTR was 1.6 months. The median DoR was not reached. Further analysis indicated that pts could benefit from timdarpacept combined with tislelizumab treatment regardless of being relapsed or refractory to anti-PD-1 treatment, or having had prior CD30-ADC treatment or not. All pts experienced treatment-related adverse events (TRAEs), 17 (48.5%) of whom experienced grade 3/4 TRAE. The most common TRAEs were WBC decreased (57.6%), PLT decreased (42.4%), anemia (39.4%), ANC decreased (39.4%), lymphocyte decreased (30.3%). Six (18.2%) pts had treatment related SAE. Three pts (9.1%) had an IMM01 dose reduction. One pt (3.0%) experienced permanent discontinuation of IMM01. No TRAEs led to death. **Conclusions:** Timdarpacept in combination with tislelizumab showed promising therapeutic efficacy and a well-tolerated safety profile in cHL patients for whom anti-PD-1 failed, providing evidence for future investigation. Clinical trial information: NCT05833984. Research Sponsor: None.

Longitudinal assessment from liquid biopsy of mutations in CD20: A pilot study using a PETE enrichment strategy.

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Background: In recent years, bispecific T cell Engagers (BsTCE) targeting CD3 and CD20 have emerged as a potent new class of therapeutics for NHL; however, a subset of patients still experience relapsed or refractory disease. Patients undergoing treatment with BsTCEs could benefit from longitudinal screening via liquid biopsy to identify baseline (primary) and treatment-induced (acquired) resistance mutations and tailor treatment accordingly. Here we present the results from a pilot study screening patients treated with Glofitamab (CD20xCD3) using a single gene Primer Extension Target Enrichment (PETE) strategy for *MS4A1* (CD20 gene) in liquid biopsies. **Methods:** Our pilot study was conducted using libraries from the plasma of 134/155 patients with relapsed or refractory large B cell lymphoma (r/r LBCL) who underwent Glofitamab treatment at approved dose in the phase I/II trial NP30179 (NCT03075696) (Dickinson, et al. N Engl J Med 2022), and paired PBMC/PDB available in 91 cases. Primers were designed against the coding regions of the *MS4A1* gene. Enrichment was performed using a workflow optimized for the detection of somatic variants in cell-free DNA isolated from plasma. Results were analyzed using a modified AVENIO circulating tumor (ct) DNA (Roche; For Research Use Only) analysis workflow. Variants detected by the analysis pipeline were further filtered based on inclusion criteria: allele fraction $>$ 0.1%, rarity in the cohort, impact on protein function *in silico*, and if sample was available, absence in germline. Tumor burden as assessed by ctDNA was obtained from retrospective sequencing data. Response to treatment was assessed by PET/CT using the Lugano Criteria. **Results:** Using inclusion criteria a total of 11/134 (8.2%) patients were identified with a total of 16 unique *MS4A1* candidate mutations at baseline or during treatment. The Best Overall Investigator Response (BOR) was progressive disease (PD) for 7 patients and partial metabolic response (PR) for 4 patients. All patients with BOR PR experienced disease progression before treatment completion. Sufficient samples were available to demonstrate expansion of the candidate mutation by the end of treatment (EOT) timepoint for 5 patients. Four of the identified mutations were previously reported in the literature, the remaining mutations were novel, and *in vitro* characterization demonstrated their functional impact. **Conclusions:** This work identifies known and novel mutations in CD20 in plasma samples as a potential contributing mechanism to relapsed or refractory cases of NHL. Although the prevalence appears to be low, this is consistent with previous reports and supports investigation of the clinical utility, including utility as a potential predictive biomarker, of sequencing this gene during treatment with CD20xCD3 BsTCE. Future and ongoing work will screen additional cohorts and therapy combinations. Research Sponsor: The NCT03075696 study was sponsored by F. Hoffman LaRoche Ltd.

7043 Poster Session

Novel analysis of 3-y results from the pivotal EPCORE NHL-1 study: Outcomes in patients (pts) with relapsed/refractory large B-cell lymphoma (R/R LBCL) and complete response (CR) at 2 y with epcoritamab (epcor) monotherapy.

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Background: Depth and duration of CR correlate with long-term outcomes in LBCL. Epcor is a subcutaneous (SC) CD3xCD20 bispecific antibody approved for the treatment (tx) of pts with DLBCL or high-grade BCL after ≥2 lines of tx (LOT). In the 3-y follow-up from the NHL-1 trial, epcor monotherapy led to durable CRs, with a 36-mo median CR duration (mDOCR), 37-mo median progression-free survival (mPFS), and not reached (NR) median overall survival (mOS) in pts with R/R LBCL who had CR. We report long-term outcomes from a post-hoc analysis of the NHL-1 trial in pts who were in CR 2 y after starting tx, referred to herein as pts in CR at 2 y. **Methods:** Pts with R/R CD20$^+$ LBCL and ≥2 prior LOT received epcor SC in 28-d cycles (C; 0.16- and 0.8-mg step-up doses in C1; 48-mg full dose thereafter; once weekly [QW], C1–3; Q2W, C4–9; Q4W, C≥10) until progressive disease (PD) or unacceptable toxicity. The primary endpoint was overall response rate. **Results:** As of the May 3, 2024 data cutoff, 41% (65/157) of pts had CR, of whom 49% (n=32) remained in CR at 2 y. Among the 32 pts in CR at 2 y, median age was 63 y, 47% were male, and 66% were refractory to ≥2 consecutive prior LOT. Pts in CR at 2 y vs pts without CR at 2 y had lower tumor burden at baseline (bulky disease >7 cm 19% vs 34%; LDH 294 vs 501 U/L); pts in CR at 2 y had lower baseline ferritin levels (383 vs 856 μg/L) and similar CAR T exposure (38% vs 39%). At data cutoff, median follow-up for pts in CR at 2 y was 37 mo (range 32–46). All but 1 had a response (CR or partial response) by the 2nd assessment at wk 12. mDOCR was NR, and ~96% of pts remained in CR at 3 y. At the data cutoff, the longest ongoing CR was >43 mo. mPFS and mOS were NR. The overall epcor safety profile in pts in CR at 2 y was consistent with that of the intention-to-treat population. Median tx duration was 35 mo (range 8–43); 81% (26/32) of pts remained on tx at 2 y. 19% (5/26) pts still on tx at 2 y had ≥1 serious infection after 2 y, most commonly pneumonia (n=4). Two pts had a fatal infection (COVID-19 pneumonia, pneumonia) after 2 y. At data cutoff, 19/32 (59%) pts with CR at 2 y were still on tx. One pt discontinued (D/C) due to PD; 12 D/C for reasons other than PD, most commonly adverse events (n=6, including the 2 pts with fatal infections above). In 12 pts who D/C due to reasons other than PD, CR was maintained for a median of 14 mo (range 2–28) after tx D/C. **Conclusions:** This novel subgroup analysis of pts with R/R LBCL in CR at 2 y after starting epcor highlights long-term disease remission, overall survival, and potential for cure with epcor in some pts. Long-term safety remained manageable. These results underscore the benefits of epcor in the 3L+ setting and may inform personalized tx strategies. Additional data to further characterize pts with R/R LBCL and a prolonged CR with epcor monotherapy will be presented. Clinical trial information: NCT03625037. Research Sponsor: Genmab.

Ibrutinib, venetoclax plus CD20 monoclonal Ab: Initial results of OASIS II, a prospective randomized phase 2 trial in previously untreated mantle cell lymphoma patients.

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Background: Ibrutinib is approved in R/R MCL. Enrich trial (Lewis, ASH 2024, abst 235) showed that Ibrutnib/CD20mAb outperforms chemotherapy front-line. We demonstrated that Ibrutnib/CD20mAb plus Venetoclax has a good safety profile in R/R and untreated MCL (Le Gouill, Blood 2021). Whether or not Ibrutnib/CD20mAb is superior to Ibrutnib/CD20/Venetoclax front-line is a key question. OASIS 2 (NCT04802590) is a phase 2 prospective randomized international trial that investigates Ibrutinib/CD20mAb (Arm A) plus Venetoclax (Arm B) in untreated MCL. **Methods:** Patients were stratified by country, age (< / >=66 years) and MIPI. All patients (18-80y) with untreated MCL, stage II-IV and nodal disease were eligible. Treatment consisted of Ibrutinib (560 mg/d, C1-24) and anti-CD20mAb (C1-6), then 2 monthly (C7-42). In Arm B, Venetoclax was added for a fixed duration of 2y (400 mg/d). The study uses a two-stage Simon's design. A preplanned interim futility analysis occurred after 39 pts with informative MRD were randomized in each arm. The primary endpoint of the futility analysis is the measurable residual disease (MRD) negativity rate assessed by digital-droplet PCR technique at the end of C6. Each treatment arm was to be considered effective if the 80% upper CI MRD negativity percentage was ≥ 64%. The interim analysis result was mandatory to re-open the trial (only for effective arms) for the second phase of recruitment. Herein, we present the results of the futility pre-planed interim analysis. **Results:** 102 pts were randomized (51 in each arm, 78 were MRD informative). Pts' characteristics were comparable between the two arms. One patient in arm B withdrew consent before any treatment. 46 in arm A and 45 in arm B completed the first 6 cycles. The median dose intensity for CD20mAb was 100%, 96% for Ibrutinib in arm A and 90% in Arm B, 91% for Venetoclax. At least one dose adjustment of Ibrutinib was more frequent in Arm B (28% vs 15.7%). At least one Venetoclax dose reduction was needed in 24% of patients in Arm B. AE, AESI, AE grade ≥ 3 were more frequent in Arm B (92% vs 82.4%; 82% vs 52.9%; 64% vs 47.1%) but not for SAE grade ≥ 3 (32% vs 31.4%). The most frequent grade 3 AE was neutropenia (11.8% vs 34%). MRD negativity was obtained in 53.8% (CI 80% 42.4% - 65%) in Arm A and 82.1% (CI 80% 71.7% - 89.7%) in Arm B. According to Lugano criteria at the end of C6, 21 out of 39 (54%) pts were in a complete metabolic remission in Arm A vs 27 out of 39 (69%) in Arm B. The export in Oct 2024 showed that the 2-y PFS and OS were 87.9% (95%CI, 79.7-92.9) and 91.9% (95%CI, 84.5-95.9). **Conclusions:** Ibrutinib/CD20mAb /Venetoclax frontline provides very high MRD negativity rate. According to the statistical analysis plan, both arms were thus re-opened for inclusion on 02APR24 and 102 new patients have been included (end of inclusion DEC 2024). Clinical trial information: NCT04802590. Research Sponsor: None.

Survival outcomes of Epstein-Barr virus-positive diffuse large B-cell lymphoma, not otherwise specified: Results from Latin American and United States cohorts.

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Background: Epstein-Barr virus-positive diffuse large B-cell lymphoma (EBV+ DLBCL), not otherwise specified, is rare in North America and Europe (2–4%) but prevalent in Latin America (LATAM, 7–14%). Most studies are limited by single-center designs, small cohorts, short follow-up, and infrequent rituximab use. Prognostic systems like the International Prognostic Index (IPI) are widely used, yet their predictive power in EBV+ DLBCL remains unclear. Additionally, the optimal threshold for EBV-encoded RNA (EBER) positivity remains controversial, with cutoffs ranging from ≥20% to ≥80%. This study aimed to characterize clinical outcomes and evaluate prognostic scores and EBER thresholds in LATAM patients treated with chemoimmunotherapy, contrasted with a U.S.-based cohort. **Methods:** This multicenter retrospective cohort study included patients diagnosed with EBV+ DLBCL from 2002–2020 in five LATAM countries (GELL registry) and a two U.S. centers (2008–2023). EBV positivity was defined per institutional EBER standards. Patients managed without anti-CD20 antibodies were excluded. Outcomes (overall survival [OS] and progression-free survival [PFS]) were assessed using Kaplan-Meier analysis, log-rank tests, and Cox regression. Prognostic systems (IPI, NCCN-IPI, R-IPI, Oyama score) were evaluated using C-indices. **Results:** In the LATAM cohort (n=139), median age was 58 years, 71% had advanced-stage (stage III-IV) disease, and 90% received R-CHOP. In the U.S. cohort (n=136), median age was 67 years, 74% had advanced-stage disease, and 74% received R-CHOP. In the LATAM cohort, with a median follow-up of 61 months (95% CI=53-68), 43 deaths were observed. The 5-year OS and PFS rates were 63% (95% CI=54-73%) and 50% (95% CI=41-60%), respectively. In the US cohort, with a median follow-up of 54 months (95% CI=45-66), 52 deaths were observed. The 5-year OS and PFS rates was 54% (95% CI=45-65%), and 41% (95% CI=32-52%), respectively. All evaluated prognostic scores had a similar performance in the LATAM (OS: C-index range 0.595-0.674; PFS: C-index range 0.553-0.633) and US (OS: C-index range 0.679-0.744; PFS: C-index range 0.701-0.782) cohorts. EBER test ≥80% was associated with mortality in the US cohort (adjusted HR=2.76, 95% CI=1.53-5.00). **Conclusions:** To the best of our knowledge this is one of the largest studies on EBV+ DLBCL. This study highlights comparable survival outcomes for EBV+ DLBCL in LATAM and the U.S. with chemoimmunotherapy, supporting its use in the management of this rare entity. Prognostic systems show variable performance across regions, emphasizing the need for further validation in EBV+ DLBCL populations. Variability in EBER thresholds underscores the need for standardized diagnostic criteria to optimize prognostication and treatment. Research Sponsor: None.

Safety and efficacy of AZD0486, a CD19xCD3 T-cell engager, in relapsed or refractory diffuse large B-cell lymphoma.

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Background: Treating relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) is challenging despite advances. AZD0486, a novel IgG4 fully human CD19xCD3 bispecific T-cell engager, showed promising safety and efficacy in patients (pts) with heavily pretreated follicular lymphoma with an overall response rate (ORR) and complete response (CR) rate of 95% and 85%, respectively, at target doses (TD) ≥2.4 mg (Hou JZ, et al. *Blood.* 2024). We present results from an ongoing phase 1 trial in pts with R/R DLBCL (NCT04594642). **Methods:** Eligible pts with R/R CD19+ B-cell lymphoma and ≥2 prior lines of therapy (pLOT) received fixed-duration AZD0486 intravenously for 2 years. Initially, pts received either no or 1 step-up dose (SUD). Subsequently, 2SUD on D1/D8 was implemented with TD on D15. TDs were given every 2 weeks in 28-day cycles. After 2 consecutive CRs, pts could receive dosing every 4 weeks. Primary objectives are safety, tolerability, pharmacokinetics, and determining the maximum tolerated dose (MTD). RECIL-based response assessment is performed by central imaging review. Measurable residual disease (MRD) in plasma ctDNA is assessed by PhasED-seq CLARITY assay. CTCAE v5.0 and ASTCT criteria are used to grade adverse events (AEs). **Results:** As of Sept 29, 2024, 70 pts with R/R DLBCL received AZD0486 at TDs ≤0.8 mg (n=2), 2.4 mg (n=18), 7.2 mg (n=22), 15 mg (n=25), and 25 mg (n=3). Median pLOT was 3 (range, 1–12) and 34 (49%) pts received prior CD19-directed CAR-T therapy. In 61 evaluable pts who received TDs ≥2.4 mg, ORR and CR rate were 46% and 33%, respectively. ORR/CR rates tended to be higher with higher doses (39%/22% at 2.4 mg, 43%/33% at 7.2 mg, and 55%/41% at 15 mg, respectively). ORR/CR rates were higher in pts without prior CAR-T vs CAR-T–exposed pts (57%/39% vs 36%/27%). For pts who received 7.2 mg or 15 mg (median follow-up 8.8 months and 5.3 months, respectively), median duration of response (DOR) was not reached; 12-mo estimated DOR was 64%. One pt who achieved CR progressed. Of the 15 pts who achieved CR and were evaluable for MRD in the 7.2-mg and 15-mg cohorts, 87% (13/15) achieved undetectable MRD. In the overall population (N=70), infections occurred in 37% of pts, with 9% grade [G] ≥3; COVID-19 occurred in 13% of pts. Febrile neutropenia occurred in 3% of pts. Neutropenia ≥G3 occurred in 23% of pts, while anemia ≥G3 occurred in 14%. In pts who received 2SUD (n=54), CRS occurred in 44% of pts, all low grade (G1/G2, 41%/4%), and 20% received tocilizumab; ICANS occurred in 17% of pts (G3, 3%). All CRS and ICANS events in the 2SUD cohort occurred in C1 (except for 1 CRS event on C2D1), were transient, and did not require treatment discontinuation. No AZD0486-related deaths or AEs leading to discontinuation occurred. **Conclusions:** AZD0486 at TDs ≥2.4 mg showed promising efficacy and manageable safety in pts with R/R DLBCL. Target doses up to 25 mg have been tested without exceeding MTD. Dose escalation is ongoing. Clinical trial information: NCT04594642. Research Sponsor: AstraZeneca.

7047 Poster Session

High HDAC I/IIb selective inhibitor purinostat mesylate in relapsed and refractory diffuse large B-cell lymphoma: A single agent phase IIb study.

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Background: Relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) has a poor prognosis. Purinostat Mesylate (PM) is a high selective HDAC I/IIb inhibitor. PM has demonstrated its safety and efficacy in r/r DLBCL in previous studies. Based on results of phase IIa, 11.2mg/m^2 was chosen to be the RP2D. The efficacy and safety of PM monotherapy in r/r DLBCL patients are evaluated in phase IIb study (NCT05563844). **Methods:** This multicenter, single-arm, phase IIb study is conducted in 37 sites in China. Key eligibilities include r/r DLBCL 2~5 lines; prior therapies include anti-CD20 monoclonal antibody and anthracycline-based chemotherapy; ECOG≤2. The IIb study plans to enroll 90 patients to receive IV of PM at 11.2mg/m^2 on day 1, 4, 8, 11 of 21-day cycle. Patients continue to receive PM until disease progression or unacceptable toxicity. Primary outcome is ORR. Secondary outcomes include PFS, OS and safety. **Results:** As of2025.1.18, 44 r/r DLBCL patients had been enrolled (median age 62.5 years, 45.5% female) with a median of 2 lines of prior therapy. 43 patients have at least one response evaluation. After a median follow-up of 6.0 months, the ORR is 60.5% (26/43) with 9 complete response (CR) and 17 partial response (PR). Most response (19/26) occurred at early cycle with median TTR of 1.3 months (95% CI, 1.25-2.00), and the mDOR is 8.6 months (95% CI, 4.24- NR). Among 26 patients with response, 16 patients remain on treatment and the longest treatment has lasted for 22 cycles (still CR at cycle 21). The mPFS is 6.2 months (95% CI, 3.22-NR) and the mOS is immature. In subgroup analysis, 16 double-expressor DLBCL patients obtained 56.3% (9/16) ORR and 32 patients with TP53 mutation by NGS/FISH test achieved 62.5% (20/32) ORR. The most common grade ≥3 treatment emergent adverse events include thrombocytopenia (81.8%), neutropenia (79.5%), leukocytopenia (47.7%), lymphocytopenia (27.3%), hypokalemia (11.4%), anemia (9.1%) and hypertriglyceridemia (9.1%). No PM-related death was reported. **Conclusion:** This ongoing study showed 11.2mg/m^2 PM in 21-day-cycle achieved remarkable efficacy in r/r DLBCL and acceptable safety profile. The strategy for pivotal study of PM in r/r DLBCL is discussed with NMPA. Clinical trial information: NCT05563844. Research Sponsor: Chengdu Zenitar Biomedical Technology Co., Ltd, Chengdu, Sichuan, China; Sichuan Province "14th Five-Year Plan" Life and Health Major Science and Technology Project (2022ZDZX0027).

Combination of mitoxantrone hydrochloride liposome with cyclophosphamide, vincristine, and prednisone (CMOP) for patients with treatment-naïve peripheral T-cell lymphomas (PTCLs): Extended follow-up analysis of a multicenter, open-label, single-arm, phase Ib study.

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Background: PTCLs represent a heterogeneous group of lymphomas generally majority of patients (pts) associated with a poor prognosis when treated with CHOP based therapy. Mitoxantrone hydrochloride liposome (Lipo-MIT) has demonstrated efficacy in relapsed/refractory PTCLs in our previous study. This study previously reported that CMOP regimen exhibits encouraging efficacy in treatment-naïve (TN) PTCLs. Here we present extended follow-up data of the final dose (NCT04548700). **Methods:** Eligible pts were aged 18-70 years with histologically confirmed TN PTCLs. Pts received Lipo-MIT combined with standard doses of COP regimen every four weeks for six cycles. The study consisted of a 3+3 dose-escalation phase (Lipo-MIT at 12, 15, 18, and 21 mg/m^2) and a specific dose-expansion phase (Lipo-MIT at the recommended phase 2 dose [RP2D]). The primary endpoints were dose-limiting toxicity (DLT) and safety. Secondary endpoints included objective response rate (ORR) assessed by an independent review committee (IRC), duration of CR (DoCR), DoR, PFS, OS, and pharmacokinetics (PK). **Results:** As of November 17, 2022,38 pts were enrolled (26 in the dose-escalation) from 7 centers in China, including 21 (55.3%) AITL, 6 (15.8%) PTCL-NOS, 4 (10.5%) ALK- ALCL, 3 (7.9%) ALK+ PTCL, and 4 (10.5%) other types,16 (42.1%) pts had stage IV disease. No DLTs were observed and a Lipo-MIT dose of 18 mg/m^2 was recommended as the RP2D. The most common treatment-related grade 3/4 adverse events were hematologic toxicities, including neutropenia (76.3%), leukopenia (73.7%), lymphopenia (44.7%), thrombocytopenia (15.8%) and anemia (13.2%). After a median follow-up of 23.8 (range 1.0-42.4) months, among the 35 response-evaluable pts, the IRC-assessed CR rate was 54.3% (95% CI, 36.6-71.2%), and the ORR was 88.6% (95% CI, 73.3-96.8%). According to the investigator assessment, the CR and ORR rate were 51.4% (95% CI, 34.0-68.6%) and 85.7% (95% CI, 69.7-95.2%), respectively. The median DoCR was not reached, while the median DoR were 20.1 (95% CI, 5.2-35.1) months. The median PFS was 20.8 (95% CI, 6.1-35.5) months, and the median OS was not reached with a 2-year OS rate of 93.3% (95% CI, 75.9-98.3%). Moreover, Lipo-MIT exhibited a favorable PK profile, with linear PK characteristics in the 12-18 mg/m^2 dose range. **Conclusions:** The CMOP regimen demonstrates a favorable PK profile, manageable safety profile, and encouraging preliminary anti-tumor activity. These results support further phase 2 and 3 trials clinical studies to confirm activity and assess efficacy in this population. Clinical trial information: NCT04548700. Research Sponsor: CSPC Zhongqi Pharmaceutical Technology Co., Ltd.

7049 Poster Session

Long-term follow-up of the phase 2 ELM-2 study: Odronextamab for patients (pts) with relapsed/refractory (R/R) follicular lymphoma (FL).

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Background: Odronextamab, an investigational off-the-shelf CD20×CD3 bispecific antibody, demonstrated compelling efficacy and a generally manageable safety profile in heavily pretreated pts with R/R FL in the primary analysis of the Phase 2 ELM-2 study (NCT03888105; Kim TM, et al. *Ann Oncol* 2024). We present updated efficacy and safety data for odronextamab in pts with R/R FL from ELM-2 after >2 yrs follow-up. **Methods:** Odronextamab was administered intravenously until disease progression/unacceptable toxicity, with Cycle (C) 1 step-up dosing to help mitigate cytokine release syndrome (CRS) risk, as reported previously. Pts with a complete response (CR) for ≥9 months (mo) switched from maintenance dosing Q2W to Q4W. Primary endpoint: objective response rate (ORR) per Lugano criteria by independent central review (ICR); secondary endpoints: CR rate, duration of response (DOR), progression-free survival (PFS), overall survival (OS). **Results:** At the updated data cutoff (Aug 15, 2024), 157 pts with centrally confirmed R/R FL Grade (Gr) 1–3a were enrolled. Median no. of treatment cycles: 19.0 (range 0.1–117.3); 96.2% (n = 151) and 82.8% (n = 130) of pts completed C1 and C4, respectively. The global cohort comprised 128 pts evaluable for efficacy. At a median efficacy follow-up of 28.3 mo, ORR was 80.5% (n = 103) by ICR and CR rate was 74.2% (n = 95); 92.2% of responders achieved CR. Responses were durable (median DOR, 26.0 mo; median duration of CR, 32.2 mo). ORR was consistent across high-risk subgroups (Follicular Lymphoma International Prognostic Index score 3–5, 78.4%; progression of disease within 2 yrs of frontline therapy, 81.0%). Median PFS was 23.0 mo (estimated 36-mo PFS rate, 37.5%), and median OS was 54.2 mo (estimated 36-mo OS rate, 62.6%). Median PFS was longer in pts who were minimal residual disease (MRD) negative (42.4 mo) versus MRD positive (21.6 mo) at Week 12. Of 47/128 pts who switched to Q4W dosing, 32 remained in CR. The odronextamab long-term safety profile was consistent with the primary analysis. All 157 pts had TEAEs (Gr ≥3, 86.0%), and 15.3% discontinued treatment due to TEAEs (most common: COVID-19 infection, 2.5%). With 0.7/4/20 mg step-up dosing (n = 89), CRS events were mostly low grade (Gr 1, 46.1%; Gr 2, 13.5%; Gr 3, n = 1; Gr ≥4, n = 0), occurred mostly in C1, and resolved in a median of 8.4 hrs. Immune effector cell-associated neurotoxicity syndrome was reported in one pt (Gr 2). Infections were reported in 79.0% of pts (124/157; Gr ≥3, 42.0%). COVID-19-related infections were reported in 38.2% of pts (Gr 5, 5.7%). **Conclusions:** With longer follow-up, odronextamab demonstrated durable responses in heavily pretreated pts with R/R FL from ELM-2, with robust efficacy in those with high-risk features, and a generally manageable safety profile. Overall, these compelling results support odronextamab as a potential off-the-shelf treatment option for pts with R/R FL. Clinical trial information: NCT03888105. Research Sponsor: Regeneron Pharmaceuticals, Inc.

7050 Poster Session

Efficacy and safety of ifupinostat (BEBT-908) in combination with rituximab for relapsed/refractory diffuse large B-cell lymphoma: Results from an exploratory phase Ib study.

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Background: Ifupinostat is a dual HDAC/PI3Kα inhibitor designed to target tumor cell signaling networks by simultaneously inhibiting HDAC and PI3Kα, thereby disrupting tumor cell proliferation and inducing apoptosis. A single-arm pivotal trial of Ifupinostat in patients who received at least two lines of systemic therapy for relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) has been completed, with data currently under NDA review by the NMPA. This exploratory trial evaluates Ifupinostat in combination with rituximab as part of a confirmatory phase 3 trial to further assess its efficacy and safety as a second-line treatment for r/r DLBCL (NCT06164327). **Methods:** This multicenter Phase 1b trial was designed to evaluate the efficacy and safety of Ifupinostat in combination with rituximab (R) with or without standard second-line regimens (R-GemOx or R-ICE). Cohort 3 included 24 r/r DLBCL patients with prior exposure to at least one systemic therapy, all involving anti-CD20 antibody. Among these, 16 patients (66.6%) were primary refractory, 4 patients (16.7%) were refractory to their most recent line of therapy, and 4 patients (16.7%) were relapsed cases. Treatment consisted of Ifupinostat administered intravenously at a dose of 22.5 mg/m^2 on days 1, 3, 5, 8, 10, and 12 of each 21-day cycle. Rituximab was administered intravenously at a dose of 375 mg/m^2 on day 1 of each cycle. Tumor assessments were conducted following treatment, and efficacy was evaluated according to the Lugano 2014 criteria. Key endpoints included the objective response rate (ORR) and safety. **Results:** Of the 24 enrolled patients, 21 completed at least one treatment dose and underwent tumor assessment. The ORR was 76.2%, with 10 patients (47.6%) achieving a complete response (CR) and 6 (28.6%) achieving a partial response (PR). The disease control rate (DCR) was 85.7%. Median progression-free survival (PFS) has not yet been reached (>7.7 months). Common grade 3-4 hematological toxicities observed during treatment included thrombocytopenia (34.8%), leukopenia (17.4%), and lymphopenia (13.0%). No unexpected toxicities were observed, and the safety profile was deemed manageable. **Conclusions:** The study results demonstrate promising efficacy and a manageable safety profile for Ifupinostat in combination with rituximab as a second-line treatment for r/r DLBCL. These findings support further investigation in confirmatory phase 3 trials, which are currently underway. Clinical trial information: NCT06164327. Research Sponsor: None.

Phase II safety and preliminary efficacy of amulirafusp alfa (IMM0306) in combination with lenalidomide in patients with relapsed or refractory CD20-positive follicular lymphoma.

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Background: Amulirafusp alfa (IMM0306) consists of anti-CD20 monoclonal antibody fused with the CD47 binding domain of SIRPα. It exerts potent anti-cancer efficacy by activating both macrophages and NK cells via blockading of CD47-SIRPα interaction and FcγR engagement. Lenalidomide was approved for relapsed or refractory (R/R) indolent non-Hodgkin's lymphoma (iNHL). Here, we report results from a Phase II study of 34 patients with R/R CD20-positive follicular lymphoma (FL) (NCT05771883). **Methods:** Eligible patients with grade 1-3a FL received amulirafusp alfa 1.6 mg/kg intravenously once a week with lenalidomide 20 mg orally once a day on Days 1 to 21 in each 28-day cycle until disease progression or intolerable toxicity. Safety was evaluated by CTCAE 5.0, tumor assessments performed every 8 weeks by Lugano 2014. **Results:** Until Dec 26, 2024, 34 patients with R/R FL were enrolled. Median age was 54, 20 (58.8%) were males, and 32 (94.1%) had stage III-IV disease. The median number of prior line therapy was 2. All patients received previous anti-CD20 therapy. Among 22 efficacy-evaluable patients, 10 CR, 8 PR, 2 SD and 2 PD were observed. The CRR and ORR were 45.5% and 81.8%, respectively. Of the 4 efficacy-evaluable patients who did not achieve response, 2 SD patients were both CD20 therapy refractory, 1 PD patient had histologic transformation and 1 PD patient were lenalidomide-resistant (had taken lenalidomide continuously for about 4 years). The most common treatment related adverse events (TRAEs) ($\geq$ 20%) were PLT decreased (70.6%), WBC decreased (58.8%), anemia (52.9%), ANC decreased (52.9%), lymphocyte decreased (52.9%), infusion-related reactions (35.3%) and hypoalbuminaemia (23.5%). Grade $\geq$3 TRAEs occurred in 22 (64.7%) patients, the most common $\geq$ grade 3 TRAEs ($\geq$ 10%) were ANC decreased (29.4%), lymphocyte decreased (26.5%), PLT decreased (23.5%) and WBC decreased (11.8%). 5 (14.7%) patients experienced serious TRAE. 1 (2.9%) patient had a dose reduction of amulirafusp alfa, 5 (14.7%) patients had dose reductions of lenalidomide due to TRAEs. 1 (2.9%) patient experienced TRAE leading to the study drug discontinuation (Grade 4 Type I hypersensitivity, recovered with sequelae within 1 month). No patient experienced TRAE leading to death. There were no significant differences between amulirafusp alfa monotherapy and combination with lenalidomide in terms of PK exposure and ADA incidence rate. Pharmacodynamics analysis demonstrated amulirafusp alfa combine lenalidomide effectively depleted $CD19^+$B cell in peripheral blood and achieved sustained long-term B cell depletion. **Conclusions:** Amulirafusp alfa in combination with lenalidomide showed a preliminary anti-tumor activity and a well-tolerated safety profile in patients with R/R FL. This phase Ib/II study is still ongoing. Clinical trial information: NCT05771883. Research Sponsor: None.

Impact of cell of origin, gene rearrangements, and frontline treatment on incidence of secondary central nervous system lymphoma in newly diagnosed diffuse large B-cell lymphoma.

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Background: Secondary central nervous system lymphoma (SCNSL) is a rare but serious complication that occurs in 2-10% of patients (pts) with diffuse large B-cell lymphoma (DLBCL). The CNS-International Prognostic Index (CNS-IPI) is a validated tool used to assess the risk of CNS relapse. However, with advancements in molecular profiling and treatments, the predictors of SCNSL, including the predictive ability of CNS-IPI combined with other molecular markers and treatment regimens, have become uncertain. This study evaluates new prognostic markers for CNS relapse in DLBCL, focusing on cell-of-origin (COO), gene rearrangements, and treatment types. **Methods:** DLBCL pts enrolled from 2002-2015 in the Mayo Clinic and University of Iowa Lymphoma Molecular Epidemiology Resource were prospectively followed for incidence of CNS relapse. Pts with primary CNS lymphoma or CNS involvement at diagnosis, and pts treated with high-dose methotrexate containing regimens were excluded. COO classification (GCB vs non-GCB) was determined using Hans algorithm and/or NanoString data. Multivariate Cox regression models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for predictors of SCNSL. Survival analysis was performed from time of DLBCL diagnosis using Cox proportional hazards model. **Results:** Among 1278 newly diagnosed DLBCL pts included (median age: 63 years; 43.6% female), SCNSL occurred in 46 (3.6%) pts. Pts with SCNSL were more likely to have intermediate/high CNS-IPI scores (80.4%) than pts without SCNSL (63.9%, p=0.02). The 3 yr SCNSL incidence was 0.016 (0.008-0.0033) in low CNS-IPI vs 0.043 (0.031-0.0060) in high CNS-IPI. Those with SCNSL were significantly more likely at baseline to have non-GCB COO (56.3% vs. 36.5%, p=0.02), and advanced stage (76.1% vs. 59.9%, p=0.03) compared to those without SCNSL. The incidence of SCNSL was not influenced by MYC, BCL2, or BCL6 rearrangements, nor by treatment with R-CHOP, R-EPOCH, or other immunochemotherapy regimens. MVA showed that intermediate CNS-IPI (HR 2.32, 95% CI 1.09-4.92, p=0.029), high CNS-IPI (HR 3.59, 95% CI 1.49-8.62, p=0.004), and non-GCB COO (HR 2.19, 95% CI 1.08-4.42, p=0.0029) were independently associated with increased SCNSL risk. After a median follow-up of 12 years (IQR 9–15), overall survival (OS) was 52.1% for the cohort, with OS significantly worse for SCNSL pts (17.4% vs. 53.4%, p<0.001). **Conclusions:** This large cohort with extensive follow-up highlights the role of COO as an additional prognostic factor for SCNSL while reinforcing CNS-IPI's prognostic value. Non-GCB COO pts had a higher risk of SCNSL even when adjusted by CNS-IPI risk. Despite advancements in management, SCNSL pts continue to have poor outcomes. Strategies to reduce the incidence of CNS relapse in high-risk pts require further investigation. Research Sponsor: None.

MER CNS relapse hazard ratios (95% CI).

Characteristics	Hazard Ratio	95% CI	P-Value
CNS-IPI Group			
0-1 Low	Ref	Ref	Ref
2-3 Intermediate	2.32	1.09 - 4.92	0.029
4+ High	3.59	1.49 - 8.62	0.004
Cell of Origin*			
GCB	Ref	Ref	Ref
non-GCB	2.19	1.08 - 4.42	0.029
Double Hit*			
non-DHL	Ref	Ref	Ref
DHL	1.08	0.14 - 8.3	0.941
Not Done/Missing	1.38	0.76 - 2.51	0.297
Double Expressor*			
Negative	Ref	Ref	Ref
Positive	2.36	0.71 - 7.85	0.162
Not Done/Missing	1.91	0.89 - 4.08	0.097
IC Group*			
R-CHOP	Ref	Ref	Ref
R-EPOCH	1.63	0.71 - 3.74	0.249
Other IC	1.18	0.57 - 2.46	0.660
Any EN Involvement*			
No	Ref	Ref	Ref
Yes	0.98	0.51 - 1.88	0.946
Albumin Group*			
>=Normal	Ref	Ref	Ref
<Normal	1.70	0.75 - 3.85	0.201
Head & Neck Involvement*			
No	Ref	Ref	Ref
Yes	0.35	0.048 - 2.63	0.310

*Adjusted by CNS-IPI risk group.

A phase I study of the EZH2 inhibitor TR115 in patients with relapsed/refractory non-Hodgkin's lymphomas and advanced solid tumors.

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Background: EZH2 gain-of-function mutations and overexpression lead to aberrant H3K27me3 levels and result in tumorigenesis and metastasis, including several categories of B cell and T cell lymphoid malignancies, and it is associated with poor clinical prognosis and outcomes. TR115, a novel, highly selective, orally administered EZH2 inhibitor, has demonstrated potent anti-tumor activity in preclinical models. This Phase I study aims to evaluate the safety, tolerability, and preliminary efficacy of TR115 in patients with relapsed/refractory non-Hodgkin's lymphomas (NHL) and advanced solid tumors. **Methods:** Dose escalation started at 200mg bid and progressed up to 1600mg bid. Patients received TR115 orally twice daily in 28-day cycles until disease progression, unacceptable toxicity, or patient withdrawal. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Efficacy was evaluated using Lugano 2014 criteria for lymphomas and RECIST v1.1 for solid tumors. **Results:** By January 10, 2025, a total of 20 patients were enrolled, including those with angioimmunoblastic T-cell lymphoma (AITL, n=4), diffuse large B-cell lymphoma (DLBCL, n=4), ovarian cancer (n=4), ALK-negative anaplastic large cell lymphoma (ALCL, n-2), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS, n=2), mycosis fungoides (n=1), follicular lymphoma (FL, n=1), extranodal marginal zone mucosa-associated lymphoid tissue lymphoma (MALT, n=1) and breast cancer (n=1). Median age was 61 (range 37-77) with 10 (50%) males. Most were heavily pretreated with a median of 2 previous lines of therapy. the most common TRAEs (all grades/Grade $\geq$3) included thrombocytopenia (50%/15%), leukopenia (45%/10%) , anemia (40%/15%), neutropenia (35%/10%), hypertriglyceridemia (35%/5%), elevated blood creatinine (35%/0%), elevated lactate dehydrogenase (25%/0%), hypokalemia (25%/5%), hyperbilirubinemia (20%/0%), adynamia (20%/5%), Hypoproteinemia (20%/0%), and upper respiratory tract infection (10%/5%). Of the 11 patients with non-Hodgkin's lymphomas evaluable for response, the overall response rate (ORR) was 63.6%, and the disease control rate (DCR) was 81.8%. 6 patients with PTCL had an ORR of 100%, and 4 continue to receive treatment with the investigational drug. One PTCL-NOS patient achieved a complete response (CR) remaining on treatment at Cycle 16. PK parameters AUC_{0-24h} and C_{max} were dose proportional with median T_{max} 2 hours. **Conclusions:** In this study, TR115 exhibited a favorable safety profile and promising efficacy in patients with relapsed/refractory non-Hodgkin's lymphoma, especially in relapsed/refractory PTCL patients. Further investigation of TR115 alone or in key therapeutic combinations is warranted. (NCT05650580). Clinical trial information: NCT05650580. Research Sponsor: Tarapeutics Pharmaceutical Science Inc.

Lorlatinib therapy in relapsed/refractory ALK+ lymphomas previously treated with tyrosine kinase inhibitors.

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Background: ALK+ Lymphomas are aggressive diseases with poor prognosis when chemo-immunotherapy (CIT) and Crizotinib fail. Lorlatinib is a 3rd-generation tyrosine kinase inhibitor (TKI), that inhibits all reported ALK kinase domain mutations responsible for resistance to Crizotinib. **Methods:** From 2019 to 2024, we enrolled 8 patients (pts) in a phase 2 open label monocentric study with Lorlatinib in relapse/refractory (r/r) ALK+ lymphomas previously treated with other TKI (EudraCT2016-003970-41). Overall response rate (ORR), the primary endpoint, was evaluated using 18F-FDG PET/CT scans and ALK RT-PCR on peripheral blood and bone marrow samples. Secondary endpoints were progression-free survival (PFS) and overall survival (OS) from the start of Lorlatinib to relapse and/or death. Side effects were classified according to CTCAEv4.03. Our cohort included 4 ALK+ Large B Cell Lymphoma (LBCL) with Clathrin-ALK (CLTC::ALK) rearrangement, 2 ALK+ Anaplastic Large Cell Lymphoma (ALCL) with ATIC::ALK fusion, 1 ALK+ ALCL Lymphoma with NPM::ALK translocation and 1 ALK+ histiocytosis with EML4::ALK rearrangement. **Results:** The median follow-up (fup) was 23 months (1,3- 62), the median age at diagnosis was 23 years (19-57); all pts were in stage IV Ann Arbor and treated with CIT and Crizotinib. 2 pts also received other TKIs (Alectinib and Ceritinib). Lorlatinib was administered daily at a dose of 100 mg. The ORR at one month (M1) was 100% (95% CI: 72-100%): 5 CR and 3 PR. 3 pts (2 ALCL [ATIC::ALK], 1 ALCL [NPM::ALK]), underwent Allogeneic Stem Cell Transplant (ASCT) while in CR and resumed Lorlatinib post-transplant. Due to hepatic GVHD and memory impairment, their Lorlatinib dosage was reduced from 100 mg to 75-50 mg/day. All of them are in CR. 2 pts (LBCL with CLTC::ALK) refused ASCT, maintained CR from M1 through their last fup at 15 and 65 months respectively, continuing with Lorlatinib at 100 mg/day. 2 ALK+ LBCL pts (CLTC::ALK) achieved PR at M1 but relapsed within 3 months and did not benefit from ASCT or salvage treatments. The pt with ALK+ histiocytosis was in PR at M1 and then obtained CR at M3 with Lorlatinib; surgical resection of a residual necrotic lung mass was performed. She has been in CR for >40 months. PFS rate at 3 months was 75%, with no additional events reported. OS was 87% at 3 and 12 months, and 72% at 24 months and stabilized thereafter. All ALK+ lymphoma pts in CR at M1 maintained a durable response, whereas those in PR died of disease progression. The type of lymphoma or of ALK translocation did not correlate with outcome. Main adverse effects (all grade I/II) included hyperlipidaemia, weight gain, muscle cramps, gastrointestinal symptoms, thrombocytopenia and memory difficulty. **Conclusions:** Our analysis confirms Lorlatinib's efficacy and safety as salvage therapy. Achieving a CR at M1 was found to be the most important prognostic factor for survival. Adverse events are manageable with dose adjustments. Clinical trial information: EudraCT2016-003970-41. Research Sponsor: None.

7055 Poster Session

Combination of mitoxantrone hydrochloride liposome with tislelizumab in patients with relapsed or refractory NK/T cell lymphoma: A phase Ib/II study.

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Background: Natural killer/T-cell lymphoma (NKTCL) is a unique subtype of non-Hodgkin lymphoma with aggressive disease course. Mitoxantrone hydrochloride liposome (Lipo-MIT) is a nano-drug that has been approved for relapsed/refractory (r/r) PTCL, and has shown certain efficacy and safety in a pivotal phase II study (Cancer. 2025, e35672). Tislelizumab is a humanized immunoglobulin G4 variant monoclonal antibody against PD-1. This study aims to investigate the safety and efficacy of combining Lipo-MIT with tislelizumab in patients (pts) with r/r NKTCL. **Methods:** Pts with r/r NKTCL and failed asparaginase-based therapy were recruited in this single-arm, multicenter phase Ib/II study (NCT05464433). Phase Ib was 3+3 dose escalation design with two dose levels of Lipo-MIT (16 mg/m^2 and 20 mg/m^2, d1) plus tislelizumab 200 mg (d1, Q4W) induction therapy for up to 6 cycles, then tislelizumab 200 mg (Q3W) maintenance therapy for up to 1 year. Phase II was conducted at the recommended phase II dose (RP2D). The primary endpoints were safety and tolerability, and determination of the maximum tolerated dose (or RP2D) of Lipo-MIT in phase Ib, and the overall response rate (ORR) of phase II. **Results:** As of the data cut-off on January 24, 2025, a total of 40 eligible pts were enrolled (phase Ib, n=6 and phase II, n=34). The median age was 46.5 (range 22-73) years. Among the pts, 62.5% had stage III or IV and 87.5% had nasal type NKTCL. No dose-limiting toxicities (DLT) were observed in the phase Ib study, and the RP2D of Lipo-MIT was determined to be 20 mg/m^2. The ORR and DCR were all of 100.0% (6/6, 95% CI 60.7%-100.0%) and the CR rate was 66.7% (4/6, 95% CI 27.1%-93.7%) in phase Ib. In the ongoing phase II stage, 30 pts were evaluable for efficacy. The ORR, DCR and CR rate were 70.0% (21/30, 95% CI 50.6%-85.3%), 76.7% (23/30, 95% CI 57.7%-90.1%) and 46.7% (14/30, 95% CI 28.3%-65.7%), respectively. Overall, combining data from phase Ib and phase II, the ORR was 75.0% (27/36, 95% CI 57.8%-87.9%) and the CR rate was 50.0 (18/36, 95% CI 32.9%-67.1%). Among the 15 pts who had not used PD-1 before, CR rate was 66.7% and ORR reached 80.0%. The median PFS and OS will be reported with longer follow-up. The most common grade 3/4 treatment-related adverse events (TRAEs) included leucopenia (37.5%), neutropenia (30.0%) and decreased lymphocyte count (27.5%). Notably, no cardiac events occurred during the study. **Conclusions:** Lipo-MIT in combination with tislelizumab demonstrated an encouraging efficacy in r/r NKTCL pts with a manageable safety profile. Clinical trial information: NCT05464433. Research Sponsor: None.

Comparative analysis of survival outcomes in infused versus not-infused patients with aggressive B-cell lymphoma referred for CART.

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Background: Chimeric antigen receptor T-cell therapy (CART) has changed the treatment paradigm for patients (pts) with relapsed/refractory (R/R) aggressive B-Cell Non-Hodgkin's Lymphoma (B-NHL). Yet, not all referrals complete the full process from harvest to re-infusion. This study evaluated a large cohort of pts "referred yet not infused" with CART to identify barriers to care and compare outcomes between pts infused vs non-infused. **Methods:** This is a retrospective analysis of adult pts with R/R B-NHL referred to Northwestern University from 2016-2024 for consideration for CART. Demographics, disease characteristics, and lines of therapy were evaluated. Survival analysis assessed median progression free survival (mPFS) and overall survival (mOS) in months (mo) from 2 starting timepoints (1) date of relapse with last line therapy prior to CART referral, denoted as PFS1 and OS1, and (2) date of treatment with CART or alternative to CART after referral, denoted as PFS2 and OS2. **Results:** Of 196 pts, 157 (80%) received CART (infused) whereas 39 (20%) were referred, but did not proceed to CART (non-infused). Comparison of demographics/disease characteristics demonstrated differences in age and ethnicity (Table 1). For infused pts, median time from apheresis to infusion was 33 days (range 9-86) and 94 pts (60%) received bridging therapy. For non-infused pts, median time from CART referral to alternative treatment was 14.5 days (range 1-80), most commonly rituximab-lenalidomide, rituximab-gemcitabine-based therapy (n=6 for each, 15%), or polatuzumab-based therapy (n=3, 8%). Death from disease progression was the most common reason for non-infusion (n=25, 64.1%). Median follow-up was 19 mo in surviving pts. Infused pts had higher mPFS1 than non-infused pts (5.6 [95% CI 3.7-7.5] vs 1.8 mo [95% CI 1.3-2.3]; p=0.05). Median PFS2 showed no significant difference. Infused pts had a markedly higher mOS1 (45.9 [95% CI 20-72] vs 2.5 mo [95% CI 1.8-3.2]; p=0.001), and mOS2 (32.3 [95% CI 0.1-64.5] vs 2.4 mo [95% CI 1.9-2.9]; p=0.001). **Conclusions:** CART infused vs non-infused pts differed with respect to age and ethnicity. The most common reason for failure to infuse was death due to disease progression. Infused pts demonstrated similar PFS to non-infused pts treated with alternative therapy. However, infused pts had a markedly improved OS. Collectively, our results suggest that survival in R/R B-NHL may be optimized by adopting measures that ensure success of proceeding to CART. Research Sponsor: None.

Baseline demographics and disease characteristics.

	Infused; N=157	Non-infused; N=39	P-value
Median Age (range)	58.5 (22-85)	67 (35-85)	0.04
Sex: Female	55 (35%)	17 (44%)	0.98
Race: Caucasian	134 (85%)	36 (92%)	0.57
Ethnicity: Hispanic	11 (7%)	8 (21%)	0.04
IPI > 3	21 (15%)	7 (20%)	0.49
Cell of Origin: GCB	64 (53%)	23 (61%)	0.46
Primary Refractory	91 (60%)	26 (68%)	0.46

7057 Poster Session

CD58 alterations and their role in regulating antitumor immune responses in diffuse large B-cell lymphoma.

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Background: Recurrent abnormalities of immune surveillance-related genes play a crucial role in DLBCL progression. Prior studies have shown that CD58, a key adhesion molecule that acts as a ligand for the T-cell costimulatory molecule CD2, is frequently mutated or deleted in certain hematological malignancies. Downregulation or loss of CD58 is linked to resistance to ICB therapy in melanoma and CAR-T therapy in B-cell malignancies. Nevertheless, the role of CD58 in cancer is not yet well understood. **Methods:** Comprehensive analysis of the genetic characteristics of *CD58* were performed through targeted deep sequencing (n=176), whole exome sequencing (n=38), and RNA-sequencing (n=162) in patients with de novo DLBCL. To investigate the mechanistic impacts of CD58 alterations on co-inhibitory molecules expression and immune cell function, we performed bulk and single-cell RNA-sequencing analysis of tumor samples and conducted co-IP, flow cytometry and co-culture assays in vitro. **Results:** We identified that *CD58* mutation rate was 9.1%, and the copy number loss rate was 44.7% among all enrolled DLBCL patients. Notably, *CD58* genetic alterations, along with low CD58 expression, significantly correlated with reduced rates of response to R-CHOP therapy and inferior progression-free and overall survival. Single-cell RNA sequencing revealed that CD58 expression in tumor cells was negatively correlated with $CD8^+$ T cell exhaustion/dysfunction status. CD58 inhibited the activity of the JAK2/STAT1 pathway by activating the Lyn/CD22/SHP1 axis, thereby limiting PD-L1 and IDO expression. Elevated PD-L1 and IDO expression in CD58 deficient DLBCL cells led to immune evasion and tumor-intrinsic resistance to CAR T-cell therapy. Direct activation of CD58-CD2 costimulatory signaling in combination with anti-PD-L1 blockade or IDO inhibitor sensitized CD58-deficient DLBCL to CAR T-cell therapy. **Conclusions:** Our study comprehensively characterized *CD58* genetic alterations in DLBCL. We demonstrated that CD58 downregulation or mutation led to upregulation of PD-L1 and IDO expression mainly by regulating the LYN/CD22/SHP1 axis. Our findings provide novel insights for individualized therapy for DLBCL patients with CD58 mutation or deletion. Research Sponsor: None.

Assessing the role of cytarabine-based regimens in mantle cell lymphoma: A real world study.

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Background: Mantle cell lymphoma (MCL) is an aggressive subtype of non-Hodgkin lymphoma. For decades, cytarabine-based regimens have been the cornerstone of MCL treatment, offering substantial efficacy but often at the cost of significant toxicity. More recently, non-cytarabine-based regimens, such as bendamustine combined with rituximab, have emerged as a promising alternative, demonstrating comparable efficacy with more favorable toxicity profile. This study aims to compare the clinical efficacy of cytarabine-based (Ara-C) versus non-cytarabine-based (non-Ara-C) regimens. **Methods:** We conducted a retrospective cohort study for patients diagnosed with MCL between 2010 and 2023 at Allegheny Health Network and Markey Cancer Center. Data pertaining to demographics, MIPIc, Lugano stage and treatments at induction were collected. Patients were divided into two groups based on whether they received cytarabine based regimen during induction (Ara-c) or not (non-Ara-c). Primary outcomes were overall survival (OS) measured from the time of diagnosis to the time of last follow up or death, and relapse free survival (RFS), calculated from the time of diagnosis to the time of relapse, persistent or progressive disease at the last day of follow up. Sensitivity analysis, with censoring on the time of autologous bone marrow transplant (ASCT) was done. RFS and OS were compared between the two groups after weighted propensity score matching (PSM). **Results:** We identified 223 patients diagnosed with MCL. The median age was 67.7 (IQ 60-74.5), Majority of patients were males (71%). The median MIPIc score was 8.1(IQR 7-9.5). 72 patients (31%) were in the Ara-c group while 151 patients (69%) were in the non-Ara-c group. The median follow-up of 5.6 years (0.95CI 4.91-6.32). Median OS was 13 years (0.95 CI 7.24-NR) and median RFS was 4.1 years (0.95 CI 3-4.96) for the entire cohort. Baseline comparison between the two groups is shown in table_1. After PSM, Median RFS for Ara-c group was 4.8 (IQR=1.8-16.2) yrs VS 3.6 (IQR=1.52-7) yrs for non-Ara-c group (P value 0.03). However, after censoring on ASCT, median RFS for Ara-c group was 4.7 (IQR 1.5-16.2) yrs VS 3.3 (IQR 1.5-6.9) yrs (P value 0.16). Median OS for Ara-c group was 16.2 yrs (IQR=4.3-16.2) vs 12.95 yrs (IQR=3.7-17.8) for non-Ara-c group (P value 0.5), which was the same after censoring on ASCT. **Conclusions:** In our cohort, cytarabine use in induction chemotherapy for MCL was associated with longer RFS and OS but it did not reach statistical significance. Larger scale studies are warranted to confirm these results. Of note, older and less fit patients received less cytarabine.
Research Sponsor: None.

	Cytarabine	Other	P value
Age	64 (57-69)	69 (63-77)	0.013
Eastern Cooperative group 0,1	96%	84%	0.05
MIPIc	7.56 (6.89-7.92)	8.28 (6.97-9.66)	0.01
Consolidation with ASCT	42%	13%	<0.01

Total metabolic tumor volume for predicting cytokine release syndrome and treatment response in patients receiving bispecific antibodies for B-cell lymphoma.

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Background: CD20xCD3 bispecific antibodies (BsAb) show high response rates with manageable cytokine release syndrome (CRS) in B-cell non-Hodgkin lymphomas (B-NHLs). While emerging data suggest that total metabolic tumor volume (TMTV) may predict treatment response and CRS, these findings have not yet been validated in real-world settings or across diverse histologic subtypes. **Methods:** We conducted a single center retrospective study evaluating B-NHL patients treated with BsAb. Baseline characteristics, efficacy, and safety outcomes were analyzed. TMTV was calculated from baseline PET scans using a semi-automated method with a threshold of 2x liver SUV_{mean}. Median TMTV separated high/low groups. **Results:** A total of81 patients are included. The baseline characteristics, efficacy outcomes, and CRS outcomes of each histological subtype are summarized in Table 1. There were no Grade 4 CRS events observed. The median TMTV for DLBCL, FL and MCL was 107.1ml, 61.7ml, and 92.2ml, respectively. In DLBCL, patients with high TMTV were more likely to have bulky disease (>7.5cm) and elevated LDH. Other baseline characteristics as outlined in Table 1 were comparable to low TMTV group. High TMTV was associated with increased risk of CRS of any grade (OR 5.0, 95% CI 1.4-18.1, p=0.017) but was not associated with ORR, CR, PFS or OS. While bulky disease and elevated LDH levels were associated with TMTV, these clinical factors were not predictive of CRS. In contrast, TMTV retained its prognostic significance in multivariate analysis. In FL, high TMTV was associated with a higher rate of bulky disease while LDH level and other baseline characteristics did not differ from the low TMTV group. High TMTV correlated with a lower CR rate (OR 0.1, 95% CI 0.0-0.6, p=0.020) but did not influence CRS risk, PFS or OS. In the small cohort of MCL patients, no significant associations between TMTV and CRS or treatment efficacy were observed. TMTV has no correlation with neurotoxicity in all cohorts. **Conclusions:** High TMTV predicts for a higher rate of CRS on multivariate analysis in DLBCL, independent of clinical factors. High TMTV was associated with a lower CR rate in FL and further evaluation in MCL is needed with larger sample sizes. Research Sponsor: None.

Baseline characteristics, efficacy outcomes, and CRS outcomes.

	DLBCL N=47	FL N=20	MCL N=14
Age, median (yr)	70	66	67
Male, n(%)	27 (57.4)	15 (75.0)	13 (92.9)
BsAb regimen, n(%)			
Epcoritamab	39 (83.0)	6 (30.0)	2 (14.3)
Glofitamab	4 (8.5)	3 (15.0)	8 (57.1)
Mosunetuzumab	4 (8.5)	11 (55.0)	4 (28.6)
Single agent BsAb treatment, n(%)	32 (68.1)	9 (45.0)	8 (57.1)
Prior lines of therapy, median (range)	3 (0-10)	3 (1-7)	3 (2-5)
Overall response rate (ORR), n(%)	25 (53.2)	16 (80.0)	9 (64.3)
Complete response (CR), n(%)	10 (21.3)	8 (40.0)	7 (50.0)
CRS, n(%)	19 (40.4)	11 (55.0)	10 (71.4)
Grade 1	13 (68.4)	4 (36.4)	5 (50.0)
Grade 2	5 (26.3)	7 (63.6)	4 (40.0)
Grade 3	1 (5.3)	0 (0.0)	1 (10.0)

DLBCL-associated PIM1 mutation and its impact on ANXA2 localization and lymphomagenesis.

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma and has an overall cure rate of approximately 60%. Previously, we observed high PIM1 mutation rates in DLBCL patients with poor outcome. However, the mechanism whether they lead to enhanced PIM1 kinase activity and contribute to lymphomagenesis is currently unknown. **Methods:** In this study, a multifaceted approach was employed to elucidate the functional consequences of PIM1 gene mutations and their implications in DLBCL. Recurrent PIM1 gene mutations that exhibited high frequencies across various lymphoma cohorts from public databases were screened and patient outcomes were stratified by PIM1 genen mutational sites. Liquid chromatography-mass spectrometry (LC-MS/MS) analysis combined with Co-IP was used to identify proteins interacting with PIM1. Transcriptomics analysis was utilized to identify proteins involved in critical cellular pathways relevant to PIM1 mutation. A high-throughput drug screening platform was leveraged to find potential therapeutic vulnerabilities unique to PIM1 mutant cells. The antiproliferative effects of PIM1 and PI3K inhibitor were evaluated in DLBCL cell lines and further validated in NSG mouse xenograft models. **Results:** We have identified PIM1 mutations, specifically P81S, E135K, L184F, and S97N, as frequently occurring variants, with the former three significantly associated with poor outcome. In particular, the $PIM1^{L184F}$ mutation promoted cell proliferation and inhibited cell apoptosis in vitro and showed faster tumor growth in vivo. Mechanistically, the $PIM1^{L184F}$ mutation was found to interact with the annexin A2 (ANXA2) gene, activating it through phosphorylation of serine 26. The activated ANXA2 gene then translocated from the cytoplasm to the cell membrane, binding with the Toll-like receptor 4 (TLR4) gene and recruiting BCAP to the cell membrane to interact with $p85\alpha$ further activating the PI3K/AKT/mTOR signaling pathway. Additionally, the high-throughput drug screening demonstrated that the $PIM1^{L184F}$ mutated cells were more sensitive to the PI3K inhibitor YY20394. PIM1 inhibitor SMI-4a combined with YY20394 showed synergistic antitumor effects both in vitro and in vivo. **Conclusions:** Taken together, these findings not only shed light on an innovative regulatory mechanism for how $PIM1^{L184F}$ mutation contributes to the pathogenesis of DLBCL but also provide a potential therapeutic strategy for effectively managing DLBCL patients harboring $PIM1^{L184F}$ mutation. Research Sponsor: None.

7061 Poster Session

Efficacy and safety of polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin and prednisone for previously untreated diffuse large B-cell lymphoma: A real-world, multi-center, retrospective cohort study.

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Background: In the POLARIX study, Pola-R-CHP showed significant improvement in progression free survival (PFS) in previously untreated DLBCL compared to R-CHOP. However, there are still few reports about the efficacy and safety of Pola-R-CHP in real-world setting in China, leaving some questions about the optimal patient population for Pola-R-CHP. Therefore, we conducted this retrospective observational study to compare the efficacy and safety of Pola-R-CHP with R-CHOP in clinical practice. **Methods:** The Pola-R-CHP group included previously untreated DLBCL patients who received Pola-R-CHP therapy across 6 medical centers in China. The control group included previously untreated DLBCL patients treated with R-CHOP. Patients treated with Pola-R-CHP were matched by propensity scores with those treated with R-CHOP. The primary endpoint was 12-month PFS based on Lugano 2014 criteria. **Results:** A total of 650 eligible patients from 6 centers were identified, 155 receiving Pola-R-CHP and 495 R-CHOP. After 1:2 propensity score matching, 150 pairs were obtained for further survival and prognosis analysis. With a median follow-up of 14.3 months, 12-month progression-free survival (PFS) was numerically higher with Pola-R-CHP versus R-CHOP (90.5% vs 84.8%, P=0.19). Benefits were consistently observed across molecular subgroups, especially advanced stage, ECOG≥2, extranodal involvement ≥2 and non-GCB group. The complete response rate of the Pola-R-CHP group was higher than that of the RCHOP group (87.2% vs 80.1%; P=0.11), but there was no statistical difference. Among 150 patients treated with Pola-R-CHP, 110 underwent gene sequencing analysis: MCD (25.5%), combined subtype (14.5%), ST2 (10.9%), and other/unclassifiable subtype (31.8%). The most common mutations (>25% of cases) were PIM1, TP53, BCL-6, KMT2D, SOCS1, BCL-2. Genetic testing results show the correlation between genotyping, gene mutations in PIM1/TP53 and therapeutic efficacy. Safety was comparable between Pola-R-CHP and R-CHOP, including rates of grade 3 to 4 AE. Prophylactic PEG-G-CSF administration was given in most of the cases. No deaths due to AE were observed. Unexpected adverse events were not observed. **Conclusions:** This large real-world study supports Pola-R-CHP as an effective frontline option for DLBCL, with sustained efficacy versus R-CHOP observed in unselected populations. While 12-month PFS failed to reach statistical significance, subgroup analyses favor Pola-R-CHP. Further research with a wider population, longer follow-up, and screening of advantageous groups are warranted. Research Sponsor: None.

Association between progression-free survival and overall survival in relapsed/refractory diffuse large B-cell lymphoma in the CAR T-cell era: A surrogate endpoint analysis.

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Background: In lymphoid malignancies, the strength of association between progression-free survival (PFS) and overall survival (OS) varies by disease aggressiveness. More-indolent malignancies such as multiple myeloma and follicular lymphoma have a weak correlation between PFS and OS, while more aggressive diseases like Hodgkin lymphoma have a stronger association. PFS has been validated as a surrogate for OS in first-line DLBCL, but its utility in R/R DLBCL in the era of CAR T-cell therapy has not been explored. This analysis is the first assessment of PFS as a surrogate endpoint for OS in DLBCL after the introduction of CAR T-cell therapy. **Methods:** A systematic review of ClinicalTrials.gov was conducted to identify phase 3 trials in DLBCL that reported hazard ratios (HR) for both PFS and OS. Trials initiated after 2015 were included to reflect the post-CAR T-cell therapy era, acknowledging that CAR T-cell therapy was approved in 2017 and most patients experience disease progression within two years. First-line trials were excluded from final analysis, resulting in an analysis focused exclusively on R/R DLBCL. Weighted linear regression analysis was performed, with the number of participants as the weighting factor. The strength of the association was evaluated using the coefficient of determination (R^2), with predefined thresholds: $R^2 > 0.80$ indicating a strong association, 0.60–0.80 indicating a moderate association, and $R^2 < 0.60$ indicating a weak association. **Results:** A total of 101 randomized clinical trials were identified. Upon screening, 20 trials reported rates for both PFS and OS. Of these, 4 trials, encompassing 1,139 patients, reported HRs and were included in the final analysis. The weighted regression analysis demonstrated a strong correlation between PFS and OS, with a correlation coefficient (r) of 0.98 and a coefficient of determination (R^2) of 0.98, indicating that 98% of the variance in OS could be explained by PFS ($p = 0.012$). **Conclusions:** This study provides the first surrogate endpoint analysis of PFS in R/R DLBCL in the post-CAR T-cell therapy era, excluding first-line trials. The findings suggest that PFS remains a strong surrogate for OS in this population. While the analysis is limited by the small number of available trials, the results highlight the need for ongoing surrogate validation as treatment landscapes evolve. Research Sponsor: None.

Trial Name	Participants	PFS* HR (95% CI)	OS HR (95% CI)
STARGLO	274	0.40 (0.28 - 0.57)	0.62 (0.43 - 0.88)
ZUMA-7	359	0.51 (0.38 - 0.67)	0.73 (0.54 - 0.98)
TRANSFORM	184	0.41 (0.25 - 0.66)	0.51 (0.26 - 1.00)
BELINDA	322	1.07* (0.82 - 1.40)	1.24 (0.83 - 1.85)
Total	**1,139**	-	-
Correlation Coefficient (r)	-	**0.98 ($p < 0.001$)**	-
Coefficient of Determination (R^2)	-	**0.98**	-

7063 Poster Session

Immune biomarkers as predictors of response to mosunetuzumab in previously untreated follicular (FL) and marginal zone lymphoma (MZL).

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Background: CD3xCD20 bispecific antibodies (BsAbs), including mosunetuzumab, induce high rates of complete response (CR) in indolent B-cell lymphomas. However, predicting the response and understanding systemic immune changes induced by the treatment (Tx) remain unmet needs. We hypothesized that changes in circulating immune biomarkers could predict Tx response in patients (pts) receiving first-line mosunetuzumab for FL and MZL. **Methods:** Immune biomarkers were measured in peripheral blood samples from pts enrolled in BrUOG-401 (NCT04792502), an investigator-initiated phase 2 trial of time-limited (8 cycles [C]) mosunetuzumab Tx for untreated, high-burden FL and MZL. Disease assessments by PET/CT occurred after C4 (MidTx) and C8 (end of Tx, EOTx). Pts without MidTx CR received additional lenalidomide in C4-8 with optional Tx extension up to C12. Samples were collected at baseline (PreTx), C1 day 8 (C1D8), C2 day 1 (C2), at MidTx, and at EOTx. We measured 25 plasma cytokines related to T-cell activation and regulation using a multiplex Luminex assay, and immune cell subsets using flow cytometry. Markers were compared by rank-sum tests or mixed-effects generalized linear models. P values were not corrected for multiplicity in this exploratory study. **Results:** Among 34 pts evaluable for EOTx response, 29 (85%) attained EOTx CR, and 22 (65%) achieved MidTx CR. Baseline cytokine levels were available for 22 pts, of whom 19 had EOTx CR, and 15 MidTx CR. No significant association was found between PreTx cytokine levels and CR at MidTx or EOTx. At C1D8, markers of T cell activation (IL2, IL7, IFNg, GZMA/B) increased overall (all P<0.05), but only lower CTLA-4 levels significantly predicted MidTx CR (P=0.0031). Persistently lower CTLA-4 at MidTx also correlated with MidTx CR (P=0.008). No cytokine was significantly associated with EOTx CR. Flow cytometry (n=26) showed an overall increase in circulating NK cells on Tx (P<0.05 at all timepoints). Higher PreTx NK cell abundance significantly correlated with MidTx CR (P=0.043), while higher PreTx CD4+CD45RA+ (naïve helper T) cells (P=0.0035) and lower CD4+CD45RO+CD25- (memory helper) T cells (P=0.0061) were associated with EOTx CR. Increased NK (P=0.011) and HLA-DR+ NK cells (P=0.0042) at C2 also correlated with MidTx CR. Although the CD8+CD45RO+CCR7-CD27- effector memory T cell subset increased overall at MidTx (P=0.025), no CD8+ subset was predictive of CR at any timepoint. **Conclusions:** Although CD8+ T cells are the main effector cells engaged by mosunetuzumab, our observations in previously untreated FL/MZL suggest that increased naïve CD4+ helper T cells and NK cells PreTx, along with lower CTLA-4 levels during Tx may better predict CR. These findings suggest that cytokine-driven immune priming could influence response to BsAbs, providing a basis for future investigations of combinations therapies to enhance their efficacy. Research Sponsor: Conquer Cancer, The ASCO Foundation.

Descriptive epidemiology of Waldenström macroglobulinemia (WM): Demographics, outcomes, and predictors of survival in the US community oncology setting.

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Background: WM is a rare, indolent subtype of non-Hodgkin lymphoma (NHL), comprising <2% of annual U.S. NHL cases. Natural history studies and registries often lack sufficient patient-level data about treatment patterns and outcomes. This study describes demographics, clinical characteristics, and outcomes of patients with WM treated in the community oncology setting. **Methods:** This retrospective cohort study included adults diagnosed with WM in the U.S. Oncology Network from 2014 to 2022, with follow-up through 2023. Data were sourced from the iKnowMed electronic health record system. Structured data were used to assess patient characteristics and overall survival (OS). Chart abstraction was performed on a random subset (n=200) to evaluate treatment characteristics and outcomes (i.e. OS, time to next treatment (TTNT), and real-world progression-free survival (rwPFS)). Multivariable Cox proportional hazard models evaluated factors associated with these outcomes. **Results:** Among 2,554 patients with WM (mean age: 72.7 years, SD: 10.1), majority were male (58.9%), and White (77.3%), consistent with SEER data reflecting the indolent nature of WM, with 82.1% alive at study conclusion and median OS was not reached. At 5-years, OS probabilities stratified by Modified Staging System for WM (MSS-WM) were 96.4% (low risk, N=135), 87.3% (low-intermediate risk, N=237), 69.2% (intermediate risk, N=267), and 50.9% (high risk, N=278; $p < 0.0001$), aligning with the externally validated MSS-WM model, demonstrating its utility in risk stratification. In the subset of 200 patients, 8.5% (N=17) had smoldering WM, and 23% (N=46) experienced disease progression. MYD88 L265P and CXCR4 mutations were present in 85.4% and 29% of patients, respectively, consistent with reported case series. Most (78%) patients initiated LOT 1 therapy. Treatment patterns aligned with NCCN guidelines, with BTK inhibitors and Rituximab-based regimens comprising 98% of LOT 1 therapies. In the multivariable model, area deprivation index was significantly linked to poorer OS (HR: 12.8, CI: 2.6–63.4), shorter TTNT (HR: 2.2, CI: 1.1–6.3) and worse rwPFS (HR: 4.1, CI: 1.2–14.3). Patients with a Charlson Comorbidity Index score ≥2, were more likely to discontinue treatment (HR: 2.2, CI: 1.3–3.5) and progress to next therapy (HR: 2.2, CI: 1.2–4.0). **Conclusions:** This natural history study of patients with WM treated in the community oncology setting confirms WM's indolent nature, with long survival and effective risk stratification using the MSS-WM. Real-world treatment patterns aligned to guidelines, while area-level socioeconomic factors and comorbidities highlighted disparities impacting outcomes. These findings emphasize the need for tailored, equitable care strategies and provide insights to enhance treatment approaches and address unmet needs in patients with WM. Research Sponsor: Oncology Center of Excellence, Food and Drug Administration of the U.S. Department of Health and Human Services; 75F40123C00199.

PET metabolic response in Lugano: Comparison of qualitative and quantitative outcome by independent central review.

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Background: The 2014 Lugano Criteria is the standard for radiographic assessment in lymphoma clinical trials, emphasizing qualitative evaluation of 18F-FDG PET-CT (PET) metabolic response (MR). In 2017, Van Heertum et al. introduced a quantitative approach defining strict percent change of standard uptake values (SUV) determination of MR, primarily for partial metabolic response (PMR) and progressive metabolic disease (PMD). Both Lugano and Van Heertum compared to baseline for determination of PMD, though industry practice frequently compare PMD to nadir. While both qualitative and quantitative approaches have been utilized in pivotal trials, few studies have compared qualitative and quantitative Lugano radiographic metabolic assessments to date. Thus, this study aims to investigate PET MR timepoint responses (TPRs) from blinded independent central review (BICR) radiologists using qualitative Lugano approach vs quantitatively derived TPRs. **Methods:** 3416 radiologist qualitatively assessed designated (desPET) responses consisting of PET TPR, 5PS, most-FDG avid lesion SUV, and liver SUV were analyzed. For desPET TPRs, radiologists compared MRs to baseline and nadir. We quantitatively derived PET (derPET) TPRs using the Van Heertum et al.,2017 %Δ utilizing SUV and 5PS, comparing to baseline and nadir, defining PMR as ≥25% decrease with a 5-point score (5PS) of 4 or 5; PMD as ≥50% increase with 5PS of 4 or 5; complete metabolic response (CMR) as 5PS of 1–3 without residual disease; and no metabolic response (NMR) as 5PS of 4 or 5, not meeting PMR or PMD criteria. To understand the merit of qualitative PET assessments, the desPET were compared to the derPET TPRs. Then, the desPET TPRs were compared among radiologists who reviewed the same case to determine concordance. **Results:** Results showed desPET differed from the derPET for 1198 TPRs (35.1%). When PMD was the derPET TPR, the desPET TPRs were: 270 PMD (53.9%), 134 NMR (26.8%) and 89 PMR (17.8%). When CMR was the derPET TPR, the desPET TPRs were: 830 CMR (51.7%), 634 PMR (39.5%), and 122 PMD (7.6%). When PMR was derPET TPR, desPET TPRs were: 177 PMR (61.9%), 55 NMR (19.2%), 51 PMD (17.8%). In the instances where desPET TPRs differed from the derPET, radiologists reviewing the same cases had concordance in desPET TPRs for 79.5% of cases. **Conclusions:** Our data show notable differences in PET MR when comparing derPET and desPET TPRs. Almost 20% BICR radiologists assessed a PMR, when our derived values were PMD and in over half the cases BICR radiologists assessed CMR when the derPET was PMR, thus suggesting that the quantitative approach results in more PD and fewer CR cases. When determining reader concordance, nearly 80% of readers aligned in desPET TPR when their TPRs differed from the derPET, suggesting that a qualitative assessment supports medical judgment in determining patient metabolic disease and consistency between readers assessments. Research Sponsor: None.

Secondary primary malignancies (SPMs) with CAR-T cell therapy in RR-DLBCL from real-world data.

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Background: Three CAR-T cell therapies i.e. axicabtagene ciloleucel, tisagenlecleucel and lisocabtagene maraleucel are currently approved for relapsed refractory DLBCL after 2 or more prior lines of treatment. Landmark trials have shown promising efficacy however, a notable concern with CAR-T therapy is the potential development of secondary primary malignancies. **Methods:** A retrospective study was performed using TriNetX, a global research de-identified database with data from 145 health care organisations as of January 2025. ICD-10 codes were used for associated diagnosis and medications. The database was queried to identify RR-DLBCL patients who had received any of axi-cel, tisa-cel or liso-cel. These treatments were set as the index event for outcome analysis. Demographics and prevalence of comorbidities were extracted. Outcome analysis queried for several hematological and solid tumor malignancies. The Measure of Association Analysis was used to calculate Odds Ratio. **Results:** 1842 adult patients with RR-DLBCL received one of the 3 CAR-T cell treatments as listed above and 12,431 patients with RR-DLBCL did not receive any of the 3 treatments. There were 1:1 propensity score matched adjusting for age, race, sex and tobacco use. Final number for both groups was 1842. For both cohorts, 1367 (73.8%) were white, 1055 were male (57%). The cohort had a mean follow up of 497 days, median follow up of 331.5 days. The CAR-T group had higher rates of MDS (3.9% vs 0.8%, p=<0.001) and AML (3.2% vs 1.2%, p=<0.001) in our database review of the US population. It did not show higher rates of other reported SPMs like Mature T/NK cell lymphoma, Hodgkin's lymphoma, multiple myeloma or solid tumours like lung, breast, prostate primary or malignant melanoma. Data on other SPMs is shown in Table 1. **Conclusions:** In our retrospective study of real-world population, RR-DLBCL patients who received CAR-T cell therapy with any of axi-cel, tisa-cel or liso-cel showed higher rates of MDS and AML compared to propensity matched patients with RR-DLBCL who did not receive CAR-T cell therapy while rates of other reported SPMs were not significantly different. Research Sponsor: None.

Frequency of SPMs in CAR-T receiving and no CAR-T receiving patients with RR-DLBCL.

SPM	Received CAR-T cohort (%)	Did not receive CAR-T cohort (%)	Odds Ratio	p-value
MDS	3.9	0.8	4.852 (2.767-8.507)	<0.001
AML	3.2	1.2	2.668 (1.624-4.382)	<0.001
Mature T/NK cell lymphoma	0.7	1.5	0.466 (0.238-0.909)	0.022
Hodgkin's lymphoma	0.9	1.9	0.469 (0.257-0.854)	0.011
Follicular lymphoma	3.8	3.6	1.055 (0.721-1.545)	0.781
Mantle cell lymphoma	1.0	0.5	1.792 (0.825-3.893)	0.135
Multiple Myeloma	1.4	2.4	0.566 (0.341-0.938)	0.025
Primary Lung site	0.7	0.5	1.292 (0.565-2.954)	0.543
Primary Breast site	0.5	0.7	0.815 (0.351-1.892)	0.634
Prostate cancer	0.5	0.6	0.902 (0.382-2.129)	0.814

Distinct outcomes with the detection of endemic Burkitt lymphoma, T-cell receptor (TCR) complementarity determining region-3s (CDR3s) matching known anti-HIV TCR CDR3s.

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Background: The adaptive immune response is represented by diverse complementary determining region 3's (CDR3s), which frequently represent antigen contact points and can be obtained from sequencing data. In particular, T-cell receptor (TCR) CDR3s in tumors have added an additional dimension to investigating the role of viruses in tumor development. Further, identifying TCR V- and J-gene segment usage, HLA allele combinations has been shown to represent outcome distinctions in various cancers. Given that endemic Burkitt lymphoma (BL) is well-known to be caused by Epstein-Barr virus (EBV), we aimed to characterize endemic BL adaptive immune features using TCR recombination reads, focusing on anti-HIV CDR3s and the presence of specific TCR V/J, HLA allele combinations. **Methods:** The Cancer Genome Characterization Initiative – Burkitt Lymphoma Genome Sequencing Project provided data available at the Genomic Data Commons website: 160 RNA-seq files from primary tumor that represented 105 cases. Phenotypic data representing these cases included gender, race, age at diagnosis, days to last follow-up, vital status, and Ann Arbor pathologic stage. The RNA-seq files were mined for TCR recombination reads using a high-stringency search algorithm (Chobrutskiy et al. 2020) and for HLA alleles utilizing xHLA (Xie et al. 2017). Anti-HIV CDR3s and specific TCR V/J, HLA allele combinations were then correlated with the progression of endemic BL as measured by overall survival (OS) and staging. **Results:** 47,302 productive TCR CDR3 recombination reads were recovered across all samples. We identified that the 22 cases with anti-HIV *TRA* CDR3s had improved OS as compared to those without an anti-HIV *TRA* recovery (median OS not reached vs. 215 days; log-rank p = 0.0013). Similarly, the 74 cases with anti-EBV *TRA* CDR3s were associated with an improved OS as compared to remaining cases (median OS 437 vs. 164 days; log-rank p = 0.005). Decreased disease progression as measured by lower pathologic stage was also noted in patients with anti-HIV *TRA* and *TRB*s compared to remaining cases (Mann-Whitney U p-value: 0.05, 0.01 respectively). Lastly, we identified five TCR V/J, HLA allele combinations which were associated with survival where the individual V or J gene segment and HLA allele was not associated with survival. An example of this were 33 cases with TRAV12-3 and DQB1*05:01, whose OS did not reach the median compared to the 199-day median OS of all other cases (log-rank p = 0.01). **Conclusions:** Early control of tumor progression via the T-cell response, whether by increased anti-viral T-cell receptors or via effective combination of antigen presentation and TCR antigen binding, appears to impact the progression of BL. Specifically, the success of anti-HIV TCRs indicates that treating co-infection with HIV may be a key factor in slowing disease progression. Research Sponsor: None.

Effect of CD73 on immune escape via tryptophan metabolic reprogramming in diffuse large B-cell lymphoma.

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Background: Immunotherapy is playing an increasingly important role in patients with relapsed or refractory DLBCL. Our previous studies have shown that high CD73 expression in DLBCL tumor cells correlates with poor prognosis and mediates immune escape. However, the underlying mechanism of CD73-mediated immune escape in DLBCL remains unclear. **Methods:** We analyzed RNA-Seq data from TCGA and de novo DLBCL patients at our center, comparing CD73 expression levels to identify enriched pathways related to tumor immune escape. These findings were validated in an syngeneic mouse model. To explore the mechanism by which CD73 regulates immune escape in DLBCL, we performed RNA sequencing and targeted tryptophan metabolism sequencing in cell lines. We further conducted co-culture, flow cytometry, Co-IP, ChIP-qPCR in vitro, and generated a mouse subcutaneous xenograft model for in vivo validation. **Results:** The syngeneic mouse model showed that CD73 knockdown significantly reduced tumor size compared to the control group, while increasing the infiltration of $CD8^+$ T cells and effector $CD8^+$ T cells in tumor tissue, and reducing $CD8^+$ T cell depletion. After systemic $CD8^+$ T cell depletion, the anti-tumor effect of CD73 monoclonal antibody was significantly weakened. RNA-seq and targeted tryptophan metabolism sequencing revealed a positive correlation between CD73 expression and tryptophan metabolism. In vitro, CD73 overexpression reduced ERK/c-Jun dephosphorylation by decreasing binding to INPPL1, leading to upregulation of IDO1 and TDO2 expression. Co-culture experiments showed weakened $CD8^+$ T cell proliferation in the CD73OE group compared to controls, while inhibition of IDO1/TDO2 significantly enhanced $CD8^+$ T cell proliferation, a result reversed in the knockdown group. The therapeutic effect of an IDO1/TDO2 inhibitor was assessed in an A20 mouse model, where both the AT-0174-treated vector and CD73 OE groups showed decreased tumor growth and increased $CD8^+$ T cell and effector $CD8^+$ T cell infiltration compared to the untreated group. Finally, we investigated whether combining CD73 monoclonal antibody with IDO1/TDO2 inhibitors could enhance immune cell infiltration in tumor tissues, and found that the combination treatment increased $CD8^+$ T cell infiltration. **Conclusions:** Our study uncovers a novel mechanism by which CD73 regulates immune escape in DLBCL through an adenosine-independent pathway. CD73 overexpression upregulates IDO1 and TDO2 levels by inhibiting ERK/c-Jun dephosphorylation via reduced binding to INPPL1. These findings offer new insights for combination therapies targeting CD73 in DLBCL patients with high CD73 expression. Research Sponsor: None.

Outcomes of patients treated for monomorphic B-cell post-transplant lymphoproliferative disorder: A single-center experience.

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Background: Patients (pts) with monomorphic B-cell post-transplant lymphoproliferative disorder (B-PTLD) have poor outcomes and high treatment-related mortality (TRM). With risk-stratified sequential treatment (RSST), some can be treated with rituximab alone. We sought to evaluate predictors of outcome in newly diagnosed B-PTLD, including involvement of extranodal (EN) sites and allograft. **Methods:** Adults diagnosed at Siteman Cancer Center with confirmed B-PTLD from 1/1/2006–12/31/2024 were identified via electronic health records. Kaplan-Meier and log-rank tests were used to evaluate progression-free survival (PFS) and overall survival (OS). Univariate analyses were done using Fisher's exact and $\chi 2$ tests with a=0.05. **Results:** 106 pts with monomorphic B-PTLD were identified (Table). The most common graft types were kidney (33%), liver (26%), and lung (15%). After diagnosis, immunosuppression was reduced in 93 (88%) pts and 105 pts received systemic therapy. 56 (53%) pts received frontline chemotherapy (chemo), most commonly R-CHOP (68%, n=38) and DA-EPOCH-R (21%, n=12), and overall response rate (ORR) was 66% (complete response [CR] 57%). 49 (46%) pts initially received rituximab monotherapy, including 39 on RSST, with ORR 36% (CR 23%). 28 (72%) were escalated to chemo, including 7 (18%) pts who progressed prior to reimaging. Treatments used were R-CHOP (71%, n=20), Pola-R-CHP (21%, n=6), and DA-EPOCH-R (7%, n=2), with ORR 59% (CR 56%). With median follow up of 58 months (mo), median PFS and OS were 33 and 64 mo, respectively. Pts who did not have CR to rituximab had worse PFS vs responders (12 mo vs 86 mo, p=0.037) and OS (27 mo vs 86 mo, p=0.04). Factors predicting CR to rituximab included early stage (p=0.001) and absence of EN disease (p=0.005). Graft type, involvement of allograft, tumor EBV status, and gene rearrangements were not predictive. Following frontline therapy, 33 (31%) pts developed relapsed/refractory disease. Elevated LDH (p=0.021) and extranodal disease (p=0.032) at diagnosis predicted relapse. 13 (12%) pts experienced graft failure, and 6 (6%) required repeat transplant. Discontinuation of antimetabolites was associated with higher rates of graft failure (p=0.020). 51 (48%) pts died, 8 (16%) due to TRM. **Conclusions:** In a large cohort of B-PTLD, ORR to rituximab on RSST and chemo confirm prior data. Pts with lack of response to rituximab monotherapy, EN disease, and elevated LDH have worse outcomes. Despite advances, TRM remains high in PTLD. Research Sponsor: None.

Demographics and predictors of response to rituximab.

Variable	Median (range)	Variable	n (%)	OR (response to rituximab)	p-value
Age	60 (22-86)	Male	66 (63)	1.7	0.65
Years since transplant	8 (0-34)	White	92 (87)	1.7	0.66
		Non-GCB	47/85 (55)	1.4	0.68
		EBV-neg	77/101 (76)	3.7	0.087
		Allograft involved	19 (18)	1.0	0.98
		FISH: MYC	20 (19)	2.4	0.46
		MYC + *BCL2*	1 (1)	NA	NA
		Early stage	15 (14)	0.04	0.001
		EN disease	85 (80)	0.14	0.005

Clinical and biological subtypes of follicular lymphoma revealed by tumor and immune cell states.

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Background: Follicular lymphoma (FL) exhibits considerable variability in biological features and clinical trajectories, compounded by a complex tumor microenvironment (TME) populated with nonmalignant immune cells. In this study, we comprehensively characterized FL by integrating multi-omics data that considered both tumor cells and microenvironmental components. This analysis revealed four subtypes of FL, each exhibiting distinct biological characteristics and differing clinical behaviors. **Methods:** Our study included 1,203 samples, 53 bulk transcriptomic samples from our center, 1,150 samples from public databases, and five single-cell RNA sequencing (scRNA-seq) cohorts. The Ecotyper algorithm was employed to identify immune cell states. Unsupervised clustering analysis using non-negative matrix factorization (NMF) was performed to identify distinct FL subtypes based on cellular infiltration. **Results:** A total of 30 unique cell states were identified from nine annotated cell populations (B cells, plasma cells, CD4 T cells, CD8 T cells, Tregs, NK cells, Tfh, monocytes/macrophages, and dendritic cells). Validation was performed across three independent scRNA-seq and bulk transcriptomic cohorts to ensure robustness. Four distinct B cell states were identified, each exhibiting unique gene expression profiles and varying prognostic implications. B cell S2 and S3 were associated with adverse outcomes. Notably, PRDM15 in B cell S2 had the most significant prognostic impact, remaining an independent adverse prognostic factor even after adjustment for m7-FLIPI. Mutational profile analysis demonstrated distinct mutation patterns across B cell states: mutations in CCND3, SPEN, and ARID1A were enriched in B cell S1; CREBBP and STAT6 mutations were prominent in B cell S2; and IRF8 and BCL2 mutations were observed in B cell S4, while no significant mutation enrichment was detected in B cell S3. Similarly, immune cells of the same type yet in different states exhibited functional and clinical heterogeneity. Four subtypes of follicular lymphoma characterized by distinct tumor cell states and varying immune infiltration were identified through unsupervised clustering analysis. FLE1 exhibits characteristics of a "cold tumor" with a high abundance of B cell S2. In contrast, FLE2 and FLE3 show moderate immune infiltration, while FLE4 is marked by abundant immune infiltration and elevated expression of immunosuppressive checkpoint molecules, resembling an "inflammatory" tumor phenotype. Prognostic analysis indicates that FLE1 has the most unfavorable prognosis, followed by FLE4. **Conclusions:** Our study stratifies FL patients based on the heterogeneity of tumor cells and the immune microenvironment, proposing an immune-based classification for FL. Targeting CREBBP and PRDM15 may offer promising new strategies for the clinical management of patients exhibiting a "cold tumor" phenotype. Research Sponsor: None.

Clinical outcomes of hemophagocytic lymphohistiocytosis in patients with HIV-related lymphomas: A multicentre observational study.

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Background: Secondary Hemophagocytic Lymphohistiocytosis (HLH) is a rare and potentially fatal inflammatory disorder triggered by infections, malignancies, autoimmune diseases or drug reactions. A very limited body of evidence is available regarding HLH in people living with HIV (PLWH). The aim of this report is to evaluate the frequency, clinical characteristics and outcomes of HLH in a multicentre cohort of patients with HIV-related lymphomas (HRL). **Methods:** We retrospectively reviewed prospectively collected data of HRL patients treated at the National Centre for HIV Malignancy, Chelsea and Westminster Hospital, London (2013-2024) and at the Department of Infectious Diseases at St. Joseph Hospital Berlin-Tempelhof, Germany (2020-2024). The diagnosis of HLH was based on both the HLH-2004 diagnostic criteria and the H-Score Saint Antoine. Statistical analyses were performed using IBM SPSS software. **Results:** We enrolled 253 patients in this study (17.4% female at birth; median age = 48.6 years, range 21.3 – 82.9). Median CD4 count was 206 cells /μL (range, 3-1.610) with 124 patients (49.2%) having a CD4 cell count <200/μL. Mean HIV viral load (VL) was 182.458 cop/mL (range, 0-26.000 .000), with 140 (55.3%) being undetectable at the time of lymphoma diagnosis. 206 (81.4%) had advanced stage disease, III (14.4%) or IV (67%). Median follow-up was 31 months and the 5-year overall survival was 51.3%. At the time of lymphoma diagnosis, 35 patients (13.5%) were diagnosed with HLH with an H-Score ≥169 points and/or ≥ 5/8 HLH criteria with a median age of 45.7 years (range 22.8-64.2), whereas 24 patients (9.5%) had an H-Score ≥ 200 points. HLH was present in 25% of patients with Primary Effusion Lymphoma, followed by 24.2% in Burkitt Lymphoma, 18.7% in Hodgkin´s Lymphoma, 9.5% in Plasmablastic Lymphoma, and 6.6% in Diffuse-large-B-cell Lymphoma. HLH patients were more likely to be diagnosed with HIV and lymphoma simultaneously ($p=0.001$), less likely to have a suppressed HIV-VL (31.4% vs 61%; $p < 0.01$) and had a lower median CD4 count (102 vs. 239 cells/μL; $p < 0.01$). A significant correlation was identified between a lower CD4 count and a higher H-Score in the bivariate analysis. Patients with HLH demonstrated a significantly poorer outcome with 1-, 2-, and 5-year overall survival of 41.2%, 32.4% and 11.8% compared to patients without HLH ($p < 0.01$). **Conclusions:** HLH is considerably more frequent in HRL in comparison to lymphomas affecting the general population. Outcome is poor and comparable to published data in HIV-negative cohorts. The acquired immune disfunction and the complex interplay of HIV and oncogenic viruses such as EBV and HHV8 in this population creates multiple potential triggers for this fatal inflammatory disorder of which the immunopathological basis is yet to be understood. Research Sponsor: None.

Effect of pre-biopsy steroids on diagnostic yield in diffuse large B-cell lymphoma (DLBCL).

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Background: DLBCL is an aggressive lymphoma, and patients (pts) often require urgent steroid administration for symptom relief or organ compromise prevention. Steroids before biopsy are avoided due to concerns about diagnostic accuracy. This supposition remains underexplored, with limited evidence supporting this practice. **Methods:** A retrospective chart review of pts with a diagnosis of DLBCL at Brown University Health between 2015 and 2024 was conducted for baseline demographics, steroid administration within 30 days of first biopsy, type and dose of steroids, markers of disease severity, type of biopsy, and biopsy results. Exclusion criteria included relapsed/refractory DLBCL. Statistical analysis was conducted using Chi-square test, T-test, and logistic regression. **Results:** 365 pts met inclusion criteria, of whom 65 received steroids prior to their first biopsy. Both steroid-treated and steroid-naive pts had similar baseline demographics (age) and markers of disease severity (LDH, "Double HIT" status, IPI score, and Stage), ($p > 0.05$). Both groups had similar rates of diagnostic first biopsies ($p > 0.05$). After initial negative biopsies, similar rates of diagnostic repeat biopsies were observed. Neither group had a significant difference in treatment delay from initial negative biopsy to start of chemotherapy ($p > 0.05$). Logistic regression analysis showed no statistical significance in the relationship between total dose of steroids and the likelihood of a diagnostic biopsy result ($p = 0.07$). Type of biopsy influenced diagnostic yield: fine needle aspiration ($n = 32$) was inferior with 28% diagnostic biopsies compared with core needle, excisional or incisional biopsies ($n = 284$) at 88% ($p < 0.001$). **Conclusions:** No significant differences were observed in biopsy success rates or treatment delays between steroid-treated and steroid-naive patients. These results support the safe use of corticosteroids when clinically indicated. Notably, biopsy type, rather than steroid exposure, was the primary determinant of diagnostic success, with fine needle aspiration yielding significantly lower diagnostic rates. These findings reinforce the importance of biopsy selection and support corticosteroid use without compromising diagnostic accuracy. Research Sponsor: None.

Characteristics	Steroids-treated (n=65)	Steroid-naive (n=283)	P value
Age (years), mean (95% CI)	67 (64 - 70)	67 (65 - 69)	0.805
Advanced Stage, proportion (95% CI)	64.15%	71.48%	0.286
LDH (U/L), mean (95% CI)	392 (297 - 487)	364 (315 - 413)	0.637
Percent "Double Hit"	13.85%	9.54%	0.304
Percent first biopsy diagnostic	86.67%	81.79%	0.219
Percent repeat biopsy diagnostic	87.50%	97.92%	0.116
Days from first negative biopsy to treatment, mean (95% CI)	39.5 (12.6 - 66.4)	50.7 (42.9 - 58.5)	0.327
Total steroid dose in prednisone equivalents (mg), mean (95% CI)	261 (193 - 329)	0	N/A
Total days on steroids, mean (95% CI)	6.8 (4.5 - 9.1)	0	N/A

The optimized HLH inflammatory index: A novel prognostic tool for newly diagnosed patients with diffuse large B-cell lymphoma—Discovery and validation.

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Background: The Optimized HLH Inflammatory (OHI) index (Zoref-Lorenz et al., *Blood*, 2022), based on serum soluble CD25 (sCD25) and ferritin, is a prognostic tool identifying inflammation in the hemophagocytic lymphohistiocytosis (HLH) spectrum and early mortality risk. Prior studies were retrospective and enriched with HLH-suspected cases. We hypothesized that the OHI index would predict outcomes in unselected diffuse large B-cell lymphoma (DLBCL). **Methods:** 670 newly diagnosed DLBCL patients from a prospective cohort (2002–2015) were analyzed: 335 for discovery and 335 for validation. Pre-treatment serum sCD25 and ferritin levels were quantified via ELISA, and we evaluated original thresholds (sCD25 ≥ 3,900 U/mL; ferritin ≥ 1,000 ng/mL) and developed DLBCL-optimized thresholds (using receiver operator curves) for predicting 500-day mortality. We also evaluated event-free survival (EFS), EFS at 24 months (EFS24), and overall survival (OS). **Results:** The median age was 64, and 51% were male. Using original thresholds, 4.2% (n=14) of patients were OHI+, with a 5.6-fold higher risk of 500-day mortality (95% CI 1.6–17; p<0.001). Optimized thresholds identified 23.6% (n=78) as OHI+ with a 9.2-fold higher 500-day mortality risk (95% CI 4.0–24; p<0.001). Optimized OHI+ also had a higher risk of EFS24 failure and inferior EFS and OS (Table). OHI+ patients had higher rates of B symptoms (35% vs. 20%; p=0.027), elevated LDH (76% vs. 34%; p<0.001), worse performance status (ECOG ≥2: 38% vs. 12%; p<0.001), and advanced-stage disease (Stage IV: 57% vs 38%; p<0.001), though IPI scores (3–5) were not significantly different (44% vs 36%; p=0.28). Adjusting for age and IPI, OHI+ independently predicted 500-day mortality (OR=5.0; CI 1.9–13; p=0.001), EFS24 failure (OR=3.2; CI 1.5–6.5; p=0.0018), and inferior long-term EFS (HR=2.2; CI 1.1–4.3; p=0.030) and OS (HR=2.0; CI 1.0–4.0; p=0.040) at a median follow up of 9.8 years in living patients. In validation, optimized OHI predicted 500-day mortality, EFS24 failure, and long-term OS and EFS (Table). Cytokine profiling revealed elevated inflammatory markers in OHI+ patients, including IL1a (p=0.008), CCL2 (p=0.03), CXCL10 (p<0.001), and CXCL9 (p<0.001), reflecting systemic hyperinflammation. **Conclusions:** The OHI index is a powerful predictor of early and long-term outcomes in DLBCL patients. Optimized thresholds identify a larger OHI+ group, highlighting hyperinflammation's critical role in poor outcomes. These findings support its use in routine management and clinical trial design for novel therapies. Research Sponsor: ASCO-ICRF; Conquer Cancer, the ASCO Foundation; The Varda and Boaz Dotan Research Center for Hemato-Oncology Research.

Odds ratios or hazard ratios and p-values for optimized OHI+ and DLBCL prognosis.

Outcome	Discovery	Validation
OR for 500-day mortality	9.2; p<0.001	4.0; p=0.002
OR for EFS24 failure	5.2; p <0.001	6.3; p<0.001
HR for OS	2.3; p<0.001	1.8; p=0.006
HR for EFS	2.4; p<0.001	2.5; p<0.001

The effect of patient self-reported confidence on psychosocial outcomes in the context of lymphoma and chronic lymphocytic leukaemia.

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Background: Adverse psycho-social outcomes (APSO's) are common side effects often under-reported which have great impact on the wellbeing of patients with lymphoma or chronic lymphocytic leukemia (CLL). As patient's traverse through their unique cancer journey, relationships with their care team yield varying degrees of confidence. We explored how confidence in both the management of their care and in the doctor coordinating their care was associated with various APSO's. **Methods:** A cross-sectional, anonymous online global survey directed at patients with lymphoma or CLL was deployed in 2024. Two questions asked how confident the patient feels about 1) the management of their care (MOC) and 2) the doctor coordinating their care (DCC). Patients were split into dichotomous groups who were and were not confident. Nominal logistic regression was used to explore how answers to these two questions influenced the prevalence of 19 different APSO's controlling for age and biological sex. Results were expressed in odds ratios with 95% confidence intervals. **Results:** Responses were received from 5,186 patients with 64% female and a median age of 61 [20-96]. Significantly increased incidence of APSO's associated with a lack of confidence in the MOC included: conflicts between beliefs and cancer treatment OR = 2.3 [1.4 – 3.6]; loss of meaning/purpose OR = 1.9 [1.5 – 2.4]; depression OR = 1.7 [1.4 – 1.99]; grief/loss OR = 1.6 [1.3 – 1.96]; loss of interest in usual activities OR = 1.6 [1.3 – 1.9]; post-traumatic stress disorder OR = 1.5 [1.2 – 1.98]; isolation/loneliness OR = 1.5 [1.3 – 1.9]; feelings of worthlessness/being a burden OR = 1.5 [1.2 – 1.9]; loss of self-esteem OR 1.5 [1.2 – 1.8]; anxiety OR = 1.5 [1.2 – 1.7]; fear of incapacitation OR = 1.4 [1.1 – 1.7]; changes in relationships OR = 1.3 [1.1 – 1.6]; worry OR = 1.3 [1.1 – 1.5]. APSO's that significantly increased due to a lack of confidence in DCC included: anger OR = 1.6 [1.2 – 2.0]; isolation/loneliness OR = 1.5 [1.2 – 1.9]; fear of incapacitation OR = 1.5 [1.1 - 1.9]. The remaining APSO's examined failed to produce significant differences regarding patient confidence levels. This analysis illustrates that approximately 73% of the APSO's reviewed in our survey had significant odds of being associated with patients who reported a lack of confidence in their MOC or the DCC. **Conclusions:** These results suggest that patients with low confidence in the management of their care plan and in the doctor coordinating their care may disproportionately experience APSO's. It is important that care teams take time to build relationships with their patients to help reinforce confidence in their care. In doing so the patient might experience fewer APSO's. Going forward, we plan to explore the effect of general practitioner involvement on patient confidence and the effect confidence has on physical side effects experienced by patients with lymphoma and CLL. Research Sponsor: Astra Zeneca; Swedish Orphan Biovitrum; Takeda Pharmaceuticals; Eli Lilly; Incyte; Kite a Gilead Company; Johnson & Johnson Innovative Medicine; Novartis; Regeneron; F. Hoffmann-La Roche Ltd; SERB Pharmaceuticals.

Clinical characteristics and treatment outcomes of hepatosplenic T-cell lymphoma: Mayo Clinic experience.

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Background: Hepatosplenic T-cell lymphoma (HSTCL) is a rare, aggressive peripheral T-cell lymphoma arising primarily from γδ T-cells. It carries a poor prognosis and resists conventional chemotherapy. Most reports on HSTCL are case-based. This study comprehensively analyzes a large cohort, evaluating treatment strategies and survival outcomes. **Methods:** This retrospective study included patients (pts) with pathologically confirmed HSTCL diagnosed between 2000-2024, consecutively seen at Mayo Clinic MN. Clinical, pathological, genomic, and treatment-related data were extracted when available. Descriptive statistics were used to summarize baseline characteristics. Time-to-event analyses, including Kaplan-Meier estimates, median overall survival (OS), and survival time estimates were conducted from the date of diagnosis. **Results:** A total of 20 patients with newly diagnosed HSTCL were included, with a median age of 57 years (range: 35-71). The cohort was predominantly male (70%) and non-Hispanic (93%). Molecular data was available for five patients, revealing abnormalities in *STAT5B, MLL3 deletion, TP53, EZH2, TERT,* and *NF1 E291D*. The median follow-up was 27.6 months (m) with a median OS of 17.6 m (95% CI: 11.2 - NA). First-line treatment was anthracycline-based in 68% of pts and non-anthracycline-based in 32%, with higher response rates in the latter group (50% vs.83%). Although non-anthracycline regimens showed a trend toward improved 3-year OS (100% vs. 29%) the difference was not statistically significant (p = 0.16). Achieving a complete response to first-line therapy was also associated with a trend towards a better 3-year OS compared to refractory disease (80% vs. 50%, p = 0.17). Most pts (79%) underwent hematopoietic stem cell transplant (HSCT), primarily allogeneic, with only one receiving autologous HSCT. First-line therapy before HSCT was evenly distributed between anthracycline (55%) and non-anthracycline (45%) regimens. HSCT recipients had significantly higher 3-year OS than non-recipients (83% vs. 33%, p = 0.017). Notably, the patient with a TP53 mutation has remained in remission for over a year post-allogeneic HSCT. **Conclusions:** HSTCL predominantly affects younger pts, with nearly half dying within a year. Allogeneic HSCT, rarely used in other NHL subtypes, improved survival. Non-anthracycline regimens and achieving CR trended toward better outcomes. Our study, leveraging a sizable cohort, highlights the need for targeted research and novel therapies to improve HSTCL management. Research Sponsor: None.

Summary of survival outcomes in HSTCL.

Characteristics	Median OS (y)	3-Year OS (95% CI)
	1.48 [0.93- NA]	46% [0.26 - 0.81]
Transplant		
Transplant	NA [NA - NA]	83% [0.58 - 1.00]
No Transplant	1.02 [0.93 - NA]	33% [0.07 - 1.00]
Treatment		
Anthracycline Based	1.02 [0.36 - NA]	29% [0.11 - 0.73]
Non-Anthracycline Based	4.61 [NA- NA]	100% [1.00 - 1.00]

Influence of HIV on outcomes in patients with diffuse large B cell lymphoma treated with CD19 targeting CAR-T cell therapy.

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Background: HIV+ patients have an 18-fold increased risk of developing diffuse large B Cell Lymphoma (DLBCL). There is uncertainty in the literature regarding the safety and efficacy of chimeric antigen receptor T-cell (CAR-T) therapy in HIV+ patients. This study aims to evaluate the influence of HIV infection on outcomes in patients treated with CD19 targeting CAR-T therapy. **Methods:** This is a multicenter retrospective cohort study that included patients with co-diagnosis of DLBCL and HIV who received a CD19 targeting CAR-T in the TriNetX Network, a database of deidentified electronic medical records with over 130 million patient records. Outcomes comprised of 5-year mortality, development of cytokine release syndrome (CRS), development of immune effector cell-associated neurotoxicity syndrome (ICANS), risk of infection, hypogammaglobinemia, and treatment with Tocilizumab, G-CSF, or IVIG. **Results:** Eighty-one patients met inclusion criteria. The mean current age was 62 years old, 75.6% were White, 16.3% were Black, 11.6% were Asian, and 73.3% were male. Approximately 72% of patients received Fludarabine/Cyclophosphamide, while 19% received Bendamustine as lymphodepletion chemotherapy. Within the cohort, 42% died within 5 years; 58% developed infection following treatment with CD19 targeting CAR-T therapy. The risks for CRS and ICANS were 65% and 14%, respectively; 53% treated with tocilizumab. Approximately 46% of patients developed hypogammaglobinemia; 31% were treated with IVIG, and 44% were treated with G-CSF. Further analysis to assess effect of development of CRS on outcomes showed no significant difference in survival probability among patients with or without CRS. **Conclusions:** CD19 CAR-T therapies have emerged for patients with refractory or relapsed DLBCL; however, HIV+ patients have been excluded from all registration CAR-T Cell clinical trials. Compared to the general population, our study demonstrates HIV+ patients with DLBCL have a similar mortality and morbidity rates when treated with CD19 targeted CAR-T therapy, indicating that in the future perhaps these patients should not be excluded from clinical trials. Research Sponsor: None.

Outcomes	Patients in Cohort	Patients with Outcome	Risk (%)
Mortality	81	34	42%
CRS	81	53	65.4%
CRS Grade 1 or 2	81	21	25.9%
CRS 3, 4, or 5	81	20	24.7%
ICANS	81	11	13.6%
Overall Infection	81	47	58%
Bacterial Infection	81	24	29.6%
Viral Infections	81	23	28.4%
Treatment with Tocilizumab	81	43	53.1%
Hypogammaglobulinemia	81	37	45.7%
Treatment with IVIG	81	25	30.9%
Treatment with G-CSF	81	36	44.4%

Frontline brentuximab vedotin (BV) and CHP in patients (pts) with peripheral T-cell lymphoma (PTCL) with <10% CD30 expression: Primary analysis results from the phase 2 SGN35-032 study.

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Background: BV, an antibody-drug conjugate targeting CD30, has shown single-agent activity in lymphomas with low CD30 expression. The combination of BV plus cyclophosphamide, doxorubicin, and prednisone (A+CHP) was effective in pts with PTCL with CD30 ≥10%. We report primary analysis results of frontline A+CHP in pts with non-systemic anaplastic large cell lymphoma (non-sALCL) PTCL with CD30 <10%. **Methods:** SGN35-032 (NCT04569032) is an open-label, multicenter, phase 2 study. Pts received 21-day cycles of A+CHP (BV 1.8 mg/kg, cyclophosphamide 750 mg/m^2, and doxorubicin 50 mg/m^2 by IV infusion on day 1 of each cycle and prednisone 100 mg by mouth daily [days 1-5]) up to 6-8 cycles. The primary endpoint, objective response rate (ORR), was assessed by blinded independent central review per Cheson 2007. Secondary endpoints included safety and complete response (CR) rate, PFS, OS, and duration of response (DOR). Efficacy endpoints are reported per central CD30 assessment unless otherwise noted. A genAI tool (12/13/24; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. **Results:** As of Jul 22, 2024, 82 pts received ≥1 dose of A+CHP, including 34 in the CD30 <1% cohort and 48 in the CD30 1% to <10% cohort per local CD30 assessment. At data cutoff, all pts were off study treatment. Overall median age was 63.5 y; most pts were male (56%), were White (77%), had an IPI score of 2-3 (66%), and had an ECOG PS ≤1 (90%). The most common (≥10%) disease subtypes were PTCL-not otherwise specified (45%), angioimmunoblastic T-cell lymphoma (32%), and nodal PTCL with T-follicular helper phenotype (10%). Overall median duration of treatment was 18.0 w (range, 3-24). The ORR at treatment completion was 77% (95% CI, 66.2-85.4) with a CR rate of 63% (95% CI, 52.0-73.8). Median (95% CI) PFS and OS were 12.7 mo (9.0-not estimable [NE]) and not reached (NR; 24.4-NE). Median (95% CI) DOR was 15.9 mo (8.3-NE), but NR in either cohort. Other efficacy parameters per cohort are listed in the table. Most pts (95%) had a treatment-emergent adverse event (TEAE), with 59% having a grade ≥3 TEAE. The most common (≥10%) overall grade ≥3 TEAEs were neutropenia (18%), febrile neutropenia (17%), and anemia (10%). Treatment-related grade 5 TEAEs were reported in 2 pts (2%); 19 pts (23%) reported a BV-related serious TEAE. **Conclusions:** As a frontline therapy, A+CHP demonstrated clinically meaningful efficacy in pts with non-sALCL PTCL regardless of CD30 expression, with a safety profile consistent with the label. Clinical trial information: NCT04569032. Research Sponsor: Pfizer.

	CD30 <1%	CD30 1% to <10%
Per local CD30	**n=34**	**n=48**
ORR (95% CI), %	74 (55.6-87.1)	79 (65.0-89.5)
CR rate (95% CI), %	56 (37.9-72.8)	69 (53.7-81.3)
Per central CD30	**n=23**	**n=31**
ORR (95% CI), %	61 (38.5-80.3)	81 (62.5-92.5)
CR rate (95% CI), %	52 (30.6-73.2)	71 (52.0-85.8)
PFS, median (95% CI), mo	10.9 (5.0-NE)	NR (8.5-NE)
OS, median (95% CI), mo	NR (11.1-NE)	NR (21.3-NE)

ALK-positive anaplastic large cell lymphoma: Statistics and survival trends.

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Background: Anaplastic lymphoma kinase positive anaplastic large cell lymphoma (ALK+ ALCL) is a rare subtype of peripheral T-cell lymphoma, characterized by CD 30+ large pleomorphic lymphoid cells with horseshoe nuclei and abundant cytoplasm. It frequently involves t(2;5) combining ALK with nucleophosmin (NPM1) gene. ALK+ ALCL is chemotherapy responsive, and CHOP, CHOEP (CHOP+etoposide) or BV-CHP (brentuximab instead of vincristine) are the popular drug combinations used. **Methods:** We extracted ALK+ ALCL cases using the ICD Code 9714/3, from Surveillance, Epidemiology and End Result (SEER) database Research Plus Data, 17 Registries, Nov 2023 Sub (2000-2021). The analysis was stratified based on age, sex, race, primary site labelled, laterality, stage, median household income inflation adjusted to 2022, and treatment options utilized. Survival curves were compared using the Log-Rank test (GraphPad Prism). **Results:** Total 3916 cases of ALK+ ALCL were identified, with median age at diagnosis of 53.5 years. Of the cases, 61% were males. Racial distribution was noted as: Caucasians 63.2%, Hispanics 16.1%, Blacks 12.4%, Asian/Pacific Islanders 6.7%, American Indians/Alaskan and unknown race were <1%, each. Overall median of survival (MoS) was 118 months, with 1-year OS of 0.696 (CI 95%, 0.68-0.71), 3-year OS of 0.61 (CI 95%, 0.596-0.63), and 5-year OS of 0.57 (CI 95%, 0.56-0.59). MoS were significant for Age: 0-30 yrs (undefined), 31-60 (233), 60+ yrs (17) ($p < 0.0001$); Gender: males (94) and females (153) (p 0.0011); Race: White (119), Black (49), Hispanics (118), Asian/Pacific Islanders (180), Alaskan/Native Americans (87), and unknown race (undefined) ($p < 0.0001$); Laterality: right (162), left (173), bilateral (144), and unknown side (66) ($p < 0.0001$). Survival based on stage was undefined for loco-regional disease, 67 for distant and 65 months for unknown stage ($p < 0.0001$). Anatomically, analysis revealed higher MoS with connective tissue (179), head/face/neck (72), and lymphoid origin (119); while lower survival with GI (21), thorax (13), and unknown site (7) ($p < 0.0001$). MoS improved with increasing income, <70,000$ (73), 70K-100K (129), and >100K (135) ($p < 0.0001$). Treatment based analysis showed: surgery (151) vs no surgery (100) ($p < 0.0001$), chemotherapy (182) vs no chemo (27) ($p < 0.0001$), radiotherapy (XRT) (173) vs no XRT (108) ($p < 0.0001$). Undefined MoS were likely observed due to insignificant numbers of death in those age categories to calculate 50% survival probability. **Conclusions:** ALK+ ALCL is a rare malignancy that favors male gender, and Caucasian race. Our analysis revealed superior survival outcomes associated with younger age, female sex, Asian/Pacific Islander origin, connective tissue involvement, unilateral and loco-regional disease, and treatment involving either surgery or non-surgical options, specifically chemotherapy. This is the first study to our knowledge to establish association of ALK+ ALCL to income, showing higher survival with increasing income bracket. Research Sponsor: None.

Safety and efficacy of chimeric antigen receptor (CAR)–T cell therapy (BRG01) targeting the Epstein-Barr virus (EBV) envelope protein in EBV+ lymphoproliferative disease patients.

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Background: Epstein-Barr virus (EBV) is a type I carcinogen which has infected more than 95% of population. EBV infection is closely associated with infectious mononucleosis and various malignancies. The envelope glycoprotein gp350 is present on EBV-infected host cells and serves as a potential tumor-specific antigen for the treatment of EBV^+ solid tumors like nasopharyngeal cancer as reported previously (NCT05864924)[1,2]. Anti-gp350 CAR-T also demonstrated robust inhibition for EBV replication and lymphoproliferation in a humanized mouse EBV infection model[3]. Here we explored the safety and efficacy of anti-gp350 CAR-T (BRG01) against EBV^+ T cell lymphoproliferative disease (LPD) in an exploratory pilot trial study. **Methods:** Patients with EBV^+ T cell LPD failing at least two lines of standard therapies were enrolled. Other criteria include $EBER^+$ and $Gp350^+$ expression on tumor biopsies. A single dose of EBV CAR-T cells (BRG01) were infused after a lymphodepletion regimen (cyclophosphamide 250-350 mg/m^2/day, fludarabine 25-30 mg/m^2/day for three days). Safety profile, pharmacokinetics (PK), EBV DNA copy number in the peripheral blood and tumor burden were monitored after BRG01 treatment. **Results:** From September 2021 to June 2023, a total of three patients with EBV^+ T cell LPD, subject 01, 02 and 03 were treated with $3*10^6$/kg, $9*10^6$/kg and $1.5*10^7$/kg BRG01 respectively. The cells expanded and proliferated well in the patients. The EBV DNA copies in the peripheral blood of subject 01 and 03 decreased significantly post BRG01 infusion and remained at less than 500 copies/ml for subject 02. The disease control rate for the three patients is 100% (3/3) and the overall response rate is 66.7% (2/3) based on Lugano 2014 criteria. One patient showed complete metabolic remission 28 days post $9*10^6$/kg BRG01 infusion and remained disease free for over three years. **Conclusions:** BRG01 is well tolerated and expanded in all treated patients. The durabler efficacy in all treated patients supports its further clinical investigation in various subtypes of EBV^+ lymphomas and LPD. 1. Zhang X, Wang T, Zhu X, et al: GMP development and preclinical validation of CAR-T cells targeting a lytic EBV antigen for therapy of EBV-associated malignancies. Frontiers in Immunology 14:1103695, 2023. 2. Zhang L, Zhao H, Ma Y, et al: 899P Safety and efficacy of a novel CAR-T cell therapy (BRG01) targeting the Epstein-Barr Virus envelope glycoprotein in advanced metastatic nasopharyngeal cancer patients. Annals of Oncology 35:S636, 2024. 3. Slabik C, Kalbarczyk M, Danisch S, et al: CAR-T cells targeting Epstein-Barr virus gp350 validated in a humanized mouse model of EBV infection and lymphoproliferative disease. Molecular Therapy-Oncolytics 18:504-524, 2020. Clinical trial information: ChiCTR2100044497. Research Sponsor: None.

Second primary malignancy in patients with diffuse large B-cell lymphoma (DLBCL) receiving chimeric antigen receptor T-cell (CAR T) therapy and other systemic anti-cancer therapy: A real-world data analysis.

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Background: CAR T therapy is a recent class of treatment for DLBCL and has been linked to the development of second primary malignancy (SPM), specifically T-cell malignancies. This study compared the risk of SPM in patients (pts) with DLBCL receiving CAR T therapy vs other systemic anti-cancer therapy (SACT). **Methods:** Adult pts with a diagnosis of DLBCL who received CAR T therapy or other SACT as second or higher line of therapy (LoT) were identified from Komodo Health claims data (10/18/2017–1/31/2024). Incident SPM (first diagnosis in pts with no history of that malignancy) was assessed from index treatment initiation through earliest report of death, disenrollment from medical coverage, or data cutoff (4/30/2024). Cumulative incidence of SPM was calculated using the Aalen–Johansen estimator with baseline risk factors, including previous treatments and number of prior LoTs (pts may contribute to multiple LoTs), demographic and lifestyle factors, and comorbidity history balanced between the treatment groups using inverse probability of treatment weighting. **Results:** The study assessed a total of 1079 (CAR T therapy) and 5836 (SACT) LoTs over a median follow-up of 10.6 months (IQR 4.3–24.3). The risk of SPM (95% CI) at 3 years post-index tended to be nominally lower in the CAR T therapy group vs the SACT group for any (37.2% [33.4, 40.7] vs 41.6% [35.5, 48.7]), hematologic (27.4% [23.8, 30.7] vs 28.5% [22.8, 35.0]; excluding DLBCL relapse), solid (14.7% [12.3, 17.1] vs 18.4% [14.8, 23.0]) (Table) and T-cell (2.6% [1.7, 3.8] vs 4.3% [2.8, 5.9]) SPM. A sensitivity analysis identifying SPM using ≥2 ICD-10 codes showed similar associations. In another sensitivity analysis excluding SPMs occurring in the first 3 months of follow-up, the risk in the CAR T therapy group remained nominally lower for any, solid, and T-cell SPMs, and higher for hematologic SPM, compared with the SACT group (Table). **Conclusions:** A large proportion of pts with DLBCL experienced SPMs with current treatment options. At 3 years post-index, there was no evidence of an increased risk of SPM in pts treated with CAR T therapy compared with those receiving SACT. Longer term studies are needed to confirm this observation. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Cumulative incidence (%) and 95% CI of SPM at 3 years post-index.

SPM	Analysis	SACT	CAR T therapy	p-value
Any	Main	41.6 (35.5, 48.7)	37.2 (33.4, 40.7)	0.20
	S1	32.4 (26.0, 40.3)	23.1 (20.0, 26.3)	0.08
	S2	34.4 (27.7, 41.2)	32.5 (28.6, 36.2)	0.81
Hematologic	Main	28.5 (22.8, 35.0)	27.4 (23.8, 30.7)	0.28
	S1	20.1 (14.4, 26.2)	16.9 (14.2, 20.3)	0.35
	S2	20.7 (15.3, 26.8)	22.9 (19.3, 25.9)	0.55
Solid	Main	18.4 (14.8, 23.0)	14.7 (12.3, 17.1)	0.34
	S1	13.8 (9.6, 18.6)	8.3 (6.4, 10.2)	0.11
	S2	17.7 (12.8, 23.5)	13.6 (11.5, 16.2)	0.41

S1: ≥2 ICD-10 codes for SPM identification; S2: excludes SPM diagnosed in the first 3 months.
S1/2, sensitivity analysis 1/2.

A phase I/II trial of high-dose methotrexate (HDMTX) followed by prophylactic glucarpidase in patients with impaired renal function and central nervous system lymphoma (CNSL).

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Background: HDMTX is a key component of treatment protocols for CNSL patients (pts), but impaired renal function in elderly or comorbid pts limits its use. The recombinant enzyme glucarpidase rapidly hydrolyzes MTX into non-toxic metabolites and is approved for therapeutic use in pts with delayed MTX elimination following HDMTX. We conducted a phase I/II study (NCT04841434) to assess the efficacy of prophylactic glucarpidase in HDMTX-treated pts with renal impairment or a history of delayed MTX elimination. **Methods:** A total of 18 pts with CNSL and pre-existing renal insufficiency (glomerular filtration rate [GFR] 40–80 mL/min) or a history of renal failure post-HDMTX were treated with up to six HDMTX cycles. HDMTX was given as a 4-hour infusion at three dose-escalation levels (3.0, 3.5, and 4.0 g/m^2; 6 pts each). Glucarpidase (2000 U IV) was administered in each cycle 24 hours after start of HDMTX. The coprimary endpoints were safety and pharmacological efficacy of glucarpidase. Plasma concentrations of MTX and its metabolites were monitored using combined liquid chromatography-tandem mass spectrometry. **Results:** Overall, 18 pts (63-86 years, median 78) were enrolled with a median baseline GFR of 69.5 mL/min. A median of 3.5 HDMTX treatment cycles was given, with 6 pts completing the maximum allowed 6 cycles. Reasons for protocol-predefined early termination included clinical non-response or radiological disease progression (n=8), investigator decision due to adverse event (AE; n=2), and termination criteria (n=2). Administration of glucarpidase resulted in a median reduction of MTX plasma levels within 15 minutes by 99.2% (95% CI: 98.4-99.1%). Results from serum samples analyses for anti-glucarpidase antibodies were performed and will be available by the meeting, but in pts with more than two HDMTX cycles, there was no statistically significant difference in the reduction of MTX plasma levels between the first and last cycles (p=0.47). Glucarpidase treatment reduced MTX plasma levels to a median of 0.05 μmol/L (range 0.00-0.84) within 15 minutes. MTX plasma levels remained consistently below 0.6 μmol/L across all cycles at 42 hours or later after start of the HDMTX infusion. A single grade III AE potentially related to glucarpidase was recorded: a transient facial flushing with a brief loss of consciousness and rapid and spontaneous full recovery. This event prompted implementation of a premedication (prednisolone, antihistaminic) in all subsequent treatment cycles. No further glucarpidase-related AE's grade >II occurred. **Conclusions:** The repeated prophylactic application of glucarpidase was feasible and safe and facilitated HDMTX treatment in pts at risk for delayed MTX elimination. This approach may enable adequate HDMTX dosing in pts with renal insufficiency and limiting comorbidities, and should be further evaluated. Clinical trial information: NCT04841434. Research Sponsor: Protherics Medicines Development Limited.

Variable response rates across chemotherapy regimens for severe idiopathic multicentric Castleman disease.

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Background: Idiopathic multicentric Castleman disease (iMCD) is a hematologic disorder treated by oncologists and characterized by diffuse lymphadenopathy and systemic inflammation that can cause multi-organ failure. iMCD subtypes include thrombocytopenia, anasarca, fever, renal dysfunction, and organomegaly (TAFRO) and not otherwise specified. Siltuximab, an interleukin 6 (IL6) antagonist, is the only FDA-approved treatment. For patients with severe disease worsening after siltuximab, consensus guidelines recommend combination chemotherapy though data is limited in guiding chemotherapy selection. **Methods:** The ACCELERATE registry leverages an expert panel who reviewed medical history and lymph node biopsy slides to rigorously confirm the diagnosis for each patient. To achieve a clinical response, the proportion of abnormal clinical and laboratory criteria assessed prior to regimen initiation has to decrease by at least 50% after regimen initiation. Regimens were grouped based on inclusion of cyclophosphamide, etoposide, doxorubicin, and bortezomib. We quantified response rates and times to next treatment for regimens containing these chemotherapies but statistical comparisons were not possible due to overlapping treatments used across these groups. Response rates for chemotherapy ± IL6 inhibition were compared. **Results:** We identified 34 (31%) chemotherapy recipients among 111 diagnosis-confirmed iMCD patients: 71% were male, 91% had iMCD-TAFRO; 35 years median age at diagnosis. All iMCD-TAFRO patients met the criteria for severe disease. We found 52 chemotherapy regimens administered to 34 patients. We observed 33 (64%) of the 52 regimens included cyclophosphamide; 23 (44%) etoposide; 21 (40%) doxorubicin; 15 (29%) bortezomib. Regimens were typically given with more than one agent. Twenty-two (42%) were co-administered with anti-IL6. Nineteen (68%) patients had a response if the regimen included cyclophosphamide; 14 (64%) etoposide, 10 (56%) doxorubicin; and 9 (69%) bortezomib. Response rates for all regimens were 60% with IL6 inhibition compared to 64% without. For cyclophosphamide, etoposide, doxorubicin, and bortezomib regimens, median time to next treatment was 9, 4, 4, 6 months, respectively. **Conclusions:** We found that almost all iMCD patients who received chemotherapy had TAFRO with severe disease. We observed relatively similar response rates across different chemotherapy containing regimens and for patients who received chemotherapy with and without IL6 inhibition. Time to next treatment was longer in the cyclophosphamide group, but this could not be statistically tested. Altogether, we provide the first study of the comparative effectiveness of chemotherapies against iMCD. Research Sponsor: U.S. Food & Drug Administration; R01FD007632.

TPS7083 **Poster Session**

SOUNDTRACK-E: A phase 1/2, open-label, multicenter study to evaluate the safety and efficacy of AZD0486 monotherapy or combination therapy in patients with mature B-cell malignancies.

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Background: AZD0486 is an IgG4 fully human CD19xCD3 bispecific T-cell engager that binds CD3 with low affinity to potentially reduce cytokine release upon T-cell activation while preserving effective T-cell cytotoxicity against malignant B cells. In a first-in-human phase 1 trial (NCT04594642), AZD0486 was active and well tolerated in patients (pts) with relapsed/refractory (R/R) follicular lymphoma or R/R diffuse large B-cell lymphoma (Gaballa S, et al. *Blood*. 2024;144:868; Hou JZ, et al. *Blood*. 2024;144:341). This study assesses fixed-duration subcutaneous (SC) AZD0486 monotherapy in B-cell malignancies and fixed-duration SC or intravenous AZD0486 in combination with other anticancer agents. This study is the first to evaluate SC AZD0486, and the first to evaluate AZD0486 in chronic lymphocytic leukemia (CLL). **Methods:** SOUNDTRACK-E (NCT06564038) is a phase 1/2 dose-escalation, global, multicenter trial of AZD0486 with 3 substudies. The study is recruiting pts aged ≥18 years with Eastern Cooperative Oncology Group performance status 0–2 and a histologically confirmed diagnosis. Pts with clinically significant central nervous system events (eg, seizure, stroke) or cardiovascular disease are excluded. Substudy 1 evaluates SC AZD0486 in R/R CLL/small lymphocytic lymphoma and includes a monotherapy cohort (1A; ≥2 prior lines of therapy [pLOT] with Bruton tyrosine kinase inhibitor exposure) and a cohort that receives combination with acalabrutinib (1B; ≥1 pLOT). Substudy 2 evaluates SC AZD0486 in R/R mantle cell lymphoma and includes a monotherapy cohort (2A; ≥2 pLOT) and a cohort that receives combination with acalabrutinib (2B; ≥1 pLOT). Substudy 3 evaluates AZD0486 in combination with R-CHOP in pts with untreated large B-cell lymphoma with International Prognostic Index ≥2, or R/R B-cell non-Hodgkin lymphoma with ≥1 pLOT. In each cohort, AZD0486 is administered via a double step-up dosing schedule in cycle 1; the target dose is given every 2 weeks. Treatment is administered for 24 (28-day) cycles in substudy 1, 12 (28-day) cycles in substudy 2, and 17 (21-day) cycles in substudy 3. Pts in cohorts 1B and 2B receive acalabrutinib 100 mg orally BID beginning at cycle 2. In substudy 3, R-CHOP is administered once every 3 weeks for 6 cycles. Dose escalation decisions will be based on a modified probability interval (mTPI-2) design. Approximately 46 pts for each cohort in substudies 1 and 2 and 36 pts in substudy 3 (~200 total pts) will be recruited. Primary objectives are to assess safety and tolerability, and to determine the recommended phase 2 dose for AZD0486 as monotherapy and combination therapy in mature B-cell malignancies. Secondary objectives include efficacy endpoints, pharmacokinetics, and immunogenicity. Enrollment opened in October 2024. Clinical trial information: NCT06564038. Research Sponsor: AstraZeneca.

TPS7084 Poster Session

A phase 2 trial to evaluate the efficacy and safety of WZTL-002, a third-generation anti-CD19 CAR T-cell therapy, in patients with relapsed or refractory large B-cell lymphoma (ENABLE-2).

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Background: Autologous chimeric antigen receptor (CAR) T-cells directed against CD19 are a standard of care for relapsed or refractory (r/r) large B-cell lymphoma (LBCL). CAR T-cells incorporating a CD28 costimulatory domain are among the most effective CAR T-cell therapies for LBCL, but are associated with high rates of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). In a phase I dose escalation and expansion study (ENABLE-1, NCT04049513), a new 'third-generation' CAR T-cell incorporating a TLR2 co-stimulatory domain alongside CD28 (WZTL-002) demonstrated low rates of CRS and ICANS and promising efficacy. a recommended phase 2 dose (RP2D) of $0.5 – 1.0 \times 10^6$ CAR^+ cells/kg was selected following dose escalation, and outpatient management and automated closed-system WZTL-002 manufacture were implemented within a dose expansion cohort. ENABLE-2 (ClinicalTrials.gov NCT06486051) is a multicentre phase 2 that aims to assess the efficacy and safety of WZTL-002 in patients with r/r LBCL. **Methods:** Eligible participants are age 18 – 75 years with relapsed or refractory LBCL (either de novo or transformed from follicular or marginal zone lymphoma) following 1 or 2 prior lines of therapy, have assessable disease and satisfactory organ function. Leukapheresis is conducted to obtain autologous T-cells, which are transduced *ex vivo* to express a third-generation CD19-directed CAR incorporating CD28, TLR2 and CD3zeta stimulatory domains (1928T2z). Bridging therapy is permitted pending WZTL-002 manufacture and product release. Lymphodepletion comprises intravenous fludarabine (30mg/m^2) and cyclophosphamide (500mg/m^2) daily for 3 days. Two days later a single dose of WZTL-002 is administered at $0.5 – 1.0 \times 10^6$ CAR^+ cells/kg (capped at 10^8 CAR^+ cells). Participants undergo daily outpatient assessments for toxicities including CRS and ICANS for the first 11 days after WZTL-002 administration, and at days 14 and 28. Disease response is assessed by PET/CT scans at day 28, 3 months and 6 months, and duration of response by CT scan at months 12 and 24. The co-primary endpoints are complete response rate (Lugano criteria) and ICANS rate (any grade) 3 months after WZTL-002 administration. Secondary outcomes include safety (with CRS, ICANS and cytopenias as adverse events of special interest), and progression-free, event-free and overall survival. The first participant was enrolled on 13 August 2024. Clinical trial information: NCT06486051. Research Sponsor: None.

TPS7085 Poster Session

ALPHA3: A pivotal phase 2 study of first-line (1L) consolidation with cema-cabtagene ansegedleucel (cema-cel) in patients (pts) with large B-cell lymphoma (LBCL) and minimal residual disease (MRD) after response to standard therapy.

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Background: R-CHOP as 1L therapy for LBCL has a cure rate of ~60%. However, ~10% of pts are refractory (Coiffier, *NEJM* 2002) and ~30% of responders relapse within 2 years (Maurer, *J Clin Oncol* 2014). Autologous CAR T cell therapies have revolutionized treatment of relapsed/refractory (R/R) LBCL and are considered standard 2L treatment due to improved overall survival (OS; Westin, *NEJM* 2023) but may not be an option due to aggressive disease, pt comorbidities, access barriers, and/or manufacturing issues/delays. Identifying responders to 1L therapy at high risk of relapse and rapidly administering an off-the-shelf CAR T cell therapy for remission consolidation may improve outcomes. Presence of circulating tumor DNA–based MRD, measured by PhasED-Seq, at the end of 1L therapy is highly prognostic for relapse (Roschewski, *Hematol Oncol* 2023). Cema-cel is an immediately available, off-the-shelf, HLA-unmatched allogeneic CD19 CAR T cell product made using Cellectis technologies. A phase 1 study of cema-cel in pts with R/R LBCL showed safety and efficacy comparable to that of autologous CAR T cell therapies (Locke, *J Clin Oncol* 2023). We describe the design of the pivotal ALPHA3 phase 2 study of cema-cel, the first randomized, open-label study to assess a CAR T cell therapy as a consolidation strategy in pts with detectable MRD measured by PhasED-Seq after standard 1L immunochemotherapy. **Methods:** ALPHA3 (NCT06500273) will evaluate efficacy and safety of cema-cel with 1 of 2 lymphodepletion (LD) regimens compared to standard-of-care (SOC) observation in pts with LBCL who are in response at the end of 1L therapy but test MRD+. Key eligibility criteria include histologically confirmed LBCL, completion of a full course of standard 1L therapy, ECOG PS 0/1, and adequate organ function. The study will consist of a 2-part seamless design. In Part A (currently enrolling), pts will be randomized to SOC observation or to 1 of 2 treatment arms (cema-cel [120×10^6 CAR T cells] following 3-day LD with fludarabine [30 mg/m^2/day] and cyclophosphamide [300 mg/m^2/day] with/without the anti-CD52 monoclonal antibody, ALLO-647 [30 mg/day]). Part A will conclude with an interim analysis to select the optimal LD regimen. Part B will assess efficacy of the selected regimen vs observation. The primary endpoint is event-free survival per independent review committee (IRC), with hierarchical testing of key secondary endpoints of progression-free survival per IRC and OS. Other secondary endpoints include MRD clearance, safety of cema-cel and ALLO-647, and disease outcomes after subsequent therapy. The study will enroll ~240 pts across ~50 sites at academic- and community-based centers. Site activation is ongoing; sites outside the US are being considered. The study was initiated in June 2024 with accrual into 2026. Clinical trial information: NCT06500273. Research Sponsor: Allogene Therapeutics, Inc.

TPS7086 **Poster Session**

A phase 2 study to confirm safety and efficacy of MB-105, an autologous CD5-directed CAR T-cell therapy, in relapsed/refractory T-cell lymphoma (R/R TCL).

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Background: R/R TCL presents an unmet clinical need with limited treatment options and 3-year survival $< 20\%$. MB-105 is an autologous CD5-targeting CAR T-cell therapy developed at Baylor College of Medicine that has been designed to address the unique challenge of treating T-cell malignancies by overcoming CAR T-cell fratricide without additional engineering. In the phase 1 trial, 44% (4/9) patients experienced objective responses, including 2/3 complete responses with survival >5 years. Mid-trial manufacturing refinements enhanced MB-105 potency and persistence without compromising safety. We have developed an industrialized, 6-day process of manufacturing MB-105 and are conducting a phase 2, multicenter study in the USA to evaluate MB-105 in patients with R/R peripheral and cutaneous TCL (PTCL, CTCL). Durable responses and safety observed across all dose levels in phase 1 guided the dose selection for this trial. **Methods:** The study follows a Simon two-stage design with a safety run-in to confirm tolerability of the recommended phase 2 dose (RP2D) of 50 million cells in 6 patients. This is followed by an efficacy evaluation first in 15 patients then 46 total. Adaptive elements allow the independent data monitoring committee to adjust doses, monitoring schedules, or lymphodepletion regimens without formal protocol amendments Primary objectives are first to confirm tolerability of the recommended dose by CTCAE v5 and ASTCT for cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (CRS/ICANS) and then evaluate efficacy through central review. Secondary/other objectives include assessing response durability, overall survival, persistence, immune correlates and manufacturing success. Adults with R/R TCL who have failed ≥ 1 prior systemic therapy for PTCL or ≥ 2 for high-volume CTCL are eligible. Local pathology for CD5 expression is required, later confirmed by central lab. Patients must have adequate organ function, Karnofsky PS $\geq 70\%$, and no prior cell therapy/transplant within 60 days of leukapheresis. Key exclusions are Sezary syndrome (potential for high circulating tumor cells to affect manufacturing), active CNS involvement, infections, graft-versus-host disease > grade 2, or comorbidities that may interfere with study participation or endpoints. Patients are closely monitored for CRS/ICANS. Safety and efficacy are assessed intensively for the first 3 months and gradually less frequently over the subsequent 21 months. Imaging and post-infusion testing, including CAR-T persistence, immune profiling and biomarkers are conducted throughout. Patients are encouraged to participate in a separate long-term follow-up study. Recruitment is ongoing. Clinical trial information: NCT06534060. Research Sponsor: None.

TPS7087 **Poster Session**

CD5-deleted chimeric antigen receptor cells (Senza5 CART5) to enhance immunotherapy against T-cell non-Hodgkin lymphoma: A first-in-human phase I clinical trial (NCT06420089).

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Background: Autologous CART options for patients with relapsed or refractory (R/R) T-cell lymphomas (TCL) have faced challenges such as T-cell fratricide during CART manufacture and safety concerns regarding depletion of normal T cells. To overcome these obstacles, we proposed a dual cell population CART product, which contained both autologous 4-1BB co-stimulated CART cells against CD5 and healthy T-cells, with both populations knocked out for CD5 (CRISPR-Cas9 CD5 short-guide RNA to delete CD5 - Senza5). In vivo experiments using the dual population product of (Senza5 CART5) demonstrated increased CART5 expansion and enhanced antitumor efficacy in TCL xenograft models compared to wild-type (WT) CART5. For clinical use, a novel 5-day manufacturing process was designed to obtain a less differentiated and less exhausted product, with enhanced in vivo expansion and fitness. **Methods:** A human phase I trial was designed to determine the safety, effectiveness and recommended phase 2 dose (RP2D) of Senza5 CART5 cells in participants with R/R TCL with ≥50% expression of CD5 on malignant cells, and no circulating CD5+ cells. Participants must have a suitable backup stem cell product or donor identified in the unlikely event of T-cell aplasia. Patients with prior allo HCT are currently excluded. Cohorts of patients are treated with escalating doses of Senza5 CART5 cells ($3x10^6$ to $1.25x10^8$) using a Bayesian Optimal Interval design following lymphodepletion. The study will enroll and treat participants until a maximum of 9 participants are infused and evaluable for dose limiting toxicity (DLT) assessments at a given dose level, or a maximum of 30 DLT-evaluable participants from all dose levels are infused. The RP2D will be determined based on both safety and biological evidence of efficacy. Study objectives include frequency and severity of treatment-related adverse events, as well as efficacy by assessing overall and complete response rates, duration of response, progression-free and overall survival. Manufacturing feasibility will be determined by the frequency of product release failures and occurrence of dose failures (inability to meet targeted dose). Exploratory objectives will evaluate the persistence and trafficking of Senza5 CART5 cells in blood and tumor by characterizing the kinetics of the infused cells by flow cytometry and qPCR gene expression. We will perform profiling of the tumor microenvironment and measure systemic soluble cytokines before and after treatment. We will also assess the impact of CART5 on normal T cells, and the persistence of CD5KO untransduced T cells that are infused as part of the Senza5 CART5 product by multicolor flow cytometry and qPCR. The trial is sponsored by Vittoria Biotherapeutics and is registered at clinicaltrials.gov as NCT06420089. Enrollment in this trial has begun. Clinical trial information: NCT06420089. Research Sponsor: Vittoria Biotherapeutics.

TPS7088 **Poster Session**

Efficacy and safety of nemtabrutinib in relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: Cohort J of the phase 2 BELLWAVE-003 study.

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Background: Treatment options for patients with relapsed or refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) can be limited if patients do not respond to both Bruton tyrosine kinase inhibitors (BTKis) and B-cell lymphoma 2 inhibitors (BCL2is). Nemtabrutinib is a once-daily, potent, noncovalent, reversible BTKi with a distinct kinase profile that inhibits BTK and other B-cell receptor relevant kinases. The multicenter, open-label, single-arm, phase 2 BELLWAVE-003 study (NCT04728893) is designed to evaluate nemtabrutinib at the recommended phase 2 dose (RP2D) in participants with R/R CLL/SLL, Richter transformation, mantle cell lymphoma, marginal zone lymphoma, follicular lymphoma, and Waldenström macroglobulinemia. Cohort J will evaluate nemtabrutinib in participants with R/R CLL/SLL who are relapsed/refractory to both a BTKi and BCL2i. **Methods:** Key eligibility criteria for cohort J include participants aged ≥18 years with CLL/SLL whose disease is R/R to prior therapy with both a BTKi (covalent or irreversible) and a BCL2i, and an ECOG PS of 0 to 2. Additional use of noncovalent or reversible BTKis is permitted if disease is R/R to such therapy. Participants must have received and not responded to, been intolerant to, or determined by their treating physician to be a poor PI3Ki candidate or ineligible for PI3Ki per local (institution) guidelines. Exclusion criteria include prior exposure to nemtabrutinib, active CNS disease, and prior systemic therapy with a monoclonal antibody within 5 half-lives or 4 weeks before allocation. Overall, the BELLWAVE-003 study comprises a dose escalation and confirmation phase (part 1) to establish the RP2D, and a cohort expansion phase (part 2). Part 1 evaluated nemtabrutinib in ≥6 to ≤20 participants with R/R CLL/SLL after ≥2 prior lines of therapy. The RP2D has been established as nemtabrutinib 65 mg QD. In part 2, ~460 participants will be enrolled across 9 expansion cohorts. Approximately 40 participants will be enrolled in cohort J. Treatment will continue until unacceptable toxicity, disease progression, or withdrawal. Adverse events will be monitored throughout and graded using NCI CTCAE version 5.0. Hematologic toxicities in participants with CLL will be assessed using iwCLL 2018 criteria. CT/MRI and/or PET will be performed every 12 weeks unless needed more frequently. The primary end point for cohort J is ORR per iwCLL 2018 criteria by independent central review (ICR). Additional end points include DOR and PFS per iwCLL 2018 criteria by ICR, OS, and safety and tolerability. Recruitment is ongoing. This is the first clinical trial with a dedicated cohort to assess noncovalent BTKis in patients whose disease has failed to respond to both BTKi and BCL2i. Clinical trial information: NCT04728893. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS7090 Poster Session

Phase 2 study of MK-3475A in relapsed or refractory classic Hodgkin lymphoma or primary mediastinal large B-cell lymphoma.

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Background: The PD-1 inhibitor pembrolizumab is approved globally for the treatment of multiple cancers, including relapsed or refractory (R/R) classic Hodgkin lymphoma (cHL) and R/R primary mediastinal large B-cell lymphoma (PMBCL). Pembrolizumab is currently administered as an intravenous infusion. Subcutaneous administration of pembrolizumab offer advantages to patients, providers, and the healthcare system. MK-3475A is pembrolizumab with berahyaluronidase alfa for subcutaneous administration (subcutaneous pembrolizumab). Berahyaluronidase alfa, a human hyaluronidase variant developed and manufactured by Alteogen Inc., is a permeation enhancer that increases dispersion and allows for subcutaneous administration of pembrolizumab in 1 injection for both Q3W and Q6W dosing. Here, we describe the methodology of a single-arm, open-label, phase 2 study (NCT06504394) designed to evaluate subcutaneous pembrolizumab in participants with R/R cHL or R/R PMBCL. **Methods:** Key eligibility criteria include participants aged ≥18 years with a histologically confirmed diagnosis of cHL or PMBCL that is FDG-avid per WHO classification criteria, radiographically measurable disease, and an ECOG performance status of 0 or 1. Participants with cHL must be anti–PD-1 naive and have not responded to or relapsed after ≥1 line of multiagent therapy, did not achieve a complete response (CR) or relapsed after autologous stem cell transplant (auto-SCT), or are ineligible for auto-SCT. Participants with PMBCL must be anti–PD-1 naive and have not responded to or relapsed after ≥2 prior lines of therapy (≥1 rituximab based), or did not achieve a CR or relapsed after auto-SCT or are ineligible for auto-SCT. Key exclusion criteria include clinically significant cardiovascular disease, pericardial effusion or clinically significant pleural effusion, or an additional malignancy that is progressing or has required active treatment within the past 2 years. Approximately 60 participants will be enrolled. All participants will receive subcutaneous pembrolizumab 790 mg every 6 weeks for up to 18 cycles (~2 years), or until disease progression or other discontinuation criteria are met. Primary end points are pharmacokinetics during cycle 1 and objective response rate per Lugano classification criteria by investigator review. Secondary end points are pharmacokinetics at steady state (cycle 3), antidrug antibody levels, safety and tolerability, and duration of response per Lugano classification criteria by investigator review. CT scans will be performed every 12 weeks; PET scans will be performed at week 12, week 24, and to confirm CR. Adverse events (AEs) will be monitored throughout the study and for ≤30 days after treatment end (90 days for serious AEs; or 30 days if new anticancer therapy is initiated) and will be graded per NCI CTCAE v5.0. Recruitment is ongoing. Clinical trial information: NCT06504394. Research Sponsor: Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS7091 Poster Session

TITANium: An open-label, global multicenter phase 1/2 study of AZD5492, a first-in-class subcutaneous CD8-guided tri-specific T-cell engager (TCE), in patients (pts) with relapsed or refractory (r/r) B-cell malignancies.

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Background: Bispecific CD20 x CD3 TCEs are changing the treatment landscape for pts with r/r non-Hodgkin lymphomas (NHL); however, they are associated with immune-related toxicities, namely cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which limit their use. AZD5492 is a first-in-class, humanized, asymmetric, subcutaneously-administered, trispecific monoclonal IgG1 antibody that harbors two Fab binding domains to CD20, one VHH binding domain to T-cell receptor and one VHH binding domain to a CD8 co-receptor. Preclinical data have shown that AZD5492 drives B-cell killing through preferential engagement of CD8+ T cells, with reduced CD4+ T-cell activation and associated cytokine production. Thus, AZD5492 may have a wider therapeutic index and safety advantage compared with first generation CD20 x CD3 TCEs which equally engage and activate CD4+ and CD8+ T cells. In an in vivo NHL model, AZD5492 showed potent antitumor activity with reduced cytokine release compared with a CD20 x CD3 comparator. TITANium is a global Phase 1/2 multicenter dose escalation (Part A) and expansion (Part B) study (NCT06542250) of AZD5492 in pts with r/r B-cell malignancies. **Methods:** We present the study design of Part A. Eligible pts are aged ≥18 years with histologically documented CD20+ mature B-cell neoplasm, specifically large B-cell lymphoma (LBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL), with ≥1 measurable lesion (except for CLL) and r/r disease after ≥2 prior lines of therapy. Pts with history of Grade ≥3 CRS or ICANS, post-transplant lymphoproliferative disease, Ritcher's transformation, Burkitt's lymphoma or Burkitt-like lymphoma are excluded. Part A will consist of two independent dose escalation groups: Part A1 will enroll pts with MCL or CLL/SLL; Part A2 will enroll pts with LBCL or FL. Dose escalation will start with pts receiving AZD5492 subcutaneously at a fixed dose per dose-level. An immune-related toxicity during Part A will trigger a double step-up strategy. Thereafter, treatment will continue for a limited duration. Each part will continue dose escalation independently, using fixed or step-up dosing. Part A will initially follow an accelerated titration design and will switch to a modified toxicity probability interval-2 design when triggered by emerging data. The primary objective is to assess safety and tolerability of AZD5492. Key secondary objectives are to evaluate preliminary efficacy, pharmacokinetics and immunogenicity of AZD5492. Enrollment began in September 2024 and is currently ongoing. Clinical trial information: NCT06542250. Research Sponsor: AstraZeneca.

TPS7092 Poster Session

waveLINE-010: Zilovertamab vedotin plus R-CHP versus R-CHOP in untreated diffuse large B-cell lymphoma.

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Background: Despite recent advances in the treatment of diffuse large B-cell lymphoma (DLBCL), 5-year survival rates range between 60% and 80%. Modest improvements have been made over standard-of-care with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) immunochemotherapy being used in the first-line setting. Zilovertamab vedotin, an ROR1-targeting antibody-drug conjugate with a monomethyl auristatin E payload, has demonstrated promising efficacy in patients with DLBCL. The randomized, open-label, phase III waveLINE-010 (NCT06717347) study will evaluate the efficacy and safety of zilovertamab vedotin in combination with rituximab plus cyclophosphamide, vincristine, and prednisone (R-CHP) versus R-CHOP in patients with untreated DLBCL. **Methods:** Eligible participants are aged ≥18 years and have histologically confirmed DLBCL per World Health Organization classification of neoplasms of the hematopoietic and lymphoid tissues (including but not limited to: DLBCL, not otherwise specified [NOS] germinal center B-cell type, or activated B-cell type; DLBCL leg-type; Epstein-Barr virus–positive DLBCL, NOS; and T-cell histiocytic-rich DLBCL), positron emission tomography–positive disease at screening (4-5 on the Lugano 5-point scale), no prior treatment for DLBCL, an International Prognostic Index (IPI) score of 2-5, and an ECOG performance status score of 0-2. Approximately 1046 patients will be randomly assigned (1:1) to receive zilovertamab vedotin 1.75 mg/kg plus R-CHP on day 1 of every 3-week cycle for 6 cycles, or R-CHOP on day 1 of every 3-week cycle for 6 cycles. Patients with high-risk DLBCL in both treatment arms will receive rituximab (or biosimilar) for an additional 2 cycles. Randomization will be stratified by 3 geographic regions (Western Europe, the United States, Canada, and Australia vs Asia vs rest of world), IPI score (2 vs 3-5), and bulk (<7.5 cm vs ≥7.5 cm). The primary end point is PFS per Lugano criteria by blinded independent central review (BICR). Secondary end points include complete response rate at end of treatment (EOT) per Lugano criteria by BICR, overall survival, event-free survival per Lugano criteria by BICR, duration of complete response, safety and tolerability, and changes from baseline in health-related quality-of-life assessments. Response assessments will be performed after day 1 of cycle 4 but before day 1 of cycle 5, and then at 12 weeks after cycle 4 scan (EOT assessment). Efficacy follow-up assessments will be completed every 24 weeks for 2 years from EOT assessment, then every year for 3 years (total of 5 years). Adverse events will be graded per NCI CTCAE v5.0. Recruitment is ongoing. Clinical trial information: NCT06717347. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS7093 Poster Session

A phase 1 first-in-human study evaluating safety, pharmacokinetics, and efficacy of ABBV-291, a CD79b-targeting antibody-drug conjugate, in patients with relapsed/refractory B-cell non-Hodgkin lymphoma.

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Background: Chemoimmunotherapy successfully treats ~60% of patients (pts) with diffuse large B-cell lymphoma (DLBCL), the most common form of B-cell non-Hodgkin lymphoma (B-NHL). However, pts who are not cured often die from relapsed/refractory (R/R) disease, highlighting the need for new therapies. CD79b is expressed on most major subtypes of B-NHL and is a validated target in DLBCL. ABBV-291 is an antibody-drug conjugate (ADC) comprising the anti-CD79b antibody conjugated to a potent topoisomerase 1 inhibitor payload, and offers potential as a best-in-class treatment in DLBCL. Preclinical data indicate that ABBV-291 has robust antitumor activity, with superior responses compared with other anti-CD79b ADCs. There is also the possibility for lower rates of key adverse events (AEs) such as neuropathy compared with monomethyl auristatin E-payload ADCs. Herein, we describe a first-in-human study evaluating the safety, pharmacokinetics (PK), and efficacy of ABBV-291 monotherapy in pts with R/R B-NHL. **Methods:** This phase 1, open-label, multicenter, dose-expansion study (NCT06667687) is enrolling pts (≥18 years) who have a documented diagnosis of B-NHL (except chronic lymphocytic leukemia), measurable disease, ECOG 0–1, and are R/R to or intolerant of ≥2 prior lines of therapy, with no other available therapies of clinical benefit. Primary objectives are to assess safety/tolerability of ABBV-291 and determine its recommended phase 1 expansion dose (RP1ED). Secondary objectives are to evaluate preliminary efficacy of ABBV-291 in specified subsets of R/R B-NHL (eg DLBCL, follicular lymphoma [FL], mantle cell lymphoma [MCL]) and to characterize its PK. Exploratory objectives include investigating the association between biomarkers, safety, efficacy, and PK. The study consists of 2 parts: dose escalation (up to ~45 pts), and dose expansion and optimization (~120 pts). ABBV-291 is administered intravenously. In the BOIN-guided dose-escalation, ABBV-291 administration for the first 2 pts is staggered by ≥24 hours at the first 2 dose levels (DLs); dose-limiting toxicities (DLTs) are assessed for 35 days from the initial dose. In dose expansion, ABBV-291 is evaluated at the RP1ED in DLBCL and FL; for dose optimization, ABBV-291 is evaluated in ≥2 DLs in MCL. Pts continue treatment until disease progression, intolerable toxicity, or other study discontinuation criteria are met. Safety evaluations include AE monitoring, DLTs, vital signs, ECG, and clinical laboratory parameters. Response evaluations are performed per disease-specific response criteria and include objective response rate, duration of response, and progression-free survival. PK parameters are determined using noncompartmental methods. The study is actively enrolling globally. Clinical trial information: NCT06667687. Research Sponsor: AbbVie, Inc.; n/a.

TPS7094 **Poster Session**

Optimizing frontline therapy for diffuse large B cell lymphoma (DLBCL) in older adults: A glofitamab-based, response-adapted, window-style study (GLORY).

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Background: Older adults (OA) with DLBCL classified as unfit or frail based on simplified geriatric assessment (sGA) do poorly with standard doses of anthracycline based chemotherapy. Bispecific antibodies have a preserved risk-benefit profile in OA and their combination with chemotherapy represents a promising strategy to increase cure rates in DLBCL. Interim PET scans have a high negative predictive value and can be harnessed to guide response adapted therapy in this setting to minimize exposure to chemotherapy for responsive patients. GLORY is a window-style, glofitamab-based, response-adapted study with polatuzumab-rituximab-miniCHP (pola-R-miniCHP) backbone specifically designed for unfit and frail older adults with DLBCL who are being treated with curative intent. The dual goals of this personalized strategy are: 1. To improve cure rates in patients with iPET2 positivity, 2. To reduce chemotherapy dosage and ensuing toxicities in patients with iPET2 negativity while maintaining/improving cure rate. **Methods:** In this Phase II, prospective, open label, single arm, single institution study, OA $\geq$ 65 years of age with newly diagnosed DLBCL, high grade or transformed B-cell lymphoma, classified as unfit or frail by simplified geriatric assessment (sGA) will be included. All patients will receive 2 cycles of glofitamab and polatuzumab followed by an interim PET scan (iPET2). If iPET2 is negative (Deauville 1-3), patients will receive 4 cycles of glofitamab-pola-R-miniCHP. If iPET2 is positive without progression, patients receive 6 cycles of glofitamab-pola-R-miniCHP. All patients undergo end of treatment (EOT) PET and are followed for 5 years. ctDNA and dynamic changes in aging biomarkers [epigenetic aging clock, senescence associated secretory phenotype (SASP)] will be measured at baseline, after cycle 1 (C1), after C2 and at the EOT and correlated with outcomes. On therapy tumor biopsy after cycle 1 of glofitamab+-polatuzumab is optional. The trial has been thoughtfully designed to be OA-friendly with pragmatic eligibility criteria and stepwise strategies (eg. prephase) to mitigate the risk of toxicities. The primary endpoints are complete response rate (CRR) after 2 cycles of glofit-pola and CRR after completion of therapy. Key secondary end points include other measures of efficacy such as overall response rate (ORR), progression free survival (PFS) and overall survival (OS) and safety. The target CRR at the end of therapy is 60% with an unacceptably low rate of 40%. Based on these assumptions, a sample size of 42 patients provides a 5% one sided type 1 error and 80% power. This is a single stage design, and the study will be considered positive if 23 of 42 patients achieve a CR at the end of therapy. Additionally, the coprimary endpoint of CR rate after 2 cycles of glofitamab+polatuzumab will be used to stop for futility. Clinical trial information: NCT06765317. Research Sponsor: Genentech; Memorial Sloan Kettering Cancer Center.

TPS7095 **Poster Session**

Sequencing-guided chemotherapy optimization using real-time evaluation in newly diagnosed DLBCL with circulating tumor DNA: SHORTEN-ctDNA (NCT06693830).

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Background: Circulating tumor DNA (ctDNA) is a clinically valid tool for detection of measurable residual disease (MRD) in patients with diffuse large B-cell lymphoma (DLBCL). Phased variant enrichment and detection sequencing (PhasED-seq), which uses multiple somatic mutations on individual DNA fragments, improves upon first-generation single nucleotide variant-based MRD tests with improved sensitivity (Kurtz et al. *Nat Biotech* 2021). To utilize ctDNA-MRD testing in a clinical setting to guide treatment decisions, the ability to test and report in a real-time manner is required. However, the feasibility of real-time MRD testing using the PhasED-seq-based Foresight CLARITY platform to inform treatment decisions has yet to be established. Therapy de-escalation after 4 cycles of standard R-CHOP therapy was non-inferior and less toxic than 6 cycles for patients with DLBCL with no baseline risk factors (Poeschel et al. *Lancet* 2019). Identification of patients who are ideal candidates for de-escalation based on treatment response remains a challenge as radiographic imaging has a high false-negative rate (Le Gouill & Casanovas, *Blood* 2017). ctDNA-MRD has a higher sensitivity and may be a better test to guide dose de-escalation decisions in patients with DLBCL. This feasibility study will have two co-primary objectives: (1) to evaluate the feasibility of ctDNA sequencing for real-time guidance of clinical decision making during frontline therapy for DLBCL; and (2) to determine the outcomes of patients with newly diagnosed DLBCL who become undetectable for ctDNA and demonstrate a radiographic complete response (CR) during standard frontline therapy and discontinue chemotherapy early. **Methods:** This single-center investigator-initiated study began enrolling in November 2024 and is enrolling patients (N=32) with newly diagnosed stage II-IV, CD20+ DLBCL with measurable disease. Patients will receive 4 cycles of standard-of-care therapy (R-CHOP or R-pola-CHP). Positron emission tomography/computed tomography (PET/CT) scans will be performed after cycle four (C4) and at the end of therapy. Additionally, whole blood samples will be drawn on C4 day 1 (C4D1) and shipped to Foresight Diagnostics, Inc. (Boulder, CO) for real-time MRD testing. Patients who experience a CR on iPET4 and have undetectable ctDNA on C4D1 will de-escalate therapy and receive rituximab alone for C5-6. Patients not meeting these response criteria or with unsuccessful real-time MRD testing for any reason will continue standard therapy for the remaining cycles. MRD will also be evaluated in a batched manner at the end of the study at other timepoints to evaluate the kinetics of ctDNA as well as correlation with clinical outcomes. The primary efficacy endpoint is the EOT CR rate on PET/CT performed 10-14 weeks after C6D1 in the patients who receive de-escalated treatment. Clinical trial information: NCT06693830. Research Sponsor: Foresight Diagnostics, Inc.; National Cancer Institute; Conquer Cancer, the ASCO Foundation.

TPS7096 **Poster Session**

A phase 1a/1b trial in relapsed/refractory T-cell non-Hodgkin lymphoma to determine the safety profile, pharmacology, and maximum tolerated dose of ST-001, an intravenous fenretinide phospholipid suspension (12.5 mg/mL).

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Background: N-(4-hydroxyphenyl)retinamide (4-HPR; fenretinide) is a synthetic amide derivative of all-trans retinoic acid. Clinical data from trials of earlier fenretinide formulations indicate that higher plasma levels of fenretinide correlate with improved patient responses. Although fenretinide intravenous emulsion (4-HPR-ILE) increased plasma concentration and yielded complete and partial responses in peripheral T-cell lymphomas, its dose-limiting hypertriglyceridemia mainly related to triglyceride from the soy oil vehicle posed a significant impediment to clinical development (Maurer BJ et al. *Clin Cancer Res.* 2017). **Methods:** A new formulation of intravenous fenretinide, designated ST-001 nanoFenretinide, is an innovative dosage form composed of phospholipid nanoparticles in a free-flowing solution (Patent number US 8709379 B2). ST-001 effectively eliminates the risk of vehicle-related hypertriglyceridemia, because it is free of triglycerides. It is also free of adjuvants, non-ionic surfactants, polyoxylated compounds, alkoxylated oils, and animal-derived substances known to cause allergy or hypersensitivity. ST-001 potentially provides a safer form of intravenous fenretinide for achieving therapeutic plasma concentrations. In this Phase 1a/1b clinical trial (NCT04234048), ST-001 is administered via intravenous infusion (IV) to patients with relapsed/refractory T-cell non-Hodgkin's lymphoma (NHL) following at least one prior treatment, including cutaneous (CTCL) and non-cutaneous T-cell lymphoma subtypes (angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, and follicular T-cell lymphoma). The U.S.-based trial will enroll up to 54 patients across three stages: up to 9 patients (single patient cohorts) for Phase 1a accelerated dose escalation, up to 15 patients (3 patient cohorts) for Phase 1a standard dose escalation and determination of maximum tolerated dose (MTD), and 30 patients for Phase 1b to determine the optimal dose. The primary objectives are to determine the MTD, toxicity profile, adverse events and dose-limiting toxicities (DLTs) based on NCI Common Toxicity Criteria, and anti-tumor activity, when administered over 4 hours daily for 5 consecutive days every 3 weeks, for a maximum of 8 cycles. Secondary objectives include pharmacokinetic profiling and investigating potential mechanisms of action using pharmacodynamic biomarkers. The accelerated stage has completed enrollment, and the standard stage is open for enrollment as of January 2025. This study investigates a novel fenretinide formulation aiming to address treatment challenges in T-cell NHL, with a focus on safety, tolerability, clinical activity, and pharmacology. Clinical trial information: NCT04234048. Research Sponsor: None.

TPS7097 **Poster Session**

A phase 1 trial of BTM-3566 in relapsed/refractory mature B cell lymphomas.

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Background: Relapsed/refractory (R/R) aggressive B-cell lymphomas, including diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL), remain challenging to treat, particularly in patients who have exhausted approved therapies. BTM-3566, a novel compound demonstrated efficacy against diverse B-cell malignancies, with the most pronounced impact observed in DLBCL and MCL. BTM-3566 initiates the mitochondrial ATF-4-mediated integrated stress response (ISR) pathway via a unique mechanism governed by the mitochondrial protein FAM210B. In vitro, BTM-3566 induces apoptosis across multiple hematological and solid tumor cell lines with several in vivo models demonstrating tumor regression or significant tumor growth inhibition. This includes complete tumor regressions in DLBCL and MCL patient-derived xenograft (PDX) mouse models carrying genetic alterations linked to unfavorable prognosis such as double hit (DH) and triple hit lymphoma (TH) and MCL PDX models from patients previously treated with CAR T, rituximab, venetoclax and/or BTK inhibitors. **Methods:** This ongoing Phase 1, single-arm, open-label, multi-center trial is evaluating the safety, tolerability, and preliminary efficacy of BTM-3566 in adult patients with mature B-cell lymphomas. Eligible participants must have histologically confirmed mature B cell lymphoma that has progressed after at least two prior lines of systemic therapy. BTM-3566 is administered orally in two weeks cycles (7 days on, 7 days off). Primary endpoints include incidence of dose-limiting toxicities (DLTs) and treatment-emergent adverse events (TEAEs). Secondary and exploratory endpoints include objective response rate (ORR), duration of response (DoR), progression-free survival (PFS) pharmacokinetics and pharmacodynamic assessments. Enrollment is scheduled to start in Q1 2025 in US and Canada. Clinical trial information: NCT06792734. Research Sponsor: None.