LBA7000 **Oral Abstract Session**

Tolerability and efficacy of BrECADD versus BEACOPP in advanced stage classical Hodgkin lymphoma: GHSG HD21, a randomized study.

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7001 Oral Abstract Session

Upfront allo-HSCT after intensive chemotherapy for untreated aggressive ATL: JCOG0907, a single-arm, phase 3 trial.

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Background: Aggressive adult T-cell leukemia-lymphoma (ATL) (i.e., acute, lymphoma and unfavorable chronic types) has poor prognosis with around a 1-year median survival time (MST) with chemotherapy. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) provides a durable response with 3-year overall survival (3-y OS) of around 40%. However, the results were mostly from retrospective studies. This single-arm, phase 3 trial by the Japan Clinical Oncology Group (JCOG) evaluated upfront allo-HSCT for aggressive ATL (jRCTs031180243). **Methods:** Patients (pts) with newly diagnosed aggressive ATL who wished to receive allo-HSCT were eligible. At trial initiation, JCOG0907 was restricted to myeloablative allo-HSCT (MAST) for pts aged ≤ 55 years. After protocol amendment in September 2014, reduced intensity allo-HSCT (RIST) for pts aged 56-65 years was allowed. The protocol treatment was VCAP-AMP-VECP as induction chemotherapy based on the phase 3 JCOG9801 trial (3-y OS 24%) followed by transplantation in pts upon first remission from an HLA-matched or 1-locus mismatched related donor, or HLA-matched unrelated (UR) donor. MAST regimens consisted of busulfan (BU)/cyclophosphamide (CPA) for related donors and total body irradiation (TBI)/CPA for UR donors. RIST regimens consisted of BU/fludarabine (FLU) for related donors and FLU/BU/TBI for UR donors. The primary endpoint was 3-y OS in all registered pts. This study evaluated whether the lower limit of the two-sided 90% CI of 3-y OS exceeded a threshold of 25%. **Results:** Between September 2010 and June 2020, 110 pts (72 acute, 27 lymphoma, 10 unfavorable chronic and 1 other) were enrolled. Of 92 pts who received allo-HSCT (all transplants), 41 pts (19 MAST and 22 RIST, 12 related and 29 UR) received per-protocol allo-HSCT (study transplant) and 51 pts (11 related, 15 UR and 25 cord blood) received allo-HSCT not specified in the protocol, 35 of whom received allo-HSCT during first remission and 16 pts after progression. The primary endpoint was met with 3-y OS of 44.0% (90% CI, 36.0-51.6). MST was 3.0 years (95% CI, 1.5-5.8) for study transplants and 2.5 years (95% CI, 1.4-4.8) for all transplants. Multivariable analysis with a time-dependent covariate for the presence or absence of transplant revealed the hazard ratio of OS for study transplants compared with non-study transplants was 0.92 (95% CI, 0.55-1.51). In 41 study transplants, treatment-related deaths (TRD) were 16.7% in related transplants and 20.7% in UR transplants. Among 70 pts who died, causes of death were disease progression in 34, TRD due to protocol treatment in 9, TRD due to post-protocol treatment in 21, and other disease in 6. **Conclusions:** Upfront allo-HSCT can be recommended for chemotherapy-sensitive pts with aggressive ATL, but its survival benefit is not clear considering immortal time bias suggested by multivariable analysis with a time-dependent covariate. Clinical trial information: jRCTs031180243. Research Sponsor: the National Cancer Center Research and Development Fund.

CLAMP: A phase II prospective study of camrelizumab combined with pegaspargase, etoposide, and high-dose methotrexate in patients with natural killer (NK)/T-cell lymphoma.

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Background: Immune checkpoint blockades have been investigated and show promising results in natural killer (NK)/T-cell lymphoma (NKTCL) patients. This study explored the efficacy and safety of camrelizumab, a PD-1 monoclonal antibody, combined with pegaspargase, etoposide, and high-dose methotrexate (CLAMP) in the treatment of NKTCL patients. **Methods:** This single-arm, phase 2 study enrolled patients with NKTCL. Patients were divided into two groups: group A, early-stage (Ann Arbor staging I/II) patients; group B, advanced-stage (Ann Arbor staging III/IV) and RR patients. Group A received involved-field radiotherapy combined with 3-4 cycles of CLAMP treatment. Group B received 6 cycles of CLAMP treatment. CLAMP regimen was administrated as follows: pegaspargase 2500 U/m^2 d1, etoposide 100 mg/m^2 per day d1-3, HD-MTX 3 g/m^2 d4, camrelizumab 200 mg d7. **Results:** A total of 41 patients, including 36 newly diagnosed and 5 relapsed NKTCL, were enrolled in this study from July 2020 to December 2022. 14 patients presented with high-risk central nervous system (CNS) infiltration with 2-4 risk factors of the NKPI (Ann Arbor stage III or IV, presence of B symptoms, regional lymph node involvement, elevated lactate dehydrogenase). One patient had complied hemophagocytic lymphohistiocytosis (HLH). On treatment completion, the overall cohort showed a complete remission (CR) rate of 87.80% (36/41) and a partial remission (PR) rate of 7.32% (3/41), giving an overall response rate (ORR) of 95.12% (39/41). The ORR for group A patients was 100% (19/19) and 90.91% (20/22) for group B patients; only 2 patients in group B progressed during the treatment. The patient with HLH obtained CR and was disease-free for more than 12 months. No patients developed HLH or CNS involvement during the follow-up period. At a median follow-up of 21 months, 5 patients (12.20%) died; among them, 3 patients died of disease progression, and 2 patients died of infection unrelated to treatment. The 2-year progression-free survival (PFS) and 2-year overall survival (OS) rates for the whole cohort were 72.81% and 88.03%, respectively. The 2-year PFS rates for group A and group B were 91.67% and 53.83%, respectively. The 2-year OS rates for group A and group B were 91.67% and 77.53%, respectively. Hematologic toxicity was common, yet nonhematologic toxicity was mild and could be well controlled by supportive treatments, except 2 patients had delayed methotrexate metabolism and received dialysis. No treatment-related death was observed. **Conclusions:** The CLAMP regimen is effective and safe and seems to reduce the incidence of CNS involvement and HLH. The CLAMP regimen may be a promising option in the treatment of NKTCL lymphoma. Clinical trial information: ChiCTR2100051208. Research Sponsor: None.

LBA7003 **Oral Abstract Session**

Tucidinostat plus R-CHOP in previously untreated diffuse large B-cell lymphoma with double expression of MYC and BCL2: An interim analysis from the phase III DEB study.

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Safety and efficacy of armored huCART19-IL18 in patients with relapsed/refractory lymphomas that progressed after anti-CD19 CAR T cells.

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Background: A substantial proportion of patients (pts) with relapsed/refractory (R/R) non-Hodgkin lymphomas (NHL) will not derive a long-term benefit from the existing anti-CD19 chimeric antigen receptor (CAR) T cells. To enhance therapeutic efficacy, we have engineered huCART19-IL18, a 4^{th} generation 4-1BB anti-CD19 construct, armored with the ability to secrete the pro-inflammatory cytokine, IL-18. **Methods:** This is a first-in-human trial using huCART19-IL18 for CD19+ B-cell malignancies (NCT04684563). Expedited 3-day manufacturing is utilized to limit T-cell exhaustion. To be eligible for the NHL cohort, pts must be R/R to prior anti-CD19 CAR T cells if indicated by FDA label. Dose levels (DL) between $3x10^6$ and $3x10^8$ of huCART19-IL18+ cells are administered as a single IV infusion following lymphodepleting chemotherapy. Bridging therapy is optional. Responses are first assessed at 3 months (mo) using Lugano criteria. **Results:** As of January 20, 2024, 21 pts with CD19+ NHL were infused with huCART19-IL18. Characteristics include median age 64 yrs (47-74), 76% male, 9 (43%) DLBCL, 6 (29%) FL, 3 (14%) MCL, 2 (10%) tFL, 1 (5%) HGBCL. Median number of prior Rx was 7 (4-14) with 20 (95%) pts R/R to prior anti-CD19 CAR T cells. Manufacturing of DL5 ($3x10^8$) was not feasible due to inability to achieve the target dose in 4/6 (67%) pts assigned to DL5. 18 (86%) pts received bridging. 3 pts received DL1 ($3x10^6$), 4 pts DL2 ($7x10^6$), 1 pt non-defined dose ($2.8x10^7$), 6 pts DL3 ($3x10^7$), 5 pts DL4 ($7x10^7$), 2 pts DL5 ($3x10^8$). No study-related deaths occurred in 21 safety-evaluable pts. CRS occurred in 15 (71%) pts: G1 in 8 (38%), G2 in 4 (19%), G3 in 3 (14%). ICANS occurred in 3 (14%) pts: G1 in 2 (10%), G2 in 1 (5%). The most common G3 adverse events at least possibly related to huCART19-IL18 included fatigue (38%), hypotension (29%), and low fibrinogen (23%). 20 pts are efficacy evaluable with median (m) follow-up of 15 mo (3-31). The 3 mo ORR was 80% (90% CI: 60-93%), with CR 50% (90% CI: 30-70%) and PR 30% (90% CI: 14-51%). mDOR was 10 mo (5.5-NR). mPFS was 8.7 mo (90% CI 5-NR), and mOS was NR (90% CI 25 mo-NR). We detected continued persistence of huCART19-IL18 in pts with 24 mo follow-up. No correlation between cell dose and outcome was identified, but response rates and mean expansion (copies/μg gDNA) were higher in pts previously exposed to CD28 CAR than those who had prior 4-1BB CAR (Table). **Conclusions:** Treatment with huCART19-IL18 has an acceptable safety profile and produced durable remissions in heavily pre-treated pts with R/R NHL despite prior CAR T-cell therapy. The subtype of the preceding CAR product may influence the expansion and effectiveness of huCART19-IL18. Clinical trial information: NCT04684563. Research Sponsor: None.

Responses and expansion by prior CAR product.

	CD28 (axi-cel, brexu-cel) N=10	4-1BB (tiso-cel, liso-cel) N=9	p-value
ORR	100%	56%	0.03*
CR	80%	22%	0.02*
Mean huCART19-IL18 expansion	26,326	5,479	0.01**

*) Fisher's exact t. **) Wilcoxon rank sum t.

LBA7005 **Oral Abstract Session**

Brentuximab vedotin in combination with lenalidomide and rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma: Results from the phase 3 ECHELON-3 study.

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Benefit of rituximab maintenance after first-line bendamustine-rituximab in mantle cell lymphoma.

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Background: Rituximab maintenance (RM) after first-line (1L) bendamustine and rituximab (BR) in MCL did not improve progression-free survival in the MAINTAIN trial (Rummel et al, ASCO 2016) but was associated with improved survival outcomes in a North American observational study (Martin et al, JCO 2023). We sought to examine the potential benefit of RM after BR using a large observational cohort from 26 US academic centers. **Methods:** Patients with MCL who received 1L BR (without stem cell transplant) outside of clinical trials were included. At the landmark of 3 months after the end of BR, patients who achieved a complete response (CR) or partial response (PR) to BR and had no evidence of progressive disease (PD) or second-line (2L) therapy were deemed eligible for RM. Event-free survival (EFS) was defined as time from landmark to progression, relapse, retreatment, or death. EFS2 was defined as time from landmark to progression, relapse, or retreatment following 2L therapy or death. RM was not considered a line of therapy for either endpoint. OS was defined as time from landmark to death. Survival analysis was done with Kaplan-Meier methods and Cox regression models adjusting for sex and simplified MIPI. **Results:** Among 796 patients who received 1L BR in 2007-2020, 693 achieved a CR or PR. At the 3-month post-BR landmark, 613 had no evidence of PD, among whom 318 (52%) received RM and 295 did not. The RM group was younger (median age 70 vs 72, p = 0.010) and more predominantly male (78% vs 69%, p = 0.047). There was no statistical difference in stage, simplified MIPI, histology (blastoid or pleomorphic vs classic), Ki-67, *TP53* alteration, complex karyotype, year of BR start, or best response to BR between the two groups. The median follow-up after the 3-month post-BR landmark was 61.3 months (95% CI 62.6-70.4). The median number of doses of RM was 10 (IQR 5-12). RM was associated with improved EFS (median 47.1 vs 29.7 months, adjusted HR 0.59, 95% CI 0.48-0.73), EFS2 (median 89.1 vs 48.3 months, adjusted HR 0.63, 95% CI 0.50-0.81), and OS (median 136.1 vs 74.3 months, adjusted HR 0.57, 95% CI 0.44-0.75) (all p values < 0.001). In patients with CR to 1L BR (n=527), 271 (51%) received RM, for a median of 11 (IQR 6-12) doses. In this subgroup, RM was associated with improved EFS (median 60.6 vs 31.5 months, adjusted HR 0.56, 95% CI 0.44-0.71), EFS2 (median 89.1 vs 48.3 months, adjusted HR 0.62, 95% CI 0.48-0.81), and OS (median 136.1 vs 75.6 months, adjusted HR 0.59, 95% CI 0.44-0.79) (all p values < 0.001). Analysis in patients with PR to 1L BR was limited by the sample size (n=86, 47 received RM). The numeric differences in median EFS (20.8 vs 11.5, log-rank p = 0.370), EFS2 (48.9 vs 30.3, log-rank p = 0.210) and OS (87.3 vs 46.9, log-rank p = 0.067) were not statistically significant. **Conclusions:** In this large multicenter study, RM after 1L BR was associated with improved EFS and OS, supporting its use in routine practice for patients with newly diagnosed MCL. Research Sponsor: None.

Efficacy and safety of ibrutinib plus venetoclax in patients with mantle cell lymphoma (MCL) and *TP53* mutations in the SYMPATICO study.

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Background: *TP53* mutations confer high risk of early progressive disease (PD) and poor outcomes with standard chemoimmunotherapy in patients (pts) with MCL. To date, data on novel treatment options for these pts are limited to small single-arm analyses. The phase 3 SYMPATICO study is evaluating ibrutinib (Ibr) + venetoclax (Ven) in 3 cohorts of pts with MCL. Primary analysis of the randomized phase showed superior PFS with Ibr+Ven vs Ibr+placebo (Pbo) in pts with relapsed/refractory (R/R) MCL (Wang M et al, ASH 2023) with similar hazard ratios for pts with and without *TP53*mutations (0.57 [95% CI, 0.33–0.97] and 0.52 [95% CI, 0.32–0.82], respectively). Here, we report efficacy and safety of Ibr+Ven in pts with *TP53* mutations across cohorts. **Methods:** The SYMPATICO cohorts are: open-label safety run-in phase to evaluate concurrent initiation of Ibr+Ven in R/R MCL (n=21); randomized phase to evaluate Ibr+Ven (n=134) vs Ibr+Pbo (n=133) in R/R MCL; and open-label cohort to evaluate first-line (1L) Ibr+Ven (n=78). Data were pooled across cohorts for pts with *TP53*mutations-treated with 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. Response was assessed by investigators per Lugano criteria. **Results:** In total, 74 pts with *TP53* mutations received Ibr+Ven in the safety run-in phase (n=5), the randomized phase (n=40), and the 1L cohort (n=29). At baseline, median age was 67 y, 96% of pts had ECOG PS of 0–1, 43% had high-risk simplified MIPI score, 36% had bulky disease ≥5 cm, 64% had bone marrow involvement, and 39% had splenomegaly. With a median time on study of 40.1 mo (range, 0.6+ to 60.7), median PFS was 20.9 mo vs not reached (NR) in pts without *TP53* mutations. ORR was 84%, and the CR rate was 57%. Median OS was 47.1 mo. Outcomes were generally comparable in 1L and R/R MCL (Table). Median duration of treatment was 15.9 mo (range, 0.3–58.9); at data cutoff, treatment was ongoing with Ibr in 24% of pts and with Ven in 4%. The most frequent grade ≥3 AEs (in ≥10% of pts) were neutropenia (32%), anemia (15%), and thrombocytopenia (15%). **Conclusions:** Ibr+Ven demonstrated promising efficacy with high CR rates and durable remissions in high-risk pts with MCL and *TP53*mutations in SYMPATICO (n=74; 29 1L and 45 R/R), the largest single-study cohort of such pts reported to date. Clinical trial information: NCT03112174. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.

Outcomes (95% CI)	1L	R/R	Total
Pts without *TP53* mutations	n=44	n=75	N=119
Median PFS, mo	NR (NE–NE)	46.9 (31.5–NE)	NR (36.4–NE)
Pts with *TP53* mutations	n=29	n=45	N=74
Median PFS, mo	22.0 (9.2–NE)	20.9 (13.0–33.1)	20.9 (14.7–30.6)
ORR, %	90 (73–98)	80 (65–90)	84 (73–91)
CR rate, %	55 (36–74)	58 (42–72)	57 (45–68)
Median duration of response, mo	20.5 (12.0–NE)	26.5 (16.8–NE)	26.0 (16.8–32.2)
Median duration of CR, mo	20.5 (5.4–NE)	NR (18.7–NE)	32.2 (18.7–NE)
Median OS, mo	NR (30.6–NE)	35.0 (14.1–NE)	47.1 (30.6–NE)

Glofitamab monotherapy in patients with heavily pretreated relapsed/refractory (R/R) mantle cell lymphoma (MCL): Updated analysis from a phase I/II study.

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Background: Glofitamab, a bispecific antibody with a novel 2:1 (CD20:CD3) format, engages and redirects T cells to eliminate malignant B cells. In a Phase I/II study (NCT03075696), fixed-duration glofitamab monotherapy showed high, durable complete responses (CR) and manageable safety in patients (pts) with heavily pretreated R/R MCL (Phillips et al. ASH 2022). We report updated efficacy and safety data for pts with R/R MCL. **Methods:** Pts received obinutuzumab pretreatment (Gpt; 1000mg or 2000mg) 7 days before their first glofitamab dose. Glofitamab step-up dosing was given on Cycle (C) 1 Day (D) 8 (2.5mg) and D15 (10mg), and target dose (16mg or 30mg) from C2D1 to C12 as a fixed-duration therapy. Efficacy endpoints were CR, overall response rate (ORR), duration of CR (DOCR), duration of response (DOR) and progression-free survival (PFS). Post-hoc PFS and overall survival (OS) landmark analyses were performed in pts with a CR at end of treatment (EOT). **Results:** As of Sept 4, 2023, 61 pts were enrolled; 60 received study treatment (1000mg Gpt, n=16; 2000mg Gpt, n=44). Median number of prior lines of therapy was 2 (range: 1–5); 73.3% were refractory to the last line of prior therapy. Median duration of glofitamab therapy was 7.4 months; median number of cycles was 12. Of the 31 pts (51.7%) who received prior Bruton's tyrosine kinase inhibitor (BTKi) therapy, 29 (93.5%) were BTKi refractory; median number of prior lines of therapy was 3 (range: 1–5); 90.0% were refractory to the last line of prior therapy. At a median PFS follow-up of 17.2 months, ORR and CR rate were 85.0% and 78.3%, respectively. Median DOCR was 15.4 months; the majority of CRs (28/47; 59.6%) were ongoing at data cut-off. Of 19 pts with a CR, 9 had disease progression and 10 died (fatal adverse event [AE], n=8; COVID, n=7; septic shock, n=1). Estimated 12-month DOCR and DOR rates were 71.0% and 66.6%, respectively. Median PFS was 16.8 months. Landmark analyses indicated that most pts with a CR at EOT were alive and progression free 15 months post-EOT (OS rate, 72.7%; PFS rate, 59.2%). Observed efficacy data were consistent across both Gpt cohorts. In post-BTKi pts after a median PFS follow-up of 26.1 months, ORR and CR rate were 74.2% and 71.0%, respectively. Median DOCR was 12.6 months; median PFS was 8.6 months. No new safety signals were observed. Cytokine release syndrome (CRS) remained the most common AE (42/60, 70.0%; Grade 1/2, 58.3%) and was lower in the 2000mg (63.6%) vs the 1000mg (87.5%) Gpt cohort. Glofitamab monotherapy (2000mg Gpt) is currently under investigation in the Phase III GLOBRYTE study (NCT06084936). **Conclusions:** Fixed-duration glofitamab continues to demonstrate compelling response rates that are maintained beyond EOT, with long-term durability observed in heavily pretreated pts with R/R MCL, including pts with prior BTKi therapy. The safety profile was manageable and CRS mainly low grade. Clinical trial information: NCT03075696. Research Sponsor: NP30179 is sponsored by F Hoffmann-La Roche Ltd.; N/A; Third-party medical writing support under the direction of authors, was provided by Deirdre Kelly, PhD and Emily Lynch, PhD (Ashfield MedComms, an Inizio company) and funded by F Hoffmann-La Roche Ltd; N/A.

7009 Rapid Oral Abstract Session

Outcomes in high-risk subgroups after fixed-duration ibrutinib + venetoclax for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): Up to 5.5 years of follow-up in the phase 2 CAPTIVATE study.

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Background: The phase 2 CAPTIVATE study evaluated first-line ibrutinib (Ibr) + venetoclax (Ven) for CLL/SLL in 2 cohorts: minimal residual disease (MRD)-guided randomized discontinuation (MRD cohort) and Fixed Duration (FD cohort). Ibr±Ven retreatment was allowed in patients (pts) who had progressive disease (PD). Here, we report outcomes for pts with high-risk genomic features from the FD cohort and retreatment outcomes in pts from the FD cohort and MRD cohort placebo arm. **Methods:** Pts aged ≤70 y with previously untreated CLL/SLL without restriction on genomic risk factors 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). On-study retreatment included single-agent Ibr (FD cohort or MRD cohort placebo arm); pts with PD >2 y after end of treatment (EOT) could be retreated with FD Ibr+Ven (FD cohort). **Results:** In the FD cohort (n=159) with a median follow-up of 61.2 mo (range, 0.8–66.3), 5-y PFS and OS rates (95% CI) were 67% (59–74) and 96% (91–98), respectively. 5-y PFS rates were higher in pts with undetectable MRD at 3 mo after EOT in peripheral blood (83%) or bone marrow (84%) vs those without (48% and 50%, respectively). 5-y PFS rates (95% CI) in pts with genomic risk factors were: del(17p)/mutated *TP53* 41% (21–59), complex karyotype 57% (37–72), del(11q) 64% (30–85), and unmutated IGHV 68% (50–80) (Table). In total, 18 second malignancies occurred in 13 pts (10 events in 8 pts during FD Ibr+Ven, 6 events in 4 pts after EOT and before retreatment, and 2 events in 2 pts during retreatment). Of 202 pts who completed Ibr+Ven (FD cohort, n=159; MRD cohort placebo arm, n=43), 63 have had PD to date; PD occurred >2 y after EOT in 43/63 pts (68%). 32/63 (51%) pts initiated retreatment with Ibr (n=25) or Ibr+Ven (n=7). With a median time on Ibr retreatment of 21.9 mo (range, 0.03–50.4), ORR was 86% in 22 evaluable pts (best response: 1 CR; 1 nodular PR; 17 PR; 2 SD; 1 PD [Richter transformation]). With a median time on Ibr+Ven retreatment of 13.8 mo (range, 3.7–15.1), ORR was 71% in 7 evaluable pts (best response: 1 CR; 4 PR; 1 PR with lymphocytosis; 1 SD). **Conclusions:** With up to 5.5 y of follow-up, FD Ibr+Ven continues to provide clinically meaningful PFS in pts with high-risk genomic features, as well as in the overall population. Ibr-based retreatment provides promising responses in pts needing subsequent therapy after the all-oral FD regimen of Ibr+Ven. Clinical trial information: NCT02910583. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.

FD cohort	With high-risk genomic feature[a]		Without high-risk genomic feature[a]	
	n	5-y PFS rate, % (95% CI)	n	5-y PFS rate, % (95% CI)
del(17p)/mutated *TP53*	27	41 (21–59)	129	73 (64–80)
CK[b]	31	57 (37–72)	102	72 (61–80)
Unmutated IGHV[c]	40	68 (50–80)	44	85 (69–93)
del(11q)[c]	11	64 (30–85)	74	79 (67–87)

[a]Among pts with known baseline status. [b]Defined as ≥3 chromosomal abnormalities. [c]Excluding pts with del(17p)/mutated *TP53* or CK.

Real-world outcomes of lisocabtagene maraleucel (liso-cel) in patients (pt) with Richter transformation (RT) from the Center for International Blood and Marrow Transplant Research (CIBMTR).

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Background: Pts with RT have poor prognosis and no standard treatment options with median OS of 3–12 mo (Eyre TA. *Hematology Am Soc Hematol Educ Program* 2023), indicating an unmet need. We report the largest cohort of real-world pts with RT treated with commercial liso-cel, an autologous, CD19-directed, 4-1BB CAR T cell product. **Methods:** This analysis included US pts with RT from the CIBMTR who received commercial liso-cel between 02/2021 and 02/2023. Primary outcomes included ORR, CR rate, duration of response (DOR), PFS, OS, and safety (including cytokine release syndrome [CRS] and immune effector cell-associated neurotoxicity syndrome [ICANS] based on Lee 2018 criteria, and prolonged cytopenia defined as grade [gr] 4 thrombocytopenia and/or neutropenia persistent at 30 d after infusion). **Results:** At data cutoff (08/04/2023), 30 pts with RT were included. Demographics and baseline characteristics at liso-cel infusion are shown in the Table; additional data regarding the pts' indolent disease and treatment history will be provided in the presentation. Median time from leukapheresis to liso-cel infusion was 35 d (range, 28–63). At median follow-up of 12.3 mo, ORR was 76% among evaluable pts (n = 29) with 66% in CR. Median time to first response was 1.1 mo (range, 0–3.1). Median DOR was not reached (NR); 12-mo DOR rate was 77% (95% CI, 49.5–91). Median PFS (n = 29) and median OS (n = 30) were NR; estimated 12-mo PFS was 54% (95% CI, 33–72) and 12-mo OS was 67% (95% CI, 44–83). Overall, 70% of pts had CRS (gr 3, 0; gr 4, 3%; gr 5, 3% [this pt also had hemophagocytic lymphohistiocytosis]); most common CRS treatments were corticosteroids and tocilizumab (23%) and tocilizumab (20%). ICANS was seen in 47% of pts (gr 3, 17%; gr 4, 10%; gr 5, 0) and most commonly treated with corticosteroids (23%), antiepileptics and corticosteroids (7%), and antiepileptics (7%). Prolonged cytopenia occurred in 17% of pts. One pt had a second primary malignancy (gastrointestinal). Eight (27%) pts died, including 7 because of progression. **Conclusions:** Pts with RT have poor prognosis with a high unmet need. Here, we show that liso-cel provided meaningful clinical benefit with low incidences of gr $\geq$ 3 CRS and ICANS observed. The high CR rate is promising in this difficult-to-treat population, and longer follow-up in a larger cohort is needed. Research Sponsor: This study was funded by BMS. All authors contributed to and approved the abstract; writing and editorial assistance were provided by Allison Green, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by BMS.

Baseline characteristics as reported after RT and before liso-cel.

	Pts With RT (N = 30)
Male[a]	20 (67)
Median (range) age, y	66 (42–82)
Histology[a]	
Diffuse LBCL	27 (90)
High-grade B-cell lymphoma	2 (7)
Other	1 (3)
ECOG PS[a]	
0–1	27 (90)
≥ 2	2 (7)
Active CNS involvement[a]	2 (7)
International Prognositic Index score[a]	
0–2	21 (70)
3–5	9 (30)
Median (range) prior lines of therapy including hematopoietic stem cell transplantation (HSCT)	3 (1–11)
Prior HSCT[a]	
Autologous	3 (10)
Allogeneic	2 (7)
Received bridging therapy, n (%)	13 (43)

[a]n (%).

7011 Rapid Oral Abstract Session

Examining two hematologic precursors and their impact on incident lymphoid malignancies.

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Background: Monoclonal B-cell lymphocytosis (MBL) is a precursor to chronic lymphocytic leukemia (CLL) but also a risk factor for other lymphoid malignancies. Clonal hematopoiesis (CH), originally defined as the presence of mutations in myeloid driver genes, is a precursor to myeloid malignancies. Recently, CH that includes genes associated with lymphoid malignancies has been reportedly associated with risk of lymphoid malignancies, and particularly CLL. Little is known about the association between CH and MBL and their joint effects on risk of hematological malignancies (HM). **Methods:** Study participants were from the Mayo Clinic Biobank, a large-scale biorepository of patients who provided a peripheral blood sample. CH at enrollment was determined using whole-exome sequencing (50x coverage). Myeloid-CH (M-CH) was based on mutations located in 56 genes associated with myeloid malignancies. Lymphoid-CH (L-CH) was based on 235 genes associated with lymphoid malignancies. Individuals were screened for MBL using eight-color flow cytometry in two different cohorts of Biobank participants. Cohort 1 (N=3883) included participants who had available sample for MBL screening at enrollment. Cohort 2 (N=5684) were participants recontacted to provide a sample for MBL screening. Incident HM were identified using ICD codes and confirmed via medical record review. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI). Cox regression was used to estimate hazard ratios (HR), with time defined as date between MBL sample and the first of incident HM, death, or 9/30/2023. Analyses were adjusted for age at MBL screening and sex. **Results:** In total, 9567 individuals (39% male, median age 66 years) were screened for MBL with available CH, of whom 17% were positive for MBL, 7% were positive for M-CH, and 2% were positive for L-CH. We found no evidence of an association between M-CH and MBL (OR=1.11, 95% CI:0.91-1.34) nor L-CH and MBL (OR=1.05, 95% CI:0.70-1.55). When subset to Cohort 1, where the same sample was used for both CH and MBL screening, the results held (M-CH OR=1.11, 95% CI: 0.83-1.48; L-CH OR=0.82, 95% CI: 0.40-1.53). Next, we investigated the effect of each of these precursors with incident HM. Median follow-up was 4 years, and 78 individuals developed incident HM (31 myeloid, 49 lymphoid overall, 8 CLL). When modeling both precursors, both L-CH (HR=6.23, 95% CI:2.46-15.79) and MBL (HR=3.89, 95% CI:2.17-6.99) were independently associated with incident lymphoid malignancy. When excluding CLL events, the association held (L-CH: HR=5.94, 95% CI:2.11-16.77; MBL: HR=2.95, 95% CI:1.54-5.66). Only M-CH was significantly associated with incident myeloid malignancies. **Conclusions:** In the largest cohort with MBL and CH precursors measured, we found no evidence of an association between them. However, both MBL and L-CH were strong independent risk factors for incident lymphoid malignancies. Research Sponsor: U.S. National Institutes of Health; R01 AG58266.

Randomized phase II/III study of R-CHOP +/- venetoclax in previously untreated MYC/BCL2 double expressor diffuse large B cell lymphoma (DLBCL): Alliance A051701.

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Background: DLBCL with expression of MYC and BCL2 (double expressor lymphoma, DEL), has an adverse prognosis. Venetoclax, an inhibitor of BCL2, was previously studied in combination with R-CHOP. A051701 is a phase II/III randomized trial of chemoimmunotherapy +/- venetoclax in DEL and double hit lymphoma cohorts. Here we report initial phase II results from the DEL cohort. **Methods:** Patients (pts) age ≥ 18 years (y) with untreated DEL were randomized 1:1 to R-CHOP (Arm 1) or R-CHOP-venetoclax (Arm 2). DEL was defined as MYC expression ≥40% and BCL2 expression ≥50%, without double hit cytogenetics. Enrollment was based on local pathology results that were centrally confirmed. Venetoclax 800 mg was given orally days 4-8 of cycle 1 and days 1-5 of subsequent cycles for up to 6 cycles. All cycles were supported by GCSF or peg-GCSF. The primary endpoint was progression-free survival (PFS) with 84% power to detect a HR of 0.518 corresponding to 2y PFS rate of 65% in Arm 1 and 80% in Arm 2 (1-sided α=0.20). **Results:** 119 DEL pts were enrolled: 60 Arm 1; 59 Arm 2. Analyses were performed for the modified intent-to-treat population, defined as eligible pts with confirmed DEL histology (n=113; 56 Arm 1, 57 Arm 2). Median age was 64 y (range 22-85); baseline demographic factors were well balanced except for advanced stage (more common in Arm 1; (77% vs 60%, p=0.051). Most pts were non-germinal center B cell-like by immunohistochemistry (Arm 1 72%, Arm 2 58%), high-intermediate/high risk IPI (Arm 1 54%, Arm 2 51%) and ECOG performance status 0-1 (Arm 1 95%, Arm 2 86%). *BCL2* rearrangements were detected in 25% and 33% of pts on Arm 1 and Arm 2, respectively. Most pts completed therapy per protocol (84% Arm 1, 75% Arm 2). Median follow up is 27 months (m). No difference in PFS was observed with 12-m PFS estimates of 77% in Arm 1, 76% in Arm 2 [HR = 0.98 (95% CI: 0.48 – 2.01), p=0.95]. The end of treatment (EOT) overall and complete response rates among patients with an EOT assessment were 87.5% and 70% in Arm 1, and 90% and 82% in Arm 2. Overall survival (OS) was not statistically significantly different with 12-mo OS estimates of 94% in Arm 1 and 79% in Arm 2 [HR = 1.27 (95% CI: 0.57 – 2.79), p=0.56]. Grade ≥3 adverse events (AEs) occurred more frequently in Arm 2 (42% vs 76%). The most commonly increased grade ≥3 AEs included neutropenia (20% vs 47%), anemia (4% vs 25.5%), thrombocytopenia (5.5% vs 24%), febrile neutropenia (7% vs 16%) and fatigue (0% vs 11%). No grade 5 AEs on treatment were reported on Arm 1, and 3 were reported on Arm 2 (lung infection and sudden death NOS, both possibly related; respiratory failure, unlikely related). **Conclusions:** Adding venetoclax to R-CHOP in DEL pts did not improve PFS and resulted in increased toxicity. The study did not meet its primary endpoint in phase II, and so did not proceed to phase III. Clinical trial information: NCT03984448. Research Sponsor: National Cancer Institute; U10CA180882.

Lisocabtagene maraleucel (liso-cel) vs standard of care (SOC) with salvage chemotherapy (CT) followed by autologous stem cell transplantation (ASCT) as second-line (2L) treatment in patients (pt) with R/R large B-cell lymphoma (LBCL): 3-year follow-up (FU) from the randomized, phase 3 TRANSFORM study.

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Background: Liso-cel is an autologous, CD19-directed, 4-1BB CAR T cell product. In prespecified interim and primary analyses of TRANSFORM (NCT03575351), liso-cel showed significant improvements in efficacy vs SOC in pts with R/R LBCL. Here we report results after ~3-y FU. **Methods:** TRANSFORM is a randomized phase 3 study comparing liso-cel vs SOC (CT [R-DHAP, R-ICE, or R-GDP] then high-dose CT [HDCT] + ASCT) in adults aged ≤ 75 y with LBCL primary refractory to or relapsed ≤ 12 mo after first-line therapy and eligible for ASCT. Liso-cel arm pts underwent lymphodepletion followed by liso-cel (100×10^6 CAR^+ T cells). Bridging therapy was allowed. SOC arm pts received 3 cycles of CT; responding pts proceeded to HDCT + ASCT. Crossover to receive liso-cel was allowed for SOC arm pts if criteria were met. The primary endpoint was event-free survival (EFS) per independent review committee (IRC). Key secondary endpoints included CR rate and PFS per IRC, and OS. Endpoints were not statistically retested and are reported descriptively. **Results:** In total, 184 pts were randomized (92 per arm); baseline characteristics were reported (Abramson et al. *Blood* 2023). Median (range) FU was 33.9 mo (0.9–53.0). Median EFS, PFS, and duration of response (DOR) were longer for liso-cel vs SOC, similar to the primary analysis (Table). A total of 61 (66%) SOC arm pts crossed over to receive liso-cel. Median OS was not reached (NR) in either arm; 36-mo OS rates were numerically higher for liso-cel. Of 76 total deaths (liso-cel, n = 34; SOC, n = 42 [crossover pts, n = 33]), 10 occurred since the primary analysis (liso-cel, n = 6; SOC, n = 4 [all crossover pts]); most were due to disease progression or complications (n = 6). Safety results were consistent with the primary analysis. Cellular kinetics and B-cell aplasia will be presented. **Conclusions:** After median FU of 33.9 mo, liso-cel as 2L treatment in pts with primary refractory or early relapsed LBCL resulted in deepening of response and continued improvement in efficacy endpoints over SOC, confirming the ongoing benefit of liso-cel. Clinical trial information: NCT03575351. Research Sponsor: This study was funded by Celgene, a BMS. All authors contributed to and approved the abstract; writing and editorial assistance were provided by Allison Green, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by BMS.

Efficacy outcomes (intent-to-treat set).

	Liso-cel Arm (n = 92)	SOC Arm (n = 92)	Liso-Cel Arm vs SOC Arm HR (95% CI)[a]
EFS[b]	29.5 (9.5–NR)	2.4 (2.2–4.9)	0.375 (0.259–0.542)
36-mo rate[c]	45.8 (35.2–56.5)	19.1 (11.0–27.3)	–
ORR[d]	80 (87) (78.3–93.1)	45 (49)(38.3–59.6)	–
CR rate[d]	68 (74) (63.7–82.5)	40 (43) (33.2–54.2)	–
PFS[b]	NR (12.6–NR)	6.2 (4.3–8.6)	0.422 (0.279–0.639)
36-mo rate[c]	50.9 (39.9–62.0)	26.5 (15.9–37.1)	–
OS[b]	NR (42.8–NR)	NR (18.2–NR)	0.757 (0.481–1.191)
36-mo rate[c]	62.8 (52.7–72.9)	51.8 (41.2–62.4)	–
DOR[b]	NR (16.9–NR)	9.1 (5.1–NR)	0.603 (0.364–1.000)

[a]Based on stratified Cox proportional hazards model;
[b]Median (95% CI), mo;
[c]% (95% CI);
[d]n (%) (95% CI). HR, hazard ratio.

Epcoritamab with rituximab + lenalidomide (R^2) in previously untreated (1L) follicular lymphoma (FL) and epcoritamab maintenance in FL: EPCORE NHL-2 arms 6 and 7.

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Background: In 1L FL, more effective, less toxic treatment (tx) options that induce durable complete responses (CRs) are needed. For responders, novel maintenance approaches are needed to improve long-term outcomes. We present data from EPCORE™ NHL-2 (phase 1/2; NCT04663347), with longer follow-up for epcoritamab + R^2 in 1L FL (arm 6) and the first disclosure for epcoritamab maintenance in patients (pts) with FL in CR or partial response (PR) after 1–2 lines of standard of care (SOC) tx (arm 7). **Methods:** Adults with $CD20^+$ FL grade (G) 1–3A received subcutaneous epcoritamab 48 mg. In arm 6, pts received R^2 for ≤12 cycles (Cs) of 28 d and epcoritamab (QW, C1–2; Q4W, C3–26). In arm 7, pts received epcoritamab (QW, C1 [28 d]; Q8W, C2–13 [56 d/C]). Pts received step-up epcoritamab dosing and corticosteroid prophylaxis in C1 to mitigate CRS. Primary endpoints were overall response rate (ORR; Lugano criteria) in arm 6 and safety/tolerability in arm 7. **Results:** As of Nov 22, 2023, 41 pts with 1L FL received epcoritamab + R^2 (arm 6) and 20 pts in CR or PR after SOC tx received epcoritamab maintenance (arm 7). In arm 6 (median follow-up, 21.1 mo), median age was 57 y and 34% had FLIPI 3– 5. ORR was 95%; CR rate was 85%. The most common treatment-emergent AEs (TEAEs) were COVID-19 (63%), CRS (56%), and neutropenia (56%). CRS was low grade (41% G1, 15% G2) and resolved; most events occurred after the first full dose and none led to epcoritamab discontinuation. Two fatal TEAEs occurred (COVID-19 pneumonia and septic shock). In arm 7 (median follow-up, 19.7 mo), median age was 54.5 y and 25% had FLIPI 3–5; 60% had CR and 40% had PR with their last tx line. All pts had prior anti-CD20 tx, 80% had prior alkylating agents, and 50% had prior anthracyclines; 80% had 1 prior tx line. The most common TEAEs were COVID-19 (70%) and CRS (55%). CRS was G1 (40%) or G2 (15%) and resolved; events mostly occurred after the first full dose, and none led to tx discontinuation. One fatal TEAE occurred (respiratory failure; post-acute COVID syndrome after 2 Cs of tx). No ICANS or clinical tumor lysis syndrome occurred in either arm. Additional efficacy data are in Table. **Conclusions:** In arm 6, epcoritamab + R^2 continued to show deep, durable responses in 1L FL; safety was manageable and consistent with prior reports. In arm 7, the first epcoritamab maintenance data in FL showed conversions from PR to CR, with manageable safety and no new safety signals. The data warrant further evaluation of epcoritamab-based, chemotherapy-free regimens in FL. Clinical trial information: NCT04663347. Research Sponsor: This study was funded by Genmab A/S and AbbVie.

Efficacy.

Arm 6 (Epcoritamab + R^2 in 1L FL) N=41	At 18 mo, %[a]
Responders remaining in response	86
Pts with CR remaining in CR	93
Pts remaining progression free	89
Pts remaining alive	90
Arm 7 (epcoritamab maintenance in FL) N=20	**Pts, %**
Converted to CR[b]	100
Remaining in response[a,c]	83
Remaining alive[a,c]	90

[a]Kaplan–Meier estimate.
[b]Of 8 pts enrolled with PR.
[c]At 21 mo.

7015 Rapid Oral Abstract Session

EPCORE NHL-1 follicular lymphoma (FL) cycle (C) 1 optimization (OPT) cohort: Expanding the clinical utility of epcoritamab in relapsed or refractory (R/R) FL.

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Background: Improving the safety of epcoritamab by reducing the incidence and severity of CRS and ICANS may enhance its accessibility and reduce healthcare resource utilization. In the pivotal EPCORE NHL-1 study (phase 1/2; NCT03625037), epcoritamab treatment (tx) led to high overall (ORR) and complete response (CR) rates of 82% and 63%, respectively, in a cohort of patients (pts) with R/R FL. Safety was manageable, with CRS events being primarily low grade. Here we report the first results from the fully enrolled EPCORE NHL-1 FL C1 OPT cohort investigating mitigation strategies for CRS with no mandatory hospitalization in pts with R/R FL receiving epcoritamab. **Methods:** Pts with $CD20^+$ R/R FL (grade [G] 1–3A) with ≥2 prior tx lines received subcutaneous (SC) epcoritamab in 3 step-up doses (0.16, 0.8, and 3 mg) in C1, followed by 48-mg full doses in 28-d Cs (QW, C1–3; Q2W, C4–9; Q4W, C≥10) until disease progression or unacceptable toxicity. Pts received dexamethasone prophylaxis and hydration recommendations in C1. Hospitalization for CRS monitoring was not mandated. The primary endpoints were rates of any-grade and G≥2 CRS. Secondary endpoints included response per Lugano criteria, minimal residual disease (MRD) in peripheral blood, and safety. **Results:** As of Jan 8, 2024, 86 pts with R/R FL were enrolled in this C1 OPT cohort (median follow-up, 5.7 mo). Pt characteristics were similar in the C1 OPT and pivotal cohorts. An overview of CRS, ICANS, and clinical tumor lysis syndrome (CTLS) events in these cohorts is in Table. CRS events primarily occurred during C1, and none led to epcoritamab discontinuation. Consistent with the lower rates of CRS with C1 OPT, IL-6 levels 24 h after the first full dose were lower than those observed in the pivotal cohort. Of 82 pts who received the first full dose in the C1 OPT cohort, 44 (54%) received outpatient CRS monitoring based on investigator discretion. Among 81 response-evaluable pts in the C1 OPT cohort, ORR was 91% and CR rate was 68%. Median times to response and CR were 1.4 mo and 1.5 mo, respectively. Among MRD-evaluable pts (n=44), MRD negativity was achieved in 64% (n=28). **Conclusions:** CRS mitigation measures in C1 further improved the safety of epcoritamab in pts with R/R FL by substantially reducing the rate and severity of CRS compared with previous reports. For pts treated in the outpatient setting, CRS was identified and appropriately treated, with few G2 events, no G≥3 events, and all events resolving. Response rates, MRD-negativity rate, and time to CR suggest that C1 OPT did not impact efficacy. These data support the potential use of SC epcoritamab as an off-the-shelf, outpatient tx option for pts with R/R FL. Clinical trial information: NCT03625037. Research Sponsor: This study was funded by Genmab A/S and AbbVie.

CRS, ICANS, and CTLS events.

n (%)	C1 OPT Cohort N=86	Pivotal Cohort[a] N=128
Any-grade CRS[b]	42 (49)	85 (66)
G1	34 (40)	51 (40)
G2	8 (9)	32 (25)
G3	0	2 (2)
ICANS[c]	0	8 (6)
CTLS	0	0

[a]Data cutoff: Apr 21, 2023.
[b]No G≥4 CRS.
[c]No G≥3 ICANS.

Lisocabtagene maraleucel (liso-cel) in patients (pt) with R/R mantle cell lymphoma (MCL): Subgroup analyses by number of prior systemic lines of therapy (LOT) and by response to prior Bruton tyrosine kinase inhibitor (BTKi) from the TRANSCEND NHL 001 MCL cohort (TRANSCEND-MCL).

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Background: In the TRANSCEND-MCL (NCT02631044) primary analysis, the CD19-directed, CAR T cell product liso-cel demonstrated a high, durable CR rate (CRR) with manageable safety in pts with heavily pretreated R/R MCL. Here, we report outcomes by number of prior LOTs and by response to prior BTKi. **Methods:** Pts had PET-positive R/R MCL after ≥ 2 prior systemic LOTs, including BTKi, alkylating, and CD20-targeted agents. Pts received liso-cel after lymphodepleting chemotherapy. Bridging therapy was allowed. Primary endpoints were treatment-emergent AEs (TEAE) and ORR by independent review committee (IRC) per Lugano 2014 criteria; secondary endpoints included CRR, duration of response (DOR), PFS, and OS. **Results:** 88 pts received liso-cel. Median follow-up was 16.1 mo (range, 0.4–60.5). For all pts, CRR was 72%; median DOR, PFS, and OS were 15.7, 15.3, and 18.2 mo, respectively (Table). ORR, CRR, and median DOR, PFS, and OS were similar to all pts for most subgroups, but numerically lower in pts with ≥ 5 prior LOTs and pts refractory to prior BTKi. Grade (gr) ≥ 3 TEAEs ranged from 67–96% across subgroups, similar to all pts (86%); most common gr ≥ 3 TEAE was neutropenia (33–58%). Most cytokine release syndrome (CRS) and neurological events (NE) were gr 1–2 (Table) with no gr 5 CRS/NE. Gr ≥ 3 infection (11–19%) and prolonged cytopenia (32–50%) in subgroups were similar to all pts (15% and 40%). Cellular kinetics will be presented. **Conclusions:** In TRANSCEND-MCL, all subgroups benefited from liso-cel and responses were generally comparable to the overall population, with numerically shorter duration in pts with ≥ 5 prior LOTs and disease refractory to prior BTKi, supporting study of liso-cel in earlier LOTs. Clinical trial information: NCT02631044. Research Sponsor: This study was funded by Juno Therapeutics, a BMS. All authors contributed to and approved the abstract; writing and editorial assistance were provided by Allison Green, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by BMS.

	Overall Population	Prior LOT ≥ 2	Prior LOT 3–4	Prior LOT ≥ 5	Refractory to BTKi	Not Refractory to BTKi
Efficacy,[a] n	**83**	**81**	**29**	**26**	**45**	**35**
ORR[b]	69 (83)	67 (83)	25 (86)	21 (81)	34 (76)	32 (91)
CRR[b]	60 (72)	58 (72)	21 (72)	17 (65)	29 (64)	28 (80)
DOR[c]	15.7 (6.2–24.0)	14.5 (5.7–NR)	17.5 (3.3–NR)	6.7 (2.4–15.8)	5.3 (2.3–15.8)	24.0 (7.6–NR)
PFS[c]	15.3 (6.6–24.9)	12.3 (6.5–NR)	16.6 (2.6–NR)	7.4 (3.3–12.3)	6.1 (3.1–16.5)	24.0 (8.6–NR)
OS[c]	18.2 (12.9–36.3)	17.1 (11.1–36.3)	18.4 (6.7–NR)	13.5 (9.5–17.1)	11.1 (6.1–17.1)	36.3 (15.3–NR)
Safety,[d] n	**88**	**85**	**31**	**26**	**47**	**36**
CRS: gr 1–2 / gr 3–4[b]	53 (60) / 1 (1)	52 (61) / 1 (1)	20 (65) / 1 (3)	18 (69) / 0	30 (64) / 0	20 (56) / 1 (3)
NE: gr 1–2 / gr 3–4[b]	19 (22) / 8 (9)	19 (22) / 7 (8)	7 (23) / 3 (10)	5 (19) / 2 (8)	12 (26) / 5 (11)	6 (17) / 2 (6)

Original protocol allowed pts with ≥ 1 LOT and was later amended to require ≥ 2 LOTs; 3 pts had 1 prior LOT; 2 pts were efficacy evaluable and both achieved CR with DORs of 16.8 and 23.3+ mo.
[a]All liso-cel–treated pts with confirmed PET-positive disease per IRC before infusion;
[b]n (%);
[c]Median (95% CI), mo;
[d]All liso-cel–treated pts. NR, not reached.

7017 Rapid Oral Abstract Session

Timdarpacept (IMM01) in combination with tislelizumab in prior anti-PD-1 failed classical Hodgkin lymphoma: An open label, multicenter, phase II study (IMM01-04) evaluating safety as well as preliminary anti-tumor activity.

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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. IMM01 showed unique property of weak human erythrocyte conjugation in preclinical studies, and low incidence of anemia in early clinical trials with no need for a priming dose. IMM01 in combination with tislelizumab has the potential to augment both innate and adaptive anti-tumor immune responses. **Methods:** Eligible patients with R/R classical Hodgkin lymphoma (cHL) who have failed prior anti-PD-1 treatment were enrolled in this open-label, multicenter phase II study (NCT05833984). IMM01 (2.0mg/kg) intravenously administered each week in each 3-week treatment cycle, while tislelizumab (200mg) will be administered once every 3 weeks 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 28 Dec 2023, 33 cHL patients were enrolled. The median age was 35 years (range 19-77) with 23 (69.7%) male patients. The median prior lines of therapy were 4. In efficacy evaluable patients (n=32) with median follow up of 5.65 month (95% CI, 2.83-6.90), the ORR was 65.6% (21/32), complete response rate was 18.8% (6/32) and DCR was 93.8% (30/32). The DoR rate at 3 months, 6 months were 92.9% and 60.8%, respectively. The mDoR was not reached. The PFS rate at 3 months, 6 months were 84.5% and 68.7%, respectively. Median TTR was 1.6 months. Further analysis indicated that regardless of primary or secondary resistance to tislelizumab treatment, other PD-1-containing regimens (non-tislelizumab), or prior CD30-ADC treatment; or the intervals from last dose of prior PD-1 treatment to first dose of IMM01 and tislelizumab, patients can benefit from IMM01 combined with tislelizumab treatment. All patients experienced at least one treatment-related adverse events (TRAEs). The most common TRAEs were WBC decreased (48.5%), PLT decreased (42.4%), anemia (36.4%), ANC decreased (33.3%), lymphocyte decreased (30.3%). TRAEs of grade $\geq$3 occurred in 15 (45.5%) patients, with the most common being lymphocyte decreased (30.3%), WBC decreased (12.1%), PLT decreased (12.1%), ANC decreased (12.1%). There was no reported hemolytic anemia or hemolysis in any of the patients. 4 (12.1%) patients had treatment related SAE. No patients experienced TRAEs leading to the study drug discontinuation or death. **Conclusions:** IMM01-04 showed a robust anti-tumor effectivity with a well-tolerated safety profile in prior anti-PD-1 failed cHL patients. The phase II study is ongoing. Clinical trial information: NCT05833984. Research Sponsor: None.

Improving the ICAHT grading criteria using time-series clustering.

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Background: Hematotoxicity is a major cause of morbidity after CAR T-cell therapy. We compared the performance of unsupervised time-series clustering versus the EHA/EBMT immune effector cell-associated hematotoxicity (ICAHT) grading system in describing ANC recovery after CAR T-cell therapy. **Methods:** Adults who underwent CAR T-cell therapy for hematologic malignancies with commercial or investigational products at our center between 2013 and 2023 were included (n = 602). Log10-transformed ANC trajectories were clustered using non-supervised longitudinal k-means based on Euclidean distances (latrend and kml packages in R). Overall survival (OS) was modeled using Cox regression. **Results:** The most common disease types were aggressive NHL (n = 293; 49%), indolent NHL (n = 150; 25%), and ALL (n = 94; 16%). The most common CAR T-cell products were the investigational CD19 CAR T-cell product JCAR014 (n = 197; 33%), axi-cel (n = 129; 21%), and liso-cel (n = 73; 12%). Median follow-up was 31 months (IQR, 11-60). The longitudinal ANC data clustered into 4 distinct trajectories ("clusters"): 1) very good (high nadir followed by rapid recovery), n = 460 (76%); 2) good (low nadir followed by rapid recovery), n = 109 (18%); 3) poor (low nadir followed by intermittent recovery), n = 20 (3%); 4) very poor (aplastic phenotype), n = 13 (2%). Grade 1, 2, 3, and 4 ICAHT occurred in 319 (53%), 96 (16%), 60 (10%), and 35 (6%) patients, respectively. Clusters were more strongly associated with OS (poor vs. very good, HR = 3.30, 95% CI, 1.88-5.80, $p < 0.0001$; very poor vs. very good, HR = 11.5, 95% CI, 6.45-20.4, $p < 0.001$), compared to ICAHT categories (grade 3 vs. 0-1, HR = 2.00, 95% CI, 1.43-2.81, $p < 0.0001$; grade 4 vs. 0-1, HR = 4.64, 95% CI, 3.10-6.96, $p < 0.0001$). When evaluating concordance of clusters versus ICAHT grades, we found that 65% of grade 3-4 ICAHT patients were in the very good (17%) or good (48%) clusters; they exhibited distinct and more favorable patterns of ANC recovery (e.g., stable ANC recovery by day +15) compared to poor/very poor clusters. Among grade 3-4 ICAHT patients, those in the good/very good clusters had longer median OS than those in the poor/very poor clusters (9 vs. 3 months, $p < 0.001$). This led us to modify the ICAHT criteria (mICAHT). When patients with grade 3-4 ICAHT and good/very good recovery were re-classified as grade 2 mICAHT, we observed greater distinction and improved model fit in median OS between mICAHT grades compared to original ICAHT grades. The median OS of grade 3-4, 2, and 1 mICAHT patients was 3, 19, and 35 months, respectively, compared to 7, 35, and 35 months using the original ICAHT criteria. **Conclusions:** Unsupervised time-series clustering identified patterns of ANC recovery not captured by the ICAHT grading system and more strongly associated with OS than ICAHT grades. Incorporating these distinct patterns of recovery into a modified ICAHT grading system improved predictions of OS compared to the original ICAHT grades. Research Sponsor: NIH National Heart, Lung, and Blood Institute; 5T32HL007093; National Cancer Institute/U.S. National Institutes of Health; 5T32CA951539; National Cancer Institute/U.S. National Institutes of Health; P30 CA15704; Swim Across America.

Glofitamab monotherapy retreatment in patients with heavily pre-treated relapsed or refractory (R/R) non-Hodgkin lymphoma (NHL): Results from a phase I/II study.

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Background: Fixed-duration glofitamab, a CD20xCD3 T-cell engaging bispecific antibody with a novel 2:1 configuration, has demonstrated efficacy and manageable safety in a Phase I/II study (NCT03075696) in heavily pre-treated patients (pts) with R/R NHL (Dickinson. N Engl J Med 2022). We report efficacy and safety data for pts with R/R NHL retreated with glofitamab monotherapy after response to initial glofitamab treatment. **Methods:** Pts who completed initial treatment and achieved complete response (CR), partial response (PR), or stable disease were eligible for retreatment after documented progression. Initial treatment included obinutuzumab pre-treatment (Gpt) 7 days before the first glofitamab dose, then glofitamab intravenously at either a fixed dose of 0.015–25mg (14- or 21-day cycles) or step-up dosing (2.5mg, then 10mg in Cycle [C] 1, followed by a target dose of 16 or 30mg [C2 onward, 21-day cycles]) for up to 12 cycles. Retreatment was administered at the escalation dose received or at the highest glofitamab dose cleared in the study at time of retreatment, with Gpt 7 days before the first glofitamab dose. As with initial treatment, retreatment was permitted for 12 cycles or until progression or unacceptable toxicity, whichever occurred first. **Results:** As of Sept 4, 2023, 13 pts (diffuse large B-cell lymphoma [DLBCL], n=4; follicular lymphoma [FL], n=4; mantle cell lymphoma [MCL], n=2; transformed FL [trFL], n=2; high grade B-cell lymphoma, n=1) had received glofitamab retreatment (retreatment dose: 10mg, n=1; 10/16mg, n=1; 2.5/10/30mg, n=11). Median age was 63.0 years (range: 44–81). With initial treatment, 9 pts had CR and 4 pts had PR (best response by investigator). Median time from end of initial treatment to initiation of retreatment was 13.0 months (range: 4.1–27.4). Median number of retreatment cycles received was 5 (range: 2–12). During retreatment, 9 pts (69.2%) responded: CR, 38.5% (FL, n=2; trFL, n=1; MCL, n=2); PR, 30.8% (FL, n=1; trFL, n=1; DLBCL, n=2). Of the 5 pts with CR at retreatment, 3 pts had CR and 2 pts had PR with initial treatment. Of the 4 pts with PR at retreatment, 3 pts had CR and 1 pt had PR with initial treatment. Median retreatment follow-up time was 25.9 months and 5 pts had responses ongoing at data cut-off (FL, n=2; MCL, n=2; trFL, n=1). The safety profile for glofitamab retreatment was consistent with prior reports of glofitamab monotherapy in R/R NHL (Hutchings. J Clin Oncol 2021). Cytokine release syndrome occurred in 7 pts (53.8%; all Grade 1/2). Exploratory data on B-cell pharmacodynamics, CD20 expression, and T-cell status before retreatment will be presented. **Conclusions:** Glofitamab monotherapy retreatment was efficacious in heavily pre-treated pts with R/R NHL who responded to initial glofitamab treatment before subsequent progression. The safety profile was consistent with that of initial treatment. Clinical trial information: NCT03075696. Research Sponsor: NP30179 is sponsored by F. Hoffmann-La Roche Ltd.; N/A; Third-party medical writing assistance, under the direction of all authors, was provided by Beth de Klerk, BSc, and Emily Lynch, PhD, of Ashfield MedComms, an Inizio company, and funded by F. Hoffmann-La Roche Ltd.; N/A.

Mosunetuzumab with polatuzumab vedotin: Subgroup analyses in patients (pts) with primary refractory or early relapsed large B-cell lymphoma (LBCL).

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Background: The primary analysis of mosunetuzumab with polatuzumab vedotin (mosun-pola) in the Phase Ib/II study (NCT03671018) demonstrated durable responses and manageable safety in pts with relapsed or refractory (R/R), transplant-ineligible LBCL (Budde et al. Nat Med 2023). Here, we present results for primary refractory (refr) or early relapse (rel) subgroups from this study after a median follow-up of 23.9 months. **Methods:** Pts with R/R LBCL (diffuse LBCL not otherwise specified [NOS], high-grade B-cell lymphoma [HGBCL], transformed follicular lymphoma (FL), and FL grade 3b) and who received ≥1 prior line of therapy (including an anti-CD20 antibody) were treated with mosun-pola. Refr was defined as SD, PD, PR, or CR with relapse <3 months after first-line (1L) therapy. Rel was defined as CR with relapse ≥3 and ≤12 months after 1L therapy. The primary endpoint was best overall response rate (ORR) by IRC using Lugano 2014 response criteria. Key secondary endpoints included CR rate, duration of response (DOR), duration of CR (DOCR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** As of July 6, 2023, of the 98 pts in the overall population, 45 (46%) and 27 (28%) pts had refr or rel LBCL, respectively. At baseline, the median age in the refr and rel subgroups was 68 and 70 years respectively; 23/45 pts (51%) and 6/27 pts (22%) were treated with mosun-pola as second-line, respectively. The majority of refr/rel pts had DLBCL NOS (71%; 78%) or HGBCL (24%; 19%), Ann Arbor stage III/IV (80%; 89%), elevated LDH (55%; 48%), and extranodal involvement (67%; 59%). In refr pts, the ORR was 49%, which was generally consistent with the overall population (59%); although the sample size was limited, higher responses (ORR: 74%) were observed in rel pts. Additional clinical outcomes are reported (Table). The safety profile was consistent with the overall population. Grade 3 CRS occurred in one pt in each subgroup. Treatment-related ICANS-like events occurred in 2/45 pts (4%; refr) and 3/27 pts (11%; rel). **Conclusions:** Mosun-pola demonstrated durable benefits in ORR and CR rates irrespective of a poor response to 1L treatment. Outcomes for pts with refr or rel LBCL are encouraging. Clinical trial information: NCT03671018. Research Sponsor: This study was sponsored by F. Hoffmann-La Roche Ltd.; N/A; Third-party medical writing assistance, under the direction of all authors, was provided by Aisling Lynch, PhD, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.; N/A.

Efficacy Endpoints, (95% CI)	Refr (n=45)	Rel (n=27)	Total Refr/rel Subgroup (n=72)	Overall Population[1] (N=98)
ORR, n (%)[95% CI]	22 (48.9) [33.7–64.2]	20 (74.1) [53.7–88.9]	42 (58.3) [46.1–69.9]	58 (59.2) [48.8–69.0]
CR, n (%) [95% CI]	16 (35.6) [21.9–51.2]	16 (59.3) [38.8–77.6]	32 (44.4) [32.7–56.6]	45 (45.9) [35.8–56.3]
Median DOR, months	20.5 (14.0–NE)	20.8 (8.8–NE)	20.5 (11.2–NE)	20.8 (14.2–NE)
Median DOCR, months	NR (16.2–NE)	NR (8.8–NE)	NR (16.2–NE)	NR (20.5–NE)
Median PFS, months	8.1 (4.8–16.5)	12.7 (8.8–NE)	10.6 (5.7–16.9)	11.4 (6.2–18.7)
Median OS, months	13.3 (8.5–NE)	NR (12.7–NE)	16.9 (10.6–NE)	23.3 (14.8–NE)

[1]Budde et al. Nat Med 2023. NE, not evaluable; NR, not reached.

7022 Poster Session

EX103: A newly designed CD20×CD3 molecule in heavily pre-treated patients with B-cell non-Hodgkin lymphoma from a phase I/II trial.

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Background: T-cell-engaging bispecific antibody (TCB) had emerged as a promising therapy for blood malignancies, including relapsed/refractory (R/R) B-NHL. However, severe cytokine release syndrome (CRS) remains to be a significant challenge in TCB treatment. To overcome this setback, we re-designed a new CD20xCD3 bispecific antibody (EX103) with a lower affinity to CD3. Clinical data from an ongoing first-in-human phase I/II study demonstrates that EX103 has an encouraging safety and promising single-agent antitumor activity in heavily pretreated R/R B-NHL patients. We present updated safety and efficacy data from the ongoing trial (CTR20212096). **Methods:** Eligible patients received EX103 with 3 step-up doses followed by target doses in 28-day cycles (iv, QW: cycle 1-2; Q2W thereafter) until disease progression or unacceptable toxicity. At data cut off (Dec 24, 2023), a total of 23 patients were evaluated, including 18 patients in dose-escalation part and 5 patients in dose-expansion part. **Results:** Among 23 evaluable patients (median age: 51 years [range 42-70]; median prior lines of treatment: 4 [range 2-10]), 13 patients had diffuse large B-cell lymphoma (DLBCL), 4 had FL 1-3a, 2 had FL grade 3B, 1 had marginal zone lymphoma, 1 had mantle cell lymphoma, and 2 had chronic lymphocytic leukemia. Median time since last therapy was 2.5 (range 0.3-39.2) months. No DLT and treatment-related death were observed. CRS was the most common treatment related adverse event. All CRS events were grade (Gr) 1-2 (Gr 1: 78.3%, Gr 2: 13.0%), no Gr 3 or higher events. Most CRS events occurred in the first or second treatment cycle, and all CRS-related clinical symptoms were resolved within 48 hours. No cases of immune effector cell-associated neurotoxicity syndrome or other clinically significant neurologic AEs were observed. For dose ≥ 6 mg cohorts, the overall response rate (ORR) for aggressive B-NHL is 78.6% and the complete response (CR) rate is 50.0% (14 patients). Meanwhile, the ORR for indolent B-NHL is 100%, and CR rate is 25.0% (4 patients). The overall DCR is 89.5%. Currently, treatment is ongoing for 18 patients. The longest duration of response is 14 months. Patients who were refractory to previous therapies achieved impressive responses to EX103 treatment. 3 patients who failed CAR-T therapy achieved either CR or partial response (PR) (2 CR and 1 PR), 2 patients who failed CD19×CD3 bispecific antibody treatment both achieved PR, and 4 patients who failed ASCT achieved either CR or PR (2 CR and 2 PR). **Conclusions:** EX103 can induce deep and durable responses in heavily pretreated patients with R/R B-NHL, such as those patients who failed CAR-T treatment (3 cases), CD19xCD3 bispecific antibody treatment (2 cases) and ASCT (4 cases). Clinical trial information: CTR20212096. Research Sponsor: Excelmab Inc.

Interim results from the ELiPSE-1 study: A phase 1, multicenter, open-label study of CNTY-101 in subjects with relapsed or refractory CD19-positive B-cell malignancies.

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Background: CNTY-101 is an allogeneic, iPSC-derived anti-CD19 Chimeric Antigen Receptor NK (CAR-iNK) cell product with Allo-Evasion edits to avoid host rejection. Potential benefits of CNTY-101 include immediate availability for treatment, repeat dosing without the need for lymphodepletion, and the potential for improved safety over T-cell based therapies. The first-in-human Phase 1 clinical trial of CNTY-101, ELiPSE-1 (NCT05336409), evaluates safety, preliminary efficacy, PK, and translational biomarkers in patients with CD19-positive B-cell malignancies. **Methods:** Subjects with R/R aggressive and indolent B-cell NHL received lymphodepletion (LDC) followed by assignment to 100e6, 300e6 or 1e9 cells at either Day 1 (Schedule A) or Days 1, 8 and 15 (Schedule B). Eligible subjects (ie, achieved SD or better at Day 28 by PET/CT) can receive additional cycles, with or without one additional regimen of LDC. Subjects also receive daily subcutaneous injections of IL-2 for 8 days (A) or 4 days (B) following each infusion. **Results:** At time of abstract submission, 10 subjects have been treated (n=4 DL1A; n=3 DL2A; n=2 DL3A; n=1 DL2B). Three subjects (1 at DL1A, 2 at DL2A) received additional cycle(s) of CNTY-101. Three subjects have not yet been evaluated for full safety and efficacy within the DLT window. Seven subjects (n=5 DLBCL; n=1 FL; n=1 MZL) had data available as of the data cut (Nov 30, 2023). All had stage 4 disease, 6/7 were refractory to last line of therapy, with a median of 4 (2-5) prior lines of therapy including CAR T (3/7). No DLTs, GvHD or ICANs were observed. Two subjects had cytokine release syndrome (n=1 Gr 1, n=1 Gr 2), all responding promptly to treatment. ORR/CRR was 25%/25% for 100e6 cells (DL1A) and 67%/33% for 300e6 cells (DL2A). Dose escalation is ongoing. In subjects from all three dose levels, CNTY-101 rapidly traffics out of circulation after infusion and is observed via cell-free DNA on Day 3 and detected up to 28 days. CNTY-101 persistence was not adversely impacted when given without lymphodepletion in two subjects who received additional cycles of CNTY-101. Induction of functional humoral immunogenicity against CNTY-101 was not observed at any of the dose levels, regardless of single or multiple cycles of CNTY-101. Adaptive immune responses were observed in the tumor microenvironment on Day 8. **Conclusions:** CNTY-101 administered as a single dose in multiple cycles has demonstrated a manageable safety profile and preliminary evidence of efficacy. Allo-Evasion edits may allow for repeat dosing for multiple cycles without allorejection in the absence of lymphodepletion. Preliminary efficacy supports dosing at higher dose levels and with more dose-intense regimens. Updated safety, efficacy, PK, and CNTY-101's impact on tumor for DL3A and DL2B will be provided. Clinical trial information: NCT05336409.
Research Sponsor: None.

Predictors of severe hematotoxicity after CAR T-cell therapy.

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Background: The EHA/EBMT immune effector cell-associated hematotoxicity (ICAHT) grading system characterizes hematotoxicity after CAR T-cell therapy based on depth and duration of neutropenia (Rejeski et al, Blood, 2023). We evaluated pre- and post-infusion factors associated with grade 3-4 ICAHT and developed a predictive model in 602 patients with hematologic malignancies undergoing CAR T-cell therapy at Fred Hutch Cancer Center. **Methods:** Grading of early hematotoxicity (day-0-30 after CAR T-cell cell infusion) was automated using the heatwaveR package. Associations with 50 patient, disease-related, and laboratory factors, and grade 3-4 ICAHT were modeled using univariate and multivariable logistic regression. **Results:** The most common disease types were aggressive non-Hodgkin lymphoma (NHL; n = 293; 49%), indolent NHL (n = 150; 25%), and acute lymphoblastic leukemia (ALL; n = 94; 16%). The most common CAR T-cell products were the investigational CD19 CAR T-cell product JCAR014 (n = 197; 33%), axicabtagene ciloleucel (n = 129; 21%), and lisocabtagene maraleucel (n = 73; 12%). Incidences of early ICAHT grades 1, 2, 3, and 4 were 319 (53%), 96 (16%), 60 (10%), and 35 (6%) patients, respectively. Baseline patient factors associated with grade 3-4 ICAHT included ALL (reference: aggressive NHL, OR = 4.18, 95% CI, 2.41-7.26, $p < 0.001$) , Hispanic or Latino ethnicity (OR = 2.17, 95% CI, 1.07-4.20, p = 0.025), and lower age (OR = 1.03, 95% CI, 1.02-1.05, $p < 0.001$). Pre-lymphodepletion (LD) laboratory factors associated with grade 3-4 ICAHT in univariate analyses included lower ANC (OR = 6.67 per log10 cells/μL, 95% CI, 4.0-11.1, $p < 0.001$), LDH (OR = 8.70per log10U/L, 95% CI, 4.03-19.4, $p < 0.001$), CRP (OR = 3.18 per log10mg/L, 95% CI, 2.06-5.07, $p < 0.001$), and ferritin (OR = 6.07 per log10mg/L, 95% CI, 3.65-10.6, $p < 0.001$). Peak CRP (OR = 15.6, 95% CI, 7.27-36.4, $p < 0.001$), peak ferritin (OR = 7.41, 95% CI, 5.02-11.3, $p < 0.001$), peak CRS grade (OR = 2.01, 95% CI, 1.59-2.56, $p < 0.001$), and peak ICANS grade (OR = 1.51, 95% CI, 1.29-1.77, $p < 0.001$) after CAR T-cell infusion were also strongly associated with grade 3-4 ICAHT. A multivariable model using restricted cubic splines and including disease type, pre-LD ANC, pre-LD LDH, peak CRP, peak ferritin, and CRS grade demonstrated high discrimination to predict grade 3-4 ICAHT (C-index = 0.89). Internal validation using bootstrapping showed near-perfect calibration without overfitting. Sensitivity and specificity based on the Youden criteria was 74% and 90%, respectively. The sensitivity and specificity of the CAR-HEMATOTOX score in predicting grade 3-4 ICAHT was 93% and 30%, respectively. **Conclusions:** We identified pre- and post-infusion predictors of grade 3-4 ICAHT and internally validated a multivariable logistic regression model including disease-type, pre-LD ANC, pre-LD LDH, peak CRP, peak ferritin, and CRS grade. We plan to further evaluate our model in an external cohort. Research Sponsor: NIH National Heart, Lung, and Blood Institute; 5T32HL007093; National Cancer Institute/U.S. National Institutes of Health; 5T32CA951539; National Cancer Institute/U.S. National Institutes of Health; P30 CA15704; Swim Across America.

7025 Poster Session

A CRISPR-edited allogeneic anti-CD19 CAR-T cell therapy with a PD-1 knockout (CB-010) in patients with relapsed/refractory B cell non-Hodgkin lymphoma (r/r B-NHL): Updated phase 1 results from the ANTLER trial.

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Background: CB-010 is an allogeneic anti-CD19 CAR-T cell therapy derived from healthy donor T cells using CRISPR hybrid RNA-DNA (chRDNA) technology. This technology is used to introduce 3 genome edits: (1) knockout of *TRAC*to eliminate TCR expression and reduce risk of GvHD, (2) insertion of a CD19-specific CAR (scFv FMC63) into the*TRAC* locus, and (3) knockout of PD-1 to prevent premature CAR-T cell exhaustion and potentially enhance antitumor activity. **Methods:** ANTLER is a Phase 1 clinical trial (NCT04637763) with a 3+3 dose escalation phase and a dose expansion phase designed to evaluate safety, tolerability, and antitumor activity of CB-010 in patients (pts) with r/r B-NHL and determine RP2D. In dose escalation, pts must have received ≥2 prior lines of chemoimmunotherapy or had primary refractory disease to 1L therapy. Pts received lymphodepletion with sequential cyclophosphamide (60 mg/kg/day x 2 days) and fludarabine (25 mg/m2/day x 5 days) followed by a single CB-010 infusion. **Results:** 16 pts with r/r B-NHL (10 LBCL, 3 MCL, 2 FL with POD24, 1 MZL) received CB-010 at 40 x 10^6 CAR-T cells (dose level 1; N=8), 80 x 10^6 CAR-T cells (dose level 2; N=5), or 120 x 10^6 CAR-T cells (dose level 3; N=3) during dose escalation. Median age was 66 years (range 55-82). Median time since first diagnosis was 2.4 years (range 0.2-16.4). Median prior lines of therapy was 2 (range 1-8). CB-010 was generally well tolerated. No GvHD was seen. CRS occurred in 7/16 (44%) pts (no CRS grade ≥3). Median time to CRS onset was 3.5 days and median duration was 3 days. ICANS occurred in 4/16 (25%) pts (13% grade ≥3). Median time to ICANS onset was 7.5 days and median duration was 2 days. The 3 most common TEAEs grade ≥3 were thrombocytopenia (11/16; 69%), neutropenia (9/16; 56%), and anemia (8/16; 50%). One grade 3 infection (antecubital cellulitis) occurred unrelated to CB-010. After a single CB-010 infusion, 15/16 (94%) pts achieved an overall response, 11/16 (69%) achieved a CR, and 7/16 (44%) achieved a CR at ≥6 months. Median time to CR was 28 days. Among LBCL pts (n=10), 9 (90%) achieved an overall response, 7 (70%) achieved a CR, and 5 (50%) achieved a CR at ≥6 months. To date,2 pts have completed the 24-month study period with ongoing CR. Peak expansion of CB-010 occurred at days 7-10 post-infusion. T and NK cells recovered rapidly in peripheral blood (<3 weeks) after lymphodepletion, and B cells remained below the limit of quantification beyond 3 months, supporting specific targeting of B cells by CB-010. **Conclusions:** CB-010 showed a manageable safety profile and promising efficacy for treatment of pts with r/r B-NHL, including aggressive subtypes. The dose escalation phase is complete. Enrollment of 2L LBCL pts in dose expansion is ongoing. Initial dose expansion data at the CB-010 RP2D and translational data will be presented for the first time at the meeting. Clinical trial information: NCT04637763. Research Sponsor: Caribou Biosciences, Inc.

Patients (pts) with R/R large B-cell lymphoma (LBCL) treated with lisocabtagene maraleucel (liso-cel) nonconforming product (NCP) under the Expanded Access Protocol (EAP).

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Background: Liso-cel is an autologous, CD19-directed, 4-1BB CAR T cell product indicated for the treatment of adults with R/R LBCL. Liso-cel NCP is defined as any product wherein one or both of the CD8 or CD4 cell components did not meet ≥ 1 of the commercial release specifications but met EAP release criteria and was considered appropriate for infusion. **Methods:** This is a prospective, multicenter EAP study of pts with R/R LBCL intended to receive commercial liso-cel but were treated with NCP due to manufacturing outcomes. Data from United States pts are reported here. The study comprised a pretreatment period for pt evaluation, a treatment period, which started at the first dose of lymphodepleting chemotherapy and continued through NCP administration at Day 1, and the posttreatment period, which followed pts up to 3 months after NCP administration for safety and disease status. Study objectives were safety (primary endpoint) and effectiveness by ORR and CR rate assessed by the treating physician per Lugano 2014 criteria (secondary endpoint). Due to the 3-month follow-up, duration of response, PFS, and OS analyses could not be estimated. **Results:** A total of 167 United States pts (third-line or later, n = 145; second line, n = 22) were included in the analysis set (data cutoff: 11/20/2023), which included pts who were infused and completed 3 months of follow-up (n = 134) or discontinued participation or died before 3 months (n = 33). Median (IQR) time from leukapheresis to NCP infusion was 50 d (44–58). Median age was 69 y (range, 29–87), 57% male, 42% diffuse LBCL (DLBCL) not otherwise specified, and 29% transformed DLBCL. The most frequent types of NCP (≥ 10 cases) were CD4 low T-cell lineage purity (n = 37 [22%]), CD4 low or high vector copy number (n = 31 [19%]), CD4 low transduction frequency (n = 24 [14%]), or CD8 high interferon-γ (n = 12 [7%]). Bridging therapy was reported in 31% of pts. In the total population (N = 167), cytokine release syndrome was reported in 42% of pts (1% grade ≥ 3), neurological events in 8% (4% grade ≥ 3), immune effector cell–associated neurotoxicity in 2% (1% grade ≥ 3), prolonged cytopenia in 40% (grade ≥ 3 on or after Day 29), grade ≥ 3 infections in 14%, infusion-related reactions in 1% (grade ≥ 3), and second primary malignancy in 1% (none grade ≥ 3). Thirteen pts died because of: AEs (n = 6), disease progression (n = 5), or unknown reasons (n = 2). Of 118 efficacy-evaluable pts for best overall response in the first 3 months, ORR was 71% (95% CI, 62–79); 53% had a CR (95% CI, 43–62) and 19% had a PR (95% CI, 12–27). **Conclusions:** These data add to current clinical experience with liso-cel, show that pts with R/R LBCL can derive clinical benefit from receiving NCP without compromising safety, and provide important evidence to facilitate clinical decision-making. Clinical trial information: NCT04400591. Research Sponsor: This study was funded by Juno Therapeutics, a BMS Company. All authors contributed to and approved the abstract; writing and editorial assistance were provided by Meredith Rogers, MS, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by BMS.

7027 Poster Session

A phase 1 study of LY007, a novel anti-CD20 CAR-T cell therapy in patients with relapsed or refractory B-cell non-Hodgkin lymphoma.

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Background: Approved chimeric antigen receptor (CAR) T cell therapies targeting CD19 with a single co-stimulatory domain in the treatment of relapsed/refractory B-cell non-Hodgkin lymphoma (r/r B-NHL) may face challenges including drug resistance and disease recurrence. This Phase 1 study was conducted to evaluate the safety and tolerability of LY007, a novel CD20-targeting CAR-T cell containing both OX40 and 4-1BB co-stimulatory domains to enhance CAR-T cell proliferation and anti-cancer cytotoxicity, for the treatment of r/r B-NHL pts. **Methods:** In this open-label, single-arm phase 1 trial, r/r B-NHL pts were infused with LY007 in 3 dose levels (DLs) (DL1, 0.5×10^6 cells/ kg; DL2, 1.5×10^6 cells/ kg; DL3, 5.0×10^6 cells/ kg) based on a standard 3+3 dose escalation design after cyclophosphamide/fludarabine lymphodepletion. The main objectives were to determine the safety and tolerability, pharmacokinetics, and preliminary efficacy of LY007. The key eligibility criteria included pts with cytologically or histologically confirmed CD20 positive r/r B-NHL according to WHO 2016 including diffuse large B cell lymphoma (DLBCL) and transformed follicular lymphoma (TFL). **Results:** As of December 25th, 2023, 9 pts were treated with single LY007 infusions at 3 dose levels with a median follow-up of 5.09 (range 0.92-18.10) months. The median age of treated pts was 65 years (range, 44 to 69), and 44% (4/9) of pts had received three prior lines of therapy. Their B-NHL subtypes were all DLBCL. Among the treated pts, 78% (7/9) relapsed after prior lines of treatment, 89% (8/9) had extranodal involvement, 78% (7/9) had an International Prognostic Index (IPI) score of ≥ 2, and 44% (4/9) had a maximum tumor length of ≥ 5 cm. The overall response rate (ORR) and complete response (CR) were 67% (6/9) and 33% (3/9) at day28, 83% (5/6), and 67% (4/6) at month 3 of the pts evaluable for efficacy. Among all study participants, the best reported ORR was 89% (8/9). The longest duration of remission was 12.3 months to date. The overall survival (OS) and progression-free survival (PFS) were 100% and 88.9% at 6 months, respectively. The LY007 was generally well tolerated. No dose-limiting toxicities (DLTs) were observed. And no immune effector cell-associated neurotoxicity syndrome (ICANS) or G3+ cytokine release syndrome (CRS) was reported. The most common G3+ AEs were lymphopenia (9/9), leukopenia (9/9), and neutropenia (7/9). No pts discontinued, withdrew, or died due to AE. 6 pts experienced G1/2 CRS. Pts at all 3 dose levels had good CAR-T expansion and long-term persistence, particularly in the LD3 cohort, where the highest mean cell copy number of 93,750 copies/μg DNA was achieved at day 11 and was still detectable to date. **Conclusions:** This phase 1 trial demonstrated that LY007 was well tolerated at the dose levels up to 5.0×10^6 cells/ kg and showed a favorable dose-response relationship for the treatment of r/r B-NHL. Clinical trial information: NCT06279611. Research Sponsor: Shanghai Longyao Biotechnology Co., Ltd.

Estimating the health care costs associated with receipt of lisocabtagene maraleucel: Insights from adults with mantle cell lymphoma (TRANSCEND NHL 001).

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Background: Anti-CD19 CAR T cell therapy is a major advancement for treating R/R B-cell malignancies such as mantle cell lymphoma (MCL). While effective disease management with CAR T cell therapy is expected to reduce patients' health care resource utilization (HCRU) over the long-term, few studies have examined the short-term impacts of this treatment on HCRU and associated health care costs. Here, we used data from the TRANSCEND NHL 001 (NCT02631044) clinical trial to estimate the HCRU-related costs incurred by patients with R/R MCL over the first 12 months after receipt of lisocabtagene maraleucel (liso-cel). **Methods:** A retrospective analysis of clinical trial data was conducted to calculate the frequency of HCRU (medications [excluding liso-cel], diagnostics, procedures, ICU and non-ICU hospitalizations) observed over the 12 months immediately after administration of liso-cel. Costs for each HCRU event were derived from public databases and literature, adjusted to 2023 United States (US) dollars, and used to estimate patient-level health care costs. **Results:** Of the patients treated (N = 88), 76.1% were male, 87.5% were White, and mean ± standard deviation (SD) age was 67.5 ± 9 years. All patients were treated in the US and completed a median (range) of 3 (1–11) prior lines of therapy before receiving liso-cel. Most patients (93.2%) received the recommended dose of 100×10^6 CAR^+ T cells. The total mean ± SD per-patient cost (excluding liso-cel) was estimated at $138,413 ± $58,555 over 12 months. Facility use accounted for 77.7% of all costs, primarily owing to non-ICU hospitalizations (98.9%), which had a mean ± SD length of stay of 19.5 ± 16.7 days per eligible patient. Half of all health care costs were incurred within the first month of infusion (53.2%), with each subsequent month contributing a fraction (1.5%–6.3%) of total costs. A total of 13 out of 88 patients received their initial infusion in an outpatient setting and incurred 23% fewer costs compared with those who received their infusion in an inpatient setting ($110,050 vs $143,418), primarily as a function of reduced first-month facility use. Total costs for patients receiving liso-cel in outpatient settings were further reduced to $72,771 upon exclusion of 3 outliers. **Conclusions:** Non-ICU hospitalizations were the largest driver of liso-cel–related costs in this R/R MCL cohort of clinical trial participants. Most of the cost burden was incurred within 1 month of treatment, with dramatic reductions in HCRU and health care costs observed thereafter. Results suggest that treatment in the outpatient setting, even in part (eg, at initial infusion only), may confer substantial cost savings to the health care system. Research Sponsor: This study was funded by BMS. All authors contributed to and approved the abstract; writing and editorial assistance were provided by Emily Burke, PhD, of The Lockwood Group (Stamford, CT, USA), funded by BMS.

Subcutaneous epcoritamab (SC epcor) administered outpatient (outpt) for relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL): Results from phase 2 EPCORE NHL-6.

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Background: Epcor is the only SC CD3xCD20 bispecific antibody approved for R/R DLBCL. In initial protocols, hospitalization after the 1st full dose of epcor was required to monitor patients (pts) for and characterize CRS. The EPCORE NHL-6 trial assessed whether R/R DLBCL/FL pts treated with SC epcor across US community and academic sites could be safely monitored in the outpt setting. **Methods:** Eligible pts had R/R DLBCL or FL and at least 2 prior lines of therapy. Epcor was given in 28-d cycles [C]; C1 SUD: 0.16 mg then 0.8 mg, followed by 48 mg; C1–3: QW; C4–9: Q2W; C≥10: Q4W. Pts received safety education, including early identification and reporting of symptoms of CRS and ICANS, and were required to stay ≤30 min of the site of care for 24 h after the 1st full dose. Based on C1 optimization (OPT) findings from EPCORE NHL-1 (Vose ASH 2023, Abs 1729), the trial was amended to implement C1 OPT with hydration and dexamethasone after enrollment of 34 pts. **Results:** At data cutoff, 36 pts (23 DLBCL, 13 FL) received ≥1 dose of epcor (median cycles, 3). 13 and 23 pts were from US academic and community sites, respectively. Median age was 65 y, 67% of pts had extranodal disease, and 39% had prior CAR T. Any grade CRS occurred in 47% of pts and were mostly low grade (G1, n=9; G2, n=7; G3, n=1). Median time to onset of CRS after 1st full dose was 23 h. No CRS events led to discontinuation; 11 pts (31%) were treated with tocilizumab, 8 (22%) with corticosteroids, and 5 (14%) with both. ICANS occurred in 8% (all G1-2) with a median time to onset of 20 days from C1D1, and all resolved. Of 31 pts receiving the 1st full dose, 3 pts (10%) received epcor in the inpatient (inpt) setting while admitted for AEs other than CRS (pain management, leg injury, UTI, n=1 each). The remaining 28 pts (90%) received epcor and were monitored in the outpt setting. 12 total pts had 13 CRS events after the 1st full dose with CRS starting in the outpt setting in 10 pts (G1, n=6; G2, n=4). 7/28 (25%) pts initially monitored as outpts were subsequently managed as inpt for CRS. All 12 pts had resolution of CRS with a median time to resolution of 45 h. **Conclusions:** Pts with R/R DLBCL and FL were successfully treated with SC epcor and monitored in the outpt setting across different types of sites. CRS events occurring in the outpt setting were appropriately managed, and the observed CRS incidence and severity was comparable to that of the pivotal EPCORE NHL-1 trial. These data suggest that SC epcor can be safely administered and pts monitored outpt, and then managed inpt as needed for CRS. Enrollment is ongoing, and a larger dataset with C1 OPT including hydration and dexamethasone, which are anticipated to further lower CRS incidence and severity, will be presented later. Clinical trial information: NCT05451810. Research Sponsor: This study was funded by AbbVie and Genmab A/S.

CRS events by dosing period.

CRS Events N=24	Priming SUD1 n=3	Intermediate SUD2 n=2	1st Full n=13	2nd Full n=4	≥3rd Full n=2
G1	3	2	7	4	0
G2	0	0	6	0	1
G3	0	0	0	0	1

No ≥G4 CRS.

Preclinical assessment of IPH6501, a first-in-class IL2v-armed tetraspecific NK cell engager directed against CD20 for R/R B-NHL, in comparison with a CD20-targeting T cell engager.

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Background: The therapeutic landscape for relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL) is evolving to include targeted T-cell based immunotherapies, including CD19-targeted CAR-T and CD3xCD20 T-cell engaging (TCE) bispecific antibodies. Yet, there remains an unmet medical need for patients who are refractory to, or ineligible for these treatments. Leveraging natural killer (NK) cells emerges as a promising strategy in hematological malignancies, as shown in a Phase 1 study with IPH6101/SAR'579 in R/R AML (Stein, ASCO 2023; Bajel, ASH 2023). **Methods:** We developed IPH6501, a tetraspecific antibody-based NK cell engager that simultaneously targets on NK cells the CD16a and NKp46 receptors, the IL-2 receptor with an engineered IL-2 variant (IL2v) and on B-NHL cells the CD20 antigen. This approach boosts NK cell activation and proliferation, cytotoxicity against tumor cells, and cytokine production. The IL-2 variant is designed with mutations that prevent binding to CD25 (IL-2Rα), limiting Treg activation and potential IL-2-related side effects. IPH6501 has been evaluated in mouse, non-human primate, and human-derived models, including cells from R/R B-NHL patients. **Results:** In vivo studies in non-human primates and tumor mouse models revealed that IPH6501, at well-tolerated doses, significantly boosted peripheral NK cell proliferation, drove their accumulation at tumor locations, and effectively eradicated CD20+ cells in blood and tissues. In human derived-models, IPH6501 significantly induced NK cell proliferation and cytotoxicity. Notably, IPH6501 showed potent activity against a range of B-NHL cell lines, including those with low CD20 expression. In addition, IPH6501 upregulated the expression of activating receptors on NK cells, such as NKG2D, essential for the recognition and killing of malignant cells, thereby introducing another mode of action enabling the elimination of CD20-negative tumor cells. In a comparative analysis with a CD3xCD20 TCE, IPH6501 induced lower cytokine secretion, suggesting a potentially safer profile. Additionally, IPH6501 showed higher killing efficacy compared to the TCE in samples from healthy individuals as well as R/R B-NHL patients, underscoring its therapeutic potential. **Conclusions:** The preclinical demonstrations of IPH6501 activities across various in vivo models and its effectiveness in ex vivo assays using cells from R/R B-NHL patients provide compelling evidence of its therapeutic potential and tolerability. IPH6501 is emerging as a promising new candidate within the treatment landscape for R/R B-NHL and is currently being investigated in a global, first-in-human phase 1/2 study (NCT 06088654). Research Sponsor: None.

Long term follow-up results of BRL-201 phase I study, a CRISPR-based non-viral PD-1 locus specific integrated anti-CD19 CAR-T cells in treating relapsed or refractory non-Hodgkin's lymphoma.

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Background: Conventional CAR-T cell therapy, often virus-based, poses tumorigenesis risks and incurs high costs and time. We developed a novel, non-viral, CRISPR/Cas9-mediated method for generating genome-specific integrated CAR-T cells, bypassing these limitations. Here, we update long term follow up data of trial of non-viral PD1 locus specifically integrated anti-CD19 CAR-T cells (BRL-201) in patients with relapsed/refractory (r/r) Non-Hodgkin's lymphoma (#NCT04213469). Recently, a phase I/II of BRL-201 (#NCT05741359) is ongoing with a large-scale and multi-center design to further evaluate of BRL-201 antitumor activity in lower dose level. **Methods:** This phase I investigator-initiated trial evaluated BRL-201 in adult patients with r/r B-NHL. Participants underwent leukapheresis followed by lymphodepletion chemotherapy with cyclophosphamide (500mg/m^2, D-3 to -2) and fludarabine (30mg/m^2, D-4 to -2) before BRL-201 infusion. Dose escalation followed a 3+3 rule across three cohorts (2×10^6/kg, 4×10^6/kg, 6×10^6/kg), with additional non-standard doses ($0.56\sim0.8\times10^6$/kg) administered to three subjects. Primary endpoint: incidence of dose-limiting toxicities (DLT). Secondary endpoint: proportion of patients achieving an objective response at 3 months as assessed by investigators. The phase I/II trial also employed the 3+3 escalation rule. **Results:** From May 3, 2020, to August 10, 2021, 25 patients with r/r B-NHL were enrolled; 21 received BRL-201, with a median age of 56 (range: 34-70) and median of 4 (range: 1-9) prior therapy lines. 17 patients were diagnosed with disease stages III or IV, and 13 patients were high-intermediate to high risk per IPI/aaIPI. Two had previous autologous HSCT, and one had primary refractory disease. As of January 10, 2024, the median follow-up was 37.0 months (95%CI: 33.82-40.18m). All 21 patients showed an objective response, with 18 (85.7%) achieving CR. 7 patients maintained CR at data cut-off. The median DOR was 18.6 months (95%CI: 4.10-33.10), with a median PFS of 19.5 months (95%CI: 5.15-33.86). The 12-month OS rate was 76.2% (95% CI: 60%-96.8%). The median OS was not reached. No severe CRS or ICANS were noted. Mild CRS (grade 1-2) occurred in 66.7%(14/21) of patients, with one requiring tocilizumab. Grade 1-2 ICANS was observed in 19.0%(4/21). No new AEs/SAEs were reported in the last follow-up. In the ongoing phase I study, 9 patients received BRL-201 with no DLTs observed within 28 days post-infusion. **Conclusions:** With a median 37.0 month follow-up, BRL-201 demonstrated durable responses, high median PFS (19.5 months), and a 12-month OS rate of 76.2%. The median OS for responders has not yet been reached. The safety profile was manageable, highlighting the clinical potential of BRL-201. Further data collection is ongoing to establish its clinical value. Clinical trial information: NCT04213469, NCT05741359. Research Sponsor: None.

Epcoritamab + R-DHAX/C in transplant-eligible patients (pts) with high-risk relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL).

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Background: While high-dose therapy (HDT)–autologous stem cell transplant (ASCT) is potentially curative for pts with R/R DLBCL, many do not receive this treatment (tx) due to insufficient response to salvage chemoimmunotherapy; better options are needed. Epcoritamab is a CD3xCD20 bispecific antibody with efficacy and safety in R/R DLBCL as a single agent and in combination. We report updated data from epcoritamab in combination with rituximab, dexamethasone, cytarabine, and oxaliplatin or carboplatin (R-DHAX/C) in pts with R/R DLBCL eligible for HDT-ASCT, including high-risk pts (progressed within 12 mo of initial tx or primary refractory), from EPCORE™ NHL-2 (phase 1/2; NCT04663347). **Methods:** Adults with R/R $CD20^{+}$ DLBCL eligible for HDT-ASCT received R-DHAX/C and epcoritamab (2 step-up doses, then 24- or 48-mg full doses) in 21-d cycles (Cs): QW, C1–3. If HDT-ASCT was deferred, pts could continue epcoritamab (21-d C: QW, C4; 28-d Cs: Q2W, C5–9; Q4W, C≥10) until disease progression. Primary endpoint was overall response rate (ORR; Lugano criteria). **Results:** As of Dec 15, 2023, 29 pts (median age, 58 y) received epcoritamab (24 mg, n=3; 48 mg, n=26) + R-DHAX/C. At baseline, 24 pts (83%) had progressed within 12 mo of initial tx, 19 (66%) had primary refractory disease (no response or relapse within 6 mo of initial tx), and 3 (10%) had prior CAR T. At 27.5 mo median follow-up, 16 (55%) pts had proceeded to HDT-ASCT and 2 (7%) remained on tx. ORR was 76% and complete response (CR) rate was 69% (Table). Median time to response was 1.4 mo (CR, 1.5 mo). At 24 mo, per Kaplan–Meier estimates, 60% of pts remained progression free, while 90% of pts who proceeded to ASCT (n=16) and 60% of pts who continued epcoritamab without ASCT (n=5) remained progression free; additionally, 90% of pts with CR who received ASCT (n=15) and 100% of high-risk pts with CR who received ASCT (n=12) remained in response. An estimated 86% of pts remained alive at 24 mo. The most common tx-emergent AEs (TEAEs) of any grade (G) were thrombocytopenia (76%), anemia (59%), nausea (48%), and neutropenia (48%; febrile neutropenia, 17%). CRS was low grade (38% G1, 7% G2), resolved, and did not lead to tx discontinuation. ICANS (G2) occurred in 1 pt and led to tx discontinuation. There were no fatal TEAEs. **Conclusions:** Longer follow-up reaffirms the efficacy and feasibility of epcoritamab + R-DHAX/C in ASCT-eligible DLBCL. Response rates were high and most pts proceeded to ASCT. Safety was manageable and consistent with prior data. These results, including new high-risk subgroup analyses, support future evaluation of epcoritamab + R-DHAX/C in ASCT-eligible DLBCL. Clinical trial information: NCT04663347. Research Sponsor: This study was funded by Genmab A/S and AbbVie.

Response and durability of response.

	n	ORR %	CR Rate %	Pts With CR Remaining in Response at 24 mo[b] %
All pts	29	76	69	81 n=20
Progressed within 12 mo of initial tx[a]	24	71	63	91 n=15

[a]For primary refractory subset (n=19), ORR/CR rates were 68%/58%.
[b]Kaplan–Meier estimate.

Secondary myeloid malignancy after CAR T cell therapy for non-Hodgkin lymphoma (NHL).

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Background: Prior studies have described toxicities associated with chimeric antigen receptor T cell therapy (CART). Recently, myeloid malignancies were identified in myeloma patients (pt) after receipt of cilta-cel. In this study, we sought to describe the cumulative incidence and characteristics of secondary myeloid malignancies in pt treated with CART for NHL. **Methods:** We conducted a single institution retrospective study among pt ages ≥18 years (yr) who received commercial CART for NHL at Ohio State between December 2017 to April 2022. Descriptive statistics were used to summarize pt/disease characteristics. Cumulative incidence was calculated from date of infusion with death/relapse as competing risks. **Results:** For 190 pt treated with CART, median age was 63 yr (23-85 yr). Disease subtypes included diffuse large B-cell lymphoma (BCL)/high grade BCL, Richter transformation, and mantle cell lymphoma (79.5%, 8.4%, and 7.4%). Products included tisa-cel (47.9%), axi-cel (43.1%), brexu-cel (7.4%), and liso-cel (1.6%). Grade 3-4 neutropenia developed in 29% and 18% of pt at 30 days and 90 days post-CART. Median follow-up was 17 mo (0.5-63 mo). 48% were alive at time of analysis. Myeloid malignancy post-CART occurred in 7 pt with a median time to development of 29 mo (18-41 mo). Characteristics (Table) included complex karyotype, TP53 and chromosome 5/7 abnormalities. Cumulative incidence of secondary malignancy was 1%, 5%, and 6% at 2, 3, and 4 yr post-CART. **Conclusions:** We report on incidence of secondary myeloid malignancy in pt receiving CART for NHL. Mutational characteristics of secondary malignancies were those classically associated with therapy-related myeloid malignancy, thus presumed to be associated with prior exposure to chemotherapy (eg. alkylators/VP-16). Further investigation in larger cohorts with additional observation time, to allow for appropriate risk discussion, is required. Research Sponsor: None.

Age, Sex	CART Product	Primary Disease	Lines of Treatment Pre-CART	Secondary Malignancy	Time to Malignancy Post-CART (Days)	Cytogenetics	FISH	NGS
61 M	Axi-cel	DLBCL	2†	AML	877	Complex	Del(17p), monosomy 16q (CBFB), monosomy 17p (TP53), RUNX1	TP53, KMT2A, DNMT3A
65 M*	Axi-cel	DLBCL	3 + autoHCT	MDS	533	Complex, del(7)	Trisomies RUNX1, RUNXIT1, CBFB, TP53, 17 centromere	TP53, NRAS
41 F	Axi-cel	RT to DLBCL	6	MDS#	1234	Monosomy 7, ring chromosome	-	Neg
61 F	Axi-cel	FL to DLBCL	5	AML#	937	Normal	Neg	DNMT3A, TET2, RUNX1
25 M*	Tisa-cel	DLBCL	2‡	MDS	1037	Unbalanced translocation t(1;7)	Neg	Neg
64 F*	Tisa-cel	DLBCL	4 + autoHCT†	CMML	835	Monosomy 7	-	RUNX1
66 M	Tisa-cel	DLBCL	2	MDS	589	Complex, monosomy 5, monosomy 6, der(6q), der(7)	Trisomies 3q27 (BCL6), 8q24.2 (MYC), 14q32.3-8q24 (IGH-MYC), 8p11.1-q11.1 (D8Z2)	-

*BM biopsy pre-CART showed no evidence of disease/mutations; biopsy unavailable in other pts.
†Received post-CART systemic tx for relapse, ‡local RT for stable disease prior to secondary malignancy.
#Underwent alloHCT.
Neg: negative.

Early prediction of severe ICANS after standard-of-care CD19 CAR T-cell therapy using gradient-boosted classification trees.

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Background: Severe immune effector cell-associated neurotoxicity syndrome (ICANS) has arisen as a major complication leading to morbidity, mortality, and increased resource utilization. There is an urgent need to accurately predict the development of severe ICANS after CAR T-cell therapy. Here, we demonstrate the high performance of the XGBoost ("eXtreme Gradient Boosting") machine learning algorithm in predicting the development of severe ICANS using commonly available laboratory and vital sign data from patients with B-cell lymphomas undergoing standard-of-care CD19 CAR T-cell therapy. **Methods:** We included patients who received axicabtagene ciloleucel (axi-cel) or brexucabtagene autoleucel (brexu-cel) per standard of care. ICANS was graded by CTCAE 4.03 criteria (pre-12/2018) or ASTCT Consensus Grading System (post-1/2019). Predictions were generated using XGBoost, a widely used supervised machine learning algorithm that trains ensembles of decision trees to learn iteratively from prior trees and allows for very flexible modeling (e.g. non-linear effects, complex high-order interaction effects). K-fold cross-validation was used to assess calibration and overfitting. Variables assessed included age, ferritin, CRP, LDH, IL-6, fibrinogen, platelet count, and temperature at pre-infusion, day 0, and day +3 post-infusion timepoints. **Results:** A total of 175 patients were included with 39 receiving brexu-cel (22%) and 136 receiving axi-cel (78%). Grade ≥3 ICANS occurred in 40 patients (23.3%). XGBoost modeling of factors demonstrated that serum ferritin level on day +3 was the most important variable predictive of grade ≥3 ICANS (accuracy gain: 0.28). Other influential factors included day 0 and +3 platelet count, patient age, day +3 IL-6 level, day 0 fibrinogen level, and day 0 and +3 CRP level, in descending order of importance. The XGBoost model maintained high discrimination (ability to distinguish high-risk from low-risk patients; mean AUROC 0.74, sensitivity 0.95, specificity 0.90). Longitudinal LOESS smoothing confirmed associations between severe ICANS and elevation in serum ferritin at day 0 (OR 3.01, 95% CI 1.41 – 6.73, p = 0.005) and day +3 (OR 5.50, 95% CI 2.31-14.5, p <0.001). **Conclusions:** A supervised machine learning model using XGBoost incorporating age, temperature and commonly accessible laboratory data including ferritin, CRP, LDH, IL-6, fibrinogen, and platelet count predicted severe ICANS prior to the development of symptoms with high discrimination (AUROC 0.74) in patients undergoing standard of care CAR T-cell therapy. This allows for the early identification of patients at highest risk for developing severe ICANS who may benefit from prophylactic interventions. Once externally validated, we plan to develop a user-friendly web application to generate individualized predictions from our model. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; 5T32CA951539; National Cancer Institute/U.S. National Institutes of Health; P30CA15704; NIH National Heart, Lung, and Blood Institute; 5T32HL007093; Swim Across America.

Follow-up on phase 1 study of AT101, a novel anti-CD19 chimeric antigen receptor cell therapy (CAR-T) in patients with relapsed or refractory (r/r) b-cell non-Hodgkin lymphoma.

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Background: All the FDA-approved CD19 CAR-T products are based on FMC63 scFv, which binds to the membrane-distal region of CD19. We developed a novel anti-CD19 antibody clone (1218) binding to a membrane-proximal epitope of CD19 with fast on/off kinetics. AT101 is an autologous CAR-T cell transduced with a lentiviral vector encoding CAR comprised of a humanized scFv of 1218, 4-1BB costimulatory, and CD3zeta domain. **Methods:** In the phase 1 trial, patients (n=3 per dose level; up to n=18 in total) are treated with AT101 in 3 dose-escalation cohorts based on a standard 3 + 3 design. Each patient received a single intravenous dose of AT101 at dose level (DL) 1 (0.2×10^6 cells/kg), DL2 (1.0×10^6 cells/kg), or DL3 (5.0×10^6 cells/kg). The primary objective is to determine the safety, the maximum tolerated dose, and the recommended phase 2 dose of AT101. Key eligibility criteria include patients aged ≥19 with histologically confirmed relapsed or refractory B-cell non-Hodgkin lymphoma (NHL). Tumor responses were evaluated using Lugano 2014 criteria at 4 weeks before AT101 infusion as well as at 4 weeks and 3, 6, 9, 12, and 18 months after AT101 infusion. **Results:** From March 2022 to December 2022, fourteen patients were enrolled and 12 patients were treated, who were their median age of 62.5 years (range 39 to 84) and received a median of three prior lines of therapy (range 2-9). Their subtypes were as follows: diffuse large B cell lymphoma (DLBCL; n=7, 58.3%), follicular lymphoma (FL; n=3, 25.0%), mantle cell lymphoma (MCL; n=1, 8.3%), or marginal zone lymphoma (MZL; n=1, 8.3%)). The data collection cut-off date was January 31, 2024. Based on the best overall response up to three months, eleven patients responded with an overall response rate (ORR) of 91.7%, and a complete response (CR) was observed in nine patients (75%). Remarkably, in DL2 and DL3 groups, the CR was 100.0%. Among nine patients who achieved CR, seven patients have remained in CR during the median follow-up of 13.6 months (1.6-22.3 months). One patient experienced relapse and another one died from septic shock. The median duration of response (DOR), progression-free survival (PFS), overall survival (OS), and event-free survival (EFS) were 19.5, 17.2, 18.9 and 17.2 months, respectively. The median DOR, PFS, OS and EFS were not reached. **Conclusions:** In this first-in-human phase 1 trial, AT101 was tolerable with limited and manageable toxicities. In comparison to current FMC63 scFv-based CD19 CAR-T therapies, AT101 exhibited potent and more enduring efficacy with a remarkable suppression of relapse after CR. A phase 2 clinical trial is currently undergoing for DLBCL patients. Clinical trial information: NCT05338931. Research Sponsor: Korea Drug Development Fund.

Association between post-CART terminal complement complex (TCC) levels and clinically significant immune effector cell–associated neurotoxicity syndrome (ICANS).

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Background: The cornerstone of ICANS pathogenesis is endothelial dysfunction leading to blood-brain barrier disruption driven by inflammatory cytokines. Endothelial dysfunction is often associated with complement activation as in thrombotic microangiopathy, but the association between complement and ICANS has not yet been investigated. Herein, we describe the association between TCC levels (sC5b-9) and ICANS after CART. **Methods:** We retrospectively included 42 patients (pts) with B-cell non-Hodgkin lymphoma treated with axi-cel or brexu-cel from 03/2022 - 09/2023 at Ohio State University who had had sC5b-9 levels available pre-lymphodepletion (pre-LD), pre-CART and post-CART infusion. sC5b-9 levels were measured once in each of the timepoints: pre-LD (between D-7 and D-4), pre-CART (between D-3 and D0) and post-CART (between D2 and D8). We defined clinically significant ICANS as peak grade ≥2 (G≥2). Median and interquartile range (IQR) were used to describe the biomarkers levels, and Wilcoxon-rank sum test was used to compare values between groups. **Results:** Median age was 64 years (26-76), 30 (71%) pts had large B-cell lymphoma and 6 (14%) had untransformed follicular lymphoma who received axi-cel (36, 86%), and 6 (14%) had mantle cell lymphoma who received brexu-cel. Following CART, cytokine-release syndrome (CRS) peak grade was 2 and 1 in 16 (38%) and 22 (52%) of the pts, respectively, and 4 pts (10%) had no CRS. The ICANS peak grade was 4, 3, 2 and 1 in 4 (10%), 2 (5%), 6 (14%) and 6 (14%) of the pts, respectively, and 24 (57%) of the pts had no ICANS. The median time from CART to ICANS peak was 6 days (2-12). Tocilizumab and steroids were used in 28 (67%) and 20 (48%) of the pts, respectively. We compared sC5b-9 levels pre-LD, pre-CART and post-CART between pts that had ICANS peak G≥2 (N = 12) vs. grade 1 or did not have ICANS (G0-1, N = 30). We found that the post-CART sC5b-9 levels were significantly higher among pts who had ICANS G≥2 [median (IQR) 254 (129) vs. 183 (82) ng/mL, p = 0.013]. There was no statistical difference in the levels pre-LD and pre-CART between pts who had ICANS G≥2 vs. G0-1, median (IQR) 176 (103) vs. 159 (94) ng/mL, p = 0.37, and 152 (64) vs. 143 (69) ng/mL, p = 0.89, respectively. We also compared levels of other biomarkers associated with tumor burden, inflammation, and endothelial dysfunction at the same time points sC5b-9 was measured between pts with ICANS G≥2 vs. G0-1 and there were no statistically significant differences: median (IQR) pre-LD LDH 171 (73) vs. 180 (115) U/L, p =0.54, post-CART ferritin 262 (546) vs. 297 (333) ng/mL, p = 0.92 and post-CART fibrinogen 302 (221) vs. 405 (146) mg/dL, p = 0.29. **Conclusions:** Our findings support an association between post-CART sC5b-9 levels and clinically significant ICANS warranting further investigation of the role of complement in the ICANS pathogenesis and as a therapeutic target. Research Sponsor: None.

7037 Poster Session

Subcutaneous epcoritamab + GemOx in patients with relapsed or refractory DLBCL: Updated results from EPCORE NHL-2.

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Background: Gemcitabine + oxaliplatin (GemOx) is commonly used with rituximab to treat relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL); however, outcomes are suboptimal: 33% complete response (CR) rate; 5 mo median progression-free survival (PFS); 10 mo median overall survival (OS; Cazelles et al, *Leuk Lymphoma* 2021). We report additional efficacy and safety results of epcoritamab + GemOx in difficult-to-treat R/R DLBCL (EPCORE™ NHL-2 phase 1/2 trial, NCT04663347). **Methods:** Adults with R/R CD20$^+$ DLBCL who failed or were ineligible for autologous stem cell transplant (ASCT) enrolled to receive subcutaneous (SC) epcoritamab (2 step-up doses followed by 48-mg full doses) in 28-d cycles (C): QW, C1–3; Q2W, C4–9; Q4W, C≥10 until unacceptable toxicity or disease progression. GemOx was given Q2W in C1–4. The primary endpoint was overall response rate (ORR) per Lugano criteria. Subgroup analyses by prior treatment (tx) and response were performed. **Results:** As of Sept 1, 2023, 97 pts with ≥6 mo of follow-up had received epcoritamab 48 mg + GemOx (median follow-up, 9.7 mo). Pts had a median of 2 prior lines of tx (pLOT; range, 1–6); 55% had primary refractory disease, 38% had bulky disease (>6 cm), 30% had prior CAR T, and 9% had prior ASCT. Median age was 72 y, with 34% of pts ≥75 y. A median of 7 cycles of epcoritamab and 4 cycles of GemOx were initiated. At data cutoff, tx was ongoing in 46% of pts. ORR was 78% and CR rate was 55%. Median time to CR was 1.7 mo; median duration of CR was 13.3 mo. Additional efficacy outcomes are shown in the Table. Safety was consistent with previous reports. The most common tx-emergent AEs (TEAEs) of any grade (G) were hematologic AEs (68% thrombocytopenia; 59% neutropenia [6% febrile neutropenia]; 51% anemia) and CRS (51%). CRS was primarily low grade (27% G1, 23% G2), with only 1 pt experiencing G3 CRS; all events resolved and none led to tx discontinuation. ICANS was reported in 3 pts (G1, n=2; G3, n=1); all events resolved, but 1 pt discontinued tx. There were 13 fatal TEAEs; in 3 cases, the contribution of epcoritamab + GemOx could not be ruled out: COVID-19, multiple organ dysfunction syndrome, and small intestinal perforation. **Conclusions:** These long-term results continue to demonstrate that SC epcoritamab in combination with GemOx leads to deep, durable responses, which translate to high rates of PFS and OS in challenging-to-treat, high-risk pts with R/R DLBCL. CR rates were consistently high across prespecified subgroups. Higher CR rates in pts with 1 vs ≥2 pLOT indicate that earlier use may further improve outcomes. No new safety signals were identified. The benefit-risk profile of this combination supports the combinability of epcoritamab in R/R DLBCL. Clinical trial information: NCT04663347. Research Sponsor: This study was funded by Genmab A/S and AbbVie.

Efficacy outcomes.

CR Rate	%
Overall (N=97)	55
1 pLOT (n=38)	63
≥2 pLOT (n=59)	49
Prior CAR T tx (n=29)	41
Primary refractory (n=53)	42
Kaplan–Meier estimates at 9 mo in pts with CR (n=53)	%
CR	78
PFS*	93
OS*	96

*COVID-19 adjusted.

Factors before leukapheresis that correlate with severe cytopenia and therapy related myeloid neoplasm post CAR-T.

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Background: While chimeric antigen receptor T-cell (CAR-T) therapy has transformed treatment for hematological malignancies, severe (≥ grade 3,Gr 3, CTCAE) cytopenias post CAR-T and therapy related myeloid neoplasms (t-MN) are particularly difficult to manage. Survival after diagnosis of t-MN is dismal. Management of ≥Gr 3 cytopenias that do not recover by month 3 after CAR-T require frequent monitoring and transfusion support. Growth factor and thrombopoietin mimetics have variable success, with stem cell boost emerging as having more consistent success. Evaluation for CAR-T eligibility, prior to leukapheresis, is the critical timepoint where factors identified at this time could inform risks and benefits of CAR-T versus alternative treatment and for consideration of stem cell collection in patients who may benefit from stem cell boost to treat severe cytopenia post CAR-T. **Methods:** We conducted a retrospective analysis comparing clinical data of patients (pts) with lymphoma (NHL) and multiple myeloma (MM) treated with FDA-approved and investigational CAR-T between 01/2016 – 06/2022 at Mayo Clinic. Prolonged cytopenias were defined as hemoglobin (Hg)<8 g/dL, absolute neutrophil count (ANC)<0.5 x 10^9/L, and/or platelet count (PLT)<50 x 10^9/L at 3 months after CAR-T. Pts with progressive disease were excluded from cytopenia analysis. Logistic regression to identify factors correlated with cytopenia and t-MN. **Results:** Among the 186 pts who received CAR-T, 42 (22%) patients developed severe cytopenia (26/102, 25%, in NHL; 16/84, 19% in MM); 15/186 (8%) had more than 1 concurrent cytopenia. Univariate analysis identified that baseline ferritin and CAR-HEMATOTOX score correlated with cytopenia. Multivariate analysis showed that advanced age (≥ 65 years) (HR 2.69, 95%CI 1.17 – 6.40, P = 0.02) and thrombocytopenia (HR 4.01, 95%CI 1.77 – 9.34, P = 0.001) were associated with severe cytopenia. Twenty (10.7%) patients [8 (40%) males] developed t-MN at a median of 9.5 months (IQR 4.8 – 19.3 months) after CAR-T (14/102, 13% in NHL; 6/84, 7% in MM). Univariate analysis identified ferritin and CAR-HEMATOTOX score correlated with t-NM. Multivariate logistic regression showed advanced age (HR 5.03; 95%CI 1.59-18.7, P= 0.009), hemoglobin ≤ 10 g/dl (HR 3.63, 95%CI 1.04-13.30, P = 0.04), and thrombocytopenia (HR 4.06, 95%CI 1.32-14.2, P 0.02) are significantly associated with development of post-CART t-MN. **Conclusions:** Advanced age, anemia and thrombocytopenia at the time of evaluation for CAR-T eligibility, prior to leukapheresis, are associated with the development of post-treatment severe cytopenia and t-MN. Larger, multi-center studies are needed to validate these findings. Research Sponsor: None.

7039 Poster Session

Extended follow-up results beyond 2.5 years from the pivotal NHL-1 EPCORE trial: Subcutaneous epcoritamab monotherapy in patients with relapsed/refractory large B-cell lymphoma (R/R LBCL).

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Background: Epcoritamab induces high complete response (CR) and MRD-negativity rates with manageable safety in patients (pts) with challenging-to-treat R/R LBCL as shown in the pivotal phase 2 study (NCT03625037). Here we present long-term data, an additional efficacy analysis from the expansion cohort, and data from the cycle 1 optimization (C1 OPT) part. **Methods:** Adults with R/R CD20$^+$ LBCL and ≥2 prior systemic therapies received subcutaneous epcoritamab (2 step-up doses, then 48-mg full doses per label) in 28-d Cs. The primary endpoint of the expansion cohort was IRC-assessed overall response rate (ORR). A subgroup analysis evaluated efficacy outcomes by investigator assessment in complete responders with longer follow-up. C1 OPT assessed CRS incidence and severity with hydration and dexamethasone prophylaxis in C1; hospitalization was not required. **Results:** Overall, 157 LBCL pts were treated in the expansion cohort; 148 had diffuse LBCL (DLBCL) or high-grade B-cell lymphoma (HGBCL). Baseline characteristics were previously reported. As of April 21, 2023, the median follow-up for LBCL was 25.1 mo (range, 0.3+ to 32.7); ORR/CR rates were 63/40% (LBCL) and 61/39% (DLBCL + HGBCL) by IRC. In a subgroup analysis of complete responders with longer follow-up (median, 31.3 mo), median duration of CR was not reached; efficacy outcomes for complete responders are shown in the Table. Long-term safety was consistent with previous reports. CRS remained the most common AE (51% all grade [G]; 32% G1, 16% G2, 3% G3). In C1 OPT, 36 pts were evaluable for CRS with a median follow-up of 1.7 mo. Overall CRS incidence was 22% and events were low grade (14% G1, 8% G2), mostly occurring following the first full dose. All CRS events resolved; none led to treatment discontinuation. Among 60 total pts in C1 OPT, 1 pt experienced ICANS (G1). Additionally, IL-6 levels were lower with C1 OPT and consistent with the observed lower rate and severity of CRS. Preliminary C1 OPT efficacy data were comparable to data observed in the expansion cohort. **Conclusions:** Epcoritamab monotherapy continues to demonstrate deep and durable responses, with most complete responders remaining in CR and without new safety signals in these long-term follow-up analyses. Implementing simple measures of adequate hydration and prophylactic dexamethasone in C1 markedly reduced the overall incidence and severity of CRS with no impact on efficacy. The continued benefit beyond 2.5 y underlines the long-term efficacy and value of epcoritamab in R/R LBCL. Clinical trial information: NCT03625037. Research Sponsor: This study was funded by Genmab A/S and AbbVie.

Efficacy outcomes in complete responders with LBCL (n=65).

Outcome, %	24 mo	30 mo	33 mo
DOCR	62.3	53.8	NA
PFS	65.4	54.7	54.7
OS	76.2	71.1	71.1

Data cutoff: October 16, 2023. Median follow-up, 31.3 mo. Per investigator assessment. Kaplan–Meier estimates. Medians were not reached (data not shown). NA, not assessed.

Phase I study of CN201, a novel CD3xCD19 bispecific antibody, in patients with relapsed or refractory B-cell non-Hodgkin lymphoma.

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Background: CN201 is a novel CD19-targeting T-cell-engager IgG4 bispecific antibody, designed to reduce cytokine release syndrome (CRS) while retaining potent T-cell mediated cytotoxicities. A silenced Fc fragment was used to prevent antibody-dependent cellular cytotoxicity while prolonging half-life of the molecule. Here, we report results of the phase I study of CN201 in patients with relapsed or refractory B-cell non-hodgkin lymphoma (R/R B-NHL) (ClinicalTrials.gov identifier: NCT06189391). **Methods:** The i3+3 dose-escalation design was used in adult patients with CD19+ R/R B-NHL to investigate safety, tolerability, maximum tolerated dose, and preliminary anti-tumor activity. Patients with R/R DLBCL who failed≧2 prior lines of therapy, or R/R indolent NHL(iNHL) who had at least 1 prior systemic therapy were eligible for enrollment. Patients received CAR-T therapy can be enrolled after 90 days washout periord provided that CD19 was still positive on tumor cells. Response were evaluated according to the Lugano 2014 criteria. Single-agent CN201 was administered intravenously once per week. Intial dose escalation was conducted in the patients at fixed ascending doses; later, a step-up dosing regimen was adopted, including a priming dose on cycle 1 Day 1 followed by an intermediate dose on Day 8 and the target dose administered on Day 15 and thereafter. **Results:** As of December 29, 2023, 58 adult patients received CN201, including 19 patients with fixed doses from 2.5μg to 600μg, 39 patients with step-up doses from 1.2mg to 40mg of the target doses. Maximum tolerated dose has not been reached. The most common treatment-related adverse effects (AEs) (≥20%) of any grade were white blood cell decreased (32%), neutropenia (30%), lymphopenia (29%), anemia (29%), pyrexia (25%) and platelet decreased (23%). The most common AEs (≥10%) of grade 3 or higher were lymphopenia (24%) and neutropenia (14%). CRS occurred in 4 (7%) patients, mainly occurred following the first dose. All of those CRS were low-grade, no ≥Grade 3. No immune effector cell-associated neurotoxicity syndrome was observed. In patients with fixed doses up to 600 μg and target dose up to 2.5mg, stable diseases (SD) were observed. The best overall responses dramatically improved in patients received full doses ≥ 5mg, ranging from 5 mg to 40 mg investigated so far. Among 22 evaluable patients with full doses ≥ 5mg, the objective response rate (ORR) was 77% and the complete remission (CR) rate was 22%. Among 11 patients with indolent B-NHL, the ORR was 91%, CR rate was 45.5%, including one patient had failed previous CAR-T therapy. The responses at higher doses are still under evaluation, and additional data will be reported. **Conclusions:** CN201 has a well tolerable safety profile and promising anti-tumor activity in patients with R/R B-NHL. Clinical trial information: NCT06189391. Research Sponsor: Curon Biopharmaceutical Limited.

Impact of late immune effector cell associated hematotoxicity (ICAHT) and prolonged neutropenia after CAR-T therapy on infection and survival outcomes.

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Background: Prolonged hematologic toxicity is a common side effect of chimeric antigen receptor T-cell (CART) therapy. The EHA/EBMT panel developed the late ICAHT grading which incorporates depth of neutropenia after Day 30. Recently, the early ICAHT grade (D 0-30) was associated with infection (infx) and survival outcomes. Here, we evaluate the impact of late ICAHT and neutropenia on survival and infx outcomes after CD19 CART. **Methods:** We included two cohorts of adult patients (pts) with large B cell lymphoma (LBCL), mantle cell lymphoma (MCL), and follicular lymphoma (FL) who received commercial CD19 CART. Late was graded based on depth of neutropenia after D30 (G1 $\leq$ 1.5; G2 $\leq$ 1.0; G3 $\leq$ 0.5; G4 $\leq$ 0.1 G/L) and pts were censored for relapse, progression, or loss of follow up. Infxs after D30 were graded per CTCAE as mild G $\leq$ 2 or severe G $\geq$ 3. Cohort 1 included pts from 8 US medical centers for survival outcomes. Only data for severe infx was collected from D30-D100 and longer term infx data was not available. Landmark survival analysis at D+100 was performed using the Kaplan-Meier method and multivariate cox proportional hazards. To assess long term late infx outcomes, cohort 2 included pts at Vanderbilt with granular cytopenia and infx data (D30-365). **Results:** Cohort 1 included 277 pts with LBCL of whom 143 received axi-cel, 61 tisa-cel, and 72 liso-cel with median follow up 395 days (range 30-1763). By D100, there were 111 (40%) without, 89 (41%) with mild to moderate (G1-G2), and 53 (19%) with severe (G3-G4) late ICAHT. There were 13 pts (6%) with severe infx which was not associated with severe ICAHT (p=0.68). In multivariate landmark survival analysis using previously published covariates, severe late ICAHT was not associated with PFS (HR 1.64, p=0.11) or OS (HR 1.54, p=0.17); however, D100 neutropenia (ANC $\leq$ 1000) was associated with inferior PFS (HR 2.00, p=0.002) and OS (HR 1.95, p=0.003). NRM was 11% and associated with D100 neutropenia (p=0.015) but not late ICAHT (p=0.15). Cohort 2 had 43 pts (35 LBCL, 7 MCL, 1 FL) with median follow up 483 days (range 233-2133). 34 pts received axi-cel, 2 tisa-cel, and 7 brexu-cel. By 1 yr, there were 10 (23%) without, 27 (63%) with mild to moderate, and 6 (14%) with severe late ICAHT. There were 52 infxs by 1 yr and 16 pts (37%) had no infx. Median time to first infx after D30 was 165 days (range 31-365). There were 31 (60%) mild and 21 (40%) severe infx. IVIG was used in 28 (65%) and G-CSF in 27 (62%). Only 1 pt with severe ICAHT had severe infx. Late ICAHT and neutropenia were not associated with severe infection in logistic regression. **Conclusions:** These data did not show an association between EHA/EBMT late ICAHT grading and infx after D30 or survival. A detailed reporting of T and B cell reconstitution data may provide clues to better predict late infx. Persistent neutropenia at D100 was associated with inferior PFS and OS which needs validation in future studies. Research Sponsor: None.

Carfilzomib plus rituximab, ifosfamide, carboplatin and etoposide (C-RICE) led to higher response, OS, and PFS in patients with transplant-eligible relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL).

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Background: The CORAL study highlighted the need to develop novel salvage regimens for R/Rr/r DLBCL previously treated with R+CHOP. Overall response rate (ORR) to second line immuno-chemotherapy was 51% with a 3-year progression free survival (PFS) of 30% following high-dose chemotherapy and autologous stem cell support (HDC-ASCS). Optimal disease control (complete remission [CR] or partial remission [PR]) prior to HDC-ADCS and more recently to chimeric antigen receptor T-cell therapy (CAR T), correlates with improved outcomes. Dysregulation of Bcl-2 family members has been associated with acquired resistance to rituximab and chemotherapy which we have previously shown may be mitigated by co-treatment with proteasome inhibition in pre-clinical model. Subsequently, we conducted a Phase I/II clinical trial evaluating the safety and efficacy of CRICE as salvage therapy for R/R DLBCL (Blood Adv. 2023 7:1146-1155). **Methods:** Here we retrospectively compared the clinical outcomes of R/R DLBCL patients treated with CRICE (N=28) versus RICE (N=38) on our prior clinical trial (NCT01959698). Demographic, clinical, and pathological characteristics were collected for both groups (Table). Study endpoints consisted of differences in overall response rate (ORR), CR/PR rates, median progression free survival (PFS) and overall survival (OS) between the two cohorts. **Results:** The addition of Carfilzomib to RICE resulted in improved clinical outcomes. A higher ORR (92.9 vs 76.3, P=0.073) and CR rates (82.1 vs. 44.7, P=0.002) were observed in CRICE vs. RICE treated patients. Multivariate analysis confirmed the higher CR rates in CRICE vs. RICE when adjusted by DLBCL subtype (GCB vs. nNon-GCB, P=0.003). More CRICE patients proceeded to HDC-ASCS (52.6% vs. 47.4%, P=0.618). The 3yr PFS rate was higher in CRICE (54%, 32-72%) vs. RICE treated patients (35%, 19-51%). While the median PFS was longer in CRICE treated patients 36.8m (0.8, 73.2) vs. 3.2m (0.5, 54.2) (RICE), it did not reach statistical significance (P=0.714). No differences in OS were observed between CRICE & RICE patients, median OS 67.3m vs. 71.8m. **Conclusions:** The CRICE outcomes were more striking in patients with non-GCB r/r DLBCL (ORR 85%, mPFS and OS not reached). CRICE led to high CR rates and longer PFS among r/r DLBCL patients, especially in non-GCB DLBCL patients. CRICE could be an attractive regimen to achieve disease control in r/r DLBCL patients undergoing consolidation therapy with HDC-ASCT or CAR T-cell therapy. Research Sponsor: None.

Patient characteristics.

	RICE	C-RICE	P value
Male/Female	22/16	15/13	NS
Median Age	59yr	59yrs	NS
Stage			NS
I	5	2	
II	7	4	
III	3	9	
IV	23	12	
IPI score			
Low (0-1)	12	6	NS
Low-Intermediate (2)	4	10	
High-Intermediate (3)	15	7	
High (4-5)	7	6	
GBC	9 (23.7%)	15 (53.6%)	0.019
Non-GCN	29 (76.3%)	13 (46.4%)	
Double hit status	4	5	NS
Refractory	21	10	NS
Relapse	15	17	

Combination of pirtobrutinib and lentiviral transduced bispecific anti-CD20/CD19 (LV20.19) CAR T-cell therapy to improve outcomes in patients with relapsed/ refractory lymphoma.

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Background: Combination trials of BTK inhibitors (BTKi) with CAR-T have suggested potential synergistic benefit by improving CAR-T immunophenotype and clinical outcomes but are limited by increased toxicity. We report immunophenotype, cytokine profile, and patient outcomes with the new non-covalent BTKi, pirtobrutinib (pirto) when given prior to LV20.19 CAR-T and compare the final CAR product to pts who did not receive pirtobrutinib prior to CAR. **Methods:** Pts received LV20.19 CAR-T as part of a phase 1/2 trial (NCT04186520). Only pts who received pirto £4 weeks prior to apheresis were included. To determine the impact of pirto on LV20.19 CAR-T, we calculated both polyfunctionality (PFA) and polyfunctional strength index (PSI) for each product using the Isoplexis. Descriptive statistics, t-tests and Kaplan-Meier method were used as appropriate. **Results:** 11 pts received pirto prior to LV20.19 CAR-T (Table). Median age was 65 (50-80) yrs and median prior lines of therapy were 4 (2-8). There were 4 MCL pts, 5 Richter's (RT)/CLL, 1 MZL and 1 DLBCL. Median duration of pirto was 4 (1-20) mo. Pts were on pirto for a median of 12 (1-22) days prior to apheresis. All except 1 pts received target CAR-T dose. The day 28 ORR was 82% (CR=7, PR=2). After a median follow up of 13 mo, 3 pts died (PD, Covid, Guillain Barre). The median PFS and OS were both 30.8 mo while the 1-year PFS and OS rates were 9 and 15 mo respectively. 9 pts had CRS and 2 had ICANS, all grades 1-2, while 4 had IEC-HS. One pt had afib recurrence and 1 pt had CMV viremia within 30 days of CAR-T. Among the pts with immunophenotypic data (n=10), there were no differences in naïve or more differentiated T-cell percentages in apheresis and final CAR-T products when compared to pts who did not receive pirto before LV20.19 CAR-T (n=57). Although not statistically significant, both PFA (CD4=61.8 vs 59, CD8= 49.8 vs 46.9) and PSI (CD4= 1752 vs 1608, CD8=1299 vs 1079) were higher with pirto pre-treated pts, suggesting a potential trend towards improved CAR-T functionality. **Conclusions:** These data represent the largest experience of pirto prior to CAR-T apheresis and demonstrate that pirto can be safely used as a bridge to LV20.19 CAR-T without negatively impacting their immunophenotype and potentially improving functionality. These data support our planned phase 1 clinical trial to assess the safety of pirto as bridging and maintenance therapy with LV20.19 CAR-T (NCT05990465). Research Sponsor: None.

Pt #	1	2	3	4	5	6	7	8	9	10	11
Disease	MZL	MCL	RT	MCL	RT	MCL	RT	MCL	RT	CLL	DLBCL
Age /Sex	80/M	65/M	65/F	50/M	65/M	62/M	55/M	55/F	79/F	68/M	59/M
Prior lines of therapy	7	4	6	4	3	5	8	2	3	7	3
CRS grade	1	1	1	2	2	0	1	1	1	1	0
ICANS grade	0	0	0	0	1	0	0	1	0	0	0
IEC-HS	N	N	Y	N	Y	N	N	Y	N	Y	N
Day 28 response	PD	CR	PR	CR	CR	CR	CR	CR	PR	SD	CR
CAR-T DOR (mo)	NA	38.2	14.8	30.8	5.8	15.2	9.2	9.2	2	NA	1.1
Alive (Y/N)/ Follow-up (mo)	Y/43.7	Y/43	N/14.8	N/ 30.8	N/12.2	Y/15.2	Y/9.2	Y/9.2	Y/2	Y/1.4	Y/1.1

Factors associated with manufacturing failure of commercial CD19 CAR-T cell products for large b cell lymphoma (LBCL).

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Background: As CD19 chimeric antigen receptor T-cell (CAR-T) therapy has shown curative potential in patients (pts) with relapsed/refractory (R/R) LBCL, indications for treatment are expanding. The reported manufacturing failure rate was 1-13% in clinical trials, but there is poor understanding of out-of-specification (OOS) products and CAR-T products on 2nd apheresis. This study aims to characterize factors associated with successful manufacturing. **Methods:** This study includes pts with R/R LBCL who underwent apheresis for CAR-T product between 12/2017 and 2/2023. Baseline variables were obtained at time of apheresis. OOS product is defined as not meeting eligibility for a commercial product but suitable for infusion on expanded access protocol. 2nd apheresis was performed due to initial manufacture failure. Progression-free survival (PFS) is the time from CAR-T conditioning to disease progression or death, whichever occurs first. Overall survival (OS) is defined as time from conditioning to death or last follow-up. A chi-square test or Fisher's exact test was used for comparison of 2 categorical variables. **Results:** 319 pts underwent apheresis; 261(78%) were axicabtagene ciloleucel, 26(8%) were tisagenlecleucel and 47(14%) were lisocabtagene maraleucel 284(85%); products were in-specification (in-spec) on 1st apheresis, 8(2%) in-spec on 2nd apheresis, 27(8%) OOS, and 15(4%) manufacturing failures. Comparison of variables are in the table. OOS rates were 10/250(4%) for axicabtagene, 4/23(17.4%) for tisagenlecleucel and 13/46(28.3%) for lisocabtagene. Reason for OOS product were low viability:14, high interferon:4, internal manufacturing issue:2, CD4 lineage purity:2, high transduction:1, low transduction:2, and low vector copies:2. No association was found with clinical factors and OOS. Factors associated with OOS were advanced stage (P=0.012), IPI score >3 (p=0.001), extranodal involvement (P=0.012) and older age (p= 0.002). In-spec product on 1st apheresis had greater OS (p= 0.011) and PFS (p=0.043) than 2nd apheresis. **Conclusions:** Factors predictive of OOS product include older age, advanced disease, extranodal involvement and high IPI. Pts requiring 2nd apheresis had worse survival. Lisocabtagene had higher likelihood for OOS product. Outcomes for OOS products are not well described. Failure to manufacture an eligible product is a barrier for LBCL pts to receive CAR-T therapy. Research Sponsor: None.

Median Baseline Clinical Variables	In-Spec (n=292)	OOS (n=27)	P-Value
Age	61.5	74	**.002**
Sex, male	193	24	**.017**
ECOG PS >2	55	9	.072
Stage III-IV	242	27	**.012**
Extranodal Sites >1	179	23	**.013**
IPI >3	185	25	**.001**
Prior lines, >3	235	19	.212
CAR-T Product			
Axicabtagene ciloleucel	240 (82.2%)	10 (37%)	
Tisagenlecleucel	19 (6.5%)	4 (14.8%)	
Lisocabtagene maraleucel	33(11.3%)	13 (48.1%)	

Key: ECOG PS: Eastern Cooperative Oncology Group performance status, IPI: International Prognostic Index.

Real world incidence, prevention, and management of tumor lysis syndrome in patients with chronic lymphocytic leukemia treated with venetoclax in the inpatient and outpatient settings.

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Background: Venetoclax (ven) is a BCL2 inhibitor used for the treatment (tx) of chronic lymphocytic leukemia (CLL) which can cause clinical or laboratory (lab) tumor lysis syndrome (TLS). A dose ramp-up schedule and prophylaxis strategies are incorporated into NCCN guidelines and prescribing information. Prior reports have of TLS focused mostly on patients (pts) with relapsed/refractory CLL receiving ven as monotherapy. **Methods:** We included pts >18y who were diagnosed with CLL or small lymphocytic lymphoma (SLL) and received tx with commercial ven in any line of therapy at our institution from 1/1/2016 to 12/31/2020. TLS was defined using the modified Cairo Bishop Criteria. TLS risk was based on the size of the largest lymph node (LN) on imaging or examination and the absolute lymphocyte count (ALC) as defined by ven prescribing information. **Results:** We included 616 ven escalations among 136 pts with CLL. Median age was 70 years and 86% were white. Ven was part of first line of tx for 48 pts (35%). 11% had high TLS risk at baseline; 37% among those escalated exclusively inpatient (IP) and 2% among those escalated exclusively outpatient (OP). Among those treated with ven, 47 pts (35%) received ven monotherapy. 74 (54%) of pts were escalated exclusively OP, 35 (26%) had at least one prophylactic hospitalization and 27 (20%) were escalated exclusively IP. During ven initiation, 86% of pts received allopurinol, 71% intravenous hydration, 18% phosphate binders, and 10% prophylactic rasburicase. Among the entire cohort, 8 pts (5.9%) developed lab TLS and zero developed clinical TLS. There were 11 TLS events; 2 pts developed TLS in more than one escalation. Incidence of TLS was 15% for those escalated exclusively IP, 5.7% for those with any prophylactic hospitalization and 2.7% for those escalated exclusively OP. Those who developed TLS were more likely to have a higher TLS risk at baseline, preceding isolated hyperuricemia, or CrCl measurement < 60 mL/min (Table). **Conclusions:** In this single institution retrospective cohort study, lab TLS was observed, though clinical TLS was not. Baseline hyperuricemia and impaired renal function were more common among those who developed lab TLS compared to those who did not. Prophylactic measures, including use of IV hydration, may have contributed to low rates of observed TLS in the outpatient setting. Research Sponsor: Sanofi.

Characteristic	Overall, N = 136[1]	Occurrence of TLS Yes, N = 8[2]	No, N = 128[2]	p-value[3]
TLS Risk				**0.001**
Low	57	0 (0%)	57 (100%)	
Medium	21	1 (4.8%)	20 (95%)	
High	10	3 (30%)	7 (70%)	
Unknown	48	4	44	
Site for Ven Escalations				0.071
All IP	27	4 (15%)	23 (85%)	
Any IP	35	2 (5.7%)	33 (94%)	
OP	74	2 (2.7%)	72 (97%)	
Ven As Front-Line TX	48	2	46	0.7
Concurrent Medication				0.11
Ritux	16	0	16	
Obinutuzumab	66	3	63	
Ibrutinib	7	2	5	
None	47	3	44	
Isolated Hyperuricemia	15	4	11	**0.005**
CrCl ≤ 60 At Least Once	36	6	30	**0.004**

[1]n
[2]n (%); n
[3]Fisher's exact test.

Evaluating CR as a surrogate endpoint for PFS in R/R chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): A meta-analysis of randomized controlled trials (RCT).

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Background: CLL/SLL is the most common leukemia in adults. Achieving a CR by International Workshop on CLL 2018 criteria indicates complete eradication of CLL/SLL in all disease compartments. Patients with R/R CLL/SLL who achieved CR tend to have delayed disease progression/death compared with patients who did not achieve CR. This is the first report to evaluate CR as a surrogate endpoint for PFS in R/R CLL/SLL using aggregate RCT data. **Methods:** A systematic literature review (SLR) identified published RCTs in R/R CLL/SLL from inception to 10/2023, reporting nonzero CR rates (CRR) and PFS. Association between treatment effects on CR and PFS across RCTs was estimated using a weighted linear model (WLM) in the primary analysis, and Daniels and Hughes (D&H) and Riley bivariate random-effects meta-analysis (BRMA) in sensitivity analyses. Strength of association was assessed based on surrogacy criteria described by D&H. Predictive performance of models was evaluated using leave-one-out cross-validation. **Results:** The SLR identified 13 RCTs with a total of 4388 patients with R/R CLL/SLL treated with a variety of therapies, including but not limited to BTKi, BCL2i, PI3Ki, CAR T cell therapy, anti-CD20 mAb, and chemotherapy. Across the evidence base, CRR ranged from 0.48% to 38.10% and median PFS was between 1 and 35.9 months (excluding unreached medians). Across RCTs, contrasting treatment and control arms, higher odds of CR resulted in lower hazards of disease progression/death (CRR improvement translated to PFS benefit). D&H surrogacy criteria were met for WLM: 1) a near-zero, statistically nonsignificant intercept, indicating that no treatment effect on CRR implies no effect on PFS; 2) a negative, statistically significant slope, suggesting that improved CRR correlates with longer PFS; and 3) a near-zero conditional variance, meaning that PFS HR variation was primarily explained by CR odds ratio. During cross-validation, treatment effects on CR were predictive of PFS benefits, as the 95% predictive interval of PFS HR contained the observed HR in all RCTs for WLM. Results were largely consistent across all 3 models(Table). **Conclusions:** Improved CRR corresponds to prolonged PFS across RCTs and treatment comparisons. The results support CRR as an important treatment goal for R/R CLL/SLL and a valid surrogate endpoint. Consistent results and predictive performance across different models indicate the robustness of the results. Research Sponsor: This study was funded by BMS. All authors contributed to and approved the abstract; writing and editorial assistance were provided by Nikola Vojtov, PhD, of The Lockwood Group (Stamford, CT, USA), funded by BMS.

Summary results for CR–PFS correlation.

Model	R^2 (95% CI)	Intercept (95% CI)	Slope/Surrogate Effect (95% CI)	Conditional Variance (95% CI)
WLM	0.41 (0.11, 0.76)	0.05 (−0.64, 0.54)	−0.64 (−1.14, −0.13)	0.49 (residual standard error)
D&H	Not applicable	−0.07 (−0.74, 0.60)	−0.52 (−1.06, 0.03)	0.25 (0.05, 0.68)
BRMA	0.49 (0.06, 0.81)	0.18 (−0.43, 1.08)	−0.76 (−1.54, −0.23)	0.15 (0.05, 0.34)

Association between treatment (tx) response and PFS and OS in R/R chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL): A 12-month landmark (LM) meta-analysis.

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Background: Despite advances in tx for CLL/SLL, CRs are rarely observed after tx in the R/R setting, thus impacting long-term outcomes. We evaluated the association between response after tx and survival outcomes in patients (pt) with R/R CLL/SLL. **Methods:** Adults with R/R CLL/SLL and ≥ 1 prior line of therapy (LOT) from 6 clinical trials (initiated after 01/01/2012 and completed before 12/31/2022) were sourced from the Medidata Enterprise Data Store. Cox models adjusted for potential prognostic factors were used to assess pt-level associations between achieving and maintaining a CR or CR with incomplete bone marrow recovery (CRi) by 12 mo after start of tx (LM date) and PFS and OS. In separate LM analyses (LMA), associations between achieving and maintaining CR/CRi, PR/nodular PR (nPR) by LM, or non-CR/non-PR (ie, those not achieving or maintaining CR/CRi or PR/nPR or not evaluated by LM), and PFS and OS were assessed. **Results:** Of 1604 pts (CLL, 97.7%; SLL, 2.3%; age ≥ 65 y, 61.8%; male, 66.6%; ECOG PS 0–1/2, 93.2%/6.8%; median [IQR] follow-up, 3.4 y [2.2–4.1]; median [IQR] LOT, 2 [1–3]; study tx, BTKi [40.4%], BCL2i [40.1%], anti-CD20 mAb [12.5%], and PI3Ki [9.9%]), 15.1% and 61.7% achieved a best overall response of CR/CRi and PR/nPR, respectively (ORR, 76.8%); 6.8% of pts had no response recorded in follow-up. A total of 1178 pts without progression, death, or censoring before LM were included in PFS LMA. Median (95% CI) PFS from LM was 64.4 mo (61.7–not reached [NR]) for CR/CRi, 43.3 mo (38.8–54.7) for PR/nPR, and 23.9 mo (18.3–50.6) for non-CR/non-PR. Pts who achieved and maintained CR/CRi had significantly longer PFS versus both non-CR/CRi and PR/nPR pts, with adjusted HR of 0.62 (P = 0.01) and 0.64 (P = 0.02), respectively (Table). For OS LMA, 1404 pts without death or censoring before LM were included. Median (95% CI) OS from LM was NR for CR/CRi and PR/nPR groups and 62.9 mo (51.2–NR) for non-CR/non-PR. At 24 mo from LM, 90% (85%–95%) CR/CRi, 87% (84%–89%) PR/nPR, and 72% (67%–77%) non-CR/non-PR pts were still alive. CR/CRi pts or PR/nPR pts had significantly longer PFS and OS versus non-CR/non-PR pts. **Conclusions:** We demonstrated that achieving and maintaining CR/CRi by 12 mo after start of tx was associated with significantly improved PFS versus achieving and maintaining PR/nPR, which was also better than not achieving/maintaining any response. These findings support the potential utility of durable CR/CRi as an informative early endpoint for assessing the value of tx in pts with R/R CLL/SLL. Adjusted HR (95% CI) Research Sponsor: This study was funded by BMS. All authors contributed to and approved the abstract; writing and editorial assistance were provided by Nikola Vojtov, PhD, of The Lockwood Group (Stamford, CT, USA), funded by BMS.

Response by LM	PFS (n = 1178)	OS (n = 1404)
CR/CRi (vs non-CR/CRi)	0.62 (0.42–0.90)[a]	0.73 (0.47–1.12)[b]
CR/CRi (vs PR/nPR)	0.64 (0.44–0.93)[c]	0.77 (0.51–1.18)[d]
CR/CRi (vs non-CR/non-PR)	0.41 (0.27–0.64)[e]	0.39 (0.25–0.60)[e]
PR/nPR (vs non-CR/non-PR)	0.65 (0.50–0.84)[e]	0.50 (0.40–0.63)[e]

[a] P = 0.01;
[b] P = 0.15;
[c] P = 0.02;
[d] P = 0.24;
[e] $P < 0.001$.

Comparative efficacy of Bruton tyrosine kinase inhibitors in the treatment of relapsed/refractory chronic lymphocytic leukemia: A network meta-analysis (NMA).

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Background: Next-generation Bruton's tyrosine kinase inhibitors (BTKis) have led to changes in the treatment algorithm for patients with high-risk relapsed/refractory (R/R) CLL; defined based on the presence of genetic mutations and a high unmet need. Given the lack of head-to-head trials comparing these treatments in R/R CLL, a NMA was performed to estimate the relative efficacy of BTKis used to treat high-risk patients. **Methods:** Randomized controlled trials ALPINE (zanubrutinib vs. ibrutinib), ELEVATE-RR (acalabrutinib vs. ibrutinib), and ASCEND (acalabrutinib vs. bendamustine + rituximab/idelalisib + rituximab [BR/IR]) were included in the NMA. High-risk populations were defined based on the pre-specified subgroups within each trial, including patients with del17p and/or TP53 mutations in ALPINE (zanubrutinib: 75/327 and ibrutinib: 75/325), ASCEND (acalabrutinib: 44/155 and BR/IR: 42/155), and del17p/del11q in ELEVATE-RR (acalabrutinib: 268/268 and ibrutinib: 265/265). Bayesian NMAs were used to estimate hazard ratios (HRs) or odds ratios (ORs) with 95% credible intervals (CrIs), and probability better (PB) for zanubrutinib versus all other treatments. Outcomes analysed included investigator-assessed progression-free survival (PFS), overall survival (OS), overall response (ORR), and complete response (CR). Given the timing of the included trials in relation to the COVID-19 pandemic, ALPINE data were analyzed with and without adjustment for COVID-19 related deaths. **Results:** The NMA found a statistically significant improvement in PFS for zanubrutinib over acalabrutinib in high-risk patients and a trend towards improvement in OS, ORR, and CR (Table). Zanubrutinib led to statistically significant improvements in PFS versus ibrutinib (HR [95% CrI]: 0.49 [0.30, 0.78], PB: 99.9%) and BR/IR (0.12 [0.05, 0.26], PB: 100.0%). For OS, zanubrutinib showed a trend towards improvement versus ibrutinib (0.59 [0.31, 1.12] PB: 94.8%) and BR/IR (0.64 [0.24, 1.74] PB: 80.7%). **Conclusions:** This NMA found zanubrutinib to be the most efficacious BTKi for patients with high-risk R/R CLL, offering significantly delayed disease progression, and favourable survival and response vs. alternative BTKi treatments. Research Sponsor: BeiGene.

Zanubrutinib vs. Acalabrutinib	High-Risk With COVID-19 Adjustment	High-Risk Without COVID-19 Adjustment
HR [95%CrI], Probability Better (%)		
PFS	0.54 [0.32, 0.92], 98.6	0.58 [0.34, 0.98], 98.0
OS	0.72 [0.35, 1.48], 81.7	0.84 (0.43, 1.65), 69.1
OR [95%CrI], Probability Better (%)		
ORR	1.91 [0.75, 5.00], 91.7	1.69 [0.61, 4.97], 84.4
CR	2.07 [0.50, 9.67], 84.4	1.84 [0.50, 7.20], 81.6

Efficacy of pembrolizumab monotherapy and in combination with BCR inhibitors for Richter transformation of chronic lymphocytic leukemia (CLL).

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Background: The management of Richter transformation (RT) of CLL represents an unmet clinical need. We previously reported modest efficacy of pembrolizumab monotherapy in an initial cohort of patients with RT (Ding, et al, Blood 2017). Here we report updated results of this trial, including an expansion cohort and a combination therapy cohort. **Methods:** Patients with biopsy proven RT to diffuse large B-cell lymphoma were enrolled and treated with single agent pembrolizumab (200 mg IV Q3W). Patients with progressive disease (PD) or stable disease (SD) after 3 months of pembrolizumab monotherapy were allowed to add a B-cell receptor (BCR) kinase inhibitor. The primary end point was overall response rate (ORR). **Results:** A total of 26 patients with RT were enrolled (9 in initial cohort and 17 in expansion cohort). The median age was 68.5 years. Ten (38%) patients had del(17p) or *TP53* mutation. The median number of prior lines of therapy was 3 (range 1-10). Fifteen (58%) patients had received ibrutinib previously (14 of whom had PD on ibrutinib). With pembrolizumab monotherapy (n=26), the ORR was 23.1%, with 2 (7.7%) complete response (CR), 4 (15.4%) partial response (PR), and 7 (26.9%) SD. Of the 6 patients with confirmed CR or PR, responses occurred after a median of 2 cycles of monotherapy. The median duration of response (DOR) was 3.2 months (95% CI 2.8-NA). The median progression-free survival (PFS) was 2.6 months (95% CI 1.6-3.6). Sixteen patients went on to receive a BCR kinase inhibitor (ibrutinib [n=15], idelalisib [n=1]) in combination with pembrolizumab, after SD or PD on pembrolizumab monotherapy. The ORR to combination therapy was 62.5%, with 4 (25.0%) CR and 6 (37.5%) PR. Of the 10 patients with confirmed CR or PR to combination therapy, responses occurred after a median of 4 cycles of therapy. The median DOR was 4.5 months (95% CI 1.6-NA). The median PFS was 7.6 months (95% CI 2.3-13.3). After a median follow-up of 50.4 (95% CI 34.0-56.0) months, the median overall survival (OS) for all 26 patients with RT was 11.6 months (95% CI 7.5-20.1), and the 2-year OS rate was 27%. Treatment-related adverse events (TRAEs) of any grade occurred in 24 (92%) patients, including anemia (54%), thrombocytopenia (58%), neutropenia (54%), leukopenia (35%), lymphopenia (23%), dyspnea (23%), diarrhea (19%), and nausea (23%). Treatment-related grade 3 or above AEs occurred in 21 (81%) patients, including neutropenia (38%), leukopenia (31%), thrombocytopenia (27%), anemia (15%), febrile neutropenia (12%), and lung infection (12%). **Conclusions:** This expanded analysis confirmed that pembrolizumab has modest single agent activity in RT. Combination therapy with pembrolizumab and a BCR kinase inhibitor is associated with increased efficacy (ORR >60%), similar to other reports. These results support further investigation of immune checkpoint inhibitor-based combination therapy in RT. Clinical trial information: NCT02332980. Research Sponsor: Merck.

A single-cell multiomics analysis of IRF4 in mediating treatment resistance in ibrutinib-treated chronic lymphocytic leukemia (CLL).

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Background: The Bruton tyrosine kinase (BTK) inhibitor ibrutinib (ibr) has revolutionized the treatment of CLL, showing efficacy in the majority of patients. Nevertheless, resistance occurs in a subset of patients, often with dismal clinical outcomes. Ibr resistance occurs through several mechanisms, including mutations affecting *BTK* or *PLCG2*, or upregulation of alternative survival pathways. We investigated at the single-cell level the molecular mechanisms that underlie ibr resistance in CLL cells and their interactions with non-malignant tumor microenvironment (TME) cell populations. **Methods:** We retrospectively identified 7 CLL patients with ibr resistance (as second line therapy). Samples were obtained before ibr treatment and at progression. Chromium Single Cell Multiome ATAC + Gene Expression (GEX) (10x Genomics) was applied to a mixture of CD19+CD5+ and CD19- cells to jointly analyze DNA accessibility and gene expression in the same single nuclei of CLL B and TME cells. An average of 4,800 cells (range 2,600-15,000) per sample was retained after QC filtering. Principal component analysis (PCA) was performed on GEX counts. ATAC peaks were called with MACS2, and latent semantic indexing was used for dimensionality reduction. We then computed a weighted nearest neighbour graph, identified clusters using the SLM algorithm and performed cell type assignment with established marker genes. **Results:** We identified 28 distinct cell clusters, representing CLL B-cells or cell types that constitute the TME, including CD4+ and CD8+ T cells, monocytes, dendritic and NK cells. CLL B-cell clusters were patient and timepoint-specific, while TME clusters were occupied by cells from multiple patients. Five patients showed multiple distinct CLL B-cell clusters pre-treatment or at progression, reflecting cellular heterogeneity within the tumor compartment. Interestingly, some clusters that were dominated by post-treatment CLL B-cells also included cells from pre-treatment samples, suggesting pre-existence of the clone giving rise to the relapse. For each patient, we performed pairwise differential expression between CLL B-cell clusters. Gene ontology analysis revealed increased activation of IRF4 and MHC-related pathways in CLL B-cells at progression compared to pre-treatment in 6 and 4 out of 7 patients, respectively. The elevated IRF4 pathway activity was underpinned by increased chromatin accessibility in IRF4 signature genes. **Conclusions:** Differential blockade of B-cell receptor signaling by ibr has been reported to downregulate activity of IRF4, a key transcription factor in B-cell activation. Our results suggest that CLL B-cells that are resistant to ibrutinib have re-activated IRF4 activity beyond pre-treatment levels, implying a potential role for IRF4 in ibrutinib resistance. Research Sponsor: Genome BC/ Genome Canada; Michael Smith Foundation for Health Research.

Real-world risk of bleeding events in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) treated with BTKi.

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Background: Bruton tyrosine kinase inhibitors (BTKis) are effective treatments for various B-cell malignancies including CLL/SLL but are known to be associated with increased bleeding risk. Current evidence indicating this association has largely been demonstrated in clinical trial research. However, bleeding risk in real-world CLL/SLL patients, who are often sicker with more comorbidities requiring anticoagulant (AC) or antiplatelet (AP) use is not well described. This study aimed to assess the prevalence of AC/AP use and explore risk factors for bleeding among real-world CLL/SLL patients receiving BTKi therapies. **Methods:** We conducted a retrospective cohort study using the claims-linked Premier PINC AI Healthcare Database of patients aged ≥18 years with a diagnosis of CLL/SLL from July 1, 2016 to March 31, 2022. Patients were followed from first BTKi prescription fill (index date) to earliest of BTKi discontinuation, death, or end of the study period. Patient comorbidities, treatments, and bleeding events were assessed using diagnosis and procedure codes and prescription claims. Multivariable-adjusted risk for bleeding events was assessed with Cox proportional-hazards regression. **Results:** Among 2091 patients with CLL/SLL receiving BTKi therapies, mean age was 65.7 years, 61.8% were men, and 77.7% were White. BTKi treatments included ibrutinib (86.3%), acalabrutinib (13.1%), and zanubrutinib (<1%). Overall, 4.3% of patients switched BTKis during follow-up; 615 (29.4%) had AC/AP use at any time during the study period, of whom 411 (66.8%) started after BTKi initiation. Bleeding events occurred in 526 (25.2%) patients during a mean BTKi exposure of 14.2 months, with an incidence of 26.6 per 100 person-years (PYs) overall, and 37.2 and 22.0 per 100 PYs in patients with and without any prescription AC/AP use, respectively. The proportion of patients with fatal bleeding was <0.3%. In adjusted models, risk of first bleeding event was higher for AC use (HR [95% CI] 2.33 [1.83–2.98]), age ≥65 years (1.32 [1.14–1.53]), women (1.28 [1.10–1.48]), and history (during 90 days prior to BTKi start) of bleeding (2.27 [1.87–2.76]), ulcers (2.21 [1.06–4.63]) or myocardial infarction (MI) (1.74 [1.31–2.33]) (all $P \leq 0.05$). Prescription AP use, race/ethnicity, and history of chronic kidney disease or thrombocytopenia were not statistically significant. **Conclusions:** In this large real-world study of bleeding risk in patients receiving BTKis, bleeding events occurred in 26.6 per 100 patients per year, with higher risk in AC users, women, and patients with history of bleeding, ulcers, or MI. However, the risk of fatal bleeding was low. Research Sponsor: AstraZeneca.

Seven-year overall survival analysis from ECHELON-1 study of A+AVD versus ABVD in patients with previously untreated stage III/IV classical Hodgkin lymphoma.

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Background: In ECHELON-1 (NCT01712490), 6-year follow-up (FU) analyses demonstrated significant improvements in overall survival (OS) and progression-free survival (PFS) with A+AVD (brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine) versus ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), with a comparable safety profile. Here, we report data at 7-year median FU. **Methods:** Analyses of OS and PFS per investigator were conducted in the intent-to-treat (ITT) population (data cut-off March 11, 2023). Patients (pts) were randomized 1:1 to receive ≤6 cycles of A+AVD (n=664) or ABVD (n=670) on days 1 and 15, every 28 days. PET scan after cycle 2 (PET2) evaluation was mandatory. Long-term safety outcomes in the safety population included resolution or improvement of peripheral neuropathy (PN), second malignancies, and pregnancies. **Results:** At median FU of 89.3 months (95% CI 87.0–90.2), 7-year OS rates were 93.5% (95% CI 91.1–95.2) with A+AVD and 88.8% (95% CI 85.8–91.1) with ABVD; OS favored A+AVD over ABVD (HR 0.62; 95% CI 0.42–0.90; p=0.011). Subgroup analyses showed consistent OS benefit for A+AVD, including in the age <40 years and Stage IV disease subgroups (Table). 7-year PFS rates with A+AVD vs ABVD were 82.3% (95% CI 79.1–85.0) vs 74.5% (95% CI 70.8–77.7; HR 0.68 [95% CI 0.53–0.86]; p=0.001). PN improved/resolved in most pts at last FU (A+AVD: 86%; ABVD: 87%). Median (range) time to complete resolution of PN (A+AVD vs ABVD) was 16 (0–373) vs 10 (0–343) weeks; median (range) time to improvement was 42 (2–182) vs 19 (15–142) weeks. PN was ongoing in 28% (4% grade ≥3) of A+AVD and 20% (1% grade ≥3) of ABVD pts. Second malignancies were reported in 5% of A+AVD and 6% of ABVD pts. Pts and their partners reported 84/92 livebirths/pregnancies with A+AVD and 59/73 with ABVD; no stillbirths were recorded. **Conclusions:** At 7-year median FU, pts with stage III/IV cHL who received A+AVD showed a sustained PFS and OS benefit vs ABVD, with PFS rates indicating potential curability. The safety profile in pts treated with A+AVD showed no new safety signals at 7 years. Clinical trial information: NCT01712490. Research Sponsor: Takeda Development Center Americas, Inc. (TDCA), Lexington, MA, USA.

7-year OS rates by subgroup (ITT).

Group, % (95% CI)	A+AVD OS Rate, % (95% CI) n=664	ABVD OS Rate, % (95% CI) n=670	HR (95% CI) p-value
All pts	93.5 (91.1–95.2) n=664	88.8 (85.8–91.1) n=670	0.62 (0.42–0.90) 0.01
PET2 negative	95.0 (92.8–96.6) n=588	90.2 (87.2–92.5) n=577	0.57 (0.37–0.87) 0.009
PET2 positive	90.7 (72.3–97.1) n=47	74.0 (59.9–83.8) n=58	0.34 (0.11–1.03) 0.05
Aged <40 years	98.2 (96.2–99.1) n=396	95.0 (91.9–96.9) n=375	0.39 (0.16–0.95) 0.032
Aged <60 years	96.4 (94.4–97.7) n=580	92.9 (90.3–94.9) n=568	0.49 (0.29–0.83) 0.007
Aged ≥60 years	72.6 (60.6–81.5) n=84	66.7 (55.9–75.5) n=102	1.01 (0.59–1.71) 0.98
Stage III	92.1 (87.6–95.1) n=237	90.3 (85.3–93.7) n=246	1.01 (0.54–1.87) 0.98
Stage IV	94.2 (91.3–96.2) n=425	88.1 (84.3–91.0) n=421	0.49 (0.30–0.79) 0.003

7055 Poster Session

A phase 1/2 study of favezelimab in combination with pembrolizumab for anti–PD-1–naive relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL): An updated analysis.

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Background: PD-1 inhibitors such as pembrolizumab are an important treatment option for patients (pts) with R/R cHL, but treatment failure remains a significant challenge. Dual immune checkpoint blockade with a PD-1 inhibitor and a lymphocyte-activation gene 3 (LAG-3) inhibitor shows promise as a treatment option for R/R cHL. In a multicohort phase 1/2 study (NCT03598608) evaluating the anti–LAG-3 monoclonal antibody favezelimab in combination with pembrolizumab for R/R hematologic malignancies, pembrolizumab plus favezelimab demonstrated sustained antitumor activity and acceptable safety in the cohort of pts with anti–PD-1–naive R/R cHL (cohort 1). We present updated results from this cohort after additional follow-up. **Methods:** Eligible pts were aged ≥18 years with R/R cHL; prior treatment with or ineligibility for autologous stem cell transplantation or no response to salvage chemotherapy; no prior PD-1 inhibitor; and an ECOG PS of 0 or 1. The study comprised a safety lead-in (pembrolizumab 200 mg IV Q3W plus favezelimab 200-mg starting dose, then dose escalation to 800 mg IV Q3W using a modified toxicity probability interval method) and a dose expansion phase (pembrolizumab 200 mg Q3W plus favezelimab at the established recommended phase 2 dose of 800 mg Q3W for up to 35 cycles). Primary end point was safety. Objective response rate (ORR) per IWG 2007 criteria by investigator review was a secondary end point. Duration of response (DOR) and progression-free survival (PFS) per IWG 2007 criteria by investigator review and overall survival (OS) were exploratory. **Results:** Cohort 1 enrolled 30 pts. The median time from first dose to data cutoff (August 15, 2023) was 36.9 months (range, 29.4-48.6). Treatment-related adverse events (AEs) occurred in 27 pts (90%), of which the most common (≥20%) were hypothyroidism (27%), infusion-related reaction (23%), and fatigue (20%). Grade 3 or 4 treatment-related AEs occurred in 7 pts (23%). Five pts (17%) discontinued treatment due to treatment-related AEs. No deaths due to treatment-related AEs were reported. AEs of clinical interest occurred in 20 pts (67%); 3 pts (10%) had grade 3 events (colitis, pneumonitis, severe skin reaction) and 1 pt (3%) had a grade 4 event (hepatitis). The ORR was 83% (n = 25; 95% CI, 65-94); 11 pts (37%) had a complete response and 14 (47%) had a partial response. Median DOR was 17.0 months (range, 2.6-30.5), and an estimated 47% of responders remained in response at 24 months. Median PFS was 19.4 months (95% CI, 9.5-28.5), and the 24-month PFS rate was 46%. Median OS was not reached (NR; 95% CI, NR-NR), and the 24-month OS rate was 93%. **Conclusions:** With additional follow-up, favezelimab plus pembrolizumab continued to demonstrate sustained antitumor activity and manageable safety in pts with anti–PD-1–naive R/R cHL. Further studies to investigate this combination are warranted. Clinical trial information: NCT03598608. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

A phase 1/2 study of favezelimab in combination with pembrolizumab for heavily pretreated anti–PD-1–refractory classical Hodgkin lymphoma (cHL): An updated analysis.

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Background: PD-1 inhibitors are standard of care for relapsed or refractory (R/R) cHL, but patients (pts) often progress after anti–PD-1 therapy. The immune checkpoint receptor lymphocyte-activation gene 3 (LAG-3) is proposed to contribute to anti–PD-1 resistance. In a phase 1/2 study (NCT03598608) evaluating favezelimab (anti–LAG-3) plus pembrolizumab (anti–PD-1) for R/R hematologic malignancies, the combination provided antitumor activity and manageable safety in pts with heavily pretreated anti–PD-1–refractory cHL (cohort 2). Updated results after additional follow-up are presented. **Methods:** Eligible pts were aged ≥18 years with R/R cHL; prior treatment with or ineligibility for autologous stem cell transplantation or no response to salvage chemotherapy; an ECOG performance status of 0 or 1; and disease progression after ≥2 doses of anti–PD-1–based therapy and within 12 weeks of the last dose of anti–PD-1 therapy. The study comprised a safety lead-in (pembrolizumab 200 mg IV Q3W + favezelimab 200-mg starting dose, then dose escalation to 800 mg IV Q3W per a modified toxicity probability interval design) and a dose expansion phase (pembrolizumab + favezelimab at the established recommended phase 2 dose of 800 mg Q3W for ≤35 cycles). Primary end point was safety. ORR per IWG 2007 criteria by investigator review was a secondary end point. DOR and PFS per IWG 2007 criteria by investigator review and OS were exploratory. **Results:** Cohort 2 enrolled 34 pts. Median time from first dose to data cutoff (August 15, 2023) was 40.7 months (range, 20.4-54.8). Treatment-related AEs occurred in 28 pts (82%); the most common (≥15%) were hypothyroidism (18%), nausea (18%), and fatigue (15%). Grade 3 or 4 treatment-related AEs occurred in 6 pts (18%). Discontinuation due to treatment-related AEs occurred in 6 pts (18%). No deaths due to treatment-related AEs were reported. AEs of clinical interest occurred in 17 pts (50%); 2 pts (6%) had grade 3 events (encephalitis, hepatitis) and 1 pt (3%) had a grade 4 event (type 1 diabetes mellitus). ORR was 29% (10/34; 95% CI, 15-48), with 3 (9%) complete responses and 7 (21%) partial responses. ORR was 35% (6/17; 95% CI, 14-62) in pts with anti–PD-1 and 24% (4/17; 95% CI, 7-50) in pts with non–anti–PD-1 as most recent therapy. Median DOR was 21.9 months (range, 0.0+ to 26.1+) and an estimated 17% of responders remained in response at 24 months. Median PFS was 9.7 months (95% CI, 5.1-14.7); 24-month PFS rate was 21%. Median OS was 39.0 months (95% CI, 25.7-not reached); 24-month OS rate was 73%. **Conclusions:** After additional follow-up, favezelimab + pembrolizumab continued to demonstrate manageable safety and antitumor activity in pts with heavily pretreated anti–PD-1–refractory cHL. The phase 3 KEYFORM-008 study (NCT05508867) will evaluate a coformulation of favezelimab and pembrolizumab in pts with anti–PD-1–refractory cHL. Clinical trial information: NCT03598608. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

A novel and selective oral PI3Kα/δ inhibitor, TQ-B3525, in patients with relapsed and/or refractory follicular lymphoma: A phase II, single-arm, open-label study.

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Background: TQ-B3525 is a novel and selective oral PI3K α/δ inhibitor. In an earlier Phase I trial, TQ-B3525 achieved outstanding efficacy in subjects with refractory/relapsed follicular lymphoma (R/R FL) (2020 ASCO Abstract #8058). Here, we report the result from a single-arm, open-label, phase II registration study evaluating the safety and efficacy of TQ-B3525 in R/R FL patients. **Methods:** This phase II study included exploratory stage 1 and confirmatory stage 2. Patients with R/R FL after ≥2 lines therapies received oral 20 mg TQ-B3525 once daily in a 28-day cycle until disease progression or intolerable toxicity. Primary endpoint was independent review committee (IRC)-assessed objective response rate (ORR). Secondary endpoints were ORR by investigator assessment; the IRC- and investigator-assessed disease control rate (DCR), time to response (TTR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Based on results (ORR, 88.0%; DOR, 11.8 months; PFS, 12.0 months) in 25 patients at stage 1, second stage study was initiated and included 82 patients for efficacy/safety analysis.Patients received a median of 3 prior lines, with 56.1% refractory to previous therapies; 73.2% experienced POD24 at baseline. At stage 2, ORR was 86.6% (71/82; 95% CI, 77.3%-93.1%), with 28 (34.2%) complete responses. Seven (8.5%) had stable disease for DCR of 95.1%. Median TTR was 1.8 months. Among 71 responders, median DOR was not reached; 18-month DOR rate was 51.6%. At median follow-up of 13.3 months, median PFS was 18.5 (95% CI, 10.2-not estimable) months; estimated 24-month OS rate was 86.1%. Response rates and survival data were consistent across all subgroups. Grade 3 or higher treatment-related adverse events occurred in 63 (76.8%) patients, with neutrophil count decreased (22.0%), hyperglycemia (19.5%), and diarrhea (13.4%) being common. **Conclusions:** TQ-B3525 exhibited favorable efficacy and manageable safety profiles, supporting its potential as a valuable treatment modality for heavily pretreated Chinese R/R/ FL patients. Clinical trial information: NCT04324879. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd. (Nanjing, China); National Natural Science Foundation of China; 81872902, 82073917, and 82070206; National Natural Science Foundation of Guangdong Province; 2023A1515011525; the Lymphoma Research Fund of China Anti-Cancer Association; the Sun Yat-sen University Cancer Center Clinical Research 308 Program; 2014-fxy-106 and 2016-fxy-079; Tianjin Key Medical Discipline (Specialty) Construction Project; TJYXZDXK-053B.

Summary of TQ-B3525 efficacy in the ITT at stage 2.

Efficacy	IRC-Assessed (n=82)	Investigator-Assessed (n=82)
Median DOR#, months (95% CI)	NR (9.2-NE)	14.8 (9.2-20.4)
12-month DOR rate (%, 95% CI)	60.2% (44.3%-72.9%)	51.5% (36.0%-65.0%)
18-month DOR rate (%, 95% CI)	51.6% (30.6%-69.2%)	41.0% (23.5%-57.7%)
Median PFS, months (95% CI)	18.5 (10.2-NE)	18.4 (11.0-22.0)
12-month PFS rate (%, 95% CI)	58.3% (44.0%-70.1%)	52.8% (38.8%-65.0%)
18-month PFS rate (%,95% CI)	58.3% (44.0%-70.1%)	52.8% (38.8%-65.0%)
Median OS, months (95% CI)	Not reached	
12-month OS rate (%, 95% CI)	91.8% (82.5%-96.3%)	
24-month OS rate (%, 95% CI)	86.1% (72.3%-93.3%)	

Data were presented as n (%) or n (%, 95% confidence interval). NE, not estimable # DOR was assessed in 71 patients achieving responses.

Phase 1/2 of EO2463 immunotherapy as monotherapy and in combination with lenalidomide and/or rituximab in indolent NHL (EONHL1-20/SIDNEY).

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Background: Follicular and marginal zone B cell lymphoma (FL; MZL) demonstrate an indolent course with heterogeneous outcomes anda potential for spontaneous remissions indicating immune system intervention. Therapeutic immunization is therefore an attractive approach but new antigens that evoke a strong immune response are needed. EO2463 expands pre-existing memory CD8+ T cells recognizing non-self protein sequences from gut bacteria which cross-react with B cell antigens and can kill HLA-A2 restricted cells (T2) loaded with target peptides. EO2463 includes 4 HLA-A2 synthetically produced epitopes which exhibit molecular mimicry with the B cell markers CD20, CD22, CD37, and CD268 (BAFF-receptor), as well as a the CD4 helper-epitope UCP2 derived from hTERT. EO2463 is being used to drive anti-tumor activity against B cell malignancies. **Methods:** Patients (pts) with FL and MZL, stage 1-3A, and HLA-A2, are eligible. In the safety lead-in pts with relapsed/refractory (R/R) disease were given EO2463 SC q2 weeks (w) x 4, then q4w, for a max of 12 months; at w7 lenalidomide (20 mg/day for 21/28 days up to 12 cycles) is added (EL), and if no complete remission (CR) at w19, rituximab (375 mg/m^2 IV, q1w x 4, then q4w x 4) is also added (ER^2). Doses evaluated: 150 μg and 300μg/peptide. **Results:** 3 pts received 150 μg/peptide and 6 pts 300 μg/peptide (EO2463 1 pat, EL 2 pts, ER^2 6 pts): 2 MZL, 7 FL pts with median 2 lines (range 1-4) of prior systemic therapy. No related grade ≥3 adverse events were seen with EO2463 monotherapy. Most common related events were grade 1 to 2 local administration site reactions in 5/9 pts. Adverse events during combination treatment were as expected for R^2. PET-CT on w6 after EO2463 monotherapy suggested clinical activity in 4/9 pts (1 PR, 1 pt size reduction 15%, 1 pt 20% reduced tracer uptake, 1 pt 5/6 target lesions reduced metabolic activity). Overall objective responses (OR) were seen in 6/9 pts (67%; 1st OR on EO2463 1 pat, EL 4 pts, ER^2 1 pat), with CR in 5/9 (56%) pts; median time to response was 18w (range 8-43w), response ongoing in 5 pts, range 24-76w. Expansion of specific CD8+ T cells against mimic peptides and targeted B cell antigens were detected in all responding pts, incl. 2 pts with no measurable B cells at baseline (prior anti-CD20). Expansion of specific T cells was detected at w5 in 5/6 pts and was maintained as long as currently tested (up to w94, 43w after last EO2463 dose). No decline in expansions were seen after start rituximab. **Conclusions:** EO2463 (300 μg/peptide) monotherapy, EL, and ER^2 are well tolerated, with encouraging clinical activity with EO2463 monotherapy and with subsequent CR in 5/9 pts on combo. Rapid and durable expansion of specific CD8+ T cells was seen in all responding pts, consistent with the preclinical hypothesis. Additional cohorts investigate EO2463 alone or in combination in newly diagnosed or R/R pts. Results will be reported at the meeting. Clinical trial information: NCT04669171. Research Sponsor: Enterome.

7059 Poster Session

A phase II multicenter study of abexinostat, an oral histone deacetylase inhibitor, in patients with relapsed/refractory follicular lymphoma.

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Background: Epigenetic alterations are major drivers of Follicular lymphoma (FL). Histone deacetylase (HDAC) inhibitors have potential to counteract the loss of histone acetylation that results from *CREBBP* or *EP300* mutations. Abexinostat (Abx) is a novel potent oral pan-HDAC inhibitor with a pharmacokinetic profile that allows maintenance of sufficient drug concentrations for anti-tumor activity with twice daily (BID) dosing. Abx was shown to be well-tolerated with significant response in pts with relapsed/refractory (R/R) FL. **Methods:** This phase II study evaluated Abx 80 mg administered orally BID 4 hours apart in a "one week on, one week off" schedule (days 1 to 7 & 15 to 21 of a 28-day cycle) in pts with R/R FL (grade 1-3a). Key inclusion criteria included age ≥18 years, ≥ 2 prior treatment regimens, ECOG of 0-2, and measurable disease per Lugano 2014 criteria. Pts undergo efficacy assessment by enhanced CT/MRI every 8 weeks for the first 24 weeks, and every 12 weeks thereafter, and PET-CT at weeks 12 and 24 and to confirm a complete response (CR), in accordance with the Lugano 2014 criteria. Bone marrow (BM) evaluation was mandated in pts with baseline BM involvement who achieved radiographic CR. The primary endpoint is independent review committee (IRC)-assessed overall response rate (ORR). Secondary endpoints include duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** At the data cut-off date of December 15, 2023, data were available for 90 pts. Median age was 55.0 (range 27-79), 57.8% of pts were male, and 22.2% had ≥ 3 FLIPI-2. Pts had a median of 3 prior lines of therapy (range 2-9), and 24.4% were refractory to the last prior regimen, 27.8% of pts had been treated with PI3K inhibitors before. With a median follow-up of 20.8 months, of 82 pts evaluable for efficacy, the IRC-assessed ORR was 67.1% (95% CI: 55.8%-77.1%), including 12.2% CR. The ORR for pts with > 3 lines of prior therapy was 69.0% (95% CI: 49.2%-84.7%). The median PFS and median DoR was 13.77 (95% CI: 9.69-not evaluable [NE]) months and 13.96 (95% CI: 8.34-NE) months, respectively. Median OS was not reached, and the 42-month OS rate was 74.3% (95% CI: 58.1%-85.0%). Of 90 pts evaluable for safety, the most common (≥ 40%) treatment-emergent adverse events (TEAEs) were thrombocytopenia (85.6%), neutropenia (58.9%), leukopenia (52.2%), nausea (50.0%), anemia (48.9%) and diarrhea (46.7%); ≥grade 3 TEAEs (≥ 5%) included thrombocytopenia (37.8%), neutropenia (23.3%), leukopenia (7.8%), and lymphopenia (5.6%). TEAEs led to dose reductions and discontinuations in 28.9% and 3.3% of all pts, respectively. **Conclusions:** Abx was well tolerated at dose of 80 mg BID as monotherapy, and demonstrated a significant response in pts with heavily pretreated R/R FL. Clinical trial information: NCT03934567. Research Sponsor: None.

Preliminary results from a phase I study of IMM0306 in patients with relapsed or refractory CD20-positive B-cell non-Hodgkin's lymphoma.

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Background: IMM0306 is a fusion protein of CD20 monoclonal antibody with the CD47 binding domain of SIRPα on both heavy chains. It exerts excellent cancer killing efficacy by activating both macrophages and NK cells via blockade of CD47-SIRPα interaction and FcγR engagement. Here, we report the safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy results of phase I study in patients (pts) with relapsed or refractory (R/R) CD20-positive B-cell non-Hodgkin's lymphoma (B-NHL). **Methods:** Eligible pts with R/R CD20-positive B-NHL were enrolled in this multicenter phase I study (NCT05805943). IMM0306 was administered as monotherapy at escalating doses of 0.04, 0.1, 0.25, 0.5, 0.8, 1.2, 1.6, 2.0 mg/kg intravenously once a week until disease progression or intolerable toxicity. Dose-limiting toxicity (DLT) was evaluated in the first 28 days. Safety was evaluated per CTCAE 5.0, PK and PD analysis were also assessed, tumor assessments performed once every 8 weeks by Lugano 2014 criteria. **Results:** As of Nov 21, 2023, 48 pts were enrolled. The median age was 56 years with 30 (62.5%) males. The median prior lines of therapy were 2. All pts received previous anti-CD20 therapy. No DLTs were observed. Recommended phase II dose was determined as 2.0 mg/kg. The most frequent treatment related adverse events (TRAEs) were WBC decreased (66.7%), anemia (64.6%), lymphocyte decreased (58.3%), ANC decreased (47.9%), PLT decreased (45.8%), infusion-related reactions (35.4%). ≥grade 3 TRAEs occurred in 33 (68.8%) pts, with the most common being lymphocyte decreased (56.3%), WBC decreased (18.8%), ANC decreased (18.8%). 8 (16.7%) pts experienced treatment related serious adverse event. Discontinuation due to AEs occurred in 1 pt (grade 4 PLT decreased at 1.6mg/kg without bleeding). No AE led to death. IMM0306 exhibited approximate dose-proportional increase in PK exposure from 0.5 to 2.0 mg/kg and no obvious accumulation was observed after repeated dosing. At 1.2 mg/kg and higher dose, CD47 receptor occupancy on peripheral lymphocytes was saturated, suggesting IMM0306 is well tolerated from perspective of CD47 engagement. B-cell depleted rapidly at doses ≥ 0.8 mg/kg. Elevated cytokines levels were observed after first dosing of IMM0306, but multiple dosing did not stimulate further cytokine activation. Among 33 pts who received doses ≥ 0.8 mg/kg, 5 CR (4 follicular lymphoma [FL], 1 marginal zone lymphoma [MZL]), 5 PR (3 FL, 1 MZL, 1 diffuse large B cell lymphoma) and 11 SD were seen; the median PFS was 10.58 months (95% CI, 2.2, NA) and the median OS was not reached. Among 17 FL pts, 7 (41%) responded including 4 CR and 3 PR; among 6 MZL pts, 2 (33.3%) responded including 1 CR and 1 PR. **Conclusions:** IMM0306 was well-tolerated and with promising preliminary anti-tumor activity especially in pts with R/R FL and MZL. The phase II study is ongoing. Clinical trial information: NCT05805943. Research Sponsor: None.

Genomic profiling in a subgroup analysis of patients (pts) with diffuse large B-cell lymphoma (DLBCL) and extranodal (EN) sites of involvement in the phase 3 Pola-R-CHP versus R-CHOP (POLARIX) study.

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Background: The prognosis and survival outcomes of pts with EN involvement remain a challenge for DLBCL management. In the Phase 3 POLARIX study (NCT03274492), Pola-R-CHP demonstrated significantly improved progression-free survival (PFS) compared with R-CHOP in previously untreated DLBCL (Tilly et al. 2022). This retrospective analysis assessed clinical outcomes and genomic patterns of pts with DLBCL and EN disease. **Methods:** POLARIX methods were previously described (Tilly et al. 2022). Using a data cutoff of June 15, 2022, this analysis assessed pts with EN involvement as determined by investigators. Additional outcomes and genomics analyses were performed on pts whose EN status was confirmed from documented radiographic lesions or bone marrow biopsy with denotation of EN disease sites. Hazard ratios (HRs) for investigator-assessed PFS were adjusted for age ($\leq$60 vs >60) and sex. Cell of origin (COO) by NanoString, mutation analysis by whole exome sequencing, and global gene expression profiling by RNAseq were performed centrally. **Results:** In POLARIX, 616/879 pts (70%) had identified EN involvement. After a median follow-up of 39.7 months, pts showed improved PFS with Pola-R-CHP vs R-CHOP (HR 0.72, 95% confidence interval [CI]: 0.55–0.96), with a 2-year PFS of 75% vs 66%. A total of 556 pts (Pola-R-CHP, n=279; R-CHOP, n=277) had confirmed sites of EN involvement, defined as pts with EN radiographic lesions or bone marrow disease. In these pts, PFS favored Pola-R-CHP vs R-CHOP but the difference was not statistically significant (HR 0.84, 95% CI: 0.63–1.13). Of pts with confirmed EN disease, 429 had COO results (activated B-cell, 145 [34%]; germinal center B-cell, 223 [52%]; unclassified DLBCL, 61 [14%]). Mutation data and frequencies of select clinically relevant mutations (Ptashkin, 2023) across EN sites were available for 364 pts (Table). Gene expression data were available for 418 pts; genes involved in proliferation (E2F or PI3K signaling targets and checkpoint genes) and regulated by IRF4, OCT2 and XBP1, were commonly upregulated in pts with EN disease. **Conclusions:** Results in pts with DLBCL with EN involvement suggest superior PFS with Pola-R-CHP vs R-CHOP. Ongoing analyses will further assess the independent impact of EN status on outcome. POLARIX represents the largest cohort of pts with annotated EN disease and systematic genomic analysis, providing new insights into the genomics of these pts. Clinical trial information: NCT03274492. Research Sponsor: The POLARIX study (NCT03274492) was sponsored by F. Hoffmann-La Roche Ltd and Genentech, Inc.; Third-party editorial assistance, under the direction of the authors, was provided by Jacob Lea, MSc, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

Mutation Frequency, %	Liver n=39	Gastric n=23	Other GI n=54	Thorax n=79	Endocrine and Reproductive n=46	Head and Neck n=34	Kidney n=24	All EN n=364	Not EN n=161
KMT2D	38	22	44	38	28	29	33	32	29
TP53	36	17	31	23	15	18	29	20	22
PIM1	26	26	30	28	43	29	46	30	30
TNFRSF14	10	22	26	25	22	12	8	21	19
MYD88	8	30	22	18	41	32	29	21	20
BCL2	3	22	30	27	11	12	4	18	24
B2M	13	22	22	14	13	6	8	14	16
CREBBP	18	9	24	13	13	15	12	18	21
CD79B	8	9	24	14	26	24	25	17	17

Frontline treatment with zanubrutinib plus rituximab (ZR) followed by short course R-DHAOx in patients with mantle cell lymphoma (MCL): Results of the phase II CHESS clinical trial.

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Background: Combining Bruton's tyrosine kinase (BTK) inhibitor and rituximab showed favourable efficacy as first-line therapy for mantle cell lymphoma (MCL). Zanubrutinib, a next-generation, highly-selective BTK inhibitor, achieved promising antitumor activity in MCL. In this multicenter phase II trial (CHESS - chemo-less), we aimed to investigate the efficacy and toxicity of zanubrutinib plus rituximab (ZR) combination, followed by short course cytarabine-based chemotherapy, then zanubrutinib maintenance as frontline therapy for MCL (NCT04624958). **Methods:** Previously untreated MCL patients enrolled and received induction therapy of ZR until complete response (CR) or to a maximum of 12 cycles, and followed by 4 cycles of R-DHAOx regimen (rituximab, dexamethasone, cytarabine and oxaliplatin). Patients achieving CR after chemotherapy would receive maintenance therapy with zanubrutinib for a maximum of 1 year. The primary endpoint was CR rate after induction therapy with ZR regimen. Minimal residual disease (MRD) of bone marrow and peripheral blood were evaluated by flow cytometry. **Results:** From Oct 2020 to Nov 2023, a total of 42 patients were enrolled and the enrollment was finished. The median age was 57 years (IQR, 51-64). Stage III-IV accounted for 92.8%, and 42.8% were intermediate or high risk simplified MIPI. Thirty-four patients (81.0%) were classic histological subtype. The median cycle of ZR was 4 (range, 2-6). As of Jan 2024, among 37/42 patients with post-treatment PET evaluation, the best CR rate of ZR regimen was 91.9% (34/37), and 94.1% (32/34) obtained CR after 2-4 cycles. The bone marrow MRD negative CR rate was 92.0% (23/25). The other 5/42 patients were still receiving ZR treatment, and PET evaluation would be performed subsequently. Among 27 patients who finished chemotherapy and were evaluable for response, only one patient experienced disease progression. With a median follow up of 11.6 months, the 1-year progression-free survival and overall survival was 90.1% and 96.7%, respectively. Two patients died due to lymphoma (n=1) and COVID-19 (n=1). Grade 3-4 adverse events on ZR regimen were neutropenia (n=3), fatigue (n=2), and amino-transferase (n=1). During chemotherapy, grade 3-4 thrombocytopenia was observed in 75.8% of patients. **Conclusions:** Induction treatment with ZR followed by short-course R-DHAOx chemotherapy yielded promising antitumor efficacy. This strategy might reduce the toxicity of cytarabine-based chemotherapy without weakening the therapeutic efficacy. Clinical trial information: NCT04624958. Research Sponsor: National Natural Science Foundation of China (82230001 and 82270199), Guangzhou Science and Technology Program (2024B03J1291), National Key Research and Development Program (2022YFC2502602), Sun Yat-Sen University Clinical Research 5010 Program (2020009).

Baseline characteristics.

Characteristics	Patients (n=42)
Age, years (median [IQR])	57 (51-64)
Sex	
Male	35 (83.3%)
Female	7 (16.7%)
Simplified MIPI	
Low risk	24 (57.1%)
Intermediate risk	15 (35.7%)
High risk	3 (7.1%)
Cytomorphology	
Classic	34 (81.0%)
Blastoid, small cell, and pleomorphic	8 (19.0%)

7063 Poster Session

Non-Hodgkin lymphoma mortality disparities across different sexes, races, and geographic locations.

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Background: Non-Hodgkin lymphoma (NHL) is one of the common hematological cancers in the United States (U.S.), accounting for 4% of new cancer cases in 2023. The mortality rate of NHL is the sixth highest among all cancers in the U.S. Our study aimed to examine the trends in NHL mortality and assess the mortality disparities among different sexes, ages, races, geographic locations, and urbanization levels. **Methods:** Our population-based cross-sectional study analyzed death certificate data from the Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) U.S. from 1999 to 2020 to determine the longitudinal trends of NHL mortality among the U.S. population aged $\geq$ 15 years. NHL (ICD-10 C82-85) was listed as the underlying cause of death. Age-adjusted mortality rates (AAMRs) per 100,000 individuals were calculated and joinpoint trend analysis were performed to determine the average annual percent change (AAPC) in AAMR trends. **Results:** From 1999 to 2020, NHL accounted for 457,143 deaths in the United States, of which 54% are men and 46% are women. Excluding unspecified NHL, there were 132,288 (n=132,288/155,957, 84.8%) B cell NHL deaths and 23,669 (n=23,669/155,957, 15.2%) T cell NHL deaths. Overall, the AAMR of NHL decreased from 10.59 (95% CI, 10.46-10.73) in 1999 to 6.21 (95% CI,6.13-6.30) in 2020 with the AAPC of -2.55 (95% CI, -2.63, -2.46). Men had a higher AAMR than women (10.10 [95% CI, 10.06-10.14] vs. 6.29 [95% CI, 6.27-6.32]). Non-Hispanic Whites recorded the highest AAMR (8.43 [95% CI, 8.40-8.45]), followed by non-Hispanic Blacks (5.71 [95% CI, 5.64-5.77]), Hispanics (6.32 [95% CI, 6.25 - 6.40]), American Indians (5.31 [95% CI, 5.04 - 5.58]), and Asians (5.10 [95% CI, 5.00 - 5.19]). Death from NHL was the most common in patients aged 75 years and above (52.50%), followed by patients aged 55-74 years (37.49%) and patients aged 15-54 years (10.41%). Those who lived in the Midwest region had the highest AAMR (8.60 [95% CI, 8.55-8.65], followed by the Northeast region (7.99 [95% CI, 7.94 - 8.05]), the South region (7.73 [95% CI, 7.70 - 7.77]), and the West region (7.58 [95% CI, 7.54 - 7.63]) . The rural population has a higher AAMR compared to the urban population (8.35 [95% CI, 8.29-8.41] vs. 7.86 [95% CI, 7.83 - 7.88]). **Conclusions:** NHL mortality has declined over the last two decades. The higher mortality rates existed among men, non-Hispanic White individuals, and the rural population warrant targeted intervention to address the mortality disparities. Research Sponsor: None.

A phase 1 study of SHR-A1912, a CD79b targeted antibody-drug conjugate (ADC), in patients (pts) with B-cell non-Hodgkin lymphoma (B-NHL).

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Background: CD79b is an attractive therapeutic target for B-NHL. SHR-A1912 is a novel ADC containing an anti-CD79b monoclonal antibody conjugated to the DNA topoisomerase I inhibitor. Here, we present results of the dose-escalation (D-ESC) and dose-expansion (D-EXP) parts of a first-in-human phase 1 study of SHR-A1912 in B-NHL. **Methods:** Pts with histologically confirmed B-NHL that had failed to respond to or had progressed after ≥1 prior anticancer therapy were enrolled. The D-ESC part commenced with accelerated titration at 0.1 and 0.3 mg/kg and then switched to an i3+3 scheme at escalated doses starting from 0.6 mg/kg (Q3W, IV). In the D-EXP part, additional pts were enrolled to selected doses (approximately 10–12 pts in total per dose level). Primary objectives were to assess the safety and tolerability of SHR-A1912 and determine the RP2D. **Results:** As of Nov 7, 2023, 49 pts were enrolled (n=1, 1, 7, 3, 13, 13, and 11 in the 0.1, 0.3, 0.6, 1.2, 1.8, 2.7, and 3.6 mg/kg dose cohorts), including 33 pts with diffuse large B-cell lymphoma (DLBCL), 12 with follicular lymphoma (FL), and 4 with marginal zone lymphoma (MZL). Pts had received a median of 2 lines of prior treatment (range, 1–9). DLTs occurred in 3 pts during D-ESC (grade 4 decreased neutrophil count lasting ≥3 days in 0.6 and 3.6 mg/kg cohorts, 1 pt for each; grade 3 pneumonia in 2.7 mg/kg cohort, 1 pt). The 1.8, 2.7, and 3.6 mg/kg cohorts were expanded. Overall, grade ≥3 treatment-related adverse events occurred in 20 (40.8%) pts, with the most common (≥20%) being decreased neutrophil count. 41 pts with baseline target lesions had at least one post-baseline assessment; ORR was 56.1% (95% CI, 39.8–71.5), and 6-mo DoR rate was 62.7% (95% CI, 26.7–84.8). As for subtypes, ORR was 51.9% in pts with DLBCL (57.1% and 77.8% in the 2.7 and 3.6 mg/kg cohorts, respectively), 63.6% in pts with FL, and 66.7% in pts with MZL (Table). The mean half-life of conjugated antibody ranged from 4.7 to 5.3 days for pts in the 1.8–3.6 mg/kg cohorts, with volume of distribution close to human plasma volume. The plasma exposure of free toxin was low, with the molar ratio of toxin/conjugated-antibody <1%, and no accumulation was observed. **Conclusions:** SHR-A1912 was tolerable up to 3.6 mg/kg and had promising anti-tumor activity in pts with previously treated B-NHL, supporting further investigations of SHR-A1912. Clinical trial information: NCT05113069. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Efficacy by subtype.

	DLBCL (n=27)	FL (n=11)	MZL (n=3)	All (n=41)
Best overall response				
CR	4 (14.8)	0	0	4 (9.8)
PR	10 (37.0)	7 (63.6)	2 (66.7)	19 (46.3)
SD	5 (18.5)	2 (18.2)	0	7 (17.1)
PD	8 (29.6)	2 (18.2)	1 (33.3)	11 (26.8)
ORR	51.9 (32.0–71.3)	63.6 (30.8–89.1)	66.7 (9.4–99.2)	56.1 (39.8–71.5)
DCR	70.4 (49.8–86.3)	81.8 (48.2–97.7)	66.7 (9.4–99.2)	73.2 (57.1–85.8)
6-mo DoR rate	65.6 (15.7–90.9)	33.3 (0.90–77.4)	100.0 (100.0–100.0)	62.7 (26.7–84.8)

Data are n (%) or % (95% CI).

7065 Poster Session

Selinexor combined with tislelizumab in patients with relapsed or refractory extranodal NK/T-cell lymphoma (R/R ENKTL): Results of dose escalation of cohort C, from a multicenter, single-arm, phase I/II study (TOUCH).

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Background: ENKTL is a rare subtype of mature T and NK/T cell lymphoma presenting features of highly aggressive clinical course and association with EBV infection.The prognosis remains poor for R/R ENKTL patients (pts) with treatment failure of L-Aspariginase (L-Asp) based regimens, highlighting the need for novel approaches. Monotherapy of tislelizumab (Tis) showed preliminary clinical activity in R/R ENKTL. Selinexor (Sel), a novel XPO1 inhibitor, has demonstrated preclinical synergistic effects when combined with PD-1 antibody. The TOUCH study (NCT04425070) includes three cohorts investigating the combination of Sel with chemotherapy (ICE or GEMOX) or Tis in R/R ENKTL. **Methods:** Cohort C was designed to evaluate the safety, tolerability, preliminary efficacy of Sel plus Tis in R/R ENKTL. Pts who received at least one prior treatment containing L-Asp were enrolled. In the escalation stage, a 3+3 design was implemented to determine the RP2D of Sel. The starting dose of Sel was 40 mg QW, followed by 60 mg QW (dose level 2), administered orally on Days 1, 8, and 15 of each 21-day cycle. Tis was administered at a fixed dose of 200 mg every 3 weeks on Day 1. DLTs were assessed during the first cycle. Efficacy was evaluated per Lyric 2016. **Results:** As of 25 Dec 2023, 12 R/R ENKTL pts were enrolled in the escalation stage [Sel 40mg (n=3); Sel 60mg (n=9)]. At study entry, the median age was 52 years (range 32-65); Five males and 7 females; 6 (50.0%) had stage III/IV disease; Seven (58.3%) pts had PINK score ≥2 and 6 (50.0%) pts were circular EBV-DNA positive. The median number of prior treatment lines was 2.5 (range 1-5); Ten (83.3%) pts were refractory to their last-line therapy. Eleven pts had prior exposure to PD-1/PD-L1 antibodies, including 7 pts who had received prior Tis. No DLT was observed and MTD was not reached. The most common TEAEs were asthenia (83.3%), neutropenia (83.3%), nausea/vomiting (58.3%), decreased appetite, weight loss, anemia, thrombocytopenia (50.0%, respectively), lymphocytopenia (41.7%), pneumonia, AST increased and proteinuria (33.3%, respectively). Only 1 pt experienced an irAE with thyroiditis. Seven pts (58.3%) had Grade≥3 TEAEs. TESAEs occurred in 3 pts (25%) with only 1 (sepsis) considered treatment related. No pt discontinued or died due to TEAEs. Among 11 efficacy evaluable patients, ORR was 72.7% (8/11), and CR rate was 36.4% (4/11). Of 7 Tis exposed pts, 2 achieved CR and 3 achieved PR. At a median follow-up of 6.8 months (range 5.5-12.6), the median PFS, DOR and OS were 6.1 months, 4.7 months, and not reached (6-month OS rate 90.9%), respectively. The RP2D of Sel in Cohort C was determined to be 60mg QW. **Conclusions:** Selinexor plus tislelizumab showed tolerable safety profile and encouraging response rate in R/R ENKTL. Expansion stage of Cohort C is ongoing. Clinical trial information: NCT04425070. Research Sponsor: None.

Glofitamab combined with poseltinib and lenalidomide for relapsed/refractory diffuse large B cell lymphoma: Interim analysis of GPL study.

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Background: Despite advanced treatments, including chimeric antigen receptor therapy (CAR-T), a significant proportion of patients succumb to relapsed and refractory diffuse large B cell lymphoma (R/R DLBCL). In vitro experiments suggest synergism between BTK inhibitor (BTKi) and T-cell engager, we initiated a multicenter trial of poseltinib and glofitamab in combination with lenalidomide in R/R DLBCL. **Methods:** This is a phase II, open label, single arm study aiming to enroll 76 participants with adult R/R DLBCL patients (NCT05335018). Patients refractory to frontline therapy or those who failed more than two lines of therapies were enrolled. Previous anti-CD19 CAR-T was allowed, while previous CD20 T-cell engager was not permitted. Participants received glofitamab (In cycle 1, dose is increased weekly from 2.5mg to 10mg, and after cycle 2, 30mg is administered on Day 1), lenalidomide (20mg daily from Day 1-14), and poseltinib (40mg twice daily from Day 1-21) (GPL) every 3 weeks for a total of 12 cycles(induction). Maintenance with poseltinib and lenalidomide for 17 cycles were given to patients after induction period. The primary endpoint is overall response rate (ORR), with secondary endpoints including duration of response (DoR), complete response rate (CRR), progression free survival (PFS), overall survival (OS), and incidence of treatment related adverse events. **Results:** No safety signals were observed in the safety cohort (n=6, 3+3 design). As of November 2023, 37 patients (median age 71) have been treated with GPL, with a median follow up duration of 3.6 months. In prior lines of therapy, 13 patients (35.1%) received treatment more than 2, and 26 patients (70.3%) were with Ann Arbor stage III/IV and 7 patients (18.9%) were refractory to frontline treatment. Previously, 3 patients (8.1%) received CAR-T. Out of 28 evaluable patients, ORR was 89.3%, with CRR of 42.9%. Six-month OS and PFS rate were 81% and 55%. DoR at 6 months was 66%. Neutropenia (45.9%) was the most common grade(gr) 3-4. Three patients (8.1%) died of gr5. There was 1 case (2.7%) of gr3 atrial fibrillation and gr1 bleeding. No incidence of gr3 or above liver/renal toxicity were observed. Overall, 3 patients (8.1%) discontinued GPL treatment due to toxicity, and cytokine release syndrome was observed in 7 patients (18.9%) and only 2 patients (5.4%) were gr3-4. **Conclusions:** Interim analysis indicates that the GPL regimen is an effective and safe regimen for R/R DLBCL patients. High response rates observed support further investigation of GPL for potential synergism between T-cell engagers and BTKi. This multicenter study is actively recruiting patients and is set to complete enrollment within this year. Clinical trial information: NCT05335018. Research Sponsor: F.Hoffmann-La Roche Ltd.

CRR	42.9% (25-61)
ORR	89.3% (78-100)
OS	3 months 91% (82-100) 6 months 81% (67-98)
PFS	3 months 81% (69-96) 6 months 55% (36-84)
DoR	3 months 94% (84-100) 6 months 66% (43-100)
Median Follow Up	3.6 months (0.3-9.4)

CODOX-M/IVAC-R versus DA-EPOCH-R in double/triple-hit large B cell lymphoma in patients ≤ 60 years.

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Background: High intensity induction with regimens such asDA-EPOCH-R, CODOX-M/IVAC-R and HyperCVAD are often used for young patients with DHL/THL despite no overall survival (OS) benefit compared to R-CHOP. Reports on the application of CODOX-M/IVAC-R are subject to selection bias as only young fit patients can tolerate it. We aimed to investigate outcomes difference between CODOX-M/IVAC-R and DA-EPOCH-R in patients ≤ 60 years with DHL/THL diagnosed via FISH. **Methods:** Retrospective review of DHL/THL patients from the Mayo Clinic diagnosed between July15th 2010-October19th 2023 treated with CODOX-M/IVAC-R or DA-EPOCH-R at age of up to 60 years. Event free survival (EFS) was defined as time from diagnosis to progression, relapse, next line of treatment or death from any cause. **Results:** 113 patients were included; CODOX-M/IVAC-R (N=49) and DA-EPOCH-R (N=64). Patient and disease characteristics are in table. 80% (N=39) achieved CR on end of treatment (EOT) PET CT with CODOX-M/IVAC-R compared to only 58% (N=37) with DA-EPOCH-R. CODOX-M/IVAC-R was associated with superior EFS on univariate (HR=0.54, 95%CI=0.31-0.97) and multivariable analysis adjusted for age, BCL2 vs BCL6 translocation and receipt of consolidation ASCT (aHR=0.53, 95%CI=0.29-0.95), however, there was no significant influence on OS (aHR=0.97, 95%CI=0.50-1.91). At a median follow-up of 5.3 years and 3.3 years for the CODOX-M-IVAC and DA-R-EPOCH group respectively; EFS was superior in the CODOX-M/IVAC-R group having 1, 2 and 5 years EFS of 68.3%, 64.1 and 61.5% respectively compared to 52.4%, 48.9% and 39.5% respectively in the DA-EPOCH-R group (p=0.035). 33%(16/49) of the CODOX-M/IVAC-R patients had R/R disease (No CR on EOT PET CT or relapsed) with a median OS of 10.3 months compared to 33.7 months in the R/R DA EPOCH-R group (54%, 35/64). Number of patients who were able to receive salvage ASCT, CAR T and Allo-SCT were 5, 17 and 4 respectively in the DA EPOCH-R group compared to 1, 6 and 3 patients respectively in the CODOX-M/IVAC-R group. None died of regimen toxicity in both groups. 19% underwent ASCT consolidation after CR with initial induction (11 patients in each group); no OS was noticed however consolidation with ASCT was associated with increased EFS regardless of the induction regimen with best outcomes being in the CODOX-M/IVAC-R group (P=0.0072). **Conclusions:** Our study showed that young patients with DHL/THL who received CODOX-M/IVAC-R had superior EFS compared to DA-EPOCH-R with no OS benefit. CODOX-M/IVAC-R can spare patients receiving more subsequent therapies. Patients who have R/R disease following CODOX-M/IVAC-R have poor outcomes. Research Sponsor: None.

Characteristic	DA-EPOCH-R N=64	CODOX-M/IVAC-R N=49	p - value
Mean Age	55	53	0.4
Female	30 (47%)	31 (63%)	0.083
FISH results			0.5
DHL MYC/BCL2	40 (63%)	26 (53%)	
DHL MYC/BCL6	9 (14%)	7 (14%)	
THL MYC/BCL2/BCL6	15 (23%)	16 (33%)	
StageIII/IV	50 (78%)	46 (94%)	0.02
DeNovo/Not transformed	46 (72%)	38 (78%)	0.5

Impact of bridging therapy (BT) on lisocabtagene maraleucel (liso-cel) treatment in patients (pt) with R/R follicular lymphoma (FL).

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Background: TRANSCEND FL primary analysis (NCT04245839) demonstrated very high response rates and manageable safety with liso-cel in second-line or later (2L+) FL, including 2L high-risk FL. Here, we report outcomes in subgroups of pts by BT status. **Methods:** TRANSCEND FL, a global, phase 2, single-arm, open-label study, evaluated liso-cel in adults with 2L+ R/R FL. Pts with 2L FL had progression of disease ≤ 24 mo (POD24) from diagnosis after treatment with anti-CD20 + alkylator ≤ 6 mo of FL diagnosis and/or met modified Groupe d'Etude des Lymphomes Folliculaires (mGELF) criteria. Pts received liso-cel after lymphodepleting chemotherapy (LDC). Optional BT per investigator was allowed during liso-cel manufacturing; reconfirmation of PET/CT-positive FL was required before LDC/liso-cel infusion to be considered efficacy evaluable (EE). PET/CT-based response assessments were performed at baseline (after end of BT and ≤ 7–14 days before LDC) and at post-infusion day 29 onward up to 60 mos. Primary endpoint was ORR per independent review committee (IRC); secondary endpoints included CR rate, duration of response (DOR), PFS, OS, and safety. Comparisons between BT and no BT (NBT) subgroups are descriptive. **Results:** Of 139 leukapheresed pts: 54 received BT; 130 were treated with liso-cel and 124 were EE (BT, n = 45; NBT, n = 79). BT pts had higher disease burden at baseline vs NBT: stage III/IV (94% vs 82%), sum of the product of perpendicular diameters ≥ 50 cm^2 before LDC per IRC (26% vs 14%), FL International Prognostic Index score 3–5 (78% vs 38%), met mGELF criteria (72% vs 48%), double refractory to anti-CD20 + alkylator (78% vs 52%), and POD24 from initial immunochemotherapy (65% vs 52%). ORR/CR rates were high and similar across subgroups, with all BT responders achieving CR (Table). Median DOR, PFS, and OS were not reached (NR) in both subgroups (Table), with a median follow-up of 18.9 mo. Grade (gr) ≥ 3 treatment-emergent AEs in BT vs NBT pts were reported in 82% vs 70%, most commonly, neutropenia (69% vs 52%), anemia (18% vs 5%), and thrombocytopenia (18% vs 5%). Gr ≥ 3 lab-based cytopenia was numerically higher in BT vs NBT at Day 29 (37% vs 14%), but most pts recovered to gr ≤ 2 by Day 90. In BT vs NBT pts, any-grade cytokine release syndrome (CRS; 51% vs 62%) and neurological events (NE; 12% vs 17%) were numerically lower, but gr 3 CRS/NEs/infections were similarly low across subgroups (BT, 0/6%/2%; NBT, 1%/0/7%, respectively), with no gr 4 or 5 events. **Conclusions:** Liso-cel showed equal clinical efficacy and safety (low rates of severe CRS/NEs/infections) in BT vs NBT pts, suggesting BT may mitigate worse outcomes and AEs associated with high tumor burden/high-risk features. Clinical trial information: NCT04245839. Research Sponsor: This study was funded by Celgene, a BMS Company. All authors contributed to and approved the abstract; writing and editorial assistance were provided by Nikola Vojtov, PhD, of The Lockwood Group (Stamford, CT, USA), funded by BMS.

	BT (EE, n = 45)	NBT (EE, n = 79)
ORR[a]	42 (93)	78 (99)
CR rate[a]	42 (93)	75 (95)
DOR[b] **12-mo DOR**[c]	NR88 (73–95)	NR81 (70–88)
PFS[b] **12-mo PFS**[c]	NR82 (67–91)	NR83 (73–90)
OS[b] **12-mo OS**[c]	NR87 (73–94)	NR96 (89–99)

[a]n (%); [b]Median, mo;[c]Rate (95% CI), %.

Frontline brentuximab vedotin and CHP (A+CHP) in patients (pts) with peripheral T-cell lymphoma with less than 10% CD30 expression: Results from the phase 2 SGN35-032 study.

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Background: Brentuximab vedotin (BV), an anti-CD30 antibody-drug conjugate, combined with cyclophosphamide, doxorubicin, and prednisone (A+CHP) was evaluated in the phase 3 ECHELON-2 trial in pts with anaplastic large cell lymphoma (ALCL) and other peripheral T-cell lymphoma (PTCL) types with ≥10% CD30 expression. Compared to conventional frontline therapy, pts treated with A+CHP had a 30% risk reduction in progression-free survival (PFS) (stratified HR=0.70 [95% CI: 0.53, 0.91], P=0.0077) and a survival benefit (HR=0.72 [95% CI: 0.53, 0.99], P=0.0424) (Horwitz 2022). Since no correlation between CD30 expression and duration of response (DOR) was found, it was hypothesized that frontline A+CHP may also be active in pts with non-sALCL PTCL with <10% CD30 expression. **Methods:** SGN35-032 (NCT04569032; EudraCT 2020-002336-74) is an ongoing phase 2 study. Pts with newly diagnosed non-sALCL PTCL with <10% CD30 expression (by local assessment) are enrolled. Pts are assigned to CD30 <1% or CD30 1% to <10% cohorts. All pts receive 21-day cycles of A+CHP (BV 1.8 mg/kg, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 by IV infusion, and prednisone 100 mg po qd on Days 1-5) for up to 6-8 cycles. The primary endpoint, overall response rate (ORR), is assessed by blinded independent central review (BICR) per Cheson 2007. Secondary endpoints are complete response (CR) rate, PFS, overall survival (OS), DOR, ORR per BICR using modified Lugano, and safety. **Results:** Seventy pts received ≥1 dose of study drug as of June 30, 2023. Median age was 63.5 years, 57% were male, and 90% had ECOG ≤1. Most had stage IV disease (63%) and were in the CD30 1% to <10% cohort per local CD30 (55%). Median treatment duration was 18 weeks (range, 0-24 weeks). Per BICR, ORR was 77% (95% CI: 65.3%, 86.7%), including 65% (95% CI: 52.4%, 76.5%) with CR among the 66 efficacy evaluable (EE) pts. ORR and CR rate per BICR are listed by cohort in the Table. Grade ≥3 treatment-emergent adverse events (TEAEs) were experienced by 43 pts (61%), most commonly neutropenia (20%), febrile neutropenia (17%), and anemia (10%). Six pts (9%) discontinued treatment due to TEAEs. Nineteen pts (27%) had BV-related serious TEAEs. There were 2 (3%) treatment-related deaths: 1 pt died of decreased appetite and 1 pt died of general physical health deterioration. **Conclusions:** In pts with non-sALCL PTCL with <10% CD30 expression, A+CHP as frontline therapy appears effective and has a safety profile consistent with label. Clinical trial information: NCT04569032. Research Sponsor: This study was sponsored by Seagen Inc., which was acquired by Pfizer Inc. in Dec. 2023.

	CD30 <1%	CD30 1% to <10%
Per local CD30[a]	**N=29**	**N=36**
ORR, % (95% CI)	79 (60.3, 92.0)	78 (60.8, 89.9)
CR rate, % (95% CI)	66 (45.7, 82.1)	67 (49.0, 81.4)
Per central CD30[a]	**N=19**	**N=25**
ORR, % (95% CI)	63 (38.4, 83.7)	80 (59.3, 93.2)
CR rate, % (95% CI)	53 (28.9, 75.6)	68 (46.5, 85.1)

[a] Analysis performed among EE set, a subset of all treated pts with postbaseline response assessment or discontinue treatment.

First-line (1L) treatment of follicular lymphoma (FL) with atezolizumab and obinutuzumab (A+O) +/- radiotherapy (RT): Results from the FLUORO study.

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Background: Standard 1L immunochemotherapy in FL is highly effective but not without significant toxicity. Up to 75% of FL patients (pts) have grade 3-5 adverse events (AEs), primarily infection and myelosuppression. More tolerable approaches are needed. PD1/PDL1 inhibitors are active in FL. A+O yield responses in 57% of rituximab-refractory FL pts (Palomba 2017). Our phase 2 study of 1L nivolumab + rituximab in FL yielded 92% overall response rate (ORR), (54% Complete Response (CR)). Toxicity compared favourably with chemotherapy: 41% grade 3-5 AEs (Hawkes 2021). FL is sensitive to low dose RT, with proven abscopal effects, is safe and synergistic with PDL1i (Hawkes 2023), potentially improving treatment efficacy with minimal extra toxicity. This investigator-led, multicentre PET-adapted phase 2 trial assessed A+O +/- RT efficacy for treatment-naïve FL. **Methods:** 'FLUORO' (NCT03245021) is an open-label, multi-centre, phase 2, Simon's 2-stage study of A+O+/-RT (N = 46; 15 in initial cohort). Key eligibility were stage II-IV grade 1-3A FL requiring therapy; ECOG ≤2; adequate organ function. All pts received 6 cycles (C) of A 1200mg + O 1000mg IV 3-weekly (plus O on C1, days 8 & 15). Pts with < CR on PET post C2 had RT (4Gy) to residual PET-avid disease. Pts with CR or PR(partial response) received 12 cycles 8-weekly maintenance O. Primary endpoint (EP) was CR rate with <5/15 CR deemed futile in 1st stage. Secondary EP included ORR, Progression-free survival (PFS), overall survival (OS) and AEs. Exploratory EP included biomarker studies and PET radiomics. **Results:** 16 pts were enrolled from 08/2021-10/2022, 1 pt was replaced due to Grade(G) 4 infusion reaction to O requiring cessation. Baseline characteristics included median age 53y (range 33-79), stage IV disease in 81%, B symptoms in 12.5%, 44% had FLIPI >2. Primary EP was met, with CR at end of induction in 13/15 (87%) evaluable pts (ORR 100%). 12 pts (80%) required RT. 2 pts (13%) discontinued due to progressive disease (Table). AEs were mostly G1-2; fatigue 44%, constipation 31%, nausea 25%. fever 25%, abdominal pain 18.6%. SAEs were reported in 7/16 (44%) pts, including grade 3 infections: COVID19 12%, upper respiratory tract 12%, urinary tract 6.2%. Median follow-up is 24m (range 16-28) and ongoing, 16m PFS & OS is 87% & 100%. Biomarker analysis is ongoing. **Conclusions:** Atezolizumab +Obinutuzumab +/- PET-adapted 4Gy RT yielded high complete response rates with low toxicity in treatment-naïve FL. CR threshold to proceed to stage 2 was met, however was not deemed commercially viable. Clinical trial information: NCT04962126. Research Sponsor: Roche Products, Pty. Limited (Australia).; Victorian Comprehensive Cancer Centre.

Response rate.

	Best Response N(%)	Post C2 O+A	End of Induction
ORR	15 (100)	15 (100)	13 (87)
CR	13 (87)	3 (20)	13 (87)
PR	2	12 (80)	0
SD	0	0	0
PD	0	0	2 (13)

Longitudinal patterns of patient-reported cognitive impairment in patients with non-Hodgkin lymphoma (NHL) treated with chemotherapy: A group-based trajectory analysis of a nationwide community-based cohort.

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Background: Cognitive problems are an important clinical concern for cancer patients. We previously published that patients with lymphoma experienced worsening in cognitive functions and perceived function from pre-to post-treatment. Limited data exists in NHL, importantly previously reported group means of cognitive function may not capture interindividual heterogeneity. Therefore, we identified distinct subgroups of NHL patients with similar trajectories of cognitive function over time and investigated potential predictors. **Methods:** We included 181 NHL patients receiving chemotherapy (mean age [SD]: 59.0 [11.8]; 63.5% male; 54% diffuse large B-cell, 22% follicular lymphoma) enrolled in the National Cancer Institute Community Oncology Research Program. Cognitive function was assessed by the patient-reported Functional Assessment of Cancer-Therapy-Cognitive Function (total score and perceived cognitive impairment [PCI]) prior to chemotherapy (T1), after chemotherapy (T2), and 6 months following T2 (T3). Patient and cancer characteristics were collected through questionnaires or medical records at T1. We utilized group-based trajectory modeling (GBTM) to identify latent clusters of individuals with similar cognitive function patterns over time. Model selection and assessment were based on the Bayes factor, group size, model diagnostics, and clinical interpretability. Multinomial logistic regression models were identified characteristics associated with group membership. **Results:** Four groups were identified by GBTM: Group A had high perceived impairment, which decreased at T2 and remained high at T3 (n=17, 9.4%); Group B had moderate perceived impairment, with a continuous decline at T2 and T3 (n=21, 11.6%); Group C had low perceived impairment and remained stable at T2 and T3 (n=95, 52.5%); Group D had moderate perceived impairment, without changes at T2 and T3 (n=48, 26.5%). Similar trajectory groups were identified for the PCI subscale. Compared to ≥ some college education, ≤ high school was associated with an increased odds of membership in Group D relative to Group C (OR 3.45, 95% CI 1.44, 8.30). Patients with a higher fatigue score (MFSI) were more likely to report worse cognitive impairment (Group A vs. C: OR 1.10, 95% CI 1.07, 1.14; Group B vs. C: OR 1.05, 95% CI 1.02, 1.08; Group D vs. C: 1.05, 95% CI 1.03, 1.07). Stage, lymphoma subtype, and treatment regimen were not associated with group membership. **Conclusions:** Our analysis revealed that patients with perceived impairment experienced stable impairment or further decline over time, which is associated with education and fatigue; a subgroup of patients did not experience cognitive worsening. These data help identify patients with different patterns of cognitive impairment to inform personalized interventions. Research Sponsor: National Cancer Institute; UG1CA189961; National Cancer Institute; R01CA231014.

Clinical and financial burden of mental health (MH) conditions in patients (pts) with low-grade non-Hodgkin lymphoma (LG-NHL).

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Background: LG-NHL is mostly incurable, imposing a prolong impact of cancer care burden for pts.This study aimed to quantify the burden of MH conditions in pts with newly diagnosed chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Waldenström macroglobulinemia (WM), or marginal cell lymphoma (MZL). **Methods:** A retrospective study was conducted using Optum Clinformatics Data Mart to identify pts ≥18 years with ≥1 new diagnosis for CLL, FL, MCL, WM, or MZL from 6/2016-6/2022 (index period). Pts were required to be continuously enrolled for 60 days pre- and 365 days post-index date, defined as the date of first cancer diagnosis. Incidence and prevalence of MH conditions of interest (anxiety, depression, stress reaction/adjustment disorder, insomnia, post-traumatic stress disorder [PTSD]) were categorized based on if diagnoses were post- or pre-index date. All-cause healthcare resource utilization (HCRU) and costs were measured during the 1-yr follow-up period. **Results:** Approximately half of newly diagnosed 36,054 LG-NHL pts (CLL/SLL=48.0%; FL=52.7%; MCL=57.2%; WM=50.5%; MZL=52.5%) had either an incident (19.4-25.7%) or prevalent (28.6-32.1%) MH condition diagnosis following their cancer diagnosis (Table). There were no significant demographic differences in pts with and without MH conditions. LG-NHL pts suffered most from anxiety (30.9-38.2%) and depression (27.5-31.9%), followed by insomnia (16-23.1%), stress (10.3-13.5%), and PTSD (1.4-1.9%). Median time from cancer diagnosis to onset of a MH condition was 334 days for CLL/SLL, 301 for FL, 248 for MCL, 351 for WM, and 328 for MZL. LG-NHL pts with an identifiable MH diagnosis had significantly higher costs and HCRU compared to those without; for example, in CLL/SLL pts with MH diagnosis, outpatient visits were 1.4 times higher, inpatient admissions 3.0 times higher, and costs 2.1 times higher than those without (all P=0.0001). HCRU and cost increases were also observed in MCL, FL, WM, and MZL pts with MH diagnosis. **Conclusions:** This real-world study uncovered a high proportion of LG-NHL patients suffer from MH conditions, incurring higher financial burden than those without. With advancements in new treatments, there remains unmet need of MH burden in these pts. Research Sponsor: BeiGene.

Rates of MH conditions by cancer type (any, prevalence, incidence), %.

%	CLL/SLL (n=19,891)	FL (n=9,715)	MCL (n=1,728)	WM (n=1,738)	MZL (n=2,982)
Anxiety	30.9 (16.9, 13.9)	35.3 (19.0, 16.3)	38.2 (18.1, 20.1)	32.3 (18.0, 14.4)	35.3 (19.7, 15.6)
Depression	27.5 (15.5, 12.0)	30.8 (16.7, 14.1)	31.9 (15.7, 16.2)	29.2 (16.6, 12.5)	29.6 (16.3, 13.3)
Stress	10.3 (4.5, 5.8)	11.9 (4.8, 7.1)	13.5 (4.6, 8.9)	12.4 (5.6, 6.9)	12.8 (5.5, 7.3)
Insomnia	16.0 (7.6, 8.4)	18.2 (7.7, 10.5)	23.1 (9.1, 14.0)	19.8 (10.0, 9.8)	17.2 (8.5, 8.7)
PTSD	1.4 (0.8, 0.7)	1.9 (0.8, 1.1)	1.8 (0.9, 0.9)	1.6 (1.0, 0.6)	1.7 (0.8, 0.9)

Survival outcomes after autologous stem cell transplantation in T follicular helper type lymphoma.

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Background: T follicular helper (TfH)-type lymphoma is the most common subtype of peripheral T-cell lymphoma (PTCL). TfH lymphoma consists of angioimmunoblastic T-cell lymphoma (AITL), PTCL-TfH and Follicular T cell lymphoma. Most patients receive first-line treatment with anthracycline-based chemotherapy regimens with a potential role for consolidation with autologous stem cell transplantation (ASCT). In this study we analyzed survival outcomes in TfH lymphoma. **Methods:** This is an IRB approved retrospective analysis of patients with TfH lymphoma followed between 1997–2023 at the MD Anderson Cancer Center. Demographics, treatment history, response and survival outcomes were collected and analyzed. Next-generation sequencing (NGS) data was collected from a panel of 162 cancer-related genes. Survival analysis was performed with Kaplan Meier curves and comparisons were made with log-rank tests. **Results:** Of the 218 patients with TfH lymphoma for whom information was known about prior history of ASCT, 84 (39%) underwent ASCT (Table). At the time of diagnosis, the majority of patients had advanced stage disease (92% with stage III or IV) and elevated LDH (89%). NGS testing was available from 31 patients and the genes with recurrent somatic mutations identified were TET2 (65% patients), DNMT3A (29%), RHOA (13%), IDH2 (10%), PLCG1 (10%), TP53 (10%), ATM (6%), CCR7 (6%), JAK3 (6%) and STAT3 (6%). The three most common first-line treatments were CHOP (37%) followed by CHOEP (14%) and combination of brentuximab with either CHP or CHEP (13%). Patients who received ASCT were significantly younger (Table). The median overall survival (OS) for the cohort was 40.3 months with median progression-free survival (PFS) after first treatment of 12.5 months. Patients who received ASCT had a significantly higher overall survival (log-rank test p-value $<$ 0.01) compared to those who did not receive ASCT. **Conclusions:** This retrospective analysis of a large single institution cohort of patients with TfH lymphoma found significantly improved OS in those who underwent ASCT compared to those who did not. Given the sizeable proportion of patients who are transplant-ineligible due to age or comorbidities, there is a need for newer consolidation approaches for TfH lymphoma. Research Sponsor: None.

Demographics	All Patients; N = 218	Autologous SCT; N = 84	No Autologous SCT; N = 134	p-value
Age > 65 years, (%)	49%	30%	61%	$<$ 0.001
Sex, female, (%)	49%	51%	44%	Not significant
Race, White, (%)	86%	87%	84%	Not significant
Elevated LDH, (%)	89%	93%	80%	Not significant
Stage III or IV, (%)	92%	90%	94%	Not significant
# Previous lines of treatment	1 (41%); 2 (22%); 3 (14%); $\geq$ 4 (16%)	1 (40%); 2 (24%); 3 (17%); $\geq$ 4 (19%)	1 (41%); 2 (21%); 3 (20%); $\geq$ 4 (14%)	Not significant
Progression-free survival	13 months	32.5 months	11 months	Not significant
Overall survival	40 months	63 months	32 months	$<$ 0.01

LBA7074 **Poster Session**

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

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P-GEMOX with sequential or sandwiched radiotherapy for early-stage extranodal natural killer/T-cell lymphoma.

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Background: Combined modality therapy (CMT), namely chemotherapy combined with radiotherapy, has been recommended for patients with localized extranodal natural killer/T-cell lymphoma (ENKTL). However, the optimal CMT has not been fully clarified. As chemotherapy is more easily accessible than immediate radiotherapy in the routine clinical practice, the "chemotherapy-first" CMT including sequential or sandwiched radiotherapy deserves further exploration. In addition, the optimal non-anthracycline-based regimen needs to be confirmed. **Methods:** The P-GEMOX regimen was administrated as follows: pegaspargase 2000 IU/m2 intramuscular on day 1, gemcitabine 1000 mg/m2 intravenous on day 1 and 8, oxaliplatin 130 mg/m2 intravenous on day 1 and was repeated every 21 days. Patients who achieved at least stable disease (SD) subsequently underwent involved field radiotherapy (IFRT). The dose of IFRT ranged from 50 to 55 Gy. Performing sequential radiotherapy (4 cycles of CT+RT) or sandwich radiotherapy (2 cycles of CT+RT+2 cycles of CT) is determined by the clinician based on the patients' conditions. The primary endpoint was the overall response rate (ORR) after 2 cycles of chemotherapy, and secondary study endpoints were CR, PFS, and OS. Safety was also evaluated. **Results:** From August 2020 to April 2023, thirty-seven patients (23 men, 14 women; median age: 55, 26-76 years) with stage I/II ENKTL who had received P-GEMOX were collected. 14 patients were stage IE and 23 were IIE. ALL patients completed at least 2 cycles of P-GEMOX, which resulted in 94.6% (35/37) of ORR including 30 patients with CR and 5 patients with PR. Among the patients in remission, 15 patients received sequential radiotherapy, 15 received sandwich radiotherapy, 4 were waiting for or in the process of radiotherapy, and 1 patient progressed before radiotherapy. With a median follow-up of 14.8 months (range: 2.6-38.1 months), the 3-year PFS and OS were 87.2% (95%CI 69.3%-95%) and 90.6% (95%CI 72%-97.1%), respectively. Sandwich radiotherapy had an obvious trend for longer PFS than sequential radiotherapy (18moths-PFS 100% vs. 78%; P=0.073). During the treatment, 21.6% (8/37) of the patients experienced grade 3–4 treatment-emergent adverse events (TEAEs). The most grade 3–4 hematological TEAEs were neutropenia (7/37, 18.9%) and thrombocytopenia (4/37, 10.8%). As for grade 3–4 non-hematological TEAEs, elevated aminotransferase, hyperbilirubinemia and hypofibrinogenemia were 16.2%, 10.8% and 8.1%, respectively. The adverse events of this CMT were well-tolerated and manageable. No treatment-related death occurred. **Conclusions:** Our study demonstrated that CMT consisted of P-GEMOX showed favorable efficacy with acceptable toxicity, and sandwich radiotherapy (CT+RT+CT) seems give more favorable PFS than sequential radiotherapy. The CMT protocol could be an effective treatment option for early-stage ENKTL patients. Research Sponsor: None.

Results from the follicular lymphoma (FL) outcomes in patients (pts) with relapsed/refractory (R/R) disease treated with systemic therapy in a real-world assessment (FLORA) study.

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Background: Odronextamab, an off-the-shelf CD20×CD3 bispecific antibody, has shown compelling efficacy (objective response rate [ORR] 80%, complete response [CR] rate 73%) and a generally manageable safety profile in pts with heavily pretreated R/R FL in the single-arm ELM-2 trial (NCT03888105; Villasboas, et al. ASH 2023). We evaluated outcomes in pts with R/R FL treated with currently available third-line or later (3L+) therapies in a real-world setting (FLORA; NCT05338879) to better evaluate the results from ELM-2 in the absence of a randomized control arm. This is the first real-world study in 3L+ FL that evaluated scans from 100% of the cohort. **Methods:** FLORA is a multicenter, retrospective, observational study, using electronic medical record or research databases, of pts with R/R FL who have received ≥2 prior lines of therapy (LoTs; including an anti-CD20 and an alkylator) and initiated 3L+ systemic therapy for FL between January 1, 2015 and December 31, 2020. After applying similar eligibility criteria to those in the ELM-2 trial, inverse-probability of treatment weighting (IPTW) was used to balance key prognostic characteristics between the trial and the real-world cohorts. Pts were followed from the start of qualifying LoT until death, end of study (December 31, 2021), or lost to follow-up, whichever occurred first. The primary endpoint was ORR assessed by independent central review (ICR). Secondary endpoints included ICR-assessed CR rate, disease control rate (DCR), progression-free survival (PFS), duration of response (DOR), and overall survival (OS) (see Bachy, et al. ASH 2022). **Results:** Pts in FLORA (N=100) generally had less severe disease than trial pts prior to IPTW. The most commonly used regimens were chemotherapy + anti-CD20, chemotherapy alone, and anti-CD20 + immunomodulatory agent. The IPTW cohort had a median age of 61 y, 59% POD24, 56% high FLIPI, 60% chemo-immuno refractory, 73% refractory to last LoT, and median (range) prior LoT: 3 (2–8). In the IPTW cohort, ORR was 52%, CR 31%, and DCR 62%. Median PFS (mPFS) was 11.5 mo, median OS was 26.1 mo, and median DOR (mDOR; responders in IPTW cohort: n=54) was 28.2 mo. Given the lack of regular scans in routine practice (37% of responders did not have any subsequent ICR assessment after CR/PR), sensitivity analysis that considered subsequent treatment as a progression event resulted in shorter mDOR (8.1 mo) and mPFS (7.2 mo). **Conclusions:** Pts in the FLORA study had markedly lower response rates than those in the R/R FL cohort of ELM-2. This study also showed that most pts still received an anti-CD20–based regimen in 3L+ in routine practice, highlighting the need for treatment options with different mechanisms of action that provide deep and durable responses and improve outcomes in this pt population. Clinical trial information: NCT05338879. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Durable complete response and overall survival in patients with heavily pretreated, poor-prognosis non-Hodgkin lymphoma to immunoactivating AVM0703 with few and mild drug-related adverse effects.

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Background: In 2022, the majority of new cancer drugs in clinical development are aimed at targets that are already saturated with approved drugs[1]. This is of concern to patients, payers, sponsor/investors, and regulatory agencies. AVM0703 activates a unique immune response mobilizing an endogenous gamma delta TCR+ and invariant TCR+ bispecific Natural Killer T-like cell ($\gamma\delta TCR^{+}iTCR^{+}NKT$) (PCT/US21/19773), that has demonstrated clinical anti-cancer activity against a variety of solid and blood cancers. The potential for AVM0703 to fill a gap in the "no-option" R/R NHL treatment landscape led to the launch of the AVM0703-001 clinical trial (The OPAL Study, NCT04329728). 1) Fougner C et al. Herding in the drug development pipeline. Nat Rev Drug Discov. 2023 Aug;22(8):617-618. **Methods:** An open-label phase 1 trial evaluating the safety and preliminary efficacy of AVM0703 was completed in patients with hematological malignancies. AVM0703 was administered as a single intravenous (IV) infusion to patients enrolled into a 3+3 dose escalation design. Consolidation therapy of investigator's choice was allowed, preferably 28 days after AVM0703. For each cohort, 3-6 patients were treated, and dose escalation permitted only after the cohort completed a 7-day dose limiting toxicity (DLT) assessment period with no more than 1 DLT. Patients ≥12 years and >40 kg diagnosed with WHO classified lymphoid neoplasms with R/R disease ineligible for transplant or CAR-T were included. The database has not been formally locked and a cutoff date of Dec 13, 2023, is used for presentation of these Phase 1 results. **Results:** In summary, 17 patients, 39-86 years of age (median 64) with a median of 4 prior lines (range: 1 to 10) received AVM0703 at 6, 9, 12, 18 and 21 mg/kg. Fifteen (88%) were poor prognosis and 4 had CNS involvement. Only 13 of 17 (76.5%) experienced study-drug related adverse events (AEs) during the DLT period; 15 AEs were grade 1 (78.9%), 2 were grade 2 (10.5%), and 2 were grade 3 (10.5%). The most common AEs were insomnia (N=5), hyperglycemia (N=3), and pruritis (N=2). The total number of All-grade TEAEs recorded in 17 patients was 114 within 30 days post dose, with 98.2% of grades 1-3. Median overall survival (OS) in all dose cohorts was 13.3 months, with 8 of 17 patients alive as of 13 Dec 2023. The recommended Phase 2 dose (RP2D) was determined as 18 mg/kg. For the 18 mg/kg group (N=6), long term durable responses were obtained in 66% (3 CR, 1 PR) with an additional patient converting to late CR, nine months survival was 100%, and median OS has not been reached with follow up between 15.9 and 27.8 months (83% still alive). No safety signals have been identified. **Conclusions:** RP2D AVM0703, with consolidation therapy at day 28 median (range 7 to 240 days) showed no concerning safety signals and promising long-term survival. Clinical trial information: NCT04329728. Research Sponsor: National Cancer Institute.

Updated efficacy and safety results of BCL-2 inhibitor lisaftoclax (APG-2575) alone or combined with ibrutinib or rituximab in patients (pts) with Waldenström macroglobulinemia (WM).

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Background: Lisaftoclax is a novel, oral, highly selective, potent BCL-2 inhibitor in development. In an ibrutinib-resistant patient-derived WM xenograft/preclinical model, lisaftoclax + ibrutinib has a strong synergistic effect. This report provides updated efficacy and safety data of lisaftoclax-based therapies (including combinations with ibrutinib) in pts with WM. **Methods:** In this global, open-label, phase 1b/2 multicenter study, pts with WM were enrolled in 3 arms: Arm A (lisaftoclax) included BTKi-resistant/intolerant pts; Arm B (lisaftoclax + ibrutinib), treatment-naïve pts; and Arm C (lisaftoclax + rituximab), BTKi-naïve relapsed/refractory pts. Lisaftoclax was escalated from 400 to 1,200 mg using a modified toxicity probability interval design. A 3-day ramp-up was used for pts at high risk of tumor lysis syndrome (TLS). Objectives were efficacy, safety, and pharmacokinetics (PK) assessments (responses assessed per IWWM criteria). **Results:** As of January 25, 2024, 46 pts were enrolled and treated at doses of up to 1,000 (Arm A), 1,200 (Arm B), and 800 mg (Arm C; Table). The median (range) treatment duration was 11 (1-28; Arm A), 23.5 (1-34; B), and 11.5 (5-33; C) months. Objective response rates (PR, VGFR, CR) were: 41.7% (Arm A), 90.9% (B), and 37.5% (C). In Arm A, pts with wild-type *CXCR4* (n = 7) had better overall response to lisaftoclax than the $CXCR4^{mut}$ group (n = 3).No significant difference was observed between pts with/without $CXCR4^{mut}$ in Arms B and C. In Arm B, 1 DLT (grade 3 clinical TLS due to preexisting renal impairment) was reported at 1,200 mg; 1 grade 3 laboratory TLS, primarily attributed to dehydration and concomitant symptomatic therapies, occurred at 1,000 mg; abnormal electrolytes resolved after 1 day of drug interruption, without recurrence. Grade ≥ 3 lisaftoclax-related AEs included neutropenia (15.2%), thrombocytopenia (4.3%), decreased leukocytes (4.3%), TLS (4.3%), anemia (2.2%), weight loss (2.2%), and septic shock (2.2%). Ventricular arrhythmia was not observed. One pt required dose reduction because of neutropenia. The MTD was not reached. Lisaftoclax + ibrutinib showed a PK exposure comparable to lisaftoclax or ibrutinib alone, indicating no potential drug-drug interactions. **Conclusions:** Lisaftoclax alone and combined with ibrutinib or rituximab was well tolerated and demonstrated measurable effects in pts with naïve or BTKi-treatment-failed WM. (CT.gov: NCT04260217; Internal ID: APG2575WU101) *Co-first authors: ML and SA. Clinical trial information: NCT04260217. Research Sponsor: Ascentage Pharma Group Corp. Ltd. (Hong Kong).

Baseline characteristics.

Arm	A (n = 14)	B (n = 24)	C (n = 8)
Median age, yr (range)	67.5 (48-75)	65.0 (51-92)	65.0 (54-72)
Male, n (%)	11 (78.6)	18 (75.0)	6 (75.0)
IPSSWM high, n (%)	8 (57.1)	4 (16.7)	2 (25.0)
Lines of prior therapies, median (range)	4.0 (1-7)	0	2.5 (1-7)
MYD88^{+}/*CXCR4*$^{+}$	4	9	1
MYD88^{+}/*CXCR4*$^{-}$	5	13	6
MYD88^{-}/*CXCR4*$^{+}$	0	0	0
MYD88^{-}/*CXCR4*$^{-}$	3	1	1

7079 Poster Session

Combined modality for localized gastric diffuse large B-cell lymphoma: Long-term outcomes of 50 patients.

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Background: R-CHOP is the primary treatment for gastric diffuse large B-cell lymphoma (GDLBCL); for localized disease, the role of consolidative radiation therapy (RT) after chemotherapy remains underexplored. This study focuses on localized GDLBCL undergoing a combined modality therapy of R-CHOP followed by gastric RT, comparing outcomes between those receiving short-course (3-4 cycles) and full-course (6 cycles) R-CHOP. **Methods:** A retrospective analysis identified 50 consecutive PGDLBCL pts treated with R-CHOP followed by RT between 1/2000-1/2021. Baseline characteristics and follow-up data were collected. Lugano PET criteria and endoscopy (EGD) assessed overall response rate. Kaplan-Meier and univariable cox regression models estimated overall survival (OS) and (PFS). **Results:** Of the 50 pts with localized (Stage I-II) disease, 34 (68%) received 3-4 cycles of R-CHOP and 16 (32%) received 6 cycles. Pre-RT disease evaluation varied, with 36 (72%) undergoing EGD and PET, 4 (8%) EGD and CT, and 6 (12%) PET alone. One pt (3%) exhibited active DLBCL post 3-4 cycle R-CHOP, while 5 (31%) did so after 6 cycles (p=0.1). Median time from last R-CHOP dose to RT start date was 1.2 months with a median 3060 cGy delivered dose for both groups (range 2340-3060 in the 3-4 cycle group, 3000-4500 in the 6-cycle group). Median follow-up time from RT end is 58 months. No in-field failures occurred post-complete response (CR); however, 1 pt did not achieve a CR following R-CHOP and RT, progressing in the stomach and subsequently at new, out-of-field (OOF) sites. 3 pts had OOF progression without relapses in the stomach in a median time of 21 months. Low-grade lymphoma in the stomach post-DLBCL CR was observed in 2 pts, 3 and 22 months from RT end, with 1 OOF marginal zone lymphoma 2 years-post RT. OS and PFS did not significantly differ between the 3-4 and 6 cycle groups (96-month OS 70% vs. 86%, p=0.8; 96-month PFS 76% vs. 86%, p=0.7). OS and DLBCL PFS were analyzed for pts with evidence of residual DLBCL pre-RT compared to those without evidence of disease after R-CHOP. The 24-month DLBCL PFS was 92% in the CR group and 67% for those with incomplete response (p=0.14), with 92% and 67% 24-month survival probability (p=0.11). On univariate analysis, pre-RT evidence of active DLBCL by PET and/or EGD, pre-RT PET FDG uptake, and achieving CR on first-post-RT imaging were not statistically significant for DLBCL PFS. **Conclusions:** Recognizing the limitations of a retrospective study, our study documents the effectiveness of short-course R-CHOP followed by RT in localized GDLBCL, with similar outcomes to the full 6-cycle regimen. Excellent disease control was observed, with few instances of DLBCL or low-grade lymphoma relapse. Further analysis will include a cohort receiving R-CHOP alone without consolidative RT. This analysis aims to contribute to the evolving standard of care for GDLBCL, providing insights for future treatment strategies. Research Sponsor: None.

Incidence of central nervous system relapse in primary mediastinal B-cell lymphoma: Implications for central nervous system prophylaxis.

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Background: Primary mediastinal large B-cell lymphoma (PMBCL) is an uncommon type of aggressive B-cell non-Hodgkin lymphoma. PMBCL has distinct clinicopathologic features compared to diffuse large B-cell lymphoma but shares some clinical and biologic features with nodular sclerosis classic Hodgkin lymphoma (cHL). Central nervous system (CNS) relapse is exceedingly rare in cHL, therefore one may expect that CNS relapse in PMBCL is also uncommon. Herein, we examined the incidence of CNS relapse in patients with PMBCL. **Methods:** Patients with newly diagnosed PMBCL seen at Mayo Clinic between 1/2002 and 4/2023 were identified from the Mayo Clinic Lymphoma Database. Clinical features, treatment details and outcomes were abstracted from medical records. The CNS relapse rate was calculated using a competing risk model, with death considered as a competing risk. **Results:** A total of 154 PMBCL cases were identified. The median age at diagnosis was 38 years (range 18-77) and 60.4% were female. The distribution of CNS-IPI was low-risk in 80 (51.9%) patients, intermediate-risk in 43 (27.9%), and high-risk in 3 (1.9%), and data were missing for 28 patients (18.2%). 78 patients (50.6%) received R-CHOP and 76 patients (49.4%) received R-DA-EPOCH as frontline therapy. High-dose methotrexate (HD-MTX) for CNS prophylaxis was administered to 5 patients (all treated with R-CHOP). 20 patients received intrathecal (IT) chemotherapy (methotrexate and/or cytarabine) for CNS prophylaxis (4 with R-CHOP [1 received HD-MTX too],16 with R-DA-EPOCH). The median follow-up was 39 months (95% CI 28.2-49.8). Only 3 patients had CNS relapse, all associated with systemic relapse (1 concurrent, 1 had CNS relapse 8.8 months after systemic relapse, 1 had CNS relapse 2 months before systemic relapse). The cumulative incidence of CNS relapse for the entire cohort was 1.43% (95% CI 0.3%-4.6%) at 1 year and 2.21% (95% CI 0.6%-5.8%) at both 2 and 5 years. For those who did not receive CNS prophylaxis (n=130), the incidence was 0.86% (95% CI 0.1%-4.3%) at 1 year and 1.82% (95% CI 0.4%-5.8%) at both 2 and 5 years. All 3 patients who experienced CNS relapse had R-CHOP as frontline therapy; two patients did not receive any CNS prophylaxis, while 1 patient received IT CNS prophylaxis. **Conclusions:** The risk of isolated CNS relapse in PMBCL appears to be very low, even in patients who did not receive CNS prophylaxis. While some patients may experience CNS relapse associated with systemic relapse, the overall incidence was low (1.43% at 1 year and 2.21% at 2 and 5 years). The rarity of isolated CNS relapse in PMBCL suggests that routine CNS prophylaxis may not be necessary as part of initial therapy.
Research Sponsor: None.

Outcomes and prognostic factors of patients diagnosed with relapsed/refractory primary B-cell lymphoma: A retrospective study.

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Background: PMBCL is an aggressive form of large B-cell lymphoma (LBCL) but has a unique gene expression profiling signature that more closely resembles Hodgkin's lymphoma. Treatment of R/R PMBCL is largely extrapolated from trials in LBCL with few PMBCL patients included. Randomized trials leading to use of CART as second line treatment for patients with primary refractory or early relapsed LBCL enrolled ≤ 10% PMBCL patients (ZUMA-7 and TRANSFORM). In the rituximab era, there is a paucity of data on the efficacy and outcomes of salvage therapy followed by high-dose chemotherapy and autologous stem cell transplant (HDT/ASCT) in PMBCL. **Methods:** We conducted a retrospective study of patients with PMBCL, histologically confirmed at the University of Michigan, diagnosed between 2001 and 2023. **Results:** 70 patients were included with a median age of diagnosis of 31.5 years and 57% female. R-DA-EPOCH was the most commonly used first line therapy (FLT) in 58 patients (83%). 10 patients (14%) were treated with R-CHOP with or without consolidative radiation. 65 patients had end of treatment (EOT) PET/CT: 45 (69%) patients achieved a Deauville (D) 1-3 response, 15 (23%) had D4 response, 5 (8%) had D5 response. 4 (26%) of patients with D4 response and all patients with D5 response ultimately developed R/R disease. 5 had EOT response assessed by CT and all deemed to have complete response. 16 patients (23%) developed R/R disease with a median time to relapse of 8.3 months. All relapses occurred within 2 years: 5 patients with primary refractory disease, 10 patients with relapse <12 months and only 1 patient with relapse >12 months. Platinum based chemotherapy with RICE, RDHAP or RGemOx were the most common salvage regimens (N=11) with ORR 60% among evaluable patients. 5 patients received HDT/ASCT with ORR of 80% and CR rate of 80%. Only 1 patient progressed following ASCT, who had relapsed >12 months after FLT. 9 patients (13%) had high-risk extranodal disease (EN) such as renal, adrenal or breast sites with 2 patients (11%) developing CNS relapse. At a median follow up time of 6.5 years, 5-year PFS and OS for the entire cohort was 76% and 96%, respectively. For patients with R/R disease, 5-year PFS and OS was 49% and 84%, respectively. **Conclusions:** We report high response rates to platinum-based salvage chemotherapy in the rituximab era, even with primary refractory or early relapsed disease. Higher PFS and OS suggests improved outcomes with HDT/ASCT compared to historical outcomes in R/R LBCL (SCHOLAR-1). Larger prospective studies are needed to determine whether HDT/ASCT or CART is the optimal approach in R/R PMBCL. Research Sponsor: None.

Characteristics and treatment in R/R PMBCL.

Female	N = 10, (63%)	N (%)
sIPI	0-1	6, (50%)
	2-3	2, (13%)
	4-5	(0%)
SLT	Platinum based salvage	11, (69%)
	HDT/ASCT	6, (50%)
	HyperCVAD	2, (13%)
	Rituximab + Bendamustine	1, (6%)
	*Rituximab + Ibrutinib + IT MTX	1, (6%)
	*Rituximab + AraC + RT	1, (6%)

*CNS relapse

Lacutamab in patients with relapsed and/or refractory mycosis fungoides: Results from the TELLOMAK phase 2 trial.

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Background: Cutaneous T-cell lymphoma (CTCL) is a rare form of non-hodgkin's lymphoma. The most common type of CTCL is Mycosis Fungoides (MF) accounting for 50-60% of cases, while Sezary Syndrome, the leukemic variant of MF accounts for 2-5% of cases. Extracutaneous involvement occurs mainly in lymph nodes or blood; 25% of patients (pts) are diagnosed at advanced stage with a 5-year survival of 15-25%. KIR3DL2 is a killer immunoglobulin-like receptor, expressed in 90% of SS pts, and 50% of MF pts. Lacutamab is a first-in-class monoclonal antibody designed to specifically deplete KIR3DL2-expressing cells via antibody-dependent cell-cytotoxicity and phagocytosis. **Methods:** TELLOMAK is an international, open-label, multi-cohort phase 2 trial (NCT03902184). MF pts who had received at least 2 prior systemic therapies were allocated to different cohorts according to KIR3DL2 expression in skin. Lacutamab 750 mg is administered as an intravenous infusion until disease progression or unacceptable toxicity. Primary endpoint was Objective Response Rate (ORR) by global response score based on the evaluation of 4 compartments: skin, blood, lymph nodes and viscera according to International Consensus criteria (Olsen 2011; sensitivity analysis vs revised Olsen 2022). Secondary endpoints included other efficacy endpoints, safety, and quality of life. Here we report data of all MF patients, and according to KIR3DL2 status. **Results:** At the data cutoff of October 13, 2023, recruitment was completed, with 107 pts enrolled. Median age was 62 years. Median number of previous systemic lines was 4 (range: 1-14). Median follow-up was 11.8 months (m) (95% CI 9.9-13.8). ORR was 16.8% (CI 10.9, 25.0; Olsen 2011), and 22.4% (CI 15.6, 31.2; Olsen 2022), response in skin and blood was 29.0% (CI 21.2, 38.2) and 40.0% (CI 24.6, 57.7) respectively. Median time to response was 1.0 months and median PFS 10.2m (CI 6.5, 16.8). Among the KIR3DL2 ≥1% pts (N=48), ORR was 20.8% (CI 11.7,34.3; Olsen 2011), and 29.2% (CI 18.2, 43.2; Olsen 2022), response in skin and in blood was observed in 33.3% (CI 21.7, 47.5) and 41.2% (CI 21.6, 64.0) respectively. Median time to response was 1.0 month and median PFS was 12.0 m (CI 5.6, 20.0). Median duration of response was not reached. Grade ≥ 3 Treatment-related (TR) Treatment-Emergent Adverse events (TEAEs) were observed in 4/107 (3.7%) pts, serious TR TEAEs were observed in 4/107 (3.7%) pts and 3/107 (2.8%) pts discontinued study drug due to TR TEAEs. The most common (>10%) TR TEAEs were fatigue (11.2%), nausea (11.2%), asthenia (10.3%), and arthralgia (10.3%). **Conclusions:** The data from the heavily pre-treated MF population enrolled to the TELLOMAK study confirms promising clinical activity of lacutamab regardless of KIR3DL2 expression, with a favorable safety and tolerability profile. These data support the further development of lacutamab in an effort to bring improved treatments to patients with CTCL. Clinical trial information: NCT03902184. Research Sponsor: INNATE PHARMA.

TPS7083 Poster Session

A phase I, first-in-human study of ONO-7018 in patients with relapsed/refractory non-Hodgkin lymphoma or chronic lymphocytic leukemia.

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Background: Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) is a key component of the caspase recruitment domain-containing protein 11 (CARD 11)-B-cell lymphoma/leukemia 10 (BCL 10)-MALT1 signalosome complex, which activates nuclear factor-kappaB (NF-κB) signaling in response to B-cell–receptor or T-cell–receptor stimulation. Activation of NF-κB signaling promotes survival and proliferation of B-cell lymphoma and T-cell lymphoma. ONO-7018 is an oral, potent, and selective MALT1 inhibitor that has demonstrated preclinical efficacy in several lymphoma models (Morishita D, et al. *Blood.* 2020). Therefore, ONO-7018 has therapeutic potential for non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). This study aims to determine the maximum tolerated dose (MTD) and to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of ONO-7018 as monotherapy in patients with relapsed or refractory NHL or CLL. **Methods:** This Phase I, first-in-human, open-label, multicenter study will be done in two parts, a dose-escalation phase (part 1) and a dose-expansion phase (part 2). An estimated 54 eligible patients will be enrolled. Patients must be adults with relapsed/refractory NHL or CLL with measurable disease; all acute toxic effects of prior antitumor therapy should be grade ≤1; have Eastern Cooperative Oncology Group performance status 0 to 2; and have adequate bone marrow, renal, and hepatic function. Exclusion criteria include history of other lymphoid malignancy, central nervous system involvement, active autoimmune disease, systemic and active infection, serious or uncontrolled medical disorder, and patient inability to swallow tablets. ONO-7018 will be administered orally. In part 1, patients will be assigned to a dose level cohort (≤4 dose levels: DL1-DL4) using a 3+3 dose-escalation design. In part 2, patients will be given the recommended dose level from part 1, following safety review. The primary endpoints include dose-limiting toxicity, MTD, and treatment-emergent adverse events. Secondary endpoints include pharmacokinetics, objective response rate, duration of response, progression-free survival, and overall survival. The study began February 13, 2023, and is currently recruiting; part 1 is ongoing. Clinical trial information: NCT05515406. Research Sponsor: Ono Pharmaceutical Co. Ltd.

TPS7084 **Poster Session**

EPCORE FL-2: Phase 3 trial of epcoritamab with rituximab and lenalidomide (R^2) vs chemoimmunotherapy or R^2 in previously untreated follicular lymphoma.

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Background: Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma. Most patients with advanced-stage FL in need of systemic therapy are treated with an anti-CD20 monoclonal antibody (eg, rituximab [R] or obinutuzumab [G]) with cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] or bendamustine [benda]). Recent studies have shown R plus lenalidomide (R^2) is a potent FL treatment in the 1L and relapsed or refractory (R/R) settings and is a promising backbone for combination therapies. Epcoritamab, a subcutaneous CD3xCD20 bispecific antibody, received breakthrough therapy designation by the FDA for R/R FL after ≥2 lines of systemic therapy. In the phase 1/2 trial (NCT04663347), epcoritamab plus R^2 demonstrated high complete response (CR) rates in the 1L and R/R settings. The objective of this trial is to evaluate the safety and efficacy of 1L epcoritamab plus R^2 vs CIT in patients with FL. **Methods:** EPCORE FL-2 (NCT06191744) is a global, randomized, open-label phase 3 trial. Eligible adult patients must have CD20+ histologically confirmed classic FL (previously grade 1–3A), stage III or IV disease (or bulky stage II), and in need of systemic treatment by meeting GELF criteria. Approximately 1080 patients will be randomized to 3 treatment arms (Table). Patients achieving CR or PR upon 6 cycles will move to epcoritamab on day 1 of cycles 7–12 (28-day cycles) and 13–21 (56-day cycles). After 120 weeks of treatment, patients will be followed for progression and survival. Dual primary endpoints will be CR rate at 30 months and progression-free survival in arm A vs arm B. Key secondary efficacy endpoints include overall survival, minimal residual disease negativity, and changes in patient-reported outcomes on the physical functioning scale of the European Organization for Research and Treatment of Cancer Quality of Life-C30 Questionnaire from baseline to week 25. Safety endpoints include incidence and severity of adverse events (AEs), including AEs of special interest (cytokine release syndrome, immune effector cell–associated neurotoxicity syndrome, and clinical tumor lysis syndrome). The study is open for enrollment. Clinical trial information: NCT06191744. Research Sponsor: This study was funded by AbbVie and Genmab A/S.

Group	Treatment
Arm A	Epcor + R^2 for 6 x 28-d cycles (24 wk); if CR or PR, epcor + lenalidomide for 6 x 28-d cycles (24 wk); then epcor for 9 x 56-d cycles (72 wk)
Arm B	Investigator's choice: either G/R-CHOP for 6 x 21-d cycles + 2 x 21-d cycles of G/R (24 wk), or G/R-benda for 6 x 28-d cycles (24 wk); if CR or PR, G/R for 12 x 56-d cycles (96 wk)
Arm C	R^2 for 6 x 28-d cycles (24 wk); if CR or PR, lenalidomide for 12 x 28-d cycles and R every 8 wk, then R for 6 x 56-d cycles (96 wk)

TPS7085 Poster Session

Phase 2 open label, multicenter study evaluating CRG-022, a CD22-directed autologous CAR T-cell therapy, in patients (pts) with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) after CD19-directed CAR T-cell therapy.

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Background: Autologous (auto) CD19-directed CAR T-cell therapy can induce long-term remissions for pts with R/R LBCL but approximately 60% will experience disease progression resulting in poor outcomes (Neelapu, 2023; Zurko, 2023). CRG-022 is a novel CAR T-cell product targeting CD22, a common B-cell antigen widely expressed in LBCL. Key features of CRG-022 include a fully human scFv derived from the m971 monoclonal antibody and 4-1BB/CD3z intracellular signaling domains (Singh, 2021). This CD22 CAR construct was developed at the National Cancer Institute and was investigated in phase (ph) 1 studies of pediatric/young adult pts with R/R CD22+ malignancies (Shah, 2020; NCT02315612) and at Stanford University in adults with R/R LBCL (Baird, 2021; NCT04088890) primarily in pts who received prior CD19-directed CAR-T therapy. The Stanford ph 1b study reported an overall response rate (ORR) and complete response rates of 66% and 52%, respectively in 29 pts treated at the recommended Phase 2 dose (RP2D) of $1x10^6$ CAR+ T cells/kg (Frank, 2023). After a median follow-up of 27.3 months, the median overall survival had not been reached at the RP2D (Su, 2023). At the RP2D, no grade >3 cytokine release syndrome (CRS), immune-effector cell associated neurotoxicity syndrome (ICANS), or immune effector cell associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) occurred; two pts (7%) developed grade 2 IEC-HS (Su, 2023; Srinagesh, 2023). Based on these notable results, this potentially pivotal ph 2 trial has been initiated. **Methods:** This Phase 2 study will evaluate the safety/efficacy of CRG-022 at $1x10^6$ CAR+ T cells/kg in pts with R/R LBCL whose disease has progressed after CD19-directed CAR T-cell therapy. The primary endpoint is ORR according to Lugano response criteria (Cheson, 2014) by blinded independent review. Adverse events (AEs) are graded per CTCAE v5 except with CRS, ICANS, and IEC-HS graded per ASTCT guidelines. Pts with diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma, DLBCL transformed from follicular or marginal zone lymphoma, follicular large B-cell lymphoma (FLBL)/FL Grade 3B, and primary mediastinal B-cell lymphoma are eligible. Other eligibility criteria include adequate hematologic and organ function, and no prior allogeneic stem cell transplant. Pts with prior treatment to both a CD19-directed auto CAR-T and a bispecific T-cell engaging antibody are also eligible within a separate cohort. Lymphodepletion with fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day for 3 days will be administered ahead of a single infusion of CRG-022. The study is designed to enroll approximately 123 pts. Study enrollment commenced in the US in August 2023, with 9 pt infused as of 08 JAN 2024. Clinical trial information: NCT05972720. Research Sponsor: None.

TPS7086 Poster Session

Phase 3 trial evaluating efficacy and safety of odronextamab plus CHOP vs rituximab plus CHOP in previously untreated diffuse large B-cell lymphoma (DLBCL; OLYMPIA-3).

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Background: Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) remains a standard of care first-line (1L) treatment for patients (pts) with DLBCL. However, poor outcomes persist for certain DLBCL pt subgroups, including those with high-risk features: activated B-cell-like (ABC) cell of origin (5-yr progression-free survival [PFS]/overall survival [OS] 48%/56%), *MYC*and *BCL2*rearrangements (median OS 15 months), or International Prognostic Index [IPI] score 4–5 (5-yr PFS/OS 46%/54%). Improving outcomes through effective 1L treatment continues to be important, highlighted by the dismal prognosis in pts who are primary refractory (2-yr OS 24%) or who relapse early after 1L treatment (4-yr OS 30%). Odronextamab, a CD20×CD3 bispecific antibody, showed encouraging efficacy (objective response rate 52%; complete response [CR] rate 31%; 47% maintained CR at 2 years) and generally manageable safety as a monotherapy in pts with heavily pretreated relapsed/refractory DLBCL, including in pts who were anti-CD20 antibody refractory (Ph 2 ELM-2 study; Ayyappan, et al. ASH 2023). These data provide the rationale to evaluate the efficacy and safety of odronextamab plus CHOP (O-CHOP) vs R-CHOP in pts with previously untreated DLBCL. **Methods:** OLYMPIA-3 (NCT06091865) is a Ph 3, randomized, open-label, multicenter study of O-CHOP vs R-CHOP in pts with previously untreated DLBCL and intermediate- or high-risk features. The study consists of Part 1A (dose escalation), Part 1B (dose optimization), and Part 2 (randomized controlled). Part 1A will assess the safety of O-CHOP. In Part 1B, pts will be randomized 1:1 to one of two O-CHOP regimens, selected based on Part 1A results. In Part 2, pts will be randomized 1:1 to O-CHOP or R-CHOP, with odronextamab dosing dependent on Part 1 results, and R-CHOP given per standard practice. Intravenous odronextamab will be administered weekly from Cycle (C) 1 Day (D) 8 until C5D8, with step-up dosing during C1 and C2, then every 2 weeks until the end of C6. CHOP will be administered in six 21-day cycles, starting on C1D1. Key inclusion criteria: aged ≥18 years; untreated CD20+ DLBCL; ECOG PS ≤2; and IPI score ≥2. Pts with central nervous system lymphoma, Grade ≥3 peripheral neuropathy, or an active infection are excluded. The primary endpoints are the incidence of dose-limiting toxicities, and incidence and severity of treatment-emergent adverse events (Part 1), and PFS by independent central review (Part 2). Part 2 key secondary endpoints are event-free survival and CR rate (both by independent central review), as well as OS. Other secondary endpoints are minimal residual disease (by ctDNA) and patient-reported outcomes (EORTC QLQ-C30, FACT-LymS, PGIS, PGIC, and EQ-5D-5L). The trial is currently recruiting and is expected to enroll up to 64 pts in Part 1 and ~840 pts in Part 2 at ~200 global sites. Clinical trial information: NCT06091865. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS7087 Poster Session

CELESTIAL-TNCLL: An ongoing, open-label, multiregional, phase 3 study of sonrotoclax (BGB-11417) + zanubrutinib vs venetoclax + obinutuzumab for treatment-naïve (TN) CLL.

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Background: The combination of venetoclax (ven), the first-generation BCL2 inhibitor, and ibrutinib, a BTK inhibitor, has demonstrated efficacy in patients with CLL (Wierda et al. *J Clin Oncol.* 2021); however, the toxicity profile of this regimen suggests a need for a more tolerable BTK/BCL2 inhibitor combination. Sonrotoclax, a next generation BCL2 inhibitor, is a more selective and more pharmacologically potent inhibitor of BCL2 than venetoclax. In a phase 1 study in patients with TN CLL treated with sonrotoclax + zanubrutinib, efficacy data was promising with ORR and 1-year progression-free survival (PFS) rates of 100% and deep responses based on undetectable measurable residual disease at $<10^{-4}$ sensitivity (uMRD4). The most common grade ≥3 TEAE was neutropenia, and no tumor lysis syndrome or cardiac toxicity was observed (Tam et al. *Blood*. 2023). Zanubrutinib, a next-generation BTK inhibitor, significantly improved PFS and had a more tolerable safety profile, including fewer cardiac adverse events vs ibrutinib in a randomized, head-to-head study of patients with CLL/SLL (Brown et al. *N Engl J Med*. 2023). Presented here is the design of a phase 3 trial aimed at comparing the efficacy of sonrotoclax + zanubrutinib vs ven + obinutuzumab (obi) in patients with TN CLL. **Methods:** CELESTIAL-TNCLL (BGB-11417-301; NCT06073821) is a randomized, open-label, phase 3 study. Eligible patients must have previously untreated CLL that requires treatment per 2018 iwCLL criteria, measurable disease by CT/MRI, an ECOG performance score of 0-2, and adequate hematologic and organ function. Approximately 640 patients will be randomized 1:1 to receive either 3 cycles of zanubrutinib monotherapy (320 mg total daily dose, orally), followed by zanubrutinib + sonrotoclax for 12 cycles, or standard ven + obi treatment for 12 cycles. Randomization will be stratified by age (<65 vs ≥65 years) and IGHV and del(17p)/*TP53* mutation status. The primary endpoint is PFS as assessed by independent review committee (IRC) according to 2018 iwCLL guidelines with modifications for treatment-related lymphocytosis for patients with CLL (Cheson et al. 2012). Key secondary endpoints include complete response rate (CRR), defined as CR or CR with incomplete hematopoietic recovery, assessed by IRC; rates of uMRD4 in bone marrow and peripheral blood at the first post-treatment follow-up visit based on next-generation sequencing by clonoSEQ; and overall survival. Other secondary endpoints include PFS as assessed by investigator (INV); CRR by INV; rate of uMRD4 based on flow cytometry; overall response rate by IRC and INV; duration of response by IRC and INV; patient-reported outcomes; and safety and tolerability. Recruitment is ongoing. Clinical trial information: NCT06073821. Research Sponsor: BeiGene, Inc.

TPS7088 **Poster Session**

BELLWAVE-011: Phase 3 randomized trial of nemtabrutinib versus ibrutinib or acalabrutinib in untreated chronic lymphocytic leukemia/small lymphocytic lymphoma.

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Background: Bruton tyrosine kinase (BTK) inhibitors have significantly improved survival in patients (pts) with chronic lymphocytic leukemia (CLL). Nemtabrutinib is a reversible non-covalent inhibitor of wild-type and C481-mutated BTK that has shown promising antitumor activity in pts with CLL (Woyach JA et al. Cancer Discovery 2023). In this ongoing trial, we evaluate the efficacy and safety of nemtabrutinib versus investigator's choice of ibrutinib or acalabrutinib in pts with untreated CLL/small lymphocytic lymphoma (SLL) requiring therapy (NCT06136559). **Methods:** This randomized, open-label, parallel group, active-controlled phase 3 trial will enroll approximately 1200 pts aged ≥18 years. Eligible pts will have confirmed CLL/SLL with active disease based on the IWCLL criteria, which include one of the following: 1) progressive marrow failure or lymphocytosis, 2) massive, progressive, or symptomatic splenomegaly or lymphadenopathy, 3) autoimmune complications, 4) extranodal involvement, or 5) disease-related symptoms. The study will enroll patients who are treatment naïve, with an ECOG performance status 0-2, adequate organ function, and provide blood, bone marrow, and/or a lymph node sample. Pts are excluded if they have Richter Transformation, central nervous system (CNS) involvement by CLL/SLL, an active second malignancy, or a severe bleeding disorder. Pts will be randomized 1:1 to receive oral nemtabrutinib 65 mg QD, or investigator's choice of oral ibrutinib 420 mg QD or acalabrutinib 100 mg BID. Randomization will be stratified by *TP53*aberration, clinical stage, investigator's choice of comparator, and region. Treatment will continue on both arms until unacceptable toxicity, disease progression, or withdrawal. Disease response assessments by physical examination, constitutional symptoms, imaging, and evaluation of blood and bone marrow will be performed Q12W up to week 97, and Q24W thereafter. Primary efficacy endpoints are objective response (OR) and progression free survival (PFS) by BICR per iwCLL 2018 criteria. Secondary endpoints are overall survival (OS), duration of response (DOR) by BICR per iwCLL 2018, and safety. OR will be tested via a non-inferiority comparison, while PFS and OS will be tested for superiority. Adverse events will be monitored throughout the trial and graded per NCI CTCAE v5.0 and iwCLL scales. Enrollment in this trial is ongoing. Clinical trial information: NCT06136559. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; N/A.

TPS7089 Poster Session

BELLWAVE-010: A phase 3 study of nemtabrutinib plus venetoclax versus venetoclax plus rituximab (VR) in previously treated patients (pts) with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

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Background: VR is a standard of care option for pts with CLL/SLL who have relapsed after ≥1 line of prior therapy. However, there is an unmet need for more effective treatments. Bruton tyrosine kinase (BTK) plays an important role in the pathogenesis of CLL. Nemtabrutinib is a BTK inhibitor that targets both wild type and C481-mutant forms of BTK. In the ongoing BELLWAVE-001 study, nemtabrutinib demonstrated manageable safety and durable antitumor activity in pts with R/R CLL/SLL with and without C481 mutations. The randomized, open-label, phase 3 BELLWAVE-010 study (NCT05947851) is designed to evaluate the efficacy and safety of nemtabrutinib + venetoclax versus VR as second-line or later treatment for pts with R/R CLL/SLL. **Methods:** Eligible pts are aged ≥18 years with active R/R CLL/SLL after ≥1 prior therapy per iwCLL 2018 criteria and an ECOG PS of 0-2. Approximately 720 pts will be enrolled in 2 parts. Part 1 is an open-label, nonrandomized dose escalation and confirmation phase to evaluate safety and determine the optimal dose of nemtabrutinib + venetoclax. Part 1 will enroll 30 pts to establish the dose of nemtabrutinib using a modified toxicity probability interval design. Pts will receive nemtabrutinib at 2 dose levels (45 mg PO QD starting dose, escalating to 65 mg PO QD) for 28 days, followed by nemtabrutinib + venetoclax (20-400 mg PO QD ramp up over 4 weeks). Part 2 is an open-label, parallel-group, randomized phase comparing the efficacy and safety of nemtabrutinib + venetoclax with VR. In part 2, approximately 690 pts will be randomly assigned 1:1 to receive either nemtabrutinib at the recommended dose for 28 days followed by the nemtabrutinib + venetoclax or venetoclax + rituximab (or rituximab biosimilar; 375 mg/m^2 at week 6, followed by 500 mg/m^2 every 4 weeks starting at week 10 until week 26 [total 6 doses]). Study treatment will continue for approximately 2 years or until unacceptable toxicity, disease progression, or other discontinuation criteria are met. Randomization will be stratified by BTK-C481 mutation status (detected vs not detected), geographic region (US/Canada vs Europe vs rest of world) and risk (high risk [del(17p) and/or *TP53*-mutated and/or IGHV-unmutated] vs low risk [absence of high-risk factors]). The primary end point for part 2 is progression-free survival by blinded independent central review (BICR) per iwCLL 2018 criteria. Secondary end points for part 2 are undetectable minimal residual disease in bone marrow at month 14 by central laboratory assessment, objective response rate (ORR), and duration of response by BICR per iwCLL 2018 criteria, overall survival, and safety. Exploratory end points are ORR including partial response with lymphocytosis, pharmacokinetics, and health-related quality of life. Recruitment is ongoing. Clinical trial information: NCT05947851. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS7090 **Poster Session**

BGB-11417-203: An ongoing, phase 2 study of sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, in patients with Waldenström macroglobulinemia.

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Background: Bruton tyrosine kinase (BTK) inhibitors and anti-CD20 antibody-based systemic therapy are included within the preferred treatment algorithms for Waldenström macroglobulinemia (WM). However, to date, no treatments have been approved for patients with WM that is refractory to both BTK inhibitors and anti-CD20 therapy. Venetoclax, the first-generation BCL2 inhibitor, has demonstrated clinical activity in patients with relapsed/refractory (R/R) WM (Castillo et al. *J Clin Oncol*. 2022), but it has no regulatory approvals in WM. Sonrotoclax, a next generation BCL2 inhibitor, is more selective and a more pharmacologically potent inhibitor of BCL2 than venetoclax. In a phase 1 trial, sonrotoclax monotherapy was well tolerated at all dose levels tested up to 640 mg and showed promising evidence of antitumor activity in patients with R/R WM (Soumerai et al. *Blood*. 2022). Based on the data from these earlier studies, a phase 2 study of sonrotoclax monotherapy in patients with WM has been initiated and is currently recruiting. **Methods:** BGB-11417-203 (NCT05952037) is an open-label, international, phase 2 study. Eligible patients have histologically confirmed WM that is R/R to both BTK inhibitor therapy and anti-CD20–based systemic therapy combined with chemotherapy or a proteasome inhibitor (PI; Cohort 1); R/R to anti-CD20–based systemic therapy combined with chemotherapy or a PI and who are intolerant to BTK inhibitor therapy (Cohort 2); or R/R to a BTK inhibitor and who are unsuitable for chemoimmunotherapy (Cohort 3). Patients who have received previous treatment with a BCL2 inhibitor are ineligible. Approximately 85 patients will be enrolled across cohorts and will receive sonrotoclax until disease progression, death, unacceptable toxicity, patient withdrawal, loss to follow-up, or study termination. The primary endpoint is major response rate (MRR; defined as partial response or better) in Cohort 1 per IWWM-11 criteria, as assessed by independent review committee (IRC). Key secondary endpoints include MRR assessed by investigator (INV) in Cohort 1 and by IRC and INV in both Cohorts 2 and 3; overall response rate, duration of response, and progression-free survival by IRC and INV; overall survival; and safety and tolerability. Patient recruitment is ongoing in Australia, the US, China, and Europe. Clinical trial information: NCT05952037. Research Sponsor: BeiGene, Inc.

TPS7091 **Poster Session**

A first-in-human study of the potent and highly selective BTK degrader ABBV-101 in patients with relapsed/refractory B-cell malignancies.

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Background: Bruton tyrosine kinase (BTK) is a clinically validated target with an integral role in the proliferation and survival of neoplastic cells in several B-cell malignancies. Inhibitors of BTK, such as ibrutinib, have revolutionized the treatment landscape for B-cell malignancies. However, long-term use can lead to disease progression and clinical resistance associated with mutations in BTK. ABBV-101 is a reversible BTK degrader. By preclinical kinome profiling, ABBV-101 has demonstrated high selectivity with the potential for best-in-class AE profile. ABBV-101 has also shown potent activity against BTK wildtype and multiple therapy-resistant mutant forms. Degradation eliminates BTK scaffolding and enzymatic functions, which has led to deeper, more durable responses vs covalent and reversible BTKi in animal models (Pan C, et al. ASH 2023). Herein, we describe the first-in-human study of ABBV-101 monotherapy in patients with relapsed/refractory B-cell NHL. **Methods:** This international phase 1, open-label, multicenter study (NCT05753501) is evaluating the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of ABBV-101. Eligible patients(≥18 years) have measurable disease, received ≥2 prior systemic therapies, and have no available therapies known to provide clinical benefit.Primary objectives are to characterize safety and tolerability of ABBV-101; secondary objectives are to evaluate PK and preliminary efficacy. The study is conducted in 2 parts: dose escalation (part 1) and dose expansion (part 2). Part 1 aims to establish the maximum administered dose and maximum tolerated dose of ABBV-101 guided by a Bayesian optimal interval design; additional patients may be enrolled to a previous dose level to further explore safety, PK, and efficacy. Patients with WHO-defined chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma (including Waldenström macroglobulinemia), and transformed indolent NHL (including Richter's transformation) are eligible. Part 2 will further characterize the safety and preliminary efficacy of ABBV-101; patients diagnosed with CLL/SLL (up to 3 dose cohorts) and non-germinal center DLBCL (1 cohort) are being enrolled. ABBV-101 is administered orally until disease progression, intolerable toxicity, or other study discontinuation criteria are met. Safety assessments include, but are not limited to, AEs, clinical laboratory parameters, vital signs, and ECG. Response evaluations are performed per disease-specific response criteria at screening and every 8 weeks (1st year), 3 months (2nd year), or 4 months (3rd year onward) until progressive disease. Enrollment is ongoing with active sites in the US and Japan. Clinical trial information: NCT05753501. Research Sponsor: AbbVie; n/a.

TPS7092 **Poster Session**

First-line treatment of follicular lymphoma (FL) with golcadamide, rituximab +/- nivolumab: An umbrella randomised phase 2 investigator-led study.

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Background: The most common therapy FL pts receive remains chemotherapy which yields high efficacy but also significant toxicity.(Marcus 2017, Rummel 2013). FL pts are largely aged over 65 and may require treatment multiple times over their disease course thus novel regimens which enhance efficacy and minimise toxicity are highly desirable. FL patient (pt) outcomes are influenced by tumor microenvironment composition and manipulation with immunotherapy. Ikaros and Aiolos, key cell development and homeostasis transcription factors are upregulated in FL. Cereblon-modulating compounds (CELMoDs) such as golcadomide (G) promote degradation of these with demonstrated efficacy alone or with rituximab (R) in FL (responses-ORR- upto 75% in heavily pre-treated FL pts) (Morschhauser 2018, Michot 2021). We reported favourable efficacy of nivolumab (N) a PD1 inhibitor plus R in 1L treatment of FL (ORR 92% complete response CR 54%). (Hawkes 2021).This study ('TOP-FLOR'; NCT05788081) builds on these findings and potential immunomodulatory synergy to explore the efficacy and safety of R + G, a novel CELMoD +/- N in treatment-naïve advanced stage FL pts. **Methods:** This is an open label multicentre umbrella Bayesian Optimal randomised Phase 2 trial (n=40). Eligibility includes: age >18 years, treatment-naïve, stage II-IV, low grade FL, ECOG 0-2. Pts from 5 Australian sites are randomised 1:1 to receive 8 cycles of R-G +/-N 8 cycles of 28 days (D) each as follows: Arm A; R 375 mg/m2 IV D1 + G 0.4 mg orally D1- 14; Arm B; R-G as above +N 480mg IV D1. All pts in partial response (PR) or CR post cycle 8 receive 8 doses of 12-weekly R maintenance. The primary endpoint (EP) is CR rate post induction in the absence of prohibitive toxicity (CTCAE V5.0). Secondary EP are overall toxicity, ORR (as per Lugano criteria), time to treatment failure, progression free survival, overall survival. Exploratory EP include: pt reported outcomes, PET radiomics, laboratory biomarkers. Study assessments include safety assessments every cycle until D28 post final study drug delivery. Response assessments (PET/CT), pt reported outcomes & biomarker bloods are performed at baseline, post cycles 2, 5 & 8, then 6 monthly during R maintenance. Futility analysis occurs after 11 pts are recruited to each arm with < 7 pts achieve the primary EP. Treatment arms will not be formally compared. Kaplan-Meier analysis will be used to report survival probabilities. This trial received IRB approval on 14 July 2023 (HREC/88597/Austin-2023). To date 15 pts have been randomised. Clinical trial information: NCT05788081. Research Sponsor: Bristol Myers Squibb.

TPS7093 Poster Session

Phase 3 trial evaluating the efficacy and safety of odronextamab versus standard-of-care (SOC) therapy in relapsed/refractory (R/R) aggressive B-cell non-Hodgkin lymphoma (B-NHL; OLYMPIA-4).

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Background: Approximately 30–40% of patients (pts) with high-risk, aggressive B-NHL are refractory to or relapse after first-line chemoimmunotherapy. Although autologous stem cell transplantation (ASCT) and chimeric antigen receptor (CAR) T-cell therapies are available in the second line, access, eligibility, tolerability, and cost pose limitations for pts, and there remains a need for well-tolerated, effective off-the-shelf therapies in this setting. Odronextamab, a CD20×CD3 bispecific antibody, demonstrated encouraging clinical activity (complete response [CR] rate 31.5%; median duration of CR 17.9 months) and a generally manageable safety profile as monotherapy in pts with heavily pretreated R/R diffuse large B-cell lymphoma (DLBCL) in the Phase 2 ELM-2 study (Ayyappan, et al. ASH 2023). This study will evaluate odronextamab versus SOC treatment in pts with DLBCL who have relapsed early (within 1 year) or were refractory to first-line therapy. **Methods:** OLYMPIA-4 (EudraCT 2022-502783-21-00) is a Phase 3, randomized, open-label, multicenter study of odronextamab versus SOC in pts with previously treated aggressive B-NHL. Odronextamab will be administered intravenously in 21-day cycles, with step-up dosing during Cycle (C) 1 to mitigate the risk of cytokine release syndrome, at 160 mg on Days 1, 8, and 15 of C2–4, then as maintenance at 320 mg Q2W until one year from the start of treatment, progressive disease, or death. Treatment in the SOC arm consists of physician's choice of salvage therapy with intent to proceed to ASCT. SOC regimens are: ifosfamide, carboplatin, and etoposide (ICE); dexamethasone, cisplatin, and cytarabine (DHAP); or gemcitabine, dexamethasone, and cisplatin (GDP), ± rituximab. Pts will receive up to three 21-day cycles of salvage therapy, followed by ASCT. Pts without an optimal response to salvage therapy or ASCT may cross over to receive one year of odronextamab treatment. Key inclusion criteria: ≥18 years of age; aggressive B-NHL that is primary refractory or relapsed within one year of first-line treatment initiation; intent to proceed to ASCT; measurable disease; ECOG performance status 0–1; and adequate organ and hematologic function. Pts with central nervous system lymphoma or active infection are excluded. The primary endpoint is event-free survival, as assessed by independent central review. Key secondary endpoints are progression-free survival, best overall response, and change from baseline in physical function, as measured by EORTC QLQ-C30. Other secondary endpoints include CR rate, duration of response, overall survival, minimal residual disease, pharmacokinetics, and incidence and severity of treatment-emergent adverse events. The trial is currently recruiting and is expected to enroll ~216 pts at ~200 global sites. Clinical trial information: 2022-502783-21-00. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS7094 Poster Session

Phase 3 trial of odronextamab plus lenalidomide versus rituximab plus lenalidomide in relapsed/refractory (R/R) follicular lymphoma (FL) and marginal zone lymphoma (MZL; OLYMPIA-5).

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Background: FL and MZL are indolent B-cell non-Hodgkin lymphomas (B-NHLs) that are treated in a similar way in the R/R setting. Despite the efficacy of rituximab–lenalidomide (R2) in patients (pts) with R/R FL, and MZL to a lesser extent, a notable proportion fail to achieve an optimal, durable response. Odronextamab is an off-the-shelf, CD20×CD3 bispecific antibody. In the Phase (Ph) 1 ELM-1 study, odronextamab monotherapy showed antitumor activity and a generally manageable safety profile across R/R B-NHL subtypes, including FL and MZL (Bannerji, et al. Lancet Haematol 2022). In the Ph 2 ELM-2 study, odronextamab elicited an objective response rate of 80% and complete response (CR) rate of 73% in pts with heavily pretreated R/R FL (Villasboas, et al. ASH 2023). The rate of treatment-related adverse events leading to treatment discontinuation was 7.8%. These positive data support the evaluation of odronextamab in R/R FL and MZL in earlier lines of therapy. Combining odronextamab with lenalidomide has the potential to improve efficacy in the R/R setting compared with R2.
Methods: OLYMPIA-5 (NCT06149286) is a Ph 3, open-label, randomized study of odronextamab plus lenalidomide versus R2 in pts with R/R FL and MZL. The study consists of Part 1 (safety run-in) followed by Part 2 (randomization). In Part 1, odronextamab and lenalidomide will be administered for 12×28-day cycles or until relapse, progressive disease, withdrawal of consent, or unacceptable toxicity. Odronextamab IV infusion will be administered in a step-up regimen during Cycle (C) 1 to mitigate the risk of cytokine release syndrome, followed by full dose starting from C1 Day 22. In Part 2, pts will be randomized 1:1 to receive 12 cycles of odronextamab plus lenalidomide, or R2 for the first 5 cycles followed by lenalidomide monotherapy for C6–12 per standard schedule (Leonard, et al. *J Clin Oncol* 2019). Key inclusion criteria: aged ≥18 years; histologically confirmed FL Grade 1–3a or MZL (nodal, splenic, or extra nodal) that is refractory or relapsed after ≥2 cycles of prior systemic therapy that included ≥1 anti-CD20 antibody; measurable disease; ECOG PS 0–2; and adequate organ function. Pts with central nervous system (CNS) lymphoma, history of or current relevant CNS pathology, histological evidence of transformation to high-grade or diffuse large B-cell lymphoma, and prior use of lenalidomide or any CD20×CD3 bispecific antibody within the past 6 months are excluded. The Part 2 primary endpoint is progression-free survival as assessed by independent central review. Key secondary endpoints are CR, best overall response, and overall survival. Minimal residual disease (by ctDNA) analysis is an exploratory endpoint. The trial is currently recruiting and is expected to enroll approximately 24–48 pts in Part 1 and 422 pts in Part 2 (352 R/R FL; 70 R/R MZL) at ~200 global sites. Clinical trial information: NCT06149286. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS7095 Poster Session

A phase 1/2, open-label, multicenter trial investigating the safety, tolerability, and preliminary antineoplastic activity of IPH6501, a first-in-class NK cell engager, in patients with relapsed and/or refractory CD20-expressing non-Hodgkin lymphoma.

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Background: The therapeutic landscape for relapsed and/or refractory B-cell non-Hodgkin lymphoma (B-NHL) is evolving to include targeted T-cell based immunotherapies. However, there remains an unmet medical need for patients who are refractory to, relapsing from, or are ineligible for these therapies. Leveraging natural killer (NK) cells emerges as a promising strategy, as demonstrated in a Phase 1 study with IPH6101/SAR'579 in R/R AML (Stein, ASCO 2023; Bajel, ASH 2023), and offers a novel approach that could complement or provide an alternative to T-cell therapies. IPH6501 is a first-in-class tetraspecific antibody-based NK cell engager that simultaneously targets the CD16a and NKp46 receptors on NK cells and CD20 on B-NHL cells. It also includes an engineered IL-2 variant designed with mutations to avoid binding to CD25 (IL-2Rα), limiting Treg activation and potential IL-2 related side effects, whilst inducing NK proliferation. In preclinical animal models, IPH6501 boosted NK cell proliferation and activation, and CD20+ target cell elimination in peripheral blood and tissues, at well-tolerated doses. In samples obtained from R/R B-NHL patients, IPH6501 demonstrated greater killing efficacy compared to a CD3xCD20 T-cell engager, and yet lower cytokine secretion, suggesting a potentially safer profile. **Methods:** This is a global first-in-human, multicenter, open-label Phase 1/2 study to evaluate the safety profile (DLTs and MTD), tolerability according to NCI-CTCAE v5.0 and to determine the RP2D of IPH6501 for patients with B-NHL (NCT06088654). Secondary objectives are to characterize the pharmacokinetic profile and evaluate the immunogenicity of IPH6501. Eligible subjects are aged ≥18 years with advanced, histologically confirmed, CD20+ B-NHL with an ECOG PS ≤2, and without established alternative therapy. Subjects must have received ≥2 prior systemic therapies which may have included astem cell transplant or CAR-T cell therapy. The Phase 1 part of the study will consist of a dose escalation part which will follow a3+3 design to determine the MTD or the highest dose to be tested as defined in protocol if the MTD has not been reached, and a dose assessment part to randomize ≥2 dose levels to determine the RP2D. The Phase 2 part will enroll one or more cohorts of selected B-cell NHL subtypes to be determined at a later stage. Up to 184 subjects will be enrolled, and the study is open in the United States, Australia and Europe. Clinical trial information: NCT06088654. Research Sponsor: Innate Pharma.

TPS7096 **Poster Session**

Phase 3 trial evaluating the efficacy and safety of odronextamab versus investigator's choice in previously untreated follicular lymphoma (OLYMPIA-1).

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Background: Follicular lymphoma (FL) is an incurable disease in which patients will relapse despite the effectiveness of first-line (1L) rituximab-based chemoimmunotherapy (CIT), indicating the need for alternative 1L treatments that can deepen and prolong response. Odronextamab, an off-the-shelf, CD20×CD3 bispecific antibody, showed compelling efficacy and generally manageable safety as a monotherapy at 3L+ for patients with relapsed/refractory (R/R) FL in the Phase 2 ELM-2 study (Villasboas, et al. ASH 2023). Objective and complete response (CR) rates were 80% and 73%, respectively, median duration of response was 22.6 months, median progression-free survival (PFS) was 20.7 months, and median overall survival was not reached. The rate of treatment-related adverse events leading to treatment discontinuation was 7.8%. The activity of odronextamab monotherapy in this heavily pretreated R/R FL population, including among patients with rituximab-refractory disease, provides a strong rationale for developing odronextamab as a chemotherapy-free option that can improve long-term outcomes in 1L. **Methods:** OLYMPIA-1 (NCT06091254) is a Phase 3, randomized, open-label, multicenter study of odronextamab versus investigator's choice of CIT (R-CHOP, R-CVP, or R-bendamustine) in patients with previously untreated FL. The study consists of Part 1 (safety run-in), followed by Part 2 (randomization). In Part 1, patients will receive six 21-day cycles (induction) of intravenous odronextamab, administered in a step-up regimen during Cycle (C) 1 to mitigate the risk of cytokine release syndrome, followed by full dose starting from C2. Patients with CR or partial response at the end of induction will receive 12 doses of odronextamab maintenance given Q8W. In Part 2, patients will be randomized 1:1 to receive induction of six cycles of odronextamab followed by odronextamab maintenance, or CIT followed by rituximab maintenance. Key inclusion criteria: aged ≥18 years; CD20+ FL Grade 1–3a, stage II bulky or stage III/IV; measurable disease; and ECOG performance status 0–2. Patients with central nervous system lymphoma or histological Grade 3b are excluded. The Part 2 primary endpoint is CR at 30 months (CR30) as assessed by independent central review. Key secondary endpoints include PFS, event-free survival, investigator-assessed CR30, and patient-reported outcomes. Biomarkers (including minimal residual disease by ctDNA) will be evaluated as exploratory endpoints. This trial is currently recruiting and is expected to enroll ~12–32 patients in Part 1 and ~446 patients in Part 2 at ~200 global sites. Clinical trial information: NCT06091254. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS7097 Poster Session

LOTIS-5: An ongoing, phase 3, randomized study of loncastuximab tesirine with rituximab (Longa-R) versus immunochemotherapy in patients with R/R DLBCL.

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Background: Patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) typically have poor outcomes following standard treatment. Loncastuximab tesirine (loncastuximab tesirine-lpyl [Lonca]), an antibody–drug conjugate (ADC) comprising a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine (PBD) dimer toxin, received accelerated (US) and conditional (EU) approval for R/R DLBCL after ≥2 lines of systemic therapy based on data from the phase 2 LOTIS-2 trial (Caimi PF et al. *Lancet Oncol.* 2021;22[6]:790). Rituximab (R), an anti-CD20 monoclonal antibody, is part of standard frontline and subsequent DLBCL immunotherapy. Preclinical evidence suggests that R + anti-CD19 ADC therapy may result in prolonged tumor control (Ryan MC et al. *Blood.* 2017; 130[18]:2018). LOTIS-5 will evaluate Lonca-R vs standard immunochemotherapy of R + gemcitabine + oxaliplatin (R-GemOx) in R/R DLBCL. **Methods:** This phase 3, randomized, open-label, 2-part, multicenter study of Lonca-R in patients with R/R DLBCL (NCT04384484) consists of part 1 (a nonrandomized safety run-in with Lonca-R) and part 2 (a randomized efficacy and safety evaluation of Lonca-R vs R-GemOx). Approximately 350 patients will be enrolled across both parts: part 1 is complete; part 2 will enroll approximately 330 patients (randomized 1:1) to achieve 262 events for the primary end point analysis of progression-free survival by independent central review. Secondary end points include overall survival, overall response rate (2014 Lugano classification), complete response rate, duration of response, frequency and severity of adverse events, change from baseline in safety assessments, concentration and pharmacokinetic parameters of Lonca (antibody [conjugated and total] and unconjugated PBD), antidrug antibody titers, and changes in patient-reported outcomes from baseline. The dosing regimen for Lonca-R is Lonca 150 μg/kg + rituximab 375 mg/m^2 every 3 weeks (Q3W) for 2 cycles, then Lonca 75 μg/kg + rituximab 375 mg/m^2 Q3W for up to 6 additional cycles. The dose regimen of R-GemOx is rituximab 375 mg/m^2, gemcitabine 1000 mg/m^2, and oxaliplatin 100 mg/m^2 every 2 weeks for up to 8 cycles. Key eligibility criteria include age ≥18 years, pathologic diagnosis of DLBCL (including patients with DLBCL transformed from indolent lymphoma) or high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements, ≥1 line of prior systemic therapy, previous stem cell transplant >30 days (autologous) or >60 days (allogenic) before start of study drug or stem cell transplant ineligibility, and measurable disease (2014 Lugano classification). The randomized part of LOTIS-5 began in January 2022; the estimated primary completion date is September 2025. Enrollment continues; 254 patients are enrolled across sites in North America, South America, Europe, and Asia. Clinical trial information: NCT04384484. Research Sponsor: ADC Therapeutics SA; Swedish Orphan Biovitrum AB.

TPS7098 **Poster Session**

An open label, single arm, multicenter phase II study of the efficacy and safety of LP-168 monotherapy for relapsed or refractory mantle cell lymphoma.

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Background: Targeting Bruton's tyrosine kinase (BTK) has demonstrated impressive efficacy in relapsed or refractory mantle cell lymphoma (R/R MCL). Covalent BTK inhibitors (cBTKi) have produced extended disease remission and durable responses in R/R MCL. However, patients with continuous cBTKi treatment tend to develop selection or outgrowth of resistant clones, which triggers disease relapse. Non-covalent binding BTKi has become a treatment option for patients who progressed on cBTKi. LP-168 is a highly selective next-generation inhibitor of BTK that can bind wild-type BTK covalently and C481-mutated BTK non-covalently (reversibly) Here, we propose to evaluate the safety and efficacy of LP-168 monotherapy in patients with R/R MCL. **Methods:** NCT05716087 is an open-label, multicenter, single-arm, phase II study to assess the efficacy, safety, tolerability, and pharmacokinetics of LP-168 in Chinese patients with R/R MCL who have failed prior cBTKi treatment. Responses were evaluated using Lugano 2014 criteria. Eligible patients with R/R MCL must show evidence of disease progression or intolerance to at least a prior cBTKi. Patients are also required to have adequate bone marrow, liver function, kidney function, and heart function, and an ECOG performance status of 0-2. Moreover, patients must have at least one measurable lesion. Key exclusion criteria include previous non-covalent BTKi or BTK proteolysis-targeting chimeras (PROTAC) treatment, uncontrolled systemic disease, active infection, central nervous system (CNS) involvement, prior history of other malignancies within two years, and current pregnancy or breastfeeding. Concomitant use of strong or moderate CYP3A4 inducers and inhibitors or OATP1B1/OATP1B3 sensitive substrates is prohibited. LP-168 is orally administered at 150mg once daily in 28-day/cycle until progressive disease (PD), unacceptable toxicity, withdrawal of consent, death, or other reasons for treatment discontinuation. In this study, the primary endpoint was ORR according to an independent review committee (IRC) assessment based on the best overall response (BOR) of PR or better per Lugano 2014 criteria. Secondary endpoints include safety evaluation, quality of life assessment, PK parameters, ORR by investigator's assessment, and other efficacy parameters, such as complete response ratio (CRR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), and time to response (TTR). First patient was enrolled on May 12, 2023. Currently 41 study sites across China are actively enrolling patients. ClinicalTrials.gov Identifier: NCT05716087. Clinical trial information: NCT05716087. Research Sponsor: None.

TPS7099 Poster Session

Phase 3 trial evaluating the efficacy and safety of odronextamab plus chemotherapy versus rituximab plus chemotherapy in previously untreated follicular lymphoma (OLYMPIA-2).

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Background: Odronextamab, an off-the-shelf, CD20×CD3 bispecific antibody, has shown compelling efficacy and generally manageable safety as monotherapy in patients with heavily pretreated relapsed/refractory (R/R) follicular lymphoma (FL), including those with rituximab-refractory disease (Villasboas et al. ASH 2023). In the Phase 2 ELM-2 study, odronextamab demonstrated objective and complete response (CR) rates of 80% and 73%, respectively, and median duration of response of 22.6 months; median overall survival was not reached. Treatment-related adverse events led to treatment discontinuation in 7.8% of patients. These encouraging results support an investigation into whether odronextamab plus chemotherapy is superior to the current FL first-line standard of care of rituximab plus chemotherapy. This study will also evaluate whether odronextamab maintenance is required to achieve progression-free survival (PFS), given the risks associated with sustained B-cell depletion. **Methods:** OLYMPIA-2 (NCT06097364) is a Phase 3, randomized, open-label, multicenter study of odronextamab plus chemotherapy (Odro-CHOP/Odro-CVP) versus R-CHOP/R-CVP in patients with previously untreated FL. The study consists of Part 1A (dose escalation), Part 1B (dose optimization), and Part 2 (randomization). In Part 1, patients will receive six 21-day cycles (induction) of Odro-CHOP, in which intravenous odronextamab will be administered in a step-up regimen starting on Cycle (C) 1 Day (D) 8 to mitigate the risk of cytokine release syndrome, followed by full dose starting from C2D8. Patients with CR or partial response at the end of induction will receive 12 doses of odronextamab maintenance given Q8W. In Part 2, patients will be randomized 1:1:1 to receive induction of 6 cycles of Odro-CHOP/Odro-CVP with no maintenance (Arm A), Odro-CHOP/Odro-CVP followed by odronextamab maintenance (Arm B), or R-CHOP/R-CVP followed by rituximab maintenance (Arm C). Key inclusion criteria: aged ≥18 years; CD20+ FL Grade 1–3a, stage II bulky or stage III/IV; measurable disease; and ECOG performance status 0–2. Part 1: patients with FL that is R/R (Part 1A only) or previously untreated with Follicular Lymphoma International Prognostic Index-1 (FLIPI-1) score 3–5. Part 2: previously untreated patients with FLIPI-1 score 0–5. Patients with central nervous system lymphoma or histological Grade 3b are excluded. The Part 2 primary endpoint is CR rate at 30 months (CR30) by independent central review. Key secondary endpoints include PFS, event-free survival, investigator-assessed CR30, and patient-reported outcomes. Biomarkers (including minimal residual disease by ctDNA) will be evaluated as exploratory endpoints. This trial is currently recruiting and is expected to enroll up to 64 patients in Part 1 and ~669 patients in Part 2 at ~200 global sites. Clinical trial information: NCT06097364. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS7100 **Poster Session**

Multicenter, randomized phase II study of epcoritamab for patients with large B-cell lymphomas achieving a partial response after CD19-directed CAR T-cell therapy (CAR-T).

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Background: Despite the promising efficacy of CAR-T for patients with relapsed or refractory (R/R) large B-cell lymphomas (LBCL), more than 60% of patients will relapse, the majority of which occur in the first 6 months. Approximately 30% of patients with LBCL treated with CAR-T achieve a partial response (PR) on day 30 (D30) PET-CT assessment. Of patients in a D30 PR, 70% will eventually progress, yet the standard of care remains close observation. Early consolidative treatment strategies utilizing therapies with a different mechanism of action may improve outcomes, but there are currently no reliable biomarkers. Epcoritamab (Epco), a bispecific antibody directed against CD20 and CD3, has been approved by the FDA for LBCL patients who relapse after at least 2 lines of therapy. In the phase 2 study, Epco was associated with an overall response rate (ORR) of 63% and a complete response (CR) rate of 39%, including similar responses in a subset of patients who were relapsed 100 days post CAR-T. This study is a trial-in-progress that will evaluate the efficacy of epco compared to observation for patients with LBCLs achieving a PR on D30 post CAR-T PET-CT assessment. **Methods:** This is an investigator-initiated, randomized, phase II, multicenter, open-label study (NCT06238648) evaluating epco monotherapy for a fixed duration of 12 cycles compared to observation for LBCL patients with D30 PR after standard of care CAR-T. A maximum of 120 patients will be randomized 1:1 to epco or observation across 10 academic centers. Stratification factors include line of CAR-T (second vs third line) and costimulatory domain (CD28 vs 4-1BB). Key inclusion criteria include PET evidence of a D30 PR. non-bulky disease ($<$7.5cm), ANC of $>$1000, hemoglobin $>$7 g/dL if asymptomatic or $>$8 if symptomatic, platelet count $>$50,000. G-CSF, pRBCs and platelet transfusions are allowed. Key exclusion criteria include prior anti CD20xCD3 bispecific antibody therapy, ongoing or uncontrolled CRS or ICANS, and active or symptomatic CNS disease. Epco is administered subcutaneously at a dose of 0.16mg on day 1, 0.8mg on day 8, prior to full dose of 48mg on day 15. Epco is administered weekly in 28 day cycles (C) for C1-3, on day 1 and 15 of C4-9 and on day 1 of C10-12. PET-CT response is assessed by the 2014 Lugano criteria after 2 cycles, and then every 3 months during active treatment. The primary objective is efficacy, measured as conversion from D30 PR to CR. The secondary endpoints include frequency and severity of treatment emergent adverse events, ORR, duration of response, duration of complete response, progression free survival, event free survival, and overall survival. Peripheral blood samples will be collected pre-treatment and during treatment to assess for biomarkers of response and resistance. The study was activated in January 2024 and recruitment is ongoing. Clinical trial information: NCT06238648. Research Sponsor: Genmab/AbbVIE.