7500 **Oral Abstract Session**

First results of a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia.

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Background: Increased selectivity of the Bruton tyrosine kinase inhibitor (BTKi) acalabrutinib (Aca) vs ibrutinib (Ib) may improve tolerability. We conducted an open-label, randomized, noninferiority, phase 3 trial to compare Aca vs Ib in patients (pts) with chronic lymphocytic leukemia (CLL). **Methods:** Previously treated CLL pts with del(17p) or del(11q) by central lab were randomized to receive oral Aca 100 mg BID or Ib 420 mg QD (stratified by del(17p) status, ECOG PS [2 vs ≤1], and number of prior therapies [1–3 vs ≥4]) until progression or unacceptable toxicity. Primary endpoint was progression-free survival (PFS) as assessed by IRC; secondary endpoints of all grade atrial fibrillation (AF), grade ≥3 infection, Richter transformation, and overall survival (OS) were assessed in hierarchical order. **Results:** 533 pts (Aca, n=268; Ib, n=265) were randomized (median age 66 y; median 2 prior therapies; del(17p) 45.2%; del(11q) 64.2%). At a median follow-up of 40.9 mo (range 0.0–59.1), Aca was noninferior to Ib with a median PFS of 38.4 mo in both arms (HR 1.00; 95% CI 0.79–1.27). Aca was statistically superior to Ib in all-grade AF incidence (9.4% vs 16.0%; *P*=0.023). Among the other secondary endpoints, incidences of grade ≥3 infection (Aca: 30.8%, Ib: 30.0%) and Richter transformation (Aca: 3.8%, Ib: 4.9%) were comparable between arms. Median OS was not reached in either arm (HR 0.82 [95% CI 0.59–1.15]), with 63 (23.5%) deaths in the Aca arm and 73 (27.5%) in the Ib arm. Among any-grade AEs in ≥20% of pts in either arm, Aca was associated with a lower incidence of hypertension (9.4%, 23.2%), arthralgia (15.8%, 22.8%), and diarrhea (34.6%, 46.0%) but a higher incidence of headache (34.6%, 20.2%) and cough (28.9%, 21.3%). AEs led to treatment discontinuation in 14.7% of Aca- vs 21.3% of Ib-treated pts. Among any-grade events of clinical interest, cardiac, hypertension, and bleeding events were less frequent with Aca (Table). **Conclusions:** In this first head-to-head trial of BTKis in CLL, Aca demonstrated non-inferior PFS with less cardiotoxicity and fewer discontinuations due to AEs vs Ib. Clinical trial information: NCT02477696. Research Sponsor: Acerta Pharma, a member of the AstraZeneca Group.

Selected events of clinical interest.

	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
Events, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
Atrial fibrillation[a]	25 (9.4)	13 (4.9)	42 (16.0)	10 (3.8)
Ventricular tachyarrhythmias	0	0	1 (0.4)	1 (0.4)
Hypertension[b]	25 (9.4)	11 (4.1)	61 (23.2)	24 (9.1)
Bleeding events	101 (38.0)	10 (3.8)	135 (51.3)	12 (4.6)
Major bleeding events[c]	12 (4.5)	10 (3.8)	14 (5.3)	12 (4.6)
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)
Second primary malignancies excluding non-melanoma skin cancers	24 (9.0)	16 (6.0)	20 (7.6)	14 (5.3)

[a]Includes atrial fibrillation and atrial flutter [b]Includes hypertension, blood pressure increased, and blood pressure systolic increased [c]Any hemorrhagic event that was serious, grade ≥3, or a CNS hemorrhage (any grade).

7501 **Oral Abstract Session**

Fixed-duration (FD) first-line treatment (tx) with ibrutinib (I) plus venetoclax (V) for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): Primary analysis of the FD cohort of the phase 2 captivate study.

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Background: CAPTIVATE (PCYC-1142) is a multicenter phase 2 study of first-line I+V in CLL. We previously reported results from the Minimal Residual Disease (MRD) cohort wherein undetectable MRD (uMRD) was achieved in over two-thirds of patients (pts) with 12 cycles of I+V, and 30-mo PFS rates were ≥95% irrespective of subsequent randomized treatment (Wierda, ASH 2020). We now present results from the FD cohort, evaluating fixed-duration tx with I+V. **Methods:** Pts aged ≤70 y with previously untreated CLL/SLL received 3 cycles of I then 12 cycles of I+V (I 420 mg/d orally; V ramp-up to 400 mg/d orally). Primary endpoint was CR rate, including CR with incomplete recovery (CRi); secondary endpoints were ORR, duration of response, uMRD rate ($<10^{-4}$ by 8-color flow cytometry), PFS, OS, tumor lysis syndrome (TLS) risk reduction, and adverse events (AEs). **Results:** 159 pts were enrolled (median age 60 y). High-risk features included del(17p)/*TP53* mutation, 17%; del(11q), 18%; complex karyotype, 19%; and unmutated IGHV, 56%. 147 (92%) and 149 (94%) pts completed planned tx with I and V, respectively. Median time on study was 27.9 mo (range, 0.8–33.2). With fixed-duration I+V, CR rate was 55% (95% CI 48–63) in the overall population and was consistent across high-risk subgroups. Of the 88 pts who achieved CR, 78 (89%) had durable CR (duration ≥1 y); 1 died 7 mo after CR, and 9 with <1 y follow-up were not evaluable. ORR was 96%. Best uMRD response was achieved in 77% of pts in peripheral blood (PB) and 60% of pts in bone marrow (BM). 24-mo PFS was 95%; 24-mo OS was 98%. Results were similar in pts without del(17p) (n=136) (Table). In pts with del(17p)/*TP53* mutation (n=27), CR rate was 56%, uMRD rate was 81% (PB) and 41% (BM), and 24-mo PFS was 84% (95% CI 63–94). Of 34 pts with high baseline TLS risk based on tumor burden, 32 (94%) shifted to medium or low risk after I lead-in; no TLS occurred. AEs were primarily grade 1/2. Most common grade 3/4 AEs were neutropenia (33%), hypertension (6%), and neutrophil count decreased (5%). AEs led to discontinuation of I in 4% and V in 2%. **Conclusions:** First-line I+V is an all-oral, once-daily, chemotherapy-free, fixed-duration regimen that provides deep, durable responses in pts with CLL/SLL, including those with genomic high-risk features. CR, uMRD rates, PFS, and OS appear favorable. The safety profile of I+V was consistent with known AEs for each agent; no new safety signals were identified. Clinical trial information: NCT02910583. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.

Efficacy	Pts without del(17p) n=136	All pts N=159
CR/CRi, n (%)	76 (56)	88 (55)
Durable CR/CRi, n/N (%)*	66/76 (87)	78/88 (89)
ORR, n (%)	130 (96)	153 (96)
uMRD in PB, n (%)	104 (76)	122 (77)
uMRD in BM, n (%)	84 (62)	95 (60)
24-mo PFS rate, % (95% CI)	96 (91-98)	95 (90-97)
24-mo OS rate, % (95% CI)	98 (93-99)	98 (94-99)

*Progression-free ≥12 cycles from first CR.

7502 **Oral Abstract Session**

First-in-human study of lisaftoclax (APG-2575), a novel BCL-2 inhibitor (BCL-2i), in patients (pts) with relapsed/refractory (R/R) CLL and other hematologic malignancies (HMs).

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Background: The BCL-2i venetoclax is active in certain HMs but can increase the risk of tumor lysis syndrome (TLS), requiring a 5-week dose ramp-up for CLL patients. Cases of severe neutropenia with venetoclax treatment have also been reported. Lisaftoclax is a novel, potent, selective BCL-2i that is active against HMs and is under clinical development. **Methods:** This first-in-human global phase I dose study assessed the safety, PK, PD, efficacy, and MTD/RP2D of lisaftoclax in patients with R/R CLL and other HMs. Lisaftoclax was orally administered daily in a 28-day cycle. Patients with CLL or intermediate-high TLS risk were initiated on a daily ramp-up schedule until the assigned dose before the study cycles. **Results:** On January 7, 2021, 35 pts had been enrolled and treated with lisaftoclax at doses ranging from 20 to 1,200 mg, with a median (range) of 2 (1-13) prior lines of treatment, and had diagnoses of R/R CLL or SLL (n = 15), MM (n = 6), FL (n = 5), WM (n = 4), and either AML, MCL, DLBCL, MDS, or HCL (n = 1 each). No DLT has been observed, even though 1,200 mg was considered as the highest dose treated. The MTD has not been reached, and no laboratory or clinical TLS has been reported. Any grade TRAEs in $>$ 10% of pts included neutropenia (22.9%) and anemia (17.1%; hematologic), and fatigue (28.6%), diarrhea (17.1%), and nausea (11.4%; nonhematologic). Grade $>$3 TRAEs were neutropenia (14.3%) and thrombocytopenia, leukopenia, lymphopenia, fatigue, and nausea (2.9% of pts each). In CLL/SLL pts, grade 3-4 TRAEs included neutropenia (13.3%) and thrombocytopenia (6.7%), which did not cause treatment-related discontinuation. In all, 12 of 35 pts (34.3%) had non-treatment-related SAEs, and only two pts experienced $>$ 1 SAE. With a median (range) treatment of 7 (3-20) cycles, 12 of 14 evaluable R/R CLL/SLL pts achieved PR, for an ORR of 85.7% and a median (range) time to response of 3 (2-7) cycles. Absolute lymphocyte counts (ALCs) were reduced at lisaftoclax doses as low as 20 mg/day. The preliminary PK profile showed that exposures increased with lisaftoclax doses from 20 to 1,200 mg (average half-life: 4-5 hours). On BH3 profiling, lisaftoclax rapidly triggered changes in BCL-2 complex in CLL/SLL pt samples, which were consistent with rapid clinical reductions in ALCs. **Conclusions:** Lisaftoclax was well tolerated up to 1,200 mg/day. No TLS was observed, even with the daily ramp-up schedule. There were no significant new or unmanageable safety findings, and the ORR in R/R CLL/SLL pts was 85.7%. Grade 3-4 TRAEs were infrequent, even at dose levels of 800 mg and above. BCL-2i lisaftoclax offers a treatment alternative for patients with R/R CLL/SLL and other HMs, with a daily ramp-up schedule that may be more pt user friendly and a favorable preliminary safety profile. Internal study identifier APG2575-001. Clinical trial information: NCT03537482. Research Sponsor: Ascentage Pharma Group Corp Limited (Hong Kong).

7503 **Oral Abstract Session**

ECOG-ACRIN E1411 randomized phase 2 trial of bendamustine-rituximab (BR)-based induction followed by rituximab (R) ± lenalidomide (L) consolidation for Mantle cell lymphoma: Effect of adding bortezomib to front-line BR induction on PFS.

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Background: Optimal initial therapy for mantle cell lymphoma (MCL) remains uncertain. The randomized phase 2 NCTN trial E1411 tested if progression-free survival (PFS) is prolonged by addition of bortezomib (V) (1.6 mg/m2 SC/IV days 1, 8) to bendamustine-rituximab (BVR vs BR) induction and/or by addition of lenalidomide (L) to rituximab (LR vs R) consolidation. Here we report efficacy and toxicity of induction BVR vs BR. **Methods:** 373 pts, accrued 2012–16, stratified by MIPI and age (≥60) received 1 of 4 arms: A) BR induction x 6 followed by R x 2 yrs, B) BVR followed by R, C) BR followed by LR or D) BVR followed by LR. Eligible pts had untreated MCL, ≥ age 18 (amended from ≥60 when S1106 for < 65 closed), ECOG PS 0-2 and adequate hematologic and organ function. Pts without progressive disease during induction proceeded to consolidation. Primary induction objective was whether adding bortezomib (BVR) (Arms B + D) to BR (Arms A + C) improves PFS, irrespective of consolidation R vs LR. Design of 360 eligible treated pts would provide 93.8% power to detect 10% improvement in 2-yr PFS from 70% hypothesized for BR, corresponding to 37.4% reduction in hazard using stratified log-rank test at 1-sided 10% alpha. Efficacy population was 179 (BVR) and 180 (BR), induction treatment completed in 144 vs 153, progressive disease during induction 6 vs 7 and registration to consolidation 140 vs 145. **Results:** Baseline demographics did not differ between the groups, with median age 67 (range 42-90) and 13% < 60 yr, 73% men, ECOG PS 0-1 97%, MIPI Low/Med/Hi 37/29/34%. Estimated PFS at 2 yrs 79.6% BVR (95% CI 73.8-85.9) vs 74.5% BR (95% CI 68.2-81.4) (1-sided stratified log-rank p = 0.268). With median PFS follow-up 51 mos, median PFS estimated at 64.1 and 64.0 mos. Overall response rate (ORR) for BVR was 88.9% (CR 65.5%) vs 89.5% (CR 60.5%) BR (z-test 1 sided p = 0.577 for ORR). Treatment related deaths during induction were 2 in BVR (cardiac arrest, hepatitis) and 1 in BR (tumor lysis). Grade ≥ 3 toxicities were 88.1% (163/185) BVR vs 77.5% (145/187) BR. For BVR vs BR grade ≥ 3 neutropenia occurred in 52 vs 39 pts, though febrile neutropenia (7 vs 6), anemia (7 vs 8) and thrombocytopenia (18 vs 16) did not differ. Peripheral neuropathy (PN) grade 2 was 8 sensory for BVR vs 2 sensory/1 motor for BR, while grade 3 PN was 6 sensory/1 motor for BVR vs 0 with BR. The only non-hematologic grade ≥ 3 toxicity in > 5% of pts was rash (9 vs 12 pts). **Conclusions:** Bortezomib did not significantly improve the primary endpoint of PFS when added to BR as initial MCL therapy. ORR and CR rates at end of induction were also similar. Follow-up continues to assess the entire treatment regimen, including consolidation R vs LR, but the PFS > 5 yrs, high ORR and MRD negativity rate (Smith et al ASH 2019) in this BR-based trial support BR as a platform for MCL induction therapy. Clinical trial information: NCT01415752. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Real-world (RW) treatment (tx) patterns and outcomes of 3,455 previously untreated mantle cell lymphoma (MCL) patients (pts) in U.S. routine clinical practice.

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Background: MCL is a non-Hodgkin lymphoma with heterogeneous biology and outcomes. We characterized RW tx patterns and outcomes of MCL pts to identify factors associated with outcomes in the US. **Methods:** This retrospective study included adult MCL pts diagnosed Jan 2011-Nov 2020 in the nationwide Flatiron Health EHR-derived deidentified database. Pt characteristics, tx patterns, time to next tx (rwTTNT, defined as start of first-line [1L] tx to subsequent tx or death) and rwOS were evaluated. **Results:** 3455 pts were included, 85.3% from a community oncology setting. In 2946 (85.2%) pts with documented 1L MCL tx, median age was 69.5 y (range 27.7-85.3); 9.5% had blastoid/pleomorphic MCL. 262 (39.6%) and 235 (35.6%) of 661 pts with available MCL international prognostic index (MIPI) had intermediate and high risk, respectively. 150/1253 pts (12.0%) with available ECOG PS had PS $\geq$ 2. Chemoimmunotherapy was the most common 1L tx, including BR in 1223 (41.5%), R-CHOP in 512 (17.4%) and cytarabine (ara-C)-containing tx in 414 (14.1%). 667 pts received R maintenance (MR). In 1036 pts $<$ 65 y, 243 pts received 1L stem cell transplant (SCT), mainly autologous. In 1L-treated pts, with median follow-up of survivors of 45.3 mos (range 0.03-117.2), median rwTTNT was 24 mos; 36-mo rwOS was 67%. The Table shows tx received and outcomes by age and SCT status. MVA analyses showed age $\geq$ 65 y, ECOG PS $\geq$ 2, LDH/ULN $\geq$ 1, WBC $\geq 10 \times 10^9$/L, bulky disease ($\geq$ 5 cm) and blastoid/pleomorphic morphology were associated with shorter rwTTNT and rwOS; MR was independently associated with longer rwTTNT and rwOS. In pts $<$ 65 y who were alive and did not initiate subsequent tx within 6 mos of 1L tx (SCT-eligible), 36-mo rwTTNT and rwOS were similar between pts treated with vs without SCT: 65% vs 59% and 86% vs 85%, respectively. **Conclusions:** In this large RW cohort of primarily community-based US practices, median 1L rwTTNT for MCL pts was ~ 2 y. BR was the most commonly used 1L tx. SCT was uncommon even in pts $<$ 65 y, suggesting RW considerations may influence SCT eligibility and availability. Also, SCT was not clearly associated with rwOS. As with other reports, older age and high-risk disease features were predictive of worse outcome in RW, while MR appeared to be associated with better outcomes. Outcomes across the board appear worse than prospective trials, suggesting a need to focus on developing tx that can be delivered effectively in the community setting. Research Sponsor: Janssen Research and Development.

Tx and outcomes in 1L MCL.

	Age < 65 y at 1L tx (n = 1036)		Age ≥ 65 y at 1L tx (n = 1910)	
	No SCT (n = 793)	Received SCT (n = 243)	No SCT (n = 1835)	Received SCT (n = 75)
1L tx received, n (%)				
Ara-C–containing	189 (23.8)	130 (53.5)	67 (3.7)	28 (37.3)
BR	244 (30.8)	42 (17.3)	914 (49.8)	23 (30.7)
R-CHOP	172 (21.7)	48 (19.8)	273 (14.9)	19 (25.3)
Pt outcome, % (95% CI)				
36-mo rwTTNT	40 (36-44)	63 (57-71)	37 (35-40)	63 (51-77)
36-mo rwOS	75 (72-79)	86 (81-91)	61 (58-63)	82 (72-94)

7505 **Oral Abstract Session**

The combination of venetoclax, lenalidomide, and rituximab in patients with newly diagnosed mantle cell lymphoma induces high response rates and MRD undetectability.

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Background: MCL is a rare lymphoma without a standard of care but several regimens have demonstrated clinical activity, the majority based on traditional chemotherapy. We hypothesized that adding venetoclax (V) to R2 would be safe and effective in MCL pts irrespective of age, morphology or stage. Here we present safety and efficacy data from the on-going phase 1b study of R2 + V in pts with newly diagnosed MCL. **Methods:** This multi-center phase 1 study (NCT03523975) enrolled pts aged ≥18 yrs with untreated MCL. The primary objective was to characterize the safety and tolerability of R2 + V and determine the MTD. During induction (12 months (m)) pts received lenalidomide (L) 20 mg daily on day 1-21, Rituximab (R) was given weekly during c1 then on day 1 of every even cycle, V was escalated over 4 weeks to 400 mg beginning day 8. Each cycle is 28 days (d). The DLT period was 42 d beginning C1D8. In maintenance, R every 8 weeks for 36m, L at 10 mg or half of last dose during induction for 24 m and V for minimum 12 m. No pts have been transplanted. Pts with progression (PD) came off study. MRD was analyzed in parallel with scans during induction by clonoSEQ assay (Adaptive Biotechnologies). **Results:** As of Feb. 1st, 2021, we have enrolled all 28 planned pts on study. Pt characteristics/responses are summarized in Table. Among the 28 pts who have received at least one dose, the median treatment duration so far is 278d (IQR 170-560), with 24 pts still on treatment (Tx). 1 pt is off from a unrelated condition. All pts escalated to V 400 mg w/o any DLTs noted. Treatment-emergent adverse events (TEAEs) were reported in 100% of pts, and grade 3+ TEAEs were reported in 26 (93%) patients. The most common all-grade TEAEs (≥50% of pts), regardless of relationship to study Tx, were fatigue, neutropenia and diarrhea. Grade ≥3 TEAEs reported in ≥50% pts were neutropenia (68%) and thrombocytopenia (50%). No pts have withdrawn or d/c Tx due to AEs. There was one grade 5 event, in a non-evaluable pt, related to a PE that occurred prior to DLT period. In the 28 evaluable pts the ORR (CR/PR) was 96% (27/28 pts) with CR/CRu of 89%. Of the responding pts, two had PD, one w/ CR and one w/ PR. All pts with PD had baseline *TP53* mutation. MRD testing was successful in all pts. At time of submission 20 of 28 (71%) were MRD - at 10^{-6}. **Conclusions:** Interim results show that at the MTD the combination of V 400 mg daily, L 20 mg, with R is safe with a manageable toxicity profile and a high ORR and MRD - in pts with newly diagnosed MCL. Safety data is consistent with the AE profile noted for each drug without any unexpected or unique AEs. Updated results including BH3 profiling will be presented at the meeting. Clinical trial information: NCT03523975. Research Sponsor: Abbvie, Rogel Cancer Center.

Sex, male, % (n)	64% (18)
Age, years, median (IQR)	65 (57, 69)
Race, white, % (n)	100% (28)
Tx duration, d, median (IQR)	278 (170, 560)
Stage IV, % (n)	96% (27)
MIPI High, % (n)	64% (18)
Blast/Pleo, % (n)	21% (6)
Ki-67 ≥30%, % (n)	68% (19)
ORR	96%
CR/CRu	89%
MRD -	71%

7506 **Oral Abstract Session**

Myeloablative versus non-myeloablative consolidative chemotherapy for newly diagnosed primary central nervous system lymphoma: Results of CALGB 51101 (Alliance).

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Background: Optimal consolidative therapy for primary central nervous system lymphoma (PCNSL) is not defined. Avoidance of whole brain radiation may reduce risk of neurotoxicity. Non-radiation consolidative options include myeloablative chemotherapy with autologous stem cell transplantation (HDT/ASCT) or non-myeloablative chemotherapy. **Methods:** This is a randomized phase 2, National Clinical Trials Network study of induction methotrexate (MTX) (8 g/m^2 days 1, 15), temozolomide (TMZ) (150-200 mg/m^2 D7-11), and rituximab (RTX) (C1 D3, 10, 17, 24 and C2 D3, 10) in four 28-day cycles followed by one cycle of cytarabine (ARA-C) (2 g/m^2 BID, D1, 2) (MTRA). After induction, patients (pts) received consolidation with thiotepa (5 mg/kg BID, D -5, -4) plus carmustine (400 mg/m^2, day -6) and ASCT (Arm A) or one cycle of ARA-C (2 g/m^2 BID, D1-4) plus infusional etoposide (40 mg/kg over 96h) (Arm B). Pts were stratified on age and performance status and randomized 1:1 before induction. The primary endpoint was progression-free survival (PFS) from randomization. With 110 pts, there was 84% power to detect an improvement in PFS using a log-rank test (1-sided α= 10%), assuming a median PFS of 3 months for pts who progress during induction, and a median PFS of 2 years (yrs) for Arm B and 4.5 yrs for Arm A consolidation. This report includes the results for the primary endpoint analysis. **Results:** 113 pts (median age 61 yrs, range 33-75) were randomized (Arm A: 57, Arm B: 56) across 27 centers. 108 eligible pts who received induction therapy were included in the primary endpoint analysis (Arm A: 54, Arm B: 54). 72/108 pts started consolidation and 70/72 completed consolidation per protocol (Arm A: 36, Arm B: 34). With a median follow-up of 3.8 years, median PFS from randomization was 6 yrs (95% CI 3.9-not reached) in Arm A vs 2.4 yrs (95% CI 0.6-not reached) in Arm B (p = 0.02). However, more pts randomized to Arm B went off treatment before consolidation due to progression or death (28% vs 11%, p = 0.05). PFS landmarked at start of consolidation demonstrated a trend for improved PFS favoring Arm A (HR 0.58, 95% CI 0.25-1.36; p = 0.21). Median OS was not reached in either arm, and 3-yr estimates were 83% (95% CI 69-91; Arm A) vs 72% (95% CI 57-82; Arm B). Toxicities were similar between arms with no treatment-related mortality during consolidation. **Conclusions:** MTRA induction followed by myeloablative consolidation (Arm A) had improved PFS vs MTRA induction followed by non-myeloablative consolidation (Arm B), though more progressions or deaths leading to treatment discontinuation prior to consolidation in Arm B were noted. Both consolidation regimens were well-tolerated with encouraging PFS and OS in newly-diagnosed PCNSL. Support: U10CA180821, U10CA180882; https://acknowledgments.alliancefound.org. Clinical trial information: NCT01511562. Research Sponsor: U.S. National Institutes of Health.

7507 **Oral Abstract Session**

CALGB 50801 (Alliance): PET adapted therapy in bulky stage I/II classic Hodgkin lymphoma (cHL).

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Background: Bulky disease is associated with inferior outcomes in patients with early stage cHL. Historically, most patients (pts) receive chemotherapy followed by radiotherapy (RT), which is associated with long-term toxicity. We tested a PET-adapted approach to reduce the need for RT in pts with early PET-negative (PET-) disease and escalate therapy in pts with PET-positive (PET+) disease. **Methods:** Eligible pts aged 18-60 years (yrs) had stage IA-IIB cHL with disease bulk $>$10 cm or $>$.33 max intrathoracic diameter on chest x-ray. Pts received 2 cycles of doxorubicin-bleomycin-vinblastine-dacarbazine (ABVD) followed by centrally reviewed PET. PET- was defined as Deauville of 1-3. Pts who achieved a negative PET scan (PET2-) received 4 additional cycles of ABVD. PET2+ pts received 4 cycles of esc-BEACOPP plus 30 Gy involved-site radiation therapy. The primary endpoint was progression-free survival (PFS) estimated from PET2. With 93 pts and assuming 30% PET2+, there was 80% power to rule out that PFS of PET2+ pts was substantially inferior to PFS of PET2- pts (HR 4.1, 3-yr PFS 40% vs 80%) if the true PFS of PET2+ pts was closer to that of PET2- pts (HR 2.29, 3-yr PFS 60% vs 80%) with one-sided alpha=0.15. With few events and mature follow-up, we report results 3 yrs after the last pt was enrolled. **Results:** Between May 2010 and October 2017, 101 pts enrolled. Excluding 6 ineligible pts (3 without baseline DLCO, 2 did not meet definition of bulk, 1 stage IIIB) and 1 pt without PET2, 94 were evaluable. 78% of pts were PET2- (73 PET2-, 21 PET2+). Median age was 30 yrs (range: 18 to 58) and 53.2% were female. Distribution of stage was: 1A - 7.4%, IB - 2.1%, IIA – 39.4%, IIB - 51.1%; 61.9% PET2+ pts had stage IIB disease. Therapy was generally well tolerated. Grade $>$ 3 neutropenia occurred in 86% of pts with 8% of PET2- and 10% of PET2+ with grade $>$ 3 febrile neutropenia. 3-yr PFS estimates were 93.1% (95% CI: 87.4-99.1%) in PET2- pts, 89.7% (95% CI: 77.2-100.0%) in PET2+ pts (HR=1.01, 85% upper bound 2.32), and 92.3% (95% CI: 87.0-98.0%) for all pts. The protocol-defined primary endpoint was met as the PFS hazard ratio for PET2+ vs PET2- was less than 4.1 (one sided p=0.04). With a median follow-up of 5.5 yrs, 3 PET2- pts died (HL, anaplastic astrocytoma and COPD) and 1 PET2+ died of progressive disease. 3-yr overall survival (not a primary or secondary outcome of the study) estimates were 98.6% (95% CI: 95.9-100.0%) in PET2- pts, 94.4% (95% CI: 85.4-100.0%) in PET2+ pts (HR: 1.2, 95% CI: 0.12, 11.60), and 97.7% (95% CI: 94.7-100.0%) for all pts. **Conclusions:** Excellent PFS outcomes were observed in all pts using a PET-adapted approach that allowed omission of RT in 78% of pts. In addition, PET2+ pts treated with escalation to BEACOPP and consolidative RT did not have inferior outcomes. Support: U10CA180821, U10CA180882; https://acknowledgments.alliancefound.org; ClinicalTrials.gov Identifier: NCT01118026. Clinical trial information: NCT01118026. Research Sponsor: U.S. National Institutes of Health.

Efficacy and safety of tisagenlecleucel (Tisa-cel) in adult patients (Pts) with relapsed/refractory follicular lymphoma (r/r FL): Primary analysis of the phase 2 Elara trial.

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Background: Most pts with r/r FL experience multiple relapses and progressively worse clinical outcomes with each line of therapy, underlining a need for novel therapies. Tisa-cel has demonstrated durable responses and manageable safety in adult pts with r/r diffuse large B-cell lymphoma. Here we report the primary analysis of ELARA, an international, single-arm phase 2 trial of tisa-cel in adult pts with r/r FL. **Methods:** Eligible pts (≥18 y) had r/r FL (grades [Gr] 1-3A) after ≥2 lines of therapy or had failed autologous stem cell transplant. Bridging therapy was permitted followed by disease assessment prior to tisa-cel infusion. Pts received tisa-cel ($0.6\text{-}6\times10^8$ CAR+ viable T cells) after lymphodepleting chemotherapy. The primary endpoint was complete response rate (CRR) by central review per Lugano 2014 criteria. Secondary endpoints included overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety, and cellular kinetics. Predefined primary analysis occurred when ≥90 treated pts had ≥6 mo of follow-up. **Results:** As of September 28, 2020, 98 pts were enrolled and 97 received tisa-cel (median follow-up, 10.6 mo). At study entry, median age among treated pts was 57 y (range, 29-73), 85% had stage III-IV disease, 60% had a FLIPI score ≥3, 65% had bulky disease, and 42% had LDH > upper limit of normal. The median number of prior therapies was 4 (range, 2-13); 78% of pts were refractory to their last treatment (76% to any ≥2 prior regimens) and 60% progressed within 2 y of initial anti-CD20–containing treatment. Of 94 pts evaluable for efficacy, the CRR was 66% (95% CI, 56-75) and the ORR was 86% (95% CI, 78-92). CRRs/ORRs were comparable among key high-risk subgroups. Estimated DOR (CR) and PFS rates at 6 mo were 94% (95% CI, 82-98) and 76% (95% CI, 65-84), respectively. Of 97 pts evaluable for safety, 65% experienced Gr ≥3 adverse events within 8 weeks post-infusion, most commonly neutropenia (28%) and anemia (13%). Any-grade cytokine release syndrome (per Lee scale) occurred in 49% of pts (Gr ≥3, 0%). Any-grade neurological events (per CTCAE v4.03) occurred in 9% of pts (Gr 3, 0%; Gr 4, 1 pt and recovered). Three pts died from progressive disease. Cellular kinetic parameters for tisa-cel were estimated using transgene levels (by qPCR) in peripheral blood. C_{max} and $AUC_{0\text{-}28d}$ were similar between responders (CR or partial response) and non-responders (stable or progressive disease). Maximum transgene levels were reached by a median of 10 days in responders and 12.9 days in non-responders; transgene persistence was detected up to 370 days and 187 days, respectively. **Conclusions:** These data demonstrate the efficacy and acceptable safety of tisa-cel in pts with r/r FL, including high-risk pts after multiple lines of prior therapy, and suggest that tisa-cel may be a promising therapy for pts with r/r FL. Clinical trial information: NCT03568461. Research Sponsor: Novartis.

Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-nave chronic lymphocytic leukemia: Elevate-TN four-year follow up.

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Background: Early results from ELEVATE-TN (NCT02475681) at a median follow-up of 28.3 mo demonstrated superior efficacy of acalabrutinib (A) ± obinutuzumab (O) compared with O + chlorambucil (Clb) in patients (pts) with treatment-nave (TN) chronic lymphocytic leukemia (CLL) (Sharman et al. Lancet 2020;395:1278-91). Results from a 4-year update are reported here. **Methods:** Pts received A±O or O+Clb. Crossover to A monotherapy was permitted in pts who progressed on O+Clb. Investigator-assessed (INV) progression-free survival (PFS), INV overall response rate (ORR), overall survival (OS), and safety were evaluated. **Results:** 535 pts (A+O, n=179; A, n=179; O+Clb, n=177) were randomized with a median age of 70 y; 63% had unmutated IGHV and 9% del(17p). At a median follow-up of 46.9 mo (range, 0.0–59.4; data cutoff: Sept 11, 2020), the median PFS was not reached (NR) for A+O and A pts vs 27.8 mo for O+Clb pts (both $P<0.0001$). In pts with unmutated IGHV, the median PFS was NR (A+O and A) vs 22.2 mo among O+Clb pts (both $P<0.0001$). In pts with del(17p), the median PFS was NR (A+O and A) vs 17.7 mo for O+Clb ($P<0.005$). Estimated 48-mo PFS rates were 87% for A+O, 78% for A, and 25% for O+Clb. Median OS was NR in any treatment arm with a trend towards significance in the A+O group (A+O vs O+Clb, $P=0.0604$); estimated 48-mo OS rates were 93% (A+O), 88% (A), and 88% (O+Clb). ORR was significantly higher with A+O (96.1%; 95% CI 92.1–98.1) vs O+Clb (82.5%; 95% CI 76.2–87.4; $P<0.0001$); ORR with A was 89.9% (95% CI 84.7–93.5; $P=0.035$ vs O+Clb). Complete response/complete response with incomplete hematologic recovery (CR/CRi) rates were higher with A+O (26.8%/3.9%) vs O+Clb (12.4%/0.6%); 10.6%/0.6% had CR/CRi with A. Common adverse events (AEs) and AEs of interest are shown in the Table. Overall treatment discontinuation rates were 25.1% (A+O), 30.7% (A), and 22.6% (O+Clb); the most common reasons were AEs (12.8%, 12.3%, 14.7%, respectively) and progressive disease (4.5%, 7.8%, 1.7%). Most pts (77.4%) completed O+Clb treatment. **Conclusions:** With a median follow-up of 46.9 mo (~4y), the efficacy and safety of A+O and A monotherapy was maintained, with an increase in CR since the interim analysis (from 21% to 27% [A+O] and from 7% to 11% [A]) and low rates of discontinuation. Research Sponsor: None.

	A+O (n = 178)		A (n = 179)		O+Clb (n = 169)	
	Any grade	G ≥ 3	Any grade	G≥3	Any grade	G≥3
Common AEs (in ≥30% of pts [any grade] in any group), n (%)						
Diarrhea	73 (41.0)	9 (5.1)	72 (40.2)	1 (0.6)	36 (21.3)	3 (1.8)
Headache	71 (39.9)	2 (1.1)	68 (38.0)	2 (1.1)	20 (11.8)	0
Neutropenia	60 (33.7)	55 (30.9)	22 (12.3)	20 (11.2)	76 (45.0)	70 (41.4)
Nausea	41 (23.0)	0	41 (22.9)	0	53 (31.4)	0
Infusion-related reaction	25 (14.0)	5 (2.8)	0	0	68 (40.2)	10 (5.9)
Selected AEs of interest, n (%)						
Bleeding	84 (47.2)	5 (2.8)	75 (41.9)	5 (2.8)	20 (11.8)	0
Hypertension	14 (7.9)	6 (3.4)	13 (7.3)	5 (2.8)	7 (4.1)	6 (3.6)
Atrial fibrillation	7 (3.9)	1 (0.6)	11 (6.1)	2 (1.1)	1 (0.6)	0

7510 **Poster Discussion Session**

Copanlisib + rituximab versus rituximab + placebo in patients with relapsed follicular (FL) or marginal zone lymphoma (MZL): Subset analysis from the phase III CHRONOS-3 trial.

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Background: Rituximab (R) monotherapy is an approved treatment for patients (pts) with relapsed indolent NHL (iNHL) who have a prolonged progression-free and treatment-free interval after last R-based therapy or who are unwilling/unfit to receive chemotherapy. Copanlisib (C) is a PI3K inhibitor approved as monotherapy in pts with relapsed FL who have progressed after ≥2 systemic therapies. The recent Phase III CHRONOS-3 study in pts with relapsed iNHL treated with C+R vs placebo (P)+R (NCT02367040) met its primary endpoint with a significant 48% reduction in the risk of disease progression or death (Matasar et al. AACR 2021). We report here a pre-planned subset analysis in pts with relapsed FL or MZL. **Methods:** Pts with relapsed iNHL who were progression- and treatment-free for ≥12 months (mo) after last R-based therapy or ≥6 mo if unwilling/unfit to receive chemotherapy were randomized 2:1 to receive C+R or P+R. C 60 mg/P was given i.v. on days 1, 8, and 15 (28-day cycle); R 375 mg/m^2 was given i.v. on days 1, 8, 15, and 22 of cycle 1 and on day 1 of cycles 3, 5, 7, and 9. Primary endpoint was centrally assessed progression-free survival (PFS) by Cheson 2014 criteria. Secondary endpoints included objective response rate (ORR), duration of response (DoR), complete response rate (CRR), time to progression (TTP), and treatment-emergent adverse events (TEAEs). All randomized pts were assessed for efficacy; pts were assessed for safety if they received ≥1 dose of C/P or R. The data cut-off date was August 31, 2020. **Results:** From a total dataset of 458 iNHL pts, 250 pts with FL/MZL (184 FL/66 MZL) were randomized to C+R and 120 (91 FL/29 MZL) to P+R. Median age was 62 years (range 28-91) and the arms were well balanced. With a median follow-up of 18.5 mo, C+R significantly reduced the risk of disease progression/death vs P+R (HR = 0.55 [95% CI 0.40, 0.76]; 1-sided p = 0.0001); median PFS was 22.2 mo (95% CI 19.1, 33.1) vs 15.4 mo (95% CI 11.0, 19.2), respectively. Median TTP was 27.5 mo for C+R vs 15.4 mo for P+R (HR = 0.500; 1-sided p = 0.00001). ORRs were 82.4% (CRR 37.6%) for C+R and 50.8% (CRR 18.3%) for P+R; median DoR was 23.9 mo vs 17.9 mo, respectively. Most common TEAEs (all grades [G]/G3+) in pts with FL/MZL receiving C+R (n = 249) were hyperglycemia (72.7%/59.0%), hypertension (53.8%/43.0% [all G3]), and diarrhea (35.3%/5.6% [all G3]). For pts receiving P+R (n = 116), the most common TEAEs were hyperglycemia (23.3%/7.8% [all G3]), hypertension (19.8%/8.6% [all G3]), neutropenia (18.1%/13.8%), and upper respiratory tract infection (18.1%/0%). **Conclusions:** C+R demonstrated superior efficacy vs P+R in pts with relapsed FL/MZL and had a manageable safety profile, consistent with C and R as monotherapy. Copanlisib is the first PI3K inhibitor to be safely combined with R in relapsed FL/MZL, representing a potential new therapeutic option. Clinical trial information: NCT02367040. Research Sponsor: Funding: Bayer AG. Writing support: Complete HealthVizion.

7511 **Poster Discussion Session**

Obinutuzumab (G)-atezolizumab (atezo)-lenalidomide (len) for the treatment of relapsed/refractory (R/R) follicular lymphoma (FL): Final analysis of a phase Ib/II trial.

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Background: G-len has promising activity and manageable toxicity in R/R FL (Morschhauser et al. 2019). We report the final analysis of an open-label, multicenter, Phase Ib/II trial (NCT02631577) that evaluated the immunomodulatory triplet G-atezo-len in pts with R/R FL. **Methods:** An initial 3+3 dose-escalation to identify the Phase II len dose was followed by an expansion phase with G-atezo-len. Enrolled pts (aged ≥18 years) received induction with 6, 28-day cycles of G 1000 mg IV on Day [D] 1, 8, and 15 of Cycle [C] 1 and D1 of C2–6, atezo 840 mg IV on D1 and 15 of C2–6, and len 15/20 mg (dose escalation) or 20 mg (expansion) orally on D1–21 of C1–6. Responders received 24 months (mos) of maintenance with G 1000 mg D1 every 2 mos, atezo 840 mg D1–2 every mo, and len 10 mg D1–21 mos 1–12. The primary endpoint was complete response at end of induction by PET-CT assessed by Independent Review Committee (modified Lugano 2014 criteria; Morschhauser et al. ICML 2019). Exploratory endpoints described herein included progression-free survival (PFS), overall survival (OS), and duration of response (DOR). Adverse events (AEs) were also assessed. **Results:** At the final analysis (October 7, 2020), 38 pts had completed the trial. Median age was 62 years, 26% had a high-risk FLIPI score, 45% were refractory to their last line of therapy, and 37% had progression of disease within 24 mos of their first-line of therapy (POD24). Median treatment duration was 26 mos (range: 0.4–30). The 36-mo PFS rate for the overall population (median observation time, 35.9 mos; range: 3–47) was 64% (95% CI, 45–79), OS was 85% (95% CI, 70–93), and median DOR was 38 mos (95% CI, 35–NE). 36-mo PFS rates for the following subgroups are provided in the table: double refractory (rituximab and an alkylator); with/without POD24; minimal residual disease (MRD) +/-. In total, 32 pts (84%) had a Grade 3/4 AE (majority hematologic), and 18 (47%) had a serious AE. Five pts (13%) during induction and six pts (16%) during maintenance had an AE that led to discontinuation of any drug. Two fatal AEs were reported (1 merkel carcinoma, 1 sarcomatoid carcinoma; both unrelated to any study drug). The most common atezo AEs of special interest were hyperthyroidism (13%), hypothyroidism (11%), increased ALT and AST (both 8%), increased lipase (8%), and hepatocellular injury (5%). **Conclusions:** G-atezo-len is efficacious in pts with R/R FL, with data from the final analysis suggesting a potential for improved outcomes versus the G-len doublet. AEs were consistent with the safety profile of the individual drugs. Clinical trial information: NCT02631577. Research Sponsor: This study was sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of all authors, was provided by A. Lynch, PhD, of Ashfield MedComms, an Ashfield Health Company, and funded by F. Hoffmann-La Roche Ltd.

36-mo PFS rates.

	Subgroup						
	MRD- (N=16)	MRD+* (N=5)	Double refractory (N=12)	Not double-refractory (N=20)	With POD24 (N=12)	Without POD24 (N=20)	Overall (N=32)
36-mo PFS rate, % (95% CI)	79 (48–93)	0	70 (33–89)	67 (40–84)	64 (30–85)	73 (46–88)	64 (45–79)

*All pts progressed before 36 mos; median PFS was 10.7 mos (range: 1.8–18).

Polatuzumab vedotin (Pola) + rituximab (R) + lenalidomide (Len) in patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): Primary analysis of a phase 1b/2 trial.

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Background: The combination of Pola-R-Len may enhance anti-tumor response in R/R DLBCL. We report the primary analysis of the R/R DLBCL cohort in a Phase 1b/2 study (GO29834; NCT02600897). **Methods:** Pts received induction with 6 x 28-Day (D) cycles (C) of: Pola 1.8mg/kg intravenous (IV; C1−6: D1); R 375mg/m^2 IV (C1−6: D1) and oral Len 10–20mg (dose escalation) or recommended Phase 2 dose (RP2D) daily on D1–21. Pts with a response at end of induction (EOI) received 6 months (mo) consolidation with R 375mg/m^2 (D1 every 2 mo) and Len 10mg (D1–21 monthly). Primary endpoints were safety/tolerability and positron emission tomography (PET)-complete response (CR) rate at EOI by independent review committee (IRC) by modified Lugano criteria. **Results:** At primary analysis (Sep 08, 2020), 57 pts were enrolled. Median age was 71 years (range 28–92); male (67%); Ann Arbor Stage III–IV (86%); International Prognostic Index 3–5 (60%); median 2 prior therapies; prior bone marrow transplant (11%); prior CAR-T therapy (5%); primary refractory (49%) and refractory to last therapy (65%). Grade 3–4 adverse events (AEs) were experienced by 75% of pts, most commonly, neutropenia (58%), thrombocytopenia (14%), infections (14%) and anemia (11%). AEs led to Len dose reduction in 25% and interruption in 63% of pts. One Grade 5 treatment-related AE (neutropenic sepsis) was reported. In total, 49 pts were treated at RP2D (Pola 1.8mg/kg + Len 20mg). IRC PET-CR rate at EOI was 29% (Table). A best overall response (BOR) assessed by investigator (INV) was seen in 36/49 (74%) pts with 17/49 (35%) pts achieving a CR; of these, 14/17 (82%) remain in remission at the cutoff date. Median duration of response (DOR) was 8.1 mo (95% confidence interval [CI]: 4.7–not evaluable [NE]). After a median follow-up of 9.7 mo, median progression-free survival (PFS) and overall survival (OS) were 6.3 mo (95% CI: 4.5–9.7) and 10.9 mo (95% CI: 7.4–NE), respectively. **Conclusions:** Our study of the novel triplet combination, Pola-R-Len, demonstrates a tolerable safety profile. This first efficacy report of Pola-R-Len shows promising activity in a difficult-to-treat R/R DLBCL population, particularly in pts achieving CR, a large proportion of whom remain in remission at the cutoff date. Further evaluation of Pola-R-Len and the impact of consolidation therapy is warranted to address the significant unmet need in this patient population. Clinical trial information: NCT02600897. Research Sponsor: Study sponsored by F. Hoffmann-La Roche Ltd/Genentech, Inc. Third-party editorial assistance, under direction of authors, was provided by Angela Rogers, PhD, of Ashfield MedComms, an Ashfield Health company, and funded by F. Hoffmann-La Roche Ltd.

Efficacy results (RP2D).

Outcome	Pola-R-Len (N=49)
PET-ORR (IRC) at EOI, n (%)	17 (35)
PET-CR (IRC) at EOI*, n (%)	14 (29)
PET-CR (INV) at EOI, n (%)	13 (27)
BOR (INV), n (%)	36 (74)
Best CR (INV), n (%)	17 (35)
Median DOR (INV), mo (95% CI)	8.1 (4.7–NE)
Median PFS (INV), mo (95% CI)	6.3 (4.5–9.7)
Median OS (INV), mo (95% CI)	10.9 (7.4–NE)

*Primary efficacy endpoint; Defined as best response of CR or partial response during the study. ORR, overall response rate.

7513 **Poster Discussion Session**

Long-term analyses from L-MIND, a phase II study of tafasitamab (MOR208) combined with lenalidomide (LEN) in patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL).

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Background: L-MIND (NCT02399085) is an ongoing, open-label, Phase II study of tafasitamab (MOR208), an Fc-modified, humanized, anti-CD19 monoclonal antibody, plus LEN in ASCT-ineligible patients (pts) with R/R DLBCL. Primary analyses and 2-year efficacy results were previously presented; we report an updated efficacy analysis with ≥35 months follow up (cut-off: October 30, 2020). **Methods:** Pts were aged ≥18 years with ASCT-ineligible R/R DLBCL, had 1–3 prior systemic therapies (Tx), including ≥1 CD20-targeting regimen, with an ECOG status of 0–2. Pts received 28-day cycles (C) of tafasitamab (12 mg/kg IV), once weekly during C1–3, with a loading dose on Day 4 of C1, then every 2 weeks (Q2W) during C4–12. LEN (25 mg PO) was administered on Days 1–21 of C1–12. After C12, progression-free pts received tafasitamab Q2W until disease progression. The primary endpoint was objective response rate (ORR), assessed by IRC. Secondary endpoints included duration of response (DoR), progression-free survival (PFS) and overall survival (OS). **Results:** Eighty of 81 enrolled pts received tafasitamab + LEN and were included in the full analysis set (1 prior Tx, n=40; 2+ prior Tx, n=40). At data cut-off, the overall ORR was 57.5% (n=46/80), including complete response (CR) in 40% of pts (n=32/80) and partial response (PR) in 17.5% of pts (n=14/80) (Table). Kaplan-Meier estimates: median DoR=43.9 months (95% CI: 26.1–not reached [NR]), and NR in pts who achieved a CR (95% CI: 43.9–NR); median PFS=11.6 months (95% CI: 6.3–45.7), with median follow-up 33.9 months; median OS=33.5 months (95% CI: 18.3–NR), with median follow-up 42.7 months. There were no unexpected toxicities or new safety signals. **Conclusions:** Combination Tx with tafasitamab + LEN followed by tafasitamab monotherapy provided durable responses in pts with R/R DLBCL not eligible for ASCT, with a manageable safety profile. These long-term data indicate the potential of tafasitamab + LEN followed by extended tafasitamab monotherapy in achieving prolonged remission and survival benefit in this patient population, especially at first relapse. Clinical trial information: NCT02399085. Research Sponsor: MorphoSys AG, Planegg, Germany.

Tafasitamab + LEN	1 prior Tx (N=40)	2+ prior Tx (N=40)	Overall (N=80)
Best Objective Response, n (%)			
CR	19 (47.5)	13 (32.5)	32 (40.0)
PR	8 (20.0)	6 (15.0)	14 (17.5)
SD	7 (17.5)	6 (15.0)	13 (16.3)
PD	5 (12.5)	8 (20.0)	13 (16.3)
NE*	1 (2.5)	7 (17.5)	8 (10.0)
ORR (CR + PR), n (%) [95% CI]	27 (67.5) [50.9–81.4]	19 (47.5) [31.5–63.9]	46 (57.5) [45.9–68.5]
Median DoR, months (95% CI)	43.9 (9.1–NR)	NR (15.0–NR)	43.9 (26.1–NR)
Median PFS, months (95% CI)	23.5 (7.4–NR)	7.6 (2.7–NR)	11.6 (6.3–45.7)
Median OS, months (95% CI)	45.7 (24.6–NR)	15.5 (8.6–NR)	33.5 (18.3–NR)

*No valid post-baseline response assessments. Two-sided 95% Clopper-Pearson exact method based on a binomial distribution. Kaplan-Meier estimate. Data cut-off: October 30, 2020.

7514 **Poster Discussion Session**

Multicenter phase II study of romidepsin plus lenalidomide for patients with previously untreated peripheral T-cell lymphoma (PTCL).

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Background: PTCL are aggressive malignancies associated with poor prognosis when treated with cytotoxic chemotherapy. Novel agents, such as HDAC inhibitor romidepsin and immunomodulatory agent lenalidomide, have shown clinical activities as single agents and in combination in R/R PTCL. We hypothesize that upfront treatment with these agents is an effective and well-tolerated option to defer chemotherapy, particularly in patients who are not candidates for intensive approach. We report the findings of the first chemo-free combination of romidepsin plus lenalidomide as initial treatment for PTCL (ClinicalTrials.gov-NCT02232516). **Methods:** Patients with untreated PTCL who were over 60 or noncandidates for chemotherapy based on comorbidity CIRS score were eligible. Treatment was initiated with romidepsin 10 mg/m2 IV on d 1, 8, 15, and lenalidomide 25 mg PO on d 1-21 of 28-day cycle for up to 1 year, unless discontinued prior due to POD, toxicities, or withdrawal of consent. The primary objective was to evaluate ORR per Cheson criteria. Secondary objectives included safety, PFS, OS, DOR, and delay to chemotherapy. The sample size was 20 evaluable patients, which allows to estimate the underlying true response rate with the margin of error of an approximate 95% confidence interval equal to 0.22, assuming the true ORR = 0.5. **Results:** The study enrolled 29 subjects at 3 US centers, including 16 (55%) AITL, 11 (38%) PTCL-NOS, 1 ATLL and 1 EATCL. The median age was 75 (range 49-84), and M:F ratio was 1:1. Nineteen (66%) had stage III/IV disease, 23 (79%) had elevated LDH, and 9 (31%) had IPI 3-5. Treatment was well tolerated with expected side effects. Grade 3-4 hematologic toxicities included neutropenia (45%), thrombocytopenia (34%) and anemia (28%). Grade 3-4 non-hematologic toxicities included hyponatremia (45%), hypertension (38%), hypoalbuminemia (24%), fatigue (17%), hyperglycemia (14%), hypokalemia (14%), dehydration (10%), lung infection (10%) and sepsis (10%). At a median follow-up of 8 months, 20 subjects were evaluable with at least one response assessment, and received a median treatment of 6 cycles. The ORR was 75% (95%CI: 50.9%, 91.3%) with CR at 30% (11.9%, 54.3%). For AITL, the ORR was 85% (54.6%, 98.1%) with CR at 38% (13.9%, 68.4%). Median DOR was 4.2 months for all responders, and 14.3 months for CR patients. The estimated 1-yr PFS was 54.3% with 3-yr PFS at 36.2%, and the estimated 1-yr OS was 76.0% with 3-yr OS at 51.3%. Two subjects moved onto consolidative ASCT in remission, and 4 received additional cytotoxic chemotherapy after progression. **Conclusions:** This study provides the first demonstration that chemo-free biologic combination of romidepsin and lenalidomide is feasible and effective as initial therapy for PTCL patients who are not candidates for cytotoxic chemotherapy. These data justify further evaluation of such novel agents as a frontline strategy. Clinical trial information: NCT02232516. Research Sponsor: BMS/Celgene.

7515 **Poster Discussion Session**

Outcomes in ZUMA-5 with axicabtagene ciloleucel (axi-cel) in patients (pts) with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) who had the high-risk feature of progression within 24 months from initiation of first anti-CD20–containing chemoimmunotherapy (POD24).

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Background: POD24 is an indicator of poor survival in iNHL (Casulo & Barr. *Blood*. 2019). In the ZUMA-5 Phase 2 study of axi-cel anti-CD19 CAR T-cell therapy in pts with R/R iNHL, overall response rates (ORR) after 17.5 months median follow-up were similarly high in those with and without POD24 (93% and 92%; Jacobson et al. ASH 2020. #700). Here, we report updated outcomes with longer follow-up in pts with POD24 in ZUMA-5. **Methods:** Adults with R/R follicular lymphoma (FL) or marginal zone lymphoma (MZL) after ≥2 lines of therapy underwent leukapheresis followed by conditioning therapy and axi-cel infusion (2×10^6 CAR T cells/kg). Axi-cel–treated pts with available data on progression after an anti-CD20 mAb + alkylating agent were included. The updated efficacy analysis occurred when ≥80 treated pts with FL had ≥18 months follow-up. **Results:** Of 129 pts at baseline, 81 pts (63%; 68 FL, 13 MZL) had POD24 and 48 pts (37%; 40 FL, 8 MZL) did not have POD24. Median prior lines of therapy in pts with and without POD24 were 3 and 3.5, respectively. High-risk characteristics of pts with and without POD24 included stage III/IV disease, 83% and 94%; ≥3 FLIPI, 44% and 43%; high tumor bulk (GELF), 51% and 44%; and refractory disease, 77% and 63%, respectively. With 23.3 months median follow-up, ORR among efficacy-evaluable pts with POD24 (n = 61) and without POD24 (n = 37) was 92% each (complete response rates, 75% and 86%). At data cutoff, 52% of pts with POD24 and 70% without POD24 had ongoing responses. Median duration of response, progression-free survival, and overall survival were not reached in pts with and without POD24; 18-month estimated rates were 60% and 78%, 55% and 84%, and 85% and 94%, respectively. Incidences of Grade ≥3 adverse events were similar in pts with and without POD24 (84% and 88%), including cytopenias (69% and 65%) and infections (15% and 21%). Grade ≥3 cytokine release syndrome (CRS) occurred in 9% and 2% of pts with and without POD24, respectively; Grade ≥3 neurologic events (NEs) occurred in 17% of pts each. Median times to onset were similar in pts with and without POD24 for CRS (4 days each) and NEs (8 days and 7 days); median durations of CRS (7 days and 5 days) and NEs (11 days and 13 days) were also similar between groups. In efficacy-evaluable pts with FL, median peak CAR T-cell levels were similar in pts with and without POD24 (35.8 cells/μL and 34.5 cells/μL). Peak levels of key inflammatory biomarkers and axi-cel product attributes were generally similar in pts with and without POD24. **Conclusions:** Axi-cel showed a high rate of durable responses in pts with POD24 iNHL, a population with high-risk disease. Efficacy results, as well as safety and pharmacological profiles, appeared largely comparable between groups, with the exception of PFS rates. Clinical trial information: NCT03105336. Research Sponsor: Kite, a Gilead Company.

Preliminary safety and efficacy of PBCAR0191, an allogeneic, off-the-shelf CD19-targeting CAR-T product, in relapsed/refractory (r/r) CD19+ NHL.

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Background: Although autologous CD19-directed CAR T products have demonstrated unprecedented efficacy in chemorefractory patients, manufacturing failure or delays remain important barriers to care, limiting utility for those with more rapidly growing disease and/or impaired T cell fitness. Here, we present an update to preliminary safety, efficacy, and correlative data for the subjects dosed with at least 3 x 10^6 CAR-T+ cells/kg, or equivalent, of PBCAR0191, an off-the-shelf allogeneic CAR T product. **Methods:** Subjects were required to have evaluable CD19+ r/r NHL, adequate organ function, 2+ prior treatment regimens, and no active GvHD, CNS disease, infections or active medical issues. Prior stem cell transplant and/or CAR-T therapy were allowed. All subjects were lymphodepleted prior to administration of PBCAR0191with either standard (sLD; 30/500mg/m2/day x 3 days fludarbine/cyclophosphamide) or enhanced (eLD; 30 x 4 days and 1000mg/m2/day x 3 days flu/cy) lymphodepletion. Correlative laboratory samples were taken at baseline and while patients remained on study for CAR T cell expansion, persistence, response to treatment and safety assessments. **Results:** As of February 2021, 13 subjects were evaluable meeting these criteria. Demographics, baseline disease characteristics, and prior therapy data are presented in the table. Median time from eligibility confirmation to PBCAR0191 infusion was 6.5 days (1 day to start LD). To date, most adverse events (AE) reported were mild, with no cases of GvHD or Grade ≥3 CRS/ ICANS. PBCAR0191 related serious AEs were reported for 31% (4/13) of the subjects and 1 subject (9%) died of Febrile neutropenia on day 42 after treatment. Infections and cytokine release related AEs occurred at higher frequency in the eLD group. Efficacy of PBCAR0191 in 13 NHL subjects with available 28 day follow up is presented in the table. Peak PBCAR0191 expansion was increased 56-fold and was associated with CR rate of 71% in eLD group versus 33% in sLD group. Duration of response assessment is ongoing. **Conclusions:** PBCAR0191 has demonstrated dose and LD-dependent cell expansion kinetics with encouraging anti-tumor activity. Host-versus-graft rejection may have a role in depth and durability of response. CR rates with PBCAR0191 are preliminarily comparable to those observed with autologous CAR T in this population. Updated response durability assessment will be presented at the time of the meeting. Clinical trial information: NCT03666000. Research Sponsor: Precision BioSciences.

		sLD (N = 6)	eLD (N = 7)	Total (N = 13)
Age (y)	*Median (min-max)*	56 (44-81)	60 (34-64)	59 (34-81)
Aggressive	*DLBCL/MCL/High grade*	6 (100%)	4 (57%)	10 (77%)
# Subjects with 4+ Prior lines of Rx (%)		3 (50%)	5 (71%)	8 (62%)
Overall response rate (Day ≥28)		3 (50%)	7 (100%)	10 (77%)
Complete response rate (Day ≥28)		2 (33%)	5 (71%)	7 (54%)
ICANS or CRS (Gr ≥3)		0	0	0
CRS (Gr 1 or 2)		3 (50%)	3 (43%)	6 (46%)
ICANS (Gr 1 or 2)		2 (33%)	2 (29%)	4 (31%)
Infection (Gr ≥3)		0	2 (29%)	2 (15%)

7517 **Poster Discussion Session**

Engineered immunostimulatory cells can convert PBMCs from chronic lymphocytic leukemia (CLL) patients into potent tumor killing immune cells.

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Background: Alloplex Biotherapeutics has developed a cellular therapeutic that uses ENgineered Leukocyte ImmunoSTimulatory cell lines called ENLIST cells to activate and expand populations of tumor killing effector cells from human peripheral blood mononuclear cells (PBMCs). This process leads to a 300-fold expansion of NK cells, CD8+ T cells, NKT cells, and TCR$\gamma\delta$ T cells that are called SUPLEXA cells, which will be cryopreserved and transferred back into patients as an autologous immune cell therapy for cancer. In this study, PBMCs from CLL patients were used to generate SUPLEXA cells as a first approach to comparatively profile SUPLEXA cells from cancer patients and normal healthy volunteers (NHVs). **Methods:** ENLIST cell lines were engineered by expressing curated immunomodulatory proteins in the SK-MEL-2 melanoma cell line. Two million (M) PBMCs from 10 CLL patients or 2 NHVs were incubated with 0.4 M freeze/thaw killed ENLIST cells for 5 days in XVIVO-15 medium with 2% heat-inactivated human AB serum (XAB2) and then split 1:15 in XAB2 containing IL-7 and IL-15 to expand. After 9 days, SUPLEXA cells were harvested and cryopreserved. **Results:** Original PBMCs and matched SUPLEXA cells from each donor were thawed and characterized by mass cytometry (CyTOF) using a 47-marker antibody panel. CyTOF staining results of PBMCs from CLL patients demonstrated approximately 95% leukemia cells and few T cells, NK cells, B cells, and monocytes. CyTOF staining of SUPLEXA cells from all 10 CLL patients showed expansion of NK cells (17%), CD8 T cells (11%), and CD4 T cells (7.5%) that were similar in phenotype to SUPLEXA cells from NHVs showing high expression of granzymes and perforin that are indicative of potent tumor cell killing activity. Cancer cells in the original CLL PBMC samples were reduced to 0.78%. However, a population of non-T/non-B cells (60% ± 9.5%) was detected in SUPLEXA cells from all CLL patients that require further characterization. Next, SUPLEXA cells from CLL and NHV patients were comparatively tested for tumor cell killing activity at 2:1, 1:1, and 1:2 effector to target cell (MEL-14 melanoma cells expressing RFP) ratios. Percent killing of tumor cells by SUPLEXA cells prepared from CLL patients (77.8% ± 2.6% at 2:1) and NHVs (81.5% ± 0.3% at 2:1) were nearly identical at all effector to target ratios. **Conclusions:** We demonstrate for the first time that PBMCs from CLL patients can be converted into SUPLEXA cells despite low numbers of normal immune cells at baseline and the known immunologic impairment present in CLL patients. Importantly, SUPLEXA cells derived from CLL patients acquire potent tumor killing activity that is indistinguishable from SUPLEXA cells prepared from NHVs. Taken together, these findings support the feasibility of converting PBMCs from CLL patients with low percentages of NK and T cells into an autologous cellular therapy for cancer. Research Sponsor: Alloplex Biotherapeutics.

7518 **Poster Discussion Session**

Subcutaneous epcoritamab in patients with relapsed/refractory B-cell non-Hodgkin lymphoma: Safety profile and antitumor activity.

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Background: Epcoritamab is a CD20xCD3 bispecific antibody that induces T-cellmediated killing of CD20positive malignant B-cells. We present updated data, including progression-free survival (PFS) from the dose escalation part of the first-in-human phase 1/2 study of epcoritamab in pts with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL; NCT03625037). **Methods:** Adults with R/R CD20+ B-NHL received flat-dose 1 mL SC epcoritamab (step-up dosing approach) in 28-day cycles (q1w: cycles 12; q2w: cycles 36; q4w thereafter) until disease progression or unacceptable toxicity. Step-up dosing and standard prophylaxis were used to mitigate severity of cytokine release syndrome (CRS). **Results:** At data cut off (1/31/2021), 68 pts with B-NHL were enrolled across histologies including diffuse large B-cell lymphoma (DLBCL; n = 46 [67.6%]; de novo and transformed), follicular lymphoma (FL; 12 [17.6%]), mantle cell lymphoma (MCL; 4 [5.9%]), and others (6 [8.8%]). Majority were heavily pretreated (median [range] prior lines: DLBCL, 3 [16]; FL, 4.5 [118]); including prior CAR-T (n = 6) and prior ASCT (n = 10). At median follow-up of 14.1 mo (DLBCL, 10.2 mo; FL, 15.2 mo), treatment was ongoing in 15 (22%) pts. Most common treatment-emergent adverse events (AEs) were pyrexia (69%), CRS (59%), and injection site reaction (47%). CRS events were all grade 1 or 2 and most occurred in cycle 1; neurotoxicity was limited (6%; grade 1: 3%; grade 3: 3%; all transient). One case of tumor lysis syndrome was observed (1.5%; grade 3); there were no cases of febrile neutropenia or treatment-related death. Overall response is shown for DLBCL ≥12 mg and ≥48 mg and FL ≥12 mg, corresponding to the minimal efficacy threshold (Table). Responses deepened over time (PR converted to CR: DLBCL, 6 pts; FL, 3 pts). Median time to response was 1.4 mo (DLBCL) and 1.9 mo (FL). Among DLBCL pts achieving CR with ≥6 mg (n = 11), none relapsed while on treatment. The median PFS for pts with DLBCL ≥12 mg (n = 22) was 9.1 mo (95% CI: 1.6, NE; median follow-up 9.3 mo) and for pts with DLBCL ≥48 mg (n = 11) median PFS was not reached (median follow-up 8.8 mo). Updated analyses will be presented. **Conclusions:** With longer follow-up, SC epcoritamab demonstrated substantial single-agent activity, inducing deep and durable clinically meaningful responses, with a consistent safety profile. Notably no severe (grade ≥3) CRS events, no febrile neutropenia, and limited neurotoxicity was observed. Clinical trial information: NCT03625037. Research Sponsor: This study was funded by Genmab A/S and AbbVie Inc.

	DLBCL		FL	MCL
	≥12 mg	4860 mg	1248 mg	0.7648 mg
Evaluable pts	22	11	5	4
ORR, n (%)	15 (68.2)	10 (91)	4 (80)	2 (50)
CR, n (%)	10 (45.5)	6 (55)	3 (60)	1 (25)
PR, n (%)	5 (22.7)	4 (36)	1 (20)	1 (25)
SD, n (%)	1 (4.5)	0	0	1 (25)
PD, n (%)	5 (22.7)	0	1 (20)	0

7519 **Poster Discussion Session**

Glofitamab step-up dosing (SUD): Complete response rates in updated efficacy data in heavily pretreated relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) patients (pts).

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Background: Glofitamab (RG6026), a T-cell-engaging, bispecific, full-length antibody, allows bivalent binding to CD20 (B-cells), and monovalent binding to CD3 (T-cells). In NP30179 (NCT03075696), an ongoing multicenter, Phase I dose-escalation and expansion study, 0.6–25mg glofitamab fixed-dosing with obinutuzumab pretreatment (Gpt), showed high, durable complete responses and manageable safety in heavily pretreated R/R NHL (Dickinson, et al. EHA 2020). Glofitamab SUD, in addition to Gpt, allowed dose escalation up to 30mg to maximize efficacy, while mitigating cytokine release syndrome (CRS) (Hutchings, et al. JCO 2021). We present updated efficacy data from glofitamab monotherapy SUD cohorts. **Methods:** Gpt (1000mg) was given to pts 7 days pre-glofitamab initial dose. Intravenous SUD of glofitamab was given on Day (D) 1 and 8 of Cycle (C) 1 and then at the target dose from C2D1 (2.5/10/16mg or 2.5/10/30mg); treatment continued for up to 12 cycles, every 21 days. Response rates were based on the Lugano criteria (Cheson, et al. JCO 2014). **Results:** Fifty-two pts received glofitamab SUD; 17 and 35 pts received 2.5/10/16mg and 2.5/10/30mg, respectively. Twenty-eight pts (53.8%) had aggressive NHL (aNHL) and 24 pts had indolent NHL (iNHL). Pts had a median age of 68 (44–85) years and received a median of 3 (1–12) prior lines of therapy. Forty (76.9%) and 38 (73.1%) pts were refractory to their most recent and any prior CD20 therapy, respectively. After a median follow-up of 6.3 months, an updated efficacy analysis was conducted on December 1, 2020. For pts with aNHL (N = 28), the best overall response (OR) and complete metabolic response (CMR) rates were 64.3% and 57.1%, respectively; a trend of improved response was observed with increased target dose, with a CMR rate of 71.4% at 2.5/10/30mg (N = 14). Notably, 4/5 pts (80%) with mantle cell lymphoma (2.5/10/16mg, n = 2; 2.5/10/30mg, n = 2) had CMR. For aNHL, 13/16 CMRs are ongoing, with 8 CMRs lasting $>$ 3 months. For pts with iNHL (N = 24), OR and CMR rates were 79.2% and 70.8%, respectively; 14/17 CMRs are ongoing, with 10 CMRs lasting $>$ 3 months. As of August 3, 2020, common adverse events (52 pts) were CRS (63.5%), neutropenia (38.5%), and pyrexia (32.7%). CRS was mostly confined to C1: 24/50 pts had CRS after 2.5mg; 20/49 pts after 10mg; 2/16 and 8/32 pts had CRS after 16 and 30mg (C2D1), respectively. Grade [Gr] 1 and 2 CRS was reported in 18 (34.6%) and 12 (23%) pts, respectively; 3 pts had Gr 3 CRS; none had Gr 4/5 events (ASTCT 2019). Updated data, including biomarker data on baseline CD20 expression and CD8 levels in the tumor, will be presented. **Conclusions:** Updated data for glofitamab monotherapy SUD show higher preliminary response rates than previously reported in pts with R/R NHL who have failed multiple lines of therapy. CRS was mostly manageable, of low grade, and confined to the first cycle of treatment. Clinical trial information: NCT03075696. Research Sponsor: NP30179 is sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under direction of authors, was provided by Khalida Rizi, MPharm, PhD, of Ashfield MedComms, an Ashfield Health company, and funded by F. Hoffmann-La Roche Ltd.

7520 **Poster Discussion Session**

Promising tolerability and efficacy results from dose-escalation in an ongoing phase Ib/II study of mosunetuzumab (M) with polatuzumab vedotin (Pola) in patients (pts) with relapsed/refractory (R/R) B-cell non-Hodgkin's lymphoma (B-NHL).

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Background: Mosunetuzumab (M), a full-length, humanized, IgG1 bispecific antibody targeting CD20 and CD3, has shown promising efficacy and safety as monotherapy for R/R B-NHL (NCT02500407; Assouline, et al. ASH 2020). The combination of M with the anti-CD79b antibody-drug conjugate, Pola, showed synergistic anti-lymphoma activity in a mouse xenograft model. These data supported a Phase Ib/II, open-label, multicenter trial of M-Pola for R/R B-NHL (GO40516, NCT03671018). Here we present early clinical data from the Phase Ib cohort. **Methods:** Pts with R/R follicular lymphoma (FL, grade [Gr] 1–3a) or aggressive NHL (aNHL), including *de novo* diffuse large B-cell lymphoma (DLBCL), transformed FL (trFL) and FL Gr 3b (FL3b), received Cycle (C) 1 step-up doses of M on Day (D) 1 (1mg) and D8 (2mg), the target dose on C1D15, then continued at the target dose on C2D1 onwards. M was given every 21 days for eight cycles (or 17 cycles if stable disease or a partial response after C8). Pola (1.8mg/kg) was given with M on D1 of each cycle for six cycles. **Results:** As of November 17, 2020, 22 pts had received M-Pola (M target doses: 9mg, n=7; 20mg, n=3; 40mg, n=6; 60mg [with D1 dose of 30mg from C3 onwards], n=6). Pts had DLBCL (n=12), FL (n=3), FL3b (n=3) and trFL (n=4). Pt characteristics include: median age of 70 (38–81) years; median of 3 (1–10) prior lines of therapy; 7 (32%) pts had prior CAR-T therapy; 17 (77%) and 19 (86%) pts had disease refractory to last prior therapy and prior anti-CD20 therapy, respectively. Median follow-up duration was 9.6 (0.7–23.7) months. The most frequent treatment-related adverse events (AEs) were neutropenia (45.4%), fatigue, nausea and diarrhea (all 36.4%). Cytokine release syndrome (CRS) was observed in 2 pts (9.1%; both Gr 1 by ASTCT 2019 criteria). One dose-limiting toxicity (Gr 3 new onset atrial fibrillation) was observed in the 40mg cohort. The maximum tolerated dose was not exceeded. The most common Gr $\geq$3 and serious AEs were both neutropenia, observed in 8 (36.4%) and 3 (13.6%) pts, respectively. Two (9.3%) Gr 5 AEs occurred: sudden cardiac death (n=1) and respiratory failure (n=1); neither was deemed treatment related. No immune effector cell-associated neurotoxicity was observed. The Table shows preliminary efficacy data. Preliminary efficacy in the dose-escalation cohort. **Conclusions:** These data indicate that M-Pola has an acceptable safety profile, with no Gr $\geq$2 CRS observed, and promising efficacy in pts with R/R NHL with predominantly aggressive disease. The Phase II expansion cohort in R/R DLBCL is ongoing, with no mandatory hospitalization required. Clinical trial information: NCT03671018. Research Sponsor: Study GO40516 is sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under direction of authors, was provided by Katie Buxton and Khalida Rizi of Ashfield MedComms, and funded by F. Hoffmann-La Roche Ltd/Genentech, Inc.

Response, n (%)	All pts (n=22)	aNHL pts (n=19)	Post-CAR-T pts (n=7)	FL pts (n=3)
Overall response rate	15 (68.2)	12 (63.2)	4 (57.1)	3 (100)
Complete response rate	12 (54.5)	9 (47.4)	2 (28.6)	3 (100)

7521 **Poster Session**

Effect of time to relapse on overall survival (OS) in mantle cell lymphoma (MCL) patients (pts) following frontline high-dose therapy and autologous hematopoietic cell transplantation (autoHCT).

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Background: In MCL, outcomes are heterogeneous and the clinical significance of the timing of relapse following autoHCT and its impact on OS is not well defined. Using the CIBMTR database, we evaluate the effect of post-autoHCT time to relapse on OS over time. **Methods:** Adult MCL pts treated with up to two lines of rituximab-based induction therapy followed by first autoHCT within 1-year of diagnosis were identified between 2000-2018. Primary outcomes included OS and post-relapse OS. A dynamic landmark analysis was performed at 6-month intervals following autoHCT to evaluate the impact of relapse on OS while adjusting for significant patient- and disease-related variables. Post-relapse OS was evaluated in pts who experienced relapse. **Results:** Of the 461 pts included in the analysis, the median age was 60 years (range 29-78), 57% had a KPS of $\geq$ 90, 83% had stage III-IV disease at diagnosis, and 76% had extranodal involvement. BEAM was the most common conditioning regimen (58%) and 23% of pts received post-autoHCT maintenance rituximab. With a median follow-up of 67 months, the 5-year progression-free survival was 45.8% with a 5-year OS of 69.6%. On multivariate analysis, age $\geq$60 years was associated with worse OS (HR= 1.55, 95% CI 1.08-2.24, p=0.0191) at all landmark timepoints. Additionally, the impact of relapse on OS varied with time (p=0.006) and was greatest at the 6-month (HR=7.68), 12-month (HR=6.68), and 18-month (HR=5.81) landmark timepoints. The risk of death for relapsing pts decreased with time and was mirrored by an improvement in adjusted OS for both relapsing and non-relapsing pts. In total, 9.3% of patients relapsed prior to the 18-month landmark timepoint. Relapse at the 6-month, 12-month, and 18-month landmark timepoints correlated with a poor median post-relapse OS of 9 months, 24 months, and 34 months, respectively (Table). Conversely, patients relapsing after the 18-month landmark timepoint experienced a median post-relapse OS ranging from 44-67 months. **Conclusions:** In MCL, early relapse ($<$ 18-months) following autoHCT defines a high-risk group with inferior post-relapse OS**.** This population should be considered for clinical trials or novel therapeutic approaches including early utilization of chimeric antigen receptor T-cell therapy. Research Sponsor: U.S. National Institutes of Health.

Median OS of relapsing and non-relapsing patients following frontline autoHCT for MCL.

Landmark timepoint	Median OS of relapsing patients, months	Median OS of non-relapsing patients, months
6 months	9	131
12 months	24	128
18 months	34	126
24 months	44	132
30 months	48	126
36 months	50	144
42 months	47	138
48 months	51	132
54 months	67	126
60 months	-	120

7522 **Poster Session**

Progression-free survival at 24 months as a landmark after autologous stem cell transplant in relapsed or refractory diffuse large B-cell lymphoma.

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Background: Patients with newly diagnoseddiffuse large B-cell lymphoma (DLBCL) who achieve event-free survival at 24 months (EFS24) following immunochemotherapy (IC) have excellent overall survival (OS) similar to that of age- and sex-matched general population. The standard of care for patients with relapsed or refractory (RR) DLBCL following frontline IC is salvage therapy followed by autologous stem cell transplant (ASCT). The goal of this study is to evaluate the role of progression-free survival (PFS) at 24 months (PFS24) as a landmark after ASCT in patients with RR DLBCL. **Methods:** Patients with RR DLBCL after frontline R-CHOP or R-CHOP-like IC who underwent salvage therapy and ASCT at Mayo Clinic or University of Iowa between 07/2000 and 4/2020 were identified from institutional lymphoma transplant databases. Clinical characteristics, treatment information, and outcome data were abstracted. Post-ASCT PFS, OS, and post-relapse survival (PRS) were plotted by Kaplan-Meier method, and cumulative incidences of relapse vs non-relapse mortality (NRM) and different causes of death were compared accounting for competing events. Statistical analyses were performed in EZR v1.54. **Results:** A total of 437 patients were identified. Median age at ASCT was 61 years (range 19-78), and 280 (64%) were male. After a median post-ASCT follow up of 8.0 years (95% CI 7.2-8.7), 215 patients had a relapse (or disease progression), 180 within 2 years and 35 after 2 years. For the entire cohort, post-ASCT relapse rate was much higher than NRM rate (48.1 vs 9.1% at 5-year). Median PFS and OS after ASCT was 2.7 and 5.4 years, respectively. Lymphoma was the primary cause of death after ASCT. In contrast, for patients who had achieved PFS24 (n = 220), rates of post-PFS24 relapse and NRM were similar (14.8% and 12.3% at 5-year). Median PFS and OS after achieving PFS24 was 10.0 and 11.5 years, respectively. Lymphoma related and unrelated death rates were similar after achieving PFS24 (Table). For all patients who had a post-ASCT relapse, median PRS was 0.7 years (95% CI 0.5-0.9), and late relapse (>2 vs ≤ 2 years after ASCT) was associated with better PRS (median 2.3 [1.7-4.8] vs 0.5 [0.3-0.7] years, $p<0.001$). **Conclusions:** Post-ASCT PFS24 is an important prognostic predictor of post-ASCT outcomes in patients with RR DLBCL following frontline IC. Research Sponsor: None.

	Starting landmark	
	ASCT (n = 437)	AchievedPFS24 (n = 220)
5-year rate of (%)		
Relapse	48.1 (43.2-52.8)	14.8 (10.1-20.3)
NRM	9.1 (6.5-12.2)	12.3 (7.8-17.8)
Median PFS, years	2.7 (1.5-4.3)	10.0 (8.4-13.1)
5-year PFS (%)	42.8 (38.0-47.6)	72.9 (65.6-78.9)
Median OS, years	5.4 (4.2-7.4)	11.5 (9.9-NA)
5-year OS (%)	51.9 (46.9-56.7)	79.3 (72.3-84.8)
5-year rate of deaths from (%)		
Lymphoma	36.0 (31.3-0.40.6)	6.5 (3.4-11.0)
Treatment-related complications	6.3 (4.2-8.9)	4.2 (1.8-8.1)
Other causes	4.8 (3.0-7.3)	8.1 (4.6-12.9)
Unknown causes	1.0 (0.3-2.5)	1.8 (0.5-4.9)

7523 **Poster Session**

Up to seven years of follow-up in the RESONATE-2 study of first-line ibrutinib treatment for patients with chronic lymphocytic leukemia.

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Background: Ibrutinib, a once-daily Bruton's tyrosine kinase inhibitor, is the only targeted therapy with significant progression-free survival (PFS) and overall survival (OS) benefit in multiple randomized phase 3 studies versus established therapies in patients (pts) with previously untreated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Extended long-term follow-up data for the RESONATE-2 study of first-line ibrutinib vs chlorambucil in older pts with CLL/SLL are reported. **Methods:** In the phase 3 RESONATE-2 study, older pts (≥65 years [y]) with previously untreated CLL/SLL and without del(17p) (N=269) were randomly assigned 1:1 to once-daily single-agent ibrutinib 420 mg until disease progression (PD) or unacceptable toxicity (n=136) or chlorambucil 0.5–0.8 mg/kg up to 12 cycles (n=133). Outcomes included PFS, OS, overall response rate (ORR), and safety. Long-term responses were investigator-assessed per 2008 iwCLL criteria. **Results:** With up to 7y of follow-up (median, 74.9 months; range, 0.1–86.8), significant PFS benefit was sustained for pts treated with ibrutinib vs chlorambucil (hazard ratio [HR] 0.160 [95% confidence interval (CI): 0.111–0.230]). At 6.5y, PFS was 61% in pts treated with ibrutinib vs 9% in pts treated with chlorambucil. This PFS benefit was observed across all subgroups, including in ibrutinib-treated pts with high-risk genomic features of unmutated IGHV (HR 0.109 [95% CI: 0.063–0.189]) or del(11q) (HR 0.033 [95% CI: 0.010–0.107]). OS at 6.5y was 78% with ibrutinib treatment. ORR was 92% for ibrutinib-treated pts with complete response (CR/CRi) rate increasing to 34% with this follow-up. Ongoing rates of grade ≥3 adverse events (AEs) of interest remained low for hypertension (5–6y interval: 5%, n=4; 6–7y: 4%, n=3) and atrial fibrillation (5–6y: 1%, n=1; 6–7y: 1%, n=1); no grade ≥3 major hemorrhage occurred in 5–7y. Dose reductions due to grade ≥3 AEs occurred in 1% (n=1) of pts during the 5–6y and 6–7y intervals. Across full follow-up, 31 pts had dose reductions due to any-grade AEs of whom 22/31 (71%) had resolution or improvement the AE. Primary reason for discontinuations in 5–7y was PD (5–6y: 5%, n=4; 6–7y: 6%, n=4). Any-grade AEs leading to discontinuations were seen in 3% (n=2) of pts from 5–6y and none in 6–7y. With over 7y of follow-up, 47% of pts remain on single-agent ibrutinib. **Conclusions:** Extended long-term data from RESONATE-2 demonstrate the sustained PFS and OS benefit of first-line ibrutinib treatment for pts with CLL, including for pts with high-risk genomic features. Responses continue to deepen over time. Rates of grade ≥3 AEs of interest continued to be low at up to 7y follow-up and further discontinuations and dose reductions due to AEs were rare; most AEs leading to dose reduction resolved or improved. Ibrutinib remains well tolerated with no new safety signals observed. Clinical trial information: NCT01722487, NCT01724346. Research Sponsor: Pharmacyclics LLC, an AbbVie Company, Pharmaceutical/Biotech Company.

7524 **Poster Session**

Survival trends in chronic lymphocytic leukemia in the era of oral targeted therapies in the United States: SEER database analyses (1985 to 2017).

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Background: The survival of chronic lymphocytic leukemia (CLL) patients has progressively improved after the approval of new targeted therapy for first-line treatment and relapsed disease. We performed a corresponding analysis from the U.S. population-based SEER database (1973–2017) to explore the trend of survival and the effect of advanced CLL treatment on overall survival in CLL patients. **Methods:** Data were extracted from SEER*Stat for all patients 15 years or older with a primary diagnosis of CLL with or without subsequent cancers. A period analysis was performed to estimate the 5- and 10-year relative survival rates for patients diagnosed (dx) during different calendar periods from 1985 to 2017, based on gender and age at time of diagnosis (15–44, 45–54, 55–64, 65–74, 75–84, 85 years or older). A mixture cure model was used to examine the proportion of long-term survivors per gender and age category among CLL patients diagnosed between 1985 and 2015. Cox proportional hazard modeling was used to calculate the hazard ratios (HRs) of death adjusted for gender and age at diagnosis for two cohorts: (a) diagnosed in 2000–2003 and followed to 2012; (b) 2004–2007 and followed to 2015. **Results:** For males, the 5-year age-adjusted relative survival rate improved progressively from 72.0% (dx 1985-1989) to 88.2% (dx 2010-2014); for females, from 76.8% (dx 1985-1989) to 90.8% (dx 2010-2014). The corresponding 10-year age-adjusted relative survival rates were 47.3% (dx 1985-1989) and 72.5% (dx 2005-2009) for males; and 58.2% (dx 1985-1989) and 78.7% (dx 2005-2009) for females. The table below shows the proportions of long-term survivors for the 1985–2017 cohort as estimated in the mixed cure model. The HRs (95%CI) of death for cohort (b) in comparison to cohort (a) were 0.58 (0.43–0.78), 0.58 (0.48–0.70), 0.57 (0.49–0.67), 0.68 (0.54–0.85); and 0.83 (0.68–1.02) for age categories of 45–54, 55–64, 65–74, 75–84, and 85 years or old. **Conclusions:** Survival is significantly improved by calendar period among patients diagnosed after 2004 and treated in the era of advanced therapies. Females and younger patients had a higher probability of long term survival. Future studies should consider such covariates as treatment type, disease stage and genetics. Research Sponsor: None.

Estimated cure proportions for CLL patients diagnosed between 1985-2015.

Age	Overall cured proportion (95%CI)	Cured proportion in males (95%CI)	Cured proportion in females (95%CI)
45-54	0.43 (0.38-0.49)	0.35 (0.29-0.42)	0.59 (0.52-0.64)
55-64	0.41 (0.37-0.44)	0.35 (0.32-0.39)	0.50 (0.46-0.54)
65-74	0.12 (0.10-0.70)*	0.08 (0.007-0.98)	0.16 (0.12-0.22)
75-84	0.003 (0.001-0.98)*	no cure	0.14 (0.11-0.20)
85+	0.02 (0.001-0.99)*	no cure	0.06 (0.02-0.26)

*Indicates a high variation in CLL survival per gender.

7525 **Poster Session**

Updated results of the selective Bruton tyrosine kinase (BTK) inhibitor TG-1701, as monotherapy and in combination with ublituximab and umbralisib (U2) in patients (pts) with B-cell malignancies.

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Background: TG-1701 is a selective, covalent BTK inhibitor administered once daily (QD). Both the U2 combination (anti-CD20 mAb ublituximab + the PI3Kδ-CK1ε inhibitor umbralisib) and BTK inhibition are highly active in treatment-nave (TN) and relapsed/refractory (R/R) CLL, each having previously demonstrated superiority over standard chemoimmunotherapy. Here we report the results of the dose escalation of TG-1701 monotherapy and TG-1701+U2. **Methods:** Pts with R/R CLL and lymphoma were enrolled in a Ph 1 study initially evaluating dose escalation (DE) of oral TG-1701 QD continuously administered in 28-day cycles (100, 200, 300, and 400 mg). After characterizing the safety profile of TG-1701 monotherapy, we implemented a parallel DE arm of TG-1701+U2. Select dose levels of TG-1701 monotherapy were expanded in CLL, MCL and Waldenström's (WM). All pts were treated until disease progression. The primary objectives are to characterize the safety profile and define the recommended Ph 2 doses for the drugs alone and in combination. **Results:** As of 03 February 2021, 123 pts were treated with TG-1701: 25 in the monotherapy DE arm, 61 in the 200 mg disease-specific cohorts (20 CLL [5 TN], 21 MCL [4 TN], 20 WM [8 TN]), 20 in the 300 mg CLL cohort (4 TN), and 17 in the 1701+U2 DE arm. The median # of prior therapies was 1 (range, 1 - 10). All pts were BTKi-nave. All 123 pts were evaluable for safety. TG-1701 was well tolerated and the maximum tolerated dose (MTD) for monotherapy was not reached at 400 mg (demonstrating near 100% saturation of the BTK at all dose levels studied). Treatment emergent adverse events (TEAE) of clinical interest included atrial fibrillation (AF 4.0% of pts, G $\geq$3 in 1 case), G $\geq$3 hypertension (2.4%), and bleeding events (18.7%, all G1-2). No cases of ventricular tachyarrhythmia were reported. TEAEs leading to TG-1701 dose reduction occurred in 6.5% of pts. TEAEs leading to treatment discontinuation occurred in 1.6% of pts (AF, COVID-19). At the data cut-off, 119 pts were evaluable for response, including 40 in DE (Table). The median duration of response has not been reached among responders overall. The median follow-up (mFU range) was 15.9 mos (1.3 - 28.6+) in DE and 8.5 mos (1.4 -15.6+) in disease-specific cohorts. **Conclusions:** TG-1701 exhibits an encouraging safety and efficacy profile. The combination of 1701+U2 has been well tolerated and dose escalation continues. The combination shows enhanced depth of response over TG-1701 monotherapy. Recruitment to this study continues. Response per investigator review by treatment group. Clinical trial information: NCT03671590. Research Sponsor: TG Therapeutics.

	DE arm (N = 23)	200 mg CLL (N = 20)	200 mg MCL (N = 20)	200 mg WM (N = 20)	300 mg CLL (N = 19)	1701+U2 DE arm (N = 17)
ORR %	56.5	95.0	60.0	95.0	100	82.3
CR %	0	0	0	0	0	23.5
Very good PR %	4.3	NA	NA	0	NA	5.9
PR %	47.8	95.0	60.0	70.0	100	52.9
Minor response %	4.3	NA	NA	25.0	NA	0
mFU mos	17.5	11.6	8.2	9.7	5.8	14.3

7526 **Poster Session**

Identification of genetic markers associated with ibrutinib-related cardiovascular toxicity.

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Background: Cardiovascular side effects (CVSEs: atrial fibrillation, hypertension, etc.) are common in patients with chronic lymphocytic leukemia (CLL) treated with ibrutinib and often lead to dose reductions or discontinuation. However, the etiology of ibrutinib related CVSEs has not been elucidated. This study sought to interrogate the association between ibrutinib related CVSEs and polymorphisms in genes of the Bruton Tyrosine Kinase (BTK) signaling pathway (identified through Ingenuity Pathway Analysis) **Methods:** Newly diagnosed and relapsed patients with CLL who underwent treatment with ibrutinib between December 2019 and November 2020 at Levine Cancer Institute were identified. Buccal swabs were collected through an IRB approved specimen collection protocol. Data extraction included: demographics, CLL stage, cytogenetics, previous treatments, ibrutinib start dates and dose, drug related SEs, and other medications. DNA isolated from buccal swabs was genotyped for 40 single nucleotide polymorphisms (SNPs) in *GATA4, SGK1, KCNQ1, KCNA4, NPPA* and *SCN5A* genes using a custom NGS panel. Logistic regression analysis evaluated the association between SNPs and CVSEs. **Results:** In 50 evaluable patients, the median age was 71 years (range:48-90) and 50% received frontline ibrutinib monotherapy. CVSEs occurred in 20% of patients (n=10). In univariate analysis, 4 SNPs in 3 genes were significantly associated with CVSEs (Table). Because the genes were in the same pathway, a genetic risk score was developed which indicated that patients with at least 2 SNPs had a 12-fold increase in risk of CVSEs (Table). **Conclusions:** Our findings provide insights into the genetic determinants of ibrutinib related CVSEs. If replicated in a larger study, this will facilitate utility of pharmacogenetic testing (for *GATA4, KCNQ1* and *KCNA5* polymorphisms*)* as a clinical tool to individualize ibrutinib treatment. Research Sponsor: Atrium foundation.

Results of logistic regression analysis.

Gene/SNP	Odds Ratio	95% Confidence Interval		P-value
		Lower limit	Upper limit	
Univariate logistic regression analysis				
GATA4				
rs804280 (AA vs. AC+CC)	4.5	1.1	19.0	0.05
KCNQ1				
rs163182 (GG vs. GC+CC)	5.3	1.1	25.0	0.04
rs2237895 (AA vs. AC+CC)	12.0	1.4	111.0	0.01
KCNA5				
rs2284136 (CC vs. CT+TT)	8.0	1.1	70.0	0.03
Genetic risk score				
Genetic risk score (1 vs. 0)*	12.2	1.4	105.4	0.01

*:score of 1 if presence of $\geq$ 2 SNPs and 0 if $\leq$ 1 SNP.

7527 **Poster Session**

Herpes zoster in chronic lymphocytic leukemia: Effect of vaccination and treatment.

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Background: Patients with Chronic Lymphocytic Leukemia (CLL) are susceptible to infections due to impaired humoral immunity as a complication of the disease, treatments received and age at diagnosis. Herpes zoster (HZ) is a painful, vesicular rash from reactivation of varicella-zoster virus that is common in immunocompromised patients. While HZ vaccines can reduce both varicella-zoster reactivation and post-herpetic neuralgia, vaccination rates are low. The aim of this study is to determine the effect of vaccination on rates of HZ infection in patients with CLL. **Methods:** We identified patients diagnosed with CLL between September 1999 and October 2015 using Veterans Administration Central Cancer Registry (VACCR). Pharmacy records were used to identify patients who received treatment for CLL and HZ. HZ events were defined as patients with International Classification of Diseases 9th Revision (ICD-9) codes for HZ infection (053) or prescriptions of acyclovir or valacyclovir at a dose of 1500 mg/day or higher or famciclovir at a dose of 1000 mg/day or higher without a diagnosis of Herpes simplex or Bell's palsy, or an ICD-9 code and prescription above. Cox proportional hazards regression model was used to assess the association between vaccination as a time-varying exposure and developing HZ while controlling age at CLL diagnosis, co-morbidity score, and receipt of first and second line chemotherapy. The study was approved by the St. Louis VA Medical Center institutional review board. **Results:** A cohort of 7155 patients with CLL was identified using VACCR. 2640 patients (36.9%) and 1161 patients (16.2%) received first and second line chemotherapy respectively. Mean age at first chemotherapy was 69.5 years. We detected 1115 cases of HZ (15.6%) using ICD-9 codes, prescriptions or both. 615 patients (8.6%) received HZ vaccinations. Patients with HZ were younger (mean 68.0 vs. 69.8 years, $p < 0.001$), had similar co-morbidities, and were more likely to get treatment for CLL (58.1% vs. 33.0%, $p < 0.001$). Using a time-varying analysis, there was a trend for HZ vaccine to decrease the risk of developing HZ (HR 0.71, 95% CI 0.49-1.04, $p = 0.082$). When adjusting for age and co-morbidity, patients with CLL treated with first line chemotherapy had a higher risk of HZ (HR 2.34, 95% CI 2.02-2.71, $p < 0.001$) compared to those never receiving therapy. Second line chemotherapy increased risk of HZ (HR 1.32, 95% CI 1.13-1.55, $p < 0.001$) beyond first line treatment. **Conclusions:** HZ is prevalent in patients with CLL and affects younger patients who require chemotherapy. The risk of developing HZ increases in recipients of first and second line chemotherapy. In the time-varying analysis, there was a trend towards decreased infection in patients who received HZ vaccination. Further studies in a more modern cohort that assess infection risk using a larger vaccinated group with the newer and more effective HZ vaccine are warranted. Research Sponsor: None.

7528 **Poster Session**

Brentuximab vedotin with chemotherapy in adolescents and young adults (AYAs) with stage III or IV Hodgkin lymphoma: A subgroup analysis from the phase 3 Echelon-1 study.

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Background: Hodgkin lymphoma (HL) is a rare disease that commonly occurs in adolescents and young adults (AYAs) which is typically defined as 15 to 39 years. Given their young age at presentation, key factors in treatment selection include a high cure rate and limiting long-term toxicities. Brentuximab vedotin (Adcetris®; A) is a CD30-directed ADC approved in combination with doxorubicin, vinblastine, and dacarbazine chemotherapy (A+AVD) for adults with previously untreated stage III/IV cHL based on results from the phase 3 ECHELON-1 trial. Recent 5-year data demonstrated a significantly improved PFS per investigator (INV) vs doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) (HR, 0.69; 95% CI, 0.54–0.9; P = 0.003) (Straus 2020). Here we describe key efficacy and safety results for AYA pts enrolled in ECHELON-1. **Methods:** ECHELON-1 (N = 1334) is a global, open-label, multicenter, randomized trial of pts with previously untreated stage III/IV cHL. A total of 771 AYAs (57.8%) received either A+AVD (n = 396) or ABVD (n = 375) with a PET scan after cycle 2 (PET2). An analysis of PFS (time from randomization to progression or death from any cause) per INV was conducted. **Results:** After a median follow-up of 60.7 months (95% CI, 60.4-61.0), there was a 36% reduction in the risk of progression or death in AYAs receiving A+AVD vs ABVD (HR 0.64; 95% CI, 0.45-0.92; P = 0.013) with a 5-year PFS of 86.3% vs 79.4%, respectively, similar to the ITT population. The PFS benefit of A+AVD vs ABVD was independent of PET2 status; PET2 positivity (Deauville 4-5) was 6% and 8%, respectively. On the A+AVD arm, 81 AYAs (20%) had at least 1 subsequent anticancer therapy vs 96 AYAs (26%) on the ABVD arm; 26 AYAs (7%) received subsequent high dose chemotherapy and autologous stem cell transplant vs 32 AYAs (9%) on the A+AVD and ABVD arms, respectively. Resolution or improvement of peripheral neuropathy (PN) were similar in both arms; 224 AYAs (88%) on the A+AVD had resolution or improvement of PN vs 133 AYAs (89%) on the ABVD arm. Ongoing PN was predominantly Gr 1 (62%) and Gr 2 (26%), with 8 AYAs (13%) on the A+AVD arm and 1 AYA (5%) on the ABVD arm reporting ongoing Gr 3 PN. Finally, 7 AYAs (1.8%) and 5 AYAs (1.4%) on the A+AVD and ABVD arms, respectively, reported a secondary malignancy. Subsequent pregnancies were reported in female pts (44 A+AVD; 26 ABVD) and partners of male pts (31 A+AVD; 30 ABVD). No stillbirths were reported. All but 1 pt in each arm was < 40. **Conclusions:** Consistent with the ITT population, AYAs treated with A+AVD compared to ABVD had a durable PFS benefit at this significant 5-year milestone. No impact on the rate of secondary malignancies and a numerically greater number of pregnancies were observed, outcomes of interest to AYAs. Additionally, the majority of PN events improved or resolved over time. A+AVD should be considered a treatment option for AYAs with stage III/IV cHL. Clinical trial information: NCT01712490. Research Sponsor: Seagen Inc., Takeda.

7529 **Poster Session**

A phase II study of penpulimab, an anti-PD-1 antibody, in patients with relapsed or refractoryclassic Hodgkin lymphoma (cHL).

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Background: Penpulimab is a humanized IgG1 monoclonal antibody (mAb) that blocks PD-1 binding to PD-L1. Penpulimab, with its unique binding epitope, was engineered to eliminate Fc-mediated effector function that compromises anti-tumor immune cell function, and to optimize receptor occupancy by improving duration of drug binding. Fc-mediated effector functions, such as ADCC/ADCP, have been observed in most IgG4 anti-PD-1 mAbs but is absent in penpulimab, thereby potentially reducing the occurrence of immune-related adverse reactions. Penpulimab also demonstrated a slower PD-1 antigen binding off-rate than marketed anti-PD-1 mAbs, thereby resulting in better cellular activity and higher receptor occupancy. Penpulimab's numerous contacts with N58 glycosylation on the BC loop of PD-1 may also contribute to a slower binding off-rate. These structural differentiations of penpulimab enhance its anti-tumor activity and produce a superior safety profile. **Methods:** AK105-201 is a multicenter, single-arm, open-label study of penpulimab in relapsed/refractory (R/R) cHL. All pts received penpulimab 200 mg Q2W until progression or unacceptable toxicity. Eligible pts had prior autologous stem cell transplant (ASCT) or at least 2 lines of prior chemotherapy. The primary endpoint was ORR based on the Lugano 2014 criteria as assessed by an independent review committee (IRC). Key secondary endpoints included CR rate, DCR, PFS, duration of response (DoR), safety, and tolerability. **Results:** As of 8 November 2020, of 94 pts (59.6% male, median age 32.0 yrs [31-71], 26.6% was ECOG 1) enrolled, 56 pts remained on treatment, 4 pts completed 24-months treatment and 25 had discontinued (17 due to disease progression, 3 due to AE). After a median follow-up of 15.8 months, the IRC-assessed ORR in the 85 pts evaluable for efficacy was 89.4% (95% CI: 80.8%, 95.0%). A total of 40 patients (47.1%) achieved CR. Median duration of response was not reached with range from 1.7 to 24.5+ months. Median PFS was not reached with 12-months PFS rate was 72.1% (95% CI: 60.5%, 80.8%). Treatment-related adverse events (TRAEs, with unlikely-related events included) occurred in 97.9% of pts ($\geq$ G3 in 26.6% [25/94], treatment discontinuation in 5.3% [5/94]). Treatment-related SAEs occurred in 10.6%. Most frequent TRAEs ($\geq$20%) were hypothyroidism (31.9%), upper respiratory tract infection (25.5%), fever (24.5%), and ALT elevations (23.4%). Grade $\geq$3 TRAEs reported in $\geq$2 pts were platelet count decreased (3.2%), hyperlipemia (3.2%), rash (3.2%), neutrophil count decreased (2.1%). Grade 3 immune-related AEs (irAEs) were reported in 4.3%: IgA nephropathy, pneumonitis, rash, psoriasis (each n = 1) and no G4 or G5 irAEs reported. **Conclusions:** Penpulimab was shown to be highly active in achieving in a CR rate of 47.1% in pts with R/R cHL while demonstrating lower rates of SAEs, TRAEs leading to discontinuation, and Grade $\geq$3 irAEs. Clinical trial information: NCT03722147. Research Sponsor: Akeso Biopharma Inc.

Salvage therapies in transplant-eligible relapsed classic Hodgkin lymphoma, are novel regimens better?

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Background: Clinical trials of novel salvage therapies (ST) have encouraging outcomes for relapsed/refractory classic Hodgkin lymphoma (R/R cHL) eligible for autologous stem cell transplant (ASCT). In this observational study, we report efficacies and outcomes of different ST in ASCT-eligible R/R cHL. **Methods:** Consecutive ASCT-eligible R/R cHL pts at 3 Mayo Clinic sites were included. Demographics and clinical variables at relapse were recorded by medical records review. Time to event endpoints were defined from relapse. Univariate associations were confirmed in multivariate models of age, sex, B symptoms, stage, bulky disease (BD, single mass $>$ 6 cm) extra nodal disease (END), primary refractory disease (PRD) and early relapse (ER, within 1 year). **Results:** From Jan 2008 to May 2020, 207 ASCT-eligible pts with R/R cHL were included. Median age was 33 (24-43) years, 53% were male, 52% had advanced stage, 24% had BD, 36% had B symptoms, 41% had END, 11% had PRD and 43% had ER. All patients received ST and underwent ASCT; 43 (21%) received 2 ST, 14 (7%) 3 ST and 4 (0.5%) received 4 ST. 6 groups of ST were identified: ifosfamide, carboplatin and etoposide (ICE), bendamustine/brentuximab (BBV), brentuximab vedotin (BV), gemcitabine-based therapy (Gem), checkpoint inhibitor (CPI), and others. Table lists response to first line ST. BBV had significantly higher overall response rate (ORR) and complete response (CR) as first ST in univariate and multivariate models. 114 (79%) after ICE, 30 (97%) after BBV, 15 (56%) after BV, 25 (76%) after Gem, 8 (73%) after CPI and 15 (79%) after other ST underwent ASCT. Higher number of pts were bridged to ASCT after BBV than ICE ($p<0.01$). 110 (53%) went to ASCT in CR, 74 (36%) in partial response (PR) and 11% in progressive disease (PD). 43 received BV maintenance (BVm) after ASCT. Pts going to ASCT in PR or PD had significantly lower progression free survival (PFS) compared to pts in CR (2 yr PFS: 62%, 18% vs 77%, respectively, $p<0.0001$) in univariate and multivariate models. There was no difference in PFS and overall survival (OS) by type of ST. BVm was associated with higher PFS (HR 0.3 (CI_{95} 0.2-0.8)) and higher number of ST was associated with lower OS (HR 2 (CI_{95} 1.4-3)) in multivariate model ($p<0.001$). For pts transplanted in CR, there was no significant difference in PFS and OS by type of ST but higher number of ST predicted lower OS (HR 2.4 (CI_{95} 1.2-3.5), $p<0.01$). **Conclusions:** Type of ST did not predict survival, response to and number of ST did. For pts with CR, number of ST not type of ST predicted survival. BBV had higher response rates, higher rates of bridge to ASCT, and may be a preferable ST than ICE. Large, randomized trials are needed to evaluate efficacy of BBV compared to ICE. Research Sponsor: None.

Type of ST	Total N(%)	ORR N(%)	CR N(%)	*P* value
ICE	136 (68)	105 (71)	68 (52)	<0.001
BBV	24 (12)	24 (100)	21 (84)	<0.001
BV	8 (3)	4 (50)	1 (12)	NS
Gem	23 (11)	20 (86)	11(50)	NS
CPI	4 (2)	3 (75)	2 (50)	NS
Others	9(4)	1 (11)	1 (11)	NS

7531 **Poster Session**

A phase Ib study of a PI3Kδ inhibitor Linperlisib in patients with relapsed or refractory peripheral T-cell lymphoma.

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Background: PI3Kδ inhibitors have been shown to have important roles in blocking mitogenic and survival signaling within the tumor cell and the tumor microenvironment and activate antilymphoma immune responses. Linperlisib is an oral highly selective small molecule inhibitor of PI3Kδ and has been demonstrated to be well-tolerated with a favorable PK profile in patients with lymphomas at the RP2D. This phase Ib study is evaluating the efficacy and safety of Linperlisib in relapsed or refractory peripheral T-cell lymphoma (PTCL), a highly aggressive malignancy with few treatment options for patients. **Methods:** Eligible PTCL patients who must have received at least 1 prior systemic conventional therapy were administrated Linperlisib 80mg orally once daily (RP2D) in 28 days cycle until disease progression, unacceptable toxicity, or withdrawal from the study. Tumor response was assessed by IWG 2007 criteria with CT performed every 2 cycles. The primary endpoint was the overall response rate (ORR), and the secondary endpoint was toxicity assessed by NCI-CTCAE5.0. **Results:** As of February 2, 2021, 36 PTCL patients were enrolled in this exploratory trial. Most patients were stage III (38.2%) or IV (50%). Of the 27 evaluable patients to date, the PTCL histologies were PTCL-NOS (n=12), AITL (n=10), ALCL (n=3), NKTCL (n=1) and MEITL (n=1). 19 of the 27 evaluable patients had Investigator confirmed responses for a 70.4% ORR including 25.9% CR (7pt) and 44.4% PR (12pt). In the major subtypes, ORR was 50% (6/12) PTCL-NOS and 80% (8/10) AITL, respectively. A disease control rate of 100% was observed, and most responses occurred by first assessment at C2D28. One subject who had a CR at C2D28 is currently in cycle 9 and continuing on Linperlisib. 36 patients experienced at least 1 AE in the trial, with 95% of AEs $\leq$ grade 2. Consistent with previously treated lymphoma patients, no unexpected toxicities were observed. The most common TRAEs ($\geq$10%) were neutrophil count decreased (55.6%), leukocyte count decreased (33.3%), hypertriglyceridemia (22.2%), aspartate aminotransferase increased (16.7%), hypercholesterolemia (16.7%), alanine aminotransferase increased (11.1%), creatinine increased (11.1%), rash (11.1%), thrombocyte count decreased (11.1%) and electrocardiogram T wave abnormal (11.1%). No AE grade 4 was observed. 6 patients (16.7%) experienced at least one SAE, in which 4 (11.1%) SAEs were considered to be drug-related, including neutrophil count and leukocyte count decreased (2.8%), gastritis (2.8%), and pneumonia (5.6%). **Conclusions:** The oral PI3Kd inhibitor Linperlisib had significant activity in patients with relapsed or refractory PTCL. Toxicities with Linperlisib therapy were generally tolerable and manageable. Further efficacy and safety is being evaluated. Clinical trial information: NCT04108325. Research Sponsor: Shanghai Yingli Pharmaceutical Co., Ltd.

7532 **Poster Session**

CD19 CAR T-cell product type independently impacts CRS and ICANS severity in patients with aggressive NHL.

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Background: CD19-targeted chimeric antigen receptor-engineered (CD19 CAR) T cells achieve high response rates in patients (pts) with relapsed or refractory (R/R) aggressive B-cell non-Hodgkin lymphoma (NHL), but are limited by cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Pivotal trial data suggested distinct toxicity risks across CD19 CAR T-cell products, but differences in pt and disease characteristics may have confounded these observations. Thus, we assessed the independent impact of 3 CD19 CAR T-cell products (axicabtagene ciloleucel[axicel], tisagenlecleucel [tisacel], and JCAR014) on CRS and ICANS severity in 136 pts with R/R aggressive NHL. **Methods:** We retrospectively analyzed aggressive NHL pts treated at our institutions with cyclophosphamide and fludarabine lymphodepletion (LD) followed by CD19 CAR T-cell therapy. Axicel and tisacel pts were treated off trial using commercial products. JCAR014 (defined-composition 4-1BB-costimulated CD19 CAR T cells) was administered in all pts at the dose of $2x10^6$/kg on a phase I/II clinical trial (NCT01865617). CRS and ICANS were graded according to the ASTCT criteria and CTCAE 4.03, respectively. We used multivariable proportional odds logistic regression to model CRS and ICANS grade. **Results:** The CAR T-cell product was axicel, tisacel, or JCAR014 in 50%, 28%, and 22% of pts, respectively. Compared to axicel pts, we observed higher preLD LDH levels in tisacel and JCAR014 pts, and lower preLD albumin with tisacel ($p < 0.001$) with comparable age and hematopoietic cell transplantation comorbidity (HCT-CI) indexes across CAR T-cell products. Higher day-28 overall response rate by Lugano criteria was observed after axicel (71%) compared to tisacel (56%) and JCAR014 (53%). Adjusting for age, HCT-CI, preLD LDH, preLD albumin, CAR T-cell product type was associated with CRS severity (tisacel versus [vs] axicel, OR = 0.45, p = 0.05; JCAR014 vs axicel, OR = 0.29, p = 0.005;). Age had limited or no impact on CRS severity (OR 95%CI, 0.97-1.02), while the effect of HCT-CI was undetermined (OR 95%CI, 0.85-1.27). In a multivariable model including the same covariates as above, CAR T-cell product type (tisacel vs axicel, OR =.14, $p <.001$; JCAR014 vs axicel, OR = 0.31, p = 0.009), preLD LDH (OR, 3.96 per log10 increase; p = 0.04) and age (OR per 10-year increase, 1.32; p =.06) were associated with ICANS severity. Interaction effect testing suggested effect modification of age by the CAR T-cell product type (tisacel/JCAR014 versus axicel, p = 0.06); using a multivariable model including this interaction term, the predicted probabilities of grade $\geq$3 ICANS in a 70 year-old after axicel, tisacel, and JCAR014 were 40%, 6%, and 8%, respectively. **Conclusions:** CAR T-cell product type independently impacts CRS and ICANS severity in NHL pts. Our findings provide key insights to guide patient and CAR T-cell product selection. Research Sponsor: U.S. National Institutes of Health.

7533 **Poster Session**

Update of a phase II, multicenter study of high-dose chemotherapy with autologous stem cell transplant followed by maintenance romidepsin for T-cell lymphoma.

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Background: Peripheral T-cell lymphomas (PTCL) have suboptimal outcomes with conventional chemotherapy. Autologous hematopoietic stem cell transplant (AHCT) is a therapeutic strategy for patients in first complete or partial remission (CR1 or PR1), with median progression-free survival (PFS) after AHCT of 36-48% by intent to treat (d'Amore et al JCO 2012, Reimer et al JCO 2009). Romidepsin (romi) is a histone deacetylase inhibitor approved for treatment of relapsed/refractory T-cell lymphoma. We present updated data of the first multicenter study to evaluate PFS of patients (pts) receiving maintenance therapy with romi after AHCT. **Methods:** This was a phase 2, open-label, investigator-initiated study (expected PFS 45%, desired PFS 70%; success achieved if 15 or more pts out of 25 were progression-free at 2 years post-AHCT). 26 pts transplanted in CR1 or PR1 were evaluable for the primary endpoint of 2-year PFS (Cohort 1, Table). An exploratory cohort (Cohort 2, n=7) enrolled pts either transplanted $\geq$ CR/PR2 (n=5) or with high risk histologies (n=2). Pts underwent AHCT with carmustine, etoposide, cytarabine and melphalan (BEAM) conditioning. Maintenance romi 14 mg/m2 started days 42-80 post AHCT; every other week through 6 mon, every 3 weeks through 1 year and every 4 weeks through 2 years post AHCT. PFS was estimated by Kaplan-Meier. **Results:** 47 pts consented; 13 did not receive romi (no AHCT, n=2; relapse before romi, n=3; cardiac comorbidity, n=3, patient declined, n=5). 1 consented pt did not have PTCL. 15 out of the first 25 pts in Cohort 1 were progression free after 2 years; median follow up of 31 mon (21 - 36 mon). Estimated 2-year PFS was 62% (45-83%, 95% CI); median PFS 30 mon (12.0- NA, 95% CI). In Cohort 2, estimated 2-year PFS was 43% (18 – 100, 95% CI); median follow up of 30 mon (range, 24 – 37 mon); median PFS 14 mon (5 – NA, 95% CI). Across cohorts, 5 pts required dose reduction. The most common toxicities ($\geq$10% of pts, all grades) were fatigue (n=24, 73%), decreased platelets (n=16, 48%) and anemia (n=16, 48%). **Conclusions:** While the study did not meet its desired primary efficacy endpoint, maintenance romi was well-tolerated with an estimated 2-year PFS of 62%, greater than historical data. A larger, randomized study would be needed to determine the superiority of this approach. Clinical trial information: NCT01908777. Research Sponsor: Celgene.

Characteristics	Cohort 1 (n=26)	Cohort 2 (n=7)
Histology		
Angioimmunoblastic T-cell Lymphoma	11 (42%)	1 (14%)
Peripheral T-cell Lymphoma, Not otherwise specified	7 (27%)	0
Anaplastic Large Cell Lymphoma, ALK-	5 (19%)	1 (14%)
Anaplastic Large Cell Lymphoma, ALK+	1 (4%)	3 (43%)
NK/T-cell Lymphoma	0	2 (29%)
Enteropathy-associated T-cell Lymphoma	1 (4%)	0
Monomorphic Epitheliotropic Intestinal T-cell Lymphoma	1 (4%)	0
Median age (range)	59 (37-73)	59 (23-68)
CR/PR, n (%)	23 (88%)/3 (12%)	6 (86%)/1 (14%)
Median time from AHCT to first romidepsin, days (range)	75 (42-102)	49 (44-80)

Polatuzumab vedotin + obinutuzumab + venetoclax in patients with relapsed/refractory (R/R) follicular lymphoma (FL): Primary analysis of a phase 1b/2 trial.

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Background: Polatuzumab vedotin (Pola) + obinutuzumab (G) demonstrated activity and tolerability in a Phase 1b/2 trial of patients (pts) with R/R FL (Phillips, et al. Blood 2016). Preclinical studies with venetoclax (Ven) showed that concurrent treatment with Pola promotes MCL-1 degradation, a known mechanism of resistance to Ven, and enhances *in vivo* anti-tumor efficacy (Amin, et al. AACR 2020). Here, we report the primary safety/efficacy analysis with Pola-G-Ven in a Phase 1b/2 study of pts with R/R FL (GO29833; NCT02611323). **Methods:** Pts received induction treatment every 21 days (D) x six cycles (C) of: Pola 1.4–1.8mg/kg intravenously (IV) in dose escalation (DE) or recommended Phase 2 dose (RP2D) on D1; G 1000mg IV (C1: D1, D8, D15; C2–6: D1); and oral Ven 200–800mg (DE or RP2D; D1–21). Pts with complete response/partial response/stable disease (CR/PR/SD) at end of induction (EOI) received maintenance with G (1000mg on D1 every 2 months [mo] for 24 mo) and Ven (200–800mg daily) for 8 mo. Primary endpoints were safety/tolerability and positron emission tomography (PET)-CR rate at EOI by independent review committee (IRC) using modified Lugano criteria. **Results:** At the primary analysis (Oct 05, 2020), 74 pts were enrolled. Median pt age was 64 years (range 36–78); male (57%); Ann Arbor Stage III–IV (86%); FL International Prognostic Index high risk ≥3 (55%); bulky disease ≥7cm (16%); prior lines of therapy ≥2 (74%); refractory to: last prior therapy (51%), any prior anti-CD20 therapy (55%), both anti-CD20 therapy and an alkylating agent (double refractory; 55%). Grade 3–4 adverse events (AEs) were experienced by 73% of pts; most commonly, neutropenia (39%), thrombocytopenia (19%), and infections (16%; mainly pneumonia). AEs led to dose reduction in 38% and interruption in 68% of pts (mainly modifications to Ven). One fatal AE was reported (pneumonia). In total, 49 pts were treated at RP2D (Pola 1.8mg/kg + Ven 800mg) and were evaluable for efficacy. PET-CR rate at EOI by IRC was 57% (Table). With a median follow-up of 14.4 mo (range 8.2–28.4), the 12-mo progression-free survival (PFS) was 73% (95% confidence interval: 59.4–86.9). Median PFS was not reached. **Conclusions:** The safety profile of Pola-G-Ven is consistent with the known profiles of the individual drugs. Response rates at EOI with Pola-G-Ven are encouraging in this R/R FL patient population. Additional follow-up is needed to assess PFS benefit during maintenance treatment and beyond. Clinical trial information: NCT02611323. Research Sponsor: The GO29833 study was sponsored by F. Hoffmann-La Roche Ltd and Genentech, Inc. Third party medical writing assistance, under the direction of authors, was provided by Carla Smith, MSc, of Ashfield MedComms, and was funded by F. Hoffmann-La Roche Ltd.

Responses at EOI by modified Lugano criteria (RP2D; N=49).

N (%)	INV	IRC
ORR	38 (78)	35 (71)
CR	28 (57)	28 (57)
PR	10 (20)	7 (14)
SD	6 (12)	8 (16)
PD	3 (6)	4 (8)
Missing/unevaluable	2 (4)	2 (4)

INV, investigator-assessed; ORR, objective response rate; PD, progressive disease.

7535 **Poster Session**

Comparative efficacy of tisagenlecleucel (tisa-cel) and lisocabtagene maraleucel (liso-cel) in patients with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL).

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Background: Chimeric antigen receptor T-cell therapies tisa-cel and liso-cel are effective treatments for r/r DLBCL (Schuster 2019, Abramson 2020). This study compared efficacy outcomes of tisa-cel and liso-cel in r/r DLBCL using matching-adjusted indirect comparison (MAIC). **Methods:** Individual patient-level data (IPD) from JULIET (tisa-cel; NCT02445248; 02/2020 datacut) were weighted to match the patient population in TRANSCEND (liso-cel; NCT02631044; 08/2019 datacut). Baseline prognostic factors available in both trials were adjusted for age, sex, histology, ECOG performance status [ECOG PS], left ventricular ejection fraction, radiologic sum of product diameters, lactate dehydrogenase, prior stem cell transplantation [SCT], use of bridging therapy, and number of and refractoriness to prior therapies, in the MAIC. Overall survival (OS), progression-free survival (PFS), complete response (CR) rate, and overall response (OR) rate were compared. Primary analyses compared infused patients in JULIET (N=106, excluding 8 without lymphodepleting chemotherapy [LDC] and 1 large cell neuroendocrine carcinoma) with efficacy-evaluable set in TRANSCEND (N=256, infused patients). A scenario analysis compared JULIET infused to TRANSCEND primary analysis set (PAS) (N=133, dose level 2, excluding those with ECOG PS 2, prior allogeneic SCT, primary mediastinal B-cell lymphoma, follicular lymphoma [FL] 3B, or transformation from indolent lymphoma besides FL). Sensitivity analyses included JULIET patients with only fludarabine-based LDC or only adjusted significantly different baseline prognostic factors. Safety outcomes were not compared because adverse event management has evolved and differed between the two trials; MAIC is unable to adjust for such differences. **Results:** After adjusting for differences in baseline characteristics, OS, PFS, and CR were comparable between tisa-cel infused patients and the liso-cel efficacy-evaluable set (Table). The results were consistent across all scenario and sensitivity analyses. OR rate trended higher in the TRANSCEND efficacy-evaluable set (72.7% vs. 62.9%, p=0.07) and was higher in TRANSCEND PAS than in the respectively matched JULIET infused set (74.4% vs. 60.9%, $p < 0.05$). **Conclusions:** The MAIC results indicate there is no evidence suggesting differences in OS, PFS and CR between tisa-cel and liso-cel in r/r DLBCL. Analyses using IPD from both trials and/or real-world evidence are warranted to confirm these findings. Research Sponsor: Novartis Pharmaceutical Corporation.

MAIC of Tisa-cel Infused vs. Liso-cel Efficacy-evaluable set.

	Tisa-cel vs. liso-cel (95% CI); p-value
OS, hazard ratio (HR)	1.12 (0.62, 2.05); p=0.71; 1-year OS rate: 55.1% vs 57.9%
PFS, HR	1.16 (0.64, 2.09); p=0.63; 1-year PFS rate: 47.4% vs 44.1%
CR, rate difference	-5.4% (-15.5%, 4.7%); p=0.29
OR, rate difference	-9.7% (-20.0%, 0.6%); p=0.07

7536 **Poster Session**

Favorable tumor immune microenvironment (TME) and robust chimeric antigen receptor (CAR) T-cell expansion may overcome tumor burden (TB) and promote durable efficacy with axicabtagene ciloleucel (axi-cel) in large B-cell lymphoma (LBCL).

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Background: Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved for patients (pts) with relapsed/refractory LBCL after ≥2 prior systemic therapies. In the pivotal ZUMA-1 study, pts with high pretreatment (preTx) TB (estimated by sum of product diameters [SPD]) had lower peak CAR T-cell expansion normalized to TB and less frequent durable response rates vs pts with low TB (< 30% vs > 60%, respectively; *Blood Adv.* 2020;4:3268). The number of $CD8^+$ and $CCR7^+CD45RA^+$ product T cells infused and favorable immune contexture in preTx TME were also associated with axi-cel response (*Blood Adv.* 2020;4:3268; Galon et al. ASCO 2020. #3022). As potential barriers to axi-cel efficacy are not fully elucidated, we systematically analyzed preTx TME characteristics, including myeloid-related biomarkers and product attributes, to identify such challenges in ZUMA-1 pts with high TB. **Methods:** Samples from evaluable pts in ZUMA-1 Phase (Ph) 1 and Ph2 Cohorts (C) 1–3 were analyzed (NCT02348216; Ph1 and Ph2 C1+2, ≥2-y follow-up; C3, ≥6-mo follow-up). PreTx immune TME was analyzed by multiplex immunohistochemistry (n = 18) and gene expression analysis (n = 30) as previously described (Rossi et al. AACR 2018. #LB-016; Galon et al. ASCO 2020. #3022). CAR T-cell product characteristics and other covariates were evaluated as previously described (*Blood Adv.* 2020;4:3268). Correlative analyses of these covariates with clinical outcomes were performed by Wilcoxon or Kruskal-Wallis test. Median TB (by SPD) from ZUMA-1 Ph1 and Ph2 C1+2 was used as a cutoff for high (> 3721 mm^2) vs low (≤3721 mm^2) TB. Durable response refers to pts in ongoing response at time of data cutoff. **Results:** PreTx immune TME features related to suppressive myeloid-related activity, most notably *ARG2*, *TREM2*, and *IL-8* gene expression, were elevated in pts who failed to respond or relapsed without documented loss of CD19 expression. *ARG2* and *TREM2* levels in preTx biopsies were negatively associated with $CD8^+$ T-cell density. Pts with high TB who achieved durable response had low preTx *ARG2* and *TREM2* levels in TME and enhanced CAR T-cell expansion after axi-cel compared to pts with high TB who relapsed. High ratio of T-cell to suppressive myeloid cell markers (T/M ratio) in preTx biopsies associated positively with CAR T-cell expansion (peak and peak normalized to TB) and durable response in pts with high TB. **Conclusions:** Axi-cel may overcome high TB in pts with a favorable immune TME alongside robust CAR T-cell expansion. Favorable immune TME is characterized by reduced suppressive myeloid cell activity (low *ARG2* and *TREM2* expression) and increased T/M ratio. These data suggest possible actionable strategies to overcome high TB in the context of CAR T-cell therapy. [JC and VP contributed equally] Clinical trial information: NCT02348216. Research Sponsor: Kite, a Gilead Company.

7537 **Poster Session**

Combination of sintilimab, anlotinib and pegaspargase "sandwich" with radiotherapy in localized natural killer/T cell lymphoma: A multicenter, phase 2 study.

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Background: NK/T-cell lymphoma (NKTL) is a rare and distinct subtype NHL**.** Most newly diagnosed NKTL cases were localized-stage. For localized NKTL, RT alone is inadequate due to high systemic failure rate. Chemoradiation has been increasingly applied. However, current chemotherapy (CT) regimens have severe toxicity and infection, which reduce the completion of RT and patients' medical compliance. Therefore, novel regimens with mild toxicity are needed. Sintilimab, a fully human anti-PD-1 monoclonal antibody, has showed encouraging antitumor efficacy in pts with r/r NKTL. Anlotinib, a multiple-targeted TKI that mainly blocks VEGF/VEGFR pathway, has been approved for several solid tumor types in china. Anti-angiogenesis therapy could improve efficacy of ICI in multiple tumor types. This multicenter, single-arm, phase 2 study aims to evaluate the efficacy and safety of sandwich chemoradiotion of sintilimab combined with anlotinib and pegaspargase (PEG-ASP) in newly diagnosed localized NKTL pts. **Methods:** Patients with pathologically confirmed previously untreated stage NKTL were enrolled. All enrolled patients received 3 cycles of sintilimab (200mg D1 ivdrip) combined with anlotinib (12mg po D1-14) and PEG-ASP (2500U/m^2 D1) every 3 weeks followed by RT, then received additional 3 cycles of combination therapy as described above. The primary endpoint was overall response rate (ORR) by LUGANO 2014 criteria. **Results:** A total of 39 pts were enrolled, and 24 pts eligible for response evaluation (70.8% men; median age, 46 y [range 20-64]; 58.3% stage). According to PINK-E system, 8 pts (33.3%) were identified as intermediate risk group and 16 patients were low risk group. 23 of 24 patients completed protocol-specified therapeutic schemes, one patient discontinued the study after the second cycle due to disease progression. ORR was 95.8% (23/24, 95%CI: 76.9%-84.1%). Surprisingly, all the responded patients achieved CR, while 66.7% (16/24, 95%CI: 44.7%-83.6%) patients achieved CR after the second cycle. Median PFS and OS have not been reached. 1-year OS and PFS was 100% and 95.8%, respectively. All grade TRAEs occurred in 84.6% of all enrolled patients and 92.1% were grade 1-2. The most common TRAE was lymphocytopenia (9.9%). Of note, grade 3-4 hematological toxicity was reported in only one patient (4.2%). All AEs were resolved after symptomatic treatment, without systematic corticosteroid intervention. **Conclusions:** Sintilimab combined with anlotinib and PEG-ASP upfront and after radiotherapy was effective and could be well tolerated in localized NKTL, achieving promising CRR and rapid and long-term remission with mild toxicity. Further investigation of survival outcome is warranted. Clinical trial information: NCT03936452.
Research Sponsor: None.

7538 **Poster Session**

Safety and efficacy of VIP152, a CDK9 inhibitor, in patients with double-hit lymphoma (DHL).

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Background: PTEFb/CDK9-mediated transcription of short-lived anti-apoptotic survival proteins and oncogenes like MCL-1 and MYC plays a critical role in a variety of cancers. VIP152 (formerly BAY 1251152), a potent and highly selective CDK9 inhibitor, has been evaluated in a Phase 1 dose-escalation study in patients with advanced cancer. The maximum tolerated dose was 30 mg once weekly administered in consecutive 21-day cycles, based on neutropenia as the dose-limiting toxicity (JCO 2018;36:2507; NCT02635672). DHL is defined as dual rearrangement of the MYC gene and either the BCL2 or BCL6 genes; the resulting overexpression of MYC and BCL2/BCL6 make it particularly difficult to treat. Patients with DHL have a poor prognosis and no standard of care. Considering the impact of CDK9 inhibition on MYC, an exploratory cohort of patients with DHL was added to the study. **Methods:** Patients with refractory or relapsed DHL were eligible. VIP152 was administered once weekly as a 30-minute IV infusion on Days 1, 8 and 15 of a 21-day cycle. Tumor response was assessed according to the revised Cheson criteria (2007). **Results:** To date a total of 7 patients have been enrolled and were evaluable at the time of data cutoff (24NOV2020). The patients were mostly men (6/7 pts, 86%) with a median (range) age of 70 (58-84) years. All patients received $\geq$2 prior therapies, including 2 patients with bone marrow transplant. Three of 7 patients (29%) had $\geq$3 prior therapies. The median time on treatment was 22 days (range 8-1361 days). The most common adverse events of any grade were: constipation, fatigue, nausea (each 3/7 pts, 43%) and abdominal pain, diarrhea, lymphocyte count decrease, neutrophil count decrease, skin infection, tumor pain, and vomiting (each 2/7 pts, 29%). Most were Grade 1 and Grade 2. The Grade 3 adverse events were fatigue, lymphocyte count decrease, neutrophil count decrease (each 1/7 pts, 14%) and tumor pain (2/7 pts, 29%). One Grade 4 lymphocyte count decrease was reported. Two patients had a serious adverse event (Grade 3 syncope and Grade 3 tumor pain). Two patients had dosing held for an adverse event; however, no patient withdrew from treatment due to any adverse events. One death occurred due to disease progression. Pharmacodynamic biomarker analysis showed significant reduction of MYC, PCNA, and MCL-1 mRNA in all patients across multiple timepoints. Antitumor activity consisted of 2 complete metabolic responses in 7 patients (29%) based on investigator-assessed FDG-PET scans. Due to the COVID pandemic, the patients withdrew consent after 3.7 and 2.3 years, respectively, of treatment. Both patients were in complete metabolic response. **Conclusions:** VIP152 had a manageable safety profile, on-target pharmacodynamic activity and signs of durable monotherapy antitumor activity in patients with DHL. These encouraging results warrant further evaluation of VIP152 in patients with MYC-driven lymphoma and solid tumors. Clinical trial information: NCT02635672. Research Sponsor: Bayer AG.

7539 **Poster Session**

Lenalidomide plus rituximab in patients with rituximab-resistant indolent B-cell and mantle cell lymphomas: 10-year follow-up.

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Background: Lenalidomide (len) plus rituximab is now a standard-of-care option for indolent B-cell non-Hodgkin lymphomas (iNHL) and mantle cell lymphomas (MCL). We previously demonstrated the efficacy of len plus rituximab in patients (pts) with rituximab-refractory iNHL and MCL (Chong *et al.* Clin Can Res 2015). We now report the longest experience to date with this regimen. **Methods:** We conducted an open-label phase II trial in pts with iNHL or MCL and rituximab resistance, defined as failure to respond or progression of disease within 6 months (mo) of rituximab or a rituximab-containing regimen. Pts received len 10 mg daily for 8 weeks, followed by 4 weekly doses of rituximab 375 mg/m^2 and continued len maintenance until disease progression, toxicity or pt choice. **Results:** 50 pts (30 FL, 14 MCL, 2 MZL, 4 SLL) were treated between 2008-2012. Median follow-up was 10.5 years (yr). Pts received a median of 3 prior therapies (range: 1–7). Progression free survival (PFS) for all pts at 5 and 10 yrs was 20.0% [95%CI 8-35] & 13% [95%CI 3-30%]; 5- and 10-yr response duration (RD) was 27% [95% CI 12-46] and 18% [95% CI 4-40], respectively; 5- and 10-yr overall survival (OS) was 58% [95%CI 43-70] and 45% [95%CI 30-58], respectively. 5-yr OS from the time pts were deemed rituximab-resistant is 64.0% and 10-yr OS 51.9%. For pts with FL, 5- and 10-yr PFS were both 13%, and 5- and 10-yr OS were 60% and 40%. For MCL, 5- and 10-yr PFS were both 25% and 5- and 10-yr OS were 50% and 36%. At 10.5 yr, 4 pts (2 FL, 1 MCL, 1 MZL) remain in complete remission (CR), 3 of whom discontinued len at 7.0-yr, 8.8-yr and 10.1-yr in CR. 1 pt with FL discontinued study in CR after 11.6-yr but continues on commercial len at 5 mg daily. The most common grade 1–2 adverse events (AEs) requiring dose reductions were neuropathy (n = 3) and diarrhea (n = 5), which all resolved with dose reduction. The most common grade 3–4 AEs requiring dose reductions were neutropenia (n = 6, 12%) and tumor flare (n = 3, 6%). Pts discontinued therapy due to toxicity at a median of 4.9 mo (range 0.3–25.7) from len start due to grade 3–4 rash (n = 2), grade 2 abdominal pain (n = 1), and grade 3–4 thrombocytopenia (n = 2). Only 1 patient discontinued len after $>$ 1 yr (25.7 mo) due to persistent diarrhea. The pt who developed grade 2 abdominal pain was retreated with len without recurrence of pain and sustained a second CR for 5 yrs. 5 (10%) pts developed secondary cancers at a median of 15.5 mo (range: 0.8–50.5) from starting len, including 2 hematological (acute myeloid leukemia, B-acute lymphoblastic leukemia) and 3 solid cancers (NSCLC, renal cell carcinoma, prostate cancer). Prior to enrollment, 4/5 of the patients with secondary cancers had received alkylating agents and 3/5 had received anthracyclines. **Conclusions:** These data represent the longest reported outcomes for len plus rituximab in NHLs. We demonstrate durable responses and a manageable safety profile with rituximab plus low-dose len. Clinical trial information: NCT00783367. Research Sponsor: Celgene.

7540 **Poster Session**

First-MIND: A phase Ib, open-label, randomized study to assess safety of tafasitamab (tafa) or tafa + lenalidomide (LEN) in addition to R-CHOP in patients with newly diagnosed DLBCL.

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Background: Tafasitamab is a humanized, Fc-modified anti-CD19 monoclonal antibody that enhances antibody-dependent cellular cytotoxicity and phagocytosis. It is FDA-approved with LEN for adult patients (pts) with relapsed/refractory (R/R) DLBCL ineligible for autologous stem cell transplantation. First-MIND (NCT04134936) is a Phase Ib, open-label, randomized study of tafa + R-CHOP or tafa + LEN + R-CHOP in newly diagnosed DLBCL. **Methods:** Eligible pts were ≥18 years, treatment-nave, with histologically confirmed DLBCL not otherwise specified, international prognostic index (IPI) 2–5 and ECOG performance status (PS) 0–2. Pts with known double- or triple-hit and transformed lymphoma were excluded. Treatment (Tx) comprised six 21-day cycles of tafa (12 mg/kg IV, Day [D] 1, 8, 15) + R-CHOP (arm A) or tafa (12 mg/kg IV, D1, 8, 15) + LEN (25 mg orally, D1–10) + R-CHOP (arm B). G-CSF and VTE prophylaxis was mandatory. Primary objective is safety; secondary objectives are ORR, PET-CR rate at end of Tx, PFS, long-term safety, pharmacokinetics, immunogenicity. **Results:** From Dec 2019 to Aug 2020, 83 pts were screened in Europe and the US; 66 were randomized (33 per arm). Data cut-off for this analysis: 9 Dec 2020; study is ongoing. Median age was 64.5 years (range 20–86). Overall, 30% (20/66) of pts were ≥70 years and many had high-risk disease: IPI 2 29%, IPI 3 46%, IPI 4 26%. ECOG PS: 47% of pts were ECOG PS 0, 44% PS 1, 9% PS 2. Most pts had stage III/IV disease (92%); 46% had bulky disease. All pts experienced a treatment-emergent adverse event (TEAE). Grade ≥3 neutropenia and thrombocytopenia occurred in 54.5% and 12.1% (arm A) and 66.7% and 30.3% (arm B) of pts, respectively (Table). Serious TEAEs occurred in 42.4% (arm A) and 51.5% (arm B) of pts. There were three deaths, unrelated to tafa and/or LEN (sepsis, urosepsis, and COVID-19 pneumonia). R-CHOP dose intensity was maintained in both arms. Among 60 pts who completed tumor assessments after cycle 3, ORR was 89.7% (arm A) and 93.5% (arm B). **Conclusions:** These data suggest R-CHOP + tafa or tafa + LEN is tolerable in pts with Tx-nave DLBCL and that R-CHOP dosing is not affected. Toxicities are similar to those expected with R-CHOP or R-CHOP + LEN. Updated safety and early efficacy data will be presented at the conference. Clinical trial information: NCT04134936. Research Sponsor: MorphoSys AG, Planegg, Germany.

	R-CHOP + tafa (n = 33)	R-CHOP + tafa + LEN (n = 33)		
TEAEs, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia	19 (57.6)	18 (54.5)	23 (69.7)	22 (66.7)
Thrombocytopenia	6 (18.2)	4 (12.1)	12 (36.4)	10 (30.3)
Febrile neutropenia	6 (18.2)	6 (18.2)	6 (18.2)	6 (18.2)
Diarrhea	8 (24.2)	1 (3.0)	10 (30.3)	2 (6.1)
Infusion related reactions*	4 (12.1)	0	6 (18.2)	1 (3.0)
Infections + infestations	16 (48.5)	7 (21.2)	16 (48.5)	9 (27.3)
Nervous system disorders	17 (51.5)	2 (6.1)	20 (60.6)	4 (12.1)

*Related to both rituximab and tafa; Related to rituximab; The majority of events were polyneuropathies related to vincristine.

7541 **Poster Session**

Preliminary results of a phase I trial of FT516, an off-the-shelf natural killer (NK) cell therapy derived from a clonal master induced pluripotent stem cell (iPSC) line expressing high-affinity, non-cleavable CD16 (hnCD16), in patients (pts) with relapsed/refractory (R/R) B-cell lymphoma (BCL).

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Background: FT516 is an investigational, NK cell cancer immunotherapy derived from a clonal master iPSC line. FT516 is engineered with a novel hnCD16 Fc receptor, demonstrated preclinically to maximize antibody-dependent cellular cytotoxicity (Zhu et al. Blood 2020). FT516 can be mass produced and made available off-the-shelf for broad pt access and multi-dose administration. **Methods:** This is a Phase I trial of FT516 combined with rituximab (R) in pts with R/R BCL. Treatment consists of 2 cycles, each with 3 days lympho-conditioning (fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2) and 1 dose of R followed by 3 weekly infusions of FT516 (planned doses 30-900 million/dose) with IL-2 (6 MIU after each FT516 dose). The primary objective is to identify the incidence of dose-limiting toxicity (DLT)/dose cohort and the recommended Phase II dose using a standard 3+3 design. Additional objectives include safety, tolerability, preliminary activity, pharmacokinetics, and immunogenicity. **Results:** Six pts (5 DLBCL, 1 FL, median age 65.5 y) have completed (5) or discontinued (1) study treatment after the DLT period (data cutoff 9 Dec 2020): 2 received 30 million cells/dose, 3 received 90 million cells/dose, and 1 received 300 million cells/dose. All pts received $>$ 1 prior R-containing regimen, and median number of prior therapies was 3 (range 2-6), including CAR-T in 3 pts. FT516 was primarily administered in the outpatient setting. No FT516-related Grade $\geq$3 adverse events (AEs) or serious AEs, and no events of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), or graft-versus-host disease (GvHD) of any grade were reported. DLT (Grade 4 neutrophil count decreased, not recovered to baseline by D29) was reported in the first pt at 30 million cells/dose and R dosing of 375 mg/m^2 weekly x 4/cycle, resulting in modification of R dosing to once/cycle; no DLTs were observed with modified R dosing. Most common all grade AEs in $\geq$3 pts: fatigue (4 pts) and decreased appetite, nausea, neutrophil count decreased, and headache (3 pts each). Grade $\geq$3 AEs in $\geq$2 pts: neutrophil count decreased (3 pts) and febrile neutropenia and platelet count decreased (2 pts each); none considered related to FT516. Host anti-product B- or T-cell immunogenicity was not observed. Three of 4 pts treated at $\geq$90 million cells/dose achieved objective response (2 complete responses [CRs] and 1 partial response). **Conclusions:** Administration of up to 6 doses of FT516 cells, including up to 300 million cells/dose, appears to be safe and tolerable, without CRS, ICANS, or GvHD. Activity was observed, including CRs, in heavily pretreated pts. Dose escalation is ongoing. Updated clinical and translational data will be presented. Clinical trial information: NCT04023071. Research Sponsor: Fate Therapeutics, Inc.

7542 **Poster Session**

Survival trends of older adult patients with diffuse large B-cell lymphoma: A National Cancer Database analysis.

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Background: 60-70% of patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) can be cured with R-CHOP or R-CHOP-like immunochemotherapy. However, patients ≥80 years of age were either excluded or underrepresented in modern DLBCL trials, and their outcomes are understudied. The aim of this study is to define the survival trends and risk factors for inferior survival in older adult patients with DLBCL. **Methods:** Patients with newly diagnosed DLBCL were identified from the National Cancer Database (2004-2017, representing the rituximab era). Clinical characteristics, treatment, and outcomes were compared between patients ages ≥ 80, 65-79, and < 65 years. The Kaplan-Meier method and Cox proportional hazards model were used for survival analysis. **Results:** A total of 231,756 patients with newly diagnosed DLBCL were identified; 46,250 (20%) were ≥80 years, 87,702 (38%) were 65-79 years, and 97,904 (42%) were < 65 years. Patients ≥80 years were more likely to have a higher Charlson-Deyo Comorbidity Index score (CDS) (CDS ≥2, 12% vs 11% vs 8%, p = 0.001), less likely to receive systemic chemotherapy (63% vs 83% vs 89%, p < 0.001), and more likely to receive treatment at a non-academic center (71% vs 65% vs 48%, p < 0.001), compared to patients 65-79 and < 65 years, respectively. Median overall survival (OS) was significantly worse for patients ≥80 years compared to patients 65-79 years (11.6 vs 61.0 months, p = 0.001) and patients < 65 years (11.6 vs 178.1 months, p = 0.001). During the study period, the median OS had only minimally improved for patients ≥80 years (10.6 months in 2004-2007 vs 11.5 months in 2008-2011 vs 12.3 months in 2012-2016, p = 0.006). In contrast, the OS improvement appears more meaningful in patients 65-79 years (median in months: 51 vs 61.2 vs 65.9, p = < 0.001) and patients < 65 years (median in years: 14.6 vs 11.3 vs not reached, p < 0.001) in the prespecified intervals (2004-07, 2008-11, and 2012-16). In multivariate analysis, the most substantial risk factor for worse survival in patients ≥80 years was not receiving systemic therapy (hazard ratio [HR] = 3.26, 95%CI = 3.01-3.54, p = 0.001). Other risk factors associated with worse survival included high-risk IPI score (HR = 2.16, 95%CI = 1.96-2.39, p = 0.001), CDS score ≥2 (HR = 1.56, 95%CI = 1.40-1.73, p = 0.001), male sex (HR = 1.16, 95%CI = 1.09-1.24, p = 0.001), B symptoms at diagnosis (HR = 1.16, 95%CI = 1.08-1.25, p = 0.001), and treatment at a non-academic center (HR = 1.1, 95%CI = 1.01-1.20, p = 0.001). **Conclusions:** Patients ≥ 80 years of age with DLBCL have a significantly inferior survival which has not meaningfully improved in recent years. More than 1/3 of patients ≥ 80 years did not receive systemic therapy. Older adult patients with DLBCL should be assessed for fitness for chemotherapy using validated geriatric assessment tools. Novel therapeutic strategies with favorable safety profiles are urgently needed for this expanding patient population. Research Sponsor: None.

7543 **Poster Session**

CNS relapse in DLBCL patients below 60 years treated with R-ACVBP, R-CHOEP, or R-CHOP: A joint analysis of LYSA and GLA/DSHNHL.

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Background: Central nervous system (CNS) relapse occurs in 2-6% of DLBCL patients (pts) increasing to 10% or more in high-risk groups. Intrathecal (IT) or intravenous high-dose methotrexate (HD MTX) have limited if any prophylactic impact on CNS relapse. To address the role of systemic first-line therapy in pts tolerating intensified strategies (R-ACVBP, R-(Mega)CHOEP, R-CHO(E)P), we compared CNS relapses occurring in a large cohort of pts ≤60 years. **Methods:** We conducted a retrospective analysis including previously untreated pts with DLBCL by central review, age 18-60 years, from multicenter clinical trials conducted by LYSA and GLA/DSHNHL (Table). We assessed the risk of CNS relapse in matched cohorts based on the aaIPI. **Results:** A total of 2203 pts were included. Median age was 47 years (18-60). 455 pts were treated with R-ACVBP, 444 with R-(Mega)CHOEP, 1304 with R-CHOP. Distribution of CNS IPI was not significantly different comparing R-ACVBP to R-CHO(E)P groups within aaIPI categories (Table). PFS and OS were comparable according to treatment within aaIPI groups, also adjusted for prognostic factors. No CNS events occured during observation time of 3 years in pts with aaIPI 0. In pts with aaIPI 1, no CNS event occured in the R-ACVPB arm, the 3y-cumulative incidence of CNS relapse for pts treated with R-CHO(E)P group was 1.0% (95%CI 0.3-1.7). In pts with aaIPI 2,3 and intermediate/high CNS IPI, four (1.6%) treated with R-ACVBP experienced relapse in the CNS compared to 15 (3.9%) pts treated with R-(Mega)CHO(E)P (3y-cumulative incidence 1.6% (95%CI 0-3.2) vs. 4.0% (95%CI 2.0-6.0). **Conclusions:** CNS relapse was extremely rare in younger DLBCL pts with aaIPI 0 or 1; prophylactic measures are not warranted. In pts with aaIPI 2,3 (and intermediate/high CNS-IPI), only 4 (1.6%) CNS relapses were seen with the R-ACVBP while 15 (3.9%) relapses did occur after R-(Mega)CHO(E)P. This analysis underlines the important role of the systemic therapy in controling CNS relapse. Research Sponsor: None.

Distribution of the clinical trials.

	aaIPI = 0 n = 652		aaIPI = 1 n = 924		aaIPI = 2,3 n = 627	
	LNH03-1B, FLYER, MInT, UNFOLDER		LNH03-2B, MInT, UNFOLDER		LNH03-3B+, LNH07-3B+, MegaCHOEP#	
	R-ACVBP n = 76	R-CHO(E)P n = 576	R-ACVBP n = 134	R-CHO(E)P n = 790	R-ACVBP n = 245	R-(Mega)CHO(E)P n = 382
CNS IPI groups						
0-1 – low risk	76 (100%)	575 (100%)	107 (80%)	641 (81%)	–	–
2-3 – int risk	0 (0%)	1 (0.2%)	27 (20%)	149 (19%)	185 (76%)	303 (79%)
4-6 – high risk	–	–	–	–	60 (24%)	79 (21%)
MTX prophylaxis (at least one course)	0 (0%)	8/554* (18%)	133 (99%)	179/742* (24%)	245 (100%)	125/309* (40%)
MTX IT	76 (100%)	0 (0%)	123 (92%)	0 (0%)	145 (59%)	0 (0%)
HD MTX IV						

Atezolizumab + obinutuzumab + venetoclax in patients with relapsed or refractory indolent non-Hodgkin's lymphoma (R/R iNHL): Primary analysis of a phase 2 trial from LYSA.

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Background: R/R iNHL treatment remains challenging. Atezolizumab (ATE) and obinutuzumab (OBI) are monoclonal antibodies acting respectively to inhibit T-lymphocyte exhaustion or by inducing lymphoma cells cytotoxicity, whereas venetoclax (VEN) is a small molecule inhibiting BCL-2. Combining tumor-targeted therapies with agents that enhance anti-tumor immunity represents an attractive treatment paradigm. This LYSA sponsored multicenter phase 2 trial (NCT03276468) evaluated ATE, OBI and VEN combination in R/R B-cell lymphomas. Herein, we present primary efficacy and safety data from the iNHL cohort including Follicular Lymphoma (FL) and Marginal Zone Lymphomas (MZL). **Methods:** Patients ≥18 years with biopsy-confirmed R/R FL and MZL who failed at least one line of therapy were eligible. OBI was given IV at 1 g on day (D) 1, 8 and 15 of cycle (C) 1 and on D1 from C2 to C8 every 3 weeks. ATE was given IV, 1.2 g every 3 weeks, started at D2 of C1, then administered at D2 of each cycle for 24 cycles. VEN was given orally at 800 mg/D at full dose, starting on D8C1 for 24 cycles. The primary endpoint was the Overall Response Rate (ORR) evaluated by Lugano criteria at the end of induction (EOI) after 8 cycles of ATE, OBI and VEN (M6) or at premature treatment discontinuation. **Results:** At the time of the primary analysis (08 Jan 2021), 78 patients were enrolled. *FL cohort* (n = 58): the median follow-up was 14.5 months. Main baseline characteristics were: Ann Arbor Stage III/IV, 85.7%; FLIPI HR, 47.3%; > 2 prior lines of therapy, 32.1%; and exposed to ASCT, 30.4%. The ORR on PET scan at EOI was measured at 53.6% [41.8%-65.1%], including 30.4% of CMR. 37 patients (63%) received the full induction treatment. *MZL cohort* (n = 20; 13 nMZL, 5 eMZL, 2 sMZL): the median follow-up was 11.9 months. Main baseline characteristics were: Ann Arbor Stage IV, 100%; bone marrow infiltration, 38.9%; ≥ 2 extra-nodal sites, 50%; and > 2 prior lines of therapy, 22.2%. The ORR on CT scan at EOI was measured at 66.76% [44.6%-84.4%], including 16.7% of CR and 50.0% PR. 11 patients (55%) received the full induction treatment. At time of the present analysis, responses in the 2 cohorts seem durable with only 21,4% of responders who have reported relapse/progression. Out of the 78 pts, a total of 55 (70.5%) pts experienced grade 3–4 adverse event (AE) and 1 patient experienced an AE that led to discontinuation of any drug. Main AE of grade 3 or more were hematologic cytopenias, with only one febrile neutropenia (1.3%). Three pts experienced immune-related AE (1 grade 2 myositis and 2 grade 3 colitis), no tumor lysis syndrome was observed. **Conclusions:** ATE, OBI and VEN triplet appears to be well tolerated, with no unexpected toxicity brought by the combination. The ORR at EOI seems to be comparable to other innovative regiments in this setting, with durable responses to date. Clinical trial information: NCT03276468. Research Sponsor: None.

7545 **Poster Session**

Obinutuzumab short-duration infusion (SDI) in previously untreated advanced follicular lymphoma: Results from the end of induction analysis of the phase IV GAZELLE study.

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Background: Obinutuzumab (G)-chemotherapy (chemo) has demonstrated improved progression-free survival compared with rituximab (R)-chemo in previously untreated advanced follicular lymphoma (FL). G is currently administered by IV infusion over ~3–4 hours. A shorter duration of infusion in Cycle (C) 2 and subsequent cycles, as is standard practice with R, could improve convenience for patients (pts) and efficiency for infusion facilities. We report the primary analysis of the prospective, open-label, multicenter, single-arm, Phase IV, GAZELLE study (NCT03817853), which evaluated the safety of G administered as a 90-minute (min) SDI from C2 onwards in pts with FL. **Methods:** Pts with previously untreated FL received G (1000mg) intravenously on Day (D) 1, 8, and 15 of C1, and on D1 thereafter, plus chemo (bendamustine, CHOP, or CVP) for 6–8 cycles. In C1, pts received G at the standard infusion rate. Pts without a Grade (Gr) ≥3 infusion-related reaction (IRR) in C1 were eligible to receive G as a 90-min SDI from C2. Pts with a Gr 3 IRR in C1 received the standard G infusion in C2, and were eligible for G SDI in subsequent cycles if no Gr ≥3 IRRs occurred. Pts with a second Gr 3/4 IRR discontinued G. At the end of induction (EOI), responding pts received maintenance G (1000mg) as SDI for 2 years or until disease progression (PD). The primary endpoint was incidence of Gr ≥3 IRRs during C2. IRRs were defined as any event occurring ≤24 hours from infusion judged to be related to treatment. Secondary endpoints included adverse events (AEs) and investigator-assessed overall response rate at EOI. **Results:** As of December 3, 2020, 113 pts had received study treatment. Median age was 62.0 years, 50.4% were male, 61.9% had stage IV FL, and 45.1% were classified as high-risk FLIPI. Of the 110 pts who were eligible for G SDI from C2, no pt experienced a Gr ≥3 IRR with SDI in C2 (Table). One pt experienced a Gr 3 IRR with SDI in C5, presenting hypertension. All other IRRs with SDI were Gr 1/2. No Gr 4/5 IRRs were reported. Other AEs were similar to those observed in previous studies. At the clinical cut-off date, 104 pts had a CT imaging-based response assessment at EOI and 9 pts had no response assessment; 76/113 (67.3%) had a complete response, 22 (19.5%) had a partial response, and six (5.8%) had PD. **Conclusions:** In GAZELLE, G SDI in C2 and beyond appeared to be safe. No Gr 3 IRRs were observed in C2 and only one Gr 3 IRR was reported in subsequent cycles. The safety profile of G SDI was comparable with the established profile of G in advanced FL. Clinical trial information: NCT03817853. Research Sponsor: GAZELLE was sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of all authors, was provided by Aisling Lynch and Louise Profit of Ashfield MedComms, and was funded by F. Hoffmann-La Roche Ltd.

IRRs by cycle.

	C1											
IRR, n (%)	**C1 overall**	**D1**	**D2***	**D8**	**D15**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**All cycles**
All Gr	65/113 (57.5)	57/113 (50.4)	4/51 (7.8)	6/112 (5.4)	5/111 (4.5)	13/110 (11.8)	9/108 (8.3)	7/108 (6.5)	6/107 (5.6)	5/105 (4.8)	2/55 (3.6)	71/113 (62.8)
Gr ≥3	6/113 (5.3)	5/113 (4.4)	1/51 (2)	0	0	0	0	0	1/107 (0.9)	0	0	7/113 (6.2)

*timepoint applicable only to pts treated with bendamustine.

7546 **Poster Session**

Duration of response to loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma by demographic and clinical characteristics: Subgroup analyses from LOTIS 2.

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Background: Outcomes for patients with refractory/relapsed diffuse large B-cell lymphoma (R/R DLBCL) are poor, particularly for those with high-risk clinical characteristics. There remains an unmet need for new treatment options for these patients. Loncastuximab tesirine (Lonca) is an antibody-drug conjugate comprising a humanized anti-CD19 antibody conjugated to a potent pyrrolobenzodiazepine dimer toxin. LOTIS 2 was a pivotal Phase 2 study that demonstrated substantial single-agent anti-cancer activity of Lonca in patients with R/R DLBCL. Efficacy and safety data were presented at ASH 2020 (Caimi *et al*, ASH 2020; abstract 1183). Here we present subgroup analyses of duration of response (DoR) to Lonca by demographic and clinical characteristics. **Methods:** Adult patients with R/R DLBCL who had received ≥2 prior therapies were enrolled in this Phase 2, multicenter, single-arm, open-label study of single-agent Lonca (150 μg/kg every 3 weeks for 2 doses, followed by 75 μg/kg thereafter for up to 1 year). The primary analysis has previously been reported, with a primary endpoint of overall response rate (ORR). Patients are being followed-up every 12 weeks for up to 3 years. DoR was a key secondary efficacy endpoint, defined as time from the first documentation of response (central review) to disease progression or death. We analyzed pre-specified demographic and clinical characteristic subgroups for DoR. **Results:** As of data cut-off (August 6, 2020), ORR in the total population (N = 145) was 48.3% (24.8% had complete response [CR] and 23.4% had partial response [PR]). Median DoR (mDoR) for the 70 responders was 12.58 months. mDoR for patients with CR and PR was 13.37 months and 5.68 months, respectively. Overall, subgroups with high-risk characteristics for poor prognosis had a DoR comparable to the whole study population. mDoR for patients with double-/triple-hit DLBCL was 13.37 months, with advanced stage disease was 12.58 months, and with transformed disease was 12.58 months. The mDoR for older patients was longer than for younger patients (≥75 years, 13.37 months; 65 to < 75 years, 12.58 months; < 65 years, 9.26 months). Patients with DLBCL refractory (defined as no response to therapy) to first-line, most recent line, and all prior lines of therapy had mDoRs of 9.63 months, 9.26 months, and 9.63 months, respectively. **Conclusions:** Durable responses were observed with the recommended Phase 2 dose regimen of Lonca in heavily pre-treated patients and those at high risk of poor prognosis, including older patients and those with double-/triple-hit, advanced stage, transformed, and primary refractory DLBCL. Updated DoR data will be presented at the meeting. Clinical trial information: NCT03589469. Research Sponsor: ADC Therapeutics SA.

7547 **Poster Session**

Outcomes with KTE-X19 in patients (pts) with relapsed/refractory (R/R) mantle cell lymphoma (MCL) in ZUMA-2 who had progression of disease within 24 months of diagnosis (POD24).

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Background: KTE-X19 is an autologous anti-CD19 CAR T-cell therapy approved in the US and EU for the treatment of R/R MCL. In the ZUMA-2 study of KTE-X19 in R/R MCL, the objective response rate (ORR) at a median 17.5-mo follow-up was 92% (67% complete responses [CR]; Wang et al. ASH 2020 #1120). Here, we report results in pts with or w/o POD24, an indicator of poor outcomes (Visco et al. *Br J Haematol* 2019). **Methods:** Eligible pts with R/R MCL underwent leukapheresis and conditioning chemotherapy followed by a single infusion of KTE-X19. Efficacy results are reported for the 60 treated pts with ≥1 y of follow-up (median 17.5 mo); safety results are presented for all 68 treated pts. **Results:** High-risk disease characteristics were common in pts with (n=33) and w/o POD24 (n=35), although pts with POD24 had higher tumor burden and lactate dehydrogenase (LDH) levels, and more had blastoid type MCL (Table). ORR in pts with (n=28) and w/o POD24 (n=32) was 93% and 91%, with CR rates of 61% and 72%. In pts with and w/o POD24, median progression-free survival (PFS) was 11.3 mo (range, 0.9–30.3) and 29.3 mo (range, 0–35.9). Medians for duration of response (DOR) and overall survival (OS) were not reached in either group. Most common Grade ≥3 adverse events (AEs) in pts with vs w/o POD24 were neutropenia (91% vs 80%), thrombocytopenia (61% vs 46%), and anemia (55% vs 51%); Grade ≥3 cytokine release syndrome (CRS) and neurologic events occurred in 9% vs 20% and 27% vs 34%, respectively. There were no cases of Grade 5 CRS, KTE-X19–related secondary cancers, or replication-competent retrovirus in either group. In pts with vs w/o POD24, median peak CAR T-cell levels and median area under the curve were 53.4 cells/μL (range, 0.2–2566) and 583.4 cells/μL (range, 1.8–27,743.6) vs 112.4 cells/μL (range, 0.2–2589) and 1588.3 cells/μL (range, 3.8–27,238.7); by 12 mo, B cells were detectable in 8/11 (73%) vs 7/15 pts (47%) in ongoing response. **Conclusions:** KTE-X19 provided a high CR rate across all pts, with median DOR and OS not reached. Pts with POD24 had more aggressive high-risk disease characteristics (tumor burden, LDH levels, and blastoid MCL) and generally lower CAR T-cell expansion and PFS vs pts w/o POD24. Earlier intervention with CD19-directed CAR T-cell therapy may benefit pts with MCL with known high-risk factors. Clinical trial information: NCT02601313. Research Sponsor: Kite, a Gilead Company.

Characteristics	With POD24 n = 33	W/o POD24 n = 35
Median age, y	65	66
Median prior therapies, n	3	3
Received ≥3 prior therapies, %	88	74
Ibrutinib	85	86
Acalabrutinib	21	26
Ibrutinib and acalabrutinib	6	11
Auto-SCT	36	49
Disease stage III/IV, %	97	97
Extranodal disease, %	52	60
LDH ≥1.5×ULN, %	24	9
Intermediate-/high-risk MIPI, %	48	63
MCL Morphology, %		
Classical	48	69
Pleomorphic	6	6
Blastoid	33	17
Median tumor burden (SPD), mm^2 (range)	2254.6(260–14,390)	1380.2(293–16,878)
Ki-67 Proliferation Index, %	n = 23	n = 20
≥50%	74	65
≥30%	83	81
TP53 status	n =20	n =16
Mutated, %	15	19

7548 **Poster Session**

Updated outcomes with axicabtagene ciloleucel (axi-cel) retreatment (reTx) in patients (pts) with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) in ZUMA-5.

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Background: ZUMA-5 is a Phase 2 study of axi-cel anti-CD19 CAR T-cell therapy in pts with R/R iNHL (follicular lymphoma [FL]; marginal zone lymphoma [MZL]). In the primary analysis, 11 pts (9 FL; 2 MZL) were retreated with axi-cel, achieving an overall response rate (ORR) of 100% (91% complete response [CR] rate) at a median follow-up of 2.3 mo post-reTx, with no Grade $\geq$3 cytokine release syndrome (CRS) or neurologic events (NEs; Chavez et al. ASH 2020. #2036). Here, we report updated clinical and translational outcomes with longer follow-up in pts retreated with axi-cel in ZUMA-5. **Methods:** Eligible pts with FL or MZL had R/R disease after $\geq$2 lines of therapy. Pts were considered for reTx if they progressed after a response at mo 3, had no evidence of CD19-negative relapse in biopsy, had no axi-cel neutralizing antibodies, and had no Grade 4 CRS or NEs with 1st Tx. Retreatment was per investigator discretion. At both Txs, pts received axi-cel (2×10^6 CAR T cells/kg) after conditioning chemotherapy. **Results:** As of 9/14/2020, 13 pts with iNHL (11 FL; 2 MZL) received axi-cel reTx, with 2 pts retreated after the primary analysis. Before their 1st Tx, pts had median 4 prior lines of therapy; 85% had stage 3–4 disease; 82% had FLIPI of $\geq$3; 46% were POD24; 77% had refractory disease. Among the 13 retreated pts, 85% had a CR to 1st Tx. Median 1st duration of response (DOR) was 8.2 mo. Detectable CD19 was confirmed in all evaluable biopsies from retreated pts at relapse, and median time from 1st Tx to reTx was 10.6 mo. Following reTx, the ORR was 100% (77% CR rate). After a median follow-up of 11.4 mo, the median DOR had not yet been reached; 46% of retreated pts had ongoing responses at data cutoff. At 1st Tx, CRS occurred in 9 pts (5 Grade 1, 4 Grade 2); NEs occurred in 5 (3 Grade 1, 1 Grade 2, 1 Grade 3). At reTx, CRS occurred in 8 pts (6 Grade 1, 2 Grade 2); NEs occurred in 4 (3 Grade 1, 1 Grade 2). Median peak levels of biomarkers typically associated with severe CRS and NEs were similar at reTx and 1st Tx (IL-6, 7.7 vs 5.7 pg/mL; IL-2, 1.8 vs 0.9 pg/mL; IFN-γ, 62.9 vs 64.2 pg/mL). In the 11 retreated pts with FL, tumor burden (median sum of product diameters [SPD]) was lower before reTx vs 1st Tx (1416 vs 4770 mm^2). Engraftment index (CAR T-cell expansion relative to SPD) is an indirect proxy for effector:target ratio and a key covariate of response to axi-cel (Locke et al. *Blood Adv*. 2020). Though median peak CAR T-cell levels appeared lower at reTx vs 1st Tx (5.2 vs 14.3 CAR+ cells/μL blood), engraftment index was similar (0.003 vs 0.005 cells/μL$\times$mm2). **Conclusions:** Axi-cel reTx achieved deep and durable responses, with an acceptable safety profile. Tumor CD19 positivity was maintained at relapse, and engraftment index was similar at both Txs, comparing favorably to previous reports in aggressive lymphomas (Locke et al. ASCO 2020. #8012). These data suggest axi-cel reTx is a promising option for pts with R/R iNHL. Clinical trial information: NCT03105336. Research Sponsor: Kite, a Gilead Company.

7549 **Poster Session**

NVG-111, a novel ROR1xCD3 bispecific antibody for non-Hodgkin lymphoma.

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Background: Receptor tyrosine kinase-like Orphan Receptor 1 (ROR1) is a type I transmembrane protein is highly expressed on an array of haematological and solid tumours. NVG-111 is a humanised, tandem scFv ROR1xCD3 bispecific antibody previously shown to elicit potent killing of tumour cells *in vitro* and *in vivo* by engaging a membrane-proximal epitope in the Wnt5a-binding Frizzled domain of ROR1 and redirecting T cell activity. The *in vitro* potency and pharmacodynamic responses to NVG-111 were assessed to support progression to a first-in-human study. **Methods:** The potency of NVG-111 *in vitro* was determined by evaluating the concentration response for cytotoxicity, T cell activation, and cytokine release in co-cultured Jeko-1 and unstimulated human T cells. Comparative data were generated for the marketed CD19xCD3 bispecific antibody, blinatumomab. Potency data for NVG-111 were used together with allometric scaling from murine PK studies to inform planned clinical doses. **Results:** NVG-111 demonstrated T cell-dependent cytotoxicity, T cell activation and levels of cytokine release similar in potency to blinatumomab. Cytotoxic responses of both NVG-111 and blinatumomab were more potent than T cell activation and cytokine release. Dose response curves for NVG-111 showed a decrease in activity beyond the concentration of maximal response (ie hook effect). We hypothesise this is due to receptor saturation, inhibiting synapse formation. NVG-111 has progressed to a Phase 1/2 first-in-human study in patients with debulked, relapsed/refractory chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), the drug given as add-on to $\geq$2nd line therapy with a Bruton's tyrosine kinase inhibitor, or venetoclax. Phase 1 includes escalating doses of 0.3 to 360 μg/day via continuous infusion over 3 cycles (each 21 days on, 7 days off) to establish safety, PK, pharmacodynamics (PD) and recommended phase 2 dose (RP2D). Predicted exposure at 0.3 μg/day is ~EC_{20} for cytotoxicity *in vitro* and below the lowest EC_{10} for cytokine release. PD biomarkers in the study include systemic cytokines. Phase 2 will study efficacy and safety of the RP2D in CLL and MCL, with primary endpoint complete response rate; other efficacy endpoints include minimal residual disease and progression free survival. **Conclusions:** NVG-111 shows potent T-cell mediated lymphoma cell cytotoxicity *in vitro* at concentrations well below those associated with extensive cytokine release. NVG-111 is in an ongoing Phase 1/2 study and may present a novel option for adoptive immunotherapy in patients with non-Hodgkin lymphoma and potentially other cancers. Clinical trial information: 2020-000820-20. Research Sponsor: NovalGen Ltd.

	NVG-111 EC_{50} (pg/mL)	NVG-111 Max. Response	Blinatumomab EC_{50} (pg/mL)	Blinatumomab Max. Response
Cytotoxicity	60	97%	56	97%
T cell activation	997	63%	887	69%
Cytokine release				
- IFNg	920	5167pg/mL	1250	6537pg/mL
- TNFa	1450	212pg/mL	1080	330pg/mL
- IL6	N/A	16.3pg/mL	N/A	9.8pg/mL

7550 **Poster Session**

Efficacy and safety of the PI3Kδ inhibitor zandelisib (ME-401) on an intermittent schedule (IS) in patients with relapsed/refractory follicular lymphoma (FL) with progression of disease within 24 months of first-line chemoimmunotherapy (POD24).

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Background: FL patients (pts) with POD24 have poorer survival and may benefit from novel therapies at relapse. Zandelisib, a potent, selective, and structurally differentiated oral PI3kδ inhibitor was evaluated in a dose escalation/expansion Phase 1b study for FL demonstrating a high objective response rate (ORR) and well tolerated when given on IS (J Clin Oncol 2020;38:#8016). We report here results based on POD24 status (NCT02914938). **Methods:** Eligible pts had $\geq$1 prior therapy, adequate bone marrow and organ function, ECOG performance status $\leq$2, and no prior PI3K therapy. Zandelisib was administered at 60 mg once daily for 8 weeks followed by IS on days 1-7 of each subsequent 28-day cycle, either as monotherapy or with rituximab at 375 mg/m^2 for 8 doses in Cycles 1-6. Treatment was continued until disease progression, intolerance, or withdrawal of consent. Imaging scans were obtained after 2 and 6 cycles, and then every 6 cycles. Response was reported based on Lugano criteria. **Results:** 37 FL pts were enrolled and received zandelisib on IS as monotherapy (N = 18) or in combination with rituximab (N = 19). Median number of prior therapies = 2 (range, 1-5). The ORR was 86.5% (32/37) with 27% CR (complete response). In the monotherapy group the ORR and CR were 77.8 % (14/18) and 27.8% and with rituximab 94.7% (18/19) and 26.3% respectively. Median duration of response (DOR) among all pts was not reached with a median follow-up of 16.9 months (mos) (1.2-33.1+). 22 pts (59%) were POD24, of which 15 (68%) had $\geq$2 prior lines of therapy. Despite more refractory disease, ORR among the POD24 pts was 81.8% (Table). Zandelisib on IS was well tolerated. 3 pts (8%) discontinued therapy due to an adverse event (AE) for any cause. Grade (Gr) 3 AE of special interest (AESI) were 2 (5.4%) diarrhea, 2 (5.4%) colitis, 3 (8.1%) rash, 3 (8.1%) ALT elevation, 1 (2.7%) AST elevation and no pulmonary infection. **Conclusions:** Zandelisib administered on IS as monotherapy or with rituximab resulted in a high-rate of durable responses in FL, both in POD24 and non-POD24 groups and therapy was well-tolerated with low rate of Gr 3 class-related AESI and discontinuation rate due to AE's. Zandelisib as monotherapy is being evaluated in a global Phase 2 study in FL and MZL after failure of 2 prior therapies (NCT03768505). A Phase 3 study of zandelisib plus rituximab in FL and MZL after failure of prior immunochemotherapy will begin enrollment in 2021. Clinical trial information: NCT02914938. Research Sponsor: MEI Pharma, Inc.

	POD24 N = 22	Non-POD24 N = 15
Age, median (range)	61.5 (38 - 82)	63 (47 - 87)
Prior therapies, median (range)	2 (1 – 4)	1 (1 –5)
Disease refractory to rituximab, N (%)	14 (63.6%)	1 (6.7%)
Disease refractory to last therapy, N (%)	14 (63.6%)	1 (6.7%)
Follow-up, median (range) in mos	19.4 (1.8- 36.5)	18.2 (3.0 – 30.4)
ORR, N (%)	18 (81.8%)	14 (93.3%)
CR rate, N (%)	4 (18.2%)	6 (40%)
KM-DOR $\geq$ 12 mos	56.7 %	80 %

7551 **Poster Session**

Long-term follow-up results of a phase II study of dose-adjusted (DA)-EPOCH-R with high-dose methotrexate (HD-MTX) for newly diagnosed stage II-IV CD5-positive diffuse large B-cell lymphoma (CD5+ DLBCL).

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Background: CD5+ DLBCL is characterized by a poor prognosis and frequent central nervous system (CNS) relapse after standard immunochemotherapy. In the primary analysis of our multicenter phase II study of DA-EPOCH-R/HD-MTX for newly diagnosed stage II-IV CD5+ DLBCL, the 2-year (yr) progression-free survival (PFS) was 79% and the 2-yr CNS relapse rate was 9% at a median follow-up of 3.1 yrs (Miyazaki, et al. 2020). The aim of this preplanned 5-yr follow-up was to assess PFS, overall survival (OS), the CNS relapse rate, and late toxicity. **Methods:** A total of 47 patients (pts) with newly diagnosed stage II-IV CD5+ DLBCL between 20-75 yrs old and ECOG PS of 0-3 were enrolled. The treatment included 4 cycles of DA-EPOCH-R followed by 2 cycles of HD-MTX (3.5 g/m^2) and 4 additional cycles of DA-EPOCH-R. Intrathecal administration of MTX and/or cytarabine was not allowed. 45 (96%) pts completed the protocol treatment. The data were updated as of December 1, 2020. **Results:** The median follow-up of alive pts was 6.0 yrs (range, 5.0-7.7). The pts' characteristics were as follows: age, 37-74 yrs (median, 62); male, 38%; ECOG PS $>$ 1, 4%; stage III/IV, 57%; IPI HI/H, 47%; CNS-IPI high, 21%; and ABC/GCB/unclassified (n = 46), 85%/9%/7%. The 5-yr PFS and OS were 72% (95% CI, 57-83%) and 79% (95% CI, 64-88%), respectively. The 5-yr PFS and OS of pts with CD5+ ABC DLBCL (n = 39) were 72% and 74%, respectively. The 5-yr CNS relapse rate in all 47 pts was 9% (95% CI, 3-22%). There were no CNS relapse events after the primary analysis. Neither grade 3/4 late adverse events nor cardiac events of any grade were observed. Possible second malignancies were recorded in 6 (13%) pts. Among them, one pt who received R-ICE as salvage therapy experienced acute myeloid leukemia. The other 2 pts had colon cancers treated with endoscopic polypectomy/mucosal resection. **Conclusions:** Both the survival benefit and safety of DA-EPOCH-R/HD-MTX were maintained during a 5-yr follow-up, indicating the excellent efficacy, and safety of this approach as a first-line therapy for CD5+ DLBCL. Clinical trial information: UMIN000008507. Research Sponsor: Japan Agency for Medical Research and Development, AMED.

7552 **Poster Session**

Real-world evidence of axicabtagene ciloleucel (Axi-cel) for the treatment of large B-cell lymphoma (LBCL) in the United States (US).

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Background: Axi-cel is approved in the US for the treatment of adult patients with relapsed or refractory LBCL after 2 or more lines of systemic therapy. Post-market long term follow up study of commercial Axi-cel recipients using the Center for International Blood and Marrow Transplant Research was recently completed. **Methods:** From October 2017 to August 2020, 1,500 Axi-cel recipients from 79 centers were enrolled. Of these, 1001 patients with at least 6 months of follow-up were included in this analysis. Outcomes include complete and overall responses rates (CR and ORR), duration of response (DOR), progression-free and overall survival (PFS and OS), cytokine release syndrome (CRS) (Lee D 2014 and American Society for Transplantation and Cellular Therapy [ASTCT]), immune effector cell associated neurotoxicity syndrome (ICANS), hematologic recovery and subsequent neoplasm (SN). Subgroup analysis by sensitivity to therapy, defined as responsive to the last line of therapy prior to Axi-cel. Median follow-up was 12 months (range, 6-28 months). **Results:** The median age overall was 62 years, 37% were $\geq$ 65 years, 83% with Eastern Cooperative Oncology Group (ECOG) performance score 0-1, 28% with transformed lymphoma, 14% with high grade lymphoma, 29% with prior autologous transplant, and 66% with chemotherapy-resistant disease prior to Axi-cel. The median time from diagnosis to Axi-cel infusion was 15 months. Best ORR was 70% (CR 53%). Landmark analysis of patients in CR at 6 months post Axi-cel demonstrates a low number of subsequent progression/death events. With respect to outcomes for chemotherapy-sensitive disease versus resistant disease, the ORR, CR, 12-month PFS and OS were 78% vs. 66%, 60% vs. 48%, 55% (95% CI, 48-62%) vs. 40% (95% CI, 37-44%), and 70% (95% CI, 63-76%) vs. 54% (95% CI, 50-58%), respectively. CRS of any grade was reported in 83% of patients. Incidence of Grades $\geq$ 3 CRS was 10% according to Lee et al 2014, and 13% according to ASTCT Consensus Grading. Median time to any grade CRS was 4 days (range, 1-28 days), and 93% of CRS cases resolved with a median duration of 7 days (range, 1-121 days). ICANS were reported in 576 (57%) patients, grade $>$3 was 26%. The median time to onset of ICANS was 7 days (range, 1-82 days), and 86% resolved with a median duration of 9 days (range, 1 to 115 days). Twenty-nine patients (2.9%) reported SN: hematologic (N = 17), solid tumors (N = 12). **Conclusions:** This is the largest report on Axi-cel in the real-world setting and demonstrates consistent efficacy outcomes and further characterizes safety outcomes. Patients in CR at 6 months have sustained disease control with low number of relapse events. Although patients with therapy-sensitive disease experience better outcomes than patients with therapy-resistant, the overall outcomes on both groups of patients are favorable. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

7553 **Poster Session**

Initial results of the combination of PI3Kδ inhibitor zandelisib (ME-401) and the BTK inhibitor zanubrutinib in patients (pts) with relapsed or refractory (R/R) B-cell malignancies.

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Background: Dual inhibition of PI3Kδ and BTK pathways may overcome existing or acquired monotherapy resistance. Dual inhibition of these pathways displays synergistic activity in cell lines that is evident even at suboptimal concentrations [Blood 2015;125(14):2306-09]. Zandelisib is a potent, selective, and structurally differentiated oral PI3Kδ inhibitor (i), and zanubrutinib is an oral BTKi. Based on their efficacy as monotherapy, we hypothesized that the combination of zandelisib and zanubrutinib can be well tolerated and may improve the depth and durability of responses. We evaluatedthis combination therapy in pts with R/R B-cell malignancies to determine the optimal dose and schedule for further evaluation in disease-specific expansion cohorts (NCT02914938). **Methods:** This is a multi-cohort Phase 1b study enrolling pts with FL, CLL, MZL, MCL, DLBCL, or high grade B-cell lymphoma (HGBCL), $\geq$1 prior therapy, adequate bone marrow and organ function, ECOG performance status $\leq$2, and no prior PI3Ki or BTKi therapy. For this combination therapy, two dose levels were evaluated in 28-day cycles: Cohort 10A: zandelisib 60 mg once daily for 2 cycles followed by an intermittent schedule (IS) on days 1-7 of subsequent 28-day cycles and zanubrutinib 160 mg twice daily (bid). Cohort 10C: zandelisib 60 mg on days 1-7 starting in Cycle 1 and zanubrutinib at 80 mg bid. Dose limiting toxicity (DLT) observation period was 28 days for cohort 10A and extended to 56 days for cohort 10C. Response was assessed at month 3, 7, 13 and then every 6 months until progression. **Results:** 20 pts treated, 7 in cohort 10A and 13 in cohort 10C: 8 FL, 5 CLL, 2 DLBCL, 2 HGBCL, 2 MZL, and 1 MCL. Median age 70 years (range, 44-85) and median prior therapies 2 (1-8). Median follow-up of 2.9 months (0.5-17.4+). There were no DLT in cohort 10A, grade (Gr) $\geq$3 adverse events (AE) occurred after day 28 in 4 pts, including Gr 4 neutropenia (1 pt), Gr 3 neutropenia, fatigue and CMV colitis (1 pt), Gr 3 AST/ALT and rash (1 pt) and Gr 3 AST/ALT (1 pt). In cohort 10C, 2 pts had DLT with Gr 3 AST/ALT in Cycle 2, with 1 pt successfully resuming both drugs and 1 discontinued treatment due to recurrence of Gr 3 AST/ALT upon rechallenge. Other Gr 3 AE were all laboratory findings: 1 pt (CLL) had laboratory TLS, neutropenia and thrombocytopenia and 2 pts (FL, DLBCL) had neutropenia. Response rate was 100% (2 CR 14 PR) in the following 16 pts with indolent NHL and MCL evaluable for response: FL (2 CR, 6 PR), CLL (5 PR), MCL (1 PR) and MZL (2 PR). No pt with aggressive B-cell lymphomas has responded. **Conclusions:** The combination of zandelisib 60 mg on IS from Cycle 1 and zanubrutinib 80 mg bid is well tolerated and achieves a high ORR in R/R indolent B-cell malignancies. This schedule is being evaluated in expansion cohorts in R/R FL and MCL. Clinical trial information: NCT02914938. Research Sponsor: None.

7554 **Poster Session**

Outpatient practice pattern and remote patient monitoring for axicabtagene ciloleucel CAR-T therapy in patients with aggressive lymphoma.

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Background: Chimeric antigen receptor T-cell therapy (CAR-T) are commonly administered inpatient due to concern for early onset cytokine release syndrome (CRS), especially with axicabtagene ciloleucel (axi-cel). We report Mayo Clinic Rochester experience for hospital-based outpatient (HBO) management of patients (pts) receiving axi-cel and identify opportunities for improvement. HBO is closely integrated with inpatient practice and includes the same specialty trained clinical team. It is the first point of contact 24/7 for pts and triage evaluations. Lymphodepletion chemotherapy and CAR-T infusion is given on HBO followed by daily monitoring till day 8 and thereafter, as clinically needed until admission criteria is met. **Methods:** We retrospectively analyzed database of pts who received axi-cel between 1/2018 and 1/2021. After 06/2020, remote patient monitoring (RPM) tools were implemented to collect patient-reported neurologic symptoms and vital signs via bluetooth-enabled devices 4 times daily through month 1. Adverse data trends are addressed by the HBO team. **Results:** Among 72 recipients, 89% received their cells outpatient; 8% remained outpatient for the entire month. CRS and neurotoxicity incidence were comparable to those reported from CIBMTR. Median time to first admission was 2 days (Table). Use of bridging therapy, increased CRP and LDH were associated with early admission ($\leq$3 days). Median time to tocilizumab, steroid, oxygen support, vasopressor was 4 days after admission. Half of HBO visits required intervention such as blood transfusions, IV medications through the first month. Nine pts had enrolled in RPM to date; with 8 having evaluable data. With 4 scheduled entries/day, a median of 1 entry/day was skipped and 2 entries/day were answered incompletely. An average of 57 additional unscheduled entries were generated per pt. Among a median of 373 (range 91-522) readings per pt over the first month, 4% (2%-20%) of the readings generated alerts. An average of 4 alerts were seen within 48 hours prior to admission. Data including additional subjects will be presented at ASCO meeting. **Conclusions:** We report a feasible outpatient care model for management of axi-cel recipients with safe outcomes. Clinical characteristics associated with more aggressive disease are associated with likelihood of early admission. Early RPM experience suggest use of digital tools could improve monitoring compliance and may predict evolution to symptoms requiring escalation of care. Research Sponsor: None.

Reason for hospitalization.

Indication (N=59)	N (%)	DOA
Fever	51 (86)	3(0-25)
Doubling CRP without fever	4 (7)	2.5 (1-7)
Neurologic symptoms	2 (3)	1.5 (1-2)
Other symptoms	2 (3)	10.5 (0-21)
Indication using RPM (N=6) *	N (%)	Time from last RPM alert, median (range), hours
Fever	6 (100)	4.6 (1.2-17.1)

DOA- Day of admission, median (range), days *Patients admitted on day 0 prior to RPM=2.

7555 **Poster Session**

Vaccine titers in lymphoma patients receiving chimeric antigen receptor T-cell therapy.

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Background: While CAR-T therapy is not myelo-ablative, patients with aggressive lymphoma treated with CD19 chimeric antigen receptor T cell therapy (CAR-T) are lymphodepleted and have prolonged B cell aplasia. The impact of CAR-T on immunologic protection from vaccine-preventable diseases (and thus the need to revaccinate) is not known. We report the vaccine titers of patients treated with axicabtagene ciloleucel (axi-cel) at Mayo Clinic. **Methods:** Retrospective chart review of adult lymphoma patients who received axi-cel from 9/2018 to 9/2020 for anti-viral and anti-bacterial titers prior to CAR-T infusion and at month 3 (MO3) post CAR-T. **Results:** Prior to CAR-T therapy, positive titer rate was highest for tetanus and lowest for Strep pneumoniae (Strep PNA) (Table). Similar trends were seen whether patients had stem cell transplant (ASCT) within 2 years of CAR-T (i.e. within immunization timeframe post ASCT) or not (Table). Compared to patients who had ASCT, those who did not had higher rate of positive titer for Strep PNA and lower rate for hepatitis B, Mumps, and VZV. The same trend for sero-positive rate were observed at MO3 post CAR-T. Patients with IgG<400 mg/dl received IVIG supplement for prophylaxis. Among the 23 patients who received IVIG, variable rate of conversion from negative to positive titers were seen for measles (1/2, 50%), mumps (2/3, 67%), rubella (2/3, 67%), varicella-zoster (VZV, 3/3, 100%), hepatitis A (6/6, 100%), hepatitis B (6/7, 86%) and Strep PNA (0/10, 0%). For patients who did not receive IVIG prophylaxis, there was one loss of seropositivity for Strep PNA (1/4, 25%). **Conclusions:** The presence of protective vaccine titers is variable for patients receiving CAR-T, regardless of recent ASCT. The loss of protective titers post CART was low. IVIG variably impacted vaccine titer status. Immunization remains important for patients with ASCT prior to CART, without completion of post ASCT immunization protocol. Further study is needed to inform the need for immunization and optimal timing post CART. Research Sponsor: None.

Positive titer/Total (%)	PRE-CAR-T			MONTH 3				
	Prior ASCT	No ASCT	Total	Prior ASCT	No ASCT	IVIG	No IVIG	Total
Strep PNA	1/12 (8)	3/18 (17)	4/30 (13)	1/10 (10)	4/25 (16)	1/14 (7)	4/21 (19)	5/35 (14)
Hepatitis B	4/13 (31)	4/22 (18)	8/35 (23)	12/14 (86)	10/17 (59)	14/15 (93)	8/16 (50)	22/31 (71)
Hepatitis A	7/14 (50)	9/20 (45)	16/34 (47)	9/13 (69)	13/18 (72)	14/15 (93)	8/16 (50)	22/31 (71)
MEASLES	11/13 (85)	21/25 (84)	32/38 (84)	10/12 (83)	12/15 (80)	12/14 (86)	10/13 (77)	22/27 (81)
MUMPS	9/13 (69)	19/25 (76)	28/38 (74)	10/12 (83)	13/15 (87)	12/14 (86)	11/13 (85)	23/27 (85)
RUBELLA	12/13 (92)	21/25 (84)	33/38 (87)	11/12 (92)	15/15 (100)	13/14 (93)	13/13 (100)	26/27 (96)
VZV	12/13 (92)	19/25 (76)	31/38 (82)	12/12 (100)	14/15 (93)	13/14 (93)	13/13 (100)	26/27 (96)
Tetanus Toxoid	13/13 (100)	23/24 (96)	36/37 (97)	12/12 (100)	15/15 (100)	14/14 (100)	13/13 (100)	27/27 (100)

Sero-positivity for routine immunization pre and post CAR-T.

7556 **Poster Session**

Phase 1/2 study of cirmtuzumab and ibrutinib in mantle cell lymphoma (MCL) or chronic lymphocytic leukemia (CLL).

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Background: Cirmtuzumab (Cirm) is a humanized monoclonal antibody that inhibits the tumor promoting activity of ROR1 and had demonstrated additive/synergistic activity with many anti-cancer agents including ibrutinib (Ibr). **Methods:** Patients (Pts) with relapsed or refractory (RR) MCL or treatment nave (TN) or RR CLL were enrolled. In Part 1 (Dose Escalation), doses of Cirm IV q2wks x5 then q4wks of 2-16 mg/kg and 300 or 600 mg were examined. Safety of Cirm alone was assessed during the first 28 days, then Ibr was started at approved doses for each indication. Cirm 600 mg IV q2wks x3 then q4wks in combination with Ibr starting day 0 was chosen as the recommended dosing regimen for use in Part 2 (Expansion) and Part 3 (CLL only, Cirm/Ibr vs. Ibr alone). **Results:** Twelve evaluable MCL pts were enrolled into Part 1, and 5 into Part 2. Median number of prior regimens was 2 (1-5), including pts relapsing after Ibr (4), auto-SCT (3), auto-SCT/ allo-SCT (1), auto-SCT/CAR-T (1). In CLL, 34 evaluable pts (12 TN and 22 RR) enrolled into Part 1 (18) or Part 2 (16). At least 74% of CLL pts in Parts 1 and 2 were high risk as determined by unmutated IGHV, del17p, and/or del11q. In Part 3, 22 evaluable pts received Cirm/Ibr (15) or Ibr (7). As of the 30OCT2020 safety cut-off for MCL and CLL, common TEAEs (all grades) included diarrhea (41%), contusion (39%), fatigue (39%), URI (31%), hypertension (25%) arthralgia (23%). Grade $\geq$3 neutropenia was 13% and thrombocytopenia 1%. There were no Cirm dose reductions or discontinuations for toxicity. Overall, Cirm did not appear to negatively impact the safety of Ibr. Efficacy (MCL): As of the 02FEB2021 efficacy cutoff, the best response of 17 evaluable pts in Parts 1 and 2 included an objective response rate (ORR) of 82%, 41% CR/CMR, 41% PR, 12% SD, and 6% PD. CR/CMR remain durable from 8-28+ mos**.** Most responses occurred rapidly after ~3 mos of Cirm/Ibr. Notably, responses were achieved in all pts who received prior SCT+/- CAR-T (4CR, 1PR) or prior Ibr (2CR, 2PR). At a median follow-up of 14.6 mos, the median PFS (mPFS) had not been reached (NR) (95% CI: 17.5, NA). Efficacy (CLL): The best response of 34 evaluable pts in Parts 1 and 2 included 91% ORR, 3% CR, 88% PR/PR-L, 9% SD, 0% PD. In Part 3, both arms achieved 100% ORR (all PRs). At a median follow-up of 20.2 mos, the mPFS was NR (95% CI: NA, NA), and the PFS estimate at 24 months was 95% for R/R, and 87% for TN, respectively, for evaluable CLL pts receiving Cirm/Ibr. **Conclusions:** Cirm/Ibr is a well-tolerated, active regimen in both MCL and CLL. For MCL, the mPFS of NR (95% CI: 17.5, NA) and CRR (41%), with all CRs remaining without PD, compare favorably to mPFS of 12.8 mos (95% CI 8.5-16.6) and CRR (20%) reported for single agent Ibr (Rule 2017). For CLL, the high ORR and PFS are encouraging, particularly for RR CLL. The study is ongoing, with MCL enrollment expanded to study Cirm + Ibr in pts who have had a suboptimal response to an Ibr regimen, or who have failed other approved BTKi agents. Clinical trial information: NCT03088878. Research Sponsor: Oncternal Therapeutics, Inc., Other Foundation.

7557 **Poster Session**

Survival outcomes, treatment toxicity, and healthcare utilization in older adults with aggressive non-Hodgkin lymphoma (NHL).

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Background: Aggressive NHLs frequently affect older adults, and are often treated with intensive systemic therapy that is potentially curative but can cause substantial toxicities. Although balancing treatment efficacy with the risk of complications is critically important for older adults with NHL, few studies have described these patients' survival outcomes, rates of toxicities, and healthcare utilization. **Methods:** We conducted a retrospective analysis of adults $>$ 65 years diagnosed with aggressive NHL and treated with systemic therapy at Massachusetts General Hospital from 4/2000-7/2020. We abstracted patient demographic and clinical information, survival outcomes, treatment toxicity (rates and grade), and healthcare utilization outcomes (intensive care unit [ICU] admissions and unplanned hospitalizations within six months of treatment initiation) from the electronic health record. Using multivariable logistic regression, we examined patient and disease factors associated with rates of grade 3+ non-hematologic toxicity and unplanned hospitalization. **Results:** Of 295 patients (median age = 73 years [age 65-69: 32.5%; age 70-74: 26.1%; age 75-79: 20.0%; age 80+: 21.4%], 39.0% female), most had advanced stage disease (59.5%) and an ECOG performance status of 0 or 1 (83.1%). The most common diagnosis was de novo diffuse large B-cell lymphoma (DLBCL) or grade 3B follicular lymphoma (69.2%). Most common therapies were CHOP (65.8%) and EPOCH (17.0%) with or without Rituximab. With a median follow up of 5.9 years, 5-year overall survival (OS) was 74.2%. Among patients age 65-69, 70-74, 75-79, and 80+ years, 5-year OS by age group were 82.1%, 72.2%, 73.5%, and 66.3%, respectively. Overall, 42.4% had grade 3+ toxicity, while 8.1% had grade 4 or 5 toxicity. The rates of unplanned hospitalization and ICU admission during the first 6 months of therapy were 41.0% and 6.1%, respectively. In multivariable analysis, hypoalbuminemia (OR 4.22, 95%, $p < 0.001$) and number of comorbidities (OR 1.75, $p < 0.001$) were associated with a greater likelihood of grade 3+ toxicity. Hypoalbuminemia (OR 2.76, $p = 0.003$), number of comorbidities (OR 1.61, $p = 0.001$), and receipt of EPOCH (OR 5.41, $p = 0.012$) were associated with a greater likelihood of unplanned hospitalization. **Conclusions:** The majority of older adults receiving upfront therapy for aggressive NHL survive beyond 5 years, yet nearly half experience substantial treatment toxicities and unplanned hospitalizations. Our findings underscore the need to develop supportive care interventions to enhance the care experience for older adults with NHL. Research Sponsor: Leukemia and Lymphoma Society.

7558 **Poster Session**

Prognostic role of lymphocyte to monocyte ratio in patients treated with CAR-T for aggressive lymphoma.

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Background: A low absolute lymphocyte to monocyte ratio (ALC/AMC) has been found to predict decreased survival in lymphoma patients receiving chemotherapy and stem cell transplant. We report its clinical significance and additional cellular phenotype changes in patients receiving chimeric antigen receptor T-cell (CART) therapy. **Methods:** Records were reviewed for patients (pts) who received axicabtagene ciloleucel between 6/2016 and 12/2020. Receiver operator curve was generated using nominal logistic regression to predict CR as best response. Survivals were calculated using Kaplan- Meier method. Blood immune phenotype were assayed by multiparametric flow. Principle component analysis (PCA) was performed using ClusterVis. **Results:** Low ALC/AMC ($\leq$0.8) prior to lymphodepletion (LD) chemotherapy on day -5 was associated with lower CR rate (AUC=0.68, Table). Our cohort of 81 pts had similar baseline characteristics except that noted in Table. Low ALC/AMC ratio is associated with shorter EFS and OS (EFS: 2.6 vs. 6.4 months, P$<$0.0001; OS: 5.3 months vs. not reached, P=0.0006), respectively. Prognostic association remained significant in multivariate analysis including ASCT, bridging therapy and CRP. Interestingly, compared to the high ALC/AMC group, the low ALC/AMC group had decreased CD8 Tem, increased CD16+CCR2+ monocytes and increased monocytes' producing IL12, IL-10, and IL-1β (n=26). Unsupervised PCA identified 3 clusters: 1. Low ALC/AMC, all non-CR; 2. High ALC/AMC, some non-CR; 3. High ALC/AMC, all CR. Compared to cluster 1 and 2, cluster 3 had increased CD4 Tnaive, CD8 Tcm and IL-17 producing CD4 T and NK cells. **Conclusions:** ALC/AMC is a clinically accessible test that is strongly associated with CAR-T response and survival. Immune characterization revealed that the biologic effect is not just associated with cell ratio. Increased inflammation has been found to negatively impact CAR-T response, with some cytokines known to be from the myeloid lineage. We show that CRP is elevated in the low ALC/AMC group with increased cytokine production by monocytes. In addition, presence of T cell subset and IL-17 producing cells, before LD, are associated with clinical response. Further investigation on optimizing host immunity may help improve clinical outcome with CAR-T. Research Sponsor: Center for Individualized medicine Mayo Clinic.

Patient demographics.

Variable	All patients (N=81)	ALC/AMC >0.8 (N=52)	ALC/AMC ≤0.8 (N=29)	P- Value
Age (yr), median (range)	58 (26-76)	57 (26-75)	59 (29-76)	0.4
Male, n (%)	53 (65)	37 (71)	16 (55)	0.09
Lymphoma stage ≥ III, n (%)	78 (94)	49 (95)	27 (93)	0.77
International prognostic index ≥3, n (%)	42 (52)	25 (48)	17 (58)	0.3
Previous ASCT, n (%)	38 (47)	30 (58)	8 (28)	0.027
Bridging therapy, n (%)	50 (61)	28 (54)	22 (76)	0.08
CRP, day 0 (mg/l), median (range)	17.2 (2.9- 251.7)	11.65 (3-251.7)	32.3 (2.9- 191.7)	0.005
Ferritin, day 0 (mcg/l), median (range)	528 (72- 12980)	487 (72-12980)	648 (72- 6058)	0.17
CR rate, n (%)	42 (52)	34 (65)	8 (28)	0.0009

7559 **Poster Session**

Efficacy and safety of zanubrutinib versus rituximab-based chemo-immunotherapy in Waldenström macroglobulinemia (WM): Matching-adjusted indirect comparisons.

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Background: Given a lack of WM randomized trials directly comparing zanubrutinib with chemoimmunotherapy, this study aimed to indirectly compare zanubrutinib with bendamustine-rituximab (BR) and with dexamethasone-rituximab-cyclophosphamide (DRC) separately through matching-adjusted indirect comparisons (MAIC). **Methods:** MAIC were conducted to re-weight the individual data of 102 WM patients (83 relapsed/refractory [R/R] and 19 treatment-nave [TN]) treated with zanubrutinib in the ASPEN trial (NCT03053440) so that the weighted average baseline characteristics of patients treated with zanubrutinib matched those of 71 R/R patients treated with BR, and 72 TN patients treated with DRC separately. Matching variables for MAIC with BR included age, prior lines of therapy, IgM concentration, International Prognostic Scoring System for WM score, and extramedullary disease (EMD); and for MAIC with DRC included age, platelet count, hemoglobin concentration, and EMD. Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) of comparators were digitized to recreate patient-level data. Comparisons of survival and adverse event incidence between treatments were conducted using Cox proportional hazards models and modified Poisson models. **Results:** Compared to DRC, zanubrutinib was associated with longer PFS (hazard ratio [HR]: 0.39 [95% confidence interval 0.18-0.82] and 0.35 [0.14-0.86] pre- and post-matching, respectively) and longer OS (HR: 0.56 [0.20-1.53] and 0.47 [0.14-1.62] pre- and post-matching, respectively), and insignificantly higher incidences of neutropenia (risk ratio [RR]: 1.63 [0.71-3.77] and 1.47 [0.58-3.74] pre- and post-matching, respectively). Compared to BR, zanubrutinib was associated with longer PFS (HR: 0.32 [0.15-0.69] and 0.37 [0.15-0.91] pre- and post-matching, respectively), longer OS (HR: 0.31 [0.12, 0.80] and 0.29 [0.10-0.85] pre- and post-matching, respectively), lower incidences of neutropenia (RR: 0.45 [0.26-0.78] and 0.50 [0.27-0.91] pre- and post-matching, respectively) and lower incidences of pneumonia (RR: 0.18 [0.02-1.55] and 0.26 [0.03-2.28] pre- and post-matching, respectively). **Conclusions:** Zanubrutinib demonstrated longer PFS than DRC, and longer PFS and OS than BR in WM, before and after matching adjustment based on patient characteristics. Research Sponsor: BeiGene, Ltd.

		MAIC of zanubrutinib vs DRC		MAIC of zanubrutinib vs BR	
Outcomes	Zanubrutinib pre-matching (N = 102)	Zanubrutinib post-matching DRC (N = 53)	DRC (N = 72)	Zanubrutinib post-matching BR (N = 50)	BR (N = 71)
PFS, 12-month rate, %	94	92	85	94	79
PFS, 24-month rate, %	85	90	68	81	59
OS, 12-month rate, %	97	95	92	98	87
OS, 24-month rate, %	90	94	85	88	77
Anaemia, %	5.0	4.2	NR	3.6	NR
Hypertension, %	5.9	3.1	4.2	9.5	NR
Neutropenia, %	15.8	14.3	9.7	17.5	35.2
Pneumonia, %	1.0	0.6	NR	1.5	5.6
Thrombocytopenia, %	5.9	4.4	0.0	5.2	NR

NR, not reported.

7560 **Poster Session**

Immune priming with nivolumab followed by nivolumab and rituximab in first-line treatment of follicular lymphoma: The phase 2 1st FLOR study.

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Background: Standard of care immunochemotherapy in front-line (1L) follicular lymphoma (FL) is highly efficacious but not without significant toxicity. High rates of grade 3-5 adverse events (AEs), primarily infection and bone marrow suppression, are experienced in up to 75% of patients. A more tolerable but equally effective approach is required. PD-1 inhibition, in combination with rituximab (R), increases T cell anti-tumour effect & enhances NK cell antibody dependent cell cytotoxicity, with proven efficacy in relapsed FL. The concept of priming' the immune system with nivolumab (N) prior to tumour-directed therapy has rationale and evidence, but the safety of this approach in 1L FL is not described. **Methods:** 1st FLOR' (NCT03245021) is an open-label, multi-centre, phase 2, Simon's 2-stage study of N + R (N = 39). Key eligibility were stage III-IV grade 1-3A FL requiring 1L systemic therapy; ECOG ≤2; adequate organ function. All patients (pts) receive induction N 240mg IV 2-weekly for 4 cycles. Pts with complete response (CR) receive 4 further cycles of 240mg IV N monotherapy then 12 cycles of maintenance N 480mg IV 4-weekly. Pts with < CR had 240mg N plus 375mg/m^2 IV R 2-weekly for 4 cycles followed by maintenance N+R (N 480mg 4 weekly for 12 cycles; R 12 weekly for 8 cycles). Primary endpoint (EP) was ≥ G3 toxicity rate during induction. Secondary EPs; response rate by Lugano response criteria, overall toxicity, PFS, OS. **Results:** Between September 2017 to March 2020, 39 pts were enrolled. Baseline characteristics included median age of 54 (range: 28-79). stage IV disease in 67%, B Symptoms & bulk (≥7cm) in 23% each, intermediate-high risk FLIPI in 74%. The primary EP was met, with only 16 pts (41%) having ≥G3 toxicity at end of induction. Non-immune AEs were predominantly G1-2; most commonly infection (67%) & fatigue (64%). G3-4 Immune-related AEs were infrequent and included pancreatitis plus hepatitis (N = 1), pancreatitis alone (N = 1), rash (N = 1), transaminitis (N = 2), hypocortisolism (N = 1), hyperglycaemia (N = 3) and asymptomatic lipase/amylase increase (N = 3). Median follow-up was 17.5 months (range: 7-39). Overall response rate was 92% (36/39) with CR in 54% (21/39). Median time to CR was 5 months (m) (range: 2-25). Nine pts (23%) discontinued treatment; 7 due to progressive disease (1 pt died of transformed FL), 2 developed constitutional symptoms (1 stable disease, 1 partial response). In 25 evaluable pts, 12m PFS & OS is 72% (CI 51-88) & 96% (CI 80-100). Biomarker analysis is in progress. **Conclusions:** Immune-priming with single-agent N, then combination N+R in 1L FL is associated with favourable toxicity and high ORR & CR rates potentially providing an alternative to chemotherapy. Acknowledgements: Bristol-myers Squibb provided funding and nivolumab for this study. Clinical trial information: NCT03245021. Research Sponsor: Bristol-Myers Squibb.

7561 **Poster Session**

Treatment free remission (TFR) and overall response rate (ORR) results in patients with relapsed/refractory Waldenstrom's macroglobulinemia (WM) treated with CLR 131.

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Background: Phospholipid ethers (PLE) provide a novel mechanism to specifically target tumor cells leveraging high lipid raft content in their cell membranes. PLE/phospholipid drug conjugates are specifically designed to have high affinity to lipid rafts which upon binding results in trans-membrane flipping with the ability to deliver an attached warhead directly to the cytosol. CLR 131 (I-131-CLR1404) is a novel PLE molecule armed with I-131 resulting in targeted tumor cell radiotherapy which is being examined in relapsed or refractory WM through an open-label, Phase 2 trial, CLOVER-1 (NCT02952508). **Methods:** The primary objective of this study is to determine the efficacy and safety of CLR 131 in select B-cell malignancies. Eligibility criteria for WM pts include receipt of at least 2 prior treatment regimens unless ineligible to receive standard agents and have measurable disease: either IgM or extramedullary disease. CLR 131 is administered in up to 4 IV infusions (15-20 min) over 3 months. Adverse events (AEs) are graded by NCI-CTCAE v4.03; responses are assessed by the VIth WM Criteria for Response Assessment [Owen 2013]. **Results:** 6 pts with WM were enrolled in the study with data current as of 8 Jan 2021. The median age was 69 (range 54-81) with 4 females and 2 males who had a median of 2 prior regimens (range 1-5) and received a mean total body dose of 92.76 mCi CLR 131. 3 of 6 patients were MYD88 wild type (WT) of which 2 were dual WT (MYD88 WT & CXCR4 WT). The overall response rate (ORR) was 100% and the major response rate (MRR) was 83%, including 1 pt with a CR, 4 PR, and 1 MR. For those pts who were dual WT, the MRR was 100% and 1 pt who was MYD88 WT (CXCR4 is unknown) had a complete response. The median time to initial response was 48 days. Median duration of response (DOR) and treatment free remission (TFR) have not been reached; ongoing mean DOR is 335 days and mean TFR is 384 days. 100% of MYD88 WT patients have exceeded 6.5 months of follow up with average TFR of 18.1 months. The primary treatment emergent AEs in pts with WM included fatigue and cytopenias, in line with prior experience with CLR 131 in other B-cell malignancies. The most commonly observed cytopenias included Grade 3 or 4 thrombocytopenia (100%), neutropenia (83%), anaemia (66%) and decreased white blood cell count (33%). Of note, no cases of bleeding or febrile neutropenia were observed. **Conclusions:** Initial results for CLR 131 show efficacy across multiple WM patient genotypes including dual WT patients with durable DOR and TFR after 2 to 4 infusions. CLR 131 represents a novel and promising approach to the treatment of MYD88 WT patients who have a historical median time to progression of 1.3 years. These encouraging data led to the pivotal global CLOVER-WaM trial (N=50) in WM patients who have failed or had a suboptimal response to a Bruton Tyrosine Kinase inhibitor. CLOVER-WaM is currently enrolling. Clinical trial information: NCT02952508. Research Sponsor: Cellectar Biosciences.

7563 **Poster Session**

A novel index using inflammatory markers improves the diagnosis of hemophagocytic lymphohistiocytosis in patients with hematologic malignancies.

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Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening inflammatory syndrome that may accompany hematologic malignancies (HM). The diagnosis of HLH in patients with HM (HM-HLH) is confounded by a number of factors: the most commonly used HLH-2004 diagnostic criteria are derived from studies in infants while the Hscore used in adults is not specific for HMs; moreover, most parameters in these scoring systems may reflect features of the underlying HM rather than HLH associated inflammation; and finally specific diagnostic cutoff values for laboratory abnormalities in HM-HLH have not been defined. We therefore conducted a study to optimize the HLH-2004 laboratory thresholds for the diagnosis of HM-HLH. **Methods:** A multi-center retrospective study in adult patients with HM in whom testing for HLH was performed. HM-HLH was defined as fulfillment of 5/8 HLH-2004 diagnostic criteria. We established the optimal diagnostic cutoff levels for HLH-2004 laboratory parameters using receiver operating curves (ROC) and combined the best performing parameters into a combined index, using binary logistic regression. We then created a clinical decision tree using a Classification and Regression Tree (CART) analysis with all available parameters, using cross validation. We also determined the prognostic value of our combined diagnostic tool. **Results:** 225 adults were analyzed (112 with HM-HLH per HLH-2004 and 113 with HM only). 35% of patients were evaluated for HLH routinely upon HM diagnosis. Soluble CD25 (sCD25) and ferritin best discriminated HM-HLH from HM, with an area under the curve (AUC) of 0.83 for each. ROC analysis demonstrated an optimal cutoff of $>$ 4190 U/mL for sCD25 (sensitivity/specificity 91%/69%) and an optimal cutoff of $>$ 2636 ng/ml for ferritin (sensitivity/specificity 64%/86%) for HM-HLH. We term the combination of elevated sCD25 and ferritin using optimized cutoff levels the optimized HLH inflammatory' (OHI) index. This OHI index was highly specific for the diagnosis of HM-HLH (specificity of 92%, sensitivity 79%). CART analysis demonstrated that OHI index positivity was sufficient to diagnose HM-HLH. In patients without a positive OHI index an Hscore $>$ 168 and either splenomegaly or triglycerides $>$ 279 ng/dL can still diagnose HM-HLH. By following this decision pathway, approximately 92% of patients were accurately classified based on HLH-2004. Furthermore, the OHI was better (odds ratio (OR) 7.9; 95% confidence interval (CI) 4.2-14.6) than Hscore $>$169 (OR 5.5; CI 3.9-9.6) and $>$ 5/8 HLH-2004 (OR 5.3; CI 3-9.3) at predicting mortality at 1 year. **Conclusions:** The OHI index derived here is a simple tool that can accurately diagnose HLH and predict mortality in patients with hematologic malignancies. Some patients may not need full HLH workup before intervening with therapy that is HLH directed and not only malignancy directed. Research Sponsor: None.

7564 **Poster Session**

Post-transplant lymphoproliferative disorder in kidney transplant patients: A multicenter report.

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Background: Post-Transplant Lymphoproliferative Disorder (PTLD) is a complication of transplantation that often arises due to reactivation of the Epstein-Bar Virus (EBV). Given the rarity of this disease, a full understanding of its presentation and optimal therapies has yet to be determined. **Methods:** A multicenter retrospective analysis was performed utilizing data from kidney transplant patients (pts) who developed PTLD at the Hospital of the University of Pennsylvania and the Cleveland Clinic. The association between categorical variables and clinical response were assessed via Fisher's exact testing. **Results:** 117 pts had diagnoses of PTLD after kidney transplantation. The median age at PTLD diagnosis was 52 yrs (range 17-89 yrs), and the median time from transplantation to diagnosis was 3.6 yrs (range: 7 days-36 yrs). Pt characteristics included: 84% Caucasian, 57% male, and 11% combined kidney and pancreas transplant patients. 68% pts had received unrelated donor transplants; 41% had prior rejection episodes. PTLD histology was 72% monomorphic and 28% polymorphic. Polymorphic PTLD was more likely to be EBV+ than monomorphic PTLD (81% vs. 54%, $p = 0.05$). At diagnosis, immunosuppression included: steroids (95%), mycophenolate (44%), azathioprine (40%), sirolimus (30%), cyclosporine (46%), and/or tacrolimus (45%). Common PTLD symptoms included fever (34%), pain (38%), weight loss (30%), fatigue (30%), and/or mass (26%). The most common sites of involvement were lymph nodes (64%), kidney allograft (22%), and/or GI tract (17%). At diagnosis, 61% of patients' tumors were EBV+ and 59% of patients had elevated serum LDH. Overall, the majority of pts responded to first-line PTLD therapy, with 61% CR and 14% PR. Reduction of immunosuppression (RI) alone (36% of pts) led to 48% CR and 12% PR; RI with rituximab (16%) led to 47% CR and 7% PR; and RI with chemotherapy (14%) resulted in 58% CR and 42% PR. Patients treated with RI as well as resection ($n = 18$) of their limited stage disease had better outcomes ($p = 0.05$). Overall survival for all patients was 10.7 years (95%CI: 5.2-13 years). PTLD patients < 40 yrs were more likely to achieve CR after first line therapy ($p < 0.001$), have allograft involvement ($p = 0.003$), and have a polymorphic histology ($p = 0.002$). Allograft involvement tended to occur sooner after transplant ($p = 0.001$) and was more likely to present with allograft failure ($p = 0.007$). PTLD with allograft involvement had better response to first therapy than regular PTLD ($p = 0.007$) and often responded well to complete resection and RI. **Conclusions:** Pts with PTLD may achieve a CR through different initial therapies. Younger patients and those able to undergo complete resection of disease and RI had better prognoses. Allograft involvement by PTLD carries a good prognosis and should be identified and treated differently from other presentations. Research Sponsor: None.

7565 **Poster Session**

Phased variants improve DLBCL minimal residual disease detection at the end of therapy.

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Background: Detection of circulating tumor DNA (ctDNA) has prognostic value in diverse tumors, including DLBCL. Despite uses for assessing molecular response to therapy, current methods using immunoglobulin or hybrid-capture sequencing have suboptimal sensitivity, particularly when disease-burden is low. This contributes to a high false negative rate at key milestones such as at the end of therapy (EOT; Kumar A, *ASH* 2020). We explored the utility of detecting multiple mutations (phased variants, PVs) on individual cell-free DNA (cfDNA) strands to improve MRD in DLBCL. **Methods:** We applied Phased Variant Enrichment and Detection Sequencing to track PVs from 485 specimens from 117 DLBCL patients undergoing first-line therapy. We sequenced cfDNA prior to, during, and after therapy to assess the prognostic value of MRD. We compared the performance of PhasED-Seq to current techniques, including SNV-based CAPP-Seq and duplex sequencing. **Results:** To establish its detection limit for ctDNA, we compared the background error-profile of of PVs and SNVs in cfDNA sequencing from healthy subjects. PV-detection by PhasED-Seq demonstrated a lower background profile than SNVs, even when considering duplex molecules (n = 12; 8.0e-7 vs 3.3e-5 and 1.2e-5; $P < 0.0001$). We also assessed analytical sensitivity within a ctDNA limiting dilution series from 3 patients, simulating tumor fractions from 0.1% to 0.00005% (1:2,000,000). PhasED-Seq outperformed SNV-based methods and duplex sequencing for recovery of expected tumor content below 0.01% ($P < 0.0001$ and $P = 0.005$ respectively by paired t-test). We then explored disease detection in clinical samples. We identified SNVs and PVs from pretreatment tumor or plasma and followed these variants in serial cfDNA. Using SNV-based methods, 40% and 59% of patients had undetectable ctDNA after 1 or 2 cycles (n = 82 and 88). However, 24% and 25% of these cases had detectable ctDNA by PhasED-Seq. Importantly, MRD detection by PhasED-Seq was prognostic for event-free survival even in patients with undetectable ctDNA by SNVs. We next explored the utility of PhasED-Seq at the EOT in 19 subjects, 5 of whom experienced eventual disease progression. While only 2/5 cases with progression had detectable disease at EOT using SNVs, PhasED-Seq detected all 5/5 cases. PhasED-Seq also correctly identified all patients (14/14) without clinical relapse as having no residual disease, including one patient who discontinued therapy after 1 cycle due to toxicity, but remains in remission > 5 years after this single treatment. This resulted in superior classification of patients for EFS using PVs compared with SNVs (C-statistic: 0.98 vs 0.60, $P = 0.02$). **Conclusions:** Tracking PVs results in significantly lower background rates than SNV-based approaches, enabling detection to parts per million range. PhasED-Seq improves on disease detection in DLBCL at the EOT, allowing possible MRD-driven consolidative approaches. Research Sponsor: U.S. National Institutes of Health, Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation.

7566 **Poster Session**

IL-1 receptor antagonist for prevention of severe immune effector cell-associated neurotoxicity syndrome.

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Background: Progress in chimeric antigen receptor (CAR) T-cell therapy has included reduction in life-threatening toxicity. Rates of severe cytokine release syndrome (CRS) have declined from 50% in early trials to 7% in the most recent real-world experience. However, rates of severe immune effector cell-associated neurotoxicity (ICANS) associated with axicabtagene ciloleucel (Axicel) remain unchanged. IL-1 is a major driver of ICANS pathophysiology that is produced upstream of IL-6. The IL-1 receptor antagonist, Anakinra, can prevent neurotoxicity in animal models when given at fever onset. We present our early experience of the first 13 participants enrolled into a phase II trial evaluating Anakinra to prevent severe ICANS (NCT4205838). **Methods:** This investigator-sponsored trial included adults eligible for standard-of-care Axicel for large B-cell lymphoma after ≥2 lines of intensive chemoimmunotherapy. Participants received Anakinra 100 mg SQ q6h x 12-36 doses until ICANS returned to grade ≤1. The trigger to initiate Anakinra was any grade ICANS or grade ≥3 CRS in the absence of ICANS. A protocol modification, made after the first 3 participants were treated, changed the trigger for Anakinra to grade ≥2 CRS. In addition to Anakinra, all participants received standard-of-care interventions for CRS and ICANS. The primary objective is to estimate the efficacy of Anakinra in preventing severe ICANS (grade ≥3) according to ASTCT 2018 consensus grading. **Results:** To date, 13 participants have been enrolled, and 7 met criteria to initiate Anakinra and received the first dose prior to severe ICANS. Median age was 56 years (range, 23-84 years). Of the 7 participants whom received Anakinra prior to severe ICANS, only 1 of 7 (14%) developed grade 3 ICANS. The most common adverse event was injection site reaction, which peaked at grade 2. There were no unexpected toxicities. Once the protocol was amended to initiate Anakinra for grade ≥2 CRS (N = 4), no participant developed severe ICANS, and only one participant met the institutional standard to receive corticosteroids (Table). **Conclusions:** Anakinra is feasible to initiate in the non-prophylactic setting in patients at increased risk for severe ICANS. These early results demonstrate potential to reduce severe ICANS associated with Axicel to a rate similar to other CAR T-cell products, and to reduce corticosteroid use. Further enrollment to the pre-planned sample size of N=36 is required to demonstrate statistical efficacy. Serum IL-1 analysis is also ongoing. Clinical trial information: NCT4205838. Research Sponsor: John Timmerman, MD study investigator-sponsor.

Maximum ICANS and CRS grades in participants who received Anakinra prior severe ICANS.

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7
Age	23	84	81	56	58	32	47
Max CRS grade	3	2	2	2	2	2	2
Max ICANS grade	3	1	2	0	0	0	2
Anakinra trigger	CRS gr 3	ICANS gr 1	ICANS gr 2	CRS gr 2	CRS gr 2	CRS gr 2	CRS gr 2
Duration of ICANS ≥ gr 3	10 hrs	-	-	-	-	-	-
Dexamethasone 10 mg-equivalent doses	10	15	6	0	0	0	3

TPS7567 **Poster Session**

Randomized, phase III study of early intervention with venetoclax and obinutuzumab versus delayed therapy with venetoclax and obinutuzumab in newly diagnosed asymptomatic high-risk patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): EVOLVE CLL/SLL study (SWOG S1925, NCT#04269902).

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Background: Currently, asymptomatic patients with CLL/SLL are observed without treatment until development of symptoms or cytopenias. Historically, early intervention studies with chemoimmunotherapy have not resulted in an overall survival (OS) benefit and have resulted in toxicity. The introduction of targeted therapies, such as venetoclax and obinutuzumab (VO), have provided tolerable/efficacious options for CLL patients. In the CLL14 study, *symptomatic* CLL patients receiving frontline therapy with VO had longer progression-free survival (PFS) and deeper remissions [more minimal residual disease-undetectable (MRDu)] compared with those receiving chlorambucil and obinutuzumab (Fischer 2019). The CLL-International Prognostic Index (CLL-IPI; Table) is a validated prognostic model to predict which patients are highest risk for a shorter time to first therapy and shorter OS. We aim to use VO as early intervention in *asymptomatic*, high-risk patients with CLL to potentially lengthen OS and thus alter the natural history of the disease. **Methods:** On 12/14/20, we activated the S1925 study for adult patients with CLL or SLL, who were diagnosed within 12 months of enrollment. Eligible patients have a CLL-IPI score ≥ 4 (Table) or complex cytogenetics ($\geq$3 cytogenetic abnormalities) and do not meet any criteria for initiation of treatment by the International Working Group for CLL (IWCLL; Hallek 2018) guidelines. Enrolled patients are randomized in a 2:1 manner to early versus delayed (at the time IWCLL indication for treatment is met) therapy with VO. VO is administered for a fixed duration of 12 months as previously described (Fischer 2019). The primary endpoint is OS. We hypothesize that early intervention with VO will improve the rate of 6-year OS from 60% to 80%. This design requires 222 eligible patients for 88% power (2-sided α=0.05) for the primary comparison. To allow for 10% ineligibility, we will enroll 247 patients. Estimated accrual time is 4 years. Secondary endpoints include: rates of response, PFS, and relapse-free survival; safety; time to 2nd CLL-directed therapy; and quality of life (FACT-Leukemia total score). The primary translational objective is to evaluate the prognostic association between OS and peripheral blood MRD status at 15 months after treatment initiation by flow cytometry. Additional exploratory objectives include the association of other clinical outcomes, baseline prognostic factors, and IWCLL-defined response with MRD status at multiple timepoints. Currently, enrollment is open. Clinical trial information: NCT04269902. Research Sponsor: U.S. National Institutes of Health.

Calculation of CLL-IPI Score.

Characteristic	Points
Del(17p) or *TP53* mutation	4
β-2-microglobulin $\geq$ 3.5mg/L	2
Unmutated IGHV status	2
Rai Stage 1-4	1
Age > 65 years	1

TPS7568 **Poster Session**

A phase 3 study to evaluate the efficacy and safety of tafasitamab plus lenalidomide and rituximab versus placebo plus lenalidomide and rituximab in patients with relapsed/refractory (R/R) follicular lymphoma (FL) or marginal zone lymphoma (MZL).

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Background: Most patients with the indolent non-Hodgkin lymphoma (NHL) subtypes FL or MZL respond to first-line treatment but relapse is common, and there is no single standard treatment for patients with R/R FL or MZL. Tafasitamab is an Fc-engineered humanized monoclonal antibody (mAb) against CD19 which is broadly expressed in FL and MZL, and regulates B-cell proliferation via B-cell receptor signaling. In preclinical studies, tafasitamab has shown activity against NHL cell lines in combination with rituximab (anti-CD20 mAb) and lenalidomide (LEN). Tafasitamab monotherapy has shown promising clinical activity in a phase 2a study in patients with R/R NHL (NCT01685008), with an ORR of 29% (n/N = 10/34) in patients with FL and 33% (n/N = 3/9) in patients with MZL. In an ongoing phase 2, single-arm study (L-MIND, NCT02399085), tafasitamab plus LEN followed by tafasitamab alone demonstrated an ORR of 57.5% (n/N = 46/80) in patients with R/R diffuse large B-cell lymphoma (FDA approved indication). These preclinical and clinical observations from phase 2 trials suggest a potential clinical benefit of tafasitamab plus LEN and rituximab for patients with R/R FL or MZL. **Methods:** This phase 3 double-blind, placebo-controlled, randomized study is designed to investigate whether tafasitamab plus LEN and rituximab provides improved clinical benefit compared with LEN and rituximab in patients with R/R FL or R/R MZL. Patients will be randomized 1:1 to receive tafasitamab (12 mg/kg IV on days 1, 8, 15, and 22 of a 28-day cycle [cycles 1–3], then days 1 and 15 [cycles 4–12]) plus LEN (20 mg PO QD, days 1–21/ cycle for 12 cycles) and rituximab (375 mg/m^2 IV on days 1, 8, 15, and 22 of cycle 1, then day 1 of cycles 2–5), or placebo (0.9% saline solution IV) plus LEN and rituximab. The primary study endpoint is PFS (investigator assessed [INV] by Lugano 2014 criteria) for patients with FL. Key secondary endpoints are PFS (INV) in overall population (FL and MZL), PET-CR rate (INV) at end of treatment (4–8 weeks after last treatment) and OS in patients with FL. Inclusion criteria include age $\geq$18 y, histologically confirmed FL (grade 1, 2, or 3a) or MZL (nodal, splenic, or extranodal), documented R/R disease, $\geq$1 prior systemic anti-CD20 therapy (including anti-CD20 refractory disease), ECOG PS $\leq$2, adequate systemic organ function, and high tumor burden (per GELF criteria). Exclusion criteria include prior rituximab plus LEN treatment, history of radiotherapy for other diseases ($\geq$25% of bone marrow), nonhematologic malignancy, congestive heart failure (LVEF $<$ 50%), active systemic infection, known CNS lymphoma, or severe immunocompromised state. inMIND (NCT04680052, EudraCT2020-004407-13) is currently enrolling patients; planned enrollment is 528 patients with R/R FL and 60–90 patients with R/R MZL. Clinical trial information: NCT04680052. Research Sponsor: Incyte Corporation.

TPS7569 **Poster Session**

Phase 3 trial (GCT3013-05) of epcoritamab versus standard of care in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

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Background: Patients (pts) with DLBCL who are refractory to/or have relapsed (R/R) after treatment with chemotherapy and anti-CD20 monoclonal antibody (mAb) have a poor prognosis. There is a need for new treatment options to improve outcomes. Epcoritamab, a novel subcutaneous (SC) bispecific antibody, binds to CD3 on T-lymphocytes and CD20 on B-cell non-Hodgkin lymphoma (NHL) cells to induce potent and selective killing of malignant CD20+ B-cells. In an ongoing phase 1/2 dose-escalation trial in heavily pretreated pts with B-cell NHL (N = 68), epcoritamab demonstrated a tolerable safety profile and substantial single-agent anti-tumor activity, with a complete response (CR) rate of 55% and an overall response rate (ORR) of 91% in pts with R/R DLBCL (at ≥48 mg doses; n = 12) (NCT04663347; Hutchings, ASH, 2020). Furthermore, all 4 evaluable R/R DLBCL pts previously treated with chimeric antigen receptor T-cell (CAR-T) therapy achieved an objective response with 2 achieving CR. These encouraging data support the potential for epcoritamab to improve clinical outcomes in pts with R/R DLBCL. Here we describe the phase 3 trial of epcoritamab versus standard of care (SOC) treatments in pts with R/R DLBCL (NCT04628494). **Methods:** GCT3013-05 is a randomized, open-label, worldwide, multicenter, phase 3 study designed to evaluate the efficacy of epcoritamab versus investigator's choice of SOC with R-GemOx (rituximab, gemcitabine, oxaliplatin) or BR (bendamustine, rituximab) in adults with R/R disease of one the following CD20+ B-cell NHL histologies: I) DLBCL, not otherwise specified including de novo DLBCL or DLBCL histologically transformed from follicular lymphoma; II) double-hit or triple-hit DLBCL (high-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 translocations); or III) follicular lymphoma grade 3B. Other key eligibility criteria include: ≥1 line of prior chemotherapy that included treatment with an anti-CD20 mAb, Eastern Cooperative Oncology Group performance status 0–2, and prior failure of/ineligibility for autologous stem cell transplantation. Prior CAR-T therapy is allowed. A total of 480 pts will be randomized 1:1 to receive either SC epcoritamab at the recommended phase 2 dose (28-day cycles; weekly, biweekly, or monthly schedule depending on cycle number) until disease progression or unacceptable toxicity; or up to 4 cycles of biweekly treatment with intravenous (IV) R-GemOx (8 doses); or up to 6 cycles of IV BR (6 doses; dosing every 3 weeks). The primary endpoint is overall survival. Key secondary endpoints include progression-free survival, ORR, duration of response, time to response, and safety. The study is currently enrolling in Australia, Belgium, Denmark, France, Spain, and will open for enrollment in additional countries. Clinical trial information: NCT04628494. Research Sponsor: This study was funded by Genmab A/S and AbbVie Inc.

TPS7570 **Poster Session**

A phase 1 dose escalation and cohort expansion study of the safety and efficacy of allogeneic CRISPR-Cas9–engineered T cells (CTX110) in patients (Pts) with relapsed or refractory (R/R) B-cell malignancies (CARBON).

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Background: Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL), and although $>$ 50% of pts achieve long-term remission with first-line therapy, pts with R/R disease as well as those with R/R grade 3b follicular lymphoma (FL), double-, or triple-hit high-grade lymphomas have poor long-term outcomes (Crump 2017; Kahl 2016; Jain 2012). Autologous (auto) chimeric antigen receptor (CAR) T cell therapy has provided additional options for pts with R/R disease, but only when leukapheresis and manufacturing prove feasible (Jacobson 2020). Allogeneic (allo) CAR-T cells were designed specifically to address these unmet needs by using healthy donor T cells to produce a readily available product and remove the need for bridging chemotherapy. We are currently investigating the safety and efficacy of CTX110, an allo anti-CD19 CAR-T cell product modified by using CRISPR/Cas9-editing to disrupt the endogenous T-cell receptor (TCR) alpha constant (TRAC) locus in order to remove TCR expression and disrupt β_2-microglobulin, which eliminates major histocompatibility complex (MHC) class I expression. Disruption of the TCR should significantly reduce or eliminate risks of graft-versus-host disease and elimination of MHC class I expression may increase CAR-T cell persistence by mitigating CTX110 rejection. In addition, the anti-CD19 CAR transgene construct is precisely inserted into the TRAC locus. **Methods:** The Phase 1 CARBON trial (NCT04035434) is an open-label, multicenter, global study evaluating the safety and efficacy of CTX110 in pts $\geq$18 y with R/R DLBCL NOS, double- or triple-hit DLBCL, or transformed or grade 3b FL with $\geq$2 prior lines of therapy or who are ineligible for/refused prior auto hematopoietic stem cell transplant (HSCT). Pts who received prior auto CAR-T or allo HSCT are excluded. Pts will receive lymphodepleting chemotherapy with fludarabine 30mg/m^2 and cyclophosphamide 500mg/m^2 for 3 days, followed by CTX110 infusion. In part A, dose escalation will be performed using a 3+3 design. Upon completion of dose finding, the cohort will be expanded to further assess safety signals and efficacy including the primary efficacy endpoint of overall response rate. Key secondary efficacy endpoints include duration of response, progression-free survival, and overall survival. The trial is currently open and enrolling. Clinical trial information: NCT04035434. Research Sponsor: CRISPR Therapeutics.

TPS7571 **Poster Session**

Brentuximab vedotin in combination with lenalidomide and rituximab in subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) (Trials in Progress).

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Background: The majority of patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who relapse after HSCT, or who are not candidates for HSCT have poor outcomes and are in need of novel therapies. Brentuximab vedotin (BV) is a CD30-directed ADC and preclinical data provide a strong rationale for combining BV, lenalidomide, and rituximab in the treatment of R/R DLBCL. In addition, in a phase 1 trial in which 37 pts with R/R DLBCL were treated with BV + lenalidomide, the ORR was 56.7% (73.3% in CD30+ pts; manuscript in preparation). The median duration of remission was 13.2 months in pts with a CR or PR and 11.7 months in pts with CR, PR, or stable disease $>$ 6 months. The PFS and median OS were 11.2 months and 14.3 months, respectively and results were similar in the CD30+ and CD30 $<$ 1% groups. The clinical activity and manageable safety profiles of BV, lenalidomide, and rituximab as single agents, make the combination a viable option in multiply relapsed and heavily pretreated pts. **Methods:** This is a randomized, double-blind, placebo-controlled, active-comparator, multicenter phase 3 study designed to evaluate the efficacy of BV vs placebo, in combination with lenalidomide + rituximab, in subjects with R/R DLBCL (NCT04404283). Prior to randomization, there will be a safety and PK run-in period where 6 pts will receive BV, lenalidomide + rituximab, and safety and PK will be evaluated after the first cycle of treatment; 6/6 subjects have been enrolled. Key eligibility criteria include: pts aged $\geq$18 with R/R DLBCL with an eligible subtype; $\geq$2 prior lines of therapy and must be ineligible for, or have declined, stem cell transplant, and chimeric antigen receptor T-cell (CAR-T) therapy; ECOG 0 to 2; fluorodeoxyglucose-avid disease by PET and bidimensional measurable disease of at least 1.5 cm by CT. Patients (n = 400) will be randomized 1:1 to receive either BV or placebo in combination with lenalidomide + rituximab and will be stratified by CD30 expression (positive [$\geq$1%] versus $<$ 1%), prior allogeneic or autologous stem cell transplant therapy (received or not), prior CAR-T therapy (received or not), and cell of origin (GCB or non-GCB). The primary endpoints are PFS per BICR in the ITT and CD30+ populations. Key secondary endpoints are OS in the ITT and CD30+ populations, and ORR per BICR. Other secondary endpoints include CR rate, duration of response, and safety and tolerability of the combination. Disease response will be assessed by BICR and the investigator according to the Lugano Classification Revised Staging System. Radiographic disease evaluations, including contrast-enhanced CT scans and PET, will be assessed at baseline, then every 6 weeks from randomization until Week 48, then every 12 weeks. PET is not required after CR is achieved. The trial is currently enrolling and will be open in 16 countries. Clinical trial information: NCT04404283. Research Sponsor: Seagen Inc.

TPS7572 **Poster Session**

ESCALADE: A phase 3 study of acalabrutinib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for patients ≤65y with untreated non-germinal center B-cell–like (non-GCB) diffuse large B-cell lymphoma (DLBCL).

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Background: R-CHOP remains the standard of care for DLBCL. Although most patients (pts) can be cured, 3540% will experience relapsed/refractory disease, leading to poor outcomes in the majority of pts. Covalent irreversible Bruton tyrosine kinase inhibitors (BTKi) have shown higher responses in pts with non-GCB DLBCL than with GCB DLBCL. In untreated non-GCB DLBCL pts, the phase 3 PHOENIX study (Younes et al. *J Clin Oncol*. 2019;37:1285-95) showed that addition of the BTKi ibrutinib to R-CHOP (R-CHOP-I) did not improve outcomes in the intent-to-treat population. However, pts age < 60y treated with R-CHOP-I had significantly improved progression-free survival (PFS) and overall survival (OS) compared with those receiving R-CHOP alone. Acalabrutinib (A) is a second-generation BTKi with enhanced kinase selectivity and potential for better efficacy and tolerability than first-generation BTKis. There is a strong rationale for combining A with R-CHOP in pts with untreated DLBCL, and safety of A + R-CHOP has been shown in a phase 1b/2 study (Davies et al. ASH 2020). The aim of this study is to determine if the addition of A to R-CHOP leads to improved PFS in pts age ≤65y with untreated non-GCB DLBCL. **Methods:** ESCALADE (ACE-LY-312; NCT04529772) is a phase 3, randomized, global, double-blind study of A vs placebo in combination with R-CHOP for treatment of newly diagnosed non-GCB DLBCL. The study is recruiting adults ≥18y and ≤65y with previously untreated DLBCL stage IIIV disease with a Revised International Prognostic Index (R-IPI) score of 25. Prior to randomization, all pts will receive an initial R-CHOP cycle (cycle 1) as standard-of-care treatment to prevent delays in therapy initiation. Based on central Gene Expression Profile (GEP) testing performed after enrollment, pts with non-GCB DLBCL (activated B-cell like or unclassified) will be randomized into 2 arms to receive A 100 mg twice daily plus R-CHOP or placebo plus R-CHOP from cycle 2 to cycle 6 followed by 2 additional cycles of rituximab + A or placebo (cycles 7 and 8). All pts will receive primary prophylaxis with granulocyte colony-stimulating factors accompanying all R-CHOP cycles. The study aims to randomize 600 pts (~300 per arm). The primary objective is to evaluate whether the addition of A to R-CHOP will prolong PFS. Secondary endpoints include event-free survival, complete response rate, OS, pharmacokinetics, and safety. Key exclusion criteria are central nervous system involvement, primary mediastinal lymphoma, high-grade B-cell lymphoma, diagnosis or treatment of malignancy other than DLBCL, and history of indolent lymphoma. Approximately 250 sites globally will enroll pts. Enrollment began in Q3 of 2020. Clinical trial information: NCT04529772. Research Sponsor: Acerta Pharma, a member of the AstraZeneca Group.

TPS7573 **Poster Session**

Coastal: A phase 3 study of the PI3Kδ inhibitor zandelisib with rituximab (R) versus immunochemotherapy in patients with relapsed indolent non-Hodgkin's lymphoma (iNHL).

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Background: Patients (pts) with iNHL treated with front-line immunochemotherapy may benefit from an alternative, chemotherapy-free regimen at relapse. Zandelisib, a potent, selective, and structurally differentiated oral PI3Kδ inhibitor, achieved an 87% response rate, with median duration of response not reached in iNHL when given as a monotherapy or in combination with R. A low rate ($<$ 10%) of Grade $\geq$ 3 immune-mediated adverse events of special interest associated with PI3kδ inhibitors is observed in patients administered zandelisib on an intermittent schedule (IS) (JCO 2020 38:15_suppl, 8016). An open-label, phase 2 study (TIDAL, NCT03768505) of zandelisib as monotherapy is ongoing in pts with relapsed/refractory follicular lymphoma (FL) and marginal zone lymphoma (MZL). **Methods:** The COASTAL study is a randomized, open-label, controlled multicenter phase 3 trial to investigate the safety and efficacy of zandelisib in combination with R versus standard immunochemotherapy in pts with iNHL. Key eligibility criteria: adults with relapsed or refractory FL or MZL who received $\geq$1 prior lines of therapy which must have included an anti-CD20 antibody in combination with chemotherapy or lenalidomide (L); at least one bi-dimensionally measured lesion $>$ 1.5 cm; adequate bone marrow, renal and hepatic function; ECOG performance status score of 0 to 1. Key exclusion criteria: histologically confirmed diagnosis of FL grade 3b or transformed disease; administration of 2 prior immunochemotherapy regimens; prior PI3K inhibitor therapy; known lymphomatous involvement of the central nervous system. Subjects will be randomized 1:1 to receive R-zandelisib or immunochemotherapy (R-CHOP or R-B) and stratified by type and number of prior treatment regimens, histology, and duration of treatment-free interval after last therapy. Zandelisib will be given in a 28-day cycle comprising of daily dosing for 2 cycles followed by IS dosing on days 1-7 of each 28-day subsequent cycle for a duration of 2 years. Rituximab or immunochemotherapy will be given for a total of 6 cycles. Disease response will be assessed by an Independent Response Review Committee according to the modified Lugano Classification. Radiographic tumor assessment will be performed approximately every 12 weeks for the first 9 months, every 16 weeks for the next 12 months, and every 24 weeks thereafter. The primary efficacy endpoint is progression-free survival. The major secondary endpoints include ORR, complete response rate, overall survival, and safety. The trial will enroll approximately 534 pts in ~200 sites globally and will begin enrollment in mid-2021. Clinical trial information: NCT04745832. Research Sponsor: MEI Pharma, Inc.

TPS7574 **Poster Session**

Phase 3 randomized study of loncastuximab tesirine plus rituximab versus immunochemotherapy in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): LOTIS-5.

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Background: Patients (pts) with DLBCL for whom frontline therapy is unsuccessful and who are ineligible for autologous stem cell transplantation have poor outcomes with salvage therapy. Single-agent loncastuximab tesirine (Lonca), an antibody-drug conjugate comprising a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine dimer (PBD) toxin, showed antitumor activity and manageable toxicity in pts with R/R B-cell non-Hodgkin lymphoma in a Phase 1 trial (Hamadani et al. *Blood* 2020; blood.2020007512) and in pts with R/R DLBCL in a Phase 2 trial (Caimi et al. *Blood* 2020; 136(Suppl 1):35–37). Rituximab (R) is part of standard immunochemotherapy for DLBCL, both as frontline therapy and in subsequent treatments. LOTIS-5 aims to evaluate Lonca + R (Lonca-R) versus (vs) standard immunochemotherapy of R + gemcitabine + oxaliplatin (R-GemOx) in pts with R/R DLBCL. **Methods:** This is a Phase 3 randomized, open-label, 2-part, 2-arm, multicenter study (NCT04384484). A non-randomized safety run-in (Part 1) will compare the safety of Lonca-R with previous safety data for Lonca after the first 20 pts have completed Cycle 1. Part 2 will be started if no significant increase in toxicity occurs; ~330 pts will be randomized 1:1 to receive Lonca-R or R-GemOx. The primary objective of the study is to evaluate the efficacy of Lonca-R vs R-GemOx. The primary endpoint is progression-free survival by independent review. Secondary endpoints include overall survival; objective response rate; complete response rate; duration of response; frequency and severity of adverse events; changes from baseline in safety laboratory and clinical variables; concentration and pharmacokinetic parameters of Lonca (conjugated and total antibody, and unconjugated warhead); immunogenicity; and changes in patient-reported outcomes. Time-to-event endpoints will be assessed for the intent-to-treat population using a stratified log-rank test. The dosing regimen of Lonca-R in both parts of the study will be 150 μg/kg Lonca + 375 mg/m^2 R every 3 weeks (Q3W) for 2 cycles and then 75 μg/kg Lonca + 375 mg/m^2 R for 6 cycles. The dose regimen of R-GemOx in Part 2 will be 375 mg/m^2 R, 1000 mg/m^2 Gem, and 100 mg/m^2 Ox Q2W for 8 cycles. Key inclusion criteria include age ≥18 years; pathologic diagnosis of DLBCL (including pts 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; not a candidate for stem cell transplantation; and measurable disease per 2014 Lugano Classification. The study opened in September 2020 and enrollment is ongoing. The trial design was presented at 62nd American Society of Hematology Annual Meeting and Exposition, December 5–8, 2020. Research Funding: ADC Therapeutics SA. Clinical trial information: NCT04384484. Research Sponsor: ADC Therapeutics SA.

TPS7575 **Poster Session**

A phase III trial evaluating glofitamab in combination with gemcitabine plus oxaliplatin versus rituximab in combination with gemcitabine and oxaliplatin in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL).

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Background: Prognosis is poor for patients with R/R DLBCL, particularly those who are ineligible for autologous stem cell transplant (ASCT) or who relapse after second-line therapy (Gisselbrecht C, et al. Br J Haematol 2018). While chimeric antigen receptor therapies have shown favorable response rates in R/R DLBCL, convenient off-the-shelf options are needed, especially for patients with rapidly progressing disease (Sermer D, et al. Blood Adv 2020). Glofitamab is a full-length, humanized, immunoglobulin G1 bispecific antibody with two regions that bind to CD20 (B cells) and one region that binds to CD3 (T cells). In an ongoing Phase I study in patients with R/R non-Hodgkin lymphoma, glofitamab monotherapy has induced high response rates with a manageable safety profile (NCT03075696; Hutchings M, et al. ASH 2020). Rituximab in combination with gemcitabine and oxaliplatin (R-GemOx) is widely used for patients with R/R DLBCL who are not eligible for ASCT (Mounier N, et al. Haematologica 2013). **Methods:** GO41944 (NCT04408638) is a Phase III, open-label, randomized trial designed to evaluate the safety and efficacy of glofitamab plus gemcitabine and oxaliplatin (glofit-GemOx) vs R-GemOx in patients with R/R DLBCL. Eligible patients must be aged $\geq$ 18 years, have histologically confirmed DLBCL (excluding transformed indolent disease, and high-grade B-cell lymphoma (BCL) with MYC and BCL2 and/or BCL6 rearrangements), and have received $\geq$ 1 prior systemic therapies; patients who have failed only one prior line of therapy must not be eligible for high-dose chemotherapy followed by ASCT. Prior treatment with GemOx, R-GemOx or a CD20xCD3 bispecific antibody is not permitted. Patients are randomized 2:1 to receive up to eight 21-day cycles of either glofit-GemOx (intravenous [IV], followed by up to four cycles of glofitamab monotherapy) or R-GemOx (IV). A single dose of obinutuzumab is administered seven days prior to the first glofitamab administration. Randomization is stratified by number of prior lines of therapy and outcome of last systemic therapy (relapsed vs refractory). The primary objective is overall survival from time of randomization. Secondary efficacy objectives include progression-free survival, complete and overall response rates, duration of response, and time to deterioration in physical functioning and fatigue, and in lymphoma symptoms. Safety objectives comprise rate of adverse events, change from baseline in targeted vital signs and clinical laboratory test results, and tolerability. Pharmacokinetic, immunogenicity and biomarker endpoints will also be explored. The study started on February 17, 2021; an estimated enrollment of 270 patients by the study completion date of March 2022 is anticipated. Clinical trial information: NCT04408638. Research Sponsor: Study GO41944 is sponsored by F. Hoffmann-La Roche Ltd/Genentech, Inc. Third--party medical writing assistance, under the direction of authors, was provided by Katie Buxton, BSc, of Ashfield MedComms, and funded by F. Hoffmann-La Roche Ltd/Genentech, Inc.

TPS7576 **Poster Session**

Randomized, double-blind, placebo-controlled phase 3 study of ibrutinib plus rituximab in patients with previously untreated marginal zone lymphoma (MZL).

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Background: First-line treatment options for patients with MZL include single-agent immunotherapy, chemotherapy, or chemoimmunotherapy. While chemoimmunotherapy has a higher toxicity profile than immunotherapy alone, it may lead to longer progression-free survival (PFS). Rituximab, an anti-CD20 antibody, is FDA approved for the first-line treatment of follicular lymphoma but not specifically for advanced MZL. Ibrutinib is a Bruton's tyrosine kinase inhibitor approved in the United States for patients with MZL who require systemic therapy and have received ≥1 prior anti-CD20-based therapy. The combination of ibrutinib and rituximab has proven effective and is well tolerated in other B-cell lymphomas; it may serve as an effective chemotherapy-free option for the treatment of previously untreated MZL. **Methods:** NCT04212013 is a multicenter, double-blind, placebo-controlled, randomized, phase 3 study designed to compare the efficacy of ibrutinib + rituximab vs placebo + rituximab in patients with previously untreated MZL. Adults (≥18 y) with histologically documented MZL (splenic, nodal, and extranodal subtypes), no prior systemic treatment for MZL (prior splenectomy or other local surgical or radiation treatment allowed), measurable disease on CT scan, documented evidence of need for treatment, and Eastern Cooperative Oncology Group performance status ≤2 are eligible. Patients will be randomly assigned 1:1 to receive ibrutinib 560 mg once daily or placebo; all patients will also receive rituximab 375 mg/m^2 on days 1, 8, 15, and 22 of cycle 1. Subcutaneous dosing after dose 1 is allowed. Treatment with ibrutinib or placebo will continue for 30 mo or until disease progression, unacceptable toxicity, patient or investigator decision to withdraw, noncompliance, death, or study termination. Clinical assessments will occur every 4 weeks until week 13, at week 25, and then every 6 mo thereafter. Imaging assessments will be conducted at week 13, at week 25, and then every 6 mo thereafter. Response will be investigator assessed per the revised International Working Group for Non-Hodgkin Lymphoma (RECIL) criteria. At month 30, patients who have a complete response (CR) will discontinue treatment; patients who have a partial response (PR) or stable disease may continue treatment at investigator discretion. Safety will be assessed throughout the study and for 30 days after the last dose of study treatment. The primary endpoint is CR rate at month 30. Secondary endpoints include overall response rate (CR + PR), duration of response, PFS, overall survival, and safety. Enrollment has started and will continue until approximately 138 patients are enrolled. Clinical trial information: NCT04212013. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.