2024 Updated on Non-Hodgkin Lymphoma

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2023 - Update Lymphoma

- **Frontline Abstracts**: 856: Smart-Stop Study; 894: Updated Zuma-12 Study
- **Relapsed/ CAR-T Abstracts**: 1729: Epco Study; 1032 : 5 year CAR-T Consortium
- **MCL Abstracts**: LBA-2: Sympatico Study; 981: Pirtobrutinib in MCL
- **Ancillary Testing Abstracts**: 192 and 225: CT-DNA – MRD study

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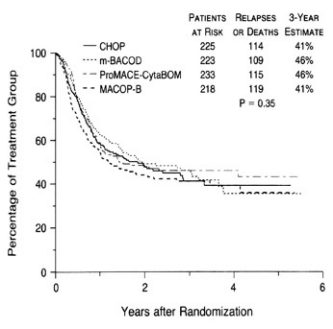
Smart Stop:
Lenalidomide, **T**afasitamab, **R**ituximab, and **A**calabrutinib Alone and with Combination Chemotherapy for the Treatment of Newly Diagnosed Diffuse Large B-Cell Lymphoma

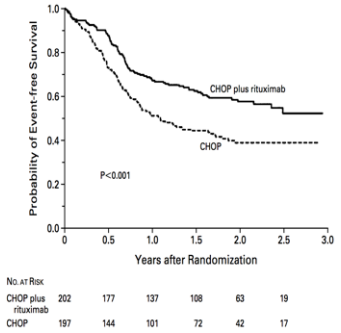
Jason Westin, MD MS FACP, Raphael E Steiner, MD, Dai Chihara, MD, PhD, Sairah Ahmed, MD, Preetesh Jain, MD, MBBS, PhD, DM, Luis Malpica, MD, Swami P. Iyer, MD, Luis Fayad, MD, Ranjit Nair, MD, Loretta J. Nastoupil, MD, Sattva S. Neelapu, MD, Jared Henderson, Maria Alma Rodriguez, MD, F. B. Hagemeister, MD, Francisco Vega, MD, PhD, Brittani Pulsifer, APRN, Jisha Tom, APRN, Isak Durmic, Gita Masand, Lei Feng, MS, Michael R. Green, PhD, Christopher R. Flowers, MD, MS and Paolo Strati, MD

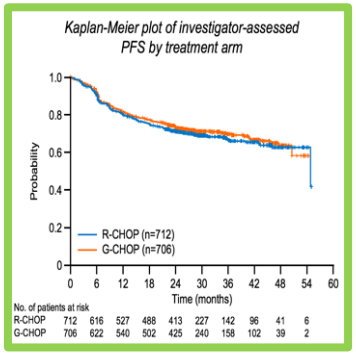
2023 ASH Abstract: 856,

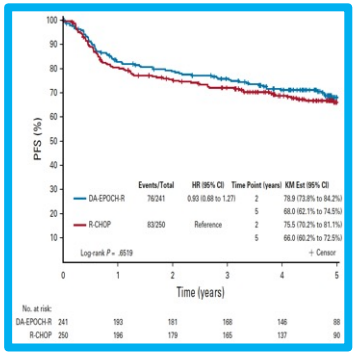
DLBCL trials

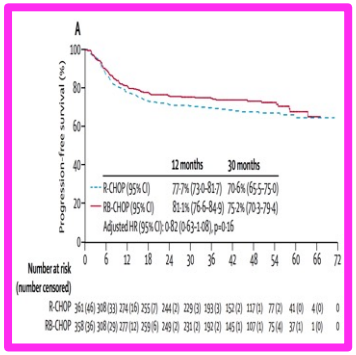
- CHOP[1,2]
- RCHOP[3]
- RCHOP vs GCHOP[4]
- RCHOP vs REPOCH[5]
- RCHOP +/- Bortezomib[6]
- RCHOP +/- Ibrutinib[7]
- RCHOP +/- Lenalidomide[8]
- RCHOP vs RCHP-Pola[10]

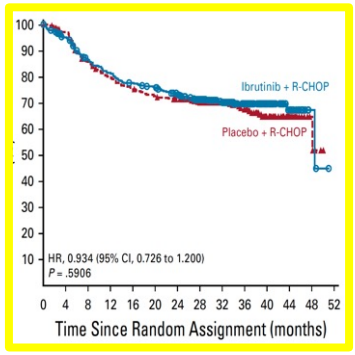


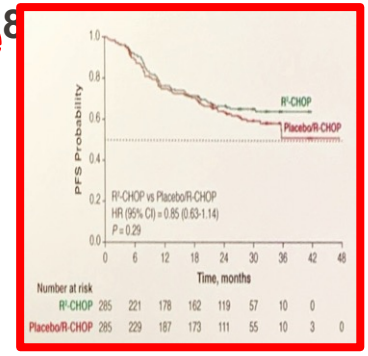


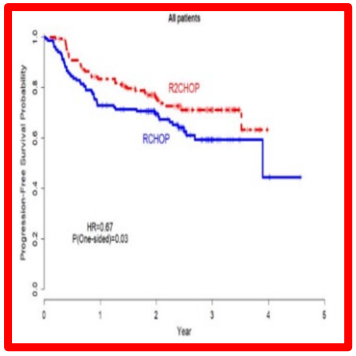


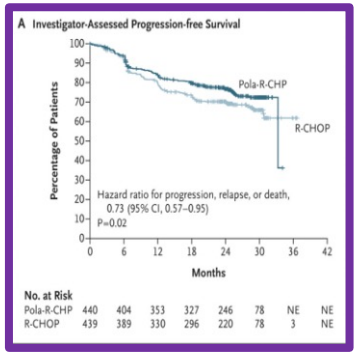








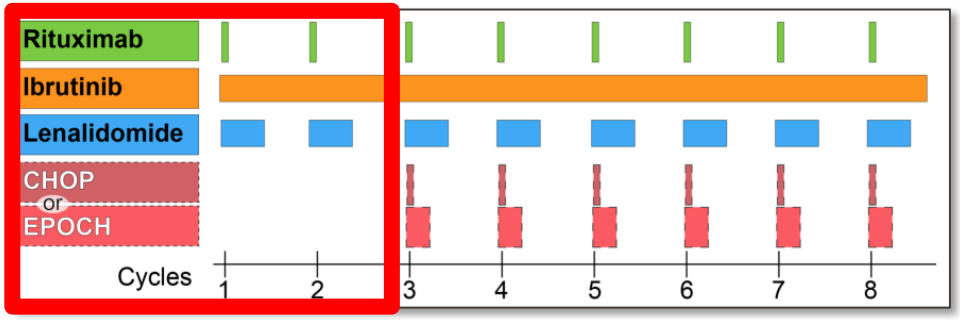


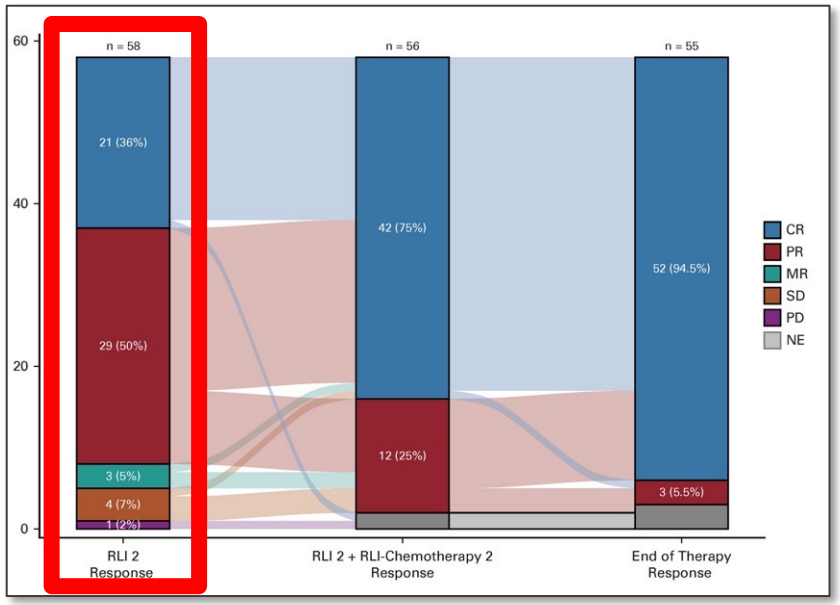


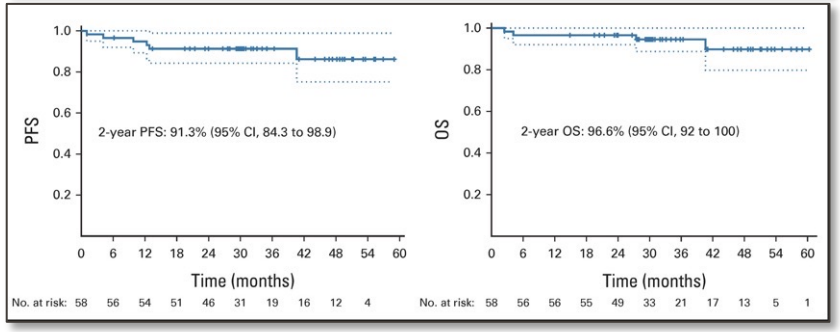
1. McKelvey et al, Cancer 1976, 2. Fisher et al, NEJM 1993, 3. Coiffier et al, NEJM 2002, 4. Vitolo et al, JCO 2018, 5. Bartlett et al, JCO 2019, 6. Davies et al, Lancet 2019, 7. Younes et al, JCO 2019, 8. Vitolo et al, ICML 2019, 9. Nowakowski et al, ICML 2019, 10. Tilly et al, NEJM 2022

Smart Start: Rituximab, Lenalidomide, and Ibrutinib in Patients With Newly Diagnosed Large B-Cell Lymphoma

Jason Westin, MD, MS[1]; R. Eric Davis, MD[1]; Lei Feng, MS[2]; Fredrick Hagemeister, MD[1]; Raphael Steiner, MD[1]; Hun Ju Lee, MD[1]; Luis Fayad, MD[1]; Loretta Nastoupil, MD[1]; Sairah Ahmed, MD[1]; Alma Rodriguez, MD[1]; Michelle Fanale, MD[1,3]; Felipe Samaniego, MD[1]; Swaminathan P. Iyer, MD[1]; Ranjit Nair, MD[1]; Yasuhiro Oki, MD[1]; Nathan Fowler, MD[1]; Michael Wang, MD[1]; Man Chun John Ma, PhD[1]; Francisco Vega, MD[4]; Timothy McDonnell, MD[4]; Chelsea Pinnix, MD, PhD[5]; Donna Griffith, RN[1]; Yang Lu, MD[6]; Sanjit Tewari, MD[6]; Ryan Sun, PhD[2]; David W. Scott, MBChB, PhD[7]; Christopher R. Flowers, MD[1]; Sattva Neelapu, MD[1]; and Michael R. Green, PhD[1,8]







Westin et al, JCO 2023

Smart Stop dosing

Lenalidomi

Tafasitamal

Rituximab

Acalabrutinib

Doses of "Smart Start" portion of the clinical trial, cycle = 21 days				
Drug Name	Dose	Route	Dosing per cycle	Day of therapy
Lenalidomide (L)	25mg	PO	Daily	1-10
Tafasitamab (T)	12mg/kg	IV	Weekly	1, 8, 15
Rituximab (R)	375mg/m2	IV	Once	1
Acalabrutinib (A)	100mg	PO	BID	1-21

LTRA

Smart Stop Eligibility

•Histopathologically confirmed diagnosis of LBCL without prior treatment with measurable disease

- Initially was restricted to Hans IHC-defined non-GCB but this criterion was removed
- Prior indolent lymphoma allowed if no CHOP-based therapy
- Any LBCL subtype could be eligible

•Age >= 18 years at the time of signing the informed consent

•Performance status of =< 3 (3 only allowed if decline in status is deemed related to lymphoma and felt potentially reversible by the treating physician)

•Adequate organ and bone marrow function

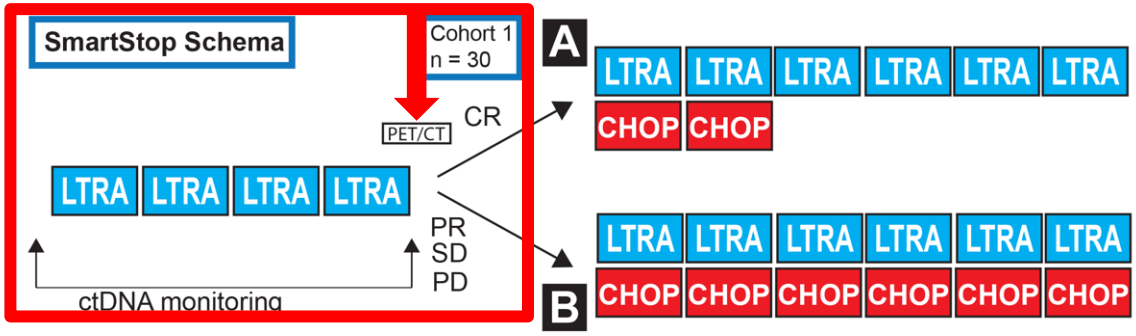
•No CNS involvement with lymphoma

Toxicities

AE	Any Grade (N=30)	Grade 3 or Higher (N=30)
Anemia	26 (87%)	5 (17%)
Neutropenia	26 (87%)	18 (60%)
Fatigue	22 (73%)	0
Platelet count decreased	22 (73%)	3 (10%)
Creatinine increased	13 (43%)	0
Rash maculo-papular	13 (43%)	4 (13%)
Headache	11 (37%)	0
Nausea	11 (37%)	0
Transaminitis	10 (33%)	0
Edema limbs	10 (33%)	0
Infections	9 (30%)	2 (7%)
Infusion related reaction	9 (30%)	0
Peripheral sensory neuropathy	9 (30%)	3 (10%)
Constipation	8 (27%)	0
Cough	8 (27%)	0
Diarrhea	7 (23%)	0
Dizziness	6 (20%)	0
Mucositis oral	5 (17%)	0
Vomiting	5 (17%)	3 (10%)
Febrile neutropenia	4 (13%)	3 (10%)
Non-cardiac chest pain	4 (13%)	0

AE >10% of any patient, electrolyte or overlapping AEs not shown

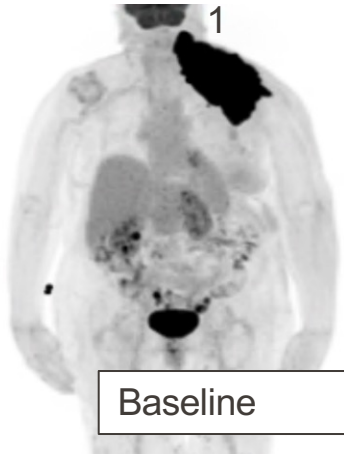
Results – after 4 cycles of LTRA



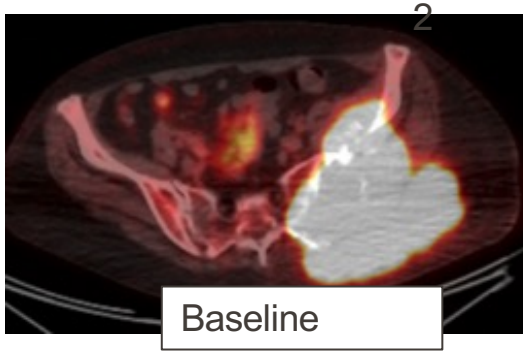
Primary Endpoint 1A: ORR after 4 LTRA is

	All (N=30)	GCB (N=5)
CR	**19 (63.3%)** (95% CI: 50.0 ~ 75.2%)	**4 (80%)**
PR	11 (36.7%)	1 (20%)
SD	0	0
PD	0	0
ORR	30 (100%) (95% CI: 92.6 ~ 100%).	

PR example 1

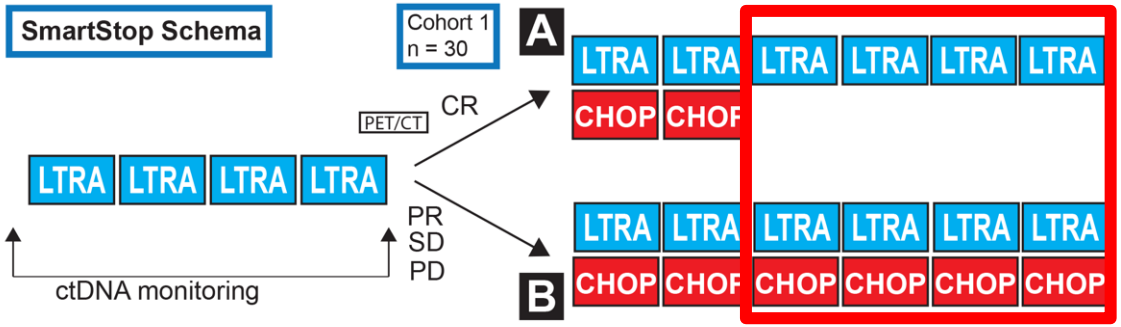


PR example 2



Results – end of treatment

Primary Endpoint 1B: CRR at EoT:
Preliminary is 100% in 22 evaluable patients



N = 22		Group A (2 CHOP, N=19)	Group B (6 CHOP, N=11)
CR	22 (100%)* (95% CI: 90.1 ~ 100%)	19 (100%)	11 (100%)*
PR	0*	0	0*
SD	0	0	0
PD	0	0	0
Pending (On treatment)	8	5	3

*FDG avid lesion biopsied with benign inflammatory response without lymphoma cells

Conclusions and Future Directions (1)

- Targeted therapy alone is safe and effective as initial treatment in 1L LBCL
  - CR rate after 4 cycles of LTRA is 63%
  - Primary endpoint 1A: ORR after 4 cycles of LTRA is 100%
- <6 cycles of CHOP appears feasible if LTRA responsive with short follow up
  - 19 of 30 patients will receive only 2 cycles of CHOP, initial patients with >1y ongoing remission
  - Primary endpoint 1B: CRR at end of treatment is 100%, including those with 2 and 6 CHOP cycles
- Limited ctDNA data shows high molecular response, including undetectable in 1/3rd

3-Year Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel as First-Line Therapy in Patients with High-Risk Large B-Cell Lymphoma

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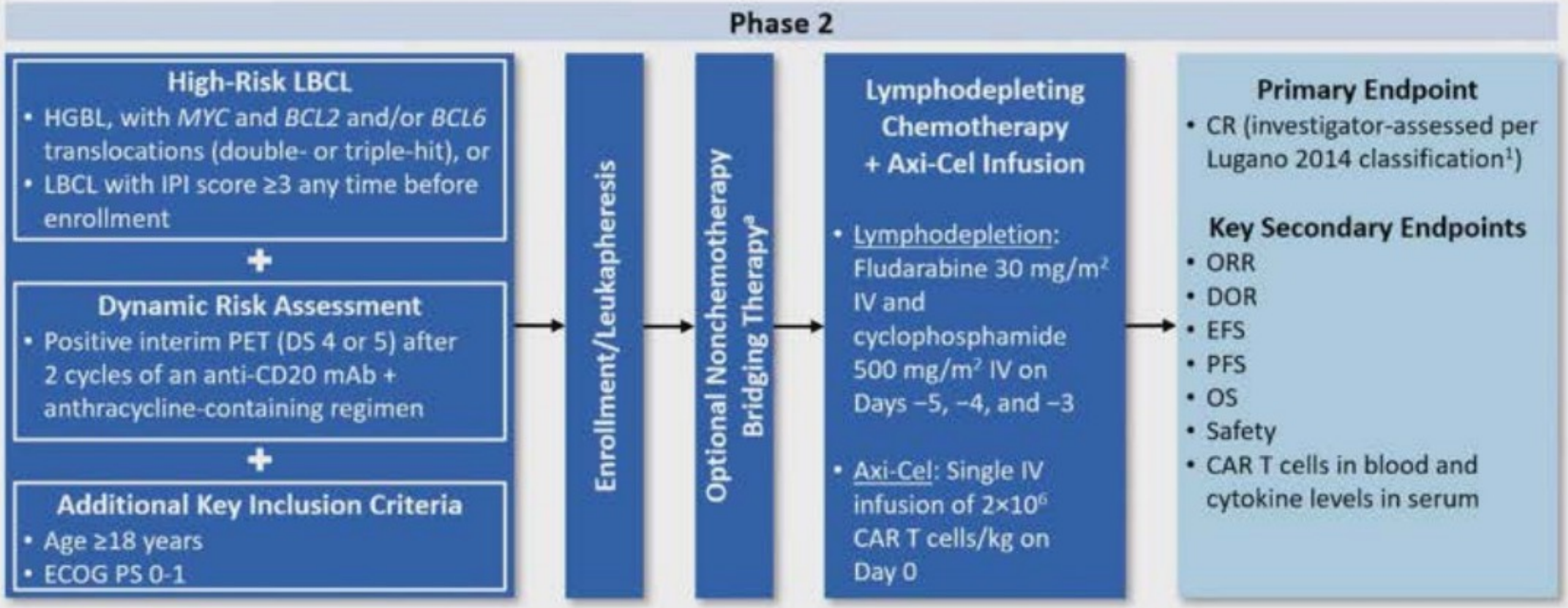
ZUMA-12 Study Design

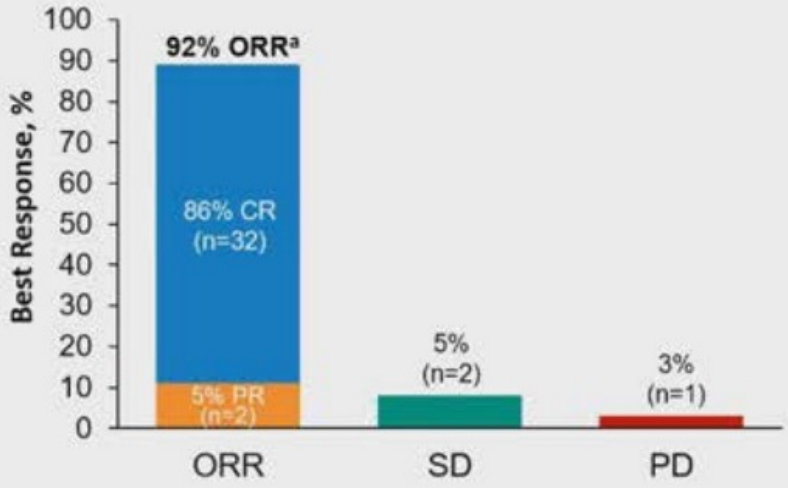


[a] Administered after leukapheresis and completed prior to initiating lymphodepleting chemotherapy. Therapies allowed were corticosteroids, localized radiation, and HDMP+R. PET-CT was required after bridging.

1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CT, computed tomography; DOR, duration of response; DS, Deauville score; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HDMP+R, high-dose methylprednisolone plus rituximab; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; IV, intravenous; LBCL, large B-cell lymphoma; mAb, monoclonal antibody; ORR, objective response rate; OS, overall survival; PET, positron-emission tomography; PFS, progression-free survival.

Objective Response Rate



	Efficacy Evaluable n=37[b]
Overall CR rate, % (95% CI)	86 (71-95)
DHL/THL and IPI score ≥3 (n/N)	4/4 100 (40-100)
DHL/THL only (n/N)	5/6 83 (36-100)
IPI score ≥3 only (n/N)	23/27 85 (66-96)
Patients converted from PR/SD to CR, n (%)	9 (24)
PR to CR	8 (22)
SD to CR	1 (3)

- In the efficacy-evaluable population, the CR rate was slightly higher than in the primary analysis[1] due to an additional number of patients converting from PR to CR
- Responses were ongoing in 73% of response-evaluable patients at data cutoff

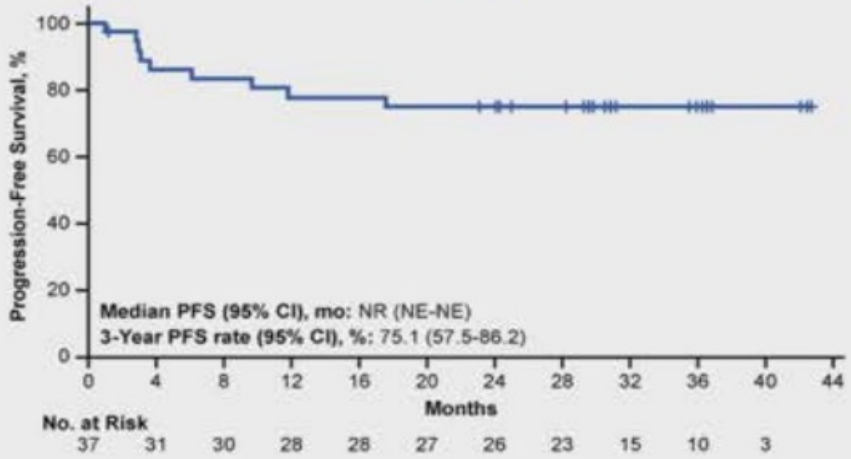
[a] Response assessments are based on best overall response. [b] Includes all treated patients with centrally confirmed disease type (DHL/THL) or IPI score ≥3 who received ≥1×10^6 CAR T cells/kg.

1. Neelapu SS, et al. *Nat Med*. 2022;28:735-742.

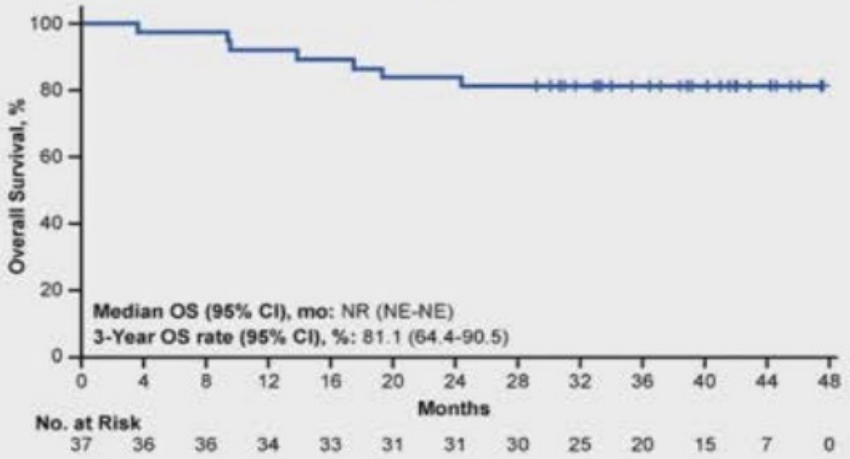
CAR, chimeric antigen receptor; CR, complete response; DHL/THL, double-hit/triple-hit lymphoma; IPI, International Prognostic Index; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Progression-Free Survival and Overall Survival[a]

PFS



OS



- Medians for PFS and OS were not reached in efficacy-evaluable patients
  - Among patients who achieved a CR as best response, the 3-year PFS and OS rates were 84.4% (95% CI, 66.5-93.2) and 90.6% (95% CI, 73.6-96.9), respectively

[a] Analyses done in all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10^6 CAR T cells/kg.
CAR, chimeric antigen receptor; CR, complete response; IPI, International Prognostic Index; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival.

Adverse Events and Deaths

New TEAEs After Primary Analysis, n (%)	All Treated (N=40)
Any TEAE[a]	5 (13)
Grade ≥3	3 (8)
Serious TEAEs	3 (8)
Any infection/infestation	4 (10)
Grade ≥3	2 (5)
COVID-related infections	3 (8)
Device related infection	1 (3)
Sinusitis	1 (3)

- In total, there were 8 deaths in ZUMA-12
  - 5 were due to PD (1 occurring after the primary analysis data cutoff)[1]
  - 1 COVID-19 (Day 350; Grade 5 and unrelated to axi-cel)
  - 1 esophageal adenocarcinoma (Day 535, occurring after the primary analysis data cutoff; Grade 5 and unrelated to axi-cel)[1]
  - 1 septic shock (Day 287; unrelated to axi-cel)
- No new cases of CRS or neurologic events of any grade occurred since the prior data cut and all cases previously reported[1] were resolved by data cutoff
- Since the primary analysis,[1] prolonged cytopenia[b] of any grade occurred in only 1 patient and was resolved by data cutoff

[a] AEs were graded per CTCAE version 5.0. Neurologic events were identified based on modified Topp et al 2015.[2] CRS events were graded according to a modification of the criteria of Lee and colleagues.[3]
[b] Present on Day ≥30 post-infusion.
1. Neelapu SS, et al. *Nat Med*. 2022;28:735-742. 2. Topp CW, et al. *Psychother Psychosom*. 2015;84:167-176. 3. Lee DW, et al. *Blood*. 2014;124:188-195.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; PD, progressive disease; TEAE, treatment-emergent adverse event.

Conclusions

- In this updated analysis of ZUMA-12, axi-cel demonstrated a high rate of durable responses
  - At data cutoff, with a median follow-up of ≥40 months, responses were ongoing in 73% of response-evaluable patients
  - Medians for DOR, EFS, PFS, and OS were not reached
- Safety outcomes were similar to previous reports,[1] with no new safety signals observed
- CAR T-cell expansion by peak and $AUC_{0\text{-}28}$ was consistent with the primary analysis[1]
- Axi-cel may benefit patients exposed to fewer prior therapies and those with high-risk LBCL, a population with high unmet need and poor outcomes after standard first-line chemoimmunotherapy
- Further investigation in randomized controlled trials is warranted in this patient population to determine the benefit of axi-cel as first-line therapy versus standard chemoimmunotherapy
  - ZUMA-23 (NCT05605899) is a Phase 3, randomized controlled study that will evaluate axi-cel as a first-line regimen versus standard of care in patients with high-risk LBCL[2]

1. Neelapu SS, et al. *Nat Med*. 2022;28:735-742. 2. Westin et al. *J Clin Oncol*. 2023;41:TPS7578.

$AUC_{0\text{-}28}$, area under the curve from Days 0-28; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; DOR, duration of response; EFS, event-free survival; LBCL, large B-cell lymphoma; OS, overall survival; PFS, progression-free survival.

1729

Mitigating the Risk of Cytokine Release Syndrome (CRS): Preliminary Results from a DLBCL Cohort of EPCORE NHL-1

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[1]University of Nebraska Medical Center, Omaha, NE, USA; [2]John Theurer Cancer Center at Hackensack Meridian Health, Hackensack Meridian Health School of Medicine, Hackensack, NJ, USA; [3]On behalf of the Lunenburg Lymphoma Phase I/II Consortium-HOVON/LLPC, Amsterdam UMC, VU University Medical Center, Amsterdam, Netherlands; [4]Samsung Medical Center, Seoul, Republic of Korea; [5]On behalf of the Lunenburg Lymphoma Phase I/II Consortium-HOVON/LLPC, Erasmus MC Cancer Institute, University Medical Center, Department of Hematology, Rotterdam, Netherlands; [6]Seoul National University Hospital, Seoul, Republic of Korea; [7]Hospital Universitario Vall d'Hebron, Barcelona, Spain; [8]Sir Charles Gairdner Hospital, Nedlands, Australia; [9]Cancer Precision Medicine, Uppsala University, Uppsala, Sweden; [10]Medical University of South Carolina, Charleston, SC, USA; [11]MSC National Research Institute of Oncology, Kraków, Poland; [12]Hematology Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori," Meldola, Italy; [13]Lifespan Cancer Institute, The Warren Alpert Medical School of Brown University, Providence, RI, USA; [14]AbbVie, North Chicago, IL, USA; [15]Genmab, Plainsboro, NJ, USA; [16]Genmab, Copenhagen, Denmark; [17]University of Iowa, Iowa City, IA, USA

Vose, et al: ASH 2023, abs 1729

Presented at the American Society of Hematology Annual Meeting; December 9–12, 2023; San Diego, CA

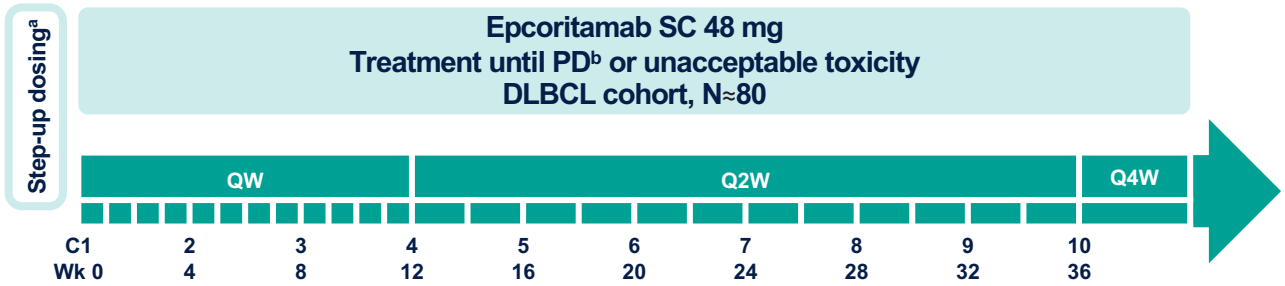
Study Design: EPCORE™ NHL-1

DLBCL Cycle 1 Optimization

Key inclusion criteria:

- R/R CD20+ DLBCL, NOS (de novo or transformed from FL)
- ECOG PS 0–2
- ≥2 prior lines of systemic antineoplastic therapy, including ≥1 anti-CD20 mAb
- FDG PET–avid and measurable disease by CT/MRI
- Prior CAR T-cell therapy allowed

Data cutoff: July 17, 2023
Median follow-up: 1.7 mo



- **Cycle 1 optimization recommendations:**
  - **Dexamethasone 15 mg premedication on D1, D8, D15, and D22 and prophylaxis on D2–4, D9–11, D16–18, and D23–25**
  - **2–3 L of fluid intake during 24 h prior to each dose**
  - **Hold antihypertensive medications for 24 h prior to each dose**
  - **Administer 500 mL of isotonic IV fluids on the day of each dose prior to administration**
  - **2–3 L of fluid intake during 24 h following each dose**
  - **Self-monitoring of temperature 3 times daily for 4 d following each dose**
  - **Hospitalization not required but patients must remain in close proximity to treatment facility for 24 h following first full dose**
- **Primary endpoint:** Rate of grade ≥2 CRS events and all-grade CRS events from first dose through 7 d following second full dose

ClinicalTrials.gov: NCT03625037. EudraCT: 2017-001748-36.

Baseline Characteristics and Prior Treatments

Demographics	N=60
Median age (range), y	66 (27–86)
≥75 y, n (%)	13 (22)
ECOG PS,[a] n (%)	
0	20 (33)
1	34 (57)
2	5 (8)
Disease Characteristics and Prior Treatments	**N=60**
DLBCL type,[b] n (%)	
De novo	37 (62)
Transformed	9 (15)
Median time from initial diagnosis to first dose (range),[c] y	1.6 (0.1–24.8)
Median time from end of last therapy to first dose (range),[c] mo	3.1 (1–220)
Median prior lines of therapy, n (range)	3 (2–10)
Prior lines of therapy, n (%)	
2	19 (32)
≥3	41 (68)
Primary refractory[d] disease,[c] n (%)	36 (60)
Refractory[d] to last systemic therapy,[c] n (%)	51 (85)
Refractory[d] to ≥2 consecutive lines of therapy,[c] n (%)	42 (70)
Prior ASCT,[c] n (%)	4 (7)
Prior CAR T therapy,[c] n (%)	33 (55)
Refractory[d] to CAR T therapy, n/n (%)	28/33 (85)

Overview of CRS Events

Cycle 1 Optimization Led to Decreased Rates and Severity of CRS

	Expansion[a] N=157	CRS-Evaluable[b] DLBCL Cycle 1 Optimization[c] n=36
CRS, n (%)[d]	80 (51)	8 (22)
Grade 1	50 (32)	5 (14)
Grade 2	25 (16)	3 (8)
Grade 3	5 (3)	0
Signs and symptoms of CRS, n (%)[e]	**n=80**	**n=8**
Fever	79 (99)	7 (88)
Hypotension	24 (30)	3 (38)
Hypoxia	14 (18)	0
Other	15 (19)	1 (13)
Median time to onset after first full dose, h[e]	20	27
Treated with tocilizumab, n/n (%)[e]	23/80 (29)	3/8 (38)
Treated with corticosteroid, n/n (%)[e]	17/80 (21)	2/8 (25)
Leading to treatment discontinuation, n (%)	1 (0.6)	0
CRS resolution, n/n (%)[e]	79/80 (99)	8/8 (100)
Median time to resolution, d (range)[e]	2 (1–27)	2.5 (1–6)

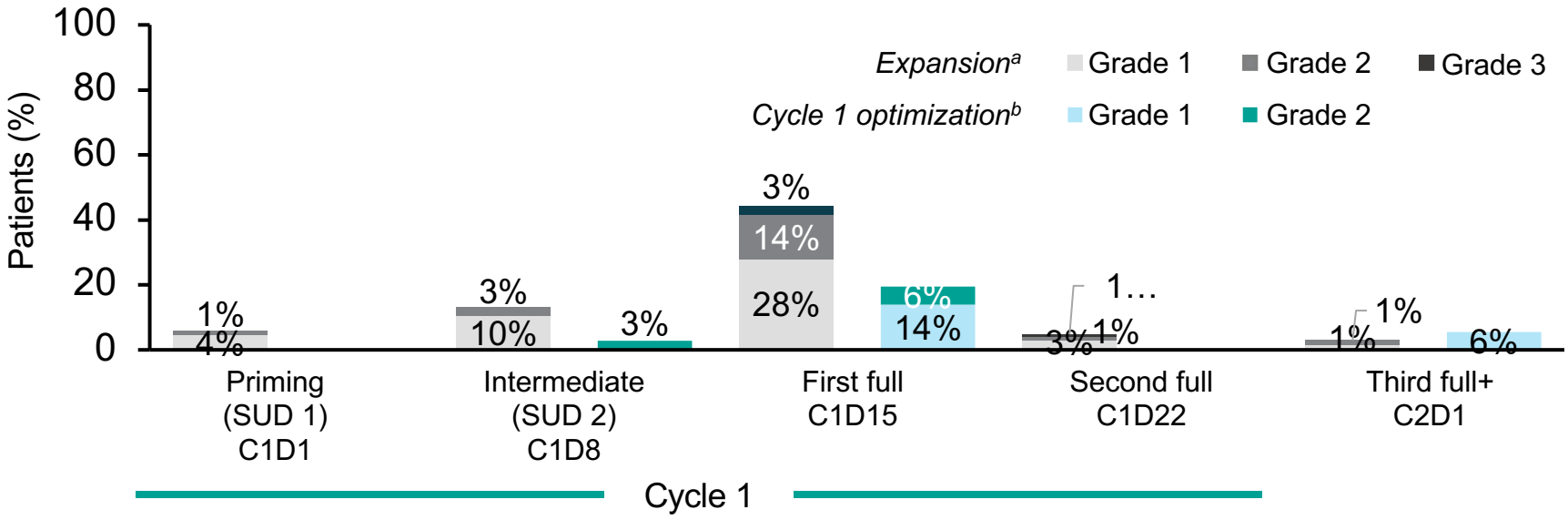
- Among the 36 CRS-evaluable patients, pretreatment prior to the first full dose included: IV fluid (86%); dexamethasone (81%); IV fluid and dexamethasone (69%); other corticosteroids (19%)

[a]Data cutoff: November 18, 2022. [b]CRS-evaluable population was defined as patients treated with epcoritamab SC who either met the minimum exposure criterion and completed the CRS-evaluation period with sufficient safety evaluations or experienced a grade ≥2 CRS event during the CRS-evaluation period. [c]Data cutoff: July 17, 2023. [d]Graded by Lee et al 2019 criteria.[1] [e]Among patients with CRS.

1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-38.

CRS Events by Dosing Period

Most Events Following First Full Dose; Lower Rates With Cycle 1 Optimization



- Preliminary efficacy data were comparable to that observed in the dose-expansion cohort

SUD 1, first step-up dose; SUD 2, second step-up dose. [a]Data cutoff: November 18, 2022. [b]Data cutoff: July 17, 2023. Based on the CRS-evaluable population (n=36), which consists of patients treated with epcoritamab SC who either met the minimum exposure criterion and completed the CRS-evaluation period with sufficient safety evaluations or experienced a grade ≥2 CRS event during the CRS-evaluation period.

Conclusions

- CRS prophylaxis with dexamethasone and hydration reduced rates and severity of CRS
  - Proactive hospitalization was not required
- Timing of CRS continues to be predictable; no patients discontinued treatment due to CRS
- IL-6 levels were lower with cycle 1 optimization and consistent with lower observed rates of CRS
  - There was no impact on T-cell activation or B-cell depletion

U.S. CAR-T Lymphoma CONSORTIUM

Five Year Outcomes of Patients with Large B-Cell Lymphoma Treated with Standard-of-Care Axicabtagene Ciloleucel: Results from the US Lymphoma CAR-T Cell Consortium .

Jay Y. Spiegel*[1], Michael Jain*[2], Loretta J. Nastoupil[3], John S. Tamaresis[4], Armin Ghobadi[5], Yi Lin[6], Lazaros Lekakis[1], Patrick M. Reagan[7], Olalekan Oluwole[8], Joseph McGuirk[9], Abhinav Deol[10], Kathleen A. Dorritie[11], Alison R Sehgal[11], Andre Goy[12], Brian T. Hill[13], Charalambos Andreadis[14], Javier Munoz[15], Matthew Ulrickson[16], Jason Westin[3], Julio C. Chavez[17], Dilan Patel[5], Miriam T. Jacobs[5], Radhika Bansal[6], N. Nora Bennani[6], Vivek G. Patel[8], Aaron P. Rapoport[17], Julie M. Vose[18], David B. Miklos[4], Sattva S. Neelapu[3], Frederick L. Locke[2], Matthew A. Lunning[18#], Saurabh Dahiya [4#]

[1]University of Miami Miller School of Medicine, Sylvester Comprehensive Cancer Center, Miami, FL; [2]Moffitt Cancer Center, Greenebaum Comprehensive Cancer Center, Baltimore, MD, [3]The University of Texas MD Anderson Cancer Center, Houston, TX;; [4]Stanford University Medical Center, Stanford, CA, Mayo Clinic, Phoenix, AZ; [5]Washington University School of Medicine, Siteman Cancer Center, St Louis, MO; [6]Mayo Clinic, Rochester, MN; [7]University of Rochester, Rochester, NY; [8]Vanderbilt-Ingram Cancer Center, Nashville, TN; [9] University of Kansas Medical Center, Kansas City, KS; [10] Wayne State University, Karmanos Cancer Institute, Detroit, MI, [11]University of Pittsburgh Medical Center, Pittsburgh, PA, [12]John Theurer Cancer Center, Hackensack Meridian Health, Hackensack, NJ; [13]Cleveland Clinic, Cleveland, OH; [14]University of California San Francisco, San Francisco, CA; [15]Mayo Clinic, Arizona; [16]Banner-MD Anderson Cancer Center, AZ; [17]University of Maryland School of Medicine, Tampa, FL; [18]University of Nebraska Medical Center, Omaha, NE

*Co-first authors; #Co-senior authors.

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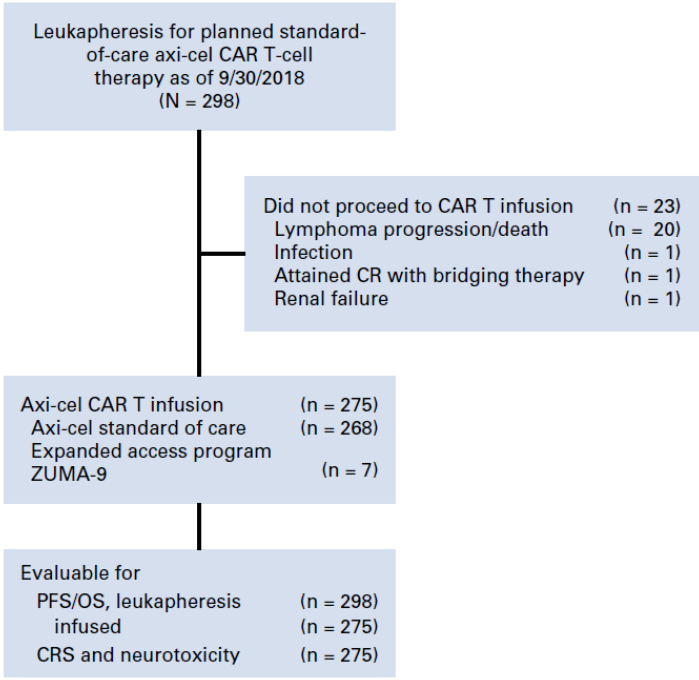
Patient Demographics of Real World Cohort

Characteristic	No. (%)	ZUMA-1
No. of patients	298	101
Age, years		
< 60	144 (48.3)	
>60	154 (51.7)	
Median (range)	60 (21-83)	58 (23-76)
Sex (male)	192 (64.0)	68 (67)
ECOG PS		
0-1	80	100
2-3	20	
Disease Stage		
I or II	52 (17.6)	15 (15)
III or IV	244 (82.4)	86 (85)
IPI		
0-2	132 (45.6)	53 (52)
3-5	162 (54.4)	48 (48)



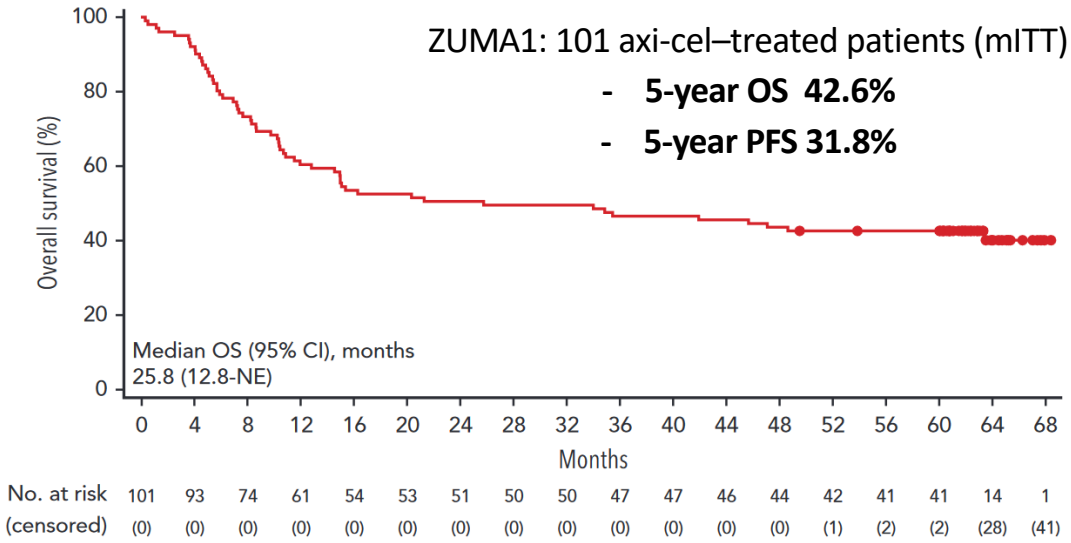
Nastoupil, Jain…Miklos, Neelapu, Locke et al. JCO 2020

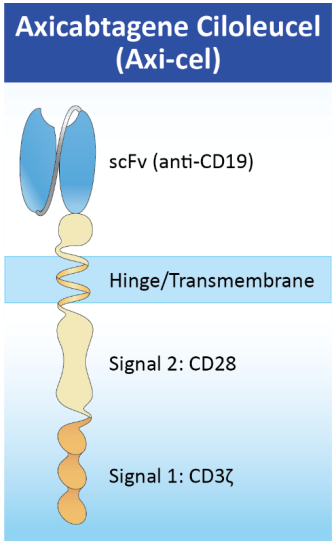
U.S. CAR-T Lymphoma CONSORTIUM

Axicabtagene Ciloleucel (Axi-Cel)

- Axicabtagene ciloleucel (Yescarta) is an autologous CD19 directed CAR T therapy with a CD3ζ/CD28-based signaling domain.

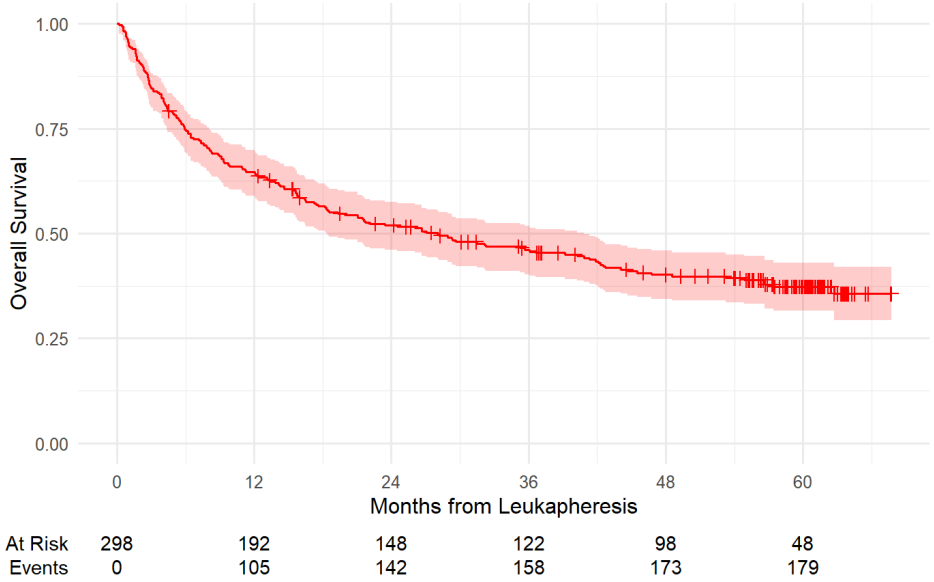
- **Regulatory timeline for Axi-Cel in large B cell lymphoma**
- FDA approval for Axi-Cel in 3L or 3L+: 10/18/2017 *(focus of this report)*
- FDA approval for Axi-Cel in 2L or 2L+: 04/01/2021



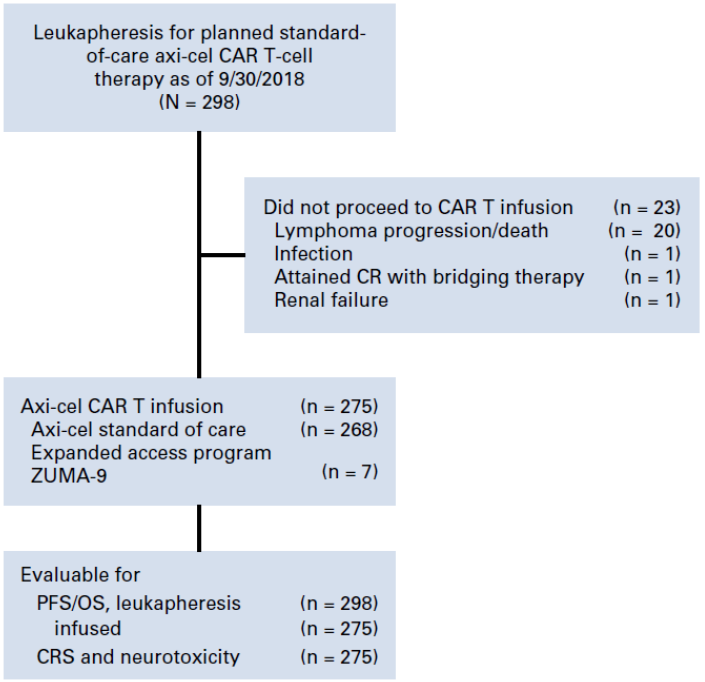


Neelapu, Locke, NEJM 2017; Neelapu Blood 2023

5 Year Intention to Treat Overall Survival was 37%



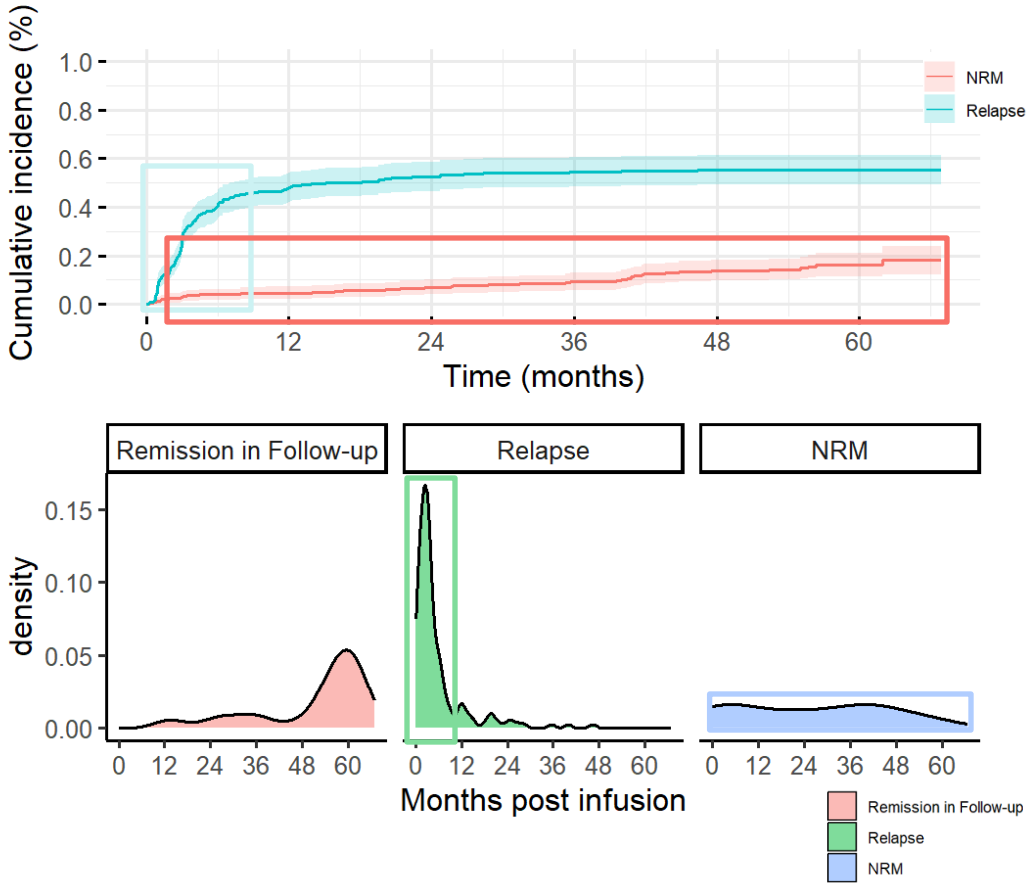
Median OS 28 mo (18 – 40.8)
5yr OS: 37% (31.5 – 43)



U.S. CAR-T Lymphoma CONSORTIUM

Relapse Occurs Early; NRM Occurs at a Steady Rate over Time

- 5 yr cumulative risk of: Relapse 55.2%, NRM 16.2%
- 151 total progression events - 20 (13%) progression events post 1 yr
- Last progression 46.4 months post infusion
- 40 total NRM events



U.S. CAR-T Lymphoma CONSORTIUM

Infection was the Leading Cause of NRM

Total Infused = 275							
Cause of Death	Year 1	Year 2	Year 3	Year 4	Year 5	After Year 5	Summary
Progressive Disease	74	28	11	4	1	0	118
Infection	8	2	4	6	1	0	21
Secondary Malignancy	0	3	1	3	1	1	9
CAR-T Toxicity[1]	3	0	0	0	0	0	3
Unknown/Other[2]	2	1	1	1	2	0	7

[1] Includes HLH, cerebral edema and intracranial hemorrhage

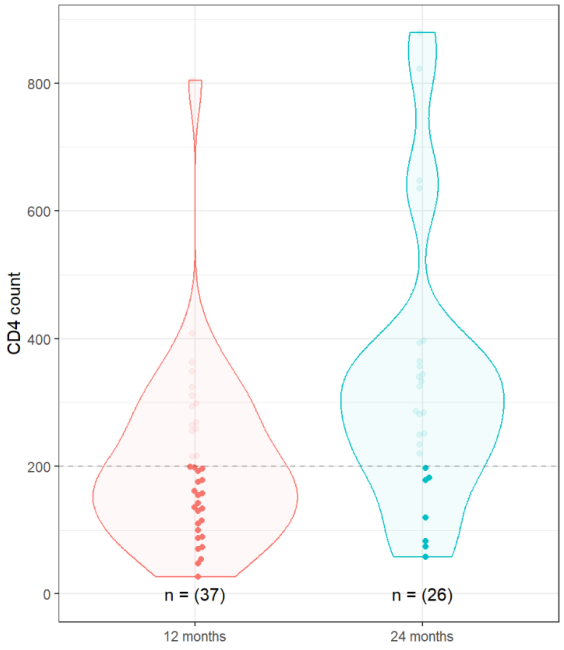
[2] Unknown = 6, Suicide = 1

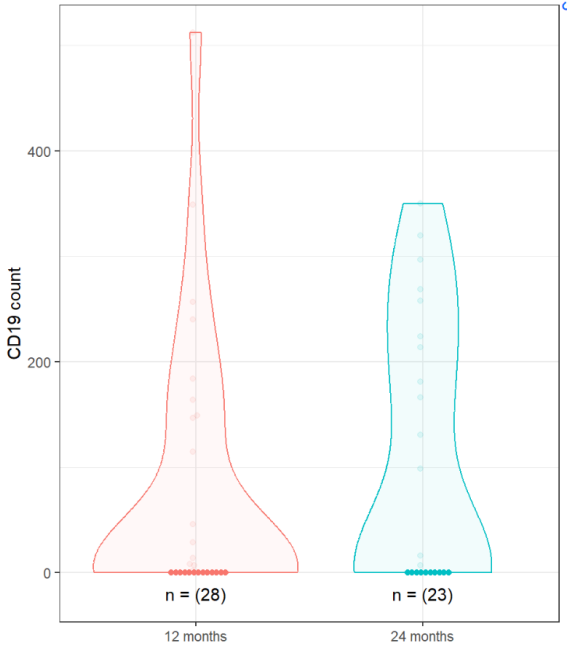
Infectious Cause of Death	N
Unclassified	6
Pneumonia	4
Sepsis	3
COVID-19	2
Candidemia	2
JC encephalitis	1
MRSA	1
Non-COVID viral pneumonia	1
PJP and Candidemia	1

U.S. CAR-T Lymphoma CONSORTIUM

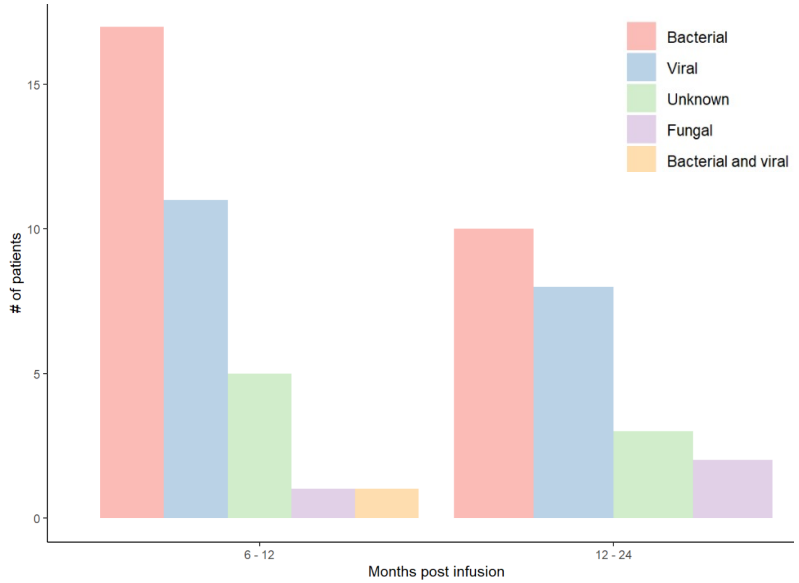
CD4 Recovery Typically >12 Months; B-cell Aplasia Not Required for Durable Remission

- CD4 recovery:
  - 38% recovery @ 1yr
  - 73% recovery @ 2yr
- B cell recovery:
  - 54% @ 1yr
  - 57% @ 2 yr
  - ZUMA 1: ~50% @ 1yr, ~ 75% @ 2 yr

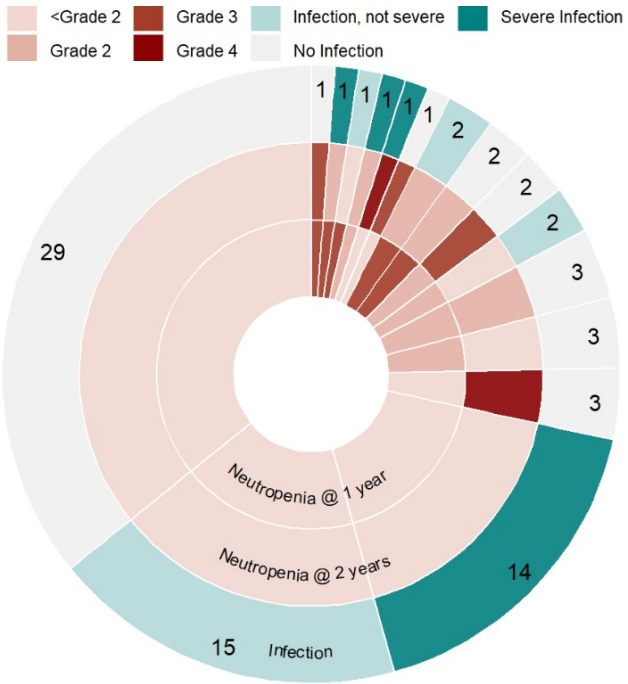




Late Infections Were Not Associated with Neutropenia



- Incidence 6-12 mo (n=109): 31.2%, 17% severe
- Incidence 12-24 mo (n=89): 24%, 11% severe

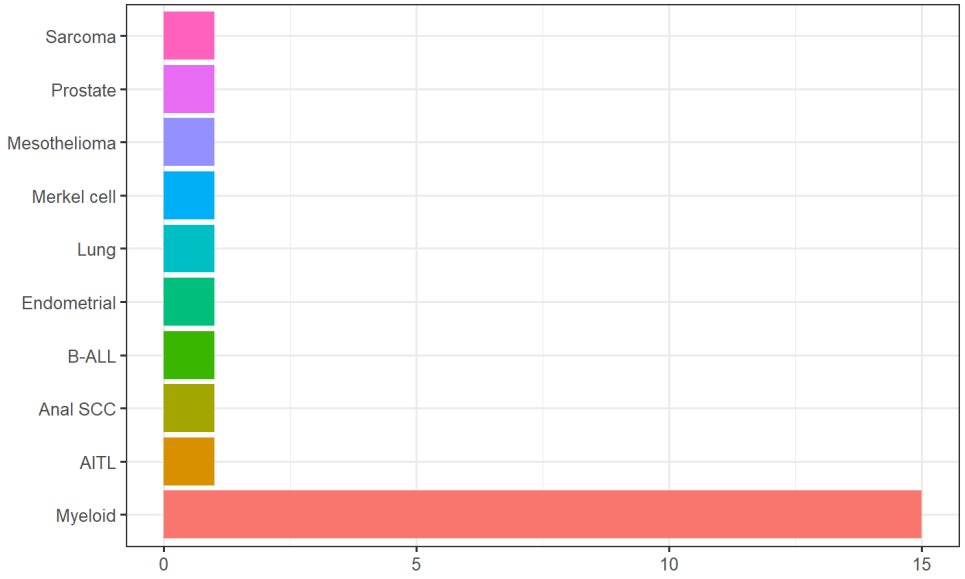


- 1 yr (n = 109): Gr 3 neutropenia 10%, Gr 3 thrombocytopenia 9%, Gr 3 anemia <1%;
- 1 yr Bicytopenia 5.5%
- 2 and 3 yr: Gr 3 neutropenia 10%

U.S. CAR-T Lymphoma CONSORTIUM

Subsequent Malignant Neoplasms

- Excluding non-melanoma skin cancer, 24/275 (9%) patients with SMN
- Patient with AITL:
  - diagnosed 3 yrs post infusion
  - after intercurrent lenalidomide + rituximab
  - no CAR testing available on biopsy tissue
- 15 secondary myeloid:
  - Median 16.2 mo post infusion
  - Median 3.5 prior lines of therapy
  - 33% with prior autoSCT



Conclusions

- ~29% of patients remain in remission with median 58 months follow-up despite 43% ZUMA-1 ineligible comorbidities
- This study highlights important survivorship issues post axi-cel
  - Infection/Immune reconstitution – 31% of patients with recorded infection (may undercount less severe infection)
  - Secondary malignancy, primarily tMN – immunosuppression driven or burden of prior therapy? Incidence in 2nd line may help determine
  - NRM overall 16.5% - focus on post-CAR management important to maximize CAR-T benefit

Ibrutinib Combined With Venetoclax in Patients With Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results From the Randomized Phase 3 SYMPATICO Study

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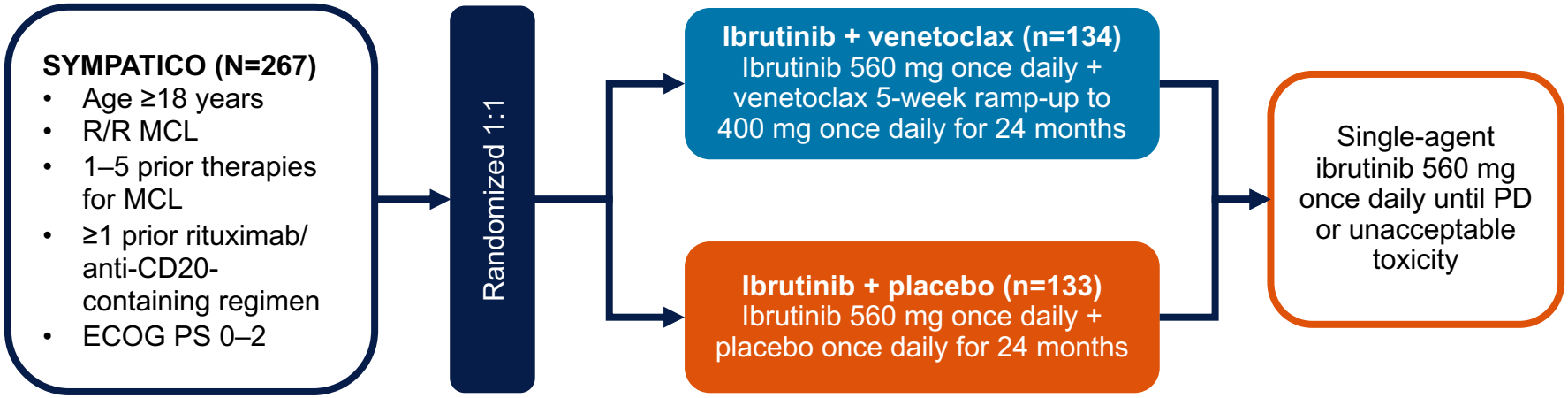
ASH 2023: Abstract LBA-2

SYMPATICO Study Design

- SYMPATICO (NCT03112174) is multinational, randomized, double-blind, placebo-controlled, phase 3 study



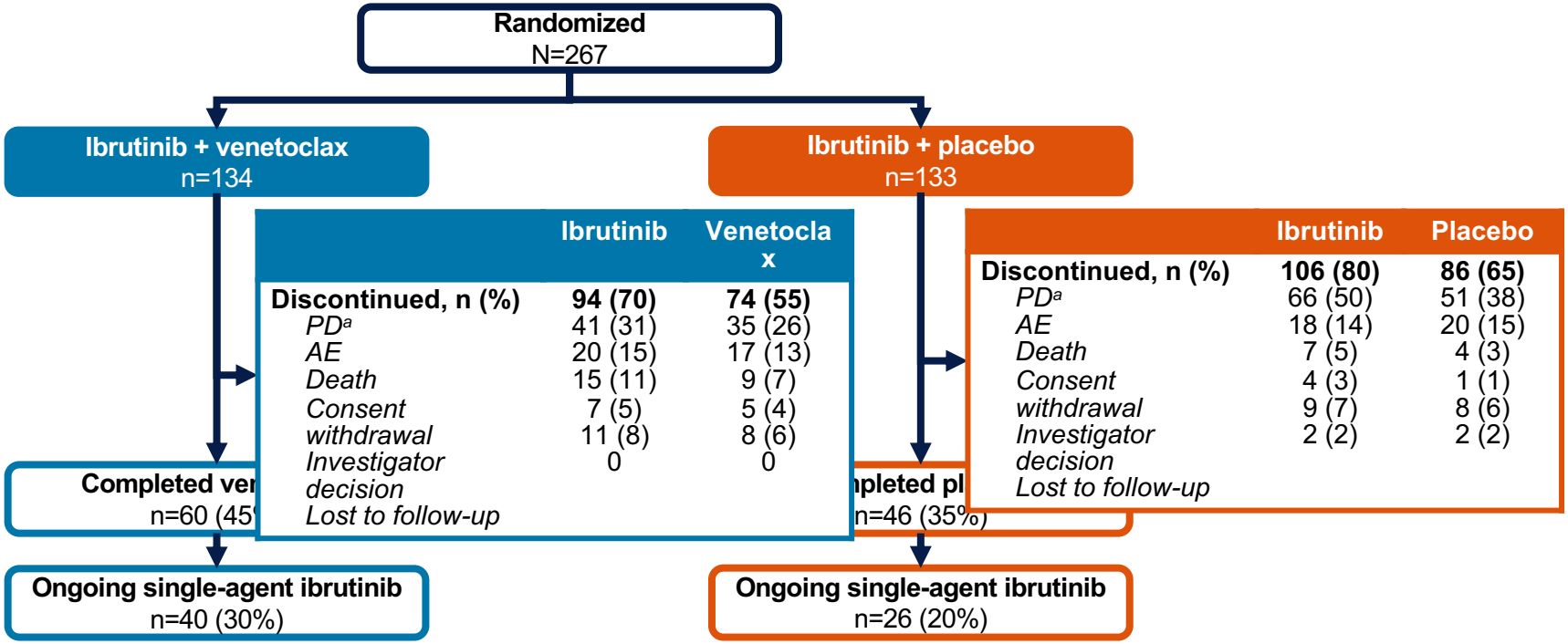
Stratification: ECOG PS, prior lines of therapy, TLS risk[a]

- **Primary endpoint:**
  - PFS by investigator assessment using Lugano criteria
- **Secondary endpoints (tested hierarchically in the following order):**
  - CR rate by investigator assessment
  - TTNT[b]
  - OS (interim analysis)
  - ORR by investigator assessment

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; OS, overall survival; TLS, tumor lysis syndrome; TTNT, time to next treatment.

[a]Increased TLS risk was defined as at least 1 lesion >10 cm, or at least 1 lesion >5 cm with circulating lymphocytes >25,000 cells/mm^3, and/or creatinine clearance <60 mL/min. [b]For hierarchical testing per US FDA censoring, TTNT was tested after OS.

Patient Disposition



- Median follow-up: 51.2 months (range, 0.1+ to 61.6) as of July 5, 2023
- Treatment discontinuations due to PD were more frequent in the ibrutinib + placebo arm
- Treatment discontinuations due to AEs were similar between arms

AE, adverse event. [a]PD per protocol criteria or clinical PD.

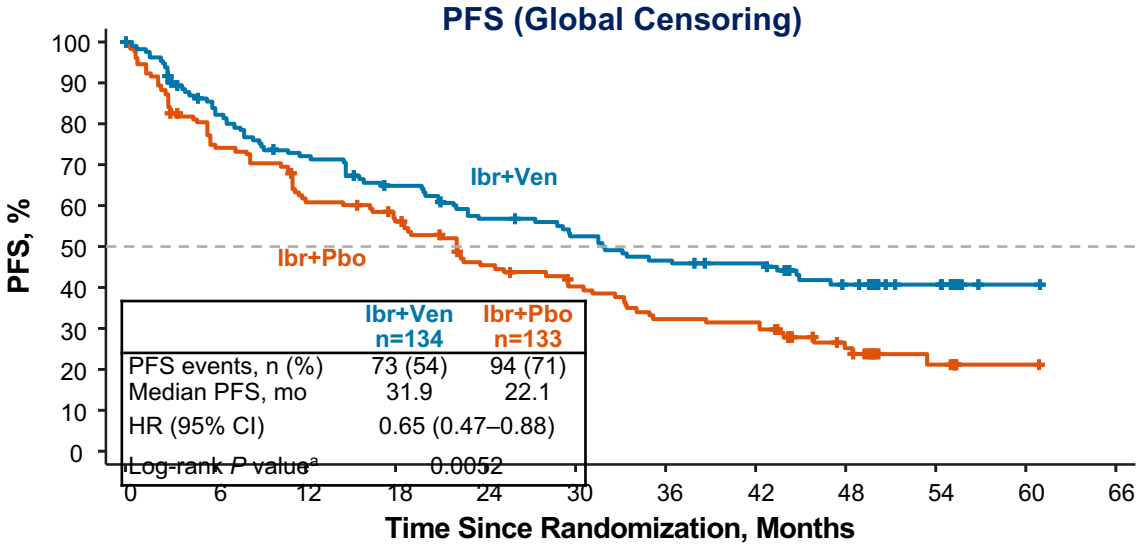
Baseline Characteristics

Characteristic	Ibrutinib + venetoclax n=134	Ibrutinib + placebo n=133
Age		
Median (range), years	69 (42–84)	67 (44–88)
≥65 years, n (%)	93 (69)	86 (65)
ECOG PS, n (%)		
0	74 (55)	74 (56)
1–2	60 (45)	59 (44)
Prior lines of treatment, n (%)	80 (60)	79 (59)
1	32 (24)	31 (23)
2	22 (16)	23 (17)
≥3		
MCL histology, n (%)		
Typical	88 (66)	95 (71)
Blastoid	19 (14)	17 (13)
Pleomorphic	8 (6)	6 (5)
Round cell (CLL-like)	1 (1)	0
Other	18 (13)	15 (11)

Characteristic	Ibrutinib + venetoclax n=134	Ibrutinib + placebo n=133
Simplified MIPI score, n (%)		
Low risk	18 (13)	23 (17)
Intermediate risk	63 (47)	68 (51)
High risk	51 (38)	41 (31)
***TP53* status, n (%)**		
Mutated	40 (30)	37 (28)
Not mutated	66 (49)	57 (43)
Missing	28 (21)	39 (29)
Bulky disease, n (%)		
≥5 cm	62 (46)	53 (40)
≥10 cm	13 (10)	10 (8)
Extranodal disease, n (%)	64 (48)	61 (46)
BM involvement, n (%)	62 (46)	54 (41)
Splenomegaly, n (%)	42 (31)	33 (25)

BM, bone marrow; MIPI, MCL International Prognostic Index.

Primary Endpoint: Investigator-Assessed PFS Was Significantly Improved With Ibrutinib + Venetoclax Versus Ibrutinib + Placebo



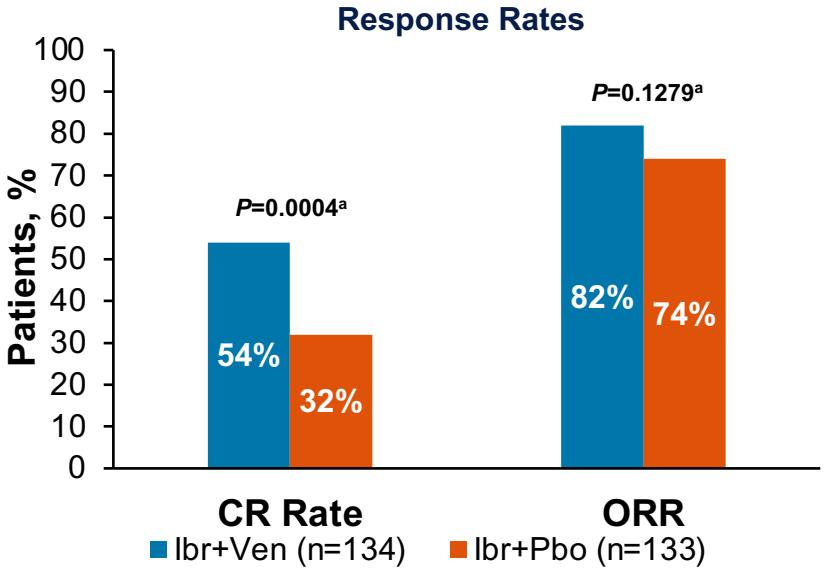
Patients at risk:

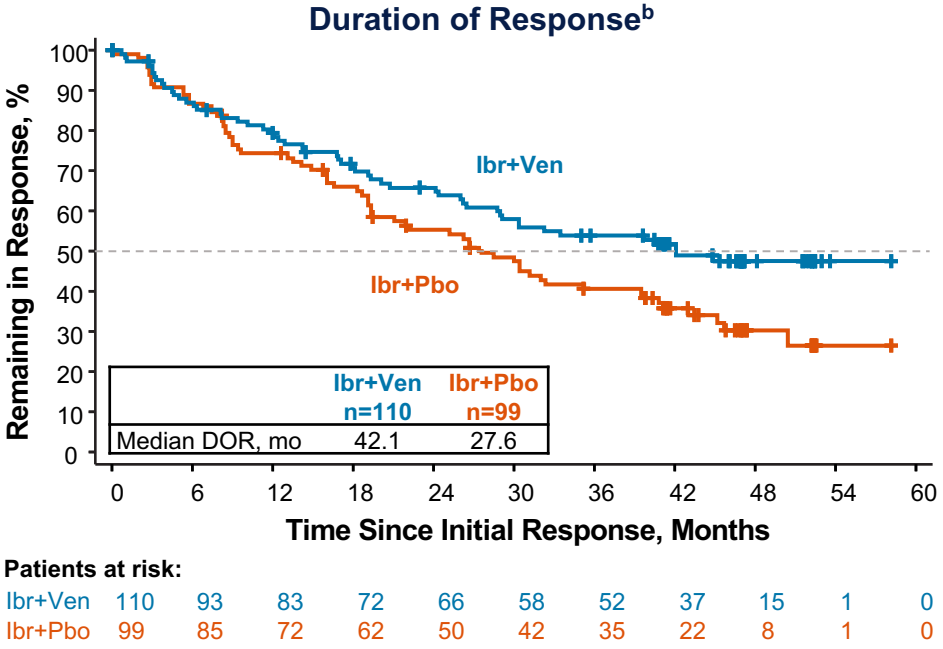
Ibr+Ven	134	107	91	80	69	63	56	53	34	15	1	0
Ibr+Pbo	133	96	79	70	54	46	37	36	18	8	1	0

Median PFS, mo	Global Censoring[b]				US FDA Censoring[c]			
	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank *P* value[a]	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank *P* value[a]
Investigator assessment	31.9	22.1	0.65 (0.47–0.88)	0.0052	42.6	22.1	0.60 (0.44–0.83)	0.0021
IRC assessment	31.8	20.9	0.67 (0.49–0.91)	0.0108	43.5	22.1	0.63 (0.45–0.87)	0.0057

HR, hazard ratio; Ibr, ibrutinib; Pbo, placebo; Ven, venetoclax.
[a]*P* values were determined by stratified log-rank test (stratification factors: prior lines of therapy [1–2 vs ≥3] and TLS risk category [low vs increased risk]). [b]Censoring at last non-PD assessment for patients without PD or death. [c]Patients were censored at last non-PD assessment before start of subsequent anticancer therapy or missing ≥2 consecutive visits prior to a PFS event, whichever occurred first.

CR Rate Was Significantly Improved With Ibrutinib + Venetoclax





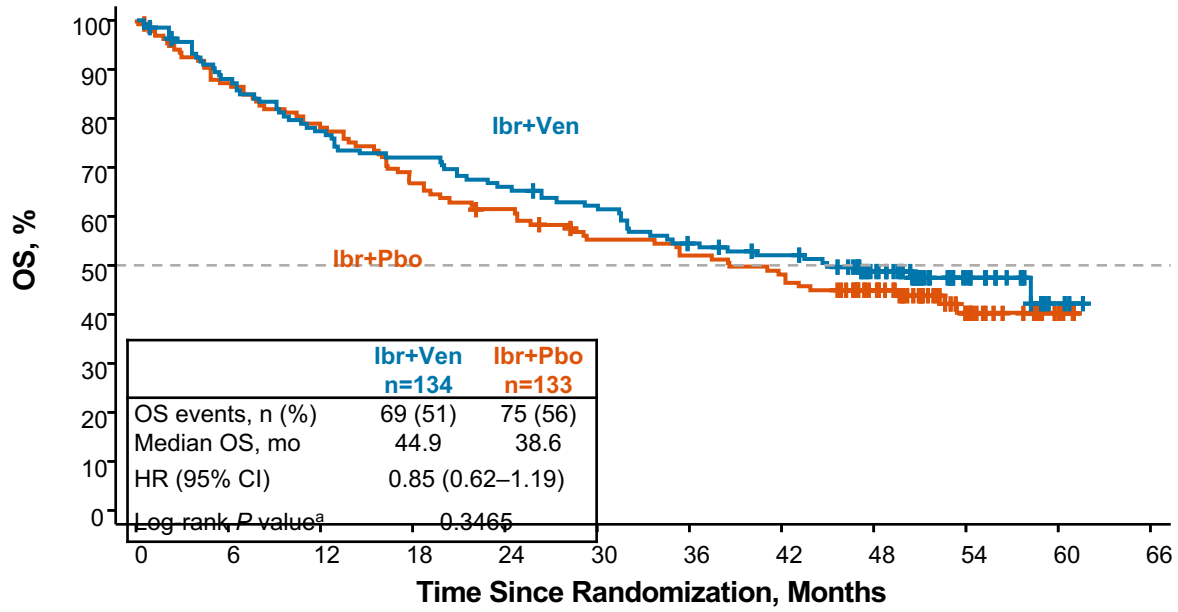
Patients at risk:

Ibr+Ven	110	93	83	72	66	58	52	37	15	1	0
Ibr+Pbo	99	85	72	62	50	42	35	22	8	1	0

DOR, duration of response.

[a]*P* values were determined by stratified Cochran-Mantel-Haenszel test (stratification factors: prior lines of therapy [1–2 vs ≥3] and TLS risk category [low vs increased risk]). [b]Global censoring (censoring at last non-PD assessment for patients without PD or death).

OS Was Numerically Improved At This Interim Analysis



Patients at risk:

Ibr+Ven	134	116	102	95	87	81	70	65	48	20	3	0
Ibr+Pbo	133	115	103	88	80	70	66	61	46	20	4	0

[a]*P* values were determined by stratified log-rank test (stratification factors: prior lines of therapy [1–2 vs ≥3] and TLS risk category [low vs increased risk]).

Conclusions

- Ibrutinib + venetoclax achieved a statistically significant improvement in PFS compared with ibrutinib + placebo, with robust benefit across all sensitivity analyses
- CR rates and TTNT were statistically significantly improved
- OS was numerically but not statistically significantly improved at this interim analysis
- The safety profile of ibrutinib + venetoclax was consistent with known AEs for each single agent, with no new safety signals observed
- Overall, addition of venetoclax to ibrutinib had a favorable benefit-risk profile in patients with R/R MCL

Pirtobrutinib in Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL) Patients with Prior cBTKi: Updated Safety and Efficacy including High-Risk Subgroup Analyses from the Phase 1/2 BRUIN Study

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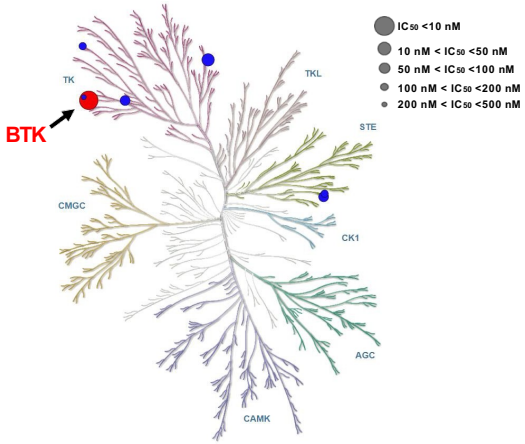
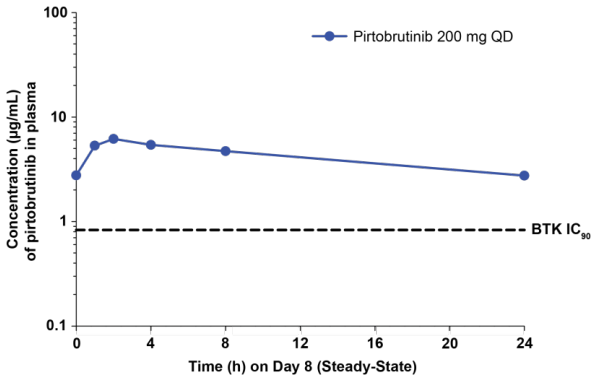
ASH 2023: Abstract 981

Pirtobrutinib is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

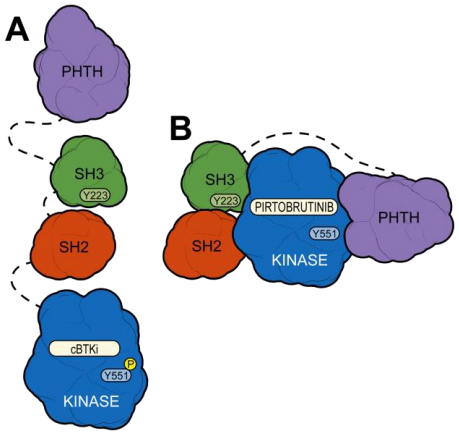
Highly selective for BTK[3,7]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[8]



- Inhibits both WT and C481-mutant BTK with equal low nM potency[8]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[8]
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[8]

[3]Mato et al. *Lancet* 2021; 397: 892–901. [7]Brandhuber et al. *Clin Lymph Myelom Leuk* 2018; 18(Suppl.1):S216. [8]Gomez et al. *Blood*.2023; 142(1):62-72.

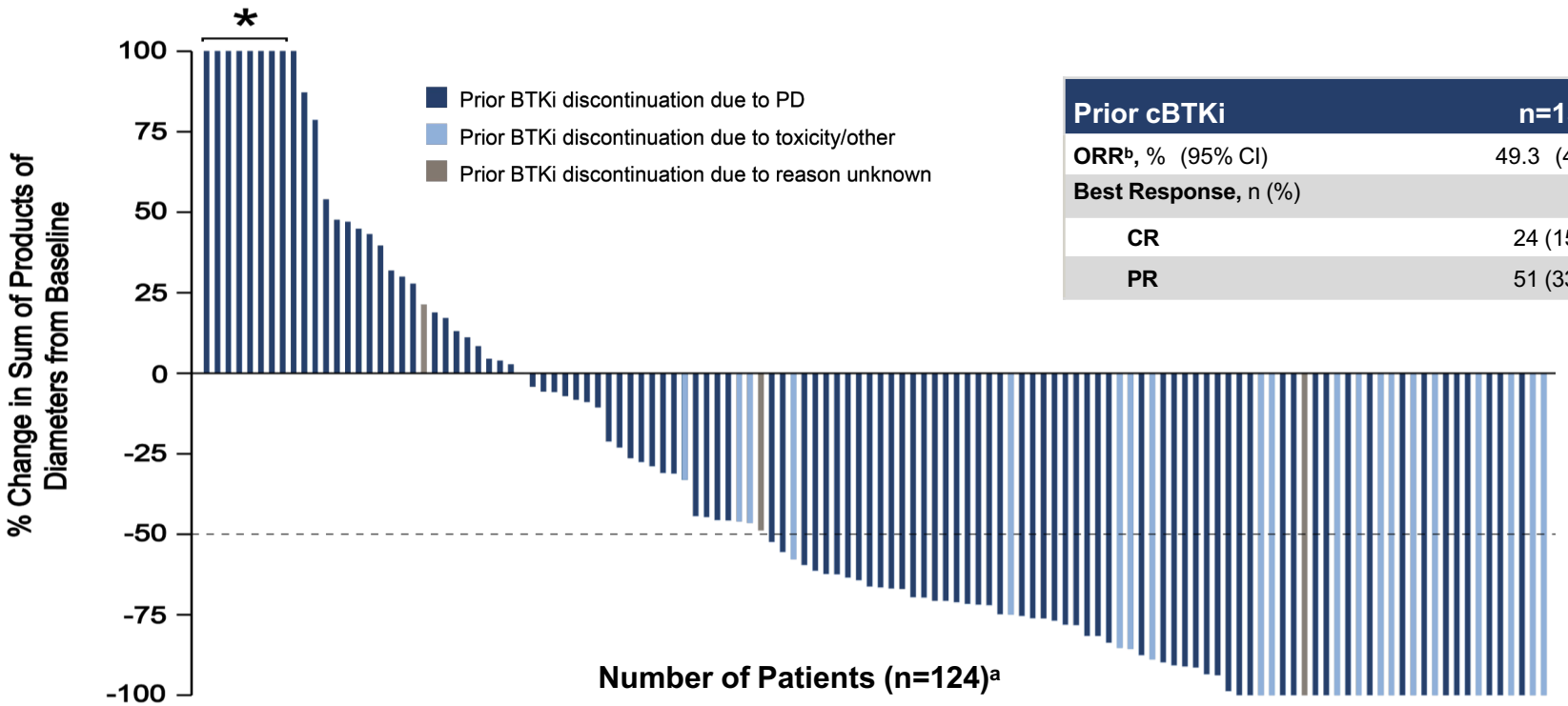
Baseline Characteristics of Patients with MCL

Characteristics	Prior cBTKi n=152	cBTKi Naïve n=14
Median age, years (range)	70 (46-88)	67 (60-86)
Male, n (%)	120 (79)	10 (71)
Histology, n (%)		
Classic/leukemic	120 (79)	11 (79)
Pleomorphic/Blastoid	32 (21)	3 (21)
ECOG PS, n (%)		
0	93 (61)	5 (36)
1	56 (37)	8 (57)
2	3 (2)	1 (7)
sMIPI score, n (%)		
Low risk (0-3)	30 (20)	3 (21)
Intermediate risk (4-5)	79 (52)	5 (36)
High risk (6-11)	43 (28)	6 (43)
Bulky Lymphadenopathy (cm), n (%)		
<5	94 (62)	8 (57)
≥5	36 (24)	5 (36)
No Measurable Lymph Node	22 (15)	1 (7)
Bone marrow involvement, n (%)		
Yes	81 (53)	4 (29)
No	71 (47)	10 (71)
Median number of prior lines of systemic therapy, n (range)	3 (1-9)	2 (1-3)

Characteristics	Prior cBTKi n=152	cBTKi Naïve n=14
Prior therapy, n (%)		
BTK inhibitor	152 (100)	0 (0)
Anti-CD20 antibody	147 (97)	14 (100)
Chemotherapy	137 (90)	14 (100)
Immunomodulator	26 (17)	1 (7)
Stem cell transplant	33 (22)	7 (50)
Autologous	30 (20)	7 (50)
Allogeneic	7 (5)	0 (0)
BCL2 inhibitor	24 (16)	0 (0)
CAR-T	13 (9)	0 (0)
PI3K inhibitor	6 (4)	1 (7)
Reason discontinued any prior BTKi[a], n (%)		
Progressive disease	128 (84)	-
Toxicity / Other	21 (14)	-
Unknown	3 (2)	-
TP53 Mutation status, n (%)		
Yes	30 (20)	3 (21)
No	30 (20)	4 (29)
Missing	92 (61)	7 (50)
Ki-67 index, n (%)		
<30%	18 (12)	2 (14)
≥30%	45 (30)	6 (43)
Missing	89 (59)	6 (43)

[a]In the event more than one reason was noted for discontinuation, disease progression took priority. Total percentages may not sum to 100% due to rounding.

Pirtobrutinib Efficacy in Patients with MCL who Received Prior cBTKi

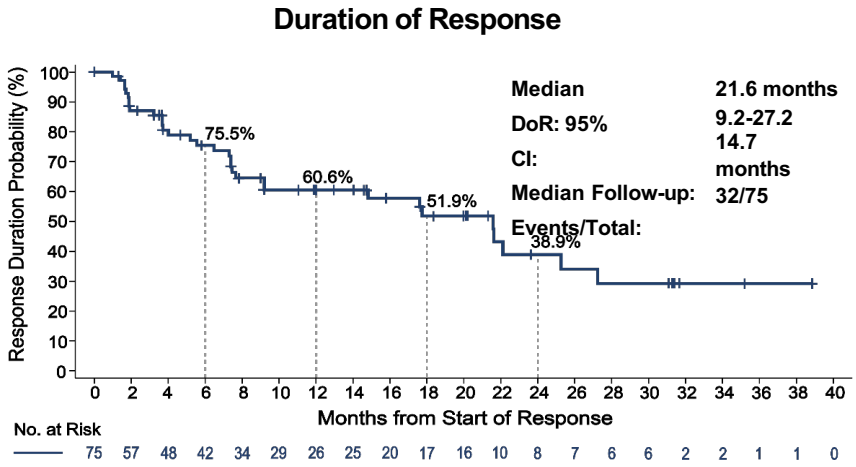


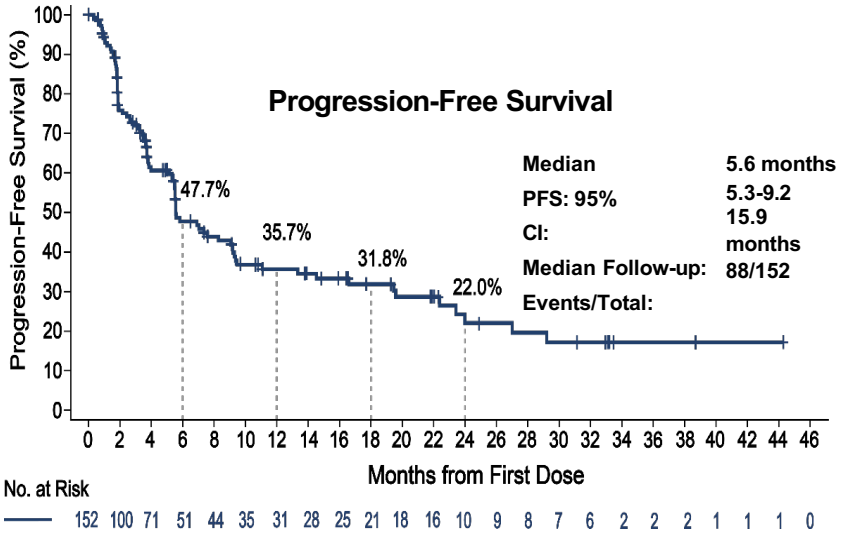
Prior cBTKi	n=152
ORR[b], % (95% CI)	49.3 (41.1-57.6)
Best Response, n (%)	
CR	24 (15.8)
PR	51 (33.6)

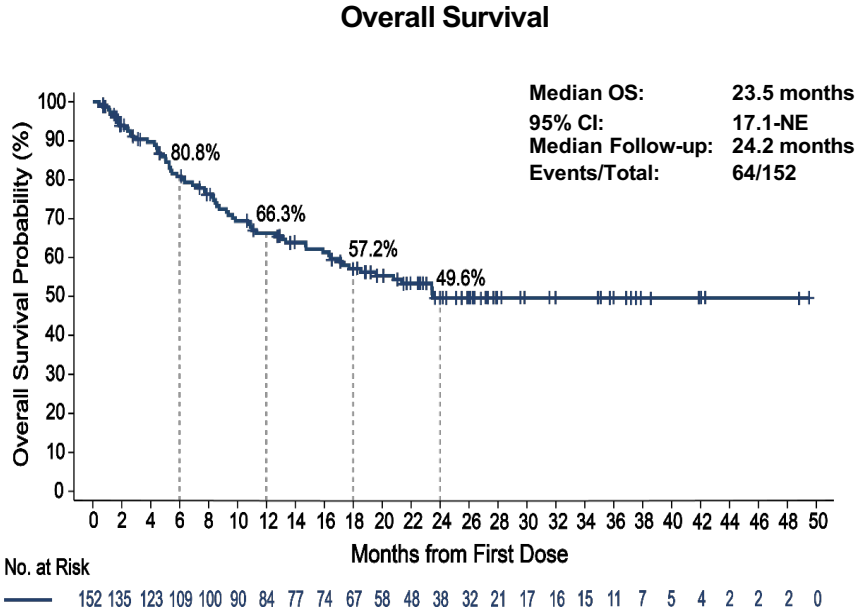
Median Time to First Response was 1.8 months (range: 0.8-13.8)

Data of patients with baseline and at least one evaluable post baseline tumor measurement. *Patients with >100% increase in SPD. [a]Data for 28/152 patients who received prior cBTKi are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [b]ORR is the number of patients with best response of CR or PR divided by the total number of patients; 13 patients with a best response of not evaluable (NE) are included in the denominator. Response status per Lugano 2014 criteria based on IRC assessment.

Pirtobrutinib Outcomes in Prior cBTKi Patients with MCL







Conclusions

- With longer follow-up, pirtobrutinib continues to demonstrate promising efficacy in heavily pre-treated patients with R/R MCL after a prior cBTKi (Median DoR was 21.6 months)
- Pirtobrutinib demonstrated clinically meaningful efficacy in a variety of MCL subgroups, including:
  - Patients with prior cBTKi treatment
  - Patients with prior cBTKi and high-risk molecular features such as Ki-67 and TP53
  - Patients with BTKi naïve MCL
- Pirtobrutinib was well tolerated with low rates of discontinuation due to drug-related toxicity
- Pirtobrutinib represents a new standard of care for patients who received a prior cBTKi
- A randomized, global, phase 3 trial comparing pirtobrutinib with investigator's choice of cBTKi is ongoing in relapsed BTKi-naïve MCL (BRUIN MCL-321; NCT04662255)

ABSTRACT #192, American Society of Hematology, December 9, 2023

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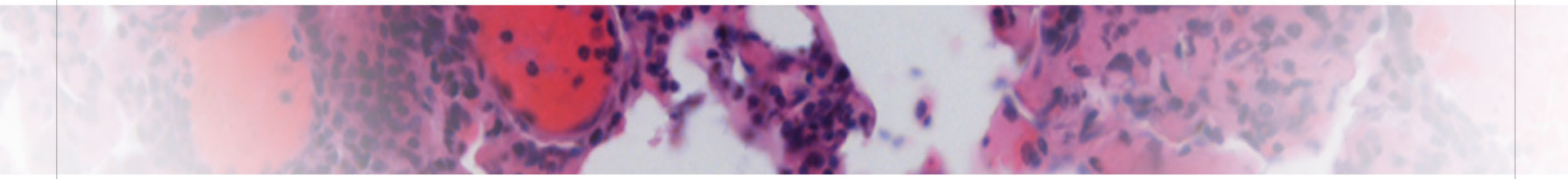
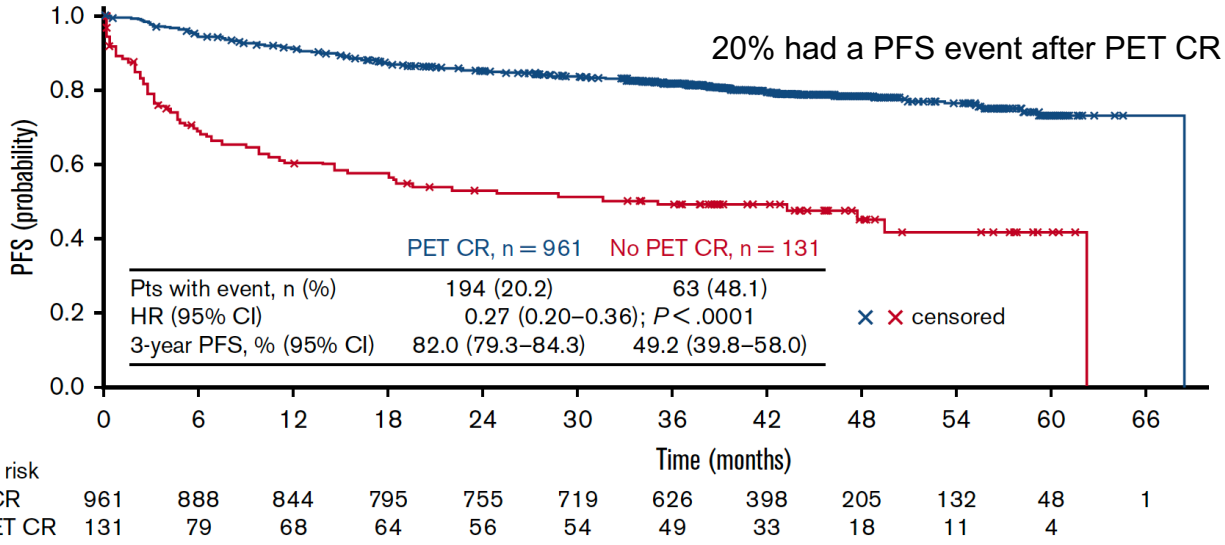


End of Treatment Response Assessment After Frontline Therapy for Aggressive B-cell Lymphoma: Landmark Comparison of a Singular PET/CT scan vs Ultrasensitive Circulating Tumor DNA

Mark Roschewski, Liza Lindenberg, Esther Mena, Rahul Lakhotia, Christopher Melani, Seth Steinberg, Andre Schultz, Gregory Hogan, Jacob Chabon, Sandra Close, Maximilian Diehn, Brian J. Sworder, David M. Kurtz, Ash A. Alizadeh, and Wyndham H. Wilson

PET Scans at EOT are Prognostic But Not Specific for Lymphoma

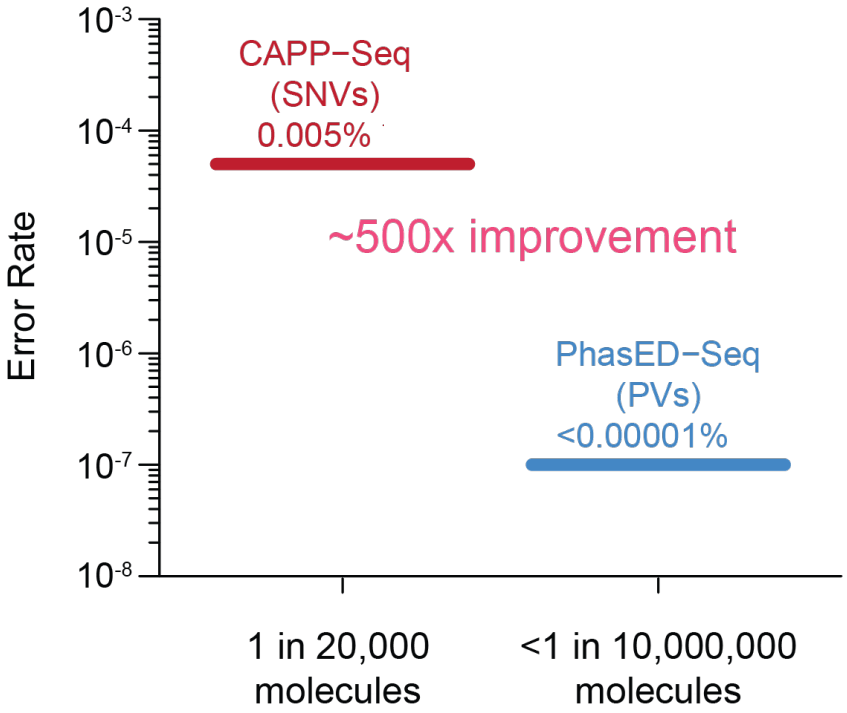
Application of the Lugano 2014 response criteria (GOYA)

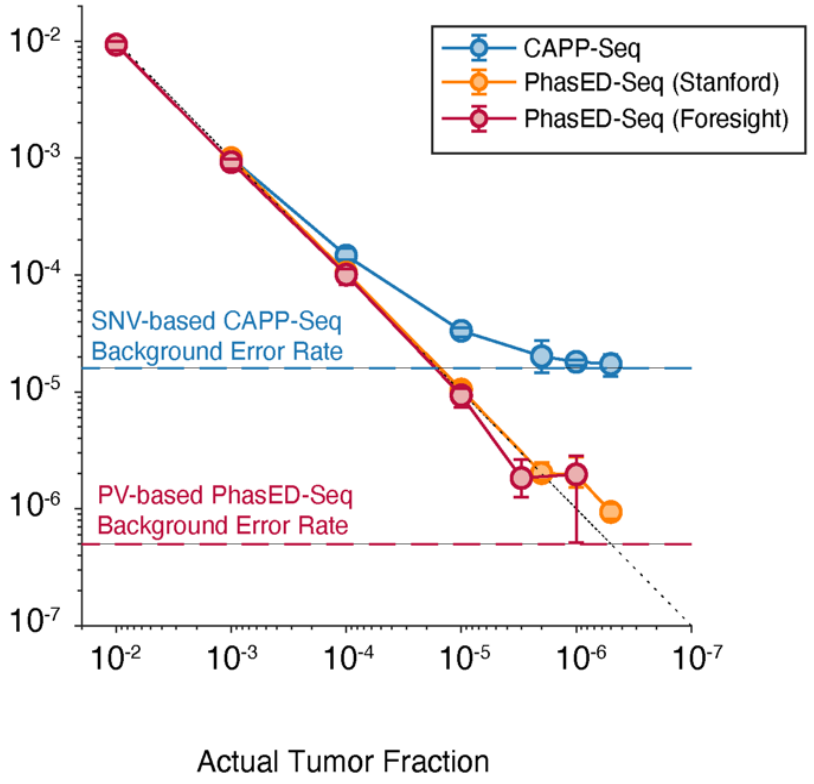


Kostakoglu et al. *Blood Adv* 2021;5(5):1283-1290

Ultrasensitive ctDNA Detection by PhasED-Seq

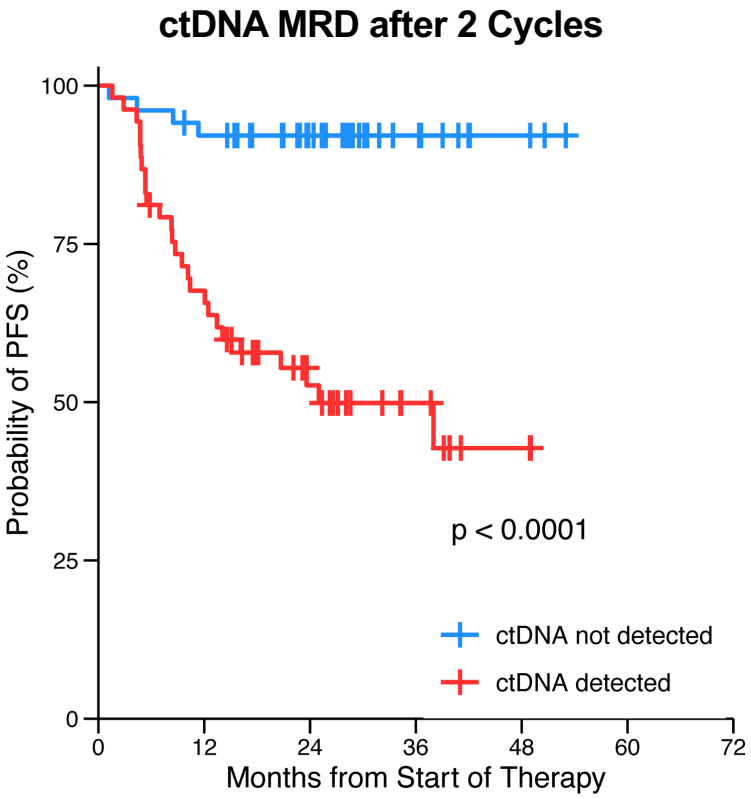
Analytical Sensitivity (~1x10^{-6})

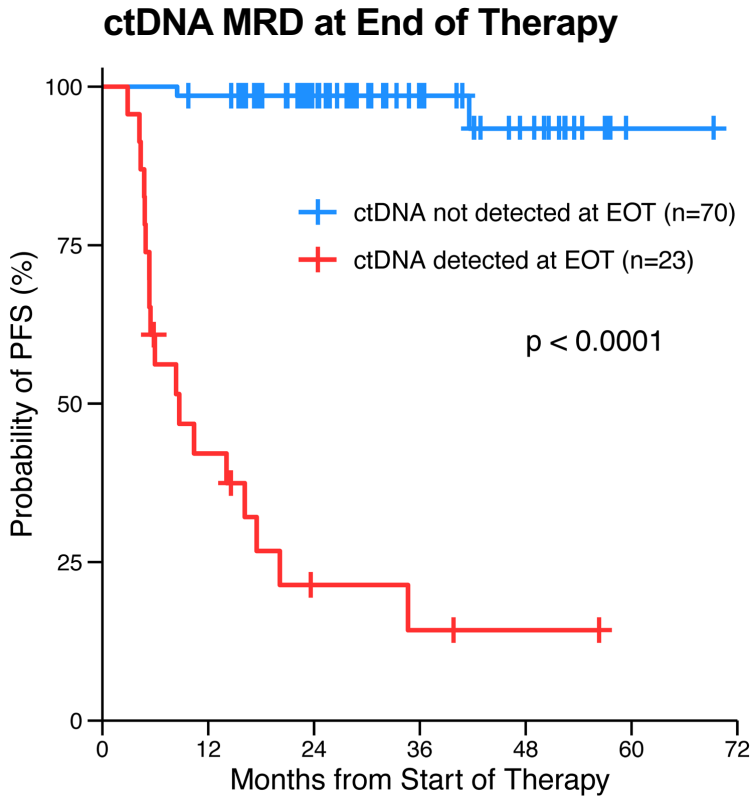




Kurtz et al. *Nat Biotechnol* 2021 Dec;39(12):1537-1547

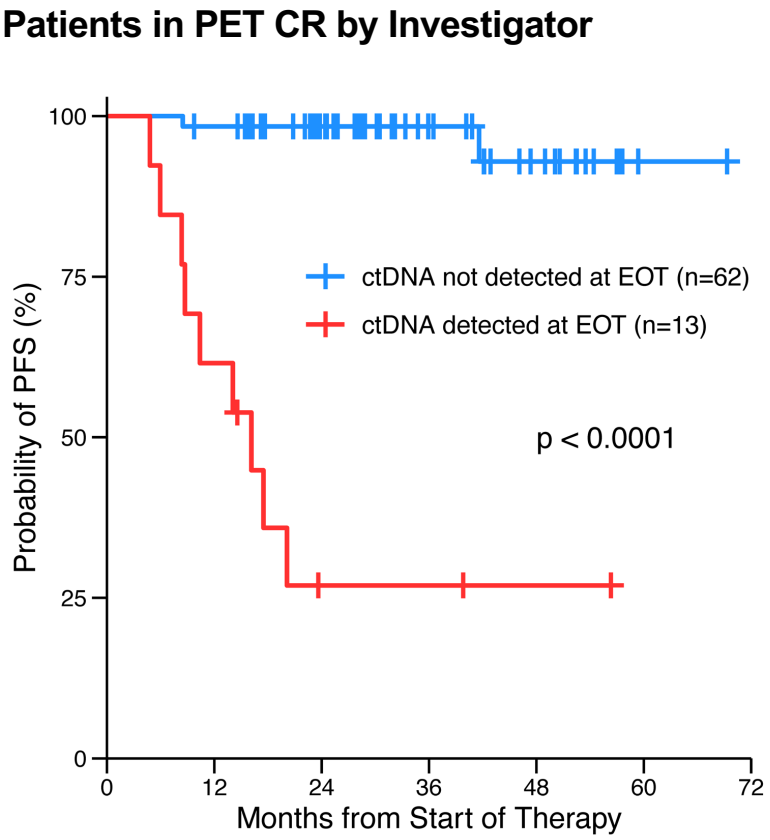
PhasED-Seq MRD Is Prognostic After 2 Cycles and EOT





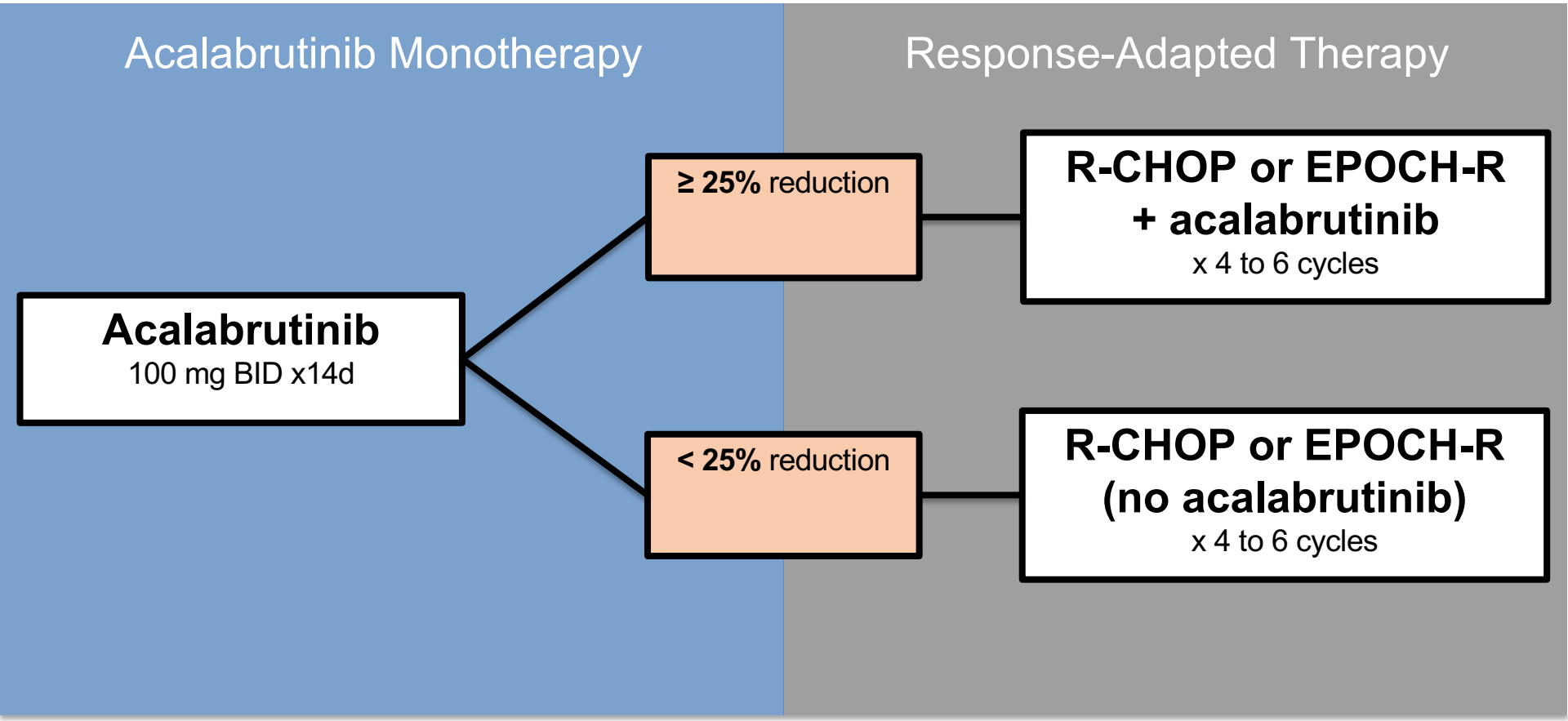
Roschewski et al. *Hematological Oncology* 41(S2):177-179, ICML 2023

PhasED-Seq MRD at EOT Stratifies PET CR



Roschewski et al. *Hematological Oncology* 41(S2):177-179, ICML 2023

Clinical Trial: Acalabrutinib Window Study



Ongoing study NCT: 04002947

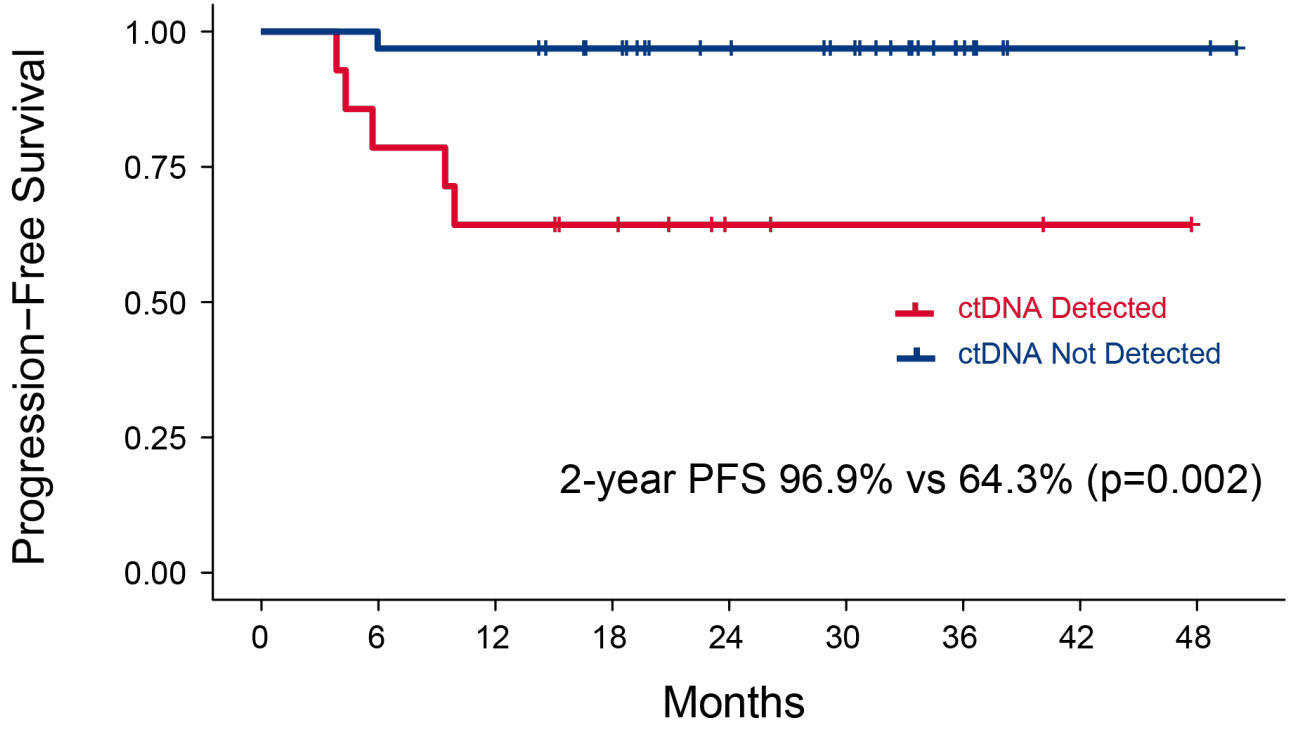
Characteristics of the Study Population

55 pts had a PET/CT and plasma at EOT
54 (98%) were successfully genotyped

Table 1. Characteristics of the Patients

Characteristic	N (%)
Number of patients	54
Female sex	22 (41%)
Age	
Median (range) - yr	62 (26-85)
< 60 years	22 (41%)
60-69 years	22 (41%)
≥ 70 years	10 (18%)
International Prognostic Index	
0-1 (low-risk)	13 (24%)
2 (low-intermediate risk)	15 (28%)
3 (high-intermediate risk)	18 (33%)
4-5 (high risk)	8 (15%)
DLBCL:NOS subtype (Hans)	46 (85%)
Non-GCB	21 (39%)
GCB	24 (44%)
T-cell/histocyte rich	1 (2%)
HGBL with MYC and/or BCL2 or BCL6	8 (15%)

Progression Free Survival By MRD Status after 2 Cycles

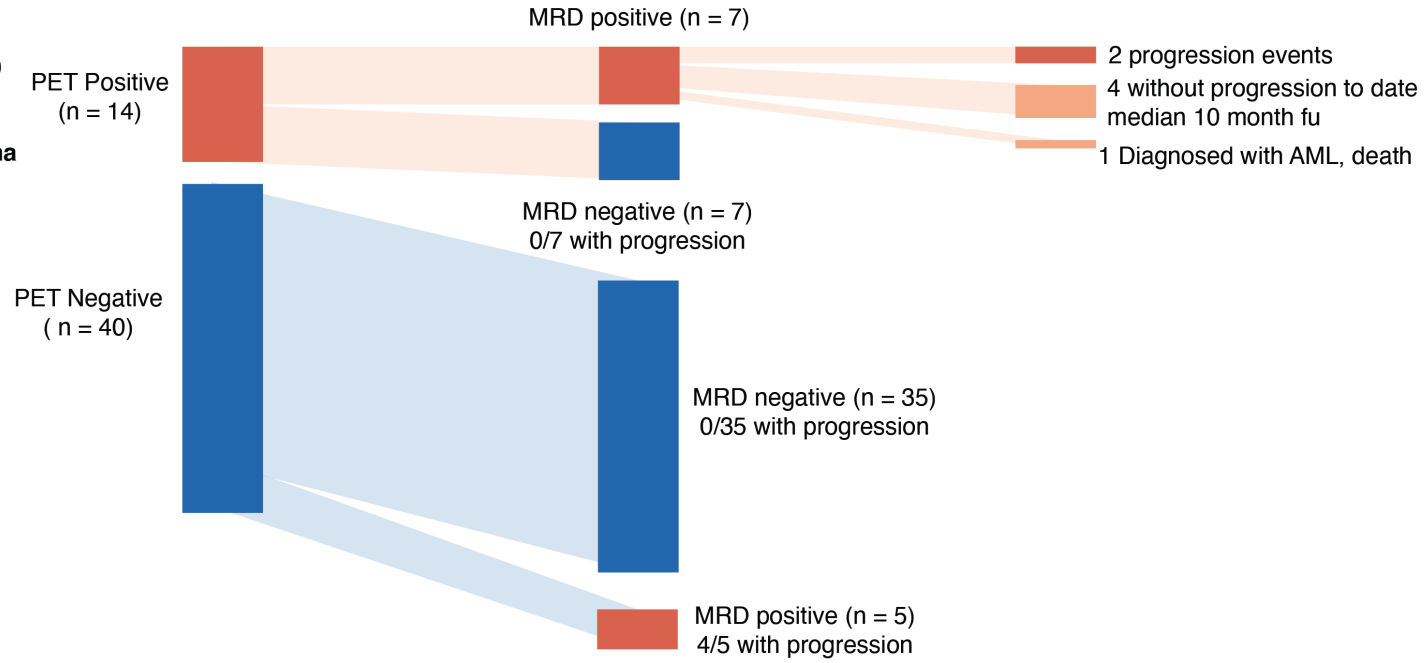


Number at risk									
ctDNA Detected	14	11	9	7	3	2	2	1	0
ctDNA Not Detected	32	31	31	27	20	17	7	2	2

Additional Procedures at EOT to Determine Remission

Additional Testing
follow-up PET/CTs (n = 5)
Biopsy (n = 4)

8/9 negative for lymphoma



Conclusions

- ctDNA by PhasED-Seq is prognostic both after 2 cycles and at EOT
- Undetectable ctDNA by PhasED-Seq at EOT predicts a very low likelihood of progression with greater predictive value than PET/CT
- Additional procedures (biopsy, repeat PET/CT scans) are often required to adjudicate EOT PET/CT scans; most do not have active lymphoma
- Salvage therapy should not be delivered based on a singular EOT PET/CT

Circulating Tumor DNA Dynamics as Early Outcome Predictors for Lisocabtagene Maraleucel as Second-Line Therapy for Large B-Cell Lymphoma from the Phase 3 TRANSFORM Study

Lara Stepan,[1*] Sahar Ansari,[1*] Abood Okal,[2] Justine Dell'Aringa,[1] Ethan Thompson,[1] Alessandro Crotta,[3] Victor A. Chow,[1] Jeremy S. Abramson,[4] Manali Kamdar,[5] Jacob J. Chabon,[6] Gregory Hogan,[6] David M. Kurtz,[7] Ash A. Alizadeh,[7] Leanne Peiser[1]

[1]Bristol Myers Squibb, Seattle, WA, USA; [2]Bristol Myers Squibb, Princeton, NJ, USA; [3]Celgene, a Bristol-Myers Squibb Company, Boudry, Switzerland; [4]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [5]University of Colorado Cancer Center, Aurora CO, USA; [6]Foresight Diagnostics, Aurora, CO, USA; [7]Stanford University, Stanford, CA, USA

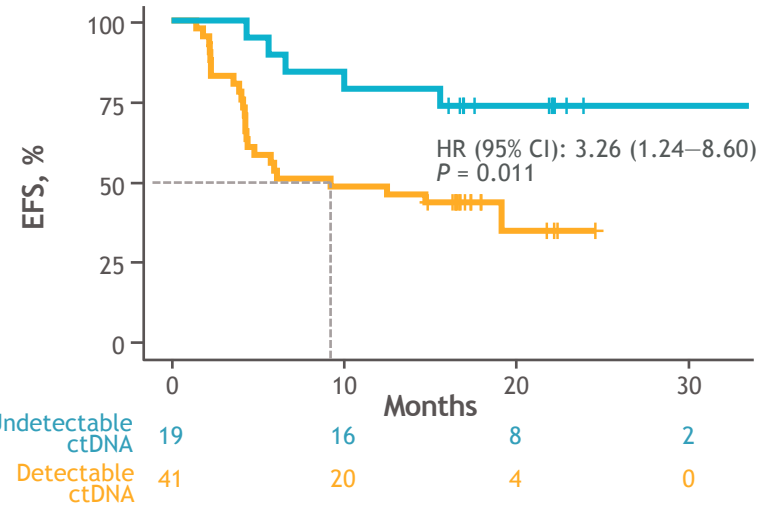
*L.S. and S.A. contributed equally to this work

ASH 2023, Presentation 225

Undetectable ctDNA after liso-cel correlates with durable benefit

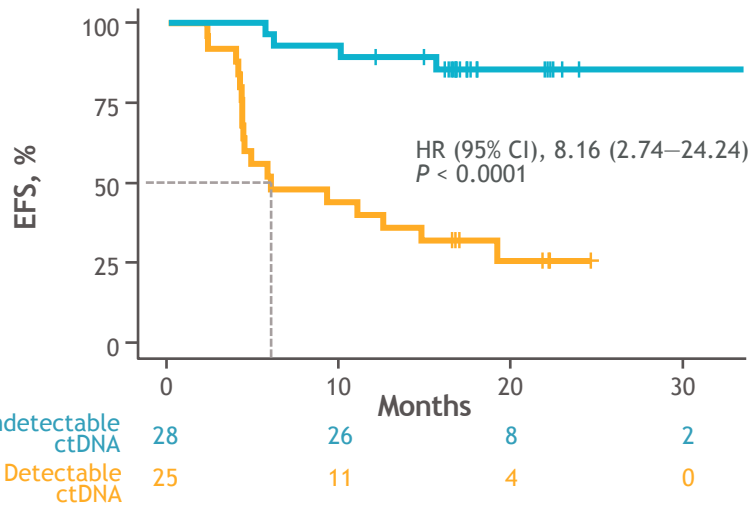
Evaluable patients treated with liso-cel

Day 15



Achieving undetectable ctDNA as early as Day 15 was strongly associated with longer durable clinical benefit

Month 3



The association of ctDNA clearance and durable outcome was most significant at Month 3

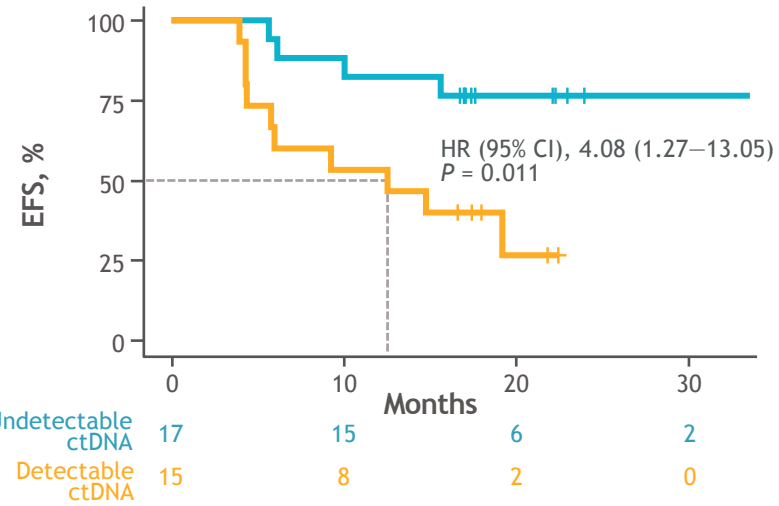
EFS is calculated from randomization. Significance was tested with log-rank test.

Stepan L, et al. ASH 2023 [Presentation #225]

Detectable ctDNA identifies patients in PET CR at risk of relapse

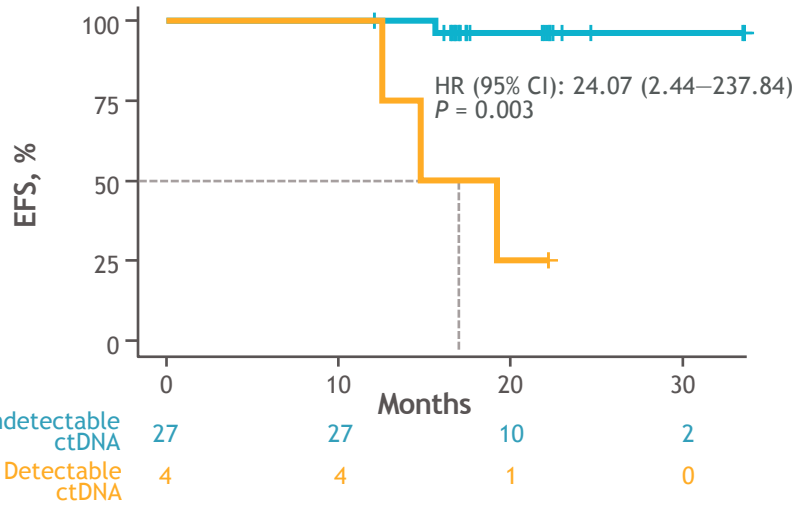
Evaluable patients treated with liso-cel with CR

Patients with CR by PET/CT at Month 1



Detectable ctDNA in patients with CR by PET/CT may be a potential biomarker for risk of PD

Patients with CR by PET/CT at Month 12



All 4 patients with detectable ctDNA and CR by PET/CT at Month 12 experienced an EFS event: PD (n = 3); COVID death (n = 1)

EFS is calculated from randomization. Significance was tested with log-rank test.

Stepan L, et al. ASH 2023 [Presentation #225]

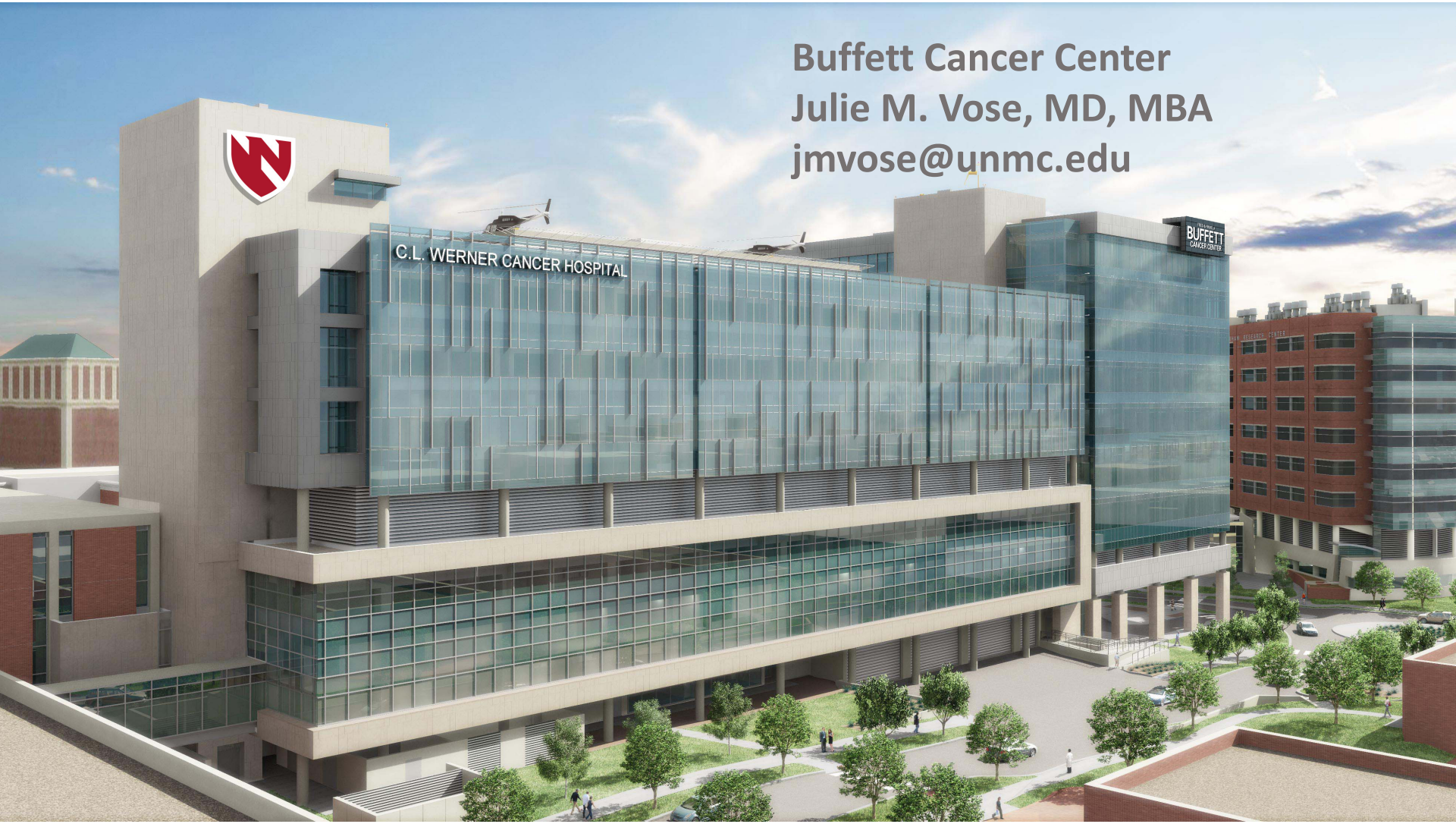
TRANSFORM ctDNA results demonstrate value of MRD for disease surveillance & early prediction of durable clinical benefit

- Liso-cel induced deep and durable responses, including both radiographic & stringent molecular remission (undetectable ctDNA MRD) for patients with 2L LBCL
  - Pretreatment ctDNA levels correlated with disease burden
  - Achieving undetectable ctDNA status strongly predicted CR and durable clinical benefit (EFS)
  - Rapid reduction of ctDNA levels by Day 15 in complete responders after liso-cel treatment allowed early prediction of durable clinical benefit
  - More patients achieved undetectable ctDNA status over time, which was durably maintained ≥1 year
- Detectable ctDNA was associated with PD risk. In patients with CR, detectable ctDNA adds prognostic value beyond PET/CT imaging
- Similar longitudinal analyses evaluating ctDNA profiling in the SOC arm are currently in progress

Stepan L, et al. ASH 2023 [Presentation #225]

Conclusions:

1. Induction chemotherapy: Future studies with consideration of DLBCL subtypes, patient characteristics, and risk models (escalation vs. de-escalation)
2. Salvage Therapy: Bi-specifics, CAR-T earlier in lines of treatment is the trend
3. MCL: BTK inhibitors: earlier in disease, new BTK inhibitor combinations
4. Ct-DNA in DLBCL: More sensitive techniques in trials – alone and in combination with PET scans are very predictive of relapse



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