VIRTUAL CHALLENGING CASE CLINIC:

B-Cell Lymphomas

Series in Review
March 9, 2022

THIS ACTIVITY JOINTLY PROVIDED BY University of Nebraska Medical Center Bio Ascend™

Course Director and Presenter

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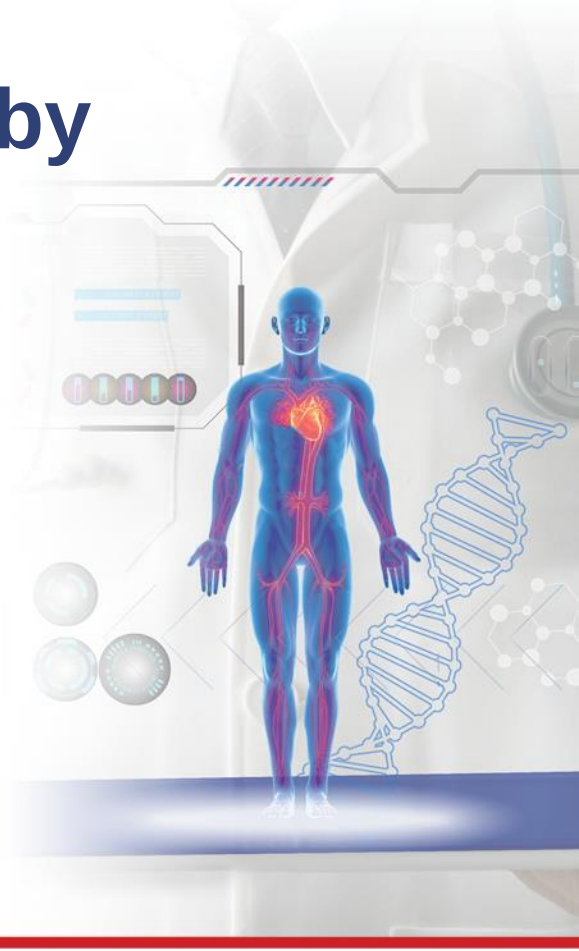

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Disclosures

John P. Leonard, MD

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Planning Committee

The following planning committee members have nothing to disclose:
UNMC: Brenda Ram, CMP, CHCP

Bio Ascend: Patti Bunyasaranand, MS; Dru Dace, PhD; Kraig Steubing

Learning Objectives

- Evaluate best available evidence regarding treatment for patients with B-cell lymphomas
- Assess the implications of emerging clinical trial data regarding B-cell lymphoma treatment approaches
- Develop strategies to address complicated B-cell lymphoma cases

Reminders

- Visit **www.oncologycaseclinic.com** to view past webinars

2021-2022 Virtual Challenging Case Studies – B-Cell Lymphoma – Series in Review

Month	Topic	Presenter
April 2021	Mantle cell lymphoma	Jonathon Cohen, MD, MS
May 2021	CAR T-cells	Mehdi Hamadani, MD
June 2021	Hodgkin lymphoma	Ann LaCasce, MD, MMSc
July 2021	US Clinical Trials Roundtable	John P. Leonard, MD Jonathan Friedberg, MD, MMSc Brad Kahl, MD
August 2021	Updates from ASCO, EHA, and ICML	Gilles Salles, MD, PhD
September 2021	CNS lymphoma	James Rubenstein, MD, PhD
October 2021	Chronic lymphocytic leukemia	Matthew Davids, MD, MMSc
November 2021	Diffuse large B-cell lymphoma	Grzegorz Nowakowski, MD
December 2021	Marginal zone lymphoma	Leo I. Gordon, MD
January 2022	Updates from ASH	John P. Leonard, MD
February 2022	Follicular lymphoma	Carla Casulo, MD
March 2022	Series in Review	John P. Leonard, MD

FDA Lymphoma Approvals in 2021-2022

Date	Agent/Regimen	Indication
February 5, 2021	Umbralisib	• R/R MZL who have received at least 1 prior anti-CD20 tx • R/R FL who have received at least 3 prior lines of tx
February 5, 2021	Lisocabtagene maraleucel	R/R LBCL after 2 or more lines of systemic therapy
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UNITY-NHL: Study Design

- Multicenter phase IIb trial evaluating umbralisib in multiple disease-specific cohorts and treatment combinations; current analysis focuses on umbralisib monotherapy in R/R iNHL

*MZL patients R/R to ≥ 1 line of therapy including ≥ 1 CD20-directed regimen; FL and SLL patients R/R to ≥ 2 lines of therapy including ≥ 1 CD20-directed regimen plus an alkylating agent.

- Primary endpoint: ORR by IRC
- Secondary endpoints: DoR, PFS, TTR, and safety

Zinzani. ASH 2020. Abstr 2934.

UNITY-NHL (iNHL Cohort): Baseline Characteristics

Baseline Characteristic	MZL Cohort (n = 69)	FL Cohort (n = 117)	SLL Cohort (n = 22)	Total Population (N = 208)
Median age, yrs (range)	67 (34-88)	65 (29-87)	65 (49-86)	66 (29-88)
Male, n (%)	33 (48)	72 (62)	13 (59)	118 (57)
ECOG PS 0/1/2, %	55/42/3	56/41/3	64/36/0	56/41/3
Disease stage III-IV, n (%)	56 (81)	85 (73)	19 (86)	160 (77)
FL grade 1/2/3A, %	--	26/45/27	--	--
MZL subtype MALT/splenic/nodal, %	55/16/29	--	--	--
Median prior therapies (range)	2 (1-6)	3 (1-10)	2 (1-4)	2 (1-10)
Prior chemoimmunotherapy, n (%) ▪ Bendamustine-based regimen ▪ Cyclophosphamide-based regimen	52 (75) 24 (35) 37 (54)	117 (100) 72 (62) 89 (76)	20 (91) 15 (68) 10 (45)	189 (91) 111 (53) 136 (65)
Refractory to last therapy, n (%)	18 (26)	42 (36)	11 (50)	71 (34)
Median time since last therapy, mos	17	13	10	14

Zinzani. ASH 2020. Abstr 2934.

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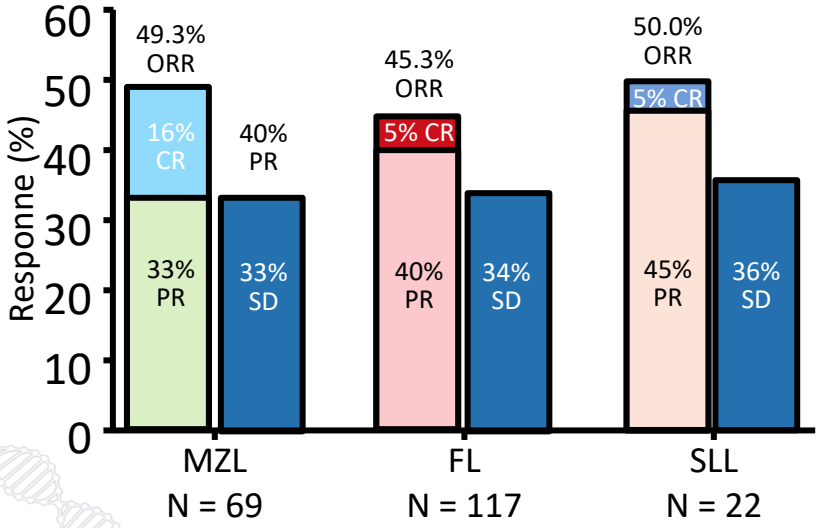
UNITY-NHL (iNHL Cohort): IRC-Assessed ORR

- Umbralisib monotherapy yielded 47.1% ORR and 81.3% DCR across iNHL population
- Investigator-assessed ORR consistent with IRC-assessed ORR (data not shown)



IRC-Assessed Efficacy Outcome	MZL Cohort (n = 69)	FL Cohort (n = 117)	SLL Cohort (n = 22)
DCR, %	82.6	79.5	86.4
Any reduction in disease, %	90.6	83.5	89.5
Median time to response, mos	2.8	4.6	2.7
Median follow up, mos	27.8	27.5	29.3

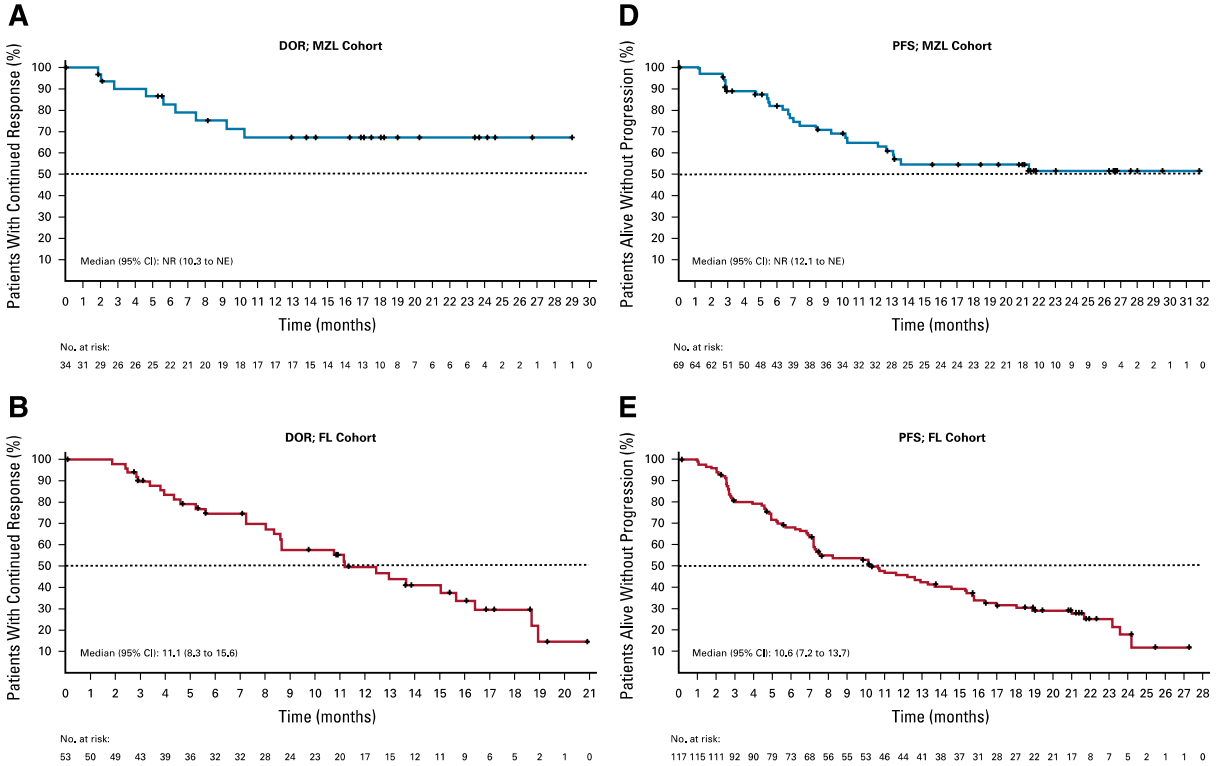
Zinzani. ASH 2020. Abstr 2934.

UNITY-NHL (iNHL Cohort): IRC-Assessed ORR by Subgroup

IRC-Assessed ORR	MZL Cohort (n = 69)	FL Cohort (n = 117)	SLL Cohort (n = 22)
All patients, %	49.3	45.3	50.0
Number of prior therapies, % (n/N)			
▪ < 3	49 (25/51)	41 (20/49)	33 (4/12)
▪ ≥ 3	50 (9/18)	49 (33/68)	70 (7/10)
Prior therapy type, % (n/N)			
▪ Anti-CD20 mAb and alkylating agent	48 (25/52)	45 (53/117)	45 (9/20)
▪ Lenalidomide	75 (3/4)	39 (7/18)	--
MZL subtype, % (n/N)			
▪ MALT	45 (17/38)	--	--
▪ Splenic	45 (5/11)		
▪ Nodal	60 (12/20)		
FL grade, % (n/N)			
▪ 1	--	57 (17/30)	--
▪ 2		45 (24/53)	
▪ 3A		34 (11/32)	

Zinzani. ASH 2020. Abstr 2934.

UNITY-NHL (iNHL Cohort): IRC-Assessed DoR and PFS



Fowler N, et al. *J Clin Oncol*. 2021;39:1609-1618.

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UNITY-NHL (iNHL Cohort): AEs

All-Cause AEs Occurring in > 15 % of Patients, %	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	59.1	30.8	18.3	10.1	0
Nausea	39.4	25.0	13.9	0.5	0
Fatigue	30.8	18.3	9.1	3.4	0
Vomiting	23.6	13.9	9.1	0.5	0
Cough	20.7	16.8	3.8	0	0
ALT increased	20.2	6.3	7.2	5.3	1.4
AST increased	18.8	9.1	2.4	7.2	0
Decreased appetite	18.8	11.1	5.8	1.9	0
Dizziness	18.3	13.9	3.8	0.5	0
Neutropenia	15.9	2.4	1.9	4.8	6.7
Headache	15.9	10.6	4.3	1.0	0

No grade 5 AEs

Zinzani. ASH 2020. Abstr 2934.

UNITY-NHL (iNHL Cohort): AEs of Special Interest

- Based on median follow-up of 27+ mos, safety profile of umbralisib distinct from previous-generation PI3K inhibitors
- Treatment discontinuations due to ALT/AST elevations (2.9%) or grade 3 diarrhea (2.9%)
- 4 patients (1.9%) developed noninfectious colitis; resolved in 3 patients, who were able to remain on umbralisib
- Additional AEs:
  - Grade 3/4 opportunistic infections (3.4%)
  - Grade 3/4 rash (1.9%)
  - Grade 3/4 pneumonitis (1.0%)

Zinzani. ASH 2020. Abstr 2934.

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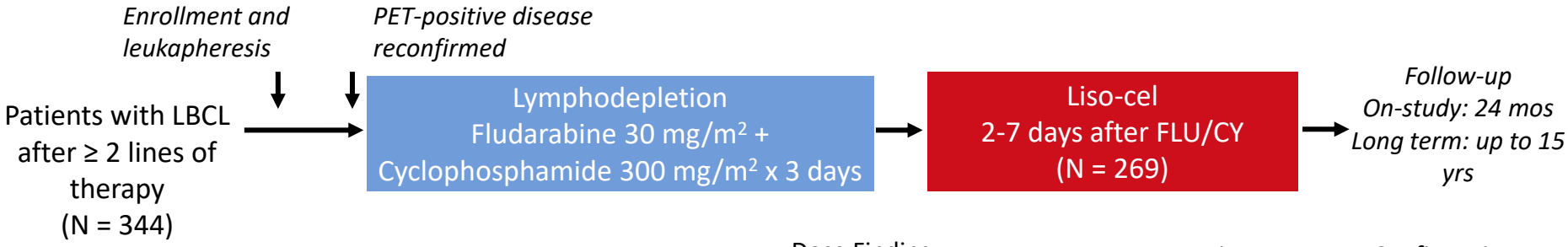
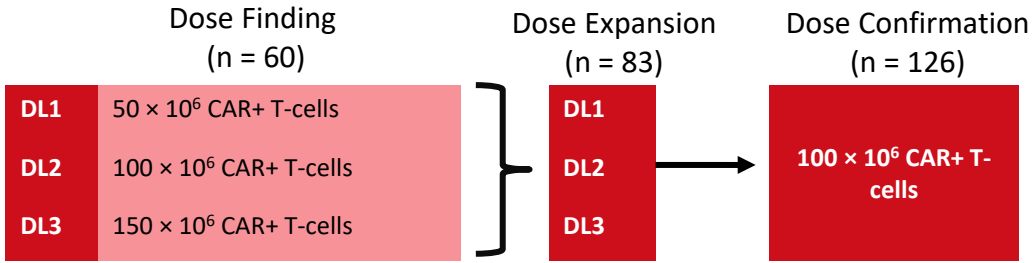
TRANSCEND NHL 001: Study Design

- Pivotal multicenter phase I study





- Primary endpoints
  - AEs, ORR by IRC
- Secondary endpoints
  - CR rate by IRC, DoR, PFS, OS, PK

Abramson. ASH 2019. Abstr 241.

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TRANSCEND NHL 001: Baseline Characteristics

Characteristic	Liso-cel (N = 269)
Median age, yrs (range) ▪ Age ≥ 65/≥ 75, n (%)	63 (18-86) 112 (42)/27 (10)
NHL subtype, n (%) ▪ DLBCL NOS ▪ Transformed from FL/other indolent lymphomas ▪ HGBCL/PBMCL/FL3B	 137 (51) 60 (22)/18 (7) 36 (13)/15 (6)/3 (1)
Secondary CNS lymphoma, n (%)	7 (3)
Screening ECOG PS 0-1/2, n (%)	265 (99)/4 (1)
High disease burden*, n (%)	103 (38)
Creatinine clearance > 30 to < 60 mL/min, n (%)	51 (19)
LVEF ≥ 40% to < 50%, n (%)	13 (5)
Previous system therapies, median (range) ▪ ≥ 4 previous therapies, n (%)	3 (1-8) 71 (26)
Previous HSCT, n (%) ▪ Autologous/allogeneic HSCT	94 (35) 90 (33)/9 (3)
Refractory to chemotherapy, n (%)	181 (67)
No previous CR, n (%)	119 (44)
Received bridging therapy, n (%)	159 (59)

Defined as LDC SPD ≥ 50 cm^2 or LDH ≥ 500 U/L.

- High-risk features associated with reduced survival in 89% of patients
  - No previous CR
  - No previous ASCT
  - ECOG PS of 2
  - Refractory to second-line or later therapy
  - Primary refractory disease
  - HGBCL/double/triple hit lymphoma

Abramson. ASH 2019. Abstr 241.

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TRANSCEND NHL 001: Treatment-Emergent AEs

AEs in ≥ 25% of Patients, n (%)	Liso-cel (N = 269) All Grades	Liso-cel (N = 269) Grade ≥ 3
Total	267 (99)	213 (79)
Neutropenia	169 (63)	161 (60)
Anemia	129 (48)	101 (38)
Fatigue	119 (44)	4 (1)
CRS	113 (42)	6 (2)
Nausea	90 (33)	4 (1)
Thrombocytopenia	84 (31)	72 (27)
Headache	80 (30)	3 (1)
Decreased appetite	76 (28)	7 (3)
Diarrhea	71 (26)	1 (< 1)

- Grade 5 events occurred in 7 patients (3%)
- Grade 5 events considered to be related to liso-cel: n = 4

AE	Liso-cel (N = 269)
CRS or NE, n (%)	127 (47)
▪ Treated with toci + steroids/toci/steroids, %	13/7/8
▪ Treated with vasopressors, %	3
CRS, n (%)	113 (42)
▪ Grade 3/4/5, n (%)	4 (1)/2 (1)/0
▪ Days to onset, median (range)	5 (1-14)
▪ Days to resolution, median (range)	5 (1-17)
▪ Treated with toci + steroids/toci/steroids, %	8/10/2
NE, n (%)	80 (30)
▪ Grade 3/4/5, n (%)	23 (9)/4 (1)/0
▪ Days to onset, median (range)	9 (1-66)
▪ Days to resolution, median (range)	11 (1-86)
▪ Treated with toci +steroids/toci/steroids, %	3/0.4/13
ICU admissions, n (%)	19 (7)
▪ For CRS and/or NE	12 (4)
▪ Other reasons	7 (3)

- CRS and NE were reversible: 1 unresolved NE (grade 1 tremor) at data cutoff; 8 had ongoing CRS/NE at time of death from other reasons

Abramson. ASH 2019. Abstr 241.

TRANSCEND NHL 001: Additional TEAEs of Interest

TEAEs, n (%)	Liso-cel (N = 269)
Prolonged grade ≥ 3 cytopenias	100 (37)
Grade ≥ 3 infections	33 (12)
▪ Bacterial	11 (4)
▪ Viral	4 (1)
▪ Fungal	2 (1)
▪ Pathogen unspecified	22 (8)
Infusion-related reactions	3 (1)
▪ Grade ≥ 3	0
Tumor lysis syndrome	2 (1)
▪ Grade ≥ 3	2 (1)
Hypogammaglobulinemia	37 (14)
▪ Grade ≥ 3	0

- Laboratory-based hypogammaglobulinemia (IgG < 500 mg/dL) in 49% (n/N = 127/258) at baseline, 58% (n/N = 136/236) at Day 29, and 61% (n/N = 68/112) at Day 365
- Intravenous immunoglobulin administered to 21% (n = 57) over entire follow-up

Abramson. ASH 2019. Abstr 241.

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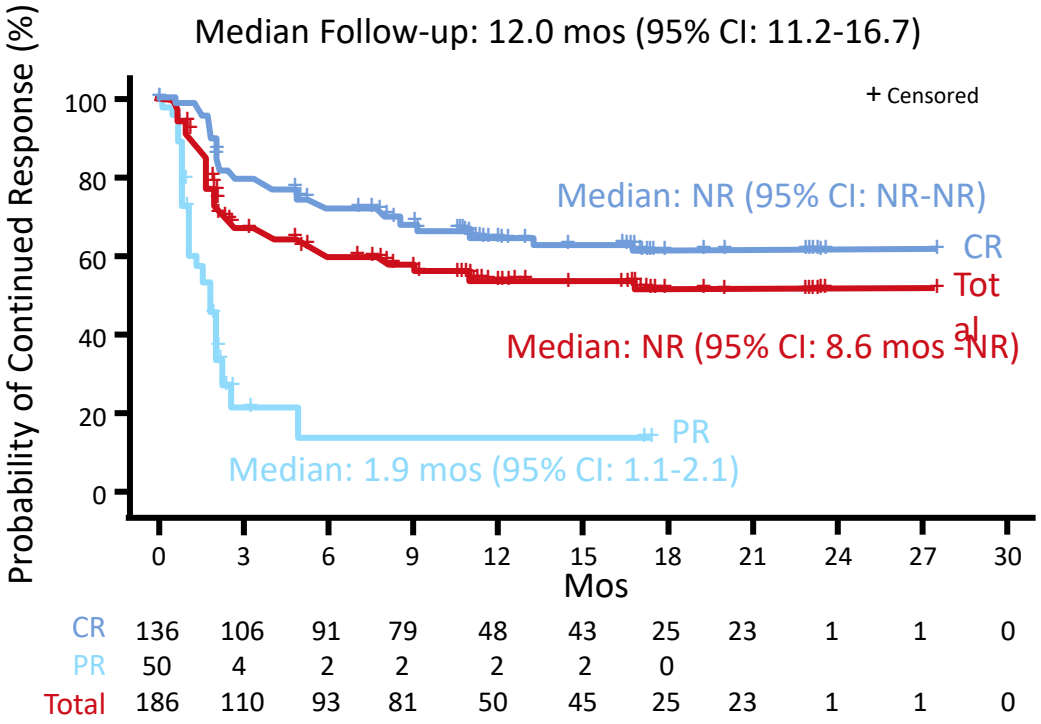
TRANSCEND NHL 001: Response and Durability by IRC

Efficacy-Evaluable Patients (N = 256)	
ORR (95% CI)	73 (67-78)
CR rate (95% CI)	53 (47-59)
Time to first CR or PR, median mos (range)	1.0 (0.7-8.9)
DoR at 6 mos, % (95% CI)	60.4 (52.6-67.3)
DoR at 12 mos, % (95% CI)	54.7 (46.7-62.0)



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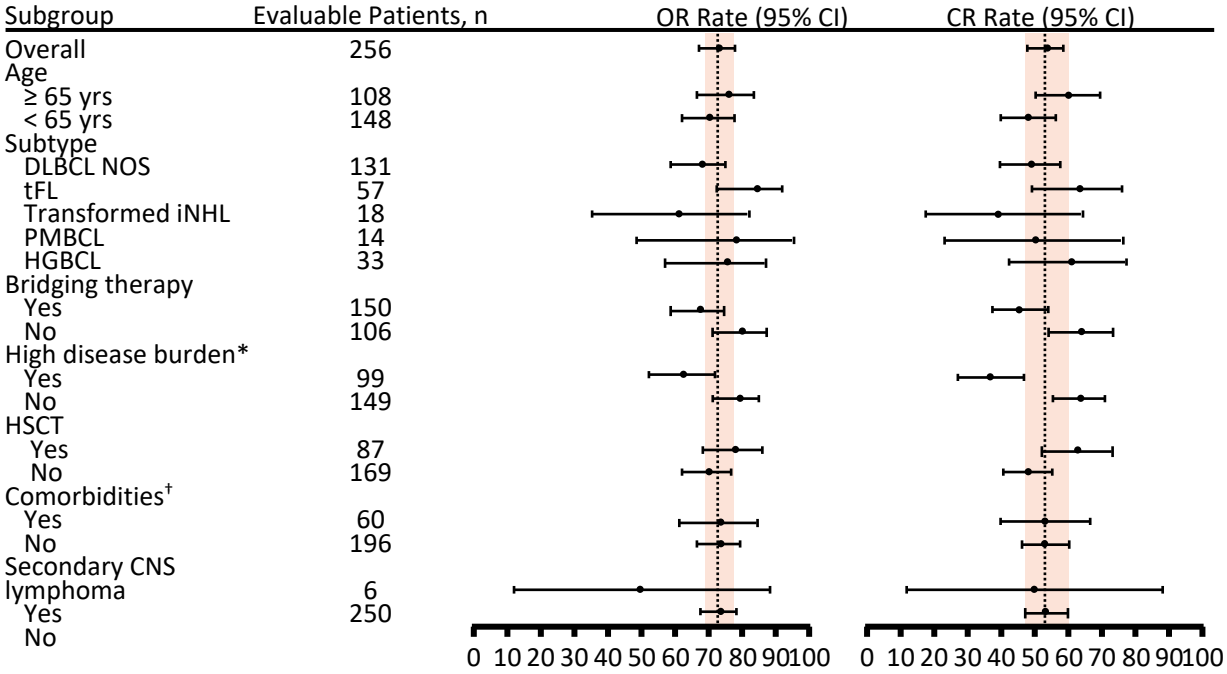
TRANSCEND NHL 001: Responses According to Patient Characteristics



*Patients with LDC SPD ≥ 50 cm^2 or LDH ≥ 500 U/L. †Patients with CrCl > 30 but < 60 mg/min or with LVEF ≥ 40% to < 50%.

Abramson. ASH 2019. Abstr 241.

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TRANSCEND NHL 001: PFS and OS Outcomes

PFS	Liso-cel (N = 256)
Median follow-up, mos (95% CI)	12.3 (12.0-17.5)
6-mo PFS, % (95% CI)	
▪ All patients	51.4 (44.6-57.7)
▪ Patients with BOR or CR	76.1 (67.9-82.4)
12-mo PFS, % (95% CI)	
▪ All patients	44.1 (37.3-50.7)
▪ Patients with BOR or CR	65.1 (56.1-72.7)
Probability of PFS by objective response, median mos (95% CI)	
▪ Total	6.8 (3.3-14.1)
▪ CR (n = 136)	NR (NR-NR)
▪ PR (n = 50)	2.8 (2.1-3.0)
▪ SD/PD (n = 70)	1.1 (1.0-1.6)

OS	Liso-cel (N = 256)
Median follow-up, mos (95% CI)	17.6 (13.5-18.0)
6-mo OS, % (95% CI)	
▪ All patients	74.7 (68.9-79.6)
▪ Patients with BOR or CR	94.1 (88.6-97.0)
12-mo OS, % (95% CI)	
▪ All patients	57.9 (51.3-63.8)
▪ Patients with BOR or CR	85.5 (78.2-90.5)
Probability of OS by objective response, median mos (95% CI)	
▪ Total	21.1 (13.3-NR)
▪ CR (n = 136)	NR (NR-NR)
▪ PR (n = 50)	9.0 (6.0-10.4)
▪ SD/PD (n = 70)	5.1 (2.9-6.5)

Abramson. ASH 2019. Abstr 241.

TRANSCEND NHL 001: PFS by Subgroup

Median PFS, Mos (95% CI)	Liso-cel (N = 256)
Disease type	
▪ HGBCL (n = 33)	5.0 (2.9-NR)
▪ tFL (n = 57)	NR (11.8-NR)
▪ PMBCL (n = 14)	NR (2.8-NR)
▪ Transformed iNHL (n = 18)	2.9 (1.3-NR)
▪ DLBCL, NOS (n = 131)	3.0 (2.8-6.3)
Bridging therapy	
▪ Yes (n = 150)	5.0 (3.0-10.0)
▪ No (n = 106)	14.1 (3.7-NR)
HR : 1.3 (95% CI: 0.9-1.9; *P* = .13)	
Comorbidities*	
▪ Yes (n = 60)	3.0 (2.5-10.0)
▪ No (n = 196)	9.5 (4.6-NR)
HR : 1.5 (95% CI: 1.0-2.2; *P* = .03)	

*Defined as CrCl > 30 but < 60 mL/min or LVEF ≥ 40 to < 50%.

Abramson. ASH 2019. Abstr 241.

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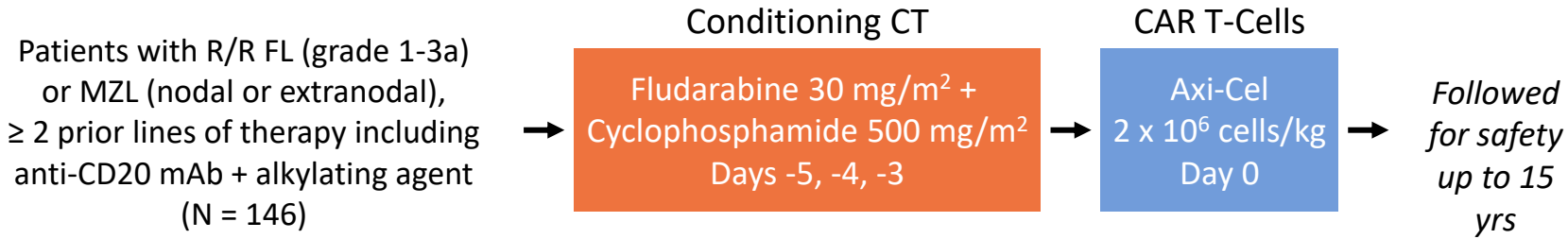
ZUMA-5: Study Design

- Multicenter, single-arm phase II trial



Patients with SD but no relapse > 1 yr from completion of last therapy ineligible. Single-agent anti-CD20 mAb not counted as line of therapy for eligibility. Median time to delivery of axi-cel: 17 days following leukapheresis.

- Primary endpoint: ORR (IRRC-assessed per Lugano classification)
- Key secondary endpoints: CR rate (IRRC-assessed), ORR (investigator-assessed), DoR, PFS, OS, AEs, CAR T-cell and cytokine levels

Jacobson. ASH 2020. Abstr 700. NCT03105336.

ZUMA-5: Baseline Patient Characteristics

Characteristic	Axi-Cel		
	FL (n = 124)	MZL (n = 22)	Overall (N = 146)
Median age, yrs (range) ▪ ≥ 65 yrs, n (%)	60 (34-79) 38 (31)	66 (48-77) 13 (59)	61 (34-79) 51 (35)
Male, n (%)	73 (59)	10 (45)	83 (57)
ECOG PS 1, n (%)	46 (37)	9 (41)	55 (38)
Stage III/IV disease, n (%)	106 (85)	20 (91)	126 (86)
≥ 3 FLIPI, n (%)	54 (44)	14 (64)	68 (47)
High tumor bulk by GELF,* n (%)	64 (52)	8 (36)	72 (49)

*Involvement of ≥ 3 nodal sites (≥ 3 cm each); any nodal or extranodal tumor mass ≥ 7 cm; B symptoms; splenomegaly; pleural effusions or peritoneal ascites; cytopenias; or leukemia.

Characteristic	Axi-Cel		
	FL (n = 124)	MZL (n = 22)	Overall (N = 146)
Median prior tx, n (range) ▪ ≥ 3 ▪ PI3K inhibitor	3 (1-10)† 78 (63) 34 (27)	3 (2-8) 15 (68) 9 (41)	3 (1-10) 93 (64) 43 (29)
Refractory disease,‡ n (%)	84 (68)	16 (73)	100 (68)
POD24§ from first anti-CD20 mAb tx, n (%)	68 (55)	11 (52)	79 (55)
Prior ASCT, n (%)	30 (24)	3 (14)	33 (23)

†n = 3 with 1 prior line of therapy before protocol amendment requiring ≥ 2. ‡PD within 6 mos of most recent prior tx. §24 mos from start of first anti-CD20–containing immunochemotherapy to progression; % based on patients ever receiving this tx.

Jacobson. ASH 2020. Abstr 700.

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ZUMA-5: IRRC-Assessed ORR

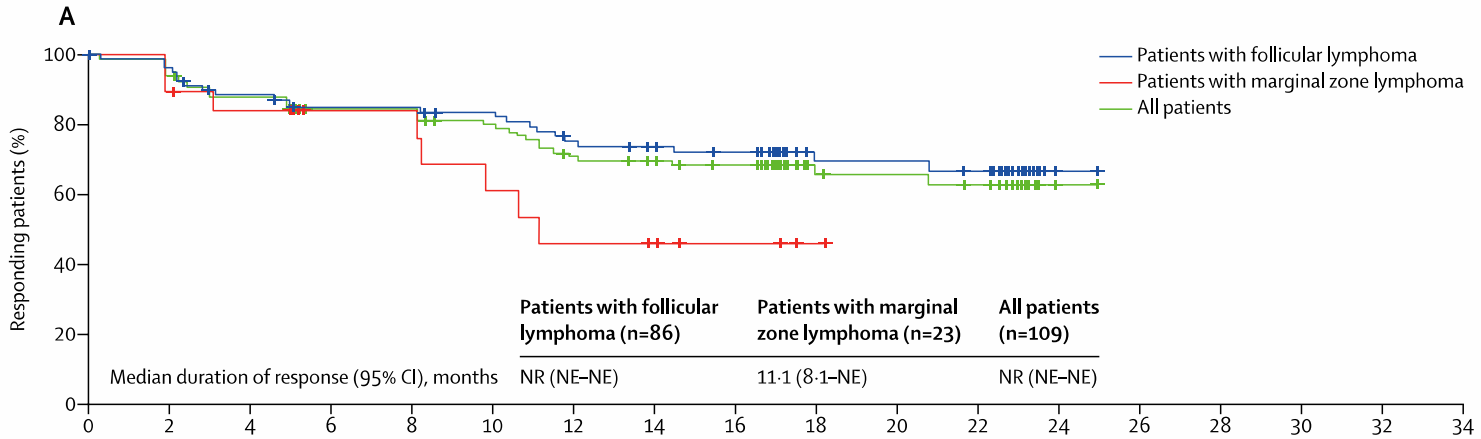
IRRC-Assessed Response,*† n (%)	Axi-Cel		
	FL (n = 84)	MZL (n = 20)	Overall (N = 104)
ORR	79 (94)	17 (85)	96 (92)
CR	67 (80)	12 (60)	79 (76)
PR	12 (14)	5 (25)	17 (16)
SD	3 (4)	0	3 (3)
ND	2 (2)	3 (15)	5 (5)

*For investigator-assessed response (N = 104): ORR, 95%; CR rate, 77%. †n = 4 (1 FL, 3 MZL) had no disease at or post BL per IRRC but were considered to have disease by investigator; n = 1 FL patient died before initial disease assessment.

- Median time to first response: 1.0 mo (range: 0.8-3.1)
- 13/25 (52%) FL patients with initial PR converted to CR after median 2.2 mos (range: 1.9-11.2)
- ORR was consistent across all subgroups analyzed including by FLIPI score, high tumor burden, and previous treatment

Jacobson. ASH 2020. Abstr 700.

ZUMA-5: Duration of Response



Number at risk (number censored)																		
Patients with follicular lymphoma	81 (0)	77 (1)	69 (3)	64 (5)	64 (5)	61 (7)	54 (8)	51 (10)	48 (12)	24 (35)	24 (35)	22 (36)	1 (57)	0 (58)	..	..	..	..
Patients with marginal zone lymphoma	19 (0)	17 (0)	15 (1)	11 (5)	11 (5)	8 (5)	6 (5)	5 (6)	3 (8)	1 (10)	0 (11)	..	..	..	..	..	..	..
All patients	100 (0)	94 (1)	84 (4)	75 (10)	75 (10)	69 (12)	60 (13)	56 (16)	51 (20)	25 (45)	25 (46)	22 (47)	1 (68)	0 (69)	..	..	..	..

Jacobson CA, et al. *Lancet Oncol*. 2022;23:91-103.

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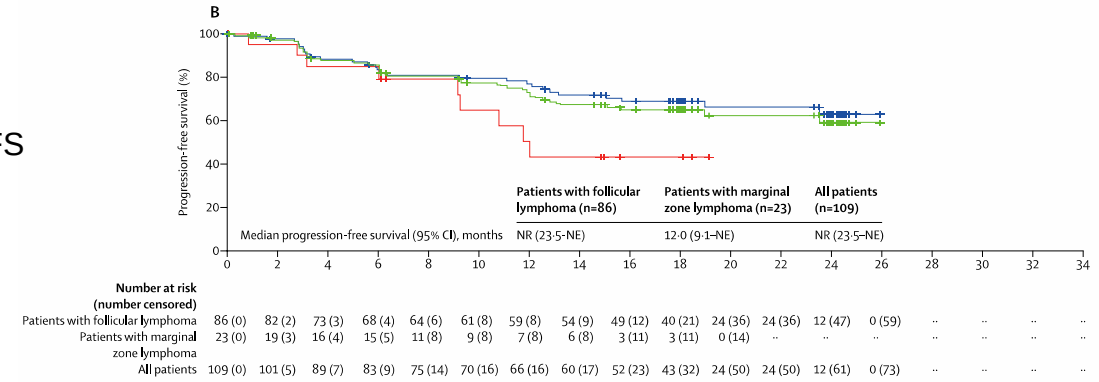
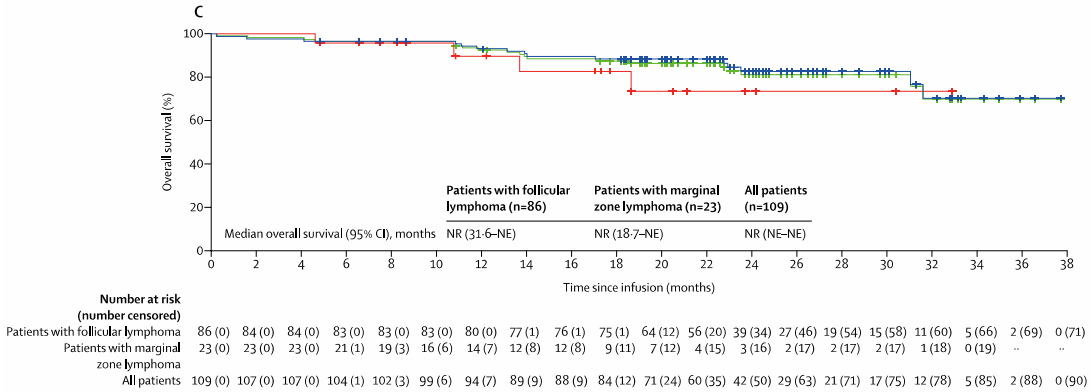
ZUMA-5: Survival

PFS



OS



Patients with follicular lymphoma
Patients with marginal zone lymphoma
All patients

Jacobson CA, et al. *Lancet Oncol*. 2022;23:91-103.

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ZUMA-5: Treatment-Emergent AEs

AEs in ≥ 25% of Patients, n (%)	FL (n = 124)	MZL (n = 22)	Overall (N = 146)
Any	123 (99)	22 (100)	145 (99)
Pyrexia	103 (83)	20 (91)	123 (84)
Neutropenia	79 (64)	15 (68)	94 (64)
Hypotension	59 (48)	13 (59)	72 (49)
Headache	54 (44)	11 (50)	65 (45)

AEs in ≥ 25% of Patients, n (%)	FL (n = 124)	MZL (n = 22)	Overall (N = 146)
Fatigue	51 (41)	13 (59)	64 (44)
Nausea	45 (36)	13 (59)	58 (40)
Anemia	44 (35)	11 (50)	55 (38)
Sinus tachycardia	41 (33)	7 (32)	48 (33)
Tremor	36 (29)	9 (41)	45 (31)
Chills	33 (27)	9 (41)	42 (29)
Constipation	35 (28)	6 (27)	41 (28)
Diarrhea	33 (27)	8 (36)	41 (28)
Decreased appetite	28 (23)	8 (36)	36 (25)

- Grade ≥ 3 AEs: n = 126 (86%); cytopenia, 70%; infection, 16%
- Grade 5 AEs: n = 3 (related, multisystem organ failure with CRS on Day 7; unrelated, aortic dissection on Day 399, coccidioidomycosis infection on Day 327)

Jacobson. ASH 2020. Abstr 700.

ZUMA-5: Cytokine-Release Syndrome

Parameter	FL (n = 124)	MZL (n = 22)	Overall (N = 146)
CRS, n (%)			
▪ Any grade	97 (78)	22 (100)	119 (82)
▪ Grade ≥ 3	8 (6)	2 (9)	10 (7)*
Most common any-grade symptoms, n/N (%)			
▪ Pyrexia	94/97 (97)	20/22 (91)	114/119 (96)
▪ Hypotension	39/97 (40)	10/22 (45)	49/119 (41)
AE management, n (%)			
▪ Tocilizumab	56 (45)	15 (68)	71 (49)
▪ Corticosteroids	19 (15)	6 (27)	25 (17)
Median time to onset, days (range)	4 (1-15)	4 (1-9)	4 (1-15)
Median duration of events, days (range)	6 (1-27)	6 (2-14)	6 (1-27)
Patients with resolved events, n/N (%)	96/97 (99)†	22/22 (100)	118/119 (99)

No ongoing events at data cut-off. *Grade 4/5, n = 1 each. †n = 1 death on Day 7 due to multisystem organ failure with CRS before CRS resolution.

Jacobson. ASH 2020. Abstr 700.

ZUMA-5: Neurologic Events

Parameter	FL (n = 124)	MZL (n = 22)	Overall (N = 146)
Neurologic events, n (%)			
▪ Any grade	70 (56)	17 (77)	87 (60)
▪ Grade ≥ 3	19 (15)	9 (41)	28 (19)*
Most common any-grade symptoms, n/n (%)			
▪ Tremor	36/70 (51)	9/17 (53)	45/87 (52)
▪ Confusional state	28/70 (40)	7/17 (41)	35/87 (40)
AE management, n (%)			
▪ Corticosteroids	38 (31)	14 (64)	52 (36)
▪ Tocilizumab	7 (6)	2 (9)	9 (6)
Median time to onset, days (range)	7 (1-177)	7 (3-19)	7 (1-177)
Median duration of events, days (range)	14 (1-452)	10 (2-81)	14 (1-452)
Patients with resolved events, n/N (%)	67/70 (96)	14/17 (82)	81/87 (93)

Ongoing events at data cutoff: grade 1 memory impairment (n = 2) and attention disturbance, intermittent paresthesia, and tremor (n = 1 each); grade 2 facial paresthesia (n = 1). *Grade 4, n = 3; no grade 5 events.

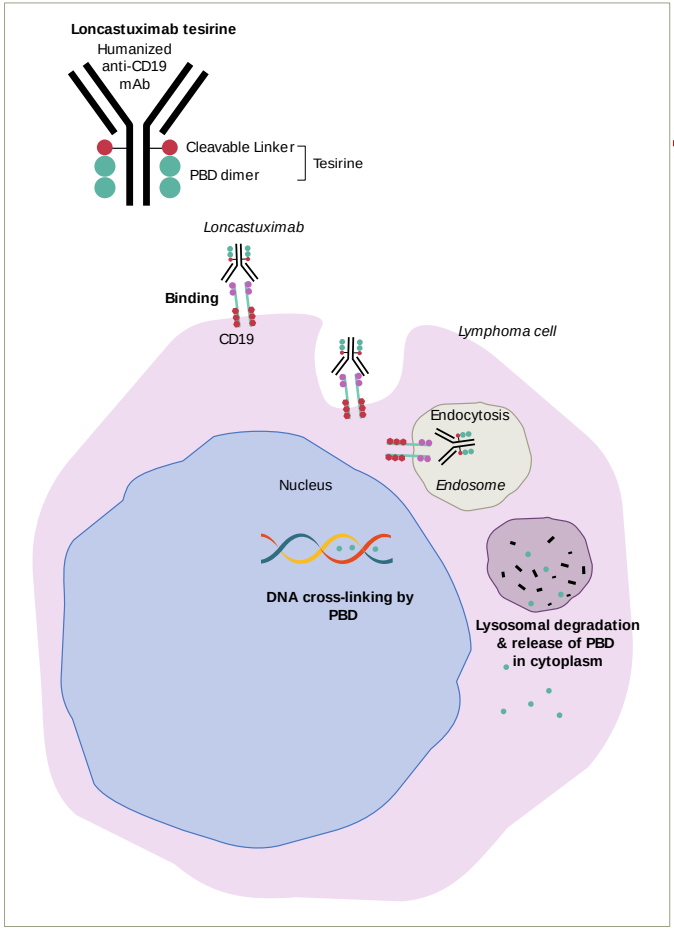
Jacobson. ASH 2020. Abstr 700.

FDA Lymphoma Approvals in 2021-2022

Date	Agent/Regimen	Indication
February 5, 2021	Umbralisib	• R/R MZL who have received at least 1 prior anti-CD20 tx • R/R FL who have received at least 3 prior lines of tx
February 5, 2021	Lisocabtagene maraleucel	R/R LBCL after 2 or more lines of systemic therapy
March 5, 2021	Axicabtagene ciloleucel	R/R FL after 2 or more lines of systemic therapy
April 23, 2021	Loncastuximab tesirine	R/R LBCL after 2 or more lines of systemic therapy
September 14, 2021	Zanubrutinib	R/R MZL after at least 1 anti-CD20-based regimen
December 2, 2021	Rituximab + chemotherapy	Pediatric patients with previous untreated, advanced, CD20+ DLBCL, Burkitt lymphoma, Burkitt-like lymphoma, or mature B-cell acute leukemia

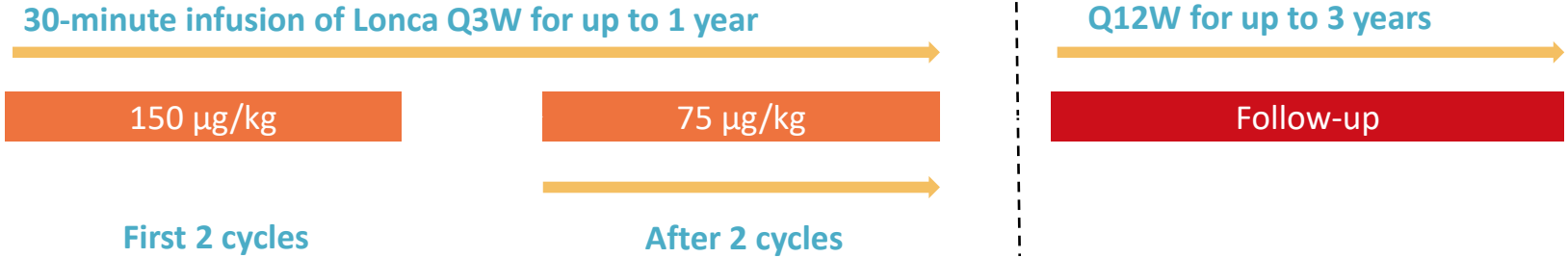
Loncastuximab Tesirine for R/R LBCL

- Loncastuximab aesirine: a humanized anti-CD19 antibody, stochastically conjugated through a cathepsin-cleavable valine-alanine linker to a pyrrolobenzodiazepine (PBD) dimer toxin causing DNA crosslinking



Single-Arm, Phase 2 LOTIS-2 Study of Loncastuximab Tesirine for R/R DLBCL: Design

Eligibility: Adults with R/R DLBCL after 2 or more lines of systemic therapy, CD19+ biopsy if prior anti-CD19 therapy received, ECOG PS 0-2, ASCT 30+ days prior or alloSCT 60+ days prior permitted



Primary endpoint: ORR
Secondary endpoints: DOR, CR, RFS, PFS, OS, Safety, PK/PD, HRQoL

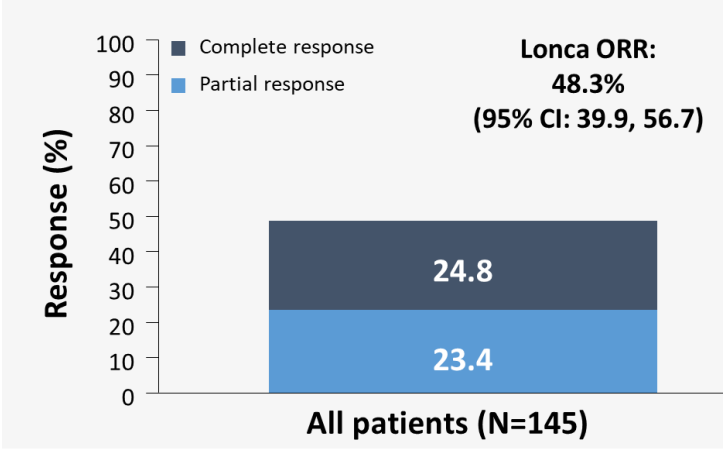
Baseline Characteristics

- 87.6% DLBCL
- 10.3% Double/triple hit
- 13.8% Double/triple expressor
- 20% Transformed disease
- 77.2% Stage III-IV
- Median number prior tx, 3 (2-7)

Carlo-Stella C, et al. EHA Congress 2020. Abstract S233.

LOTIS-2 Trial: Efficacy Results

ORR was assessed by independent reviewer. Data cut-off: 06 Aug 2020. *4 patients had treatment ongoing at data cut-off. Caimi PF, et al. ASH 2020. Abstract 1183.



mDoR for the 70 responders:
12.58 months
(95% CI: 6.87, -)

Median PFS:
5.09 mo
(95% CI, 2.89-8.31)

mDoR for patients with a CR:
13.37 months
(95% CI: 12.58, -)

Median OS:
9.53 mo
(95% CI, 6.93-11.24)

- ORRs seen in high-risk subgroups (eg, double/triple hit, transformed disease)
- Most responders had response after 2 cycles; median time to first response was 41.0 days (range: 35–247)
- Mean lonca cycles: 4.5 (Std: ± 3.89) (Min, max: 1, 18)*
- Subsequent treatment
  - 15 pts received CD19-directed CAR-T therapy with an INV-assessed ORR of 46.7% (6 CR; 1 PR)
  - 9 patients proceeded to SCT as consolidation after response to lonca

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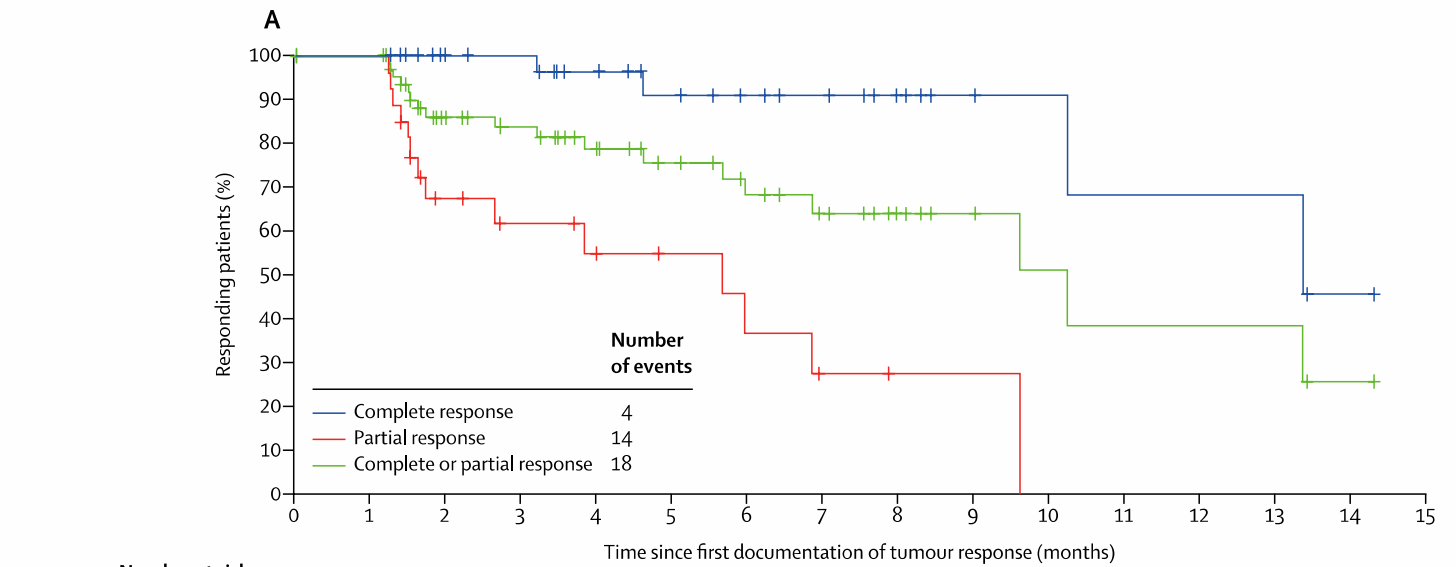
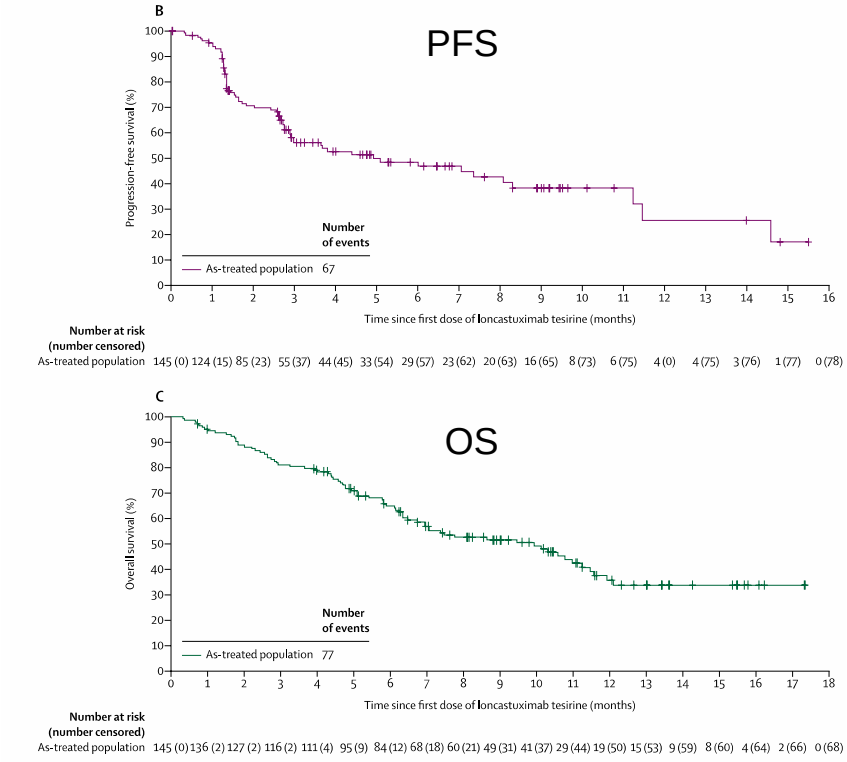
LOTIS-2 Trial: Duration of Response



Number at risk (number censored)																
Complete response	35 (0)	34 (1)	28 (7)	26 (9)	21 (13)	17 (16)	14 (19)	12 (21)	8 (25)	5 (28)	4 (29)	3 (29)	3 (29)	3 (29)	1 (30)	0 (31)
Partial response	35 (0)	28 (7)	13 (14)	10 (16)	8 (17)	6 (19)	4 (19)	2 (20)	1 (20)	1 (21)	0 (21)	0 (21)	0 (21)	0 (21)	0 (21)	0 (21)
Complete or partial response	70 (0)	62 (8)	41 (21)	36 (25)	29 (30)	23 (35)	18 (38)	14 (41)	9 (46)	6 (49)	4 (50)	3 (50)	3 (50)	3 (50)	1 (51)	0 (52)

Caimi PF, et al. *Lancet Oncol*. 2021;22:790-800.

LOTIS-2 Trial: Survival



Caimi PF, et al. *Lancet Oncol*. 2021;22:790-800.

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LOTIS-2 Trial: Safety Results

	Patients n (%)		
Preferred term	**<65 years (N=65)**	**≥65 (N=80)**	**Total (N=145)**
Patients with any TEAE	65 (100)	78 (97.5)	143 (98.6)
GGT increased	33 (50.8)	27 (33.8)	60 (41.4)
Neutropenia	34 (52.3)	24 (30.0)	58 (40.0)
Thrombocytopenia	28 (43.1)	20 (25.0)	48 (33.1)
Fatigue	21 (32.3)	19 (23.8)	40 (27.6)
Anemia	23 (35.4)	15 (18.8)	38 (26.2)
Nausea	17 (26.2)	17 (21.3)	34 (23.4)
Cough	19 (29.2)	13 (16.3)	32 (22.1)
Alkaline phosphatase increased	18 (27.7)	11 (13.8)	29 (20.0)
Peripheral edema	11 (16.9)	18 (22.5)	29 (20.0)

Most common (≥10%) grade ≥3 TEAEs were:

- Neutropenia (38 patients; 26.2%)
- Thrombocytopenia (26 patients; 17.9%)
- GGT increased (25 patients; 17.2%)
- Anemia (15 patients; 10.3%)

Treatment-related TEAEs leading to treatment discontinuation occurred in 26 (17.9%) patients, most commonly (≥2%):

- GGT increased (16 patients; 11.0%)
- Peripheral edema (4 patients; 2.8%)
- Localized edema (3 patients; 2.1%)

No increase in toxicity was seen in patients aged ≥65 years compared with younger patients

TEAEs were reported for the all-treated population. Data cut-off: 06 Aug, 2020.
GGT, gamma-glutamyltransferase; **TEAE**, treatment-emergent adverse event.

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December 2, 2021	Rituximab + chemotherapy	Pediatric patients with previous untreated, advanced, CD20+ DLBCL, Burkitt lymphoma, Burkitt-like lymphoma, or mature B-cell acute leukemia

MAGNOLIA: Zanubrutinib in R/R Marginal Zone Lymphoma

- Single-arm, multicenter, open-label phase II trial

Adult pts with R/R MZL, ≥1 prior therapy including anti-CD20
(N = 68)

→ **Zanubrutinib** 160 mg BID

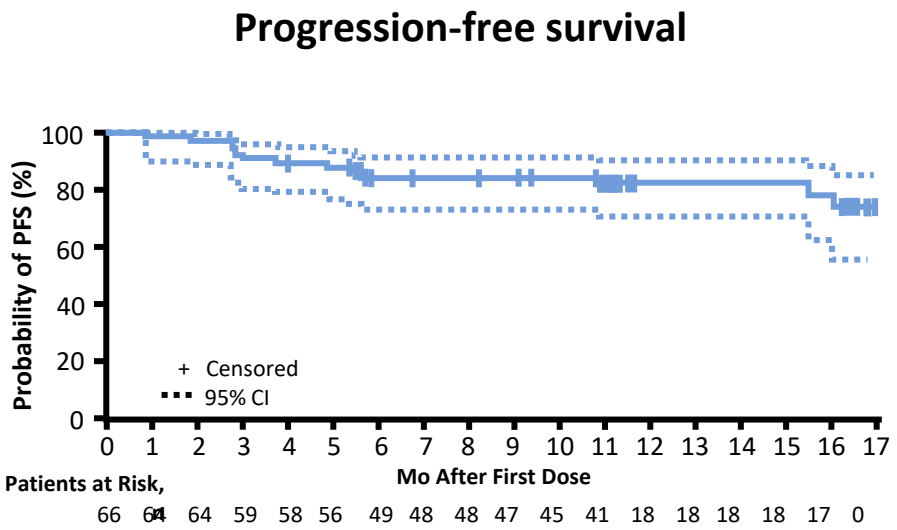
- **Primary endpoint:** ORR by IRC using Lugano
- **Key secondary endpoints:** ORR by PI, PFS, OR, DOR, safety

Best response, n (%)	Extranodal (n = 25)	Nodal (n = 25)	Splenic (n = 12)	Unknown (n = 4)	Total (N = 66)
ORR (95% CI)	16 (64.0)	19 (76.0)	8 (66.7)	2 (50.0)	68.2 (55.56-79.11)
▪ CR	10 (40.0)	5 (20.0)	1 (8.3)	1 (25.0)	17 (25.8)
▪ PR					28 (42.4)
▪ SD					13 (19.7)
▪ PD					6 (9.1)

- Median follow-up of 15.7 months (range 1.6-21.9)
- Progression-free rate: 82.5% at 12 months and 15 months (by IRC)

Opat. Clin Cancer Res. 2021; Epub Sept 15.

MAGNOLIA: Efficacy and Toxicity



TEAE of interest, n (%)	All patients (N = 68)	
	All grade	Grade ≥3
Infection	31 (45.6)	11 (16.2)
Hemorrhage	25 (36.8)	0
Diarrhea	15 (22.1)	2 (2.9)
Neutropenia	9 (13.2)	7 (10.3)
Thrombocytopenia	10 (14.7)	3 (4.4)
Second primary malignancy	5 (7.4)	3 (4.4)
Atrial fibrillation/flutter	2 (2.9)	1 (1.5)
Hypertension	2 (2.9)	1 (1.5)
Major hemorrhage	0	0

- Zanubrutinib received accelerated approval for R/R MZL September 2021

Opat. Clin Cancer Res. 2021; Epub Sept 15.

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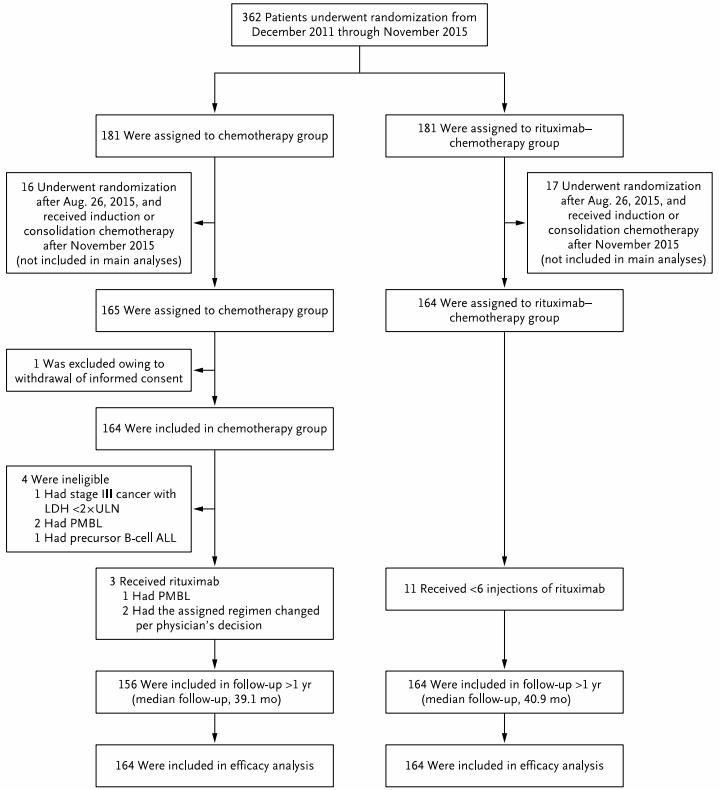
December 2, 2021	Rituximab + chemotherapy	Pediatric patients with previous untreated, advanced, CD20+ DLBCL, Burkitt lymphoma, Burkitt-like lymphoma, or mature B-cell acute leukemia

Rituximab for High-Risk, Mature B-Cell NHL in Children – Randomization, Treatment, and Follow-Up of Patients



Minard-Colin V, et al. *N Engl J Med*. 2020;382:2207-2219.

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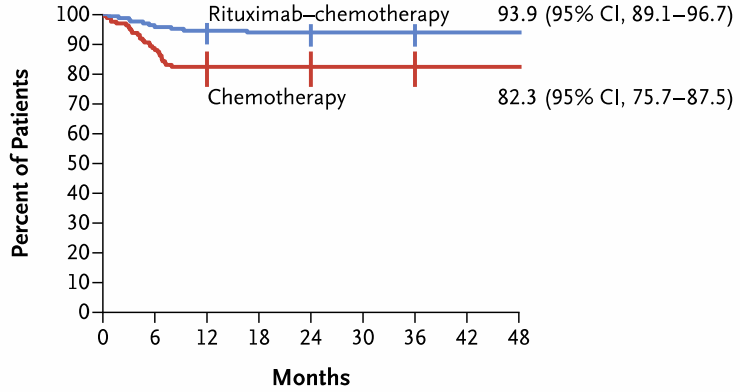
Rituximab for High-Risk, Mature B-Cell NHL in Children – EFS and OS

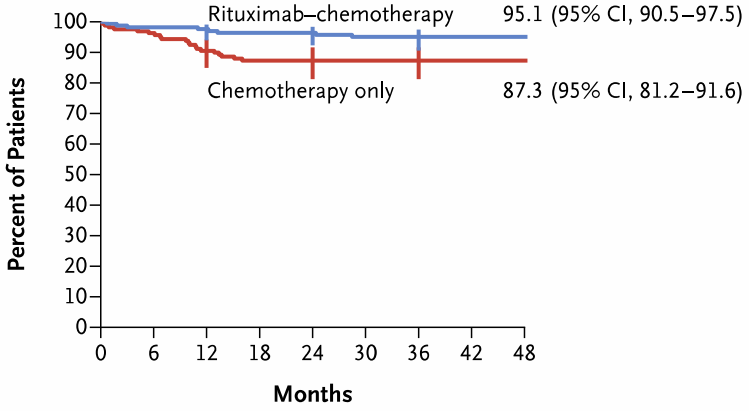
A Event-free Survival



No. at Risk

Rituximab–chemotherapy	164	157	155	154	150	138	102	74	42
Chemotherapy	164	140	128	127	122	112	82	52	38

B Overall Survival



No. at Risk

Rituximab–chemotherapy	164	161	160	158	154	140	103	75	43
Chemotherapy	164	152	141	135	130	119	89	57	42

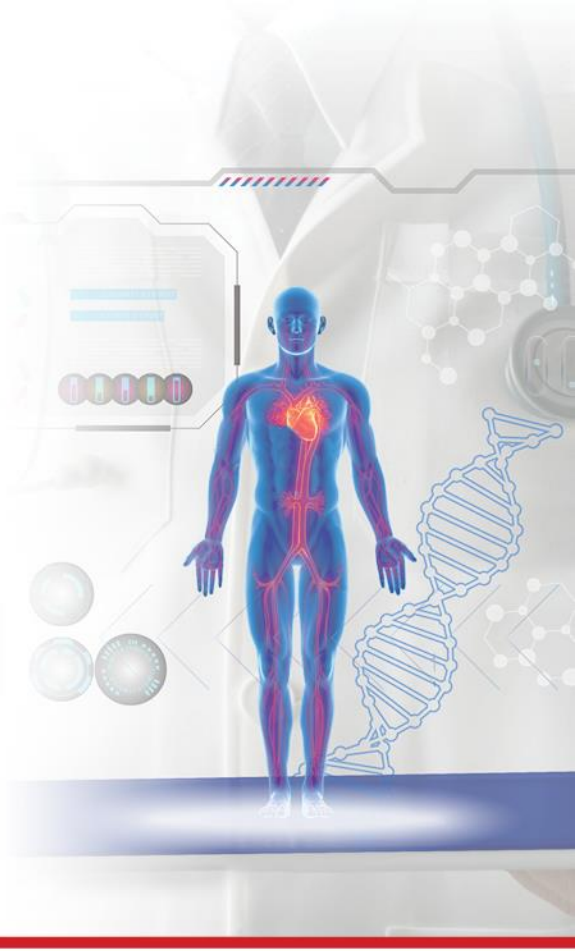
Minard-Colin V, et al. *N Engl J Med*. 2020;382:2207-2219.

Rituximab for High-Risk, Mature B-Cell NHL in Children – Acute AEs

Event	All Patients (N = 315)	Chemotherapy Group (N = 153)	Rituximab–Chemotherapy Group (N = 162)	P Value
		no. of patients (%)		
During all therapy				
≥1 Adverse event	306 (97.1)	148 (96.7)	158 (97.5)	
≥1 Adverse event of grade ≥4	111 (35.2)	50 (32.7)	61 (37.7)	0.36
During COP prephase treatment				
≥1 Adverse event	63 (20.0)	31 (20.3)	32 (19.8)	
≥1 Adverse event of grade ≥4	27 (8.6)	17 (11.1)	10 (6.2)	0.12
After COP prephase treatment				
≥1 Adverse event	303 (96.2)	147 (96.1)	156 (96.3)	
≥1 Adverse event of grade ≥4	91 (28.9)	37 (24.2)	54 (33.3)	0.07
Most frequent adverse events after COP prephase treatment				
Febrile neutropenia	289 (91.7)	139 (90.8)	150 (92.6)	
Grade 3	260 (82.5)	129 (84.3)	131 (80.9)	
Grade ≥4	29 (9.2)	10 (6.5)	19 (11.7)	0.11
Stomatitis	244 (77.5)	115 (75.2)	129 (79.6)	
Grade 3	224 (71.1)	108 (70.6)	116 (71.6)	
Grade ≥4	20 (6.3)	7 (4.6)	13 (8.0)	0.21
Enteritis	63 (20.0)	24 (15.7)	39 (24.1)	
Grade 3	62 (19.7)	24 (15.7)	38 (23.5)	
Grade ≥4	1 (0.3)	0	1 (0.6)	1.00
Infection	170 (54.0)	75 (49.0)	95 (58.6)	
Grade 3	123 (39.0)	58 (37.9)	65 (40.1)	
Grade ≥4	47 (14.9)	17 (11.1)	30 (18.5)	0.07
Main types of infection				
Sepsis	45 (14.3)	17 (11.1)	28 (17.3)	
Central venous catheter–related infection	38 (12.1)	17 (11.1)	21 (13.0)	
Lung infection	32 (10.2)	13 (8.5)	19 (11.7)	
Enterocolitis infection	32 (10.2)	18 (11.8)	14 (8.6)	
Biologic adverse events				
Alanine aminotransferase increased	41 (13.0)	18 (11.8)	23 (14.2)	
Grade 3	25 (7.9)	12 (7.8)	13 (8.0)	
Grade ≥4	16 (5.1)	6 (3.9)	10 (6.2)	0.36
Hypokalemia	36 (11.4)	15 (9.8)	21 (13.0)	
Grade 3	28 (8.9)	11 (7.2)	17 (10.5)	
Grade ≥4	8 (2.5)	4 (2.6)	4 (2.5)	1.00

Minard-Colin V, et al. *N Engl J Med*. 2020;382:2207-2219.

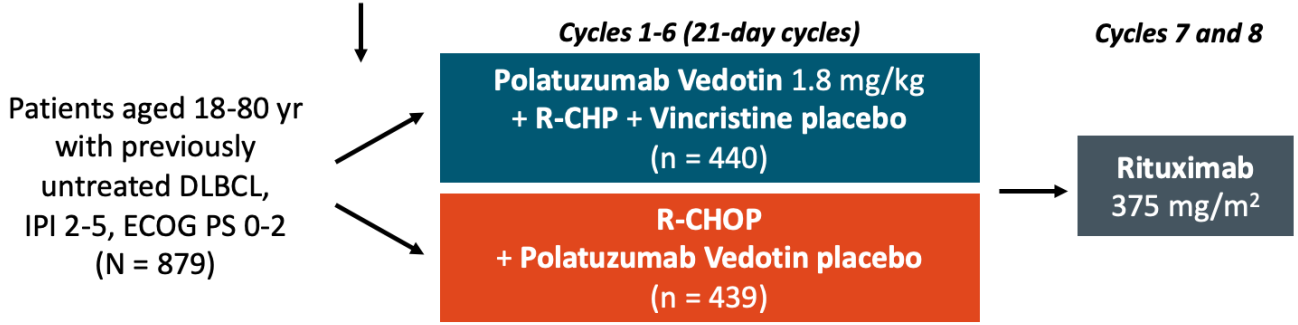
ASH 2021 – Potentially Practice Changing Studies



R-CHOP vs Polatuzumab-R-CHP in DLBCL (IPI 2-5) – Schema

- Multicenter, double-blind, placebo-controlled phase III trial

Stratification by IPI score (2 vs 3-5); bulky disease (<7.5 vs ≥7.5 cm); and geographic region (Western Europe, US, Canada and Australia vs Asia vs rest of world)



R-CHOP: IV rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² administered on Day 1 + oral prednisone 100 mg QD Days 1-5.

- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoints:** EFS, CRR at end of treatment, DFS, OS, safety

Tilly H, et al. ASH 2021 (abstr LBA1). Tilly H, et al.. NEJM. 2021 [Epub]

R-CHOP vs Polatuzumab-R-CHP in DLBCL – Baseline Characteristics

Characteristic	Pola-R-CHP (N=440)	R-CHOP (N=439)
Median age (range) — yr	65 (19–80)	66 (19–80)
Age category — no. (%)		
≤60 yr	140 (31.8)	131 (29.8)
>60 yr	300 (68.2)	308 (70.2)
Female sex — no. (%)	201 (45.7)	205 (46.7)
Geographic region — no. (%)†		
Western Europe, United States, Canada, and Australia	302 (68.6)	301 (68.6)
Asia	81 (18.4)	79 (18.0)
Rest of world	57 (13.0)	59 (13.4)
Ann Arbor stage — no. (%)‡		
I or II	47 (10.7)	52 (11.8)
III or IV	393 (89.3)	387 (88.2)
No. of extranodal sites — no. (%)		
0 or 1	227 (51.6)	226 (51.5)
≥2	213 (48.4)	213 (48.5)
Bulky disease — no. (%)†§	193 (43.9)	192 (43.7)

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R-CHOP vs Polatuzumab-R-CHP in DLBCL – Baseline Characteristics (cont.)

ECOG performance status score — no. (%)¶		
0 or 1	374 (85.0)	363 (82.7)
2	66 (15.0)	75 (17.1)
Lactate dehydrogenase level — no. (%)‖		
Normal	146 (33.2)	154 (35.1)
Elevated	291 (66.1)	284 (64.7)
IPI score — no. (%)†**		
2	167 (38.0)	167 (38.0)
3 to 5	273 (62.0)	272 (62.0)
Median time from initial diagnosis to treatment initiation (IQR) — days	26 (16.0–37.5)	27 (19.0–41.0)
Cell of origin — no./total no. (%)††		
Germinal-center B-cell–like subtype	184/330 (55.8)	168/338 (49.7)
Activated B-cell–like subtype	102/330 (30.9)	119/338 (35.2)
Unclassified	44/330 (13.3)	51/338 (15.1)
Double-expressor lymphoma — no./total no. (%)††	139/362 (38.4)	151/366 (41.3)
Double-hit or triple-hit lymphoma — no./total no. (%)††	26/331 (7.9)	19/334 (5.7)

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R-CHOP vs Polatuzumab-R-CHP in DLBCL – Toxicity

Adverse Event	Pola-R-CHP (N = 435)		R-CHOP (N = 438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Peripheral neuropathy†	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
Nausea	181 (41.6)	5 (1.1)	161 (36.8)	2 (0.5)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.8)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Constipation	125 (28.7)	5 (1.1)	127 (29.0)	1 (0.2)
Fatigue	112 (25.7)	4 (0.9)	116 (26.5)	11 (2.5)
Alopecia	106 (24.4)	0	105 (24.0)	1 (0.2)
Decreased appetite	71 (16.3)	5 (1.1)	62 (14.2)	3 (0.7)
Pyrexia	68 (15.6)	6 (1.4)	55 (12.6)	0
Vomiting	65 (14.9)	5 (1.1)	63 (14.4)	3 (0.7)
Febrile neutropenia	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)
Headache	56 (12.9)	1 (0.2)	57 (13.0)	4 (0.9)
Cough	56 (12.9)	0	53 (12.1)	0
Decreased weight	55 (12.6)	4 (0.9)	52 (11.9)	1 (0.2)
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0

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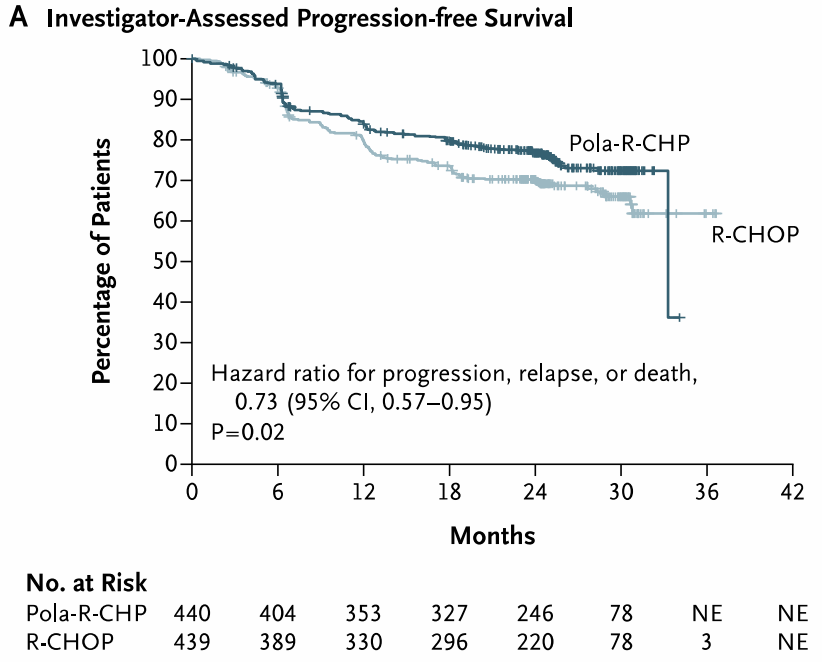
R-CHOP vs Polatuzumab-R-CHP in DLBCL – PFS



24 mo PFS:
76.7% Pola-R-CHP
70.2% R-CHOP

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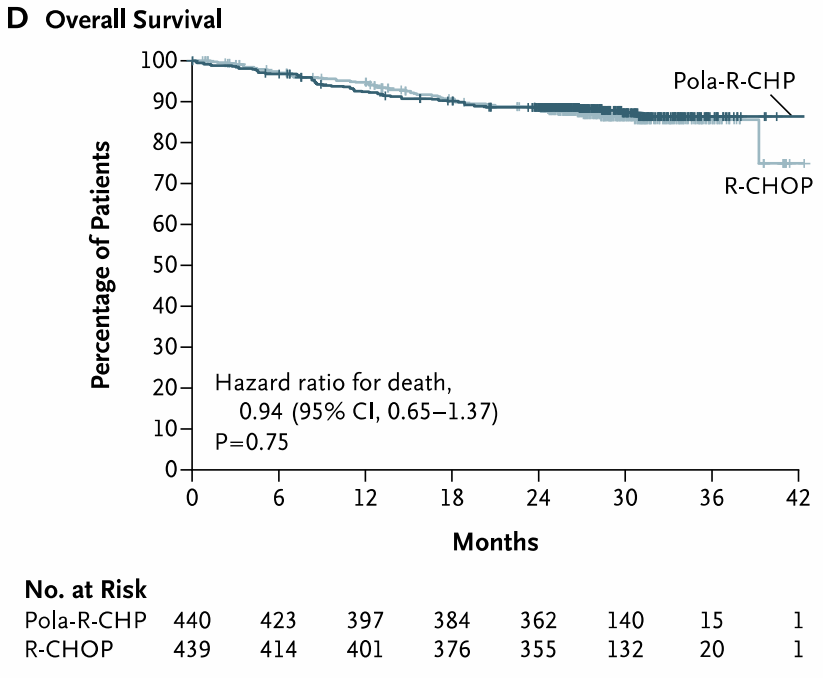
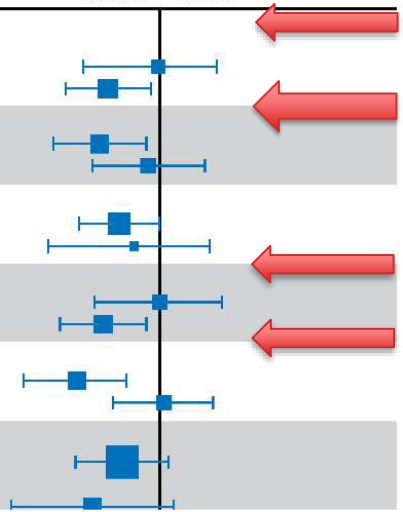
R-CHOP vs Polatuzumab-R-CHP in DLBCL – OS



Tilly H, et al. ASH 2021 (abstr LBA1). Tilly H, et al.. NEJM. 2021 [Epub]

R-CHOP vs Polatuzumab-R-CHP in DLBCL – Subgroups

Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)



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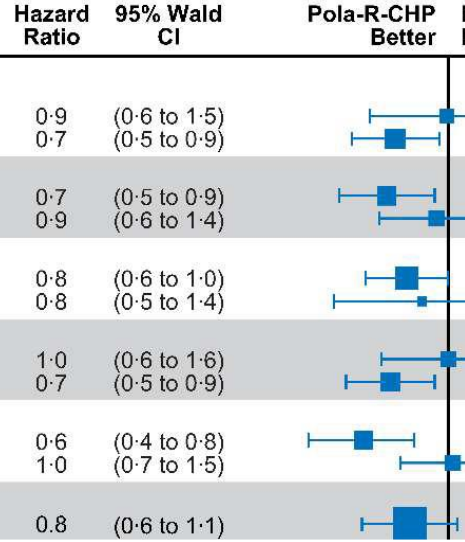
R-CHOP vs Polatuzumab-R-CHP in DLBCL – Subgroups (cont.)

Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States,	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)



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Impact of the POLARIX Study

- Positive trial (6.5% benefit in PFS), no OS benefit in IPI 2-5 DLBCL patients
- Generally comparable toxicity
- Older, male patients, higher risk and ABC subtype benefitted most
- Saves 6.5% (1 of 15 patients) from relapse and more therapy
- 6 doses x $15,669/dose/80kg pt x 15 patients

= $1.4 million/relapse saved

Axicabtagene Ciloleucel for 2nd line (<12m) relapsed DLBCL – Schema

- Global, multicenter, randomized phase III trial

Stratified by 1L treatment response, 2L age-adjusted IPI

Patients ≥18 yr with LBCL, ECOG PS 0-1, R/R disease with ≤12 mo of adequate 1L CIT (including anti-CD20 mAb and an anthracycline), and intent to proceed to HDT-ASCT (N = 359)

Axi-cel 2 x 10^6 CAR T-cells/kg after conditioning chemotherapy (n = 180)

Conditioning regimen: cyclophosphamide 500 mg/m²/day + fludarabine 30 mg/m²/day on Days 5, 4, and 3 prior to CAR t-cell infusion. Optional bridging therapy limited to corticosteroids (no CIT).

SoC*
(2-3 cycles of investigator-selected, protocol defined, platinum-based CIT)
(n = 179)

CR/PR → **HDT-ASCT** (n = 64)

No CR/PR → **Off-protocol Tx**‡

*SoC included R-GDP, R-DHAP, R-ICE, or R-ESHAP. ‡56% received subsequent cellular immunotherapy.

- Primary endpoints: EFS (BICR)
- Key secondary endpoints: ORR and OS (tested hierarchically)
- Other secondary endpoints: PFS, safety, PROs
- Median follow-up: 24.9 mo

Locke F, et al. ASH 2021 (abstr 2). Locke F, et al.. NEJM. 2021 [Epub]

Axicabtagene Ciloleucel for 2nd line (<12m) relapsed DLBCL – Baseline Characteristics

Characteristic	Axi-cel (N=180)	Standard Care (N=179)	Total (N=359)
Age			
Median (range) — yr	58 (21–80)	60 (26–81)	59 (21–81)
≥65 yr — no. (%)	51 (28)	58 (32)	109 (30)
Male sex — no. (%)	110 (61)	127 (71)	237 (66)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	0	1 (1)	1 (<1)
Asian	12 (7)	10 (6)	22 (6)
Black	11 (6)	7 (4)	18 (5)
Native Hawaiian or other Pacific Islander	2 (1)	1 (1)	3 (1)
White	145 (81)	152 (85)	297 (83)
Other	10 (6)	8 (4)	18 (5)
Hispanic or Latino ethnic group — no. (%)†			
Yes	10 (6)	8 (4)	18 (5)
No	167 (93)	169 (94)	336 (94)
Not reported	3 (2)	2 (1)	5 (1)
ECOG performance-status score of 1 — no. (%)‡	85 (47)	79 (44)	164 (46)
Disease stage — no. (%)			
I or II	41 (23)	33 (18)	74 (21)
III or IV	139 (77)	146 (82)	285 (79)
Second-line age-adjusted IPI of 2 or 3 — no. (%)§	82 (46)	79 (44)	161 (45)

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Axicabtagene Ciloleucel for 2nd line (<12m) relapsed DLBCL – Baseline Characteristics (cont.)

Molecular subgroup according to central laboratory — no. (%)¶			
Germinal center B-cell–like	109 (61)	99 (55)	208 (58)
Activated B-cell–like	16 (9)	9 (5)	25 (7)
Unclassified	17 (9)	14 (8)	31 (9)
Not applicable	10 (6)	16 (9)	26 (7)
Missing data	28 (16)	41 (23)	69 (19)
Response to first-line therapy at randomization — no. (%)			
Primary refractory disease	133 (74)	131 (73)	264 (74)
Relapse at ≤12 mo after the initiation or completion of first-line therapy	47 (26)	48 (27)	95 (26)
Disease type according to central laboratory — no. (%)			
Diffuse large B-cell lymphoma‖	126 (70)	120 (67)	246 (69)
High-grade B-cell lymphoma, not otherwise specified	0	1(1)	1 (<1)
High-grade B-cell lymphoma, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	31 (17)	25 (14)	56 (16)
Not confirmed or missing data	18 (10)	28 (16)	46 (13)
Other	5 (3)	5 (3)	10 (3)
Disease type according to the investigator — no. (%)			
Large B-cell lymphoma, not otherwise specified	110 (61)	116 (65)	226 (63)
T-cell– or histiocyte–rich large B-cell lymphoma	5 (3)	6 (3)	11 (3)
Epstein–Barr virus–positive diffuse large B-cell lymphoma	2 (1)	0	2 (1)
Large-cell transformation from follicular lymphoma	19 (11)	27 (15)	46 (13)

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Axicabtagene Ciloleucel for 2nd line (<12m) relapsed DLBCL – Safety

Table 2. Most Common Adverse Events, Cytokine Release Syndrome, and Neurologic Events.*

Event	Axi-cel (N=170)		Standard Care (N=168)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cytokine release syndrome — no. (%)	157 (92)	11 (6)	—	—
Pyrexia — no./total no. (%)	155/157 (99)	14/157 (9)	—	—
Hypotension — no./total no. (%)	68/157 (43)	18/157 (11)	—	—
Sinus tachycardia — no./total no. (%)	49/157 (31)	3/157 (2)	—	—
Chills — no./total no. (%)	38/157 (24)	0/157	—	—
Hypoxia — no./total no. (%)	31/157 (20)	13/157 (8)	—	—
Headache — no./total no. (%)	32/157 (20)	2/157 (1)	—	—
Neurologic event — no. (%)	102 (60)	36 (21)	33 (20)¶	1 (1)
Tremor	44 (26)	2 (1)	1(1)	0
Confusional state	40 (24)	9 (5)	4 (2)	0
Aphasia	36 (21)	12 (7)	0	0
Encephalopathy	29 (17)	20 (12)	2 (1)	0
Paresthesia	8 (5)	1 (1)	14 (8)	0
Delirium	3 (2)	3 (2)	5 (3)	1 (1)

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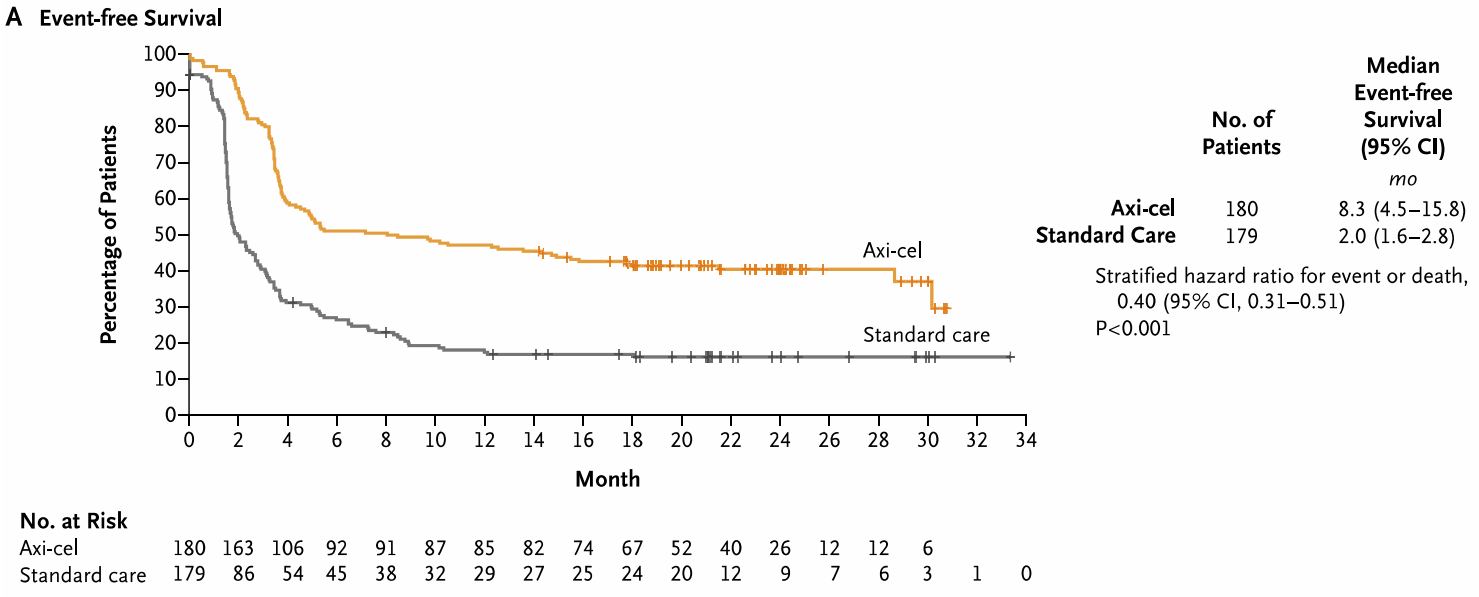
Axicabtagene Ciloleucel for 2nd line (<12m) relapsed DLBCL – EFS



	No. of Patients	Median Event-free Survival (95% CI)
		mo
Axi-cel	180	8.3 (4.5–15.8)
Standard Care	179	2.0 (1.6–2.8)

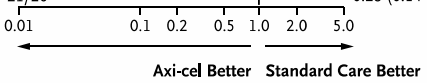
Stratified hazard ratio for event or death, 0.40 (95% CI, 0.31–0.51)
P<0.001

Locke F, et al. ASH 2021 (abstr 2). Locke F, et al.. NEJM. 2021 [Epub]

Axicabtagene Ciloleucel for 2nd line (<12m) relapsed DLBCL – Subgroups

B Subgroup Analysis

Subgroup	Axi-cel	Standard Care	Hazard Ratio for Event or Death (95% CI)
	no. of patients with event/total no.		
Overall	108/180	144/179	0.40 (0.31–0.51)
Age			
<65 yr	81/129	96/121	0.49 (0.36–0.67)
≥65 yr	27/51	48/58	0.28 (0.16–0.46)
Response to first-line therapy at randomization			
Primary refractory disease	85/133	106/131	0.43 (0.32–0.57)
Relapse ≤12 mo after initiation or completion of first-line therapy	23/47	38/48	0.34 (0.20–0.58)
Second-line age-adjusted IPI			
0 or 1	54/98	73/100	0.41 (0.28–0.58)
2 or 3	54/82	71/79	0.39 (0.27–0.56)
Prognostic marker according to central laboratory			
HGBL, double- or triple-hit	15/31	21/25	0.28 (0.14–0.59)
Double-expressor lymphoma	35/57	50/62	0.42 (0.27–0.67)
Molecular subgroup according to central laboratory			
Germinal center B-cell–like	64/109	80/99	0.41 (0.29–0.57)
Activated B-cell–like	11/16	9/9	0.18 (0.05–0.72)
Unclassified	8/17	12/14	—
Disease type according to investigator			
DLBCL, not otherwise specified	68/110	97/116	0.37 (0.27–0.52)
Large-cell transformation from follicular lymphoma	10/19	24/27	0.35 (0.16–0.77)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	23/43	18/27	0.47 (0.24–0.90)
Disease type according to central laboratory			
DLBCL	79/126	95/120	0.44 (0.32–0.60)
HGBL, including rearrangement of *MYC* with *BCL2* or *BCL6* or both	15/31	21/26	0.28 (0.14–0.59)



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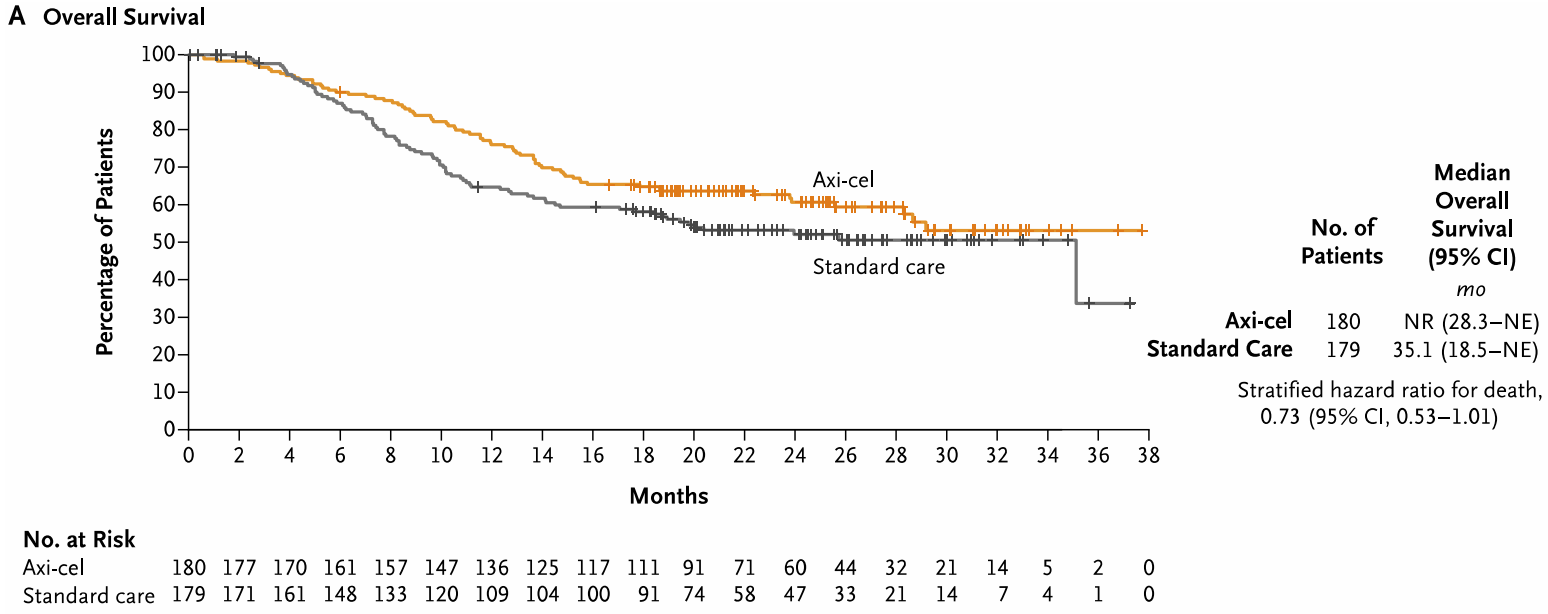
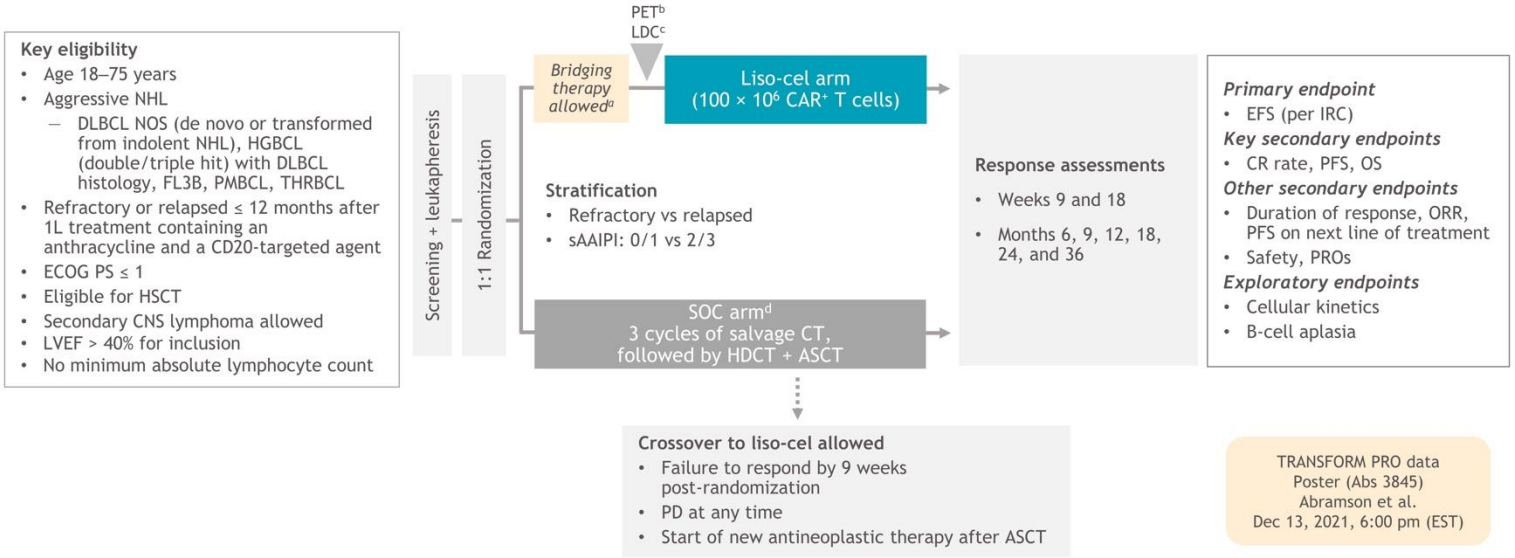
Axicabtagene Ciloleucel for 2nd line (<12m) relapsed DLBCL – OS



Locke F, et al. ASH 2021 (abstr 2). Locke F, et al.. NEJM. 2021 [Epub]

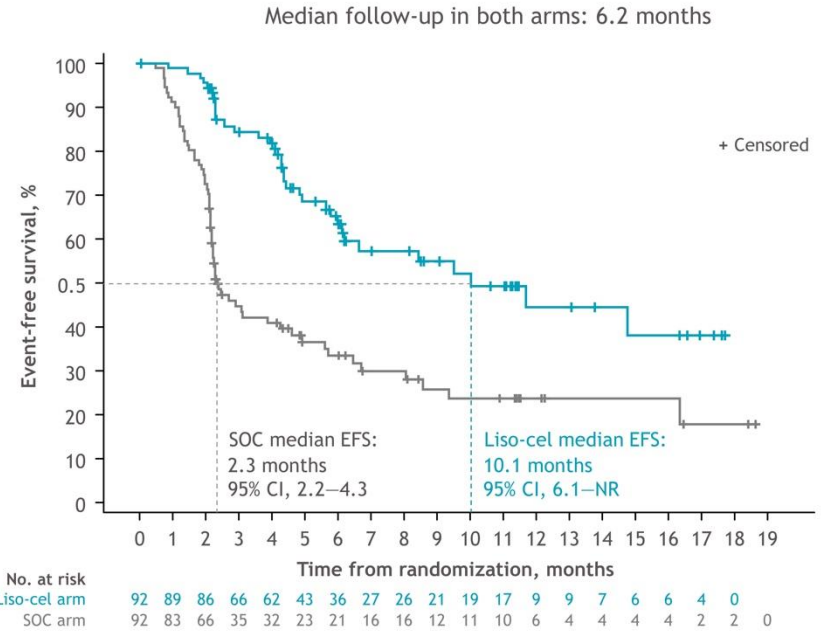
Lisocabtagene maraleucel for 2nd line (<12m) relapsed DLBCL - Schema



- **EFS is defined as time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy, whichever occurs first**

Kamdar M, et al. ASH 2021 (abstr 91).

Lisocabtagene maraleucel for 2nd line (<12m) relapsed DLBCL – EFS per IRC (ITT set; primary endpoint)



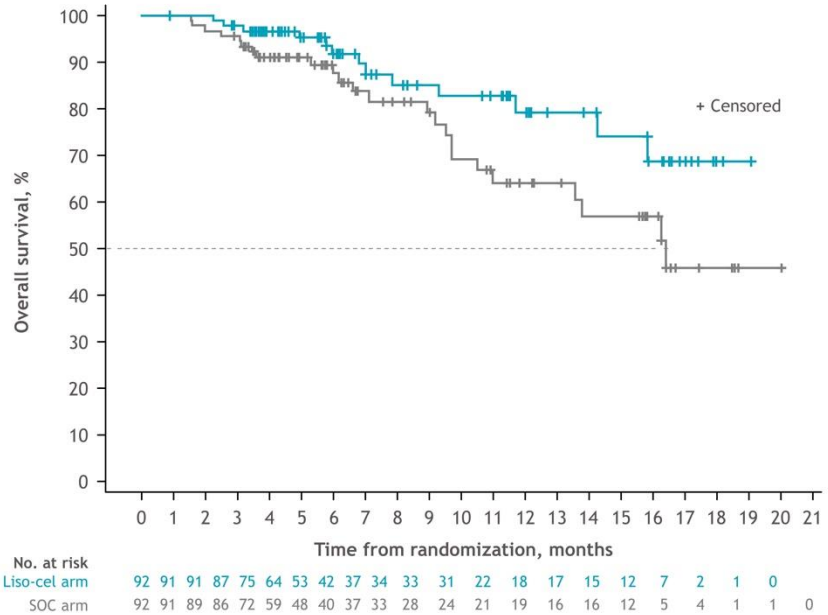
	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	35	63
Stratified HR (95% CI)	0.349 (0.229–0.530)	
	P < 0.0001	
6-month EFS rate, % (SE)	63.3 (5.77)	33.4 (5.30)
Two-sided 95% CI	52.0–74.7	23.0–43.8
12-month EFS rate, % (SE)	44.5 (7.72)	23.7 (5.28)
Two-sided 95% CI	29.4–59.6	13.4–34.1

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

EFS is defined as the time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization or start of a new antineoplastic therapy due to efficacy concerns, whichever occurs first.

Kamdar M, et al. ASH 2021 (abstr 91).

Lisocabtagene maraleucel for 2nd line (<12m) relapsed DLBCL – OS (ITT set)



	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	13	24
Stratified HR (95% CI)	0.509 (0.258–1.004)	
	P = 0.0257	
Median OS (95% CI), months	NR (15.8–NR)	16.4 (11.0–NR)
6-month OS rate, % (SE)	91.8 (3.29)	89.4 (3.36)
Two-sided 95% CI	85.4–98.2	82.9–96.0
12-month OS rate, % (SE)	79.1 (6.13)	64.2 (6.99)
Two-sided 95% CI	67.1–91.1	50.5–77.9

Patients in the SOC arm that crossed over to receive liso-cel continue to be followed for OS in the SOC arm

One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

OS is defined as the time from randomization to death from any cause.

12

Kamdar M, et al. ASH 2021 (abstr 91).

University of Nebraska Medical Center

Bio Ascend

Summary of second line CAR-T studies

Randomized trials of CAR T-cells vs. SOC in 2nd line transplant-eligible DLBCL with primary refractory disease or relapse within 1 year of 1st line therapy

	ZUMA-7	TRANSFORM	BELINDA
CAR T-cell	Axicabtagene Ciloleucel	Lisocabtagene Maraleucel	Tisagenlecleucel
n	359	184	322
% infused in CAR arm	94%	98%	96%
Median EFS	8.3 mo vs. 2 mo	10.1 mo vs. 2.3 mo	3 mo vs. 3 mo
Hazard ratio	0.398 (*P*<0.0001)	0.349; (*P* < 0.0001)	1.07 (*P*=0.69)
Median follow-up	25 months	6 months	10 months
CR rate	65% vs 32%	66% vs 39%	28% vs 28%
Grade ≥3 CRS/NT	6% / 21%	1% / 4%	5% / 3%
	Locke, et al. Abstract 2	Kamdar, et al. Abstract 91	Bishop, et al. Abstract LBA-6

Toby Eyre

Implications of second line CAR-T studies

- In patients with chemoresistant disease (short first remission), more chemo (and AutoSCT) is not effective
- Why different outcome in BELINDA study with tisagenlecleucel?
  - Chemotherapy bridging (sicker patients), additional chemo cycles for standard group, longer time (52d) to get CAR-T (and 25.9% pre-infusion PD), different agent, less lymphodepletion, event definitions
- CAR-T will be SOC for those with PD < 1 year
  - For practical reasons seems likely there will still be 2nd line chemo for many patients
- AutoSCT remains SOC for those with later relapses

Conclusions

- Multiple new agents approved for various lymphoma subtypes
- Polatuzumab-R-CHP likely will be a standard for higher risk DLBCL
- CAR-T will likely be employed in second line therapy for early relapsing DLBCL

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