Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Hodgkin and Non-Hodgkin Lymphomas

Wednesday, February 1, 2023
5:00 PM – 6:00 PM ET

Faculty

Christopher R Flowers, MD, MS
Laurie H Sehn, MD, MPH

Moderator

Neil Love, MD

RTP Year in Review 2023

Faculty

Christopher R Flowers, MD, MS
Chair, Professor
Department of Lymphoma/Myeloma
The University of Texas
MD Anderson Cancer Center
Houston, Texas

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

Laurie H Sehn, MD, MPH
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BC Cancer Centre for Lymphoid Cancer
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Division of Medical Oncology
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Associate Editor, *Blood*
Vancouver, British Columbia, Canada

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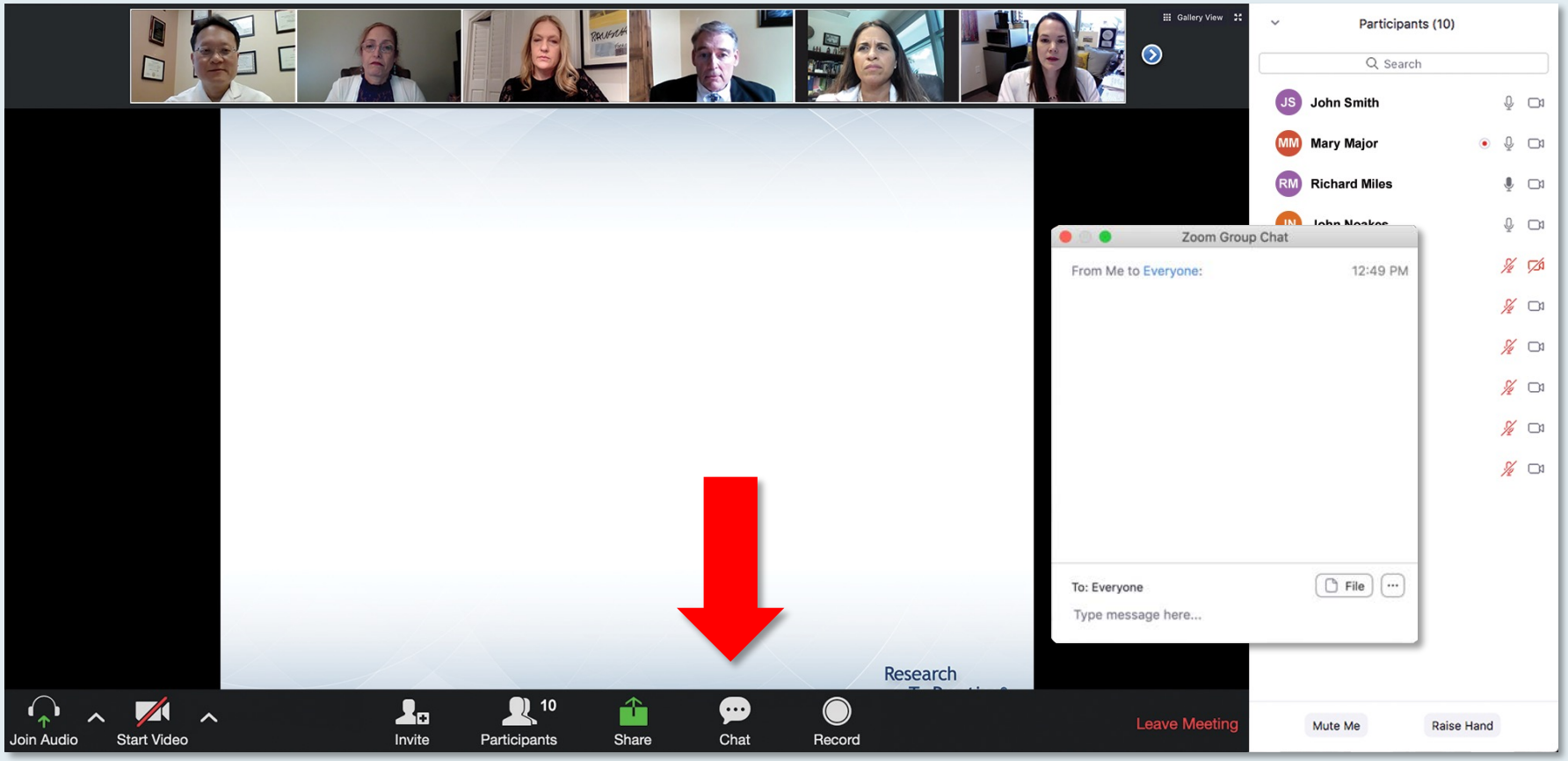
We Encourage Clinicians in Practice to Submit Questions



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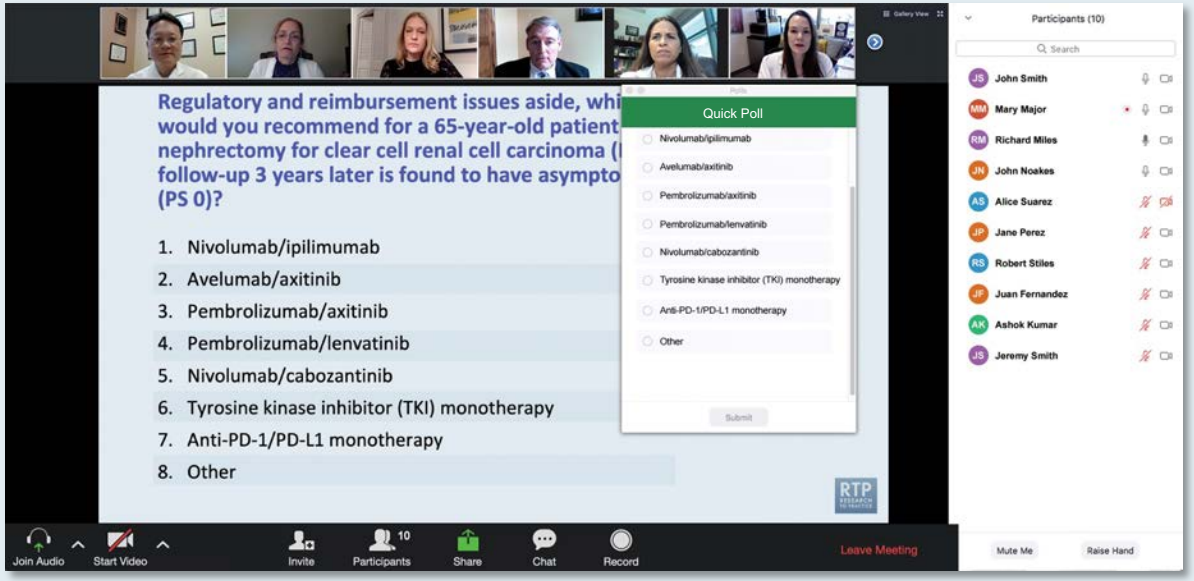

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Maha Hussain, MD, FACP, FASCO

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Dr Love — Disclosures

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Dr Sehn — Disclosures

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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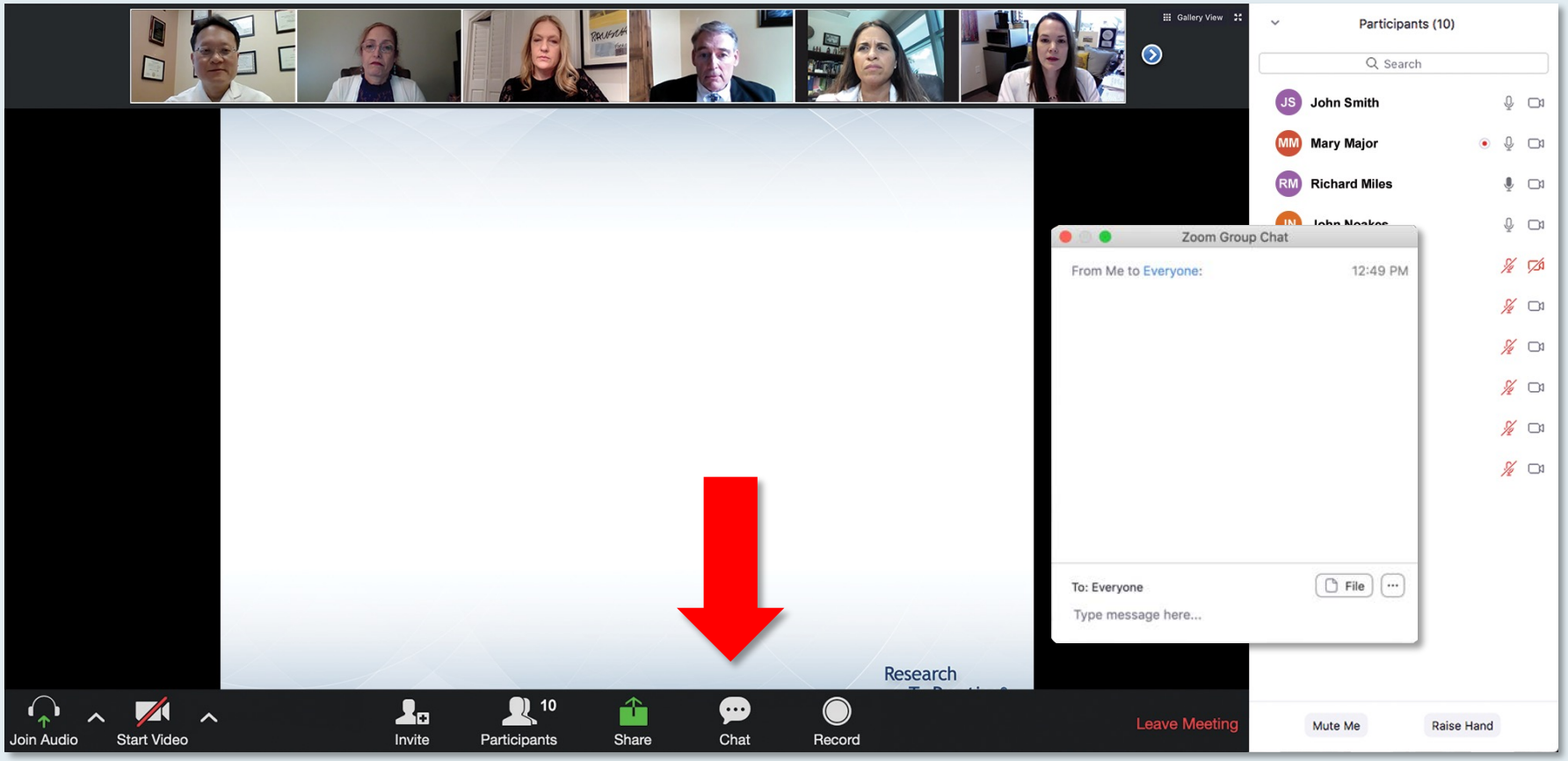

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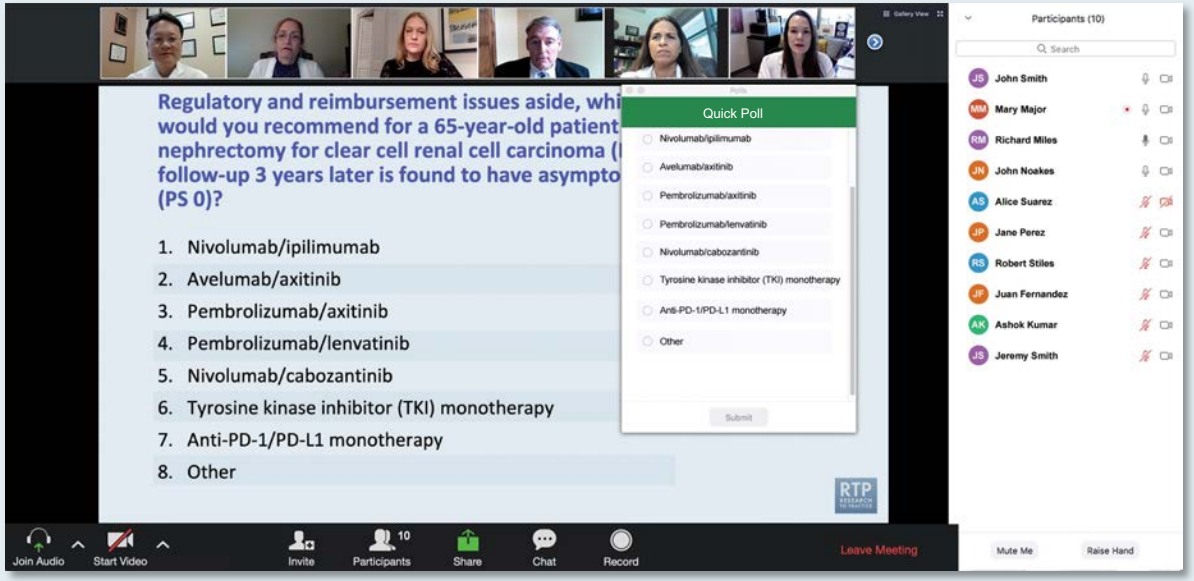

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Research To Practice CME Planning Committee Members, Staff and Reviewers

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Diffuse Large B-Cell Lymphoma (DLBCL) and Hodgkin Lymphoma (HL)

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Follicular Lymphoma (FL) and Mantle Cell Lymphoma (MCL)

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Key Data Sets

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- Tilly H et al. Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. *N Engl J Med* 2022;386(4):351-63.
- Duell J et al. L-Mind: A safety and efficacy analysis of tafasitamab in patients with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) receiving treatment for at least 2 years. ASH 2022;Abstract 2937.
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- Alderuccio JP et al. Loncastuximab tesirine in relapsed/refractory high-grade B-cell lymphoma: A subgroup analysis from the LOTIS-2 study. *Blood Adv* 2022;6(16):4736-9.
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Key Data Sets

Christopher R Flowers, MD, MS (continued)

- Schuster M et al. Effect of prior therapy and disease refractoriness on the efficacy and safety of oral selinexor in patients with diffuse large B-cell lymphoma (DLBCL): A post-hoc analysis of the SADAL study. *Clin Lymphoma Myeloma Leuk* 2022;22(7):483-94.
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Key Data Sets

Christopher R Flowers, MD, MS (continued)

- Kim W et al. Odronextamab in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): Results from a prespecified analysis of the pivotal Phase II study ELM-2. ASH 2022;Abstract 444.
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Key Data Sets

Laurie H Sehn, MD, MPH

- Townsend W et al. Obinutuzumab plus chemotherapy demonstrates long-term benefit over rituximab plus chemotherapy in patients with previously untreated FL: Final analysis of the GALLIUM study. EHA 2022;Abstract S206.
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- Salles G et al. Tazemetostat in combination with lenalidomide and rituximab in patients with relapsed/refractory follicular lymphoma: Phase 1b results of SYMPHONY-1. ASH 2022;Abstract 954.
- Proudman DG et al. Tazemetostat in relapsed/refractory follicular lymphoma: A propensity score-matched analysis of E7438-G000-101 trial outcomes. *Oncotarget* 2022;13:677-83.
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Key Data Sets

Laurie H Sehn, MD, MPH (continued)

- Dreyling M et al. Long-term clinical outcomes and correlative efficacy analyses in patients (pts) with relapsed/refractory follicular lymphoma (R/R FL) treated with tisagenlecleucel in the ELARA trial. ASH 2022;Abstract 608.
- Budde LE et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: A single-arm, multicentre, phase 2 study. *Lancet Oncol* 2022;23(8):1055-65.
- Bartlett N et al. Mosunetuzumab monotherapy demonstrates durable efficacy with a manageable safety profile in patients with relapsed/refractory follicular lymphoma who received ≥2 prior therapies: Updated results from a pivotal Phase II study. ASH 2022;Abstract 610.
- Falchi L et al. Subcutaneous epcoritamab in combination with rituximab + lenalidomide (R^2) for first-line treatment of follicular lymphoma: Initial results from Phase 1/2 trial. ASH 2022;Abstract 611.

Key Data Sets

Laurie H Sehn, MD, MPH (continued)

- Falchi L et al. Subcutaneous epcoritamab with rituximab + lenalidomide in patients with relapsed or refractory follicular lymphoma: Phase 1/2 trial update. ASH 2022;Abstract 609.
- Kim TM et al. Odronextamab in patients with relapsed/refractory (R/R) follicular lymphoma (FL) Grade 1-3a: Results from a prespecified analysis of the pivotal Phase II study ELM-2. ASH 2022;Abstract 949.
- Wang ML et al. Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma. *N Engl J Med* 2022;386(26):2482-94.
- Dreyling M et al. Efficacy and safety of ibrutinib combined with standard first-line treatment or as substitute for autologous stem cell transplantation in younger patients with mantle cell lymphoma: Results from the randomized TRIANGLE trial by the European MCL Network. ASH 2022;Abstract 1.

Key Data Sets

Laurie H Sehn, MD, MPH (continued)

- Wang M et al. Acalabrutinib plus venetoclax and rituximab in patients with treatment-naïve (TN) mantle cell lymphoma (MCL): 2-year safety and efficacy analysis. ASH 2022;Abstract 2884.
- Ruan J et al. Phase 2 trial of acalabrutinib-lenalidomide-rituximab (ALR) with real-time monitoring of MRD in patients with treatment-naïve mantle cell lymphoma. ASH 2022;Abstract 73.
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- Wang M et al. Three-year follow-up of outcomes with KTE-X19 in patients with relapsed/refractory mantle cell lymphoma in ZUMA-2. ASCO 2022;Abstract 7518.

Agenda

INTRODUCTION

MODULE 1: Diffuse Large B-Cell Lymphoma

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FDA Grants Accelerated Approval to Pirtobrutinib for Patients with Relapsed or Refractory Mantle Cell Lymphoma

Press Release: January 27, 2023

On January 27, 2023, the Food and Drug Administration (FDA) granted accelerated approval to pirtobrutinib for relapsed or refractory mantle cell lymphoma (MCL) after at least 2 lines of systemic therapy, including a BTK inhibitor.

“Pirtobrutinib was approved under the FDA's Accelerated Approval pathway based on response rate from the open-label, single-arm, international, Phase 1/2 study, called the BRUIN trial. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.”

“In the BRUIN Phase 1/2 trial, covalent BTK inhibitor pre-treated patients with relapsed or refractory MCL achieved an overall response rate of 50%, with 13% of patients achieving a complete response [with pirtobrutinib].”

“Pirtobrutinib, a highly selective kinase inhibitor, utilizes a novel binding mechanism and is the first and only FDA approved non-covalent (reversible) BTK inhibitor. Pirtobrutinib can reestablish BTK inhibition in MCL patients previously treated with a covalent BTK inhibitor (ibrutinib, acalabrutinib, or zanubrutinib) and extend the benefit of targeting the BTK pathway.”

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-relapsed-or-refractory-mantle-cell-lymphoma?utm_medium=email&utm_source=govdelivery; https://finance.yahoo.com/news/u-fda-approves-jaypirca-pirtobrutinib-190700019.html

RTP RESEARCH TO PRACTICE

FDA Approves Zanubrutinib for Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Press Release: January 19, 2023

“On January 19, 2023, the Food and Drug Administration (FDA) approved zanubrutinib for chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

Efficacy in patients with treatment-naïve CLL/SLL was evaluated in SEQUOIA (NCT03336333). In the randomized cohort including patients without 17p deletion, a total of 479 patients were randomized 1:1 to receive either zanubrutinib until disease progression or unacceptable toxicity or bendamustine plus rituximab (BR) for 6 cycles.

Efficacy in patients with relapsed or refractory CLL/SLL was evaluated in ALPINE (NCT03734016). A total of 652 patients were randomized 1:1 to receive either zanubrutinib or ibrutinib.

The recommended zanubrutinib dosage is 160 mg taken orally twice daily or 320 mg taken orally once daily until disease progression or unacceptable toxicity.”

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-zanubrutinib-chronic-lymphocytic-leukemia-or-small-lymphocytic-lymphoma

Agenda

INTRODUCTION

MODULE 1: Diffuse Large B-Cell Lymphoma

MODULE 2: Hodgkin Lymphoma

MODULE 3: Follicular Lymphoma

MODULE 4: Mantle Cell Lymphoma

Diffuse Large B-Cell Lymphoma

POLARIX – Polatuzumab vedotin/R-CHP

RE-MIND2 – Tafasitamab/lenalidomide

LOTIS-2 – Loncastuximab tesirine

CAR T-cell therapy

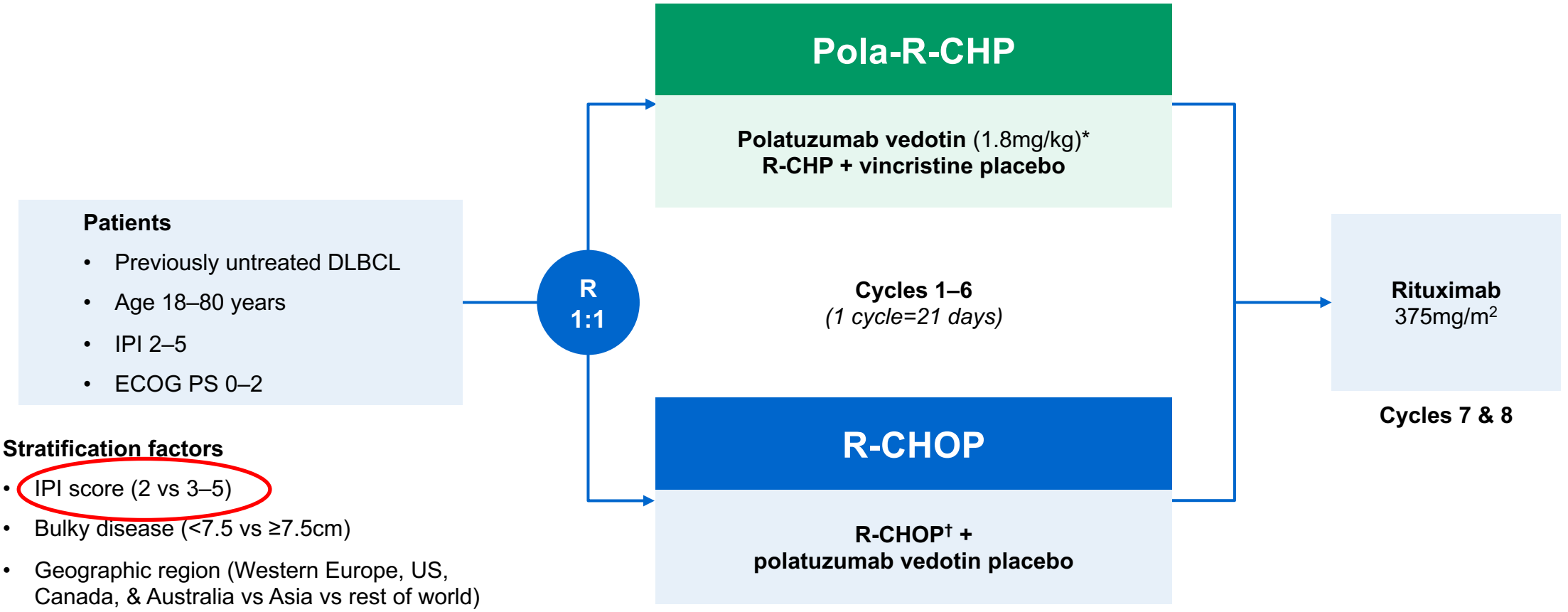
- ZUMA-7 – Axicabtagene ciloleucel
- TRANSFORM – Lisocabtagene maraleucel

SADAL – Selinexor

Bispecific antibodies

- Glofitamab, epcoritamab, odronextamab

POLARIX: A randomized double-blinded study



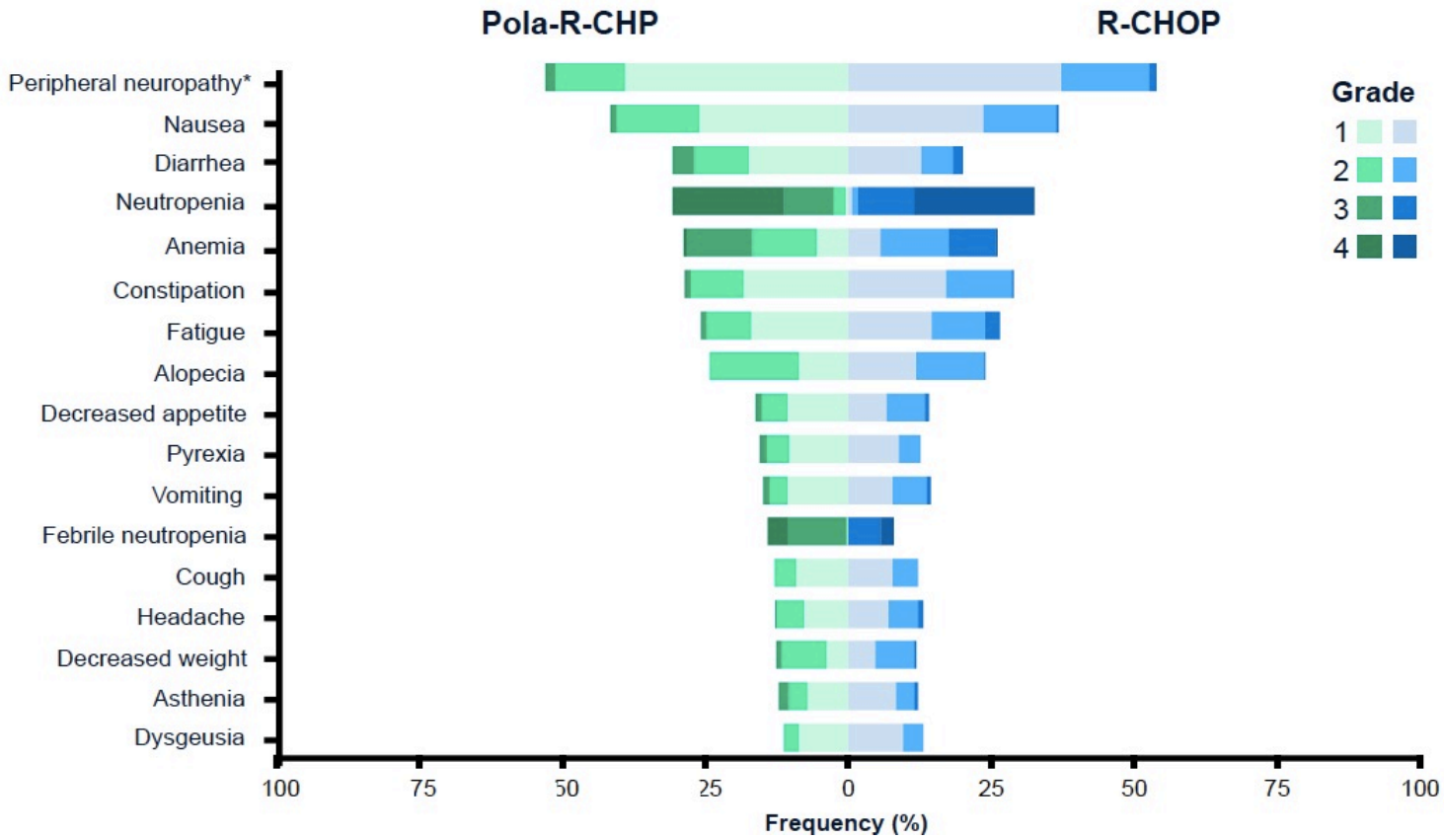
*IV on Day 1; †R-CHOP: IV rituximab 375mg/m², cyclophosphamide 750mg/m², doxorubicin 50mg/m², and vincristine 1.4mg/m² (max. 2mg) on Day 1, plus oral prednisone 100mg once daily on Days 1–5.
IPI, International prognostic index; ECOG PS, Eastern Cooperative Oncology Group performance status; R, randomized.

Courtesy of Christopher R Flowers, MD, MS

Tilly H et al, NEJM 2021

POLARIX: Safety and Adverse Events

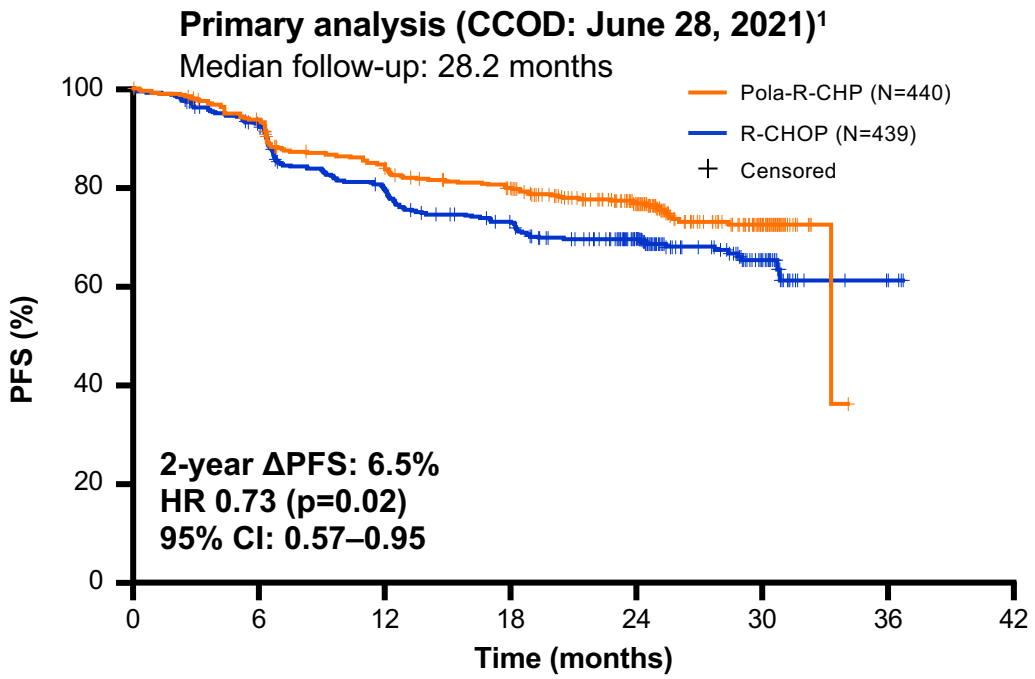
n (%)	Pola-R-CHP (N=435)	R-CHOP (N=438)
Any-grade adverse events	426 (97.9)	431 (98.4)
Grade 3–4	251 (57.7)	252 (57.5)
Grade 5	13 (3.0)	10 (2.3)
Serious adverse events	148 (34.0)	134 (30.6)
Adverse events leading to:		
Discontinuation of any study drug	27 (6.2)	29 (6.6)
Polatuzumab vedotin / vincristine	19 (4.4)	22 (5.0)
Dose reduction of any study drug	40 (9.2)	57 (13.0)

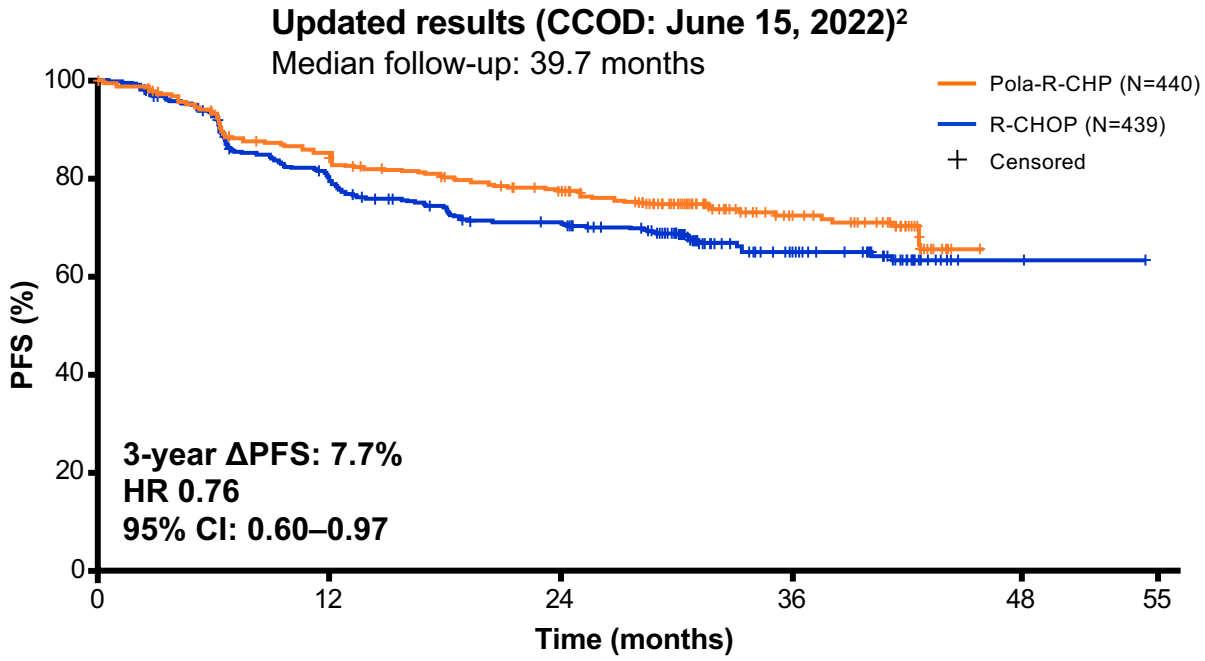


Courtesy of Christopher R Flowers, MD, MS

Tilly H et al, NEJM 2021

POLARIX Updated Efficacy Results: 3-Year Progression Free Survival





No. of patients at risk								
Pola-R-CHP	440	404	353	327	246	78	0	0
R-CHOP	439	389	330	296	220	78	3	0

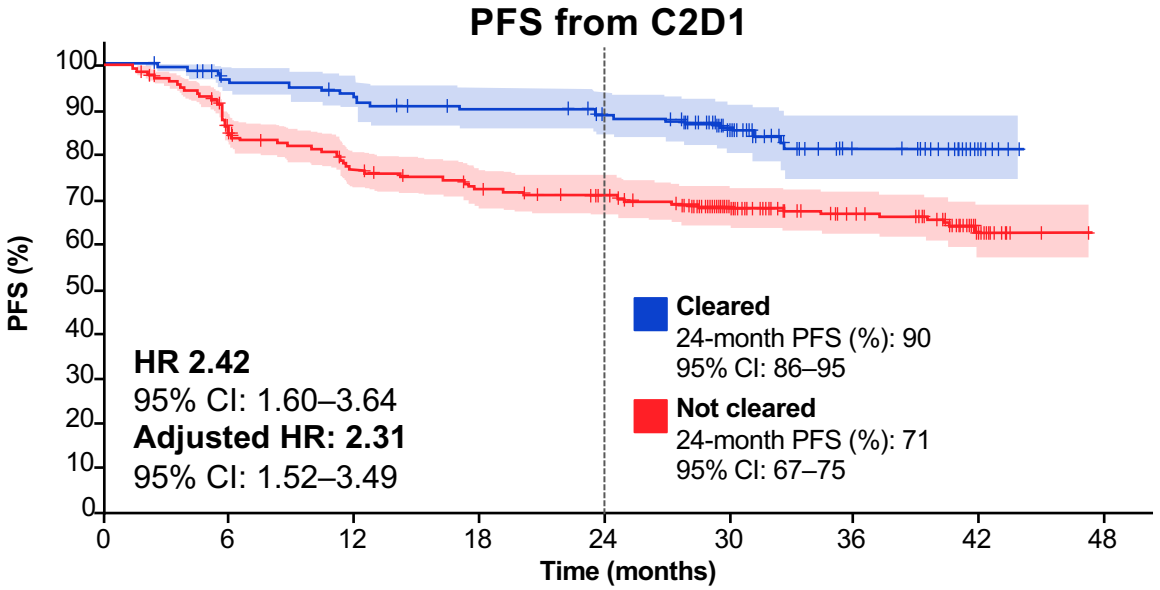
No. of patients at risk										
Pola-R-CHP	440	405	354	331	313	242	103	66	0	0
R-CHOP	439	390	331	300	284	222	94	59	2	1

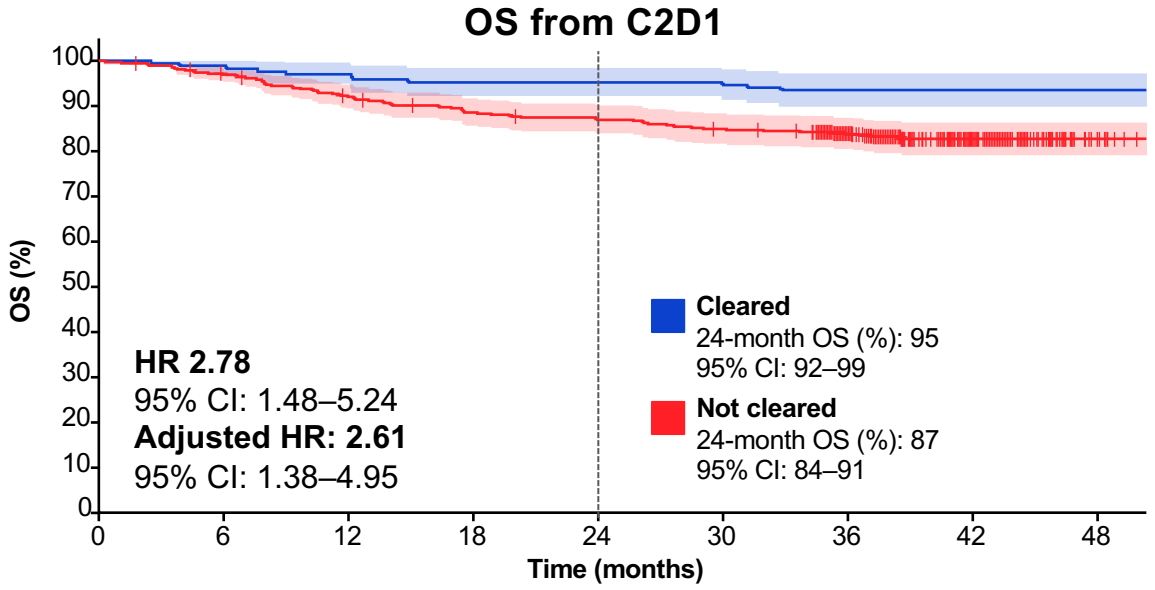
Analysis based on the ITT population.
ITT, intention-to-treat; NE, not evaluable; no., number.

Courtesy of Christopher R Flowers, MD, MS

1. Tilly H, et al. N Engl J Med 2022;386:351–63
2. Herrera A, ASH abstract 2022.

POLARIX: Patients with ctDNA clearance after one cycle of treatment had longer PFS and OS than those without ctDNA clearance





No. of patients at risk									
Cleared	175	163	156	148	141	89	47	9	0
Not cleared	443	371	327	306	290	167	111	28	0

No. of patients at risk									
Cleared	175	170	165	162	162	159	136	50	2
Not cleared	443	427	403	386	378	368	308	127	14

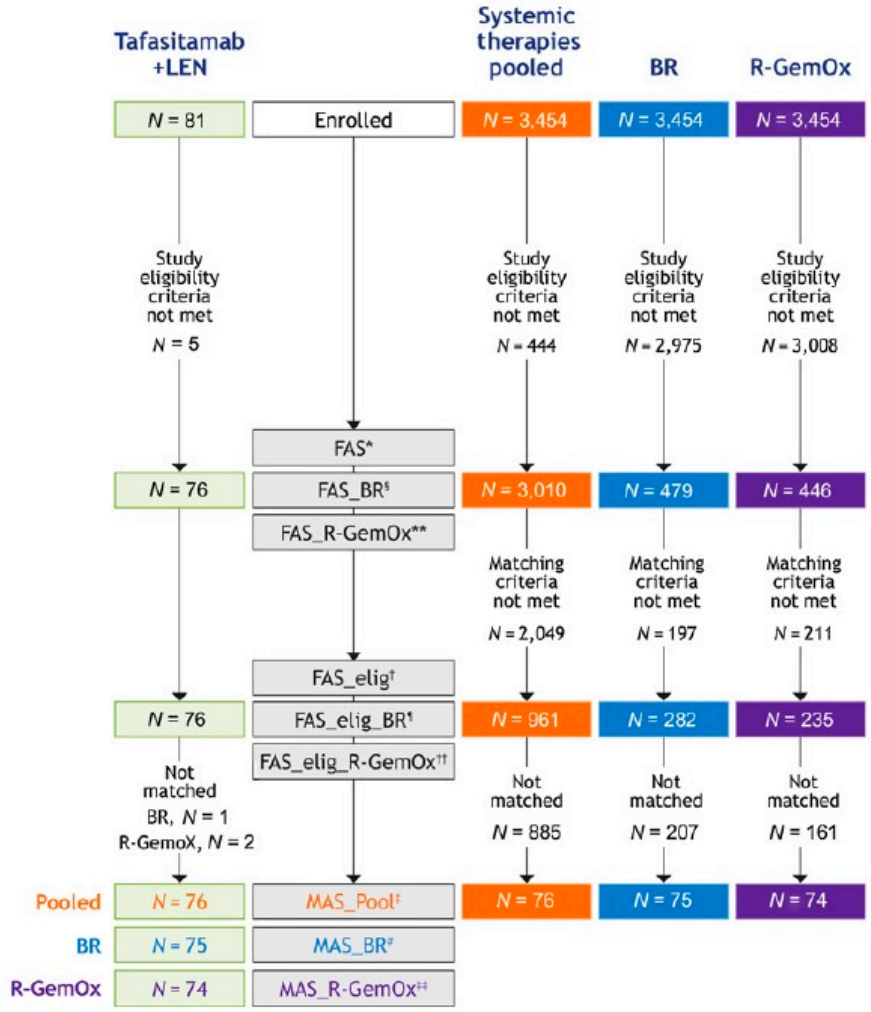
	24-month PFS, %			
	ctDNA not cleared at C2D1 (95% CI)	ctDNA cleared at C2D1 (95% CI)	HR (95% CI)	Adjusted HR (95% CI)
Pola-R-CHP (n=319)	72 (66–78)	90 (84–96)	**3.08** (1.63–5.80)	**2.93** (1.53–5.61)
R-CHOP (n=299)*	69 (63–76)	90 (84–97)	**1.95** (1.14–3.36)	**2.00** (1.15–3.47)

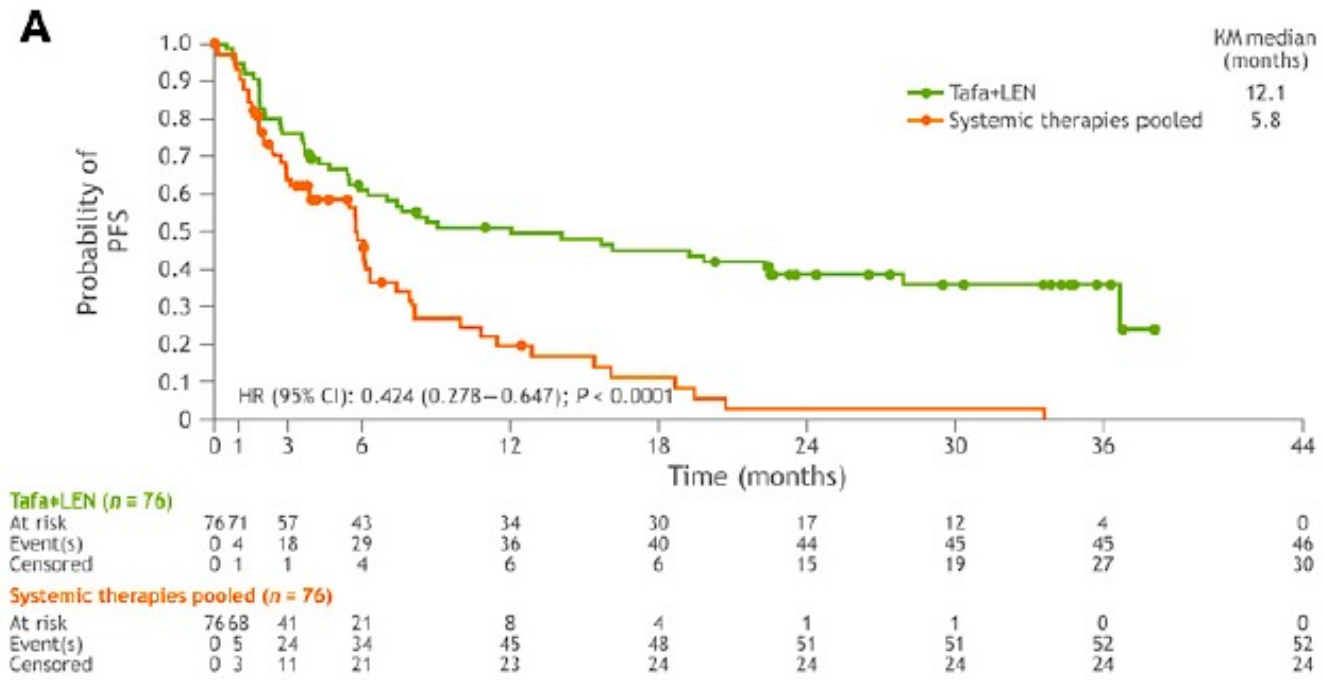
	24-month OS, %			
	ctDNA not cleared at C2D1 (95% CI)	ctDNA cleared at C2D1 (95% CI)	HR (95% CI)	Adjusted HR (95% CI)
Pola-R-CHP (n=319)	87 (83–92)	95 (90–99)	**2.75** (1.16–6.49)	**2.27** (0.95–5.45)
R-CHOP (n=299)	88 (84–92)	96 (92–100)	**2.81** (1.10–7.17)	**2.88** (1.12–7.45)

*Three patients were censored between C1D1 and C2D1, and were therefore not included in this analysis.
Analysis based on the BEP. Relationships between ctDNA and PFS and OS were evaluated using univariate and multivariate Cox regression. Adjusted HRs are reported for Cox regression including the study stratification factors (geographic region, baseline IPI score, bulky disease status), age >60 years, and cell of origin.

Courtesy of Christopher R Flowers, MD, MS

RE-MIND2: Observational Matched Cohort Study Tafasitamab/Lenalidomide vs Systemic Therapies





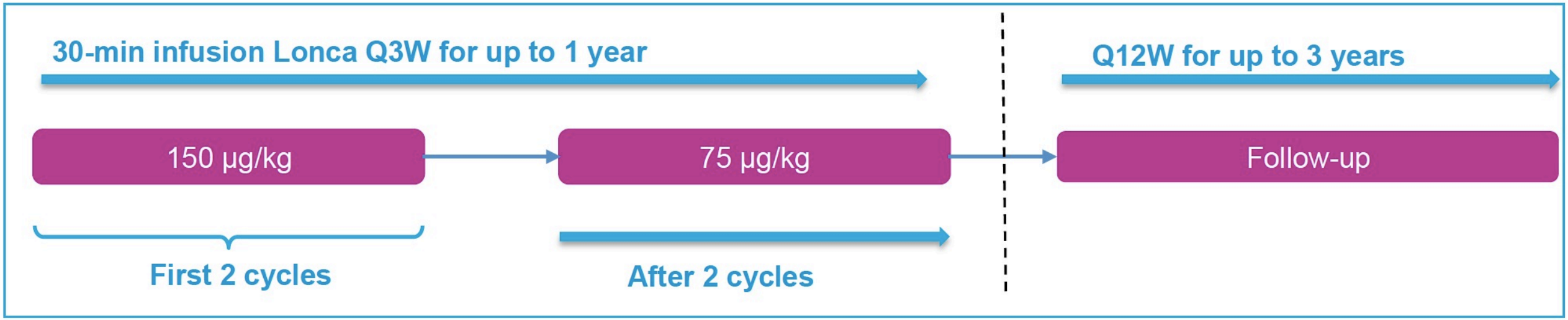
Nowakowski et al, Clin Cancer Res 2022

Courtesy of Christopher R Flowers, MD, MS

Loncastuximab Tesirine: LOTIS-2 Trial
Single Arm Open Label Phase 2 Study in DLBCL

Patient population:
Patients with R/R DLBCL following ≥2 lines of prior systemic therapy

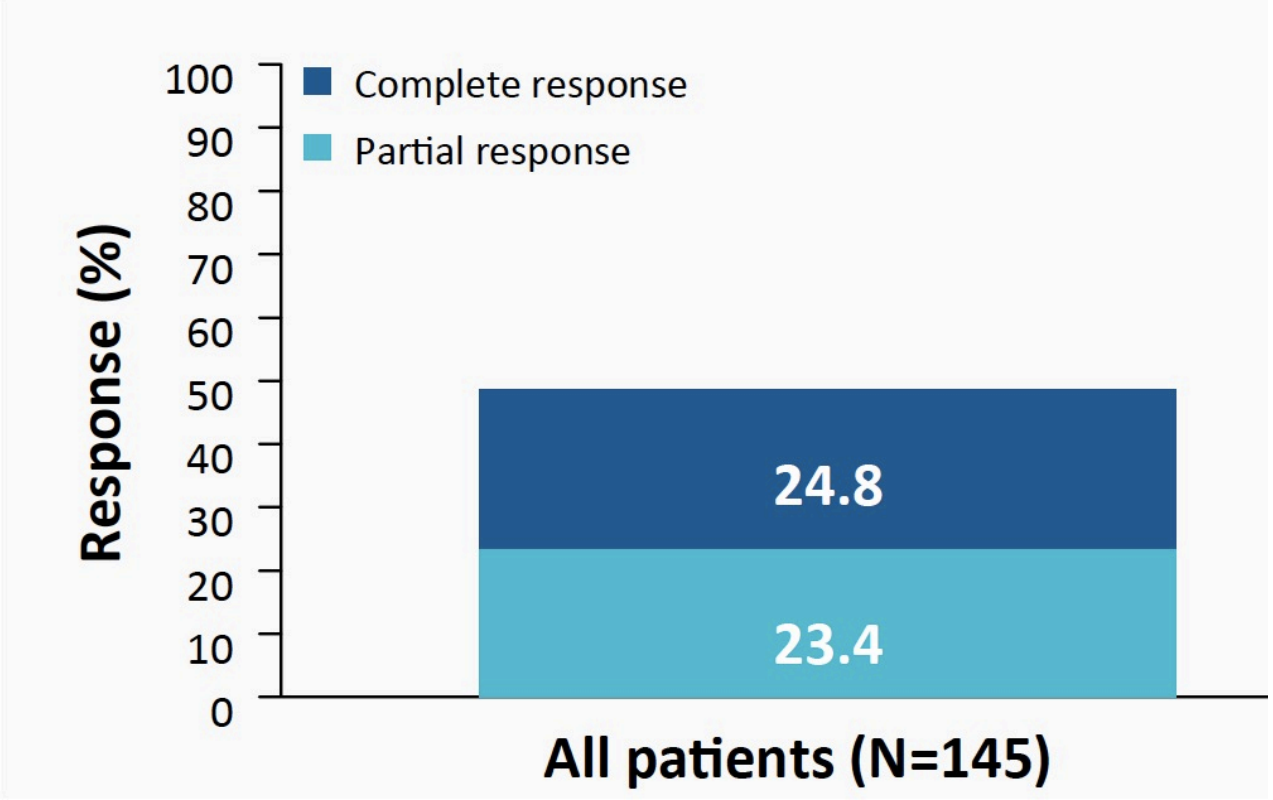
Primary objective:
Evaluate efficacy, **using ORR** (central review), and **safety** of the full Phase 2 study population

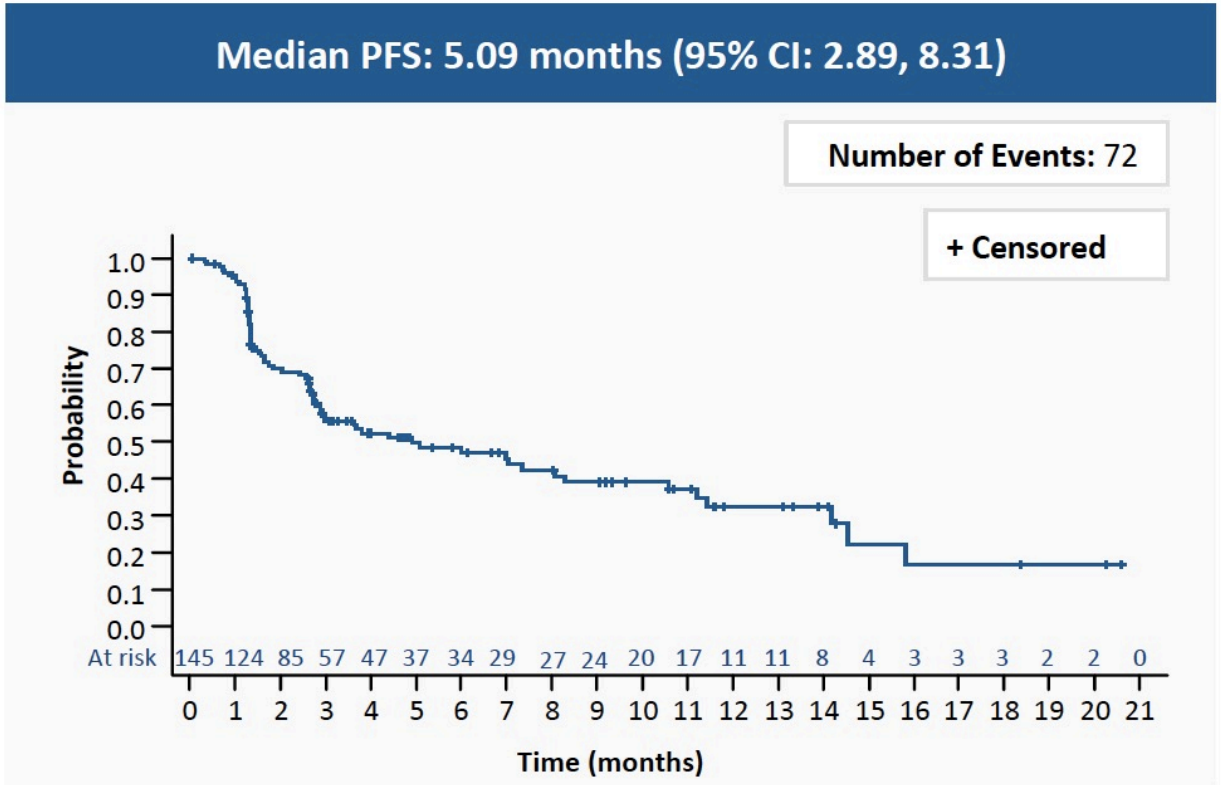


Courtesy of Christopher R Flowers, MD, MS

Caimi et al, Lancet Oncology 2021

Loncastuximab Tesirine: LOTIS-2 Trial
Single Arm Open Label Phase 2 Study in DLBCL

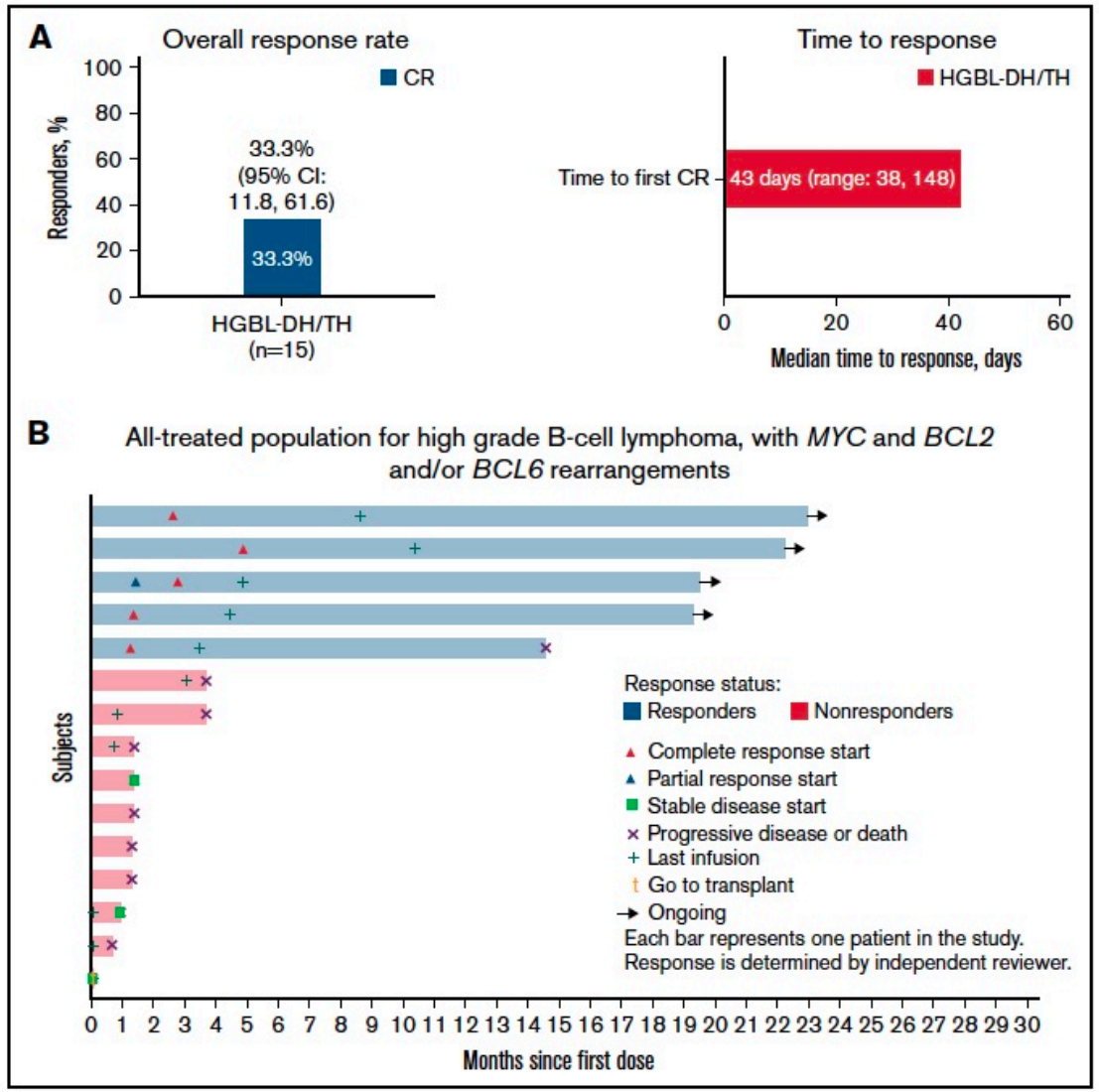




Courtesy of Christopher R Flowers, MD, MS

Caimi et al, Lancet Oncology 2021

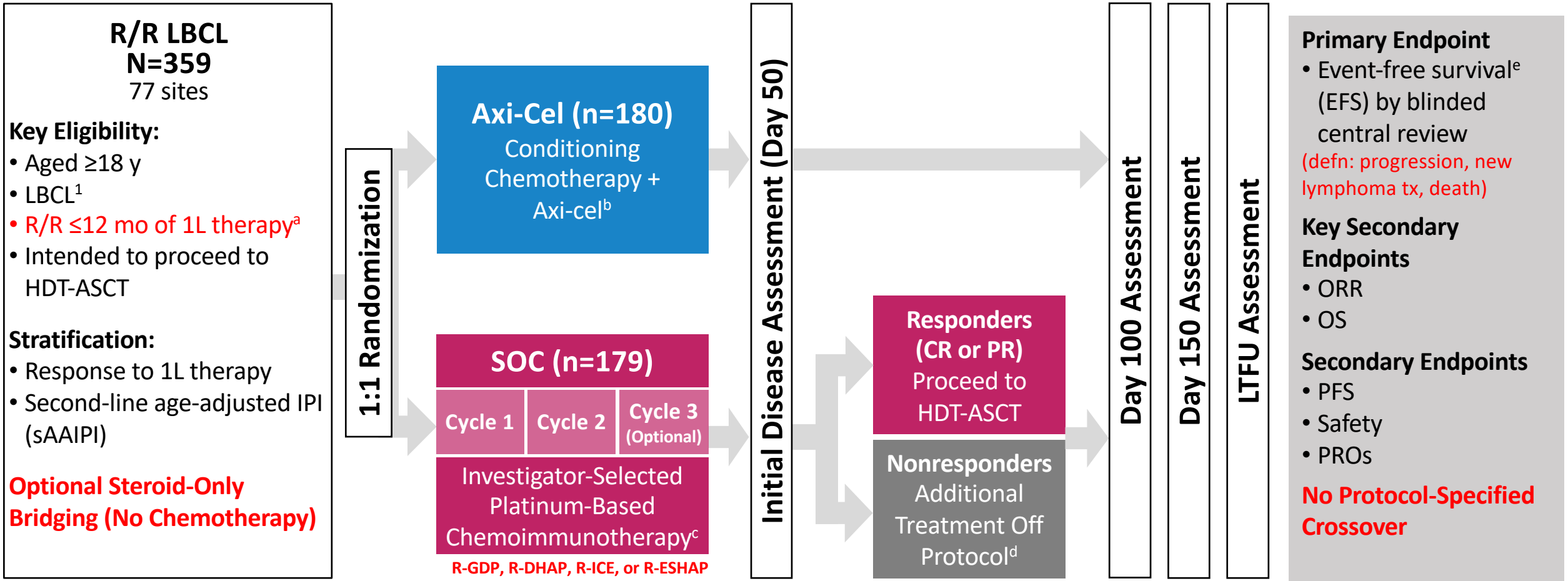
Loncastuximab Tesirine: HGBCL Subgroup



Courtesy of Christopher R Flowers, MD, MS

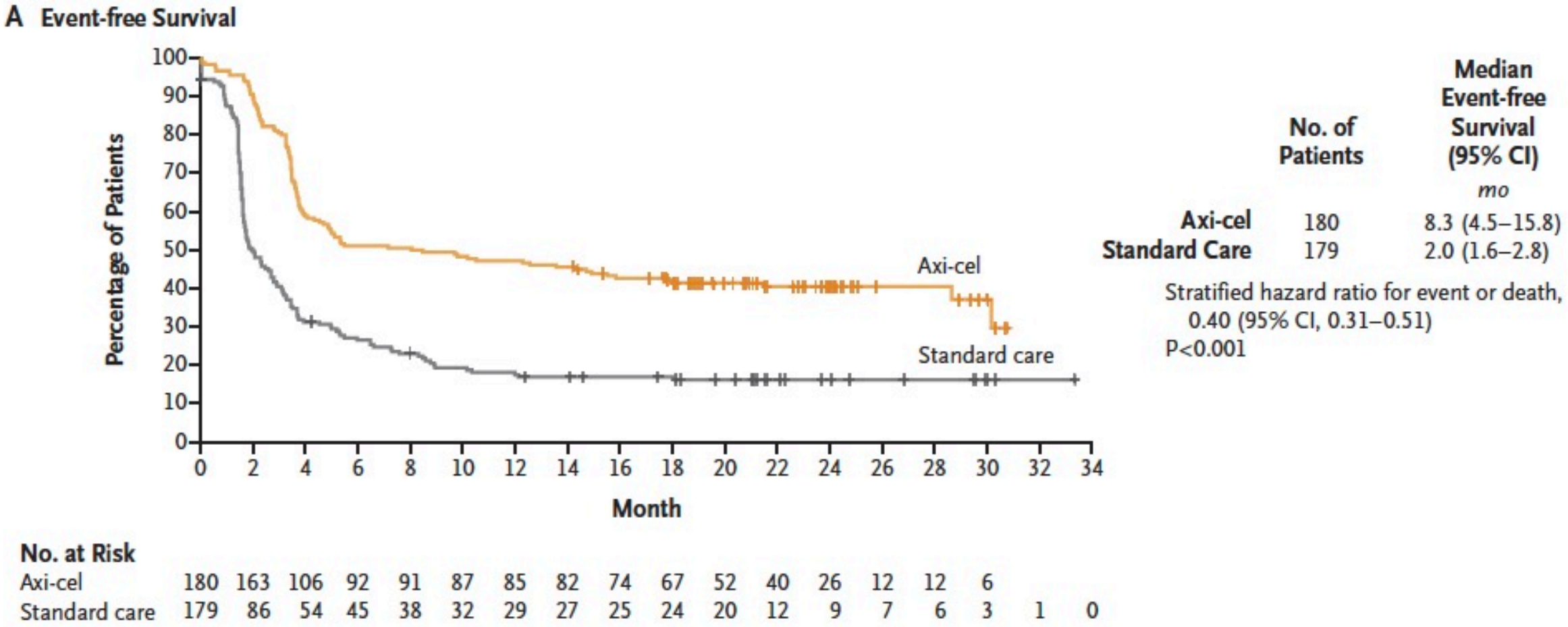
Alderuccio et al, Blood Advances 2022

ZUMA-7 Study Schema and Endpoints: Axi-Cel Versus SOC as Second-Line Therapy in Patients With R/R LBCL



Courtesy of Christopher R Flowers, MD, MS

ZUMA-7: Axicabtagene Ciloleucel as Second-Line Therapy for LBCL



	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)

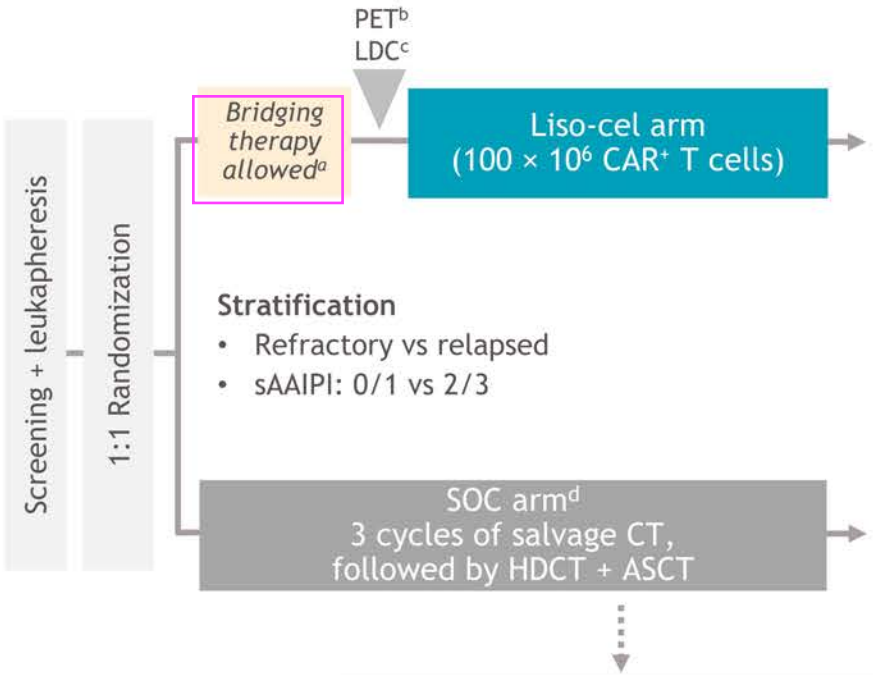
Stratified hazard ratio for event or death, 0.40 (95% CI, 0.31–0.51)
P<0.001

Courtesy of Christopher R Flowers, MD, MS

Locke et al, NEJM 2022

TRANSFORM study design

Key eligibility
- Age 18–75 years
- Aggressive NHL
  - DLBCL NOS (de novo or transformed from indolent NHL), HGBCL (double/triple hit) with DLBCL histology, FL3B, PMBCL, THRBCL
- Refractory or relapsed ≤ 12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG PS ≤ 1
- Eligible for HSCT
- Secondary CNS lymphoma allowed
- LVEF > 40% for inclusion
- No minimum absolute lymphocyte count



Response assessments
- Weeks 9 and 18
- Months 6, 9, 12, 18, 24, and 36

Primary endpoint
- EFS (per IRC)

Key secondary endpoints
- CR rate, PFS, OS

Other secondary endpoints
- Duration of response, ORR, PFS on next line of treatment
- Safety, PROs

Exploratory endpoints
- Cellular kinetics
- B-cell aplasia

TRANSFORM PRO data
Poster (Abs 3845)
Abramson et al.
Dec 13, 2021, 6:00 pm (EST)

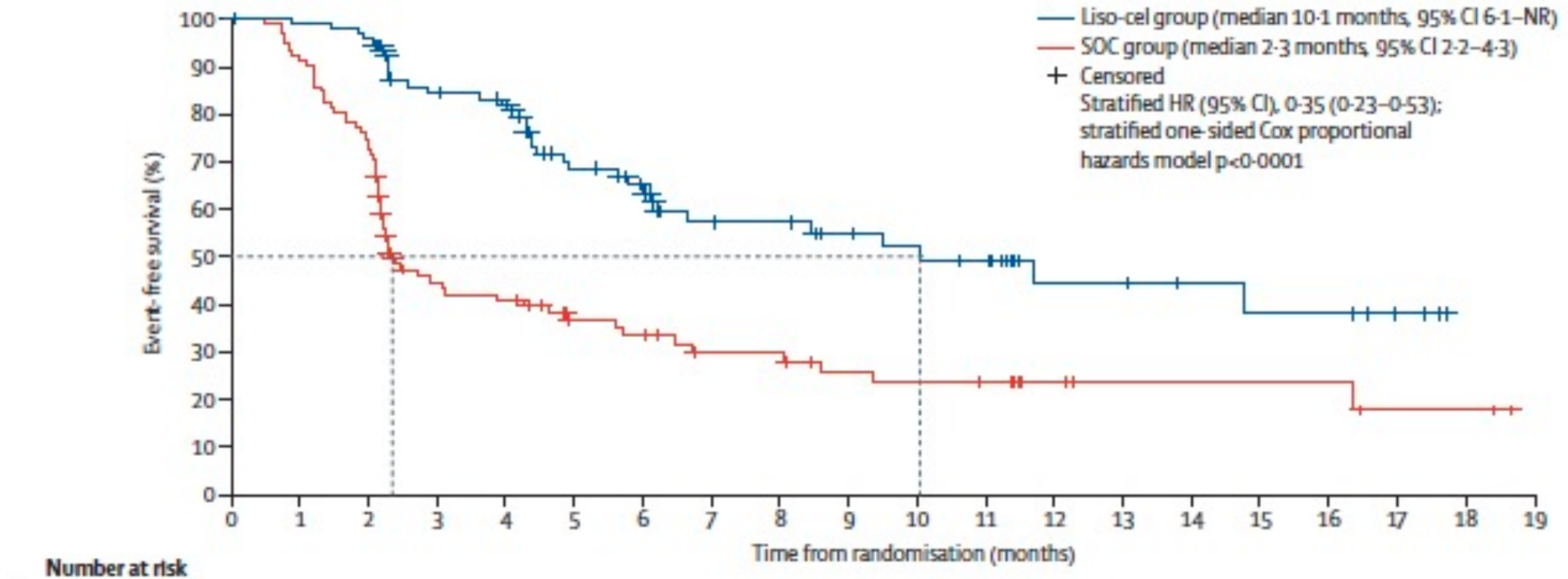
- **EFS is defined as time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy, whichever occurs first**

[a]Patients may have received a protocol-defined SOC regimen to stabilize their disease during liso-cel manufacturing; [b]Only for patients who received bridging therapy; [c]Lymphodepletion with fludarabine 30 mg/m^2 and cyclophosphamide 300 mg/m^2 for 3 days; [d]SOC was defined as physician's choice of R-DHAP, R-ICE, or R-GDP.
DLBCL, diffuse large-B cell lymphoma; FL3B, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; LDC, lymphodepleting chemotherapy; NOS, not otherwise specified; PD, progressive disease; PMBCL, primary mediastinal large B-cell lymphoma; PRO, patient-reported outcome; sAAIPI, secondary age-adjusted International Prognostic Index; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma.

Kamdar M, et al. ASH 2021 [Abstract #91]

Courtesy of Christopher R Flowers, MD, MS

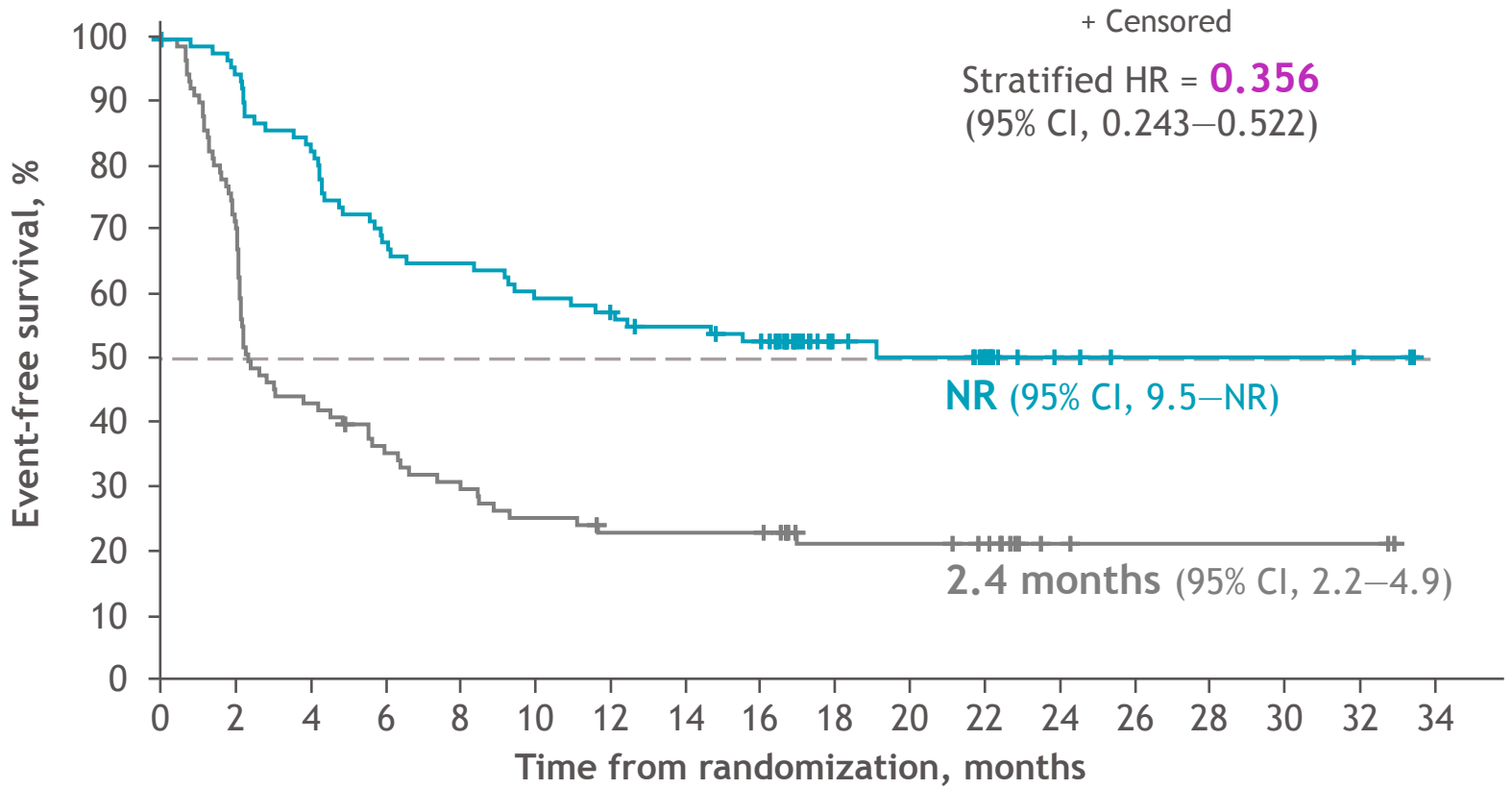
TRANSFORM: Lisocabtagene Maraleucel vs Salvage and ASCT in Second-line LBCL



Courtesy of Christopher R Flowers, MD, MS

Kamdar et al, Lancet 2022

TRANSFORM: EFS per IRS (ITT set; primary endpoint)



No. at risk

Liso-cel	92	87	76	62	59	55	52	48	45	24	20	17	5	3	3	3	3	0
SOC	92	66	39	32	27	22	19	19	19	12	12	10	3	2	2	2	2	0

18-month EFS rate	
Liso-cel	**SOC**
52.6%	**20.8%**
(95% CI, 42.3–62.9)	(95% CI, 12.2–29.5)

Median follow-up: 17.5 months

EFS was defined as the time from randomization to death due to any cause, PD, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy due to efficacy concerns, whichever occurred first. This endpoint was not statistically retested for the primary analysis.
NR, not reached.

Abramson JS, et al. ASH 2022

Courtesy of Christopher R Flowers, MD, MS

Abramson et al, ASH 2022

SADAL Study: Post-hoc Analysis of Oral Selinexor

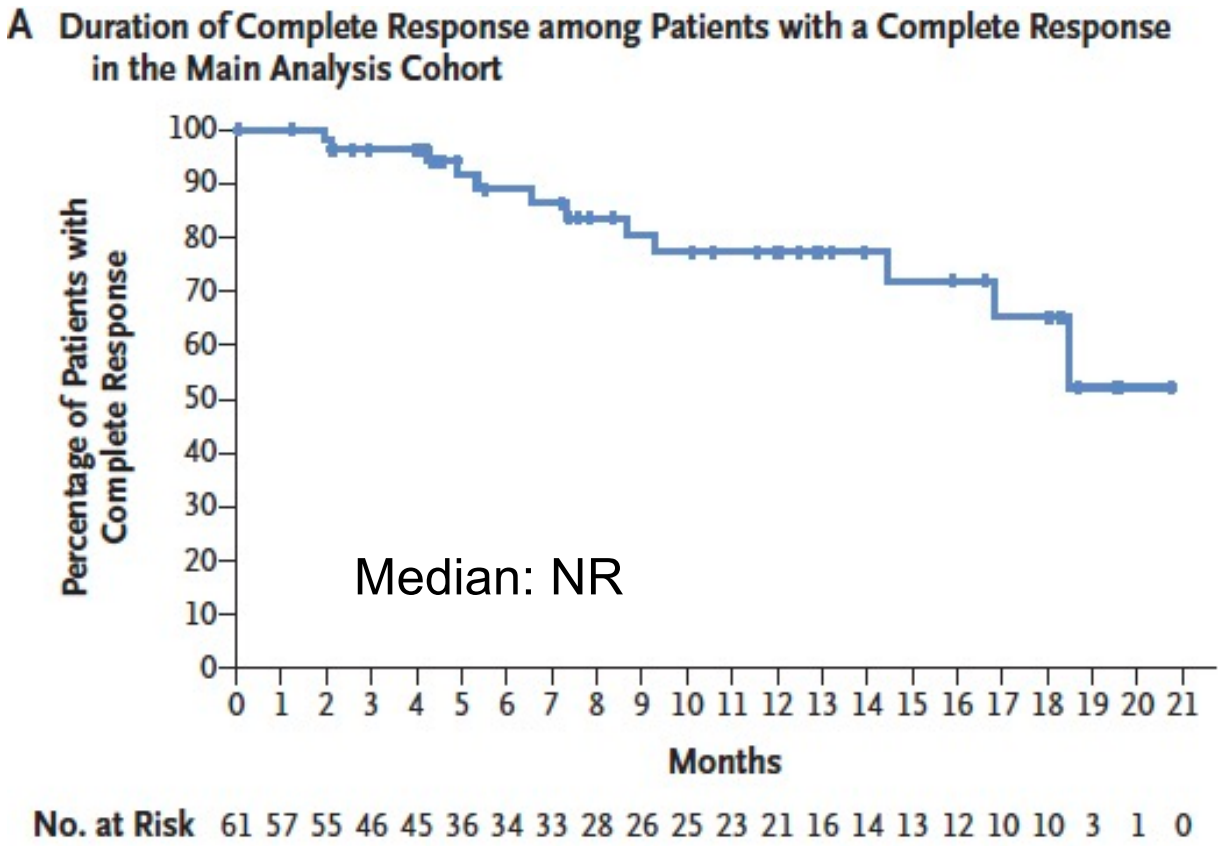
Table 2 Response Rates According to Prior Treatment/Refractory Status

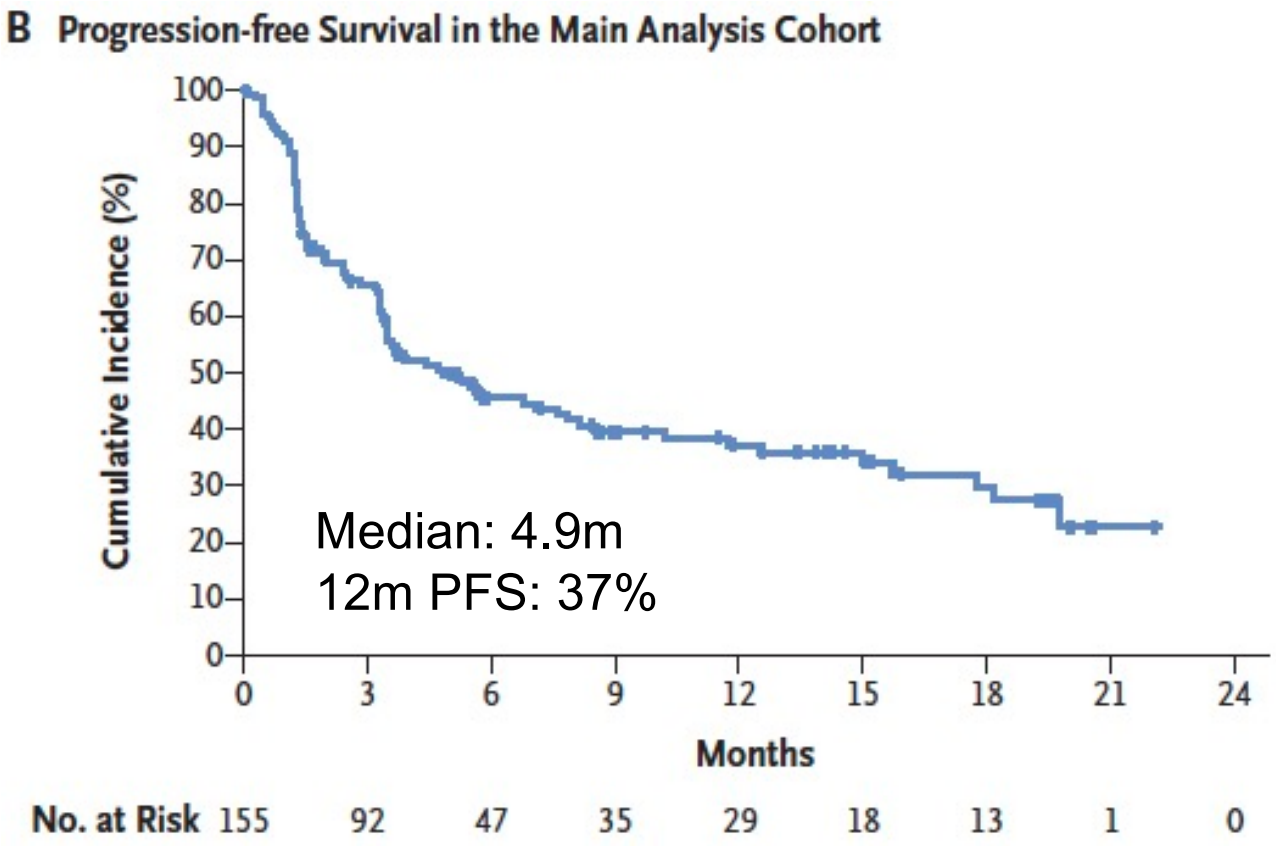
Patients	ORR, % (95% CI)	*P value*
Prior treatments		
2 Lines of Prior Therapies (n = 79)	27.8 (18.3, 39.1)	
3 or More Lines of Prior Therapies (n = 55)	30.9 (19.1, 44.8)	*.8490*
Prior ASCT (n = 40)	42.5 (27.0, 59.1)	
No Prior ASCT (n = 94)	23.4 (15.3, 33.3)	*.0435*
Response to Last Therapy		
PR or CR (n = 92)	35.9 (26.1, 46.5)	
No PR or CR (n = 37)	16.2 (6.2, 32.0)	*.0470*

Courtesy of Christopher R Flowers, MD, MS

Schuster M et al. Clin Lymphoma Myeloma Leuk 2022

Glofitamab in R/R DLBCL: Efficacy





Median follow-up: 12.6m
ORR 52%; CR rate 39%

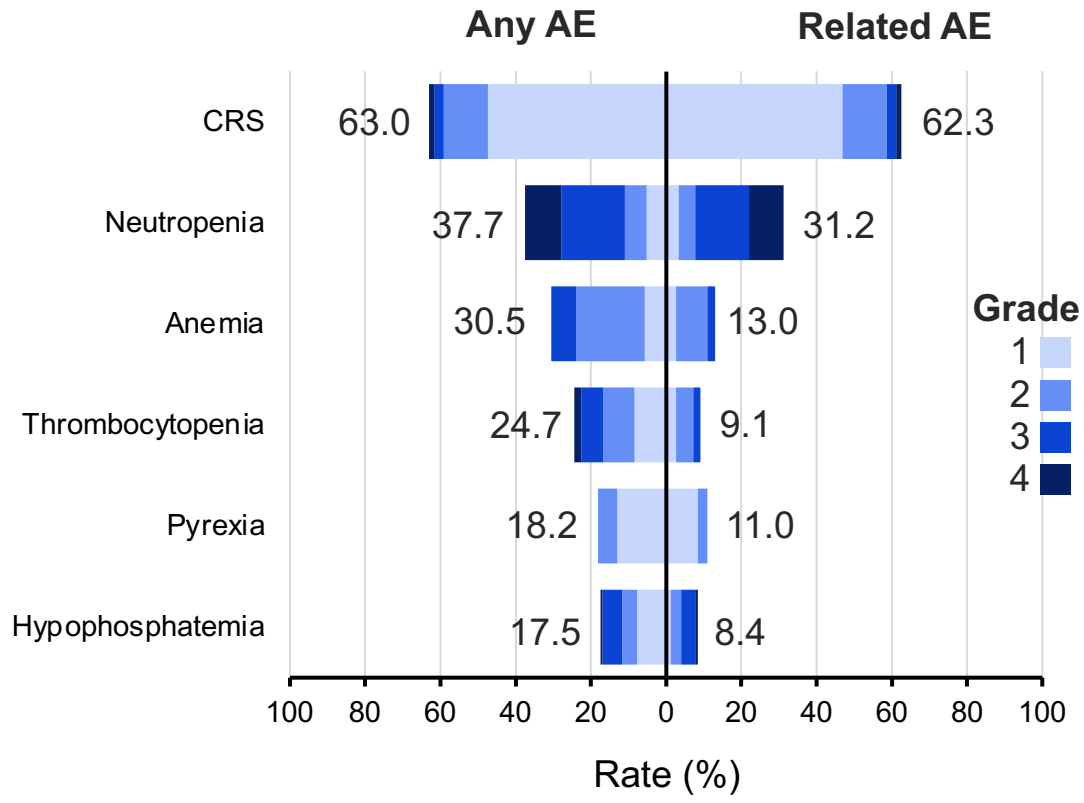
Courtesy of Christopher R Flowers, MD, MS

Dickinson et al, NEJM 2022

Glofitamab Safety Profile

n (%)*	N=154
Median no. of cycles received (range)	5 (1–13)
Median relative dose intensity, % (range)	100 (94–100)
AE	152 (98.7)
Related AE	140 (90.9)
Grade 3–4 AE	87 (56.5)
Related AE	64 (41.6)
Serious AE	73 (47.4)
Related AE	46 (29.9)
Grade 5 (fatal AE)	8 (5.2)†
Related AE	0
AE leading to treatment discontinuation	14 (9.1)
Related AE	5 (3.2)

AEs (≥15%) by grade and relationship with glofitamab



Courtesy of Christopher R Flowers, MD, MS

Dickinson et al, ASCO 2022/NEJM 2022

EPCORE NHL-1 (Expansion Cohort) – Study Design and Endpoints

Subcutaneous Epcoritamab in Patients with Relapsed or Refractory Large B-cell Lymphoma (EPCORE NHL-1): Pivotal Results from a Phase 2 Study

Epcoritamab SC Dose Escalation
(not presented here)

- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Acceptable safety profile
- ✓ Encouraging antitumor activity

→ **Phase 2 EPCORE NHL-1 LBCL Cohort**
R/R DLBCL, HGBCL, PMBCL, & FL grade 3B
N=157

Step-up dosing[a]
Priming dose C1D1 (0.16 mg)

Intermediate dose C1D8 (0.8 mg)

Epcoritamab SC RP2D 48 mg
QW C1–3,
Q2W C4–9,
Q4W C10+

Data cutoff: January 31, 2022
Median follow-up: 10.7 mo

→ Until progressive disease* or unacceptable toxicity

*Radiographic disease evaluation was performed every 6 weeks for the first 24 weeks (W6, 12, 18, 24) and then every 12 weeks (W 36, 48) and Q6 months thereafter

INCLUSION CRITERIA

- R/R CD20+ mature B-cell neoplasm
- ECOG PS 0–2
- Prior treatment with ≥2 prior lines of antineoplastic therapy including ≥1 anti-CD20 mAb
- Measurable disease by CT, MRI, or FDG PET-CT[b]
- Prior CAR-T was allowed

To ensure patient safety and to better characterize CRS, inpatient monitoring was required at the first full dose for 24 hours. Later doses were outpatient.

OBJECTIVES

Primary: ***ORR by IRC***

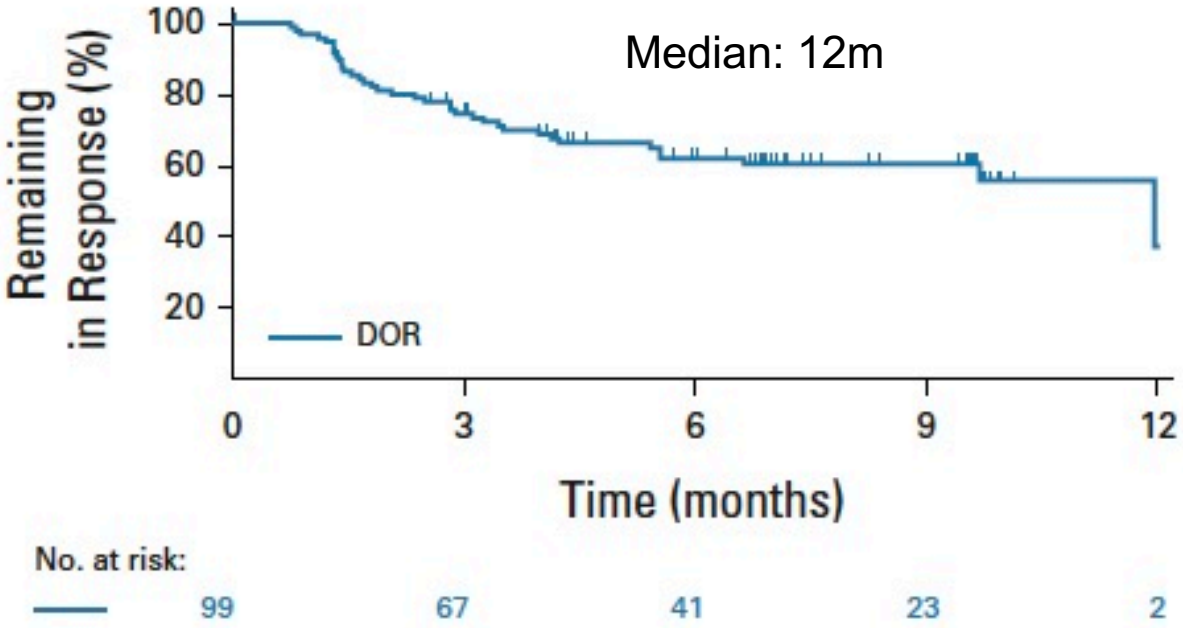
Secondary: ***DOR, TTR, PFS, OS, CR rate and safety/tolerability***

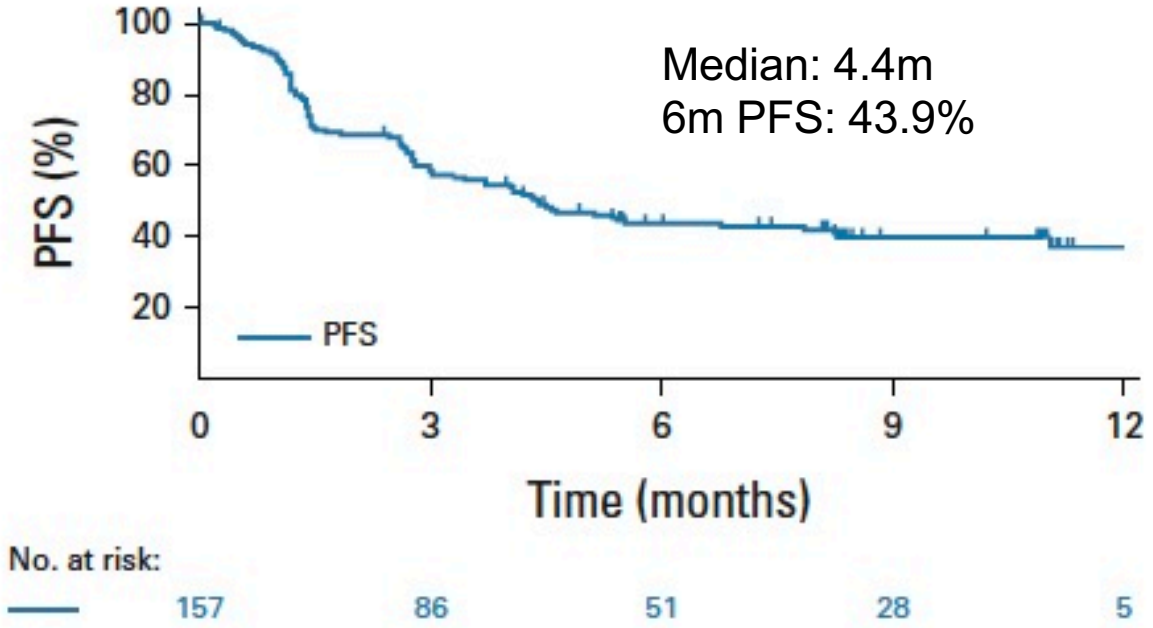
[a]Step-up dosing (priming 0.16 mg and intermediate 0.8 mg dosing before first full dose) and corticosteroid prophylaxis were used to mitigate CRS.
[b]Measurable disease with computerized tomography (CT) (or magnetic resonance imaging [MRI]) scan with involvement of 2 or more clearly demarcated lesions/nodes with a long axis >1.5 cm and short axis >1.0 cm (or 1 clearly demarcated lesion/node with a long axis >2.0 cm and short axis ≥1.0 cm) and FDG positron emission tomography (PET) scan that demonstrates positive lesion(s) compatible with CT (or MRI) defined anatomical tumor sites for FDG avid lymphomas. (Acronyms in notes)

Data Cutoff: January 31, 2022.
Thieblemont C, et al. Oral LB2364. 27th EHA Congress. June 9-12, 2022. Vienna, Austria.

Courtesy of Christopher R Flowers, MD, MS

Epcoritamab in R/R LBCL: Efficacy





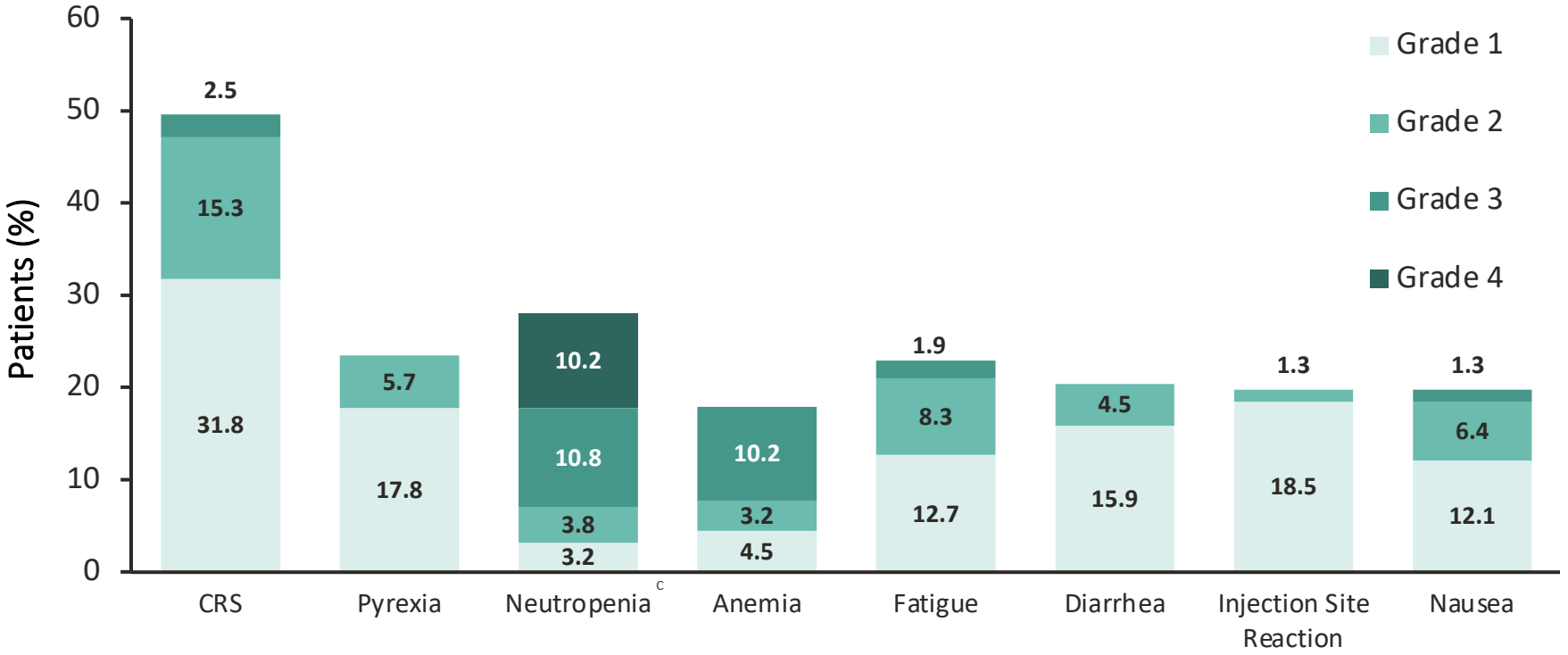
Median follow-up: 10.7m
ORR 63.1%; CR rate 38.9%

Thieblemont et al, J Clin Oncol 2022

Courtesy of Christopher R Flowers, MD, MS

EPCORE NHL-1 (Expansion Cohort) – Safety

Treatment-Emergent Adverse Events[a] (TEAEs) in ≥15% Patients by Grade



- Most AEs were low grade and occurred early in treatment (Cycles 1-3)
  - The incidence of AEs declined after 12 weeks
- 10 (6.4%) patients experienced ICANS
  - 9 grade 1-2 (resolved)
  - 1 grade 5 (confounded by multiple factors[b])

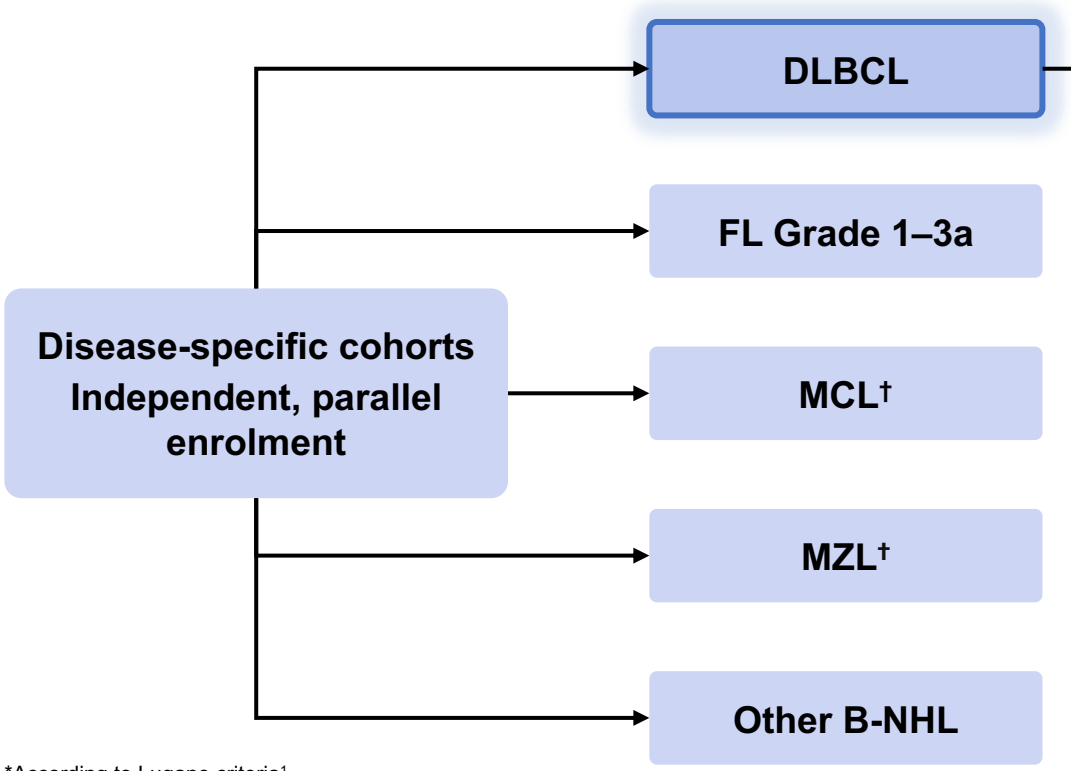
[a]COVID incidence: 4.5%.
[b]Patient experienced ICANS after intermediate dose with multiple confounders, including opioid use for grade 3 pancreatitis, hyperammonemia, multifocal cerebral infarcts in setting of possible microangiopathy, and tocilizumab administration.
*Combined term included neutropenia and decreased neutrophil count.
AE=Adverse Event. CRS=Cytokine Release Syndrome. ICANS=Immune Effector Cell-Associated Neurotoxicity Syndrome.

Data Cutoff: January 31, 2022.
Thieblemont C, et al. Oral LB2364. 27th EHA Congress. June 9-12, 2022. Vienna, Austria.

Courtesy of Christopher R Flowers, MD, MS

ELM-2 Phase 2 Study– Odronextamab in R/R DLBCL

- Phase 2, open-label, multi-cohort, multicenter study of odronextamab monotherapy for patients with R/R B-NHL (NCT03888105)
  - R/R FL cohort results presented at ASH 2022: oral presentation #949



Key eligibility criteria
- DLBCL per WHO 2016 classification
- ECOG PS 0 or 1
- Refractory to or relapsed after ≥2 prior lines of therapy, including an anti-CD20 antibody and an alkylator

Primary endpoint
- ORR* by ICR

Key secondary endpoints
- ORR* by local investigator
- CR, DOR, PFS, and OS
- Safety and tolerability

Odronextamab administration:
- IV, 21-day cycles
- Cycle 1 Step-up
- Cycles 2-4 160mg Days 1, 8,15
- Cycle 5 onwards 320mg Q2W
- Treatment until disease progression

*According to Lugano criteria[1]
†New enrolment is currently paused.
B-NHL, B-cell non-Hodgkin's lymphoma; CD, cluster of differentiation; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; FL, follicular lymphoma; ICR, independent central review; IV, intravenous; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; R/R, relapsed/refractory; WHO, World Health Organization.
1. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059–3068.

Courtesy of Christopher R Flowers, MD, MS

Kim et al, ASH 2022

Odronextamab Efficacy: Objective Response Rate in Relapsed/Refractory DLBCL

Best overall response	Independent central review N=130*	Investigator evaluation N=130*
Objective response rate (ORR)†	**49.2%** [95% CI 40.4%–58.1%]	**50.0%** [95% CI 41.1%–58.9%]
Complete response	**30.8%**	**36.2%**
Partial response	18.5%	13.8%
Stable disease	3.8%	3.1%
Progressive disease	22.3%	21.5%

Week 12 response assessment by independent central review	1/20 step-up regimen N=67	0.7/4/20 step-up regimen N=63
ORR	46.3% [95% CI: 34.0–58.9%]	42.9% [95% CI: 30.5–56.0%]
Complete response	26.9%	20.6%

- 63% of responders achieved a complete response
- Consistent efficacy observed at Week 12 regardless of Cycle 1 step-up regimen

- Median opportunity of follow-up: 21.3 months (range 2.6–29.8)

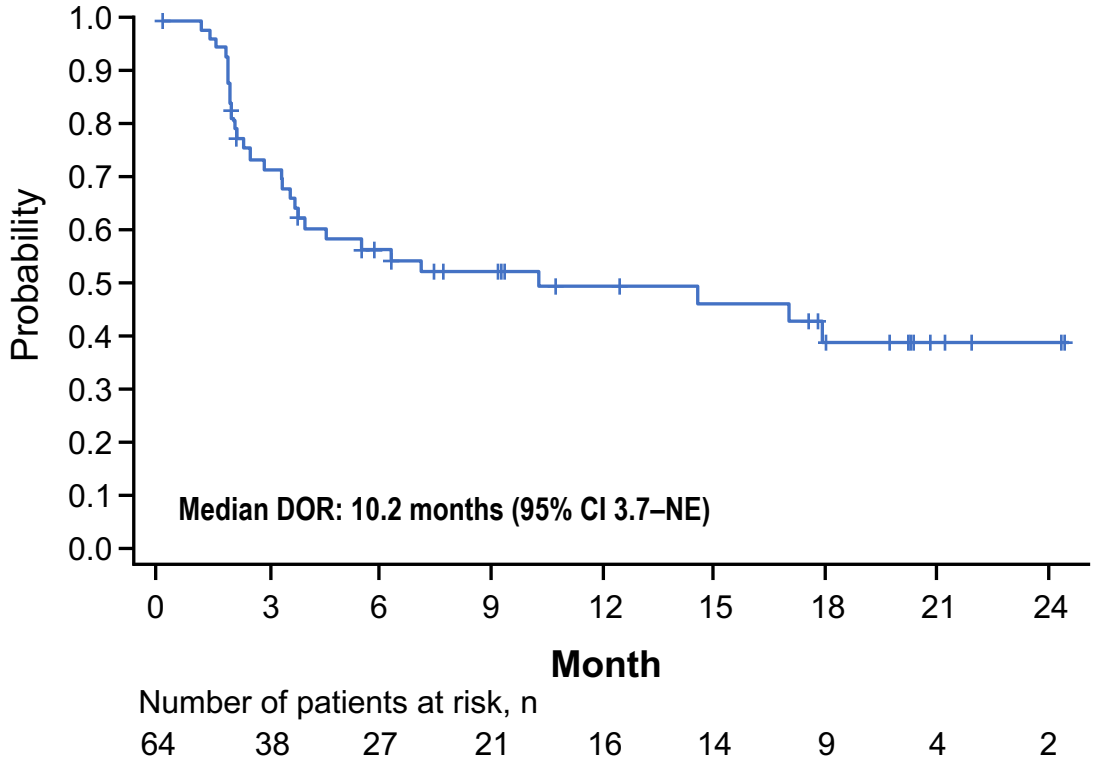
Kim et al, ASH 2022

Data cut-off date: Sep 15, 2022.
*Efficacy evaluable (with an opportunity for assessment at 12 weeks); †ORR = complete responses + partial responses.
CI, confidence interval; ORR, objective response rate.

Courtesy of Christopher R Flowers, MD, MS

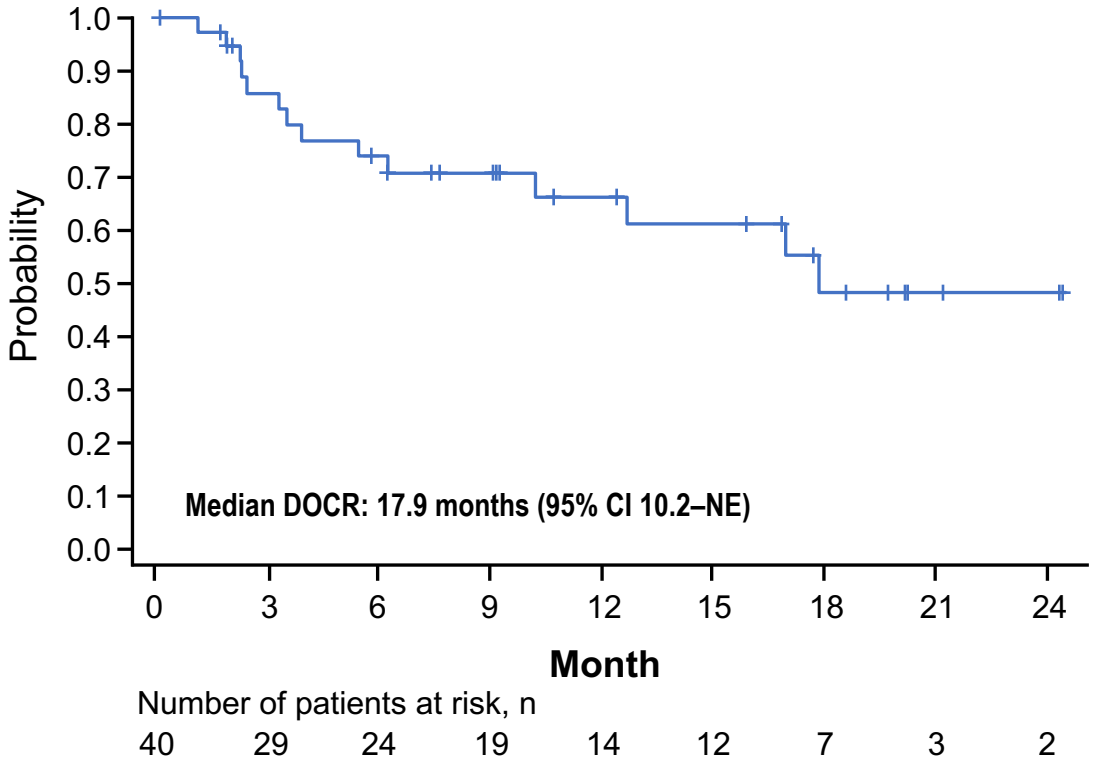
Odronextamab efficacy: Responses appear durable

Duration of response – Independent central review



- 12-month DOR: 49.4% (95% CI: 35.0–62.2)
- 18-month DOR: 38.9% (95% CI: 23.9–53.6)

Duration of complete response – Independent central review



- 12-month DOCR: 66.4% (95% CI: 47.1–80.1)
- 18-month DOCR: 48.3% (95% CI: 26.1–67.4)

Kim et al, ASH 2022

Data cut-off date: Sep 15, 2022.

CI, confidence interval; DOCR, duration of complete response; DOR, duration of response; NE, not evaluable.

Courtesy of Christopher R Flowers, MD, MS

Agenda

INTRODUCTION

MODULE 1: Diffuse Large B-Cell Lymphoma

MODULE 2: Hodgkin Lymphoma

MODULE 3: Follicular Lymphoma

MODULE 4: Mantle Cell Lymphoma

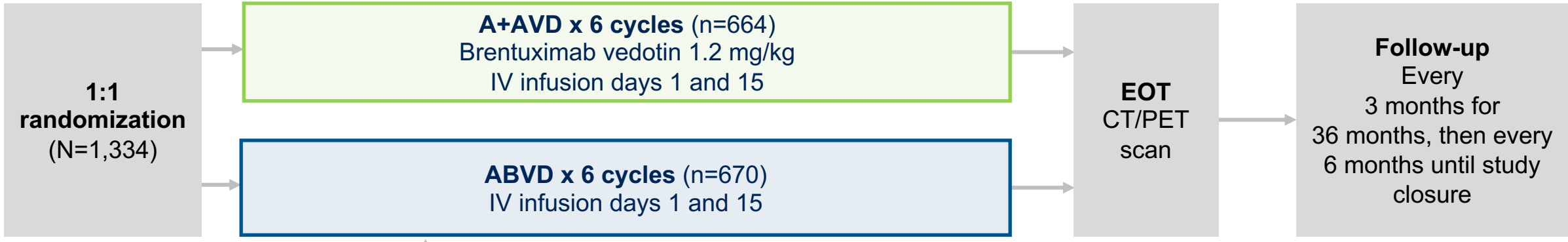
Hodgkin Lymphoma

ECHELON-1 – Brentuximab vedotin/AVD

BREACH – Brentuximab vedotin/AVD first line for early-stage unfavorable disease

Camidanlumab tesirine

Phase 3 ECHELON-1: AVD + Brentuximab Vedotin in Stage 3/4 Hodgkin Lymphoma



End-of-cycle-2 PET scan by IRF per Deauville 5-point scale
- PET–: 1–3
- PET+: 4–5

Primary endpoint: modified PFS per IRF (previously reported[1])

Key secondary endpoint: alpha-controlled, event-driven analysis of OS

Long-term follow-up assessments:
- Exploratory analysis of OS among patients who were PET2-positive and PET2-negative.
- PFS per investigator
- Subsequent treatment use
- Safety outcomes including:
  - PN resolution and improvement rates
  - Second malignancies
  - Outcomes of pregnancy among patients and their partners

Data cut-off for current analysis, June 1, 2021
CT, computerized tomography; EOT, end of treatment; ITT, intention to treat; IV, intravenous; PET2, PET status at the end of cycle 2.

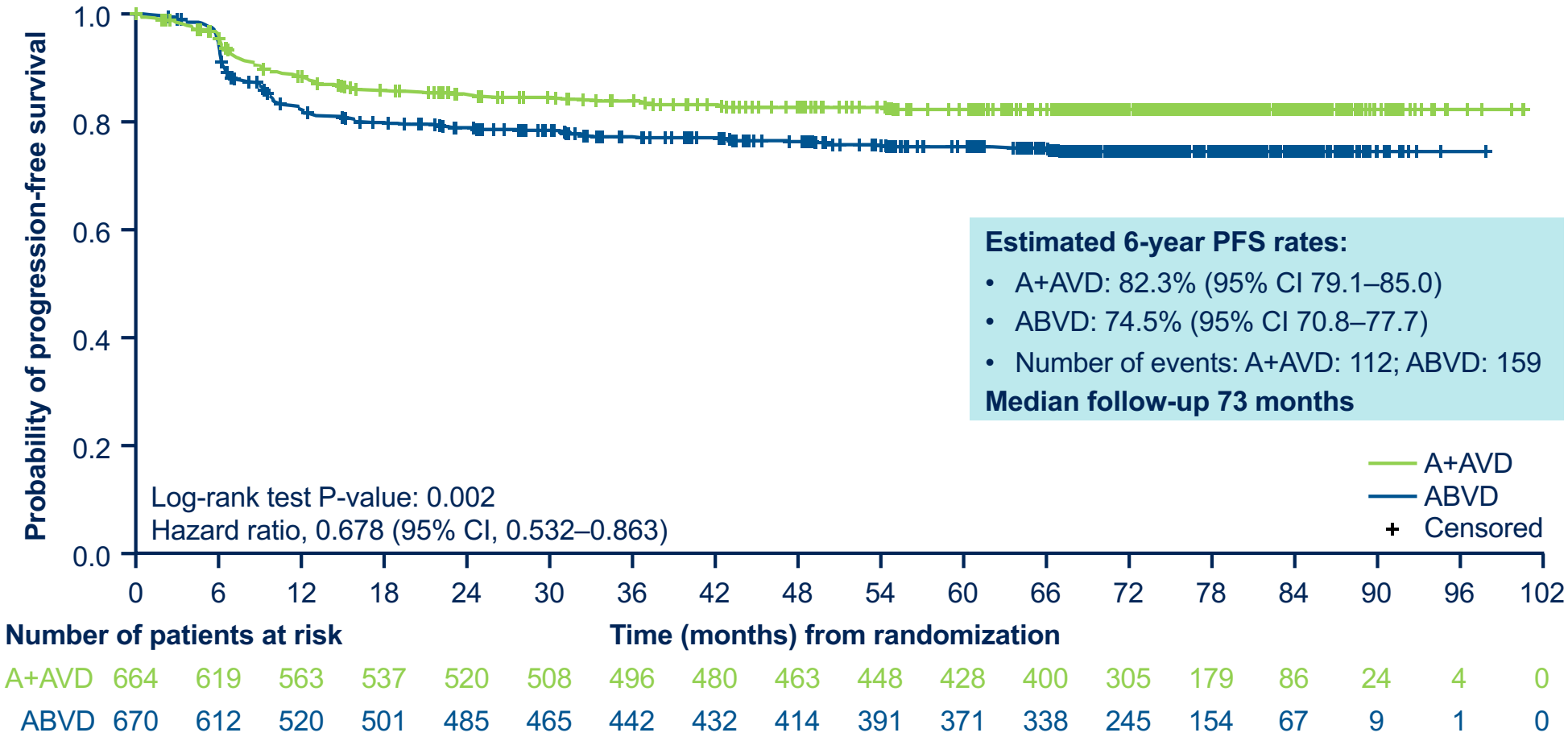
1. Connors JM, et al. N Engl J Med 2018;378:331–44.

Dr Stephen M. Ansell

Ansell et al, NEJM 2022

Courtesy of Christopher R Flowers, MD, MS

ECHELON-1: PFS per investigator continued to favor A+AVD vs ABVD, with a 32% risk reduction

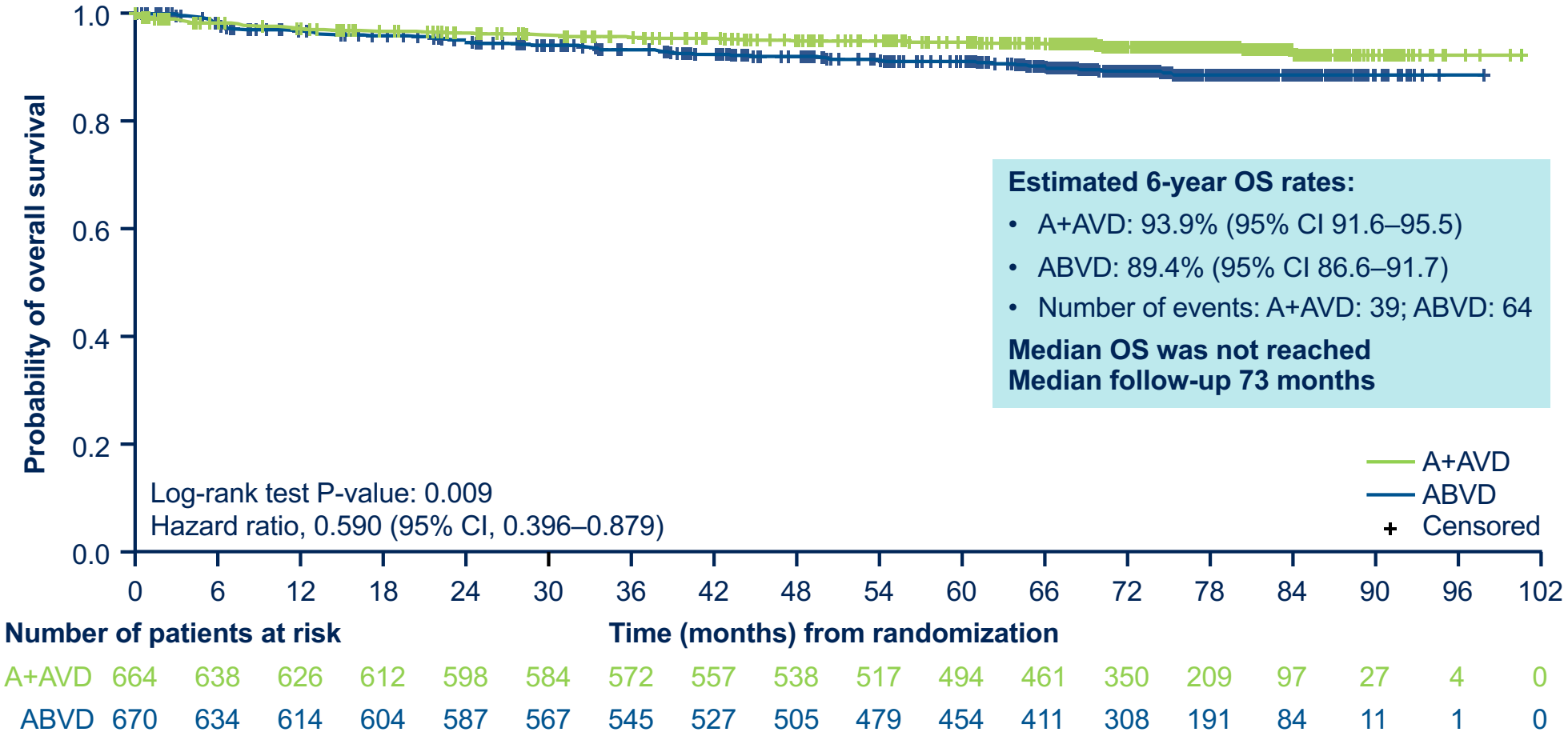


Ansell et al, NEJM 2022

Dr Stephen M. Ansell

Courtesy of Christopher R Flowers, MD, MS

ECHELON-1: OS significantly favored A+AVD vs ABVD corresponding to a 41% risk reduction



Fewer patients died from HL and disease- or treatment-related complications with A+AVD vs ABVD

Dr Stephen M. Ansell

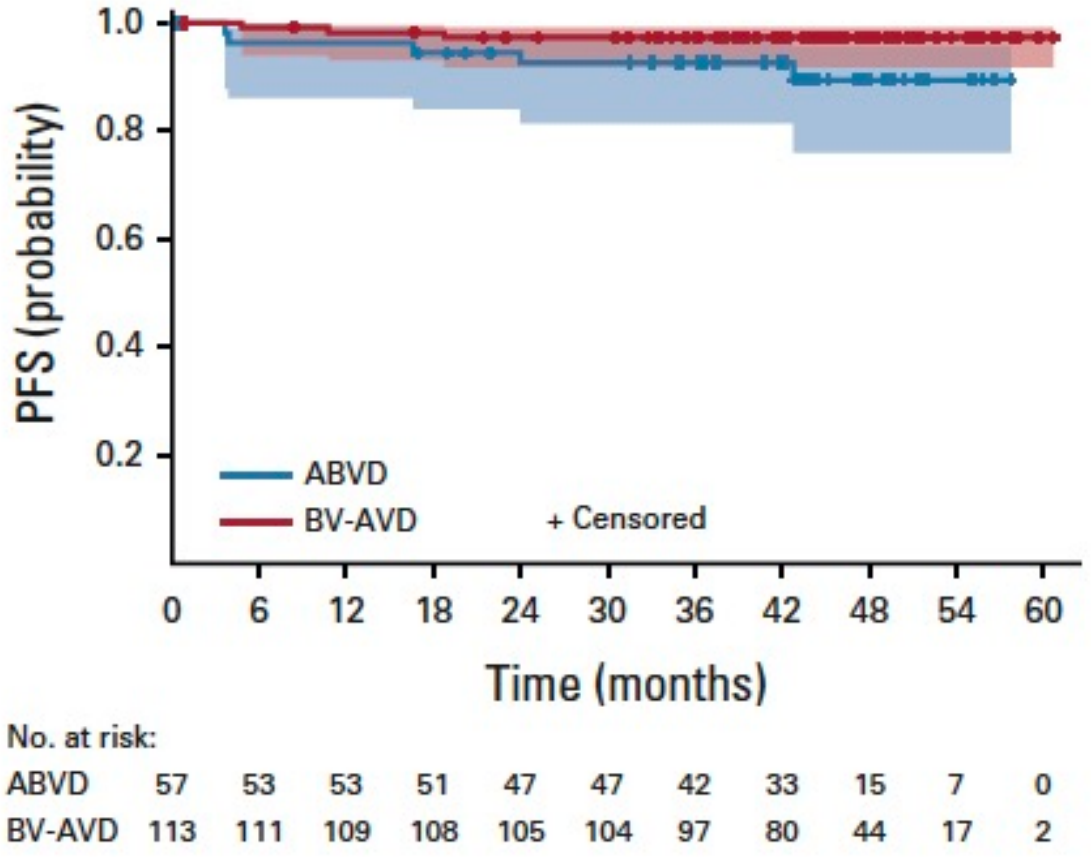
Ansell et al, NEJM 2022

Courtesy of Christopher R Flowers, MD, MS

BREACH: Brentuximab Vedotin plus AVD for First-line Treatment of Early-stage Unfavorable HL

- Randomized Phase 2 Trial
- Age 18-60y with ≥1 unfavorable EORTC/LYSA risk criterion
- 2:1 randomization to 4 cycles BV-AVD vs ABVD followed by 30Gy INRT
- Primary endpoint PET response after 2 cycles (D1-3)

- N=170
- BV-AVD vs ABVD
  - PET-neg: 82.3% vs 75.4%
  - 2-y PFS: 97.3 v 92.6%



Courtesy of Christopher R Flowers, MD, MS

Fornecker et al, JCO 2022

Camidanlumab Tesirine – anti-CD25 monoclonal antibody conjugated to a PBD dimer

Ongoing, Phase 2, single-arm, multicenter, open-label study in patients with R/R cHL[a]

30-minute IV infusion of Cami on Day 1 of each 3-week cycle

Cycles 1 & 2

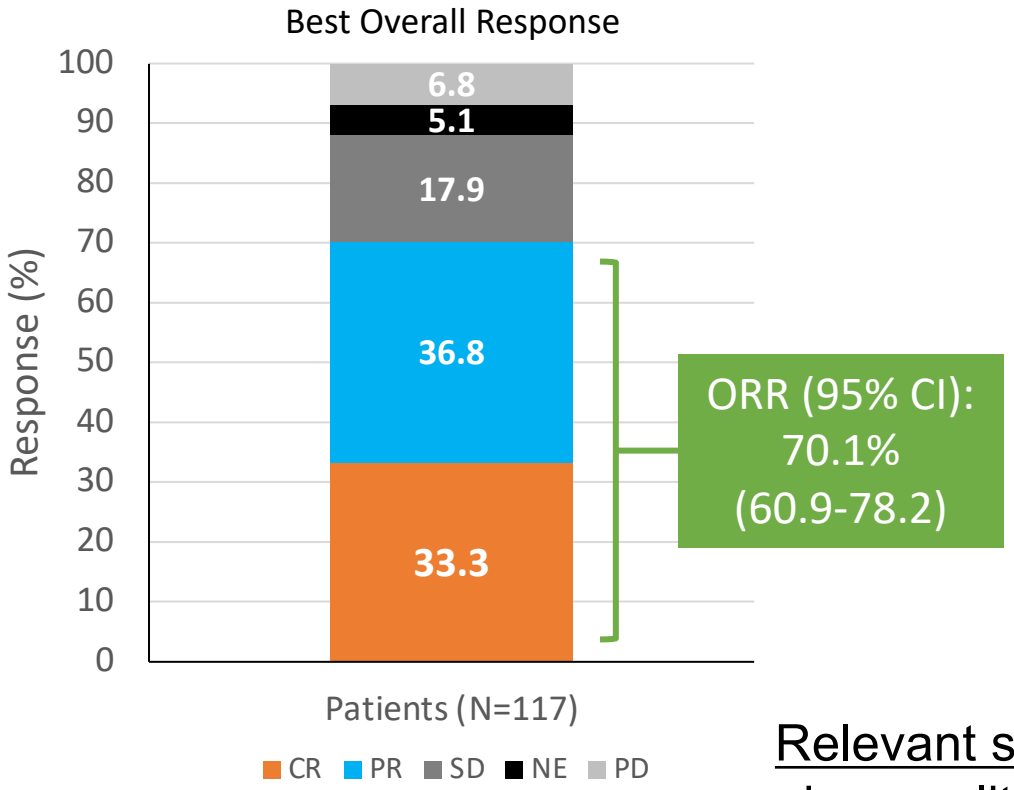
Cycle 3 onwards, up to 1 year[b]

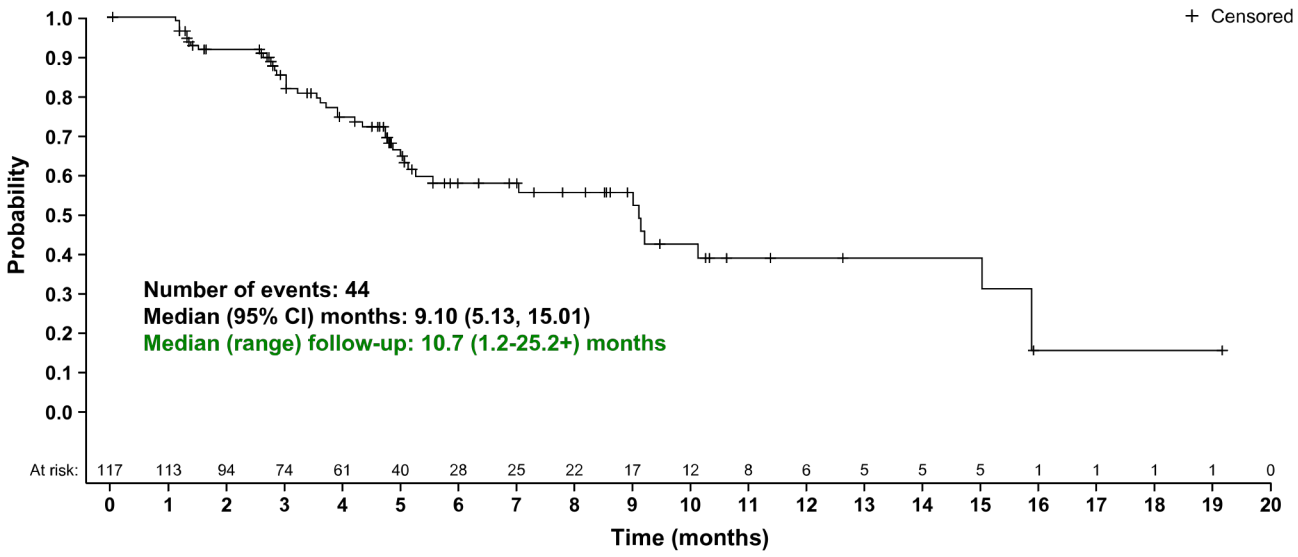
- Primary endpoint: ORR (per 2014 Lugano classification) assessed by central review
- Secondary endpoints: DoR, PFS, safety (frequency and severity of adverse events)
- As of November 1, 2021, enrollment was complete **(N=117)**
- R/R HL who have previously received BV and PD1 inhibitor

Courtesy of Christopher R Flowers, MD, MS

Herrera et al, SOHO 2022

Efficacy – Overall Response Rate and PFS with Camidanlumab Tesirine





Relevant side effects: skin/nail reactions, hepatobiliary test abnormalities, edema, auto-immune-related abnormalities similar to PD1 inhibitors, Guillain-Barre Syndrome (polyradiculopathy)

Courtesy of Christopher R Flowers, MD, MS

Herrera et al, SOHO 2022

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Follicular Lymphoma

GALLIUM – Obinutuzumab/chemotherapy versus rituximab/chemotherapy

RELEVANCE – Lenalidomide/rituximab (R^2)

Tazemetostat monotherapy

Bispecific antibodies

- Mosunetuzumab, odronextamab

Bispecific antibodies in combination

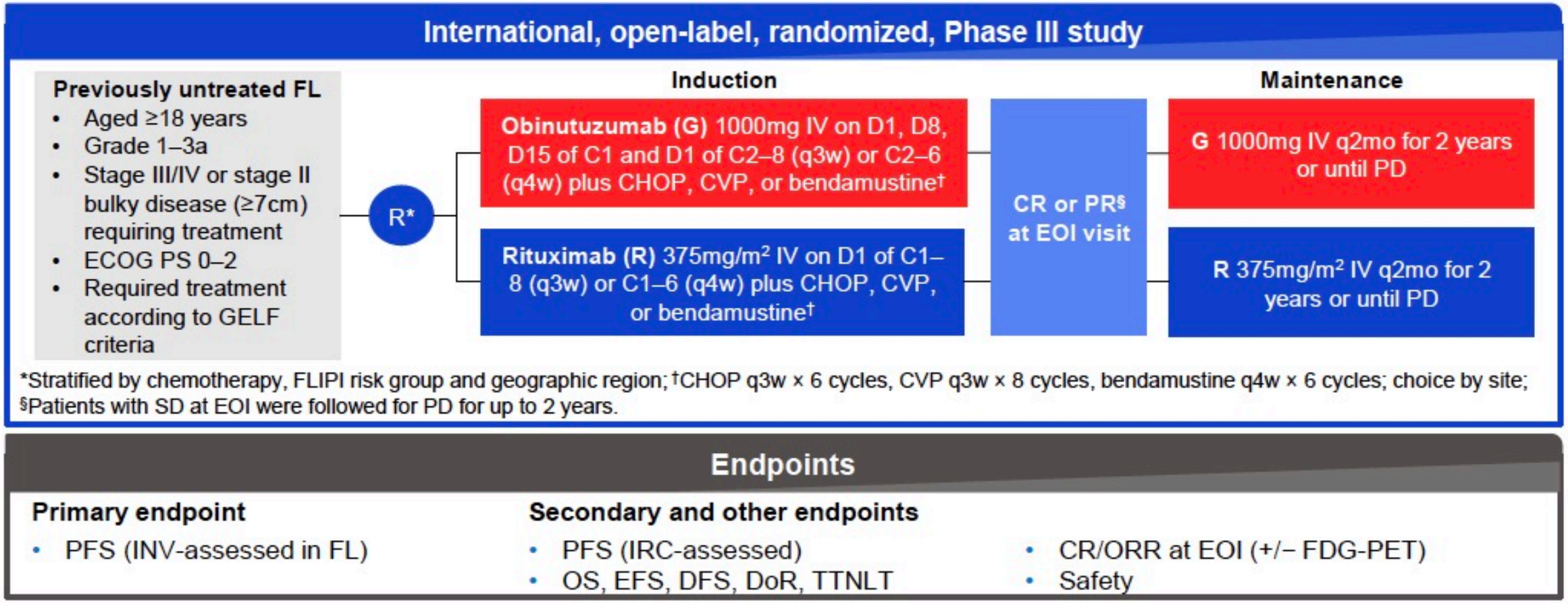
- Epcoritamab, lenalidomide/rituximab

SYMPHONY-1 – Tazemetostat in combination with lenalidomide/rituximab

CAR T-cell therapy

- ZUMA-5 – Axicabtagene ciloleucel
- ELARA – Tisagenlecleucel

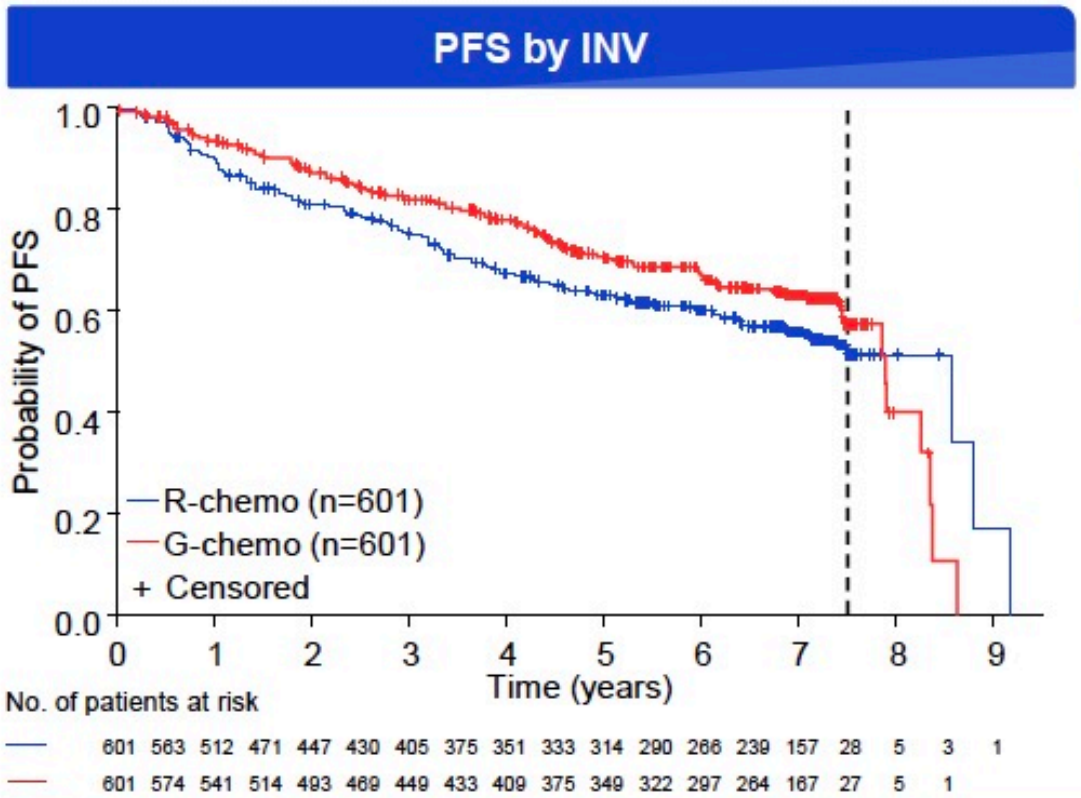
GALLIUM Study: Long-term Follow-up



Townsend et al, EHA 2022

Courtesy of Laurie H Sehn, MD, MPH

GALLIUM: PFS benefit was maintained with G- vs R-chemo after 8 years of follow-up



KM estimates became unreliable beyond 7.5 years, due to low numbers of patients at risk[1]

Median observation time: 7.9 (0.0–9.8) years

INV-assessed PFS	G-chemo (n=601)	R-chemo (n=601)
Patients with event, n (%)	206 (34.3)	244 (40.6)
7-year PFS, % (95% CI)	63.4 (59.0–67.4)	55.7 (51.3–59.9)
HR (95% CI)*	0.77 (0.64–0.93)	
P-value	0.006	

Townsend et al, EHA 2022

Courtesy of Laurie H Sehn, MD, MPH

GALLIUM Safety Summary: No new safety signals identified

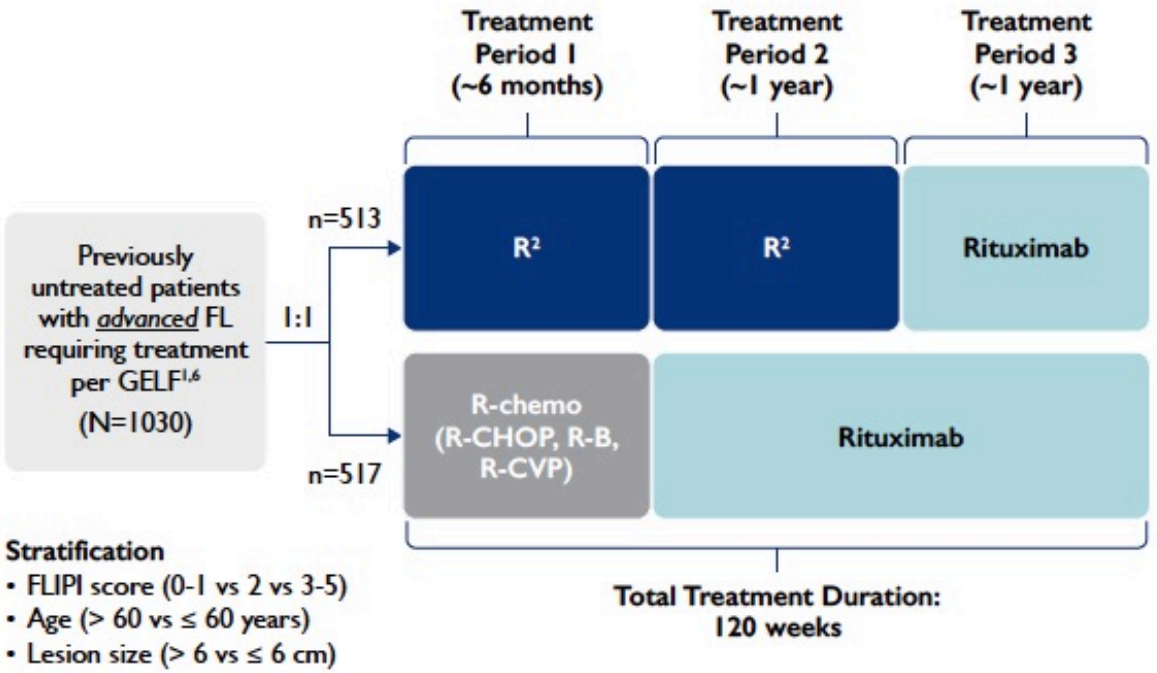
	Induction phase		Maintenance phase		Observation/follow-up phase	
	G-chemo (n=595)	R-chemo (n=597)	G-chemo (n=540)	R-chemo (n=526)	G-chemo (n=577)	R-chemo (n=572)
Any Grade AE,* n (%)	589 (99.0)	585 (98.0)	517 (95.7)	479 (91.1)	254 (44.0)	208 (36.4)
Grade ≥3, n (%)	368 (61.8)	350 (58.6)	216 (40.0)	174 (33.1)	123 (21.3)	90 (15.7)
SAEs, n (%)	168 (28.2)	147 (24.6)	132 (24.4)	114 (21.7)	99 (17.2)	83 (14.5)
Most common AEs of interest, n (%)						
Neutropenia	270 (45.4)	257 (43.0)	114 (21.1)	79 (15.0)	21 (3.6)	12 (2.1)
Grade ≥3	241 (40.5)	223 (37.4)	100 (18.5)	63 (12.0)	20 (3.5)	10 (1.7)
Infections	309 (51.9)	294 (49.2)	382 (70.7)	317 (60.3)	131 (22.7)	105 (18.4)
Grade ≥3	45 (7.6)	45 (7.5)	65 (12.0)	54 (10.3)	50 (8.7)	33 (5.8)
Infusion-related reactions	410 (68.9)	354 (59.3)	45 (8.3)	45 (8.6)	1 (0.2)	1 (0.2)
Grade ≥3	72 (12.1)	43 (7.2)	4 (0.7)	2 (0.4)	0	0

Townsend et al, EHA 2022

Courtesy of Laurie H Sehn, MD, MPH

Six-Year Results from the Phase 3 RELEVANCE Study: Similar Outcomes for Previously Untreated FL Receiving Lenalidomide Plus Rituximab (R^2) versus R-Chemotherapy Followed by R Maintenance

Figure 1. RELEVANCE Study Design



- Co-primary endpoints: CR/CRu at 120 weeks and PFS by IRC based on 1999 IWG criteria
- The prespecified second interim analysis was done after 75% of total PFS events were reached

Figure 3: Progression-Free Survival by IRC, FDA Censoring Rules

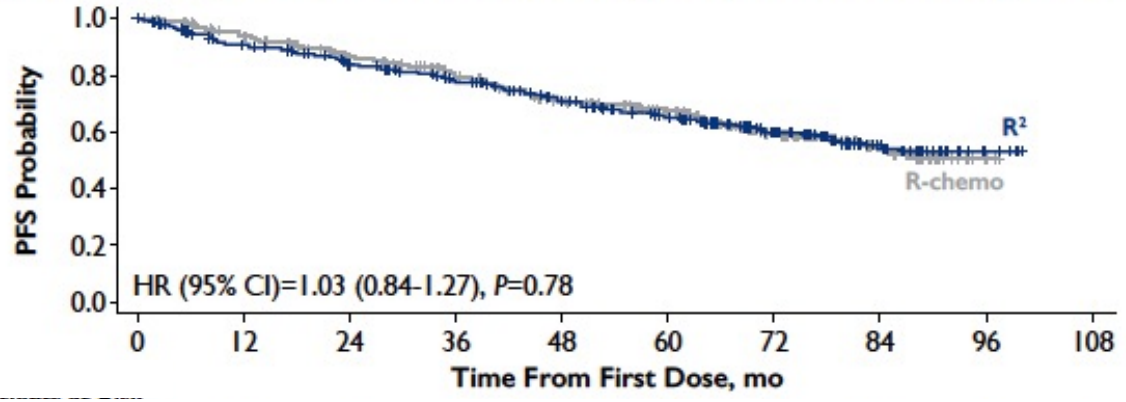
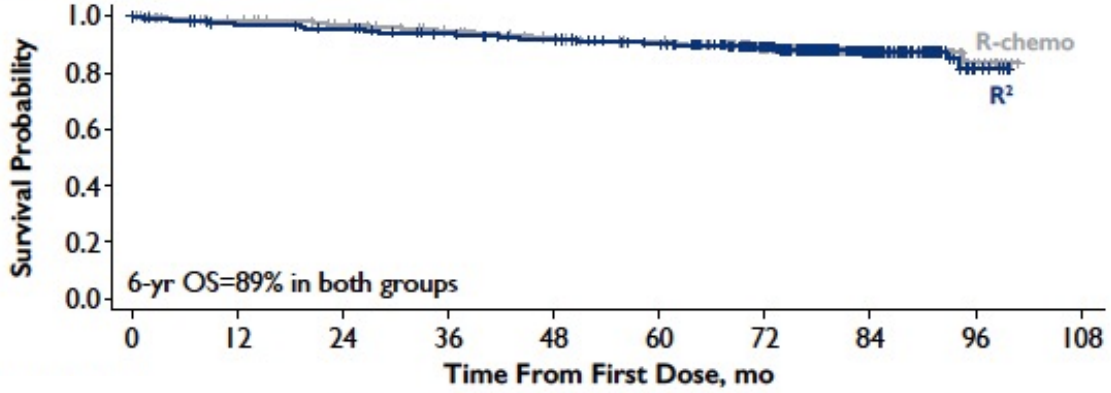


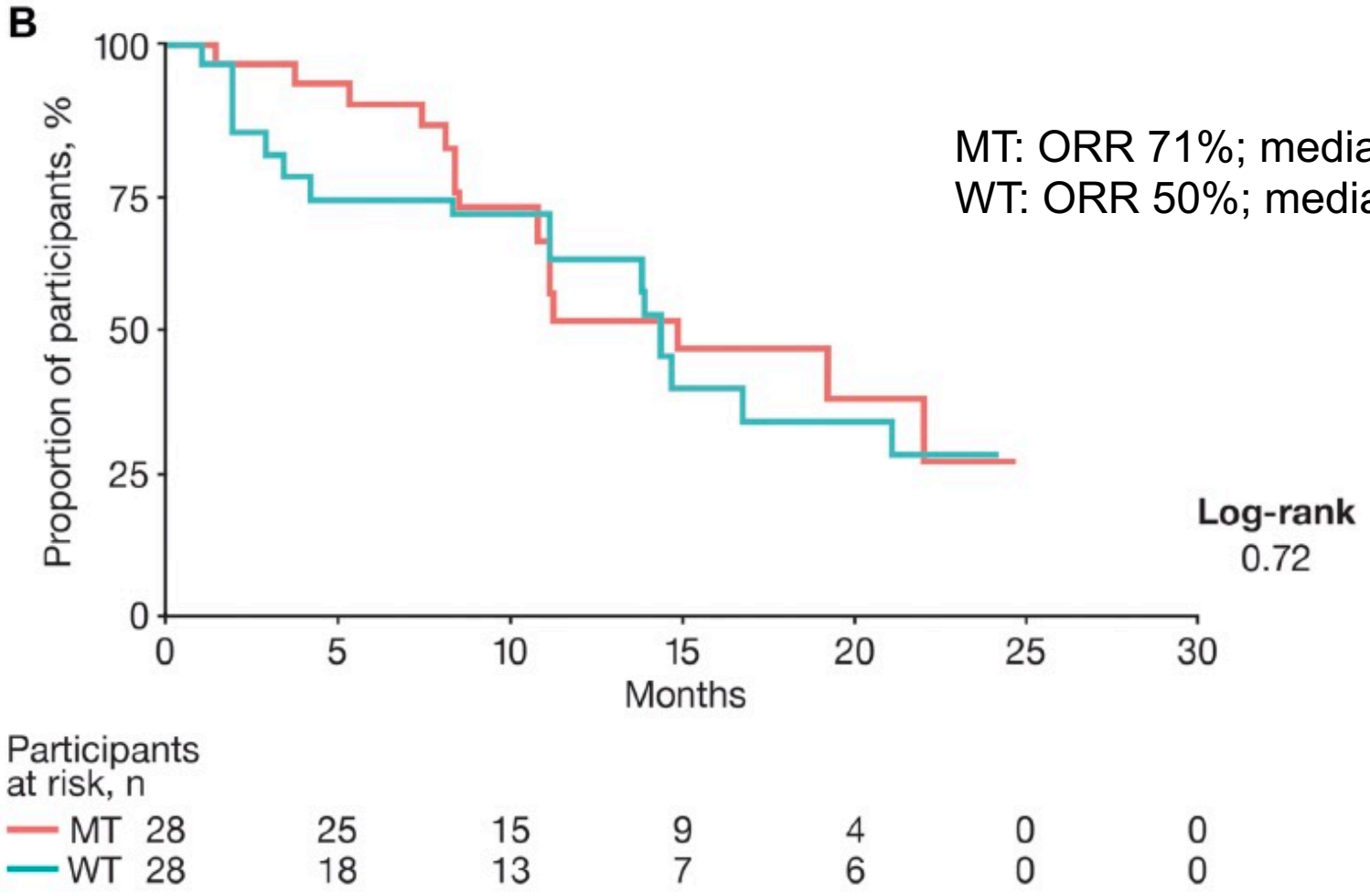
Figure 6: Overall Survival



Courtesy of Laurie H Sehn, MD, MPH

Morschhauser F, et al J Clin Oncol 2022

Tazemetostat in R/R Follicular Lymphoma: Propensity Score Matched Analysis



MT: ORR 71%; median PFS 14.8 m
WT: ORR 50%; median PFS 14.3m

Proudman et al, Oncotarget 2022

Courtesy of Laurie H Sehn, MD, MPH

Mosunetuzumab Monotherapy: Update from Pivotal Phase II Study in Relapsed/Refractory Follicular Lymphoma

Pivotal, single-arm, multicenter, Phase II expansion in patients with R/R FL and ≥2 prior therapies

Key inclusion criteria

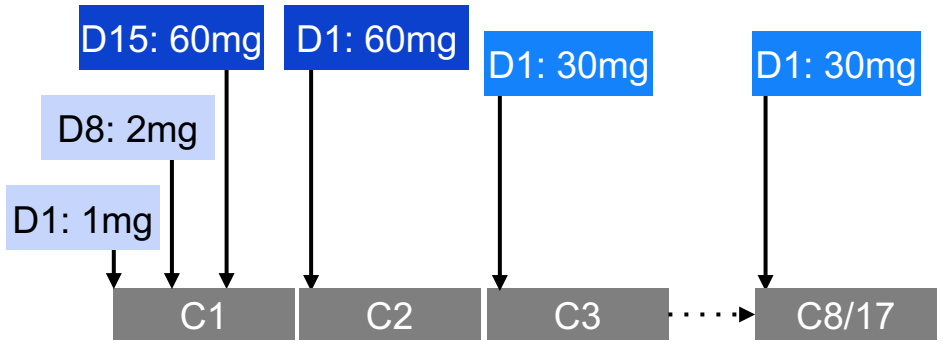
- FL Grade 1–3a
- ECOG PS 0–1
- ≥2 prior therapies including an anti-CD20 antibody and an alkylator

Data analysis

- Study met its primary endpoint: 60% CR rate versus 14% historical control ($p<0.0001$)[1,2]
- Updated efficacy and safety analysis with median 28.3 months of follow up (10 months after the previous report)

Mosunetuzumab administration

- IV mosunetuzumab administered in 21-day cycles with step-up dosing in C1
- Fixed-duration treatment: 8 cycles if CR after C8; 17 cycles if PR/SD after C8
- Re-treatment with mosunetuzumab permitted at relapse for patients who achieved CR
- No mandatory hospitalization



Bartlett, N et al. ASH 2022

1. Dreyling M, et al. J Clin Oncol 2017;35:3898–3905; 2. Budde LE, et al. Lancet Oncol 2022;23:1055–1065.

Courtesy of Laurie H Sehn, MD, MPH

Mosunetuzumab Monotherapy: Response Rates

Efficacy endpoint in the overall population by investigator assessment; % (95% CI)	N=90
ORR	**78%** (68–86)
CR	**60%** (49–70)

Time to first response (median [range]): **1.4 months** (1.0–11)
Time to first CR (median [range]): **3.0 months** (1.0–19)

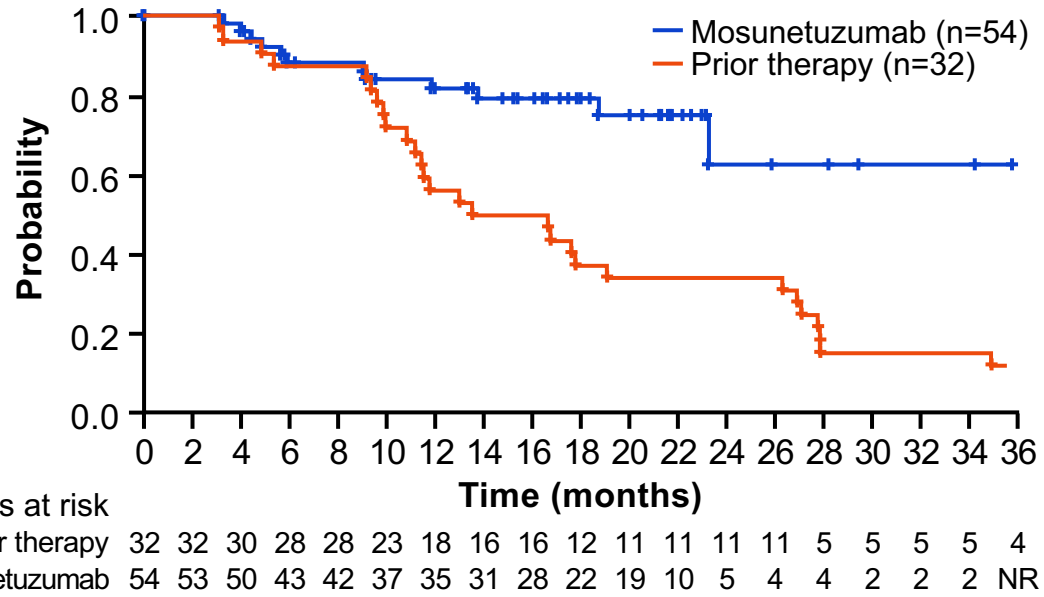
High ORR and CR rate were consistent with published results[1]

Courtesy of Laurie H Sehn, MD, MPH

1. Budde LE, et al. Lancet Oncol 2022;23(8):1055–1065.

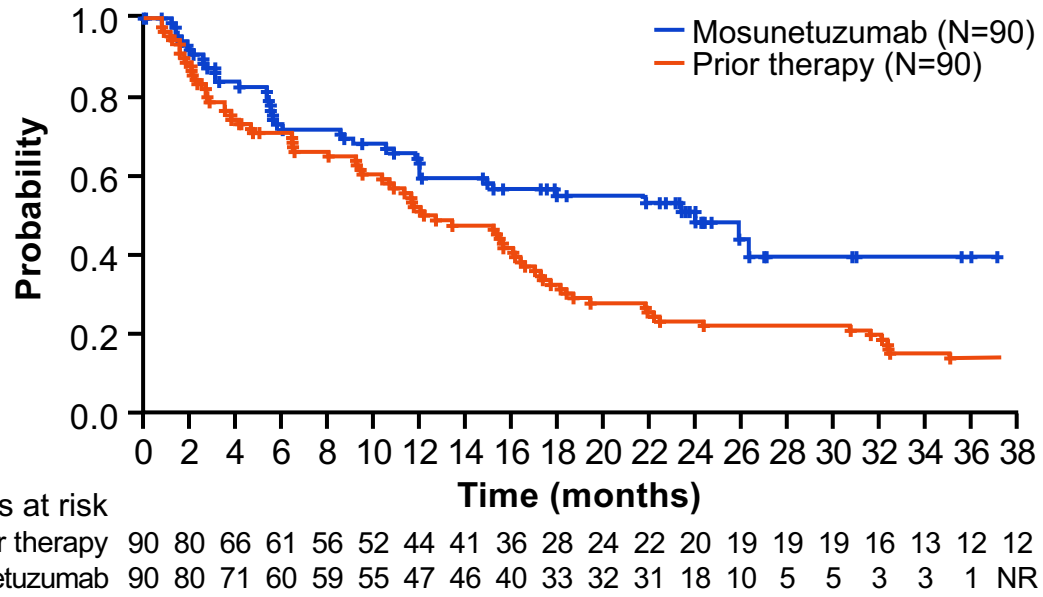
DOCR and PFS with mosunetuzumab versus last prior therapy

DOCR



	Mosunetuzumab (n=54)	Last prior therapy (n=32)
Median DOCR, months (95% CI)	**NR** (23–NR)	**15** (11–26)

PFS



	Mosunetuzumab (N=90)	Last prior therapy (N=90)
Median PFS, months (95% CI)	**24** (12–NR)	**12** (10–16)

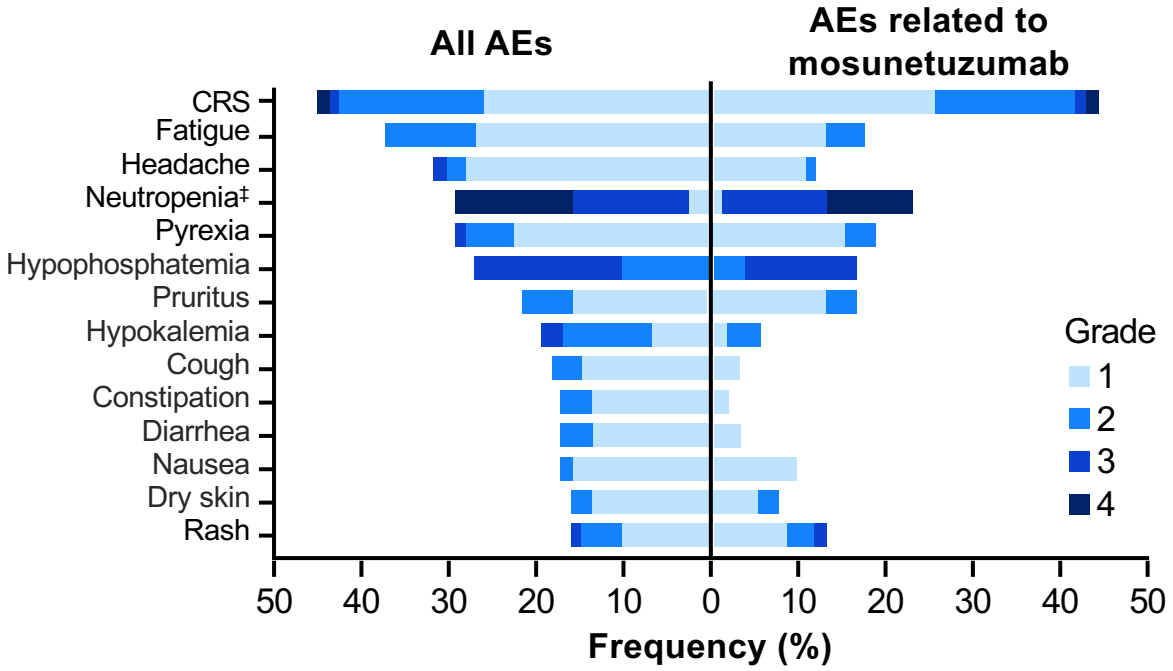
Extended DOCR and 12-month improvement in median PFS with mosunetuzumab compared with last prior therapy

Courtesy of Laurie H Sehn, MD, MPH

Mosunetuzumab Monotherapy: Safety profile

Adverse events (AEs)	N=90
AE Mosunetuzumab related	100% 92%
Grade 3/4 AE Mosunetuzumab related	70% 51%
Serious AE Mosunetuzumab related	47% 33%
Grade 5 (fatal) AE Mosunetuzumab related	2%* 0
AE leading to treatment discontinuation Mosunetuzumab related	4%† 2%

AEs (≥15%) by grade and relationship with mosunetuzumab



No new serious AEs, Grade ≥3 AEs, or treatment-related AEs were reported with 10 additional months of follow-up

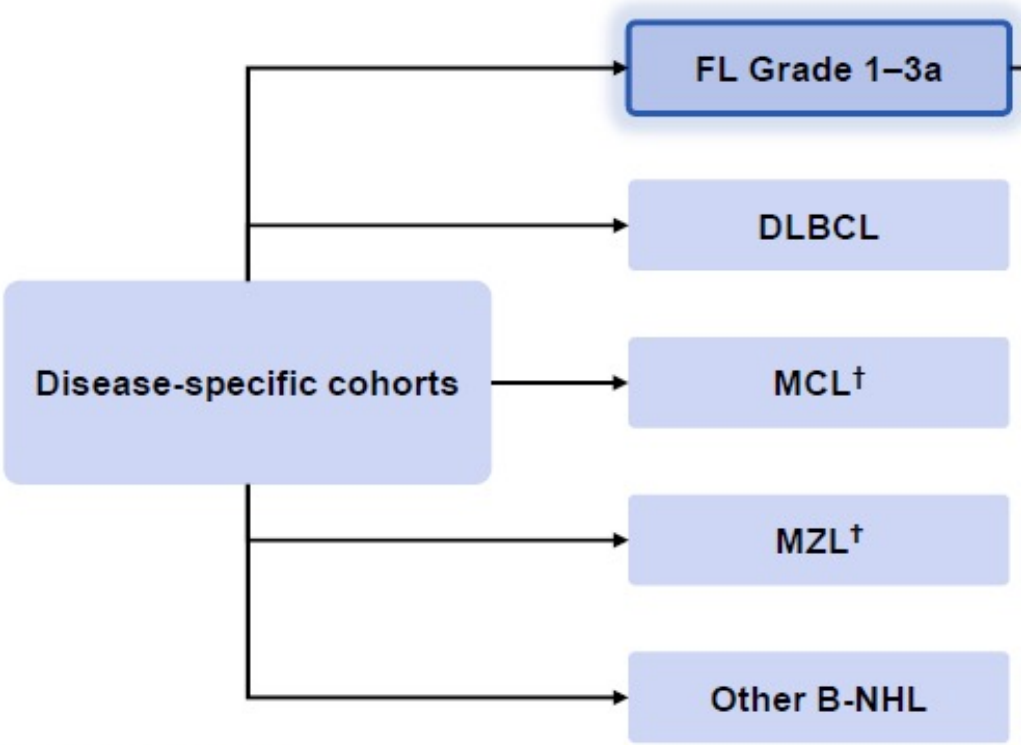
*Malignant neoplasm progression (n=1) and unexplained death (n=1). †Mosunetuzumab related: CRS (2 patients); mosunetuzumab unrelated: Epstein-Barr viremia and Hodgkin's disease (1 patient each). ‡Grouped term including preferred term 'neutropenia' and 'neutrophil count decreased'.

Courtesy of Laurie H Sehn, MD, MPH

ELM-2 study design – FL cohort

Odronextamab

- ELM-2 Phase 2, open-label, multi-cohort, multicenter study of odronextamab monotherapy for patients with R/R B-NHL (NCT03888105)
  - R/R DLBCL cohort results also presented at ASH 2022: oral presentation #444



Key eligibility criteria
- FL grades 1–3a
- ECOG PS 0 or 1
- Refractory to or relapsed after ≥2 prior lines of therapy, including an anti-CD20 antibody and an alkylator

Primary endpoint
- ORR* by ICR

Key secondary endpoints
- ORR* by local investigator
- CR, DOR, PFS, and OS
- Safety and tolerability

Odronextamab administration:
IV, 21-day cycles
- Cycle 1 Step-up
- Cycles 2–4 80mg Days 1, 8,15
- Cycle 5 onwards 160mg Q2W
- Treatment until disease progression

*According to Lugano criteria[1]
†New enrolment is currently paused.
B-NHL, B-cell non-Hodgkin's lymphoma; CD, cluster of differentiation; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance score; FL, follicular lymphoma; ICR, independent central review; IV, intravenous; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; Q2W, every 2 weeks.

1. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059–3068.

Courtesy of Laurie H Sehn, MD, MPH

Kim et al, ASH 2022

Odronextamab efficacy: Objective response rate

Best overall response	Independent central review N=121*	Investigator evaluation N=121*
Objective response rate (ORR)†	**81.8%** [95% CI: 73.8–88.2%]	81.8% [95% CI: 73.8–88.2%]
Complete response	**75.2%**	70.2%
Partial response	6.6%	11.6%
Stable disease	5.8%	2.5%
Progressive disease	4.1%	5.8%

Week 12 response assessment by independent central review	1/20 step-up regimen N=68	0.7/4/20 step-up regimen N=53
ORR	72.1% [95% CI: 59.9–82.3%]	75.5% [95% CI: 61.7–86.2%]
Complete response	61.8%	71.7%

- Majority of R/R FL patients achieved a complete response
- 92% of responders were complete responders
- Consistent efficacy observed at Week 12 regardless of Cycle 1 step-up regimen

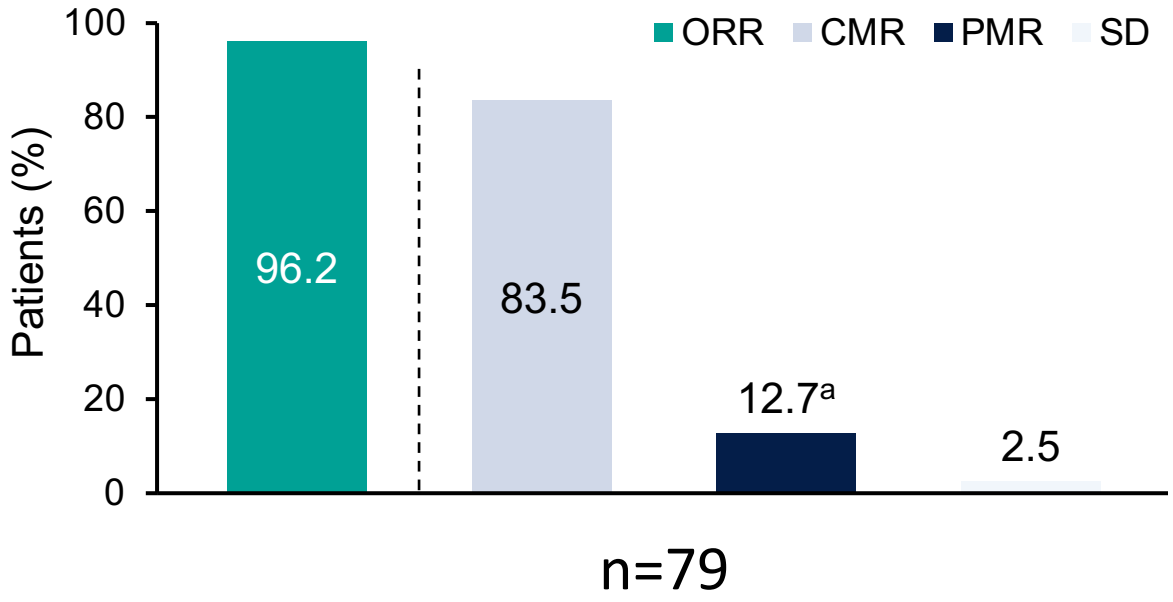
- Median opportunity of follow-up: 22.4 months (range 2.6–33.0)

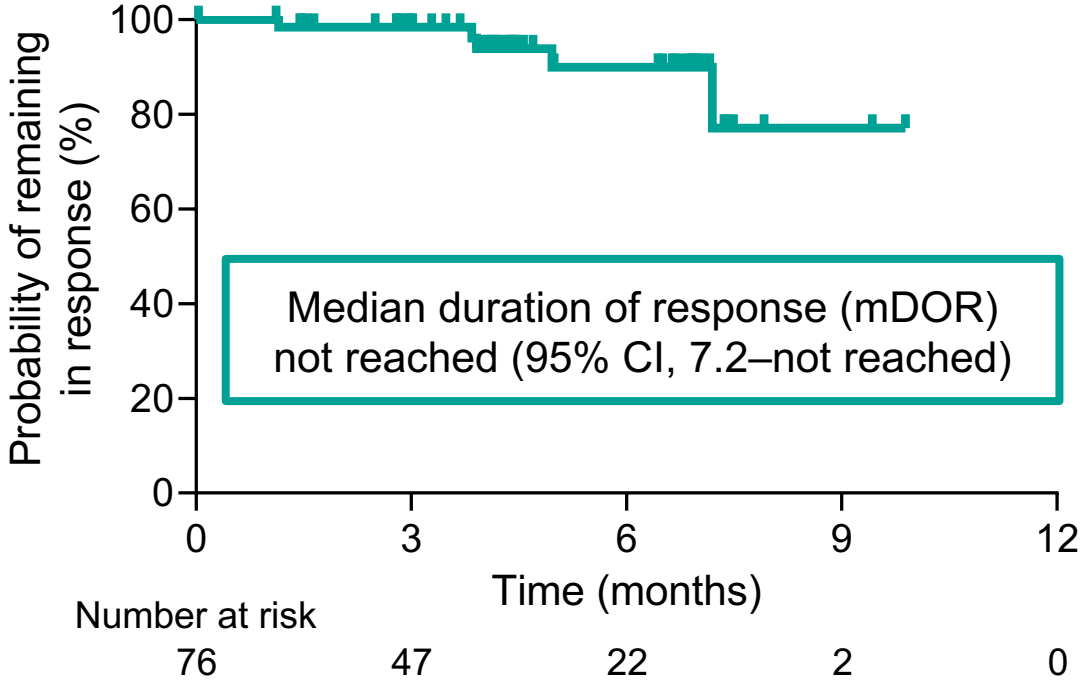
Data cut-off date: Sep 15, 2022.
*Efficacy evaluable (with an opportunity for assessment at 12 weeks); †ORR = Complete responses + Partial responses.
CI, confidence interval; FL, follicular lymphoma; ORR, objective response rate; R/R relapsed/refractory.

Courtesy of Laurie H Sehn, MD, MPH

Kim et al, ASH 2022

Subcutaneous Epcoritamab with Rituximab and Lenalidomide in Relapsed/Refractory FL: Efficacy





Data cutoff: October 31, 2022

Median follow-up: 5.6 mo (range, 1.2+ to 11.5+)

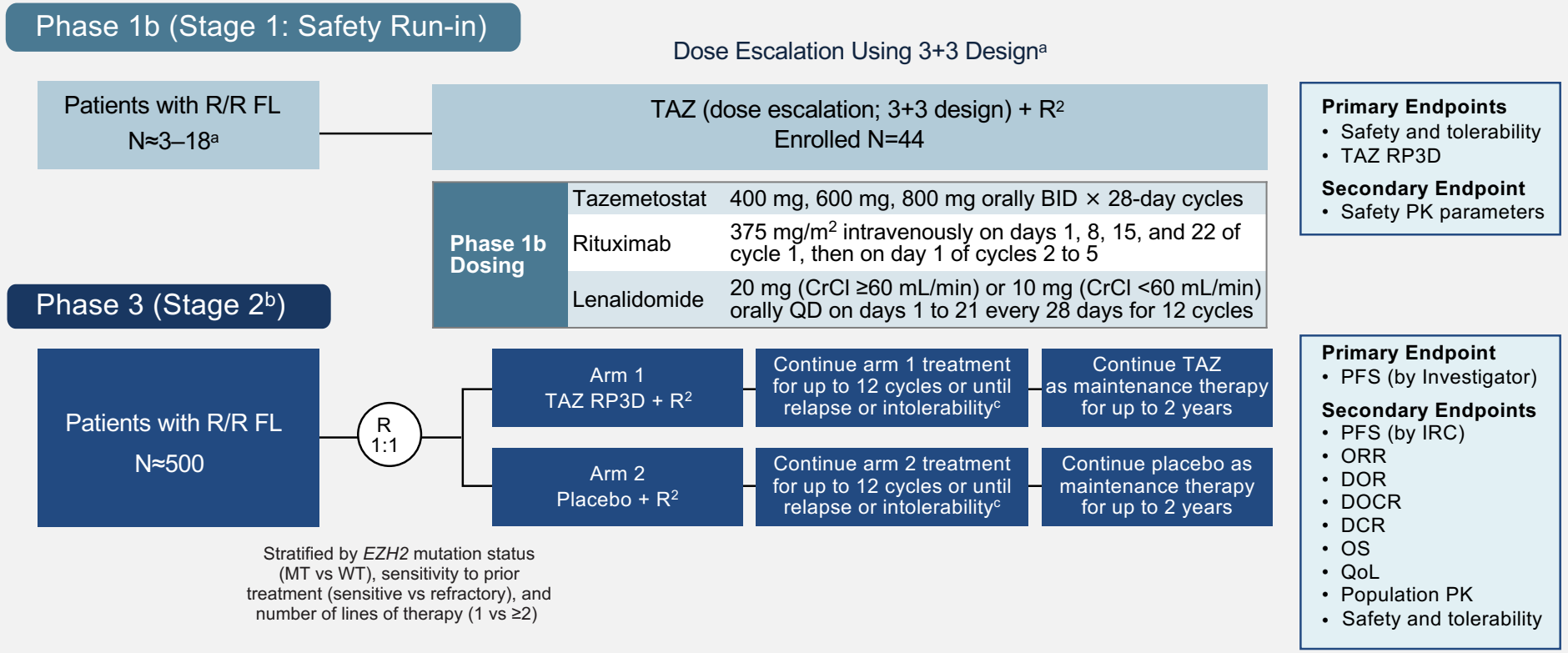
[a]Ongoing PMR in 6 patients.

Courtesy of Laurie H Sehn, MD, MPH

Falchi, L et al, ASH 2022

SYMPHONY-1: Tazemetostat with Lenalidomide and Rituximab in R/R FL

This international, multicenter, randomized, double-blind, active-controlled, 3-stage, biomarker-enriched, phase 1b/3 study (NCT04224493) is evaluating TAZ + R² in patients with R/R FL



- Preliminary efficacy analysis was performed on the response-evaluable population[d]
  - Efficacy was reported as best overall response, PFS, and DOR[e]
- The safety population[f] was used for all safety analyses

[a]Additional patients enrolled to further study safety in the 600- and 800-mg groups. [b]An optional stage 3, for patients with MT *EZH2* FL only, will be executed if the efficacy in stage 2 fails for all patients but is sufficiently promising for patients with MT *EZH2* FL (as assessed in a futility analysis during stage 2). [c]All patients receive treatment in 28-day cycles. [d]The response-evaluable population consists of patients from the intent-to-treat population who had adequate baseline and ≥1 postbaseline tumor assessment, per the International Working Group criteria for non-Hodgkin lymphoma. [e]Per investigator assessment, according to Lugano 2014 response criteria. [f]The safety population is defined as all patients who receive ≥1 dose of study drug

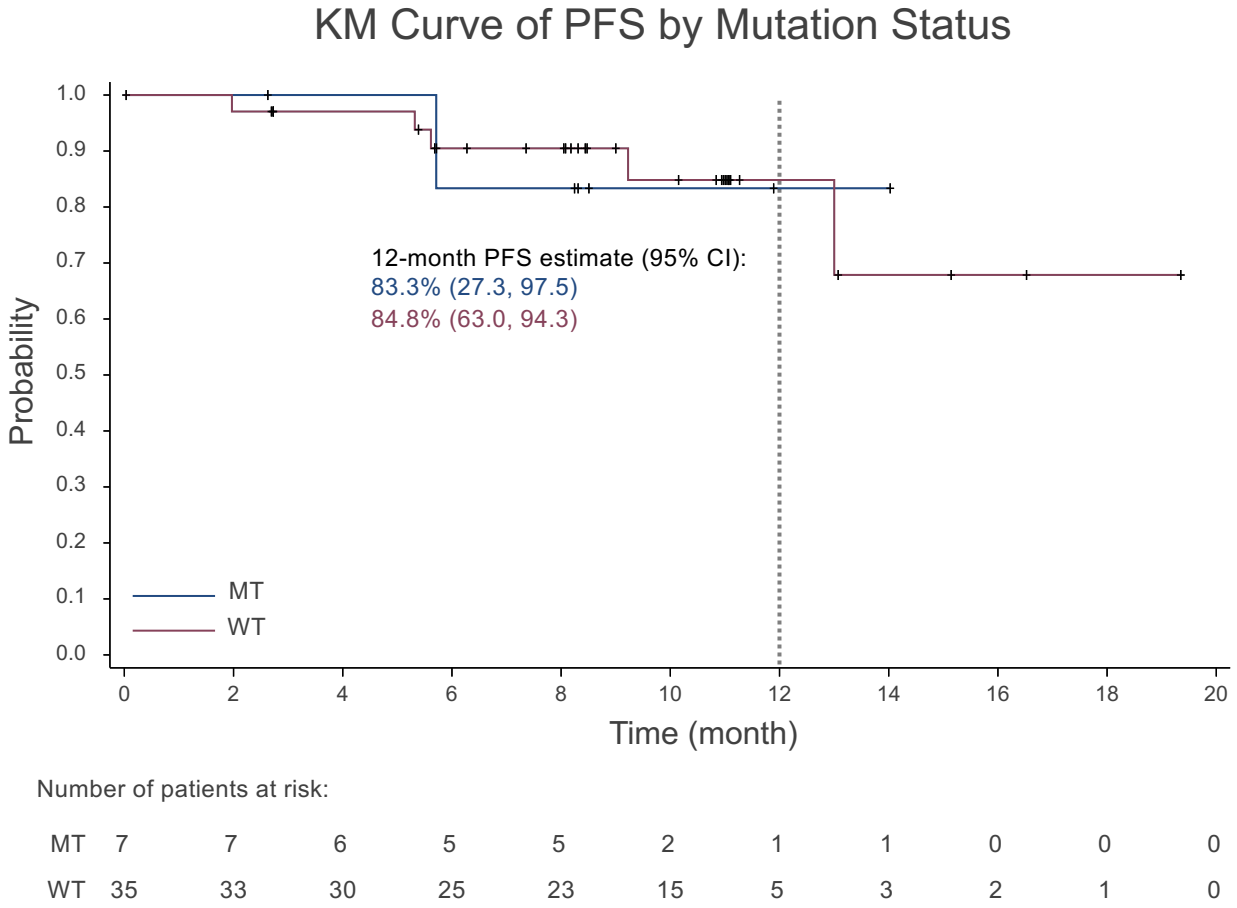
Batlevi et al, ASH 2022

Courtesy of Laurie H Sehn, MD, MPH

SYMPHONY-1: Tazemetostat + R^2 Phase Ib: Efficacy by mutation status

Best Overall Response,[a] % (n)	WT (n=33)	MT (n=7)
ORR	97.0 (32)	100 (7)
Complete response	45.5 (15)	71.4 (5)
Partial response	51.5 (17)	28.6 (2)
Stable disease	3.0 (1)	0

- ORR was 97.0% in patients with WT *EZH2* (n=32)
- ORR was 100% in patients with MT *EZH2* (n=7)
- mPFS and mDOR were not reached
- Recommended phase 3 dose: tazemetostat 800 mg po BID
- No new safety signals

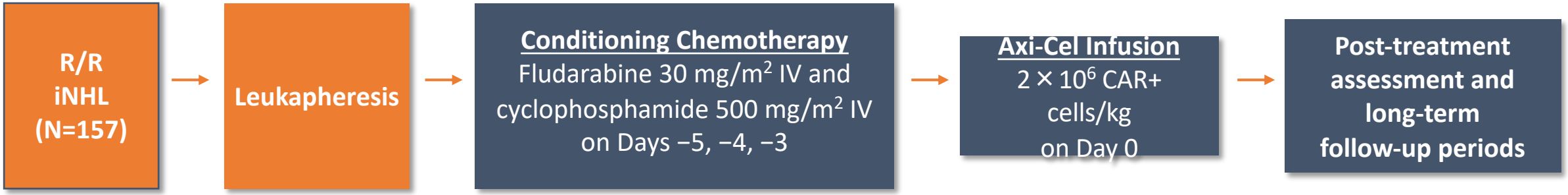


[a]*EZH2* status for 1 patient with best overall response was unknown.
KM, Kaplan-Meier; mDOR, median duration of response; mPFS, median progression-free survival; MT, mutant; NE, not evaluable; ORR, objective response rate; WT, wild-type.

Batlevi et al, ASH 2022

Courtesy of Laurie H Sehn, MD, MPH

ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) in R/R Indolent NHL - Long-term Follow-up



Key ZUMA-5 Eligibility Criteria

- R/R FL (Grades 1–3a) or MZL (nodal or extranodal)[a]
- ≥2 Prior lines of therapy that must have included an anti-CD20 mAb combined with an alkylating agent[b]

Primary Endpoint

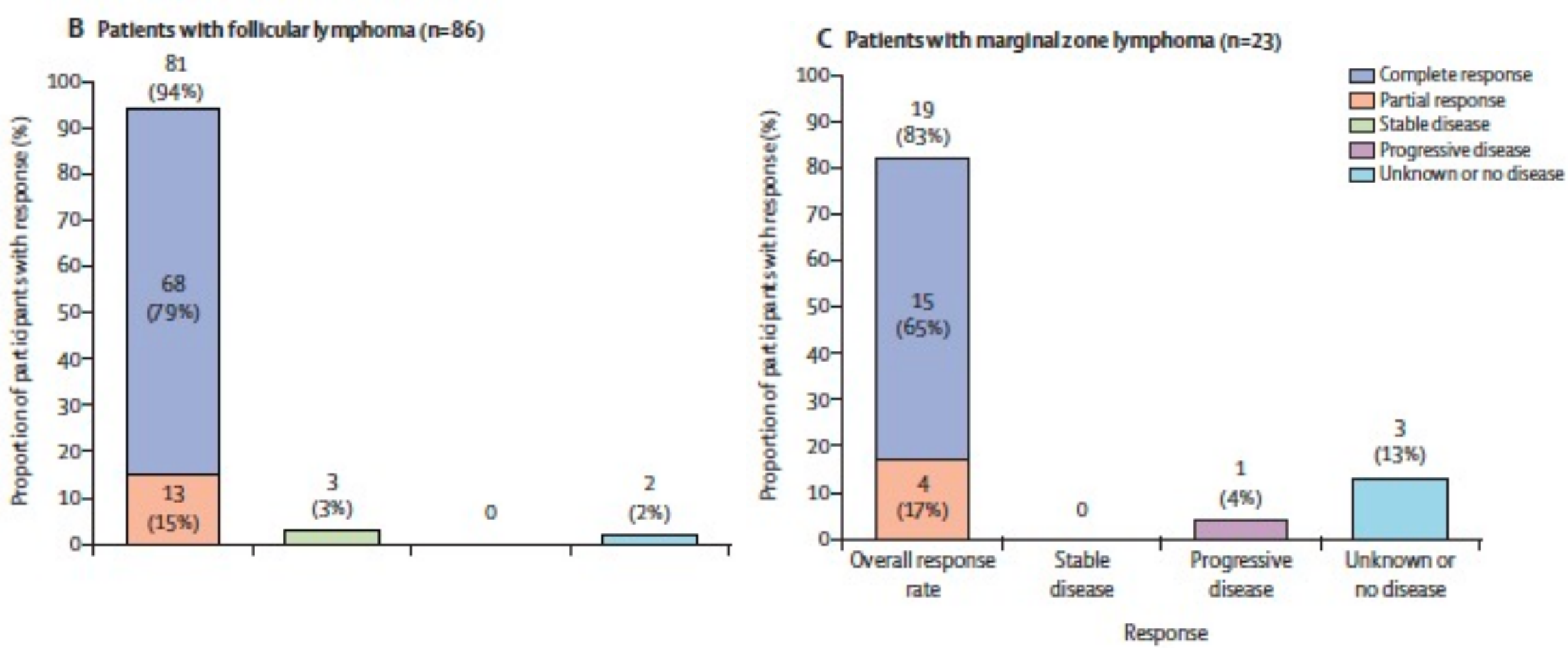
- ORR (IRRC assessed per the Lugano classification[1])

Key Secondary Endpoints

- CR rate (IRRC assessed)
- Investigator-assessed ORR[a]
- DOR, PFS, OS
- AEs
- CAR T-cell and cytokine levels

Courtesy of Laurie H Sehn, MD, MPH

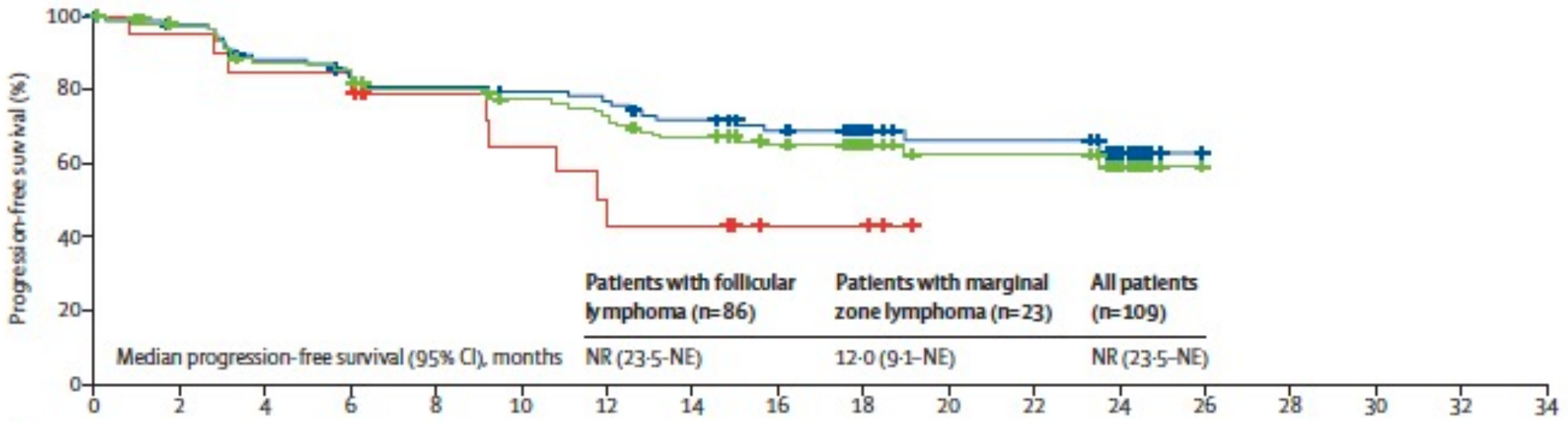
ZUMA-5: Overall Response Rate



Jacobson et al, Lancet 2022

Courtesy of Laurie H Sehn, MD, MPH

ZUMA-5: Progression-free Survival



	Patients with follicular lymphoma (n=86)	Patients with marginal zone lymphoma (n=23)	All patients (n=109)
Median progression-free survival (95% CI), months	NR (23·5-NE)	12·0 (9·1-NE)	NR (23·5-NE)

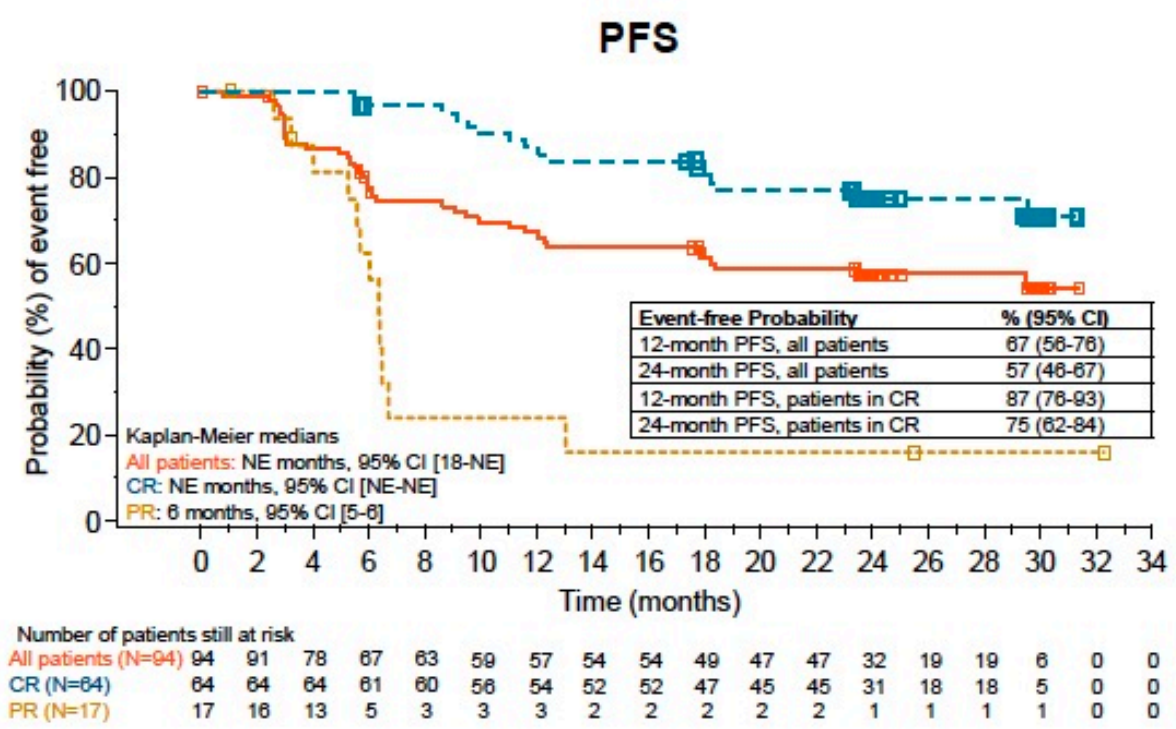
Number at risk (number censored)																		
Patients with follicular lymphoma	86 (0)	82 (2)	73 (3)	68 (4)	64 (6)	61 (8)	59 (8)	54 (9)	49 (12)	40 (21)	24 (36)	24 (36)	12 (47)	0 (59)	–	–	–	–
Patients with marginal zone lymphoma	23 (0)	19 (3)	16 (4)	15 (5)	11 (8)	9 (8)	7 (8)	6 (8)	3 (11)	3 (11)	0 (14)	–	–	–	–	–	–	–
All patients	109 (0)	101 (5)	89 (7)	83 (9)	75 (14)	70 (16)	66 (16)	60 (17)	52 (23)	43 (32)	24 (50)	24 (50)	12 (61)	0 (73)	–	–	–	–

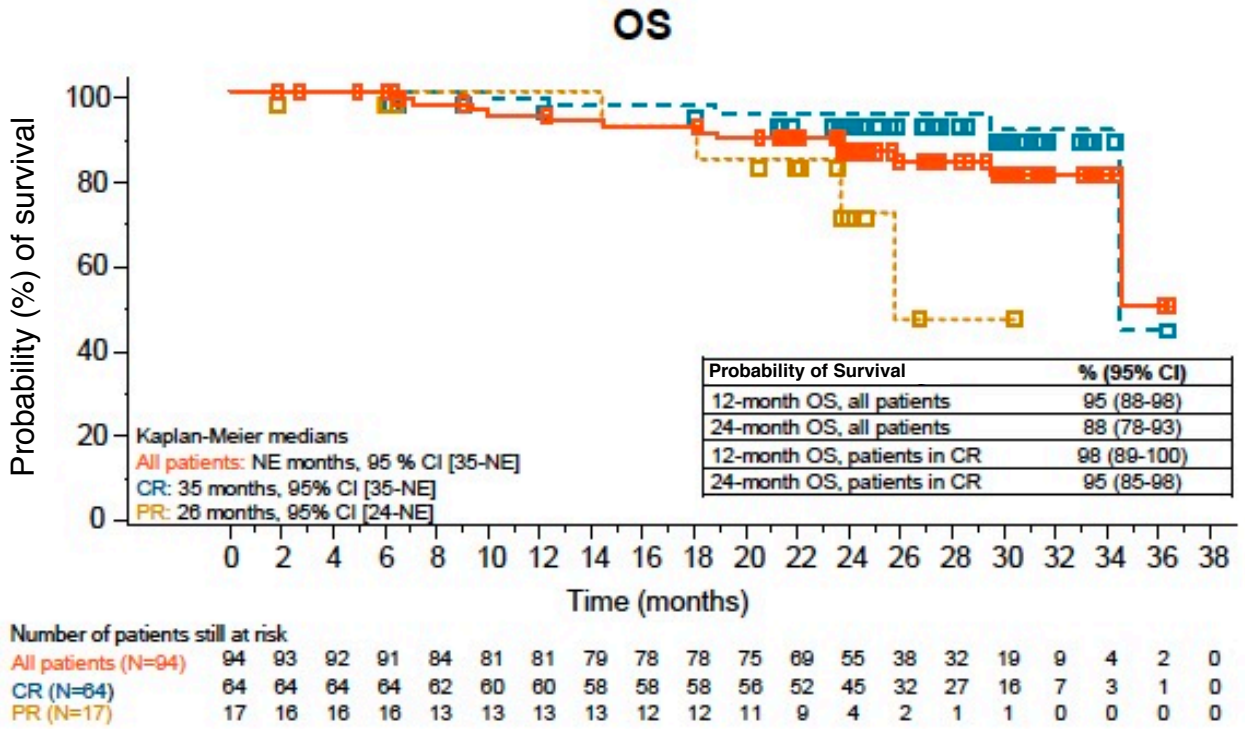
Median follow-up: 17.5m

Jacobson et al, Lancet 2022

Courtesy of Laurie H Sehn, MD, MPH

ELARA: Tisagenlecleucel in Patients with R/R FL



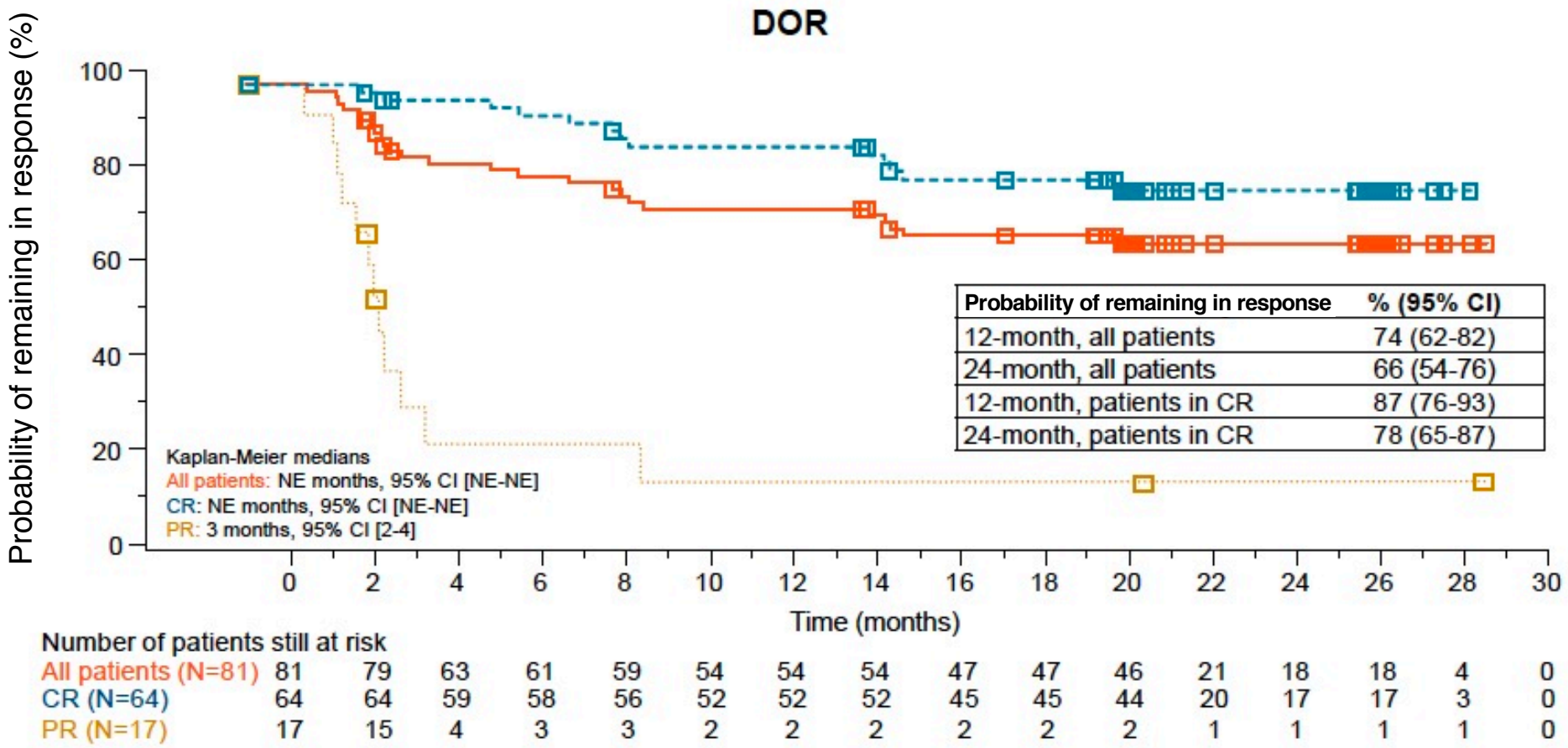


Median follow-up: 29 m

Courtesy of Laurie H Sehn, MD, MPH

Dreyling et al, ASH 2022

ELARA: Tisagenlecleucel in Patients with R/R FL



Median follow-up: 29 m

Dreyling et al, ASH 2022

Courtesy of Laurie H Sehn, MD, MPH

Agenda

INTRODUCTION

MODULE 1: Diffuse Large B-Cell Lymphoma

MODULE 2: Hodgkin Lymphoma

MODULE 3: Follicular Lymphoma

MODULE 4: Mantle Cell Lymphoma

Mantle Cell Lymphoma

First-line BTK inhibitors

- SHINE – Ibrutinib/bendamustine/rituximab
- TRIANGLE: European Mantle Cell Lymphoma Consortium
- Acalabrutinib/R^2 (lenalidomide/rituximab)

Venetoclax

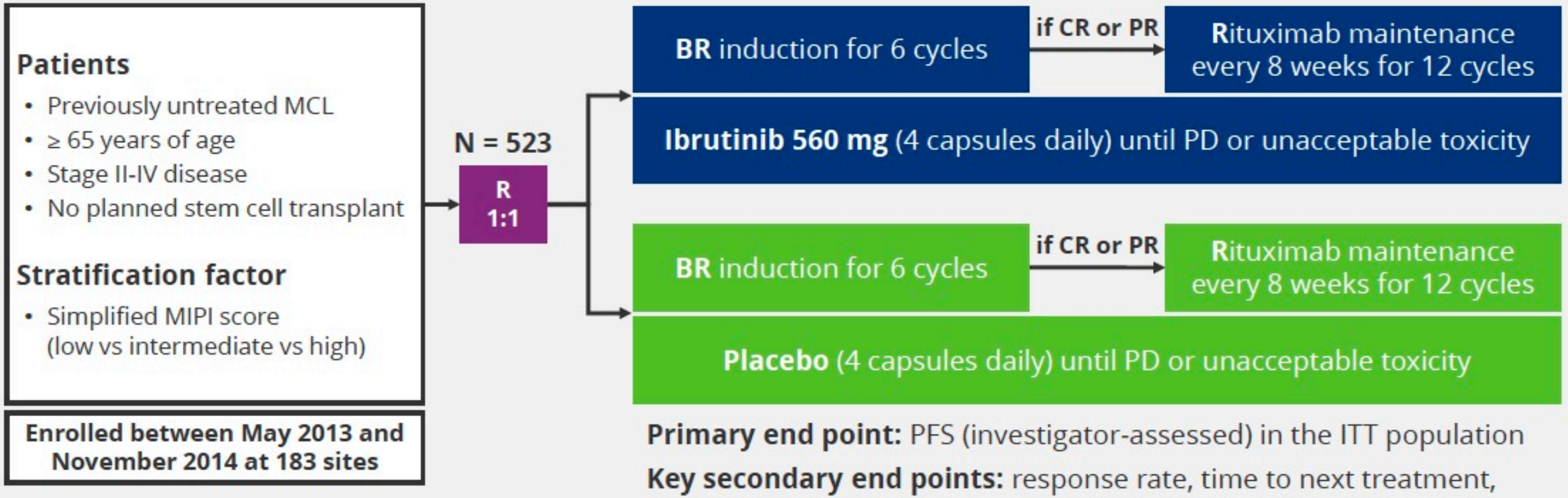
- Venetoclax/rituximab/acalabrutinib

CAR T-cell therapy

- ZUMA-2 – Brexucabtagene autoleucel

Zanubrutinib

SHINE: A Randomized, Double-Blind, Phase III Study



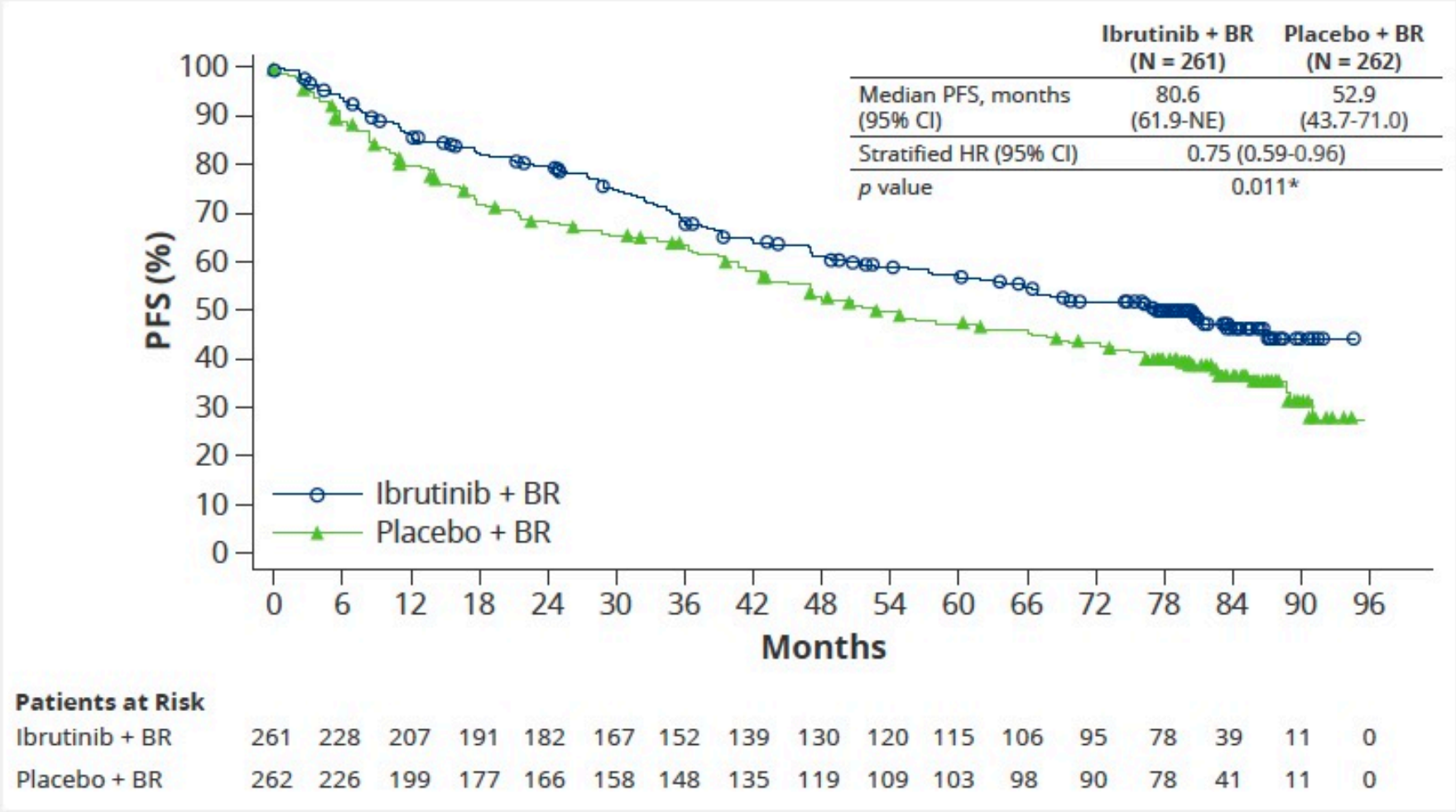
Induction: Bendamustine 90 mg/m2 Days 1 and 2, Rituximab 375 mg/m2 Day 1, Q4W. A cycle is defined as 28 days.

CR, complete response; ITT, intent-to-treat; MIPI, Mantle Cell Lymphoma International Prognostic Index; PD, progressive disease; PFS, progression-free survival; PR, partial response.

Wang et al, NEJM 2022

Courtesy of Laurie H Sehn, MD, MPH

SHINE: Primary End Point of Improved PFS Was Met



CI, confidence interval; HR, hazard ratio; NE, not evaluable.
*Significance boundary for superiority was $p < 0.023$.

Ibrutinib + BR and R maintenance achieved:

- **Significant improvement in median PFS by 2.3 years** (6.7 vs 4.4 years)
- **25% reduction** in risk of PD or death

Wang et al, NEJM 2022

Courtesy of Laurie H Sehn, MD, MPH

SHINE: TEAEs of Clinical Interest With BTKis

	Ibrutinib + BR (N = 259)		Placebo + BR (N = 260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any bleeding*	42.9%	3.5%	21.5%	1.5%
Major bleeding	5.8%	–	4.2%	–
Atrial fibrillation*	13.9%	3.9%	6.5%	0.8%
Hypertension	13.5%	8.5%	11.2%	5.8%
Arthralgia	17.4%	1.2%	16.9%	0

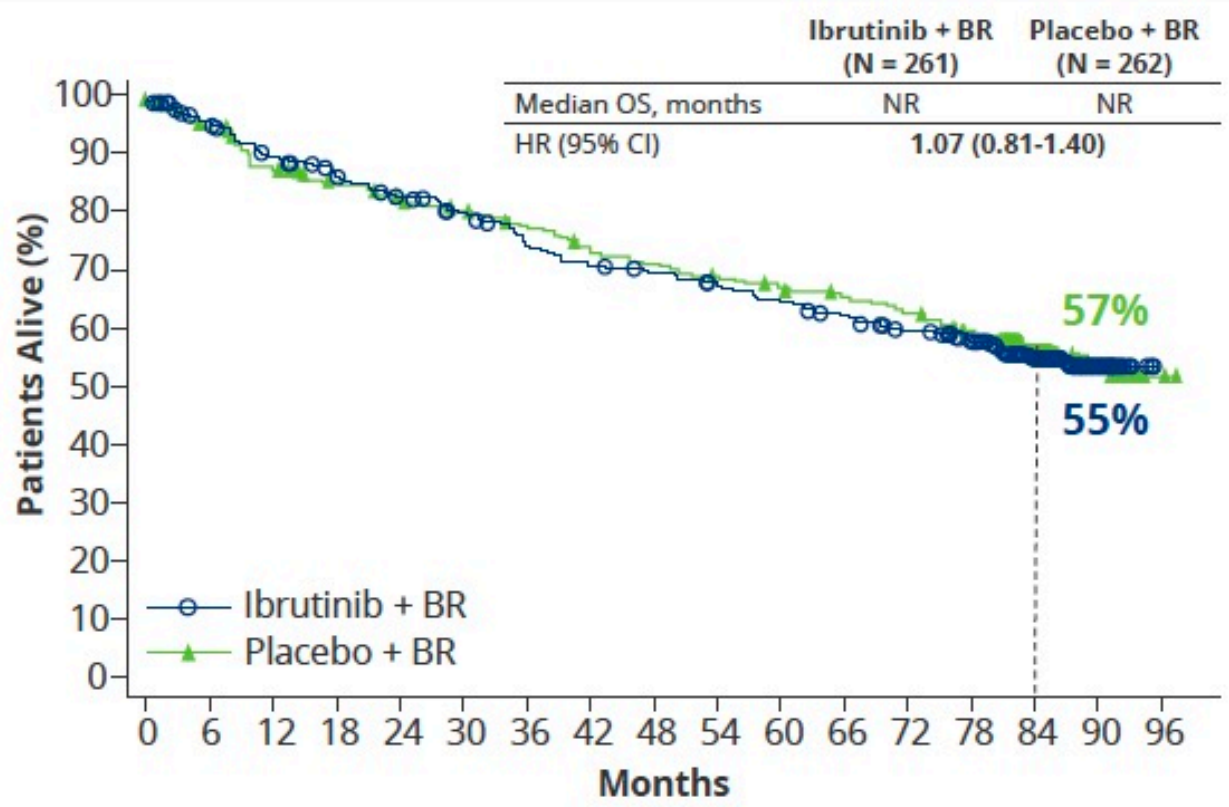
- These adverse events were generally not treatment limiting
- During the entire study period, second primary malignancies (including skin cancers) occurred in 21% in the ibrutinib arm and 19% in the placebo arm; MDS/AML in 2 and 3 patients, respectively

Wang et al, NEJM 2022

Courtesy of Laurie H Sehn, MD, MPH

*Difference of ≥ 5% in any grade TEAE; MDS/AML, myelodysplastic syndromes/acute myeloid leukemia;
Any bleeding is based on Haemorrhage Standardized MedDRA Query (SMQ) (excluding laboratory terms). Major bleeding includes any grade 3 or higher bleeding and serious or central nervous system bleeding of any grade.

SHINE: Overall Survival



Patients at Risk

Ibrutinib + BR	261	239	221	208	197	187	171	163	158	152	145	138	128	118	70	25	0
Placebo + BR	262	244	223	212	203	197	188	177	171	165	159	154	147	137	90	31	2

Cause of death	Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Death due to PD and TEAE	**58 (22.2%)**	**70 (26.7%)**
Death due to PD	**30 (11.5%)**	**54 (20.6%)**
Death due to TEAEs*	**28 (10.7%)**	**16 (6.1%)**
Death during post-treatment follow-up excluding PD and TEAEs	**46 (17.6%)**	**37 (14.1%)**
Total deaths	**104 (39.8%)**	**107 (40.8%)**

- Death due to Covid-19: 3 patients in the ibrutinib arm during the TEAE period and 2 patients in the placebo arm after the TEAE period
- Exploratory analysis of cause-specific survival including only deaths due to PD or TEAEs showed an HR of 0.88

*The most common grade 5 TEAE was infections in the ibrutinib and placebo arms: 9 versus 5 patients. Grade 5 TEAE of cardiac disorders occurred in 3 versus 5 patients, respectively.
CI, confidence interval; HR, hazard ratio; NR, not reached; PD, progressive disease; TEAE, treatment-emergent adverse event.

Wang et al, NEJM 2022

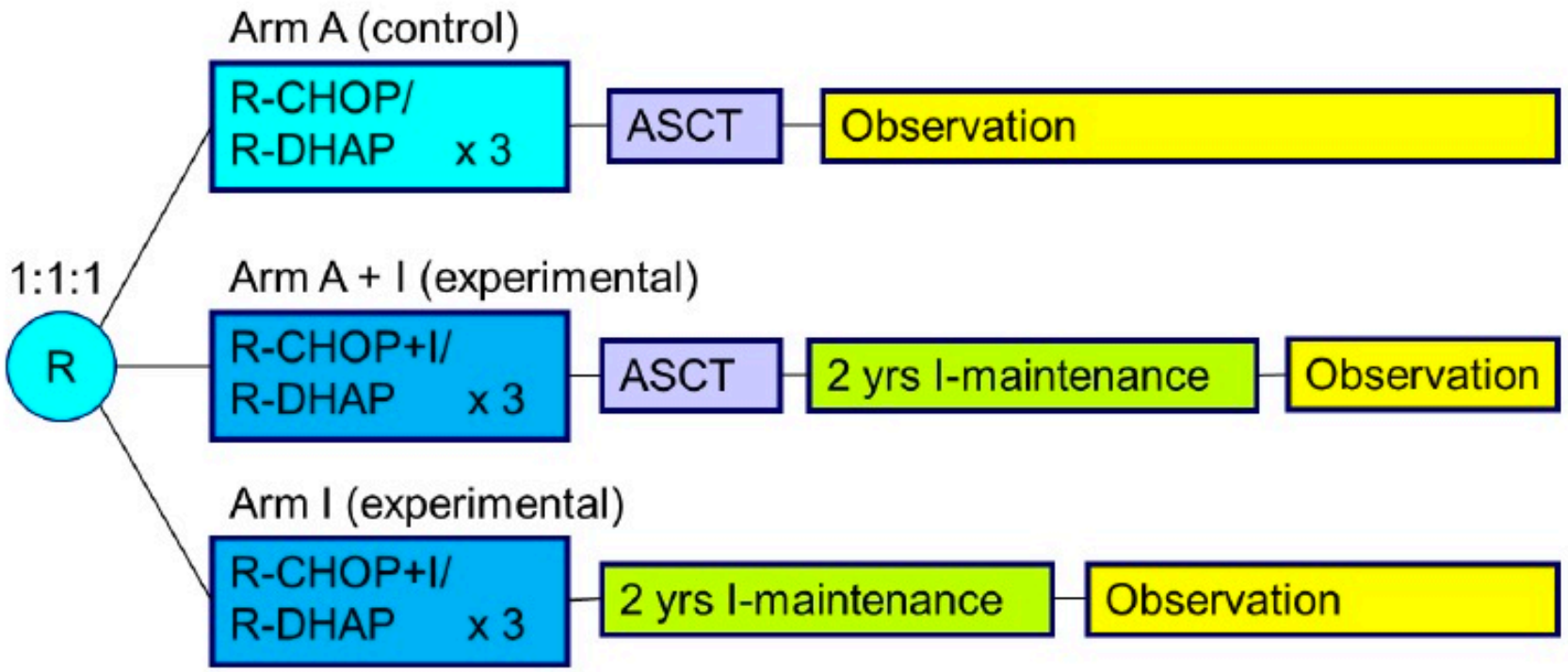
Courtesy of Laurie H Sehn, MD, MPH

TRIANGLE Study: Ibrutinib combined with first-line treatment or as a substitute for ASCT in untreated MCL

- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA and ASCT
- ECOG 0-2

- Primary outcome: FFS

- Secondary outcomes:
  - Response rates
  - PFS, RD
  - OS
  - Safety

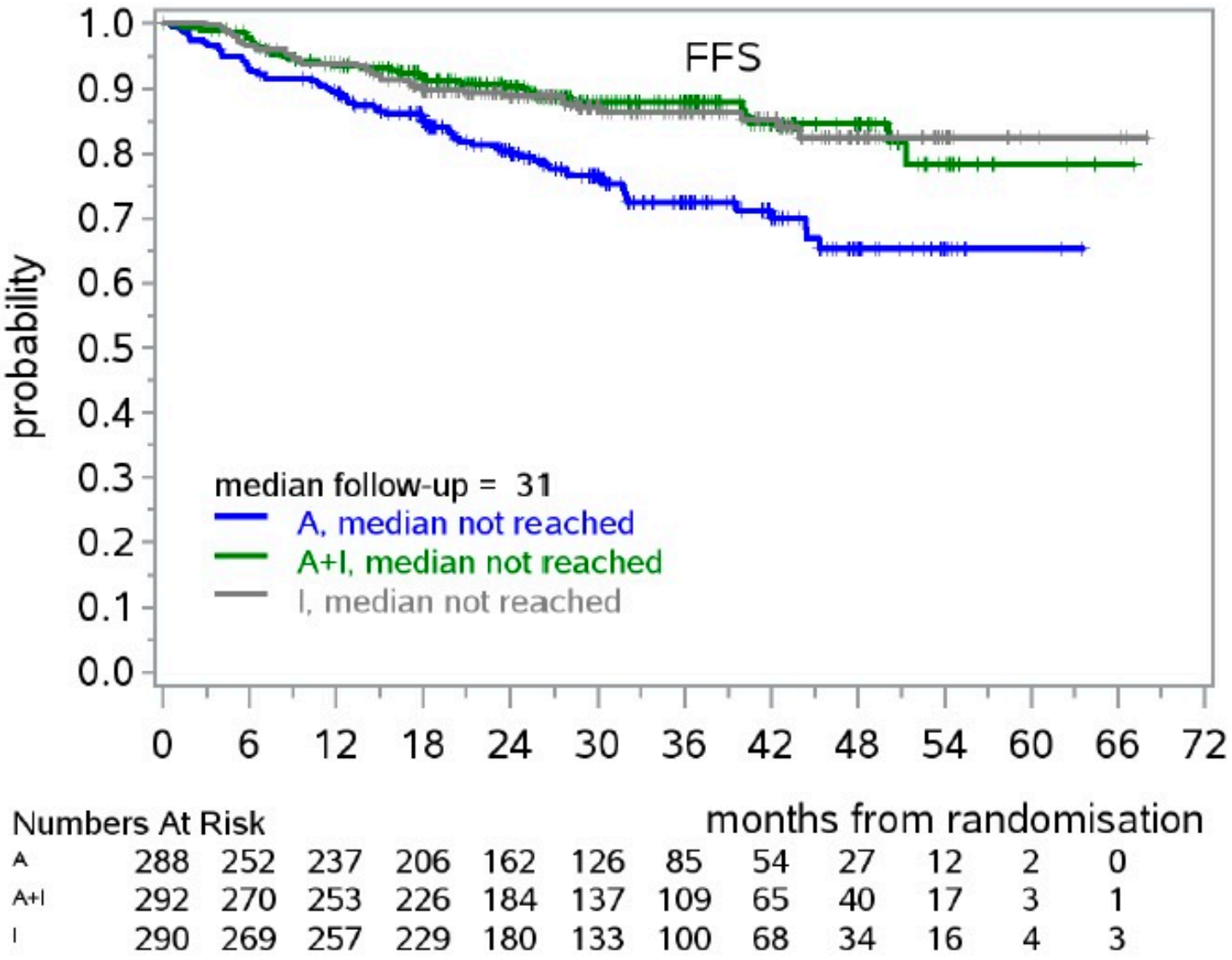


- R maintenance was added following national guidelines in all 3 trial arms
- Rituximab maintenance (without or with Ibrutinib) was started in 168 (58 %)/165 (57 %)/158 (54 %) of A/A+I/I randomized patients.

Dreyling et al, ASH 2022

Courtesy of Laurie H Sehn, MD, MPH

TRIANGLE: FFS Superiority of A+I vs. I ?



- Test A+I vs. I ongoing, no decision yet

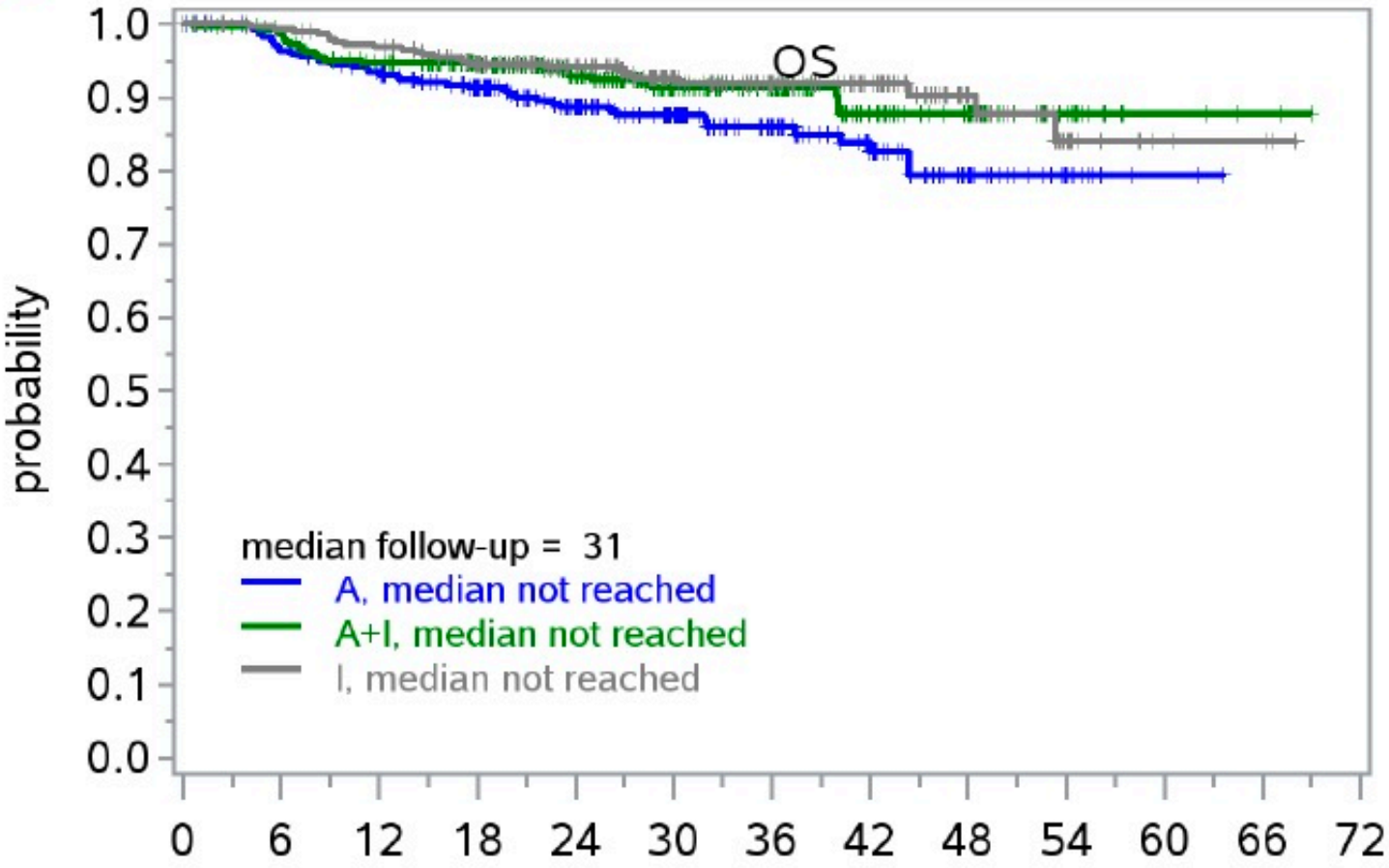
Next lymphoma treatment (among patients with first treatment failure)	A (n=68)		A+I (n=35)		I (n=37)	
Treatment with Ibrutinib	34	79%	4	24%	3	11%
Treatment without Ibrutinib	9	21%	13	76%	24	89%
No treatment	25		18		10	

A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Dreyling et al, ASH 2022

Courtesy of Laurie H Sehn, MD, MPH

TRIANGLE: Overall survival



Numbers At Risk												
A	288	270	256	230	181	145	97	63	32	15	2	0
A+I	292	280	262	238	195	142	113	67	42	19	4	2
I	290	281	272	248	197	145	109	77	38	16	4	3

- 3-year OS:
  - A: 86% (MCL Younger exp.: 84%)
  - A+I: 91%
  - I: 92%
- Too early to evaluate statistical significance

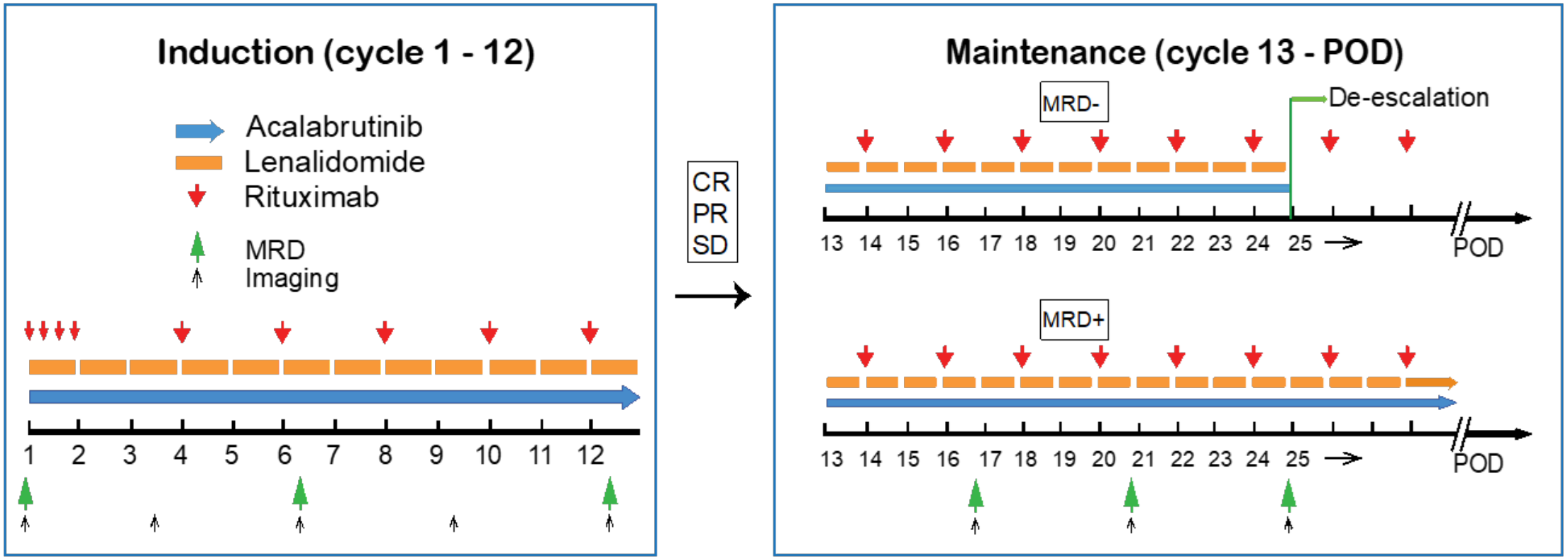
Dreyling et al, ASH 2022

A arm: R-CHOP/R-DHAP+ASCT; A+I arm: IR-CHOP/R-DHAP+ASCT+I; I arm: IR-CHOP/R-DHAP+I. I: ibrutinib

Courtesy of Laurie H Sehn, MD, MPH

Phase 2 Trial of Acalabrutinib-Lenalidomide-Rituximab (ALR) with Real-time Monitoring of MRD in Patients with Untreated MCL

Sample size N=24



1st – CR rate after induction
2nd – ORR, safety and survival
Exploratory: MRD, NGS

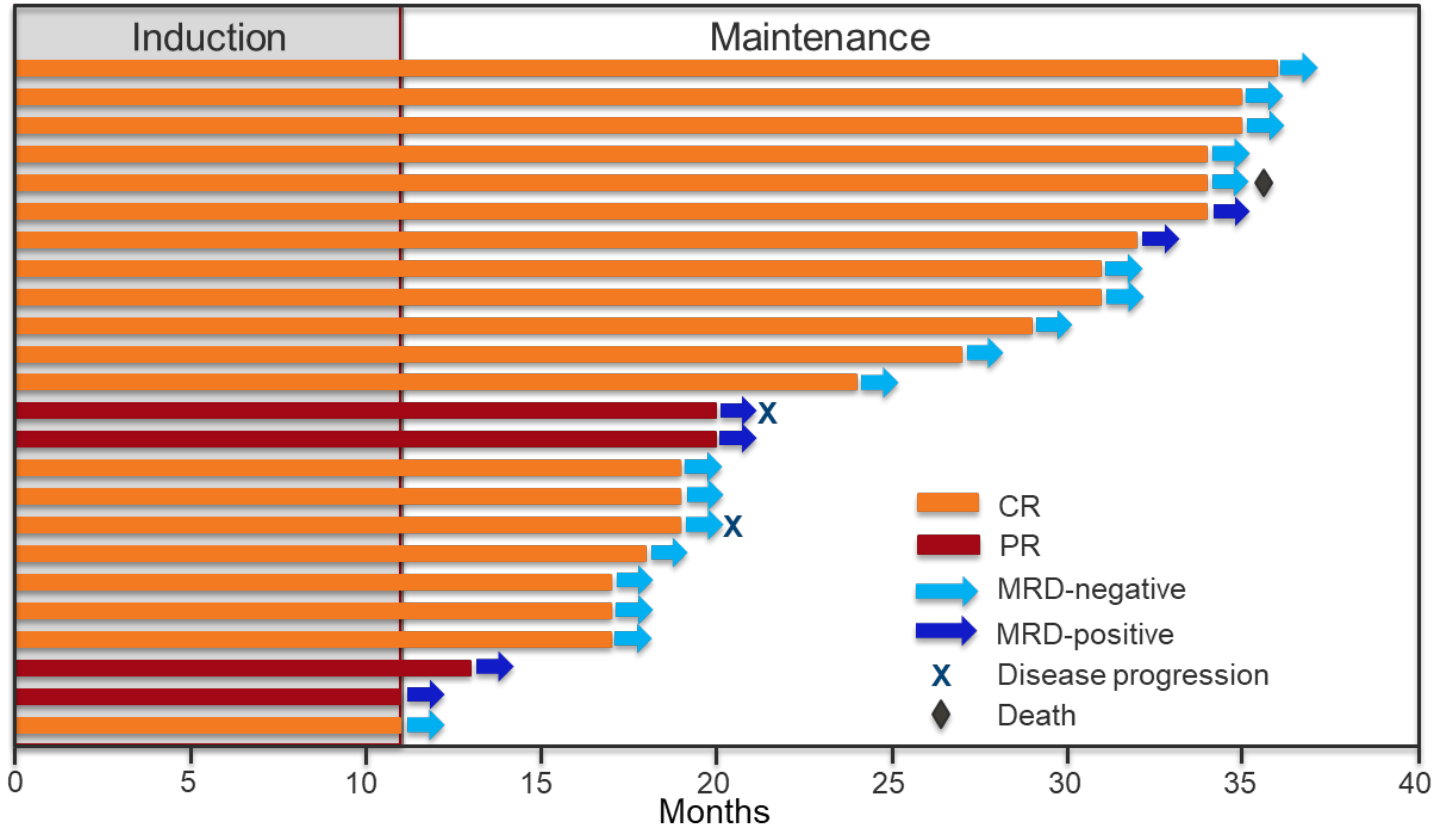
- Acalabrutinib and lenalidomide can be discontinued after 24 cycles of treatment for subjects achieving MRD-negative CR during maintenance.
- Imaging studies: PET/CT is required at baseline and time to confirm CR.

Courtesy of Laurie H Sehn, MD, MPH

Ruan et al, ASH 2022

Efficacy: Objective Responses and Duration with ALR

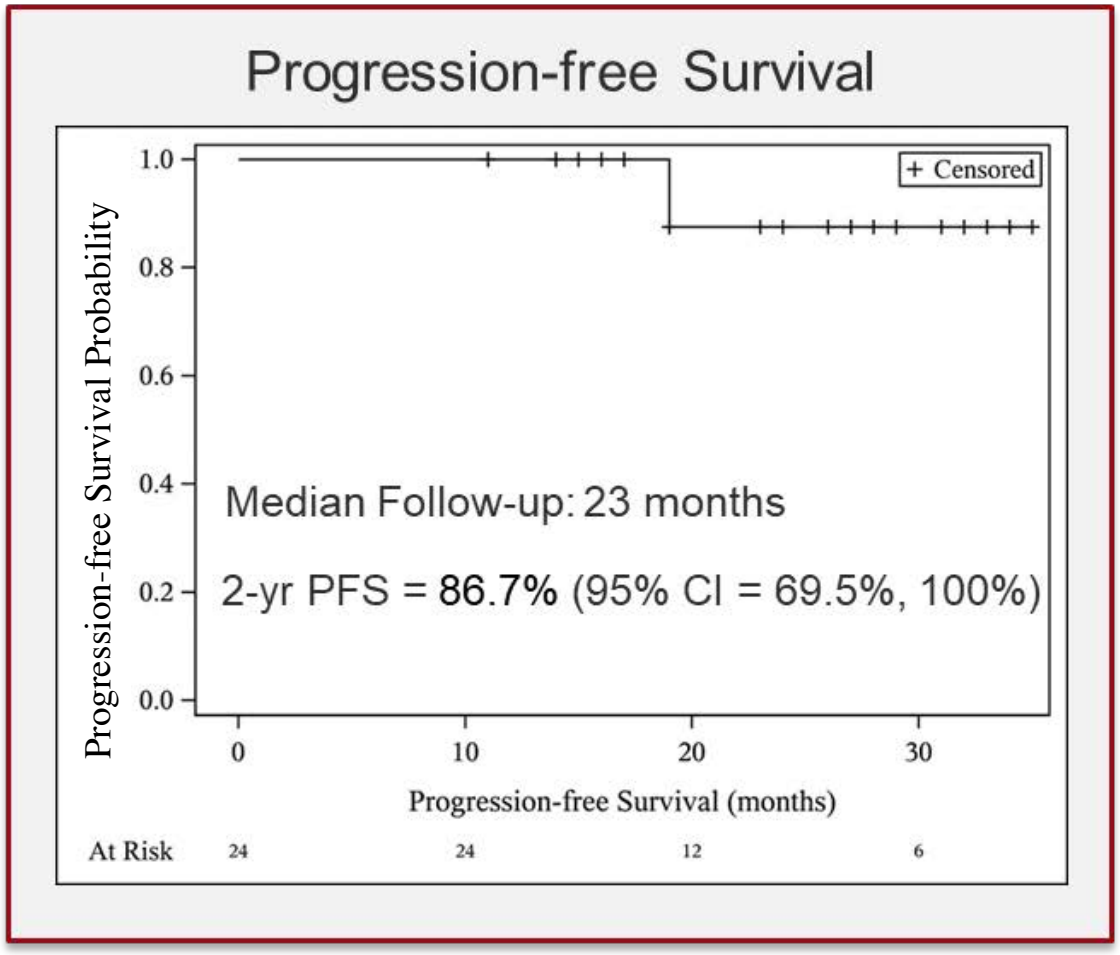
Response	End of Induction* (12 cycles)	
	No. Pt	ITT
ORR	24	100%
CR	20	**83%**
PR	4	17%
SD	0	0
PD	0	0
Median Follow-up	23 months (range 12-36)	
"*": EOI following 12 cycles of treatment; response per Lugano criteria		

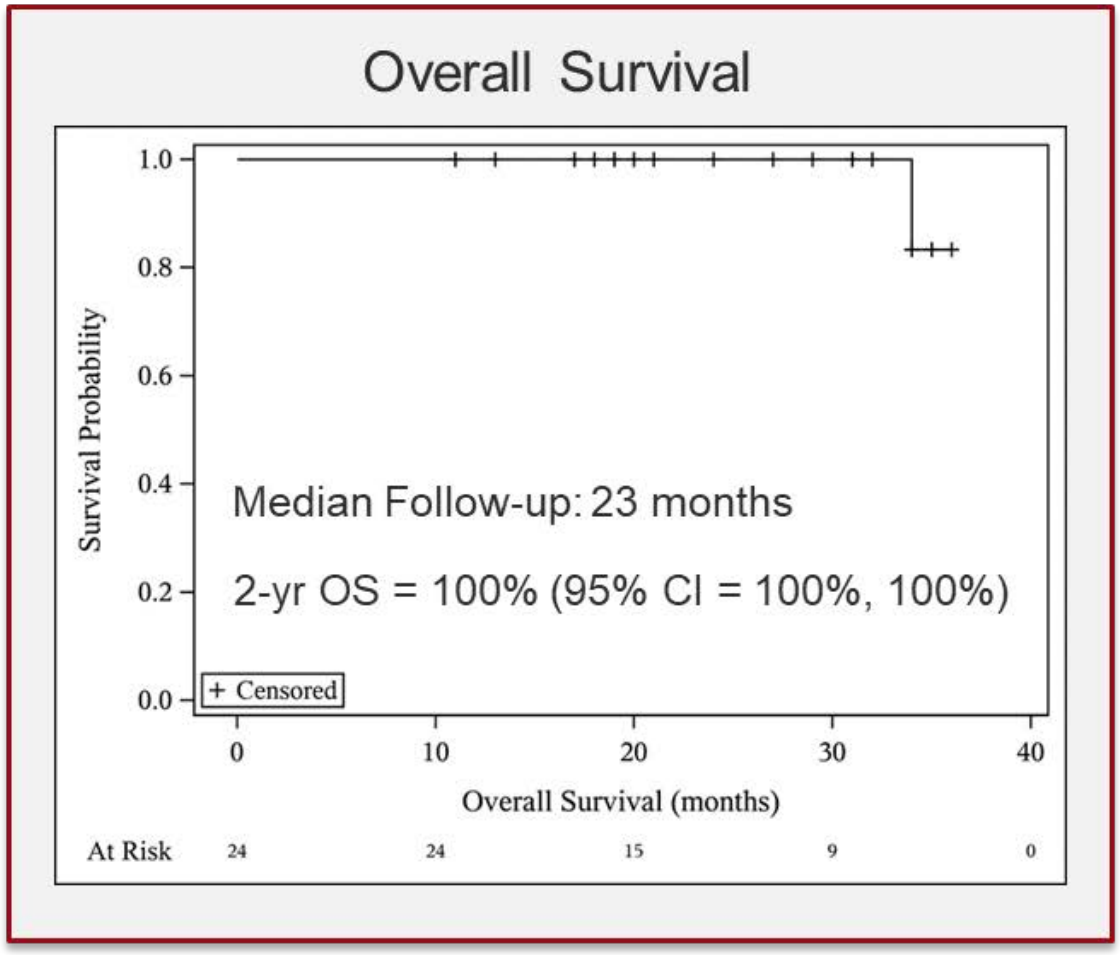


Courtesy of Laurie H Sehn, MD, MPH

Ruan et al, ASH 2022

Efficacy: Survival with ALR





Courtesy of Laurie H Sehn, MD, MPH

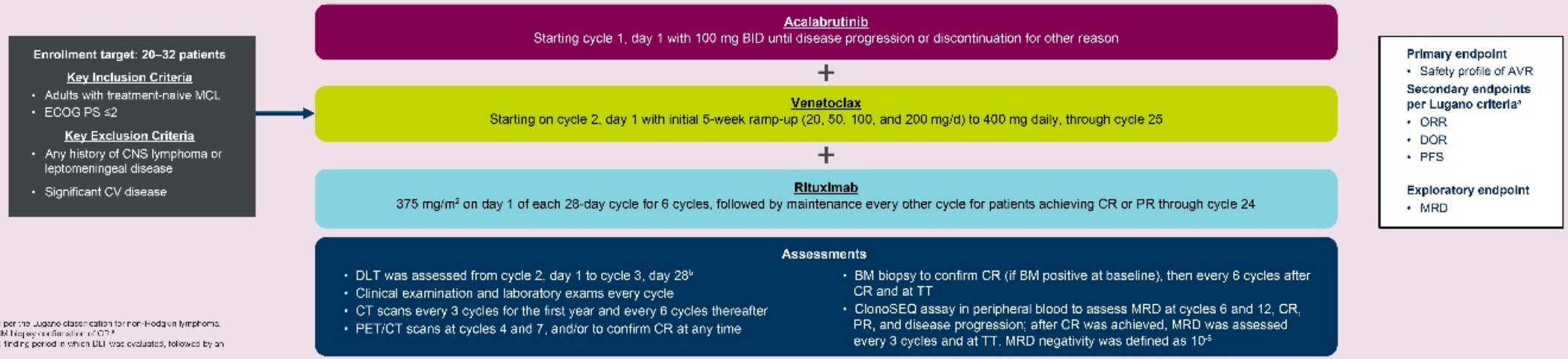
Ruan et al, ASH 2022

Acalabrutinib with Venetoclax and Rituximab in Patients with Untreated MCL

Methods

- The inclusion and exclusion criteria, treatment protocol, assessment schedule, and endpoints are detailed in **Figure 1**

Figure 1. Study Design



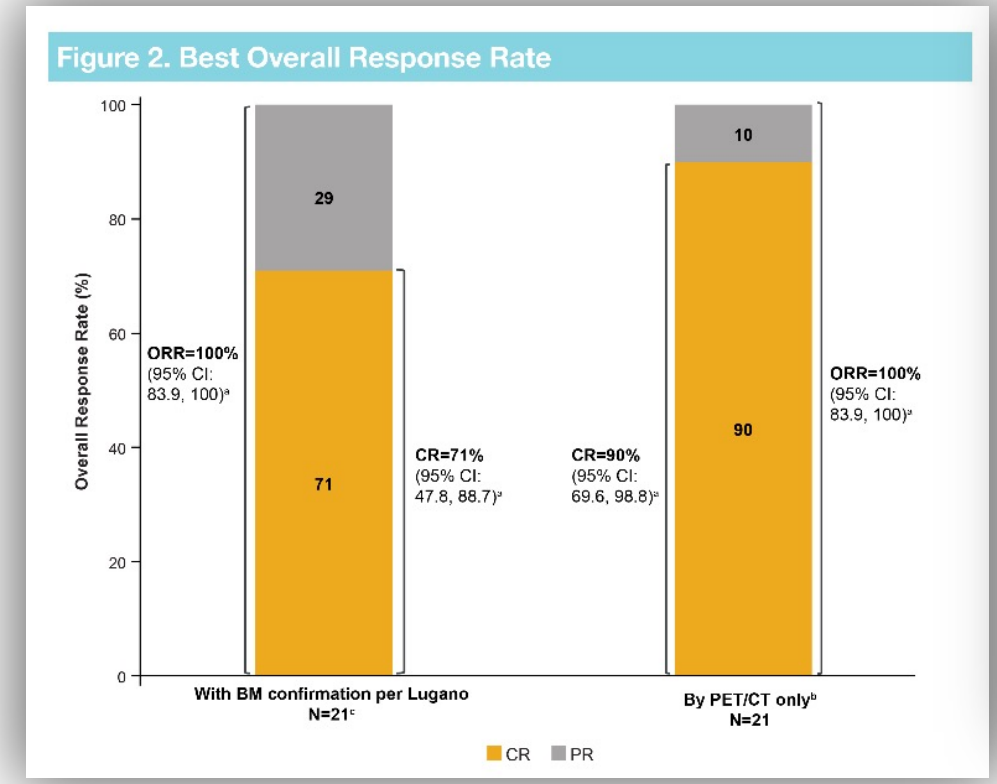
[a]Efficacy endpoints evaluated per the Lugano classification for non-Hodgkin lymphoma, which requires PET/CT and BM biopsy confirmation of CR.
[b]The study had an initial dose finding period in which DLT was evaluated, followed by an expansion phase.

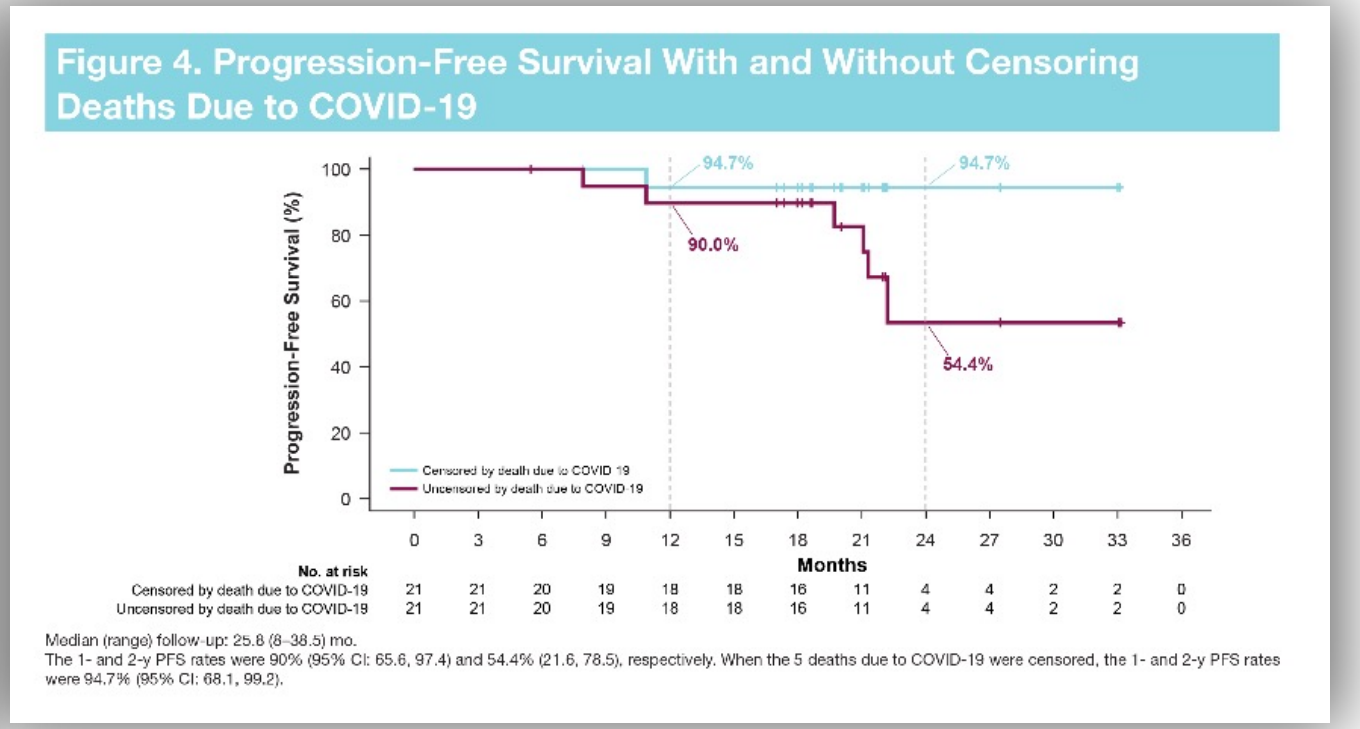
Median follow-up: 25.8 m
N=21
Median age 66 y

Wang et al, ASH 2022

Courtesy of Laurie H Sehn, MD, MPH

Acalabrutinib with Venetoclax and Rituximab in Patients with Untreated MCL



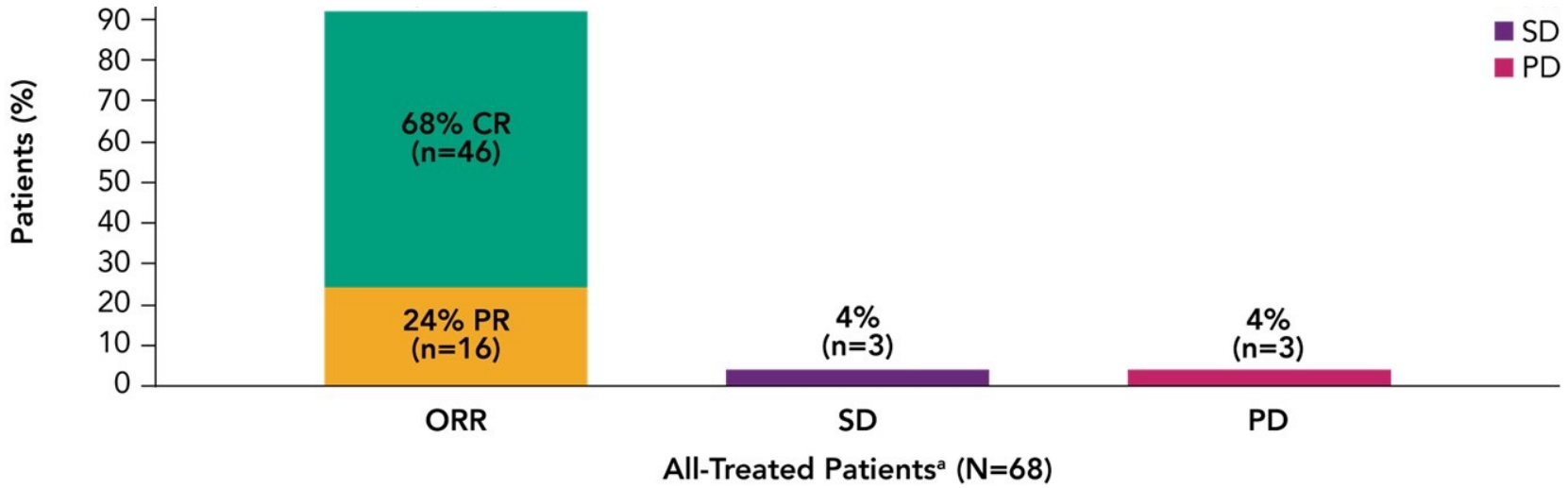


5 Covid-related deaths

Wang et al, ASH 2022

Courtesy of Laurie H Sehn, MD, MPH

ZUMA-2: Three-year follow-up of outcomes with KTE-X19 in R/R MCL



- After a median follow-up of 35.6 months (range, 25.9-56.3), the ORR (CR + partial response [PR]) was 91% (95% CI, 81.8-96.7), with a 68% CR rate (95% CI, 55.2-78.5) and a median DOR of 28.2 months (95% CI, 13.5-47.1)
- In the ITT population, ORR was 84% (95% CI, 73.4-91.3), with a 62% CR rate (95% CI, 50.1-73.2)

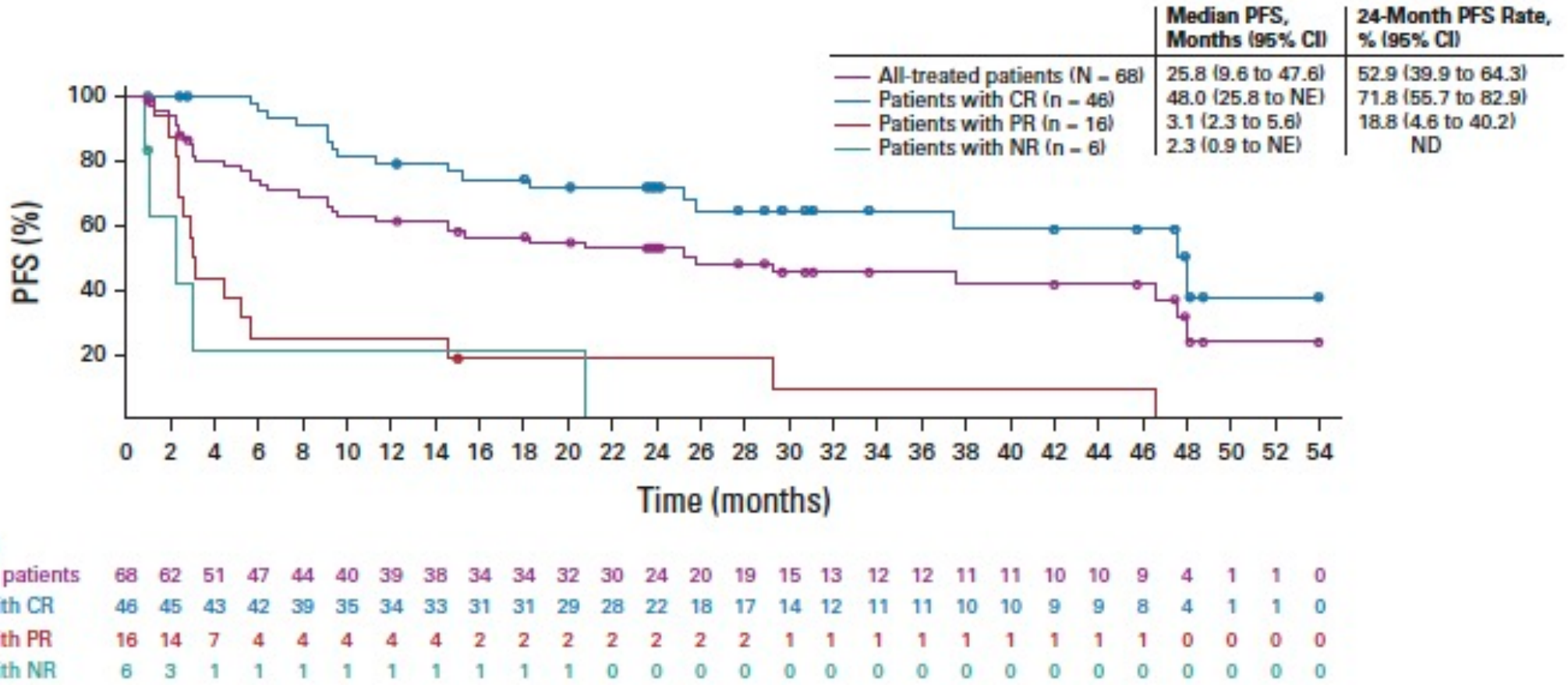
With 3-years of follow-up, these data demonstrate that a single infusion of KTE-X19 resulted in high rates of durable responses in R/R MCL.

Assessed by an IRRC according to the Lugano Classification.[1] [a] Since the previous report,[2] IRRC review determined that 1 patient who was previously reported as best response of PR had no disease at baseline; this patient is reported as PD in the current report. CR, complete response; DOR, duration of remission; IRRC, Independent Radiology Review Committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

1. Cheson BD, et al. J Clin Oncol. 2014;32:3059-3068. 2. Wang M, et al. *Blood*. 2020;136(suppl 1):20-22.

Courtesy of Laurie H Sehn, MD, MPH

ZUMA-2: Three-year follow-up of outcomes with KTE-X19 in R/R MCL



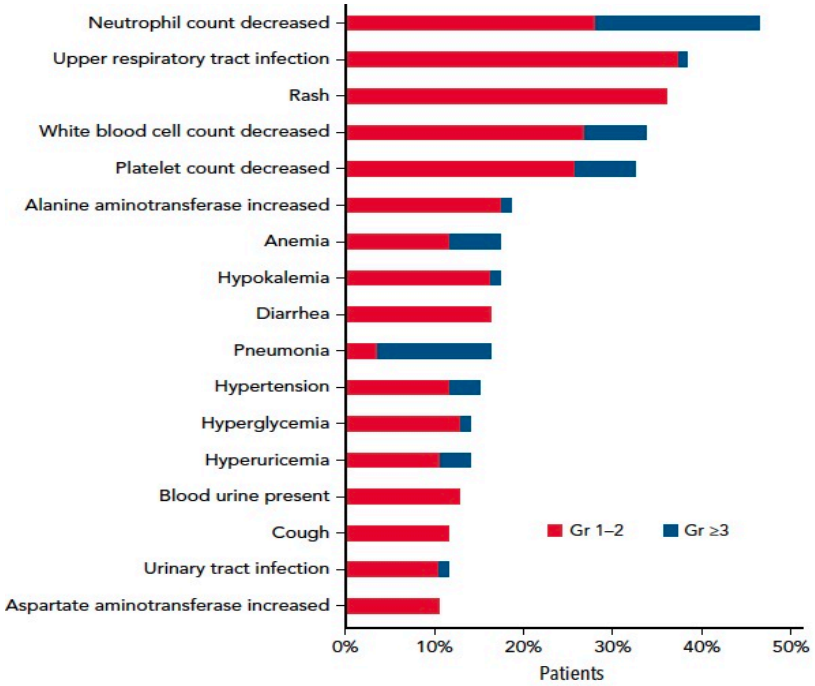
Median OS: 46.6 m

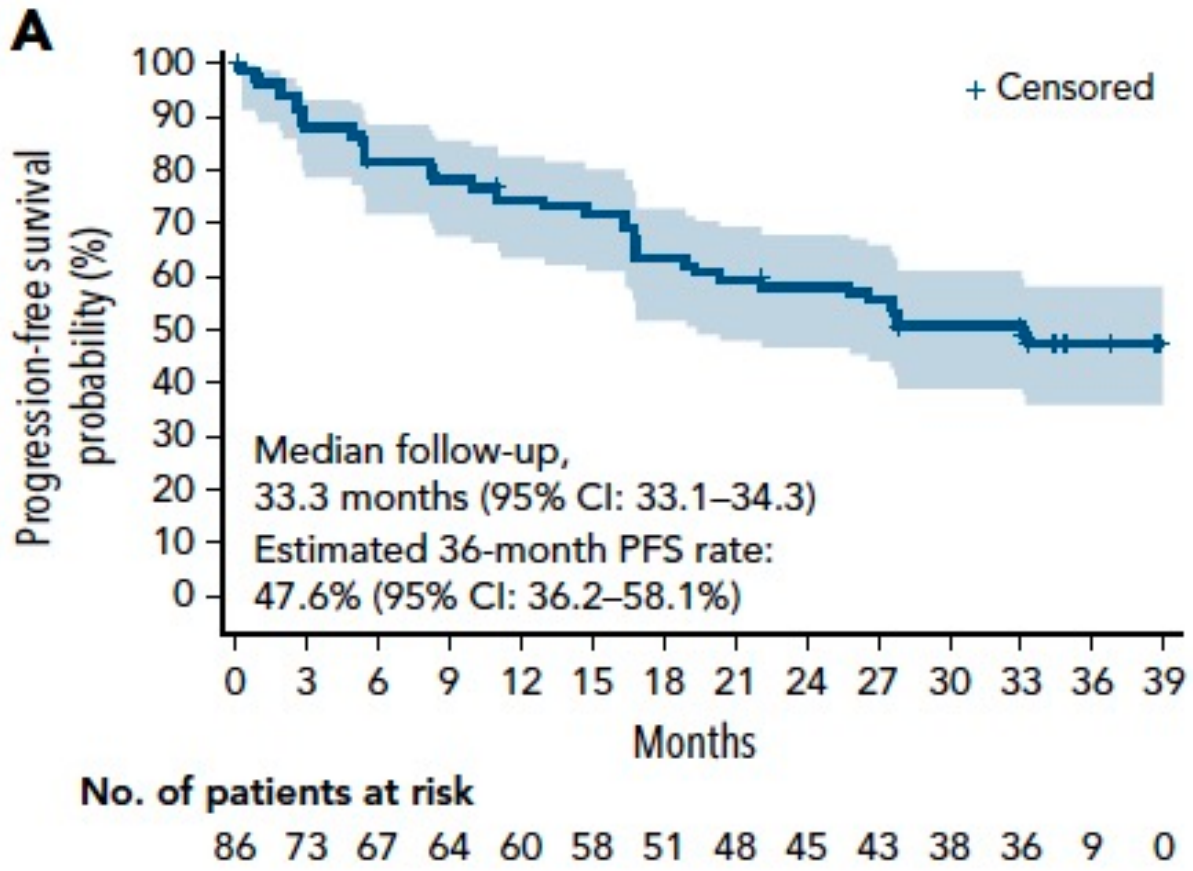
Courtesy of Laurie H Sehn, MD, MPH

Wang et al, JCO 2022

Zanubrutinib in R/R Mantle Cell Lymphoma: Long-term Follow-up of Phase 2 Trial

Efficacy variable	n = 86
ORR (CR + PR), % (95% CI)*	83.7 (74.2-90.8)
Best response, n (%)	
CR	67 (77.9)
PR	5 (5.8)
SD	1 (1.2)
PD	8 (9.3)
Discontinued before first assessment	5 (5.8)





Song et al, Blood 2022

Courtesy of Laurie H Sehn, MD, MPH

Inside the Issue — Optimizing the Management of Adverse Events Associated with BTK Inhibitors

A CME/MOC-Accredited Virtual Event

Thursday, February 2, 2023
5:00 PM – 6:00 PM ET

Faculty

Farrukh T Awan, MD
Kerry A Rogers, MD

Moderator

Neil Love, MD

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RESEARCH
TO PRACTICE

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

RTP Year in Review 2023