Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

A CME Hybrid Symposium Held in Conjunction with the 2022 ASCO Annual Meeting

Sunday, June 5, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty

Ian W Flinn, MD, PhD
Brian T Hill, MD, PhD
John P Leonard, MD
Matthew Lunning, DO
Laurie H Sehn, MD, MPH
Mitchell R Smith, MD, PhD

Moderator

Neil Love, MD

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Faculty

Ian W Flinn, MD, PhD
Director of Lymphoma Research Program
Sarah Cannon Research Institute
Tennessee Oncology
Nashville, Tennessee

Brian T Hill, MD, PhD
Director, Lymphoid Malignancy Program
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio

John P Leonard, MD
Richard T Silver Distinguished Professor of
Hematology and Medical Oncology
Senior Associate Dean for Innovation and Initiatives
Executive Vice Chair, Joan and Sanford I Weill
Department of Medicine
Weill Cornell Medicine
New York, New York

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Associate Professor
Fred and Pamela Buffett Cancer Center
Associate Vice Chair of Research, Department of Medicine
Assistant Vice Chancellor of Clinical Research
University of Nebraska Medical Center
Omaha, Nebraska

Laurie H Sehn, MD, MPH
Chair, Lymphoma Tumour Group
BC Cancer Centre for Lymphoid Cancer
Clinical Professor of Medicine
Division of Medical Oncology
University of British Columbia
Associate Editor, *Blood*
Vancouver, British Columbia, Canada

Mitchell R Smith, MD, PhD
Clinical Professor of Medicine
George Washington University
Washington, DC

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Friday June 3	**Acute Myeloid Leukemia and Myelodysplastic Syndromes** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Lung Cancer 6:30 PM – 9:00 PM CT (7:30 PM – 10:00 PM ET)
Saturday June 4	**Prostate Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Gastrointestinal Cancers 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Sunday June 5	**Ovarian Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Monday June 6	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Breast Cancer 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Tuesday June 7	**Multiple Myeloma** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

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Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2022 ASCO Annual Meeting

Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

Sunday, June 5, 2022
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Brian T Hill, MD, PhD
John P Leonard, MD
Matthew Lunning, DO
Laurie H Sehn, MD, MPH
Mitchell R Smith, MD, PhD

Breast Cancer

Monday, June 6, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty
Javier Cortés, MD, PhD
Matthew P Goetz, MD
Erika Hamilton, MD
Ian E Krop, MD, PhD
Hope S Rugo, MD
Sara M Tolaney, MD, MPH

Urothelial Bladder Cancer

Monday, June 6, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Yohann Loriot, MD, PhD
Elizabeth R Plimack, MD, MS
Jonathan E Rosenberg, MD

Multiple Myeloma

Tuesday, June 7, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Ajai Chari, MD
Elizabeth O'Donnell, MD
Robert Z Orlowski, MD, PhD

Spencer H Bachow, MD
Lynn Cancer Institute
Boca Raton, Florida

Shaachi Gupta, MD, MPH
Florida Cancer Specialists
Lake Worth, Florida

Philip L Brooks, MD
Northern Light Eastern Maine Medical Center and Lafayette Family Cancer Institute
Brewer, Maine

Zanetta S Lamar, MD
Florida Cancer Specialists
Naples, Florida

Shams Bufalino, MD
Advocate Aurora Health
Park Ridge, Illinois

Neil Morganstein, MD
Atlantic Health System
Summit, New Jersey

Lionel A Kankeu Fonkoua, MD
Mayo Clinic
Rochester, Minnesota

Vignesh Narayanan, MD
Colorado Permanente Medical Group (CPMG)
Lone Tree, Colorado

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Namrata I Peswani, MD
Harold C Simmons
Comprehensive Cancer Center
Richardson, Texas

Matthew R Strickland, MD
Massachusetts General Hospital
Cancer Center
Boston, Massachusetts

Erik Rupard, MD
The Reading Hospital
West Reading, Pennsylvania

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Commercial Support

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Dr Love — Disclosures

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Dr Flinn — Disclosures

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Dr Hill — Disclosures

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Contracted Research	AbbVie Inc, ADC Therapeutics, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol-Myers Squibb Company, Genentech, a member of the Roche Group, Kite, A Gilead Company, MorphoSys, Novartis

Dr Leonard — Disclosures

Consulting Agreements	AbbVie Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Bristol-Myers Squibb Company, Calithera Biosciences, Celgene Corporation, Constellation Pharmaceuticals, Epizyme Inc, Genentech, a member of the Roche Group, Genmab, Grail Inc, Incyte Corporation, Janssen Biotech Inc, Karyopharm Therapeutics, Lilly, Merck, Mustang Bio, Pfizer Inc, Roche Laboratories Inc, Second Genome, Sutro Biopharma
Contracted Research	Epizyme Inc, Genentech Foundation, Janssen Biotech Inc
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Dr Lunning — Disclosures

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Dr Sehn — Disclosures

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Contracted Research	Genentech, a member of the Roche Group, Teva Oncology

Dr Smith — Disclosures

Advisory Committee	Janssen Biotech Inc
Speakers Bureau	Acrotech Biopharma

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

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Mitchell R Smith, MD, PhD

Moderator

Neil Love, MD

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Agenda

Module 1 – Newly Diagnosed Chronic Lymphocytic Leukemia (CLL) — Dr Flinn

Module 2 – Relapsed/Refractory (R/R) CLL; Novel Investigational Strategies — Dr Smith

Module 3 – Follicular Lymphoma (FL) — Dr Leonard

Module 4 – Mantle Cell Lymphoma (MCL) — Dr Lunning

Module 5 – Diffuse Large B-Cell Lymphoma (DLBCL) — Dr Sehn

Module 6 – Chimeric Antigen Receptor (CAR) T-Cell Therapy — Dr Hill

MODULE 1: Newly Diagnosed CLL – Dr Flinn

An 88-year-old woman with CLL, well controlled atrial fibrillation and a history of COPD and pneumonia

Dr Erik Rupard (West Reading, Pennsylvania)

A 73-year-old woman with CLL who developed severe basal cell carcinomas during ibrutinib therapy

Dr Zanetta Lamar (Naples, Florida)

An 80-year-old man with newly diagnosed del(13q) CLL and life-threatening anemia

Dr Namrata Peswani (Richardson, Texas)

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Treatment Naïve CLL

Ian W. Flinn, MD, PhD
Sarah Cannon Research Institute
Tennessee Oncology

Current Approaches to Treatment of TN CLL: NCCN Guidelines®

Without Del(17p)/*TP53* Mutation

Patients age ≥65 years OR patients age <65 years with significant comorbidities (CrCl <70 mL/min)

Preferred

- Acalabrutinib ± obinutuzumab[a]
- Ibrutinib[a]
- Venetoclax + obinutuzumab[a]
- Zanubrutinib

Other Regimens

- Bendamustine + anti-CD20
- Chlorambucil + obinutuzumab
- Obinutuzumab
- High-dose methylprednisolone + rituximab or obinutuzumab
- Ibrutinib + obinutuzumab
- Chlorambucil
- Rituximab

Patients age <65 years without significant comorbidities

Preferred

- Acalabrutinib ± obinutuzumab[a]
- Ibrutinib[a]
- Venetoclax + obinutuzumab
- Zanubrutinib

Other Regimens

- Bendamustine + anti-CD20
- Fludarabine + cyclophosphamide + rituximab[b]
- Ibrutinib + rituximab
- Fludarabine + rituximab
- High-dose methylprednisolone + rituximab or obinutuzumab

With Del(17p)/*TP53* Mutation

Preferred

- Acalabrutinib ± obinutuzumab
- Ibrutinib
- Venetoclax + obinutuzumab
- Zanubrutinib

Other Regimens

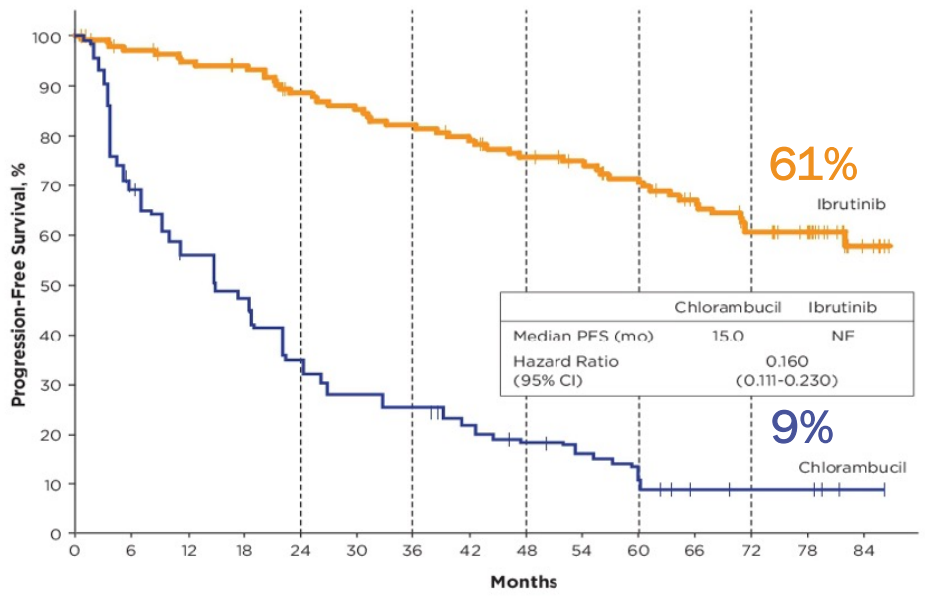
- Alemtuzumab ± rituximab
- High-dose methylprednisolone + rituximab
- Obinutuzumab

[a] Category 1 preferred regimen. [b] Preferred for patients with *IGHV*-mutated CLL.

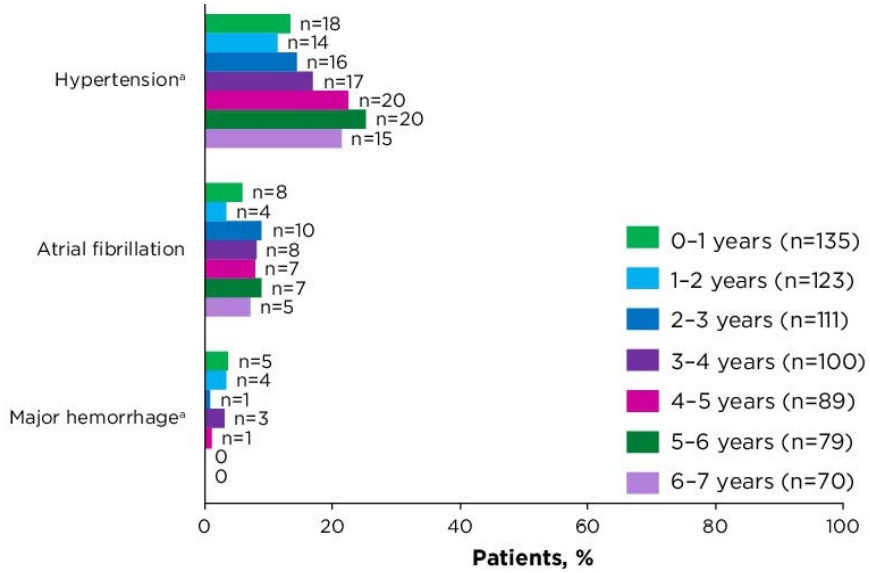
NCCN Clinical Practice Guidelines® in Oncology for Chronic Lymphocytic Leukemia V.2.2022.

Up to 7 Years of Follow-Up in the RESONATE-2 Study of Ibrutinib for Patients With TN CLL: Treatment and Summary

PFS: Ibrutinib vs Chlorambucil



AEs of Clinical Interest Over Time With Ibrutinib



Most common reason for discontinuation over 7 years was adverse event (23%); limited data available on next therapies

Ibrutinib Treatment Disposition	Ibrutinib n=136
Median (range) duration of ibrutinib treatment, years[a]	6.2 (0.06-7.2)
Continuing ibrutinib on study, n (%)	64 (47)
Discontinued ibrutinib, n (%)	
Adverse event	31 (23)
Progressive disease	16 (12)
Death	11 (8)
Withdrawal by patient	9 (7)
Investigator decision	4 (3)

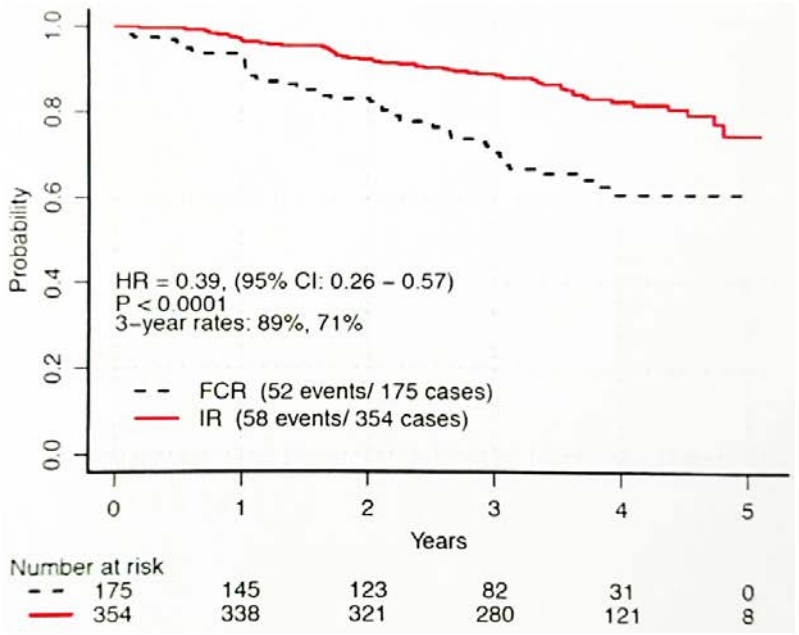
[a]74.0 months (0.7-86.8).

Barr PB, et al. ASCO 2021. Abstract 7523.

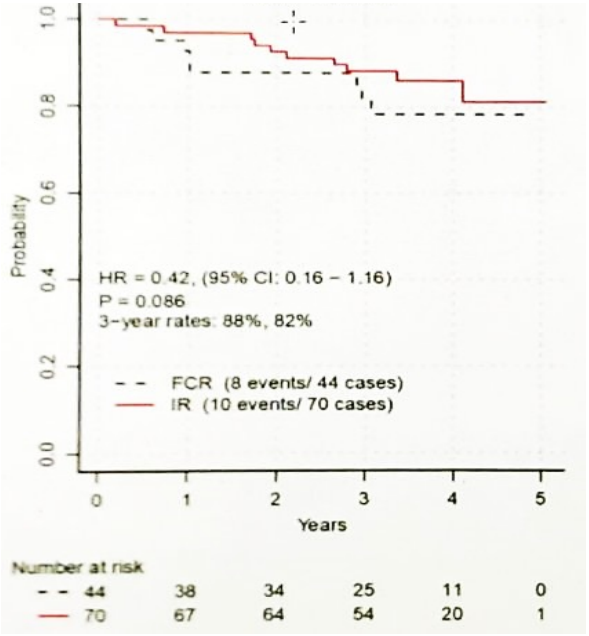
ECOG 1912: IR vs FCR in Younger Patients With TN CLL

- Phase 3 trial of 529 patients with TN CLL aged ≤70 years who received either ibrutinib + rituximab (IR, n=354) or FCR (n=175)
- With a median follow-up of 48 months, 3-year PFS was 89% vs 71% in the IR and FCR arms, respectively (*P*<0.0001)
  - In *IGHV*-mut patients, difference in PFS between the IR and FCR arms was not statistically significant
- 3-year OS was 99% vs 93% in the IR and FCR arms, respectively (*P*=0.009)

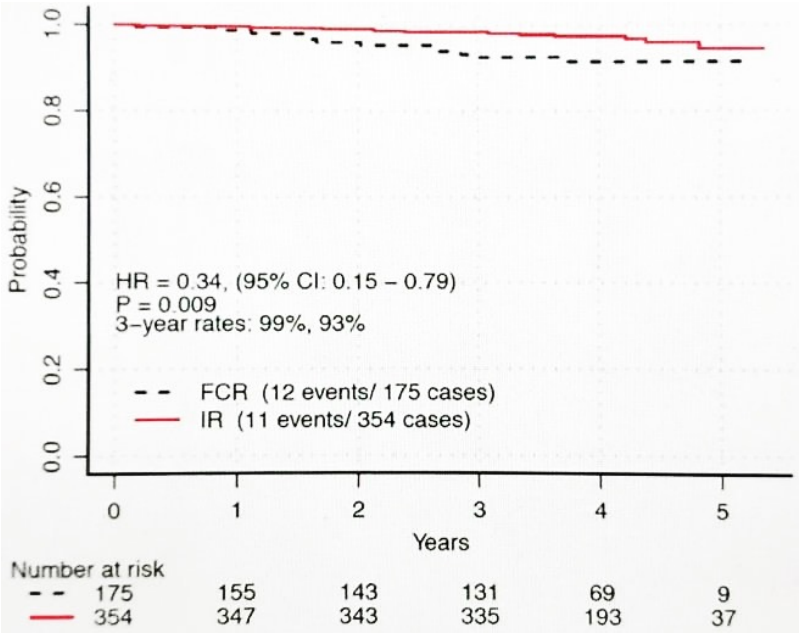
Progression-Free Survival



Progression-Free Survival, *IGHV*-mut



Overall Survival

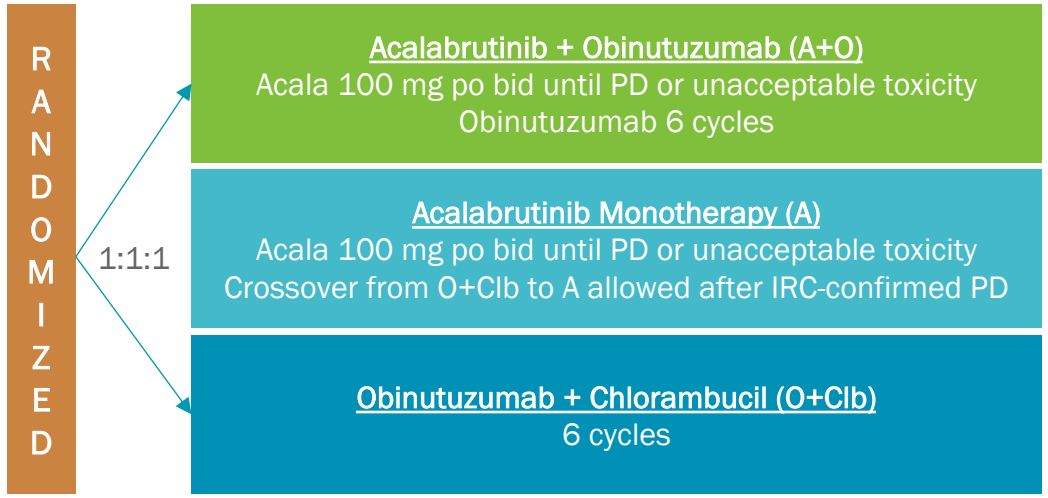


Shanafelt TD, et al. ASH 2019. Abstract 33.

4-Year Follow-Up of ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL – Study Design and Patient Characteristics

Key Eligibility Criteria

- Age ≥65 years or >18 to <65 years with comorbidities (defined as CrCl 30-69 mL/min and CIRS-G >6)
- Untreated CLL requiring treatment per iwCLL 2008 criteria
- ECOG PS ≤2
- No significant cardiovascular disease



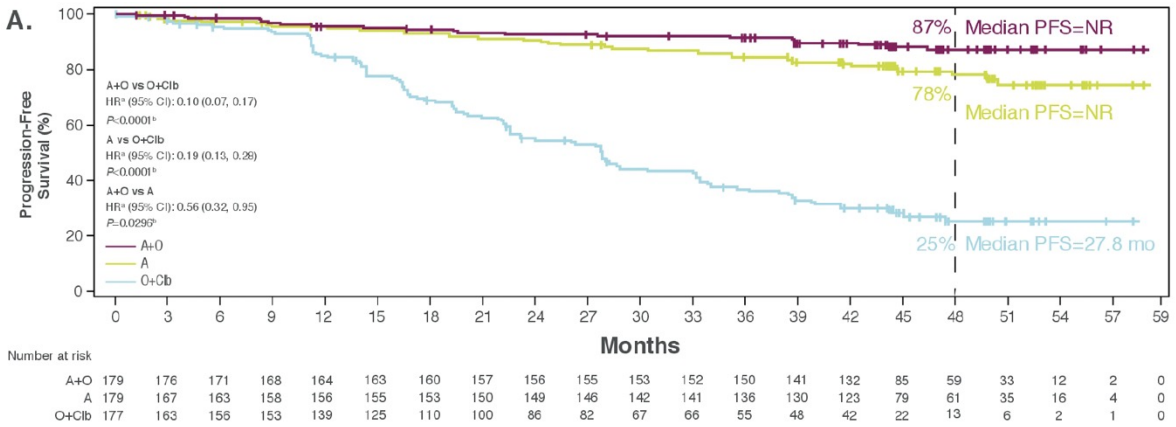
Primary endpoint: IRC-assessed PFS (A+O vs O+Clb)
Secondary endpoints: IRC-assessed PFS (A vs O+Clb), INV-assessed PFS, IRC- and INV- assessed INV- assessed ORR, TTNT, OS, uMRD, safety

Patient Characteristics		A+O (n=179)	A (n=179)	O+Clb (n=177)
Median age (range), years		70 (41-88)	70 (44-87)	71 (46-91)
ECOG PS, n (%)	0-1	169 (94.4)	165 (92.2)	167 (94.4)
	2	10 (5.6)	14 (7.8)	10 (5.6)
Bulky disease ≥5 cm, n (%)		46 (25.7)	68 (38.0)	54 (30.5)
Rai stage, n (%)	III	47 (26.3)	51 (28.5)	40 (22.6)
	IV	38 (21.2)	37 (20.7)	38 (21.5)
Cytogenetics, n (%)	del(17p)	17 (9.5)	16 (8.9)	16 (9.0)
	del(17p) and/or mut *TP53*	25 (14.0)	23 (12.8)	25 (14.1)
	del(11q)	31 (17.3)	31 (17.3)	33 (18.6)
	Complex karyotype[a]	15 (8.4)	13 (7.3)	25 (14.1)
Mutated *TP53*, n (%)		21 (11.7)	19 (10.6)	21 (11.9)
Unmutated *IGHV*, n (%)		103 (57.5)	119 (66.5)	116 (65.5)
Treatment ongoing, n (%)		134 (74.9)	124 (69.3)	0

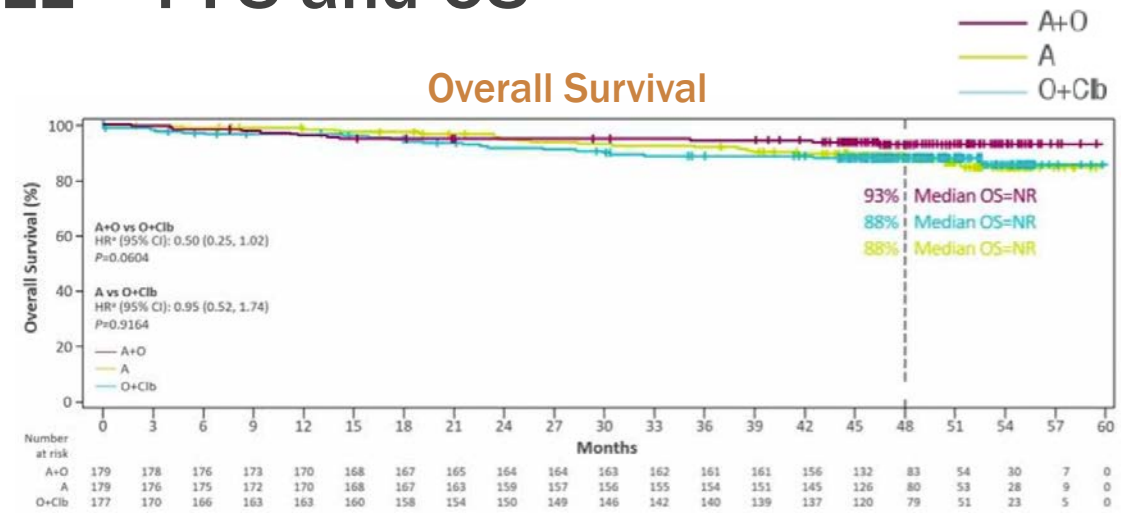
Data cutoff: September 11, 2020
[a] Patients with ≥3 chromosomal abnormalities.
Sharman JP, et al. EHA 2021. Abstract S148.

4-Year Follow-Up of ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL – PFS and OS

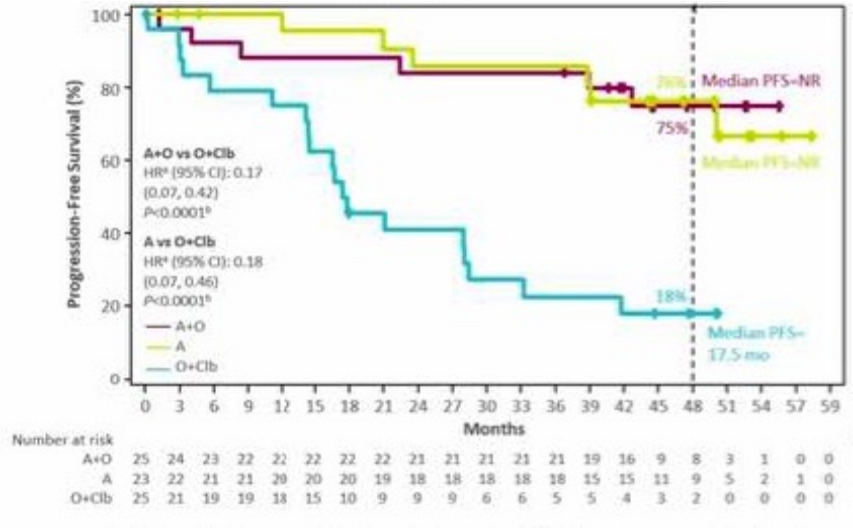
INV-Assessed PFS Overall



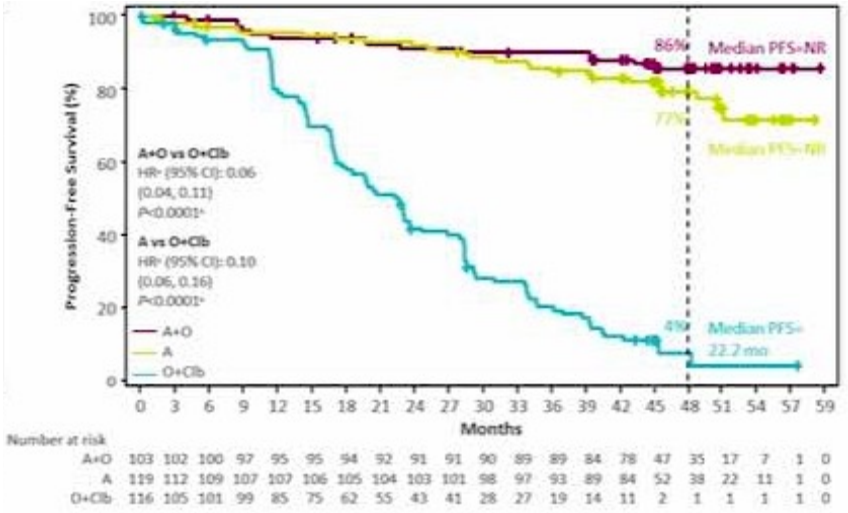
Overall Survival



INV-Assessed PFS In Del(17p) and/or Mutated *TP53*



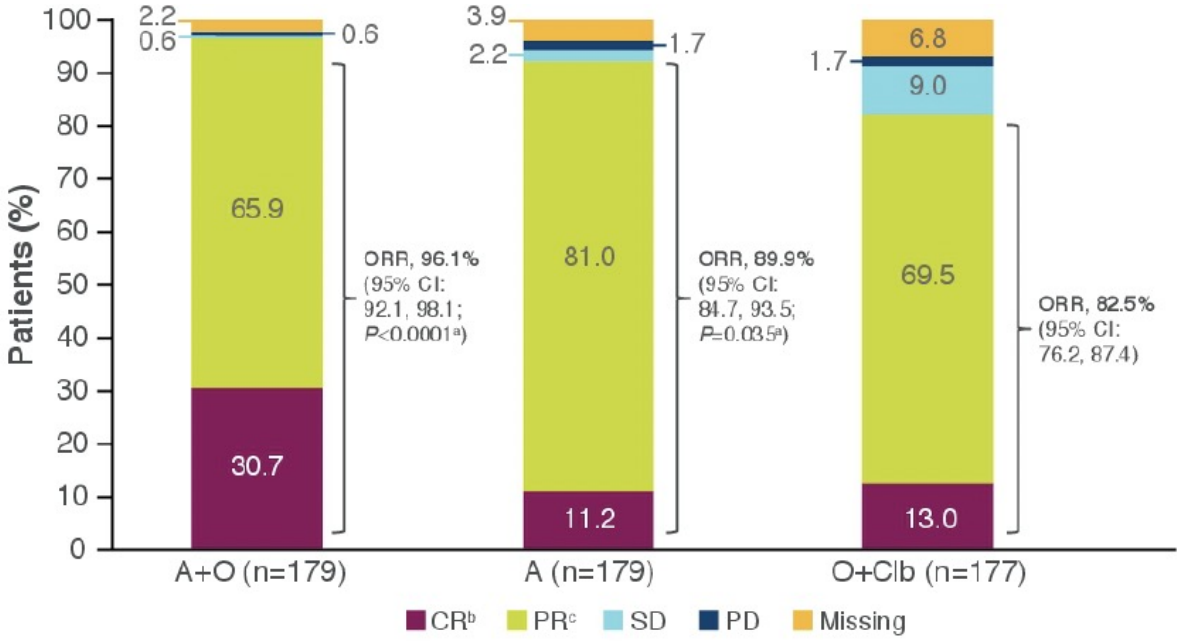
INV-Assessed PFS In Unmutated *IGHV*



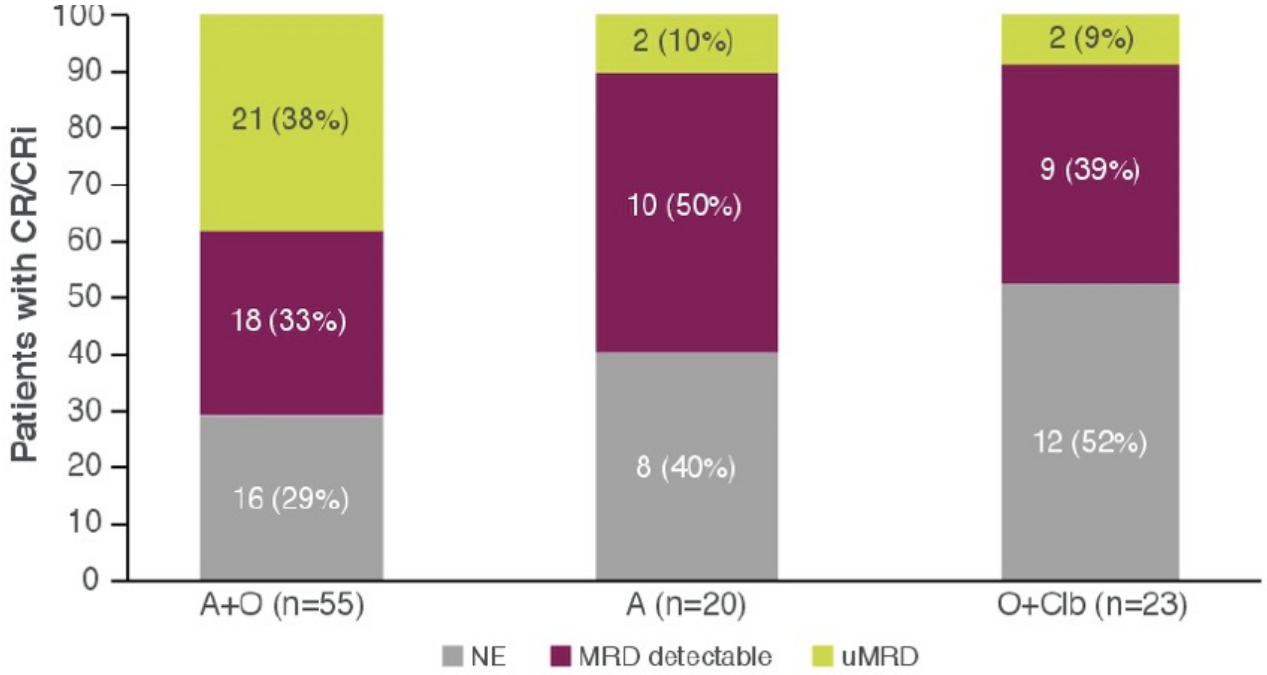
Sharman JP, et al. EHA 2021. Abstract S148.

4-Year Follow-Up of ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL – Response

INV-Assessed ORR



MRD Status in Patients With CR/CRi



Sharman JP, et al. EHA 2021. Abstract S148.

4-Year Follow-Up of ELEVATE-TN: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL – Safety

AEs of Clinical Interest, n (%)	A+O (n=178)		A (n=179)		O+Clb (n=169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	37 (20.8)	14 (7.9)	34 (19.0)	15 (8.4)	13 (7.7)	3 (1.8)
Atrial fibrillation	7 (3.9)	1 (0.6)	11 (6.1)	2 (1.1)	1 (0.6)	0
Bleeding	84 (47.2)	5 (2.8)	75 (41.9)	5 (2.8)	20 (11.8)	0
Major bleeding	7 (3.9)	5 (2.8)	7 (3.9)	5 (2.8)	2 (1.2)	0
Hypertension	14 (7.9)	6 (3.4)	13 (7.3)	5 (2.8)	7 (4.1)	6 (3.6)
Infections	134 (75.3)	42 (23.6)	132 (73.7)	29 (16.2)	75 (44.4)	14 (8.3)
Secondary primary malignancies	28 (15.7)	13 (7.3)	24 (13.4)	5 (2.8)	7 (4.1)	3 (1.8)
Excluding nonmelanoma skin	15 (8.4)	10 (5.6)	11 (6.1)	4 (2.2)	3 (1.8)	2 (1.2)

Sharman JP, et al. EHA 2021. Abstract S148.

SEQUOIA: Phase 3 Open-Label Study of Zanubrutinib vs Bendamustine + Rituximab in TN CLL/SLL – Study Design and Efficacy

Key Eligibility Criteria

- TN CLL/SLL
- Without del(17p)
- ≥65 years of age or unsuitable for FCR treatment

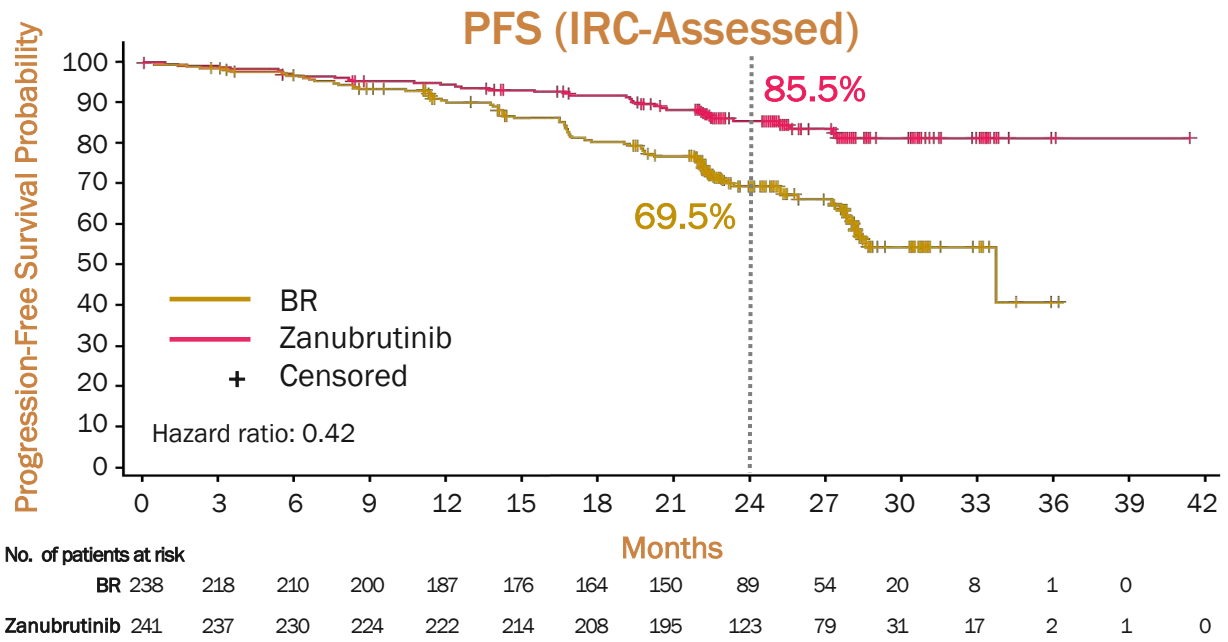
RANDOMIZE 1:1

Arm A
Zanubrutinib
160 mg po bid
n=241

Arm B
Bendamustine + rituximab[a] (BR)
n=238

Primary endpoint:
- PFS (IRC-assessed) for zanubrutinib vs BR

Secondary endpoints:
- PFS (INV-assessed)
- ORR
- OS
- Safety



Select Patient Characteristics	Zanubrutinib (n=241)	BR (n=238)
Median age, (range) y	70 (66-75)	70 (66-74)
Unmutated *IGHV*	125/234 (53.4)	121/231 (52.4)
Del(11q)	43 (17.8)	46 (19.3)

	Zanubrutinib (n=241)	BR (n=238)
IRC-assessed PFS HR (95% CI) P value	0.42 (0.27–0.63) <0.0001	
24-mo PFS, % (95% CI)	85.5 (80.1–89.6)	69.5 (62.4–75.5)
IRC-assessed ORR, % (95% CI)	94.6 (91.0–97.1)	85.3 (80.1–89.5)
CR, n (%)	16 (6.6)	36 (15.1)

[a] Bendamustine 90 mg/m^2 on day 1 and 2 and rituximab 375 mg/m^2 in cycle 1, 500 mg/m^2 in cycles 2-6 for 6 × 28-day cycles.

1. Tam CS, et al. ASH 2021. Abstract 396. 2. https://www.clinicaltrials.gov/ct2/show/NCT03336333.

ELEVATE-RR: Phase 3 Study of Acalabrutinib vs Ibrutinib in Patients With R/R CLL – Study Design and Results

Key Eligibility Criteria

- Previously treated CLL
- Presence of del(17p) and/or del(11q)
- ECOG PS ≤2
- No significant CV disease, no concomitant treatment with warfarin or equivalent VKA
- No prior treatment with ibrutinib, a BCRi, or a BCL-2i

RANDOMIZED 1:1

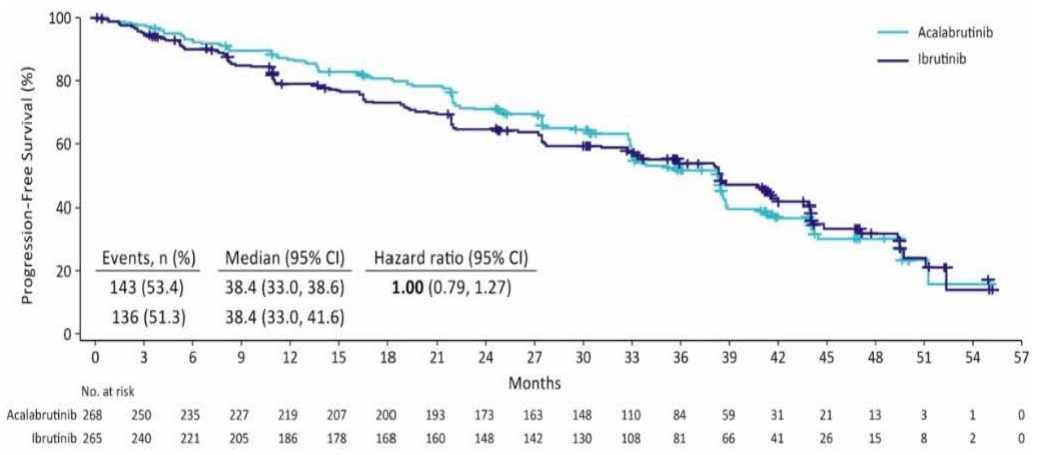
Acalabrutinib
100 mg po bid until PD or unacceptable toxicity

Ibrutinib
420 mg po qd until PD or unacceptable toxicity

Primary Endpoint Noninferiority on IRC-assessed PFS

Secondary Endpoints Incidence of any-grade atrial fibrillation/flutter, incidence of grade ≥3 infection, incidence of RT, OS

Primary Endpoint: Noninferiority on IRC-Assessed PFS



Patient Characteristics		Acala (n=268)	Ibr (n=265)
Median age, years (range)		66 (41-89)	65 (28-88)
ECOG PS 0-1, n (%)		247 (92)	243 (92)
Bulky disease ≥5 cm, n (%)		128 (48)	136 (51)
Rai stage 3 or 4, n (%)		131 (49)	134 (51)
Cytogenetics, n (%)	del(17p)	121 (45)	120 (45)
	del(11q)	167 (62)	175 (66)
	Complex karyotype[a]	124 (46)	125 (47)
	TP53 mutated	100 (37)	112 (42)
	IGHV unmutated	220 (82)	237 (89)
Prior therapies, n (%)	Median (range)	2 (1-9)	2 (1-12)
	1-3	234 (87)	237 (89)
	≥4	33 (12)	28 (11)

[a] Patients with ≥3 chromosomal abnormalities.

Hillmen P, et al. EHA 2021. Abstract S145. Seymour JF, et al. ASH 2021. Abstract 3721.

ELEVATE-RR: Phase 3 Study of Acalabrutinib vs Ibrutinib in Patients With R/R CLL – Post Hoc Safety Analysis

AEs	Incidence, %				Exposure-Adjusted Incidence[a]				Exposure-Adjusted Time With Event[b]			
	Any Grade		Grade ≥3		Any Grade		Grade ≥3		Any Grade		Grade ≥3	
	Acala[c]	Ibr[d]	Acala[c]	Ibr[d]	Acala[c]	Ibr[d]	Acala[c]	Ibr[d]	Acala[c]	Ibr[d]	Acala[c]	Ibr[d]
Events of clinical interest												
Cardiac events	24%	30%	9%	10%	1.2	1.9	0.4	0.5	7.1	13.0	0.4	0.2
Atrial fibrillation/flutter	9%	16%*	5%	4%	0.4	0.7	0.2	0.1	1.3	3.8	0.3	0.1
Hypertension[e]	9%	23%*	4%	9%*	0.4	1.2	0.1	0.4	4.1	15.0	1.6	4.0
Bleeding events[f]	38%	51%*	4%	5%	2.4	3.8	0.1	0.2	13.7	24.6	0.1	0.1
Major bleeding events[g]	5%[h]	5%[i]	4%	5%	0.2	0.2	0.1	0.2	0.1	0.3	0.1	0.1
Infections[j]	78%	81%	31%	30%	8.9	10.4	1.6	2.0	14.6	15.6	1.5	1.1
Selected common AEs[k]												
Diarrhea	35%	46%*	1%	5%*	1.9	2.8	<0.1	0.2	6.7	9.6	<0.1	0.1
Headache	35%*	20%	2%*	0	1.8	1.1	<0.1	0	7.8	5.4	<0.1	0
Cough	29%*	21%	1%	<1%	1.3	1.1	<0.1	<0.1	5.6	4.9	<0.1	<0.1
Fatigue	20%	17%	3%*	0	0.9	0.9	0.1	0	7.4	7.0	0.6	0
Arthralgia	16%	23%*	0	1%	0.6	1.3	0	<0.1	7.5	10.4	0	<0.1
Back pain	8%	13%*	0	1%	0.3	0.5	0	<0.1	1.9	3.2	0	0.1
Muscle spasms	6%	13%*	0	1%	0.2	0.7	0	<0.1	0.8	10.0	0	0.1
Dyspepsia	4%	12%*	0	0	0.1	0.5	0	0	1.0	2.4	0	0

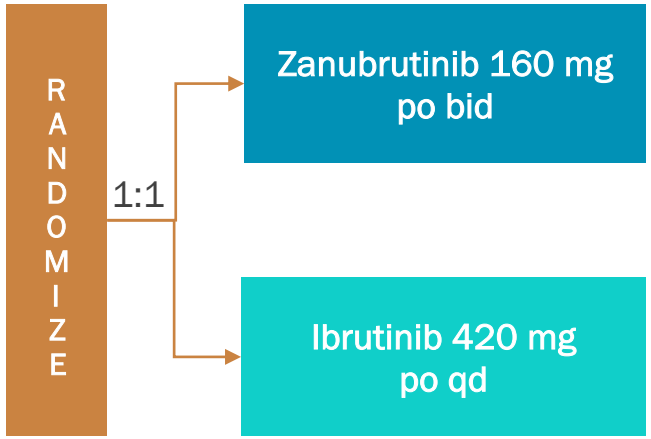
- **Median follow-up** 40.9 months
- **Treatment ongoing** 46% (Acala) and 41% (Ibr)
- **Most common reasons for discontinuation** PD (31% Acala vs 26% Ibr), AEs (15% Acala vs 22% Ibr)
- **Median (range) treatment exposure** 38.3 months (0.3-55.9) Acala vs 35.5 (0.2-57.7) Ibr

≥5% incidence difference between arms are highlighted; **green** favors acalabrutinib, **red** favors ibrutinib.
* Two-sided *P* value <0.05 without multiplicity adjustment, for comparison of incidence based on Barnard's exact test.
[a] Reported as events per 100 person-months. [b] Reported as months with event per 100 person-months. [c] n=266. [d] n=263. [e] Includes hypertension, blood pressure increased, and blood pressure systolic increased. [f] Bleeding events occurring in ≥10% of patients in either treatment arm include contusion and epistaxis. [g] Any hemorrhagic event that was serious, grade ≥3, or a CNS hemorrhage (any grade). [h] Of 12 patients with major hemorrhage events in the Acala arm, CNS-related hemorrhage events were reported in 4 patients. [i] Of 14 patients with major hemorrhage events in the Ibru arm, CNS-related hemorrhage events were reported in 1 patient who had 2 events. [j] Infections occurring in ≥10% of patients in either treatment arm include upper respiratory tract infection, pneumonia, bronchitis, nasopharyngitis, and urinary tract infection. [k] AEs occurring in ≥10% of patients in either treatment arm that are not already captured in the ECIs presented.
Seymour JF, et al. ASH 2021. Abstract 3721.

ALPINE: Phase 3 Study of Zanubrutinib vs Ibrutinib in Patients With R/R CLL/SLL – Study Design and Results

Key Eligibility Criteria

- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI
- No current or past RT, prior BTKi therapy, or warfarin/other VKA



Primary endpoint:

- ORR (CR+PR) noninferiority and INV-assessed superiority

Secondary endpoints:

- Any-grade atrial fibrillation
- DOR
- PFS
- OS
- Time to treatment failure
- PR-L or higher
- PROs
- Safety

Data cutoff ~12 months after randomization of 415 patients

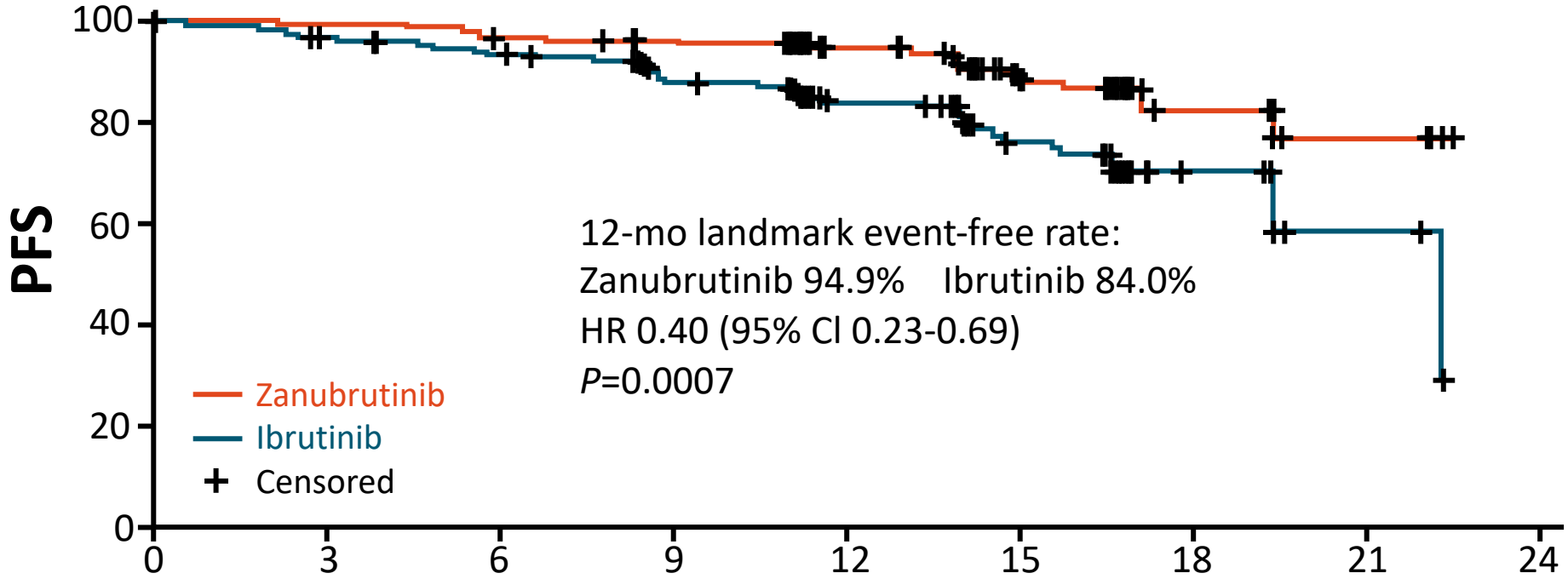
Select Patient Characteristics	Zanubrutinib (n=207)	Ibrutinib (n=208)
Median age (range), y	67 (35-90)	67 (36-89)
Del(17p) and/or mut *TP53*	41 (19.8)[a]	38 (18.3)
Del(11q)	61 (29.5)	55 (26.4)

Efficacy, n (%)	Zanubrutinib (n=207)	Ibrutinib (n=208)
ORR (CR+PR), 95% CI	162 (78.3), 72.0-83.7	130 (62.5), 55.5-69.1
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
PR	157 (75.8)	127 (61.1)
ORR (CR+PR+PR-L)	183 (88.4)	169 (81.3)
PR-L	21 (10.1)	39 (18.8)
SD	17 (8.2)	28 (13.5)
PD	1 (0.5)	2 (1.0)

AEs of Special Interest[b] n (%)	Zanubrutinib (n=204)		Ibrutinib (n=207)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders[c]	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation/flutter	5 (2.5)	2 (1.0)	21 (10.1)	4 (1.9)
Hemorrhage	73 (35.8)	6 (2.9)	75 (36.2)	6 (2.9)
Major hemorrhage[d]	6 (2.9)	6 (2.9)	8 (3.9)	6 (2.9)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia[e]	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[e]	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies	17 (8.3)	10 (4.9)	13 (6.3)	4 (1.9)
Skin cancer	7 (3.4)	3 (1.5)	10 (4.8)	2 (1.0)

[a] 2 patients with missing values. [b] In safety analysis population. [c] Cardiac disorders leading to treatment discontinuation: 0 patients (zanubrutinib) vs 7 (3.4%) patients (ibrutinib). [d] Includes hemorrhages that were serious or grade ≥3 or CNS hemorrhages of all grades.
[e] Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.
Hillmen P, et al. EHA 2021. Abstract LB1900.

ALPINE: PFS



Patients at Risk, n

Zanubrutinib	207	200	194	190	152	70	19	5	0
Ibrutinib	208	196	188	170	125	57	8	3	0

- Guidelines include zanubrutinib as an option in patients with relapsed/refractory CLL/SLL or frontline CLL with *TP53* mutation and an intolerance or contraindication to other BTKis

Hillmen. EHA 2021. Abstr 1900.

CLL14: 4-Year Follow-Up of Phase 3 Study of Venetoclax + Obinutuzumab vs Chlorambucil + Obinutuzumab – Study Design and Efficacy

Key Eligibility Criteria

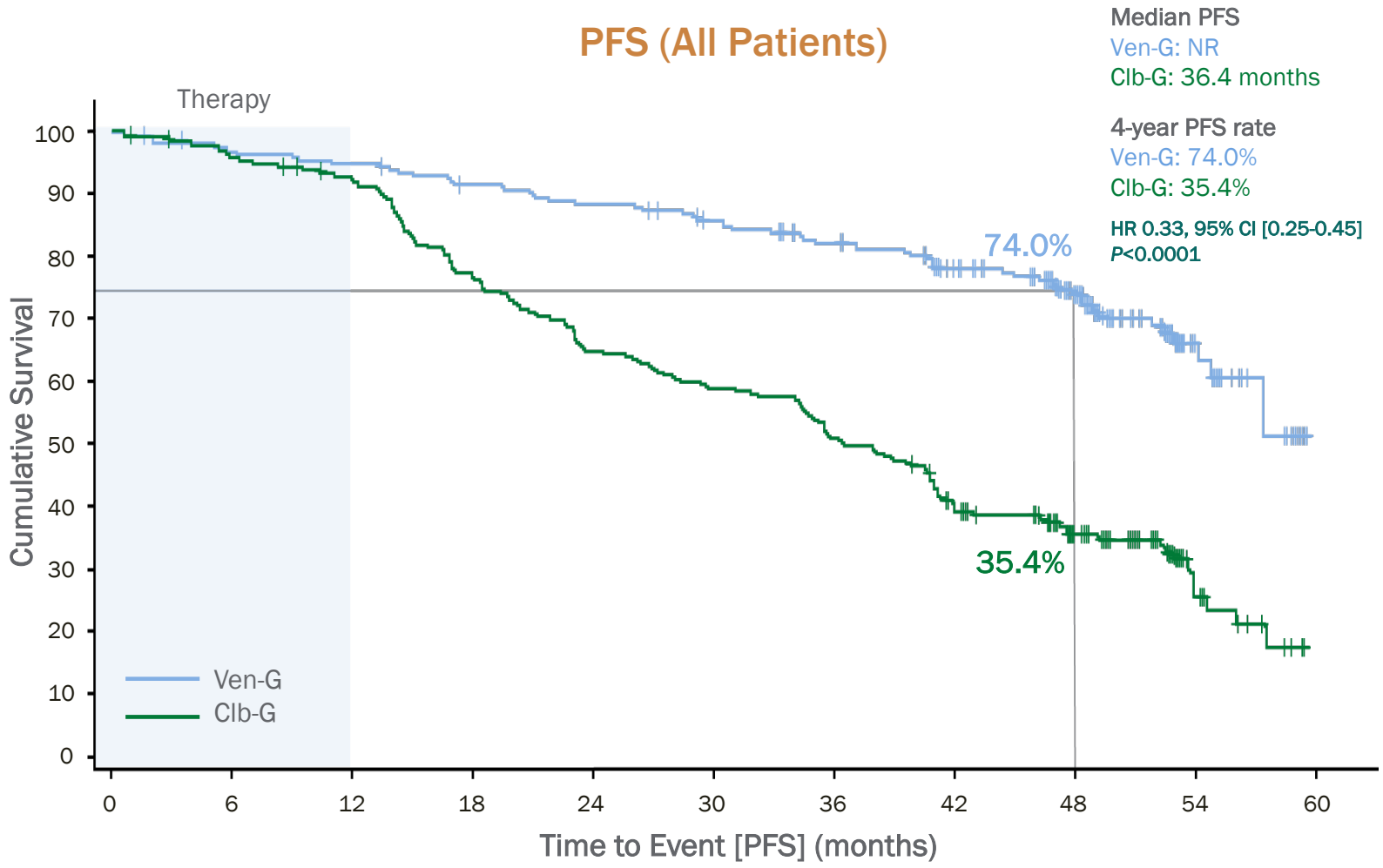
- Patients with TN CLL and coexisting medical conditions
- CIRS >6 and/or CrCl <70 mL/min

RANDOMIZE → 1:1

- **Venetoclax-Obinutuzumab (Ven-G)** (6 cycles) followed by venetoclax (6 cycles)
- **Chlorambucil-Obinutuzumab (Clb-G)** (6 cycles) followed by chlorambucil (6 cycles)

Primary endpoint:
- PFS

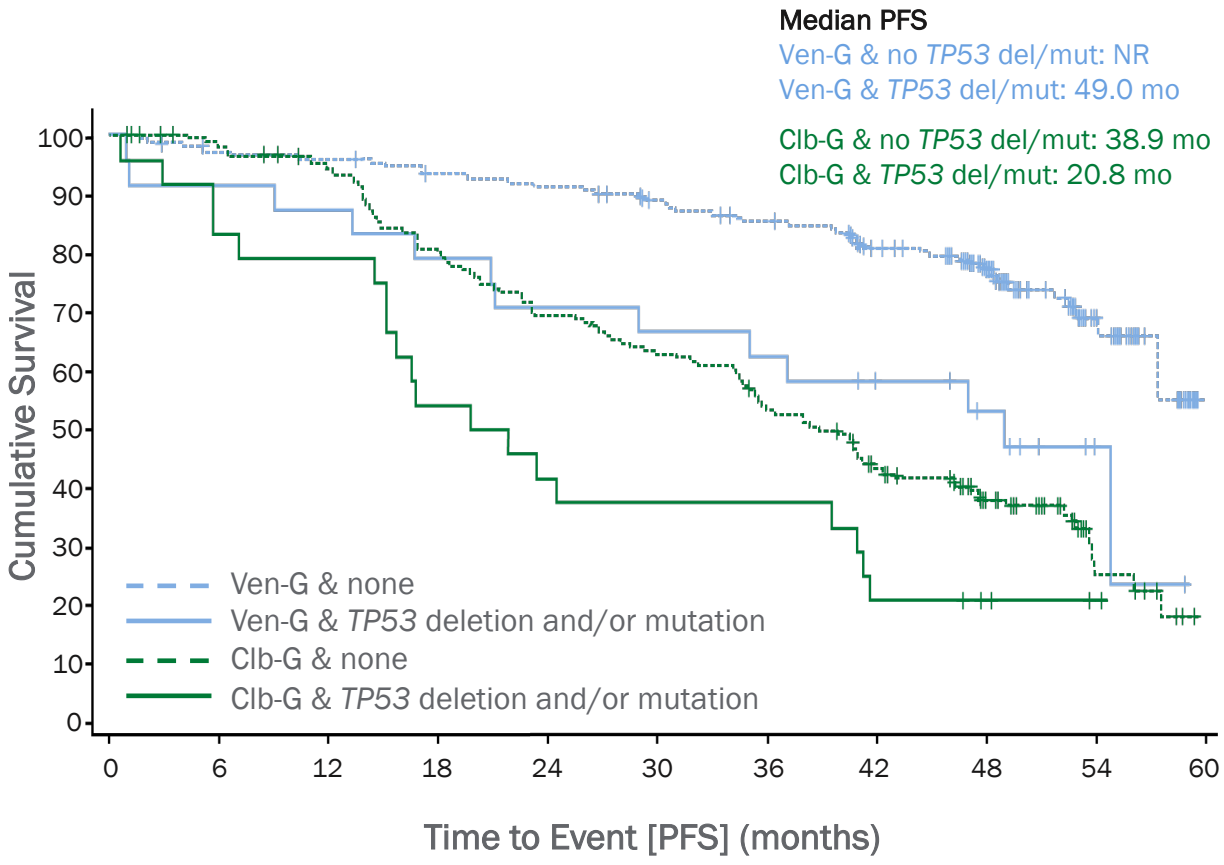
Secondary endpoints:
- Response
- MRD
- OS



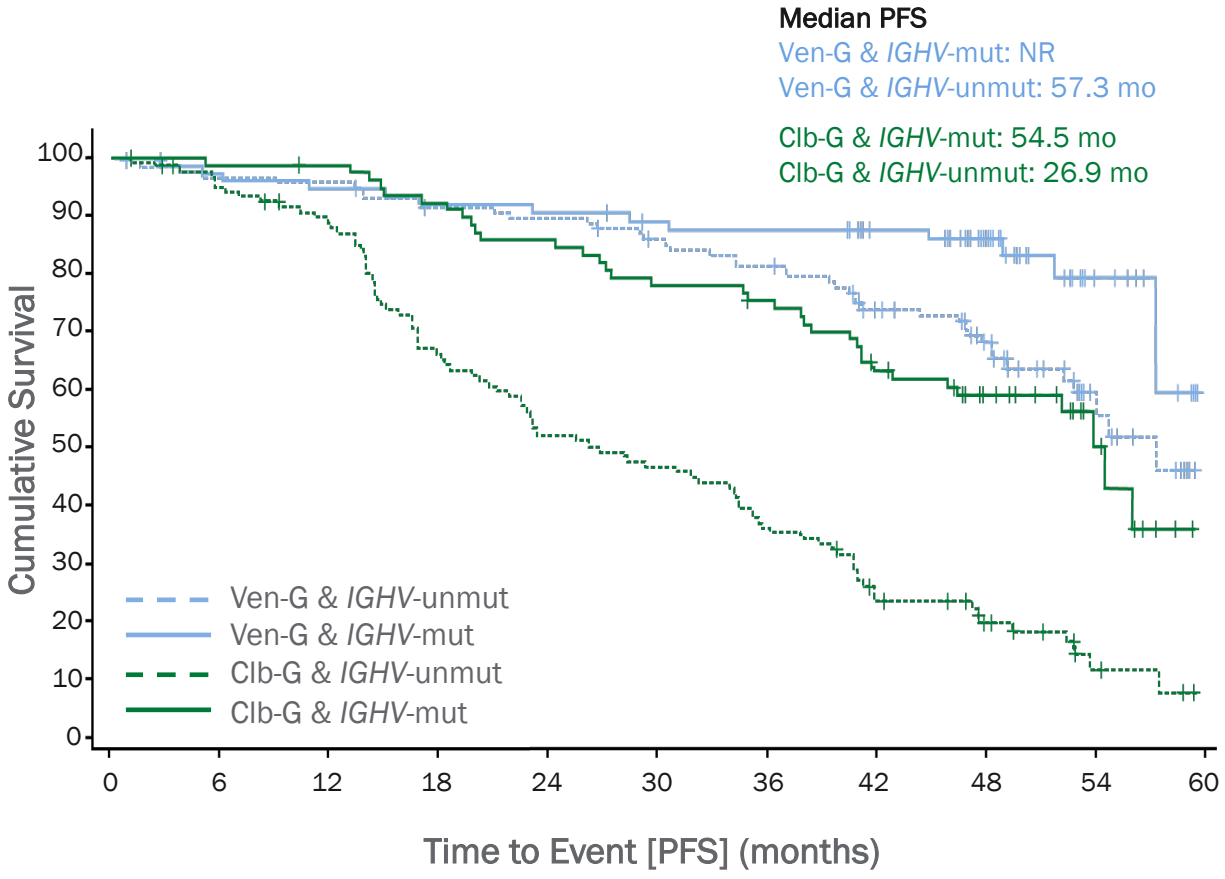
Al-Sawaf O, et al. EHA 2021. Abstract S146.

CLL14: 4-Year Follow-Up of Phase 3 Study of Venetoclax + Obinutuzumab vs Chlorambucil + Obinutuzumab – PFS by Mutational Status

PFS by *TP53* Status



PFS by *IGHV* Status



Al-Sawaf O, et al. EHA 2021. Abstract S146.

CLL14: 4-Year Follow-Up of Phase 3 Study of Venetoclax + Obinutuzumab vs Chlorambucil + Obinutuzumab – Safety

Most Frequent Grade ≥3 AEs,%	Ven-G (n=212)		Clb-G (n=214)	
	During treatment	After treatment	During treatment	After treatment
Neutropenia	51.9	4.0	47.2	1.9
Thrombocytopenia	13.7	0.5	15.0	0.0
Anemia	7.5	1.5	6.1	0.5
Febrile neutropenia	4.2	1.0	3.3	0.5
Leukopenia	2.4	0.0	4.7	0.0
Pneumonia	3.3	3.0	2.8	1.4
Infusion-related reaction	9.0	0.0	9.8	0.5
Tumor lysis syndrome	1.4	0.0	3.3	0.0

Secondary Primary Malignancies (SPM)	Ven-G (n=212)	Clb-G (n=214)
Overall total number of events, n	47	42
Number of pts with ≥1 SPM, n (%)	40 (18.9)	30 (14.0)
Non-melanoma skin cancer	19 (8.9)	18 (8.4)
Melanoma	8 (3.7)	3 (1.4)
Prostate cancer	4 (1.8)	3 (1.4)
Colon cancer	2 (0.9)	2 (0.9)
Lung cancer	2 (0.9)	2 (0.9)
Bladder cancer	2 (0.9)	0
Breast cancer	2 (0.9)	0
Hepatocellular carcinoma	0	1 (0.5)
Pancreatic cancer	0	1 (0.5)
Hematologic cancer	3 (1.4)	1
Other	2 (0.5)	3 (1.4)

Al-Sawaf O, et al. EHA 2021. Abstract S146.

GLOW: Phase 3 Study of Fixed-Duration Ibrutinib + Venetoclax vs Chlorambucil + Obinutuzumab in TN CLL – Study Design and Results

Key Eligibility Criteria

- Previously untreated CLL
- ≥65 years of age or <65 years with CIRS >6 or CrCl <70 mL/min
- No del(17p) or known *TP53* mutation
- ECOG PS ≤2

RANDOMIZE 1:1

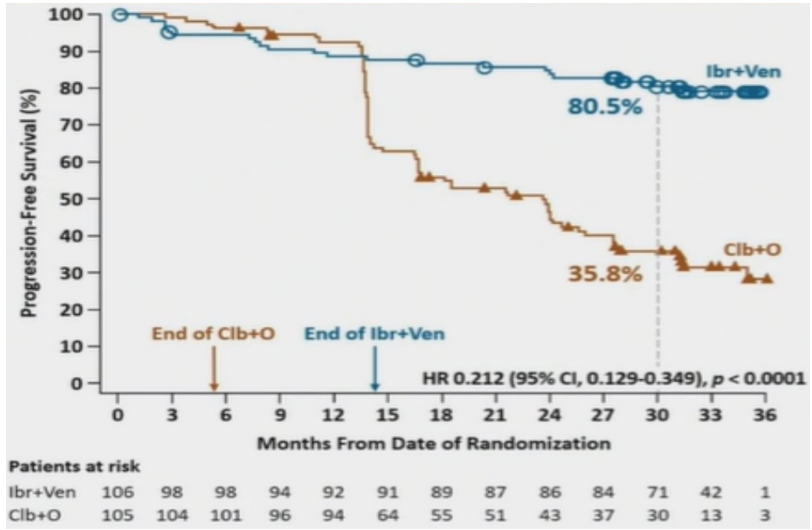
- Ibrutinib 420 mg po qd lead-in (3 cycles) followed by Ibrutinib + Venetoclax (I+V) (12 cycles; venetoclax ramp-up 20-400 mg over 5 weeks beginning C4) n=106
- Chlorambucil (Clb) 0.5 mg/kg on D1 & D15 x 6 cycles + Obinutuzumab (O) 1000 mg D1-2, D8, D15 of C1, and D1 of C2-6 n=105

Primary endpoint: IRC-assessed PFS

Current MRD analysis

- MRD reported with cutoffs of $<10^{-4}$ and $<10^{-5}$
- PB/BM concordance calculated for patients with uMRD in PB at EOT+3 who had paired BM sample
- PFS results updated with 34.1 months of follow-up

PFS at 34.1 Months of Follow-Up[1]



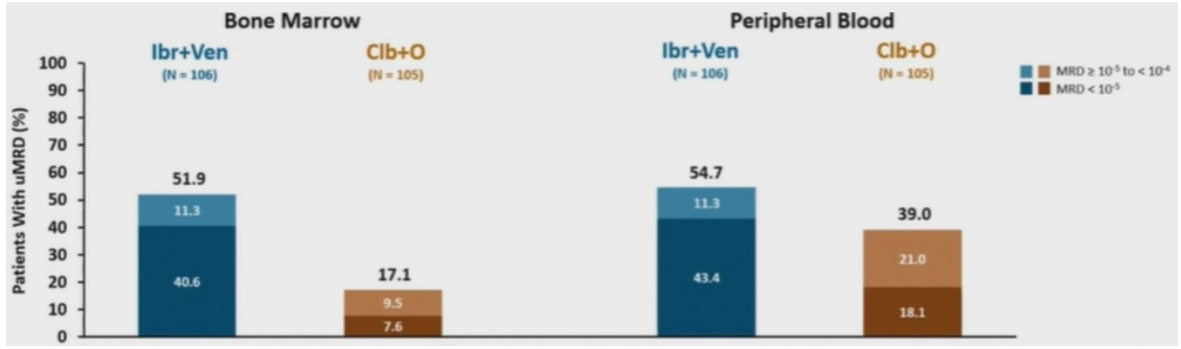
Safety (Median Follow-Up of 27.7 Months)[2]	I+V (N=106)	Clb+O (N=105)
Median exposure, mo (range)	13.8 (0.7-19.5)	5.1 (1.8-7.9)
Grade 3 or Higher AEs in ≥5% of Patients, %	75.5	69.5
Neutropenia[a]	34.9	49.5
Infections[b]	17.0	11.4
Thrombocytopenia	5.7	20.0
Diarrhea	10.4	1.0
Hypertension	7.5	1.9
Atrial fibrillation	6.6	0
Hyponatremia	5.7	0
TLS	0	5.7

[a] Includes neutrophil count decreased; grade ≥3 febrile neutropenia: 1.9% for I+V vs 2.9% for Clb+O. [b] Includes multiple preferred terms.

1. Munir T, et al. ASH 2021. Abstract 70. 2. Kater A, et al. EHA 2021.Abstract LB1902.

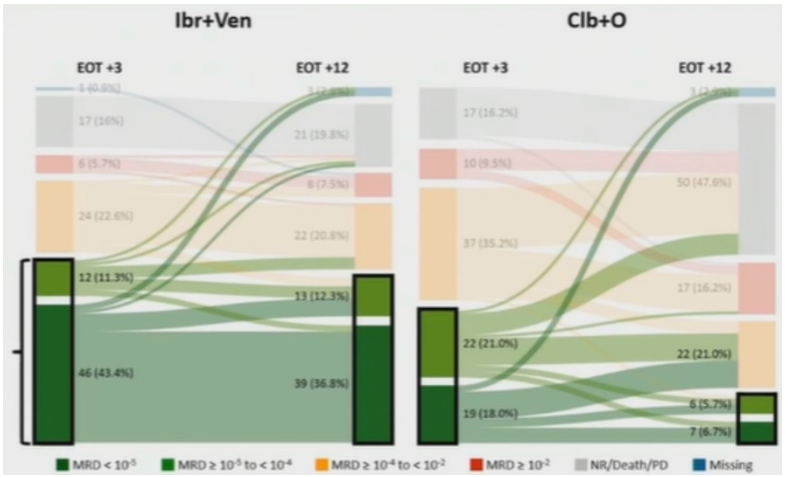
GLOW: Phase 3 Study of Fixed-Duration Ibrutinib + Venetoclax vs Chlorambucil + Obinutuzumab in TN CLL – MRD Response

MRD at EOT+3



- In the Ibr+Ven arm, most patients with uMRD $<10^{-4}$ had deep responses of uMRD $<10^{-5}$

uMRD in PB from EOT+3 to EOT+12



uMRD concordance in PB/BM, %	Ibr + Ven	Clb + O
At $<10^{-4}$	92.9	43.6
At $<10^{-5}$	90.9	36.8

Patients with sustained uMRD, %	Ibr+Ven	Clb+O
uMRD $<10^{-4}$	84.5	29.3
uMRD $<10^{-5}$	80.4	26.3

uMRD in patients with unmutated *IGHV* CLL

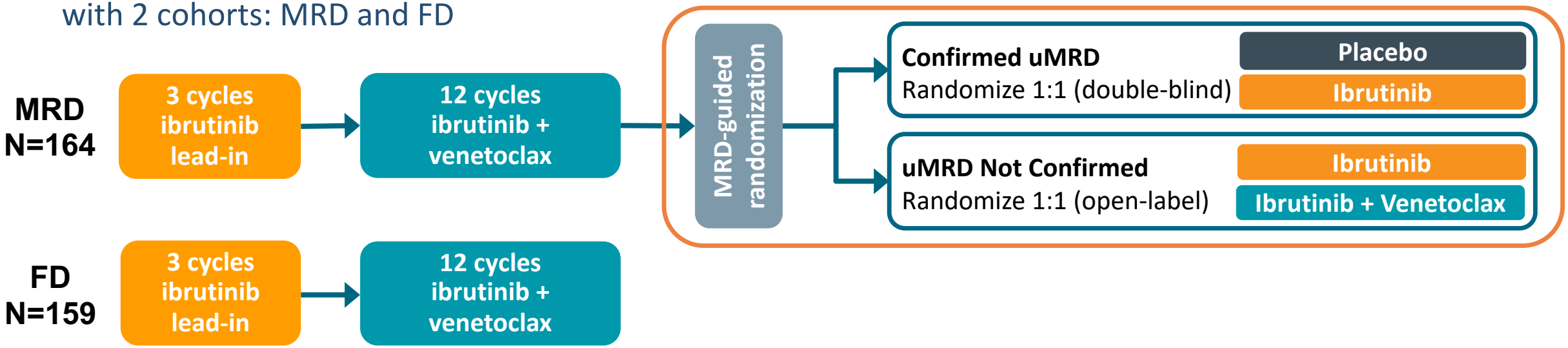
- With Ibr+Ven, depth of MRD response was similar in BM and PB for patients with unmutated *IGHV* CLL
- Among patients with mutated *TP53*, 5 of 7 achieved uMRD $<10^{-5}$ in both BM and PB with Ibr+Ven

- uMRD $<10^{-4}$ rate decreased 6% with Ibr+Ven vs 27% with Clb+O
- Patients with detectable MRD $\geq 10^{-4}$ in the Ibr+Ven arm were less likely to convert to PD vs those in the Clb+O arm or have worsening of detectable MRD levels

Munir T, et al. ASH 2021. Abstract 70.

Phase 2 CAPTIVATE Study

- CAPTIVATE (PCYC-1142) is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax with 2 cohorts: MRD and FD

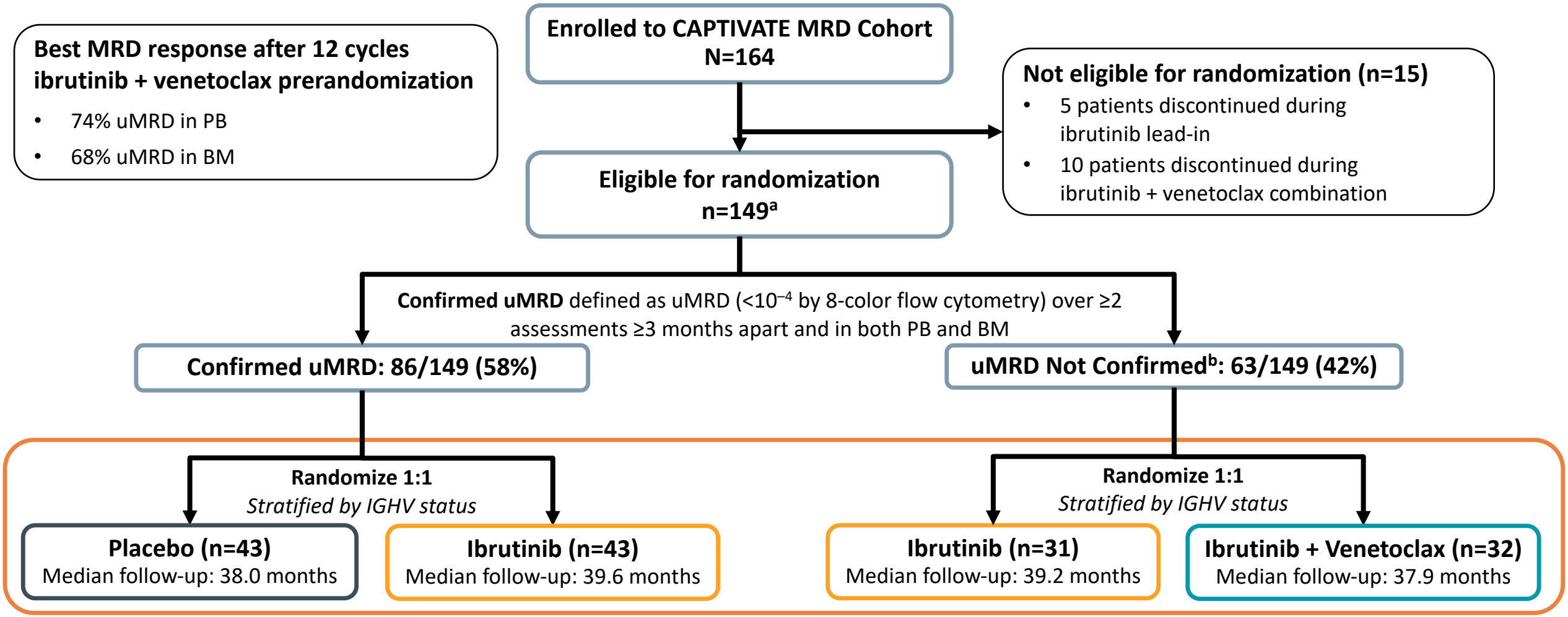


- Primary analyses of both cohorts have been previously reported[1,2]
- Presented are updated results from the MRD cohort, with median time on study: 38.2 months (range, 15.0–47.9)
  - Median postrandomization follow-up: 24.0 months (range, 5.8–33.1)

MRD, minimal residual disease; FD, fixed-duration.

1. Wierda WG et al. ASH 2020. Abstract #123. 2. Ghia P et al. ASCO 2021. Abstract #7501.

MRD Cohort: Patient Disposition and Randomization (cont.)



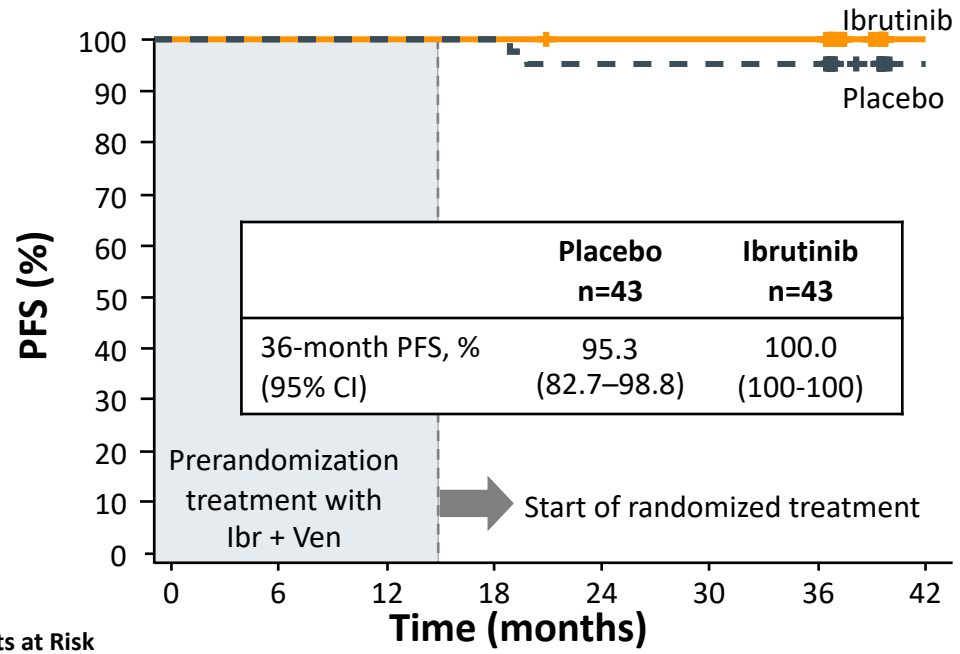
BM, bone marrow; PB, peripheral blood.

[a]Includes 1 patient who discontinued venetoclax but completed planned treatment with ibrutinib. [b]Did not meet criteria for uMRD because of detectable MRD in PB and/or BM *or* undetectable MRD in PB that was not confirmed at consecutive assessments.

ASH 2021, CAPTIVATE-MRD; Ghia et al.

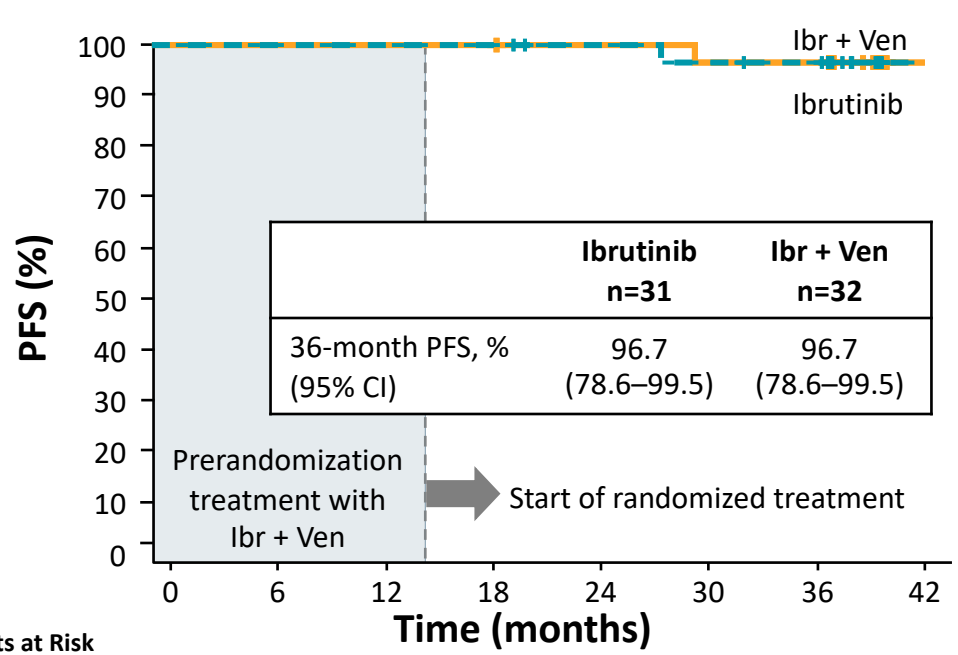
3-Year PFS Rates Were ≥95% Across All Randomized Arms

Confirmed uMRD



Patients at Risk								
Ibr + Ven → Ibr	43	43	43	43	42	42	42	5
Ibr + Ven → Plb	43	43	43	43	41	41	41	4

uMRD Not Confirmed



Patients at Risk								
Ibr + Ven → Ibr + Ven	32	32	32	32	30	29	28	2
Ibr + Ven → Ibr	31	31	31	31	30	29	29	1

Median follow-up = 38 months

- With an additional year of follow-up since the primary analysis, only 1 new PFS event occurred on study; a patient in the uMRD Not Confirmed ibrutinib arm who had PD after 42 months
- 36-month OS was 99% overall (97%–100% across randomized treatment arms)

PFS, progression-free survival; Plb, placebo. Tick marks indicate patients with censored data.

ASH 2021, CAPTIVATE-MRD; Ghia et al.

MODULE 2: Relapsed/Refractory (R/R) CLL: Novel Investigational Strategies – Dr Smith

RTP
RESEARCH
TO PRACTICE

A 71-year-old man with CLL who received pirtobrutinib in combination with venetoclax/rituximab on a clinical trial

Dr Shaachi Gupta (Lake Worth, Florida)

RTP
RESEARCH
TO PRACTICE

Use of monoclonal antibody therapy for COVID-19 prevention and treatment

Dr Vignesh Narayanan (Lone Tree, Colorado)

RTP
RESEARCH
TO PRACTICE

Relapsed/Refractory (R/R) CLL; Novel Investigational Strategies

RTP Symposium

ASCO 2022

Mitchell R. Smith

NCCN CLL/SLL Guidelines: *Relapsed/Refractory Regimens*

R/R without del(17p)/*TP53* mutation

	Preferred	Other recommended regimens
Frail w/significant comorbidities OR ≥65 y and younger pts w/significant comorbidities	• **Acalabrutinib (category 1)** • **Ibrutinib (category 1)** • Venetoclax + rituximab (category 1) • Duvelisib • Idelalisib + rituximab	• Alemtuzumab ± rituximab • Chlorambucil + rituximab • Reduced-dose FCR • HDMP + rituximab • Idelalisib • Lenalidomide ± rituximab • Obinutuzumab • Ofatumumab • Reduced-dose PCR • Venetoclax • Zanubrutinib (for patients with intolerance or contraindication to other BTKi) • Dose-dense rituximab • Bendamustine, rituximab ± **ibrutinib**, or idelalisib
< 65 y without significant comorbidities	• **Acalabrutinib (category 1)** • **Ibrutinib (category 1)** • Venetoclax + rituximab (category 1) • Duvelisib • Idelalisib + rituximab	• Alemtuzumab ± rituximab • Bendamustine + rituximab • FC + ofatumumab • FCR • HDMP + rituximab • Idelalisib • Lenalidomide ± rituximab • Obinutuzumab • Ofatumumab • PCR • Venetoclax • Zanubrutinib (for patients with intolerance or contraindication to other BTKi) • Bendamustine, rituximab + **ibrutinib**

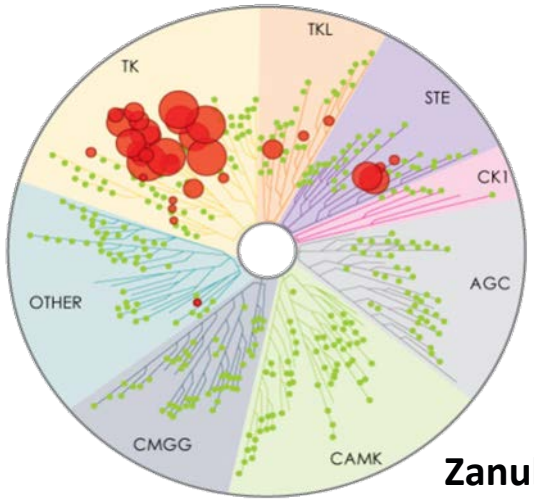
R/R with del(17p)/*TP53* mutation

Preferred	Other recommended regimens
• **Acalabrutinib (category 1)** • **Ibrutinib (category 1)** • Venetoclax + rituximab (category 1) • Duvelisib • Idelalisib + rituximab • Venetoclax	• Alemtuzumab ± rituximab • HDMP + rituximab • Idelalisib • Lenalidomide ± rituximab • Ofatumumab • **Zanubrutinib** (for patients with intolerance or contraindication to other BTKi)

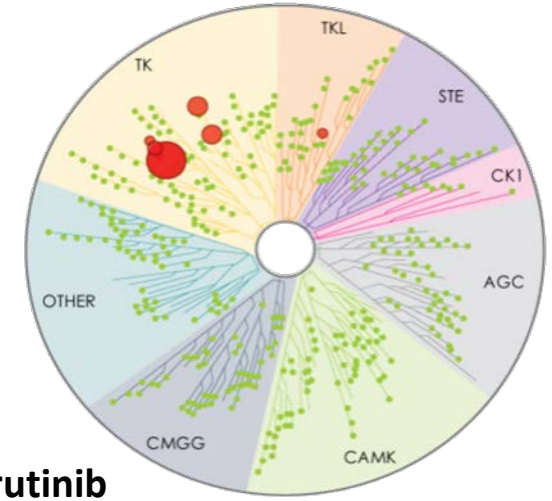
NCCN Clinical Practice Guidelines. CLL/SLL. Version 4.2021.

Kinomes of BTK Inhibitors

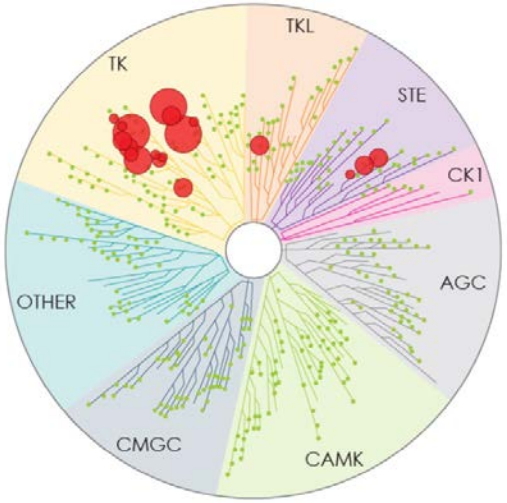
Ibrutinib



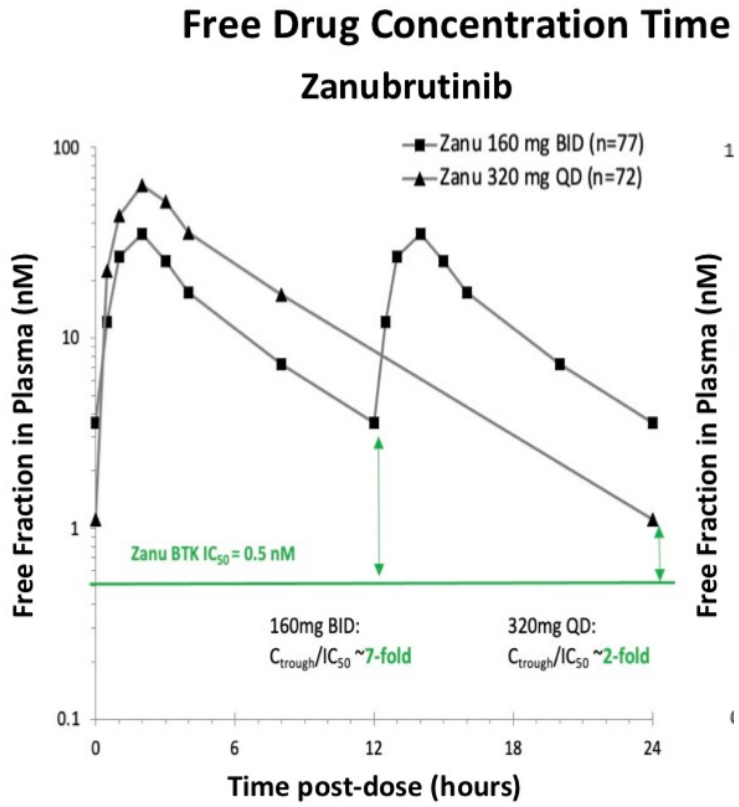
Acalabrutinib



Zanubrutinib



BID vs QD Dosing



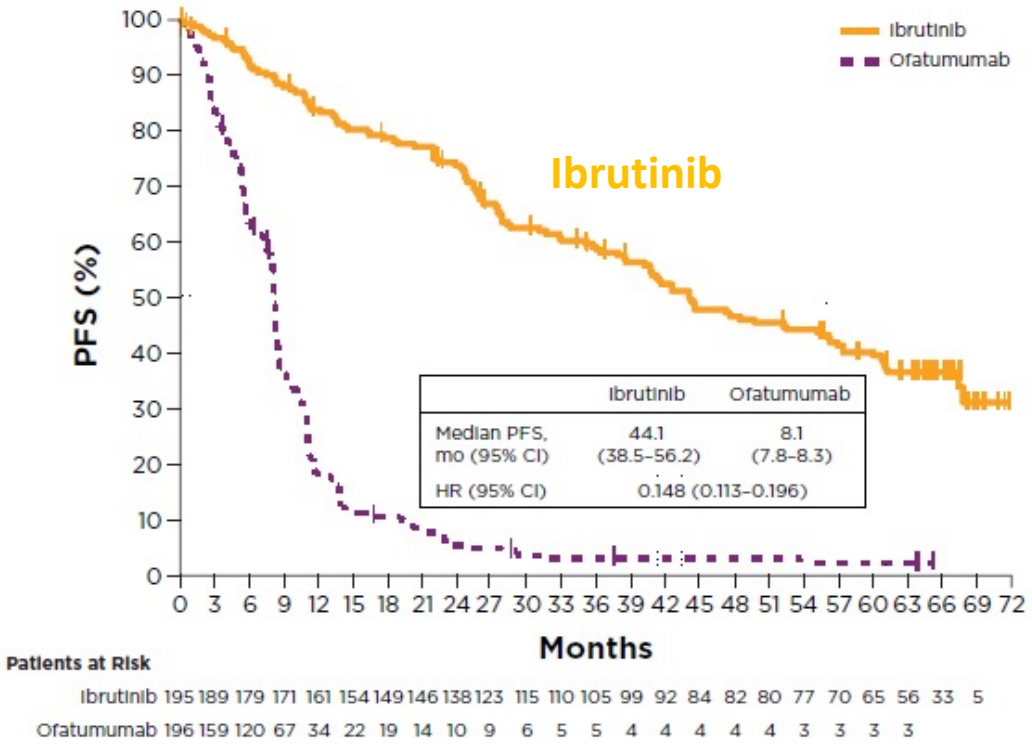
Efficacy depends on covalent, prolonged BTKi
Toxicity may depend on peak vs AUC?

Kaptein, et al. *Blood*. 2018. 132 (Supplement 1): 1871. doi.org/10.1182/blood-2018-99-109973.

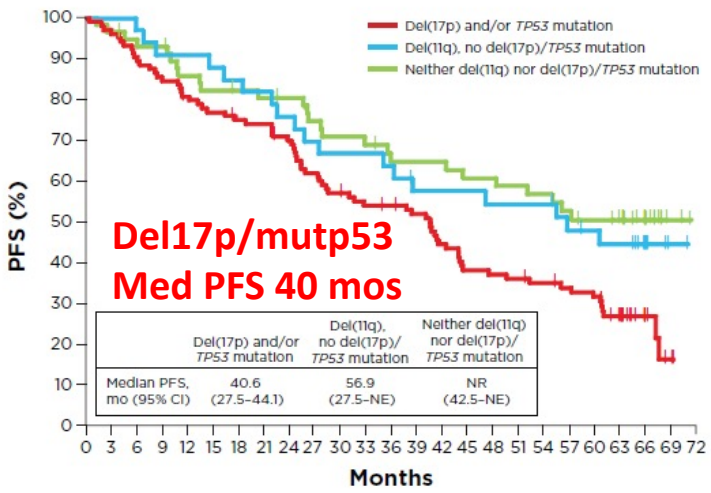
RESONATE Final Analysis, 6-year F/U of PFS: Ibrutinib vs Ofatumumab in Previously Treated CLL/SLL

- ≥ 1 prior therapy (N=391)
- ECOG PS 0-1
- Measurable nodal disease by CT

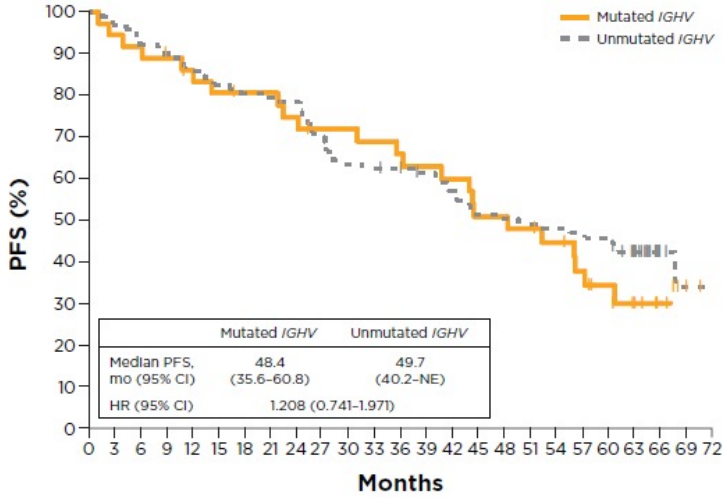
ITT Population



Ibrutinib overcomes Unmutated *IGHV, del11q* and largely *p53* as prognostic factors



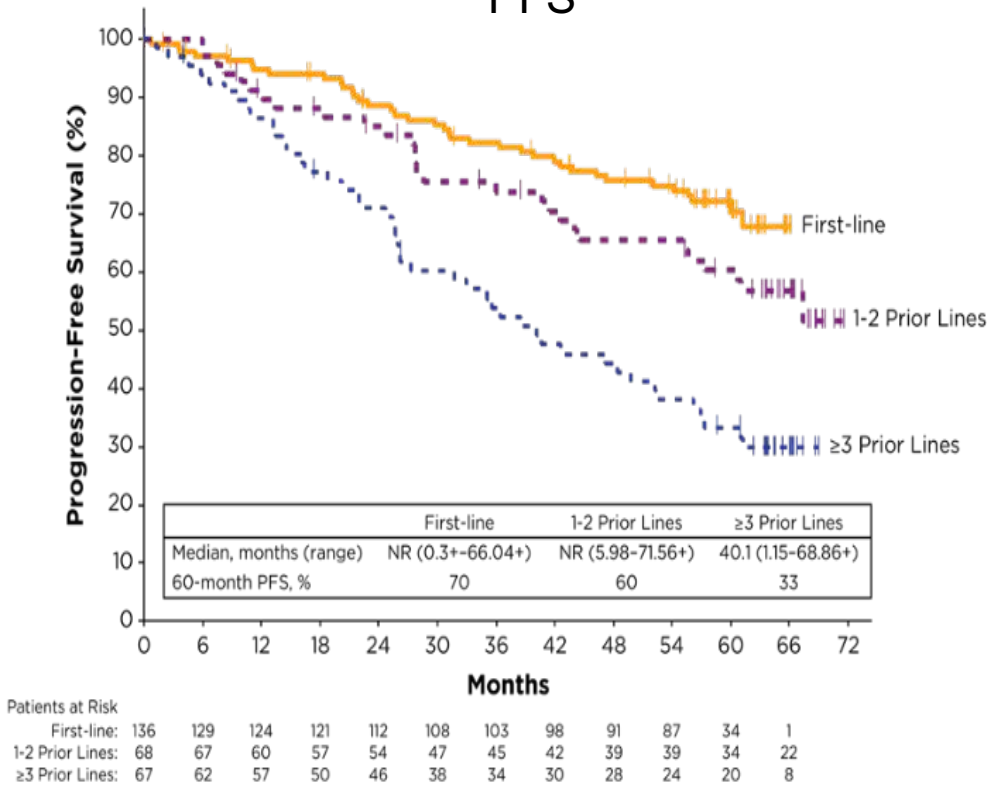
IGHV mutation status



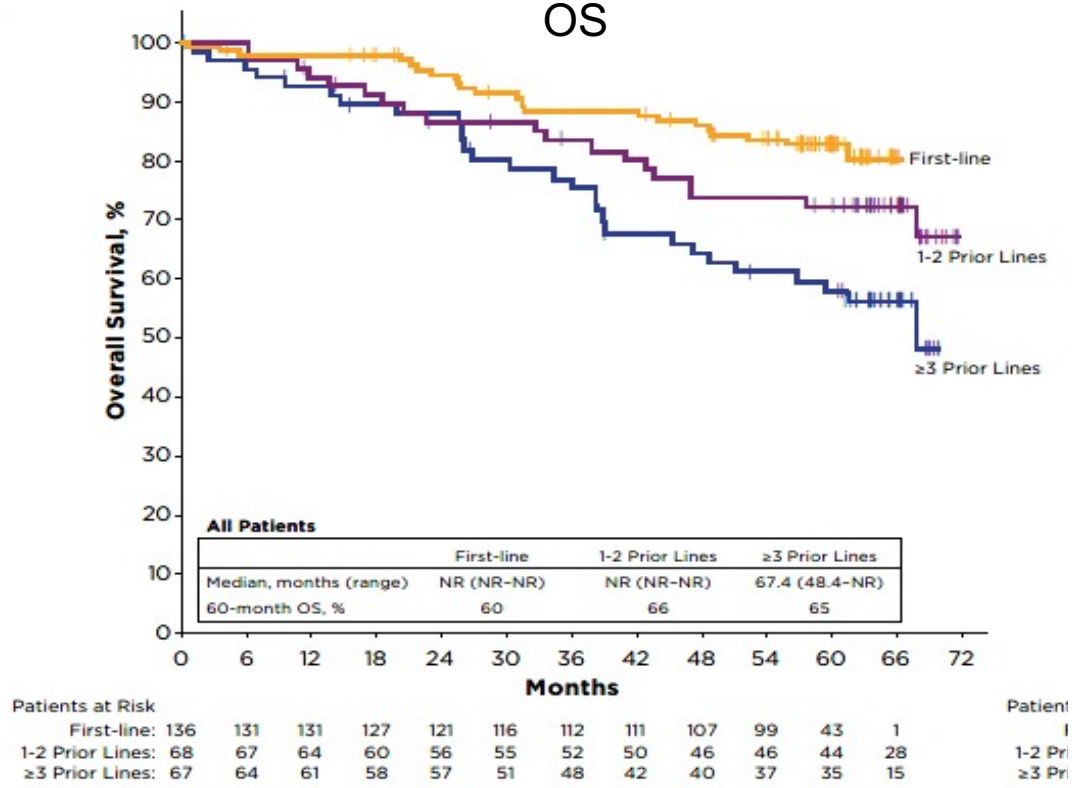
RESONATE PCYC-1112; Munir T et al. *Am J Hematol.* 2019;94:1353-63

Ibrutinib Outcome by Prior Lines of Therapy

PFS



OS



- PFS rates at 5 years higher for ibrutinib treatment in earlier lines (first-line: 70%; 1-2 prior lines: 60%; ≥3 prior lines: 33%)
- Treatment in earlier lines resulted in better PFS for patients with high-risk prognostic features

- OS rates at 5 years higher for ibrutinib treatment in earlier lines (first-line: 83%; 1-2 prior lines: 72%; ≥3 prior lines: 58%)
- Median OS for overall population not reached for first-line and 1-2 prior, and was 67 months for ≥3 prior lines

Barr PM et al. *Blood*. 2019;134(Suppl 1):Abstract 3054.

BR ± Ibrutinib for R/R CLL/SLL
Phase III HELIOS

Pts with previously treated R/R CLL/SLL (N = 578)

- ECOG PS 0-1
- Measurable LN
- **No del(17p)**

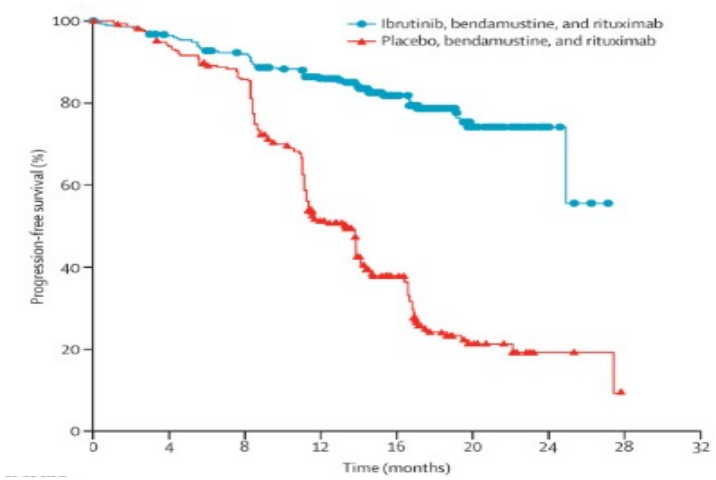
Bendamustine-Rituximab (BR) + Ibrutinib
(starting Day 2, cycle 1)

Bendamustine-Rituximab + Placebo
(starting Day 2, cycle 1)

Crossover upon PD

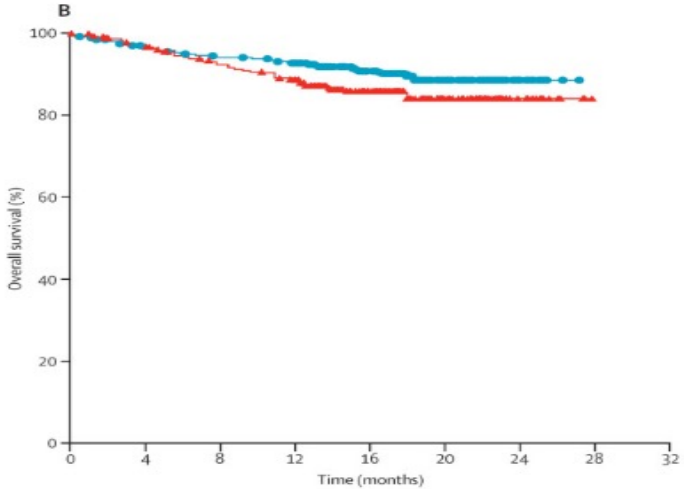
Treat to PD or unacceptable toxicity

PFS



	BR+I	BR
Median PFS, mo	NR	13.3
HR (95% CI)	0.203 (0.150-0.276); *P*<.0001	

OS



	BR+I	BR
Median OS, mo	NR	NR
HR (95% CI)	0.628 (0.385-1.024); *P* = .0598	

- ORR
  - Ibrutinib + BR, 82.7%
  - Placebo + BR, 67.8%
  - *P* < .0001
- Similar toxicity in both arms except more mild bleeding events and atrial fibrillation with BR + I

Chanan-Khan AAA, et al. *Lancet Oncol*. 2016;17:200-211.

Acalabrutinib Monotherapy in R/R CLL (ASCEND)

R/R CLL (N=310)

Stratified by:
- Del(17p)
- ECOG PS 0-1 vs 2
- 1-3 vs ≥ 4 prior therapies

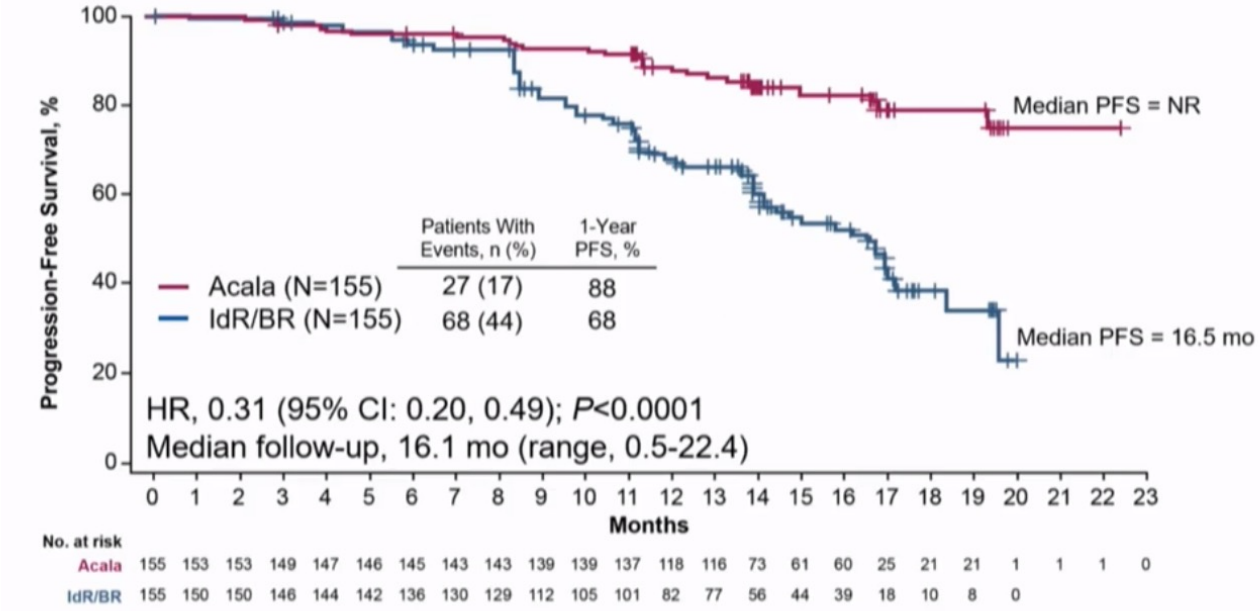
Randomized 1:1

- **Acalabrutinib**
- **Idelalisib + Rituximab (IdR)**
  -OR-
  Bendamustine + Rituximab (BR)

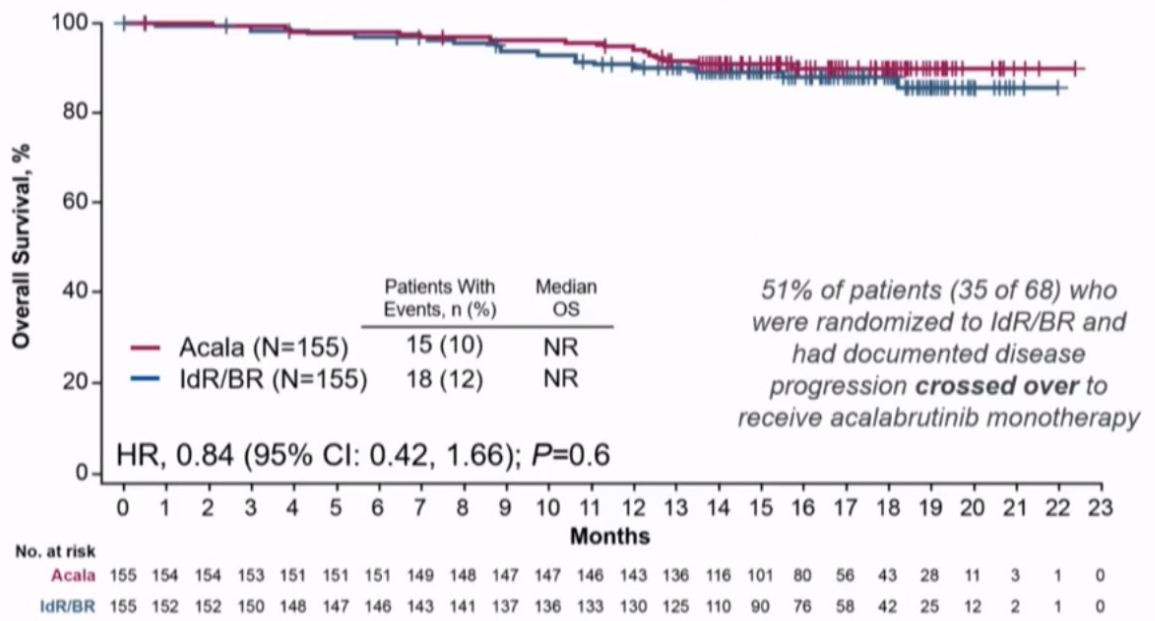
Primary Endpoint: PFS (IRC)

Crossover from IdR/BR allowed after confirmed PD

IRC-Assessed PFS Superior for Acalabrutinib vs IdR/BR



Overall Survival (Median Follow-Up, 16.1 Months)



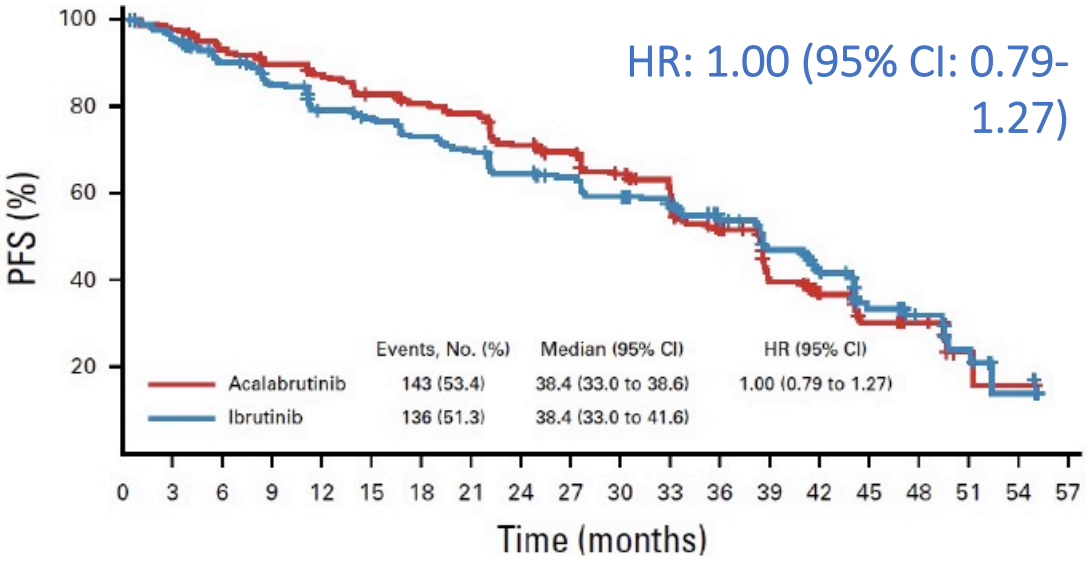
Ghia, P et al JCO 2020

ELEVATE-RR: PHASE III COMPARISON ACALABRUTINIB vs IBRUTINIB FOR RELAPSED/REFRACTORY CLL [with del(17p) or del(11q)]:

NON-INFERIORITY DESIGN AND SAFETY ENDPOINTS: **Median follow-up: 41 months**

EFFICACY

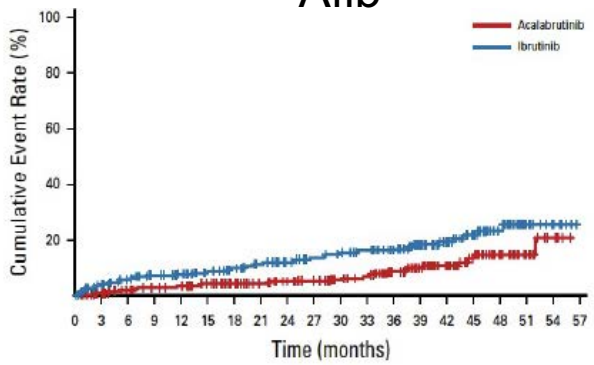
PFS-non-inferior



HR: 1.00 (95% CI: 0.79-1.27)

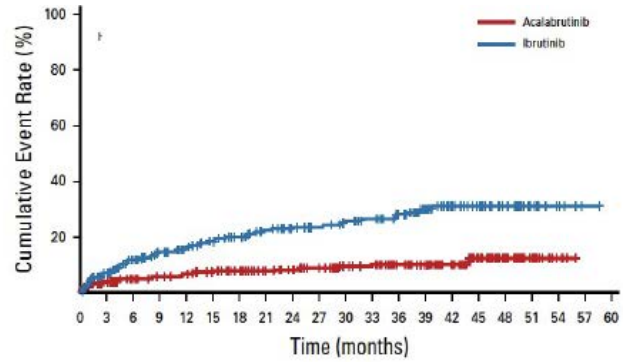
TOXICITY: ALL GRADES

Afib



Acalabrutinib:Ibrutinib
HR (95% CI): 0.52 (0.32 to 0.86)

HBP



Acalabrutinib:Ibrutinib
HR (95% CI): 0.34 (0.21 to 0.54)

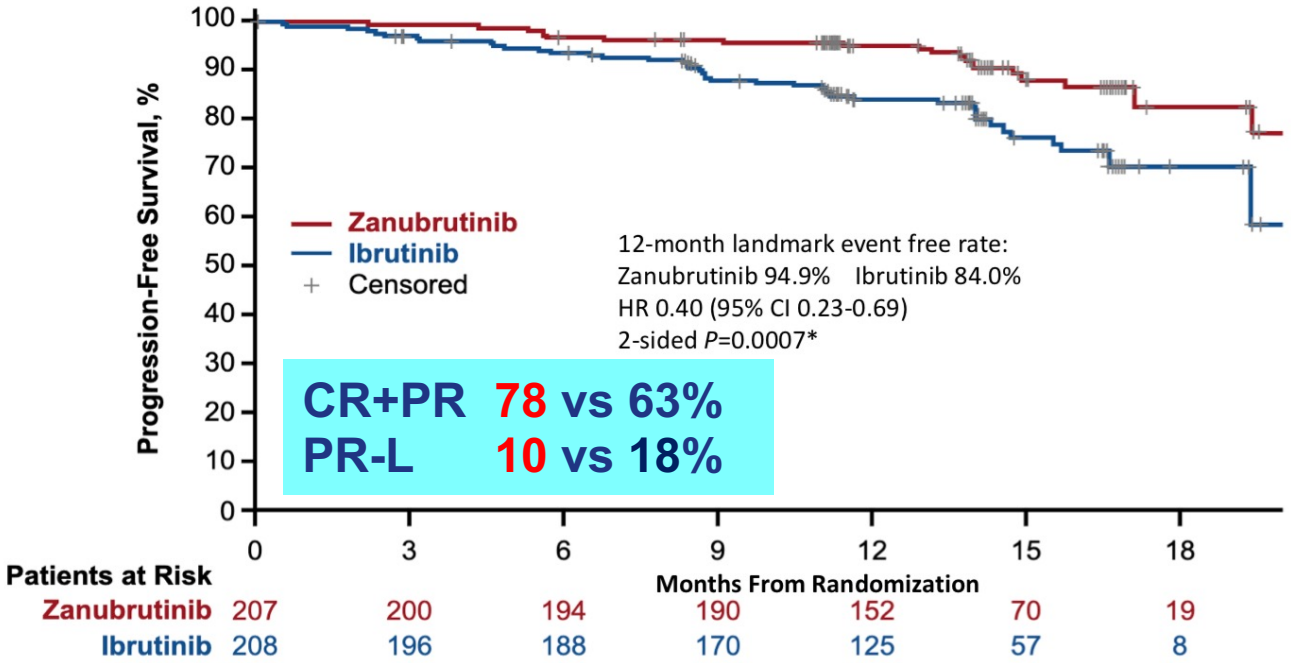
	ACALABRUTINIB N = 266		IBRUTINIB N = 263	
GRADE	**All**	**≥ 3**	**All**	**≥ 3**
Afib	**9%**	**5%**	**16%**	**4%**
HBP	**9%**	**4%**	**23%**	**9%**
AE to DC	**15%**		**21%**	

Byrd J et al. JCO 2021

ALPINE: Phase 3 Rel/Ref CLL Comparing Zanubrutinib and Ibrutinib

≥ 1 prior line; no prior BTKi
Median age 67 yrs
19% del17p and/or mutp53
Data cutoff 1 yr after 415th pt randomized

PFS by Investigator Assessment



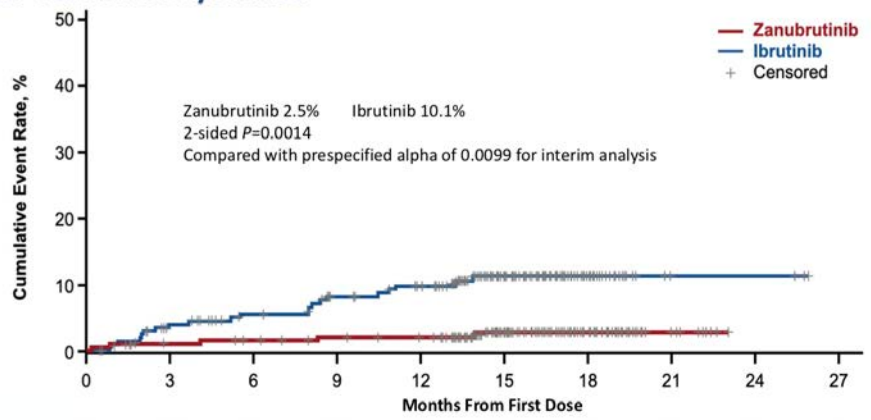
DID PR-L COMPROMISE THIS RESULT?

For del17p (N=50 total): ORR 83% vs 54%

TOXICITY

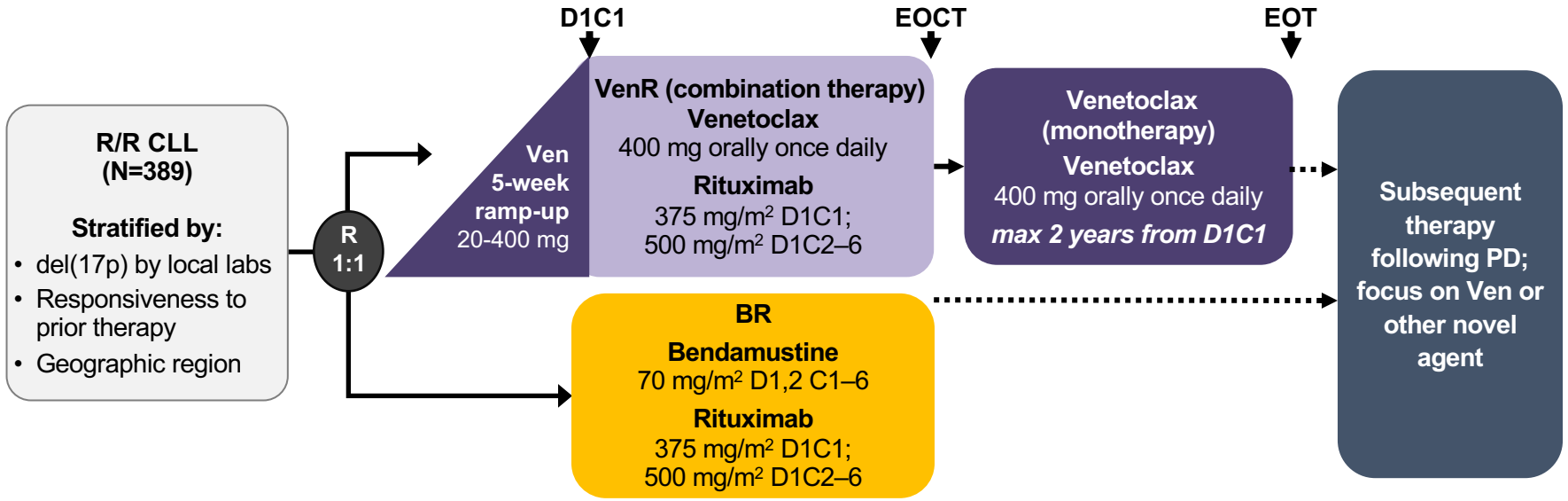
	ZANUBRUTINIB N = 207		IBRUTINIB N = 208	
Grade	All	≥ 3	All	≥ 3
Afib	2.5%	1%	10%	2%
AEs		56%		51%
AE to DC	8%		13%	

Atrial Fibrillation/Flutter



Hillman P et al EHA 2021

MURANO Study Design VR vs. BR

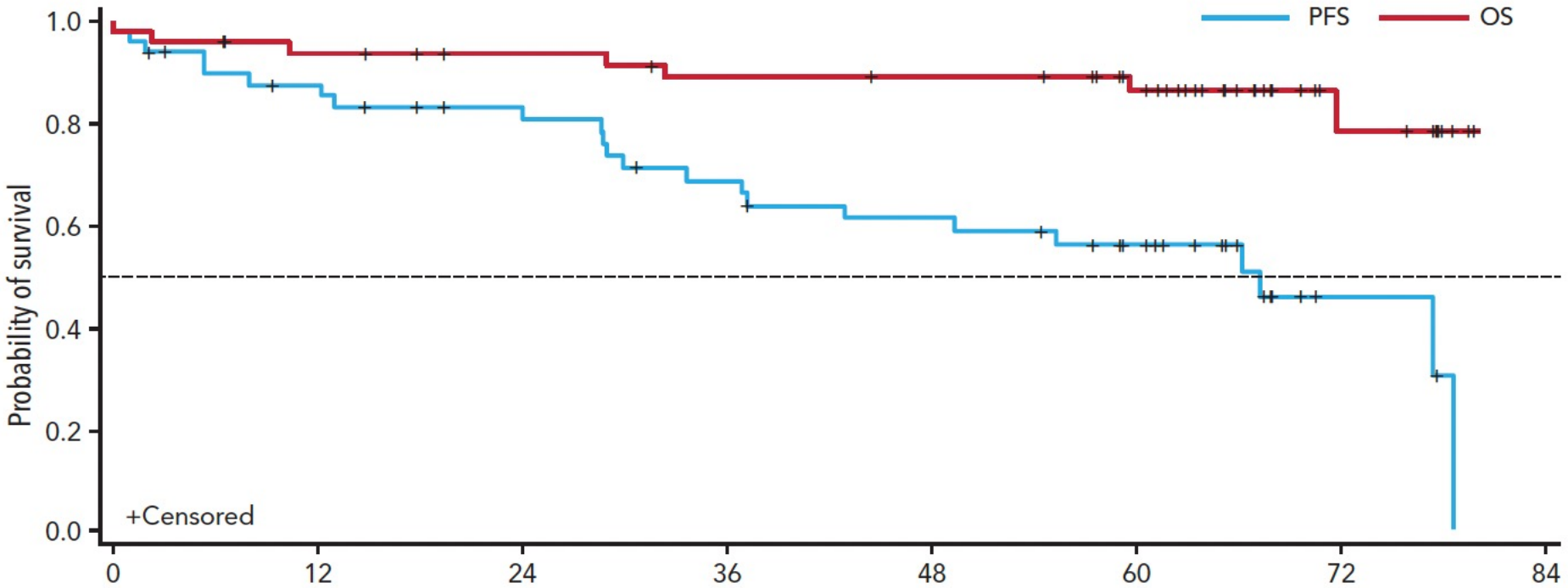


- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoint:** rates of clearance of MRD
- Clinical response and MRD* in PB during Ven monotherapy and follow-up visits were assessed every 3 months for 3 years, then every 6 months thereafter, or until PD

*Undetectable MRD defined as <1 CLL cell/10,000 leukocytes, determined by ASO-PCR or flow cytometry per iwCLL recommendations for reporting of MRD.
BR, bendamustine–rituximab; D1C1, day 1, cycle 1; D1C2-6, day 1, cycles 2-6; EOCT, end of combination treatment; EOT, end of treatment; MRD, minimal residual disease; PB, peripheral blood; PD, progressive disease/disease progression; R, randomization; R/R, relapsed/refractory VenR, venetoclax–rituximab

Seymour JF et al. *N Engl J Med.* 2018;378(12):1107-1120. Kater AP et al. *J Clin Oncol.* 2020;JCO2000948.

MURANO 5-Year Follow-Up: Overall and Progression-Free Survival (All Patients)



Patients at risk

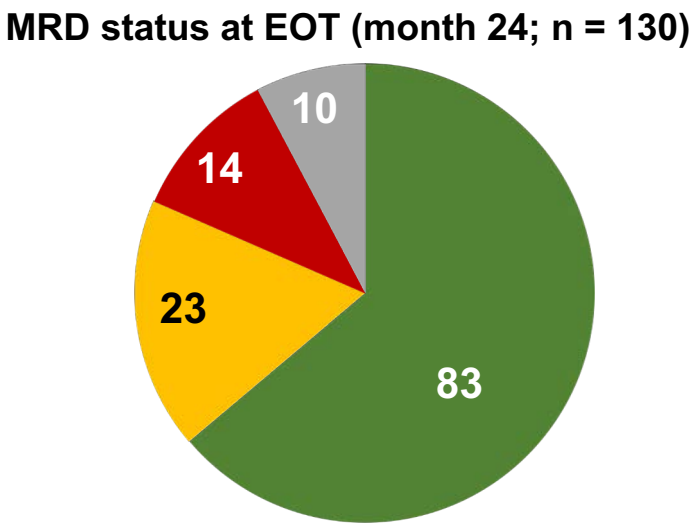
PFS	49	40	34	28	24	18	3	0
OS	49	44	41	38	37	31	10	0

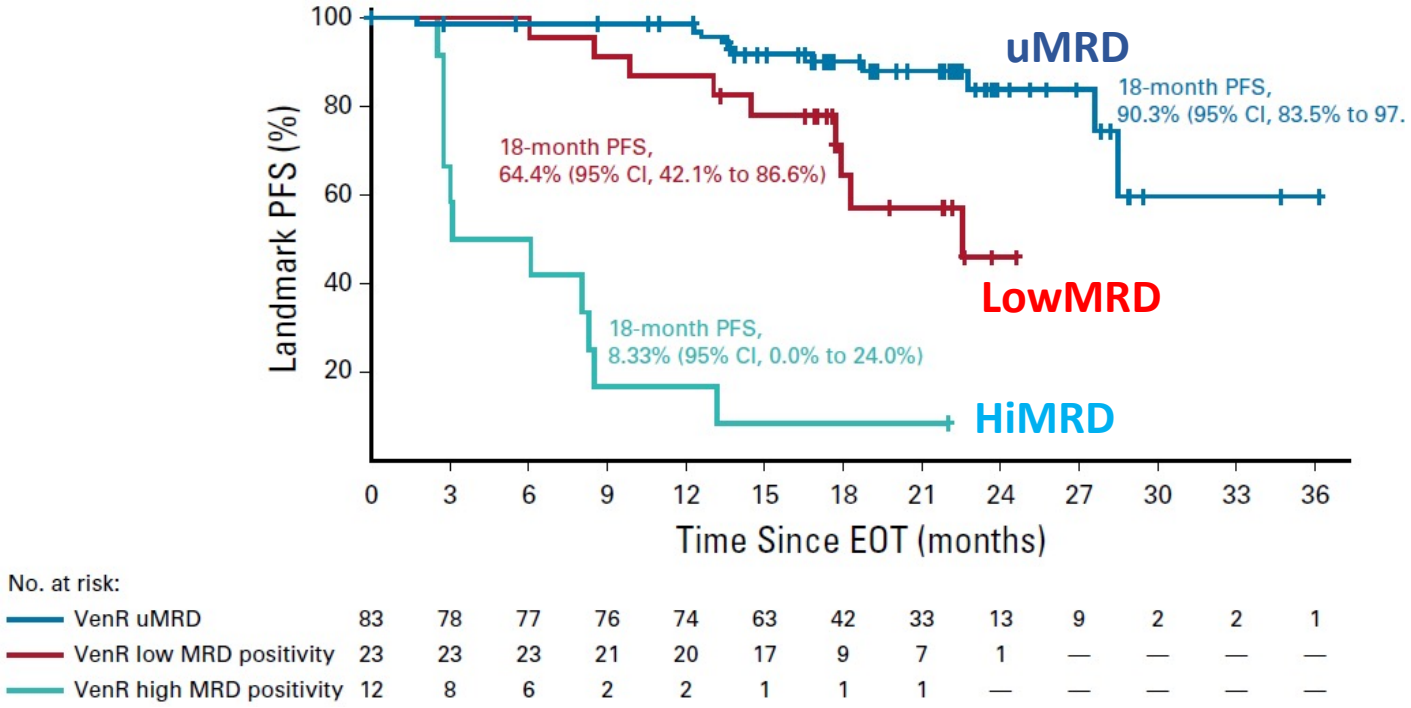
Survival estimate (95% CI)

	Events	Month 24	Month 36	Month 60	Month 72	Median months (95% CI)
PFS (N = 49)	23	80.7% (66.2–89.5)	68.8% (52.9–80.3)	56.1% (39.9–69.5)	45.9% (27.8–62.2)	67.3 (37.1–78.6)
OS (N = 49)	7	93.8% (82.0–98.0)	89.2% (75.8–95.3)	86.4% (71.9–93.7)	78.5% (54.7–90.8)	NR (NR–NR)

Ma S et al. *Blood* 2021;138(10):836-46.

MURANO: PFS by Depth of Response (MRD) at End of Treatment

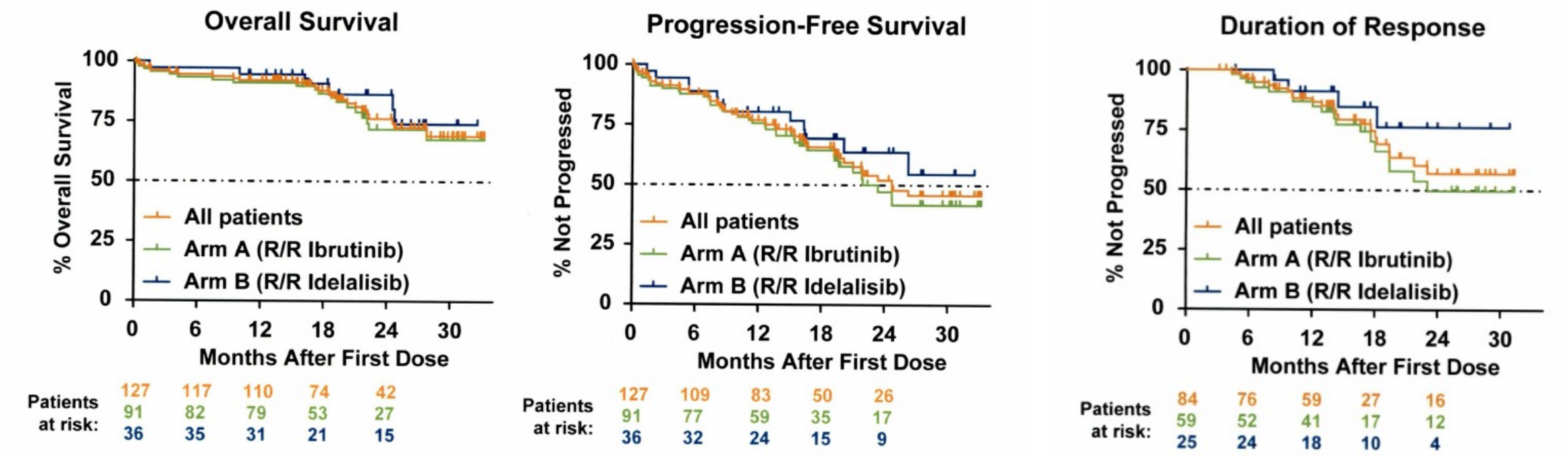




Status off-therapy, n (%)	uMRD ($<10^{-4}$) n = 83	Low-MRD+ (10^{-4}–10^{-2}) n = 23	High-MRD+ ($>10^{-2}$) n = 14	Unknown n = 10
Progression-free	72 (86.7)	14 (60.9)	1 (7.1)	8 (80.0)
PD	11 (13.3)	9 (39.1)	13 (92.9)	2 (20.0)

Seymour JF et al. *N Engl J Med.* 2018;378(12):1107-1120. Kater AP et al. *J Clin Oncol.* 2020;JCO2000948.

Venetoclax Responses Durable in Patients with CLL Relapsed/Refractory After Prior Ibrutinib and/or Idelalisib



- In patients with CLL R/R to ibrutinib and/or idelalisib treated with venetoclax monotherapy, median PFS was 24.7 months
- Median DoR and median OS were not reached after 24 months of follow-up

Median number of prior therapies in all patients: 4 (1-15)

Byrd JC et al. *J Clin Oncol.* 2018;36(Suppl 15):Abstract 7512; Jones JA et al. *Lancet Oncol*. 2018;19(1):65-75; Coutre S et al. *Blood.* 2018;131(15):1704-1711.

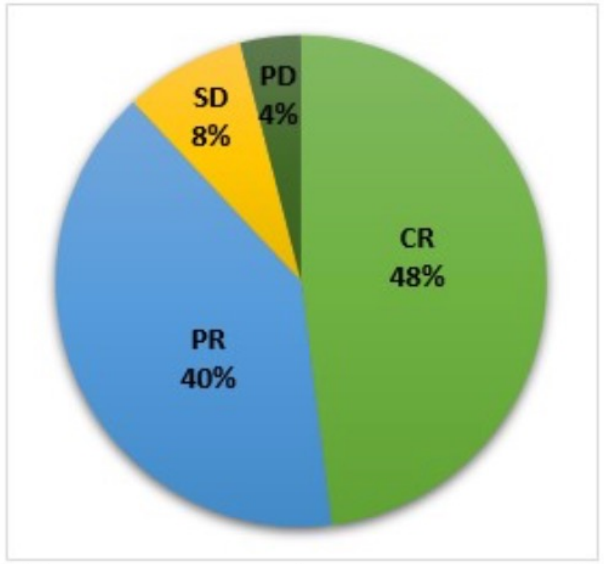
What About Treatment Post-Venetoclax?

MURANO: post-Ven-R treatment outcomes

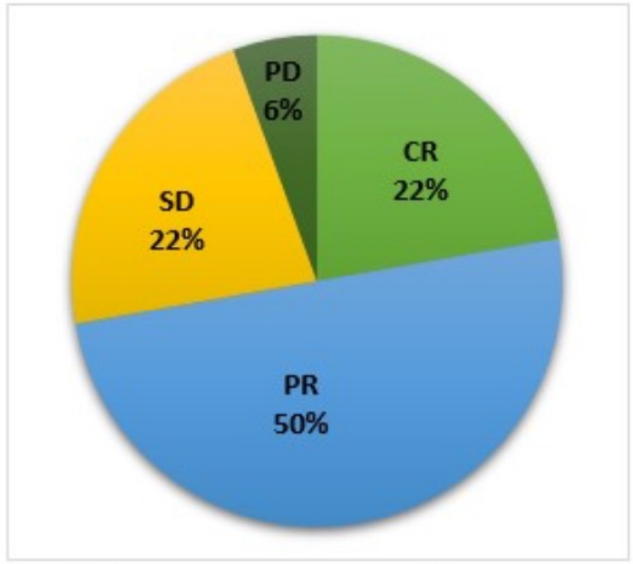
	ALL	Novel Agents	BTKi	Ven-based
N =	99	52	18	32
ORR	71%	79%	100%	72%
Median duration (mos)	6	14	22	11

Harrup RA et al. ASH 2020 A3139.

A. Response to initial ven regimen (n=25)



B. Response to ven re-treatment regimen (n=18)



Abbreviations: CR: complete response, PR: partial response, SD: stable disease, PD: progression of disease

Thompson MC et al. 2020 ASH 2020, A3136.

Therapy Post-Venetoclax Discontinuation in CLL:

Multicenter, retrospective cohort study (31 centers internationally, UK CLL Forum and Collaborative Study of Real World Evidence (CORE)

Post-Ven Therapy	BTKi	BTKi	BTKi	PI3Ki	CAR-T	Anti-CD20 abs
Agents	Ibrutinib Acalabrutinib	Ibrutinib Acalabrutinib Non-covalent BTKi	Ibrutinib Acalabrutinib Non-covalent BTKi	Idelalisib Duvelisib	Anti-CD19	Rituximab Obinutuzumab Ofatumumab
Pre-Ven Exposure	BTKi-naïve	BTKi-exposed BTKi-resistant	BTKi-exposed BTKi-intolerant	PI3Ki-naïve BTKi-exposed	BTKi-exposed	
Patient Number	44	20	10	17	18	19
ORR	83.9%	53%	70%	46.9%	66.6%	32%
CR	9%	6.6%	20%	5.9%	33.3%	16%
PR	56.8%	26.4%	30%	35.2%	33.3%	16%
PR-L	18.1%	20%	20%	5.8%	0%	0%
SD	11.6%	20%	-	23.7%	5.7%	32%
PD	4.5%	27%	30%	29.4%	27.7%	37%

Ven DC'd for:

CLL PD	38%
AE	14%
Richter	14%
Pt pref	8%
alloSCT	6%

Mato AR et al. *Blood.* 2019;134(Suppl 1):Abstract 502.

What about Combining BTKi + BCL2i? Already in 1st Line
Ibrutinib-Venetoclax in R/R CLL: BM MRD4 Responses

Treatment schema

	C1	C2	C3	C4-->27
Ibrutinib	420mg daily	420mg daily	420mg daily	420mg daily
Venetoclax	-	-	-	20mg daily 1 week; 50mg daily 1 week; 100mg daily 1 week; 200mg daily 1 week; 400mg daily continuous

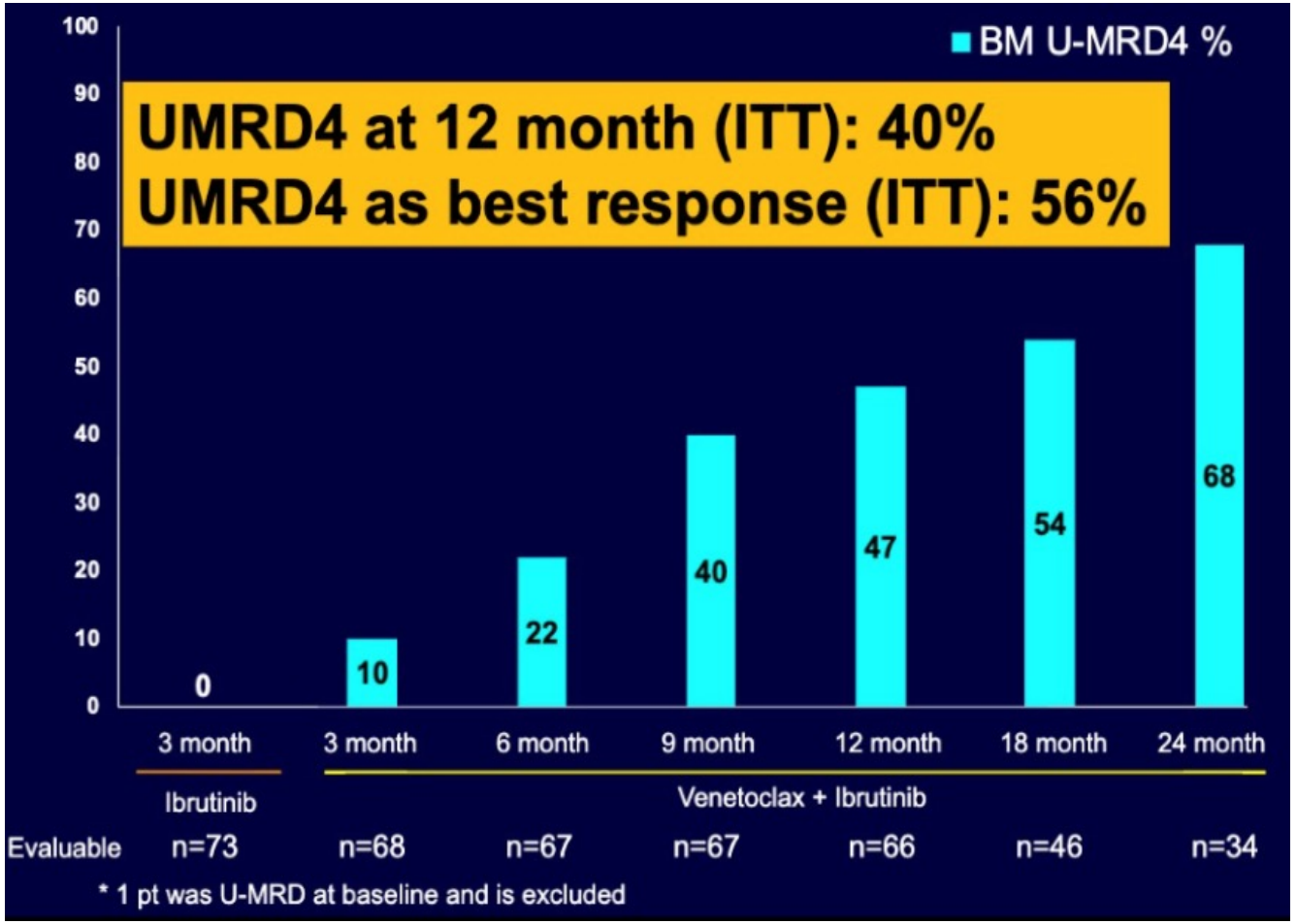
Duration of therapy: 24 cycles of combination treatment

- **If BM MRD+ at 24 cycles, ibrutinib alone continues until PD**

74 patients initiated combination

- 5 patients off-study during ibrutinib monotherapy

Median follow-up 27 months



Jain N et al. *Blood.* 2019;134(Suppl 1):Abstract 359.

Summary of Approved PI3K Inhibitors

	Idelalisib	Copanlisib	Duvelisib	Umbralisib
Isoform	δ	αδ	γδ	δ (and CK1-epsilon)
FDA-approved indications	• R CLL (w/rituximab) • ~~R SLL (≥2 prior systemic tx)~~ • ~~R FL (≥2 prior systemic tx)~~	• R FL (≥2 prior systemic tx)	• R/R CLL (≥2 prior systemic tx) • R/R SLL (≥2 prior systemic tx) • ~~R/R FL (≥2 prior systemic tx)~~	• ~~R/R MZL (≥1 prior anti-CD20–based tx)~~ • ~~R/R FL (≥3 prior systemic tx)~~
Use w/o rituximab	No—CLL Yes—SLL FL	Yes	Yes	No
Method of administration	Oral	IV	Oral	Oral
Dosing	150 mg twice daily	60 mg as a 1-hour intravenous infusion on Days 1, 8, and 15 of a 28-day treatment cycle	25 mg twice daily	800 mg orally once daily with food
Black box Warnings	Hepatotoxicity, diarrhea or colitis, pneumonitis, infection, intestinal perforation	None	Infection, diarrhea or colitis, cutaneous reactions, pneumonitis	None

ZYDELIG® (idelalisib) tablets, for oral use [prescribing Information]. Foster City, CA: Gilead; Revised 10/2018. Aliqopa™ (copanlisib) for injection [prescribing Information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals; Revised 2/2020.
Copiktra® (duvelisib), capsules for oral use [prescribing information]. Needham, MA: Verastem; Revised 7/2019. UKONIQ™ (umbralisib) tablets, for oral use [prescribing information]. Edison, NJ: TG Therapeutics, Inc; Revised 2/2021.

What's on the Horizon?

- New BTKi: non-covalent
- New BCL2i: which members of BCL2 family need to be affected
- New PI3Ki: dosing/scheduling being re-evaluated
- New antibody-based therapy: Targets (ROR1); ADC; Bispecifics
- Immune modulatory agents
- CART
- COMBINATIONS/SEQUENCES
- What do we do when everything has been used in initial therapy?
  - CLONAL DYNAMICS/Mechanisms of Resistance to personalize therapy

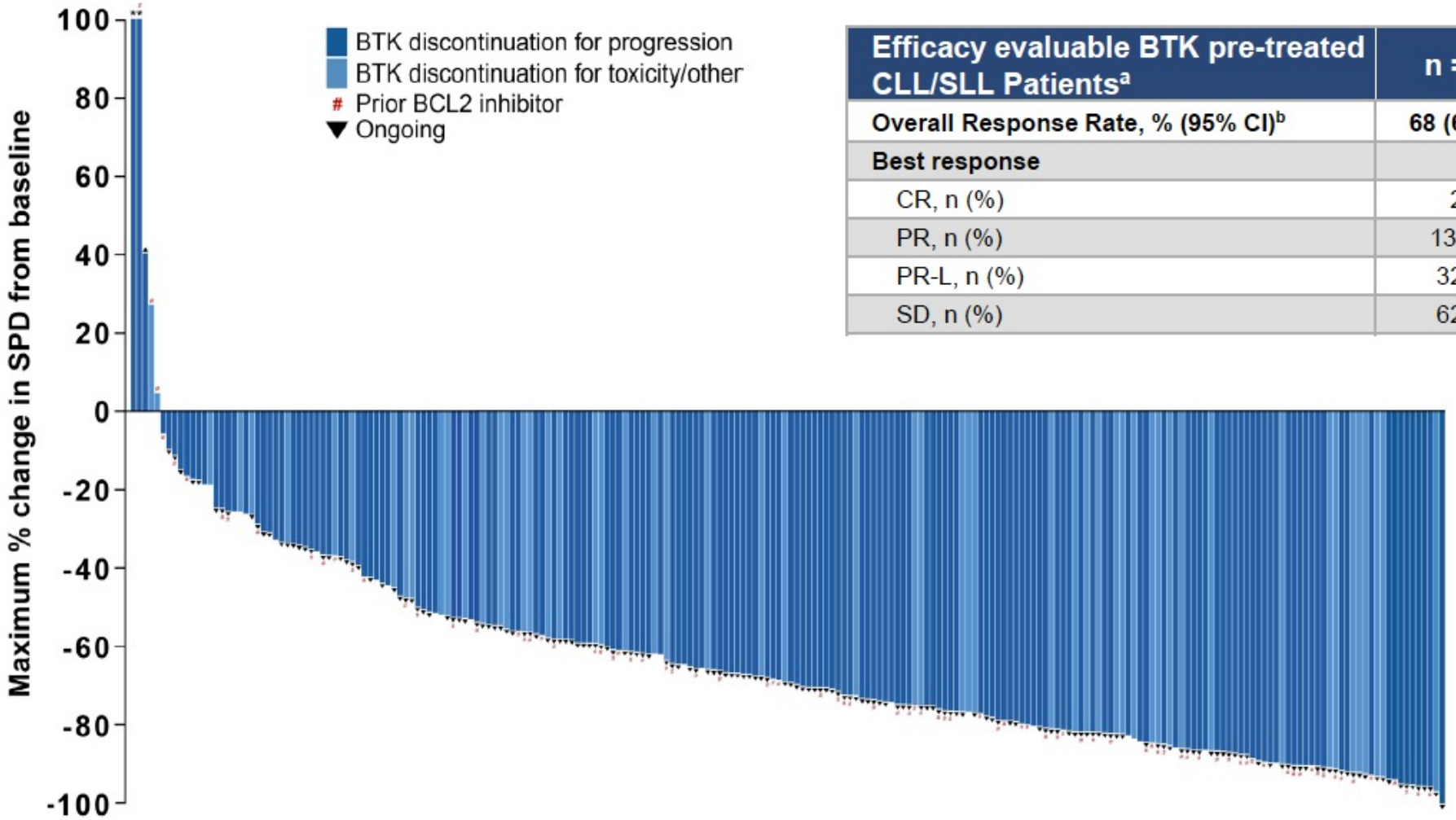
Non-Covalent BTK Inhibitors

- Resistance to covalent BTKi often due to mutation in binding site
- Non-covalent BTKi are not inhibited by such mutations
- Pirtobrutinib (LOXO-305) blocks the ATP binding site in BTK, with minimal off-target inhibition
  - ARQ-531 hydrogen binds to amino acids 475&476, may block downstream of PLCgamma2 (another mechanism of BTKi resistance)
- In Phase 1/2 BRUIN trial no MTD was reached, RP2D is 200 mg/d

  >100 mg/d inhibited BTK at > IC90 throughout the dosing interval
- Most common Gr 3-4 AE neutropenia (10%); well tolerated
- In CLL/SLL (N=121) with prior BTKi, ORR = 62%
  - Prior BTKi resistance 67%
  - Prior BTKi intolerance 52%
  - C481 mutant 71%/BTK wt 66%

Mato AR et al. BRUIN Trial. Lancet 2021

BRUIN: Updated Pirtobrutinib Efficacy Findings



Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	**68 (62 – 74)**
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Mato AR et al. ASH 2021;Abstract 391.

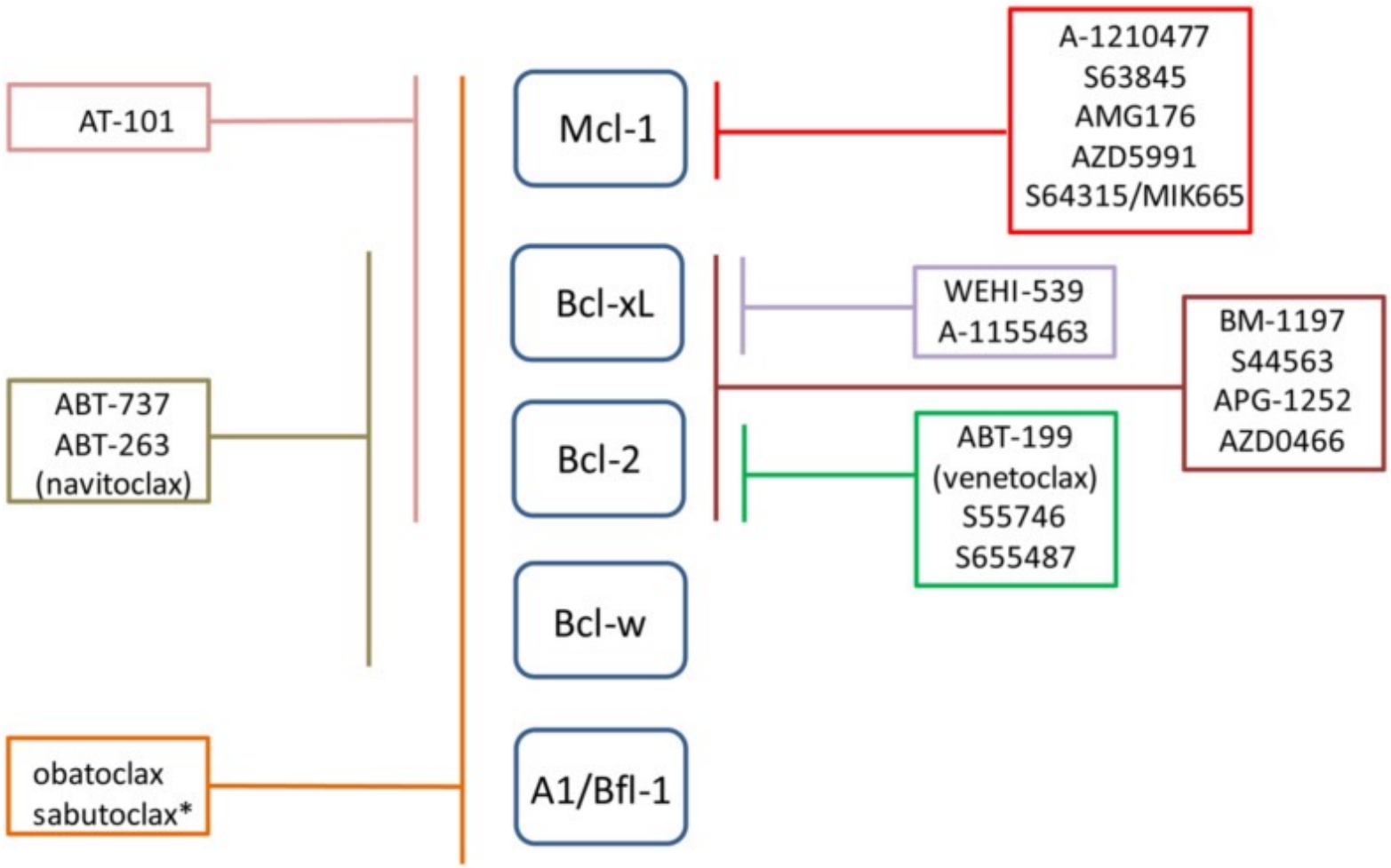
BRUIN: Updated Pirtobrutinib Safety Findings

	All doses and patients (n=618)						
	Treatment-emergent AEs, (≥15%), %					Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

No DLTs reported and MTD not reached
96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily
1% (n=6) of patients permanently discontinued due to treatment-related AEs

Mato AR et al. ASH 2021;Abstract 391.

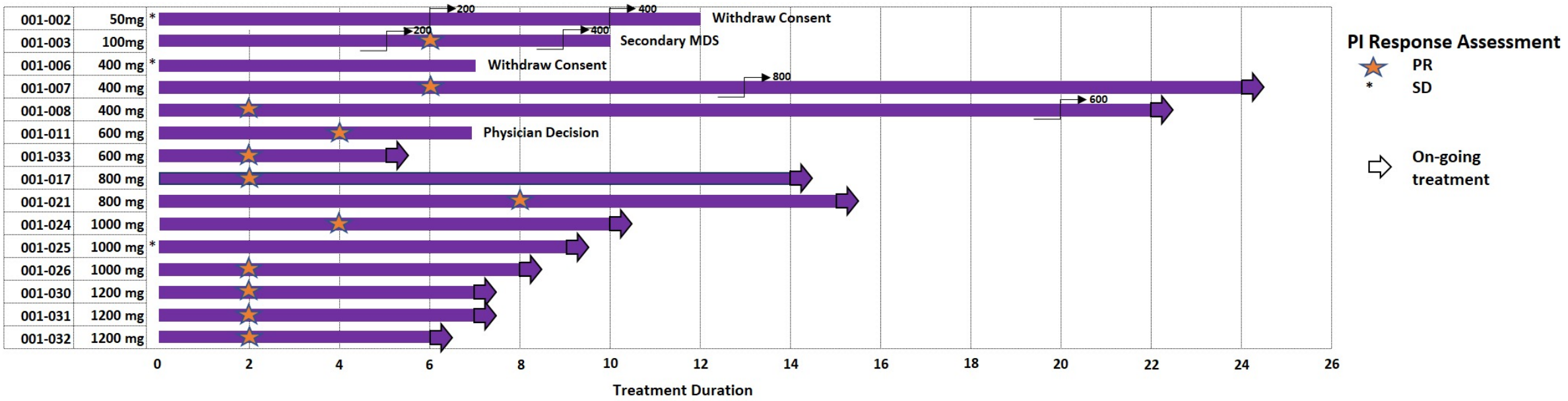
Will Other BH3 Mimetics Be Useful?



D'Aguanno Cells 2020 May; 9(5): 1287

Lisaftoclax (APG-2575), efficacy in patients with CLL/SLL (ORR = 80%)

SLIDE COURTESY OF DR. ASHER CHANANKHAN

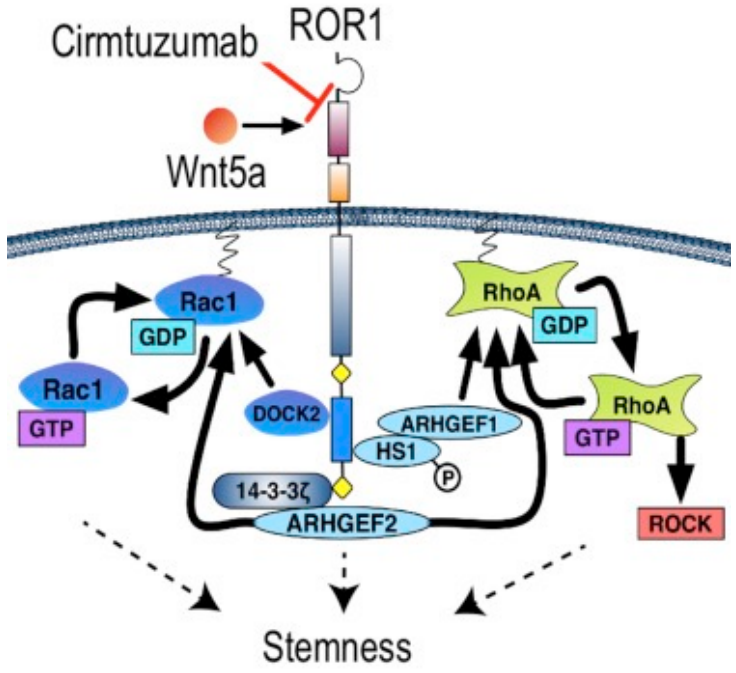


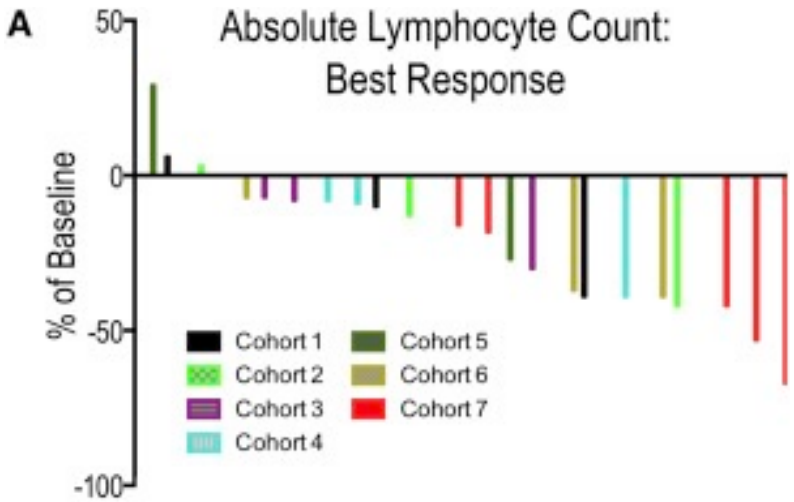
001-003: The nodal size reduction reached by 48% after 4 cycles of treatment at 100mg. The patient dose escalated to 200mg and achieved PR after 1 cycle of treatment at 200mg.

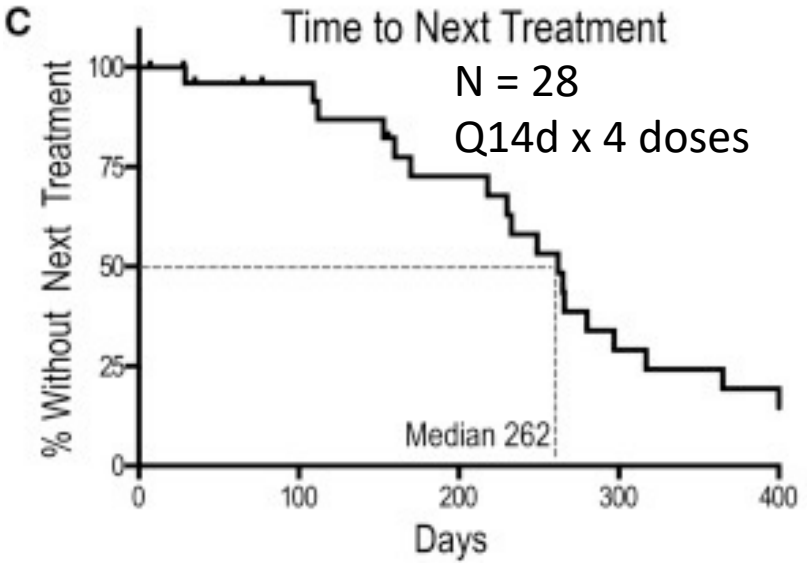
- **Median (range) treatment of 9 cycles (Range 5-24 cycles)**
- **12 of 15 evaluable R/R CLL/SLL patients achieved partial response (PR) by 2008 iwCLL definition, for an objective response rate of 80%**
- **Median time to response of 2 cycles (Range 2-8 cycles)**

Anti-ROR1 Cirmtuzumab in CLL

"Naked" Antibody Phase 1, **Choi MY et al Cell Stem Cell 22:951-959, 2018**







Zilovertamab vedotin (ZV; previously VLS-101), ADC of cirmtuzumab, Phase I
Wang M et al NEJM 2021

7/15 ORR MCL, not very active in CLL but N = 7

MODULE 3: Follicular Lymphoma (FL) – Dr Leonard

RTP
RESEARCH
TO PRACTICE

A 76-year-old woman with Stage III, Grade 1/2 FL now requiring treatment

Dr Shams Bufalino (Park Ridge, Illinois)

RTP RESEARCH TO PRACTICE

A 77-year-old man with newly diagnosed Grade I to II/III FL and a Ki-67 score of 80%

Dr Philip Brooks (Brewer, Maine)

RTP
RESEARCH
TO PRACTICE

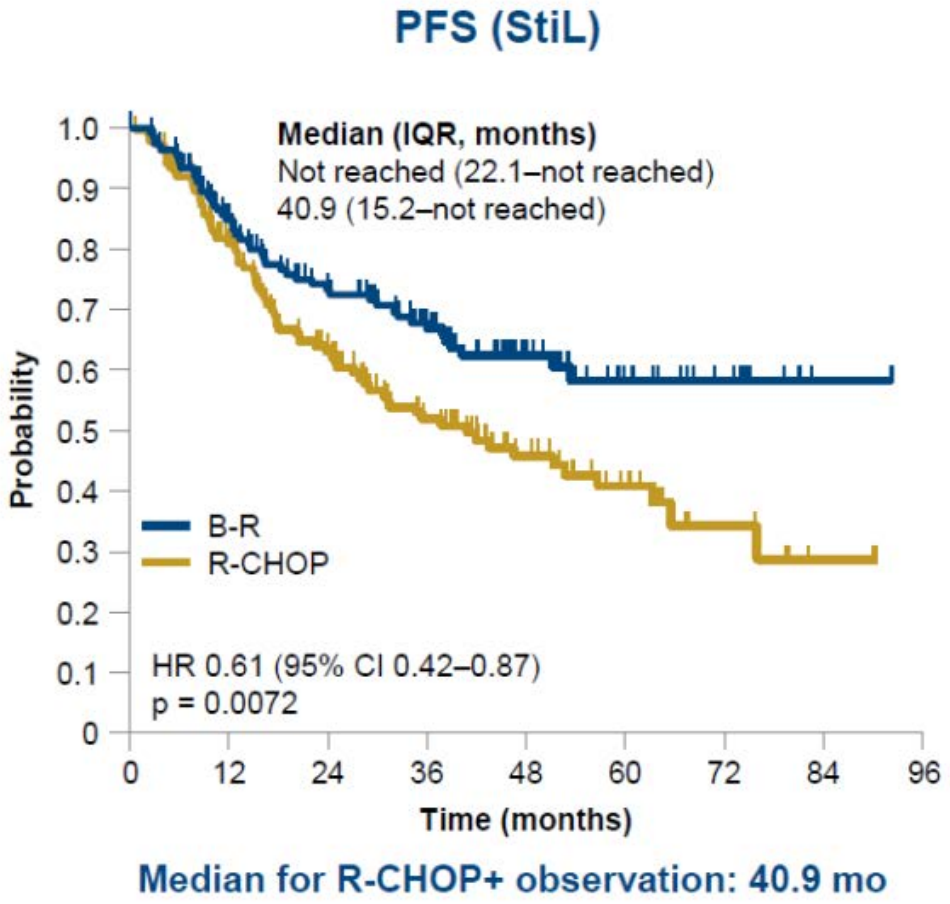
A 77-year-old woman with EZH2 wild-type R/R FL who received tazemetostat

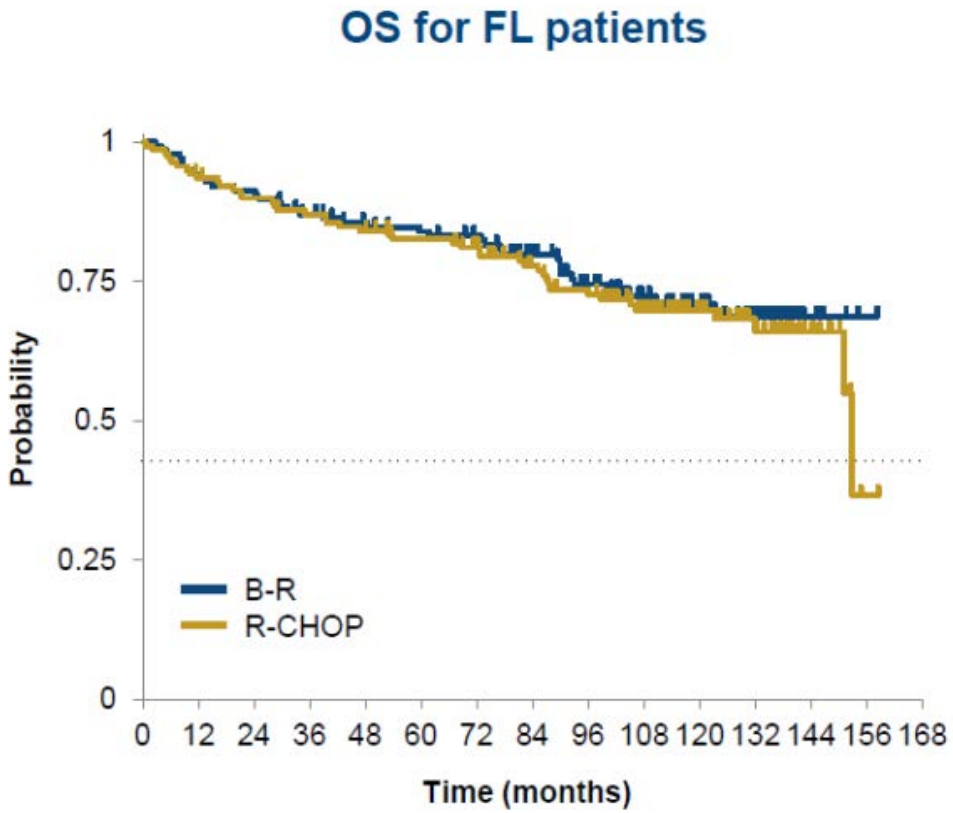
Dr Spencer Bachow (Boca Raton, Florida)

Updates in follicular lymphoma

John P Leonard, MD
Richard T Silver Distinguished Professor of Hematology
and Medical Oncology
Senior Associate Dean for Innovation and Initiatives
Executive Vice Chair, Joan and Sanford I Weill
Department of Medicine
Weill Cornell Medicine
New York, New York

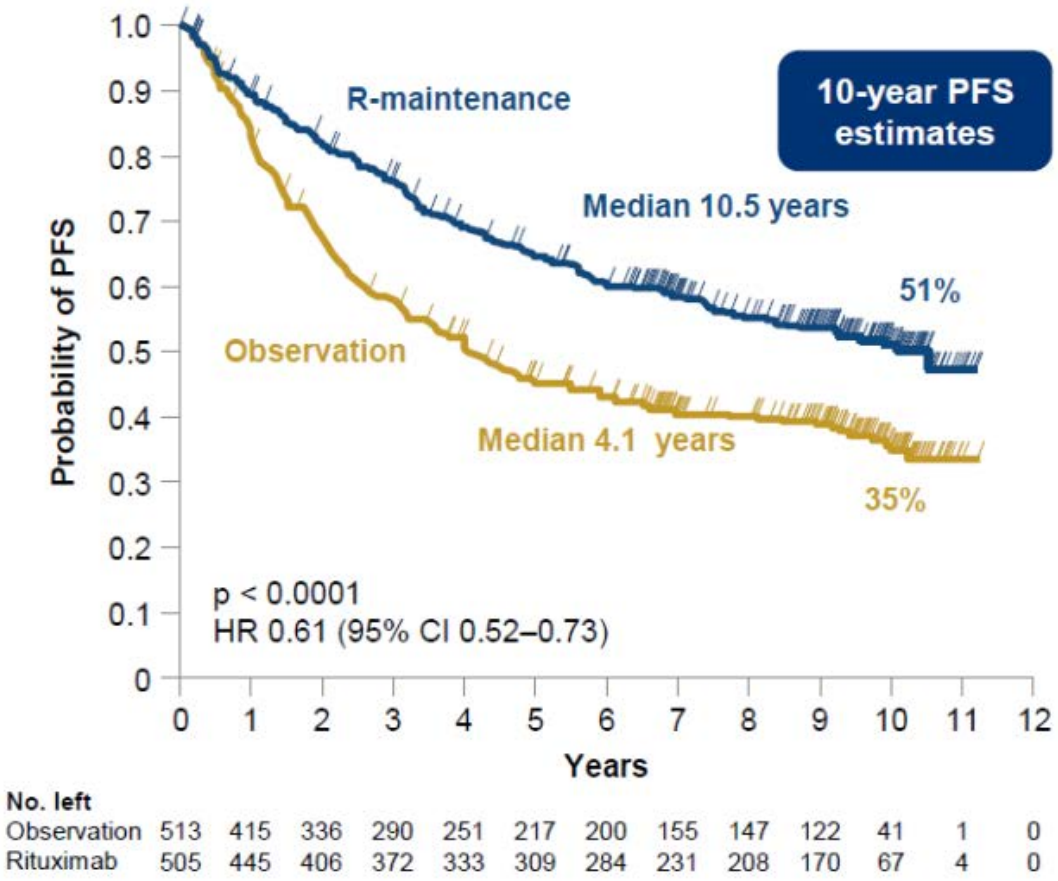
How to treat advanced stage, high tumor burden FL?
One approach: Bendamustine-Rituximab vs R-CHOP

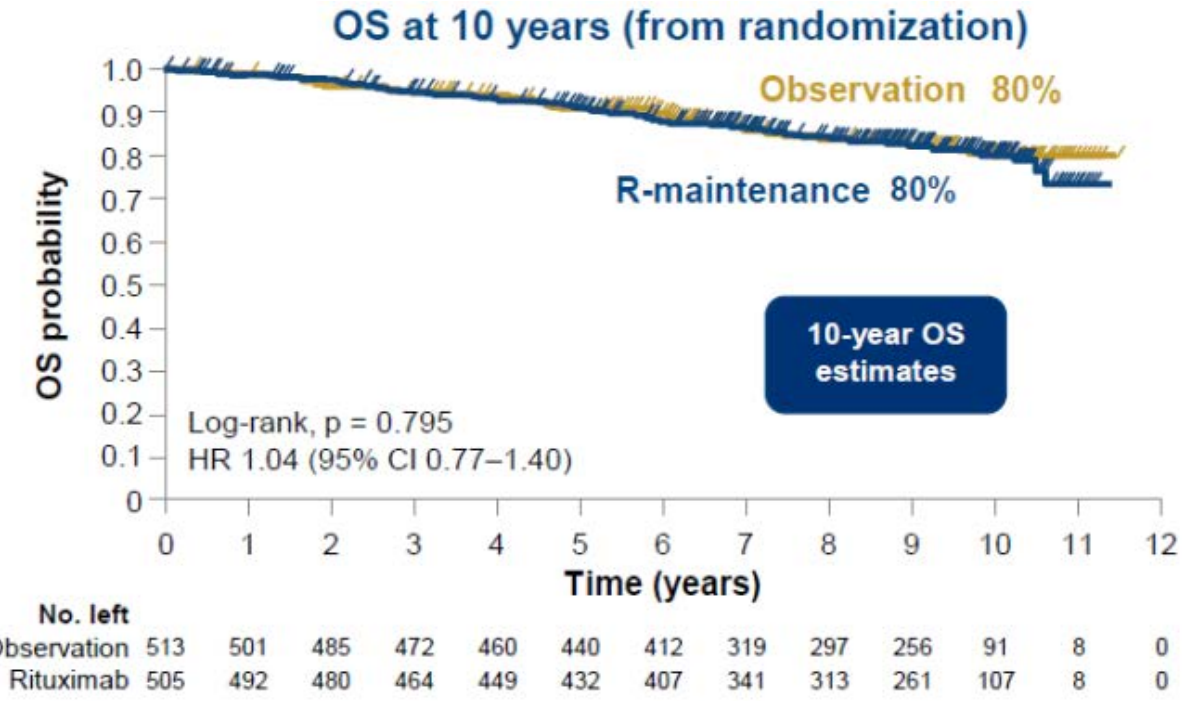




Rummel MJ, et al. Lancet. 2013:381:1203-10. and updated ASCO 2017

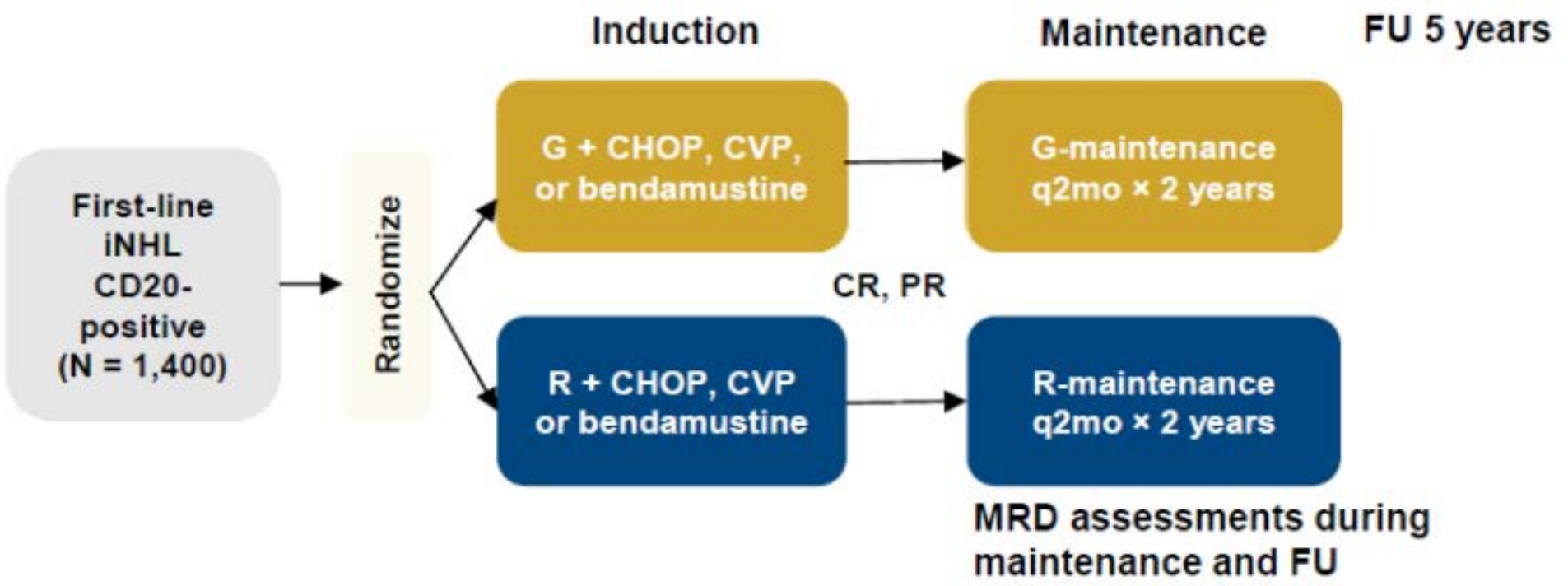
PRIMA: Maintenance R after R-CHOP/R-CVP improves PFS but not OS





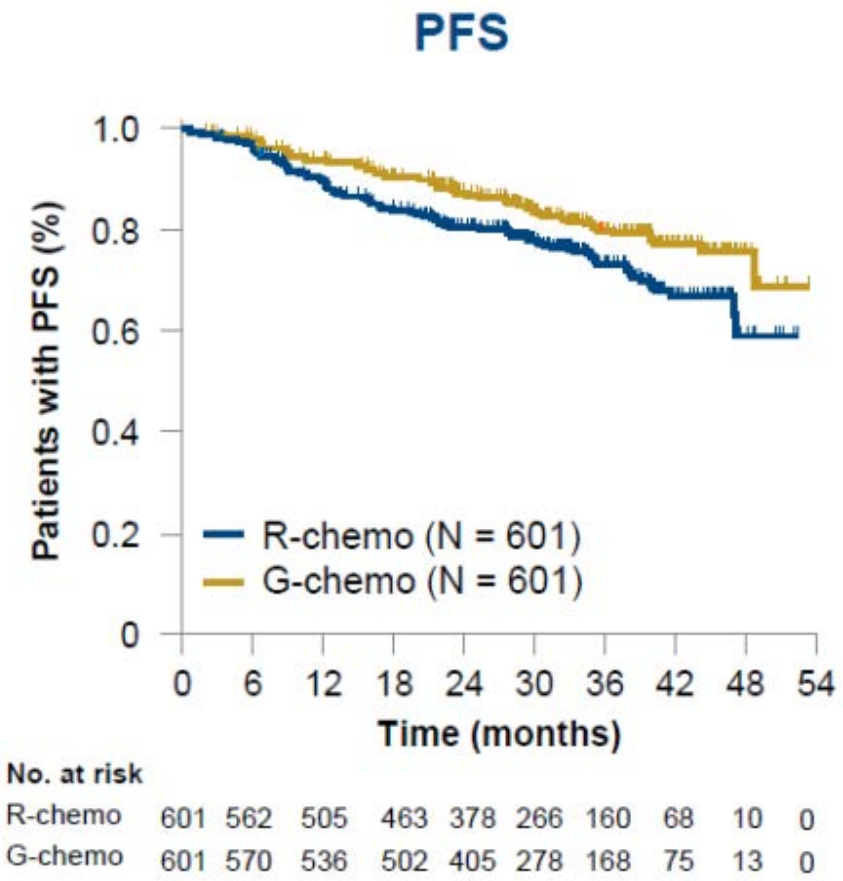
Salles G, et al, ASH 2017

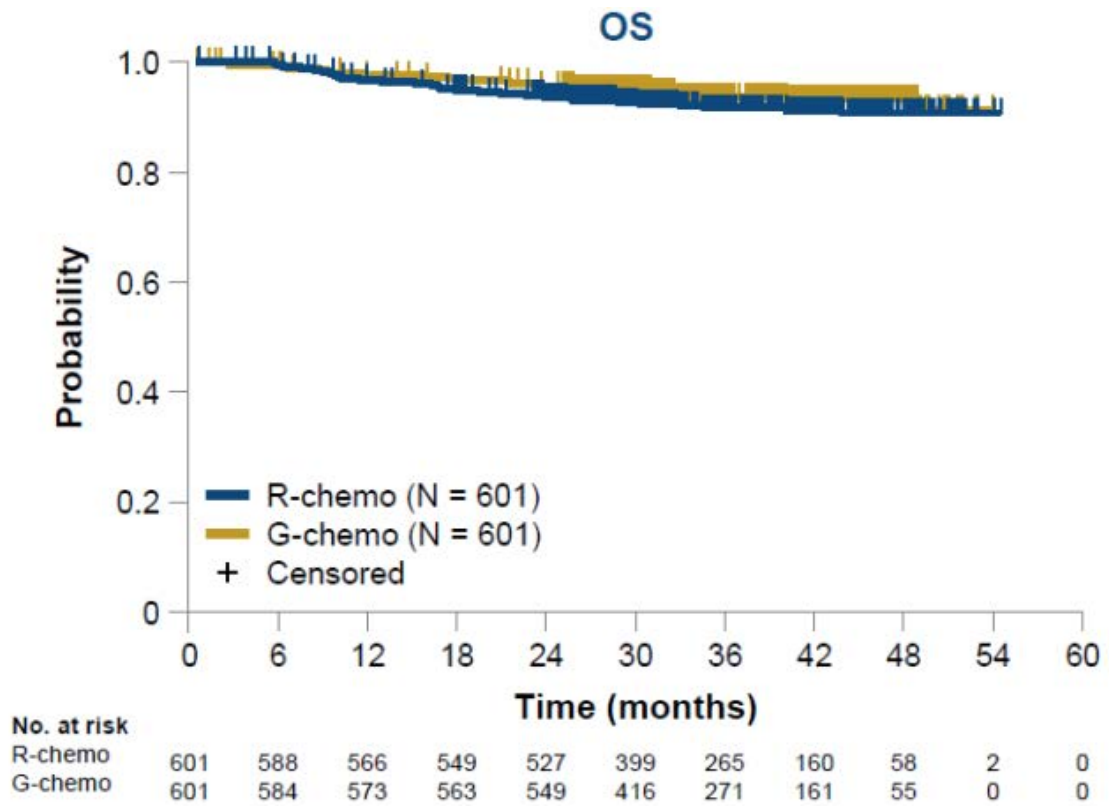
GALLIUM: Obinutuzumab vs Rituximab with chemotherapy (and as maintenance)



Marcus R, et al. N Engl J Med. 2017; 377:1331-44.

GALLIUM: Obinutuzumab vs Rituximab with chemotherapy (and as maintenance) improves PFS but not OS





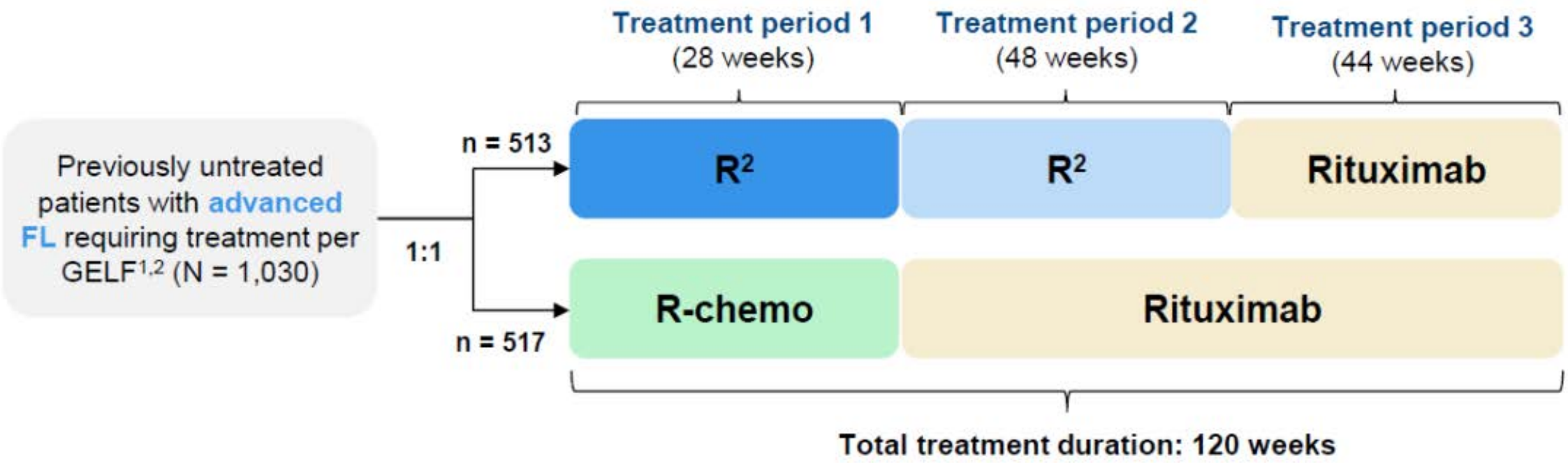
Marcus R, et al. N Engl J Med. 2017; 377:1331-44.

Can we give Obinutuzumab short infusions? Gazelle study

- Phase IV study of Obinutuzumab administered in 90 min infusion in upfront FL patients from cycle 2 onwards
  - Cycle 1 day 1, 8, 15 standard rate, if no G3 IRR, onward 90 min
- 113 patients, only one had grade 3 tox with subsequent 90 min infusion rate
- > 90% pts completed infusions in under 2 hours
- Now FDA approved regimen

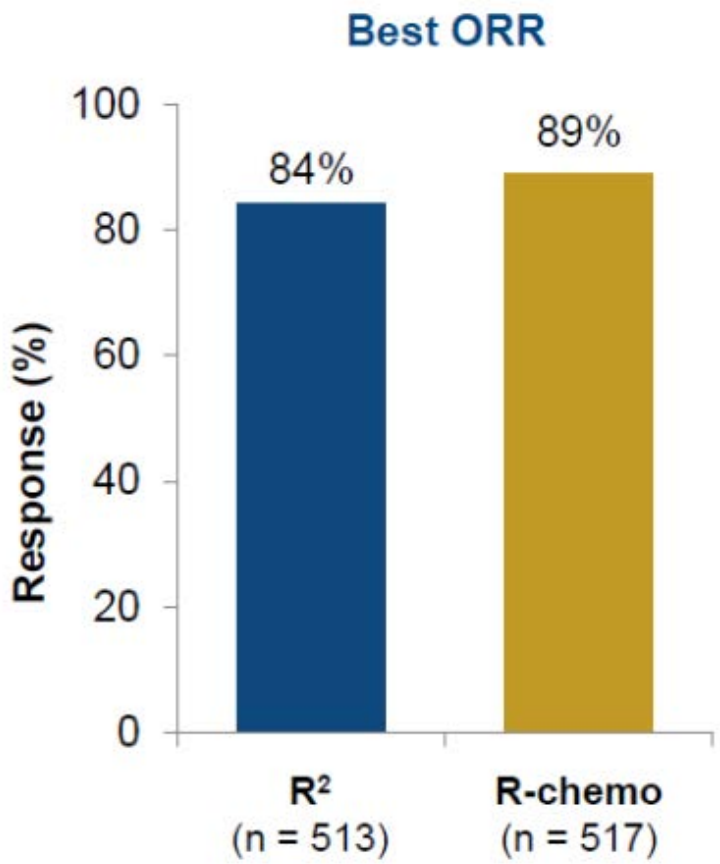
Hubel et al, ICML 2021
Trask et al, ASH 2021

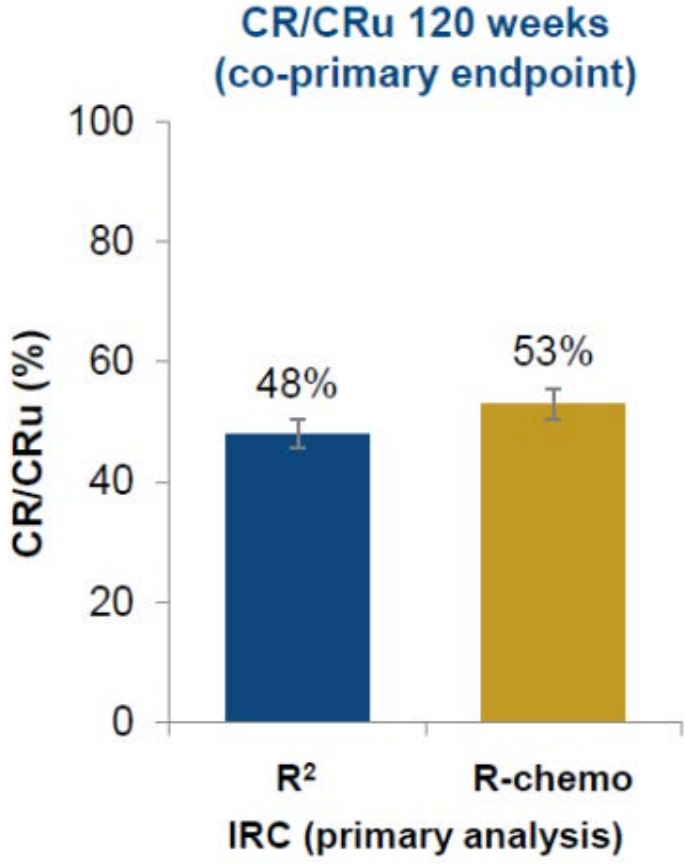
RELEVANCE: Lenalidomide-Rituximab (R2) vs Chemo-R



Morschhauser F, et al, NEJM 2018

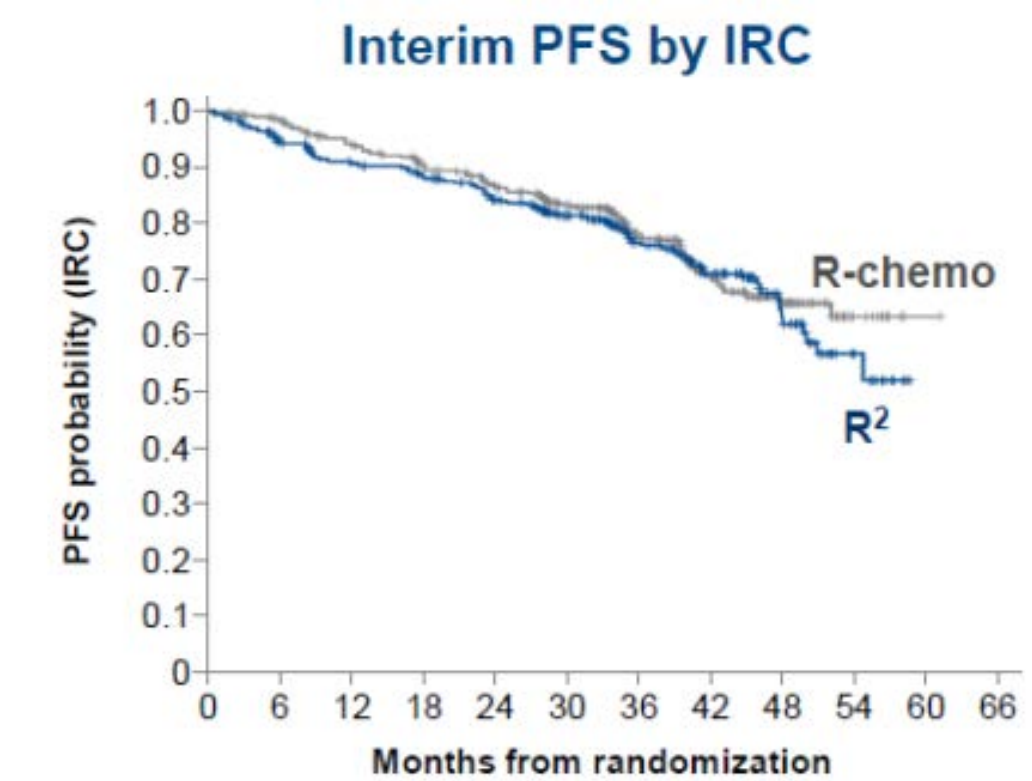
RELEVANCE: Lenalidomide-Rituximab (R2) vs Chemo-R
Similar ORR and CR as initial therapy for FL





Morschhauser F, et al, NEJM 2018

RELEVANCE: Lenalidomide-Rituximab (R2) vs Chemo-R
Similar PFS and OS as initial therapy for FL



Morschhauser F, et al, NEJM 2018

Long term f/u of RELEVANCE study

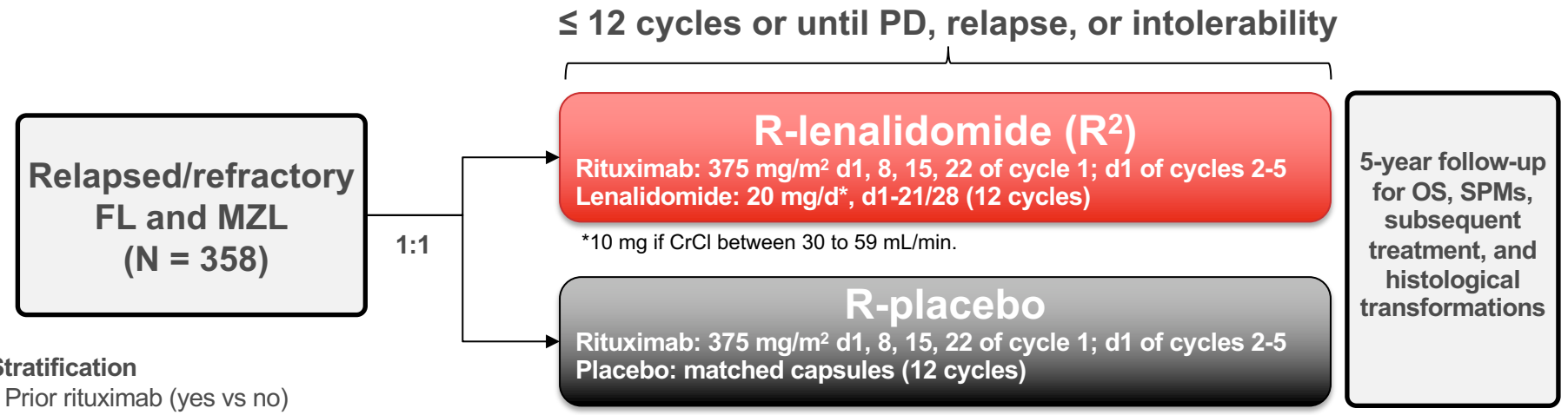
- Median f/u 6 years
- 6 year PFS 60% R2 vs 59% R chemo
- Transformation rates similar (2% range)
- Similar ORR and OS with subsequent therapy in both groups
- Similar rates of second primary malignancies
- 6 year OS 89% in both groups

Morschhauser et al, ASH 2021

Key agents for recurrent FL

- Rituximab retreatment
- Obinutuzumab combination
- Radioimmunotherapy
- Lenalidomide + rituximab
- PI3K inhibitors
- EZH2 inhibitors
- Auto/Allo SCT
- CAR-T
- Novel agents

AUGMENT: R^2 vs rituximab monotherapy in R/R iNHL



Stratification
- Prior rituximab (yes vs no)
- Time since last therapy (≤ 2 vs > 2 y)
- Histology (FL vs MZL)

Key eligibility criteria
- MZL or FL (grades 1-3a) in need of treatment
- ≥ 1 prior chemotherapy, immunotherapy or chemoimmunotherapy
- Not rituximab refractory

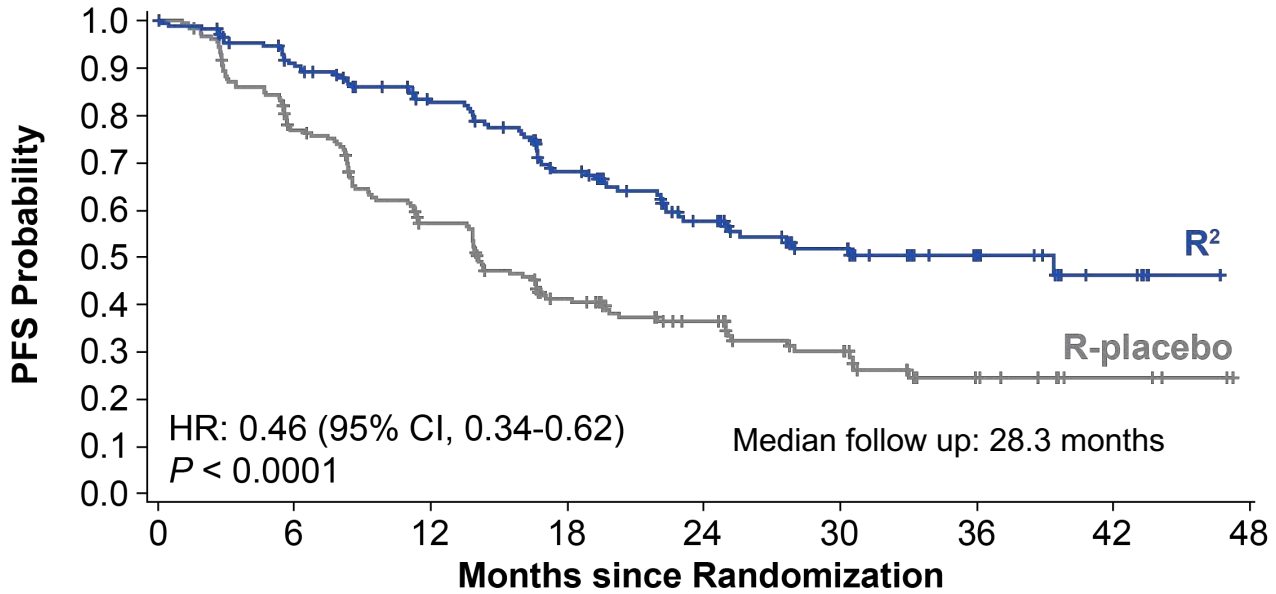
- Primary endpoint: PFS by IRC (2007 IWG criteria w/o PET)

NCT01938001

1. Crawford et al. *Ann Oncol.* 2010;21 Suppl 5:248-251. 2. Smith et al. *J Clin Oncol.* 2015;33:3199-3212.

Leonard et al. JCO 2019

AUGMENT primary endpoint: Progression-free survival (ITT, IRC)



No. at Risk									
R^2	178	148	124	91	59	39	20	7	0
R-placebo	180	132	92	58	40	26	10	4	0

Median PFS	R^2 (n = 178)	R-placebo (n = 180)	HR (95% CI)	*P* Value
By IRC, mo (95% CI)	39.4 (22.9-NE)	14.1 (11.4-16.7)	0.46 (0.34-0.62)	< 0.0001
By investigator, mo (95% CI)	25.3 (21.2-NE)	14.3 (12.4-17.7)	0.51 (0.38-0.69)	< 0.0001

*Censoring rules based on FDA guidance.
Data cutoff June 22, 2018.

Leonard et al. JCO 2019

GADOLIN study: bendamustine vs bendamustine + obinutuzumab in rituximab-refractory iNHL

Rituximab-refractory CD20 + iNHL (including FL, MZL, and SLL), n = 413

Stratification factors

- NHL subtype (FL vs other)
- Prior therapies (≤ 2 vs > 2)
- Refractory type (R-mono vs R-chemo)
- Geographic region

R 1:1

Obinutuzumab
1,000 mg i.v. Days 1, 8, and 15 Cycle 1;
Day 1 Cycles 2–6 (28-day cycles)

Bendamustine
90 mg/m^2/day i.v. Days 1 and 2
Cycles 1–6 (28-day cycles)

CR/PR/SD

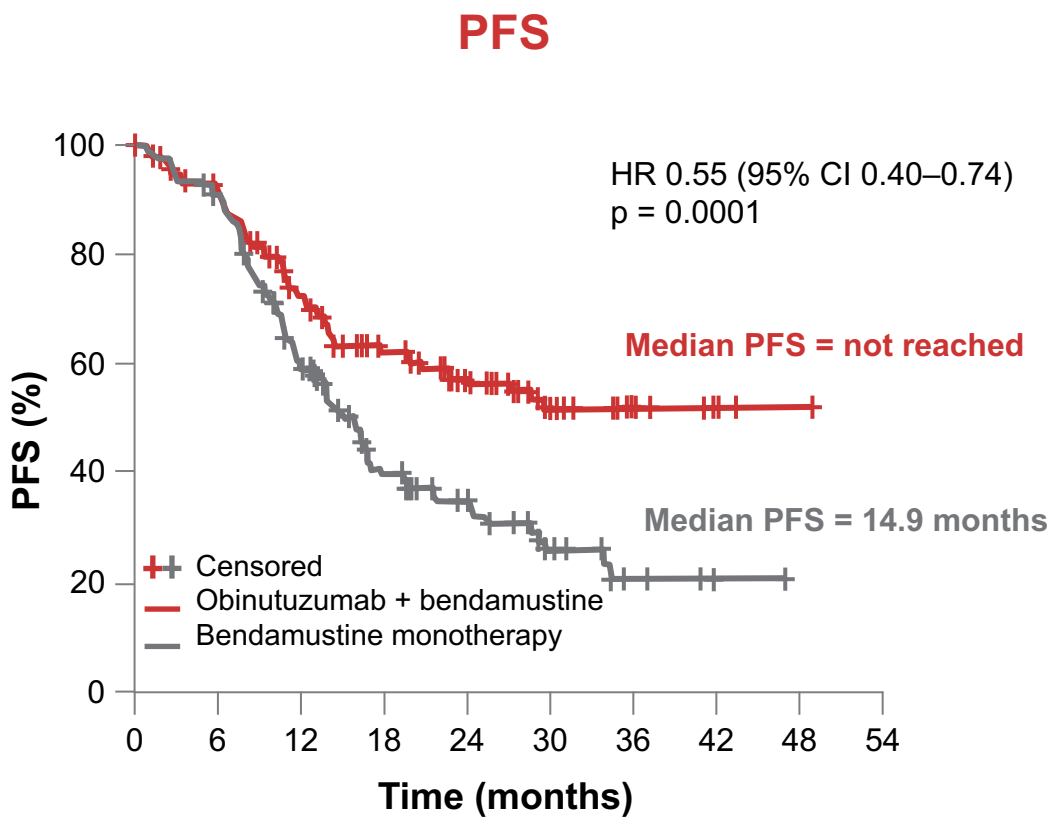
Obinutuzumab maintenance
1,000 mg i.v. q2mo
for 2 years
or until progression

Bendamustine
120 mg/m^2/day
Days 1 and 2
Cycles 1–6 (28-day cycles)

Response monitored by CT scan post-induction, then every 3 months for 2 years, then every 6 months

Sehn LH, et al. Lancet Oncol. 2016;17:1081-93.

GADOLIN study: obinutuzumab improves PFS and OS in recurrent iNHL when added to bendamustine



The addition of obinutuzumab also improved PFS in patients who were refractory to both alkylators and rituximab

- HR 0.56 (0.40–0.78)

Final analysis: Median OS was 88.3 months with the addition of obinutuzumab vs 65.6 months

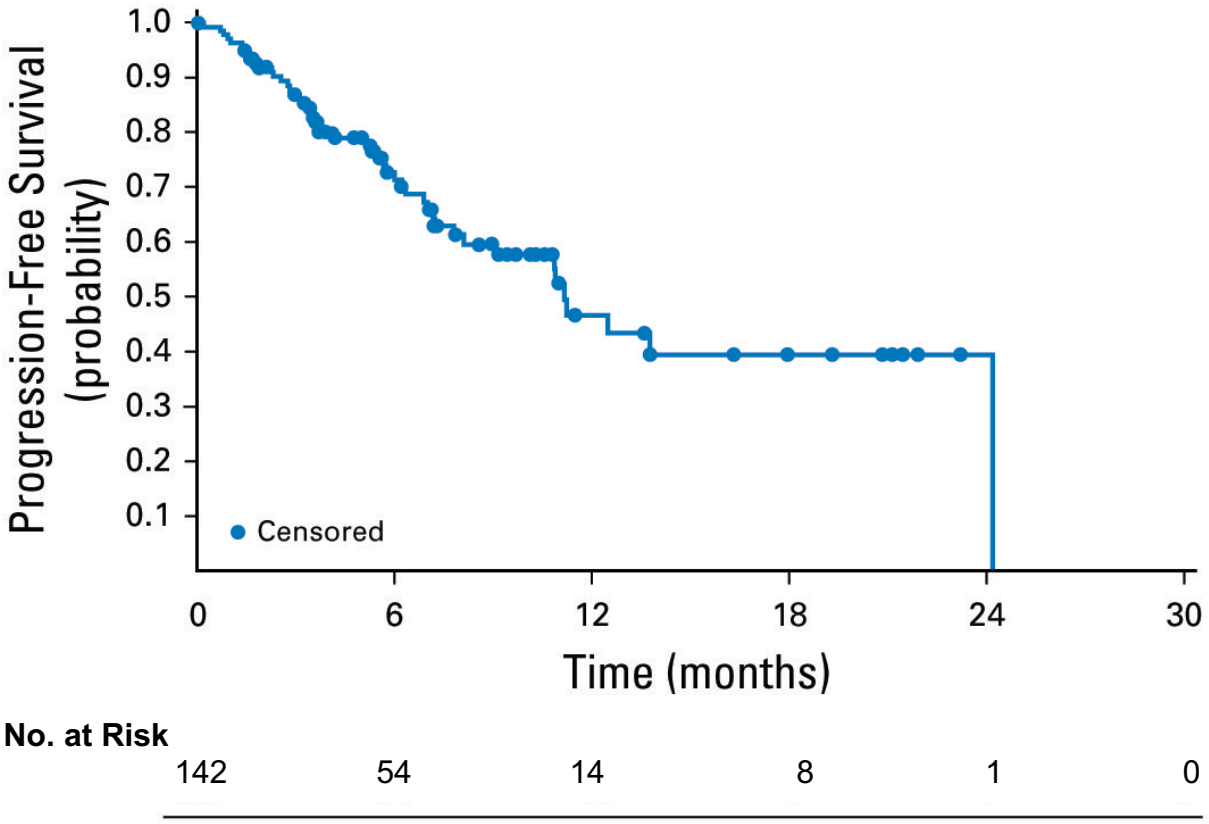
- HR 0.77; p = 0.0810

Sehn LH, et al. Lancet Oncol. 2016;17:1081-93. Sehn LH et al. ASH 2019;Abstract 2822.

PI3K inhibitors with FL FDA indications withdrawn from market

- Idelalisib (Gopal NEJM 2014)
  - ORR in iNHL 59%, median duration 11.2 mo
- Duvelisib (Zinzani ICML 2017)
  - ORR iNHL 46%, median duration 9.9 mo
- Umbralisib (FDA 2021)
  - ORR FL 43%, median duration 11.1 mo

PFS of Copanlisib in R/R Indolent Lymphoma



Median, mo	11.2
Range	0.2-24.0
95% CI	8.1-24.0

ORR 59% (12% CR)

Dreyling M et al. J Clin Oncol. 2017;35:3898-3905.

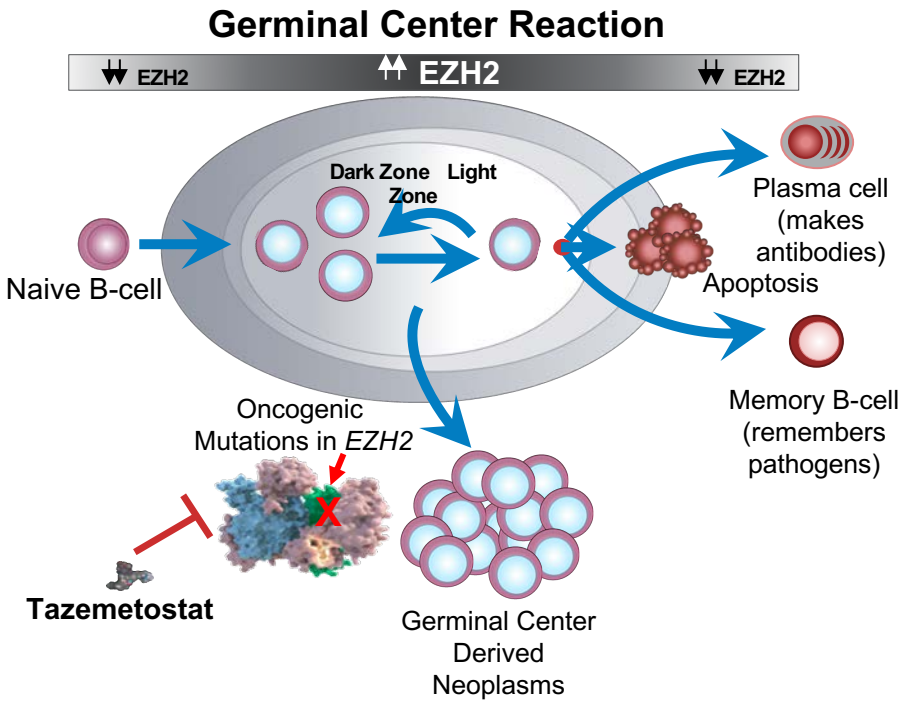
Chronos-3 study (Copanlisib + Rituximab vs Placebo + Rituximab)

- Randomized trial of Copanlisib/R vs Placebo/R (Lancet Oncol 2021)
  - 307 pts, recurrent indolent lymphoma
  - 79% ORR/34% CR in C/R arm, 20.4 months DoR
  - Favored C/R vs P/R by primary endpoint
  - Followup analysis (ASH 2021) – longer response for those remaining on therapy vs d/c for toxicity but some durable responses after early discontinuation

Matasar et al, Lancet Oncol 2021

Follicular Lymphoma and EZH2

- *EZH2* an epigenetic regulator of gene expression and cell fate decisions[1]
- *EZH2* is required for normal B-cell biology and germinal center formation[2]
  - Oncogenic mutations in *EZH2* suppress exit from germinal state and “lock” B cells in this state thereby transforming into a cancer[2]
- *EZH2* biology relevant in both mutant (MT) and wild-type (WT) *EZH2* FL
  - ~20% of patients with FL also have *EZH2* gain of function mutations[3]



1. Gan L, et al. *Biomark Res*. 2018;6(1):10; 2. Béguelin W, et al. *Cancer Cell*. 2013;23(5)677-692. 3. Bödör C, et al. *Blood*. 2013;122:3165-3168. 4. Italiano A, et al. *Lancet Oncol*. 2018;19(5):649-59; 5. Morschhauser F, et al. *Hematol*

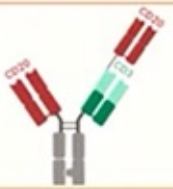
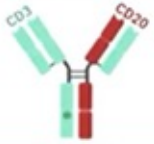
Tazemetostat, an investigational, selective, oral inhibitor of EZH2 has shown antitumor activity in non-Hodgkin’s lymphoma patients with either MT or WT EZH2[4,5]

Tazemetostat ORR in EZH2 mutant and wild type populations (recurrent FL)

	EZH2 Mutant Cohort (n=45)		*EZH2* WT Cohort (n=54)	
Parameter	**Investigator**	**IRC**	**Investigator**	**IRC**
ORR, n (%)	**35 (78)**	**31 (69)**	**18 (33)**	**19 (35)**
CR, n (%)	4 (9)	6 (13)	3 (6)	2 (4)
PR, n (%)	31 (69)	25 (56)	15 (28)	17 (31)
SD, n (%)	10 (22)	13 (29)	16 (30)	18 (33)
PD, n (%)	0	1 (2)[c]	16 (30)	12 (22)
DOR, months, median (95% CI)	8.3 (5.5–13.8)	10.9 (7.2–NE)	14.7 (7.6–NE)	13.0 (5.6–NE)

Morschhauser, ICML 2019

Structure of selected BITE and bispecific antibodies

Bispecific Antibody	Targets	Design	Ig Fragment Formats	Ref.
blinatumomab	CD19 x CD3		• two murine scFv joined by a glycine-serine linker • monovalent CD19 and monovalent CD3 binding • cloned from anti-CD19 (clone HD37) and anti-CD3 (clone L2K-07) murine mAbs	1, 2, 3
mosunetuzumab	CD20 x CD3		• humanized mouse heterodimeric IgG1-based antibody • monovalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	4
glofitamab	$(CD20)_2$ x CD3		• humanized mouse IgG1-based antibody • bivalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding	5
odronextamab	CD20 x CD3		• fully human IgG4-based heterodimeric antibody • monovalent CD20 and monovalent CD3ε binding • Fc-dependent effector function-minimized antibody with Fc of the anti-CD3ε heavy chain modified to reduce Protein A binding • common κ light chain from anti-CD3ε mAb	6
epcoritamab	CD20 x CD3		• humanized mouse IgG1-based heterodimeric antibody • monovalent CD20 and monovalent CD3 binding • IgG1 Fc modified to minimize Fc-dependent effector functions and to control Fab-arm exchange of mAb half-molecules, resulting in high bispecific product yield	7

Ig, immunoglobulin; scFv, single-chain variable fragment; mAb, monoclonal antibody; Fc, fragment crystallizable; FcγR, Fc gamma receptor

[1]Dufner V, *et al.* Blood Adv (2019) 3:2491; [2]Goebeler ME, *et al.* J Clin Oncol (2016) 34:1104; [3]Viardot *et al.* Blood (2016) 127(11):1410; [4]Schuster SJ, *et al.* ASH 2019, Plenary Abstract 6; [5]Hutchings M, *et al.* ASH 2020, Abstract 403; [6]Bannerji R, *et al.* ASH 2020, Abstract 400; [7]Hutchings M, *et al.* ASH 2020, Abstract 406

Schuster et al, ICML 2021

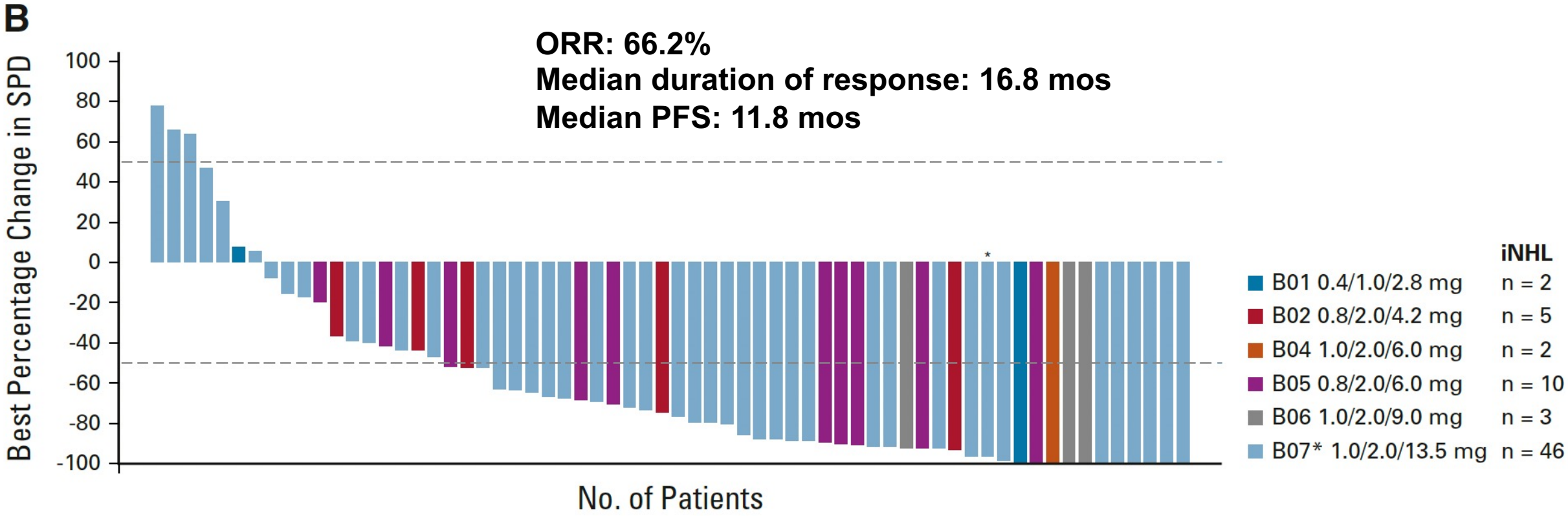
original reports

Single-Agent Mosunetuzumab Shows Durable Complete Responses in Patients With Relapsed or Refractory B-Cell Lymphomas: Phase I Dose-Escalation Study

Lihua E. Budde, MD[1]; Sarit Assouline, MD[2]; Laurie H. Sehn, MD[3]; Stephen J. Schuster, MD[4]; Sung-Soo Yoon, MD, PhD[5]; Dok Hyun Yoon, MD, PhD[6]; Matthew J. Matasar, MD[7]; Francesc Bosch, MD, PhD[8]; Won Seog Kim, MD, PhD[9]; Loretta J. Nastoupil, MD[10]; Ian W. Flinn, MD, PhD[11]; Mazyar Shadman, MD, MPH[12]; Catherine Diefenbach, MD[13]; Carol O'Hear, MD, PhD[14]; Huang Huang, MSc[15]; Antonia Kwan, MBBS, PhD[14]; Chi-Chung Li, PhD[14]; Emily C. Piccione, PhD[14]; Michael C. Wei, MD, PhD[14]; Shen Yin, PhD[14]; and Nancy L. Bartlett, MD[16]

J Clin Oncol 2022; 40(5):481-91.

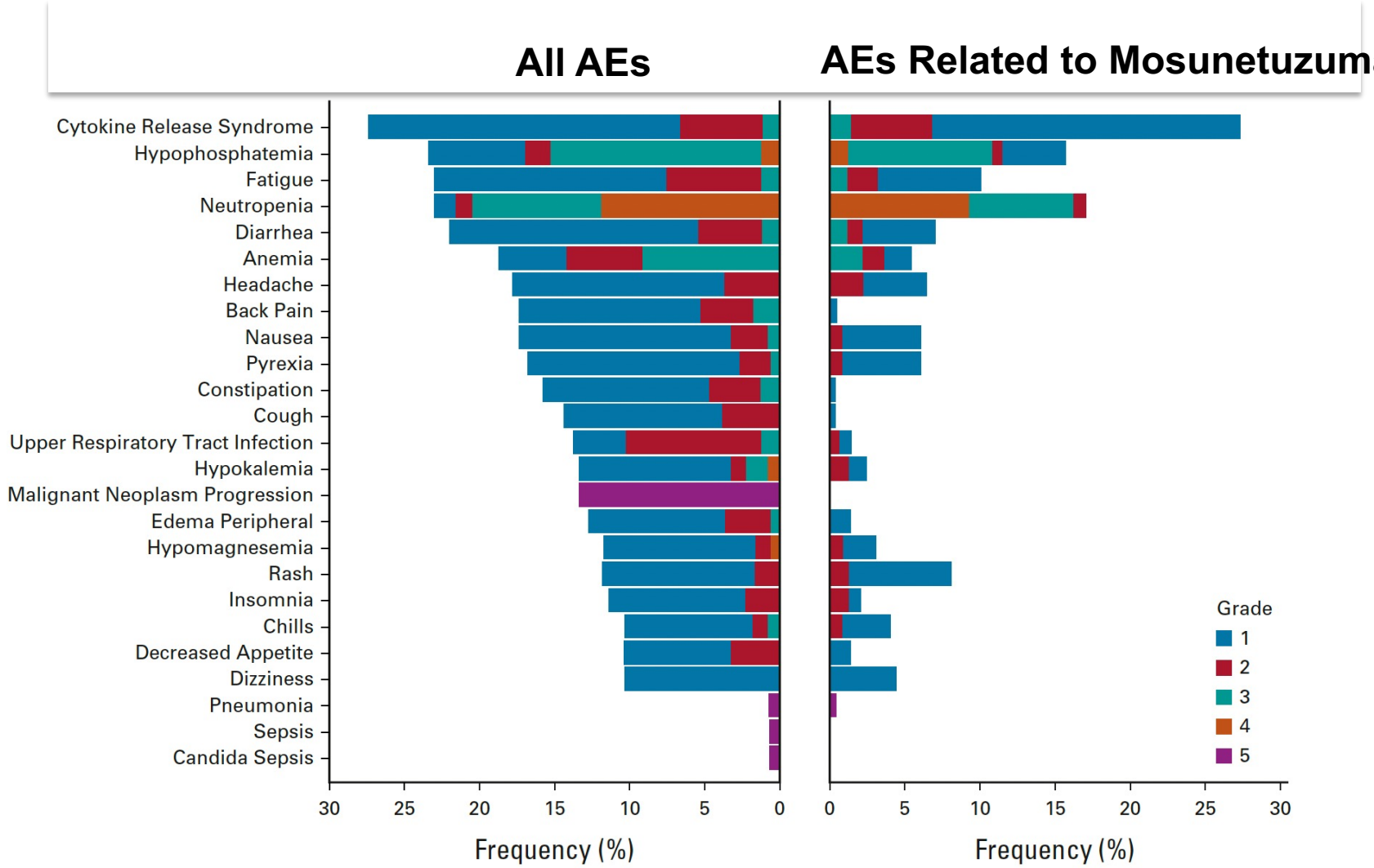
Best Percentage Change from Baseline in Indolent NHL, Including Grade 1-3a FL



Weill Cornell Medicine NewYork-Presbyterian

Budde LE et al. *J Clin Oncol* 2022;40(5):481-91.

Adverse Events with Incidence ≥ 10%



Budde LE et al. *J Clin Oncol* 2022;40(5):481-91.

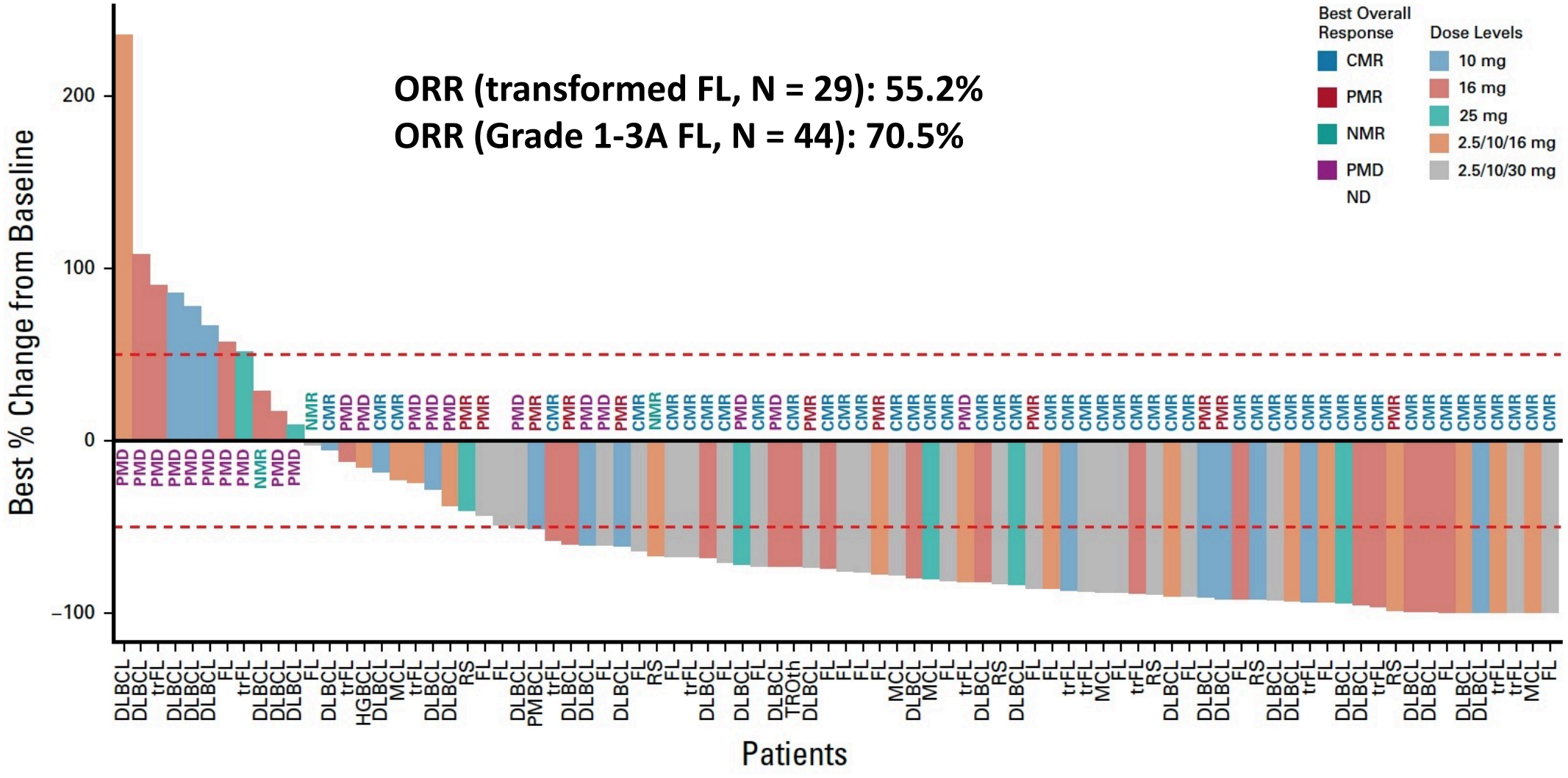
rapid communications

Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell–Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial

Martin Hutchings, PhD[1]; Franck Morschhauser, MD, PhD[2]; Gloria Iacoboni, MD[3,4]; Carmelo Carlo-Stella, MD[5]; Fritz C. Offner, MD, PhD[6]; Anna Sureda, MD, PhD[7]; Gilles Salles, MD[8]; Joaquín Martínez-Lopez, MD, PhD, MBA[9]; Michael Crump, MD[10]; Denise N. Thomas, MSc[11]; Peter N. Morcos, PharmD[11]; Cristiano Ferlini, MD[11]; Ann-Marie E. Bröske, PhD[12]; Anton Belousov, PhD[13]; Marina Bacac, PhD[13]; Natalie Dimier, PhD[14]; David J. Carlile, PhD[14]; Linda Lundberg, PhD[15]; David Perez-Callejo, MD, PhD[15]; Pablo Umaña, PhD[13]; Tom Moore, MD[12]; Martin Weisser, MD[12]; and Michael J. Dickinson, MBBS, DMedSci[16]

J Clin Oncol 2021;39:1959-70.

Response to Glofitamab in Patients with R/R B-Cell Lymphomas



Hutchings M et al. *J Clin Oncol* 2021;39:1959-70.

128

Glofitamab as Monotherapy and in Combination with Obinutuzumab Induces High Complete Response Rates in Patients with Multiple Relapsed or Refractory (R/R) Follicular Lymphoma (FL)

Franck Morschhauser,[1] Carmelo Carlo-Stella,[2] Michael Dickinson,[3] Tycel Phillips,[4] Roch Houot,[5] Fritz Offner,[6] Corinne Haioun,[7] Paolo Corradini,[8] Martin Hutchings,[9] Anna Sureda,[10] Joaquin Martinez-Lopez,[11] Tomasz Wróbel,[12] Shang-Ju Wu,[13] Linda Lundberg,[14] Estefania Mulvihill,[14] David Perez-Callejo,[14] James Relf,[15] Anesh Panchal,[15] Kathryn Humphrey,[15] Emmanuel Bachy[16]

[1]CHU Lille, Service des Maladies du Sang, F-59000 Lille, France; [2]Humanitas University and Humanitas Research Hospital, Milan, Italy; [3]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, Australia; [4]University of Michigan Medical School, Ann Arbor, Michigan, USA; [5]CHU de Rennes, Université de Rennes, INSERM U1236, EFS, Rennes, France; [6]Universitair Ziekenhuis Gent, Ghent, Belgium; [7]Hôpital Henri Mondor, AP-HP, Créteil, France; [8]University of Milan; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [9]Rigshospitalet, Copenhagen, Denmark; [10]Institut Català d'Oncologia Hospitalet, IDIBELL, Universitat de Barcelona, Barcelona, Spain; [11]Hospital Universitario 12 de Octubre (H12O), Centro Nacional de Investigaciones Oncológicas (CNIO)-H12O and Universidad Complutense de Madrid, Madrid, Spain; [12]Wroclaw Medical University, Wroclaw, Poland; [13]National Taiwan University Hospital, Taipei, Taiwan; [14]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [15]Roche Products Ltd, Welwyn Garden City, United Kingdom; [16]Hospices Civils de Lyon and Université Claude Bernard, Pierre-Bénite, France.

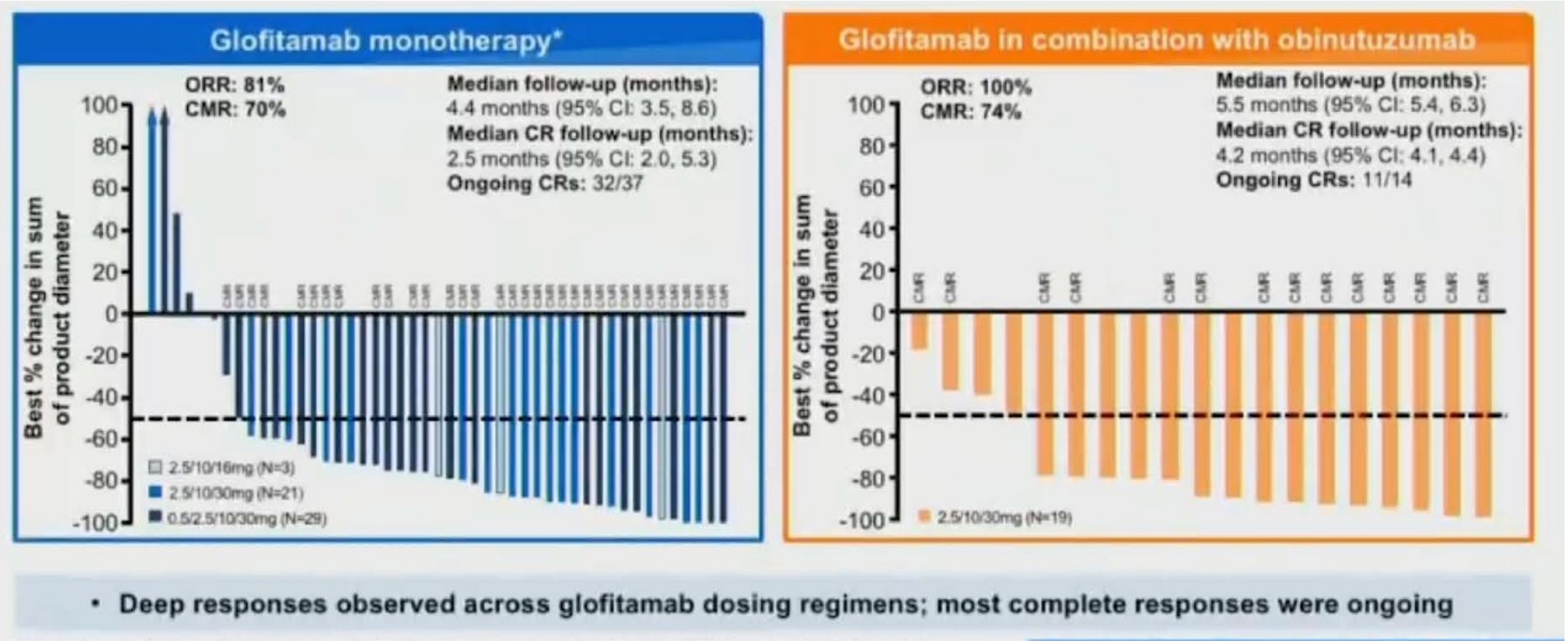
Accepted as an Oral Presentation at the 63rd ASH Annual Meeting and Exposition

63rd ASH® Annual Meeting and Exposition

Weill Cornell Medicine NewYork-Presbyterian

ASH 2021;Abstract 128.

Phase I/II Study of Glofitamab as Monotherapy or in Combination with Obinutuzumab for R/R FL



- Myelosuppression was more common with the combination
- CRS rates were high and comparable, and cases were mainly low grade

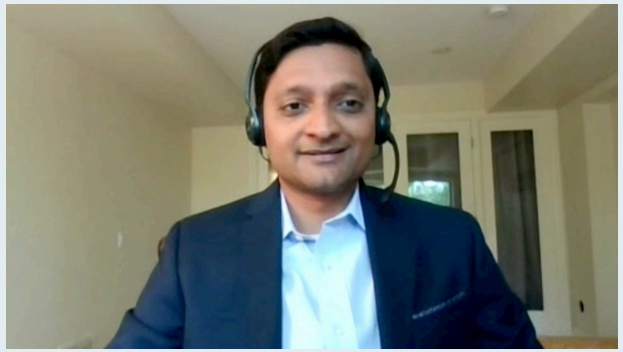
Weill Cornell Medicine NewYork-Presbyterian

Morschhauser F et al. ASH 2021;Abstract 128.

Key challenges in management of follicular lymphoma

- **What will it take to "dislodge" watch and wait as a standard option?**
  - Randomized trial with OS benefit? Clear QOL benefit? Evidence of "cure"?
- **How will we ever define a "cure"?**
  - Potentially "cured" patients can relapse 15+ years later
  - Should "functional cure" be the goal and how is that defined?
- **How can we better choose individualized "QOL targeted" rx?**
  - For regimens with similar OS, value of PFS benefit vs QOL
- **Can we move to risk-adapted rx (induction, consolidation, maintenance)?**
  - Prognostic scores, tumor/patient profiling, PET, MRD, ctDNA

MODULE 4: Mantle Cell Lymphoma (MCL) – Dr Lunning



Dr Vignesh Narayanan
(Lone Tree, Colorado)

A 77-year-old woman with newly diagnosed asymptomatic MCL with extranodal involvement

A 56-year-old man with blastoid variant MCL with a TP53 mutation

RTP
RESEARCH
TO PRACTICE

An 83-year-old man with MCL and disease progression on acalabrutinib

Dr Shams Bufalino (Park Ridge, Illinois)

RTP
RESEARCH
TO PRACTICE

Mantle Cell Lymphoma

Wrestle Mania

Matthew Lunning D.O. FACP
Associate Professor

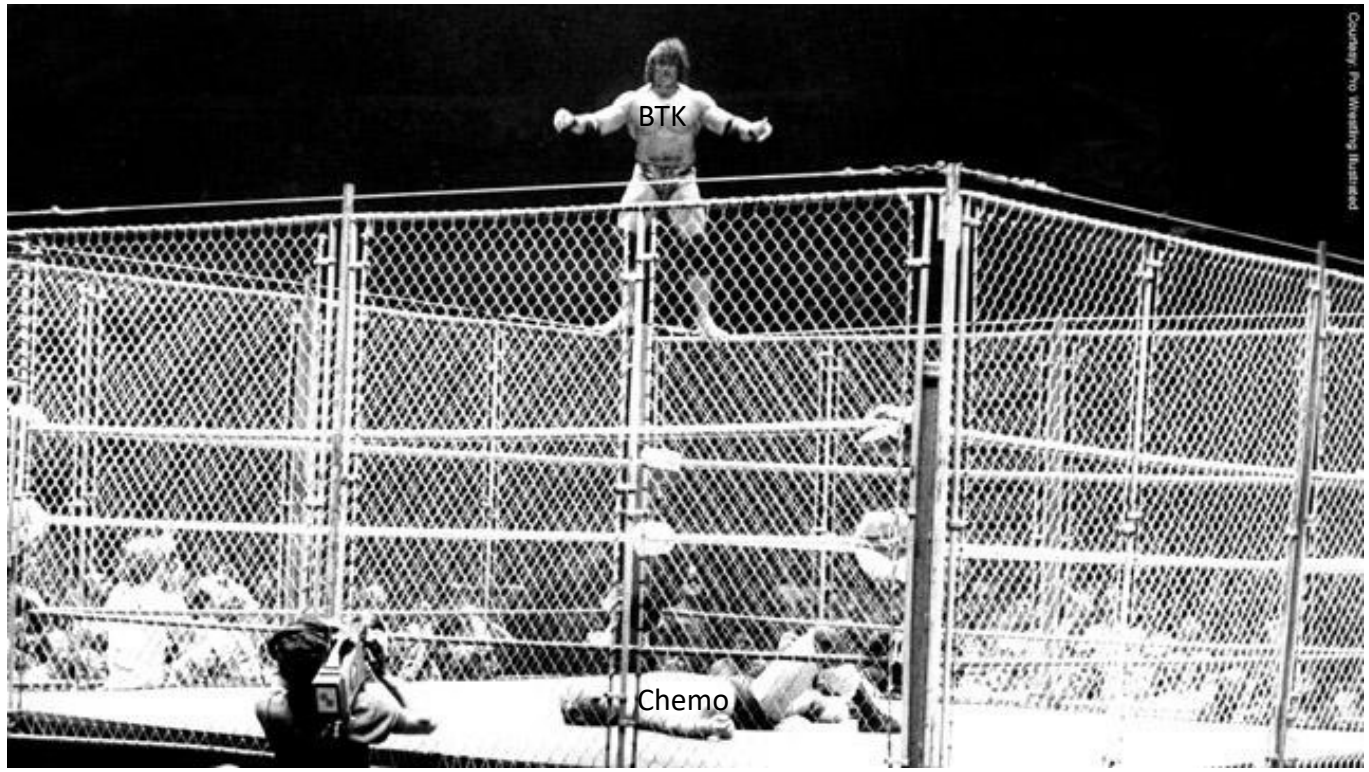
A National Cancer Institute
Designated Cancer Center

FRED & PAMELA
BUFFETT CANCER CENTER

Objectives

- Discuss current use of Bruton Tyrosine Kinase (BTK) inhibitors (i) in 1st line and relapsed/refractory (rel/ref) mantle cell lymphoma (MCL)
- Discuss results from studies presented at ASCO 2022 in MCL
- Discuss trial outcomes with BTK in combination with other systemic therapies for patients with MCL
- Discuss the outcomes of pirtobrutinib in patients with rel/ref MCL
- Discuss new agents and strategies in MCL

BTK Cage Match



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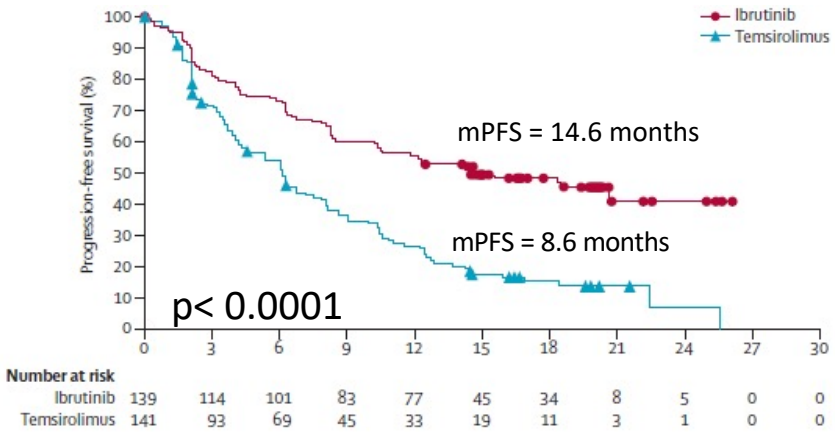
BTK Cage Match

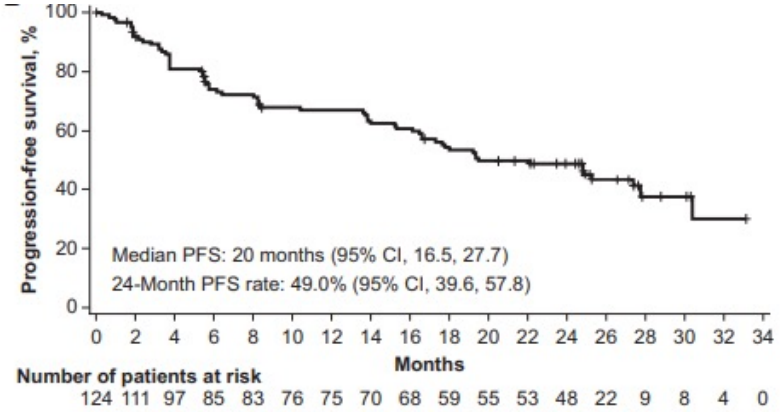
Ibrutinib

Median prior txts = 2



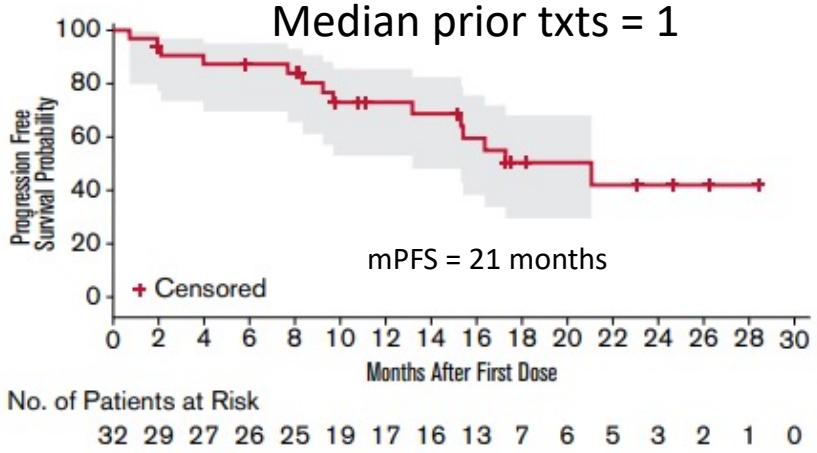
Acalabrutinib

Median prior txts = 2



Zanubrutinib

Median prior txts = 1



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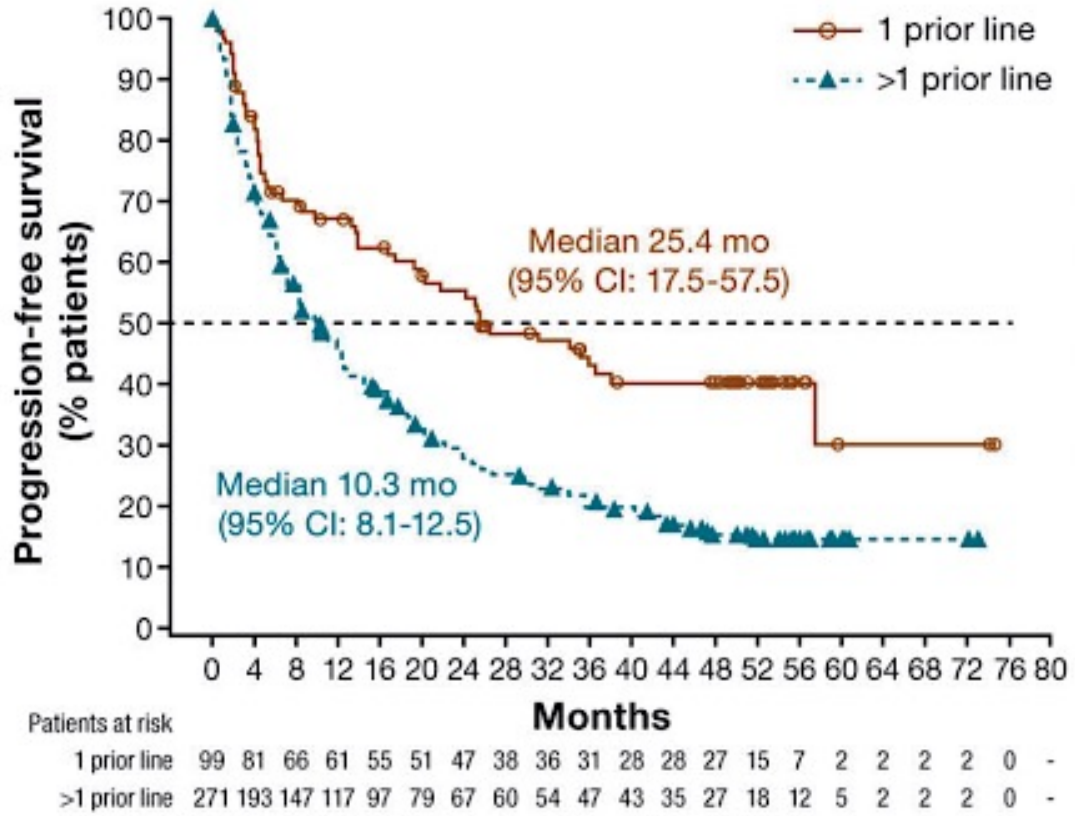
Dreyling M et al. Lancet 2016; Wang et al. Leukemia 2019; Tam et al. Blood Advances 2021

Entering the Cage Match

Ibrutinib



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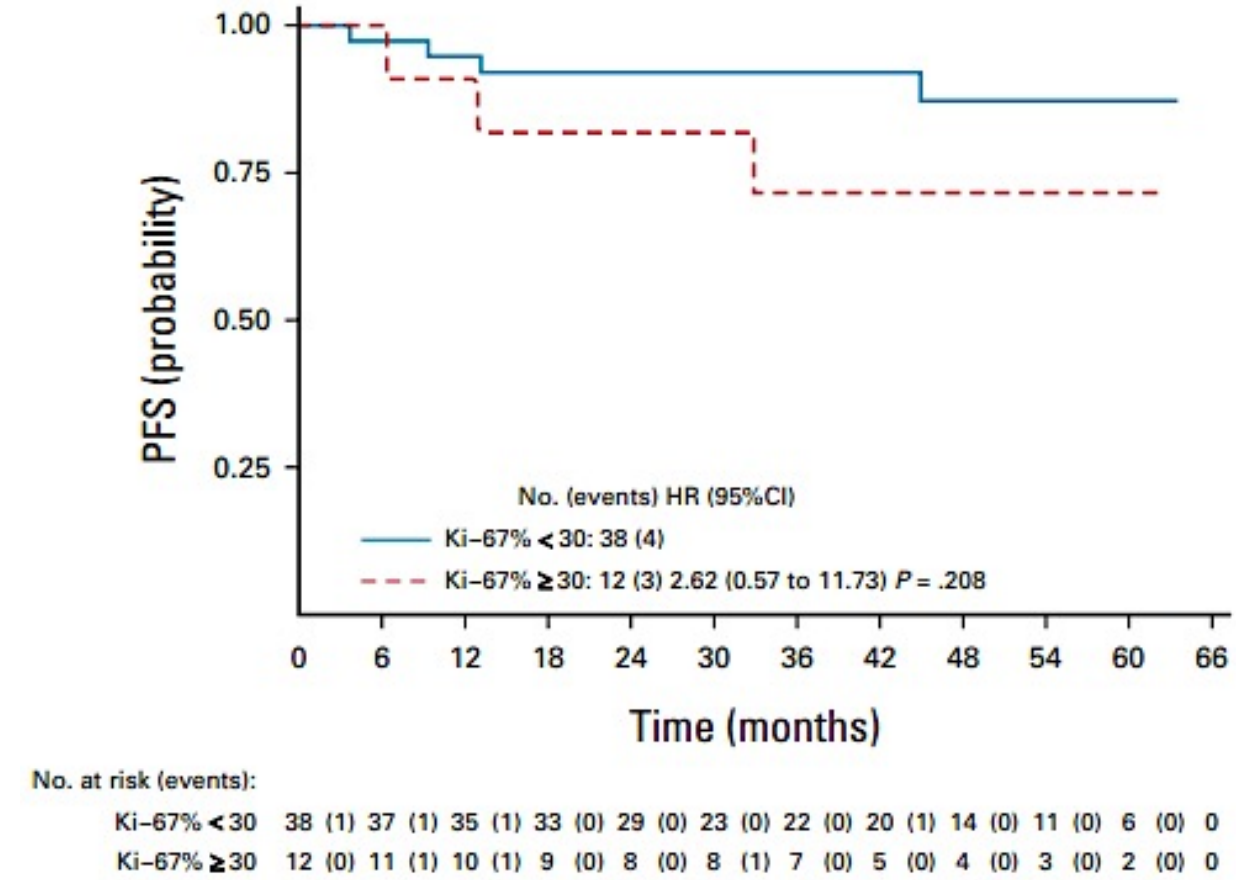
Rule et al. Haematologica 2019

Starting The Cage Match

Ibrutinib



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Jain et al. JCO 2022

Elimination Chamber

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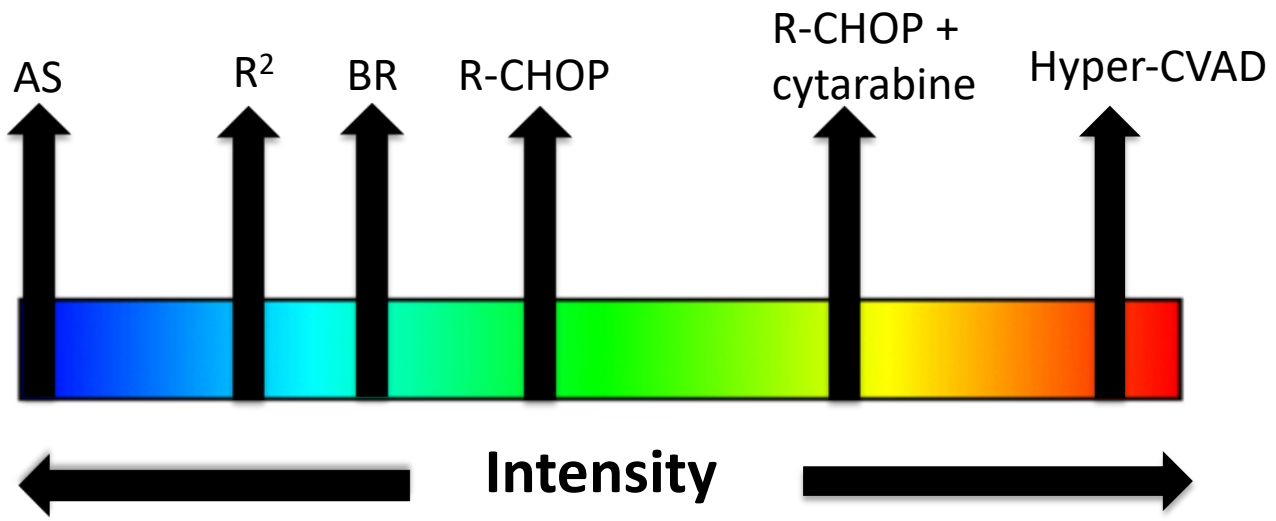
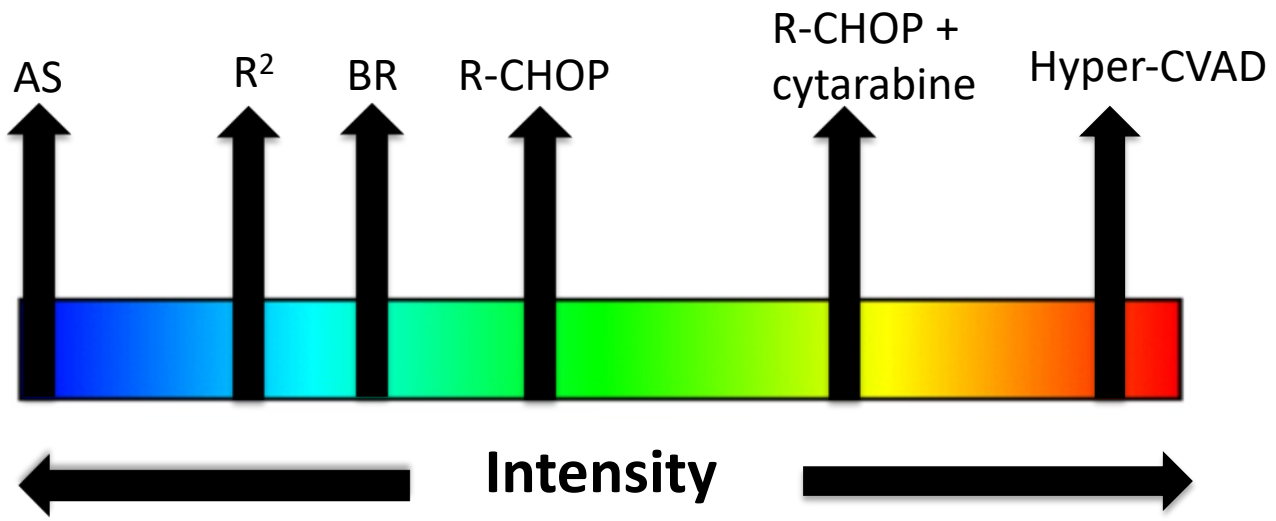
Elimination Chamber



Elimination Chamber



Where Does BTKi Fit?

Shine 2022

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BUFFETT CANCER CENTER

Shine 2022

		Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median age (range), years		71 (65-86)	71 (65-87)
≥ 75 years, n (%)		74 (28.4)	82 (31.3)
Male, n (%)		178 (68.2)	186 (71.0)
ECOG PS 1, n (%)		127 (48.7)	118 (45.0)
Simplified MIPI, n (%)	Low risk	44 (16.9)	46 (17.6)
	Intermediate risk	124 (47.5)	129 (49.2)
	High risk	93 (35.6)	87 (33.2)
Bone marrow involvement, n (%)		198 (75.9)	200 (76.3)
Blastoid/pleomorphic histology, n (%)		19 (7.3)	26 (9.9)
Extranodal, n (%)		234 (89.7)	226 (86.3)
Bulky (≥ 5 cm), n (%)		95 (36.4)	98 (37.4)
TP53 mutated, n (%)		26 (10.0)	24 (9.2)
TP53 mutation status unknown, n (%)		121 (46.4)	133 (50.8)

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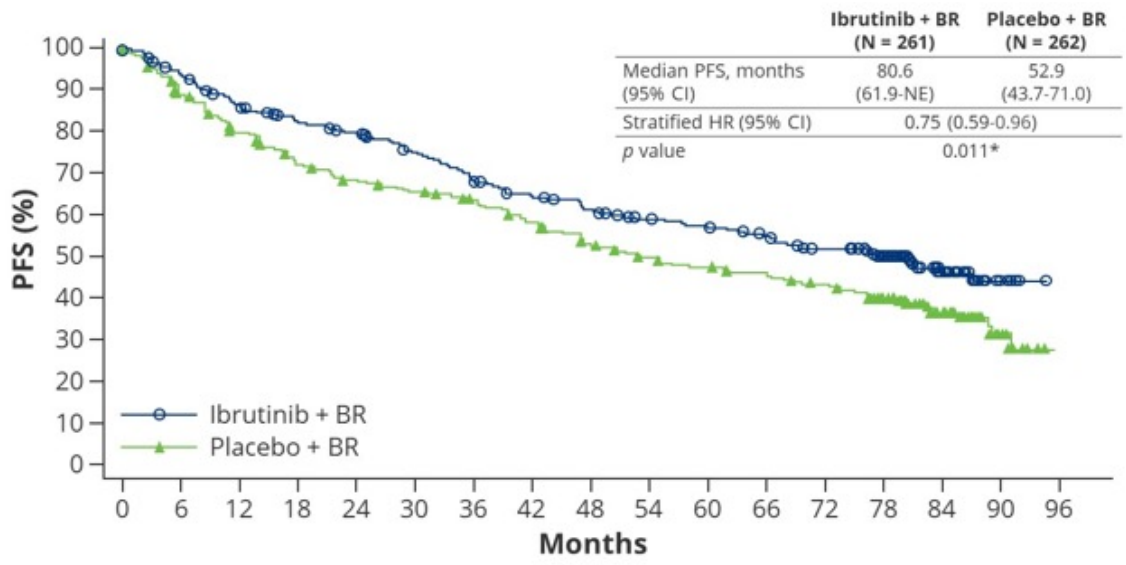
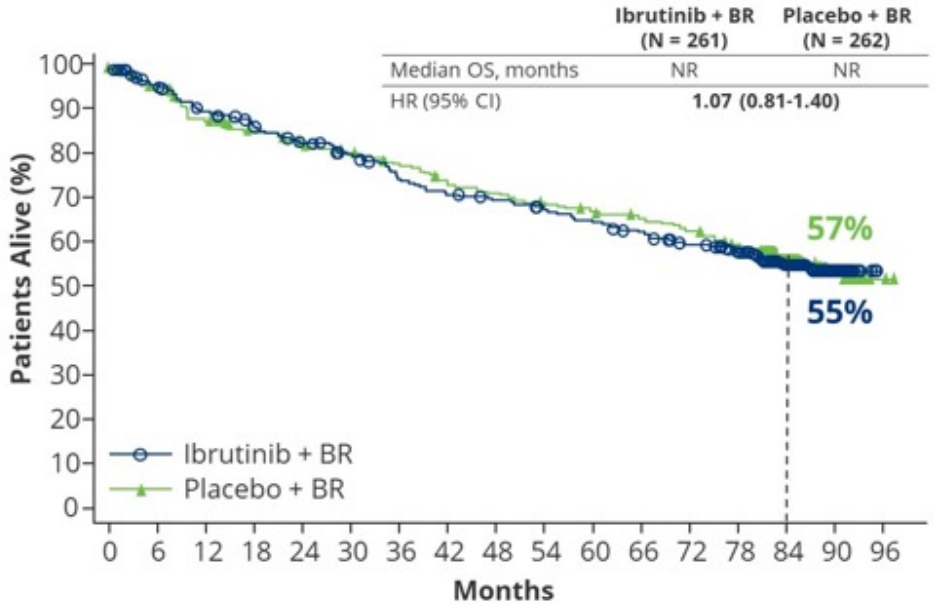
Wang et al. ASCO 2022 LBA7502

Shine 2022



Patients at Risk

Ibrutinib + BR	261	228	207	191	182	167	152	139	130	120	115	106	95	78	39	11	0
Placebo + BR	262	226	199	177	166	158	148	135	119	109	103	98	90	78	41	11	0



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

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Wang et al. ASCO 2022 LBA 7502

Shine 2022

	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

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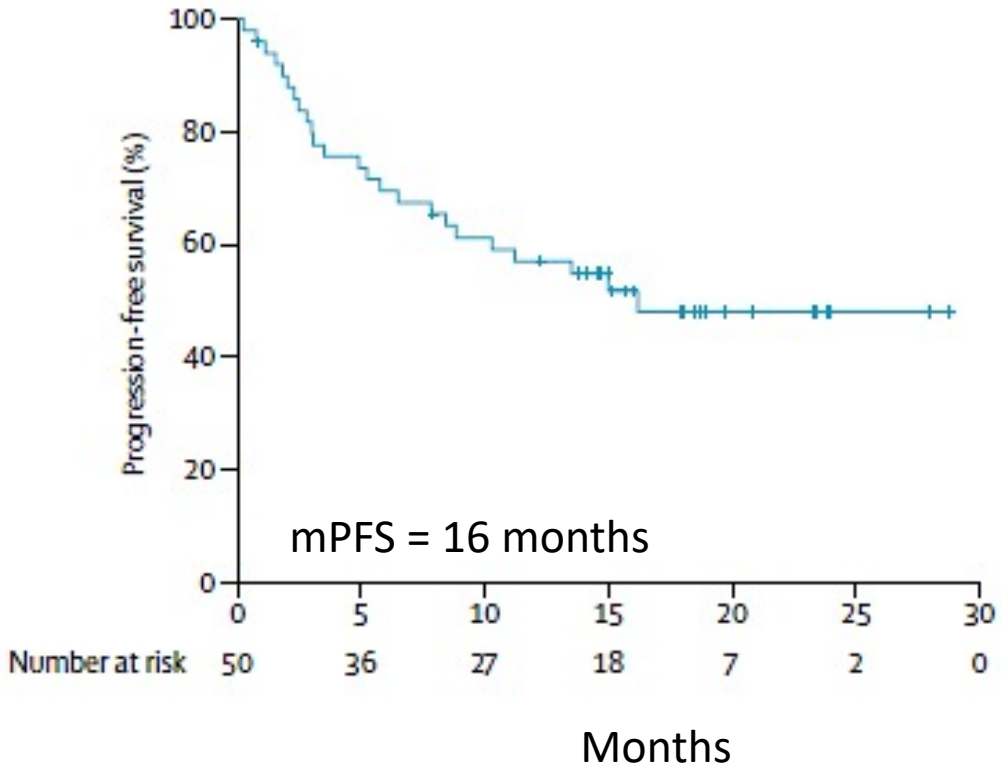
Wang et al. ASCO 2022 LBA 7502

Tag Teaming MCL

Legion of Doom

Tag Teaming MCL: Ibrutinib + R^2

	All patients (n=50)
Age (years)	69 (45–85)
Sex	
Female	14 (28%)
Male	36 (72%)
ECOG performance status score 0–1	45 (90%)
MIPI score	
Low risk (<5·7)	8 (16%)
Intermediate risk (5·7–6·1)	15 (30%)
High risk (>6·2)	23 (46%)
Missing	4 (8%)
Ann Arbor stage IV disease	42 (84%)
Bone marrow involvement	34 (68%)
Refractory disease	8 (16%)
Number of previous therapies	2 (1–7)
Previous therapy	
Autologous stem-cell transplantation	21 (42%)
Allogeneic stem-cell transplantation	3 (6%)
Ibrutinib	4 (8%)
Lenalidomide	1 (2%)



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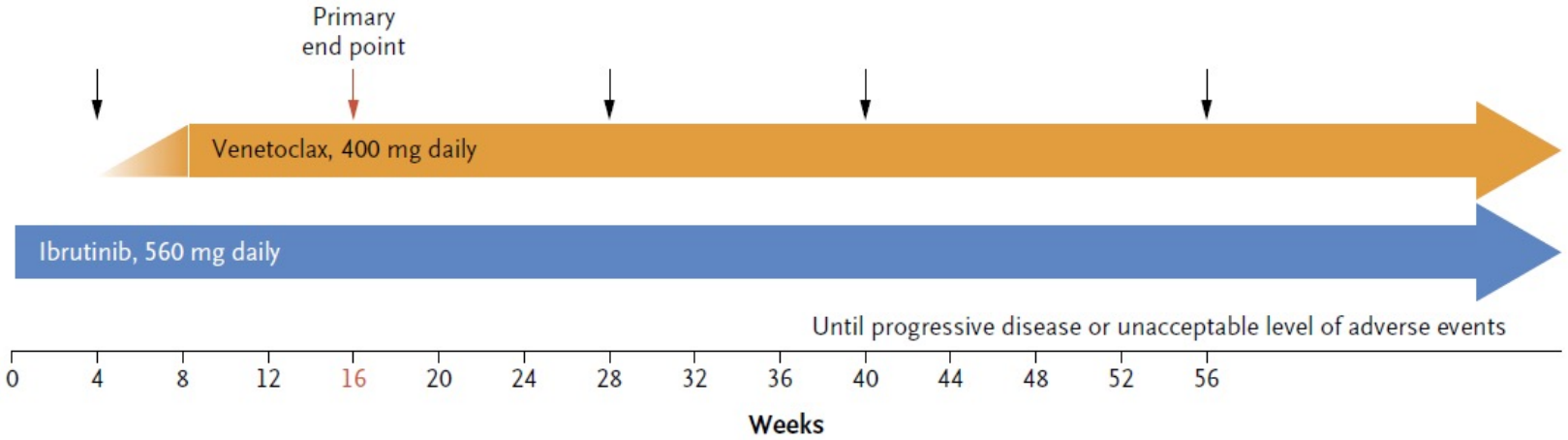
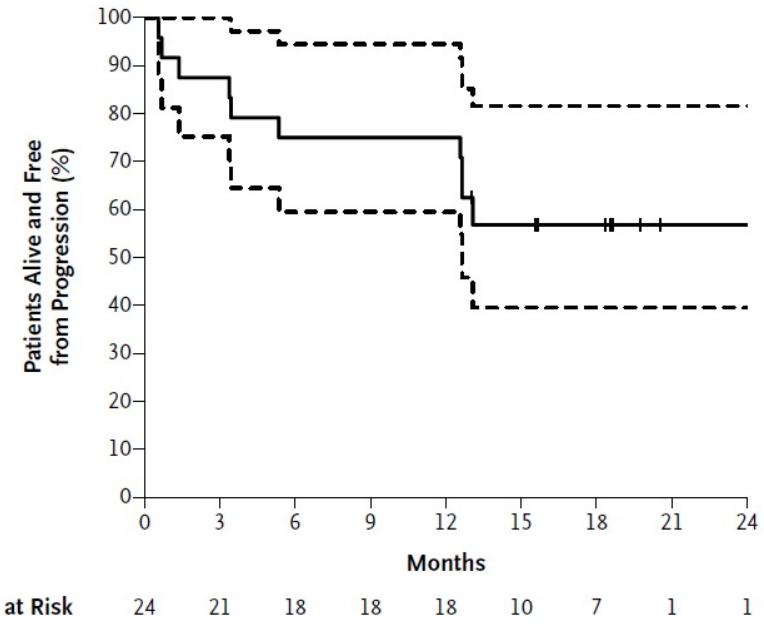
Jerkeman et al. Lancet Haematology 2018

Tag Teaming MCL: Venetoclax + Ibrutinib





CR=62%

Tam C et al. NEJM 2018

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Tag Teaming MCL: 3-year Follow-up

Figure 1. Progression free survival (Dashed lines represent 95% confidence interval)

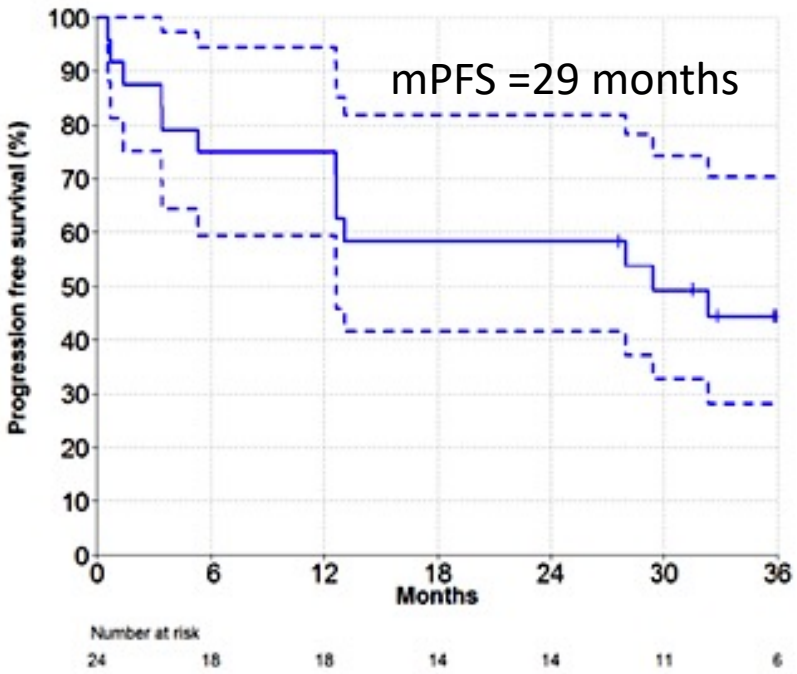
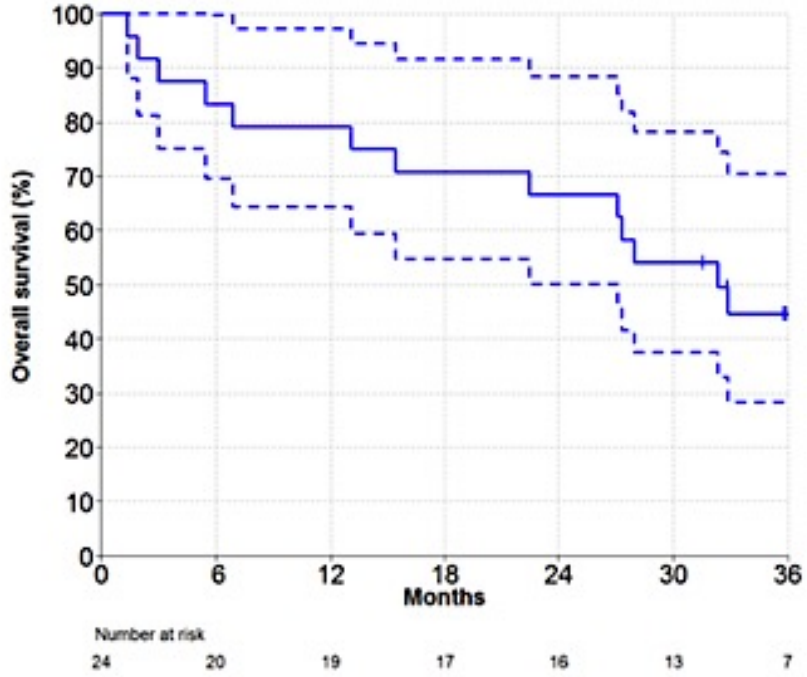


Figure 2. Overall survival (Dashed lines represent 95% confidence interval)



4 of 5 MRD neg at 18 months remains off txt

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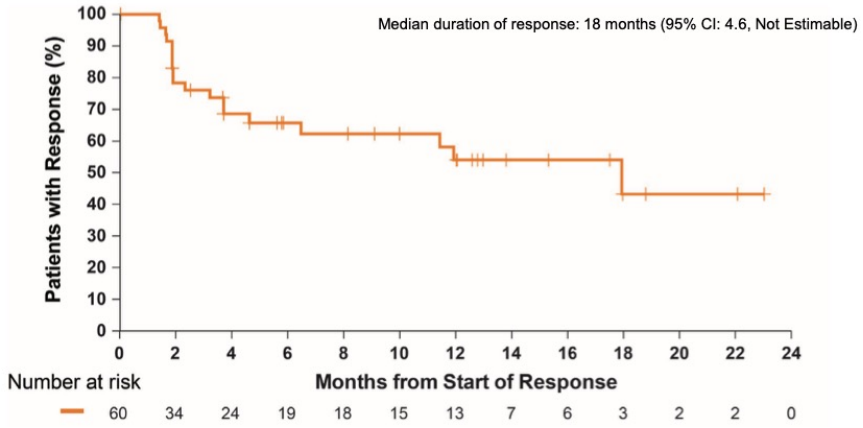
Handunnetti et al. ASH 2019

New Opponent: Pirtobrutinib

Characteristics	MCL (n=134)
Median age (range), years	70 (46, 88)
Female / Male, n (%)	30 (22) / 104 (78)
Histology	
Classic	108 (81)
Pleomorphic/Blastoid	26 (19)
ECOG PS, n (%)	
0	82 (61)
1	50 (37)
2	2 (2)
Median number prior lines of systemic therapy (range)	3 (1, 9)
Prior therapy, n (%)	
BTK inhibitor	120 (90)
Anti-CD20 antibody	130 (97)
Chemotherapy	122 (91)
Stem cell transplant[b]	30 (22)
IMiD	23 (17)
BCL2 inhibitor	20 (15)
Proteasome inhibitor	17 (13)
CAR-T	7 (5)
PI3K inhibitor	5 (4)
Reason discontinued prior BTKi[a]	
Progressive disease	100 (83)
Toxicity/Other	20 (17)

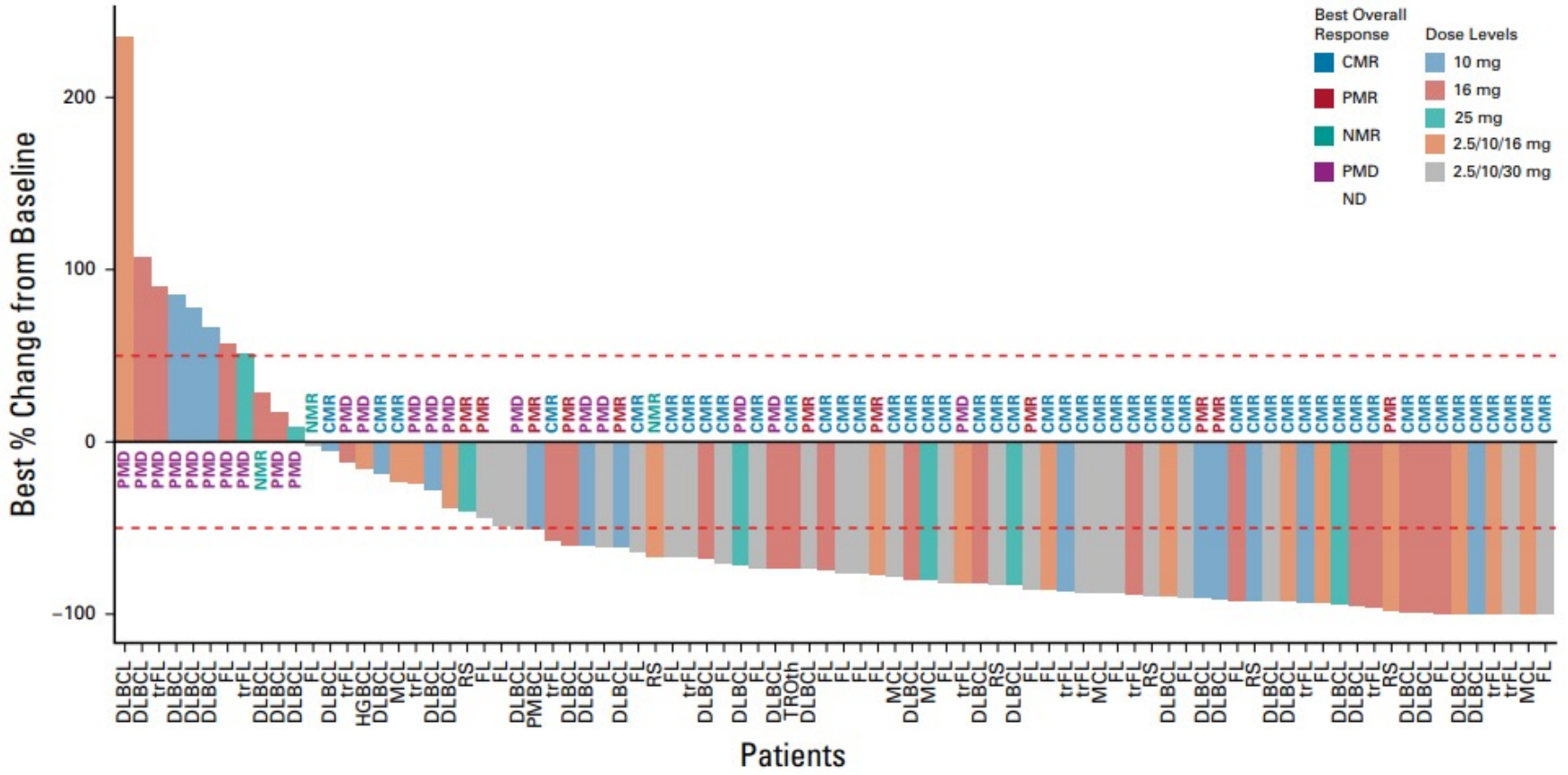
BTK Pre-Treated MCL Patients[a]	n=100
Overall Response Rate[b], % (95% CI)	51% (41-61)
Best Response	
CR, n (%)	25 (25)
PR, n (%)	26 (26)
SD, n (%)	16 (16)
BTK Naive MCL Patients[a]	**n=11**
Overall Response Rate[b], % (95% CI)	82% (48-98)
Best Response	
CR, n (%)	2 (18)
PR, n (%)	7 (64)
SD, n (%)	1 (9)



FRED & PAMELA BUFFETT CANCER CENTER

Wang M, et al. ASH 2021, Abstr 381

New Opponent: Glofitamab



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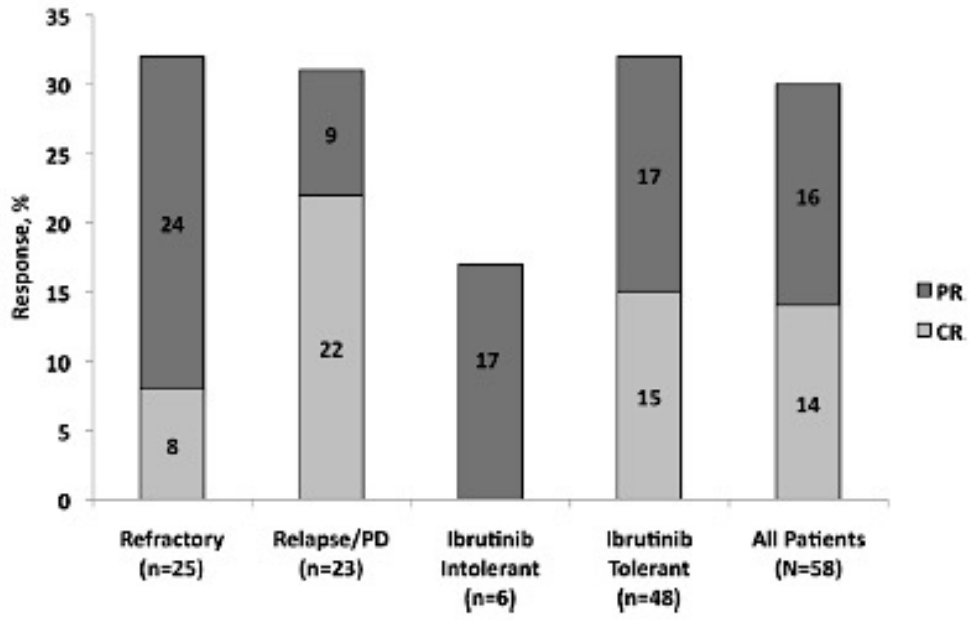
Hutchings et al JCO 2021

Put Into Retirement in MCL: Lenalidomide post BTK



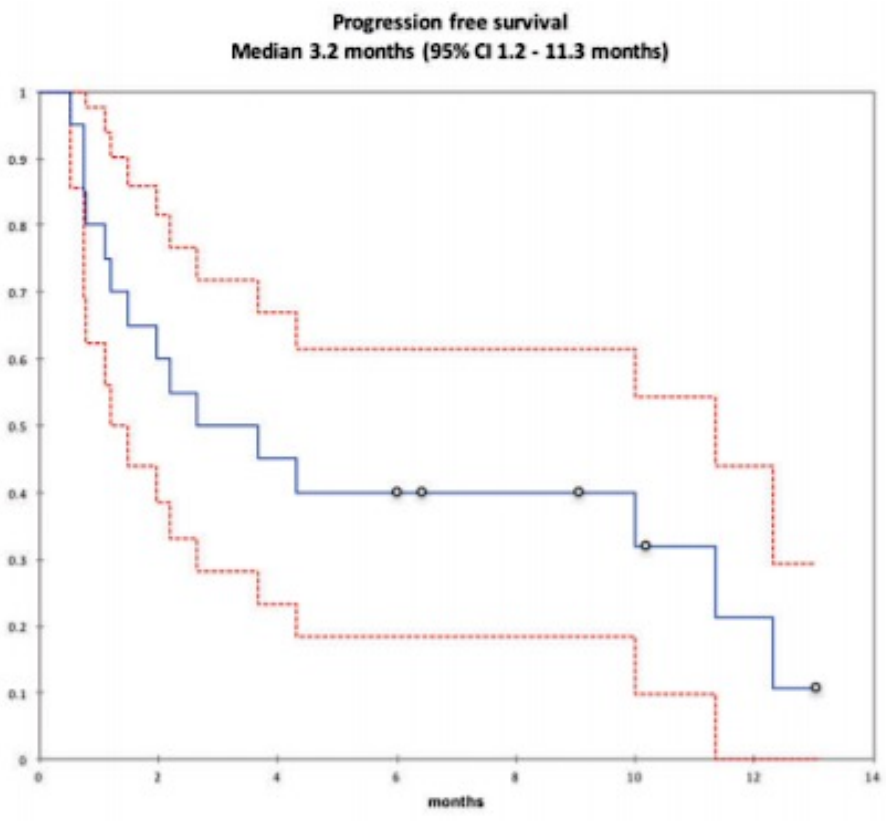
	L (*n* = 13)	L + R (*n* = 11)	L + other (*n* = 34)	Overall (*N* = 58)
Lenalidomide treatment duration, weeks				
Median	8.4	14.0	7.0	8.4
Range	0.4 to 30.0	0.9 to 37.9	1.1 to 77.9	0.4 to 77.9
Number of lenalidomide cycles				
Median	2.0	2.0	1.0	2.0
Range	1.0 to 7.0	1.0 to 9.0	0.0 to 11.0	0.0 to 11.0
Duration of other therapy combined with lenalidomide, weeks				
Median	NA	8.3	7.2	7.4
Range	NA	0.1 to 35.9	0.7 to 77.7	0.1 to 77.7

FRED & PAMELA BUFFETT CANCER CENTER

Wang M et al. J Hema & Onc 2017

Put Into Retirement in MCL: Venetoclax Post BTKi

All patients (N = 20)	n (%)
Gender	
Male	17 (85%)
Female	3 (15%)
First-line therapy	
CHOP ± R or CHOP-like	6
Fludarabine-based ± R	4[a]
Maxi-CHOP/HDAC ± R	8
Other	2[b]
ASCT consolidation in first remission	
Yes	6 (30%)
No	14 (70%)
Rituximab maintenance in first remission	
After immunochemotherapy	2 (10%)
After ASCT	0 (0%)
Neither	18 (90%)
Duration of exposure to BTK inhibitor	
Median	4.77 months
Range	0.66 – 34.85 months
Response to prior BTK inhibitor	
Overall response	11/20 (55%)
Complete response	3 (15%)
Partial response	8 (40%)
Stable disease	4 (20%)
Progressive disease	5 (25%)
Reason for BTK inhibitor discontinuation (n = 20)	
Progressive disease	17
Stable disease	1
Toxicity	2



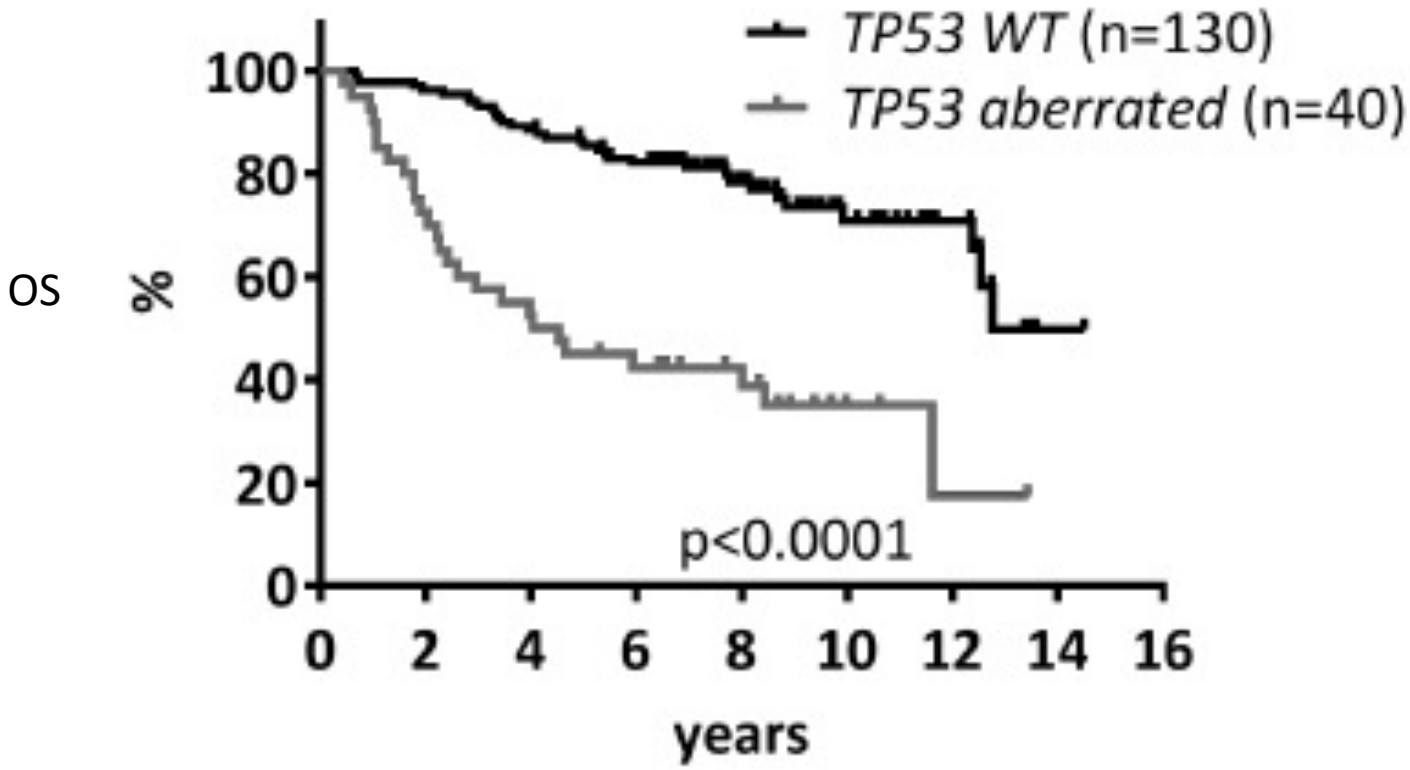
FRED & PAMELA BUFFETT CANCER CENTER

Eyre et al. Haematologica 2019

Elephant in The Ring

TP53 Matters

N=183 from MCL2 & MCL3 trials



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Eskelund C et al. Blood 2017

CIRLL Study

- Zilovertamab + Ibrutinib
- MCL or CLL
- ORR of 81%
  - Historic ORR of 66%, the addition of zilovertamab to ibrutinib was favorable.
- CR rate observed in the MCL cohort was 35% compared with the historic ibrutinib monotherapy CR rate of 20%.
- Zilo and ibrutinib median PFS of 35.9 months in patients with MCL who were followed for a median of 14.4 months
  - Compared with 12.8 months with ibrutinib alone.
- ZILO-301 (Ibrutinib +/- Zilo) in MCL
- ZILO-302 (ZILO + Ibrutinib) with POD to ibrutinib

MODULE 5: Diffuse Large B-Cell Lymphoma (DLBCL) – Dr Sehn

RTP
RESEARCH
TO PRACTICE

Dr Zametta Lamar
Naples, Florida

A 23-year-old man with limited-stage DLBCL, germinal center B-cell (GCB) subtype

Dr Shams Bufalino
Park Ridge, Illinois

A 72-year-old man with pleural effusion and tamponade who is diagnosed with large B-cell lymphoma

An 88-year-old woman with newly diagnosed DLBCL who developed pneumonia after the first dose of R-CHOP

Dr Erik Rupard (West Reading, Pennsylvania)

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Diffuse Large B-Cell Lymphoma (DLBCL)

Laurie H. Sehn, MD, MPH

Chair, Lymphoma Tumour Group

BC Cancer Centre for Lymphoid Cancer
Vancouver, Canada

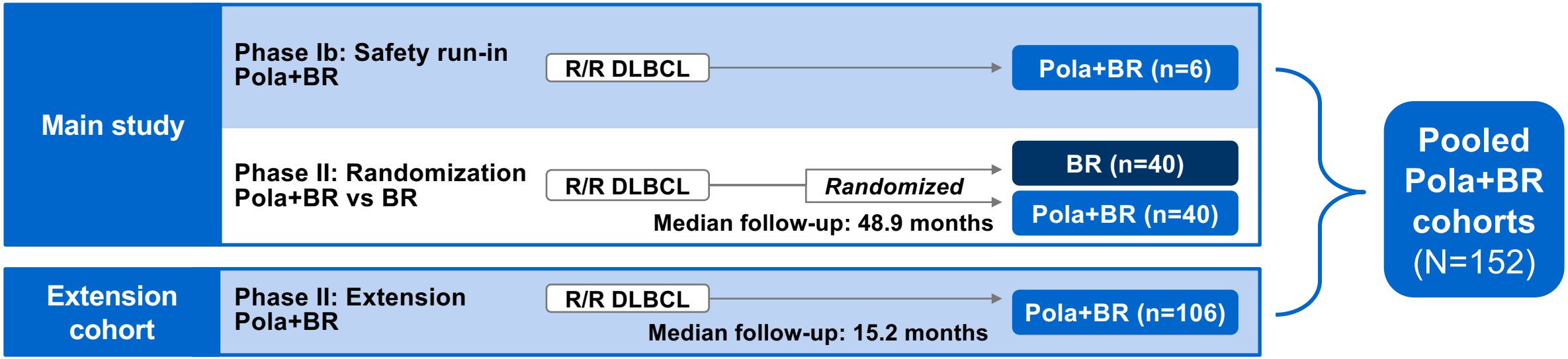
Novel Agents Recently Approved in R/R DLBCL

	Pola-BR	Selinexor	Tafasitamab/ Lenalidomide	Loncastuximab Tesirine
MOA	Anti-CD79b ADC	XPO-1 inhibitor	Anti-CD19 MAb/Immunomodulator	Anti-CD19 ADC
ORR	45%	28%	58%	48%
CR rate	40%	10%	40%	24%
PFS	9.2m	2.6m	11.6m	4.9m
DOR	12.6m	9.3m	43.9m	10.3m
OS	12.4m	NR	33.5m	9.9m

GO29365 Phase 1b/2 Study: Pola-BR in ASCT-Ineligible DLBCL

Inclusion: transplant-ineligible DLBCL, ≥1 line of therapy

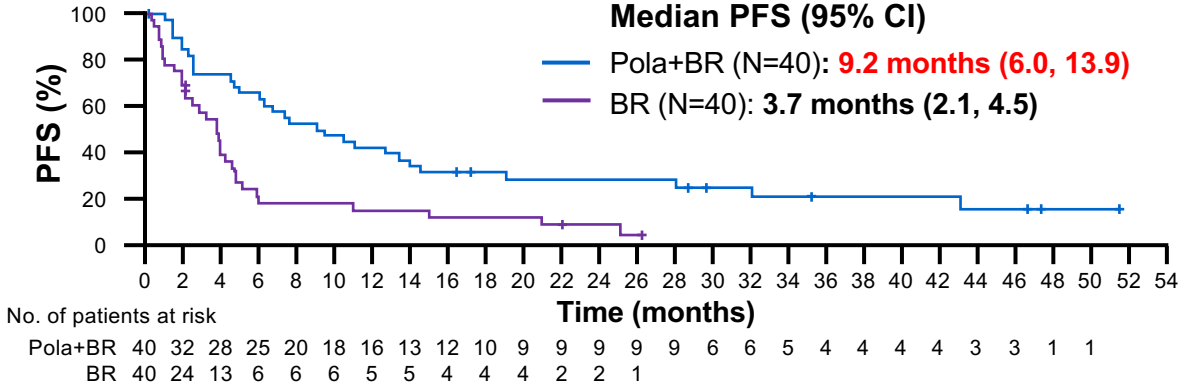
Exclusion: prior allo-SCT; history of transformation; current grade >1 PN

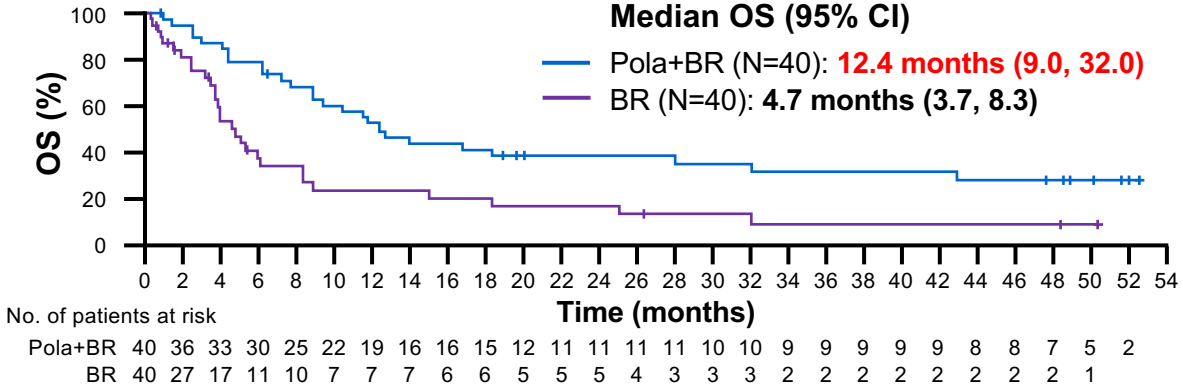


*Pola 1.8 mg/kg on D1 of each cycle of BR; up to 6 cycles at 3-weekly interval

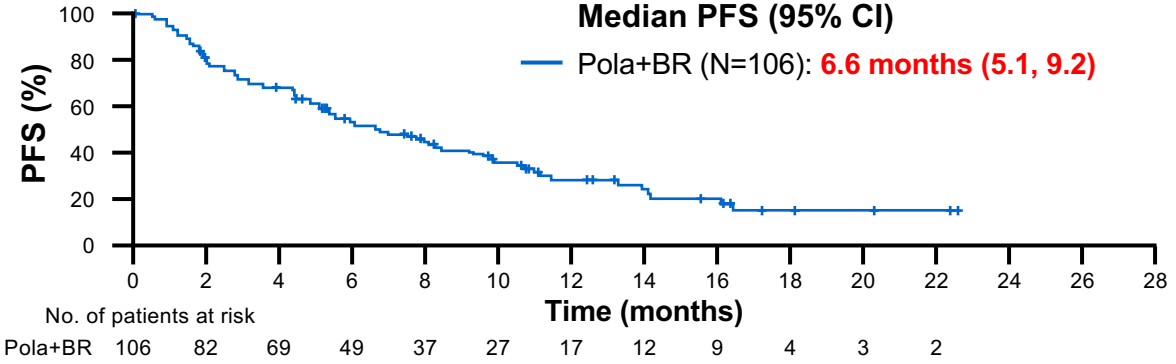
PFS and OS in Randomized and Extension Cohorts

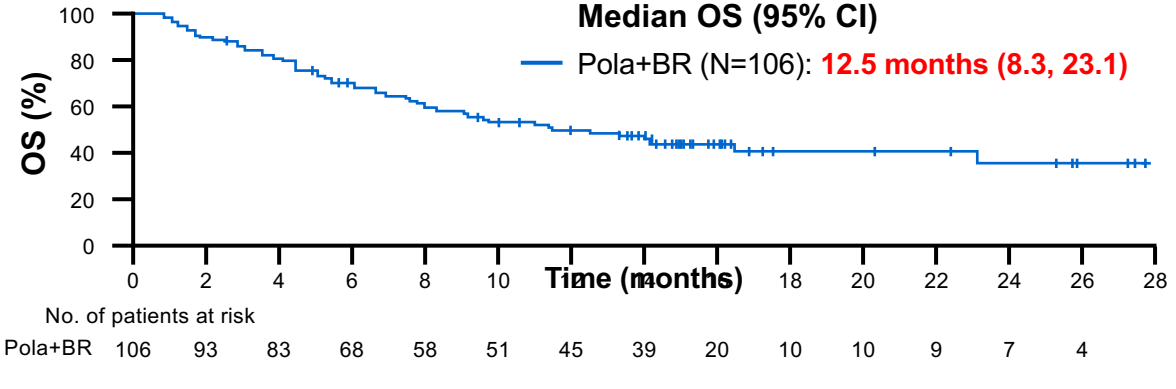
Randomized





Extension cohort





<u>Randomized cohort</u>:

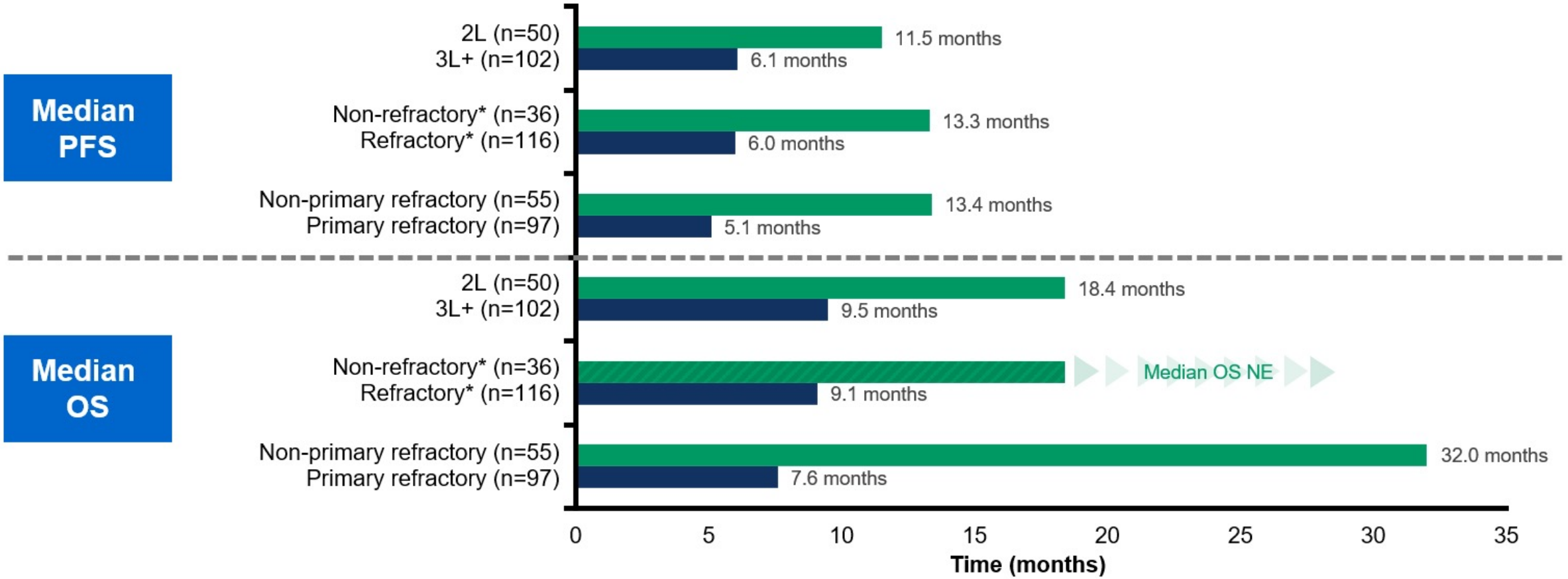
- Survival benefit persists with longer follow-up
- 2-y PFS: 28.4%, 2-y OS was 38.2%

<u>Pooled cohort</u>:

- Non-primary refractory patients:
  Median PFS: 13.4 m, median OS: 32 m

Sehn et al, Blood Advances 2022

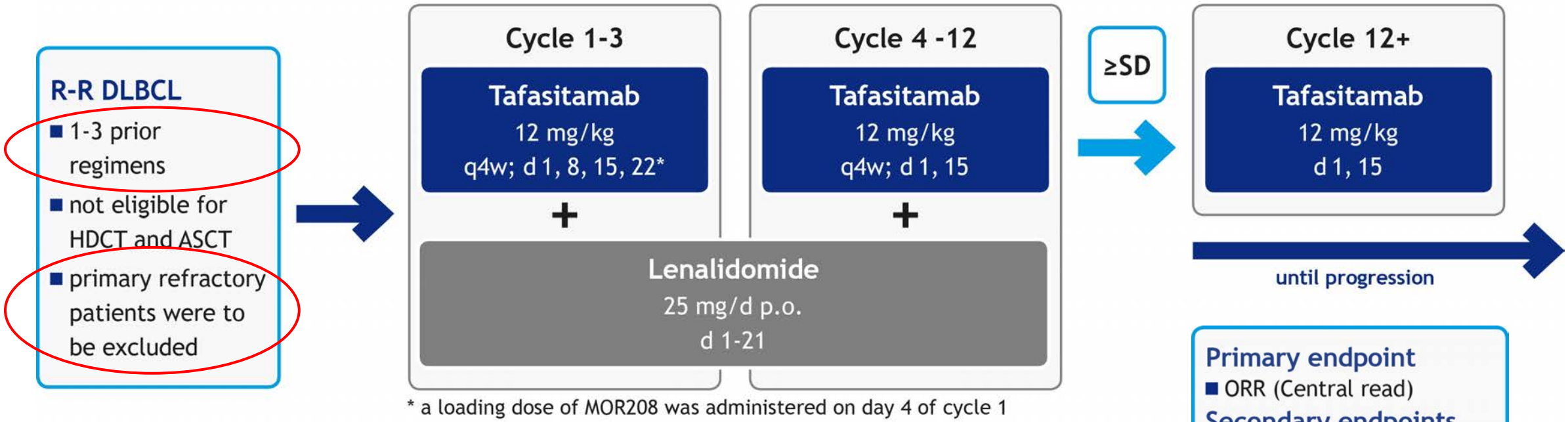
Median PFS and OS in the Pooled Pola+BR cohort according to line of therapy and refractory status



Sehn et al, Blood Advances 2022

Tafasitamab and Lenalidomide: L-MIND Study

Phase 2, single-arm, open-label, multicenter study (NCT02399085)



- Sample size suitable to detect ≥15% absolute increase in ORR for Tafasitamab/LEN combination vs. LEN monotherapy at 85% power, 2-sided alpha of 5%
- Mature Data: Primary Endpoint Analysis with data cut-off 30 Nov 2018; minimum Follow-Up 12 months, median Follow-Up 17.3 months

Primary endpoint
- ORR (Central read)

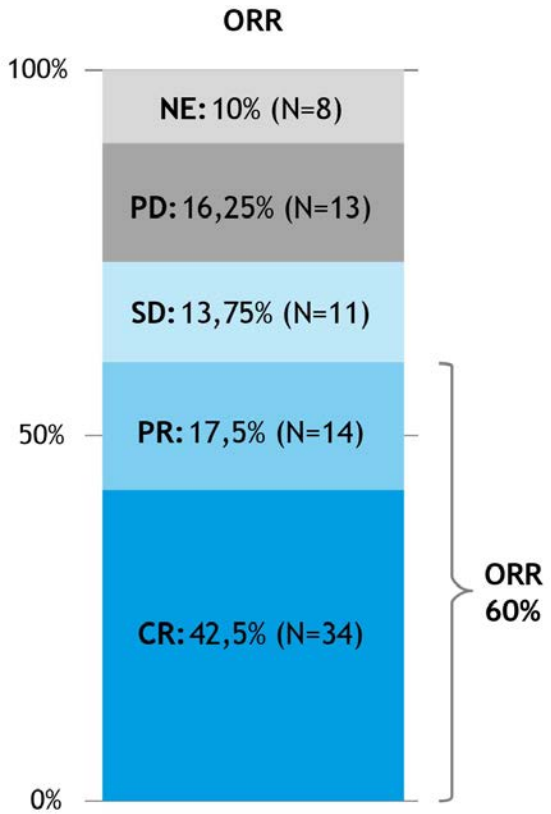
Secondary endpoints
- PFS
- DoR
- OS
- Safety of the Tafasitamab + LEN combination
- Exploratory and biomarker-based analyses

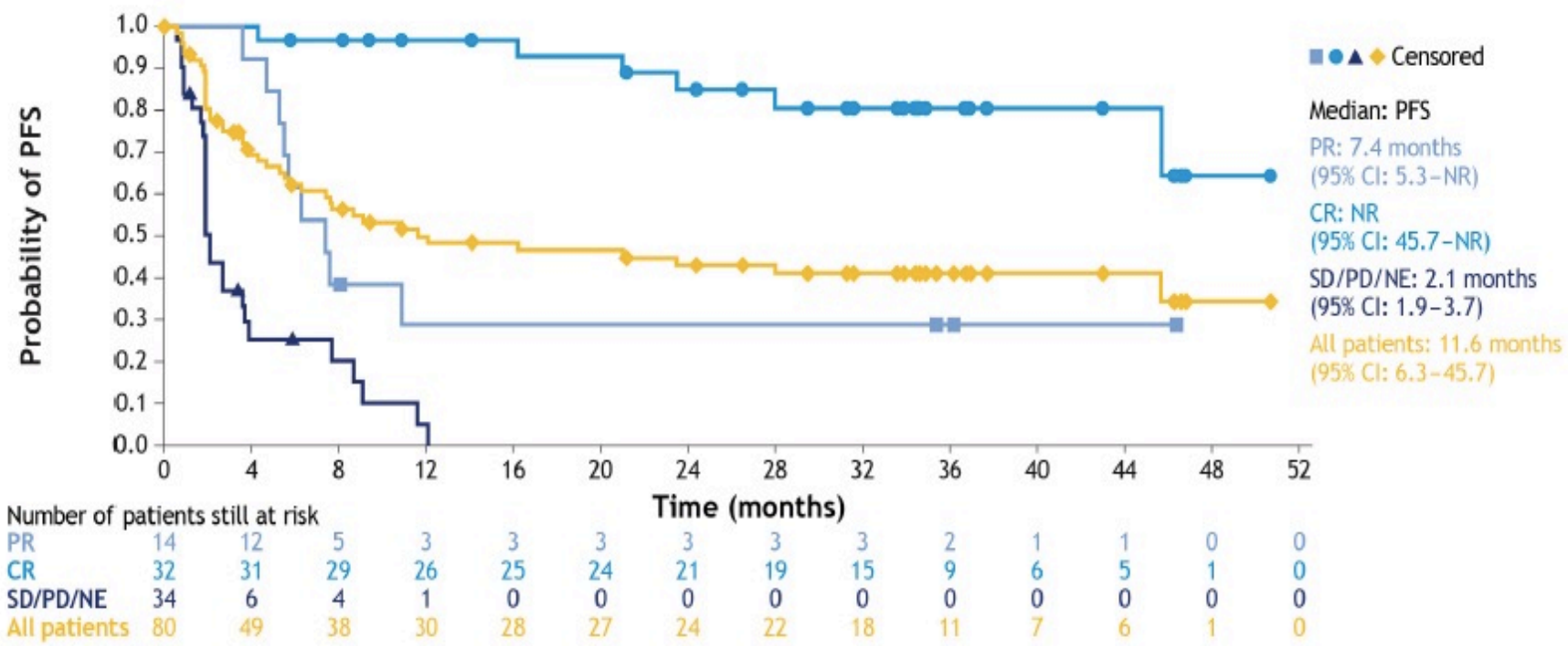
Salles G et al, Lancet Oncology 2020

L-MIND: Efficacy (n=80)

ORR 60%, CR rate 43% by IRC

➔ Median follow-up 33.9 months
➔ Median PFS: 11.6 mos (95% CI: 6.3 - 45.7 mos)



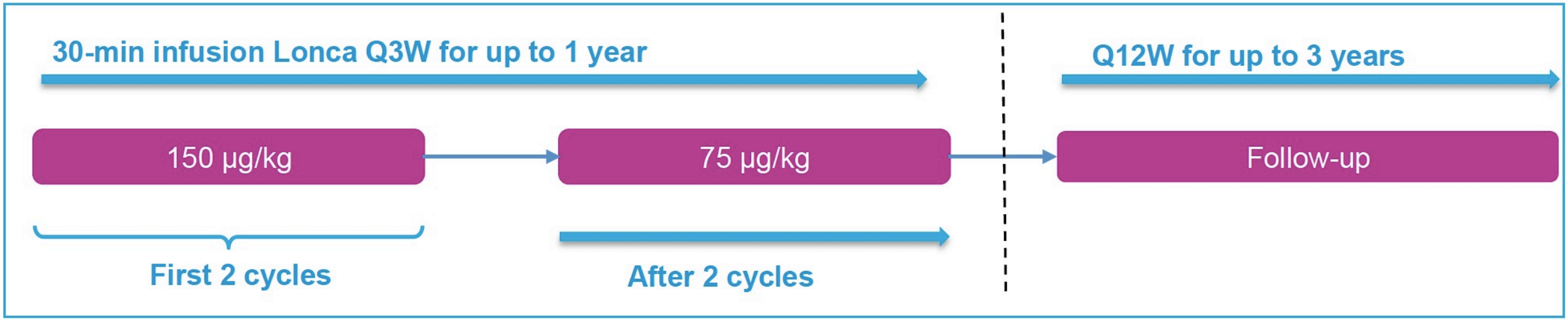


Salles G et al, Lancet Oncology 2020, Duell J et al, Haematologica 2021

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

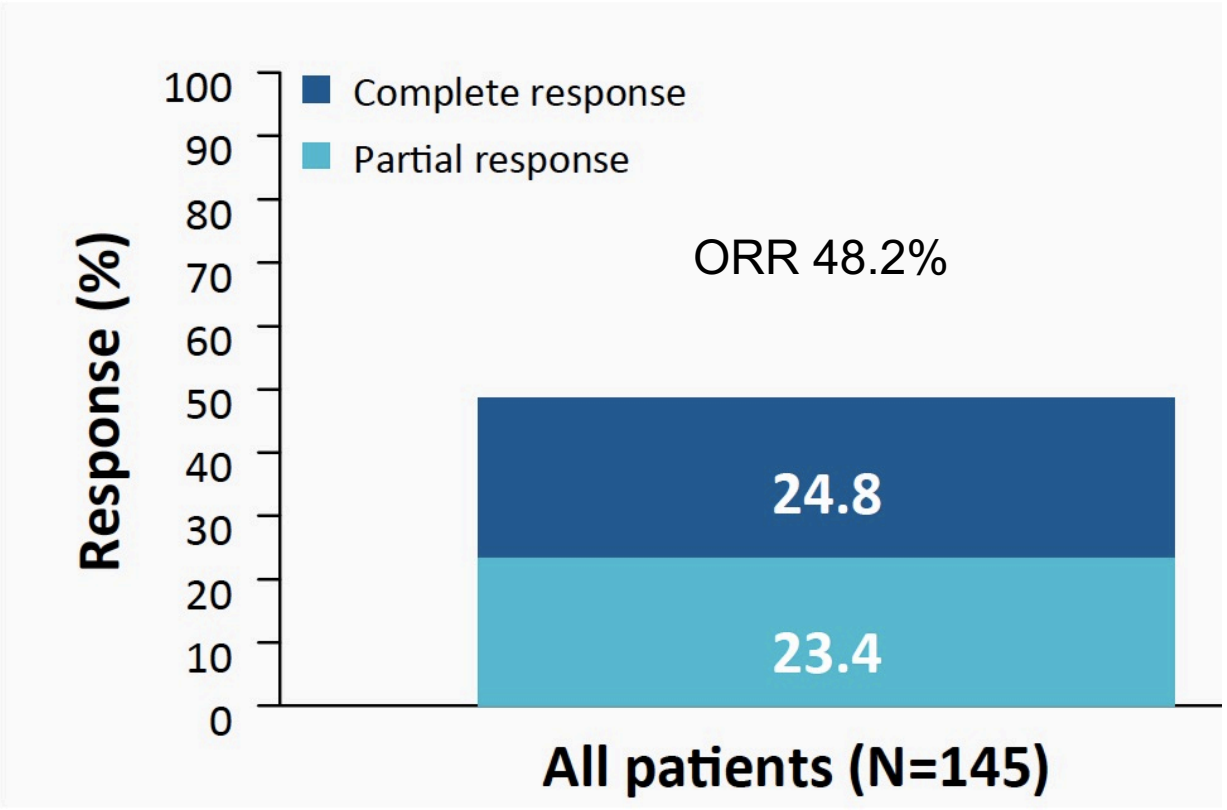
Patient population:
Patients with R/R DLBCL following ≥2 lines of prior systemic therapy

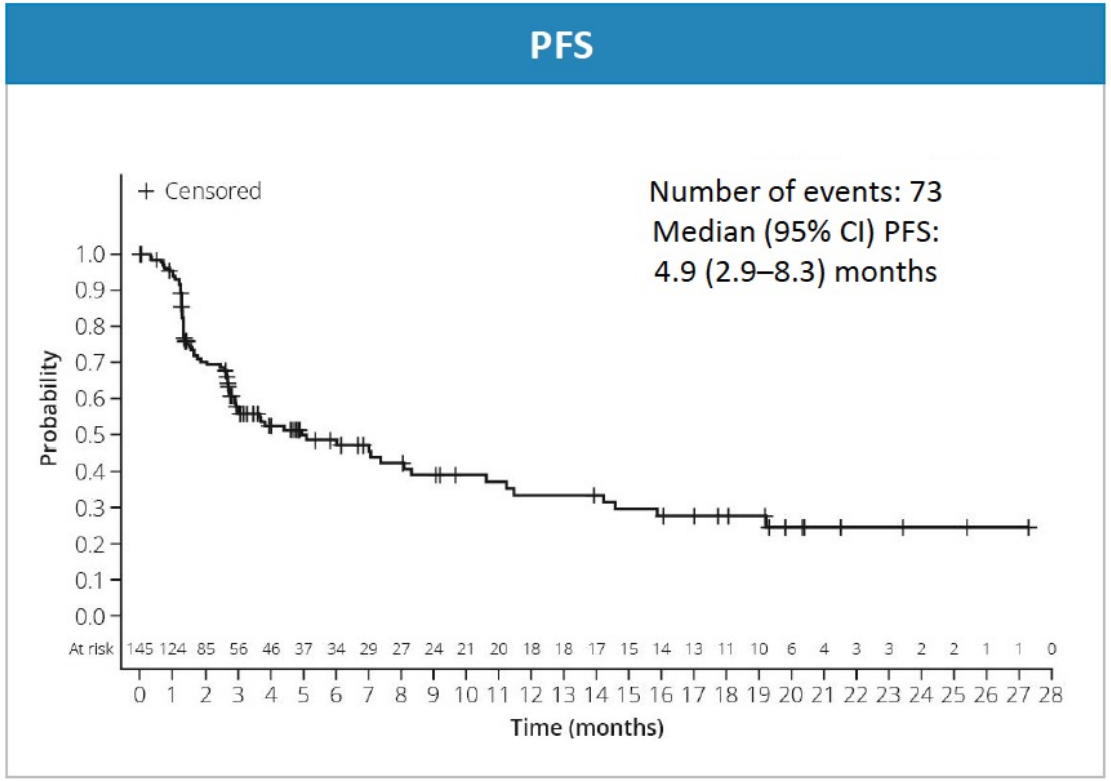
Primary objective:
Evaluate efficacy, **using ORR** (central review), and **safety** of the full Phase 2 study population



Caimi et al, Lancet Oncology 2021

Efficacy Results – OR





Caimi et al, Lancet Oncology 2021; Kahl et al, SOHO 2021

Glofitamab Pivotal Phase II Trial: Baseline characteristics

n (%)*		N=154†
Median age, years (range)		66.0 (21–90)
Male		100 (64.9)
ECOG PS‡	0	69 (44.8)
	1	84 (54.5)
Ann Arbor stage	I	10 (6.5)
	II	25 (16.2)
	III	31 (20.1)
	IV	85 (55.2)
NHL subtype	DLBCL	110 (71.4)
	trFL	27 (17.5)
	HGBCL	11 (7.1)
	PMBCL	6 (3.9)
Bulky disease	>6cm	64 (41.6)
	>10cm	18 (11.7)

n (%)*	N=154
Median no. of prior lines, n (range)	3 (2–7)
2 prior lines	62 (40.3)
≥3 prior lines	92 (59.7)
Prior anti-CD20 Ab	154 (100.0)
Prior anthracycline	149 (96.8)
Prior CAR-T	51 (33.1)
Prior ASCT	28 (18.2)
Refractory to any prior therapy	139 (90.3)
Refractory to last prior therapy	132 (85.7)
Primary refractory	90 (58.4)
Refractory to prior CAR-T	46 (29.9)
Refractory to any prior anti-CD20	128 (83.1)

- **Heavily pre-treated, highly refractory population**

Clinical cut-off date: March 14, 2022; *unless otherwise specified; †safety-evaluable population (all treated patients); ‡ECOG PS 2, n=1 (0.6%); Ab, antibody; ASCT, autologous stem cell transplant; trFL, transformed follicular lymphoma.

Dickinson et al, ASCO 2022

Response rates – primary endpoint met

Efficacy endpoint[1]	Glofitamab 2.5/10/30mg (n=155)
CR rate*	**61 (39.4%)** [95% CI: 31.6%, 47.5%]
ORR*	**80 (51.6%)** [95% CI: 43.5%, 59.7%]

- Median duration of follow-up: 12.6 months (range: 0–22)
- Responses were achieved early: median time to first CR was 42 days (95% CI: 42, 44)

– At time of primary analysis, primary endpoint met in the primary efficacy population (n=108)†: 35.2% CR rate by IRC significantly greater (p<0.0001) than 20% historical control CR rate‡

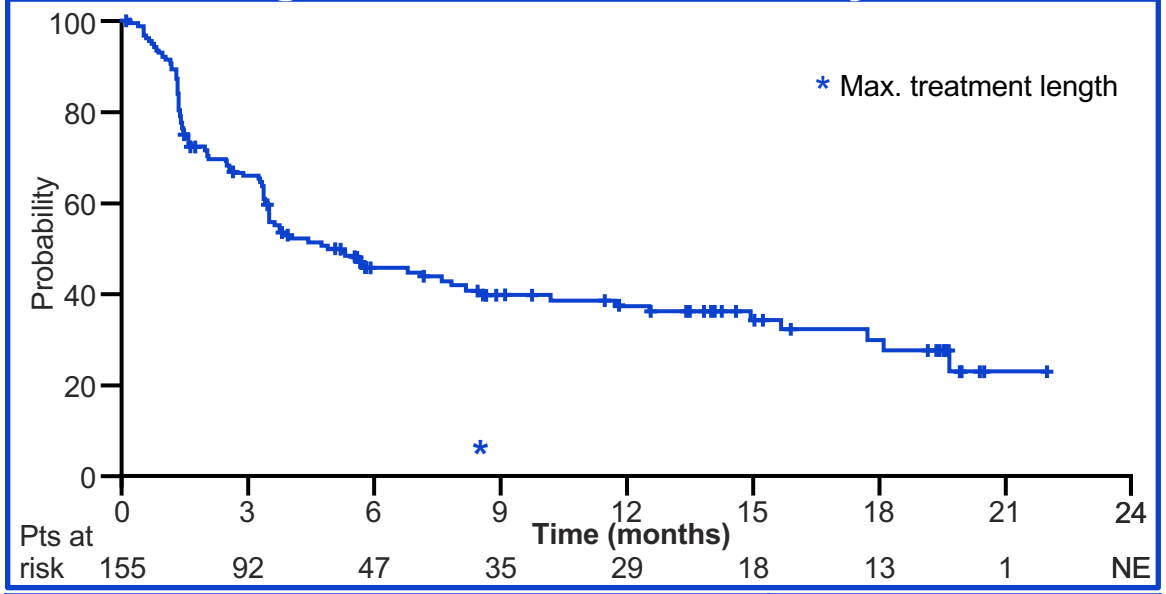
- **High CR/ORR rate at RP2D**

*best response by intent-to-treat population; †the pivotal expansion cohort population; ‡the historical control CR rate was pre-specified based on a meta-analysis in patients with R/R DLBCL (where most [≥50%] had received ≥2 prior therapies) and compared with the CR rate in the primary efficacy-evaluable population using an exact binomial test (2-sided alpha level: 5%).

Dickinson et al, ASCO 2022

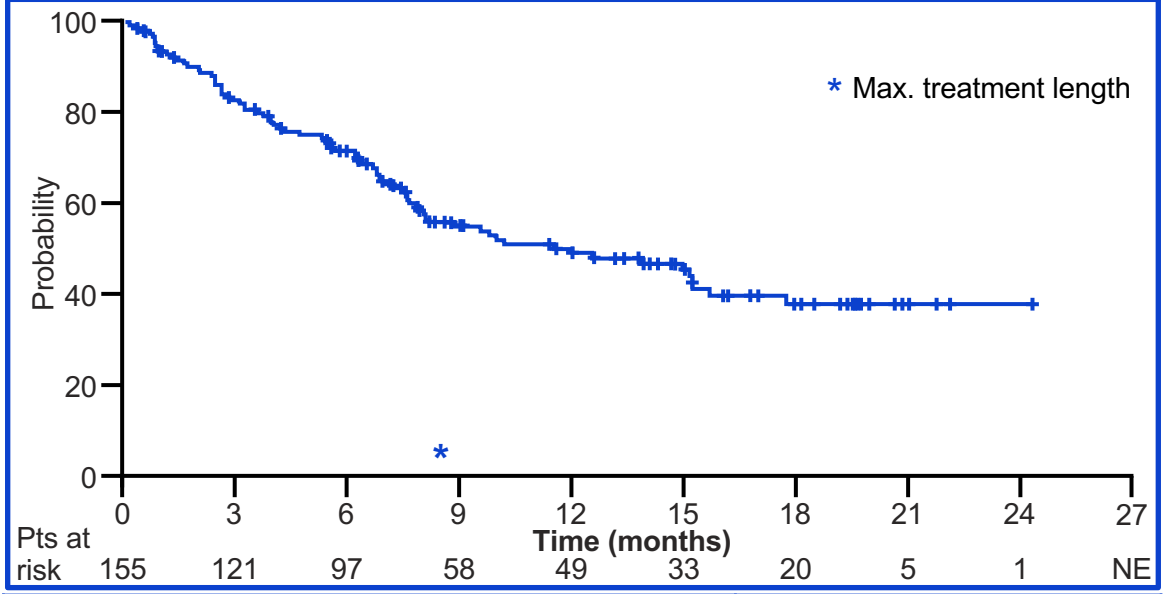
Time-to-event endpoints

Progression-free survival by IRC



	N=155
Median PFS follow-up, mo (range)	12.6 (0–22)
Median PFS, months (95% CI)†	4.9 (3.4, 8.1)
6-month event-free rate, % (95% CI)	45.5 (37.2, 53.8)
12-month event-free rate, % (95% CI)	37.1 (28.5, 45.8)

Overall survival*



	N=155
Median OS, months (95% CI)†	11.5 (7.9, 15.7)
12-month OS rate, % (95% CI)	49.8 (41.1, 58.5)

Median DOR 18.4 m (13.7,NE)

- **Clinically significant freedom from progression at 12 months and long-term overall survival**

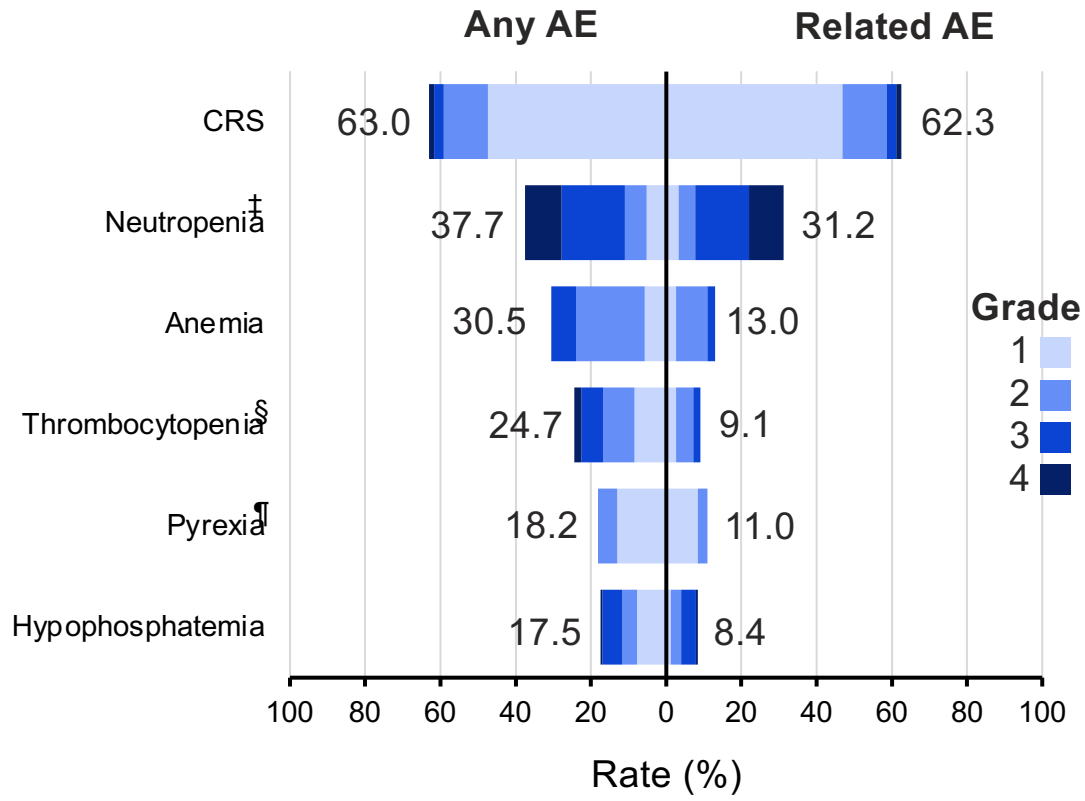
*including five deaths due to COVID-19; †KM estimates

Dickinson et al, ASCO 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

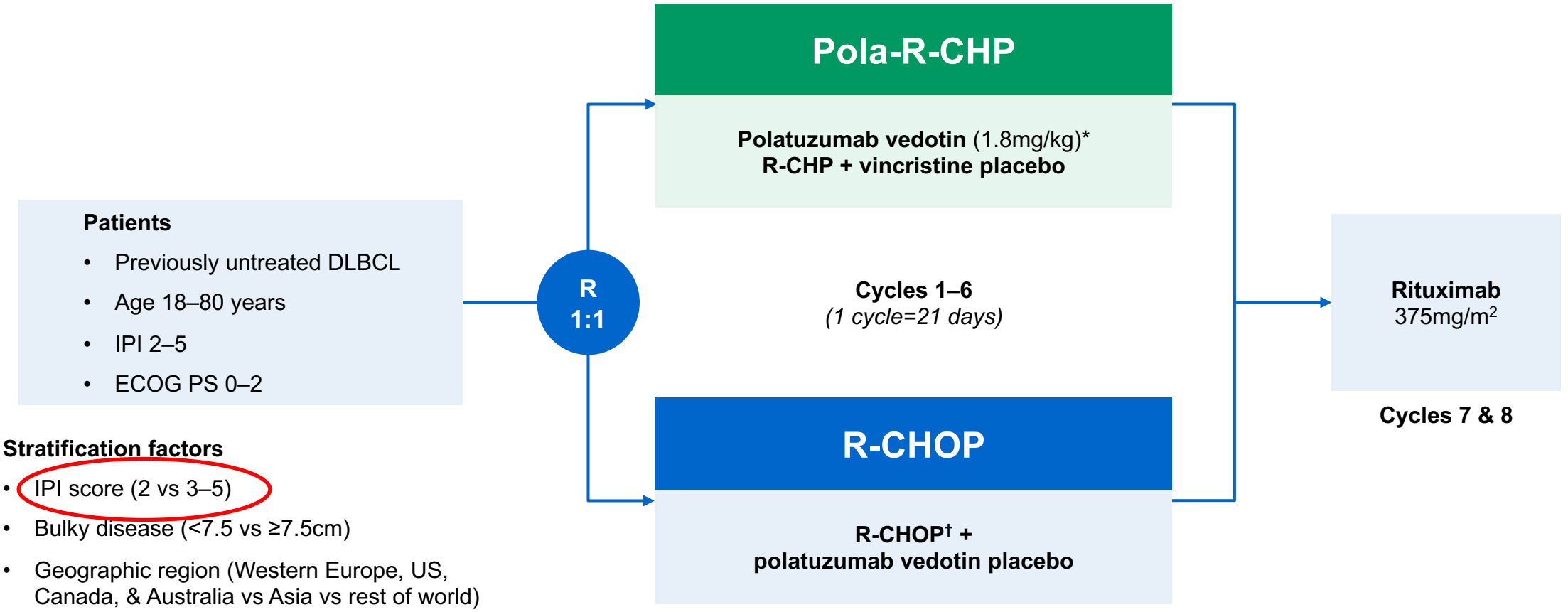


- **Glofitamab was well tolerated, with a favorable safety profile**

*unless otherwise specified; †COVID-19/COVID-19 pneumonia (n=5); sepsis (n=2); delirium (n=1); ‡includes neutrophil count decreased; §includes platelet count decreased; ¶pyrexia events separate from CRS

Dickinson et al, ASCO 2022

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.

Tilly H et al, NEJM 2022

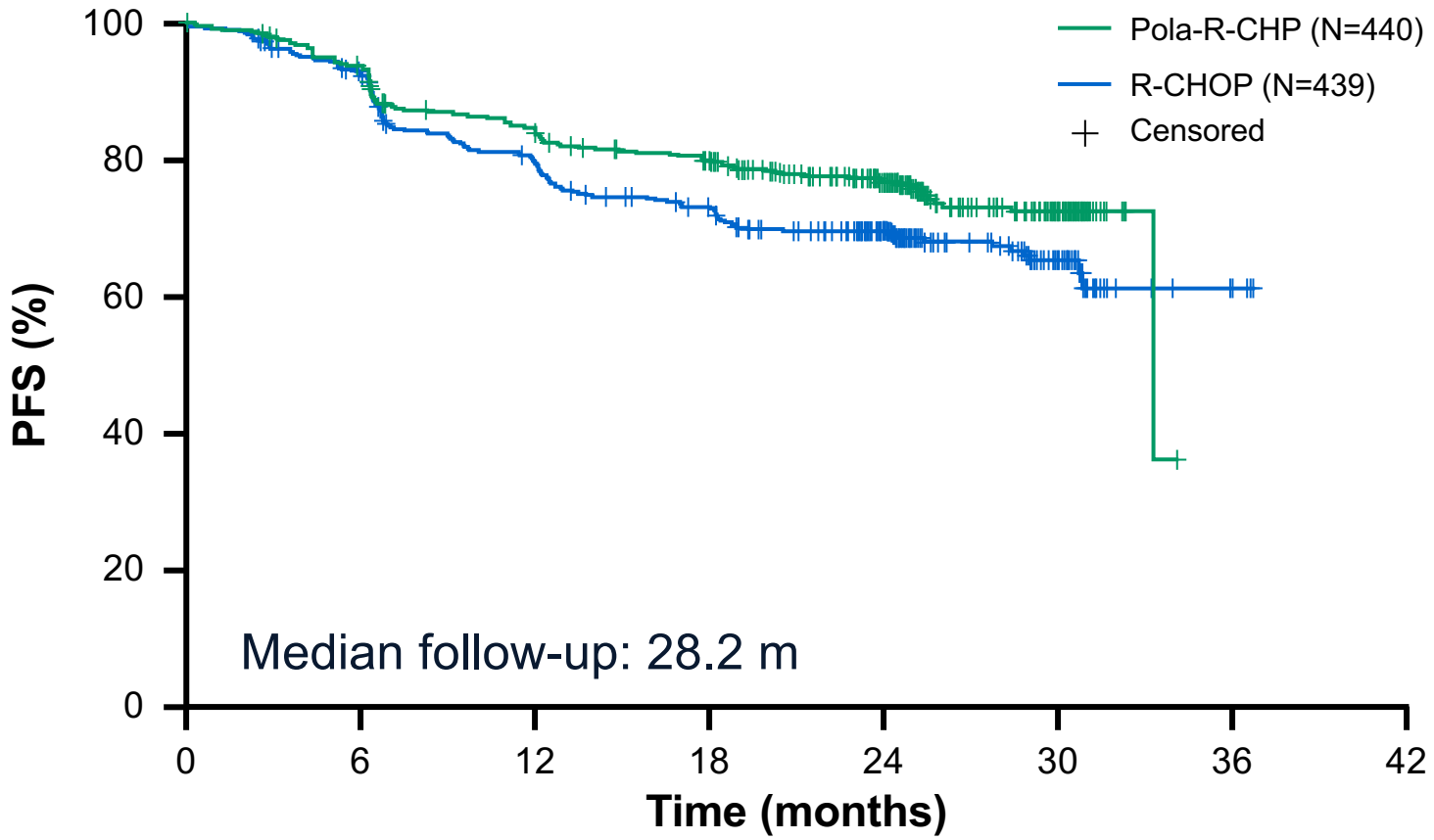
Baseline characteristics

ITT population		Pola-R-CHP (N=440)	R-CHOP (N=439)
Age	Median (range), years	65.0 (19–80)	66.0 (19–80)
Sex, n (%)	Male	239 (54)	234 (53)
ECOG PS, n (%)	0–1 2	374 (85) 66 (15)	363 (83) 75 (17)
Bulky disease (≥7.5cm), n (%)	Present	193 (44)	192 (44)
Elevated LDH, n (%)	Yes	291 (66)	284 (65)
Time from diagnosis to treatment initiation	Median, days	26	27
Ann Arbor Stage, n (%)	III–IV	393 (89)	387 (88)
Extranodal sites, n (%)	≥2	213 (48)	213 (49)
IPI score, n (%)	2 3–5	167 (38) 273 (62)	167 (38) 272 (62)
Cell-of-origin, (%)*	ABC GCB Unclassified	102 (31) 184 (56) 44 (13)	119 (35) 168 (50) 51 (15)
MYC/BCL2 expression, n (%)*	Double expression	139 (38)	151 (41)
MYC/BCL2/BCL6 rearrangement, n (%)*	Double-/triple-hit	26 (8)	19 (6)

Tilly H et al, NEJM 2022

Primary endpoint: Progression-free survival

Pola-R-CHP significantly improved PFS versus R-CHOP



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

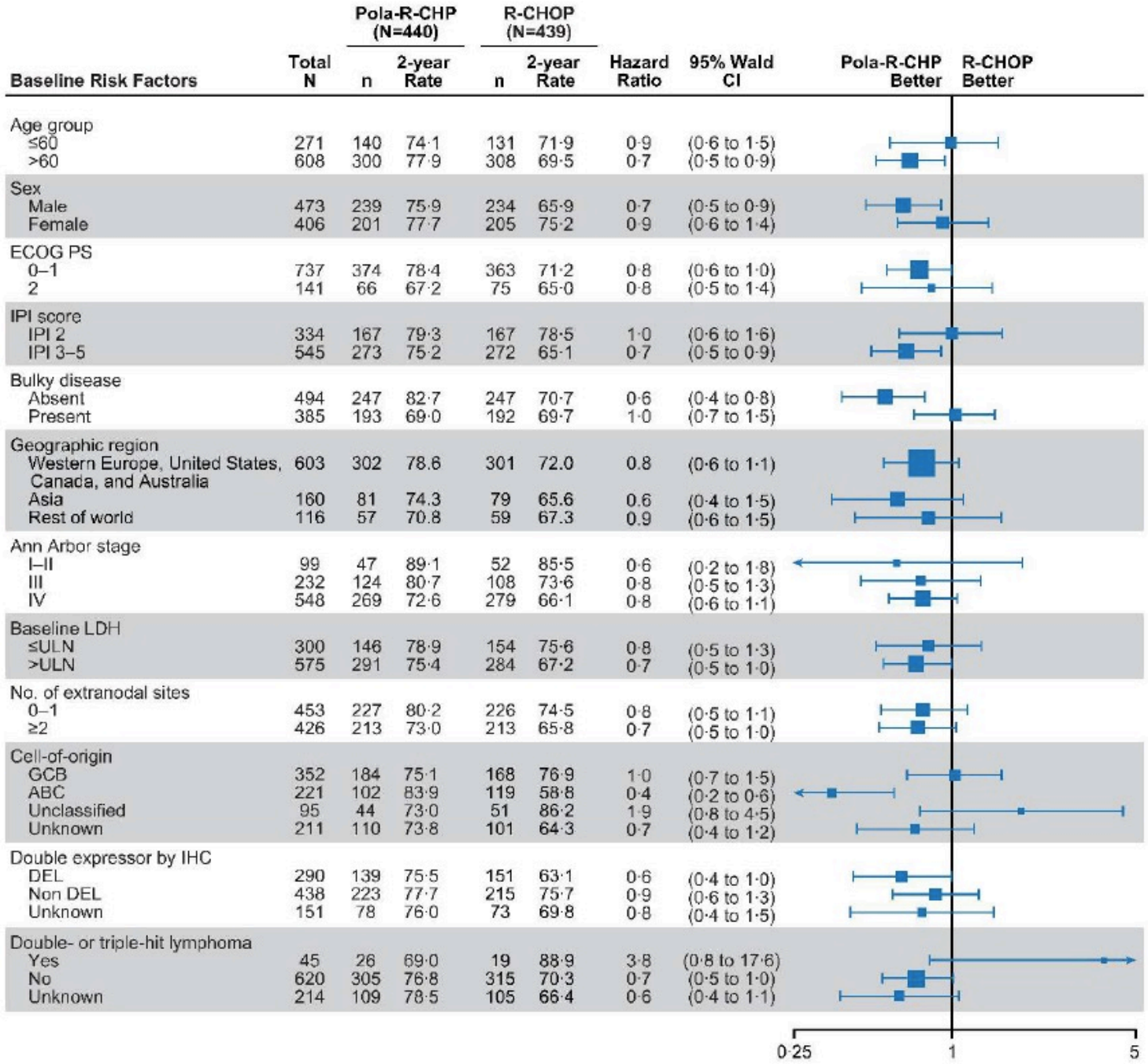
HR 0.73 **(P<0.02)**

95% CI: 0.57, 0.95

- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** versus R-CHOP
- **24-month PFS:**
  76.7% with Pola-R-CHP versus
  70.2% with R-CHOP (**Δ=6.5%**)

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
NE, not evaluable.

Tilly H et al, NEJM 2022



? Benefit

Younger ≤ 60y

Females

IPI = 2

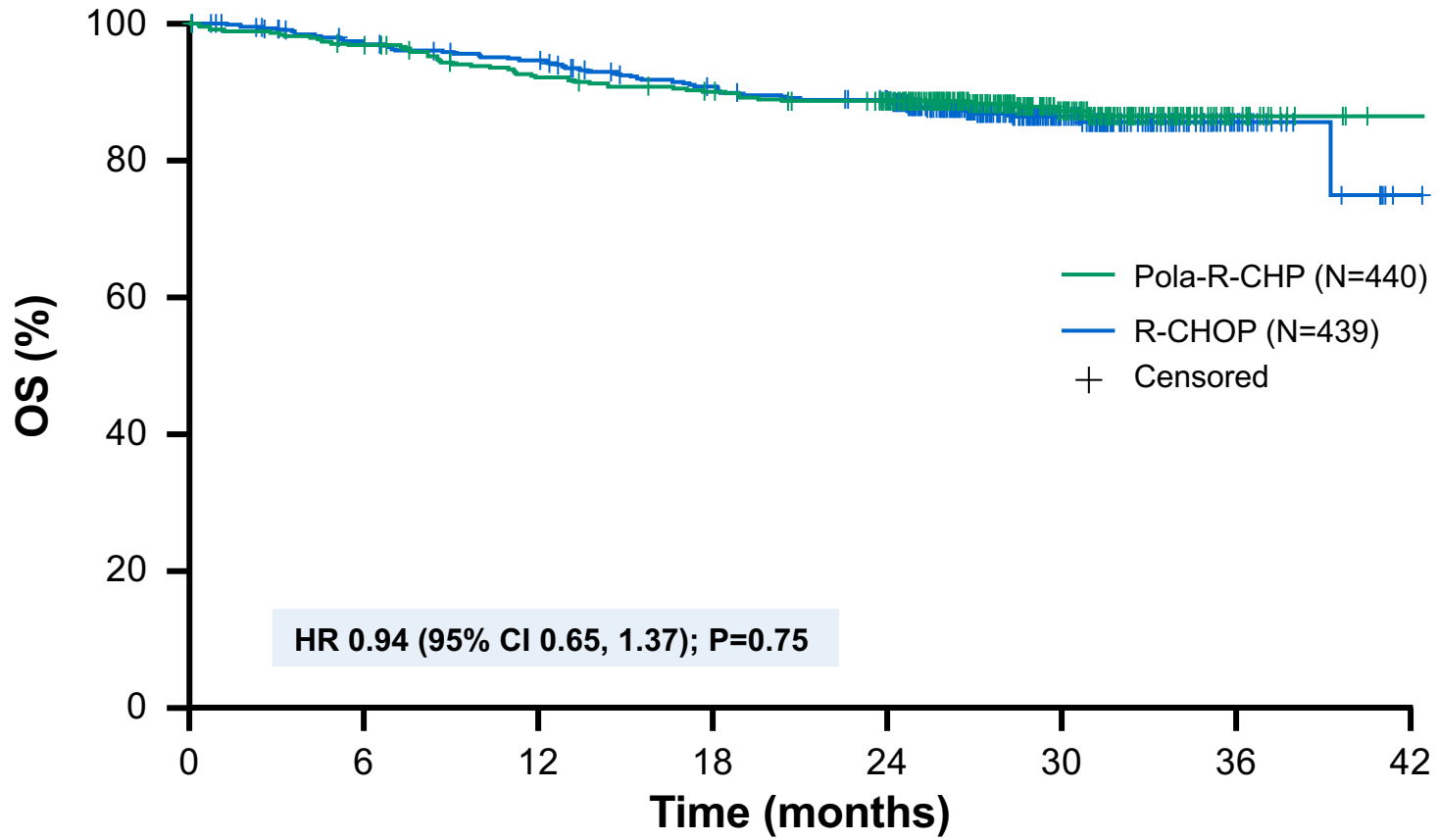
Bulk ≥ 7.5 cm

GCB Subtype

DH/TH lymphoma

Tilly H et al, NEJM 2022

Overall survival

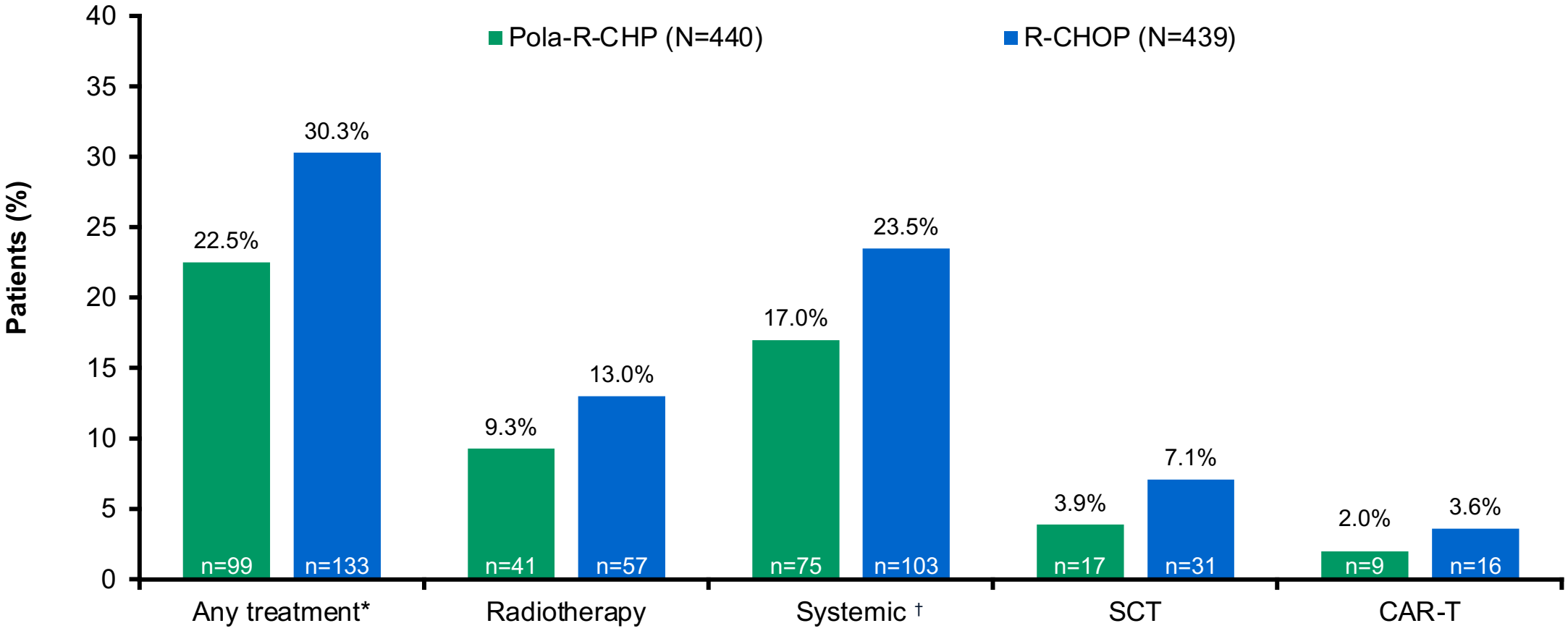


No. of patients at risk								
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	1

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.

Tilly H et al, NEJM 2022

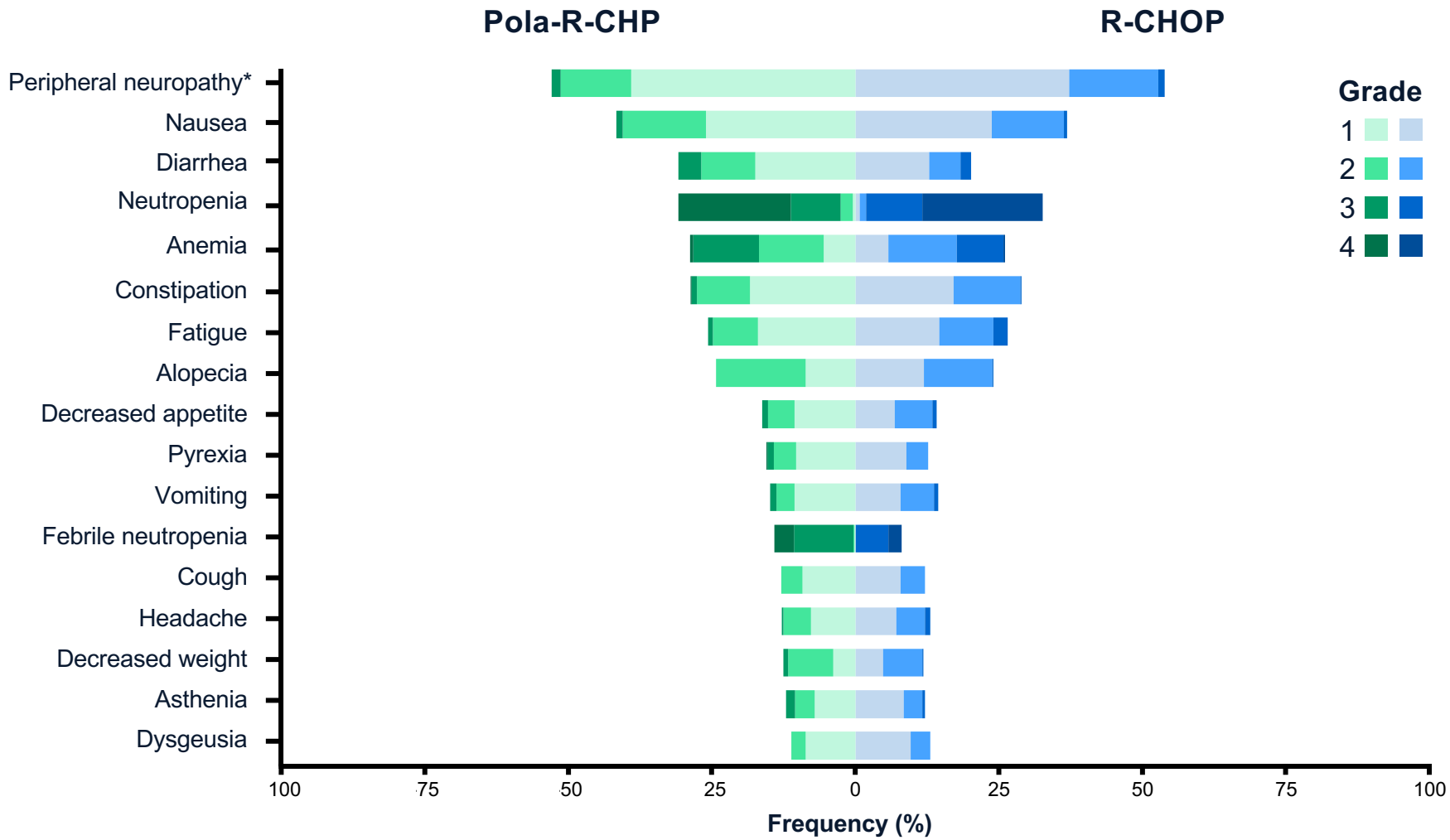
Patients receiving subsequent treatments



Data cut-off: June 28, 2021. *Subsequent lymphoma treatment was defined as non-protocol anti-lymphoma therapy; †Includes any monotherapy, multi-drug, or cell-based regimen.

Tilly H et al, NEJM 2022

Common adverse events



Data cut-off: June 28, 2021. Adverse events are Medical Dictionary for Regulatory Activities version 24.0 preferred terms; shown are all-grade adverse events occurring in ≥12% of patients in any treatment arm. *Peripheral neuropathy is defined by standard organ class group of preferred terms.

Tilly H et al, NEJM 2022

Ongoing/Planned Trials in Upfront DLBCL

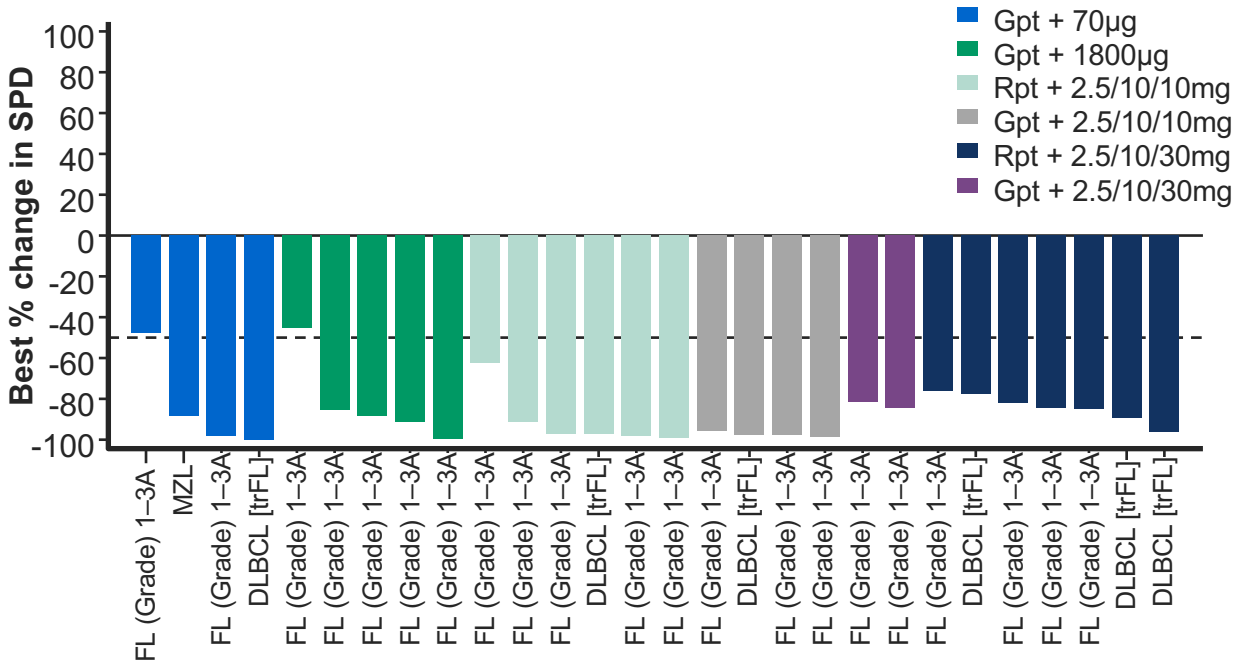
- **BTK-inhibitor R-CHOP trials**
  - Escalade (acala); UK trial; zanubrutinib
- **First-Mind Trial**
  - Tafasitamab/Lenalidomide + R-CHOP
- **Bispecific antibodies + R-CHOP**
- **Biology-driven trials**
- **Response-adapted trials (ctDNA, quantitative PET/CT)**

Glofit + R-CHOP shows encouraging clinical activity in R/R NHL

INV-assessed BOR rate (unconfirmed)	R/R NHL Dose-escalation phase (N=31)	
	Indolent NHL (FL + MZL) (n=24)	Aggressive NHL (trFL + MCL) (n=7)
ORR*	22 (91.6)	6 (85.7)
CMR	20 (83.3)	5 (71.4)
PMR	2 (8.3)	1 (14.3)
NMR	0	0
PMD	1 (4.2)	1 (14.3)
Missing/NE	1 (4.2)	0

- In efficacy-evaluable patients (n=31), after a median 9.0 months' (range: 0–29) follow-up, the ORR was 90% (n=28); the CMR rate was 81% (n=25)
- Median duration of response was not reached in the R/R NHL cohort (range: 1–993 based on censored observation)

Best % change in SPD from baseline by Glofit dose and histology in the dose-escalation phase†



- Across all dose levels and histologies, Glofit + R-CHOP demonstrated encouraging anti-tumour activity in patients with R/R NHL

Ghosh et al, ASH 2021

7523

First-line treatment (Tx) with subcutaneous (SC) epcoritamab (epco) + R-CHOP in patients (pts) with high-risk diffuse large B-cell lymphoma (DLBCL): phase 1/2 data update

Lorenzo Falchi, MD,[1]* Fritz Offner, MD, PhD,[2] David Belada, MD, PhD,[3] Joshua Brody, MD,[4] Kim M. Linton, MBChB, PhD,[5] Yasmin Karimi, MD,[6] Raul Cordoba, MD, PhD,[7] Sylvia Snauwaert, MD, PhD,[8] Aqeel Abbas, MS,[9] Liwei Wang, PhD,[9] Jun Wu, MD, MS,[10] Brian Elliott, MD,[9] Michael Roost Clausen, MD, PhD[11]

[1]Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Universitair Ziekenhuis Gent, Ghent, Belgium; [3]4th Department of Internal Medicine – Hematology, University Hospital and Faculty of Medicine, Hradec Králové, Czech Republic; [4]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [5]The Christie NHS Foundation Trust and Manchester Cancer Research Centre, Manchester, UK; [6]University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA; [7]Fundacion Jimenez Diaz University Hospital, Health Research Institute IIS-FJD, Madrid, Spain; [8]Department of Hematology, AZ Sint-Jan Hospital, Bruges, Belgium; [9]Genmab, Princeton, NJ, USA; [10]AbbVie, North Chicago, IL, USA; [11]Vejle Hospital, Vejle, Denmark

*Email address for questions: falchil@mskcc.org

Objectives

- The EPCORE NHL-2 trial (phase 1/2; NCT04663347) is evaluating epcoritamab combined with different standard of care therapies in patients with B-cell NHL
- To present data from arm 1, which is investigating epcoritamab + R-CHOP in patients with previously untreated high-risk DLBCL

Conclusions

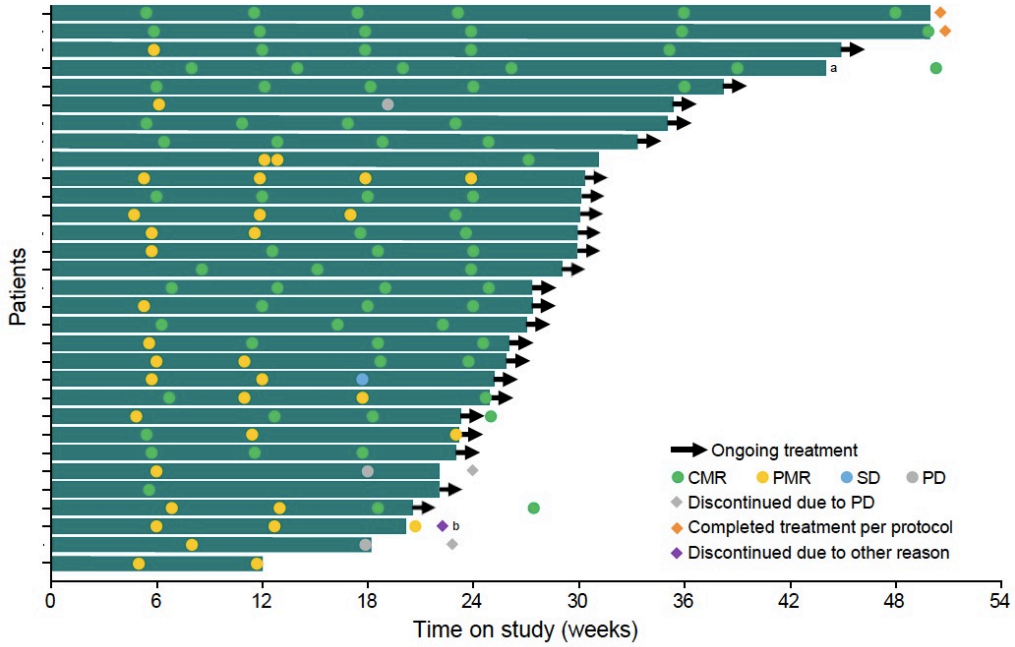
- Epcoritamab + R-CHOP showed encouraging responses:
  - ORR 100%, CMR 77%
- Epcoritamab + R-CHOP has a manageable safety profile; no new safety signals were detected
  - CRS was predictable and generally low grade
  - All CRS events resolved
- These updated data support further exploration of epcoritamab + R-CHOP in first-line DLBCL

Best Overall Responses

Response, n (%)[a]	Total n=31
Overall response	31 (100)
CMR	24 (77)
PMR	7 (23)
Stable disease	0
Progressive disease	0

Data cutoff: March 25, 2022. [a]Based on modified response-evaluable population, defined as patients with ≥1 target lesion at baseline and ≥1 postbaseline response evaluation and patients who died within 60 d of first dose.

Response Profile



Falchi et al, ASCO 2022

MODULE 6: Chimeric Antigen Receptor (CAR) T-Cell Therapy – Dr Hill

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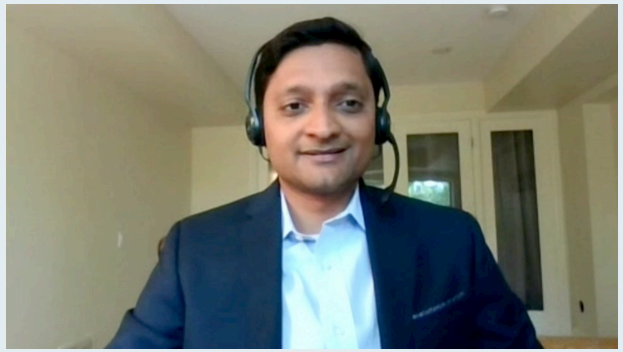

Dr Vignesh Narayanan
(Lone Tree, Colorado)

A 75-year-old woman with recurrent DLBCL and significant cardiac comorbidity

A 57-year-old man with double-hit DLBCL

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An 84-year-old man with recurrent DLBCL

Dr Namrata Peswani (Richardson, Texas)

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A 59-year-old man with R/R MCL and multiple comorbidities

Dr Spencer Bachow (Boca Raton, Florida)

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Chimeric Antigen Receptor (CAR) T-Cell Therapy

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Cleveland Clinic
Taussig Cancer Institute

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Research To Practice
ASCO Update
June 5, 2022

@BrianHill_MDPhD

Long-Term Survival and Gradual Recovery of B Cells in Patients With Refractory Large B-Cell Lymphoma Treated With Axicabtagene Ciloleucel

- Caron A. Jacobson, MD, MMSc[1]; Fredrick L. Locke, MD[2]; Armin Ghobadi, MD[3]; David B. Miklos, MD, PhD[4]; Lazaros J. Lekakis, MD[5]; Olalekan O. Oluwole, MD, MPH, MBBS[6]; Yi Lin, MD, PhD[7]; Ira Braunschweig, MD[8]; Brian T. Hill, MD, PhD[9]; John M. Timmerman, MD[10]; Abhinav Deol, MD[11]; Patrick M. Reagan, MD[12]; Patrick Stiff, MD[13]; Ian W. Flinn, MD, PhD[14]; Umar Farooq, MD[15]; Andre H. Goy, MD[16]; Peter A. McSweeney, MB, ChB[17]; Javier Muñoz, MD, MS, FACP[18]; Tanya Siddiqi, MD[19]; John M. Rossi, MS[20]; Adrian A. Bot, MD, PhD[20]; Lianqing Zheng, PhD[20]; Remus Vezan, MD, PhD[20]; Zahid Bashir, MBBS, MS[20]; Jenny J. Kim, MD, MS[20]; Rong Chu, PhD[20]; and Sattva S. Neelapu, MD[21]

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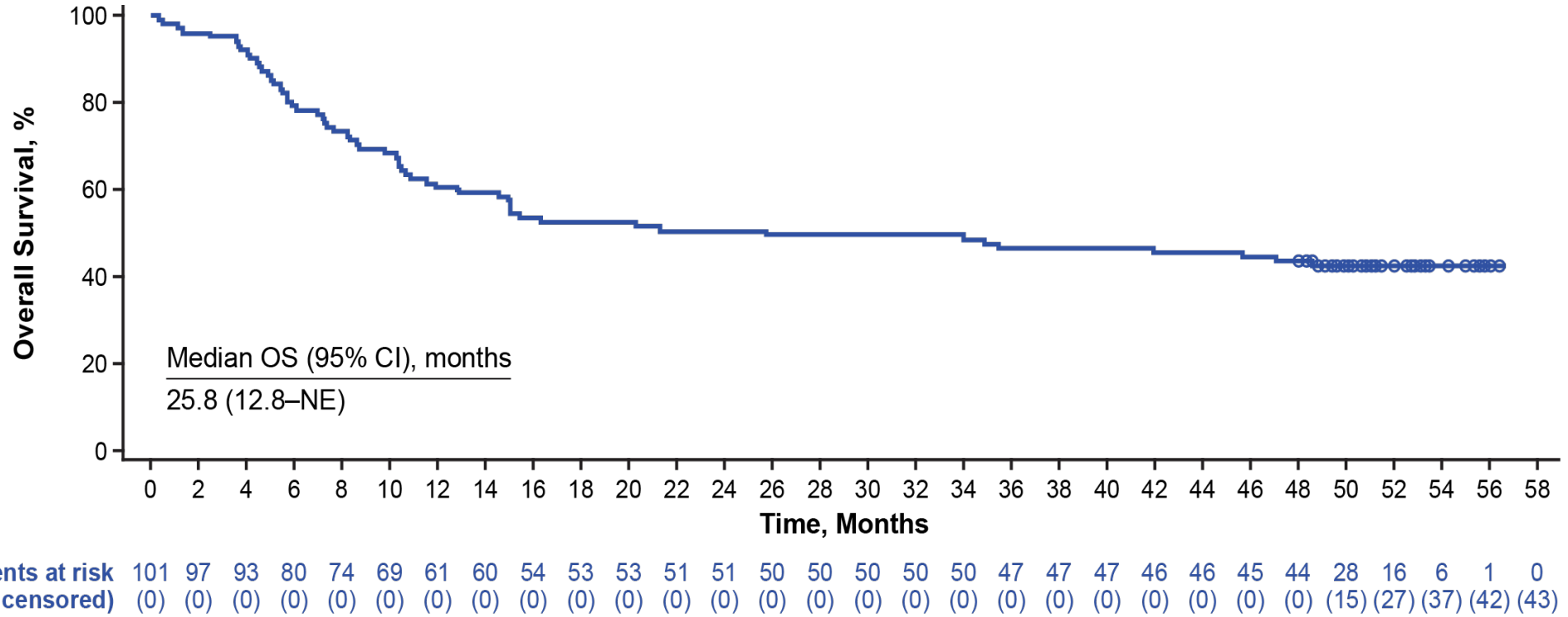
Overall Survival At 4 Years (mITT, n=101)



- Among axi-cel–treated patients (mITT, n=101), with ≥4 years of follow-up (median, 51.1 months), median OS was 25.8 months, and the KM estimate of the 4-year OS rate was 44%
- Among the entire enrolled population (ITT, n=111), median OS was 17.4 months, and the KM estimate of the 4-year OS rate was 41%

Axi-cel, axicabtagene ciloleucel; KM, Kaplan-Meier; mITT, modified intent-to-treat; NE, not estimable; OS, overall survival.

CAR T-Cell and B-Cell Detection in Blood

- As previously reported, patients in ongoing response after 2 years had significantly greater peak CAR T-cell expansion in blood 7–14 days after axi-cel infusion than did patients with relapse (*P*=.014) or no response (*P*=.0003)[1]

- Blood samples from 21 patients in ongoing response (per institutional standard of care) at ≥3 years were available for analysis of CAR T cells and evaluation of B-cell presence
  - All evaluable patients had detectable B cells in blood at 3 years after axi-cel treatment
  - 67% of patients (n=14/21) had detectable CAR gene-marked cells and polyclonal B cells in blood at 3 years

1. Locke FL, et al. *Lancet Oncol*. 2019;20:31-42.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor.

Second Line CAR-T vs. Standard of Care

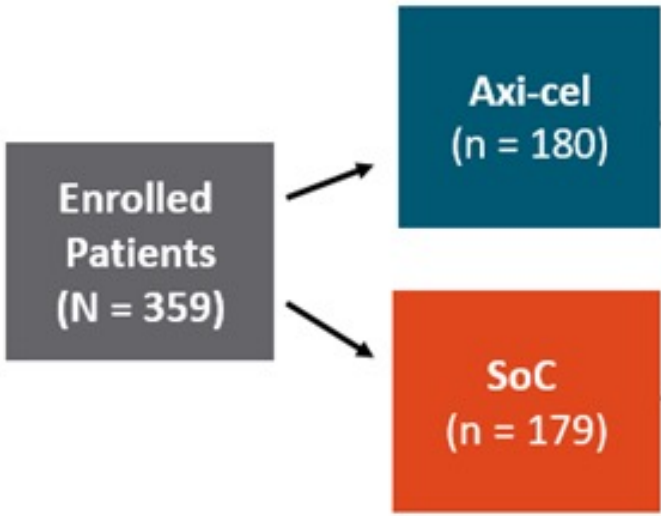
3 Randomized Phase III Trials*

1. ZUMA-7 – Axi-cel
2. TRANSFORM – Liso-cel
3. BELINDA - Tisa-cel

*All required patients to have relapsed <12 months of completion of frontline treatment

ZUMA-7: Axi-cel vs. Standard of Care

- 94% of patients received axi-cel, whereas 36% of patients received HDT-ASCT



Locke. ASH 2021. Abstr 2.

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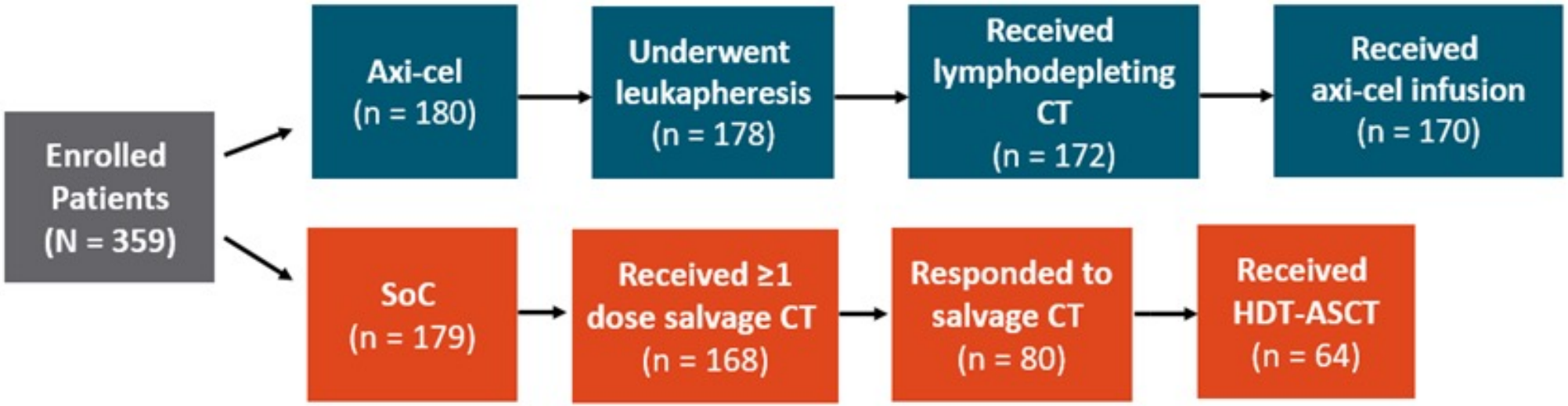
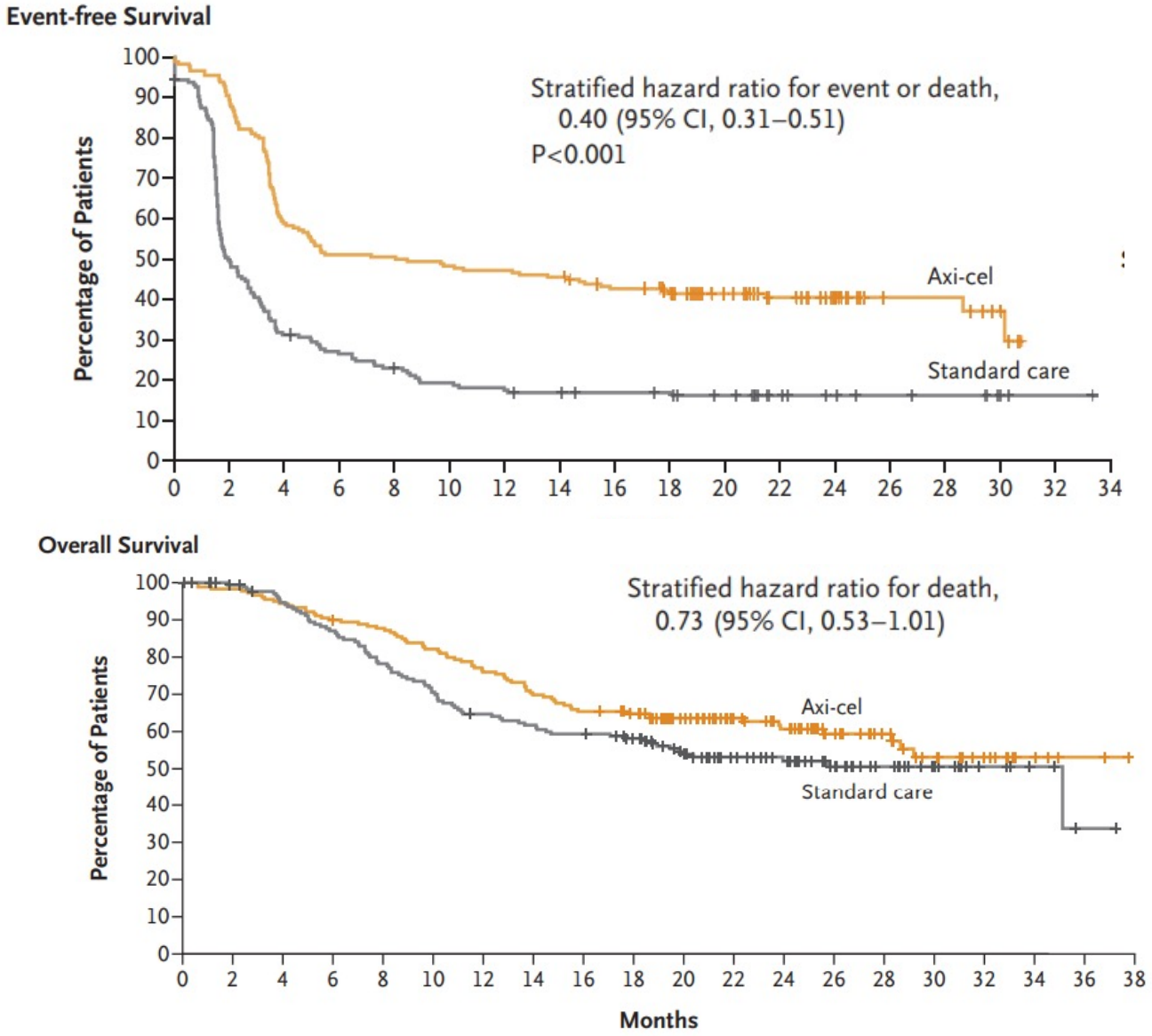


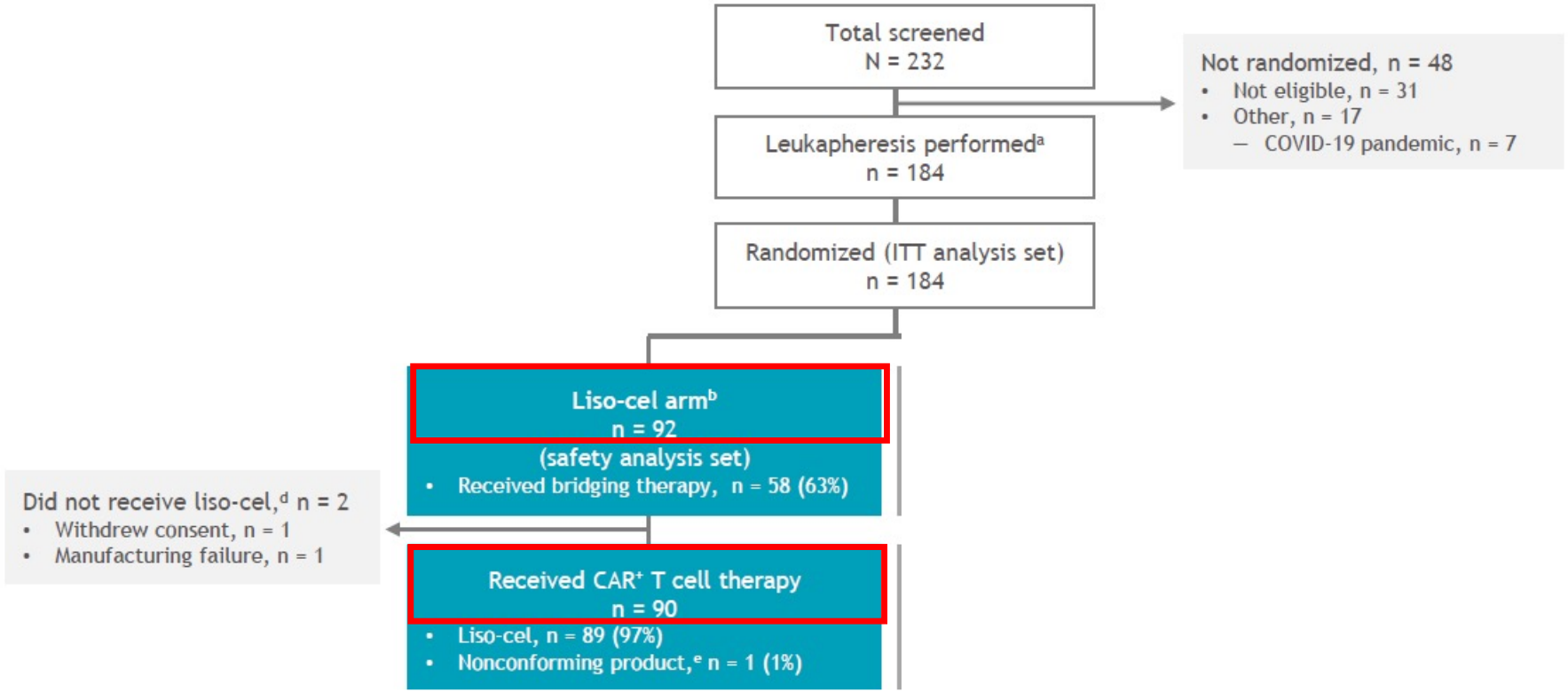
Locke. ASH 2021. Abstr 2.

ZUMA-7: Axi-cel vs. Standard of Care



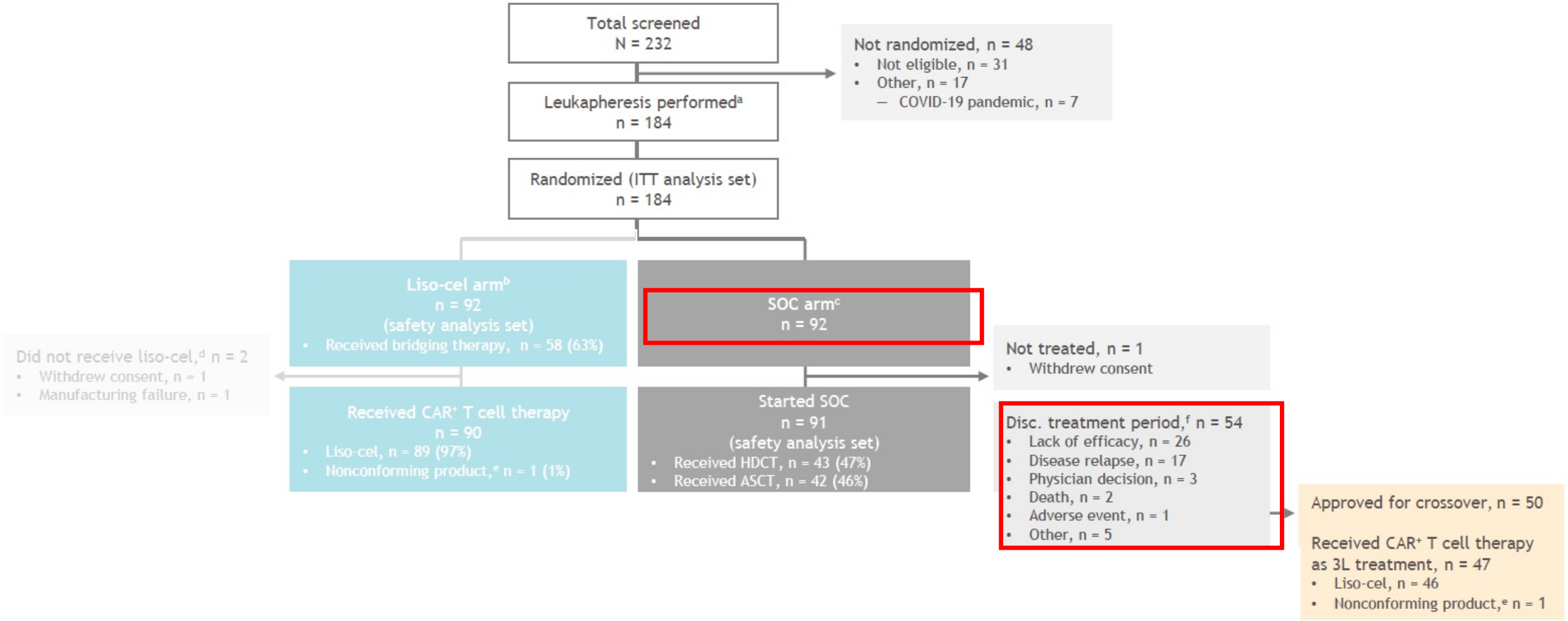
Locke FL et al. NEJM 2022

TRANSFORM: Liso-cel vs. Standard of Care



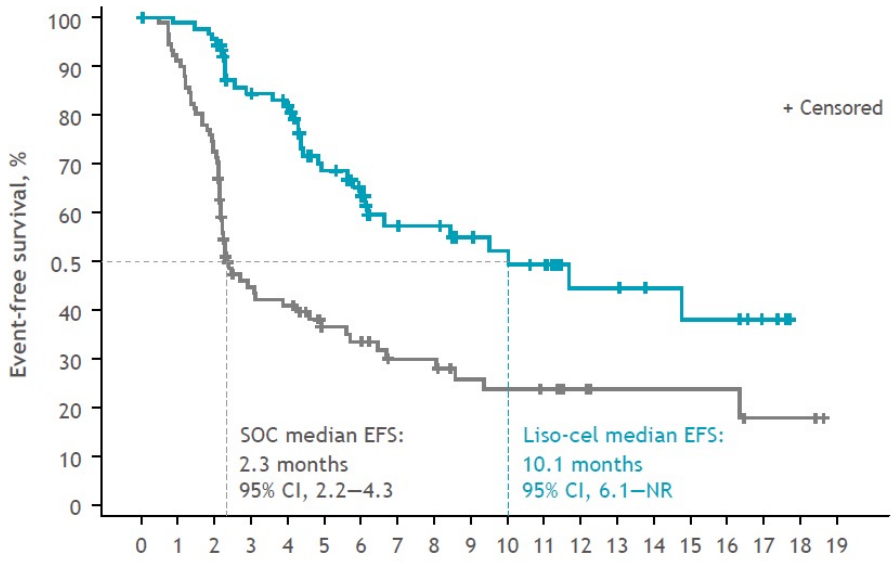
Kamdar et al. ASH 2021

TRANSFORM: Liso-cel vs. Standard of Care

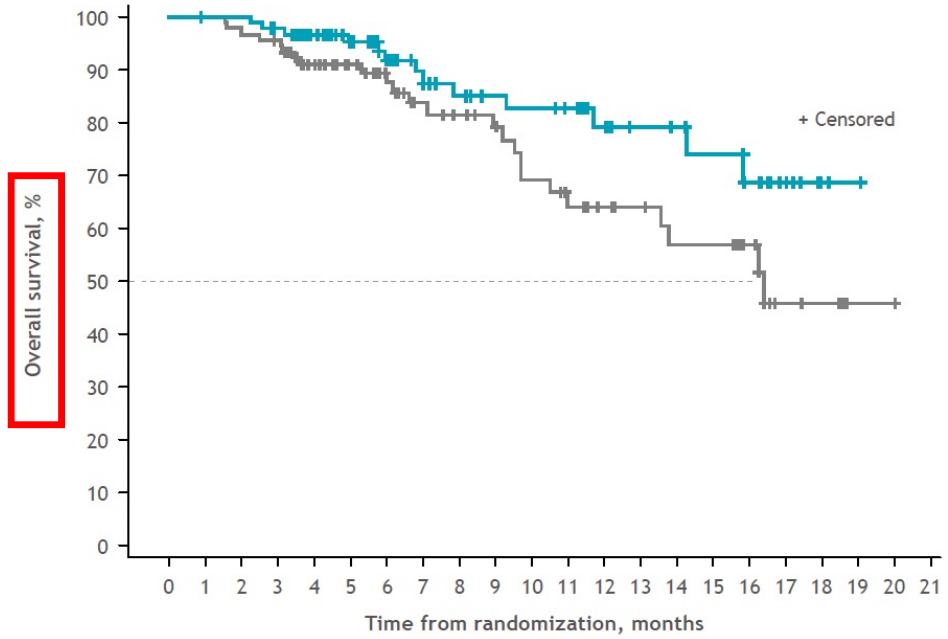


Kamdar et al. ASH 2021

TRANSFORM: Liso-cel vs. Standard of Care



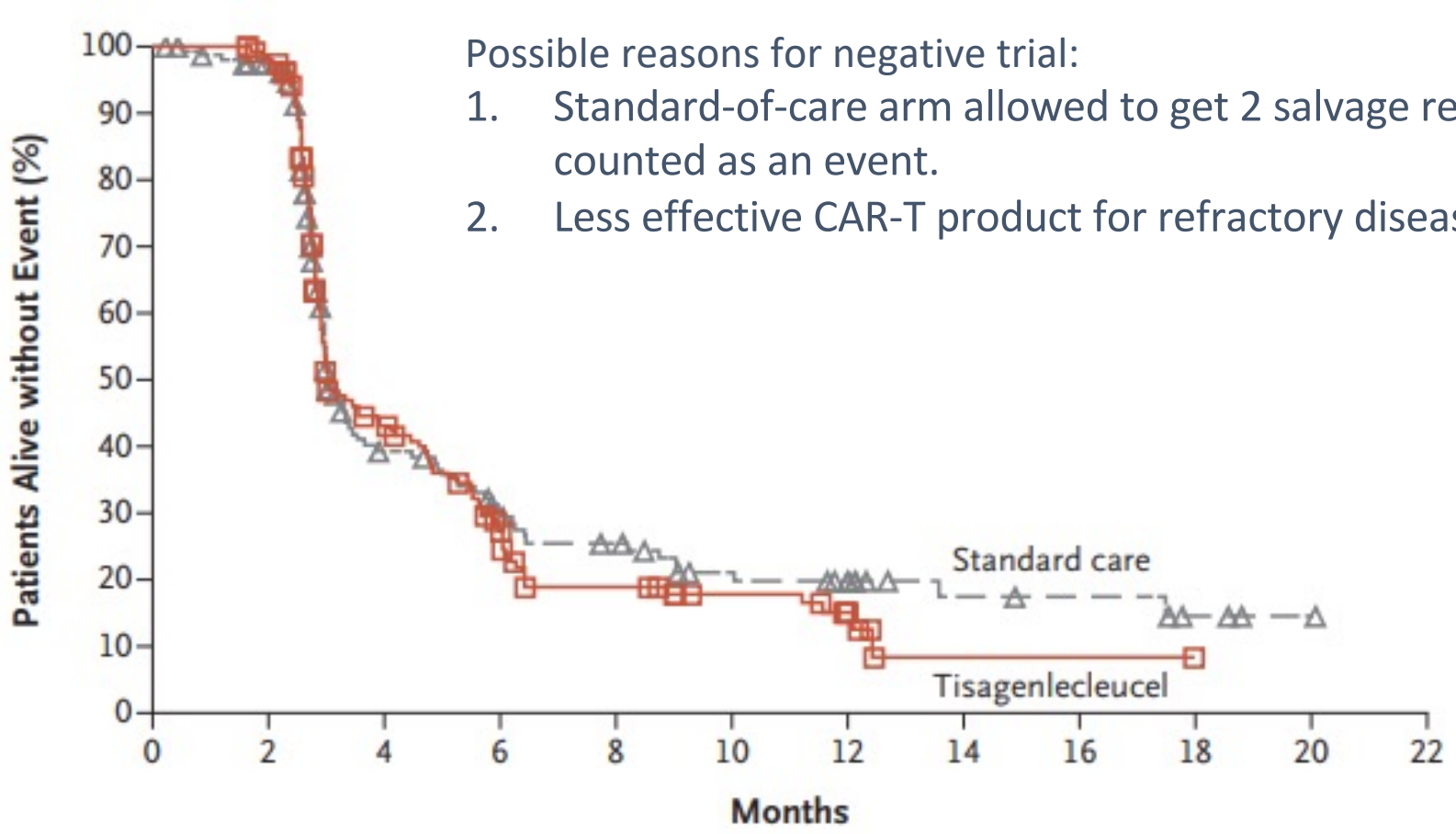
	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	35	63
Stratified HR (95% CI)	0.349 (0.229–0.530)	
	P < 0.0001	



	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	

Kamdar et al. ASH 2021

BELINDA: Tisa-cel vs. Standard of Care



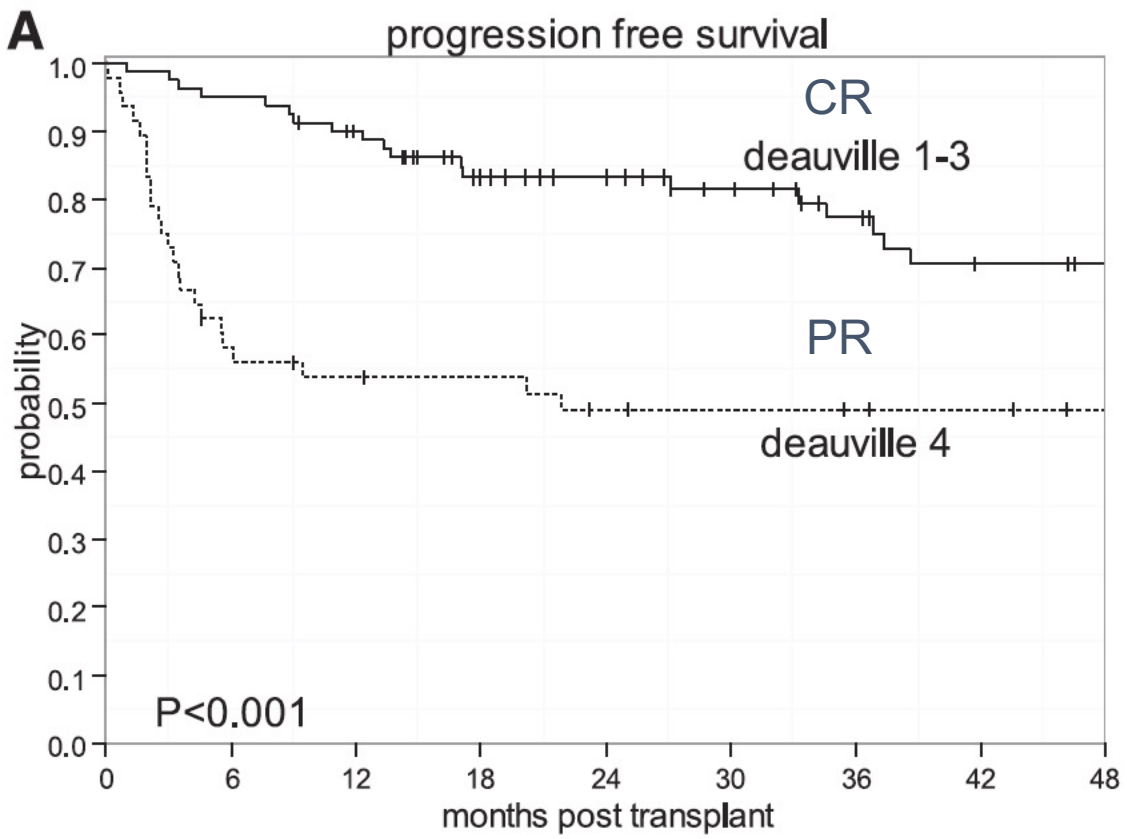
Possible reasons for negative trial:

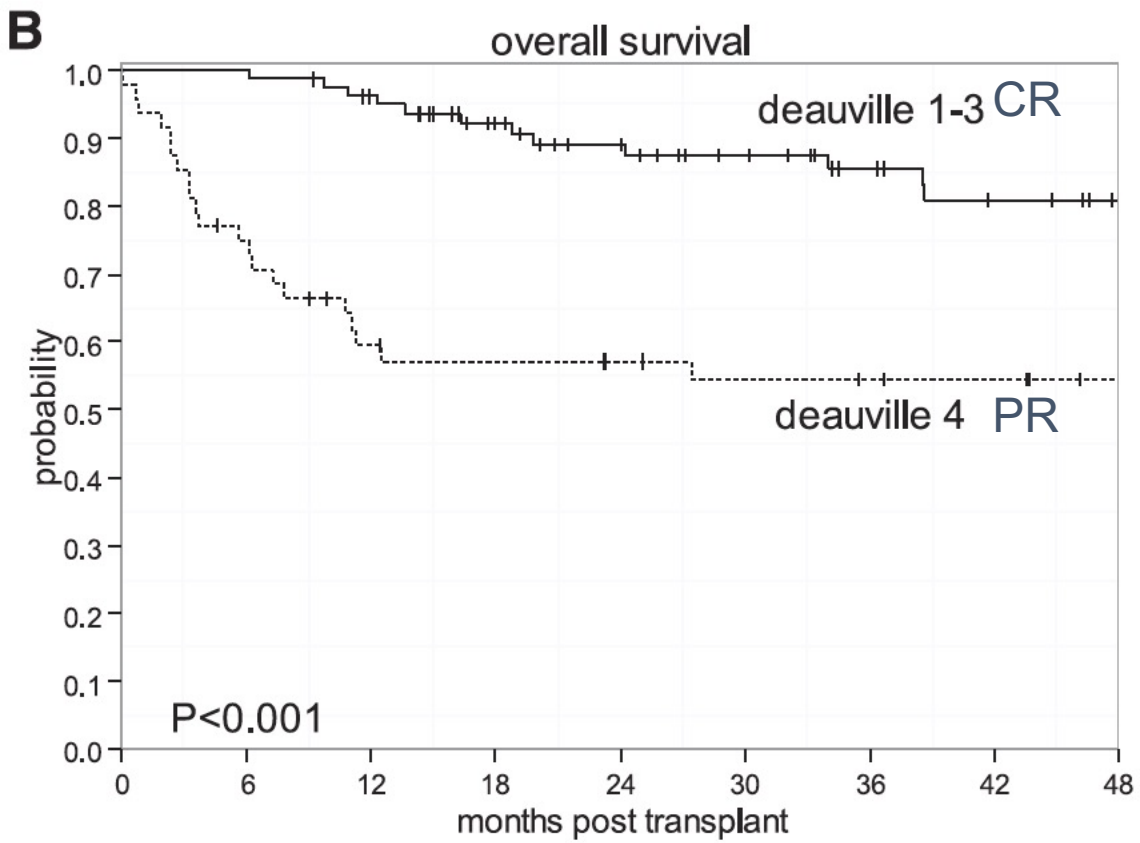
1. Standard-of-care arm allowed to get 2 salvage regimens without being counted as an event.
2. Less effective CAR-T product for refractory disease

Bishop, et al. NEJM 2021

Confused?

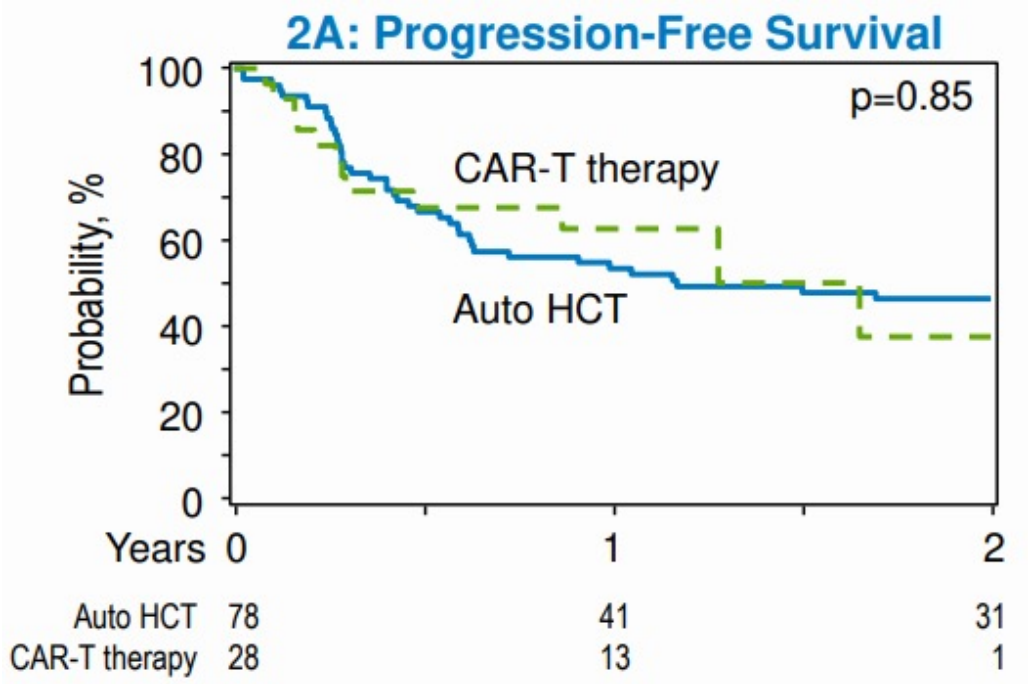
Favorable Outcomes of ASCT in Complete Remission: Prognostic Value of Chemosensitivity

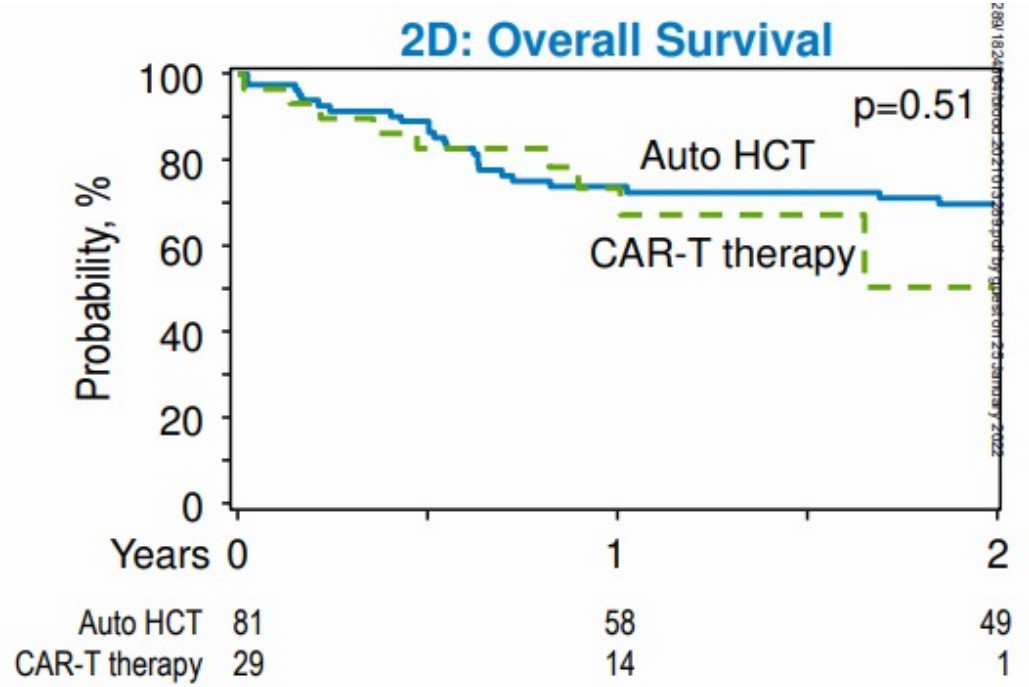




Sauter, *et al* Blood, 2015

Registry Comparison of patients in PR after ≤2 Lines of Prior Therapy





Mayzar, *et al.* Blood 2021

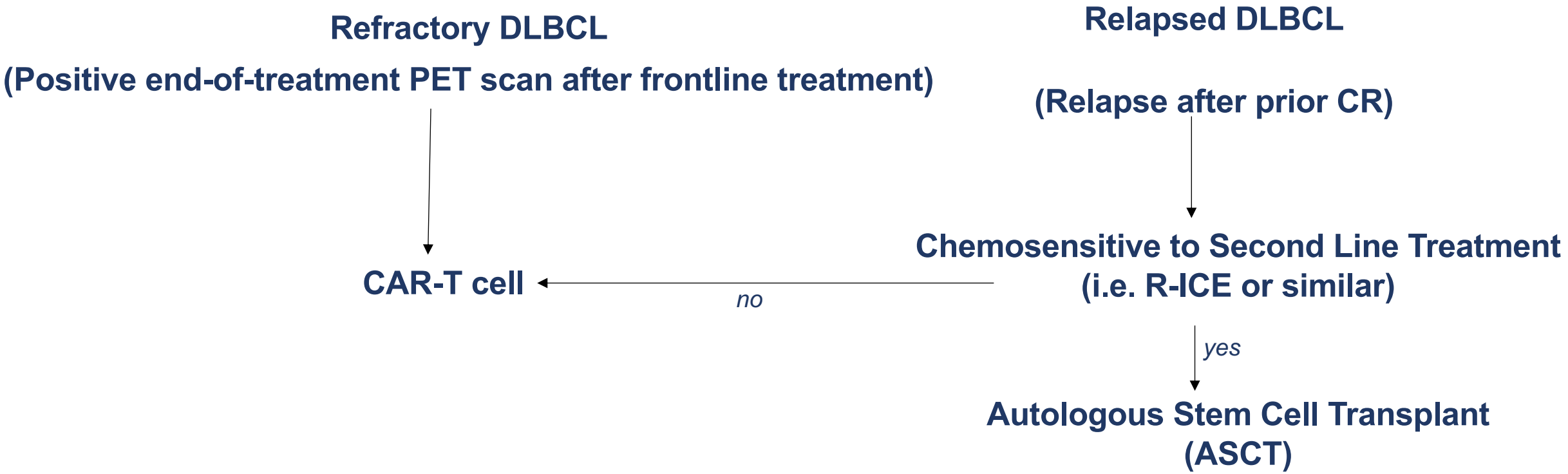
Proposed Approach

Refractory DLBCL

(Positive end-of-treatment PET scan after frontline treatment)

CAR-T cell

Proposed Approach



Frontline CAR-T for High Risk DLBCL

nature medicine

FOCUS | ARTICLES

https://doi.org/10.1038/s41591-022-01731-4

Check for updates

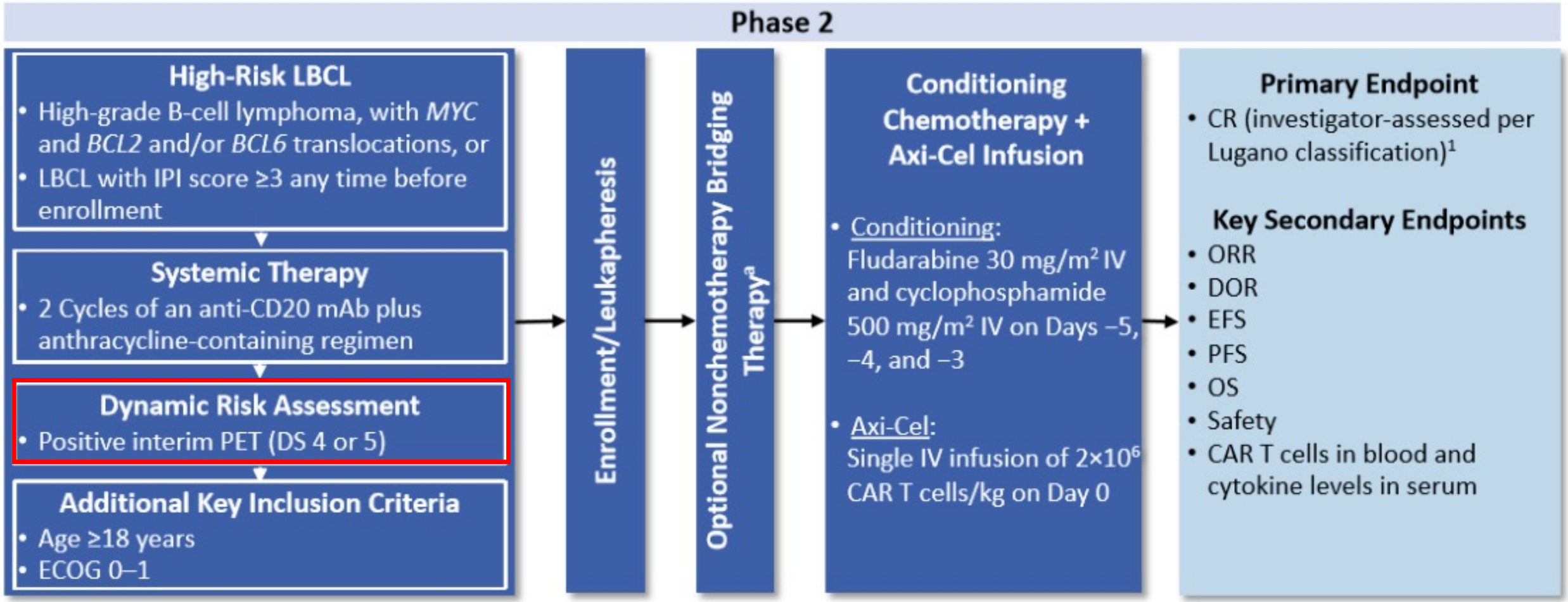
OPEN

Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial

Sattva S. Neelapu[1]✉, Michael Dickinson[2], Javier Munoz[3], Matthew L. Ulrickson[3], Catherine Thieblemont[4,5], Olalekan O. Oluwole[6], Alex F. Herrera[7], Chaitra S. Ujjani[8], Yi Lin[9], Peter A. Riedell[10], Natasha Kekre[11], Sven de Vos[12], Christine Lui[13], Francesca Milletti[13], Jinghui Dong[13], Hairong Xu[13] and Julio C. Chavez[14]

Neelapu, et al Nature Medicine 2022

ZUMA-12 Study Design

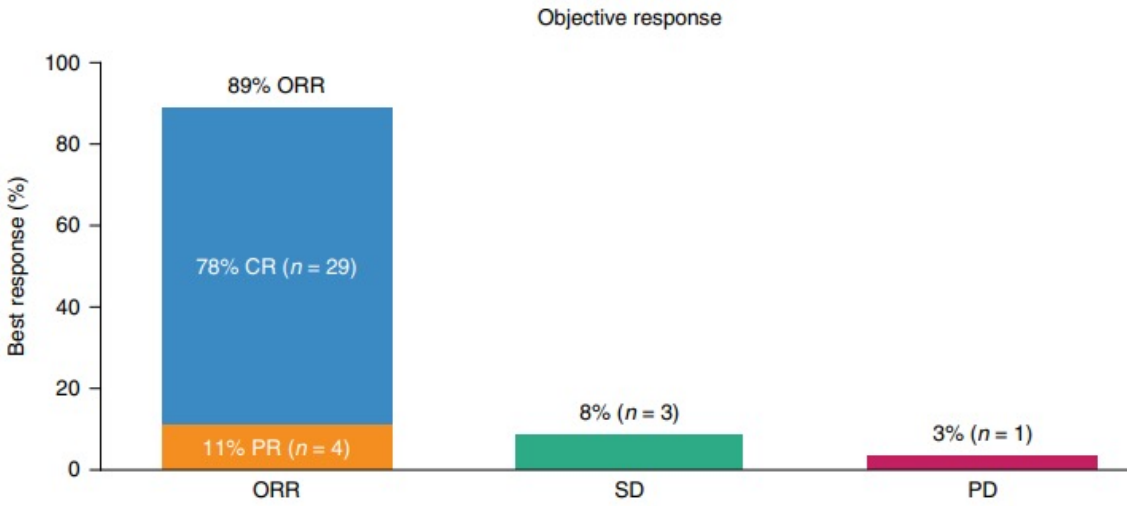


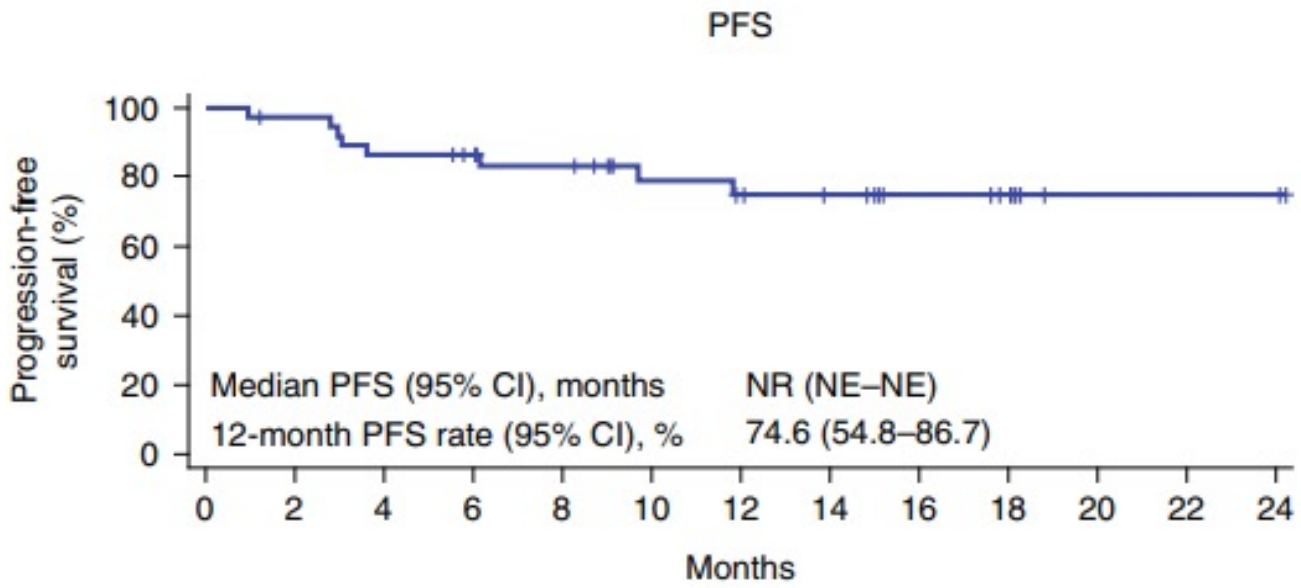
[a] Administered after leukapheresis and completed prior to initiating conditioning chemotherapy; PET-CT was required after bridging.

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

Axi-cel, axicabtagene ciloleucel; BCL, B-cell lymphoma; CAR, chimeric antigen receptor; CR, complete response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; DS, Deauville score; ECOG, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; IPI, International Prognostic Index; IV, intravenous; LBCL, large B-cell lymphoma; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PET, positron-emission tomography; PFS, progression-free survival.

Frontline CAR-T for High Risk DLBCL





Caveat: Need prospective randomized control trial, as value of interim PET scan during R-CHOP has not been demonstrated. Continuation of R-CHOP may have resulted in favorable outcomes in a significant proportion of patients.

Neelapu, et al Nature Medicine 2022

CAR-T for Mantle Cell Lymphoma: Brexu-Cel

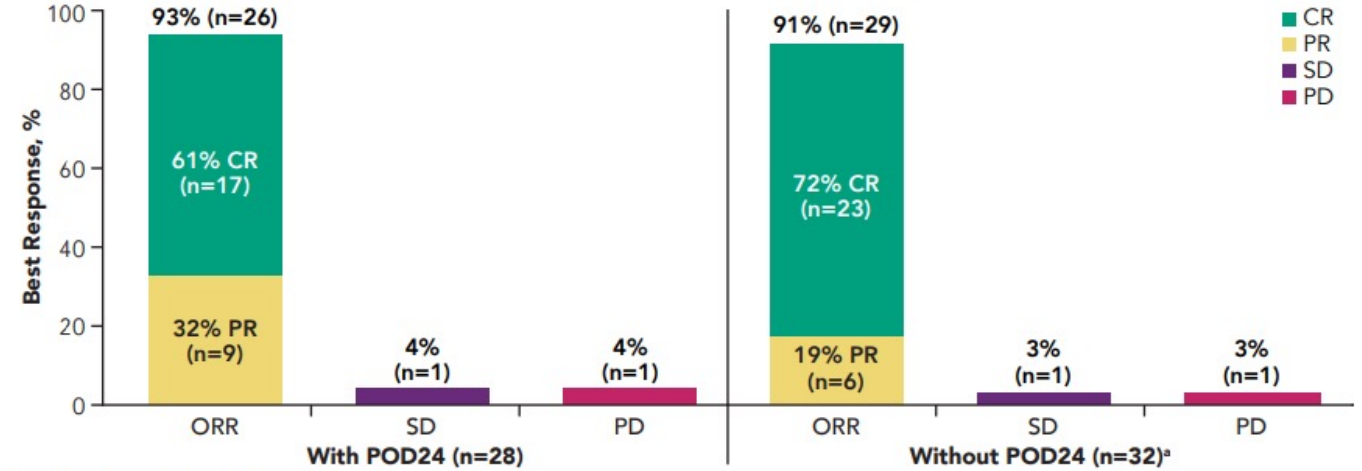
Outcomes with KTE-X19 in patients (pts) with relapsed/refractory (R/R) mantle cell lymphoma (MCL) in ZUMA-2 who had progression of disease within 24 months of diagnosis (POD24).

Michael Wang, Javier Munoz, Andre Goy, Frederick Lundry Locke, Caron A. Jacobson, Brian T. Hill, John Timmerman, Houston Holmes, Samantha Jaglowski, Ian Flinn, Peter A. McSweeney, David Bernard Miklos, Marie José Kersten, Krimo Bouabdallah, Max S. Topp, Rhine Shen, Ioana Kloos, Weimin Peng, Xiang Fang, Patrick M. Reagan

The University of Texas MD Anderson Cancer Center, Houston, TX; Banner MD Anderson Cancer Center, Gilbert, AZ; John Theurer Cancer Center, Hackensack, NJ; Moffitt Cancer Center, Tampa, FL; Dana-Farber Cancer Institute, Boston, MA; Cleveland Clinic Foundation, Cleveland, OH; UCLA David Geffen School of Medicine, Los Angeles, CA; Texas Oncology, Dallas, TX; The Ohio State University Comprehensive Cancer Center, Division of Hematology, Columbus, OH; Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN; Colorado Blood Cancer Institute, Denver, CO; Stanford University School of Medicine, Stanford, CA; Amsterdam UMC, University of Amsterdam, and on behalf of HOVON/LLPC, Amsterdam, Netherlands; CHU Bordeaux, Service d'Hématologie et Thérapie Cellulaire, Bordeaux, France; Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany; Kite, A Gilead Company, Santa Monica, CA; University of Rochester Medical Center, Rochester, NY

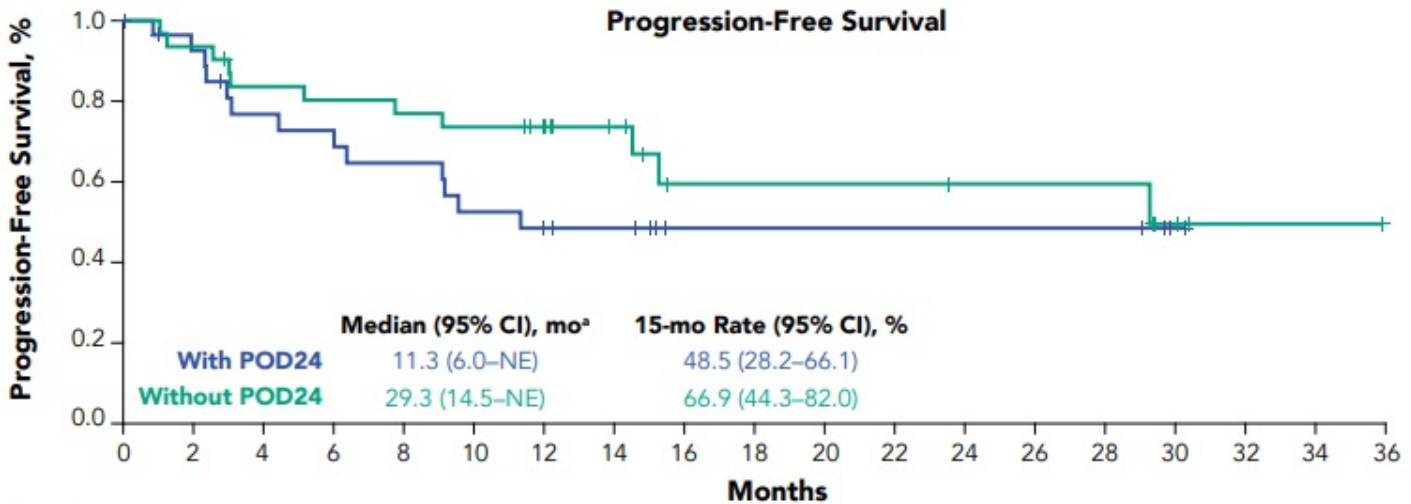
CAR-T for Mantle Cell Lymphoma: Brexu-Cel

Figure 2. ORR by IRRC Assessment in Patients With and Without POD24



Assessed by an IRRC according to the Lugano Classification.[7]
[a]One patient was not evaluable.
CR, complete response; IRRC, Independent Radiology Review Committee; ORR, objective response rate; PD, progressive disease; with POD24, progression of disease <24 months after initial diagnosis; without POD24, progression of disease ≥24 months after initial diagnosis; PR, partial response; SD, stable disease.

- The ORR was similar among patients with and without POD24, with a slightly higher CR rate in patients without POD24 (**Figure 2**)
- Similar rates of MRD-negativity were also observed among patients with (82%; n=9/11) and without (79%; n=15/19) POD24



Wang, et al EHA 2021

CAR-T for Mantle Cell Lymphoma: Liso-Cel

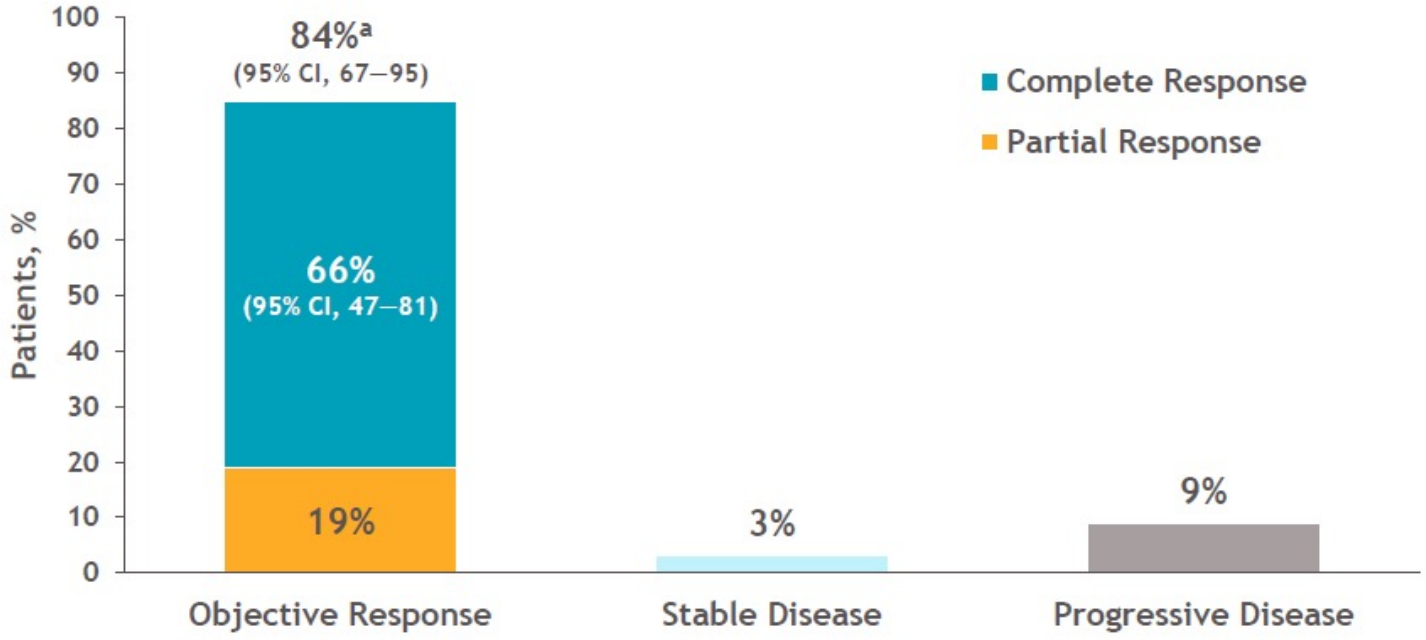
Safety and Preliminary Efficacy in Patients with Relapsed/Refractory Mantle Cell Lymphoma Receiving Lisocabtagene Maraleucel in TRANSCEND NHL 001

M. Lia Palomba,[1] Leo I. Gordon,[2] Tanya Siddiqi,[3] Jeremy Abramson,[4] Manali Kamdar,[5] Matthew Lunning,[6] David G. Maloney,[7] Charalambos Andreadis,[8] Jon E. Arnason,[9] Nilanjan Ghosh,[10] Amitkumar Mehta,[11] Scott R. Solomon,[12] Thalia Farazi,[13] Jacob Garcia,[13] Christine Dehner,[13] Ken Ogasawara,[14] Jie Gao,[13] Michael Wang[15]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Northwestern University Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, USA; [3]City of Hope National Medical Center, Duarte, CA, USA; [4]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [5]University of Colorado Cancer Center, Aurora, CO, USA; [6]University of Nebraska Medical Center, Omaha, NE, USA; [7]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [8]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA, USA; [9]Beth Israel Deaconess Medical Center, Boston, MA, USA; [10]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [11]University of Alabama at Birmingham, Birmingham, AL, USA; [12]Immunotherapy Program, Northside Hospital Cancer Institute, Atlanta, GA, USA; [13]Bristol Myers Squibb, Seattle, WA, USA; [14]Bristol Myers Squibb, Princeton, NJ, USA; [15]University of Texas MD Anderson Cancer Center, Houston, TX, USA

CAR-T for Mantle Cell Lymphoma: Liso-Cel

Best Overall Response by Investigator Assessment



- Median on-study follow-up: 5.9 (range, 0.4–24.8) months
- Median time to first CR or PR: 0.95 (range, 0.9–2.0) months

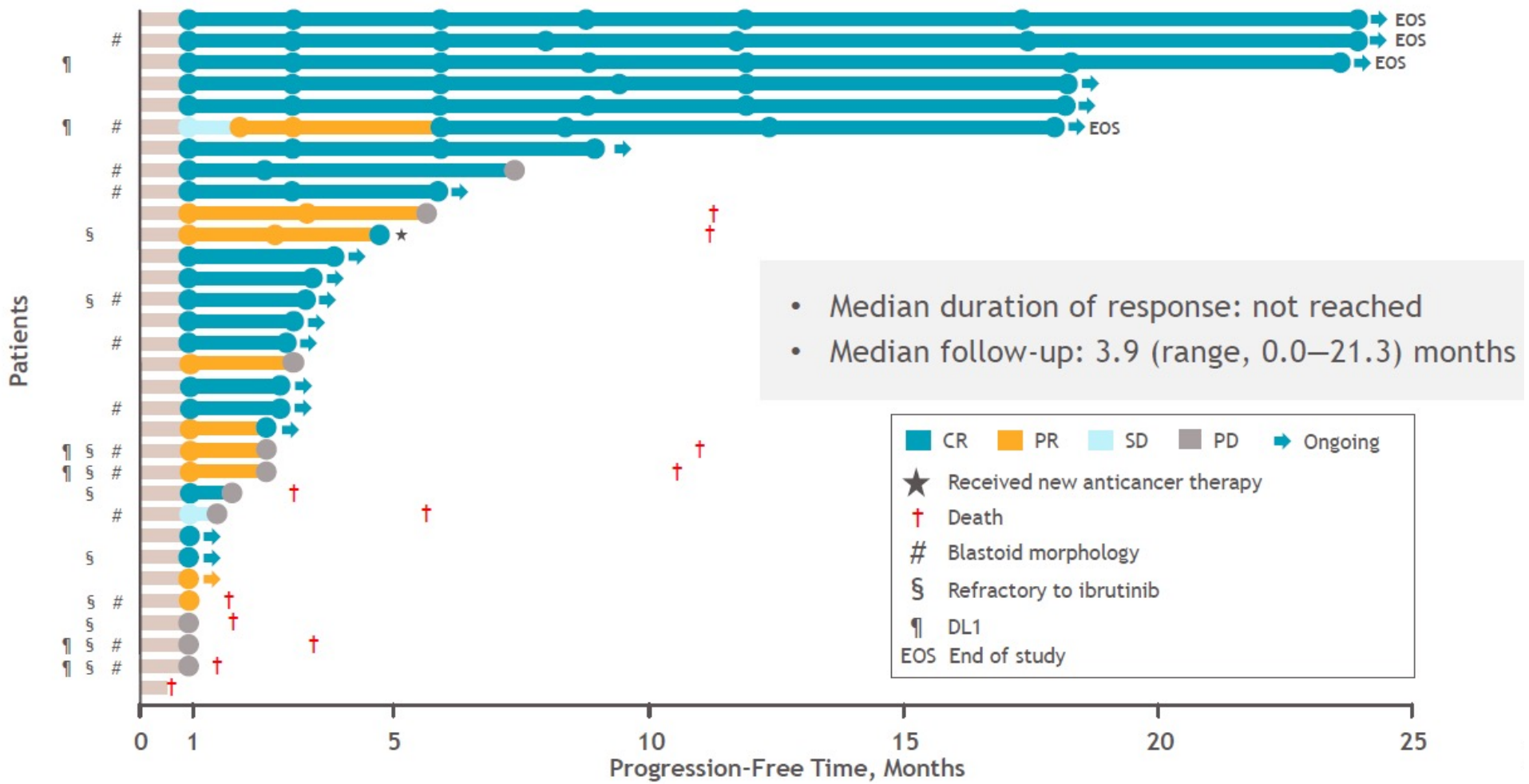
- ORR and CR rate, respectively, for patients with high-risk features:
  - Ki67 ≥30% (n = 23): 83% and 65%
  - Blastoid morphology (n = 13): 77% and 54%
  - *TP53* mutations (n = 7): 100% and 57%

[a]Based on 32 patients treated; one patient was not evaluable and is not shown in the figure.

Palomba, et al ASH 2020

CAR-T for Mantle Cell Lymphoma: Liso-Cel

Patient Responses over Time



Palomba, et al ASH 2020

CAR-T for Indolent Lymphoma: Axi-cel

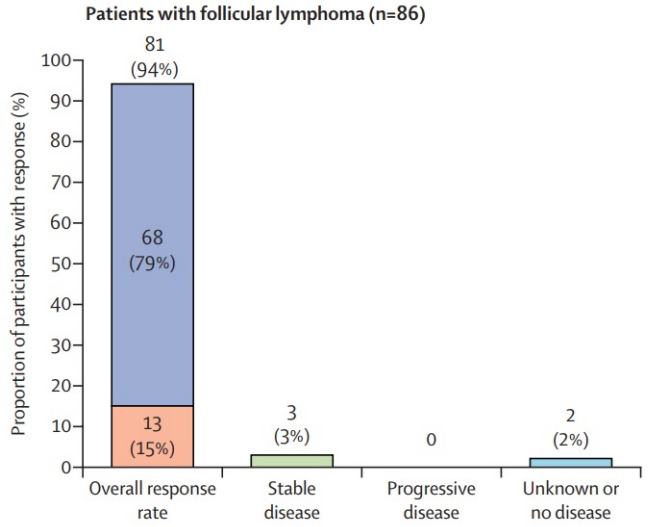
Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial

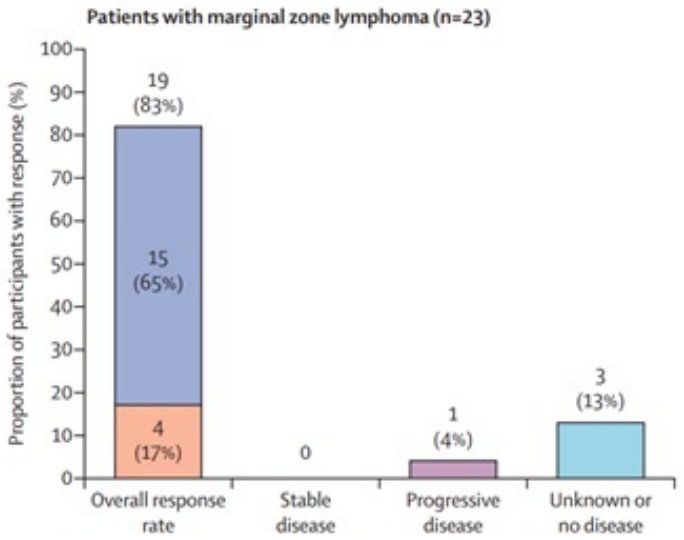
THE LANCET

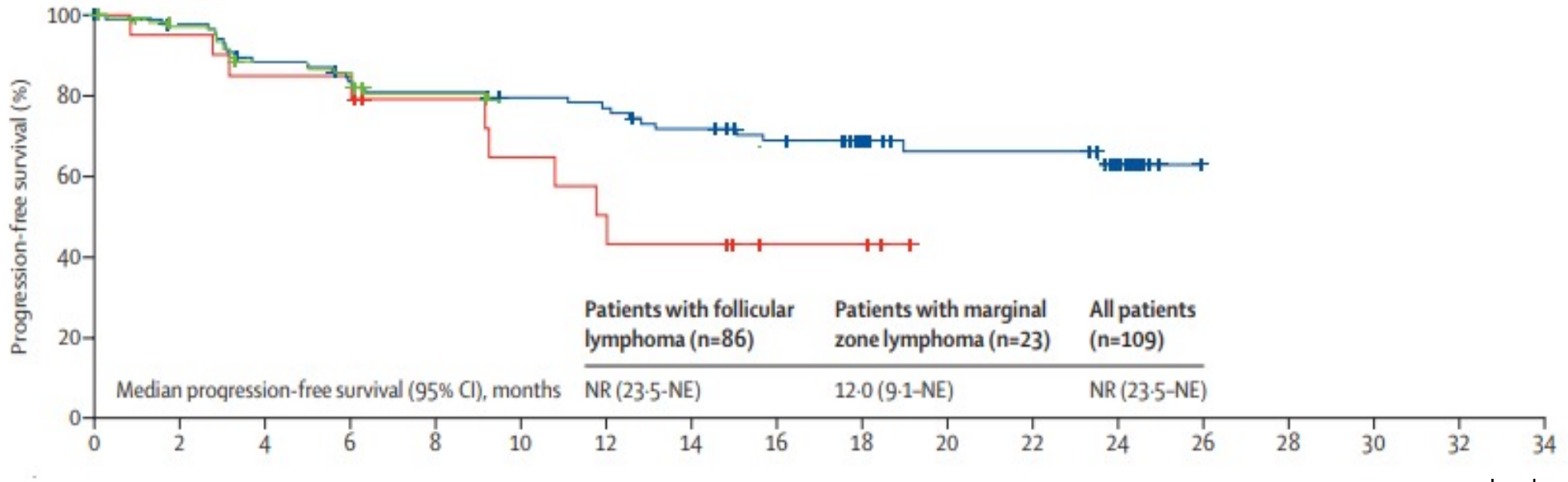
Caron A Jacobson, Julio C Chavez, Alison R Sehgal, Basem M William, Javier Munoz, Gilles Salles, Pashna N Munshi, Carla Casulo, David G Maloney, Sven de Vos, Ran Reshef, Lori A Leslie, Ibrahim Yakoub-Agha, Olalekan O Oluwole, Henry Chi Hang Fung, Joseph Rosenblatt, John M Rossi, Lovely Goyal, Vicki Plaks, Yin Yang, Remus Vezan, Mauro P Avanzi, Sattva S Neelapu

Jacobson, *et al.* Lancet, 2022

CAR-T for Indolent Lymphoma: Axi-cel







Jacobson, *et al.* Lancet, 2022

FDA Approves Tisagenlecleucel for Relapsed or Refractory Follicular Lymphoma

Press Release: May 27, 2022

"On May 27, 2022, the Food and Drug Administration granted accelerated approval to tisagenlecleucel for adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

The approval was based on the ELARA trial (NCT03568461), a multicenter, single-arm, open-label trial evaluating tisagenlecleucel, a CD19-directed chimeric antigen receptor (CAR) T cell therapy, in adult patients who were refractory or relapsed within 6 months after completion of two or more lines of systemic therapy (including an anti-CD20 antibody and an alkylating agent) or relapsed after autologous hematopoietic stem cell transplant."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tisagenlecleucel-relapsed-or-refractory-follicular-lymphoma

RTP RESEARCH TO PRACTICE

CAR-T for CLL: Liso-Cel

TRANSCEND CLL 004: Phase 1 Cohort of Lisocabtagene Maraleucel (liso-cel) in Combination with Ibrutinib for Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

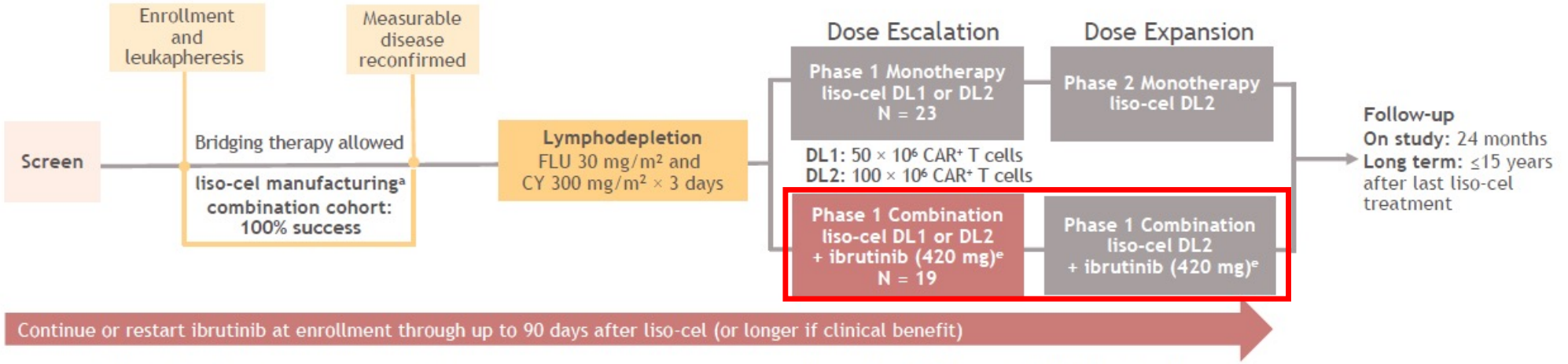
William G. Wierda,[1] Kathleen A. Dorritie,[2] Javier Munoz,[3] Deborah M. Stephens,[4] Scott Solomon,[5] Heidi H. Gillenwater,[6] Lucy Gong,[6] Lin Yang,[6] Ken Ogasawara,[7] Jerill Thorpe,[6] Tanya Siddiqi[8]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA; [3]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [4]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [5]Immunotherapy Program, Northside Hospital Cancer Institute, Atlanta, GA, USA; [6]Bristol Myers Squibb, Seattle, WA, USA; [7]Bristol Myers Squibb, Princeton, NJ, USA; [8]City of Hope National Medical Center, Duarte, CA, USA

Wierda, *et al.* ASH 2020

CAR-T for CLL: Liso-Cel

TRANSCEND CLL 004 Phase 1/2 Study Design[1] of liso-cel, a CD19-Directed, Defined Composition, CAR T Cell Product



Key Eligibility for Combination Cohort

- R/R CLL/SLL, and
- Progressing on ibrutinib at enrollment,[b] ***or***
- High-risk features[c] and received ibrutinib for ≥6 months with less than a CR, ***or***
- *BTK* or *PLCγ2* mutations,[d] ***or***
- Prior ibrutinib with no contraindication to reinitiating ibrutinib

Dose Escalation: mTPI-2 Design[2]

28-day dose-limiting toxicity period

Primary Objectives

- Safety
- Determine recommended dose

Exploratory Objectives

- Antitumor activity (iwCLL 2018)[3]
  - Testing for MRD[f]
- Cellular kinetic profile (qPCR)

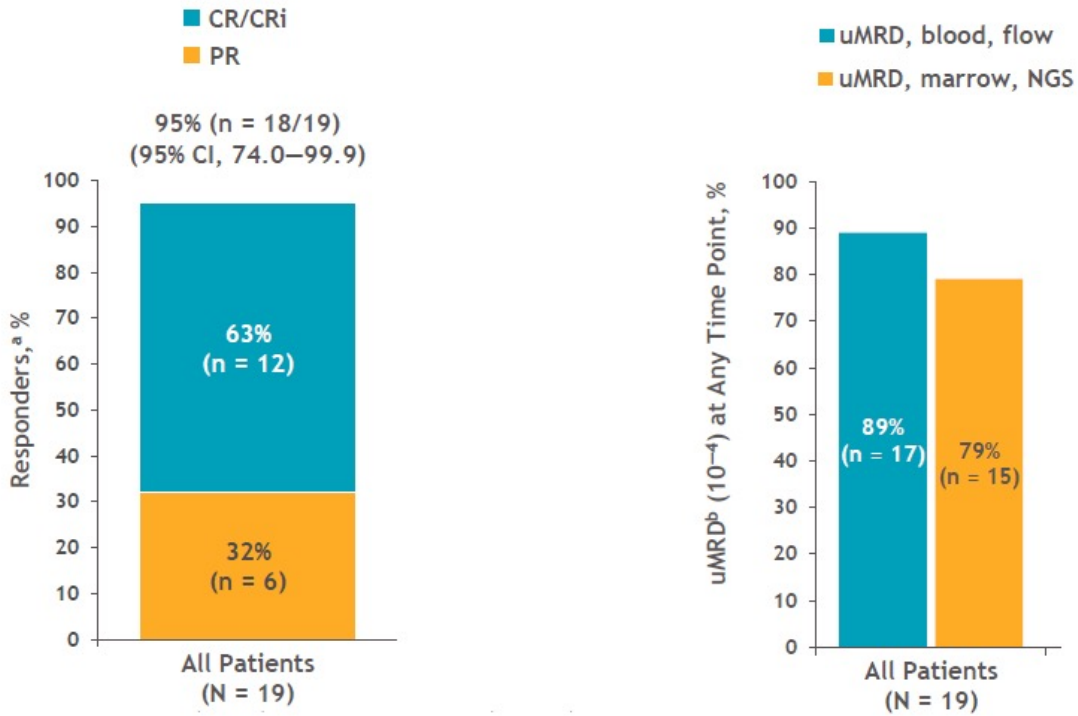
Oral presentation (Abs 546)
Siddiqi et al.
Phase I monotherapy update
Dec 7, 2020, 8:00 AM (PST)

[a]No patient in the combination phase 1 cohort received nonconforming product. [b]Defined as SD or PD as best response, or PD after previous response. [c]Complex cytogenetic abnormalities, del(17p), *TP53* mutated, or unmutated *IGHV*. [d]*BTK* or *PLCγ2* gene mutation, with or without progression on ibrutinib. [e]Lower dose was used if prior dose reduction was necessary to manage toxicity. [f]MRD was assessed in blood by flow cytometry and/or in bone marrow by next-generation sequencing (both with a sensitivity of $\leq 10^{-4}$).
CY, cyclophosphamide; DL, dose level; FLU, fludarabine; iwCLL, International Workshop on CLL; mTPI, modified toxicity probability interval; SD, stable disease.
1. ClinicalTrials.gov. NCT03331198; 2. Guo W, et al. *Contemp Clin Trials*. 2017;58:23-33; 3. Hallek M, et al. *Blood*. 2018;131:2745-2760.

Wierda, *et al.* ASH 2020

CAR-T for CLL: Liso-Cel

Best Overall Response and uMRD ($\leq 10^{-4}$) at 10-Month Follow-Up



- No patients had PD during the first month after liso-cel
- One patient at DL1 had SD for 6 months but later progressed

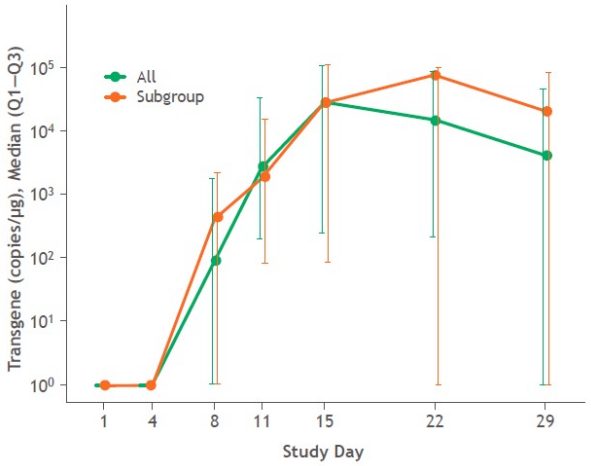
[a]Evaluated according to iwCLL 2018 criteria. [b]Assessed in blood by flow cytometry and/or in bone marrow by NGS.
CRi, CR with incomplete blood count recovery; NGS, next-generation sequencing.

Wierda, *et al.* ASH 2020

CAR-T for CLL: Liso-Cel

Cellular Kinetics—Expansion and Persistence

Liso-cel

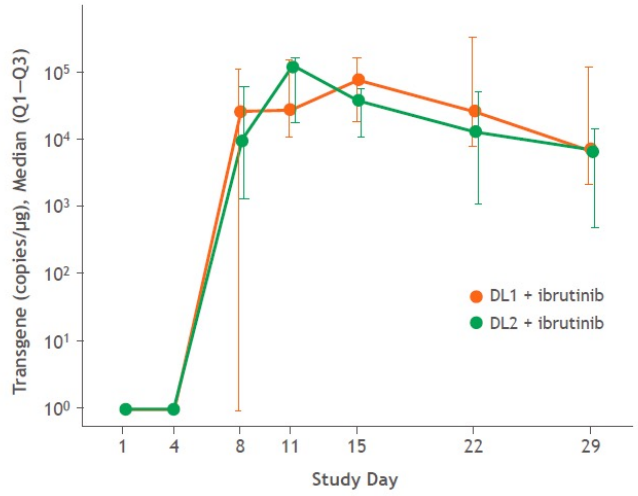


Parameter[a,b]	Monotherapy Cohort (N = 23)
C_{max} (copies/µg)	67,300 (2510–139,000)
t_{max} (day)	15 (14–21)
$AUC_{0–28d}$ (day × copies/µg)	470,000 (17,400–1,740,000)

[a]Median (interquartile range, Q1–Q3). [b]Evaluated using qPCR. [c]Defined as patients whose disease progressed on BTKi and failed venetoclax due to progression, intolerance, or failure to respond after at least 3 months of therapy.

- Long-term persistence
  - 50% of patients (n = 6/12) at 12 months
  - 18% of patients (n = 2/11) at 18 months

Liso-cel + ibrutinib



Parameter[a,b]	Combination Cohort (N = 19)
C_{max} (copies/µg)	128,000 (47,100–344,000)
t_{max} (day)	11 (10–15)
$AUC_{0–28d}$ (day × copies/µg)	682,000 (390,000–2,720,000)

[a]Median (interquartile range, Q1–Q3). [b]Evaluated using qPCR.

- Long-term persistence
  - 38% of patients (n = 6/16) at 6 months
  - 20% of patients (n = 1/5) at 12 months

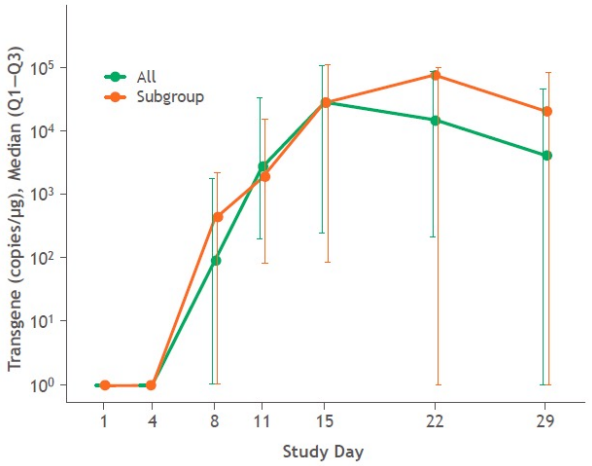
$AUC_{0–28d}$, area under the curve for transgene levels from 0 to 28 days postinfusion; C_{max}, maximum transgene levels; Q, quartile; t_{max}, time to C_{max}.

Siddiqi *et al*, ASH 2020
Wierda, *et al*. ASH 2020

CAR-T for CLL: Liso-Cel

Cellular Kinetics—Expansion and Persistence

Liso-cel



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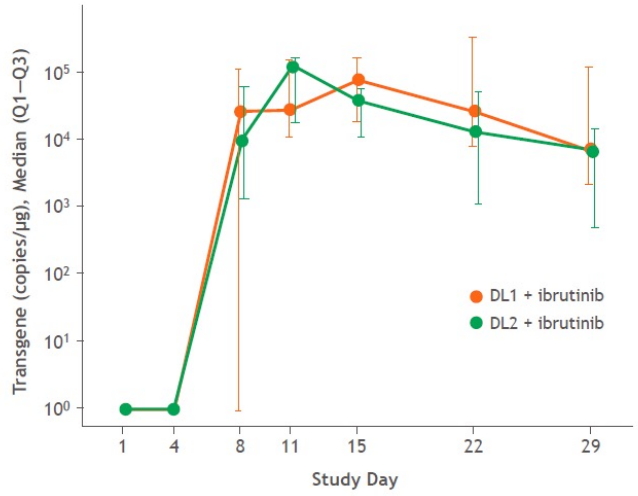

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Siddiqi *et al*, ASH 2020
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Breakfast with the Investigators: Urothelial Bladder Cancer

A CME Hybrid Symposium Held in Conjunction with the 2022 ASCO Annual Meeting

Monday, June 6, 2022

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Yohann Loriot, MD, PhD

Elizabeth R Plimack, MD, MS

Jonathan E Rosenberg, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

CME links will be posted in the chat (Zoom participants only) and emailed to all participants within 24 hours of the program.