The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

A CME/MOC- and NCPD-Accredited Event

Saturday, October 22, 2022
7:30 AM – 5:30 PM ET

RTP
RESEARCH
TO PRACTICE

Agenda

Module 1 — Lung Cancer: *Drs Langer and Lovly*

Module 2 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs LaCasce and Smith*

Module 3 — Prostate and Bladder Cancers: *Drs Morgans and Yu*

Module 4 — Renal Cell Carcinoma: *Prof Powles*

Module 5 — Multiple Myeloma: *Dr Usmani*

Module 6 — Hepatobiliary Cancers: *Prof Abou-Alfa*

Agenda

Module 7 — Breast Cancer: *Drs Goetz and Krop*

Module 8 — Endometrial Cancer: *Dr Westin*

Module 9 — Ovarian Cancer and PARP Inhibitors: *Dr O'Malley*

Module 10 — Gastrointestinal Cancers: *Drs Messersmith and Strickler*

Module 11 — Melanoma: *Prof Long*

Chronic Lymphocytic Leukemia and Lymphomas Faculty

Ann S LaCasce, MD, MMSc
Director, Dana-Farber/Mass General Brigham
Fellowship in Hematology/Oncology
Associate Professor of Medicine
Harvard Medical School
Lymphoma Program
Dana-Farber Cancer Institute
Boston, Massachusetts

Mitchell R Smith, MD, PhD
Clinical Professor of Medicine
George Washington University
Washington, DC
Chief Medical Officer
The Follicular Lymphoma Foundation
London, United Kingdom

Chronic Lymphocytic Leukemia

Current Approaches to Treatment of Treatment-Naïve CLL: NCCN Guidelines®

Without Del(17p)/*TP53* Mutation

Patients age ≥65 OR patients age <65 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 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.

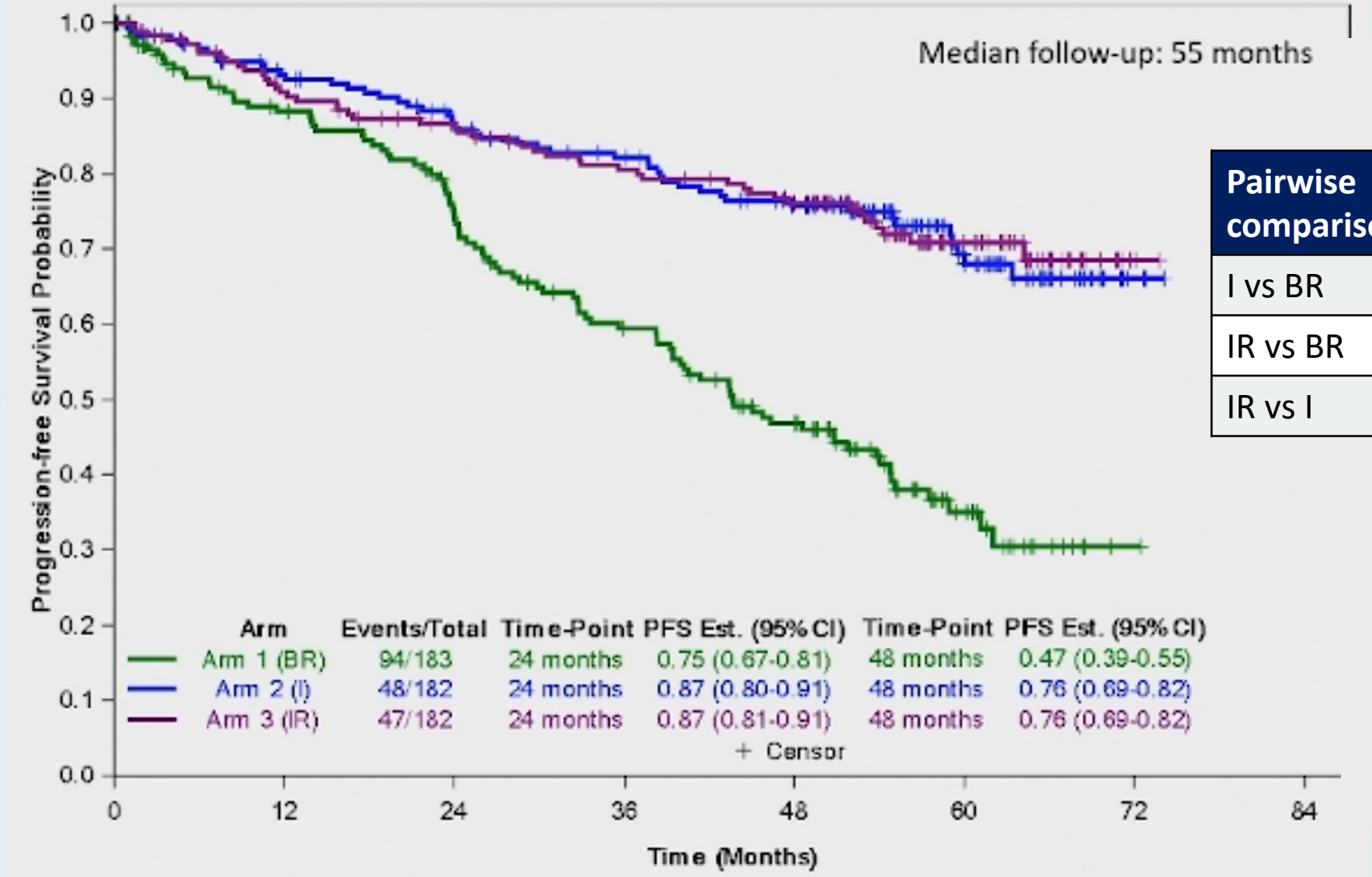
Courtesy of Ian W Flinn, MD, PhD

Long-Term Results of Alliance A041202 Show Continued Advantage of Ibrutinib-Based Regimens Compared with Bendamustine plus Rituximab (BR) Chemoimmunotherapy

Woyach JA et al.

ASH 2021;Abstract 639.

Alliance A041202: Progression-Free Survival



Pairwise comparisons	Hazard ratio	*p*-value
I vs BR	0.36	<0.0001
IR vs BR	0.36	<0.001
IR vs I	0.99	0.96

I = ibrutinib; BR = bendamustine/rituximab; IR = ibrutinib/rituximab

Woyach JA et al. ASH 2021;Abstract 639.

RTP RESEARCH TO PRACTICE

Blood 2022 July 14;140(2):112-20.

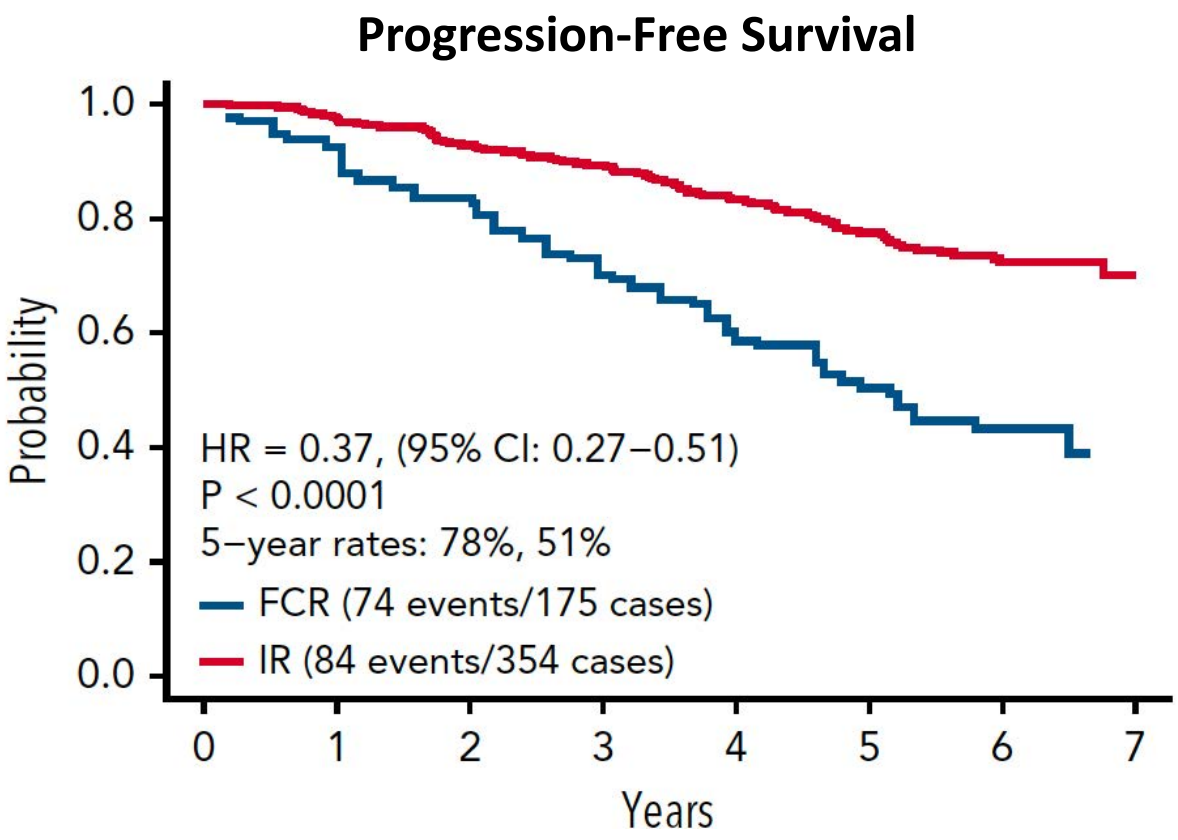
Regular Article

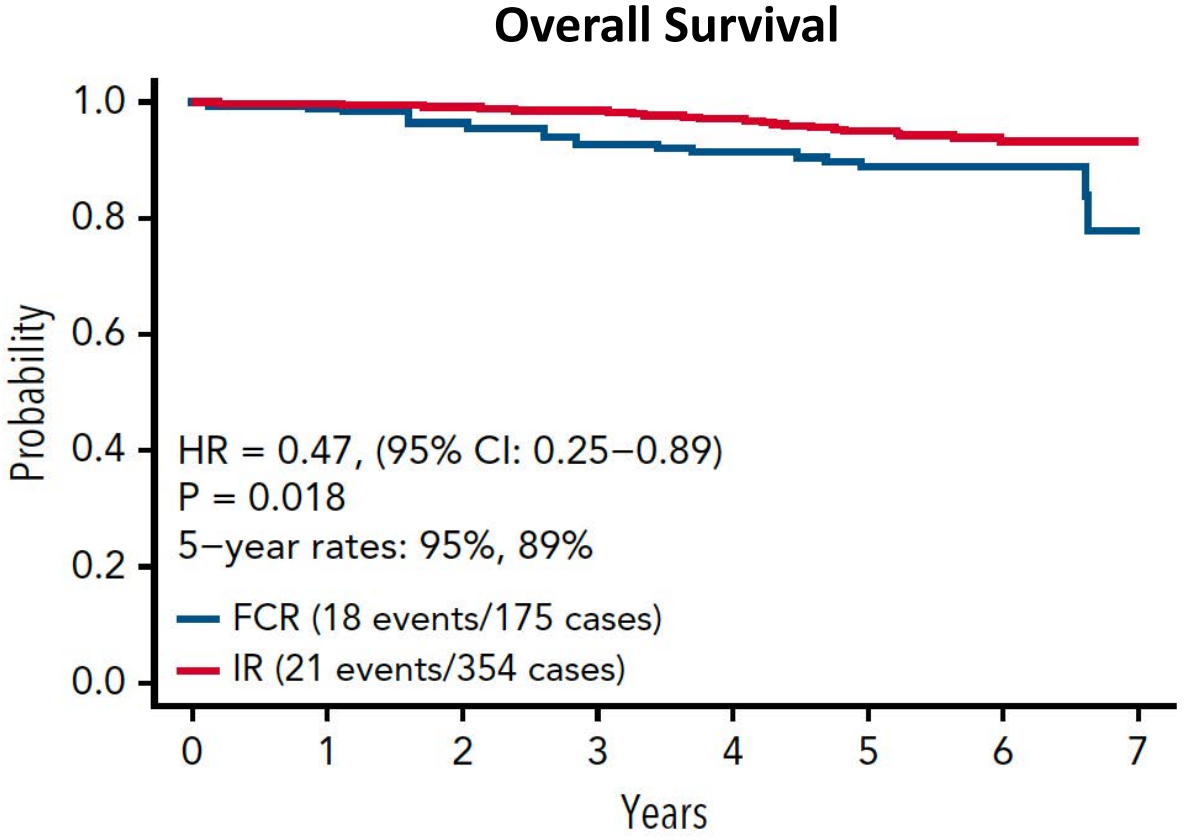
LYMPHOID NEOPLASIA

Long-term outcomes for ibrutinib–rituximab and chemoimmunotherapy in CLL: updated results of the E1912 trial

Tait D. Shanafelt,[1] Xin Victoria Wang,[2] Curtis A. Hanson,[3] Elisabeth M. Paietta,[4] Susan O'Brien,[5] Jacqueline Barrientos,[6] Diane F. Jelinek,[3] Esteban Braggio,[3] Jose F. Leis,[3] Cong Christine Zhang,[7] Steven E. Coutre,[1] Paul M. Barr,[8] Amanda F. Cashen,[9] Anthony R. Mato,[10] Avina K. Singh,[11] Michael P. Mullane,[12] Richard F. Little,[13] Harry Erba,[14] Richard M. Stone,[2] Mark Litzow,[3] Martin Tallman,[10] and Neil E. Kay[3]

E1912: Progression-Free and Overall Survival





FCR = fludarabine/cyclophosphamide/rituximab; IR = ibrutinib/rituximab

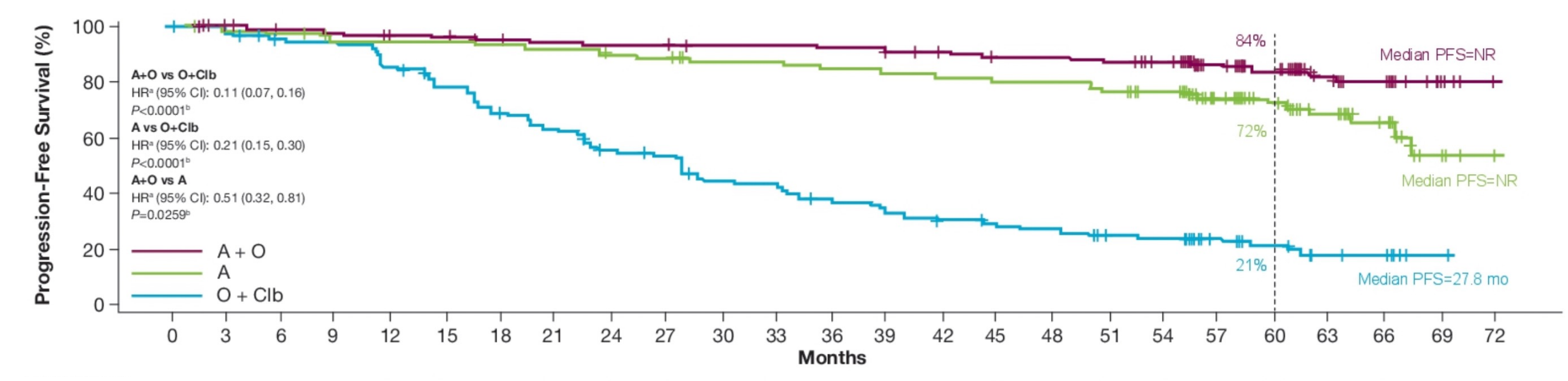
Shanafelt TD et al. *Blood* 2022 July 14;140(2):112-20.

Acalabrutinib ± Obinutuzumab versus Obinutuzumab + Chlorambucil in Treatment-Naïve Chronic Lymphocytic Leukemia: Five-Year Follow-Up of ELEVATE-TN

Sharman JP et al.

ASCO 2022;Abstract 7539.

ELEVATE-TN: Investigator-Assessed PFS



A = acalabrutinib; O = obinutuzumab; Clb = chlorambucil; PFS = progression-free survival; NR = not reached

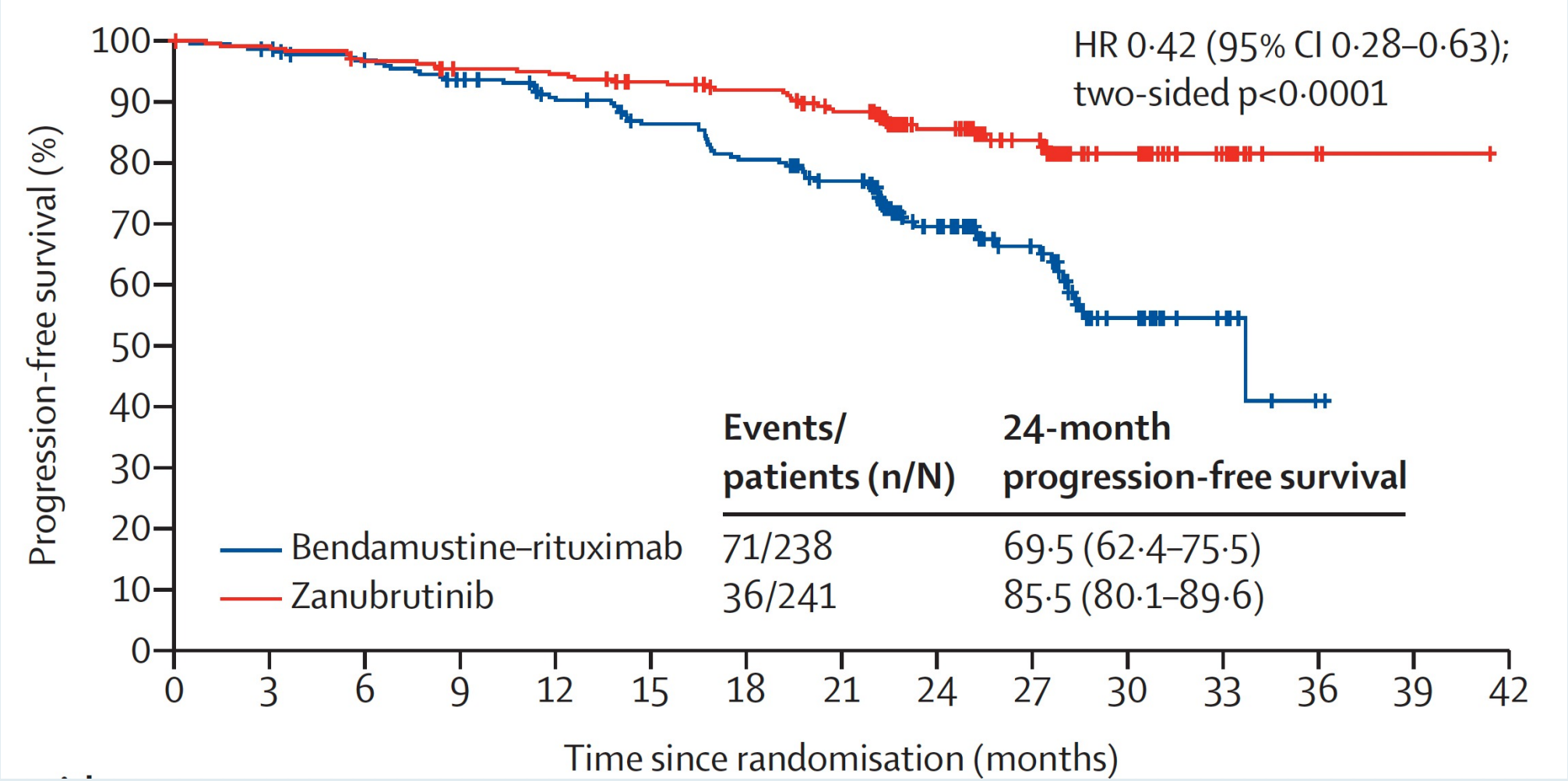
Sharman JP et al. ASCO 2022;Abstract 7539.

Lancet Oncol 2022 July 7;[Online ahead of print].

Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial

Constantine S Tam, Jennifer R Brown, Brad S Kahl, Paolo Ghia, Krzysztof Giannopoulos, Wojciech Jurczak, Martin Šimkovič, Mazyar Shadman, Anders Österborg, Luca Laurenti, Patricia Walker, Stephen Opat, Henry Chan, Hanna Ciepluch, Richard Greil, Monica Tani, Marek Trněný, Danielle M Brander, Ian W Flinn, Sebastian Grosicki, Emma Verner, Alessandra Tedeschi, Jianyong Li, Tian Tian, Lei Zhou, Carol Marimpietri, Jason C Paik, Aileen Cohen, Jane Huang, Tadeusz Robak, Peter Hillmen**

SEQUOIA: Progression-Free Survival by Independent Review Committee (Intent-to-Treat Population)



Tam CS et al. *Lancet Oncol* 2022 July 7;[Online ahead of print]. Kahl BS et al. SOHO 2022;Abstract CLL-137.

original reports

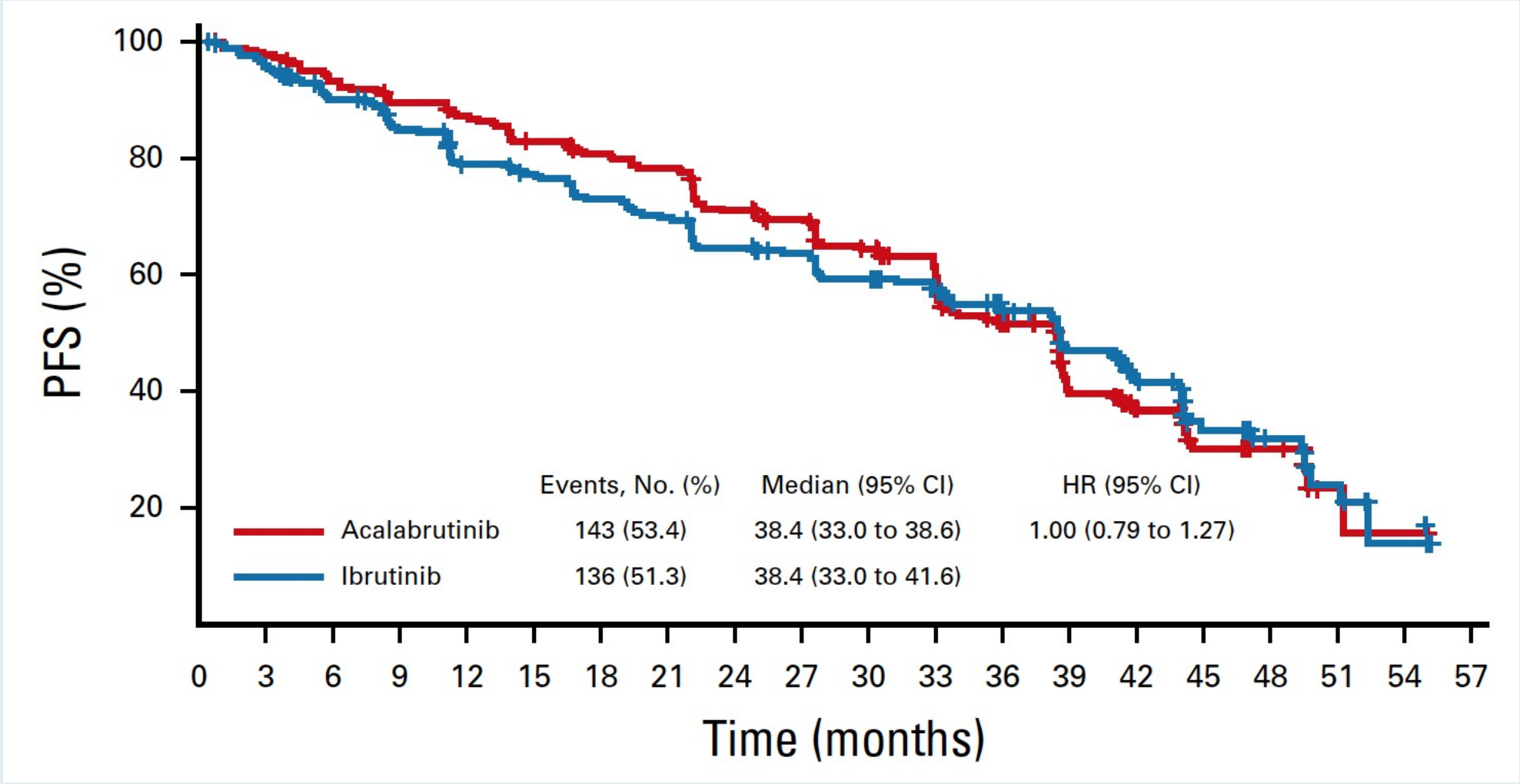
Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial

John C. Byrd, MD[1]; Peter Hillmen, MD, MBChB, PhD[2]; Paolo Ghia, MD, PhD[3,4]; Arnon P. Kater, MD, PhD[5]; Asher Chanan-Khan, MD[6]; Richard R. Furman, MD[7]; Susan O'Brien, MD[8]; Mustafa Nuri Yenerel, MD[9]; Arpad Illés, MD[10]; Neil Kay, MD[11]; Jose A. Garcia-Marco, MD, PhD[12]; Anthony Mato, MD[13]; Javier Pinilla-Ibarz, MD, PhD[14]; John F. Seymour, PhD[15]; Stephane Lepretre, MD[16,17]; Stephan Stilgenbauer, MD[18]; Tadeusz Robak, PhD[19]; Wayne Rothbaum, MS[20]; Raquel Izumi, PhD[20]; Ahmed Hamdy, MD[20]; Priti Patel, MD[21]; Kara Higgins, MS[21]; Sophia Sohoni, MD[21]; and Wojciech Jurczak, MD, PhD[22]

J Clin Oncol 2021 November 1;39(31):3441-52.

RTP RESEARCH TO PRACTICE

ELEVATE-RR: Independent Review Committee-Assessed PFS



Byrd JC et al. *J Clin Oncol* 2021;39(31):3441-52.

ELEVATE-RR: Characterization of Adverse Events with Acalabrutinib versus Ibrutinib

	Incidence, %				Exposure-Adjusted Incidence[b]				Exposure-Adjusted Time With Event[c]			
	Any grade		Grade ≥3		Any grade		Grade ≥3		Any grade		Grade ≥3	
	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]	Acala[d]	Ibru[e]
ECIs												
Cardiac events	24%	30%	9%	10%	1.2	1.9	0.4	0.5	7.1	13.0	0.4	0.2
Afib/flutter	9%	**16%***	5%	4%	0.4	0.7	0.2	0.1	1.3	3.8	0.3	0.1
HTN[f]	9%	**23%***	4%	**9%***	0.4	1.2	0.1	0.4	4.1	15.0	1.6	4.0
Bleeding events[g]	38%	**51%***	4%	5%	2.4	3.8	0.1	0.2	13.7	24.6	0.1	0.1
Major bleeding events[h]	5%[i]	5%[j]	4%	5%	0.2	0.2	0.1	0.2	0.1	0.3	0.1	0.1
Infections[k]	78%	81%	31%	30%	8.9	10.4	1.6	2.0	14.6	15.6	1.5	1.1
Selected Common AEs (preferred term)												
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

Seymour JF et al. ASH 2021;Abstract 3721.

Positive Topline Results from Final PFS Analysis Announced from the Phase III ALPINE Trial

Press Release: October 12, 2022

“Today [it was] announced that zanubrutinib achieved superior Progression-Free Survival (PFS) versus ibrutinib in a final analysis of the Phase 3 ALPINE trial, as assessed by an independent review committee (IRC) and investigator. Zanubrutinib was generally well tolerated; safety findings at the final PFS analysis were consistent with prior reports.

‘This positive result adds to the growing body of evidence underpinning our belief in the potential for zanubrutinib to provide new hope for CLL patients facing this intractable disease. With this final PFS analysis, zanubrutinib has achieved superior progression free survival, as well as superiority in overall response rate versus ibrutinib,’ said Mehrdad Mobasher, M.D., M.P.H., Chief Medical Officer. ‘We look forward to sharing the full results with the medical and patient communities and will submit for presentation at a medical congress and for publication.’

A supplemental New Drug Application for zanubrutinib for the treatment of adult patients with CLL or small lymphocytic lymphoma (SLL) is currently under review with the FDA, with a target action date of January 20, 2023.”

https://www.businesswire.com/news/home/20221012005491/en/BeiGene-Announces-Positive-Topline-Results-from-Final-Progression-Free-Survival-Analysis-of-BRUKINSA®-zanubrutinib-Compared-to-IMBRUVICA®-ibrutinib-in-Phase-3-Chronic-Lymphocytic-Leukemia-CLL-Trial

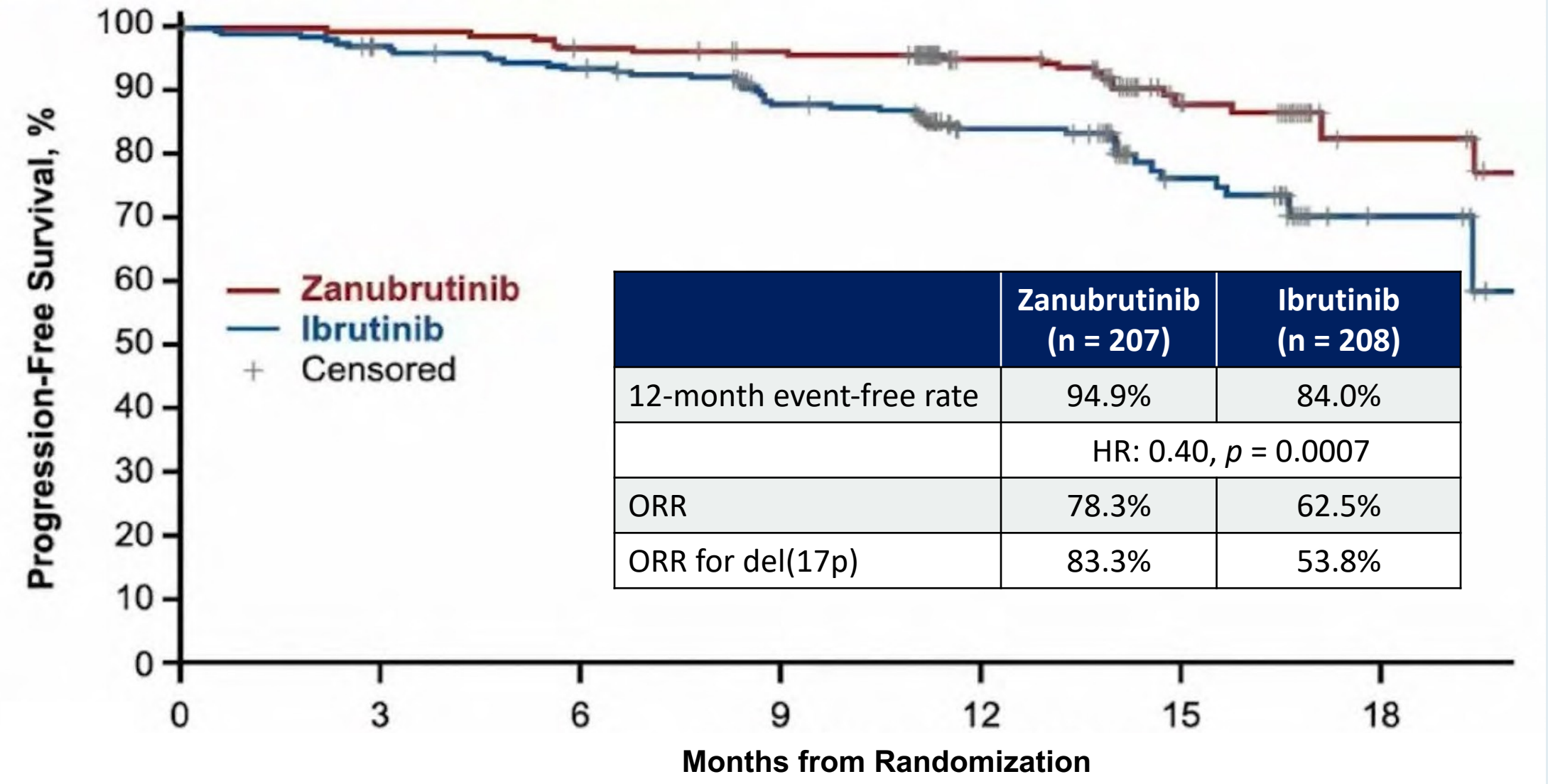
RTP RESEARCH TO PRACTICE

First Interim Analysis of ALPINE Study: Results of a Phase 3 Randomized Study of Zanubrutinib vs Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Hillmen P et al.

EHA 2021;Abstract LBA1900.

ALPINE: Response and Investigator-Assessed PFS



	Zanubrutinib (n = 207)	Ibrutinib (n = 208)
12-month event-free rate	94.9%	84.0%
	HR: 0.40, *p* = 0.0007	
ORR	78.3%	62.5%
ORR for del(17p)	83.3%	53.8%

ORR = overall response rate

Hillmen P et al. EHA 2021;Abstract LBA1900.

ALPINE: Adverse Events of Special Interest

Safety Analysis Population	Zanubrutinib (n=204), n (%)		Ibrutinib (n=207), n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders[a]	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter (key 2º endpoint)	**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[b]	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[c]	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[c]	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 cancers	7 (3.4)	3 (1.5)	10 (4.8)	2 (1.0)

Hillmen P et al. EHA 2021;Abstract LBA1900.

EHA EUROPEAN HEMATOLOGY ASSOCIATION

EHA2022 HYBRID JUNE 9-17 VIENNA

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Abstract S148

EHA2022 HYBRID VIRTUAL

UNIKLINIK KÖLN | Department I of Internal Medicine University Hospital of Cologne

DEUTSCHE STUDIENGRUPPE CLL

Othman Al-Sawaf

Abstract S148

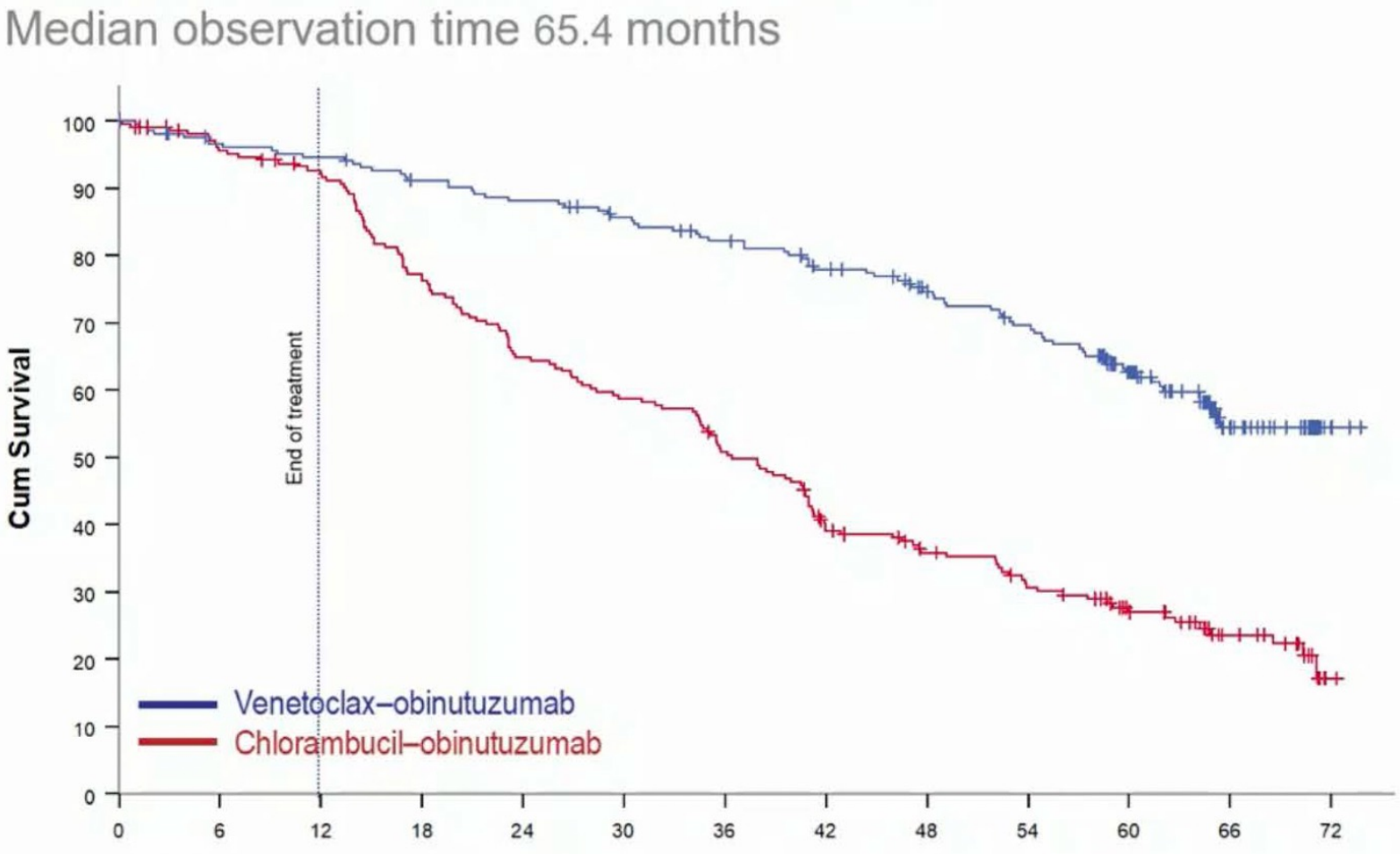
Venetoclax-Obinutuzumab for previously untreated chronic lymphocytic leukemia: 5-year results of the randomized CLL14 study

Othman Al-Sawaf, Can Zhang, Sandra Robrecht, Alex Kotak, Naomi Chang, Anna Maria Fink, Eugen Tausch, Christof Schneider, Matthias Ritgen, Karl-Anton Kreuzer, Brenda Chyla, Barbara Eichhorst, Yanwen Jiang, Stephan Stilgenbauer, Michael Hallek, Kirsten Fischer

June 12th, 2022
Clinical CLL Session

RTP RESEARCH TO PRACTICE

CLL14: Progression-Free Survival



Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

5-year PFS rate

Ven-Obi: 62.6%

Clb-Obi: 27.0%

HR 0.35, 95% CI [0.26-0.46]

P<0.0001

Al-Sawaf O et al. EHA 2022;Abstract S148. Al-Sawaf O et al. SOHO 2022;Abstract CLL-246.

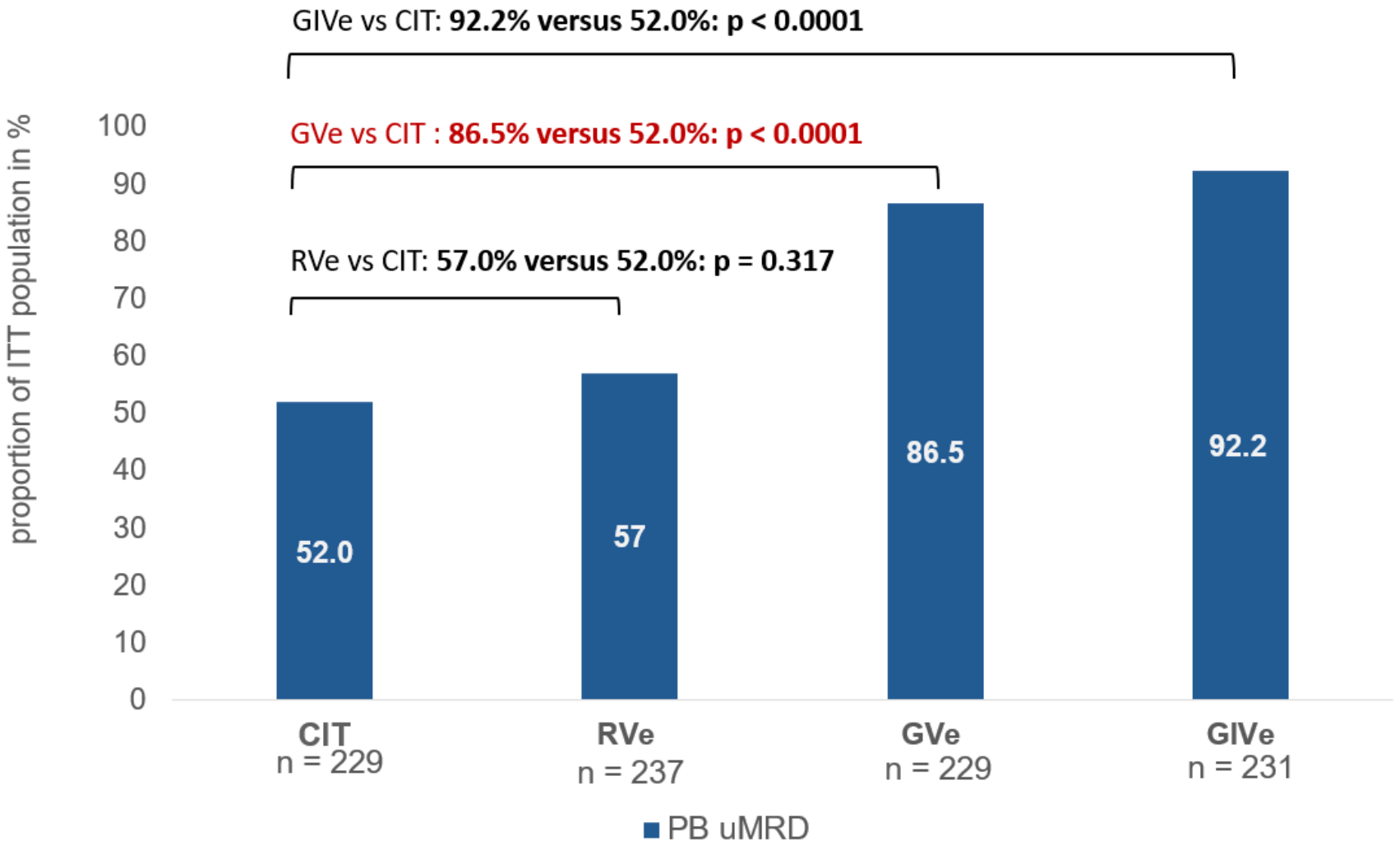
RTP RESEARCH TO PRACTICE

A Randomized Phase III Study of Venetoclax-Based Time-Limited Combination Treatments (RVe, GVe, GIVe) vs Standard Chemoimmunotherapy (CIT: FCR/BR) in Frontline Chronic Lymphocytic Leukemia (CLL) of Fit Patients: First Co-Primary Endpoint Analysis of the International Intergroup GAIA (CLL13) Trial

Eichhorst B et al.

ASH 2021;Abstract 71.

GAIA/CLL13 Coprimary Endpoint: Undetectable Minimal Residual Disease (uMRD) ($<10^{-4}$) at Month 15 in Peripheral Blood (PB) by 4-Color Flow



CIT
- BR >65
- ≤FCR 65

RVe
Rituximab/venetoclax

GVe
Obinutuzumab/venetoclax

GIVe
Obinutuzumab/ibrutinib/venetoclax

Eichhorst B et al. ASH 2021;Abstract 71.

CLINICAL TRIALS AND OBSERVATIONS

Blood 2022 June 2;139(22):3229-30.

Comment on Tam et al, page 3278

A CAPTIVATE-ing new regimen for CLL

Kerry A. Rogers and Jennifer A. Woyach | The Ohio State University

Blood 2022 June 2;139(22):3278-89.

CLINICAL TRIALS AND OBSERVATIONS

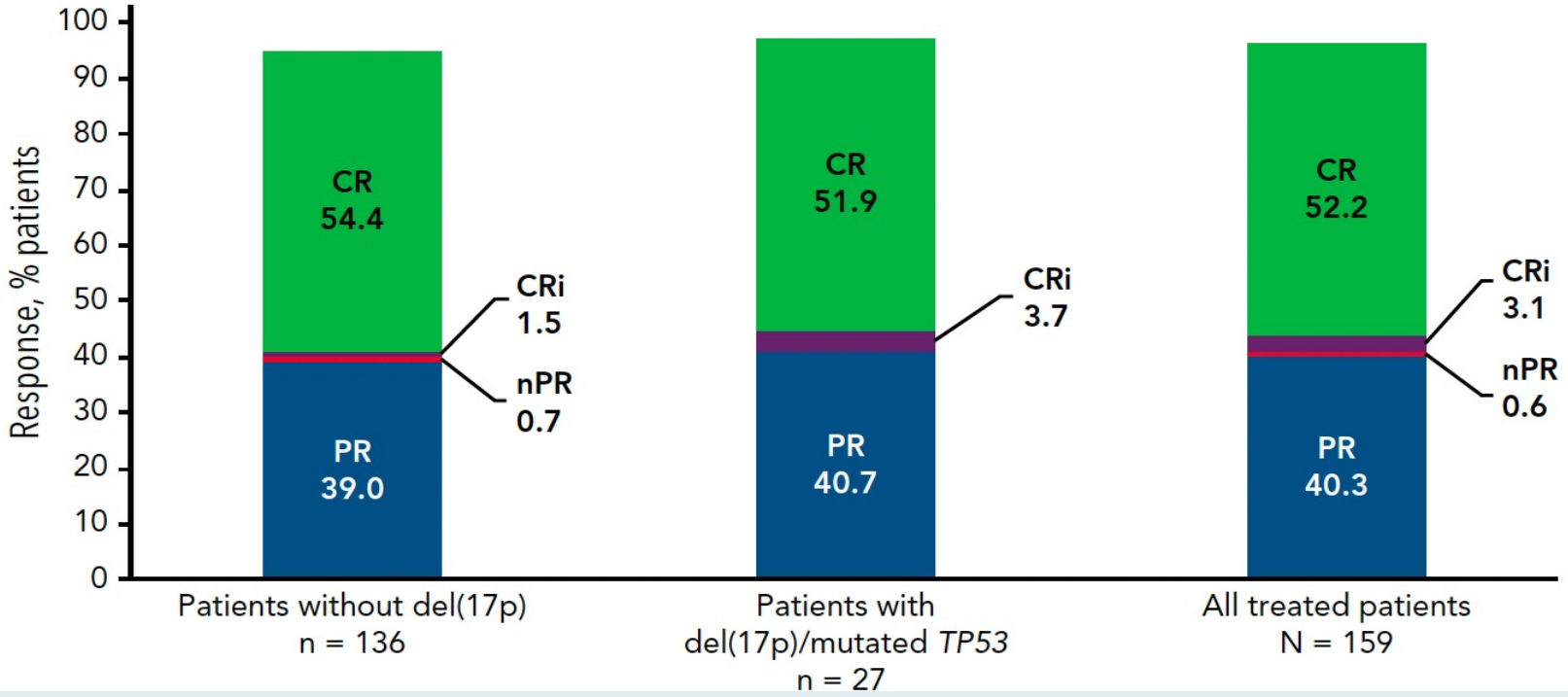
Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort

Constantine S. Tam,[1-3] John N. Allan,[4] Tanya Siddiqi,[5] Thomas J. Kipps,[6] Ryan Jacobs,[7] Stephen Opat,[8] Paul M. Barr,[9] Alessandra Tedeschi,[10] Livio Trentin,[11] Rajat Bannerji,[12] Sharon Jackson,[13] Bryone J. Kuss,[14] Carol Moreno,[15] Edith Szafer-Glusman,[16] Kristin Russell,[16] Cathy Zhou,[16] Joi Ninomoto,[16] James P. Dean,[16] William G. Wierda,[17,*] and Paolo Ghia[18,19,*]

RTP RESEARCH TO PRACTICE

CAPTIVATE Fixed-Duration Cohort: Best Overall Response

	Patients without del(17p) n = 136	Patients with del(17p)/mutated *TP53* n = 27	All treated patients N = 159
Best response, % (95% CI)			
CR/CRi	56 (48-64)	56 (37-74)	55 (48-63)
ORR	96 (92-99)	96 (89-100)	96 (93-99)
Duration of CR ≥12 cycles, n/N (%)	66/76 (87)	13/15 (87)	78/88 (89)*



CR = complete response; CRi = CR with incomplete blood count recovery; ORR = overall response rate

Tam CS et al. *Blood* 2022 June 2;139(22):3278-89.

RTP RESEARCH TO PRACTICE

NEJM Evidence

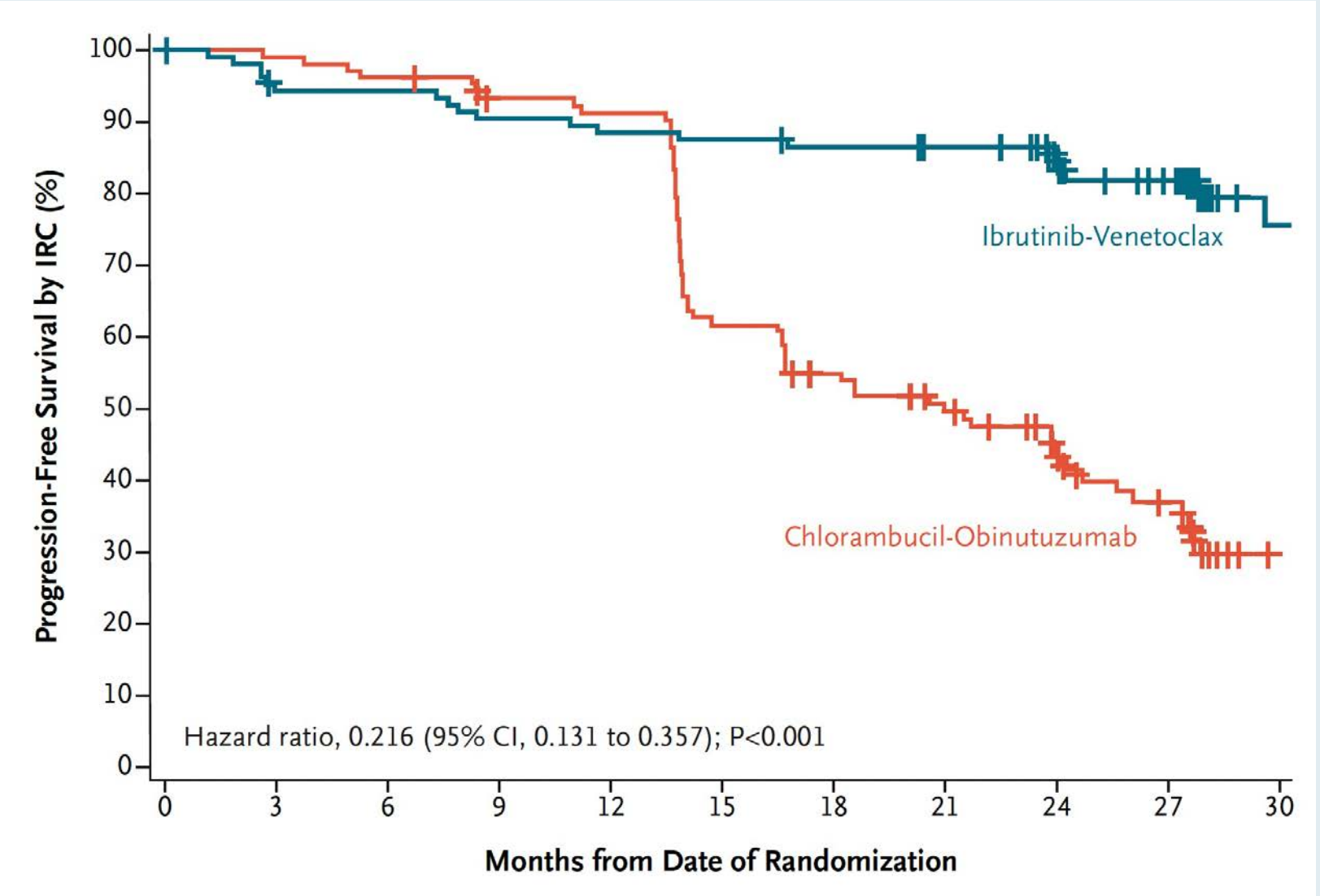
Published May 13, 2022;1(7).

ORIGINAL ARTICLE

Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities (27.7 months follow up)

Arnon P. Kater, M.D., Ph.D.,[1] Carolyn Owen, M.D.,[2] Carol Moreno, M.D.,[3] George Follows, B.M.Bch., Ph.D.,[4] Talha Munir, M.B.B.S.,[5] Mark-David Levin, M.D.,[6] Ohad Benjamini, M.D.,[7] Ann Janssens, M.D., Ph.D.,[8] Anders Osterborg, M.D., Ph.D.,[9] Tadeusz Robak, M.D., Ph.D.,[10] Martin Simkovic, M.D., Ph.D.,[11] Don Stevens, M.D.,[12] Sergey Voloshin, M.D., Ph.D.,[13] Vladimir Vorobyev, Ph.D.,[14] Loic Ysebaert, M.D., Ph.D.,[15] Rui Qin, Ph.D.,[16] Andrew J. Steele, Ph.D.,[17] Natasha Schuier, M.D.,[18] Kurt Baeten, Ph.D.,[19] Donne Bennett Caces, M.D., Ph.D.,[16] and Carsten U. Niemann, M.D., Ph.D.,[20] for the GLOW Investigators*

GLOW Primary Endpoint: Progression-Free Survival by IRC

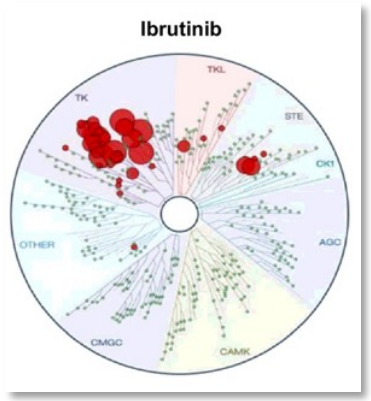


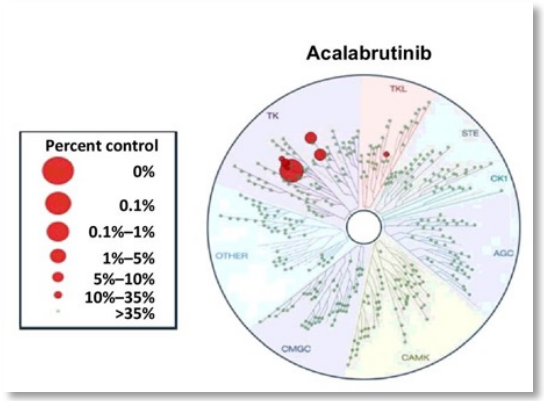
Kater AP et al. *NEJM Evid* 2022 May 13;1(7).

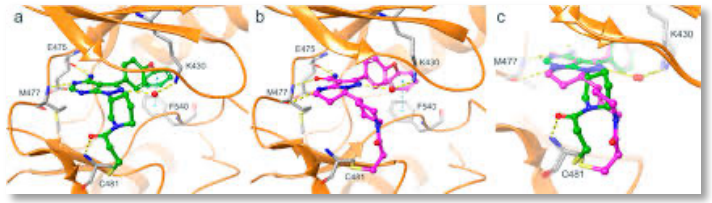
Irreversible and Reversible Bruton Tyrosine Kinase Inhibitors (BTKi) in CLL

BTKi	Binding	T1/2 (hours)	IC50 (nM)	Dosing
Ibrutinib	Covalent irreversible C481	4-8	0.5	420 mg
Acalabrutinib	Covalent irreversible C481	0.9	5.1	100 mg BID
Zanubrutinib	Covalent irreversible C481	2-4	0.5	160 or 320 mg BID
Pirtobrutinib	Noncovalent reversible	Not available	0.85	200 mg

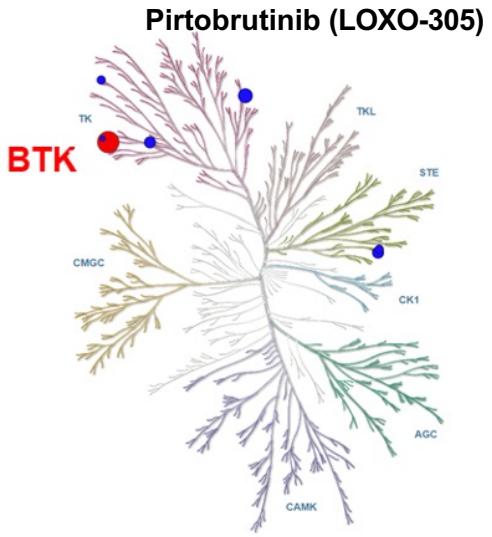
Irreversible







Reversible



Robak T et al. *Cancers* 2022 February 2;14(3):771.

RTP RESEARCH TO PRACTICE

EHA EUROPEAN HEMATOLOGY ASSOCIATION

EHA2022 HYBRID JUNE 9-17 VIENNA

Pirtobrutinib, A Highly Selective, Non-Covalent (Reversible) BTK Inhibitor In Previously Treated CLL/SLL: Updated Results From The Phase 1/2 BRUIN Study

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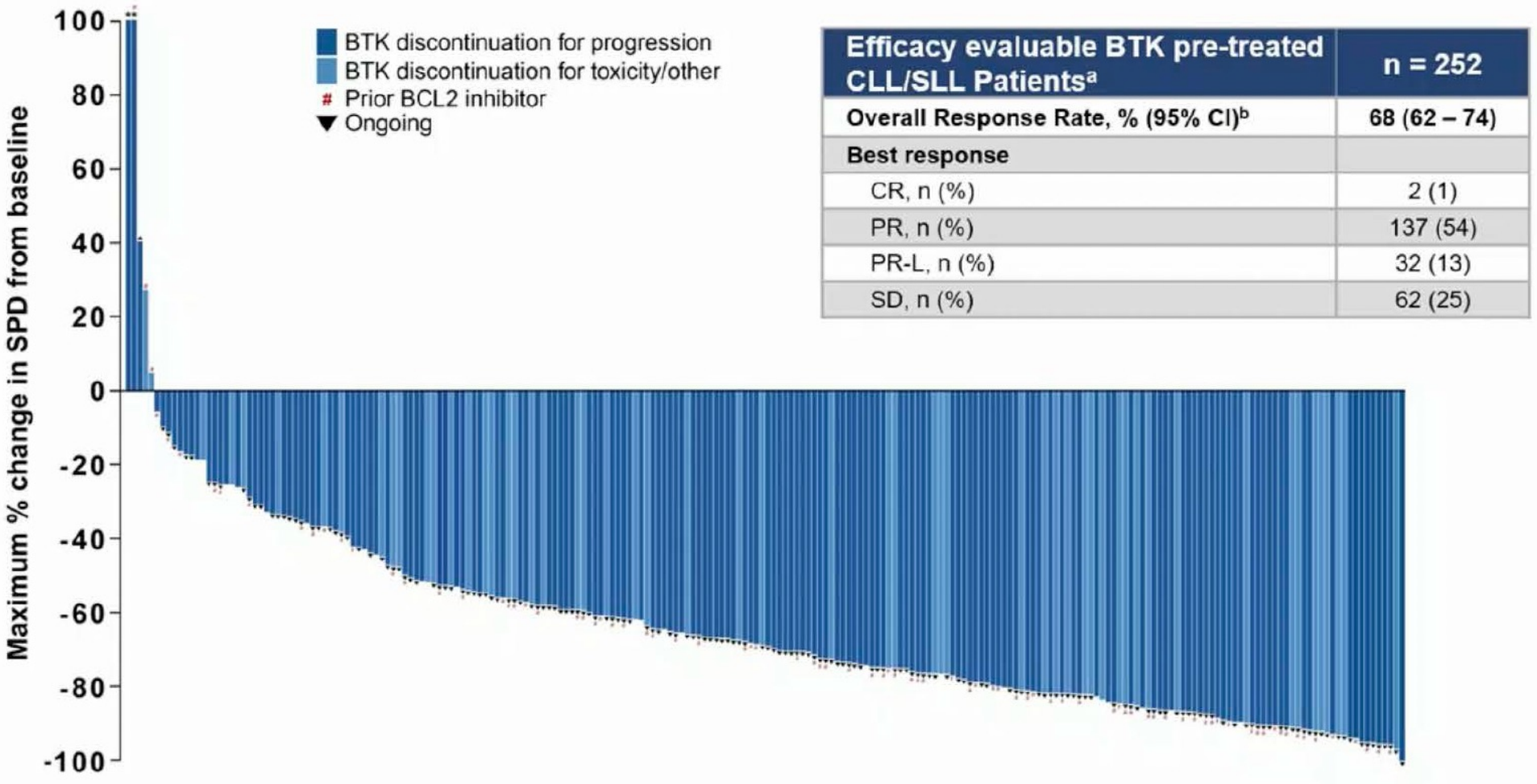
Anthony R. Mato

Abstract S147

RTP RESEARCH TO PRACTICE

BRUIN: Pirtobrutinib Efficacy in BTK-Pretreated CLL/SLL

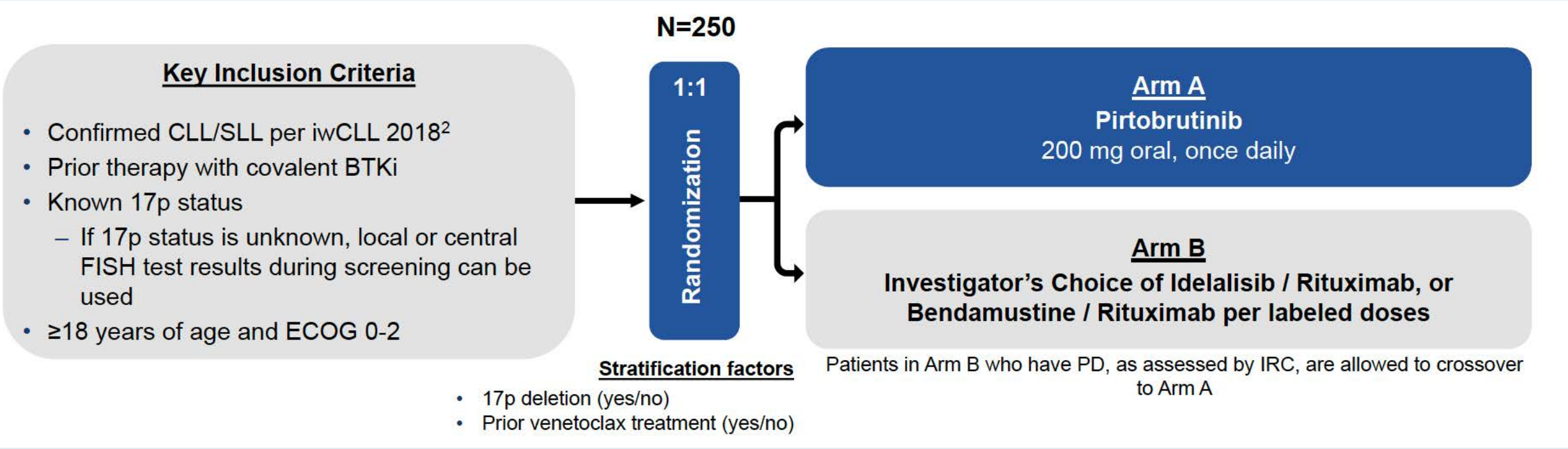


Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	**68 (62 – 74)**
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Mato AR et al. EHA 2022;Abstract S147. Coombs CC et al. SOHO 2022;Abstract CLL-120.

RTP RESEARCH TO PRACTICE

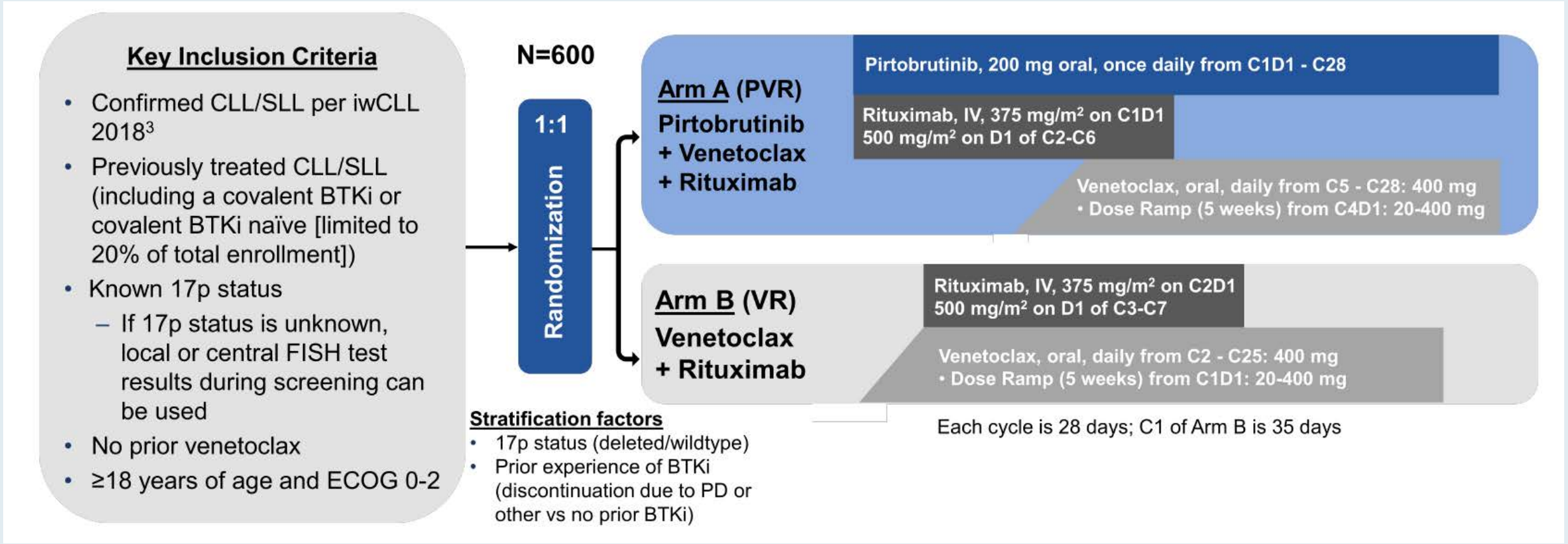
BRUIN CLL-321 Phase III Study Design



iwCLL = International Workshop on Chronic Lymphocytic Leukemia; FISH = fluorescence in situ hybridization

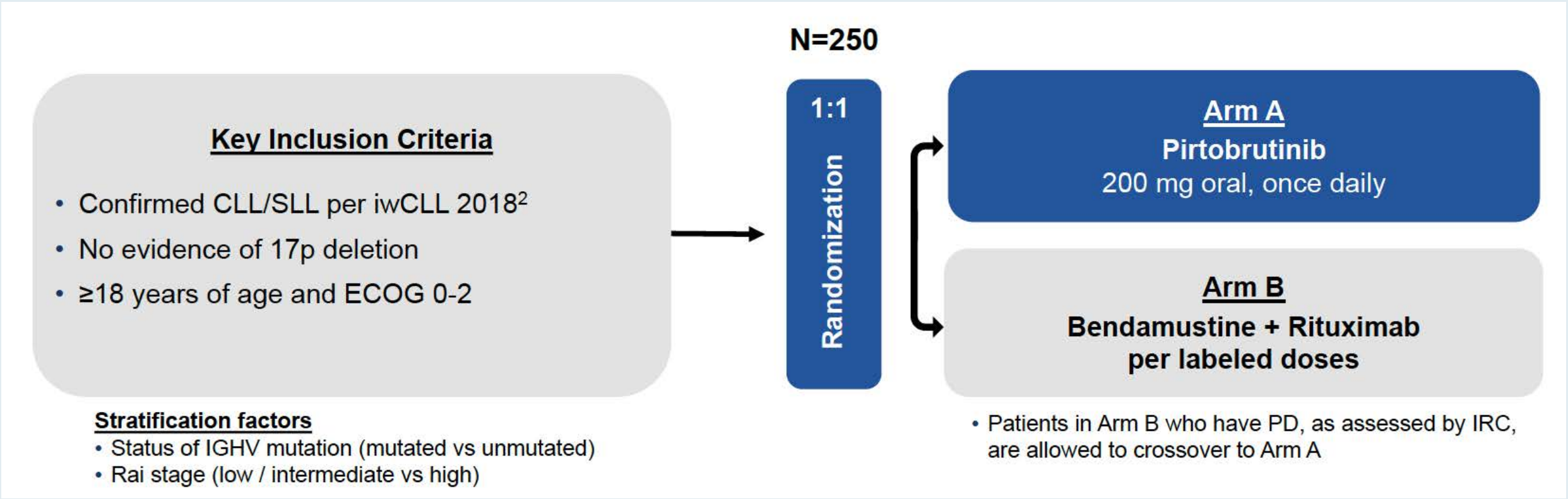
Hill M et al. SOHO 2022;Abstract CLL-114.

BRUIN CLL-322 Phase III Study Design



Wierda WG et al. SOHO 2022;Abstract CLL-116.

BRUIN CLL-313 Phase III Study Design



Levy A et al. SOHO 2022;Abstract CLL-129.

Blood 2022 March 24;139(12):1794-806.

blood®

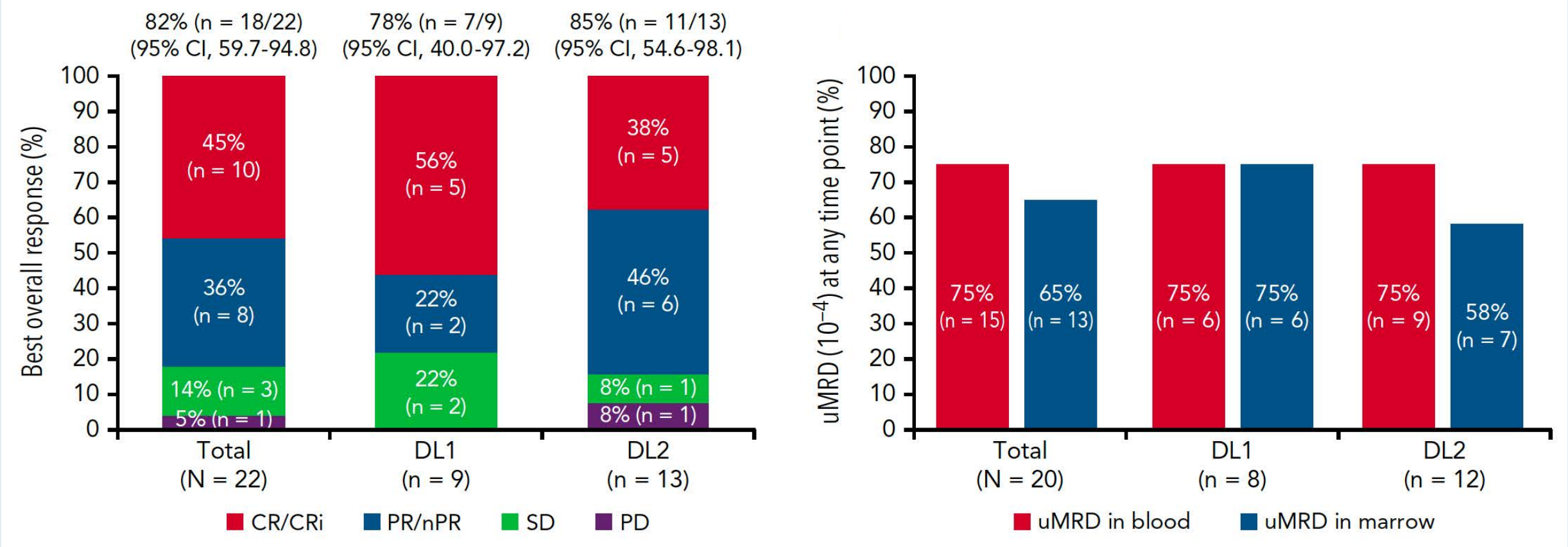
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Phase 1 TRANSCEND CLL 004 study of lisocabtagene maraleucel in patients with relapsed/refractory CLL or SLL

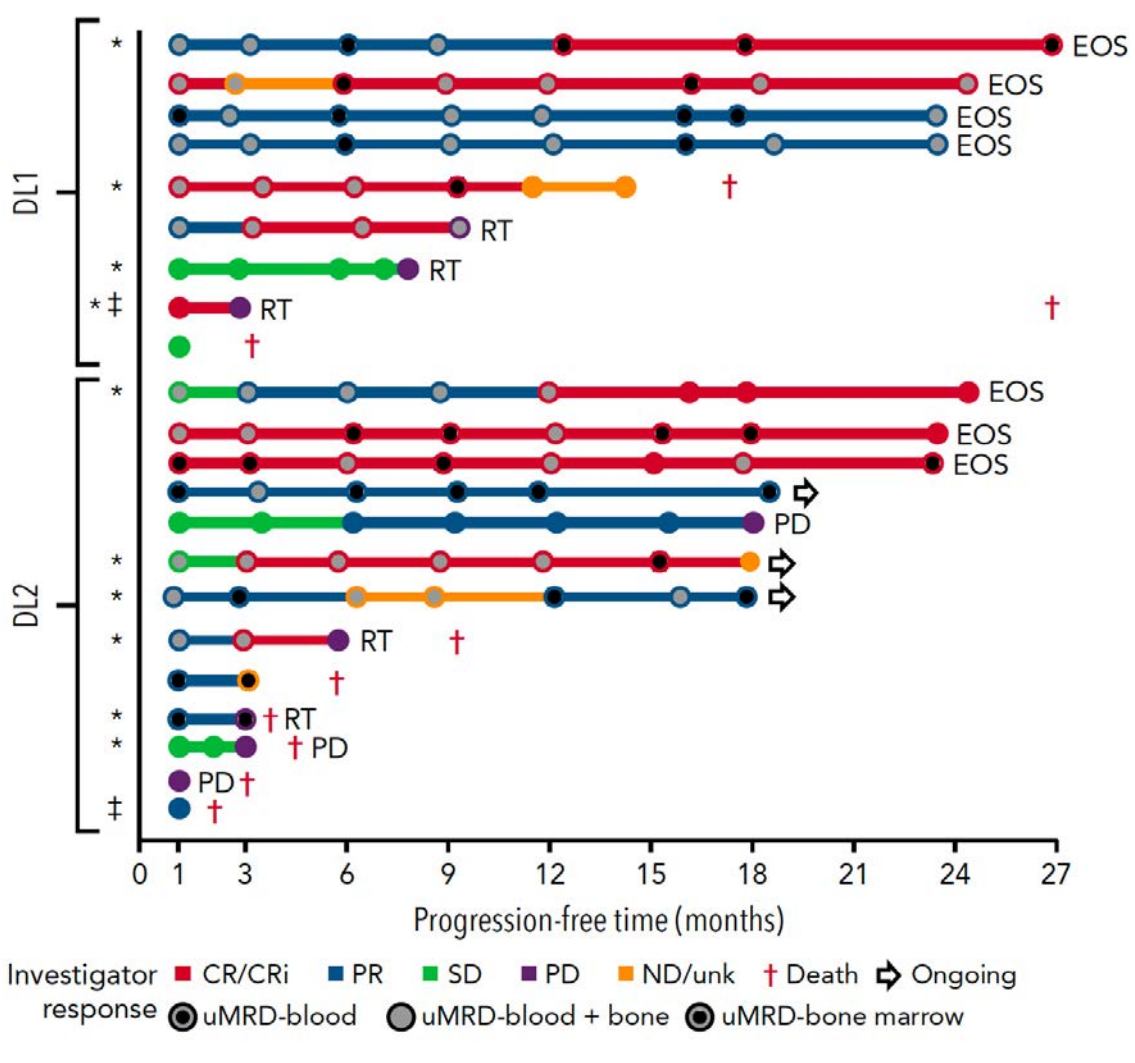
Tanya Siddiqi,[1] Jacob D. Soumerai,[2] Kathleen A. Dorritie,[3] Deborah M. Stephens,[4] Peter A. Riedell,[5] Jon Arnason,[6] Thomas J. Kipps,[7] Heidi H. Gillenwater,[8] Lucy Gong,[8] Lin Yang,[8] Ken Ogasawara,[9] Jerill Thorpe,[8] and William G. Wierda[10]

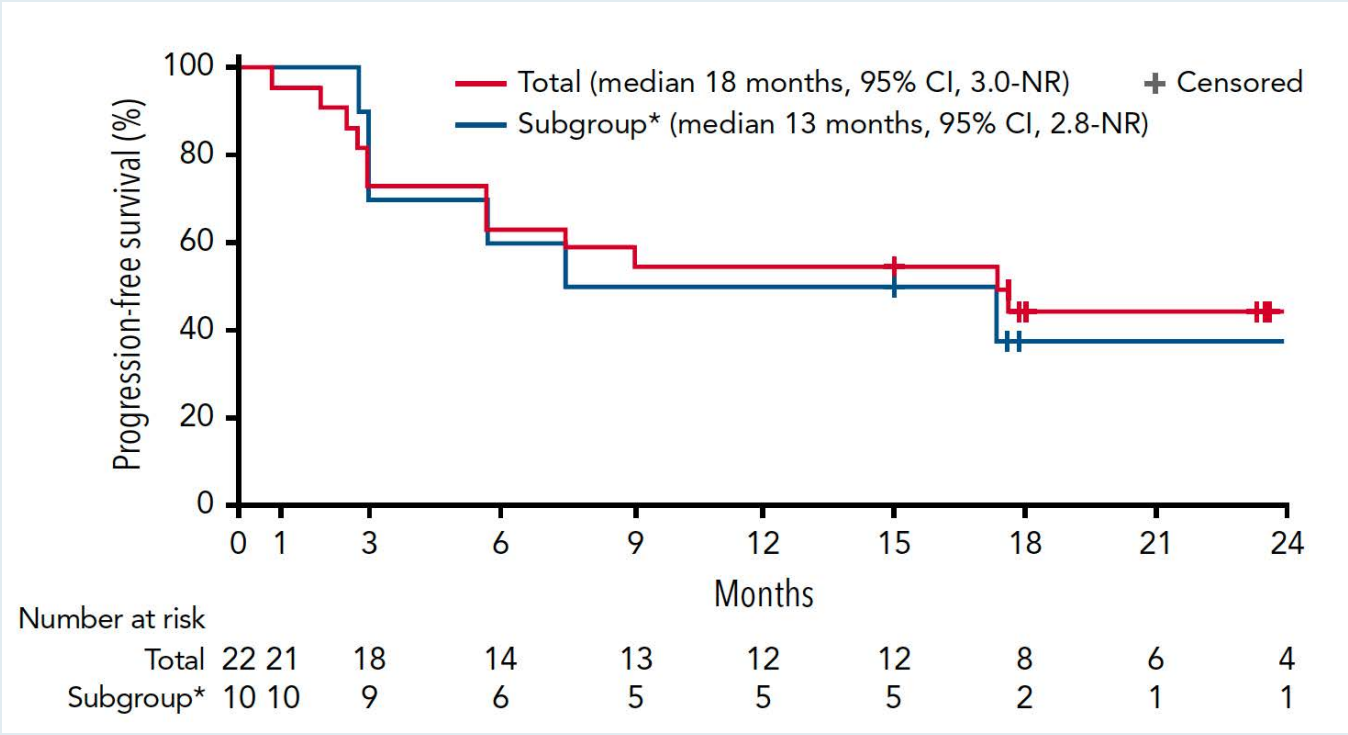
TRANSCEND CLL 004: Responses and uMRD



Siddiqi T et al. *Blood* 2022 March 24;139(12):1794-806.

TRANSCENDENT CLL 004: Swim Lane Plot and PFS





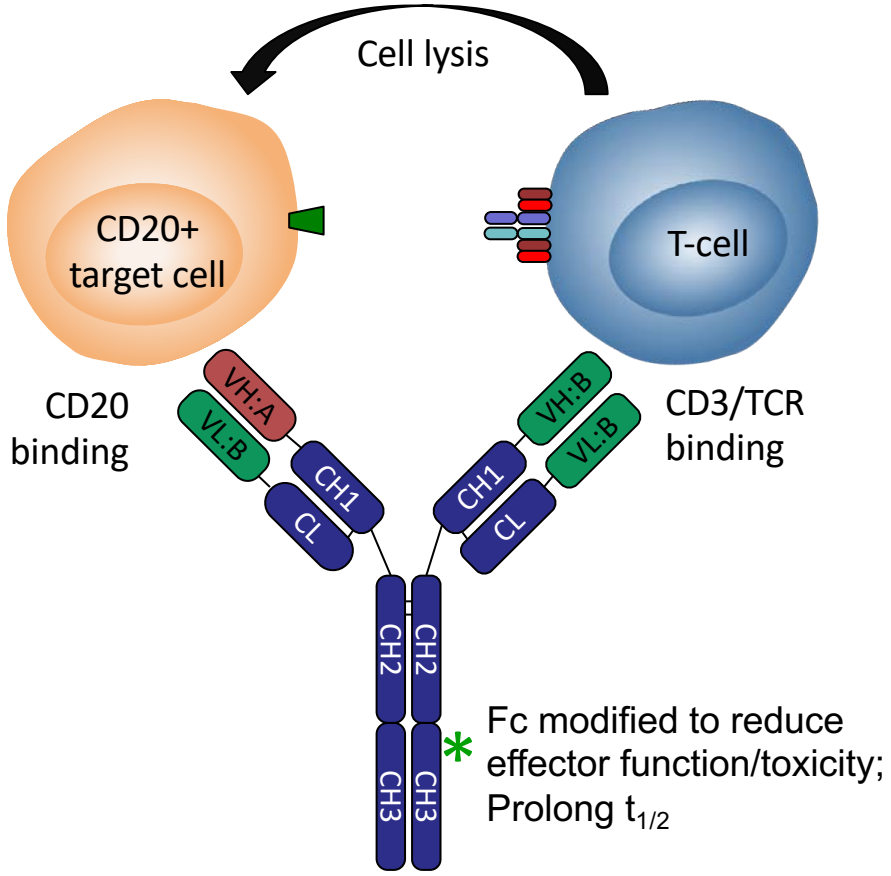
Siddiqi T et al. *Blood* 2022 March 24;139(12):1794-806.

RTP RESEARCH TO PRACTICE

Diffuse Large B-Cell Lymphoma

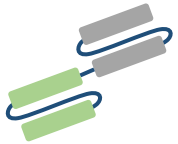
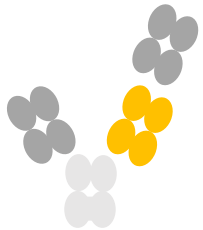
BiSpecific Antibodies
CD3-CD20

Mitchell R. Smith, M.D., Ph.D.



T-cell-mediated killing of CD20+ B-cells independent of TCR-mediated recognition

Structure of Selected BITE/Bispecific Antibodies

Bispecific Ab	Targets	Design	Distinguishing Structural Features
Blinatumomab	CD19 x CD3		• 2 murine scFv with glycine-serine linker • No Fc
Mosunetuzumab	CD20 x CD3		• Humanized mouse IgG1 • Modified Fc
Glofitamab	$CD20_2$ x CD3		• Murine IgG1-based Ab • Modified Fc • 2:1 configuration (Bivalent CD20)
Odronextamab	CD20 x CD3		• Fully human IgG4 heterodimeric Ab • Fc modified to reduce Protein A binding • Common κ light chain from antiCD3ε mAb
Epcoritamab	CD20 x CD3		• Humanized mouse IgG1 DUOBODY • Modified Fc modified to minimize effector functions and Fab-arm exchange

Modified from Schuster, SJ

CD3-CD20 BITE/Bispecific Antibodies: ADMINISTRATION/EFFICACY (caveat: simplified)

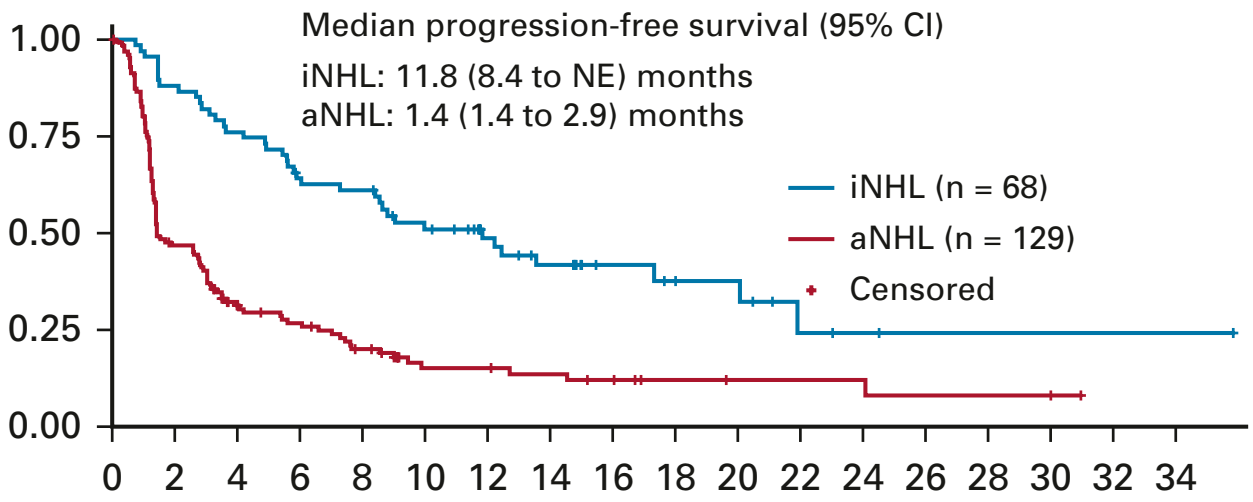
	Mosunetuzumab	Odronextamab	Epcoritamab	Glofitamab
ROUTE	IV	IV	SQ	IV
CYCLES	Q21d Weekly c1 Q21d ≥ cycle 2	Q21d 2x/wk cycle 1 Weekly cycles 2-4 Then q14d	Q28d Weekly x 3 cycles Q14d x 6 cycles Q28d ≥ cycle 10	Q21d Q21d x 12
DURATION	PD/toxicity	PD/toxicity	PD/toxicity	Fixed duration
CRS MITIGATION	Step-up dosing Steroids	Step-up dosing Split dosing Steroids	Step-up dosing Steroids	Step-up dosing Steroids OBINUTUZUMAB
EFFICACY – R/R aNHL	35% ORR/19% CR Budde LE JCO 2022	40% ORR/35% CR (>80 mg dose) Bannerji Lancet Haem 2022	68% ORR/45% CR (>12 mg dose) Hutchings M Lancet 2021	48% ORR/33% CR Hutchings M JCO 2021
EFFICACY – R/R FL	66% ORR/49% CR Budde LE JCO 2022 N=90; 60% CR Budde LE Lancet Onc 2022	91% OR/72% CR (>5mg dose) Bannerji Lancet Haem 2022	90% OR/50% CR (>0.76 mg dose) Hutchings M Lancet 2021	71% OR/48% CR Hutchings M JCO 2021

Bi-Specific ABs: TOXICITY

Antibody	CD20/CD3			
	Glofitamab	Mosunetuzumab	Odronextamab	Epcoritamab
N	64 (> 60 ug)	131	136	58
CRS any CRS ≥3	64% 4%	29% 1%	61% 7%	59% 0
NEURO any NEURO ≥3	43% NR	49% 1%	NR 4%	7% 3%

CRS = cytokine release syndrome; NEURO = neurotoxicity;

Mosunetuzumab (Dose-Escalation) DOR and PFS in iNHL and aNHL



Budde et al. J Clin Oncol 2022

Mosunetuzumab in Previously Untreated Older DLBCL Patients

- DLBCL > 60 unfit/ > 80 yrs
- Step up dose (D1/D8/D15)
- Optional pretreatment with prednisone + vincristine
- **ORR: 63%; CR: 45%. Durable**
- CRS mostly grade 1 and limited to first administration

Olszewski et al. Clin Lymph Myel Leuk 2021

CD3-CD20 T cell engagers work: Now what?

- Good option for R/R B cell lymphomas (Not FDA approved yet)
- As single agents
  - Move to 2nd line?
  - Before or after CART?
  - 1st line elderly DLBCL trial?

- Combinations: bispecifics +
  - Lenalidomide (CelMODS) ± αCDC20
    - CELESTIMO IN R/R FL Mosun-Len vs R-Len
  - Polatuzumab vedotin
  - Chemo + αCDC20
    - 1L + R-chemo (e.g. EPCORE - Falci L et al ASCO 2022)

- Later generation molecules
  - Tri-specifics (2nd target, costimulatory T cell signal, NK or monocyte targets) or adding a second molecule with these

DLBCL Treatment in Flux

- Is Pola-R-CHP the new standard for initial therapy of DLBCL?
  - ABC only? Age 60-80? Not IPI 0-1?
  - Ibrutinib R-CHOP for a few uncommon subtypes?
    - Re-analysis of PHOENIX trial
  - CART for high-risk primary refractory?
    - ZUMA-12
- Is CART the current standard for relapsed/refractory DLBCL?
- How to choose 3rd line therapy?

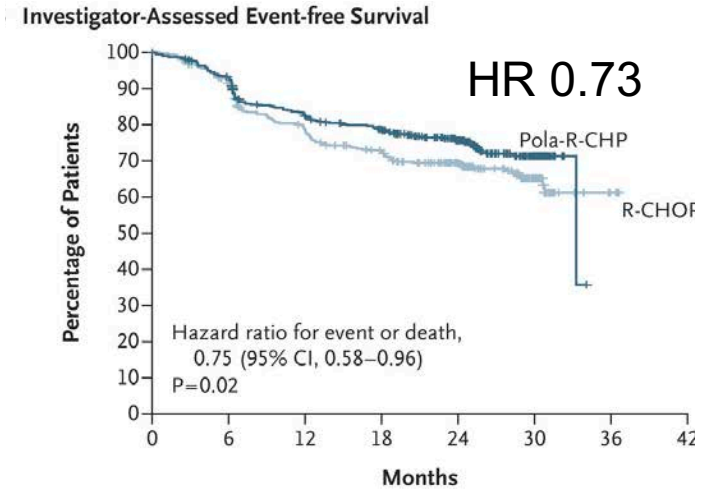
Targeted Trials in Up-Front DLBCL: R-CHOP ± X

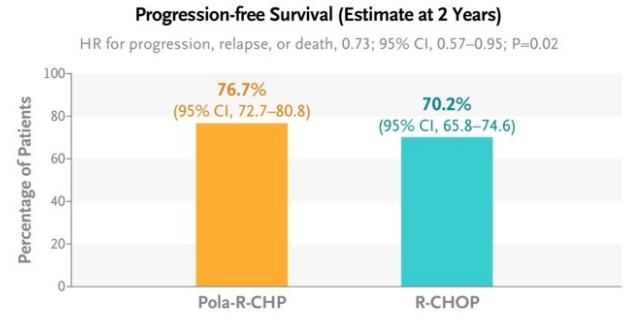
Target	Randomized Phase II/III Studies	n	R-CHOP ±	Primary Endpoint Outcome	Result
NF-κB	PYRAMID	399	Bortezomib	No PFS improvement in non-GCB DLBCL	Neg
NF-κB	REMoDL-B	201	Bortezomib	No PFS improvement in GCB/ABC DLBCL	Neg
CD20	GOYA	1418	GA101-CHOP vs R-CHOP	No PFS improvement	Neg
BTK	PHOENIX	838	Ibrutinib	No EFS improvement in non-GCB DLBCL	Neg
iMiD	ROBUST	570	Lenalidomide	No PFS improvement in ABC	Neg
iMiD	ECOG ACRIN 412	280	Lenalidomide	PFS and OS improvement	?

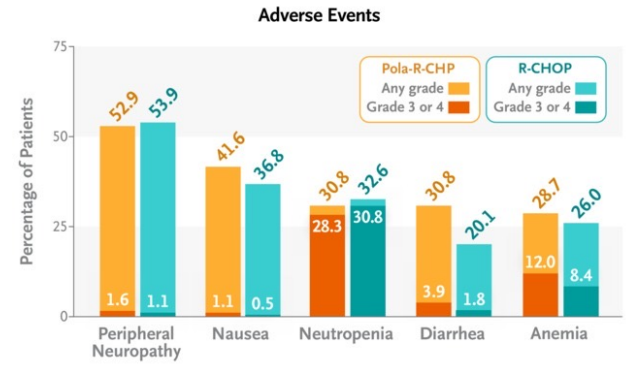
Courtesy of Kieron Dunleavy, modified

POLARIX: Polatuzumab vedotin-R-CHP vs. R-CHOP 1L DLBCL

- International, randomized phase 3, double-blind placebo-controlled trial (N = 879)
- Eligibility:
  - Int- or High-Risk IPI 2-5 (38% IPI 2/62% 3-5)
  - age 18-80 (median 70)
  - PS 0-2 (16% PS2)
  - No transformed lymphoma, no PMBCL
- R-CHOP vs pola-R-CHP x 6 (then + R x 2)
- *Met primary endpoint with 27% reduction in relative risk of PD, relapse or death*
  - No difference in CR rate (78% Pola-R-CHP vs 74% R-CHOP)
  - No difference in overall survival (median f/u 28 months)
- Similar rates of AEs, dose reductions or drug discontinuation
- Exploratory analyses:
  - no benefit if ≤ 60, or GC subtype



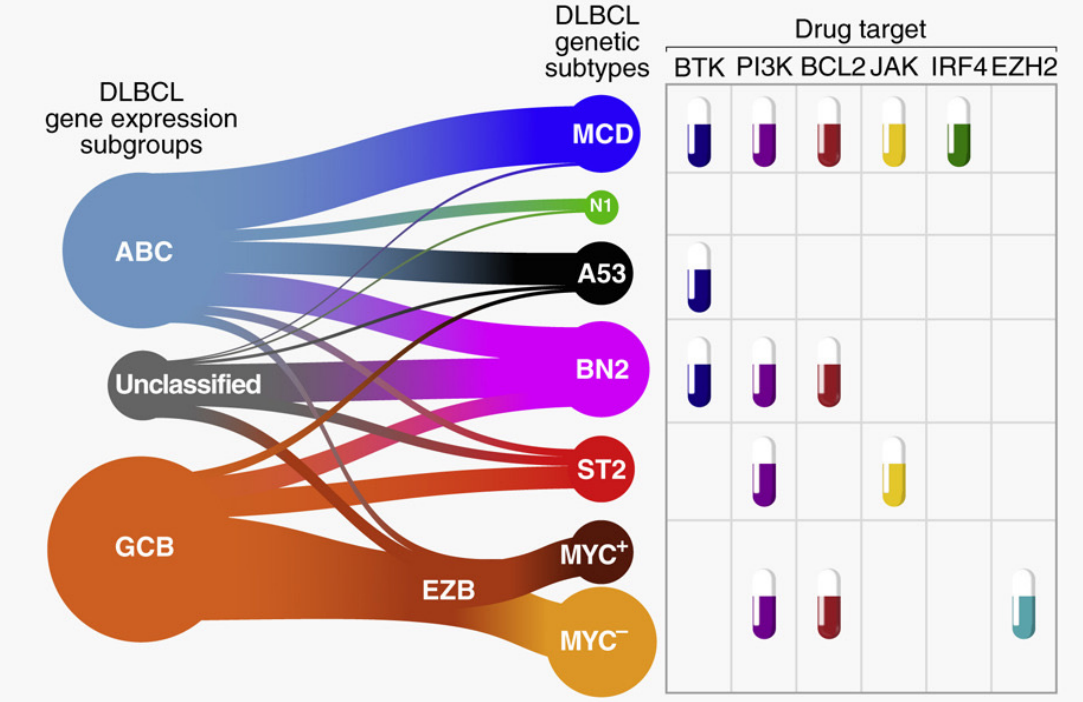


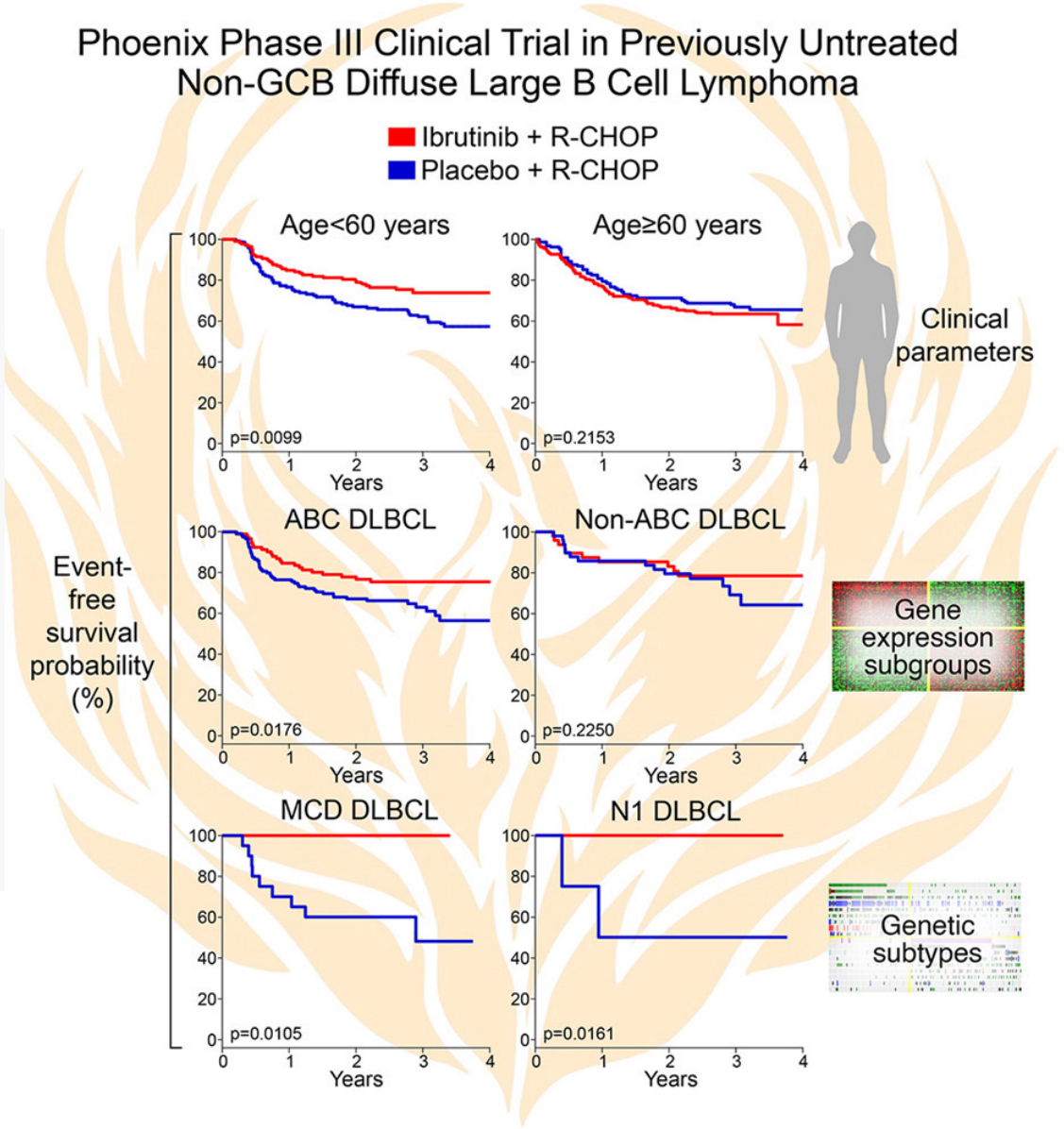


Tilly et al. NEJM 2022

Ibrutinib + R-CHOP in genetic subtypes of DLBCL: A Post-Hoc analysis

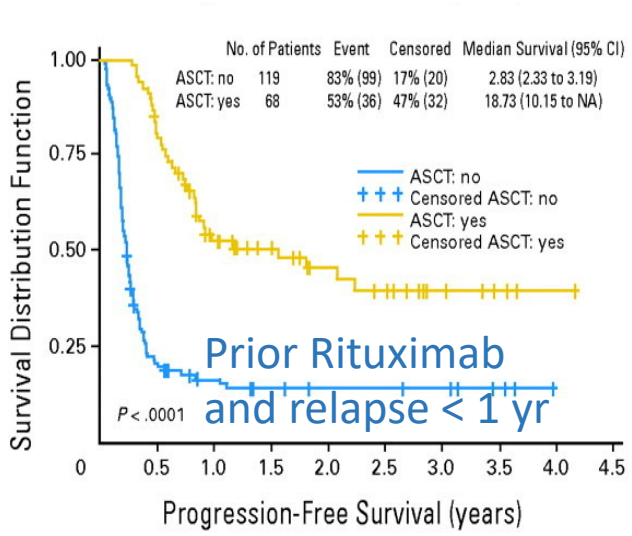
This was a NEGATIVE trial overall

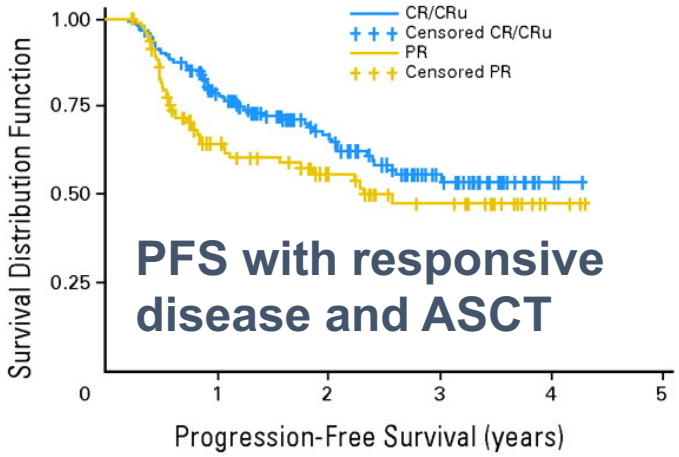




Wright GW et al Cancer Cell 2020
Wilson WH et al Cancer Cell 2021

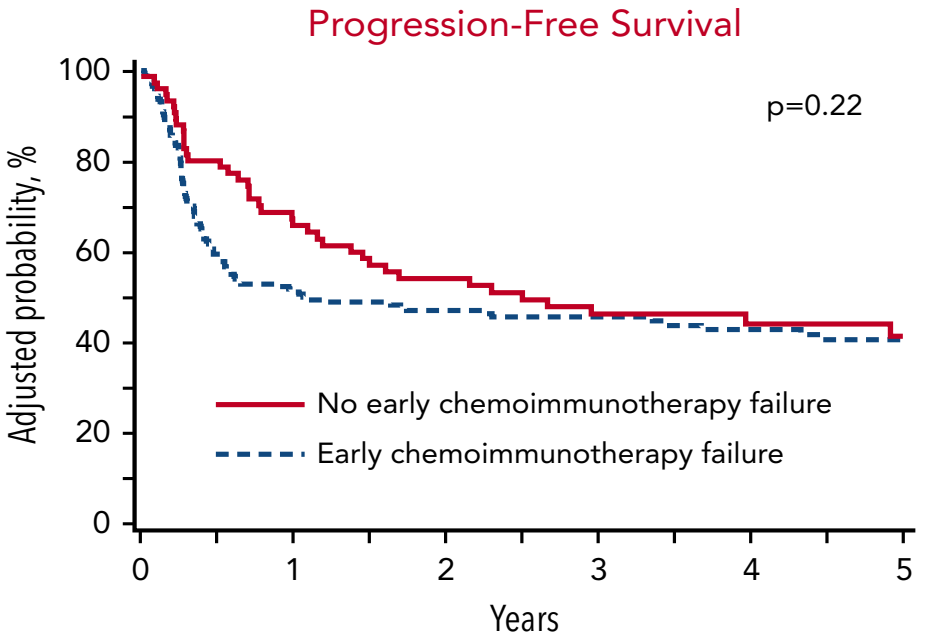
CORAL Study: CD20+ DLBCL 1st Relapse/1° Refractory R-ICE vs R-DHAP → HDC/SCT (then ± Rituximab)





Gisselbrecht C et al. JCO 2010;28:4184-4190

ASCT benefit in chemosensitive DLBCL even with early relapse: CIBMTR

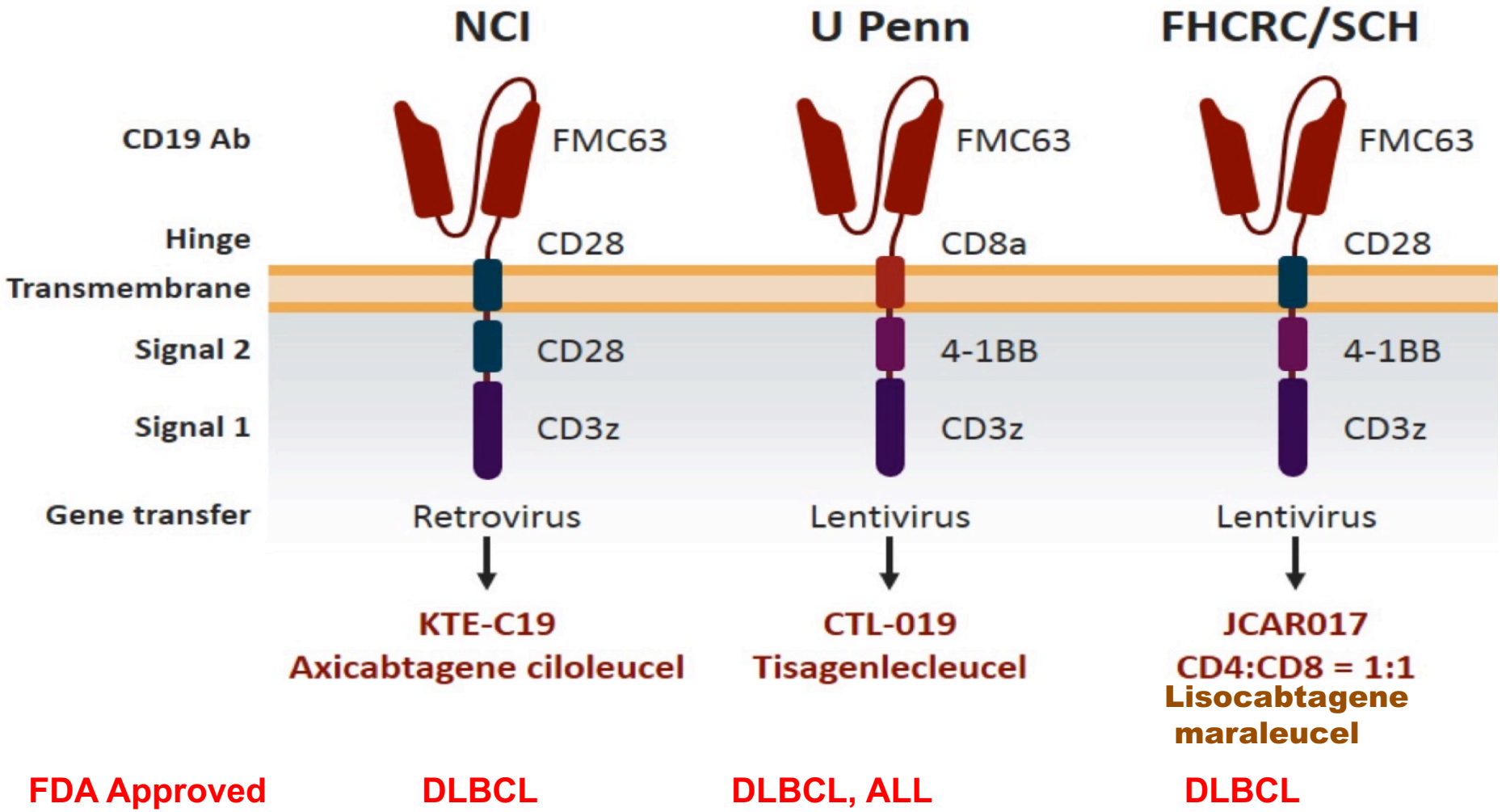


Shah N et al. Blood 2021; Bal S et al. Trans Cell Ther 2021

The issue with early relapses is often not chemosensitive, so do not proceed to ASCT.

This affects interpretation of CART vs SOC trials in 1st relapse

Anti-CD19 CAR T-cell constructs in clinical use



Has CD19 CART Replaced ASCT for R/R DLBCL?

ZUMA-7
Axi-cel
Locke NEJM 2022

TRANSFORM
Liso-cel
Kamdar Lancet 2022

CART better than SOC

BELINDA
Tisagenlecleucel
Bishop NEJM 2022

No differences

BRIDGING Rx VARIED → **CART therapy**

Eligibility: DLBCL 1 prior Rx
1^0 Refractory (65-75% in each trial)
Relapsed < 1 yr
PS 0-1

1^0 Endpoint PFS/EFS

(≥ week 12 BELINDA)

2^{nd} line
(ICE, GDP, DHAP)

If CR/PR → **HDC/autoSCT**

NCT03391466. NCT03570892. NCT03575351.

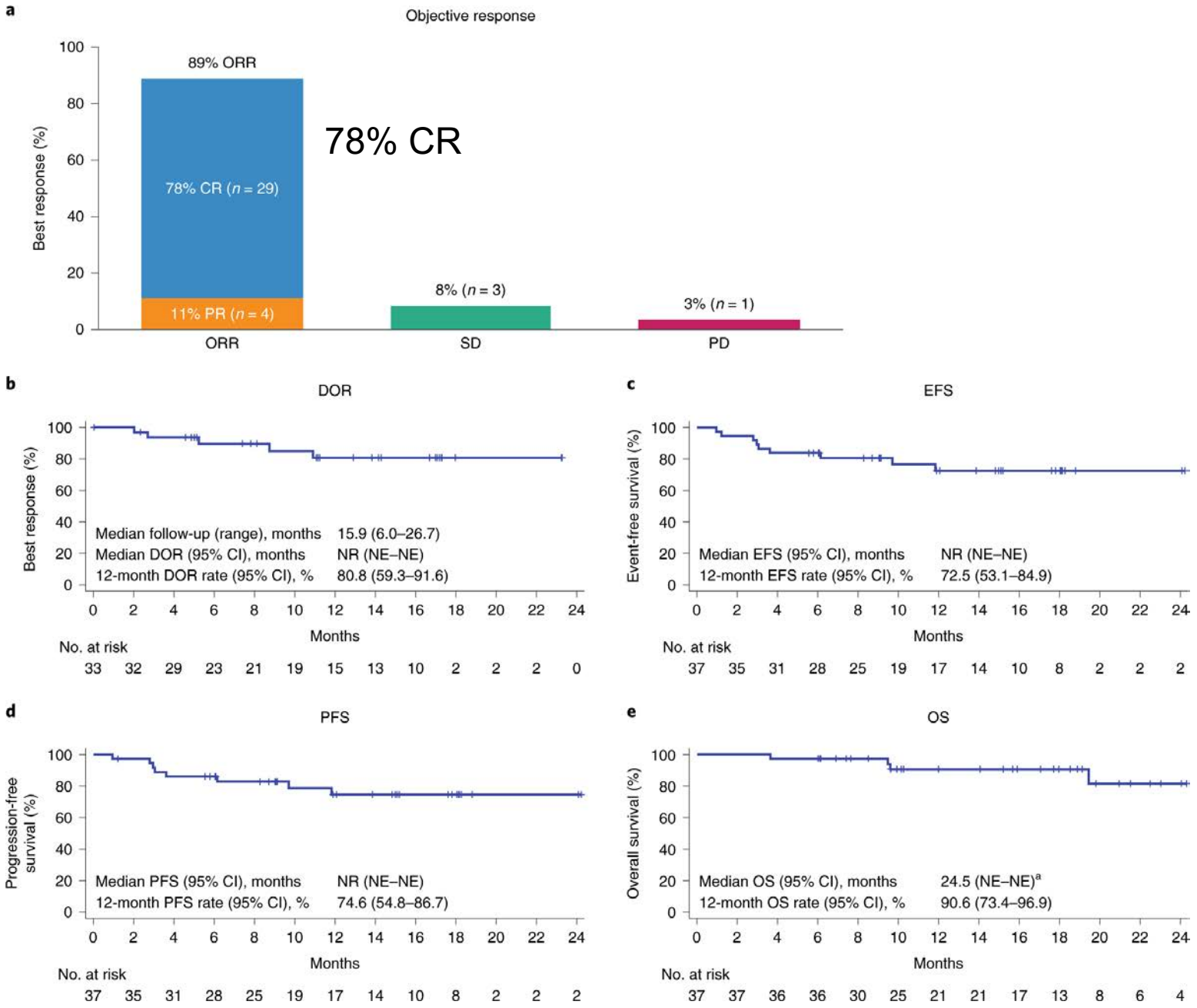
Phase 3 DLBCL trials (CART vs SOC)

	ZUMA-7	TRANSFORM	BELINDA
CART arm	AXI-CEL	LISO-CEL	TISA-CEL
Construct	CD19-**CD28**-CD3z	CD19-**41BB**-CD3z	CD19-**41BB**-CD3z
Bridging chemoTX	Steroids only (36%)	63% (SOC CIT)	83% (SOC CIT) 2nd regimen permitted
Conditioning regimen	Flu 30 mg/m^2 x3d Cy 500 mg/m^2 x3d	Flu 25/m^{2}x 3d Cy 250 mg/m^2 x3d	Flu 30 mg/m^2 x3d Cy 300 mg/m^2 x3d
Median time to CART	29 days	34 days	52 days
ORR/CR	83%	86%	46%
CR	65%	66%	28%
EFS median	8.3 months	10.1 months	3.1 months
HR vs SOC	0.39 (p<0.0001)	0.34 (p<0.0001)	1.07 (p=0.69)
G3+ CRS/G3+ ICANS	6%/21%	1%/4%	5%/3%
SOC arm			
ASCT	36%	46%	33%
ORR/CR	50%/32%	48%/39%	43%/28%
EFS median	2 months	2.3 months	3.1 months
Crossover CART	56%	55%	51%

ZUMA 12:
Axi-cel 1st Line therapy in Primary Refractory High-Risk Large B-cell Lymphoma

Eligibility:
DLBCL with high-risk features:
- Double hit/triple hit HGBCL, or
- DLBCL with IPI score ≥ 3,

AND
- **PET + (DS 4-5) after 2 cycles chemoimmunotherapy**



Neelapu SS et al Nature Medicine 2022, 28:735

PILOT Trial: Phase 2 of liso-cel as 2nd line therapy for LBCL patients not planned for ASCT

- PATIENT CHARACTERISTICS
  - Median age 74
  - 26% PS 2
  - 54% 1^0 Ref/21% Rel < 12 months
- TREATMENT
  - Of 74 leukapheresed, 61 (82%) received liso-cel
- EFFICACY
  - 1^0 Endpoint ORR achieved in 49/61 = 80%
- TOXICITY
  - CRS 38% (grade 3 in 1)
  - ICANS 31% (grade 3 in 3)

Seghal A et al Lancet Oncology 2022

Tafasitamab + Lenalidomide in R/R DLBCL

- Tafasitamab (MOR208): Fc-engineered antibody targeting CD19
- FDA granted a priority review designation for tafasitamab + LEN for patients with R/R DLBCL
- L-MIND[1-3]: Phase II of tafasitamab + LEN for R/R DLBCL (1-3 prior therapies, including ≥1 αCD20) who are ineligible for ASCT
- RE-MIND (retrospective observational matched control study): Tafa + LEN significantly improved ORR vs lenalidomide monotherapy in R/R DLBCL ineligible for ASCT

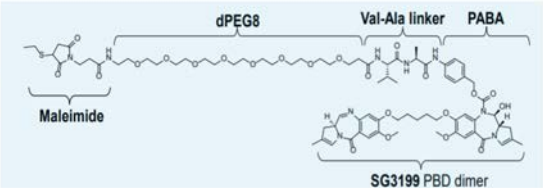
	L-MIND[1-3] Tafasitamab + LEN (N= 80)
Median follow-up	17.3 months
ORR	60%
CR	42.5%
mDOR	21.7 months
12-month DOR	71.6%
mOS	NR
12-month OS	73.7%
mPFS	12.1 months

- Ongoing studies include
  - COSMOS (Phase 2): Tafasitamab + idelalisib or venetoclax for R/R CLL/SLL
  - First-MIND (Phase 1b): Tafasitamab + R-CHOP or tafasitamab/LEN + R-CHOP for newly diagnosed, previously untreated DLBCL
  - B-MIND (Phase 2/3): Tafasitamab + bendamustine vs rituximab + bendamustine for R/R DLBCL

1. Salles, et al. Hemat Oncol. 2019;37(52):173-174. doi.org/10.1002/hon.130_2629. 2. Maddockes, et al. *J Clin Oncol.* 2019; 37(15_suppl):7521. doi: 10.1200/JCO.2019.37.15_suppl.7521.
3. Duell, et al. *Blood* . 2019;134 (supplement_1): 1582. doi.org/10.1182/blood-2019-122573.

Loncastuximab Tesirine in R/R DLBCL

Tesirine/
SG3249



Overall Response Rate: By Clinical Characteristics

Characteristic	Subgroup	All ≥120 µg/kg, % (responders/total)
Age group	<65 Years	33.3 (23/69)
	65–74 Years	52.8 (19/36)
	≥75 Years	59.1 (13/22)
Bulky disease	Absent	46.8 (51/109)
	Present	22.2 (4/18)
Double/Triple hit	Absent	47.6 (50/105)
	Present	22.7 (5/22)
Transformed	No	39.6 (38/96)
	Yes	54.8 (17/31)

Characteristic	Subgroup	All ≥120 µg/kg, % (responders/total)
Number of prior therapies	≤3 lines	43.8 (35/80)
	>3 lines	42.6 (20/47)
Response to first-line therapy	Relapsed	53.1 (43/81)
	Refractory	23.1 (6/26)
Response to most recent therapy	Relapsed	59.1 (26/44)
	Refractory	35.1 (26/74)
Overall		**43.3 (55/127)**

- The most common grade ≥3 TEAEs (≥10%):
  - Gamma-glutamyl transferase increase (20.2%)
  - Decreased neutrophils (38%)
  - Decreased platelets (27.1%)
  - Anemia (11.6%)

Monitor for:
3rd space fluid/effusions
Rash (may be photosensitive)

Figures from Radford, et al. *Hematol Oncol*. 2019;37(52):93-95. doi.org/10.1002/hon.60_2629

DLBCL Treatment in Flux

- 1st Line:
  - Pola-R-CHP for IPI 2-5 (though no OS benefit)
    - ABC only? Age 60-80?
  - Many clinical trial options
- High-risk primary refractory change early to axi-cel?
  - Feasibility?
- CART for primary refractory/relapse < 12 months
  - Should be planned to avoid delay
  - If get 2nd line chemo and respond, proceed to ASCT?
- Later relapses: "salvage" chemo ⟹ ASCT
  - If not ASCT candidate consider CART?
- "3rd line" therapy: increasing options
  - CART, BsAb, tafa-len, lonca-T, pola-V, selinexor

N Engl J Med 2022 January 27;386(4):351-63.

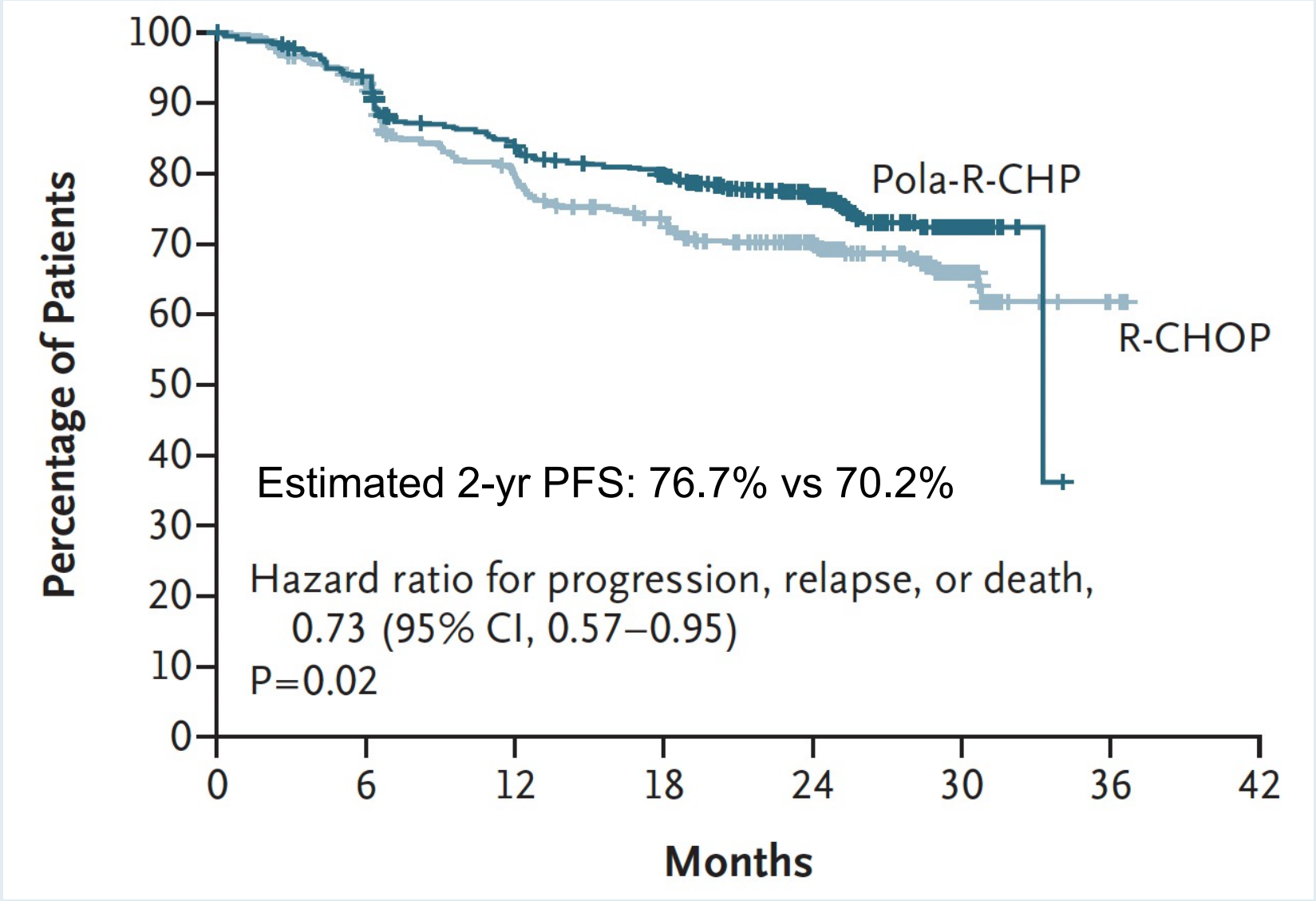
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma

H. Tilly, F. Morschhauser, L.H. Sehn, J.W. Friedberg, M. Trněný, J.P. Sharman, C. Herbaux, J.M. Burke, M. Matasar, S. Rai, K. Izutsu, N. Mehta-Shah, L. Oberic, A. Chauchet, W. Jurczak, Y. Song, R. Greil, L. Mykhalska, J.M. Bergua-Burgués, M.C. Cheung, A. Pinto, H.-J. Shin, G. Hapgood, E. Munhoz, P. Abrisqueta, J.-P. Gau, J. Hirata, Y. Jiang, M. Yan, C. Lee, C.R. Flowers, and G. Salles

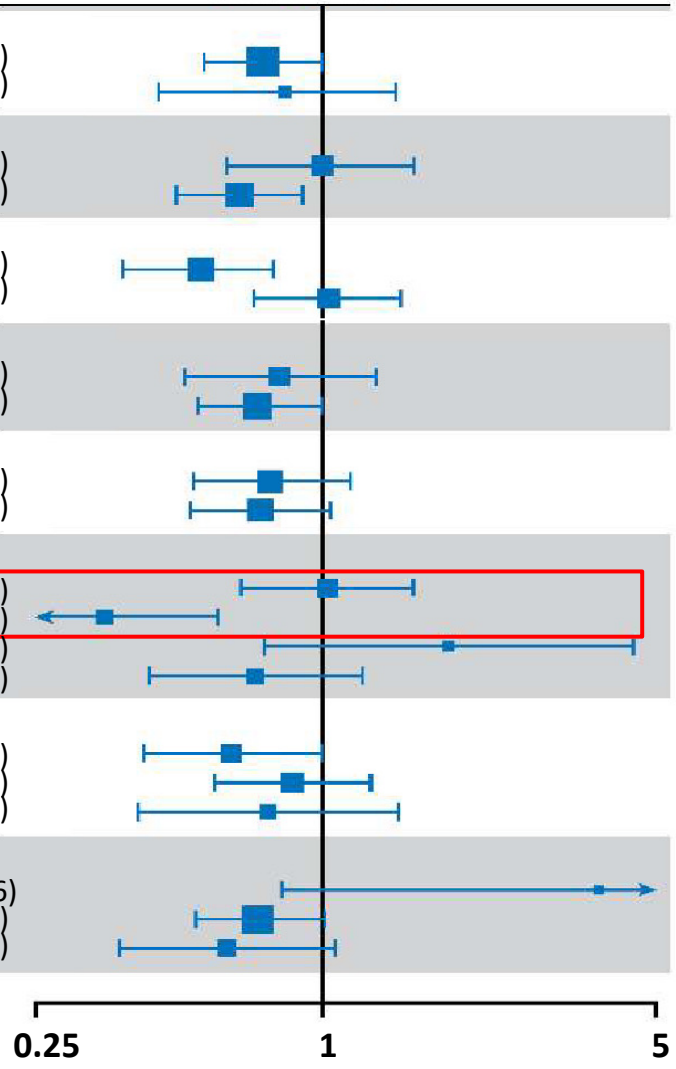
POLARIX: Investigator-Assessed Progression-Free Survival (Primary Endpoint)



Tilly H et al. *N Engl J Med* 2022;386(4):351-63. Flowers C et al. SOHO 2022;Abstract ABCL-073.

POLARIX: Subgroup Analysis

Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
ECOG PS							
0-1	737	374	78.4	363	71.2	0.8	(0.6 to 1.0)
2	141	66	67.2	75	65.0	0.8	(0.5 to 1.4)
IPI score							
IPI 2	334	167	79.3	167	78.5	1.0	(0.6 to 1.6)
IPI 3-5	545	273	75.2	272	65.1	0.7	(0.5 to 0.9)
Bulky disease							
Absent	494	247	82.7	247	70.7	0.6	(0.4 to 0.8)
Present	385	193	69.0	192	69.7	1.0	(0.7 to 1.5)
Baseline LDH							
≤ULN	300	146	78.9	154	75.6	0.8	(0.5 to 1.3)
>ULN	575	291	75.4	284	67.2	0.7	(0.5 to 1.0)
No. of extranodal sites							
0-1	453	227	80.2	226	74.5	0.8	(0.5 to 1.1)
≥2	426	213	73.0	213	65.8	0.7	(0.5 to 1.0)
Cell-of-origin							
GCB	352	184	75.1	168	76.9	1.0	(0.7 to 1.5)
ABC	221	102	83.9	119	58.8	0.4	(0.2 to 0.6)
Unclassified	95	44	73.0	51	86.2	1.9	(0.8 to 4.5)
Unkown	211	110	73.8	101	64.3	0.7	(0.4 to 1.2)
Double expressor by IHC							
DEL	290	139	75.5	151	63.1	0.6	(0.4 to 1.0)
Non DEL	438	223	77.7	215	75.7	0.9	(0.6 to 1.3)
Unknown	151	78	76.0	73	69.8	0.8	(0.4 to 1.5)
Double- or triple-hit lymphoma							
Yes	45	26	69.0	19	889	3.8	(0.8 to 17.6)
No	620	305	76.8	315	70.3	0.7	(0.5 to 1.0)
Unknown	214	109	78.5	105	66.4	0.6	(0.4 to 1.1)



Tilly H et al. *N Engl J Med* 2022;386(4):351-63.

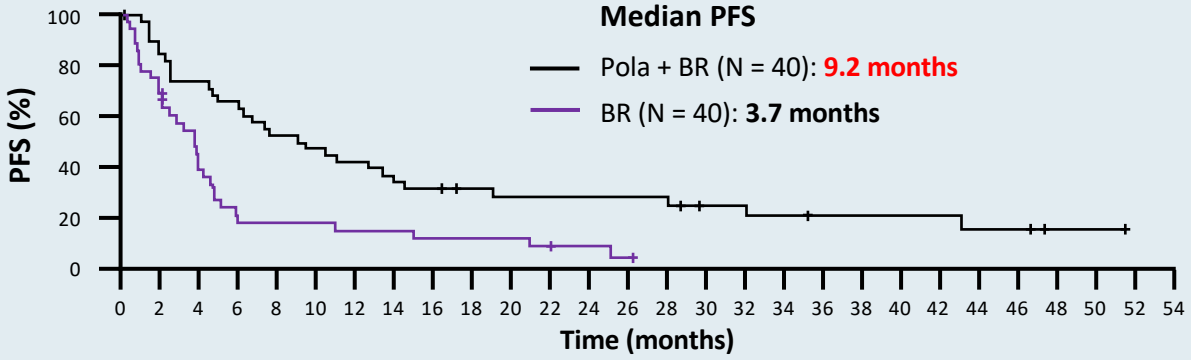
Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data

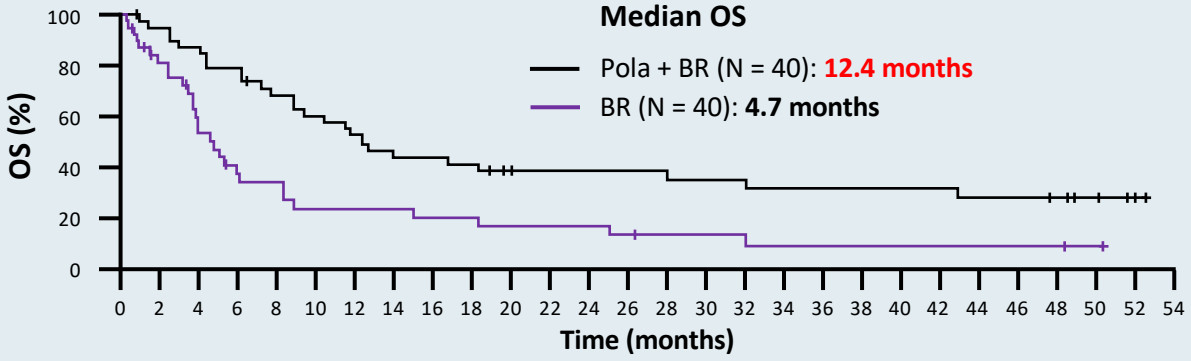
Laurie H. Sehn,[1] Mark Hertzberg,[2] Stephen Opat,[3] Alex F. Herrera,[4] Sarit Assouline,[5] Christopher R. Flowers,[6] Tae Min Kim,[7] Andrew McMillan,[8] Muhit Ozcan,[9] Violaine Safar,[10] Gilles Salles,[10] Grace Ku,[11] Jamie Hirata,[11] Yi Meng Chang,[12] Lisa Musick,[11] and Matthew J. Matasar[13]

***Blood Adv* 2022 January 25;6(2):533-43.**

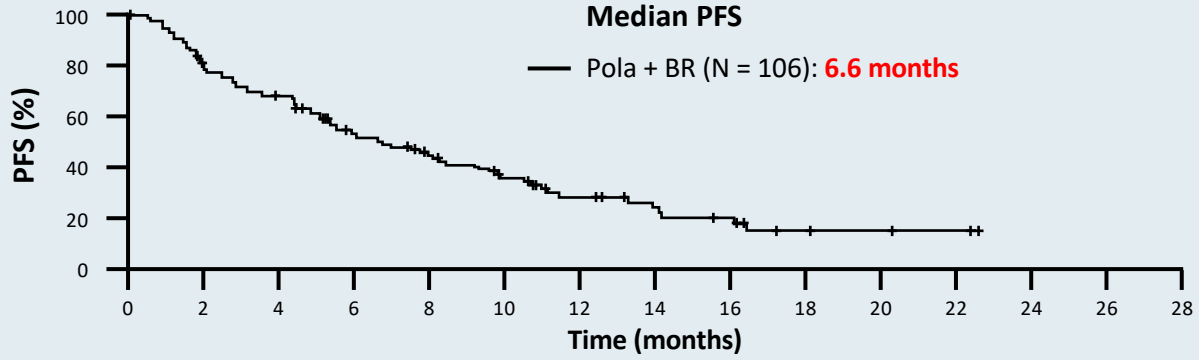
GO29365: PFS and OS in Randomized and Extension Cohorts

Randomized

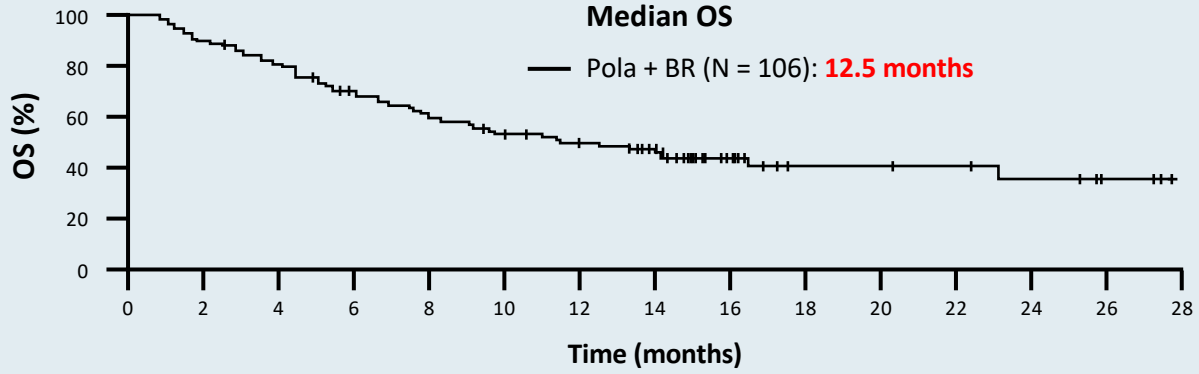




Extension cohort



Pola+BR



Randomized cohort

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

Pooled cohort

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

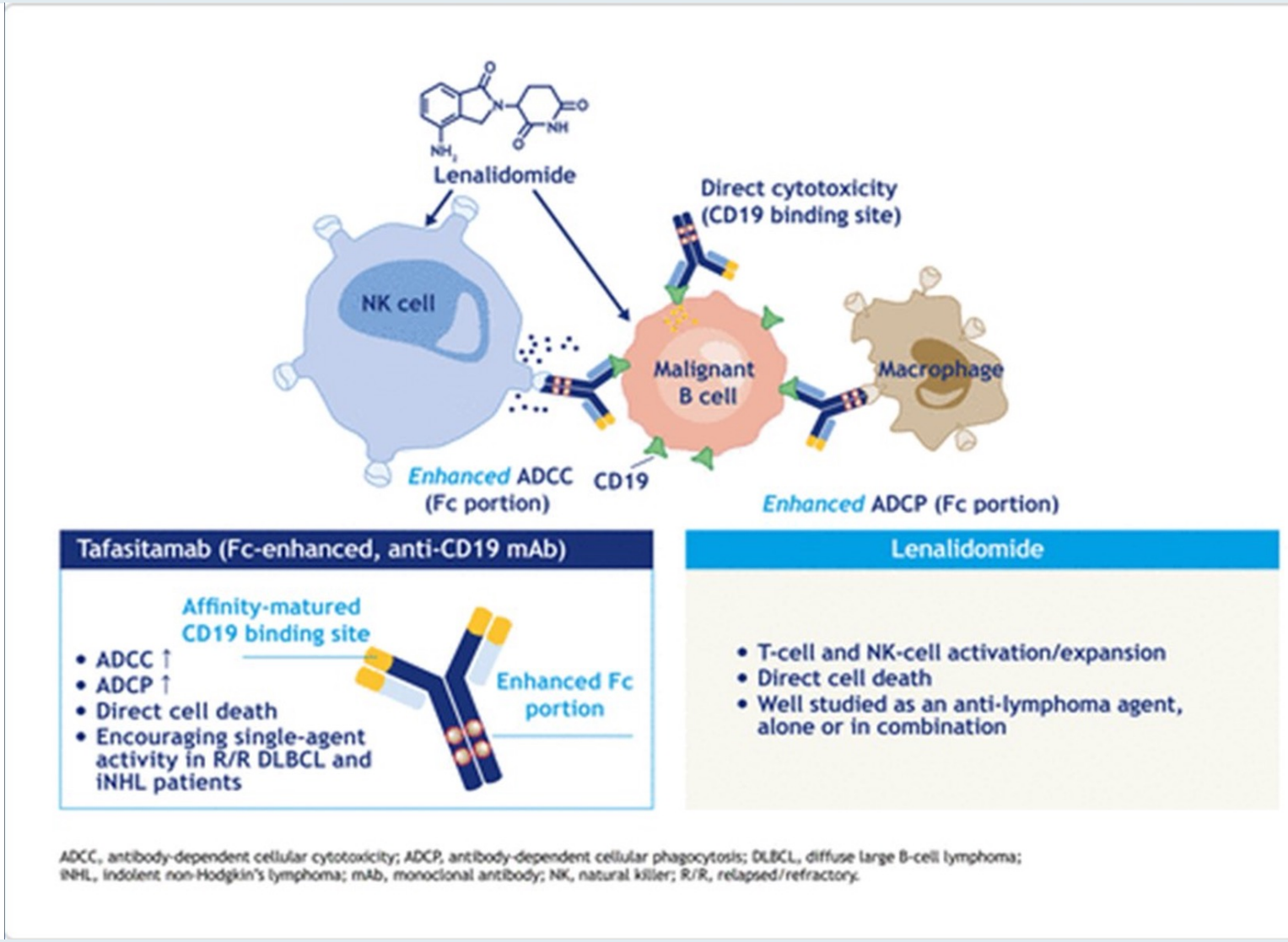
Sehn LH et al. *Blood Adv* 2022;6(2):533-43.

RTP RESEARCH TO PRACTICE

Tafasitamab Mechanism of Action

Mechanism of action: cytolytic

- Apoptosis,
- Antibody-dependent cellular cytotoxicity (ADCC) and
- Antibody-dependent cellular phagocytosis (ADCP)
- In combination with lenalidomide increase NK cell stimulation and proliferation



ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; DLBCL, diffuse large B-cell lymphoma; iNHL, indolent non-Hodgkin's lymphoma; mAb, monoclonal antibody; NK, natural killer; R/R, relapsed/refractory.

Rodriguez MA. Education Session. ASCO 2022; Dull J et al. *Ther Adv Hematol* 2021;12:1-13.

Non-Hodgkin Lymphoma

ARTICLE

Long-term outcomes from the phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma

Johannes Duell,[1] Kami J. Maddocks,[2] Eva González-Barca,[3] Wojciech Jurczak,[4] Anna Marina Liberati,[5] Sven de Vos,[6] Zsolt Nagy,[7] Aleš Obr,[8] Gianluca Gaidano,[9] Pau Abrisqueta,[10] Nagesh Kalakonda,[11] Marc André,[12] Martin Dreyling,[13] Tobias Menne,[14] Olivier Tournilhac,[15] Marinela Augustin,[16] Andreas Rosenwald,[17] Maren Dirnberger-Hertweck,[18] Johannes Weirather,[18] Sumeet Ambarkhane[18] and Gilles Salles[19*]

Ferrata Storti Foundation

Haematologica 2021
Volume 106(9):2417-2426

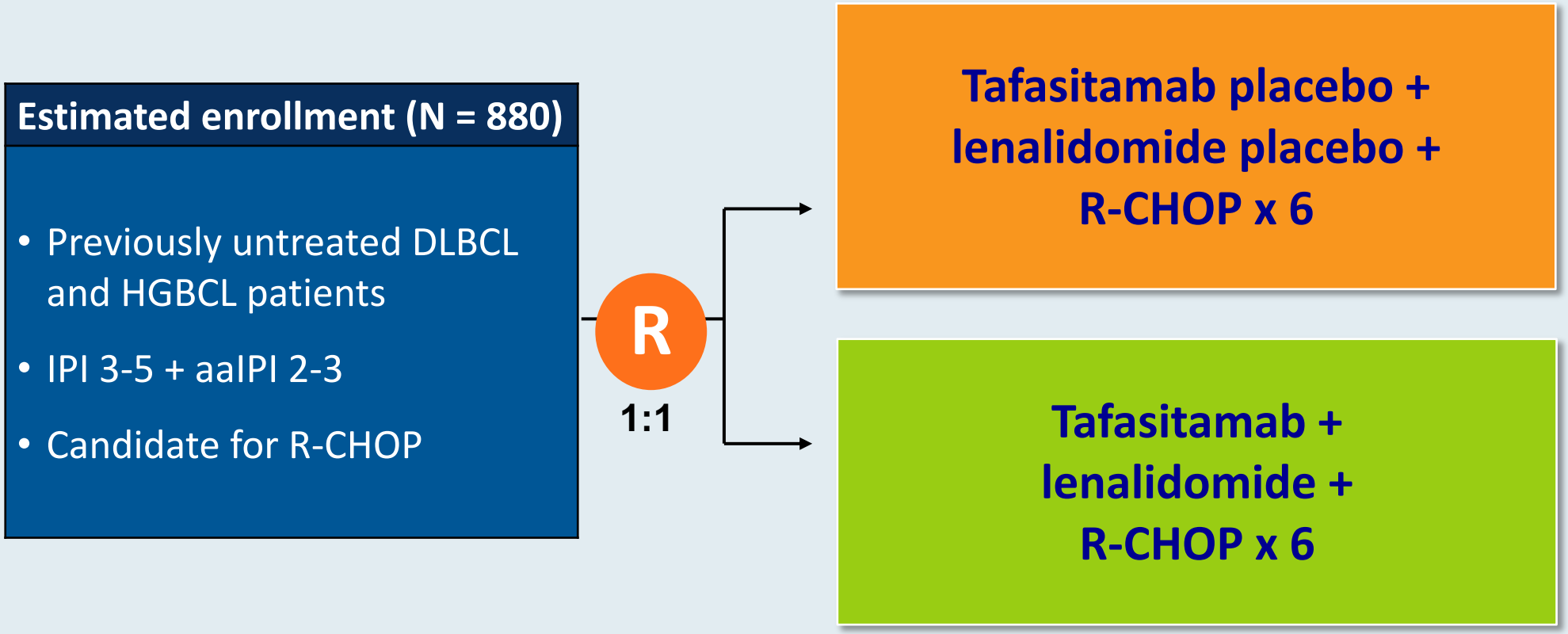
L-MIND: Efficacy Outcomes in the Primary and Follow-Up Analyses

	Tafasitamab plus lenalidomide (N=80)‡		Clinically relevant subgroups (follow-up analysis)		
	Primary analysis (data cut-off: Nov 30, 2018)[8]	Follow-up analysis (data cut-off: Oct 30, 2020)	Primary refractory disease (n=15)	Rituximab-refractory disease (n=33)	Last-therapy-refractory (n=35)
Best objective response, n (%)					
Complete response	34 (42.5)	32 (40.0)	5 (33.3)	13 (39.4)	14 (40.0)
Partial response	14 (17.5)	14 (17.5)	3 (20.0)	5 (15.2)	7 (20.0)
Stable disease	11 (13.8)	13 (16.3)	2 (13.3)	4 (12.1)	3 (8.6)
Progressive disease	13 (16.3)	13 (16.3)	3 (20.0)	7 (21.2)	7 (20.0)
Not evaluable*	8 (10.0)	8 (10.0)	2 (13.3)	4 (12.1)	4 (11.4)
ORR (CR + PR), n (%) [95% CI]†	48 (60.0) [48.4-70.9]	46 (57.5) [45.9-68.5]	8 (53.3) [26.6-78.7]	18 (54.5) [36.4-71.9]	21 (60.0) [42.1-76.1]
Median DoR (IRC), months (95% CI)	21.7 (21.7-NR)	43.9 (26.1-NR)	NR (1.8-NR)	NR (5.8-NR)	NR (5.8-NR)
Median PFS (IRC), months (95% CI)	12.1 (5.7-NR)	11.6 (6.3-45.7)	5.3 (0.9-NR)	7.6 (2.7-NR)	7.6 (2.7-NR)
Median OS, months (95% CI)	NR (18.3-NR)	33.5 (18.3-NR)	13.8 (1.3-NR)	15.5 (8.6-NR)	15.5 (8.6-NR)

ORR = objective response rate; CR = complete response; PR = partial response; NR = not reached; DoR = duration of response; PFS = progression-free survival; OS = overall survival

Duell J et al. *Haematologica* 2021;106(9):2417-26.

frontMIND Phase III Study Design



Primary endpoint: PFS by investigator

Key secondary endpoints: EFS by investigator, OS

Vitolo U et al. SOHO 2022;Abstract ABCL-023.

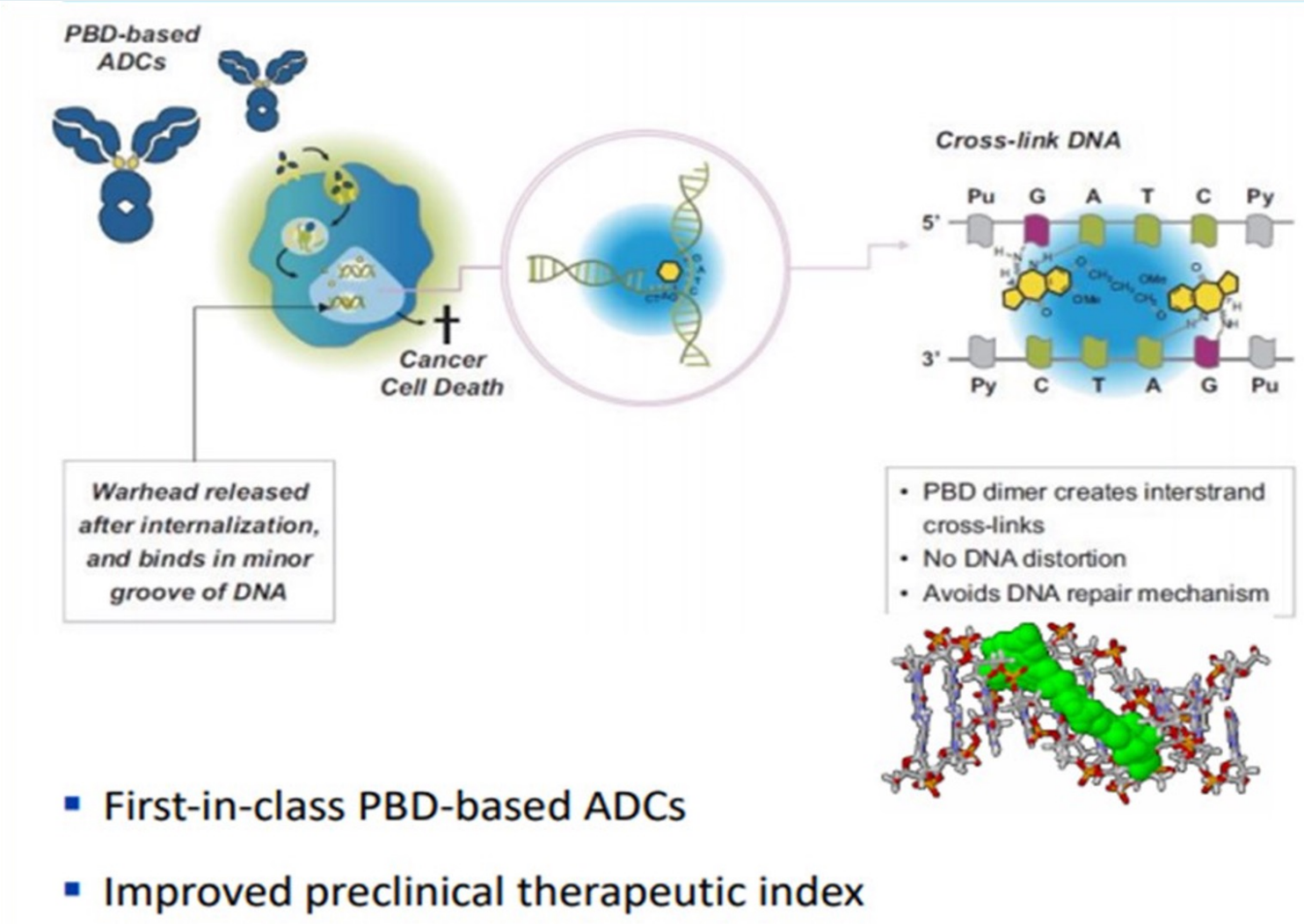
Mechanism of Action of Loncastuximab Tesirine

Design: Humanized anti-CD19 antibody-drug conjugate (ADC)

Active drug agent: Tesirine is a pyrrolobenzodiazepine (PBD) dimer ("warhead" – more potent than systemic chemotherapy)

Mechanism of action:

- ADC is internalized by the cell,
- Tesirine is enzymatically lysed from the antibody and
- It intercalates into the DNA of the cell forming cytotoxic DNA interstrand crosslinks



Rodriguez MA. Education Session. ASCO 2022; Zammarchi F et al. *Blood* 2018;131(10):1094-105.

Lancet Oncol 2021 June;22(6):790-800.

Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial

Paolo F Caimi, Weiyun Ai, Juan Pablo Alderuccio, Kirit M Ardeshna, Mehdi Hamadani, Brian Hess, Brad S Kahl, John Radford, Melhem Solh, Anastasios Stathis, Pier Luigi Zinzani, Karin Havenith, Jay Feingold, Shui He, Yajuan Qin, David Ungar, Xiaoyan Zhang, Carmelo Carlo-Stella

As a result of the LOTIS-2 trial, loncastuximab tesirine was FDA approved for relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from low-grade lymphoma and high-grade B-cell lymphoma.

LOTIS-2: Response and Survival with Loncastuximab Tesirine for R/R DLBCL

Response	As-treated population (N = 145)
Overall response rate	70/145 (48.3%)
• Complete response rate	35/145 (24.1%)
• Complete response	35 (24%)
• Partial response	35 (24%)
• Stable disease	22 (15%)
• Progressive disease	30 (21%)
• Not evaluable	23 (16%)
Survival	**As-treated population (N = 145)**
Median progression-free survival	4.9 months
Median overall survival	9.9 months

Caimi PF et al. *Lancet Oncol* 2021;22(6):790-800.

RTP RESEARCH TO PRACTICE

Initial Safety Run-In Results of the Phase III LOTIS-5 Trial: Novel Combination of Loncastuximab Tesirine with Rituximab (Lonca-R) versus Immunochemotherapy in Patients with R/R DLBCL

Kingsley E et al.

SOHO 2022;Abstract ABCL-320.

Results for LOTIS-5 Safety Run-In (N = 20)

Efficacy in patients with R/R DLBCL		
	n (%)	95% CI
Overall response rate[a]	15 (75%)	(50.9, 91.3)
Complete response	8 (40%)	(19.1, 63.9)
Partial response	7 (35%)	(15.4, 59.2)
Safety endpoints		
Any grade TEAE, n (%)	19 (95%)	
Rash	5 (25%)	
Fatigue	4 (20%)	
Increased gamma-glutamyltransferase	4 (20%)	
Grade ≥3 TEAEs, n (%)	10 (50%)	
Increased gamma-glutamyltransferase	3 (15%)	
Increased alanine aminotransferase	2 (10%)	
Neutropenia	2 (10%)	

TEAE = treatment-emergent adverse event

Kingsley E et al. SOHO 2022;Abstract ABCL-320.

Patient Characteristic and Efficacy Outcomes of Phase II Trials Leading to Approval of CAR-T Therapy for Multiregimen R/R DLBCL

	Axi-cel: ZUMA-1[13,37]	Tisa-cel: JULIET[16,17]	Liso-cel: TRANSCEND[11]
Disease type	▪ DLBCL: 76% ▪ Transformed follicular lymphoma: 16% ▪ Primary mediastinal B-cell lymphoma: 8%	▪ DLBCL: 79% ▪ Transformed follicular lymphoma: 19% ▪ Other: 2%	▪ DLBCL: 51% ▪ Transformed DLBCL: 29% ▪ High-grade B-cell lymphoma: 13% ▪ Primary mediastinal B-cell lymphoma: 6% ▪ Follicular lymphoma, grade 3: 1%
Median age, y (range)	58 (23-76)	56 (22-76)	63 (54-70)
Median No. of prior therapies	3	3	3
% patients with prior stem cell transplant	21%	49%	33%: autologous 3%: allogeneic
CAR T-cell dose	2×10^6 cells/kg body weight	$0.6\text{-}6.0 \times 10^8$ cells	Median dose 91×10^6 cells
Median time for CAR T-cell preparation	17 days (time from leukapheresis to delivery of axi-cel to treatment facility)	54 days (time from enrollment to infusion of tisa-cel)	37 days (time from leukapheresis to infusion of liso-cel)
ORR	83% (CR, 58%; PR, 25%)	53% (CR, 39%; PR, 13%)	73% (CR, 53%; PR, 20%)
Median DOR, m	11.1 (4.2-NR)	NR (at median follow-up of 40.3 m)	NR (at median follow-up of 12 m)
Median PFS, m	5.9 (95% CI, 3.3-15)	2.9 (95% CI, 2.3-5.2)	6.8 (95% CI, 3.3-14.1)
Median OS, m	25.8 (after median follow-up of 4 y); 4-y OS rate, 44%	11.1 (95% CI, 6.6-23.9) after median follow-up of 40.3 mo	21.1 (95% CI, 13.3-NR)

Kesireddy M, Lunning MA. *Oncology* 2022 June;36(6):360-9.

N Engl J Med 2022;386(7):640-54.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma

F.L. Locke, D.B. Miklos, C.A. Jacobson, M.-A. Perales, M.-J. Kersten, O.O. Oluwole, A. Ghobadi, A.P. Rapoport, J. McGuirk, J.M. Pagel, J. Muñoz, U. Farooq, T. van Meerten, P.M. Reagan, A. Sureda, I.W. Flinn, P. Vandenberghe, K.W. Song, M. Dickinson, M.C. Minnema, P.A. Riedell, L.A. Leslie, S. Chaganti, Y. Yang, S. Filosto, J. Shah, M. Schupp, C. To, P. Cheng, L.I. Gordon, and J.R. Westin, for All ZUMA-7 Investigators and Contributing Kite Members*

Lancet 2022;399(10343):2294-308.

Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial

Manali Kamdar, Scott R Solomon, Jon Arnason, Patrick B Johnston, Bertram Glass, Veronika Bachanova, Sami Ibrahimi, Stephan Mielke, Pim Mutsaers, Francisco Hernandez-Ilizaliturri, Koji Izutsu, Franck Morschhauser, Matthew Lunning, David G Maloney, Alessandro Crotta, Sandrine Montheard, Alessandro Previtali, Lara Stepan, Ken Ogasawara, Timothy Mack, Jeremy S Abramson, for the TRANSFORM Investigators†*

N Engl J Med 2022;386(7):629-39.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma

M.R. Bishop, M. Dickinson, D. Purtill, P. Barba, A. Santoro, N. Hamad, K. Kato, A. Sureda, R. Greil, C. Thieblemont, F. Morschhauser, M. Janz, I. Flinn, W. Rabitsch, Y.-L. Kwong, M.J. Kersten, M.C. Minnema, H. Holte, E.H.L. Chan, J. Martinez-Lopez, A.M.S. Müller, R.T. Maziarz, J.P. McGuirk, E. Bachy, S. Le Gouill, M. Dreyling, H. Harigae, D. Bond, C. Andreadis, P. McSweeney, M. Kharfan-Dabaja, S. Newsome, E. Degtyarev, R. Awasthi, C. del Corral, G. Andreola, A. Masood, S.J. Schuster, U. Jäger, P. Borchmann, and J.R. Westin

Randomized Trials Comparing Second-Line CAR T-Cell to Standard Therapy for Patients with Transplant-Eligible DLBCL with Primary Refractory Disease or Relapse within 1 Year of First-Line Therapy

	ZUMA-7	TRANSFORM	BELINDA
CAR T-cell therapy	Axicabtagene ciloleucel	Lisocabtagene maraleucel	Tisagenlecleucel
n	359	184	322
Patients infused in CAR arm	94%	98%	96%
Median EFS	8.3 mo vs 2 mo	10.1 mo vs 2.3 mo	3 mo vs 3 mo
Hazard ratio	0.398 ($p < 0.0001$)	0.349 ($p < 0.0001$)	1.07 ($p = 0.69$)
Median follow-up	25 mo	6 mo	10 mo
CR rate	65% vs 32%	66% vs 39%	28% vs 28%
Grade ≥3 CRS/NT	6%/21%	1%/4%	5%/3%
	Locke et al. ASH 2021;Abstract 2	Kamdar et al. ASH 2021;Abstract 91	Bishop et al. ASH 2021;Abstract LBA-6

EFS = event-free survival

Content Courtesy of Jeremy Abramson, MD

RTP RESEARCH TO PRACTICE

Recent FDA Approvals of CAR (Chimeric Antigen Receptor) T-Cell Therapy as Second-Line Treatment for Large B-Cell Lymphoma

June 24, 2022: The FDA approved lisocabtagene maraleucel for large B-cell lymphoma (LBCL) in adult patients who have refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy, or refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age. It is not indicated for the treatment of primary central nervous system lymphoma. Based on the TRANSFORM study.

April 1, 2022: The FDA approved axicabtagene ciloleucel for large B-cell lymphoma (LBCL) that is refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy. It is not indicated for the treatment of primary central nervous system lymphoma. Based on the ZUMA-7 study.

www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lisocabtagene-maraleucel-second-line-treatment-large-b-cell-lymphoma
www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-axicabtagene-ciloleucel-second-line-treatment-large-b-cell-lymphoma

RTP RESEARCH TO PRACTICE

nature medicine

FOCUS | ARTICLES

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

OPEN

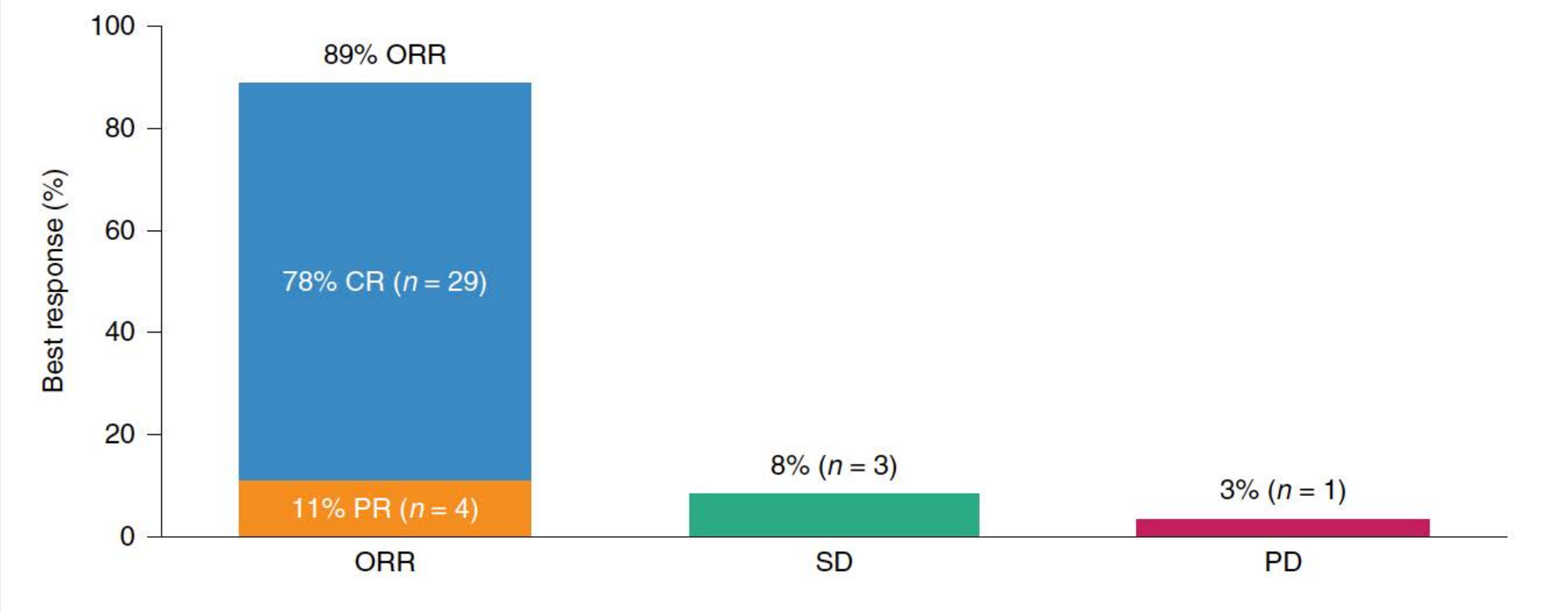
Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial

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]

Nat Med 2022;[Online ahead of print].

ZUMA-12: Efficacy Results with Axicabtagene Ciloucel as First-Line Treatment

ORR and CR in efficacy-evaluable patients (N = 37)



- At median follow-up of 15.9 months, 73% of patients remained in objective response
- Median DOR, EFS and PFS were not reached

Neelapu SS et al. *Nat Med* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

Structure of IgG-Like Bispecific Antibodies

Bi-specific Anti-body	Targets	Administration	Structure
Mosunetuzumab	CD20 x CD3	IV or SC Step-up doses on C1 (D1, D8, D15) Subsequent 21-day cycles for 8 cycles for patients in CR and up to 17 cycles for those with PR or SD	Humanized mouse IgG1-based heterodimeric antibody
Glofitamab	$(CD20)_2$ x CD3	IV 21-day cycles up to 12 cycles Seven days before 1,000 mg obinutuzumab	Humanized mouse IgG1-based antibody. Bivalent CD20 binding
Epcoritamab	CD20 x CD3	SC Weekly dosing in C1-C2 (D1,D8, D15, D22); every 2 weeks in C3–C6 (D1, D15), every 4 weeks from C7 onward Until disease progression or unacceptable toxicity	Humanized mouse heterodimeric IgG1-based heterodimeric antibody
Odronextamab	CD20 x CD3	IV Step-up doses on C1 (D1, D2, D8, D9, D15, D16) Weekly dosing C2–C4 (D1,D8, D15), in 21-day cycles After C4, maintenance treatment every 2 weeks Until disease progression or unacceptable toxicity	Fully human IgG4-based heterodimeric antibody

Ig, immunoglobulin; SC, subcutaneous; IV, intravenous; C,cycle; D, day.

Barca EG. *Front Immunol* 2022 July 19;[Online ahead of print].

Glofitamab in Patients with Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL) and ≥ 2 Prior Therapies: Pivotal Phase II Expansion Results

Dickinson M et al.

ASCO 2022;Abstract 7500.

Response Rates with Glofitamab for R/R DLBCL (≥2 Prior Therapies)

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)

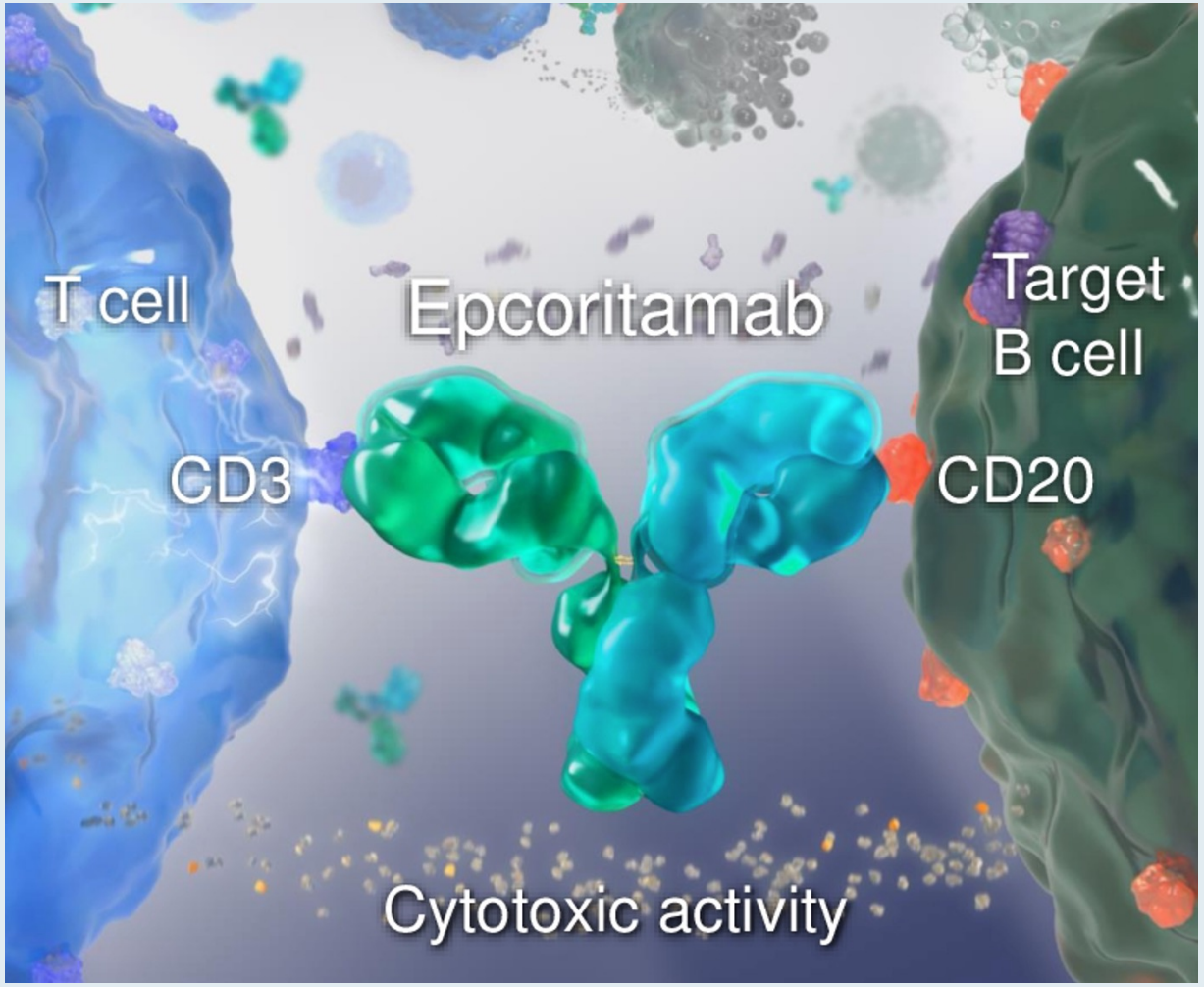
– At time of primary analysis, primary endpoint met in the primary efficacy population (n=108)†: 35.2% CR rate by IRC significantly greater ($p<0.0001$) than 20% historical control CR rate‡

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

RTP RESEARCH TO PRACTICE

Dickinson M et al. ASCO 2022;Abstract 7500. Dickinson M et al. EHA 2022;Abstract S220.

Mechanism of Action of the Subcutaneous Bispecific Antibody Epcoritamab



Falchi L et al. ASCO 2022;Abstract 7524.

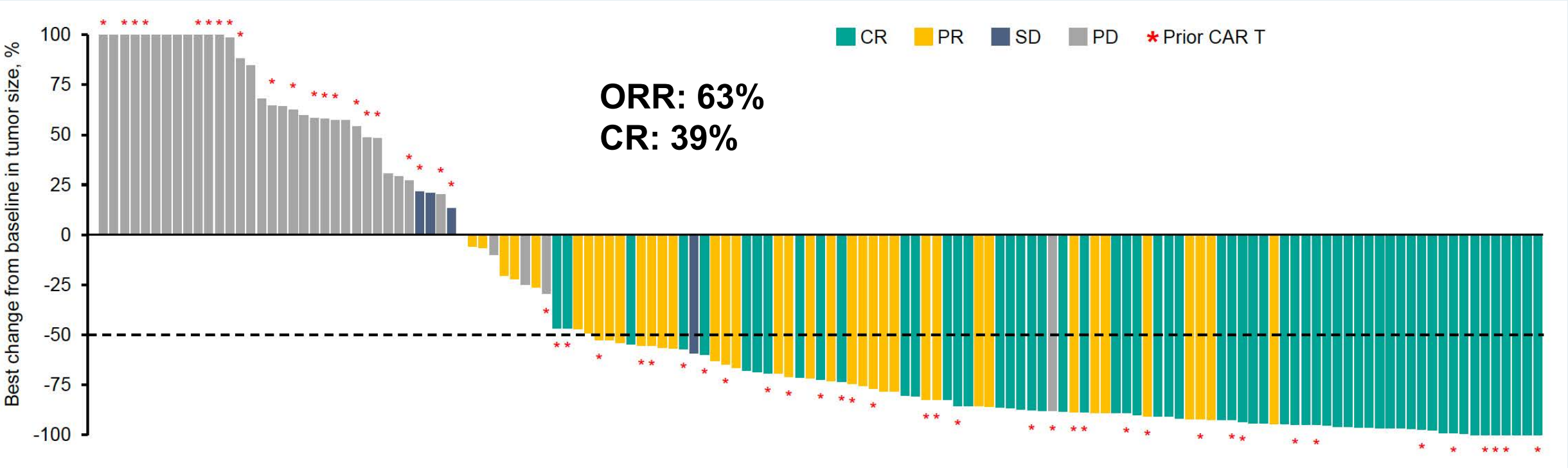
RTP
RESEARCH
TO PRACTICE

SOHO 2022;Abstract ABCL-422.

Subcutaneous epcoritamab in patients with relapsed or refractory large B-cell lymphoma (EPCORE NHL-1): pivotal results from a phase 2 study

Catherine Thieblemont, MD, PhD,[1] Tycel Phillips, MD,[2] Herve Ghesquieres, MD, PhD,[3] Chan Y. Cheah, MBBS, FRACP, FRCPA, DMSc,[4] Michael Roost Clausen, MD, PhD,[5] David Cunningham, MD, FRCP, FMedSci,[6] Young Rok Do, MD, PhD,[7] Tatyana Feldman, MD,[8] Robin Gasiorowski, MBBS, FRACP, FRCPA, PhD,[9] Wojciech Jurczak, MD, PhD,[10] Tae Min Kim, MD, PhD,[11] David John Lewis, MD,[12] Marjolein van der Poel, MD, PhD,[13] Michelle Limei Poon, MBBS, MRCP,[14] Thomas Doerr, MS,[15] Nurgul Kilavuz, PharmMS,[16] Menghui Chen, PhD,[16] Mariana Sacchi, MD,[16] Brian Elliott, MD,[16] Martin Hutchings, MD, PhD,[17] Pieternella Lugtenburg, MD, PhD[18]

Epcoritamab Responses in R/R DLBCL



Thieblemont C et al. SOHO 2022;Abstract ABCL-422.

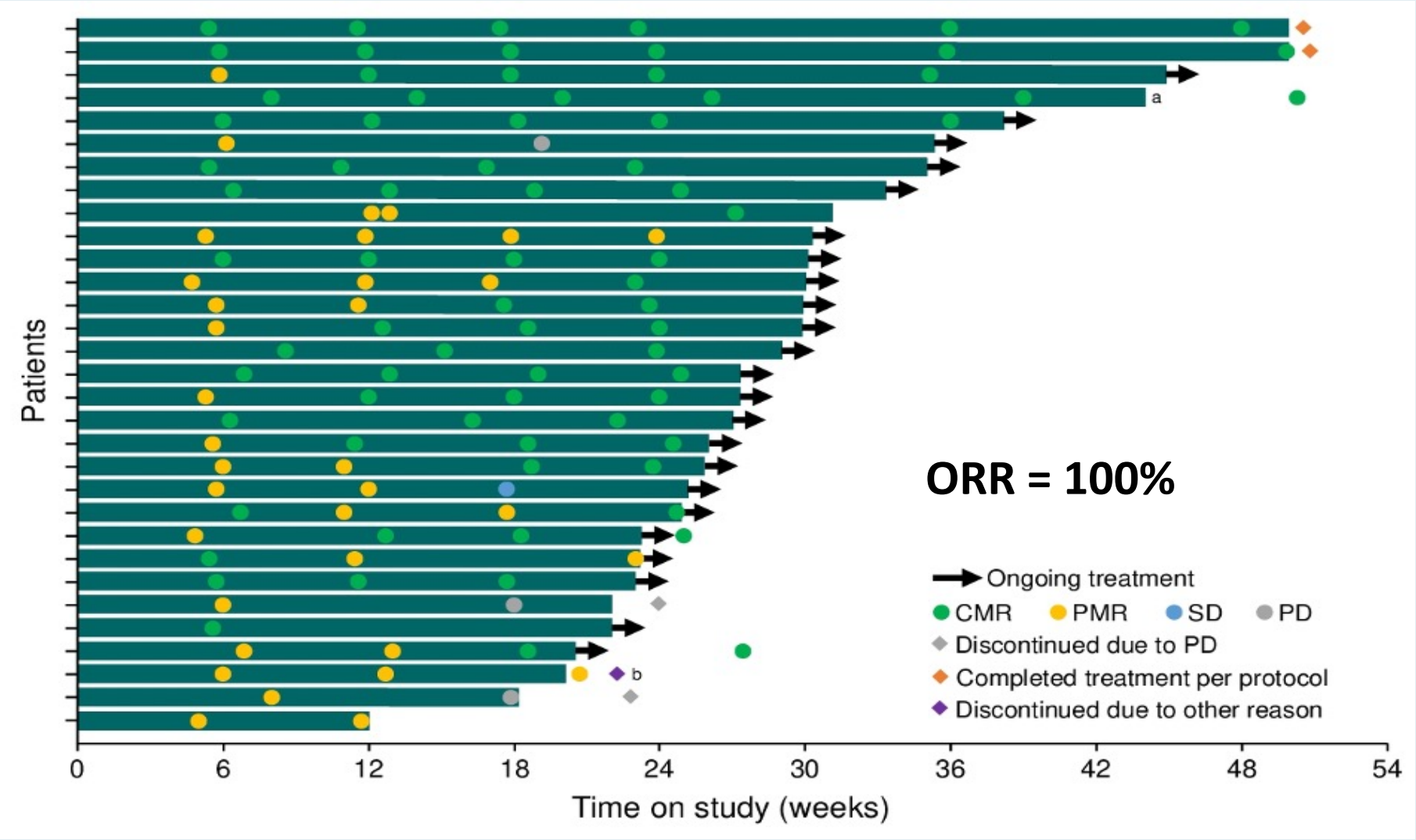
7523

ASCO 2022

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]

EPCORE NHL-2: Response Profile



CMR = complete metabolic response; PMR = partial metabolic response; SD = stable disease; PD = progressive disease

Falchi L et al. ASCO 2022;Abstract 7523. Falchi L et al. SOHO 2022;Abstract ABCL-452.

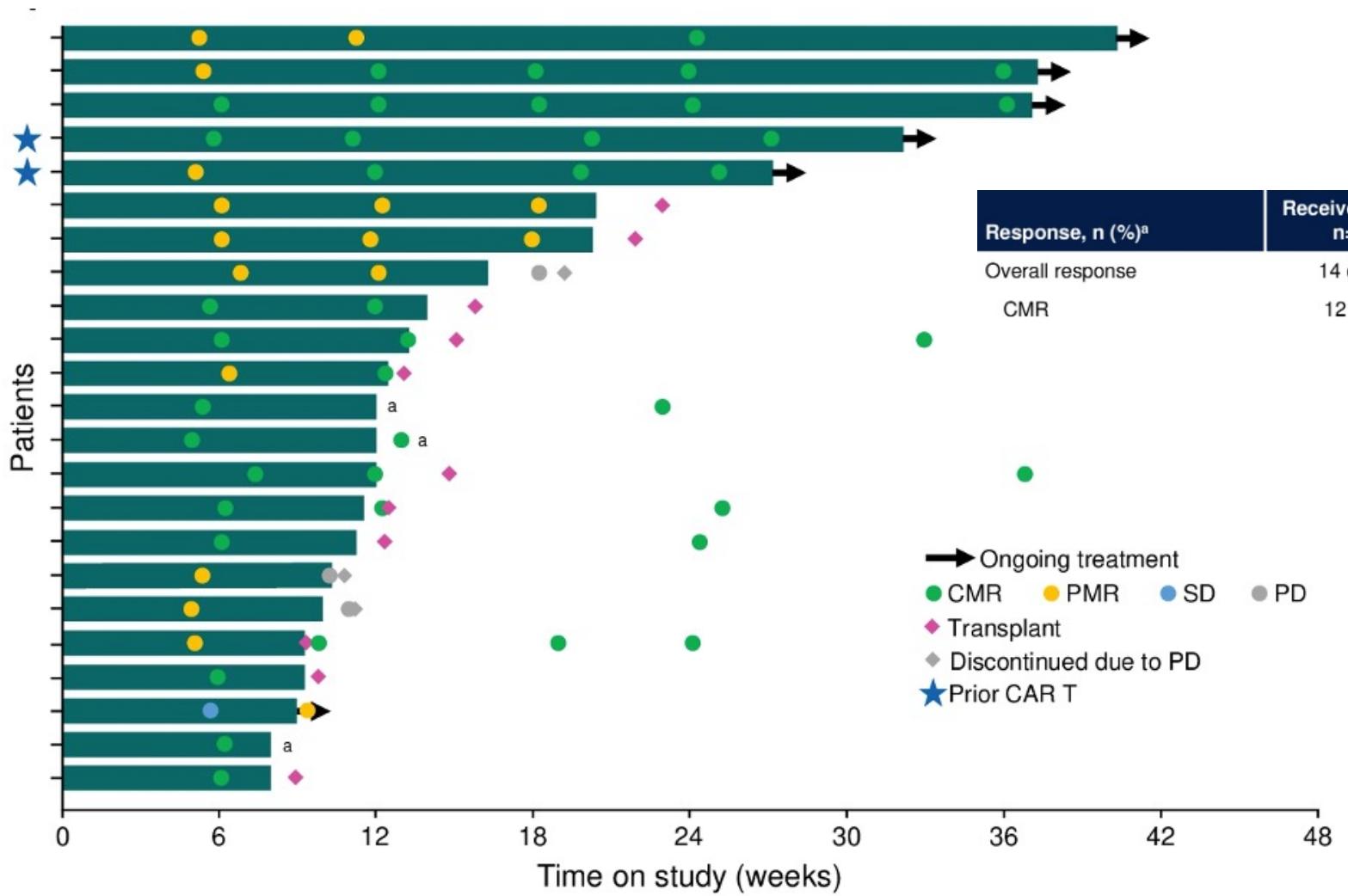
7528

ASCO 2022

Subcutaneous epcoritamab + R-DHAX/C in patients (pts) with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) eligible for autologous stem cell transplant (ASCT): preliminary phase 1/2 results

Pau Abrisqueta, MD, PhD,[1*] Lorenzo Falchi, MD,[2] Tycel Phillips, MD,[3]
Sven de Vos, MD, PhD,[4] Marcel Nijland, MD, PhD,[5] Fritz Offner, MD, PhD,[6]
Irina Bykhovski, PharmD,[7] Jun Wu, MD, MS,[8] Liwei Wang, PhD,[7]
Ali Rana, MD, PhD,[7] Raul Cordoba, MD, PhD[9]

EPCORE NHL-2 Arm 4: Response Profile



Response, n (%)[a]	Received ASCT n=14	Did not receive ASCT n=12	Total n=26
Overall response	14 (100)	9 (75)	23 (88)
CMR	12 (86)	5 (42)[b]	17 (65)

CMR = complete metabolic response; PMR = partial metabolic response; SD = stable disease; PD = progressive disease

Abrisqueta P et al. ASCO 2022;Abstract 7528.

RTP RESEARCH TO PRACTICE

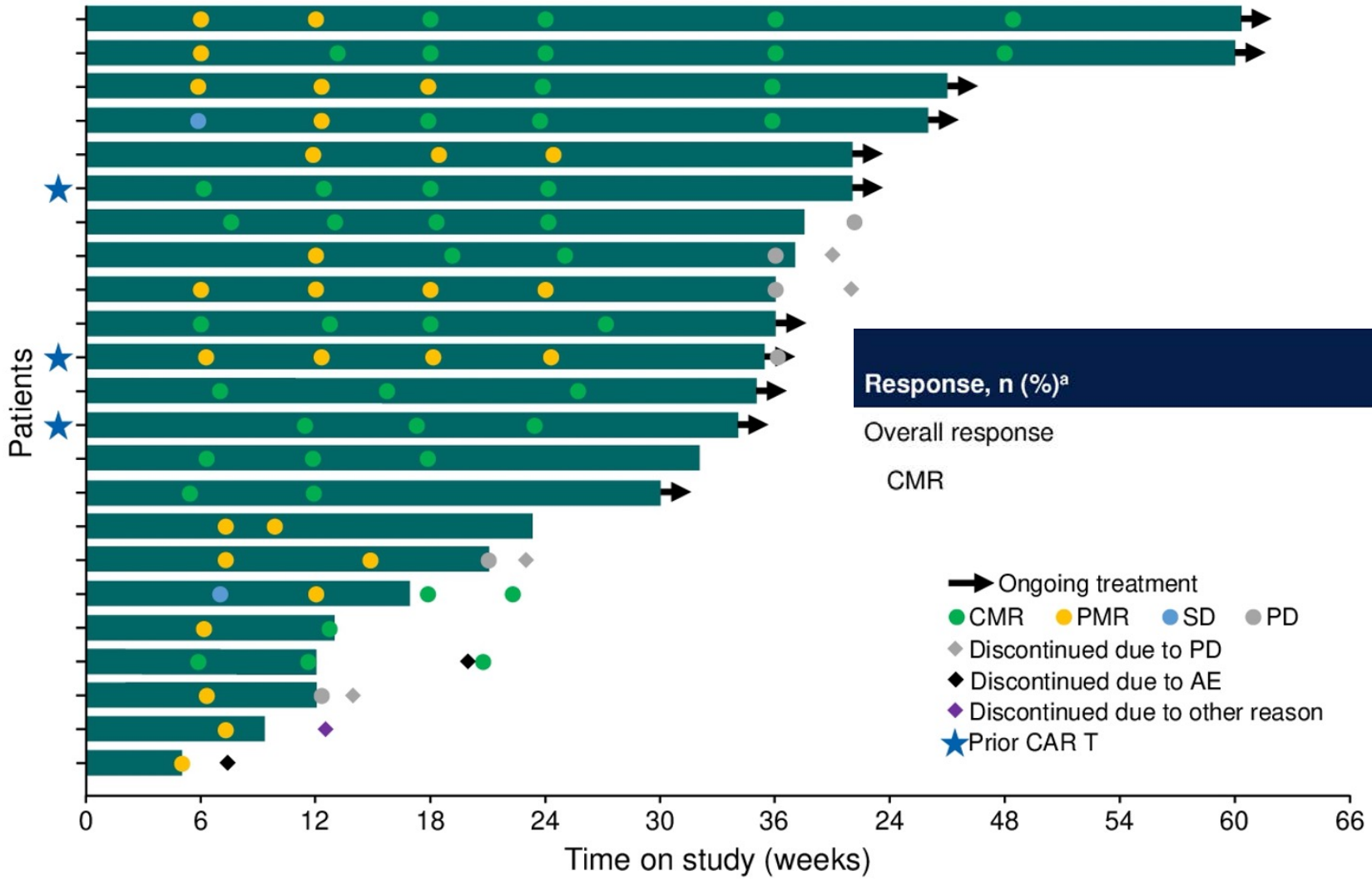
7527

ASCO 2022

Epcoritamab (epco) with gemcitabine + oxaliplatin (GemOx) in patients (pts) with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) ineligible for autologous stem cell transplant (ASCT) induces high response rate even in pts failing CAR T therapy

Joshua Brody, MD,[1]* Björn E. Wahlin, MD, PhD,[2] Tycel Phillips, MD,[3]
Régis Costello, MD, PhD,[4] Pieternella Lugtenburg, MD, PhD,[5]
Raul Cordoba, MD, PhD,[6] Liwei Wang, PhD,[7] Jun Wu, MD, MS,[8]
Brian Elliott, MD,[7] Aqeel Abbas, MS,[7] Judit Jørgensen, MD, PhD[9]

EPCORE NHL-2 Arm 5: Response Profile



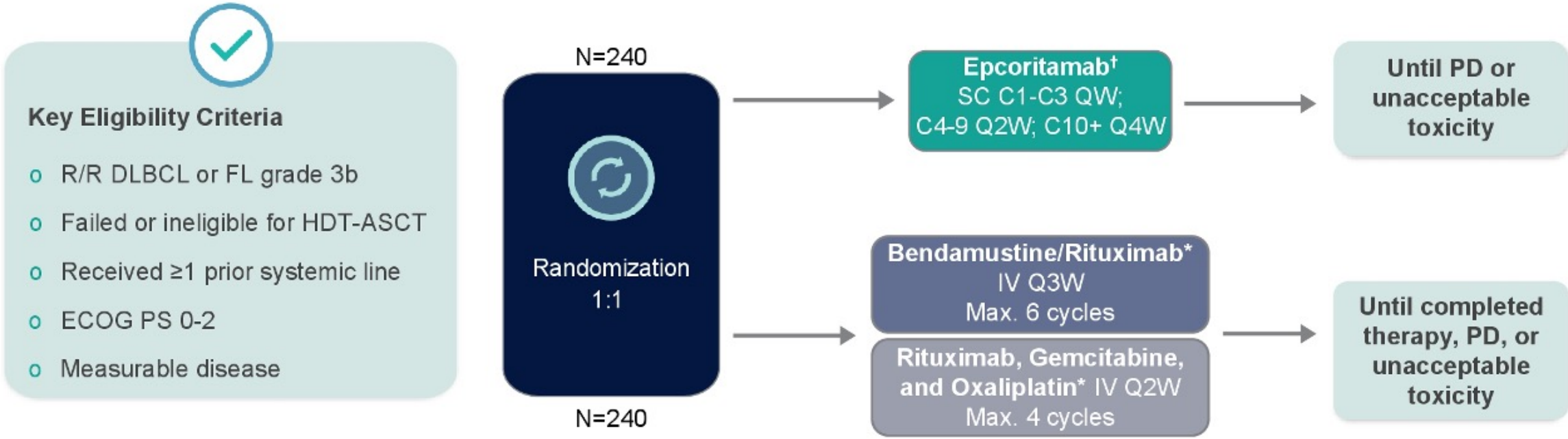
Response, n (%)[a]	Total n=25
Overall response	23 (92)
CMR	15 (60)

CMR = complete metabolic response; PMR = partial metabolic response; SD = stable disease; PD = progressive disease; AE = adverse event

Brody J et al. ASCO 2022;Abstract 7527. Brody J et al. SOHO 2022;Abstract ABCL-439.

RTP RESEARCH TO PRACTICE

EPCORE DLBCL-1 Pivotal Phase III Trial Design



Primary Endpoint: Overall Survival
Key Secondary Endpoints: ORR, CR, PFS, DOR and TTR

PD = progressive disease; ORR = overall survival; CR = complete response; PFS = progression-free survival; DOR = duration of response; TTR = time to response

Thieblemont C et al. ASCO 2022;Abstract TPS7569.

LOTIS-9 Phase II Study Design

Eligibility
- Stage I-IV DLBCL
- No prior therapy for DLBCL
- No clinically significant third space fluid accumulation

Patients will be followed for up to 5 years

Cohort A:
unfit[a] patients

Target enrollment, n = 40

Lonca-R:
Lonca IV Q3W 0.15 mg/kg for cycles 1 and 2, then 0.075 mg/kg for 3 cycles[c]
+
Rituximab IV[c]:
375 mg/m² for cycles 1-3

CR → **Lonca-R: cycle 4[e]**

PR → **Lonca-R: cycles 4-6[e]**

Cohort B:
frail[b] or patients with ≥1 cardiac comorbidity

Target enrollment, n = 40

Lonca-R:
Lonca IV Q3W 0.15 mg/kg for cycles 1 and 2, then 0.075 mg/kg for 3 cycles
+
Rituximab IV[d]:
375 mg/m² for cycles 1-3

CR → **Lonca-R: cycle 4[e]**

PR/SD → **Lonca-R: cycles 4-6[e]**

End of treatment

PRIMARY ENDPOINTS

- Cohort A: CR rate (2014 Lugano classification)
- Cohort B: CR rate, tolerability (number of patients who completed 4 cycles/total number of patients)

KEY SECONDARY ENDPOINTS

- ORR (2014 Lugano classification), 2-year PFS, 3-year OS, DOR, frequency and severity of AEs and SAEs, changes from baseline in safety laboratory variables, vital signs, physical examinations, ECOG PS, PK/PD parameters[f], PROs[g]

Westin J et al. SOHO 2022;Abstract ABCL-272.

Follicular Lymphoma

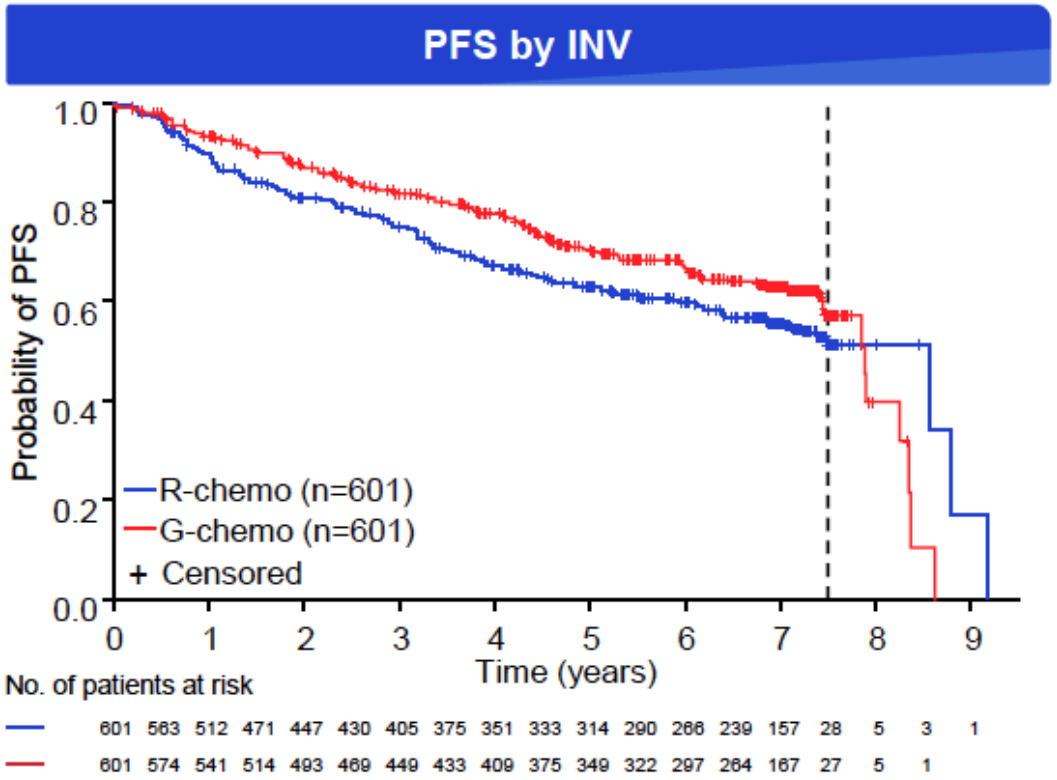
Obinutuzumab plus chemotherapy demonstrates long-term benefit over rituximab plus chemotherapy in patients with previously untreated follicular lymphoma: final analysis of the GALLIUM study

William Townsend,[1] Wolfgang Hiddemann,[2] Christian Buske,[3] Guillaume Cartron,[4] David Cunningham,[5] Martin JS Dyer,[6] John G Gribben,[7] Elizabeth Phillips,[8] Martin Dreyling,[2] John F Seymour,[9] Andrew Grigg,[10] Judith Trotman,[11] Tong-Yu Lin,[12] Xiao-Nan Hong,[13] Dirk Kingbiel,[14] Tina G Nielsen,[14] Andrea Knapp,[14] Michael Herold,[15] Robert Marcus[16]

[1]Cancer Research UK and UCL Cancer Trials Centre, University College Hospitals London, London, United Kingdom; [2]Ludwig-Maximilians-University Hospital Munich, Munich, Germany; [3]Universitätsklinikum Ulm, Ulm, Germany; [4]CHU Montpellier, Montpellier, France; [5]Royal Marsden Hospital, Sutton, United Kingdom; [6]Ernest and Helen Scott Haematological Research Institute, University of Leicester, Leicester, United Kingdom; [7]Queen Mary, University of London, St Bartholomew's Hospital, London, United Kingdom; [8]University of Manchester, The Christie Hospital and National Institutes of Health Research Manchester Biomedical Research Centre, Manchester, United Kingdom; [9]Peter MacCallum Cancer Centre, the Royal Melbourne Hospital, and University of Melbourne, Melbourne, Australia; [10]Austin Hospital, Austin, Australia; [11]Concord Repatriation General Hospital, University of Sydney, Concord, Australia; [12]Sun Yat-Sen University Cancer Centre, State Key Laboratory of Oncology in South China, and Collaborative Innovation Centre for Cancer Medicine, Guangzhou, China; [13]Fudan University Shanghai Cancer Centre, Shanghai, China; [14]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [15]HELIOS-Klinikum Erfurt, Erfurt, Germany; [16]Kings College Hospital, London, United Kingdom*

EHA 2022;Abstract S206.

GALLIUM Final Analysis: PFS Benefit After 8-Year Follow-Up



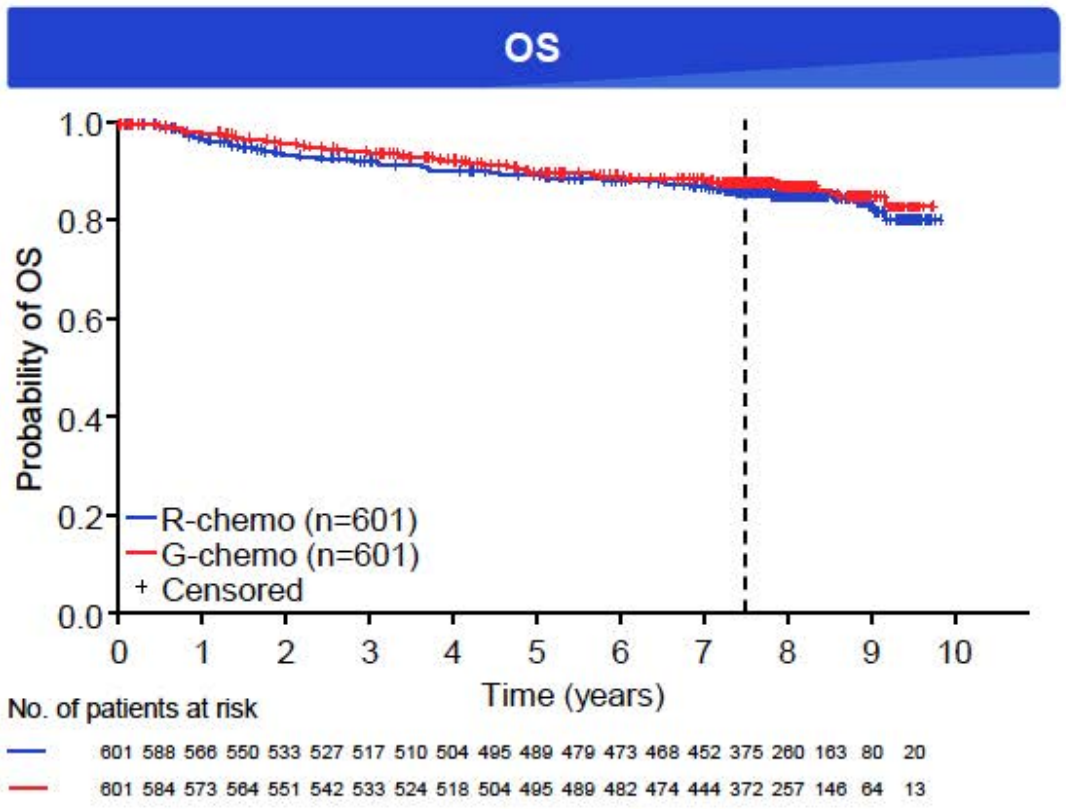
KM estimates became unreliable beyond 7.5 years, due to low numbers of patients at risk[1]

Median observation time: 7.9 (0.0–9.8) years

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

Townsend W et al. EHA 2022;Abstract S205.

GALLIUM Final Analysis: Overall Survival



OS	G-chemo (n=601)	R-chemo (n=601)
Patients with event, n (%)	76 (12.6)	86 (14.3)
7-year OS, % (95% CI)	88.5 (85.6–90.9)	87.2 (84.1–89.7)
HR (95% CI)*	0.86 (0.63–1.18)	
P-value	0.36	

- G-chemo: 4% died due to PD, 4% due to AEs†
- R-chemo: 6% died due to PD, 5% due to AEs†

Townsend W et al. EHA 2022;Abstract S205.

clinical trial updates

Six-Year Results From RELEVANCE: Lenalidomide Plus Rituximab (R^2) Versus Rituximab-Chemotherapy Followed by Rituximab Maintenance in Untreated Advanced Follicular Lymphoma

Franck Morschhauser, MD, PhD[1]; Loretta Nastoupil, MD[2]; Pierre Feugier, MD, PhD[3]; Jean-Marc Schiano de Colella, MD[4]; Hervé Tilly, MD[5]; Maria Lia Palomba, MD[6]; Emmanuel Bachy, MD, PhD[7]; Christophe Fruchart, MD[8]; Edward N. Libby, MD[9]; Rene-Olivier Casasnovas, MD[10]; Ian W. Flinn, MD, PhD[11]; Corinne Haioun, MD[12]; Hervé Maisonneuve, MD[13]; Loic Ysebaert, MD, PhD[14]; Nancy L. Bartlett, MD[15]; Kamal Bouabdallah, MD[16]; Pauline Brice, MD[17]; Vincent Ribrag, MD[18]; Steven Le Gouill, MD, PhD[19]; Nicolas Daguindau, MD[20]; Stéphanie Guidez, MD[21]; Gian Matteo Pica, MD[22]; Alejandro Martín García-Sancho, MD, PhD[23]; Armondo López-Guillermo, MD[24]; Jean-François Larouche, MD[25]; Kiyoshi Ando, MD[26]; Maria Gomes da Silva, MD, PhD[27]; Marc André, MD[28]; Wu Kalung, MD[29]; Laurie H. Sehn, MD, MPH[30]; Koji Izutsu, MD, PhD[31]; Guillaume Cartron, MD, PhD[32]; Argyrios Gkasiamis, MD[33]; Russell Crowe, MA[33]; Luc Xerri, MD, PhD[4]; Nathan H. Fowler, MD[2]; and Gilles Salles, MD[6]

J Clin Oncol 2022;40(28):3239-45.

RELEVANCE 6-Year Follow-Up: Coprimary Endpoints of Response and PFS by IRC

Variable	R² (n = 513)	R-Chemo (n = 517)	P
Response and PFS Independent Review Committee Review			
Overall response, No. (%)	313 (61)	338 (65)	
Complete response + complete response unconfirmed, No. (%; 95% CI)	247 (48; 44 to 53)	276 (53; 49 to 58)	.10
Complete response, No. (%)	142 (28)	169 (33)	
Complete response unconfirmed, No. (%)	105 (21)	107 (21)	
Partial response, No. (%)	66 (13)	62 (12)	
Stable disease, No. (%)	2 (0.4)	0	
PD/death, No. (%)	89 (17)	78 (15)	
Not evaluated/not done/missing, No. (%)	109 (21)	101 (20)	
PFS at 6 years, % (95% CI)	60 (55 to 64)	59 (54 to 64)	
HR (95% CI)	1.03 (0.84 to 1.27)		.78

Morschhauser F et al. *J Clin Oncol* 2022;40(28):3239-45.

RTP RESEARCH TO PRACTICE

original report

AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma

John P. Leonard, MD[1]; Marek Trneny, MD[2]; Koji Izutsu, MD[3]; Nathan H. Fowler, MD[4]; Xiaonan Hong, MD[5]; Jun Zhu, PhD[6]; Huilai Zhang, MD[7]; Fritz Offner, MD, PhD[8]; Adriana Scheliga, MD[9]; Grzegorz S. Nowakowski, MD[10]; Antonio Pinto, MD[11]; Francesca Re, MD[12]; Laura Maria Fogliatto, MD, PhD[13]; Phillip Scheinberg, MD[14]; Ian W. Flinn, MD, PhD[15]; Claudia Moreira, MD[16]; José Cabeçadas, MD[17]; David Liu, MD, PhD[18]; Stacey Kalambakas, MD[18]; Pierre Fustier, PhD[19]; Chengqing Wu, PhD[18]; and John G. Gribben, MD, DSc[20]; for the AUGMENT Trial Investigators

J Clin Oncol 2019;37(14):1188-99.

AUGMENT: Efficacy of R^2 for FL

	Lenalidomide + rituximab (n = 147)	Placebo + rituximab (n = 148)	HR (*p*-value)
IRC-assessed best response			
ORR	80%	55%	NA (<0.0001)
CR	51%	29%	NA (0.0040)
PR	46%	36%	NR
IRC-assessed median PFS	39.4 mo	14.9 mo	0.40 (<0.0001)
2-year OS probability	95%	86%	0.45 (0.02)

Leonard JP et al. *J Clin Oncol* 2019;37(14):1188-99.

RTP RESEARCH TO PRACTICE

FDA Accelerated Approvals of CAR T-Cell Therapies for Relapsed or Refractory Follicular Lymphoma

Tisagenlecleucel – 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."

Axicabtagene ciloleucel – March 5, 2021

"The Food and Drug Administration granted accelerated approval to axicabtagene ciloleucel for adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. Approval in FL was based on a single-arm, open-label, multicenter trial (ZUMA-5; NCT03105336) that evaluated axicabtagene ciloleucel, a CD19-directed chimeric antigen receptor (CAR) T cell therapy, in adult patients with relapsed or refractory FL after two or more lines of systemic therapy, including the combination of an anti-CD20 monoclonal antibody and an alkylating agent."

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tisagenlecleucel-relapsed-or-refractory-follicular-lymphoma; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-axicabtagene-ciloleucel-relapsed-or-refractory-follicular-lymphoma

ASH 2021;Abstract 131.

Efficacy of Tisagenlecleucel in Adult Patients with High-Risk Relapsed/Refractory Follicular Lymphoma: Subgroup Analysis of the Phase II ELARA Study

Catherine Thieblemont,[1] Michael Dickinson,[2] Joaquin Martinez-Lopez,[3] Arne Kolstad,[4] Jason P. Butler,[5] Monalisa Ghosh,[6] Leslie L. Popplewell,[7] Julio C. Chavez,[8] Emmanuel Bachy,[9] Koji Kato,[10] Hideo Harigae,[11] Marie José Kersten,[12] Charalambos Andreadis,[13] Peter A. Riedell,[14] P. Joy Ho,[15] José Antonio Pérez-Simón,[16] Andy I. Chen,[17] Loretta J. Nastoupil,[18] Bastian von Tresckow,[19] Andrés José María Ferreri,[20] Takanori Teshima,[21] Piers EM Patten,[22] Joseph P. McGuirk,[23] Andreas Petzer,[24] Fritz Offner,[25] Andreas Viardot,[26] Pier Luigi Zinzani,[27] Ram Malladi,[28] Aiesha Zia,[29] Chiara Lobetti Bodoni,[29] Aisha Masood,[30] Stephen J. Schuster,[31] Nathan H. Fowler,[32] Martin H. Dreyling,[33]

[1]Department of Hemato-Oncology, Saint Louis Hospital, Paris, France; [2]Department of Clinical Haematology, Peter MacCallum Cancer Centre and The Royal Melbourne Hospital, Melbourne, Australia; [3]Centro de Investigación Biomédica en Red Cáncer (CIBERONC), Hospital Universitario 12 de Octubre, Complutense University, CNIO, Madrid, Spain; [4]Oslo University Hospital Radiumhospitalet, Oslo, Norway; [5]Royal Brisbane and Women's Hospital, Brisbane, Australia; [6]Michigan Medicine University of Michigan, Ann Arbor, MI, USA; [7]Department of Hematology/HCT, City of Hope National Medical Centre, Duarte, CA, USA; [8]Division of Malignant Hematology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; [9]Hospices Civils de Lyon and Université Claude Bernard, Pierre-Bénite, France; [10]Kyushu University Hospital, Fukuoka, Japan; [11]Tohoku University Hospital, Sendai, Japan; [12]Amsterdam UMC, Department of Hematology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands; [13]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA, USA; [14]The University of Chicago Medical Center, Chicago, IL, USA; [15]Royal Prince Alfred Hospital and Department of Medicine, The University of Sydney, Sydney, Australia; [16]Department of Hematology, Hospital Universitario Virgen del Rocio, Instituto de Biomedicina de Sevilla (IBIS)/CSIC/Universidad de Sevilla, Spain, Sevilla, Spain; [17]Oregon Health and Science University, Portland, OR, USA; [18]Department of Lymphoma and Myeloma, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [19]University of Cologne, Cologne, Germany; [20]Lymphoma Unit, Department of Onco-Haematology, IRCCS San Raffaele Scientific Institute, Milano, Italy; [21]Department of Hematology, Hokkaido University Hospital, Sapporo, Japan; [22]Department of Haematological Medicine, King's College Hospital, London, UK; [23]Division of Hematologic Malignancies & Cellular Therapeutics, University of Kansas Medical Center, Kansas City, KS, USA; [24]Internal Medicine I, Ordensklinikum Linz GmbH Elisabethinen, Linz, Austria; [25]University Hospital Ghent, Gent, Belgium; [26]Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany; [27]Institute of Hematology "L. e A. Seràgnoli", University of Bologna, Bologna, Italy; [28]Cambridge University Hospitals NHS Foundation Trust, Cambridge, CA, UK; [29]Novartis Pharma AG, Basel, Switzerland; [30]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [31]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [32]Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [33]Klinikum Der Universität München-Grosshadern, Medizinische Klinik und Poliklinik III, München, Germany

ELARA: Efficacy Analysis with Extended Follow-Up

- As of March 29, 2021, 97 patients received tisagenlecleucel and 94 were evaluable for efficacy
- CR rates are consistent and durable for the interim, primary analyses, and this extended follow-up analysis
- Complete response correlated with durability and prolonged PFS
  - **Among patients who achieved CR, 12-month PFS was 85.5% (95% CI, 74-92) and estimated DOR rate at 9 months was 86.5% (95% CI, 75-93)**

Efficacy Results of Extended Follow-up Analysis

Endpoint	% (95% CI)
ORR[a]	**86.2** (77.5-92.4)
CRR[a]	**69.1** (58.8-78.3)
12-mo PFS	**67.0** (56.0-75.8)
9-mo DOR	**76.0** (64.6-84.2)

[a]ORR and CRR were comparable with the primary efficacy analysis (ORR 86.2% and CRR 66.0%).

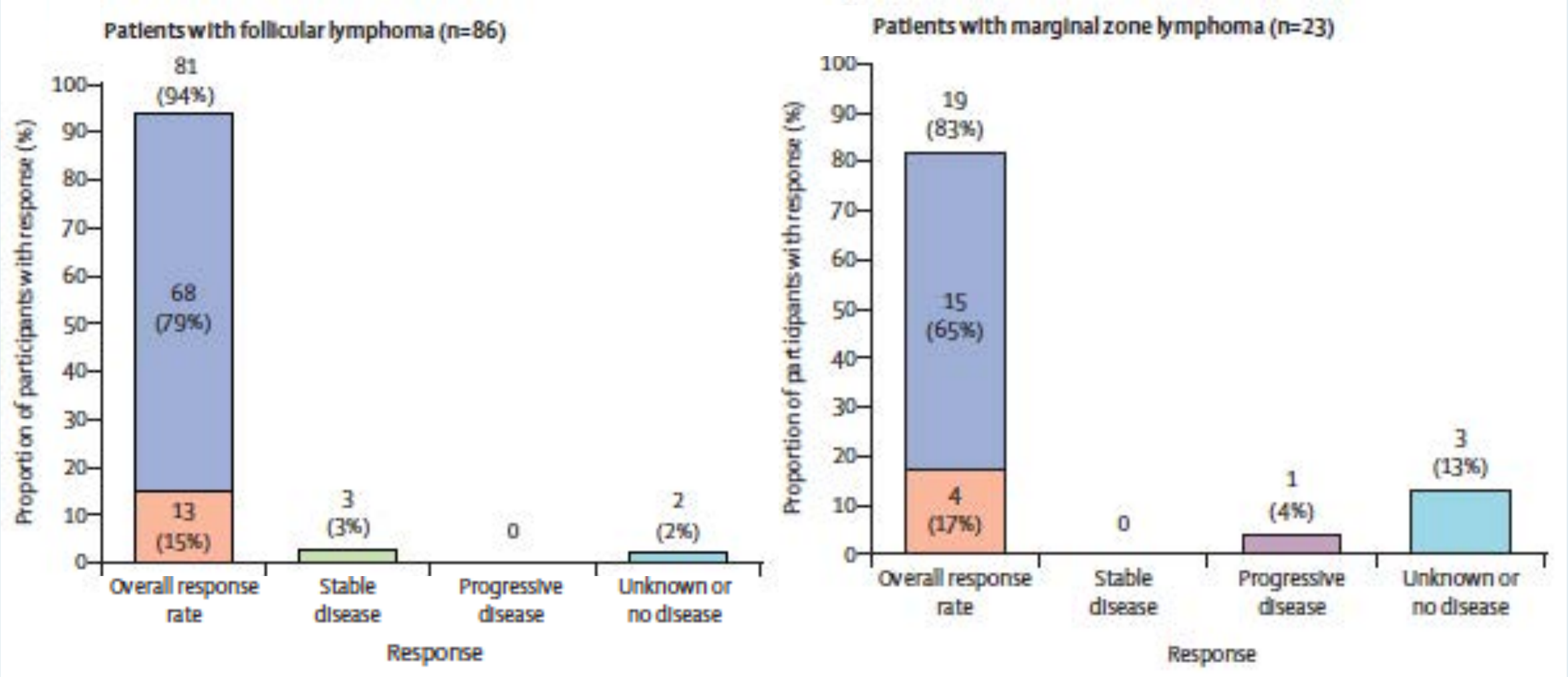
Thieblemont C et al. ASH 2021;Abstract 131.

Lancet Oncol 2022;23(1):91-103.

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

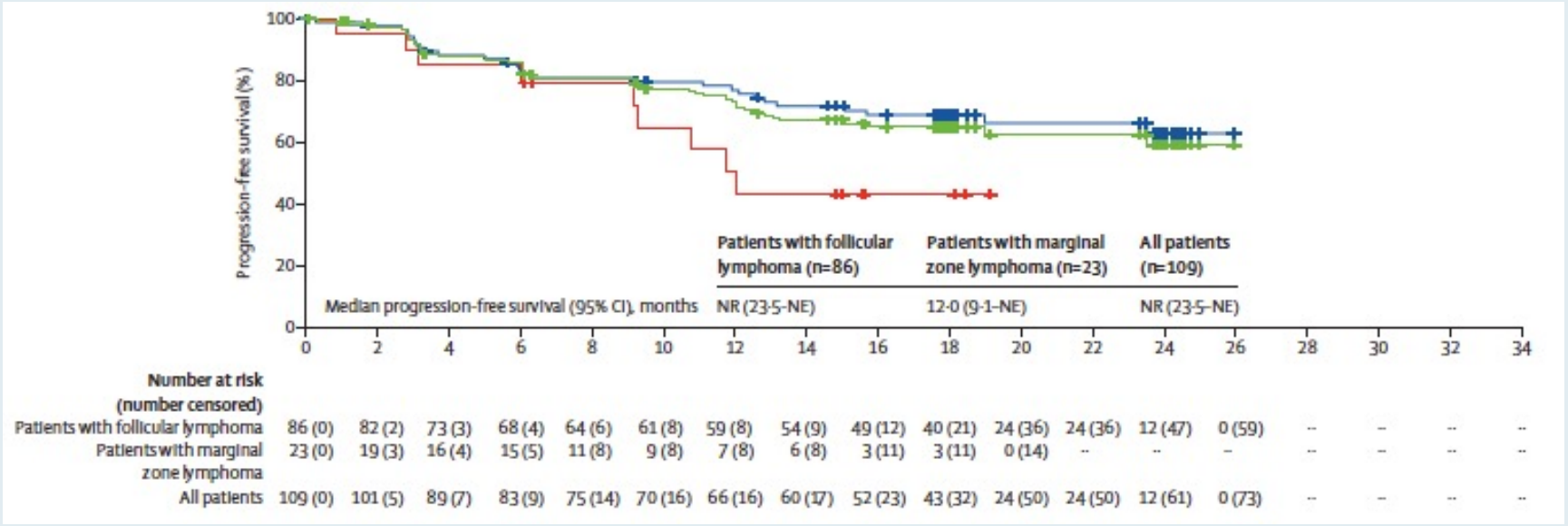
Caron A Jacobson, Julio C Chavez, Alison R Sehgal, Basem M William, Javier Munoz, Gilles Salles, Pashna N Munshi, Carla Casulo, David G Maloney, Sven de Vos, Ran Reshef, Lori A Leslie, Ibrahim Yakoub-Agha, Olalekan O Oluwole, Henry Chi Hang Fung, Joseph Rosenblatt, John M Rossi, Lovely Goyal, Vicki Plaks,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

ZUMA-5: Overall Response Rate (ORR) by Central Review

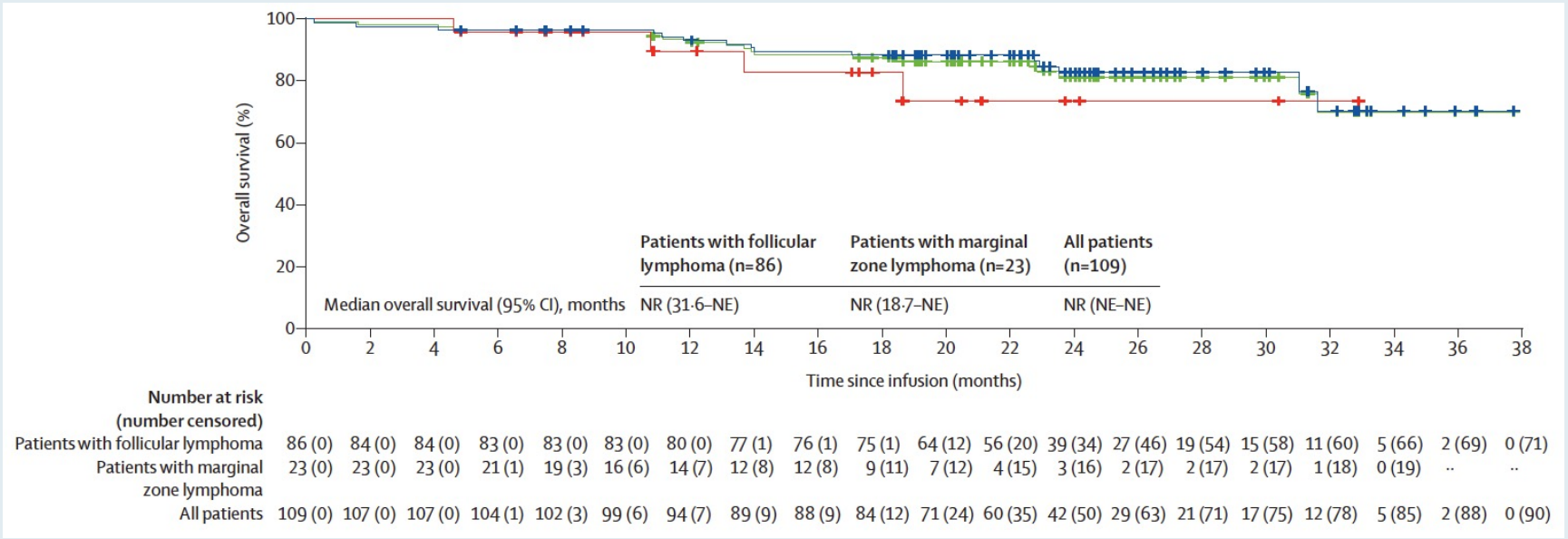


Jacobson CA et al. *Lancet Oncol* 2022;23(1):91-103.

ZUMA-5: Progression-Free and Overall Survival



PFS



OS

Jacobson CA et al. *Lancet Oncol* 2022;23(1):91-103.

RTP RESEARCH TO PRACTICE

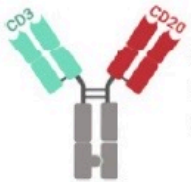
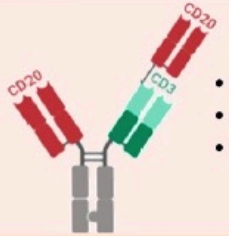
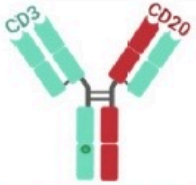
ZUMA-5: Safety Summary

Select treatment-emergent AEs	Grade 1-2	Grade 3	Grade 4
Anemia	14%	24%	1%
Hypophosphatemia	7%	11%	0
Neutropenia	3%	10%	23%
Encephalopathy	11%	9%	0

- Cytokine release syndrome occurred in 121 (82%) of 148 patients (97 [78%] of 124 with follicular lymphoma, 24 [100%] of 24 with marginal zone lymphoma). Most cases were Grade 1 or 2.
- Neurological events occurred in 87 (59%) of 148 patients (70 [56%] of 124 with follicular lymphoma, 17 [71%] of 24 with marginal zone lymphoma). No Grade 5 neurological events occurred.

Jacobson CA et al. *Lancet Oncol* 2022;23(1):91-103.

Structure of Selected Bispecific Antibodies

Bi-Specific Antibody	Targets	Design	Ig Fragment Formats
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
mosunetuzumab	CD20 x CD3		• humanized mouse heterodimeric IgG1-based antibody • monovalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding
glofitamab	$(CD20)_2$ x CD3		• humanized mouse IgG1-based antibody • bivalent CD20 and monovalent CD3ε binding • modified Fc devoid of FcγR and complement binding
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
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

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

Schuster SJ. *Hematol Oncol* 2021;39(S1):113-16.

FDA Grants Priority Review to the CD20 x CD3 Bispecific Antibody Mosunetuzumab for Relapsed/Refractory Follicular Lymphoma

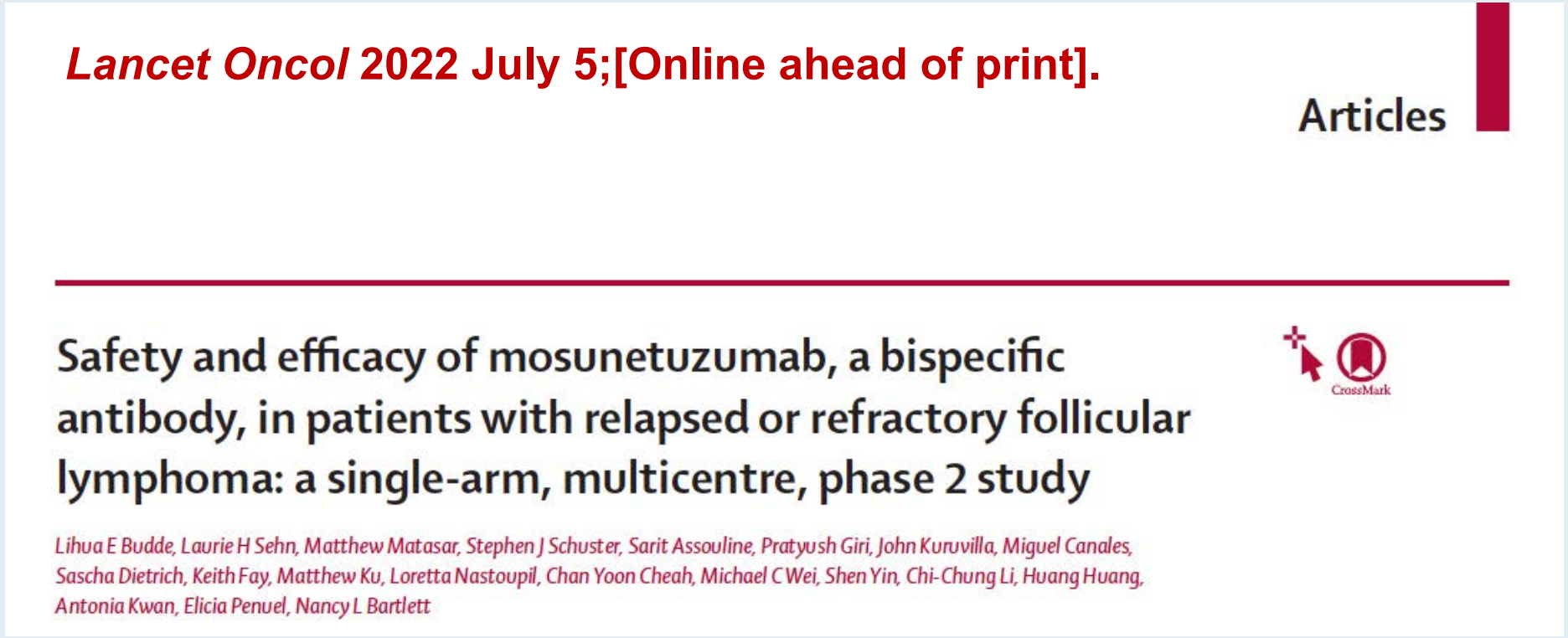
Press Release: July 6, 2022

"The US Food and Drug Administration has accepted the Biologics License Application (BLA) and granted Priority Review for mosunetuzumab, a potential first-in-class CD20xCD3 T-cell engaging bispecific antibody, for the treatment of adults with relapsed or refractory (R/R) follicular lymphoma (FL) who have received at least two prior systemic therapies.

The BLA is based on positive results from the pivotal phase I/II GO29781 study of mosunetuzumab, which showed high complete response (CR) rates, with the majority of responders (57% [95% CI: 49-70]) maintaining responses for at least 18 months, and manageable tolerability in people with heavily pretreated FL."

https://www.globenewswire.com/news-release/2022/07/06/2474498/0/en/FDA-grants-Priority-Review-to-Roche-s-Lunsumio-for-people-with-relapsed-or-refractory-follicular-lymphoma.html

Lancet Oncol 2022 July 5;[Online ahead of print].

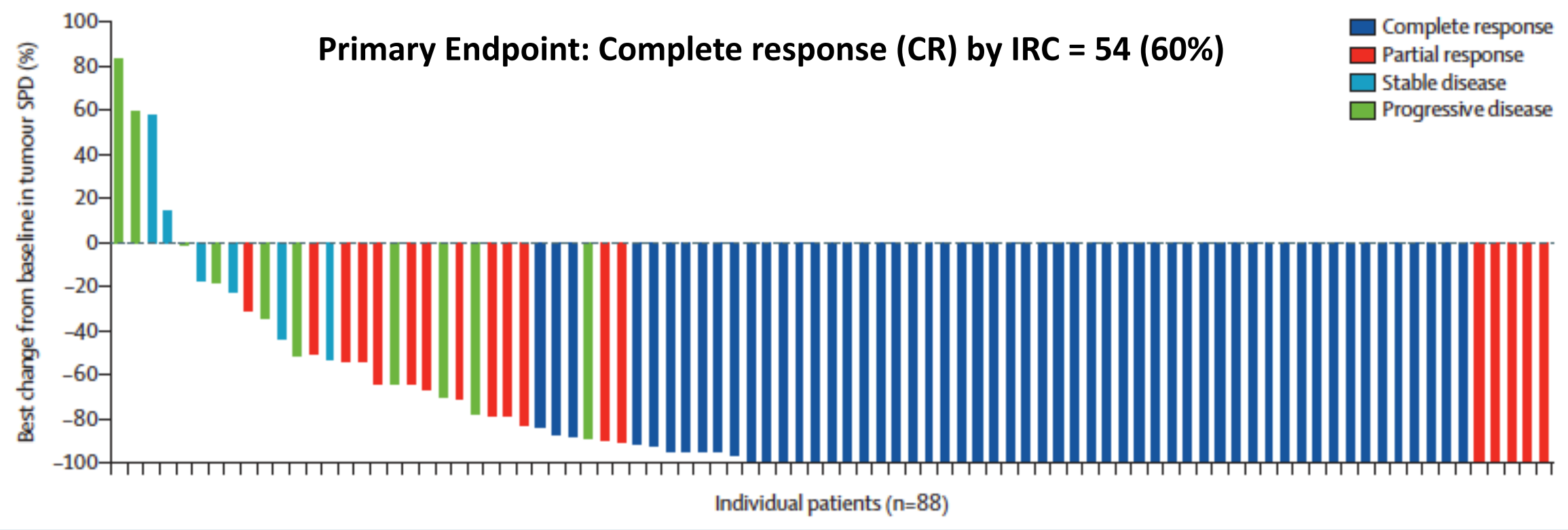


Mosunetuzumab Monotherapy Is an Effective and Well-Tolerated Treatment Option for Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) Who Have Received ≥2 Prior Lines of Therapy: Pivotal Results from a Phase I/II Study

Budde EL et al.
SOHO 2022;Abstract ICBL-249.

RTP RESEARCH TO PRACTICE

Response to Mosunetuzumab Monotherapy in Patients with R/R FL Who Have Received ≥2 Lines of Therapy



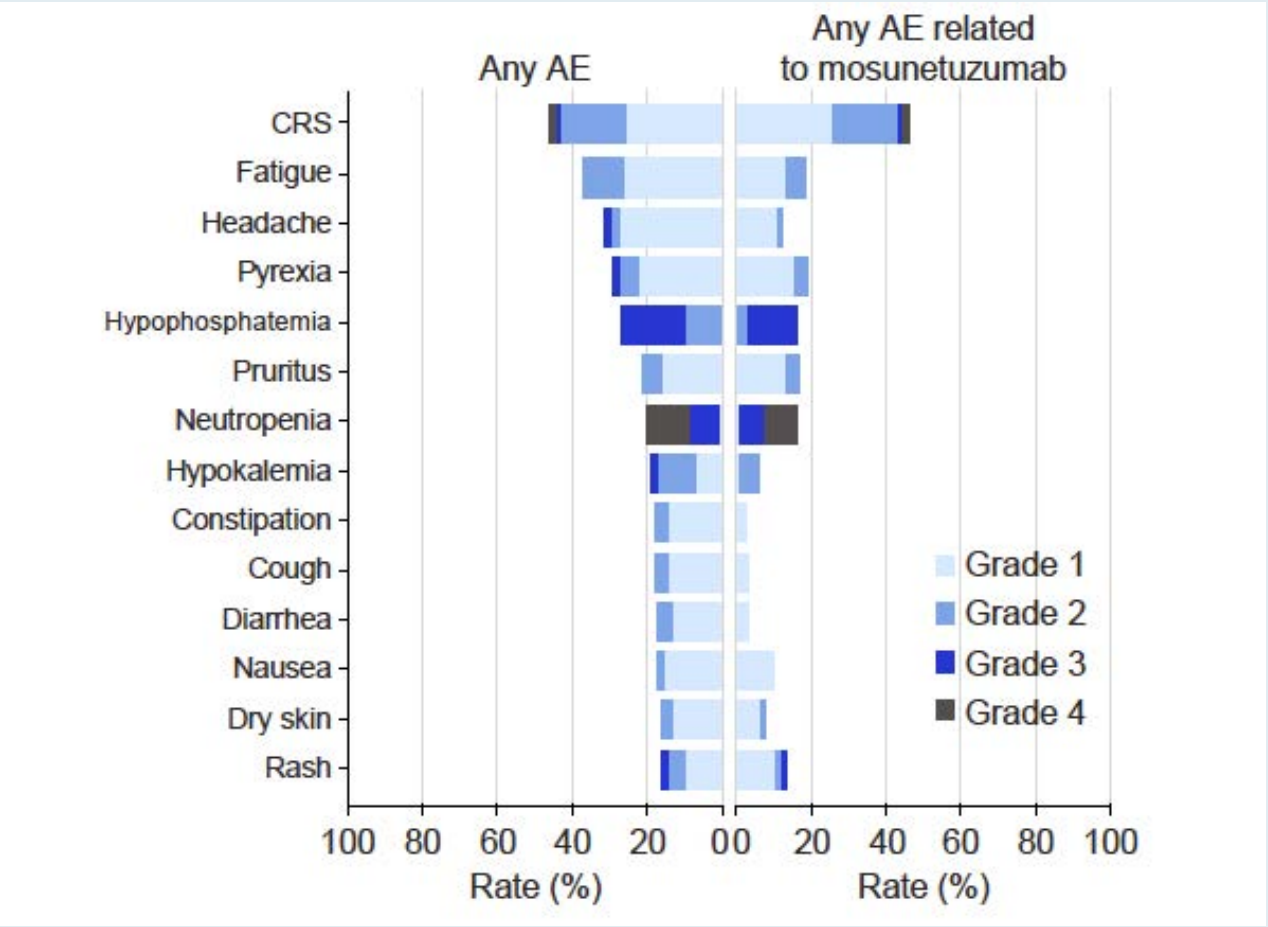
Budde LE et al. *Lancet Oncol* 2022 July 5;[Online ahead of print].

Efficacy Summary for Mosunetuzumab Monotherapy in Patients with R/R FL Who Have Received ≥2 Lines of Therapy

	Response to mosunetuzumab per IRC (n = 90)
Objective response rate (ORR)	72 (80%)
CR	54 (60%)
Median duration of response	22.8 mo
Median duration of response in patients with CR	22.8 mo
Median PFS	17.9 mo
Median OS	Not reached

Budde LE et al. *Lancet Oncol* 2022 July 5;[Online ahead of print]; Budde LE et al. SOHO 2022;Abstract IBCL-249.

Select Adverse Events Associated with Mosunetuzumab Monotherapy in Patients with R/R FL Who Have Received ≥2 Lines of Therapy



	N=90
Any grade CRS, n (%)*	40 (44.4)
Grade 1	23 (25.6)
Grade 2	15 (16.7)
Grade 3	1 (1.1)
Grade 4	1 (1.1)†
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–23.7)
C1D15	26.6 (0.1–390.9)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management, n (%)	10 (11.1)
Tocilizumab for CRS management, n (%)	7 (7.8)

*Assessed using American Society for Transplantation and Cellular Therapy (ASTCT) criteria;[10] †patient with leukemic-phase FL.

Budde LE et al. SOHO 2022;Abstract IBCL-249.

Lancet Oncol 2021;398(10306):1157-69.

Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study

Martin Hutchings, Rogier Mous, Michael Roost Clausen, Peter Johnson, Kim M Linton, Martine E D Chamuleau, David John Lewis, Anna Sureda Balari, David Cunningham, Roberto S Oliveri, Brian Elliott, Dena DeMarco, Ada Azaryan, Christopher Chiu, Tommy Li, Kuo-mei Chen, Tahamtan Ahmadi, Pieternella J Lugtenburg

Response Rates with Phase I/II Study Subcutaneous Epcoritamab in Patient Subgroup with R/R FL

	Epcoritamab 0.76-48 mg (n = 10)	Epcoritimab 48 mg (n = 1)
Overall response rate	9 (90%)	0
Complete response	5 (50%)	0
Partial response	4 (40%)	0
Time to response	1.9 mo	NA

Hutchings M et al. *Lancet* 2021;398(10306):1157-69.

Treatment-Emergent Adverse Events with Subcutaneous Epcoritamab in the Full Analysis Population of Patients with R/R FL, DLBCL and MCL (N = 68)

	Grade 1–2	Grade 3	Grade 4
Pyrexia*	43 (63%)	4 (6%)	0
Cytokine release syndrome	40 (59%)	0	0
Injection site reaction	32 (47%)	0	0
Fatigue	26 (38%)	4 (6%)	0
Diarrhoea	18 (26%)	0	0
Hypotension*	17 (25%)	4 (6%)	0
Dyspnoea	16 (24%)	0	1 (1%)
Tachycardia*	14 (21%)	0	0
Anaemia	7 (10%)	9 (13%)	0

*Most pyrexia, hypotension, and tachycardia events were associated with cytokine release syndrome.

Hutchings M et al. *Lancet* 2021;398(10306):1157-69.

RTP RESEARCH TO PRACTICE

Adverse Events of Special Interest with Subcutaneous Epcoritamab in the Full Analysis Population of Patients with R/R FL, DLBCL and MCL

	Epcoritamab dose			Total (n=68)
	≤24 mg (n=53)	48 mg (n=12)	60 mg (n=3)	
Cytokine release syndrome				
Total	30 (57%)	8 (67%)	2 (67%)	40 (59%)
Grade 1	15 (28%)	4 (33%)	1 (33%)	20 (29%)
Grade 2	15 (28%)	4 (33%)	1 (33%)	20 (29%)
Neurological symptoms				
Total	4 (8%)	0	0	4 (6%)
Grade 1	2 (4%)	0	0	2 (3%)
Grade 3	2 (4%)	0	0	2 (3%)
Clinical tumour lysis syndrome				
Total	0	1 (8%)	0	1 (1%)
Grade 3	0	1 (8%)	0	1 (1%)

Hutchings M et al. *Lancet* 2021;398(10306):1157-69.

RTP RESEARCH TO PRACTICE

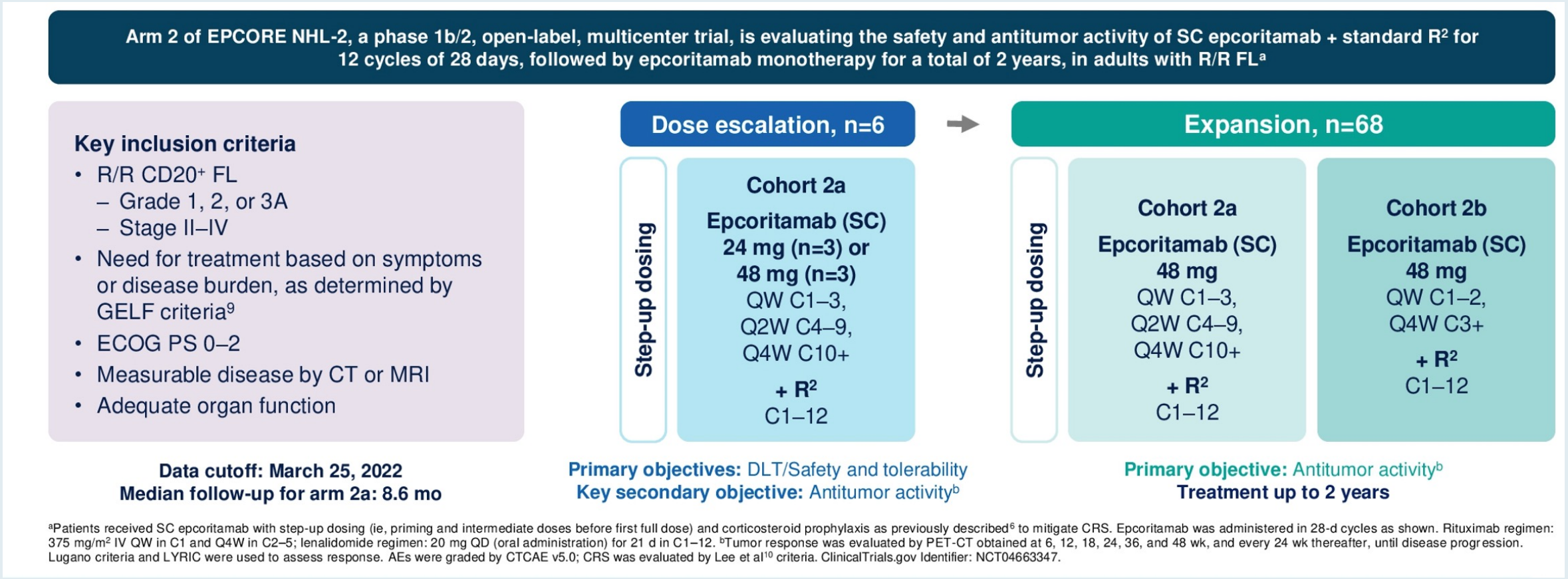
Subcutaneous epcoritamab with rituximab + lenalidomide (R^2) in patients with relapsed or refractory (R/R) follicular lymphoma (FL): update from phase 1/2 trial

Lorenzo Falchi, MD,[1] Sirpa Leppä, MD,[2] Björn E. Wahlin, MD, PhD,[3] Marcel Nijland, MD, PhD,[4] Jacob Haaber Christensen, MD, PhD,[5] Sven de Vos, MD, PhD,[6] Harald Holte, MD, PhD,[7] Kim M. Linton, MBChB, PhD,[8] Aqeel Abbas, MS,[9] Liwei Wang, PhD,[9] Minh Dinh, MD,[10] Brian Elliott, MD,[9] David Belada, MD, PhD[11]

[1]Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Helsinki University Hospital Comprehensive Cancer Center and University of Helsinki, Helsinki, Finland; [3]Karolinska Institutet, Stockholm, Sweden; [4]University Medical Center Groningen and University of Groningen, Groningen, Netherlands; [5]Odense University Hospital, Odense, Denmark; [6]Ronald Reagan University of California Los Angeles Medical Center, Los Angeles, CA, USA; [7]Oslo University Hospital and KG Jebsen Center for B-cell Malignancies, Oslo, Norway; [8]The Christie NHS Foundation Trust and Manchester Cancer Research Centre, Manchester, UK; [9]Genmab, Princeton, NJ, USA; [10]AbbVie, North Chicago, IL, USA; [11]4th Department of Internal Medicine – Hematology, University Hospital and Faculty of Medicine, Hradec Králové, Czech Republic

SOHO 2022;Abstract IBCL-460.

EPCORE NHL-2 Arm 2 Study Design



[a]Patients received SC epcoritamab with step-up dosing (ie, priming and intermediate doses before first full dose) and corticosteroid prophylaxis as previously described[6] to mitigate CRS. Epcoritamab was administered in 28-d cycles as shown. Rituximab regimen: 375 mg/m² IV QW in C1 and Q4W in C2–5; lenalidomide regimen: 20 mg QD (oral administration) for 21 d in C1–12. [b]Tumor response was evaluated by PET-CT obtained at 6, 12, 18, 24, 36, and 48 wk, and every 24 wk thereafter, until disease progression. Lugano criteria and LYRIC were used to assess response. AEs were graded by CTCAE v5.0; CRS was evaluated by Lee et al[10] criteria. ClinicalTrials.gov Identifier: NCT04663347.

Falchi L et al. SOHO 2022;Abstract IBCL-460.

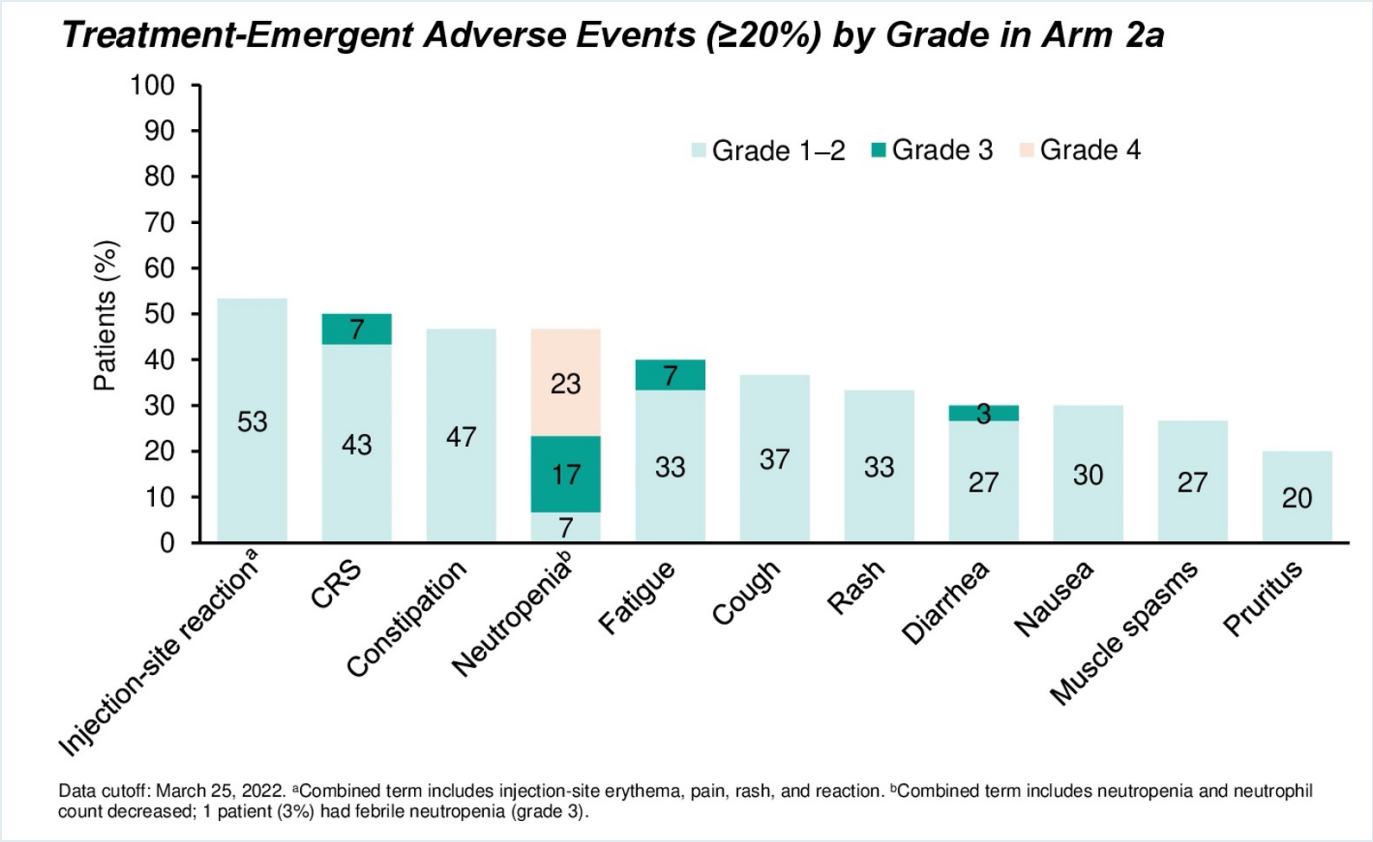
EPCORE NHL-2 Arm 2a: Best Overall Response at Any Time and at 6 Weeks (First Assessment)

Response, n (%)[a]	At any time Arm 2a n=28[b]	At 6 weeks Arm 2a n=27	At 6 weeks Arm 2b n=28
Overall response	28 (100)	25 (93)	26 (93)
CMR	27 (96)	19 (70)	17 (61)
PMR	1 (4)	6 (22)	9 (32)
Stable disease	0	2 (7)	1 (4)
Progressive disease	0	0	1 (4)

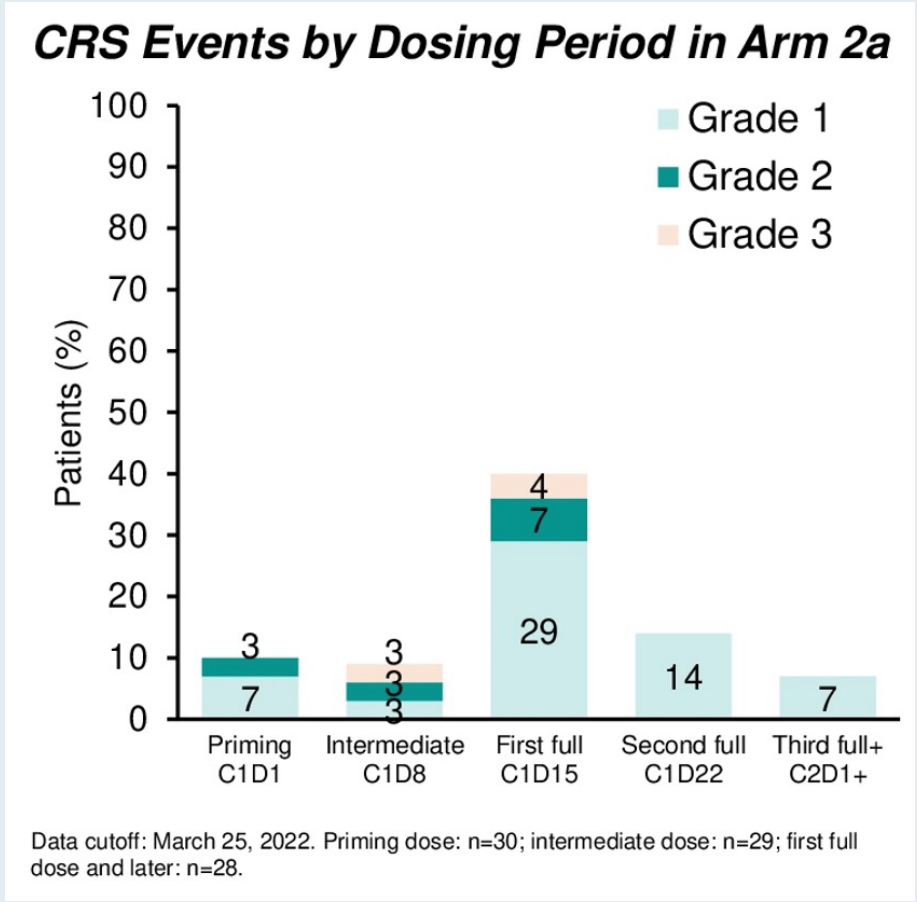
Data cutoff: March 25, 2022. [a]Based on modified response-evaluable population, defined as patients with ≥1 target lesion at baseline and ≥1 postbaseline response evaluation and patients who died within 60 d of first dose. [b]Excludes 2 patients who discontinued before first assessment.

Falchi L et al. SOHO 2022;Abstract IBCL-460.

EPCORE NHL-2 Arm 2a: Adverse Event Summary



Data cutoff: March 25, 2022. [a]Combined term includes injection-site erythema, pain, rash, and reaction. [b]Combined term includes neutropenia and neutrophil count decreased; 1 patient (3%) had febrile neutropenia (grade 3).



Data cutoff: March 25, 2022. Priming dose: n=30; intermediate dose: n=29; first full dose and later: n=28.

Falchi L et al. SOHO 2022;Abstract IBCL-460.

RTP RESEARCH TO PRACTICE

rapid communications

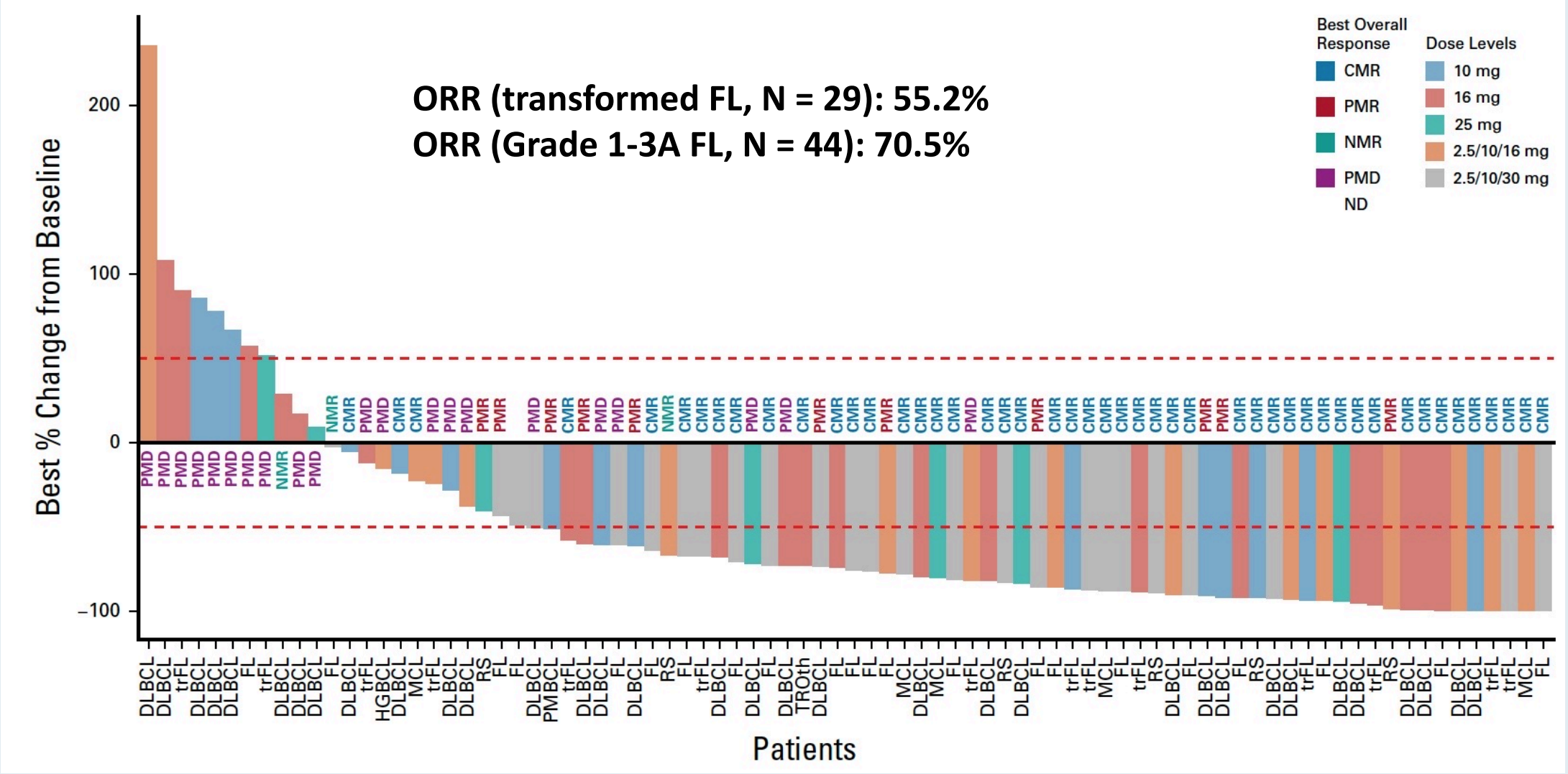
Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell–Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial

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(18):1959-70.

RTP RESEARCH TO PRACTICE

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



Hutchings M et al. *J Clin Oncol* 2021;39(18):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]

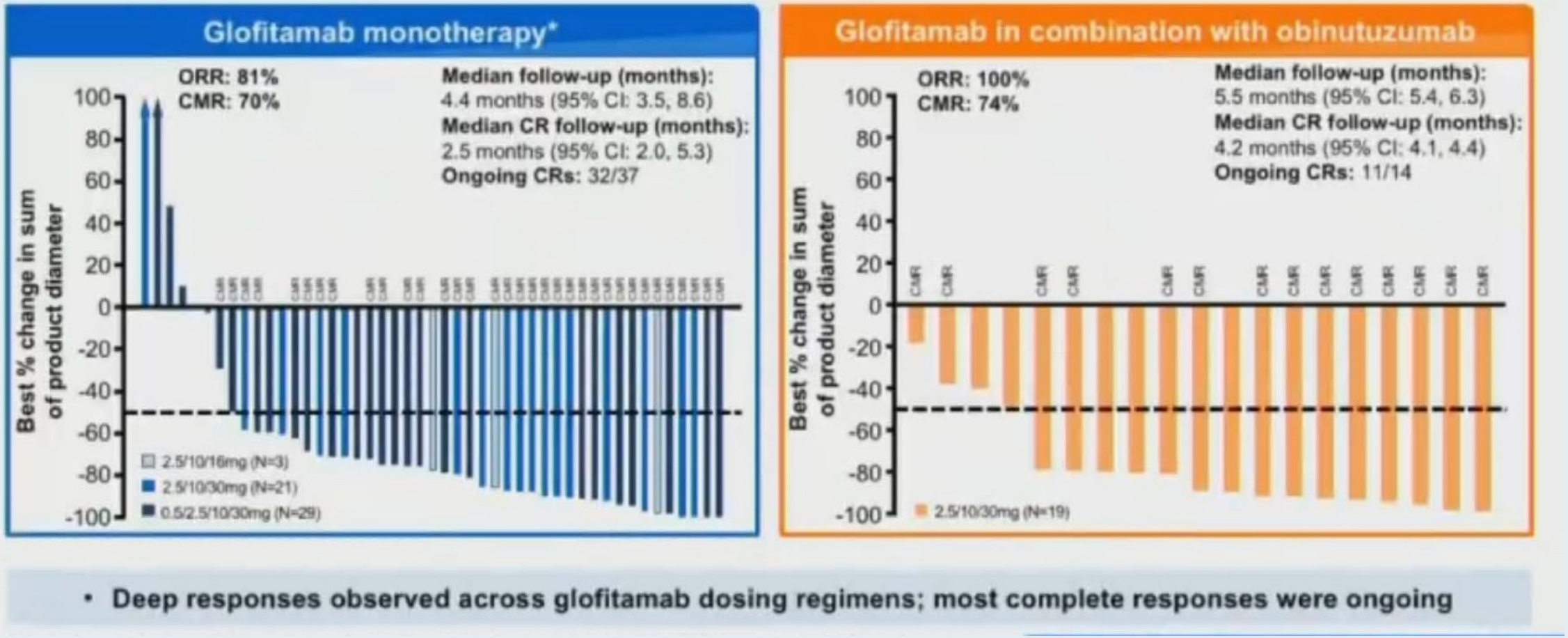
[1]CHU Lille, Service des Maladies du Sang, F-59000 Lille, France; [2]Humanitas University and Humanitas Research Hospital, Milan, Italy; [3]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne, Melbourne, Australia; [4]University of Michigan Medical School, Ann Arbor, 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

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

Morschhauser F et al. ASH 2021;Abstract 128.

RTP RESEARCH TO PRACTICE

Hodgkin Lymphoma

Dana-Farber Cancer Institute

Advanced Stage Hodgkin Lymphoma Initial Therapy in CLL

Ann S. LaCasce, MD, MMSc

October 22, 2022

Dana-Farber
Cancer Institute

Advanced Stage Hodgkin Lymphoma

Systemic therapy in HL

ABVD

Very low risk of infertility

Not stem cell toxic

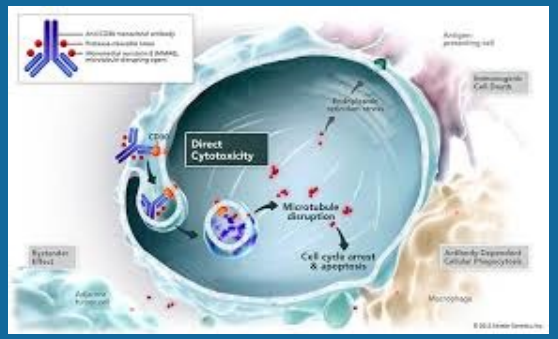
Bleomycin lung toxicity

BEACOPP

Improved PFS compared with ABVD

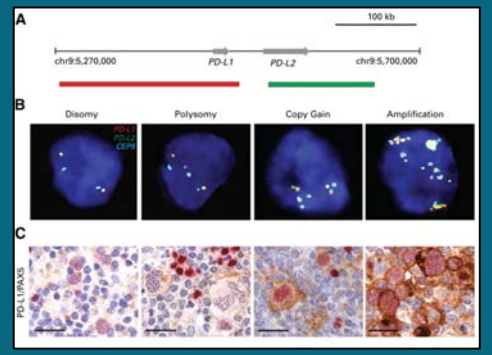
Associated with Infertility/stem cell damage

Brentuximab vedotin



Peripheral neuropathy

PD-1 inhibitors

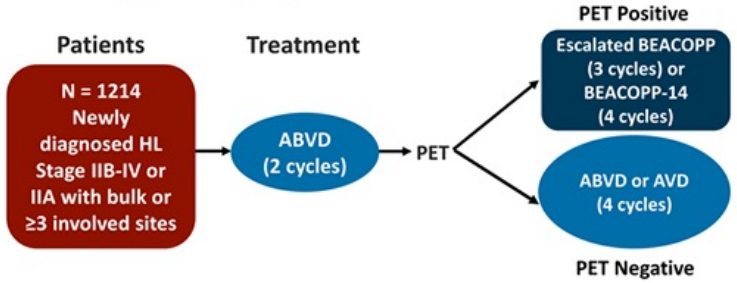


Low rates of irreversible toxicity but rare severe

Roemer et al JCO 2016

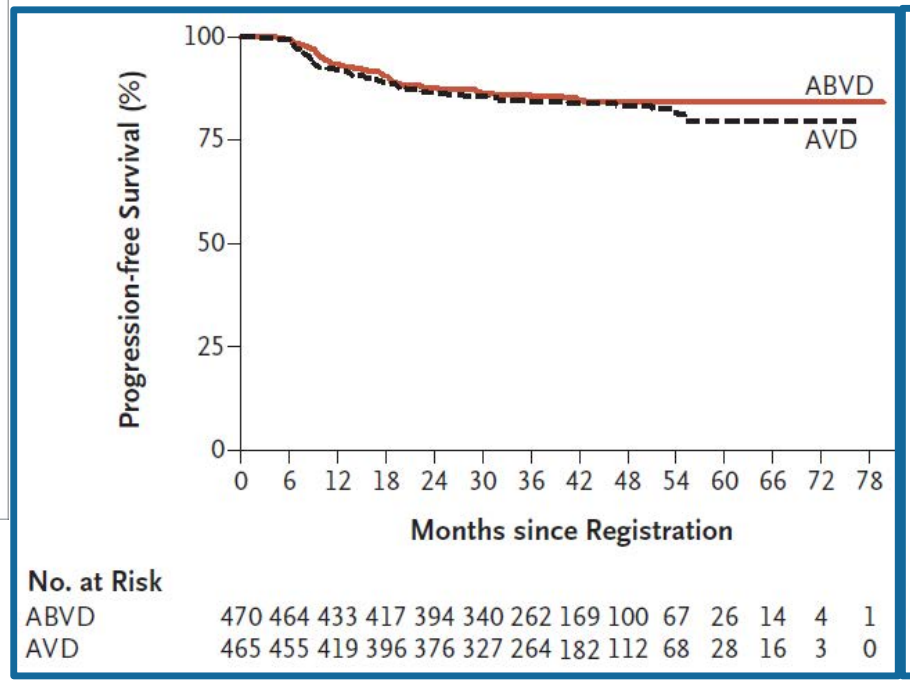
PET adapted therapy in unfavorable II-IV cHL

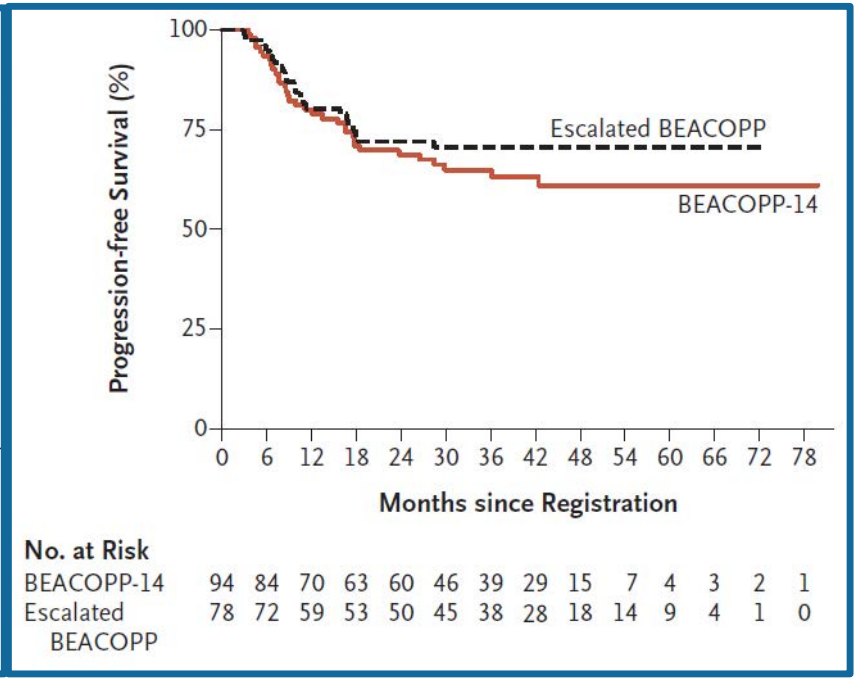
RATHL: Response-adapted Treatment in Hodgkin Lymphoma FDG-PET



Outcomes	ABVD or AVD	eBEACOPP or BEACOPP-14
3 y PFS, %	85	68
3-y OS, %	97	86

Johnson PW, et al. [ICML abstract 008]. *Hematol Oncol*. 2015;33:102-103.[86]

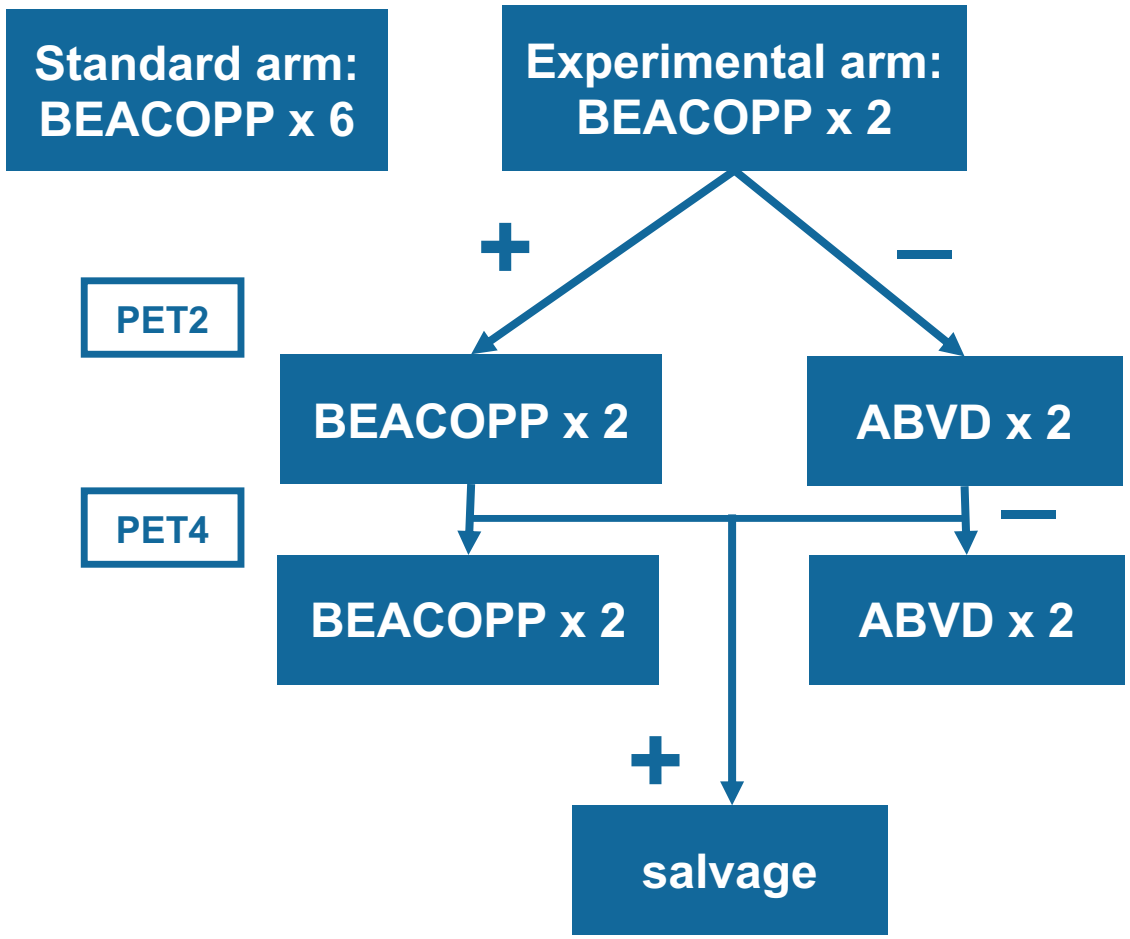


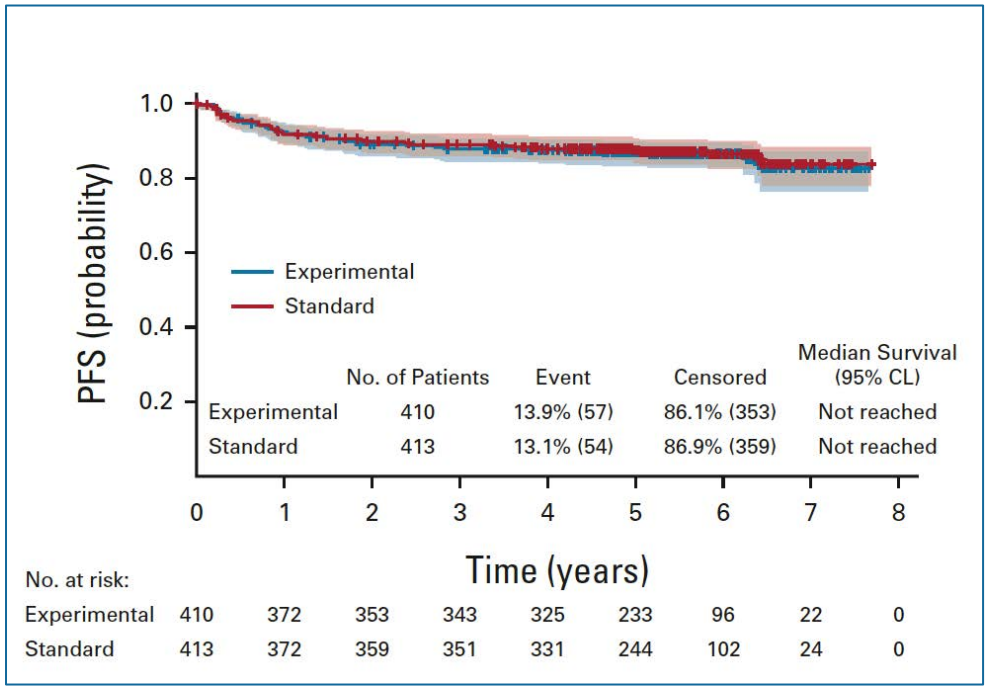


Stage III/IV ≤ 60
3 yr PFS: 82%

Johnson et al. NEJM 2016

PET driven de-escalated approach with favorable outcomes

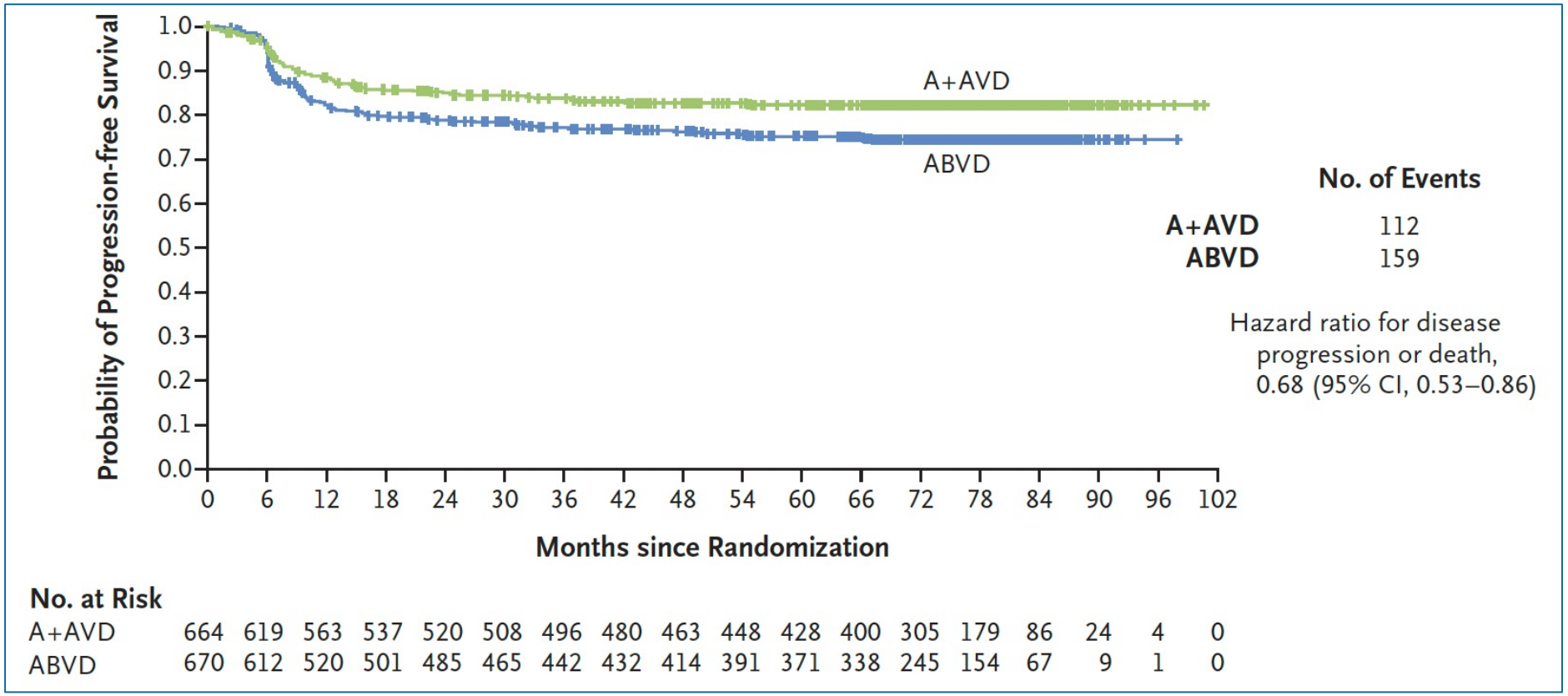




Risk Factors	No. (%)	5-Year PFS, % (95% CI)
PET2/PET4		
PET2–/PET4–	654 (79)	92.3 (89.9 to 94.1)
PET2+/PET4–	62 (7.5)	75.4 (62.5 to 84.4)
PET4+	43 (5.2)	46.5 (31.2 to 60.4)
IPS		
0-2	343 (42)	90.3 (85.8 to 93.4)
≥ 3	475 (58)	82.8 (78.5 to 86.3)

Cassanovas et al. JCO 2021

BV-AVD with improved PFS (7.8% improvement) compared with ABVD with median f/u 6 yrs



Ansell et al. NEJM 2022

BV-AVD with improved OS (4.5% absolute with median f/u 6 yrs)

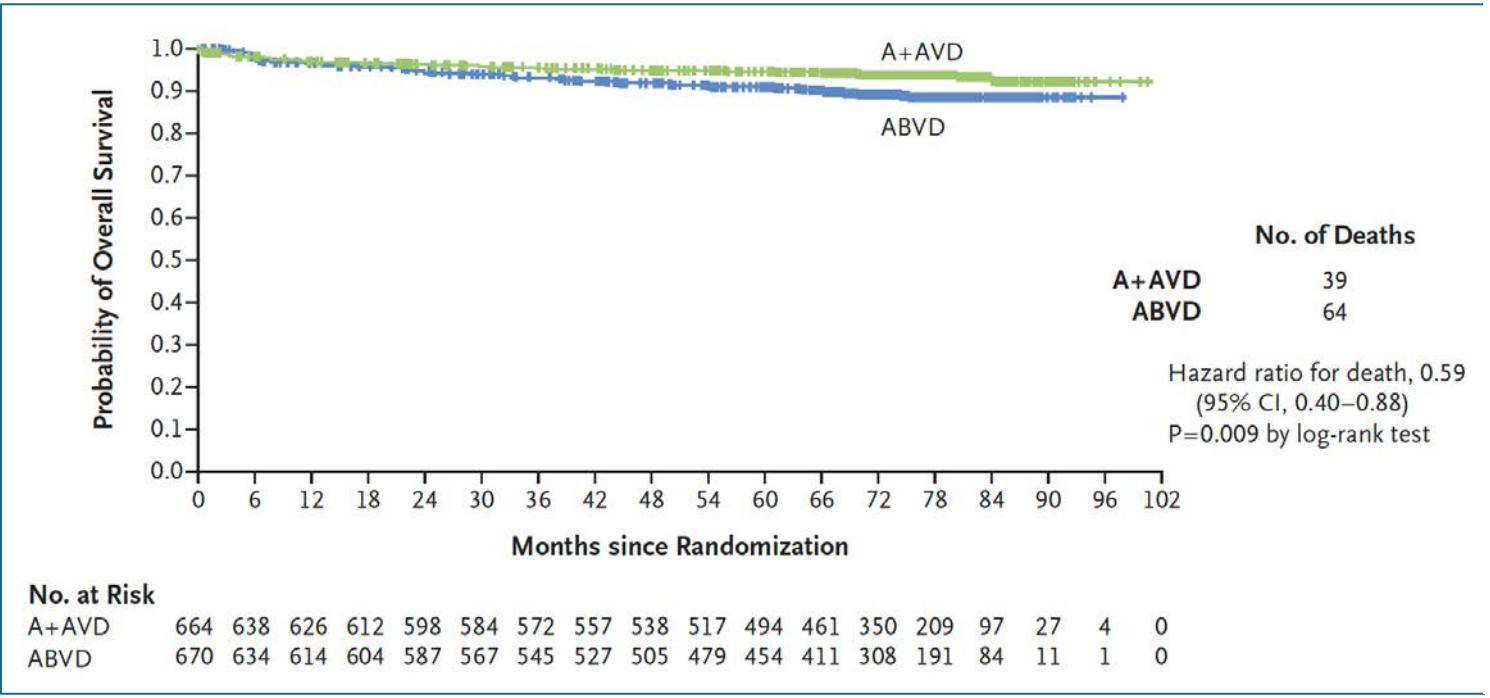


Table 1. Summary of Causes of Death (Safety Population).*

Cause of Death	A+AVD (N=662)	ABVD (N=659)
Any cause — no. (%)	39 (5.9)	64 (9.7)
Hodgkin's lymphoma or complications — no.	32	45
Second cancer — no.	1	11
Other cause — no.	6	8
Unknown cause	1	5†
Accident or suicide	3	0
Covid-19	0	1
Heart failure	1	1
Intracranial hemorrhage	1	0
Lower respiratory tract infection	0	1

Caution: PN and bone pain

Ansell et al. NEJM 2022

Current options for the management of advanced HL

RATHL	BEACOPP	LYSA	BV-AVD
Lower toxicity in PET2- with less bleomycin	Better PFS without OS benefit	Excellent PFS	Moderate improvement in PFS compared with ABVD but with OS benefit.
Escalation to BEACOPP not highly effective	High toxicity and not appropriate for > 60	Limited exposure to BEACOPP for PET2 negative patients	Sequential for elderly
PET2 – patients with lower PFS than other strategies	Inexpensive	Inexpensive	Peripheral neuropathy
Inexpensive			Expensive

Pembrolizumab+AVD in early unfavorable and advanced stage HL

Pembrolizumab x 3

↓

PET

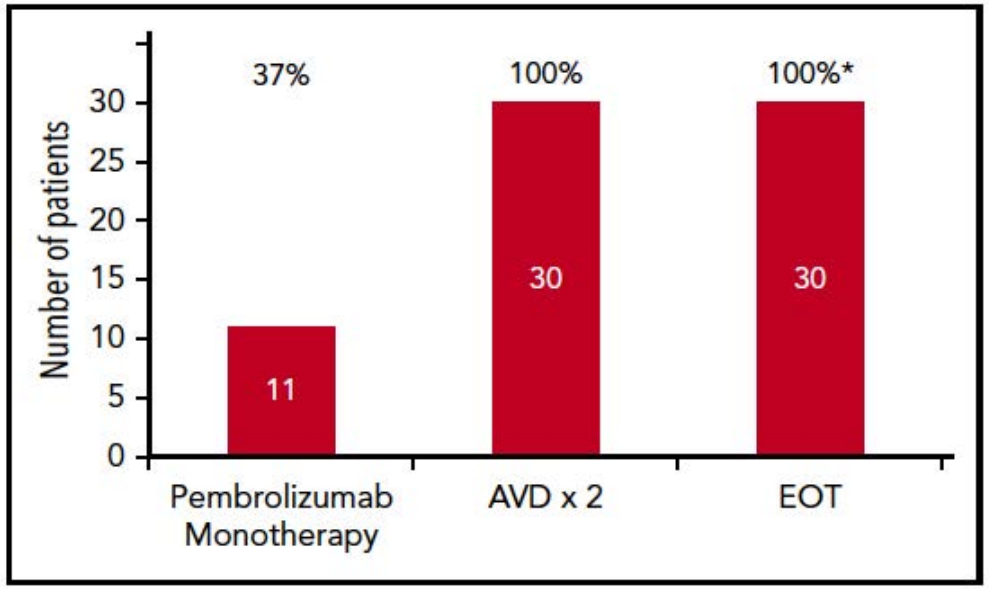
AVD x 4-6

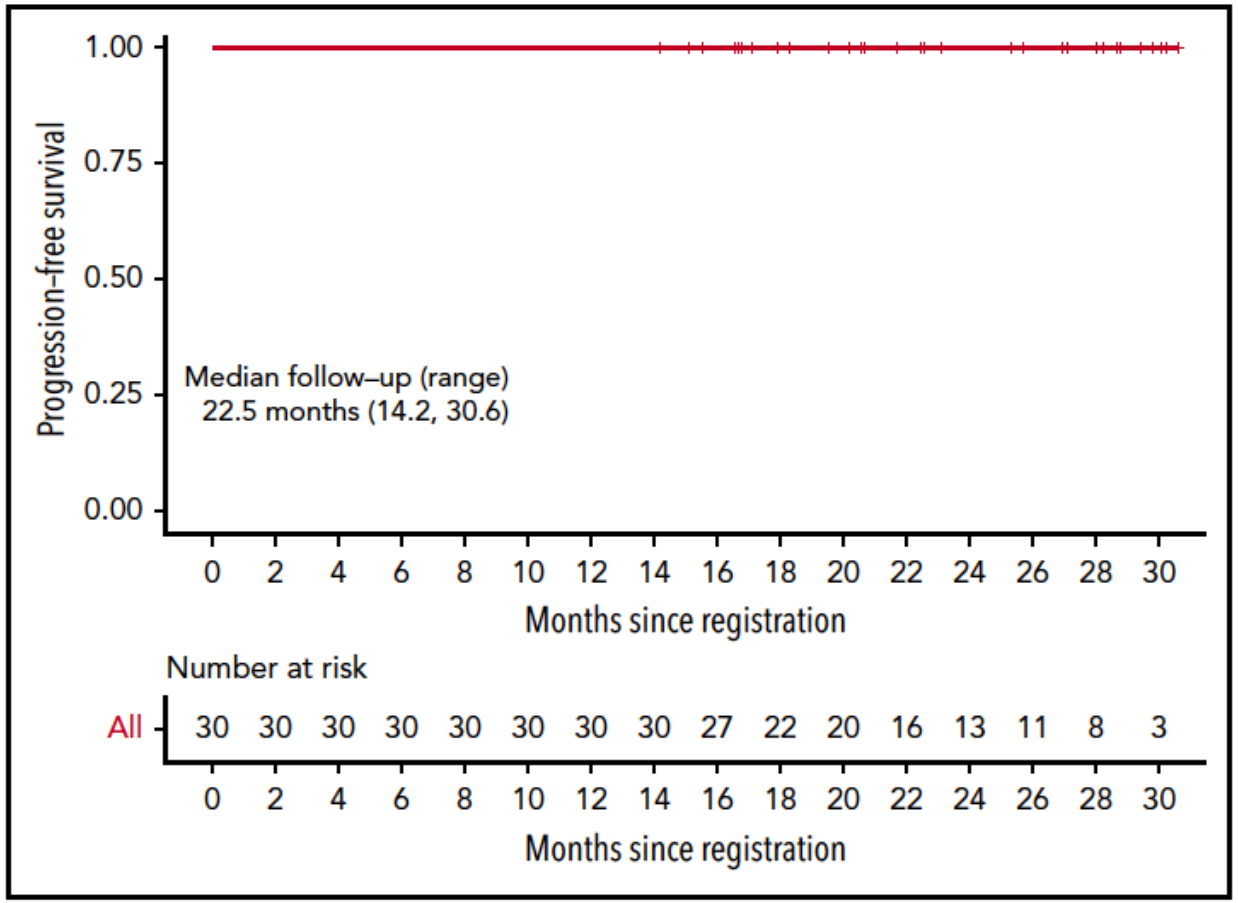
Characteristic	Patients (N = 30)	
	n	%
Median age, y (range)	29 (21-77)	
Age 45-60	4	13.3
Age >60	4 (67-77)	13.3
Sex		
Male	11	36.7
Female	19	63.3
Disease stage		
IIA	6	20.0
IIB	6	20.0
IIB with >10 cm mass	5	16.7
IIIA	4	13.3
IIIB	1	3.3
IVA	6	20.0
IVB	7	23.3

Characteristic	Patients (N = 30)	
	n	%
IPS Score*		
0-1	4	13.3
2	6	20.0
3	6	20.0
≥4	2	6.7
ESR >50†	6	50
B symptoms	14	46.7
Extranodal disease	16	53.3
Bone‡	14	46.7
Lung‡	3	10.0
Bulky		
>7 cm†	11	91.7
>10 cm	10	33.3
MMR >1/3	9	30.0
>10 cm or MMR >1/3	12	40.0

Allen et al. Blood 2021

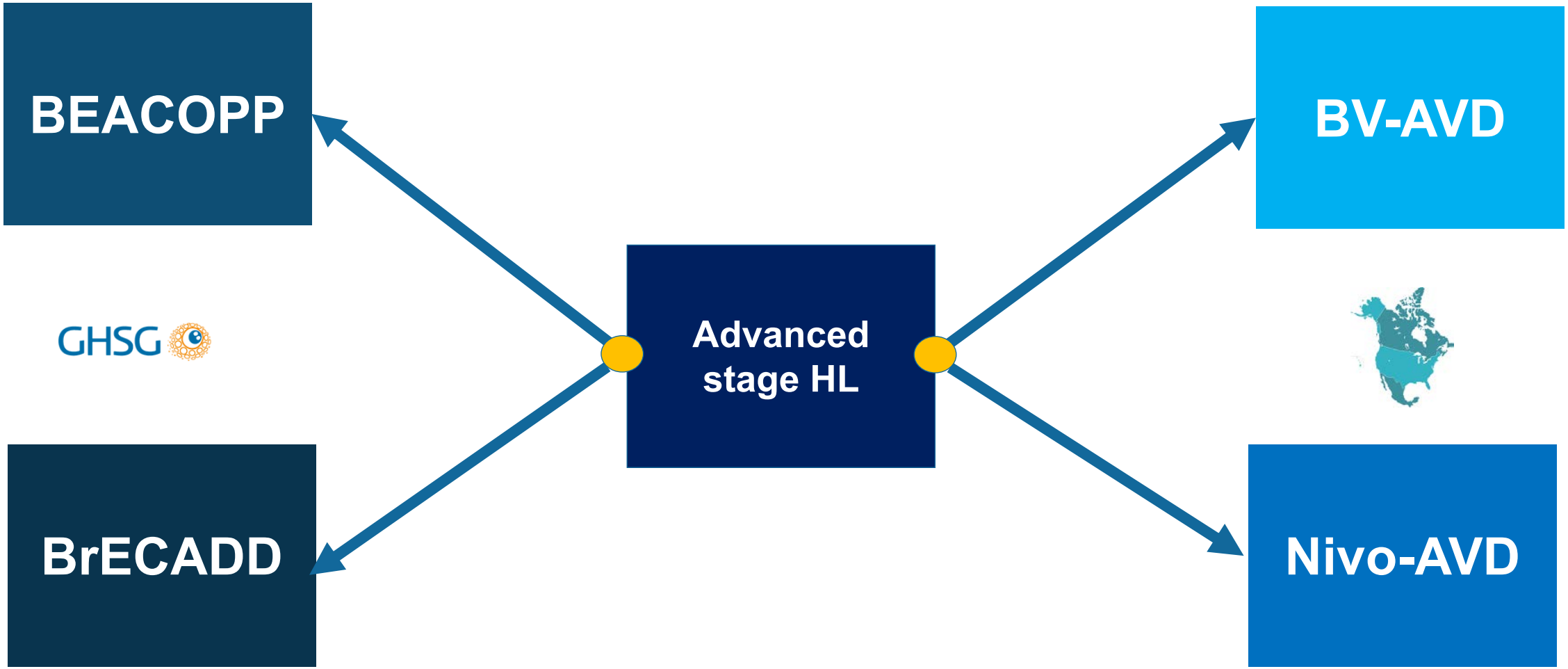
Pembrolizumab+AVD in early unfavorable and advanced stage HL





Allen et al. Blood 2021

On-going trials in advanced stage HL



Dana-Farber
Cancer Institute

CLL

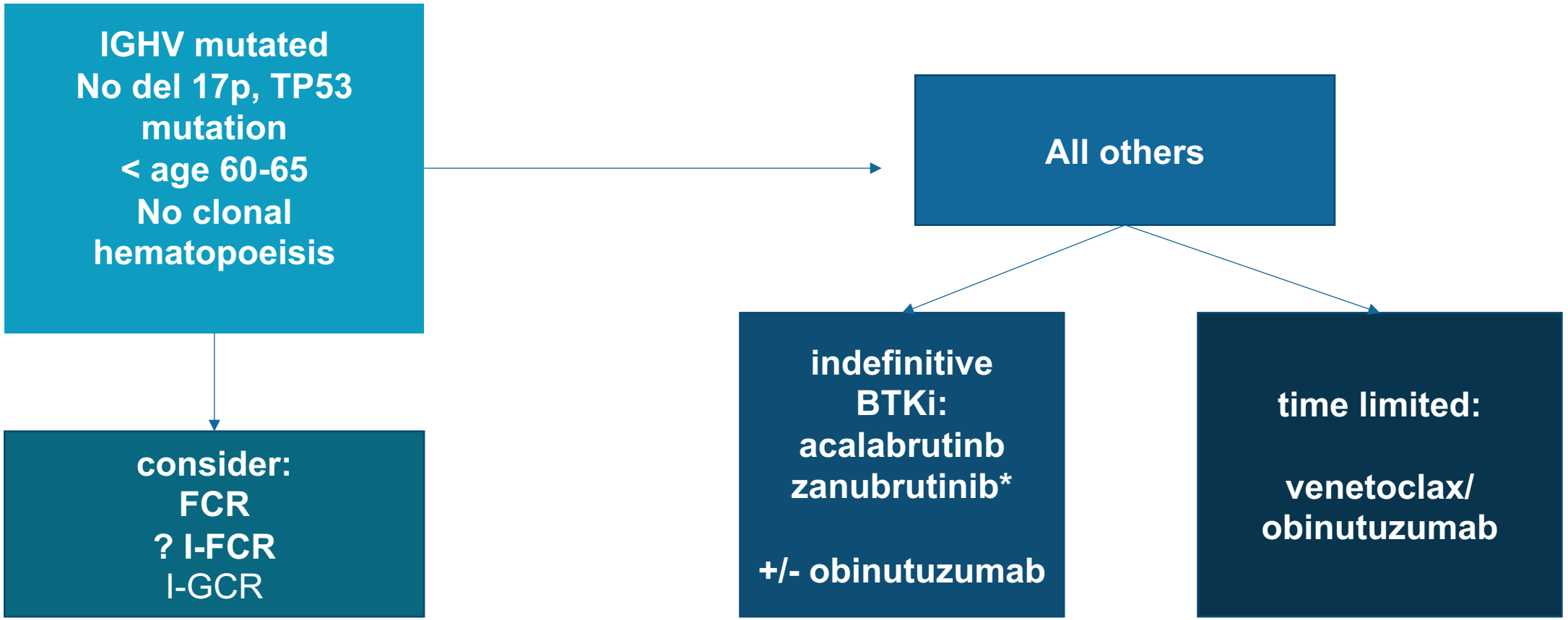
Treatment for previously untreated CLL

Regimen	ORR (CR)	PFS	OS
FCR	90% (44%)	57 months	13 yrs
BR	96% (31%)	42 months	92 % at 3 yr
Ibrutinib	92% (20%)	70% at 5 yr	83% at 5 yr
Acalabrutinib	86% (1%)	82% at 30 months	94% at 30 months
Venetoclax/obin	85% (49%)	74% at 4 yr	92% at 24 months

Unfavorable prognostic/predictive factors in CLL

IGHV	FISH	TP53
unmutated	del 11q del 17p complex	mutated

Choice of initial therapy



Patient specific factors to consider

BTKi	Venetoclax/ obinutuzumab
Ibrutinib – higher risk of atrial fibrillation, ? Hypertension Acalabrutinib: headache early in course. Tablet formulation facilitating co-administration with PPI Zanubrutinib: well tolerated All BTKi: risk of bleeding, indefinite administration, low rates of MRD neg	Obinutuzumab: IV administration, infusion reactions common Venetoclax: risk of tumor lysis, slow ramp up with multiple appointments, admission required for high risk patients. Generally well tolerated.

N Engl J Med 2022 July 28;387(4):310-20.

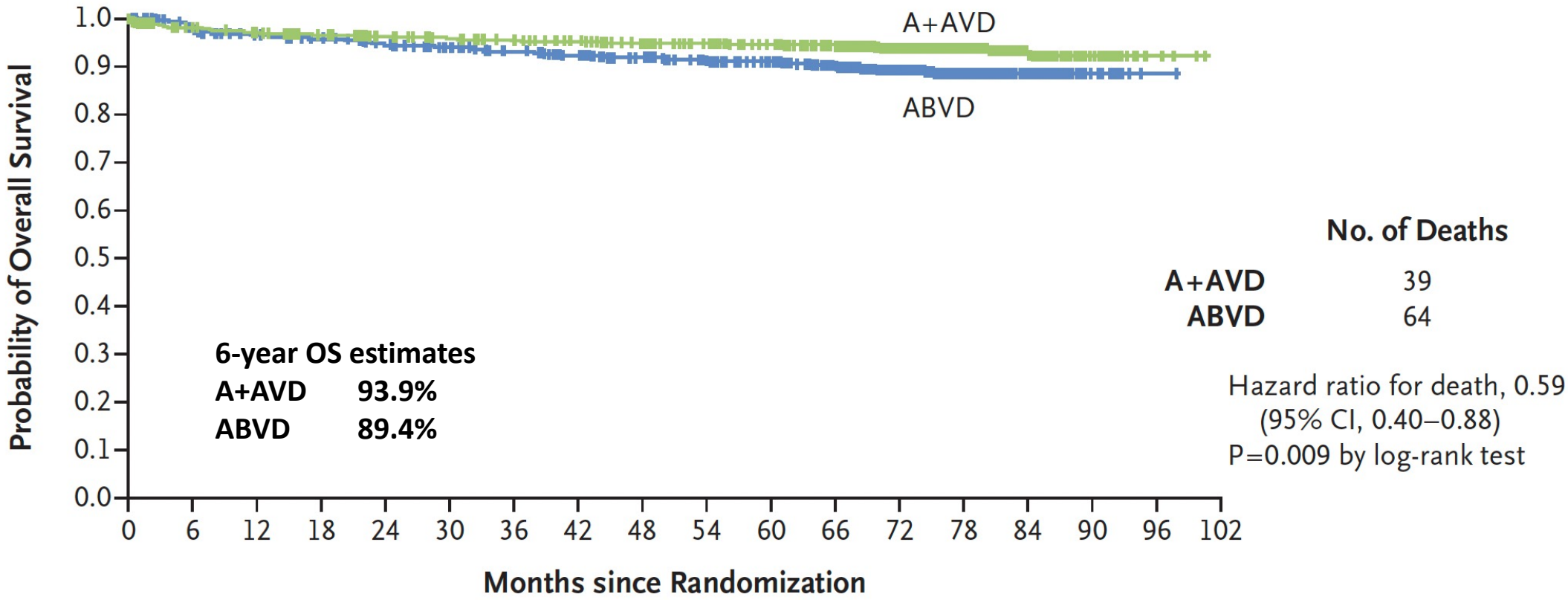
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Brentuximab Vedotin in Stage III or IV Hodgkin's Lymphoma

Stephen M. Ansell, M.D., Ph.D., John Radford, M.D., Joseph M. Connors, M.D., Monika Długosz-Danecka, M.D., Ph.D., Won-Seog Kim, M.D., Andrea Gallamini, M.D., Radhakrishnan Ramchandren, M.D., Jonathan W. Friedberg, M.D., Ranjana Advani, M.D., Martin Hutchings, Ph.D., Andrew M. Evens, D.O., Piotr Smolewski, M.D., Ph.D., Kerry J. Savage, M.D., Nancy L. Bartlett, M.D., Hyeon-Seok Eom, M.D., Ph.D., Jeremy S. Abramson, M.D., Cassie Dong, Ph.D., Frank Campana, M.D., Keenan Fenton, M.D., Markus Puhlmann, M.D., and David J. Straus, M.D., for the ECHELON-1 Study Group*

ECHELON-1 Primary Endpoint: Overall Survival (ITT Population)

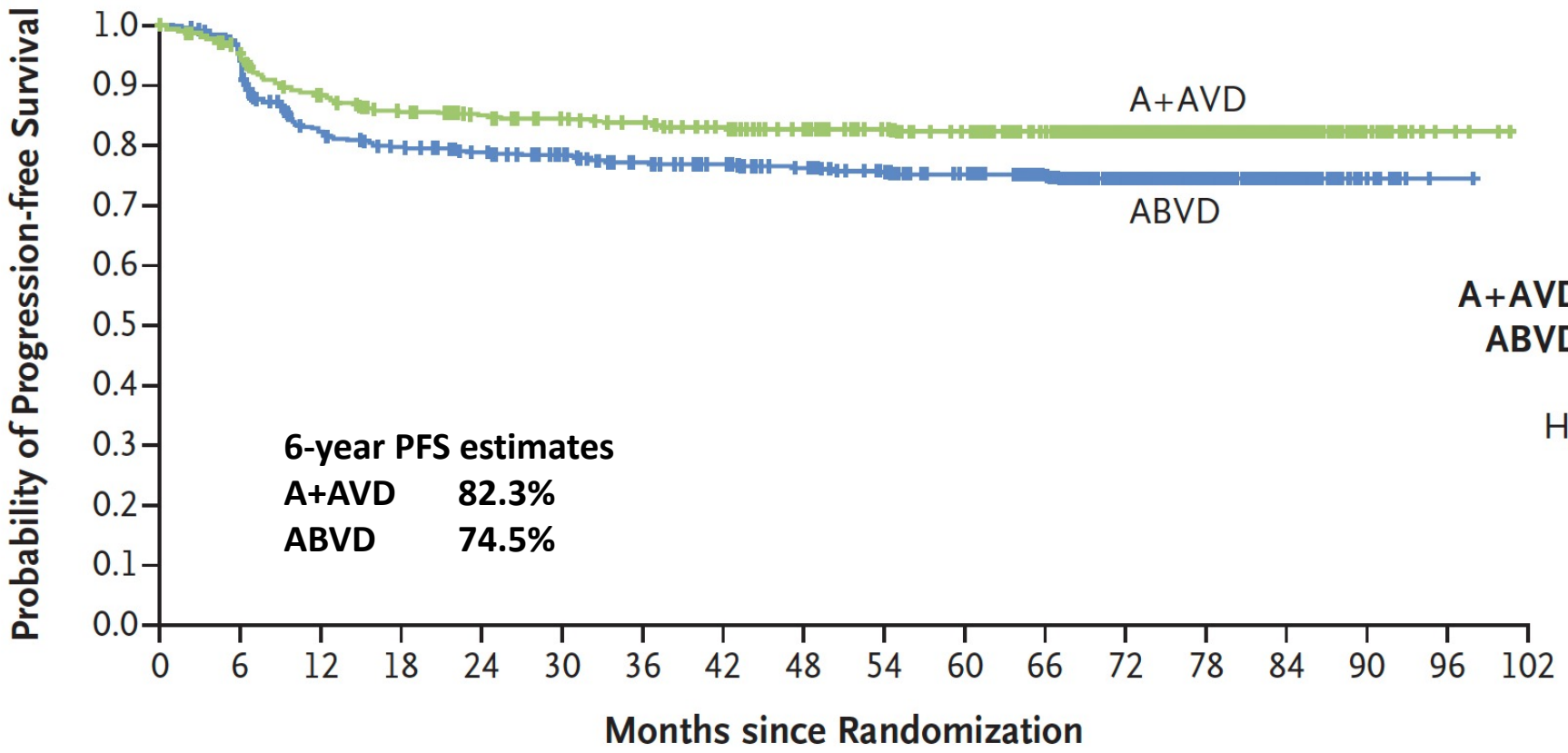


A + AVD = brentuximab vedotin with doxorubicin, vinblastine and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine and dacarbazine

Ansell SM et al. *N Engl J Med* 2022 July 28;387(4):310-20. Straus DJ et al. SOHO 2022;Abstract HL-507.

RTP RESEARCH TO PRACTICE

ECHELON-1: Progression-Free Survival (ITT Population)



No. of Events

A+AVD	112
ABVD	159

Hazard ratio for disease progression or death, 0.68 (95% CI, 0.53–0.86)

No. at Risk

A+AVD	664	619	563	537	520	508	496	480	463	448	428	400	305	179	86	24	4	0
ABVD	670	612	520	501	485	465	442	432	414	391	371	338	245	154	67	9	1	0

A + AVD = brentuximab vedotin with doxorubicin, vinblastine and dacarbazine; ABVD = doxorubicin, bleomycin, vinblastine and dacarbazine

Ansell SM et al. *N Engl J Med* 2022 July 28;387(4):310-20. Straus DJ et al. SOHO 2022;Abstract HL-507.

ARTICLE

Ferrata Storti Foundation

Older patients (aged ≥60 years) with previously untreated advanced-stage classical Hodgkin lymphoma: a detailed analysis from the phase III ECHELON-1 study

Andrew M. Evens,[1] Joseph M. Connors,[2] Anas Younes,[3*] Stephen M. Ansell,[4] Won Seog Kim,[5] John Radford,[6] Tatyana Feldman,[7] Joseph Tuscano,[8] Kerry J. Savage,[2] Yasuhiro Oki,[9] Andrew Grigg,[10] Christopher Pocock,[11] Monika Dlugosz-Danecka,[12] Keenan Fenton,[13] Andres Forero-Torres,[13] Rachael Liu,[14] Hina Jolin,[14] Ashish Gautam[14] and Andrea Gallamini[15]

Haematologica 2022
Volume 107(5):1086-1094

ECHELON-1: Summary of Modified PFS in Older Patients (≥60 Years) and Younger Patients with HL

	Aged ≥60 years (n=186)		Aged ≥60 years with stage III disease (n=65)*		Aged ≥60 years with stage IV disease (n=118)*		Aged <60 years (n=1,148)		ITT population (n=1,334)	
	A+AVD (n=84)	ABVD (n=102)	A+AVD (n=31)	ABVD (n=34)	A+AVD (n=51)	ABVD (n=67)	A+AVD (n=580)	ABVD (n=568)	A+AVD (n=664)	ABVD (n=670)
24-month modified PFS† per IRF, % (95% CI)[20]	70.3 (58.4-79.4)	71.4 (60.5-79.8)	67.7 (44.9-82.6)	80.9 (66.2-90.9)	71.3 (56.3-81.9)	66.1 (51.8-77.1)	83.7 (80.2-86.6)	78.2 (74.4-81.6)	82.1 (78.8-85.0)	77.2 (73.7-80.4)
24-month PFS‡ per INV, % (95% CI)	74.4 (62.2-82.7)	70.8 (60.6-78.8)	74.8 (54.2-87.1)	85.3 (68.2-93.6)	74.1 (59.6-84.1)	62.7 (49.5-73.5)	86.5 (83.4-89.1)	80.4 (76.8-83.5)	84.5 (81.4-87.1)	78.3 (74.9-81.4)
60-month PFS‡ per INV, % (95% CI)	67.1 (55.1-76.5)	61.6 (50.9-70.7)	70.1 (48.7-83.9)	69.9 (51.3-82.6)	65.1 (49.9-76.8)	57.0 (43.5-68.5)	84.3 (81.0-87.1)	77.8 (74.0-81.1)	80.7 (77.1-83.8)	73.1 (69.0-76.7)

Evens AM et al. *Haematologica* 2022;107(5):1086-94.

RTP RESEARCH TO PRACTICE

original reports

Brentuximab Vedotin Plus AVD for First-Line Treatment of Early-Stage Unfavorable Hodgkin Lymphoma (BREACH): A Multicenter, Open-Label, Randomized, Phase II Trial

Luc-Matthieu Fornecker, MD, PhD[1]; Julien Lazarovici, MD[2]; Igor Aurer, MD, PhD[3]; René-Olivier Casasnovas, MD[4]; Anne-Claire Gac, MD[5]; Christophe Bonnet, MD[6]; Krimo Bouabdallah, MD[7]; Pierre Feugier, MD[8]; Lena Specht, MD[9]; Lysiane Molina, MD[10]; Mohamed Touati, MD[11]; Cécile Borel, MD[12]; Aspasia Stamatoullas, MD[13]; Emmanuelle Nicolas-Virelizier, MD[14]; Laurent Pascal, MD[15]; Pieternella Lugtenburg, MD, PhD[16]; Nicola Di Renzo, MD[17]; Thierry Vander Borght, MD, PhD[18]; Alexandra Traverse-Glehen, MD[19]; Peggy Dartigues, MD[2]; Martin Hutchings, MD[20]; Annibale Versari, MD[21]; Michel Meignan, MD[22]; Massimo Federico, MD[23]; and Marc André, MD[18] for the LYSA-FIL-EORTC Intergroup

J Clin Oncol 2022 July 22;[Online ahead of print].

BREACH: PET Response After 2 Cycles

Response	BV-AVD (n = 113)	ABVD (n = 57)
PET response after two cycles		
Deauville 1	4 (4)	4 (7)
Deauville 2	34 (30)	22 (39)
Deauville 3	55 (49)	17 (30)
Deauville 4	13 (12)	8 (14)
Deauville 5	3 (3)	3 (5)
Not evaluated	4 (4)	3 (5)

BV-AVD = brentuximab vedotin with doxorubicin, vinblastine and dacarbazine; ABVD = doxorubicin, bleomycin, vincristine and dacarbazine

Fornecker LM et al. *J Clin Oncol* 2022;[Online ahead of print].

original reports

Brentuximab Vedotin Combined With Chemotherapy in Patients With Newly Diagnosed Early-Stage, Unfavorable-Risk Hodgkin Lymphoma

Anita Kumar, MD[1]; Carla Casulo, MD[2]; Ranjana H. Advani, MD[3]; Elizabeth Budde, MD[4]; Paul M. Barr, MD[2]; Connie L. Batlevi, MD, PhD[1]; Philip Caron, MD[1]; Louis S. Constine, MD[2]; Savita V. Dandapani, MD[4]; Esther Drill, MD[1]; Pamela Drullinsky, MD[1]; Jonathan W. Friedberg, MD[2]; Clare Grieve, BA[1]; Audrey Hamilton, MD[1]; Paul A. Hamlin, MD[1]; Richard T. Hoppe, MD[3]; Steven M. Horwitz, MD[1]; Ashlee Joseph, BA[1]; Niloufer Khan, MD[1]; Leana Laraque, BA[1]; Matthew J. Matasar, MD[1]; Alison J. Moskowitz, MD[1]; Ariela Noy, MD[1]; Maria Lia Palomba, MD[1]; Heiko Schöder, MD[1]; David J. Straus, MD[1]; Shreya Vemuri, BA[1]; Joanna Yang, MD[5]; Anas Younes, MD[6]; Andrew D. Zelenetz, MD, PhD[1]; Joachim Yahalom, MD[1]; and Craig H. Moskowitz, MD[7]

J Clin Oncol 2021 July 10;39(20):2257-65.

Multicenter Pilot Study of Brentuximab Vedotin (BV) and AVD with or without Consolidative Radiation Therapy for Early-Stage, Unfavorable-Risk Hodgkin Lymphoma

- Patients who achieved a negative end-of-therapy (EOT) PET-4 scan after 4 cycles of BV + AVD were studied with de-escalating radiation dose and field.

Clinical endpoint	Cohort 1 30-Gy ISRT (n = 29)	Cohort 2 20-Gy ISRT (n = 29)	Cohort 3 30-Gy CVRT (n = 29)	Cohort 4 No radiation (n = 29)	All patients (n = 114)
EOT CR rate	27 (93%)	29 (100%)	27 (93%)	28 (97%)	111 (96%)
2-year PFS rate	93.1%	96.6%	89.7%	96.6%	94%

"BV + AVD x four cycles is a highly active and well-tolerated treatment program for ES, unfavorable-risk Hodgkin lymphoma, including bulky disease. The efficacy of BV + AVD supports the safe reduction or elimination of consolidative radiation among PET-4-negative patients."

Kumar A et al. *J Clin Oncol* 2021 July 10;39(20):2257-65.

Blood 2021 August 12;138(6):427-38.

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results

Ranjana H. Advani,[1] Alison J. Moskowitz,[2] Nancy L. Bartlett,[3] Julie M. Vose,[4] Radhakrishnan Ramchandren,[5] Tatyana A. Feldman,[6] Ann S. LaCasce,[7] Beth A. Christian,[8] Stephen M. Ansell,[9] Craig H. Moskowitz,[10] Lisa Brown,[11] Chiyu Zhang,[11] David Taft,[11] Sahar Ansari,[11] Mariana Sacchi,[12] Linda Ho,[11] and Alex F. Herrera[13]

SGN35-025: Response and Survival Outcomes

Response (all patients, N = 91)		All	Patients proceeding to ASCT	
ORR	CR	Est 3-yr PFS	Est 3-yr PFS	OS
85%	67%	77%	91%	93%

Advani RH et al. *Blood* 2021 August 12;138(6):427-38.

Camidanlumab tesirine: updated efficacy and safety in an open-label, multicenter, phase 2 study of patients with relapsed or refractory classical Hodgkin lymphoma (R/R cHL)

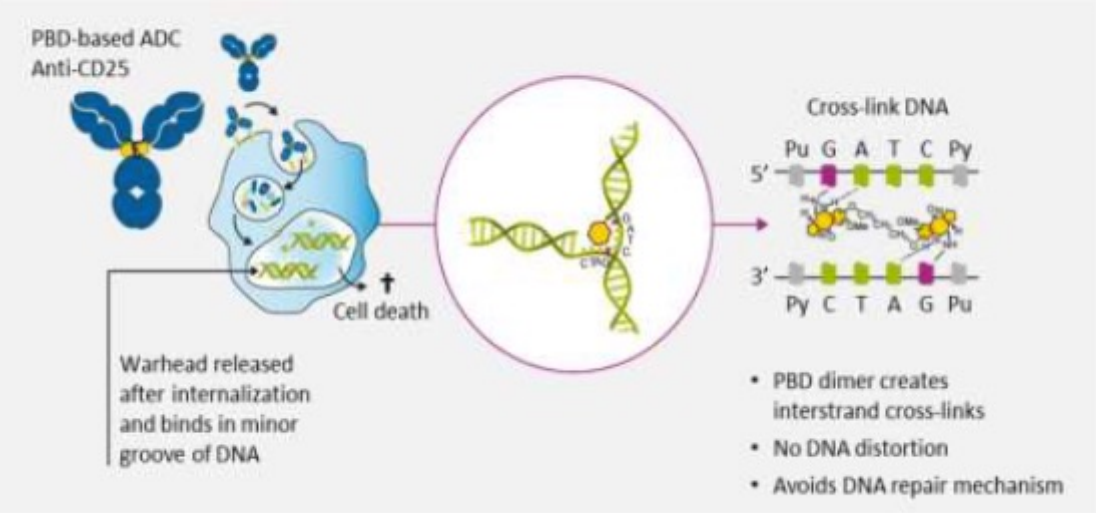
Carmelo Carlo-Stella[1]*, Stephen Ansell[2], Pier Luigi Zinzani[3], John Radford[4], Kami Maddocks[5], Antonio Pinto[6], Graham P. Collins[7], Veronika Bachanova[8], Nancy Bartlett[9], Isabelle Bence-Bruckler[10], Mehdi Hamadani[11], Justin Kline[12], Jiri Mayer[13], Kerry J. Savage[14], Ranjana Advani[15], Paolo Caimi[16], René-Olivier Casasnovas[17], Tatyana Feldman[18], Brian Hess[19], Mariana Bastos-Oreiro[20], Sunil Iyengar[21], Sandy Eisen[22†], Yanina Negievich[22], Luqiang Wang[23], Jens Wuerthner[22], Alex F. Herrera[24]

EHA 2022;Abstract S201.

Camidanlumab Tesirine: Mechanism of Action and Study Rationale

Limited therapeutic options are available for patients with R/R cHL who are unresponsive to, or whose disease progresses after, BV and PD-1 blockade therapy.[1–5] Novel treatments are required to address this unmet need

Camidanlumab tesirine (Cami) is an Ab-drug conjugate comprising a human IgG1 anti-CD25 monoclonal Ab conjugated to a potent PBD dimer warhead[6]



Treatment with Cami demonstrated encouraging antitumor activity and manageable toxicity:

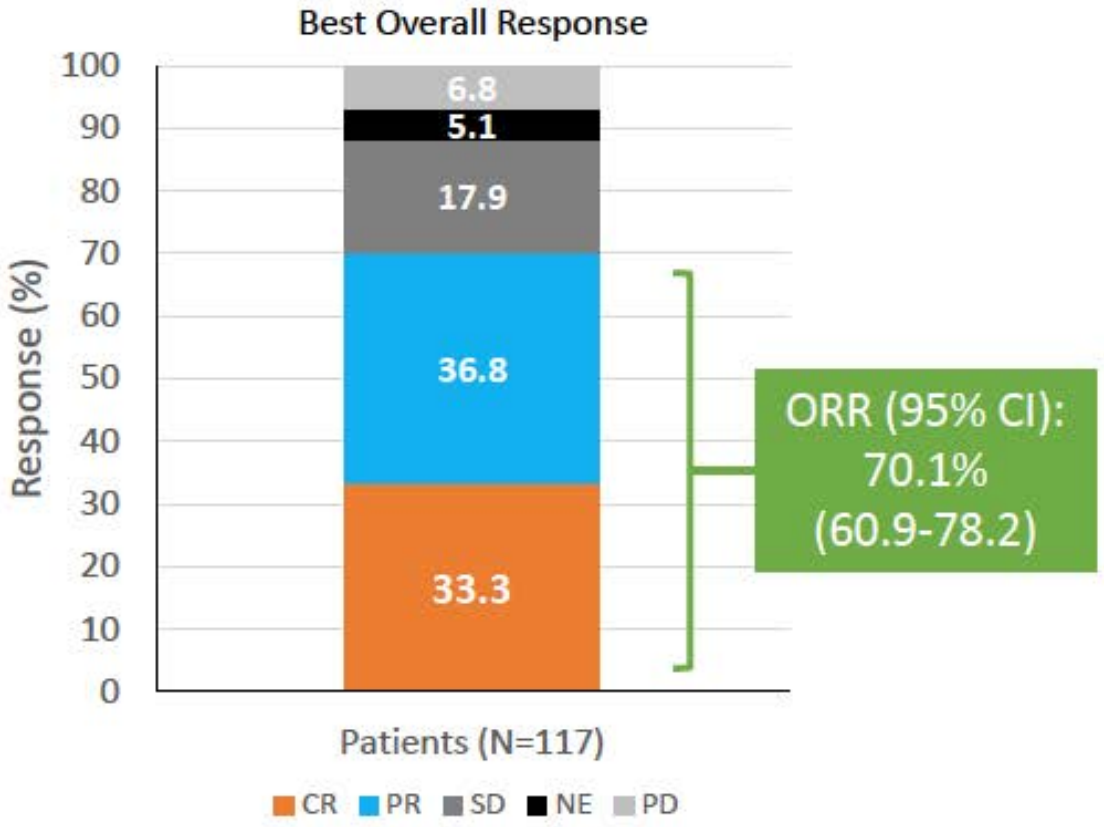
- In a Phase 1 trial that included patients with R/R cHL who received Cami at a dose of 45 µg/kg and achieved an overall response rate (ORR; CR + PR) of 86.5%[7]
- In the initial findings of this Phase 2 study of patients with R/R cHL, who achieved an ORR of 83.0%[8]

Here, we present preliminary results from this Phase 2 study of patients with R/R cHL (NCT04052997) after meeting target enrollment (100 patients)

Zinzani PL et al. ICML Virtual Congress 2021;Abstract 075.

RTP RESEARCH TO PRACTICE

Response to Camidanlumab Tesirine for R/R cHL (Primary Study Endpoint)



Best Overall Response in Patients with or without prior SCT

Best Overall response, n (%)[b]	BV and CHPi With Prior SCT (n=73), n (%)	BV and CHPi Without Prior SCT (n=43), n (%)
CR	30 (41.1)	8 (18.6)
PR	24 (32.9)	19 (44.2)
SD	13 (17.8)	8 (18.6)
NE[c]	3 (4.1)	3 (7.0)
PD	3 (4.1)	5 (11.6)
ORR 95% CI for ORR	54 (74.0) 62.4-83.5	27 (62.8) 46.7-77.0

Carlo-Stella C et al. EHA 2022;Abstract S201. Carlo-Stella C et al. SOHO 2022;Abstract HL-339.

Mantle Cell Lymphoma

FDA Approvals, Indications and Key Efficacy Endpoints of BTKi for MCL

	Ibrutinib	Acalabrutinib	Zanubrutinib
FDA approval date	Nov 13, 2013	October 31, 2017	November 14, 2019
Indication	MCL after at least 1 prior therapy	MCL after at least 1 prior therapy	MCL after at least 1 prior therapy
Pivotal study ID	NCT01236391	ACE-LY-004 (NCT02213926)	BGB-3111-206 (NCT03206970)
Study phase	Phase II R/R MCL	Phase II R/R MCL	Phase II R/R MCL
Median # prior therapies	3	2	2
No. of patients	111	124	86
Primary endpoint: ORR	67% (CR: 23%)	81% (CR: 40%)	84% (CR: 78%)
Median DOR	17.5 mo	26 mo	Not estimable
Median PFS	13 mo	20 mo	33 mo
Median OS	22.5 mo	Not reached	Not reached

Wang ML et al. *NEJM* 2013 August 8;369(6):507-16. Wang ML et al. *Blood* 2015 August 6;126(6):739-45. Wang M et al. *Lancet* 2018 February 17;39(10121):659-667. Wang M et al. *Leukemia* 2019;33:2762-2766. Song Y et al. *Clin Cancer Res* 2020 Aug 15;26(16):4216-4224. Song Y et al. *Blood* 2022 May 26;139(21): 3148-3158. Ibrutinib PI, Rev 8/21. Acalabrutinib PI, Rev 8/2022. Zanubrutinib PI, Rev 9/2021.

ORIGINAL ARTICLE

Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma

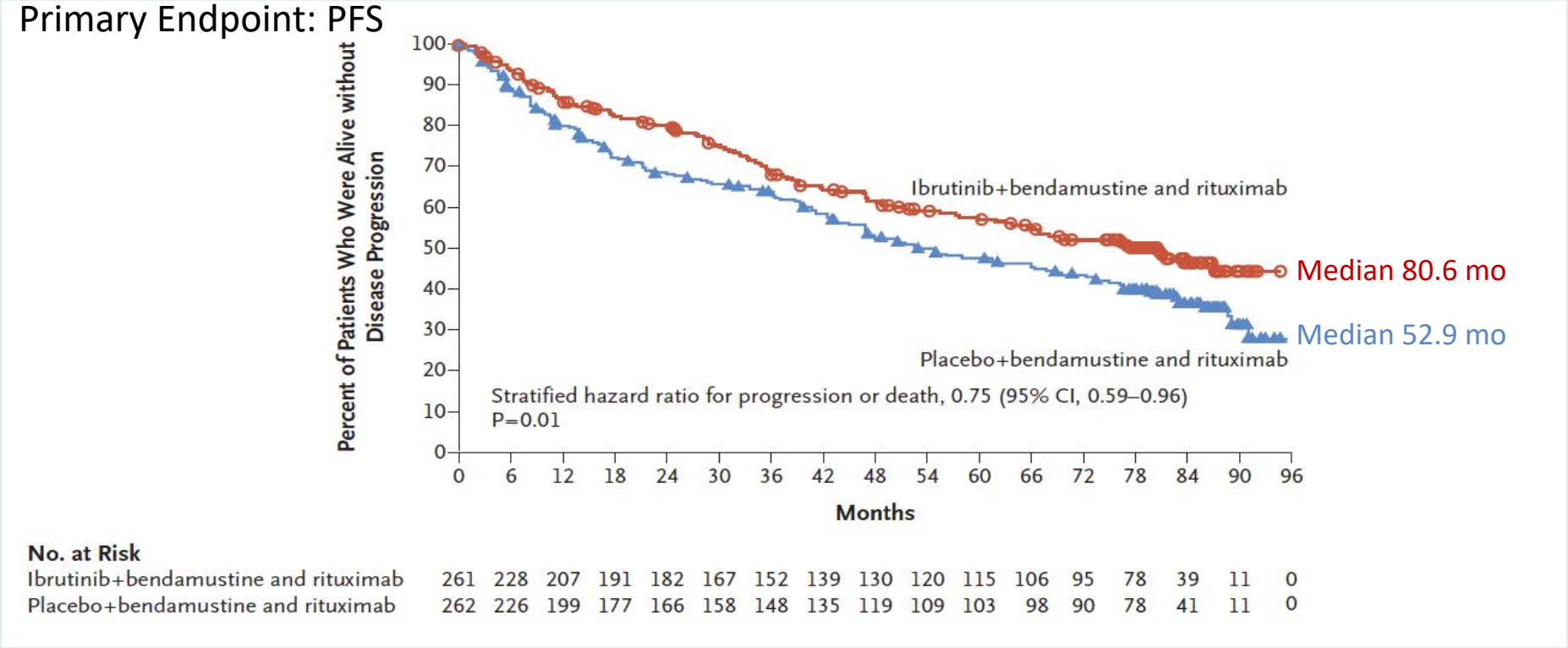
Michael L. Wang, M.D., Wojciech Jurczak, M.D., Ph.D., Mats Jerkeman, M.D., Ph.D., Judith Trotman, F.R.A.C.P., Pier L. Zinzani, M.D., Ph.D., David Belada, M.D., Ph.D., Carola Boccomini, M.D., Ian W. Flinn, M.D., Ph.D., Pratyush Giri, F.R.A.C.P., Andre Goy, M.D., Paul A. Hamlin, M.D., Olivier Hermine, M.D., Ph.D., José-Ángel Hernández-Rivas, M.D., Ph.D., Xiaonan Hong, M.D., Seok Jin Kim, M.D., Ph.D., David Lewis, F.R.C.Path., Ph.D., Yuko Mishima, M.D., Ph.D., Muhit Özcan, M.D., Guilherme F. Perini, M.D., Christopher Pocock, M.D., Ph.D., Yuqin Song, M.D., Ph.D., Stephen E. Spurgeon, M.D., John M. Storring, M.D., Jan Walewski, M.D., Jun Zhu, M.D., Ph.D., Rui Qin, Ph.D., Todd Henninger, Ph.D., Sanjay Deshpande, M.D., Angela Howes, Ph.D., Steven Le Gouill, M.D., Ph.D., and Martin Dreyling, M.D., for the SHINE Investigators*

***N Engl J Med* 2022 June 30;386(26):2482-94.**

RTP RESEARCH TO PRACTICE

SHINE: A Phase III Trial of Ibrutinib with Bendamustine and Rituximab for MCL

Primary Endpoint: PFS



- The proportion of patients with a complete response was 65.5% in the ibrutinib group and 57.6% in the placebo group (p = 0.06)
- Overall survival was similar in the 2 groups (HR 1.07)
- The safety profile of the combined therapy was consistent with the known profiles of the individual drugs

Wang ML et al. *N Engl J Med* 2022 June 30;386(26):2482-94.

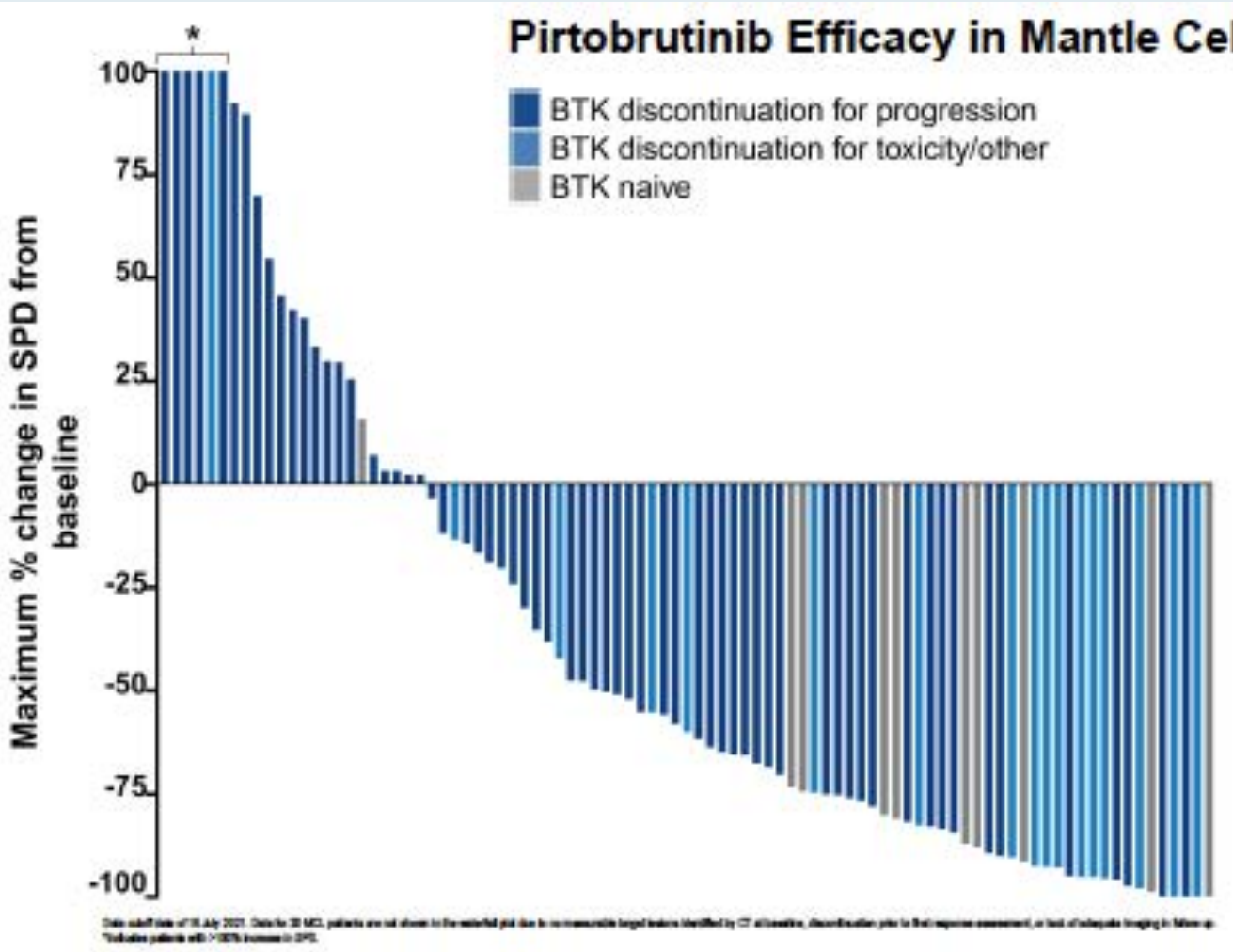
RTP RESEARCH TO PRACTICE

Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Previously Treated Mantle Cell Lymphoma: Updated Results from the Phase 1/2 BRUIN Study

Lewis K et al.

Pan Pacific Lymphoma Conference 2022.

BRUIN: Updated Results with Pirtobrutinib for MCL



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)

- Efficacy also seen in patients with prior:
  - Stem cell transplant (n=28): ORR 64% (95% CI: 44-81)
  - CAR-T therapy (n=6): ORR 50% (95% CI: 12-88)

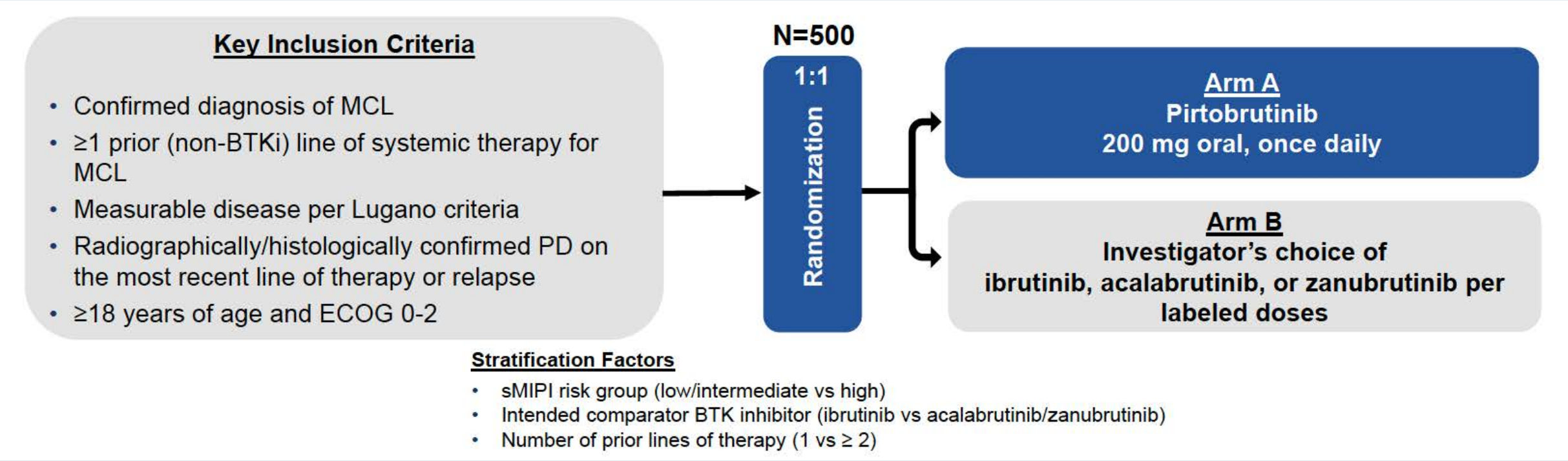
Lewis K et al. Pan Pacific Lymphoma Conference 2022. Cohen JB et al. SOHO 2022;Abstract MCL-133.

Single-Agent Venetoclax in Relapsed or Refractory MCL

Study	N	Median # prior therapies	ORR (CR)	Median PFS	Median DoR	Median OS
Eyre *Haematologica* 2019	20	3	53% (18%)	3.2 mo	8.1 mo	9.4 mo
Zhao *Amer J Hematol* 2020	24	5	50% (21%)	8 mo	4 mo	13.5 mo
Davids *Clin Cancer Res* 2021	28	3	67% (21%)	11.3 mo	15.7 mo	Not reported

Eyre TA et al. *Haematologica* 2019;104(2):e68-71. Zhao S et al. *Am J Hematol* 2020;95(6):623-9. Davids MS et al. *Clin Cancer Res* 2021;27(17):4690-5.

BRUIN MCL-321 Phase III Study Design



Ito R et al. SOHO 2022;Abstract MCL-135.

Leukemia 2022;36(9):2165-76.

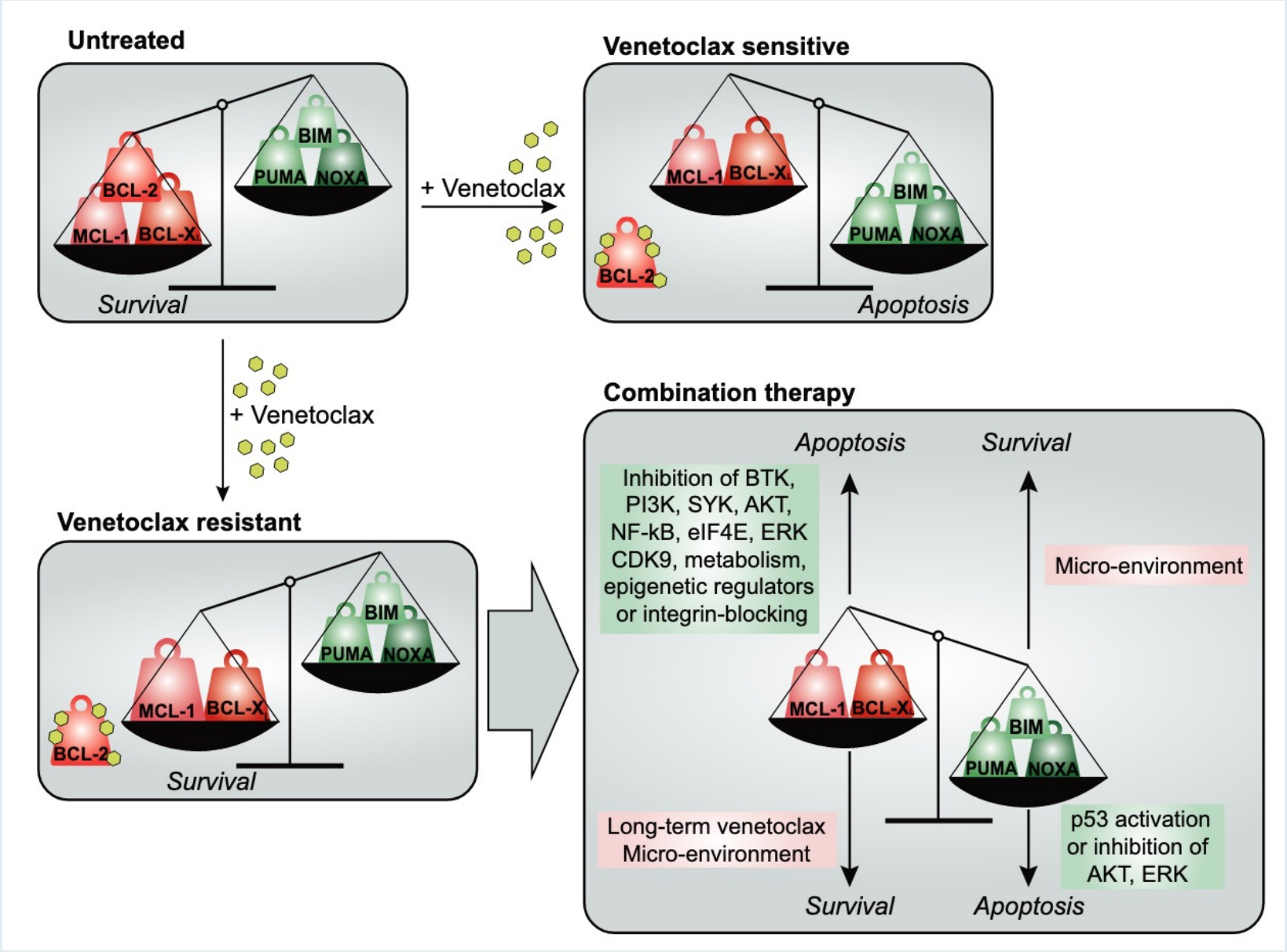
REVIEW ARTICLE OPEN

MOLECULAR TARGETS FOR THERAPY

Tipping the balance: toward rational combination therapies to overcome venetoclax resistance in mantle cell lymphoma

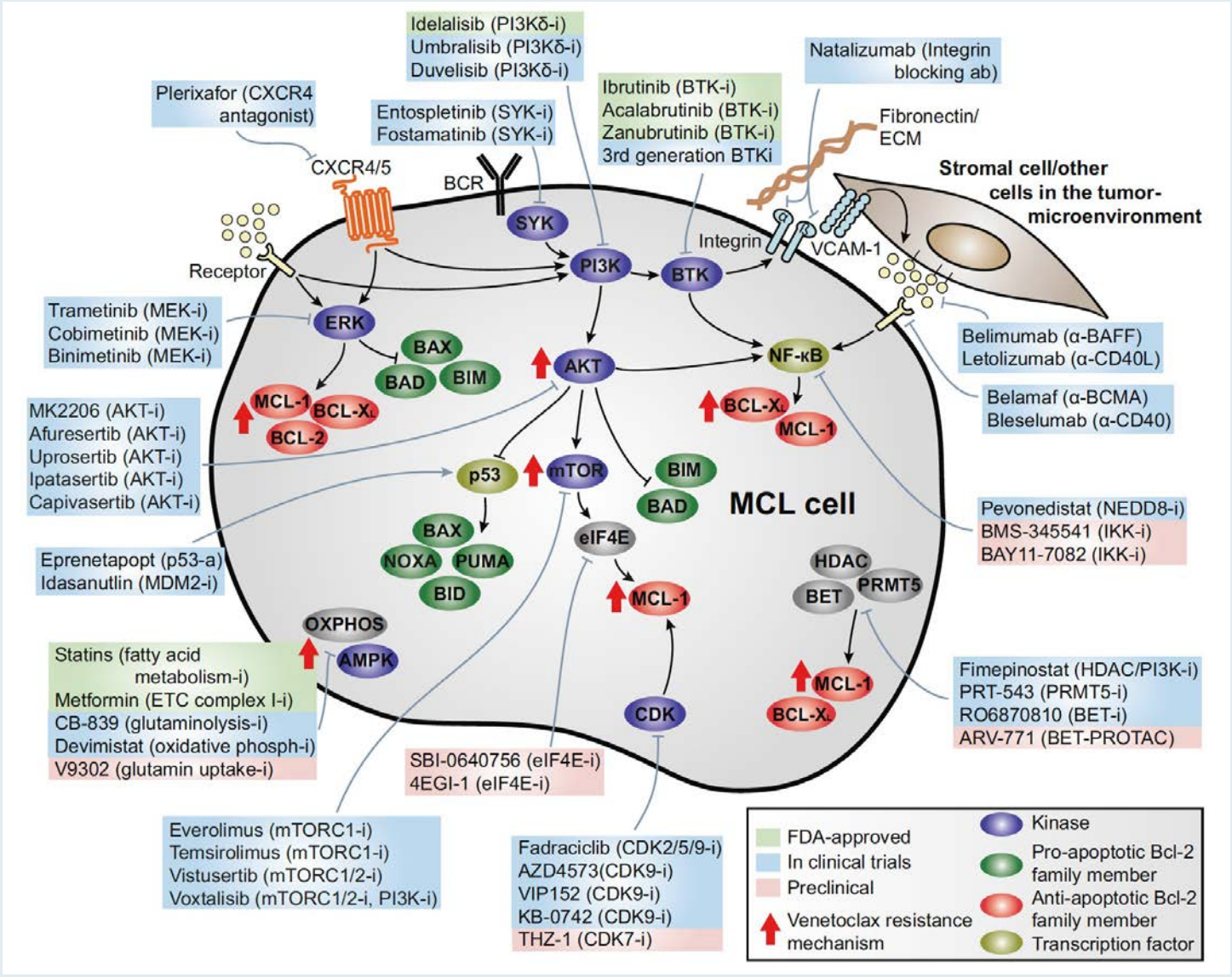
Yvonne J. Thus[1,2,3], Eric Eldering[2,3,4,5], Arnon P. Kater[2,3,6] and Marcel Spaargaren[1,2,3] ✉

Tipping the Balance of MCL Toward Venetoclax Sensitivity



Thus YJ et al. *Leukemia* 2022;36(9):2165-76.

Rational Drug Combinations to Enhance Venetoclax Sensitivity in MCL Cells



Thus YJ et al. *Leukemia* 2022;36(9):2165-76.

Clinical Trials with Venetoclax in MCL

Interventions	Conditions	Phase	NCT Identifier	Start date
Ven + **Ibrutinib**	R/R MCL	I	NCT02419560	Apr 2015
Ven + **Ibrutinib** (AIM) [53]	R/R MCL	II	NCT02471391	Jun 2015
Ven + **Ibrutinib**	R/R MCL	II	NCT04477486	Sep 2020
Ven + **Ibrutinib** (SYMPATICO) [55]	TN & R/R MCL	III	NCT03112174	Jun 2017
Ven + **Acalabrutinib**	R/R MCL	II	NCT03946878	Aug 2019
Ven + *Rituximab*	TN MCL	II	NCT05025423	Jun 2022
Ven + **Ibrutinib** + *Obinutuzumab* (OASIS) [54]	R/R MCL	I/II	NCT02558816	Oct 2015
Ven + **Ibrutinib** + *a-CD20* (OASIS-II)	TN MCL	II	NCT04802590	Jan 2022
Ven + **Pirtobrutinib** + *Rituximab* (BRUIN)	R/R MCL/CLL/NHL	I/II	NCT03740529	Nov 2018
Ven + **Zanubrutinib** + *Obinutuzumab* (BOVen) [96]	TN *TP53*-mut MCL/CLL	II	NCT03824483	Feb 2019
Ven + **Acalabrutinib** + *Obinutuzumab*	TN & R/R MCL	I/II	NCT04855695	Jul 2021
Ven + **Ibrutinib** + Chemoimmunotherapy (WINDOW-2) [97]	TN MCL	II	NCT03710772	May 2019
Ven + **Ibrutinib** + Lenalidomide + *Obinutuzumab* + Prednisone (VIPOR) [98]	TN & R/R MCL	I/II	NCT03223610	Feb 2018
Ven + Lenalidomide + *Rituximab* [99]	TN MCL	I	NCT03523975	Dec 2018
Ven + Lenalidomide + *Rituximab* (VALERIA)	R/R MCL	I/II	NCT03505944	Jul 2018
Ven + Bendamustine + *Rituximab*	TN MCL	II	NCT03834688	Jan 2020
Ven + Bendamustine + *Obinutuzumab*	TN MCL	II	NCT03872180	Apr 2019
Ven + Bendamustine + *Rituximab* + **Ibrutinib**	R/R MCL	I	NCT03295240	Sep 2017
(Ven or Bendamustine) + *Rituximab* + **Acalabrutinib** [95]	TN MCL	I	NCT02717624	May 2016
Ven + Bendamustine + *Rituximab* + Cytarabine	TN high-risk MCL	II	NCT03567876	Sep 2018
(Ven + *Rituximab* or Bendamustine) + APR-246	R/R *TP53*-mut MCL/CLL/RT	I/II	NCT04419389	Mar 2021
Ven + Polatuzumab Vedotin + *Rituximab*/Hyaluronidase	R/R MCL	II	NCT04659044	Apr 2021
Ven + Copanlisib	R/R MCL	I/II	NCT04939272	Jun 2022
(Ven or Lenalidomide) + *Ublituximab* + Umbralisib	R/R MCL/CLL/NHL	I/II	NCT03379051	Mar 2018

Drugs in bold target BTK, drugs in italic target CD20, drugs in underline are current standard chemoimmunotherapy regimens.

Thus YJ et al. *Leukemia* 2022;36(9):2165-76.

RTP RESEARCH TO PRACTICE

N Engl J Med 2018;378(13):1211-23.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma

Constantine S. Tam, M.B., B.S., M.D., Mary Ann Anderson, M.B., B.S., Ph.D., Christiane Pott, M.D., Ph.D., Rishu Agarwal, M.B., B.S., Sasanka Handunnetti, M.B., B.S., Rodney J. Hicks, M.B., B.S., Kate Burbury, M.B., B.S., Gillian Turner, B.N., M.I.P.H., Juliana Di Iulio, Ph.D., Mathias Bressel, M.Sc., David Westerman, M.B., B.S., Stephen Lade, M.B., B.S., Martin Dreyling, M.D., Sarah-Jane Dawson, M.B., B.S., Ph.D., Mark A. Dawson, M.B., B.S., Ph.D., John F. Seymour, M.B., B.S., Ph.D., and Andrew W. Roberts, M.B., B.S., Ph.D.

AIM Primary Endpoint: Rate of Complete Response at Week 16

Response	Without PET (N = 24)	With PET (N = 24)
Overall		
Response at wk 4 — no. (%)		
Complete response	0	—
Unconfirmed complete response	1 (4)	—
Partial response	10 (42)	—
Stable disease	10 (42)	—
Progressive disease	2 (8)	—
Could not be evaluated	1 (4)†	—
Response at wk 16 — no. (%)		
Complete response	10 (42)	15 (62)
Unconfirmed complete response	4 (17)	—
Partial response	4 (17)	2 (8)
Stable disease	2 (8)	1 (4)
Progressive disease	3 (12)	4 (17)
Could not be evaluated	1 (4)‡	2 (8)‡§

Tam CS et al. *N Engl J Med* 2018;378(13):1211-23.

Wang *et al. J Hematol Oncol* (2021) 14:179
https://doi.org/10.1186/s13045-021-01188-x

Journal of Hematology & Oncology

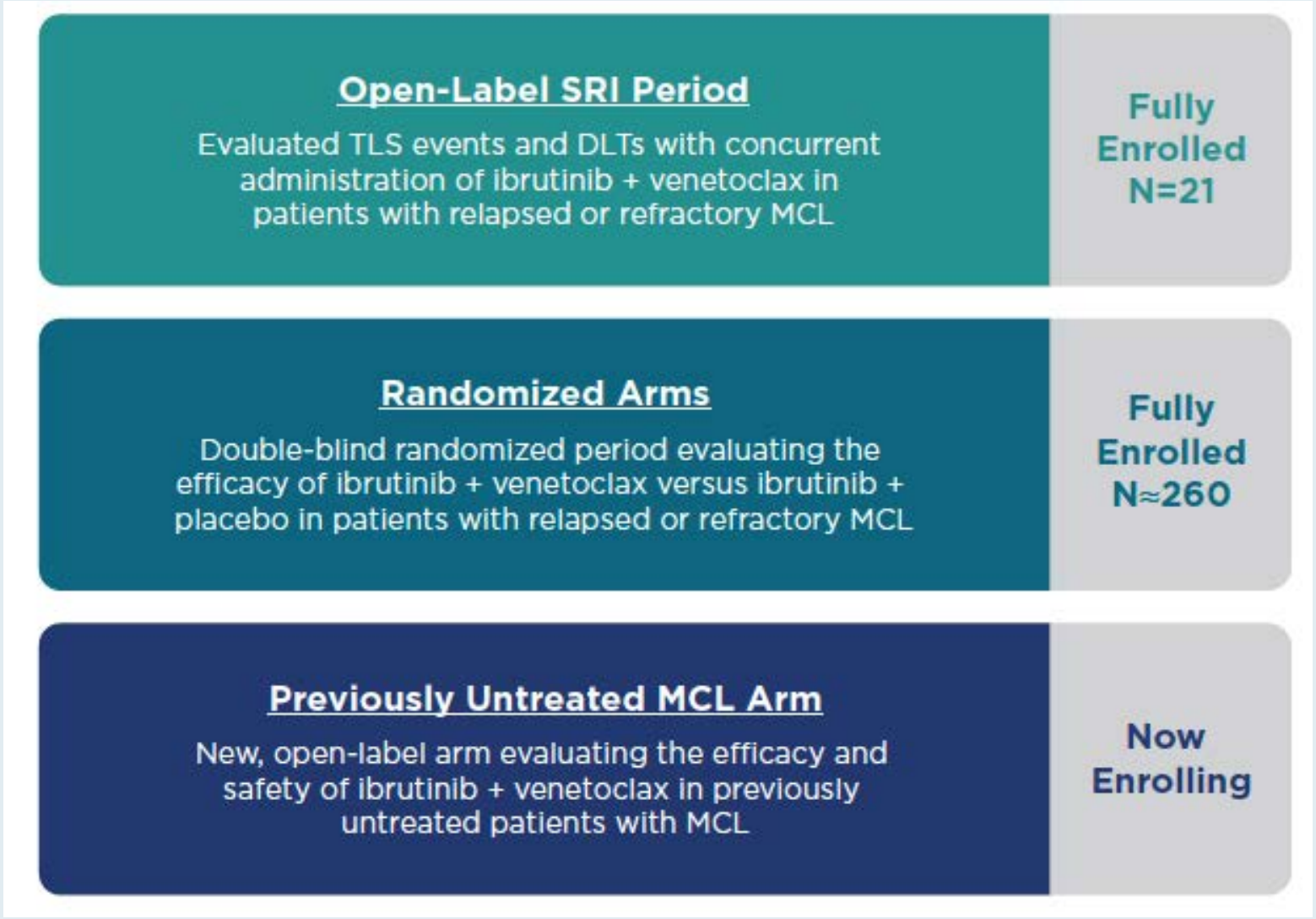
RAPID COMMUNICATION

Open Access

Concurrent ibrutinib plus venetoclax in relapsed/refractory mantle cell lymphoma: the safety run-in of the phase 3 SYMPATICO study

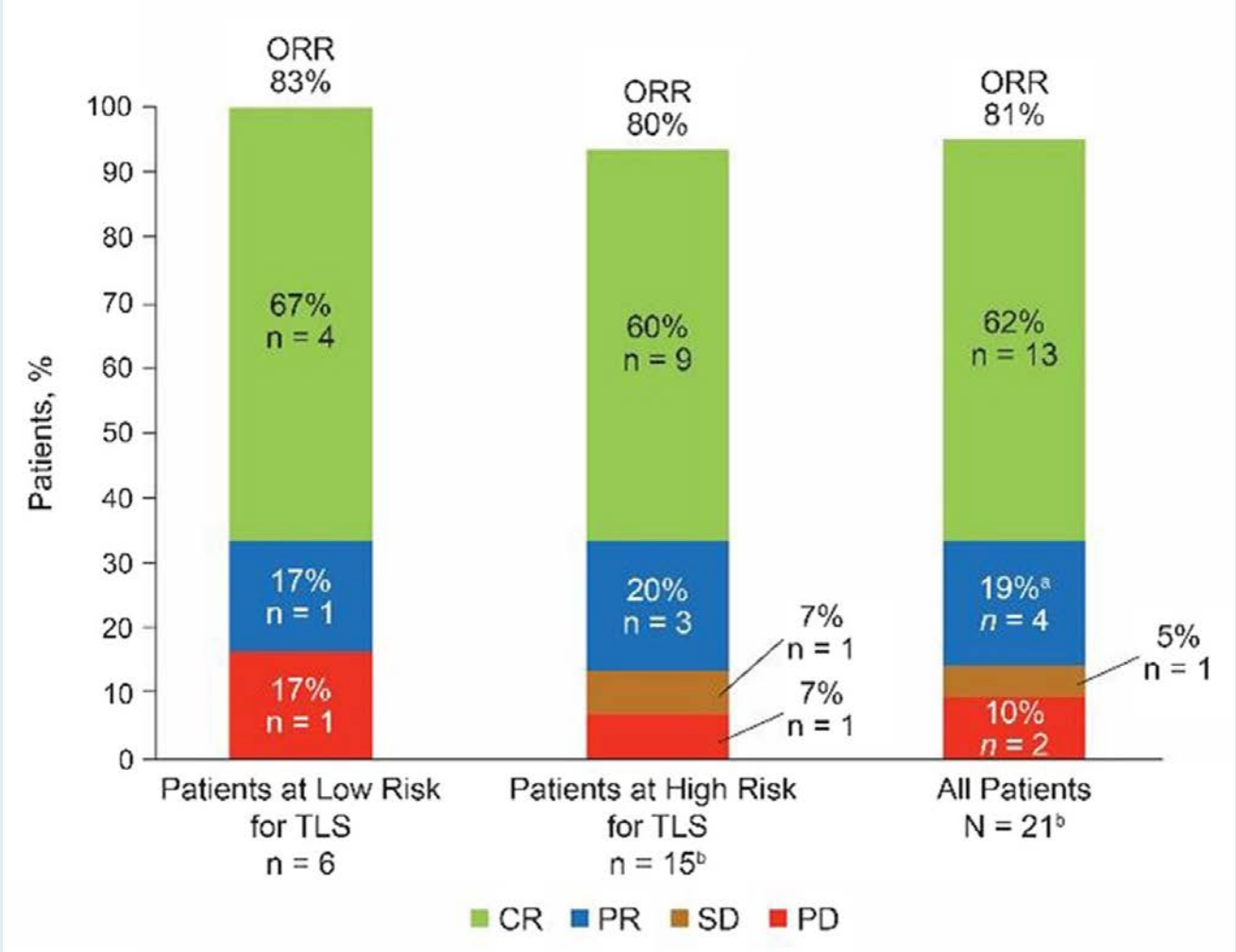
Michael Wang[1*], Radhakrishnan Ramchandren[2], Robert Chen[3], Lionel Karlin[4], Geoffrey Chong[5], Wojciech Jurczak[6], Ka Lung Wu[7], Mark Bishton[8], Graham P. Collins[9], Paul Eliadis[10], Frédéric Peyrade[11], Yihua Lee[12], Karl Eckert[12], Jutta K. Neuenburg[12] and Constantine S. Tam[13]

SYMPATICO Study Design: Safety Run-In (SRI), Phase III Randomized Arms in R/R MCL and Open-Label Arm in Previously Untreated MCL



Jurczak ICM 2021;Abstract 1143TiP.

SYMPATICO Safety Run-In: Response



Wang M et al. *J Hematol Oncol* 2021;14(1):179.

Blood 2021;137(7):877-87.

Plenary Paper

CLINICAL TRIALS AND OBSERVATIONS

Ibrutinib, obinutuzumab, and venetoclax in relapsed and untreated patients with mantle cell lymphoma: a phase 1/2 trial

Steven Le Gouill,[1] Franck Morschhauser,[2] David Chiron,[3] Krimo Bouabdallah,[4] Guillaume Cartron,[5] Olivier Casasnovas,[6] Caroline Bodet-Milin,[7] Sylviane Ragot,[8] Céline Bossard,[9] Nathalie Nadal,[6] Charles Herbaux,[10] Benoit Tessoulin,[1] Emmanuelle Tchernonog,[11] Cédric Rossi,[6] Rory McCulloch,[12] Thomas Gastinne,[13] Mary B. Callanan,[8,*] and Simon Rule[12,*]

Ibrutinib, Obinutuzumab and Venetoclax for Relapsed and Untreated MCL: Response at End of Cycle 6

	Cohort A: relapsed patients, ibrutinib and obinutuzumab (n = 9)	Cohort B: relapsed patients, ibrutinib, obinutuzumab, and venetoclax (n = 24)	Cohort C: untreated patients, ibrutinib, obinutuzumab, and venetoclax (n = 15)
Response at end of cycle 6 (Cheson 99)			
CR/CRu	7 (78)	16 (67)	12 (80)
PR	0 (0)	2 (8)	2 (13)
SD	1 (11)	—	—
PD	1 (11)	4 (17)	1 (7)
Not done	—	2 (8)†	—
Response at end of cycle 6 (Lugano)			
CR	7 (78)	16 (67)	13 (86)
PR	1 (11)	1 (4)	1 (7)
PD	1 (11)	5 (21)	1 (7)
Not done	—	2 (8)†	—

Le Gouill S et al. *Blood* 2021;137(7):877-87.

Three-Year Follow-Up of Outcomes With KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma in ZUMA-2

Michael L. Wang, MD[1]; Javier Munoz, MD, MS, FACP[2]; Andre Goy, MD[3]; Frederick L. Locke, MD[4]; Caron A. Jacobson, MD, MMSc[5]; Brian T. Hill, MD, PhD[6]; John M. Timmerman, MD[7]; Houston Holmes, MD, MBA, FACP[8]; Ian W. Flinn, MD, PhD[9]; David B. Miklos, MD, PhD[10]; John M. Pagel, MD, PhD, DSc[11]; Marie José Kersten, MD, PhD[12]; Roch Houot, MD, PhD[13]; Amer Beitinjaneh, MD[14]; Weimin Peng, PhD[15]; Xiang Fang, PhD[15]; Rhine R. Shen, PhD[15]; Rubina Siddiqi, PhD[15]; Ioana Kloos, MD[15]; Patrick M. Reagan, MD[16]

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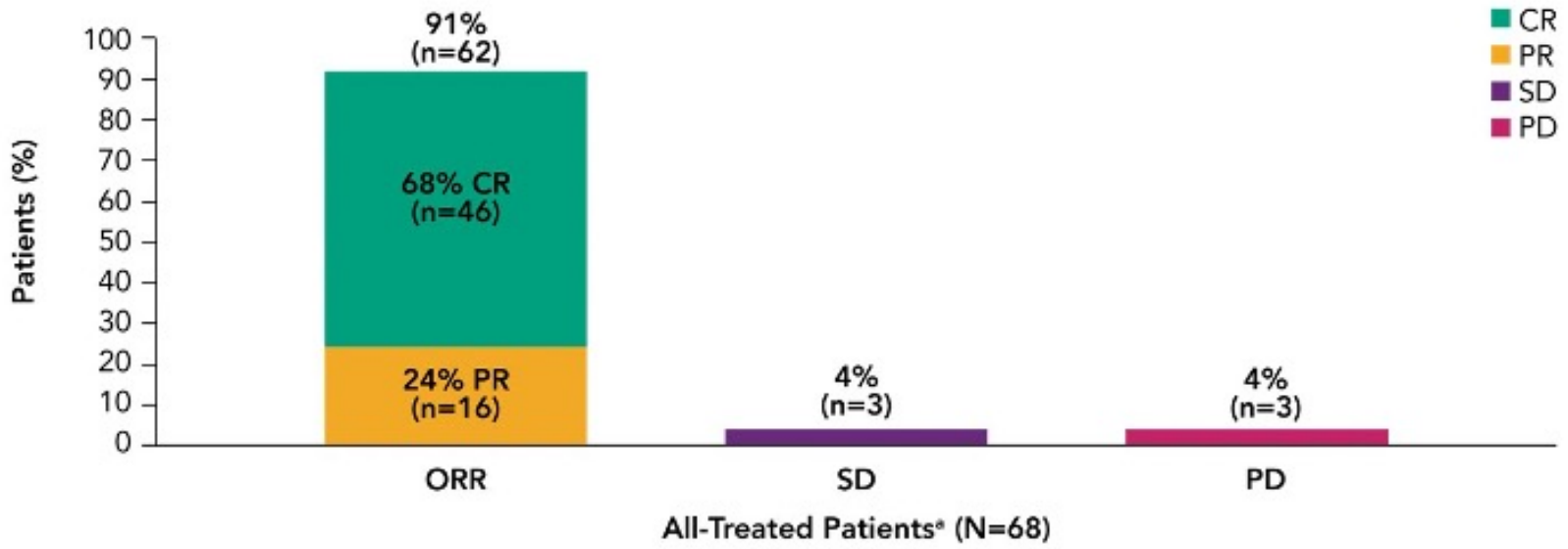
Disclosures

Michael L. Wang: honoraria from Janssen, Acerta Pharma, OMI, Physicians' Education Resources, Dava Oncology, CAHON, Hebei Cancer Prevention Federation, Clinical Care Options, Mumbai Hematology Group, Anticancer Association, Newbridge Pharmaceuticals; consultancy or advisory role for InnoCare, Loxo Oncology, Juno, Oncternal, CStone, AstraZeneca, Janssen, VelosBio, Pharmacyclics, Genentech, Bayer Healthcare; research funding from Kite, Pharmacyclics, Janssen, AstraZeneca, Celgene, Loxo Oncology, Juno, BioInvent, VelosBio, Acerta Pharma, Oncternal, Verastem, Molecular Templates, Lilly, InnoCare.

ASCO 2022;Abstract 7518.

ZUMA-2 Three-Year Follow-Up: Objective Response Rate (ORR) with Brexucabtagene Autoleucel for All Patients Receiving Treatment (N = 68)



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

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

Wang ML et al. ASCO 2022;Abstract 7518.

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

Palomba ML et al.

ASH 2020;Abstract 118.

TRANSCEND NHL-001: Preliminary Efficacy and Safety of Lisocabtagene Maraleucel for R/R MCL at 2 Dose Levels

No. of Patients		Median # prior therapies (range)	ORR		CR		CRS		NE	
DL1	DL2		DL1	DL2	DL1	DL2	DL1	DL2	DL1	DL2
6	26	3 (1-7)	67%	88%	33%	65%	33%	54%	0	28%

DL1, 50 x 10^6 CAR T cells, DL2, 100 x 10^6 CAR T cells
CRS = cytokine release syndrome; NE = neurologic event

Palomba ML et al. ASH 2020;Abstract 118.

Thank you for joining us!

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

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