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: *Dr 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 and Lymphomas Agenda

MODULE 1: Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

MODULE 2: Bispecific Antibodies; Diffuse Large B-Cell Lymphoma

MODULE 3: Mantle Cell Lymphoma

Chronic Lymphocytic Leukemia and Lymphomas Agenda

MODULE 1: Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

MODULE 2: Bispecific Antibodies; Diffuse Large B-Cell Lymphoma

MODULE 3: Mantle Cell Lymphoma

RTP
RESEARCH
TO PRACTICE

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

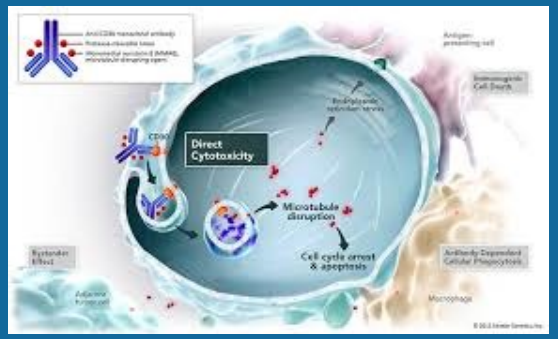
Bleomycin lung toxicity

BEACOPP

Improved PFS compared with ABVD

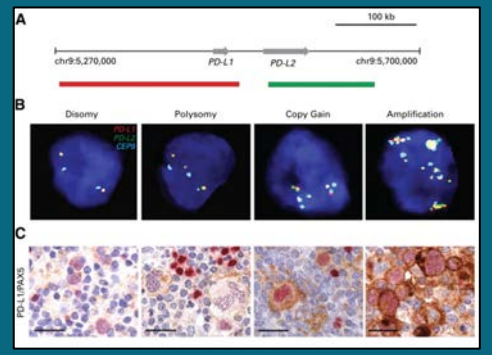
Associated with Infertility/stem cell damage

Brentuximab vedotin



Peripheral neuropathy

PD-1 inhibitors

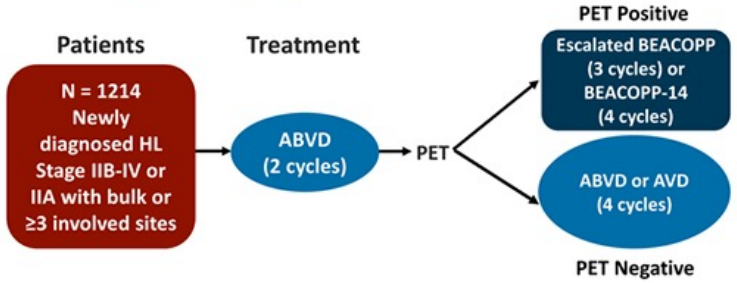


Low rates of irreversible toxicity but rare severe

Roemer et al JCO 2016

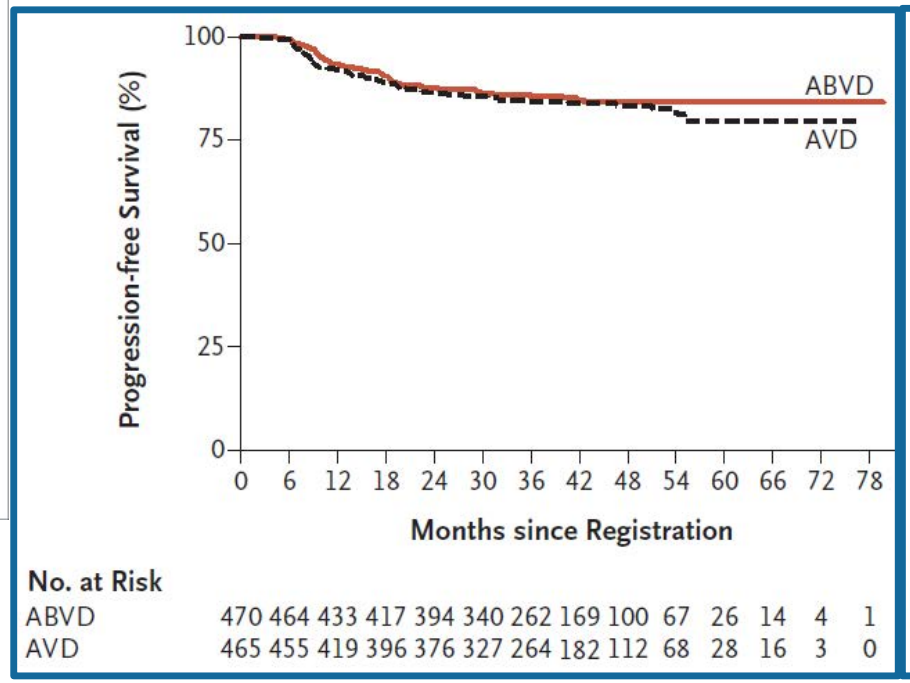
PET adapted therapy in unfavorable II-IV cHL

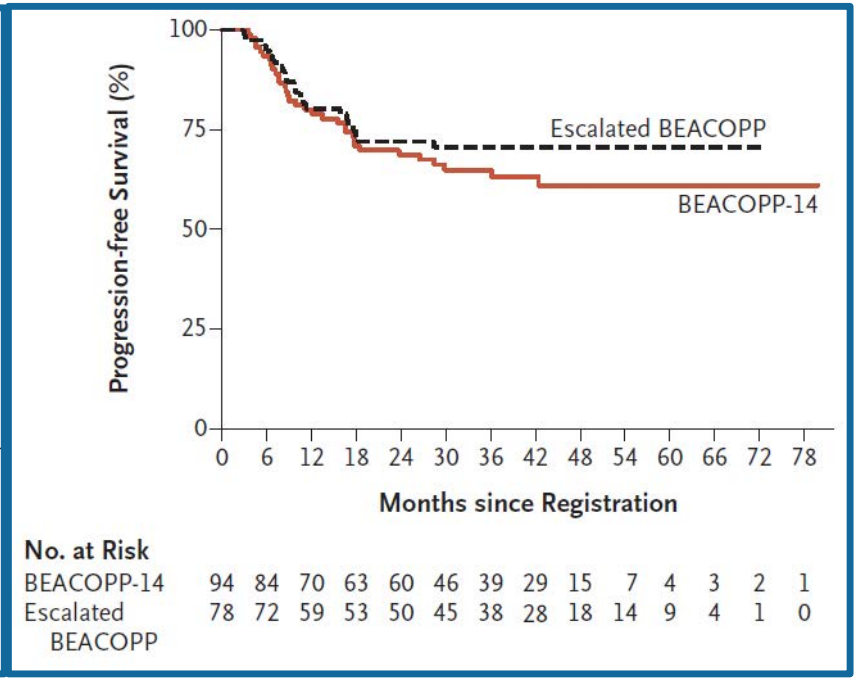
RATHL: Response-adapted Treatment in Hodgkin Lymphoma FDG-PET



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]

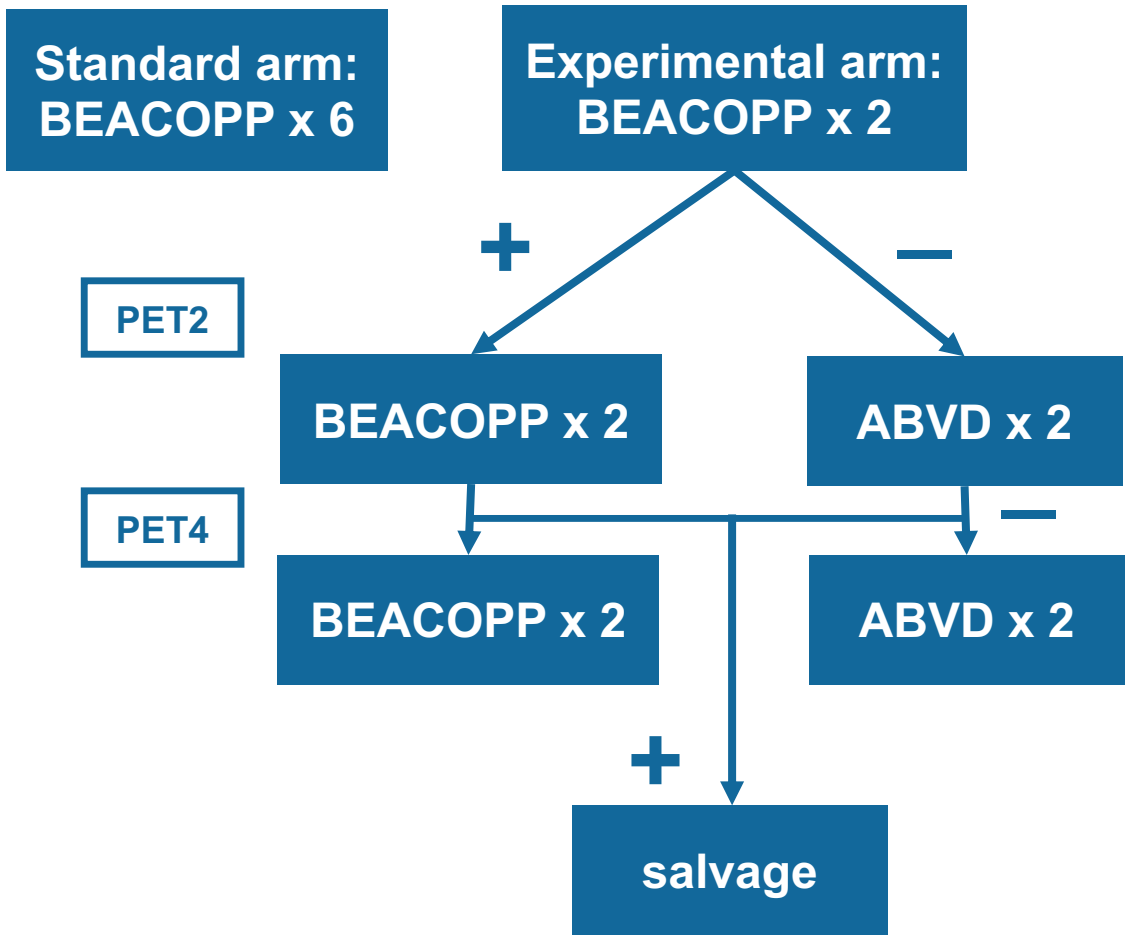


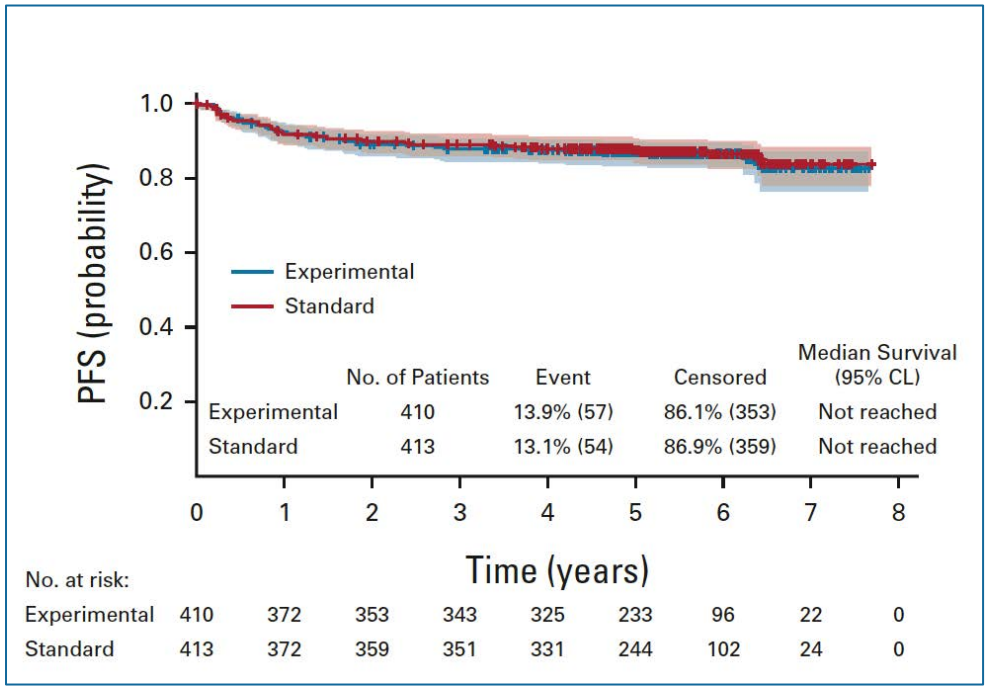


Stage III/IV ≤ 60
3 yr PFS: 82%

Johnson et al. NEJM 2016

PET driven de-escalated approach with favorable outcomes

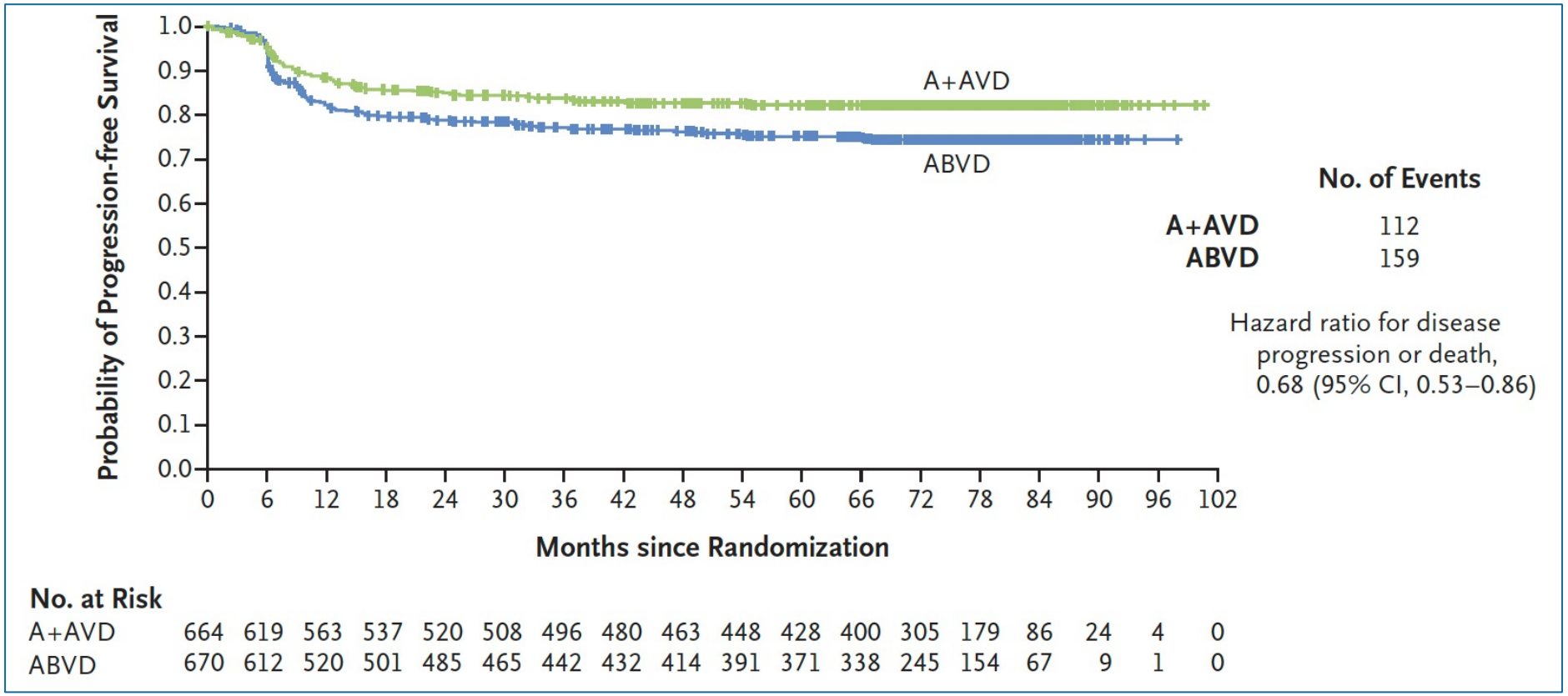




Risk Factors	No. (%)	5-Year PFS, % (95% CI)
PET2/PET4		
PET2–/PET4–	654 (79)	92.3 (89.9 to 94.1)
PET2+/PET4–	62 (7.5)	75.4 (62.5 to 84.4)
PET4+	43 (5.2)	46.5 (31.2 to 60.4)
IPS		
0-2	343 (42)	90.3 (85.8 to 93.4)
≥ 3	475 (58)	82.8 (78.5 to 86.3)

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)

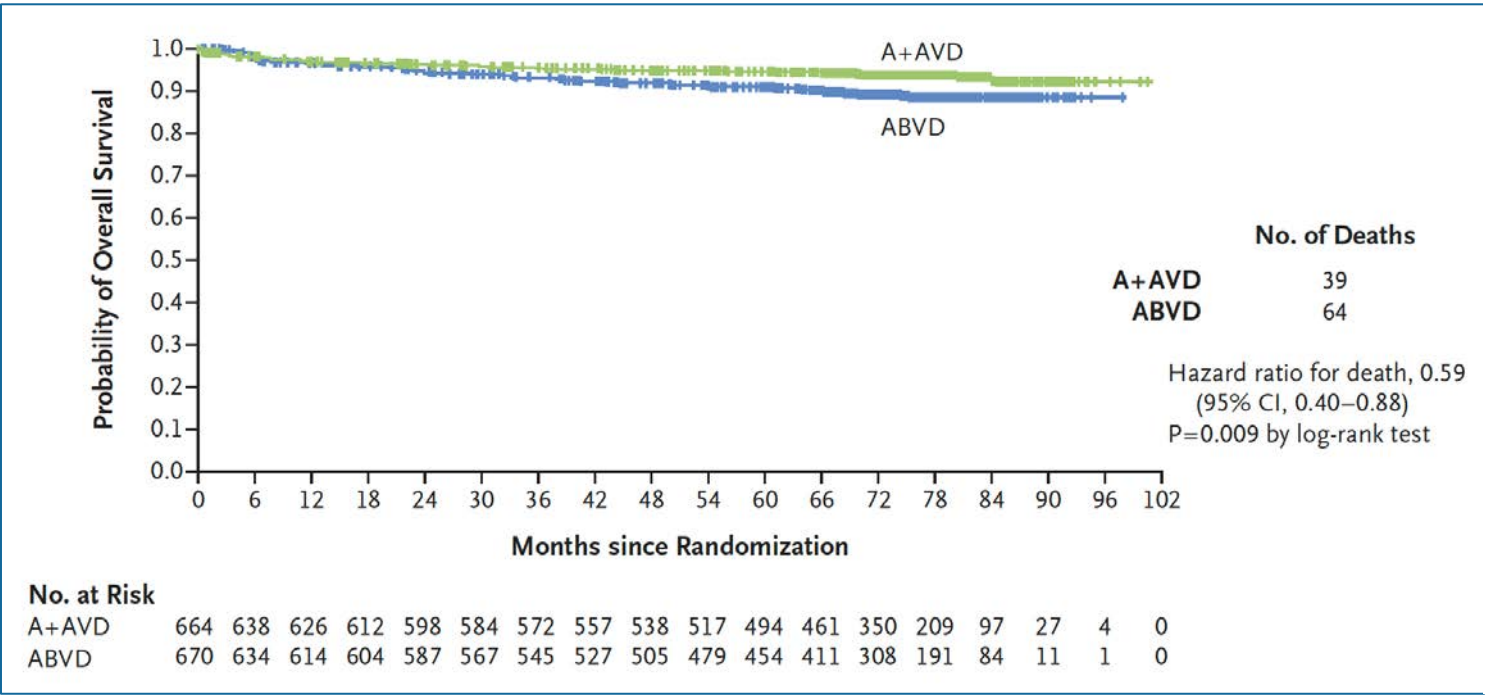


Table 1. Summary of Causes of Death (Safety Population).*

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

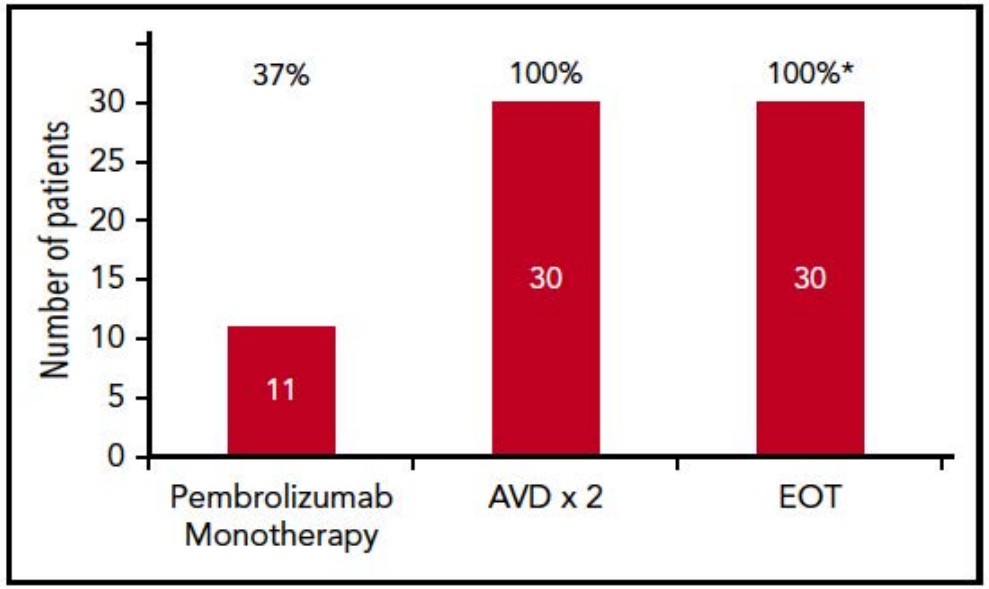
AVD x 4-6

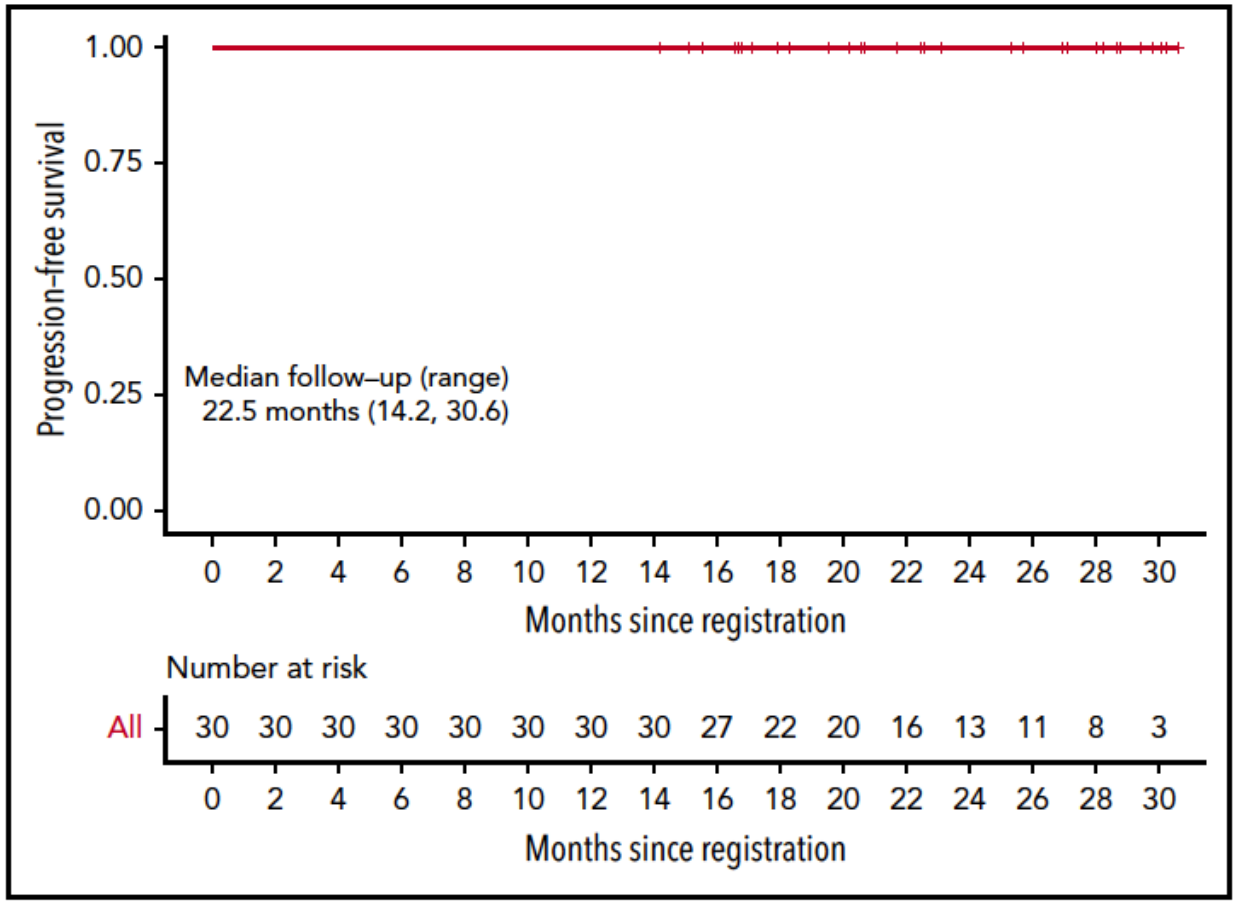
Characteristic	Patients (N = 30)	
	n	%
Median age, y (range)	29 (21-77)	
Age 45-60	4	13.3
Age >60	4 (67-77)	13.3
Sex		
Male	11	36.7
Female	19	63.3
Disease stage		
IIA	6	20.0
IIB	6	20.0
IIB with >10 cm mass	5	16.7
IIIA	4	13.3
IIIB	1	3.3
IVA	6	20.0
IVB	7	23.3

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

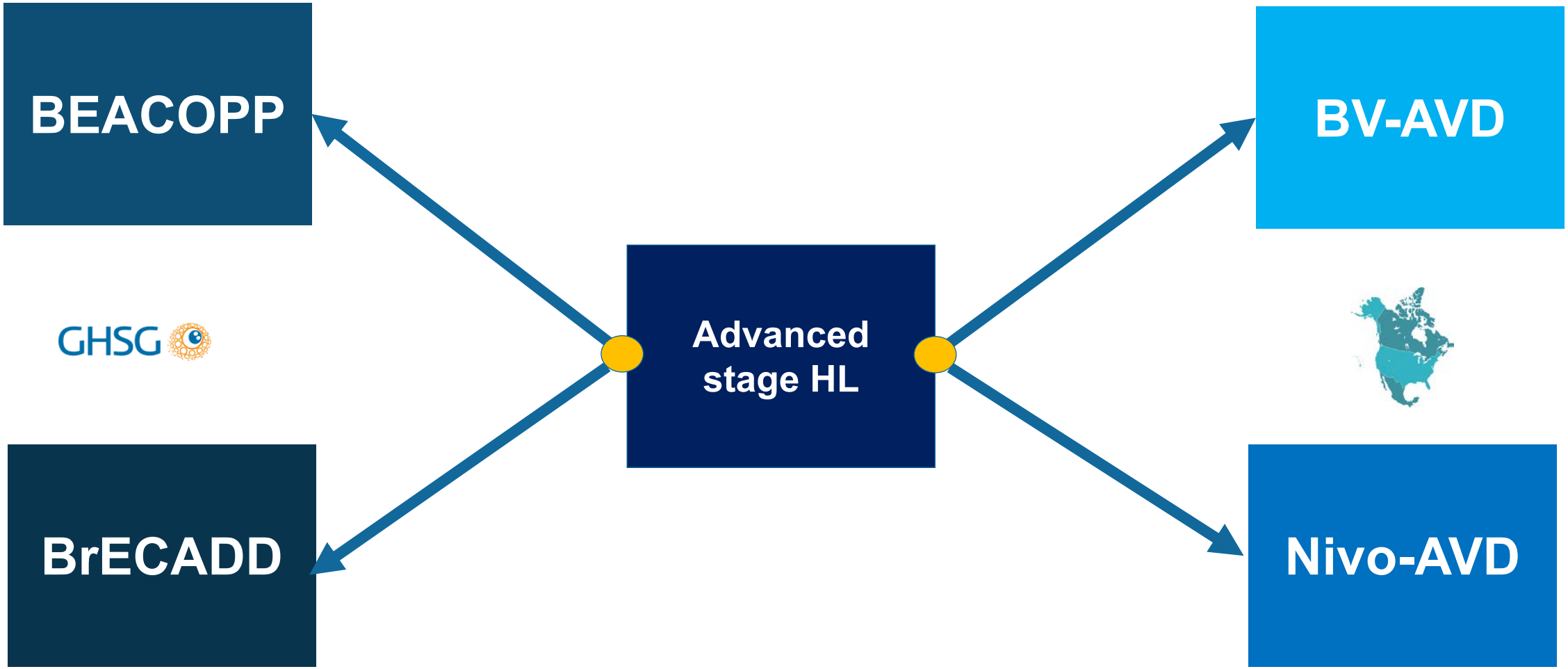
Pembrolizumab+AVD in early unfavorable and advanced stage HL





Allen et al. Blood 2021

On-going trials in advanced stage HL



Dana-Farber
Cancer Institute

CLL

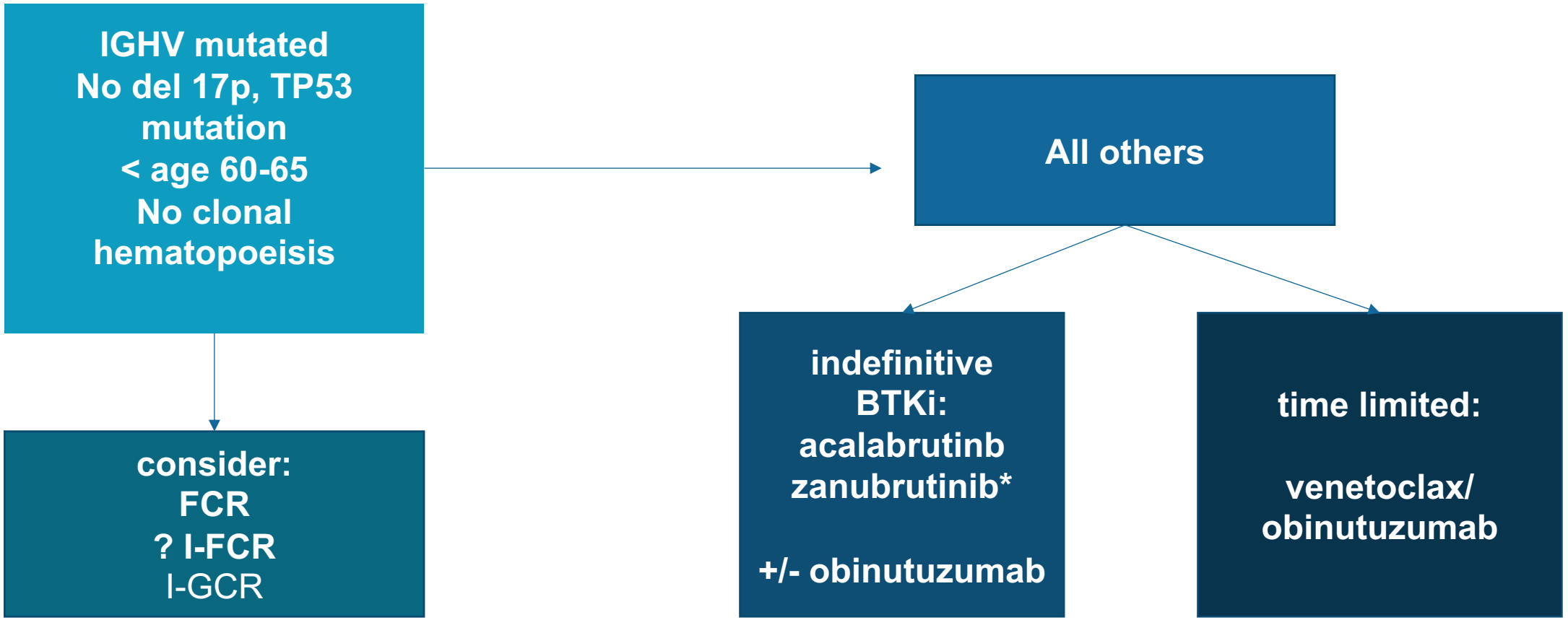
Treatment for previously untreated CLL

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.

Hodgkin Lymphoma

Discussion Questions

Hodgkin Lymphoma

- Regulatory and reimbursement issues aside, in which situations do you generally feel brentuximab vedotin (BV)/AVD is the preferred first-line treatment for advanced-stage HL?
- What is generally your preferred first-line treatment for patients with advanced-stage HL who are not fit and have comorbidities?
- Regulatory and reimbursement issues aside, in which situations do you generally feel BV/AVD is the preferred first-line treatment for limited-stage HL?
- What do you predict will be the preferred first-line treatment for advanced-stage HL in 5 years?

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

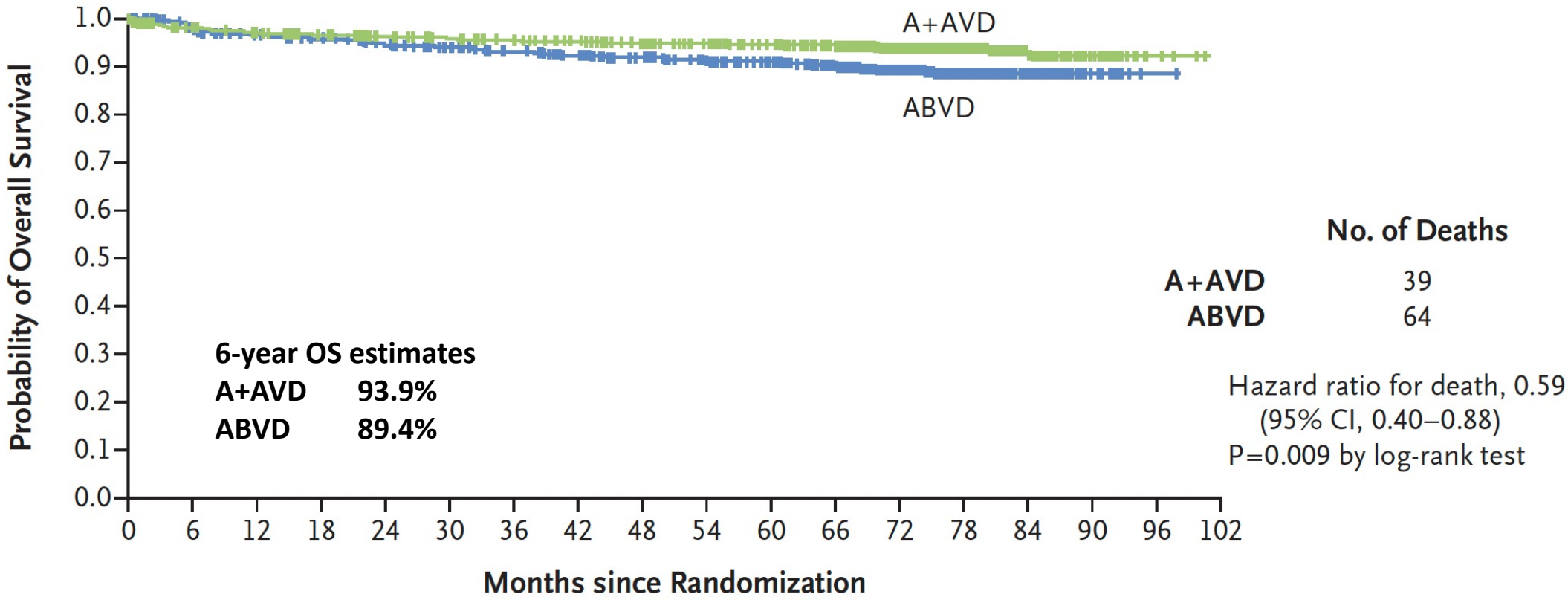
The NEW ENGLAND JOURNAL of MEDICINE

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*

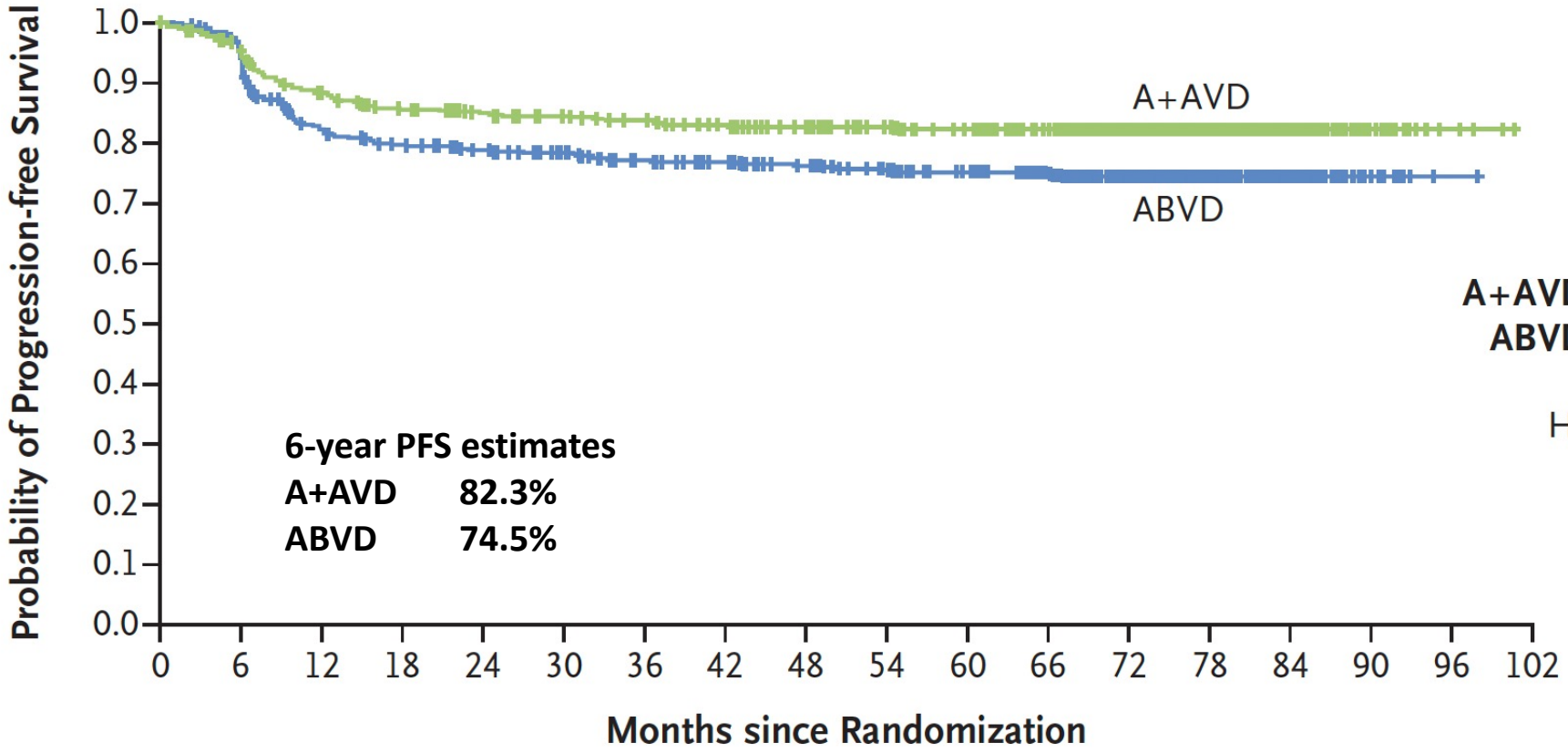
ECHELON-1 Primary Endpoint: Overall Survival (ITT Population)



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.

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



6-year PFS estimates

A+AVD	**82.3%**
ABVD	**74.5%**

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

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].

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)

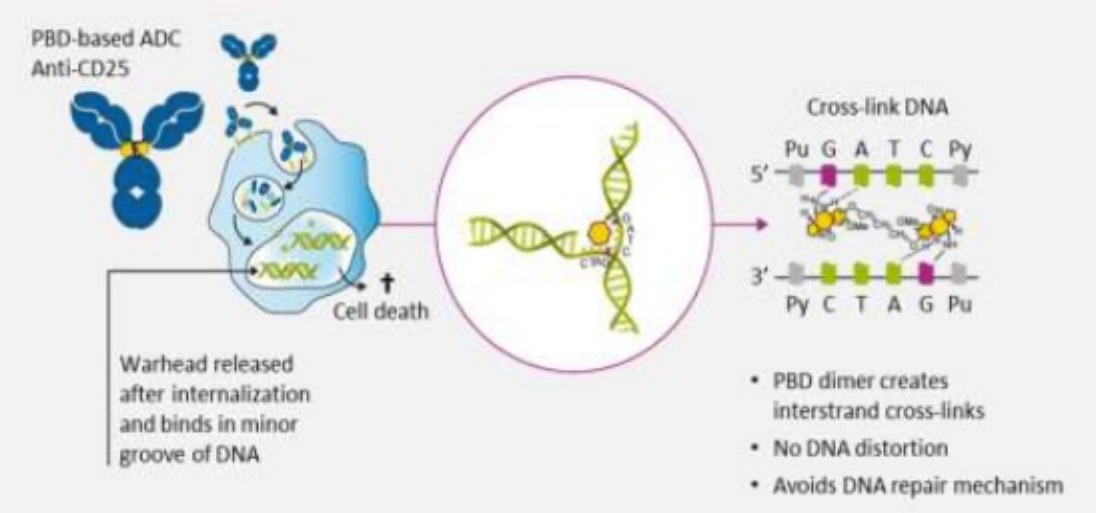
Carmelo Carlo-Stella[1]*, Stephen Ansell[2], Pier Luigi Zinzani[3], John Radford[4], Kami Maddocks[5], Antonio Pinto[6], Graham P. Collins[7], Veronika Bachanova[8], Nancy Bartlett[9], Isabelle Bence-Bruckler[10], Mehdi Hamadani[11], Justin Kline[12], Jiri Mayer[13], Kerry J. Savage[14], Ranjana Advani[15], 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:

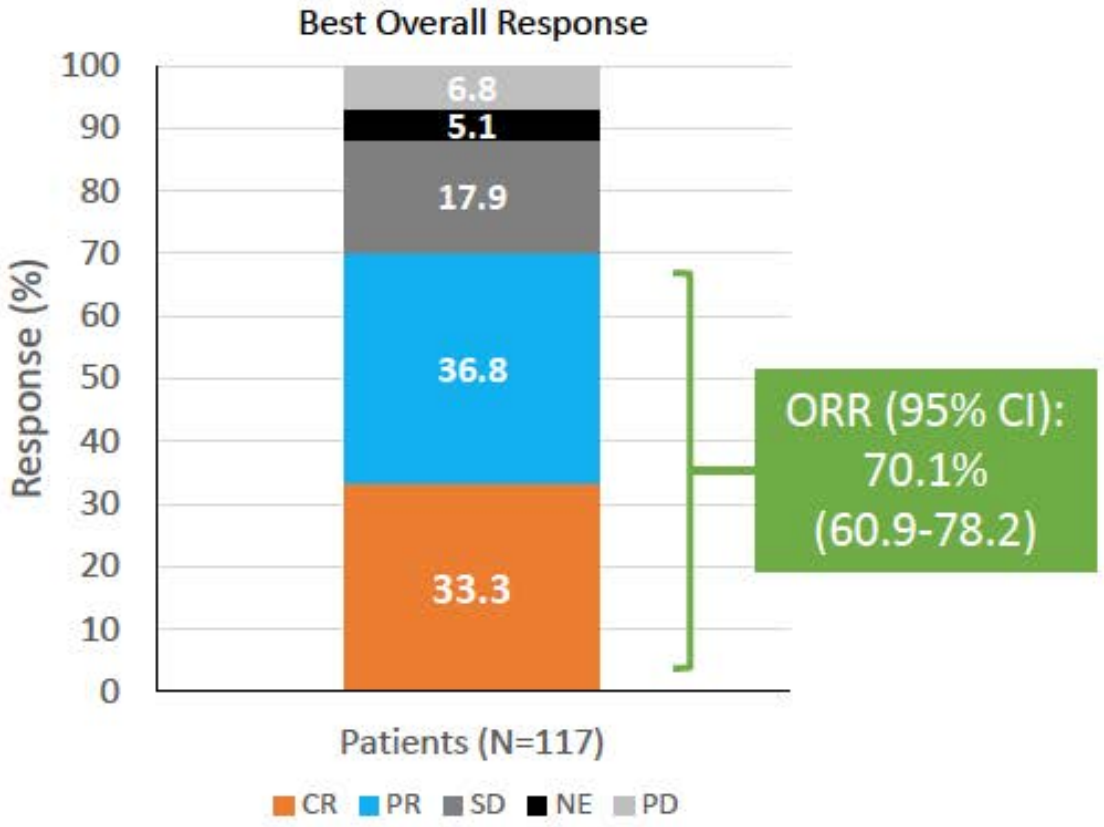
- In a Phase 1 trial that included patients with R/R cHL who received Cami at a dose of 45 µg/kg and achieved an overall response rate (ORR; CR + PR) of 86.5%[7]
- In the initial findings of this Phase 2 study of patients with R/R cHL, who achieved an ORR of 83.0%[8]

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.

Chronic Lymphocytic Leukemia

Discussion Questions

Chronic Lymphocytic Leukemia

- What do you consider the minimal biomarker workup for a patient requiring treatment?
- In which situations, if any, will you treat a patient with CLL who doesn't meet the classic indications for treatment (eg, adverse risk factors, fatigue)?
- In a patient who requires treatment, how do you choose between a BTK inhibitor and venetoclax-based strategies? Which BTK inhibitor do you choose, and when do you add an anti-CD20 monoclonal antibody? Which anti-CD20 antibody do you add to venetoclax, and which agent do you initiate first?
- Regulatory and reimbursement issues aside, are there situations in which you believe the optimal first-line treatment is a BTK inhibitor in combination with venetoclax?
- How do you manage high-risk CLL (eg, del[17p] disease)?

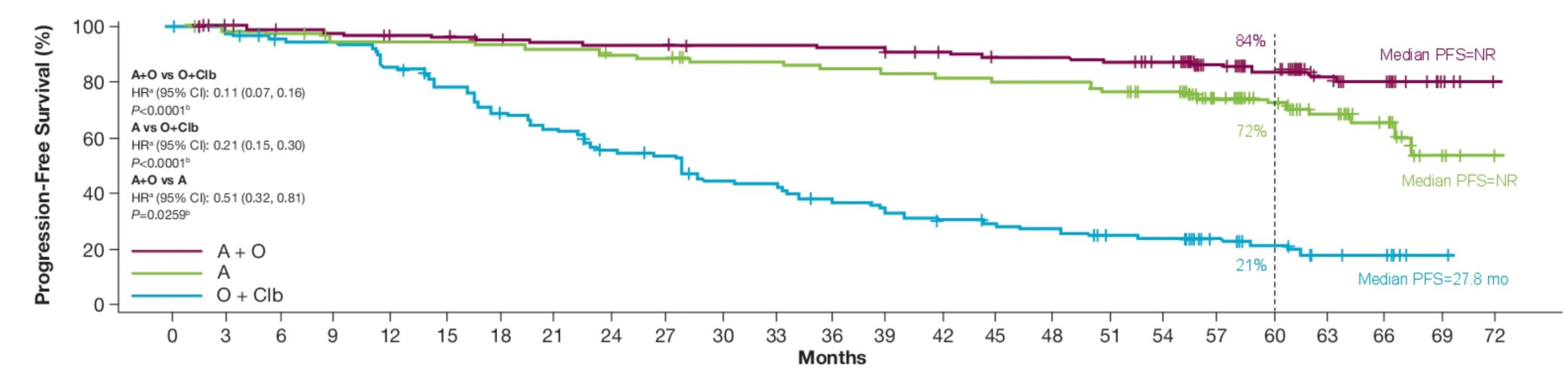
RTP RESEARCH TO PRACTICE

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.

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

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

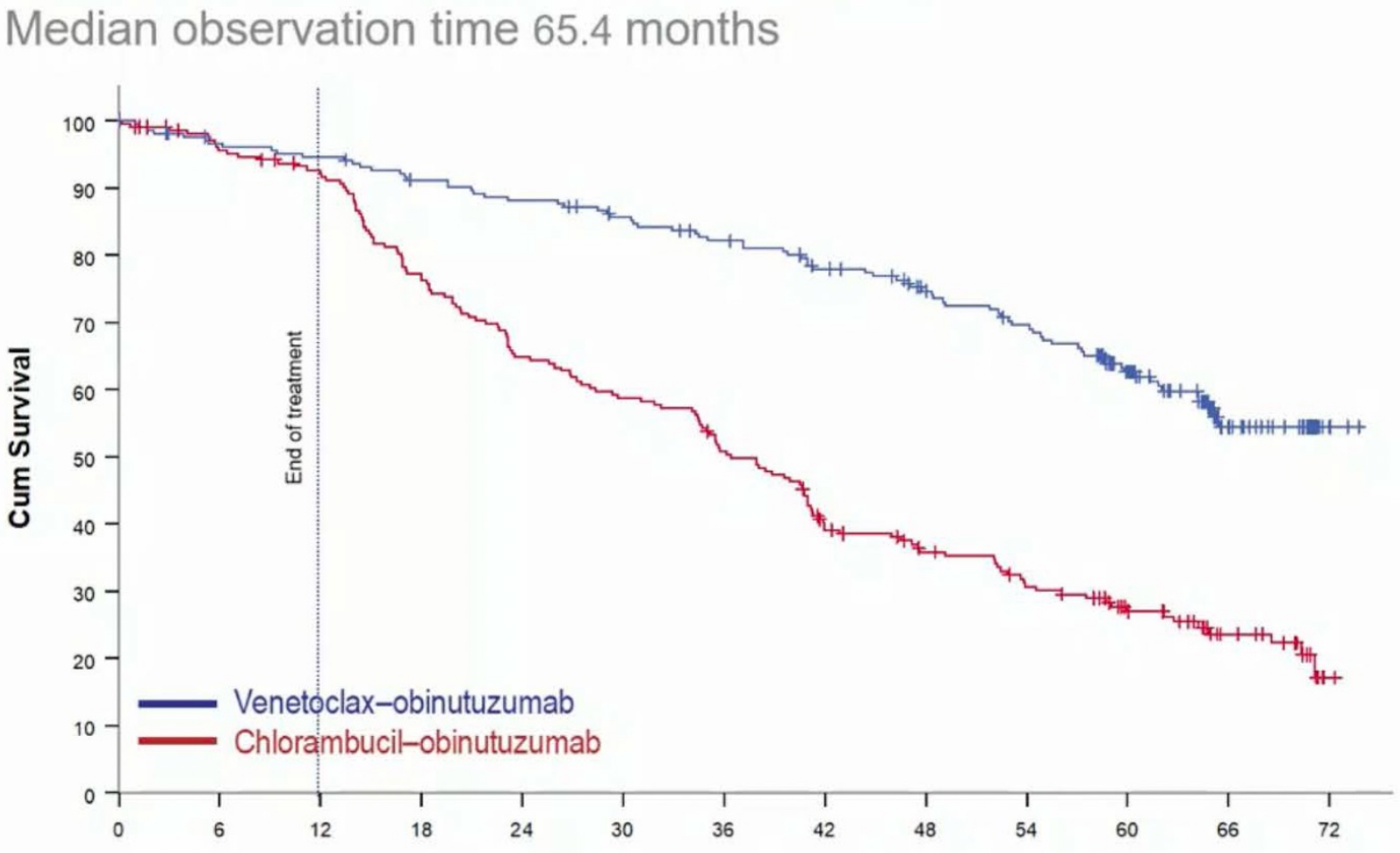
Venetoclax-Obinutuzumab for previously untreated chronic lymphocytic leukemia: 5-year results of the randomized CLL14 study

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

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

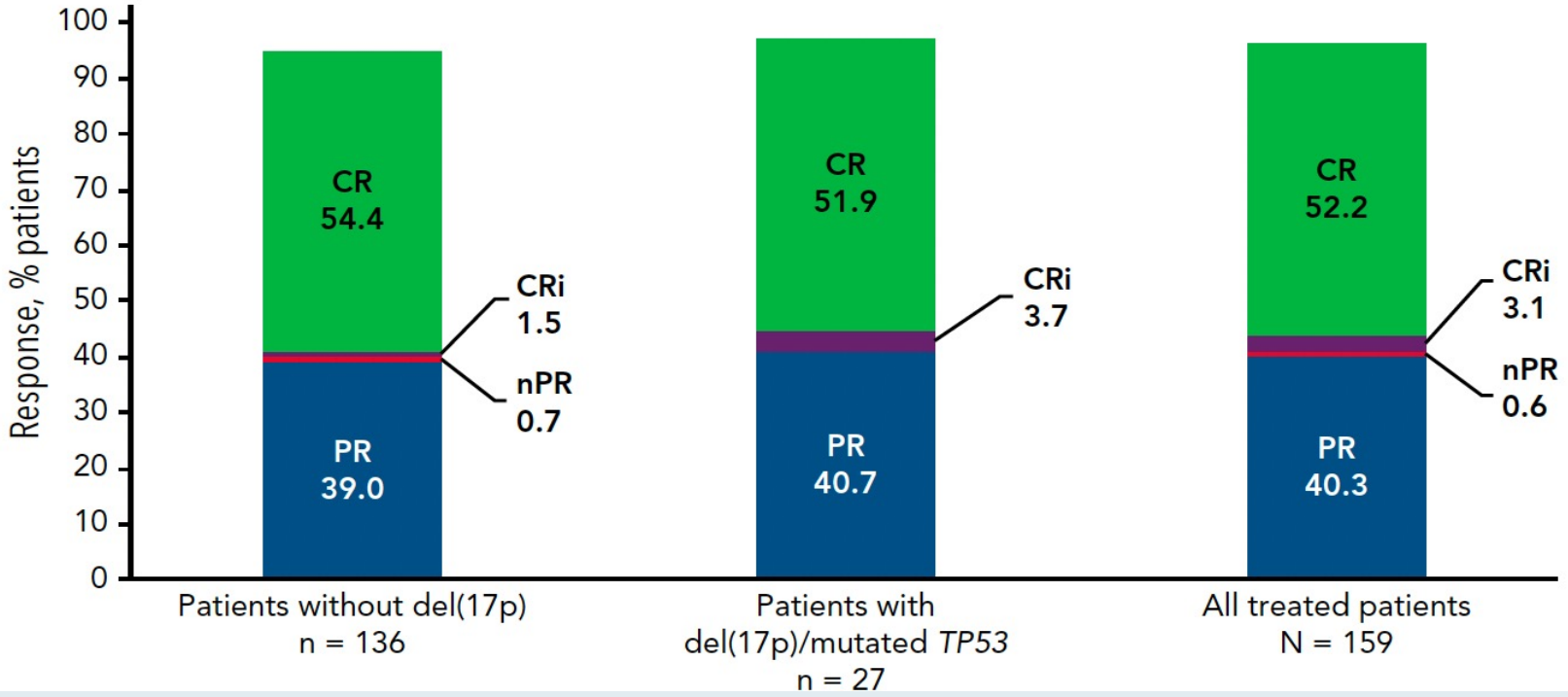
Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort

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

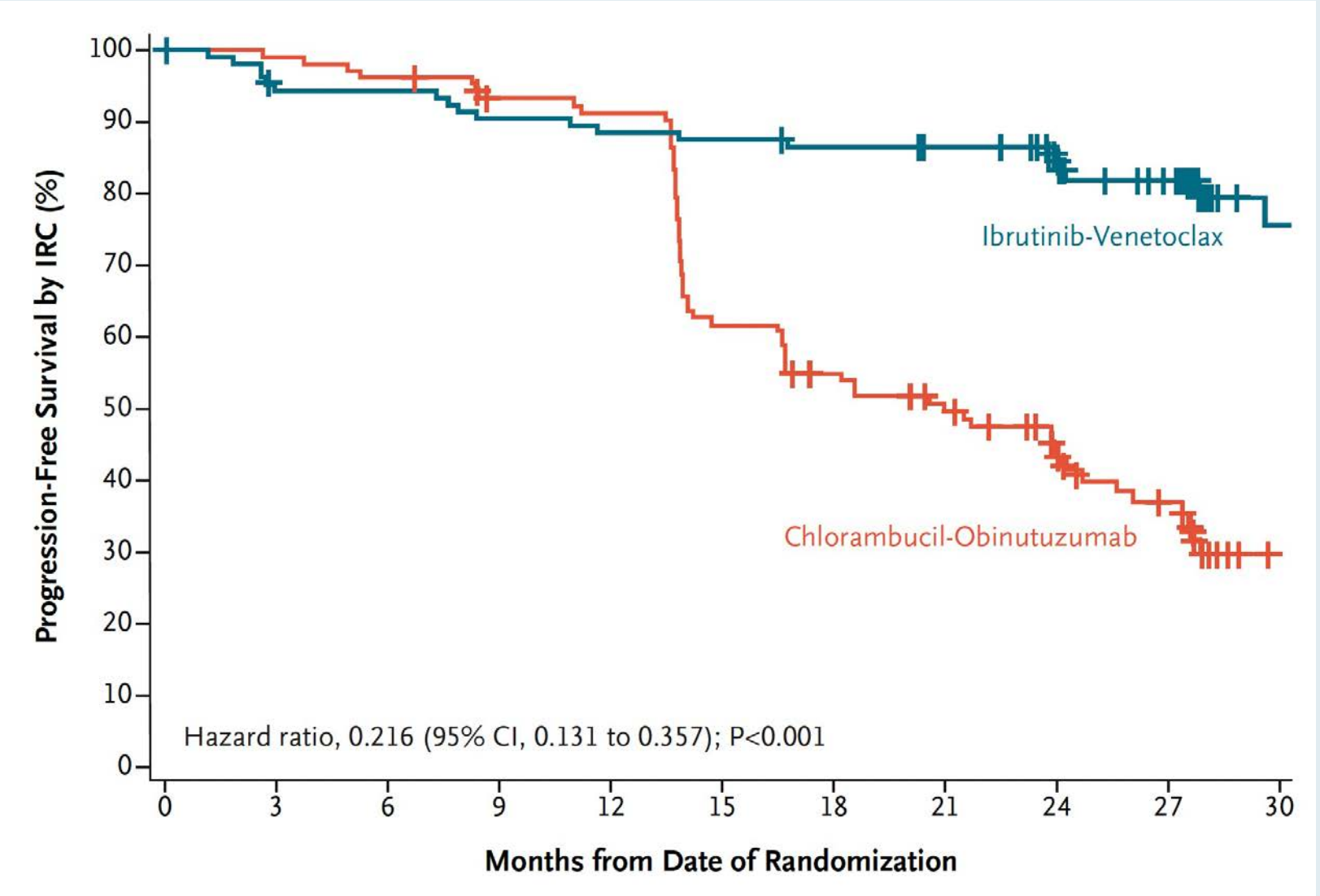
Published May 13, 2022;1(7).

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).

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

Anthony R. Mato[1], John M. Pagel[2], Catherine C. Coombs[3], Nirav N. Shah[4], Nicole Lamanna[5], Talha Munir[6], Ewa Lech-Maranda[7], Toby A. Eyre[8], Jennifer A. Woyach[9], William G. Wierda[10], Chan Y. Cheah[11], Jonathon B. Cohen[12], Lindsey E. Roeker[1], Manish R. Patel[13], Bita Fakhri[14], Minal A. Barve[15], Constantine S. Tam[16], David J. Lewis[17], James N. Gerson[18], Alvaro J. Alencar[19], Chaitra S. Ujjani[20], Ian W. Flinn[21], Suchitra Sundaram[22], Shuo Ma[23], Deepa Jagadeesh[24], Joanna M. Rhodes[25], Justin Taylor[19], Omar Abdel-Wahab[1], Paolo Ghia[26], Stephen J. Schuster[18], Denise Wang[27], Binoj Nair[27], Edward Zhu[27], Donald E. Tsai[27], Matthew S. Davids[28], Jennifer R. Brown[28], Wojciech Jurczak[29]

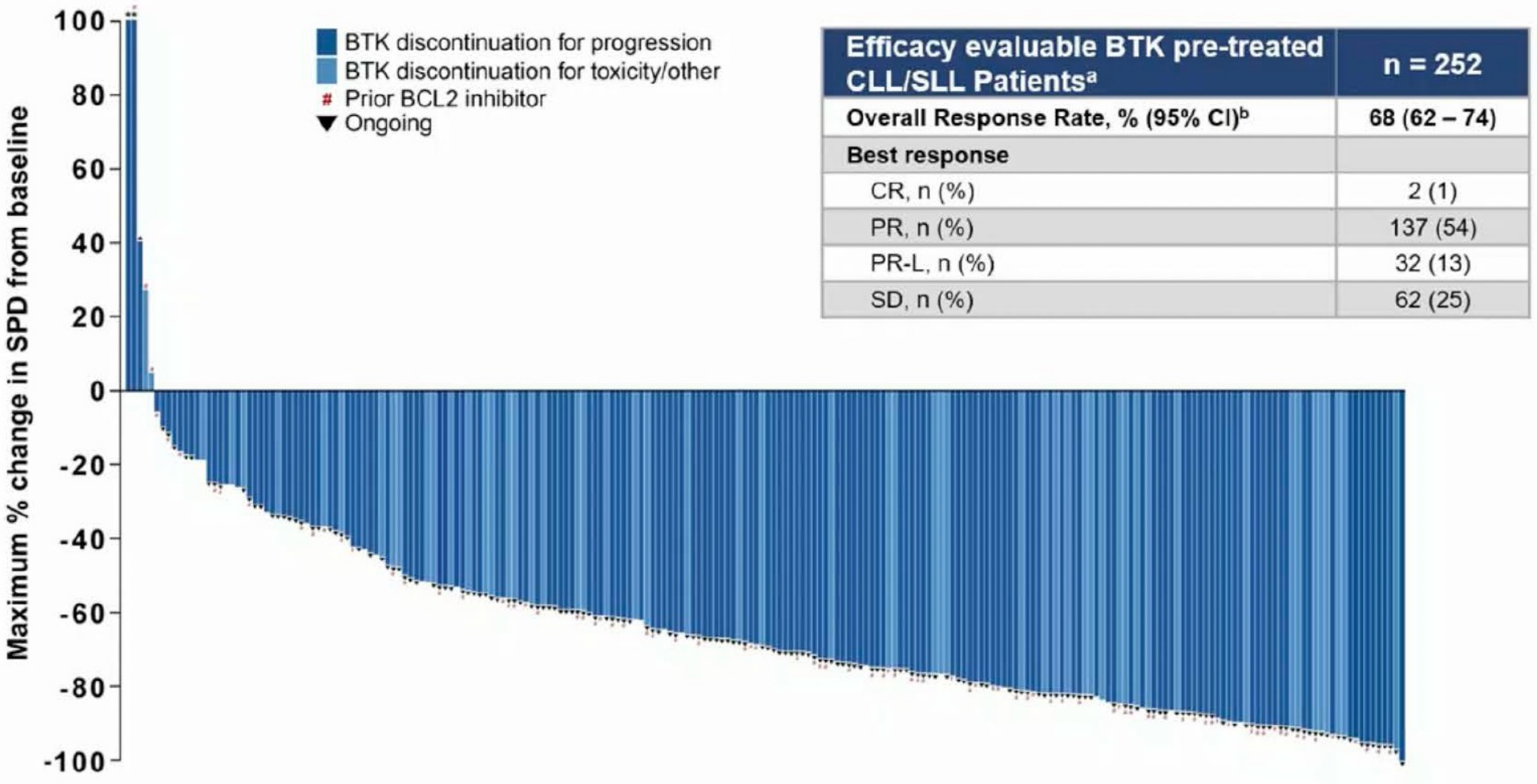
[1]Memorial Sloan Kettering Cancer Center, New York, USA; [2]Swedish Cancer Institute, Seattle, USA; [3]University of North Carolina at Chapel Hill, Chapel Hill, USA; [4]Medical College of Wisconsin, Milwaukee, USA; [5]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, USA; [6]Department of Haematology, St. James's University Hospital, Leeds, UK; [7]Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [8]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, Oxford, UK; [9]The Ohio State University Comprehensive Cancer Center, Columbus, USA; [10]MD Anderson Cancer Center, Houston, USA; [11]Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia; [12]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [13]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, USA; [14]University of California San Francisco, San Francisco, USA; [15]Mary Crowley Cancer Research, Dallas, USA; [16]Peter MacCallum Cancer Center, Royal Melbourne Hospital, and University of Melbourne, Melbourne, Australia; [17]Plymouth Hospitals NHS Trust - Derriford Hospital, Plymouth, UK; [18]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, USA; [19]University of Miami Miller School of Medicine, Miami, USA; [20]Fred Hutchinson Cancer Research Center, [21]Sarah Cannon Research Institute, Nashville, USA; [22]Department of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, [23]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; [24]Cleveland Clinic, Cleveland, OH, USA; [25]Northwell Health Cancer Institute, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Health, New Hyde Park, NY; [26]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [27]Loxo Oncology at Lilly, Stamford, CT, USA; [28]Dana-Farber Cancer Institute and Harvard Medical School, Boston, USA; [29]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland

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

Chronic Lymphocytic Leukemia and Lymphomas Agenda

MODULE 1: Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

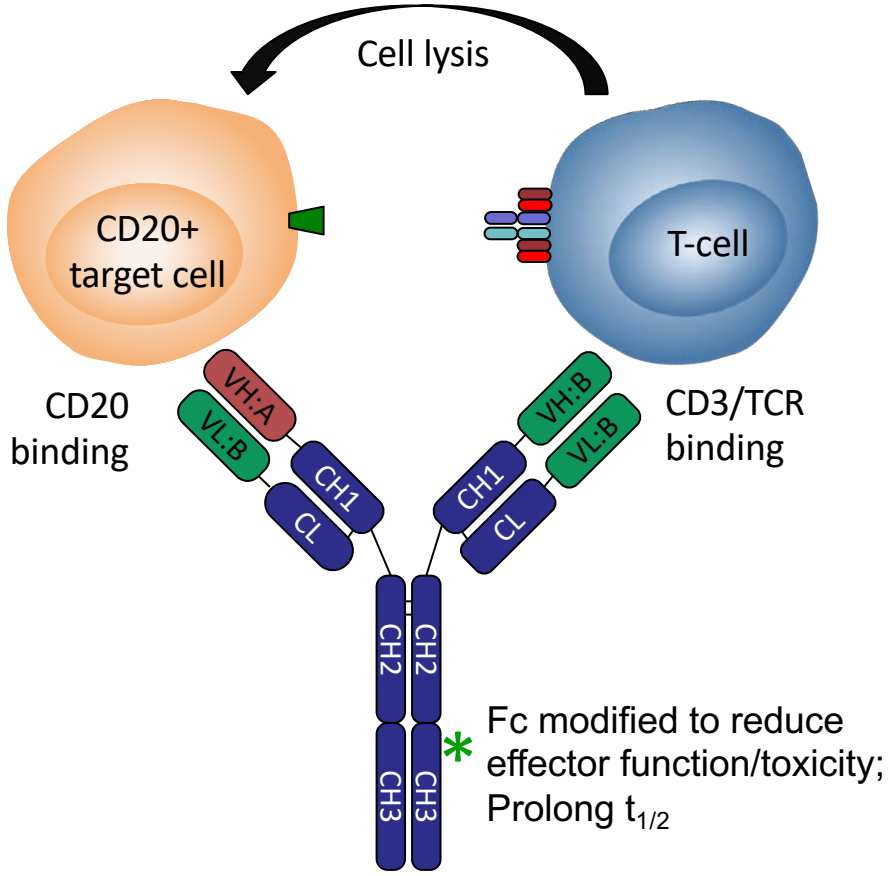
MODULE 2: Bispecific Antibodies; Diffuse Large B-Cell Lymphoma

MODULE 3: Mantle Cell Lymphoma

RTP RESEARCH TO PRACTICE

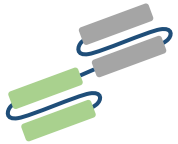
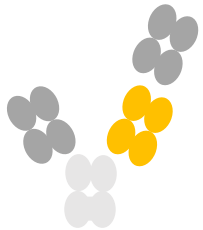
BiSpecific Antibodies
CD3-CD20

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)

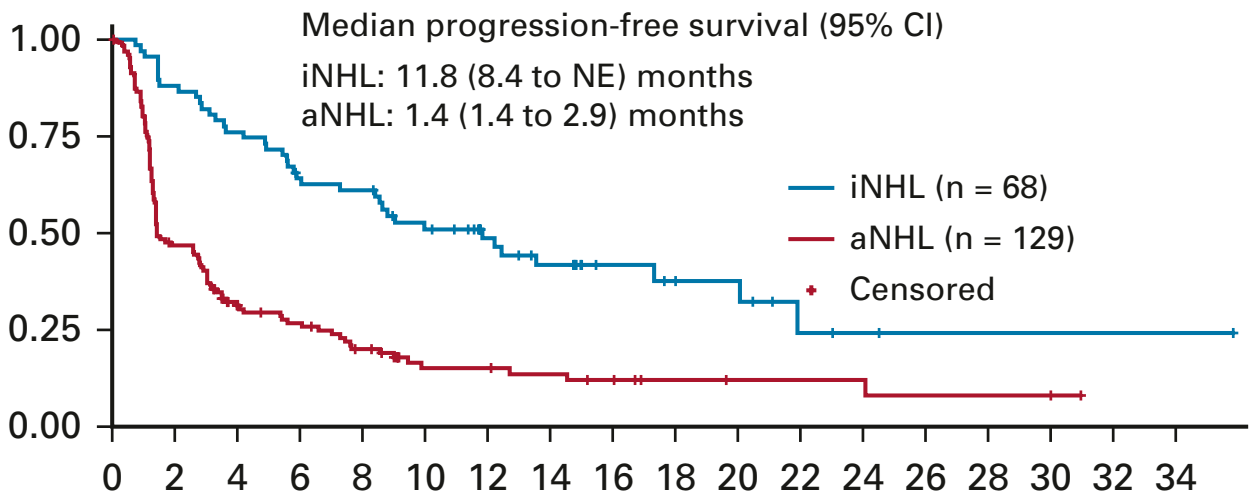
	Mosunetuzumab	Odronextamab	Epcoritamab	Glofitamab
ROUTE	IV	IV	SQ	IV
CYCLES	Q21d Weekly c1 Q21d ≥ cycle 2	Q21d 2x/wk cycle 1 Weekly cycles 2-4 Then q14d	Q28d Weekly x 3 cycles Q14d x 6 cycles Q28d ≥ cycle 10	Q21d Q21d x 12
DURATION	PD/toxicity	PD/toxicity	PD/toxicity	Fixed duration
CRS MITIGATION	Step-up 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?

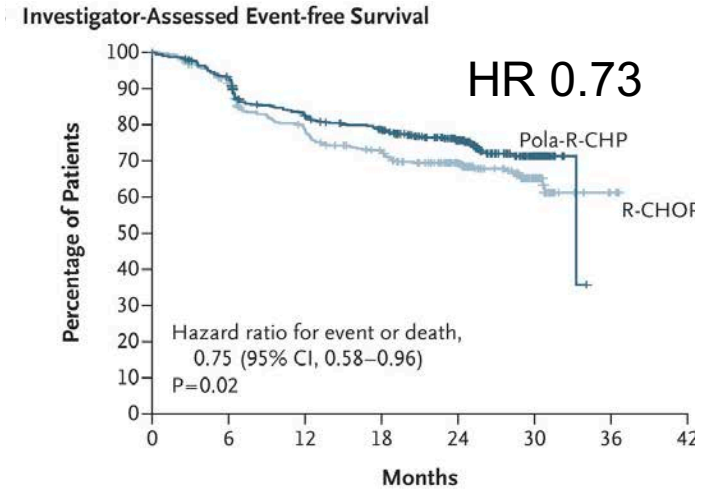
Targeted Trials in Up-Front DLBCL: R-CHOP ± X

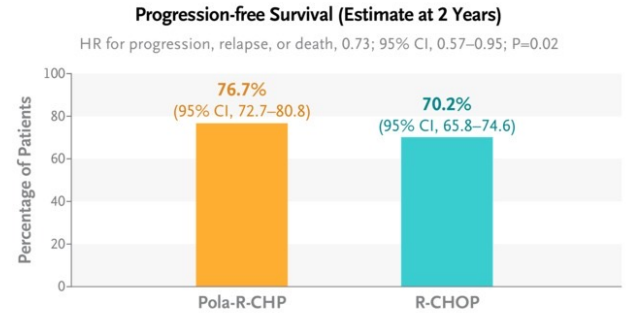
Target	Randomized Phase II/III Studies	n	R-CHOP ±	Primary Endpoint Outcome	Result
NF-κB	PYRAMID	399	Bortezomib	No PFS improvement in non-GCB DLBCL	Neg
NF-κB	REMoDL-B	201	Bortezomib	No PFS improvement in GCB/ABC DLBCL	Neg
CD20	GOYA	1418	GA101-CHOP vs R-CHOP	No PFS improvement	Neg
BTK	PHOENIX	838	Ibrutinib	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	?

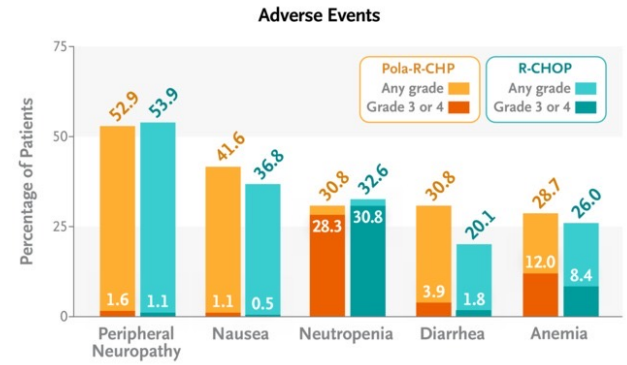
Courtesy of Kieron Dunleavy, modified

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



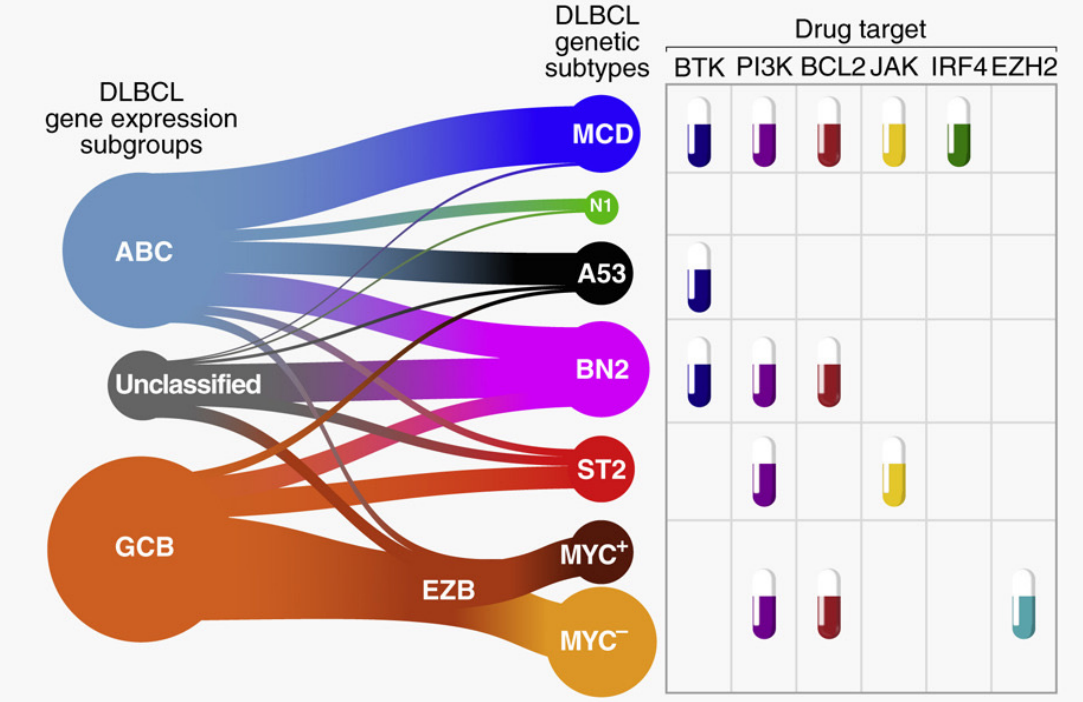


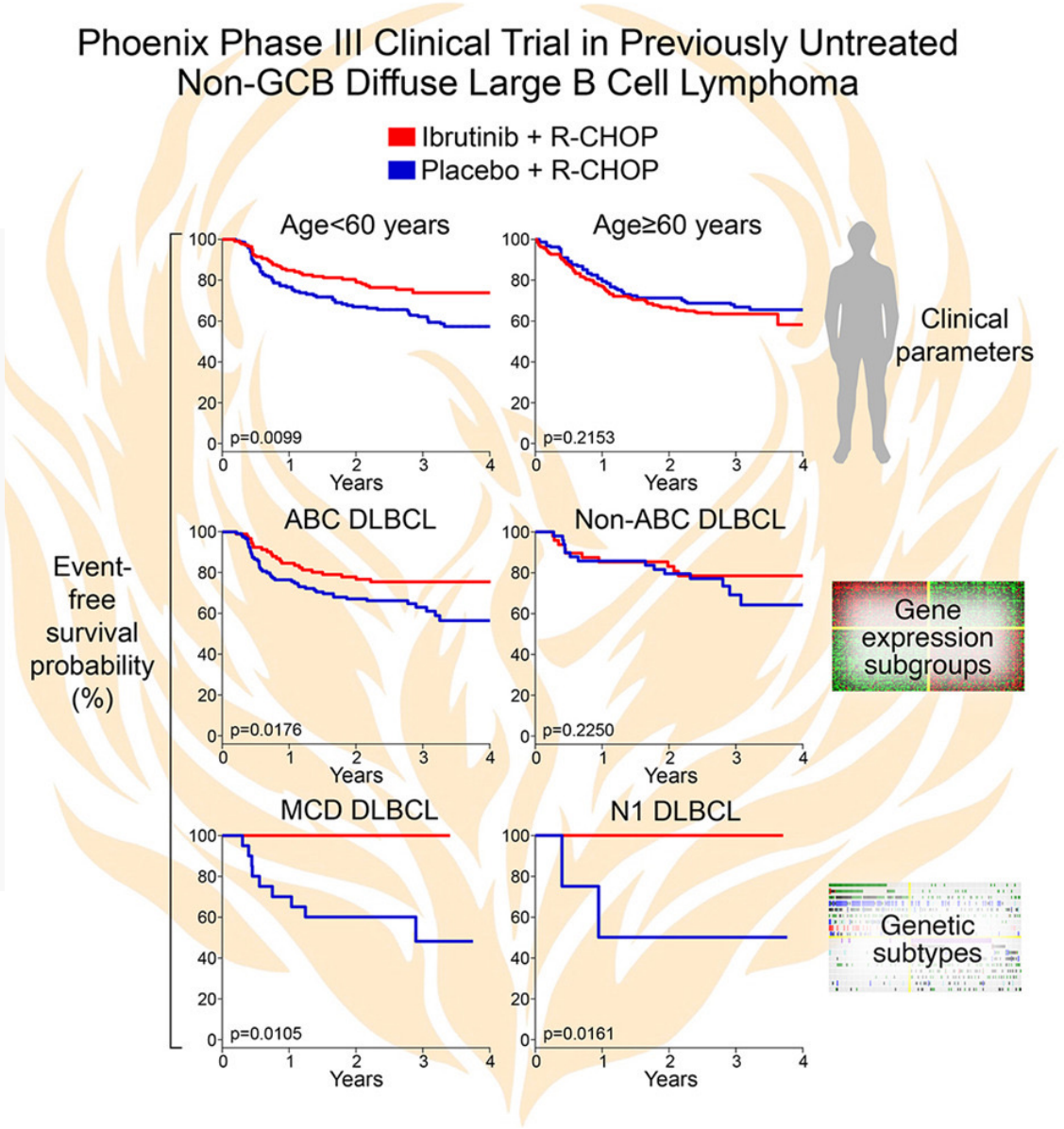


Tilly et al. NEJM 2022

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

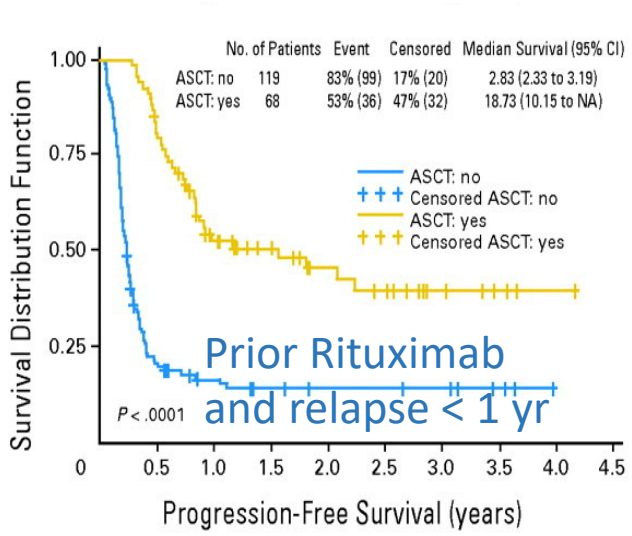
This was a NEGATIVE trial overall

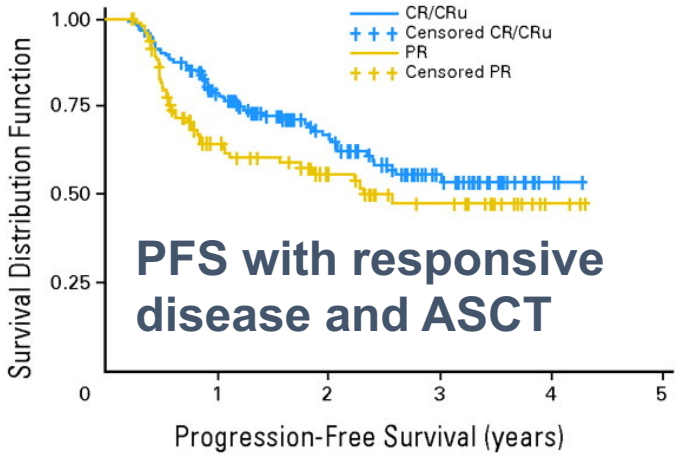




Wright GW et al Cancer Cell 2020
Wilson WH et al Cancer Cell 2021

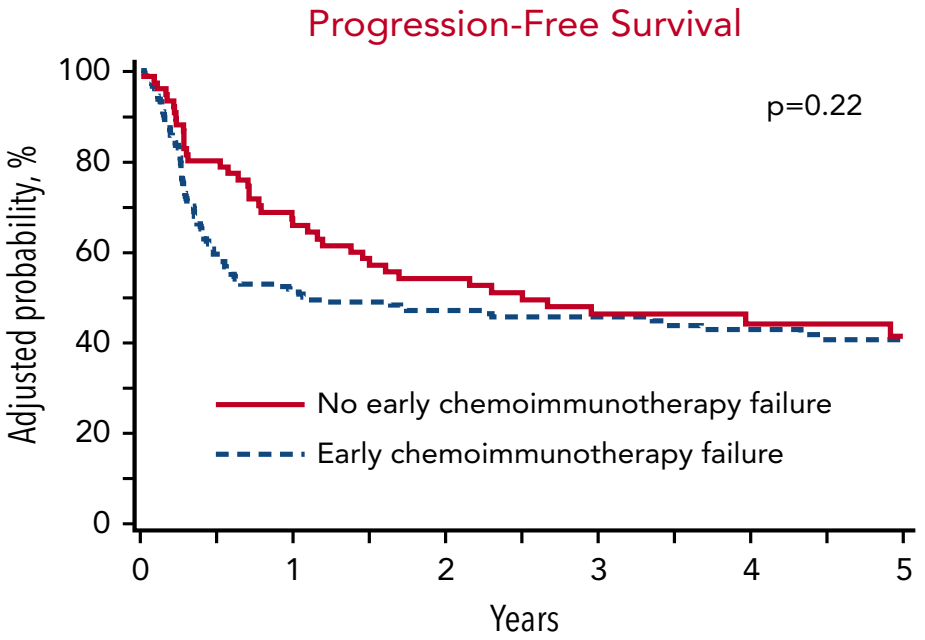
CORAL Study: CD20+ DLBCL 1st Relapse/1° Refractory R-ICE vs R-DHAP → HDC/SCT (then ± Rituximab)





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

ASCT benefit in chemosensitive DLBCL even with early relapse: CIBMTR

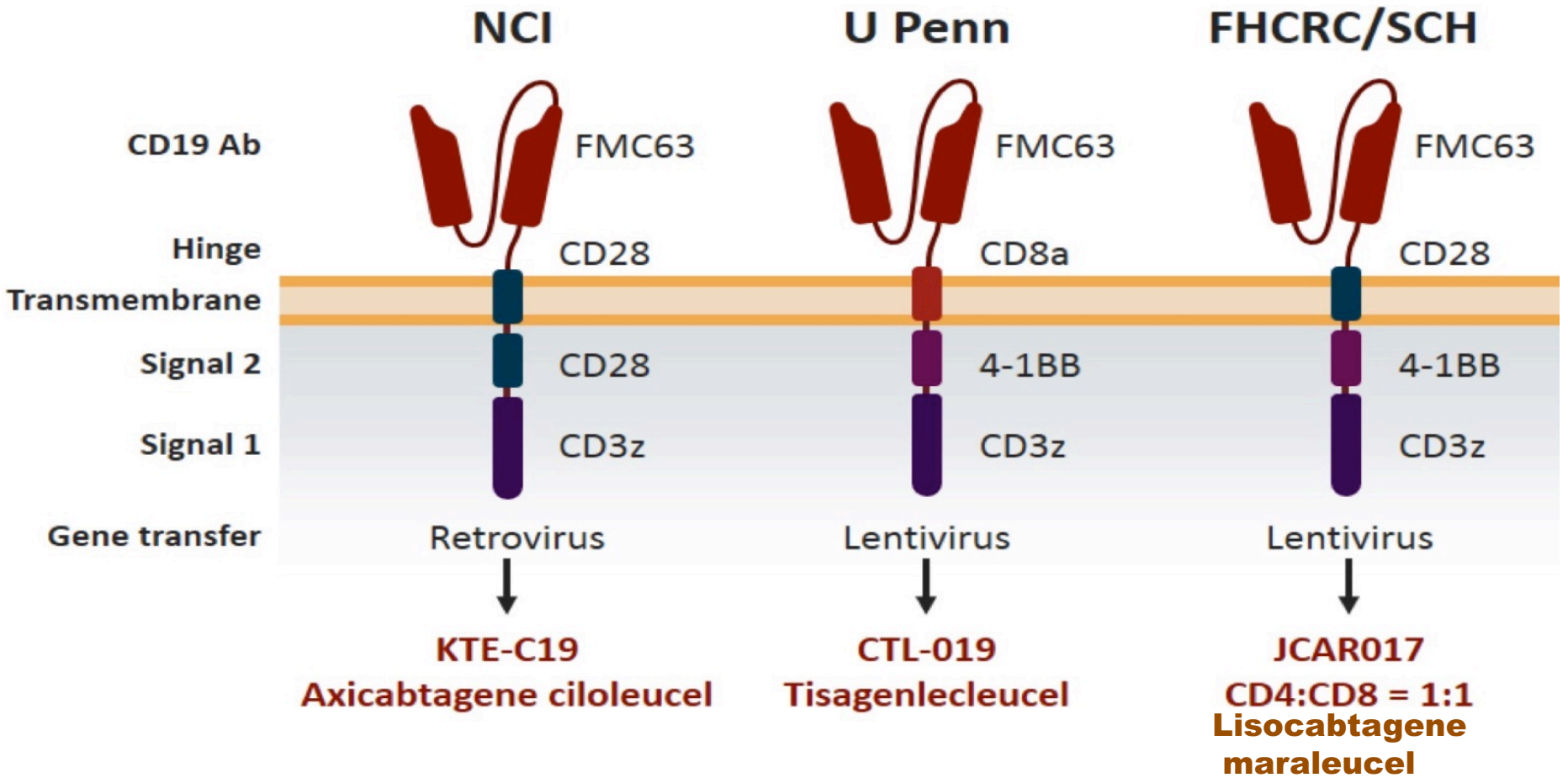


Shah N et al. Blood 2021; Bal S et al. Trans Cell Ther 2021

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 DLBCL



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.

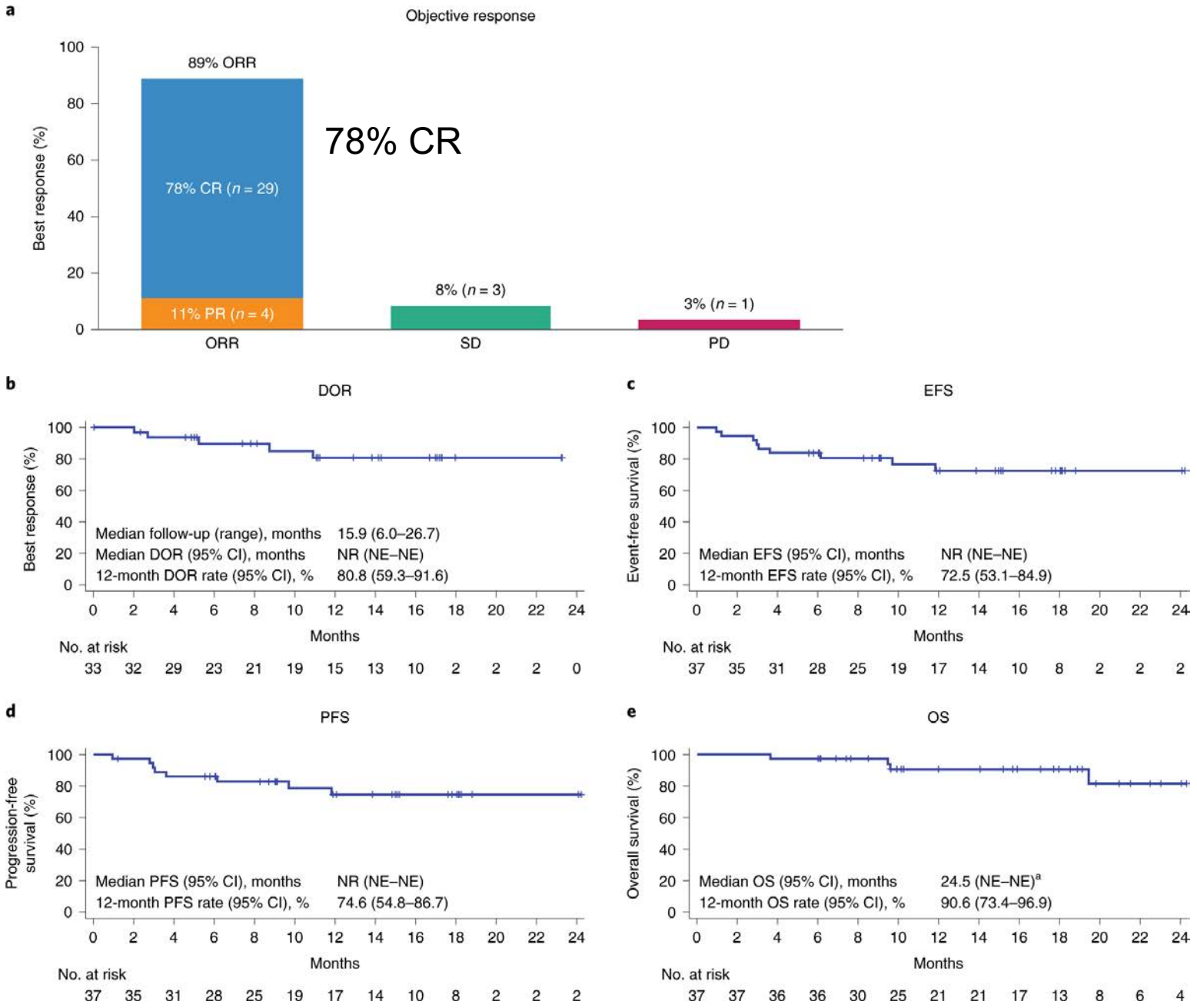
Phase 3 DLBCL trials (CART vs SOC)

	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

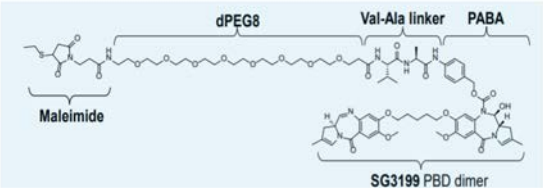
	L-MIND[1-3] Tafasitamab + LEN (N= 80)
Median follow-up	17.3 months
ORR	60%
CR	42.5%
mDOR	21.7 months
12-month DOR	71.6%
mOS	NR
12-month OS	73.7%
mPFS	12.1 months

- 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

Diffuse Large B-Cell Lymphoma

Discussion Questions

Bispecific Antibodies/CAR T-Cell Therapy/Diffuse Large B-Cell Lymphoma

- In which situations, if any, do you consider the POLARIX approach to be optimal?
- In which situations is ASCT ideal at first relapse, and when is CAR T-cell therapy preferable?
- Where do you see bispecifics being used as part of treatment for younger, fit and older, less fit patients with DLBCL and FL?
- Do you believe bispecifics will be administered by community-based general medical oncologists?
- Is there a preferred CAR T-cell platform in younger, fit and older, less fit patients with DLBCL?
- Are there a significant number of patients who are not fit enough to receive ASCT who can safely receive CAR T-cell therapy?
- What is the optimal sequence of tafasitamab/lenalidomide, selinexor, loncastuximab tesirine and polatuzumab vedotin/BR?

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

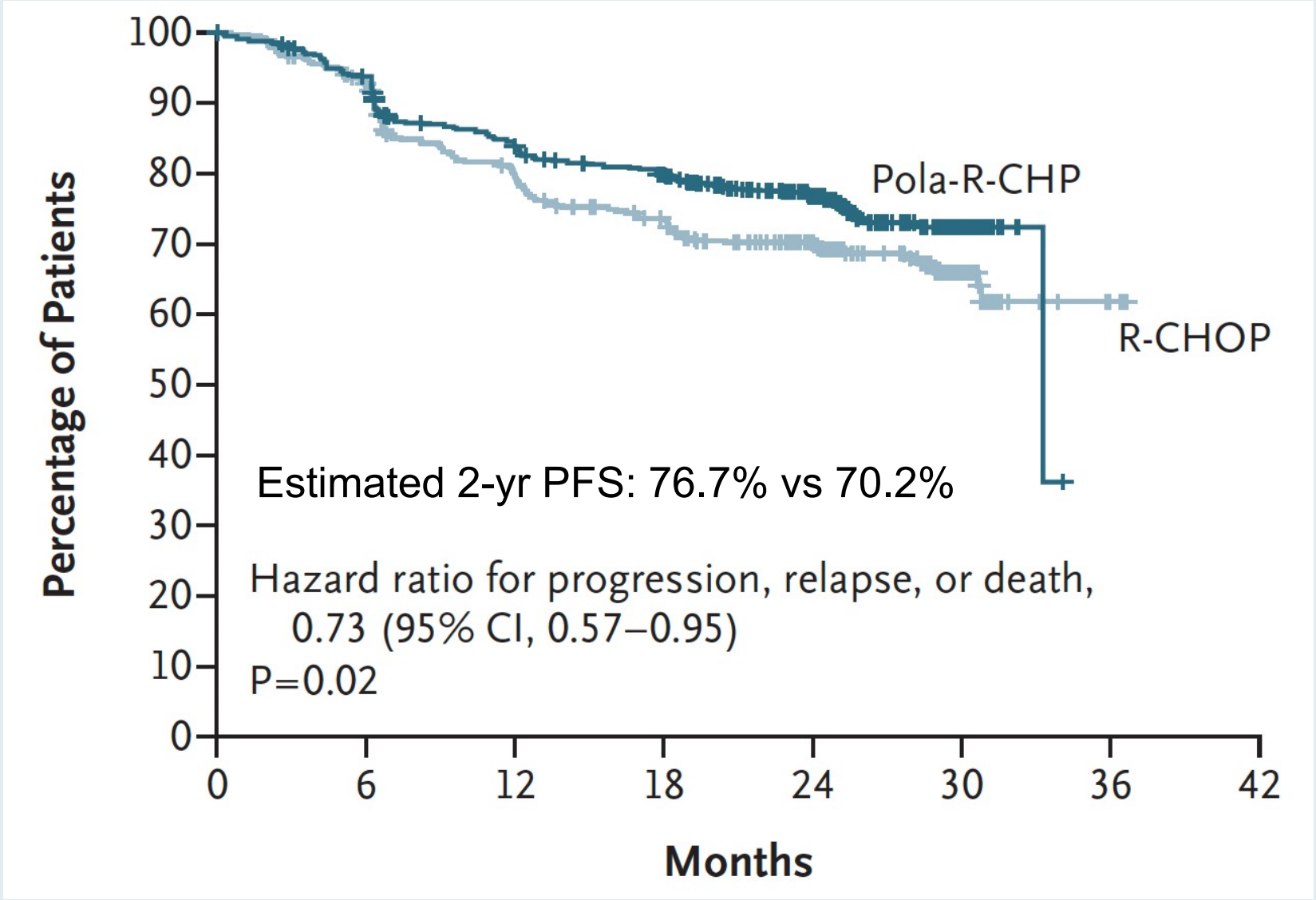
The NEW ENGLAND JOURNAL of MEDICINE

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

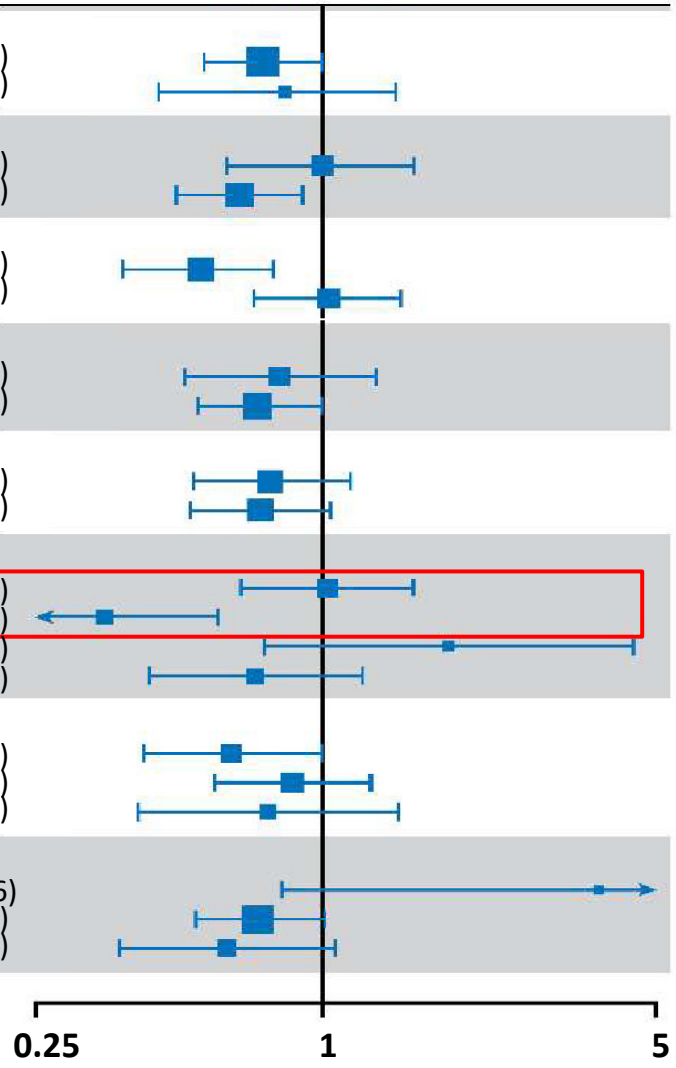
POLARIX: Investigator-Assessed Progression-Free Survival (Primary Endpoint)



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.

RTP RESEARCH TO PRACTICE

Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study

Alison Sehgal, Daanish Hoda, Peter A Riedell, Nilanjan Ghosh, Mehdi Hamadani, Gerhard C Hildebrandt, John E Godwin, Patrick M Reagan, Nina Wagner-Johnston, James Essell, Rajneesh Nath, Scott R Solomon, Rebecca Champion, Edward Licitra, Suzanne Fanning, Neel Gupta, Ronald Dubowy, Aleco D'Andrea, Lei Wang, Ken Ogasawara, Jerill Thorpe, Leo I Gordon

Lancet Oncology 2022;August;23(8):1066-77.

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‡

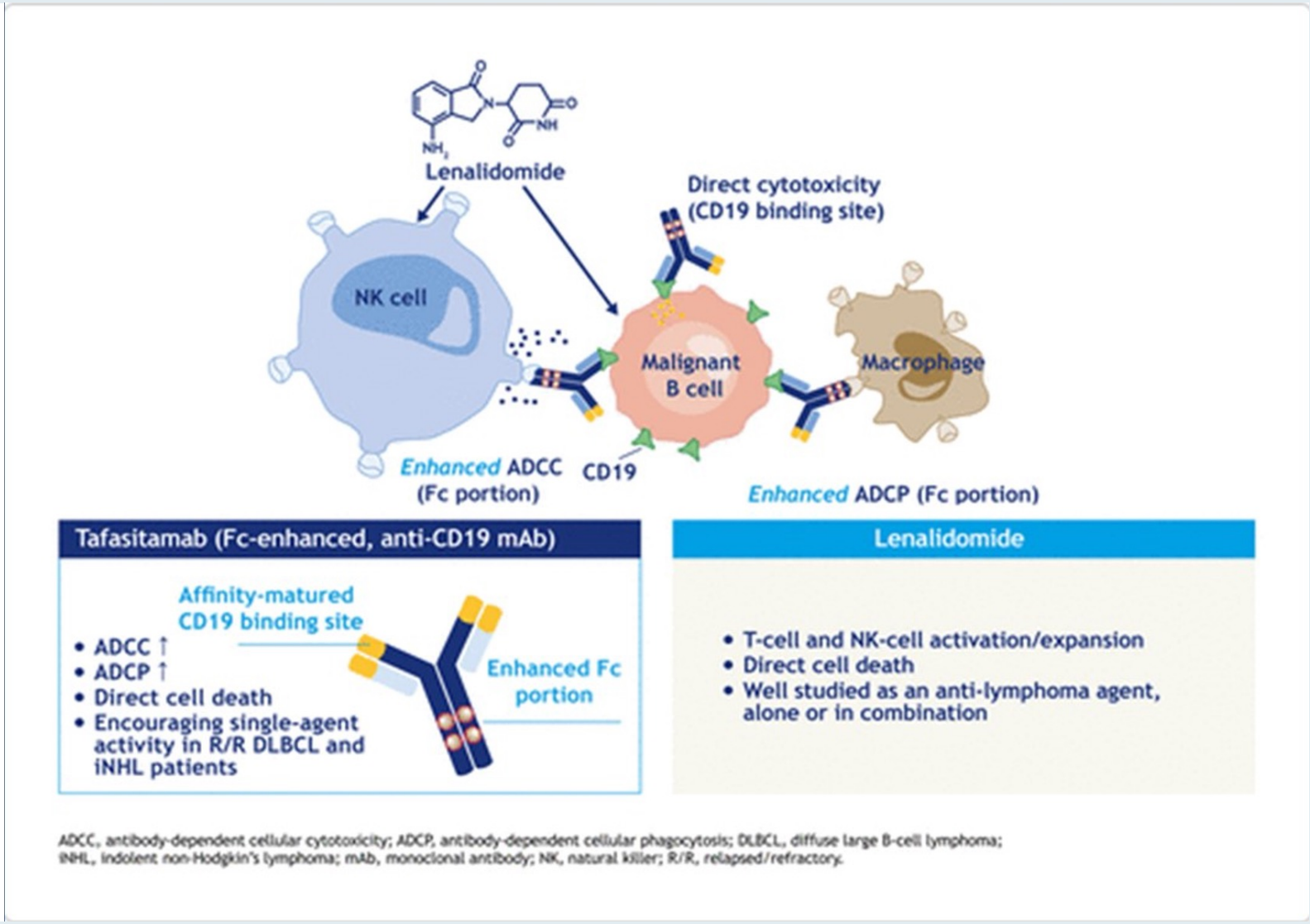
- **High CR/ORR rate at RP2D**

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

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.

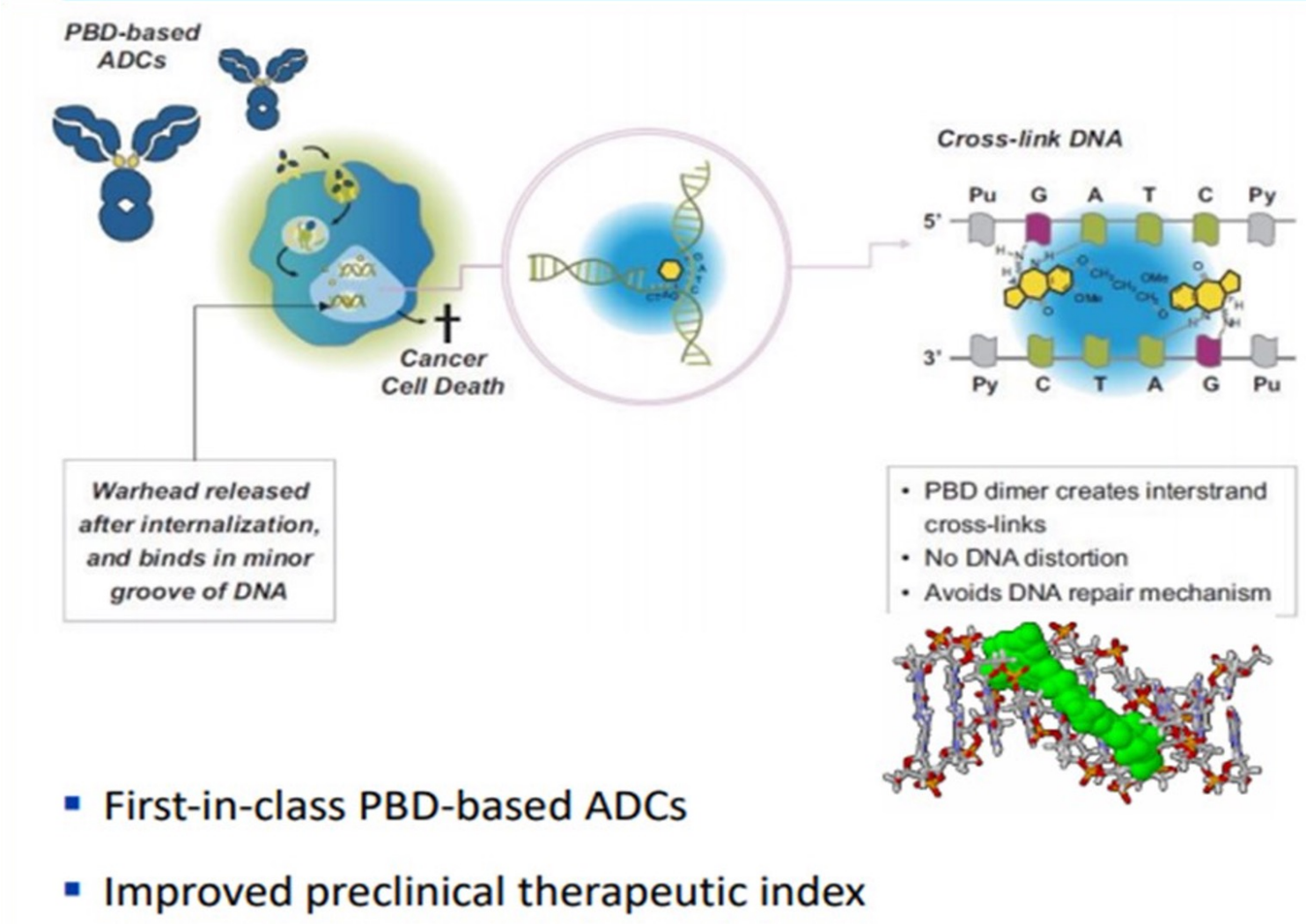
Mechanism of Action of Loncastuximab Tesirine

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.

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.

Chronic Lymphocytic Leukemia and Lymphomas Agenda

MODULE 1: Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

MODULE 2: Bispecific Antibodies; Diffuse Large B-Cell Lymphoma

MODULE 3: Mantle Cell Lymphoma

RTP
RESEARCH
TO PRACTICE

Discussion Questions

Mantle Cell Lymphoma

- Regulatory and reimbursement issues aside, in which situations would you use a BTK inhibitor as part of first-line treatment (as monotherapy or as maintenance)?
- What is the optimal timing of CAR T-cell therapy in MCL?

ORIGINAL ARTICLE

Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma

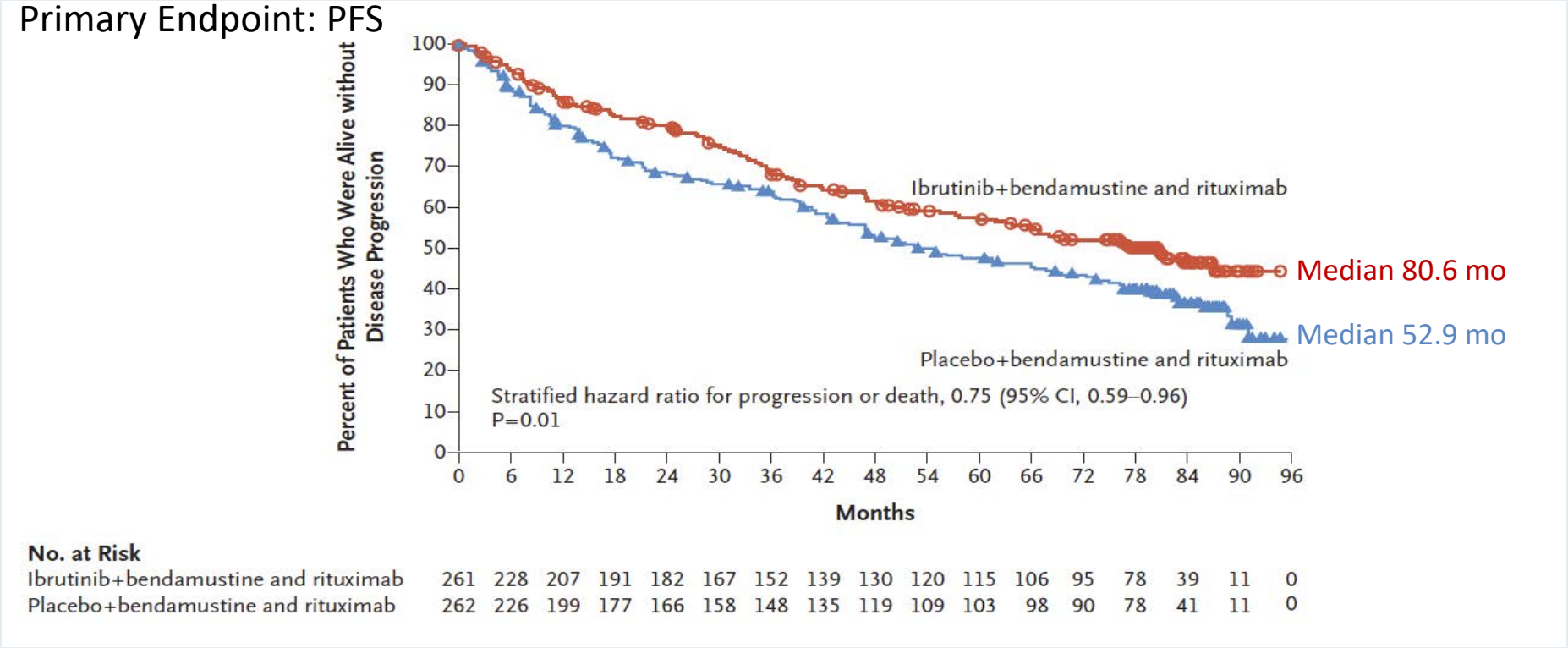
Michael L. Wang, M.D., Wojciech Jurczak, M.D., Ph.D., Mats Jerkeman, M.D., Ph.D., Judith Trotman, F.R.A.C.P., Pier L. Zinzani, M.D., Ph.D., David Belada, M.D., Ph.D., Carola Boccomini, M.D., Ian W. Flinn, M.D., Ph.D., Pratyush Giri, F.R.A.C.P., Andre Goy, M.D., Paul A. Hamlin, M.D., Olivier Hermine, 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.

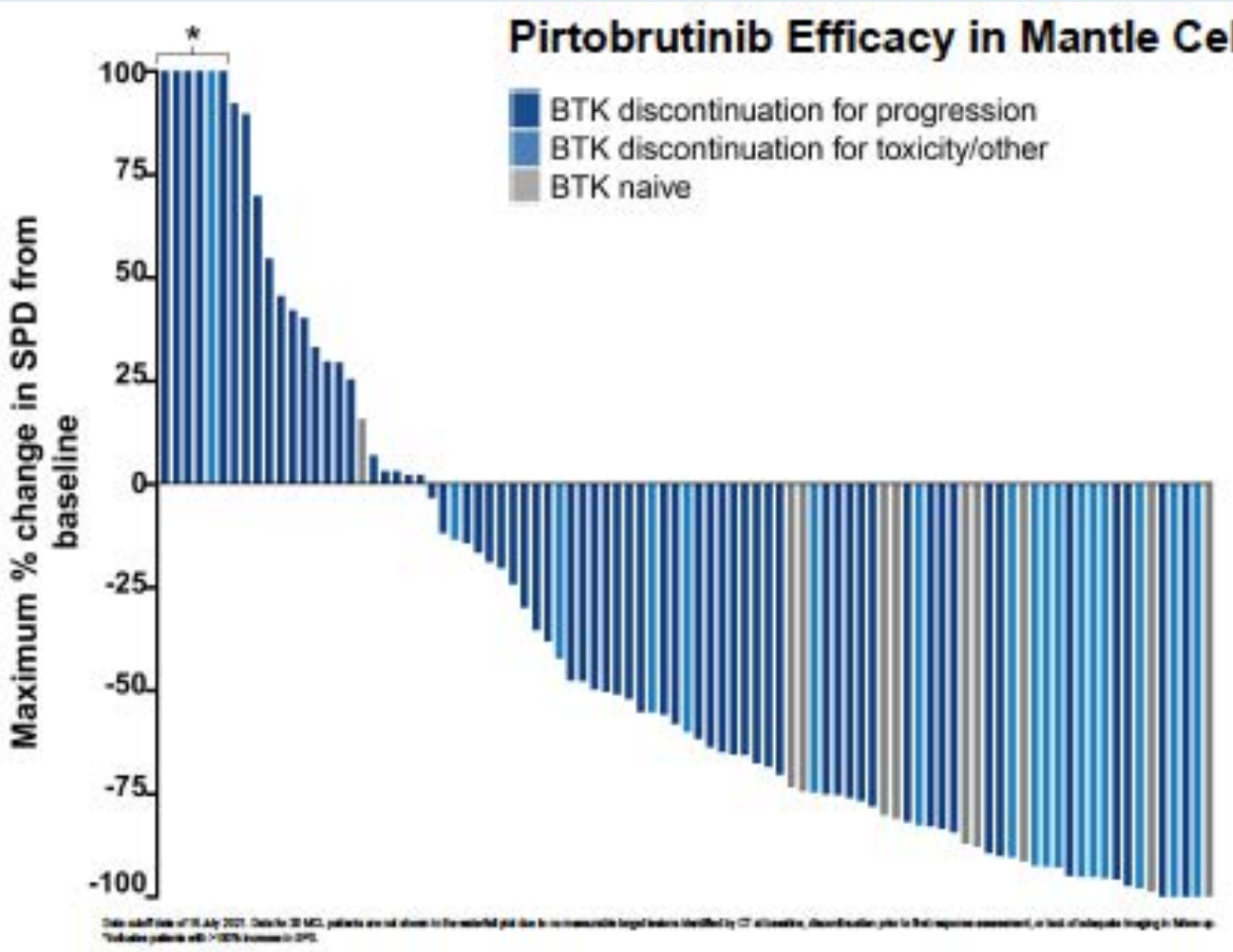
RTP RESEARCH TO PRACTICE

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.

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.

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]

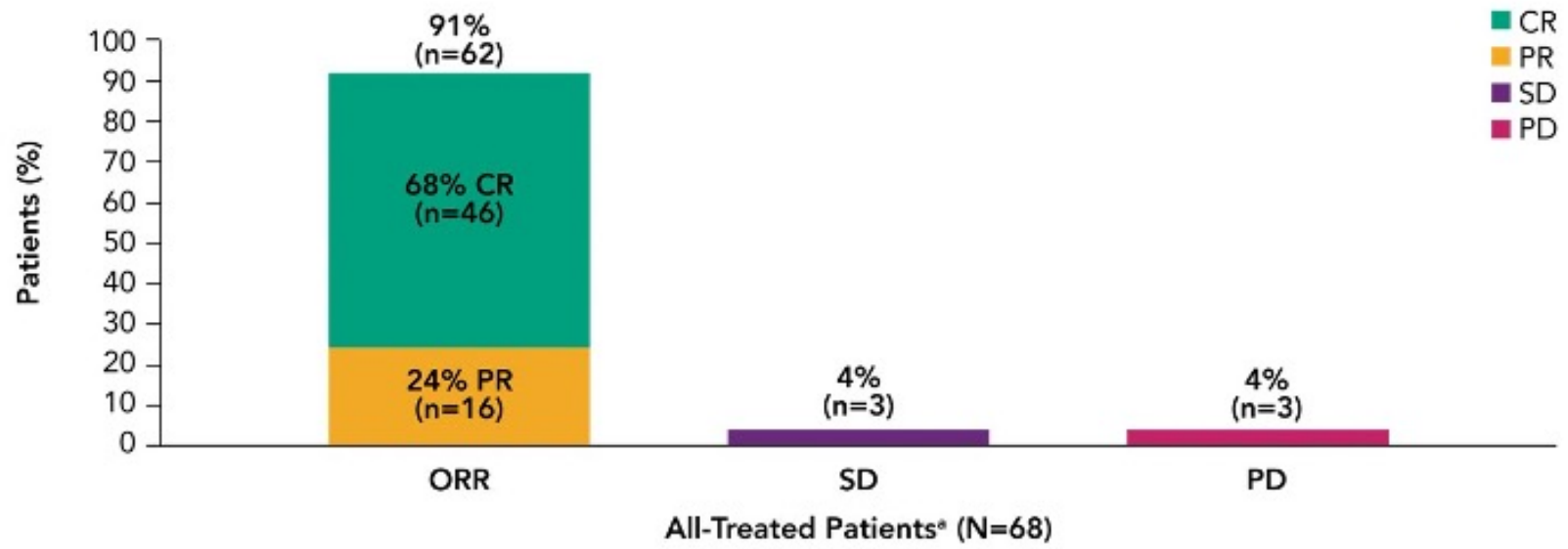
[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [3]John Theurer Cancer Center, Hackensack University, Hackensack, NJ, USA; [4]Moffitt Cancer Center, Tampa, FL, USA; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]Cleveland Clinic Foundation, Cleveland, OH, USA; [7]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [8]Texas Oncology, Dallas, TX, USA; [9]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; [10]Stanford University School of Medicine, Stanford, CA, USA; [11]Swedish Cancer Institute, Seattle, WA, USA; [12]Amsterdam UMC, University of Amsterdam, Amsterdam, Cancer Center Amsterdam, The Netherlands, on behalf of HOVON/LLPC; [13]CHU Rennes, Université Rennes, INSERM & EFS, Rennes, France; [14]University of Miami, Miami, FL, USA; [15]Kite, a Gilead Company, Santa Monica, CA; and [16]University of Rochester Medical Center, Rochester, NY, USA

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.

Thank you for joining us!

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

RTP
RESEARCH
TO PRACTICE

We are taking a short break!

The program will resume at 10:00 AM ET

Up Next…

Drs Alicia Morgans and Evan Yu discuss the management of prostate and bladder cancers

RTP
RESEARCH TO PRACTICE