Recent Advances in Cancer Care — New Paradigms, Novel Agents and What It Means for the Oncology Nurse

A Complimentary NCPD Symposium Series Held During the 51st Annual ONS Congress

Bispecific Antibodies and Antibody-Drug Conjugates for Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia

Friday, May 15, 2026

6:00 PM – 8:00 PM

Faculty

Farrukh T Awan, MD, MS, MBA
Robin Klebig, MSN, APRN, CNP, AOCNP
Mollie Moran, APRN-CNP, AOCNP

Moderator

Brad S Kahl, MD

RTP RESEARCH TO PRACTICE

Faculty

Farrukh T Awan, MD, MS, MBA
Professor of Internal Medicine
Associate Director, Section of Hematologic Malignancies/Transplantation and Cellular Therapies
Director of Lymphoid Malignancies Program
Harold C Simmons Comprehensive Cancer Center
University of Texas Southwestern Medical Center
Dallas, Texas

Robin Klebig, MSN, APRN, CNP, AOCNP
Hematology Outpatient APP Supervisor
Assistant Professor of Medicine
Nurse Practitioner, Lymphoma Group
Division of Hematology
Mayo Clinic
Rochester, Minnesota

Mollie Moran, APRN-CNP, AOCNP
Nurse Practitioner
The James Cancer Hospital and Solove Research Institute
The Ohio State University
Columbus, Ohio

Moderator

Brad S Kahl, MD
Professor of Medicine
Washington University School of Medicine
Director, Lymphoma Program
Siteman Cancer Center
St Louis, Missouri

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Dr Awan — Disclosures

Consulting Agreements	AbbVie Inc, Adaptive Biotechnologies Corporation, AstraZeneca Pharmaceuticals LP, BeOne, Bristol Myers Squibb, DAVA Oncology, Genmab US Inc, Incyte Corporation, Invivyd, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Miltenyi Biotec, Pierre Fabre
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Data and Safety Monitoring Boards/Committees	Ascentage Pharma, AstraZeneca Pharmaceuticals LP, Caribou Biosciences Inc

Ms Klebig — Disclosures

No relevant financial relationships to disclose.

Ms Moran — Disclosures

No relevant financial relationships to disclose.

Dr Kahl — Disclosures

Advisory Committees	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeOne, Bristol Myers Squibb, Genentech, a member of the Roche Group, GSK, Incyte Corporation, Lilly, Merck, Pfizer Inc, Roche Laboratories Inc
Contracted Research	BeOne, Roche Laboratories Inc
Data and Safety Monitoring Boards/Committees	BeOne, Bristol Myers Squibb, Roche Laboratories Inc

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This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

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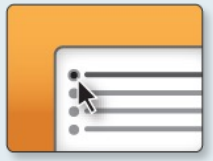
Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

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

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

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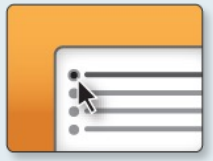
Clinicians Attending via Zoom

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



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

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

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

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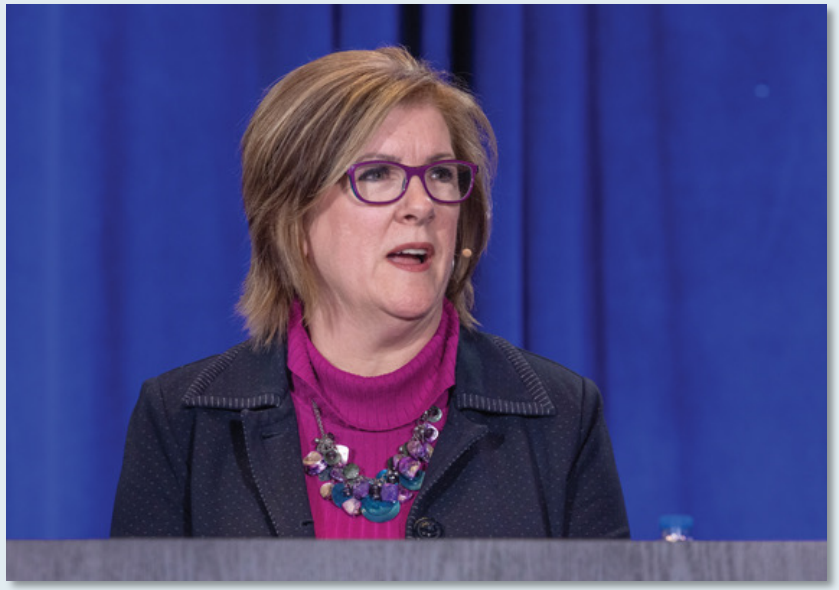
About the Enduring Program



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

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RTP RESEARCH TO PRACTICE ONCOLOGY NURSING UPDATE WITH NEIL LOVE, MD

NONMELANOMA SKIN CANCERS
Check out our recent program with Dr Nikhil I Khushalni from Moffitt Cancer Center in Tampa, Florida. Published May 7, 2026.

Overview of nonmelanoma skin cancers (12 min)

Systemic therapy for nonmelanoma skin cancers (8 min)

Immune checkpoint inhibitors for special patient populations (12 min)

Hedgehog inhibitors for basal cell carcinoma (6 min)

New developments in therapy for nonmelanoma skin cancers (5 min)

CASE: A man in his early 70s with cutaneous squamous cell carcinoma receives cemiplimab (8 min)

CASE: A man in his mid 70s with a history of basal cell carcinoma presents with disease of the ocular surface and receives immunotherapy (6 min)

CASE: A man in his early 70s with recurrent metastatic basal cell carcinoma receives vismodegib followed by cemiplimab on disease progression (6 min)

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Feedback (Please!)

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“Recent Advances in Cancer Care — New Paradigms, Novel Agents and What It Means for the Oncology Nurse”
Eighteenth Annual RTP-ONS NCPD Symposium Series

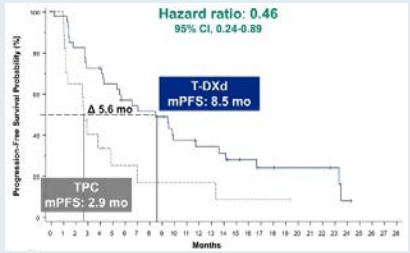
Wednesday May 13	**Antibody-Drug Conjugates** 11:15 AM – 12:45 PM CT
	Ovarian Cancer 6:00 PM – 7:30 PM CT
Thursday May 14	**Immunotherapeutic Approaches for Endometrial Cancer** 6:00 AM – 7:30 AM CT
	Prostate Cancer 12:15 PM – 1:45 PM CT
	Non-Muscle-Invasive and Muscle-Invasive Bladder Cancer 6:00 PM – 7:30 PM CT
Friday May 15	**Pancreatic Cancer** 6:00 AM – 7:30 AM CT
	Targeting the PI3K/AKT/mTOR Pathway in HR-Positive Metastatic BC 12:15 PM – 1:45 PM CT
	Non-Hodgkin Lymphoma and Chronic Lymphocytic Leukemia 6:00 PM – 8:00 PM CT
Saturday May 16	**CDK4/6 Inhibitors for HR-Positive Breast Cancer** 6:00 AM – 7:30 AM CT
	Relapsed/Refractory Multiple Myeloma 12:15 PM – 1:45 PM CT
	Oral SERDs for Breast Cancer 6:00 PM – 7:30 PM CT

RTP RESEARCH TO PRACTICE

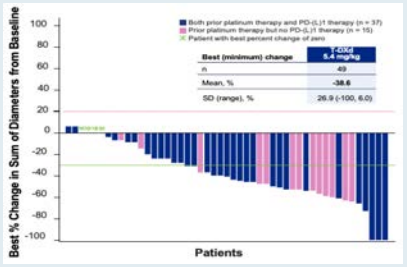
Recent Advances in Cancer Care — New Paradigms, Novel Agents and What It Means for the Oncology Nurse

New Agents, Therapies and Regimens

- When should it be used, for whom and why?
- How to prevent and manage side effects: dose holds and reductions
  - Kaplan Meier curves — HR and absolute benefit



  - Waterfall plots



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RTP RESEARCH TO PRACTICE

Agenda

Introduction: Biology of Non-Hodgkin Lymphoma (NHL)

Module 1: Current Role of CD20 x CD3 Bispecific Antibodies in NHL

Module 2: Role of Polatuzumab Vedotin in Diffuse Large B-Cell Lymphoma (DLBCL)

Module 3: Optimal Application of Loncastuximab Tesirine for Patients with DLBCL and Follicular Lymphoma

Module 4: Role of BTK Inhibitors Alone or with Anti-CD20 Antibodies for Patients with Newly Diagnosed Chronic Lymphocytic Leukemia (CLL)

Module 5: Combining BTK Inhibitors with Bcl-2 Inhibitors

Module 6: Current and Future Role of Noncovalent BTK Inhibitors in CLL

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Discussion Questions

At a very basic level, how do you counsel your patients with newly diagnosed DLBCL about the nature of their disease and what their treatment journey might look like?

How does this conversation differ for patients with newly diagnosed FL?

Agenda

Introduction: Biology of Non-Hodgkin Lymphoma (NHL)

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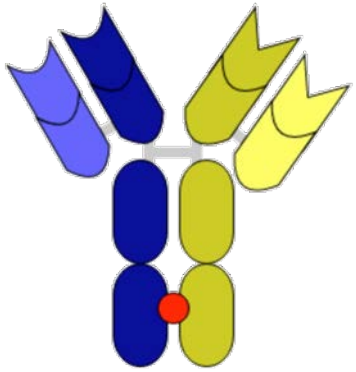
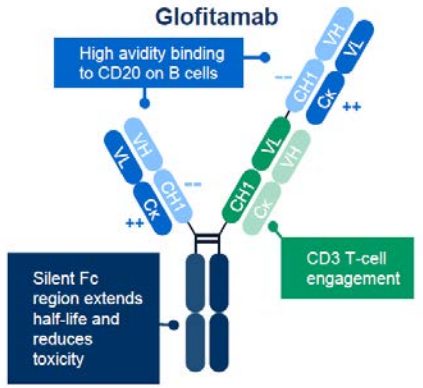
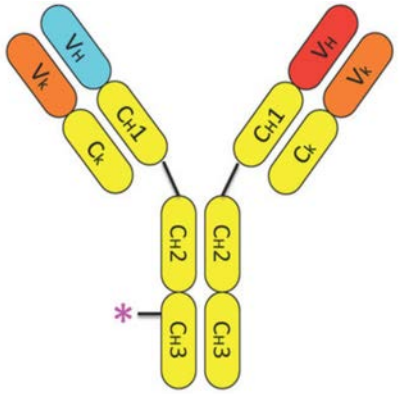
Biologic Rationale for and Current Role of CD20 x CD3 Bispecific Antibodies in Non-Hodgkin Lymphoma (NHL)

Farrukh T. Awan, M.D., M.S., M.B.A.
Professor of Internal Medicine
Associate Director, Section of
Hematologic Malignancies/Transplantation and Cellular Therapies
Director of Lymphoid Malignancies Program
Harold C. Simmons Comprehensive Cancer Center
University of Texas Southwestern Medical Center
Dallas, TX

New and Emerging Bispecific Antibodies in Non-Hodgkin Lymphomas

Anti-CD20/CD3 bispecific monoclonal antibodies in the development for B-cell NHL

Epcoritamab[1]	Mosunetuzumab[2,3] (approved in FL)	Glofitamab[4]	Odronextamab[5,6]
			
DuoBody – CD3 x CD20 BsAb SC	CD3 x CD20 Knobs-into-holes Fc BsAb IV/SC	CD3 (Fab) x CD20 (Fab x2) Fc BsAb IV	CD3 x CD20 common LC Fc BsAb IV

Odronextamab is an investigational therapy for the management of NHL.

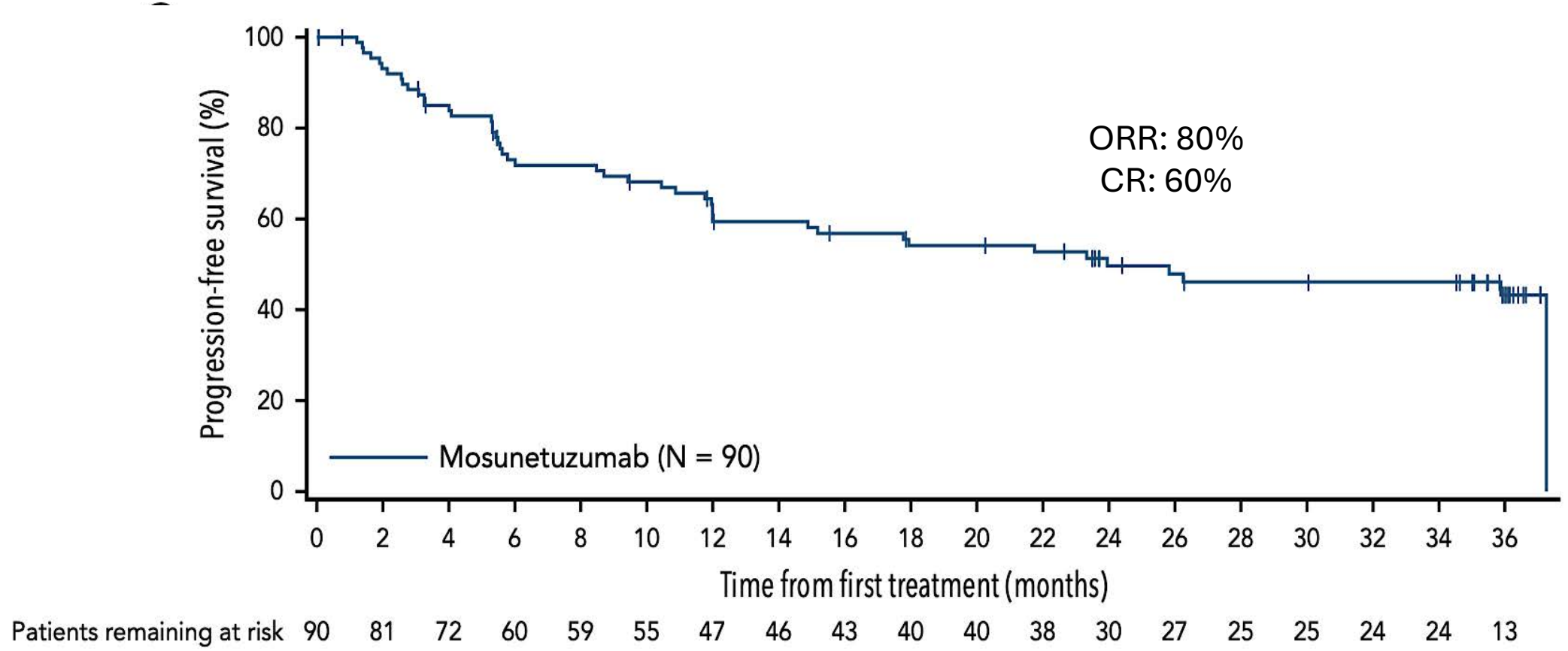
Ab = antibody; BsAb = bispecific Ab; Fc = crystallizable fragment; FL = follicular lymphoma; Fab = fragment antigen binding; IV = intravenous; LC = liquid chromatography; SC = subcutaneous.

1. Hutchings M, et al. *Lancet*. 2021;398:1157-1169. 2. Budde LE, et al. *J Clin Oncol*. 2022;40:481-491. 3. Hosseini I, et al. *NPJ Syst Biol Appl*. 2020;6:28. 4. Minson A, Dickinson M. *Leuk Lymphoma*. 2021;62:3098-3108. 5. Zhu M, et al. *Clin Transl Sci*. 2022;15:954-966. 6. Smith EJ, et al. *Sci Rep*. 2015;5:17943.

Approved or Late-Stage Development Bispecifics: Administration Schedules

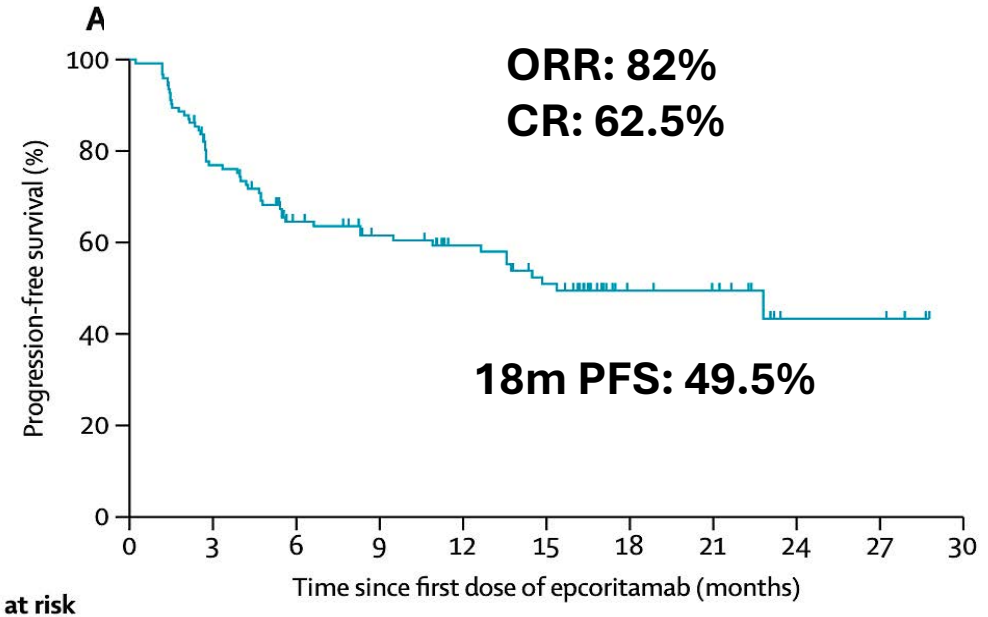
Bispecific	Route	Schedule	Duration
Glofitamab	IV	Weekly C1, every 3 weeks	12 cycles
Mosunetuzumab	IV	Weekly C1, every 3 weeks	8 cycles if complete response (CR); 17 cycles if partial response (PR)
Odronextamab	IV	Twice weekly C1, weekly C2 to C4, every 2 weeks C ≥5	Until progressive disease (PD)
Epcoritamab	SC	Weekly C1 to C3, every 2 weeks C4 to C9, every 4 weeks C ≥10	Until PD

Efficacy of mosunetuzumab in R/R FL

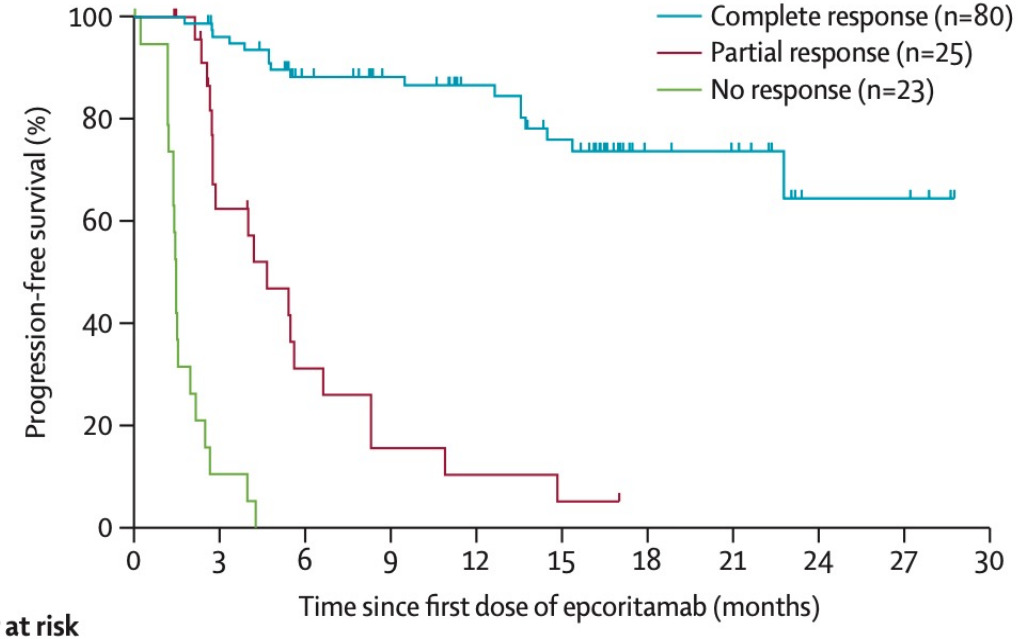


Sehn et al., Blood, 2025

Efficacy of Epcoritamab in R/R FL



Number at risk (number censored)											
Pivotal cohort	128 (0)	90 (10)	67 (19)	57 (26)	43 (38)	35 (40)	14 (60)	12 (62)	4 (69)	4 (69)	0 (73)



Number at risk (number censored)											
Complete response	80 (0)	75 (2)	61 (10)	54 (17)	41 (29)	34 (31)	14 (50)	12 (52)	4 (59)	4 (59)	0 (63)
Partial response	25 (0)	13 (4)	6 (5)	3 (5)	2 (5)	1 (5)	0 (6)	0 (6)	0 (6)	0 (6)	0 (6)
No response	23 (0)	2 (4)	0 (4)	0 (4)	0 (4)	0 (4)	0 (4)	0 (4)	0 (4)	0 (4)	0 (4)

Linton et al. Lancet Haematol., 2024

Summary of CD20-Directed Bispecifics for R/R FL

Bispecific antibody	Number of patients	ORR %	CR %	Duration of CR (median; months)	PFS months
Glofitamab[1]	44	71	48	NR	11.8
Mosunetuzumab[2]	90	79	60	NR	18
Odronextamab[3]	128	80	72	21.7	20.7
Epcoritamab[4]	10	90	50	NA	NR

Odronextamab is an investigational therapy for the management of NHL.

1. Hutchings M, et al. *J Clin Oncol.* 2021;39:1959-1970. 2. Budde LE, et al. *Lancet Oncol.* 2022;23:1055-1065. 3. Villasboas JC, et al. *Blood*. 2023;142(suppl 1):3041. 4. Hutchings M, et al. *Lancet.* 2021;398:1157-1169.

Glofitamab Monotherapy at RP2D Induces Durable Complete Responses

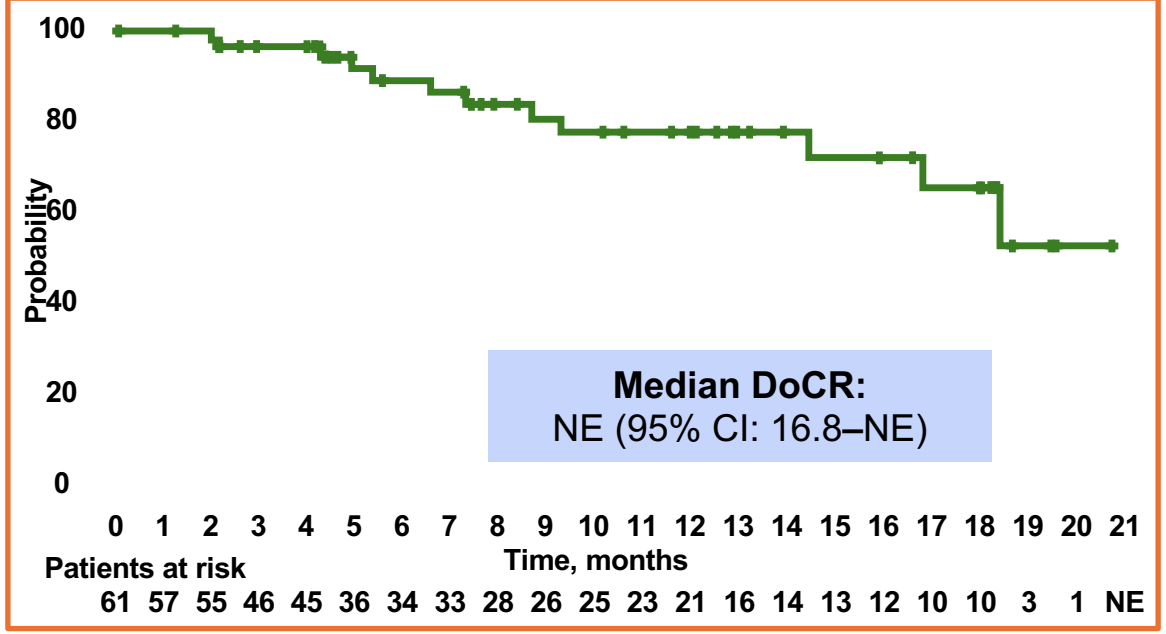
Heavily pretreated, highly refractory population

Pivotal phase 2 results

- DLBCL NOS, HGBCL, trFL or PMBCL; ≥2 prior therapies
- Glofitamab 2.5/10/30 mg (N = 155)
  - Efficacy
    - CR rate: 39.4% (61/155)
    - ORR: 51.6% (80/155)

Received FDA approval on June 15, 2023, for R/R DLBCL after 2 prior therapy lines

Pivotal phase 2 cohort (ASCO 2022) – DoCR* by IRC



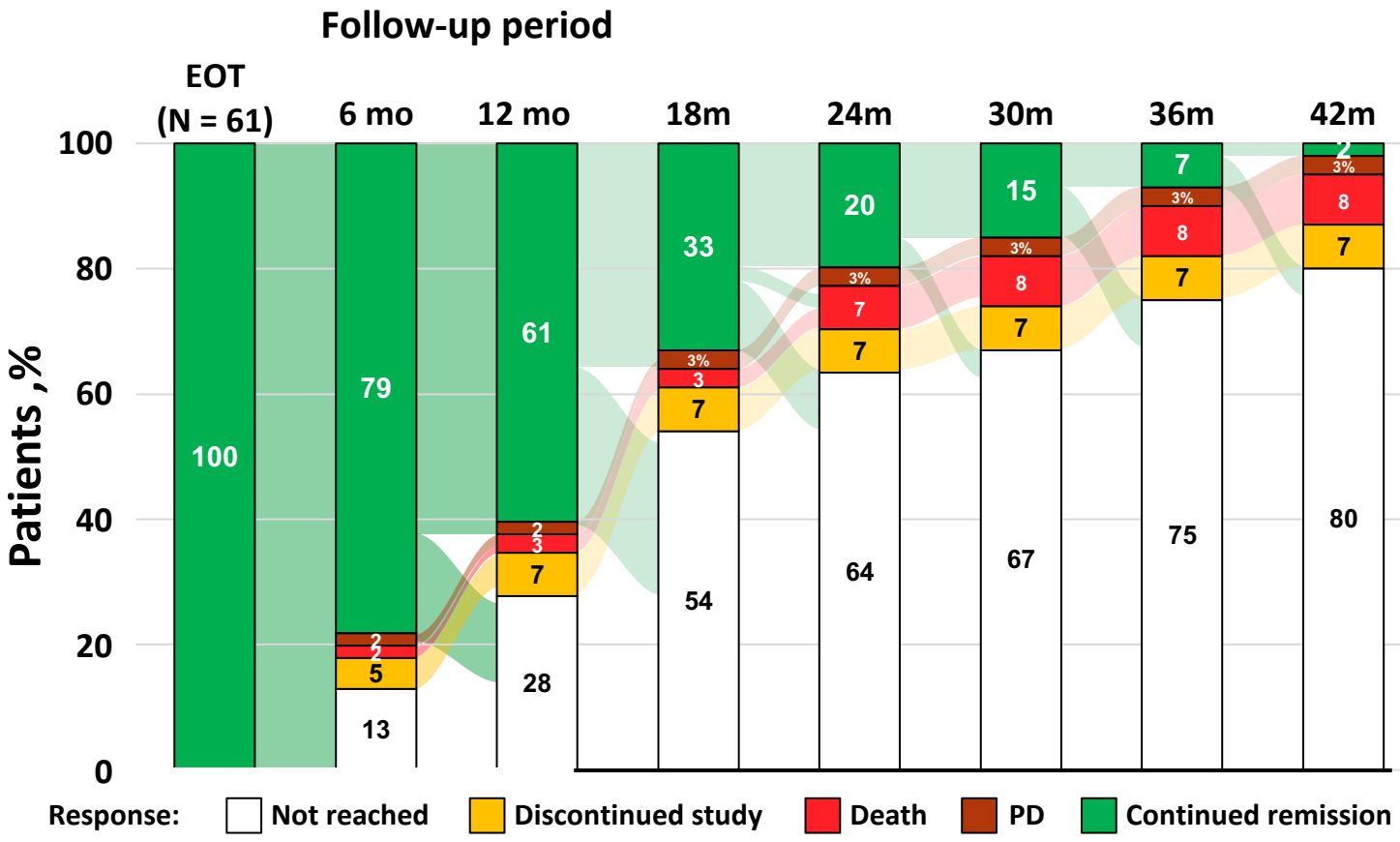
	N = 61
Median DoCR follow-up, months (range)	
12-months DoCR, % (95% CI)	
CRs ongoing at CCOD, n (%)	

Clinical cutoff date: March 14, 2022. *Time from the initial occurrence of a CR until PD or death due to any cause, whichever occurs first.

RP2D = recommended phase II doseCCOD = clinical cutoff date; CI = confidence interval; CRS = cytokine release syndrome; DoCR = duration of complete response; IRC = independent review committee; PD = progressive disease.

Dickinson M, et al. American Society of Clinical Oncology (ASCO) 2022; Abstract 7500. Dickinson M, et al. *N Engl J Med*. 2022;387:2220-2231.

Glofitamab: Remission at 12-Month Post-EOT in Patients With CR at EOT



The majority of patients remain in remission

- 6-month follow-up: 79% (48/61)
- 12-month follow-up: 61% (37/61)

After 12-month follow-up, 7 patients had discontinued

- 1 PD
- 2 deaths (due to lymphoma)
- 4 discontinued study (2 received allogeneic transplant, 1 due to physician decision, 1 lost to follow-up)

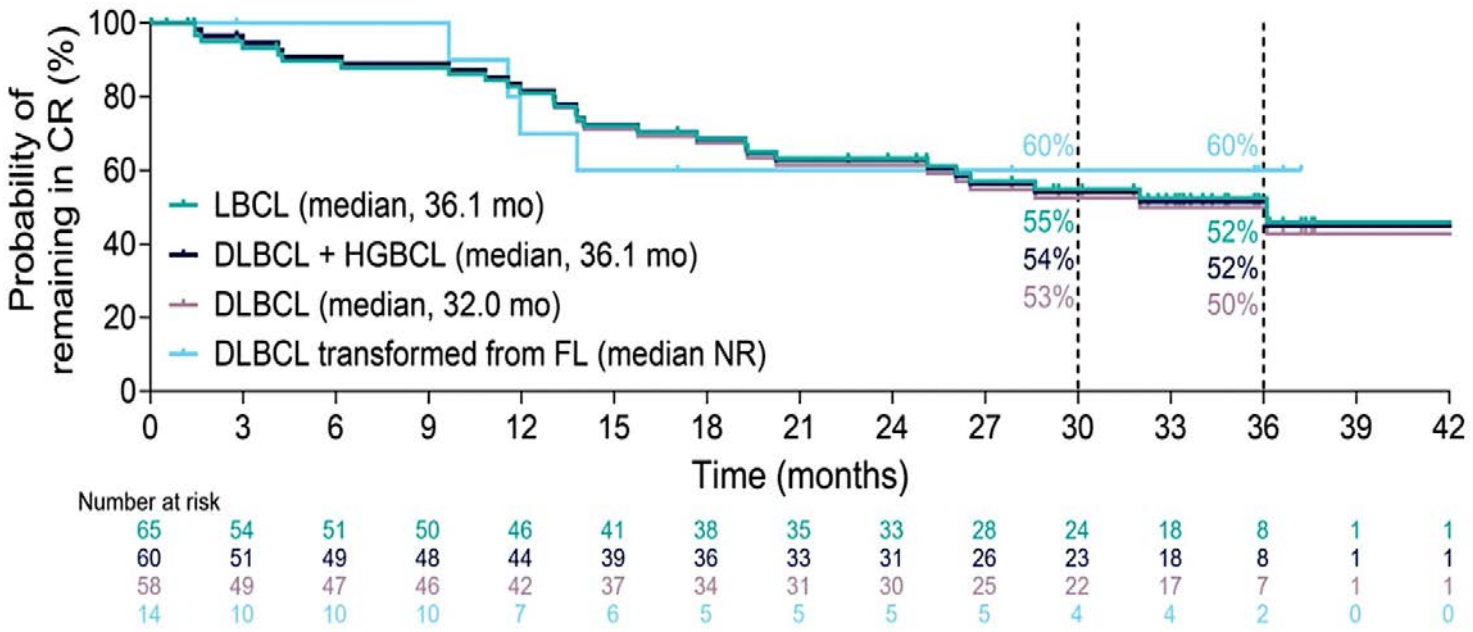
17 patients remained in follow-up but had not yet reached 12 months

The majority of patients remain in remission 12 months after cessation of therapy.

Hutchings M, et al. Presented at ASH 2022. Abstract 441

EPCORE NHL-1 Trial: Efficacy

Response and DOR	LBCL (N=157)	DLBCL Transformed From FL (n=32)
ORR, n (%)	92 (59)	16 (50)
CR,	65 (41)	14 (44)
PR,	21 (17)	2 (6)
Median DOR, months (95% CI)	20.8 (13.0-32.0)	NR (10.6-NR)
36-month estimate, %	39	55

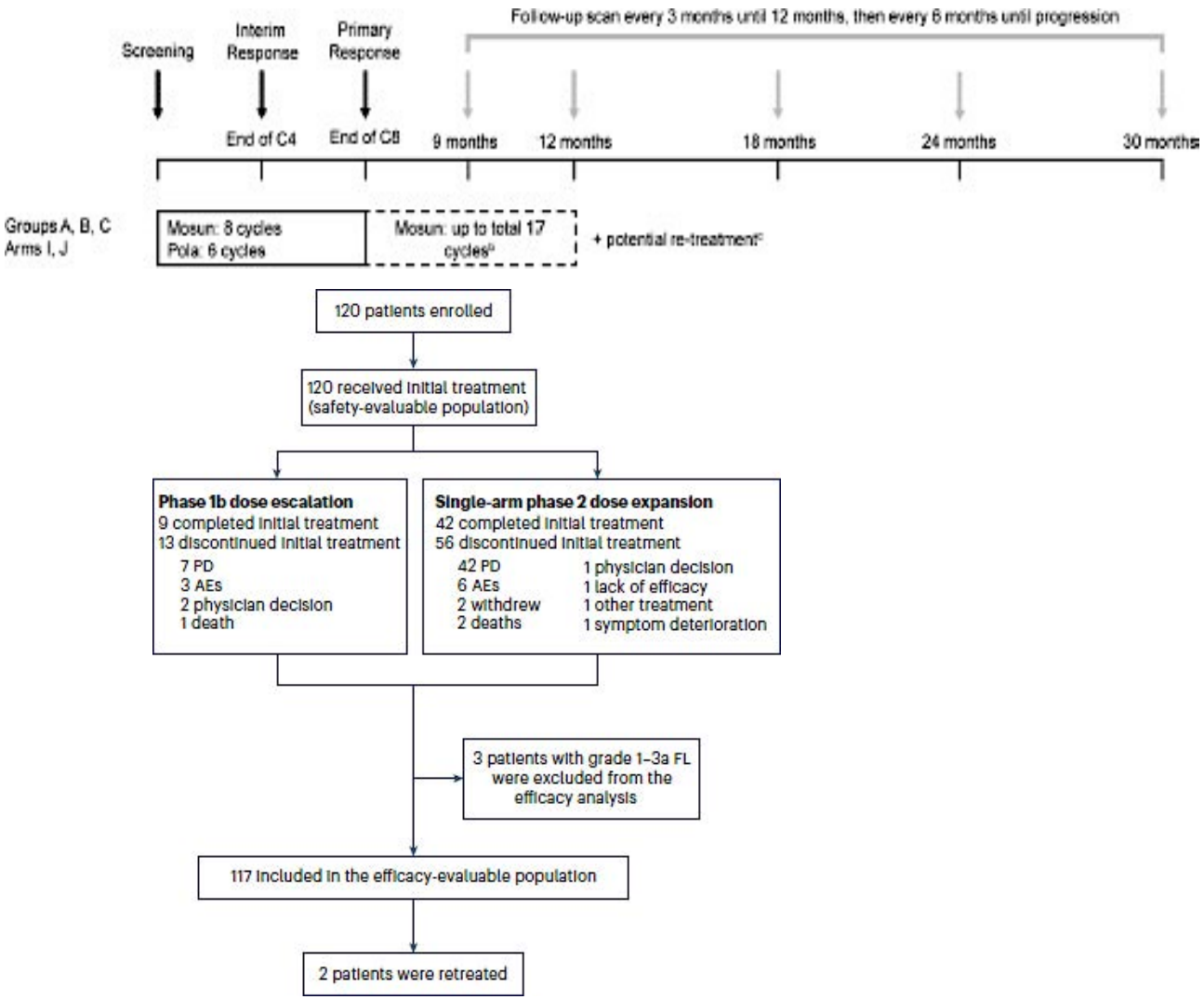


Durable complete responses and overall median DOCR of 36.1 months (95% CI, 20.2-NR)

•Vose JM, et al. ASH 2024. Abstract 4480.

Mosunetuzumab + polatuzumab vedotin for R/R DLBCL

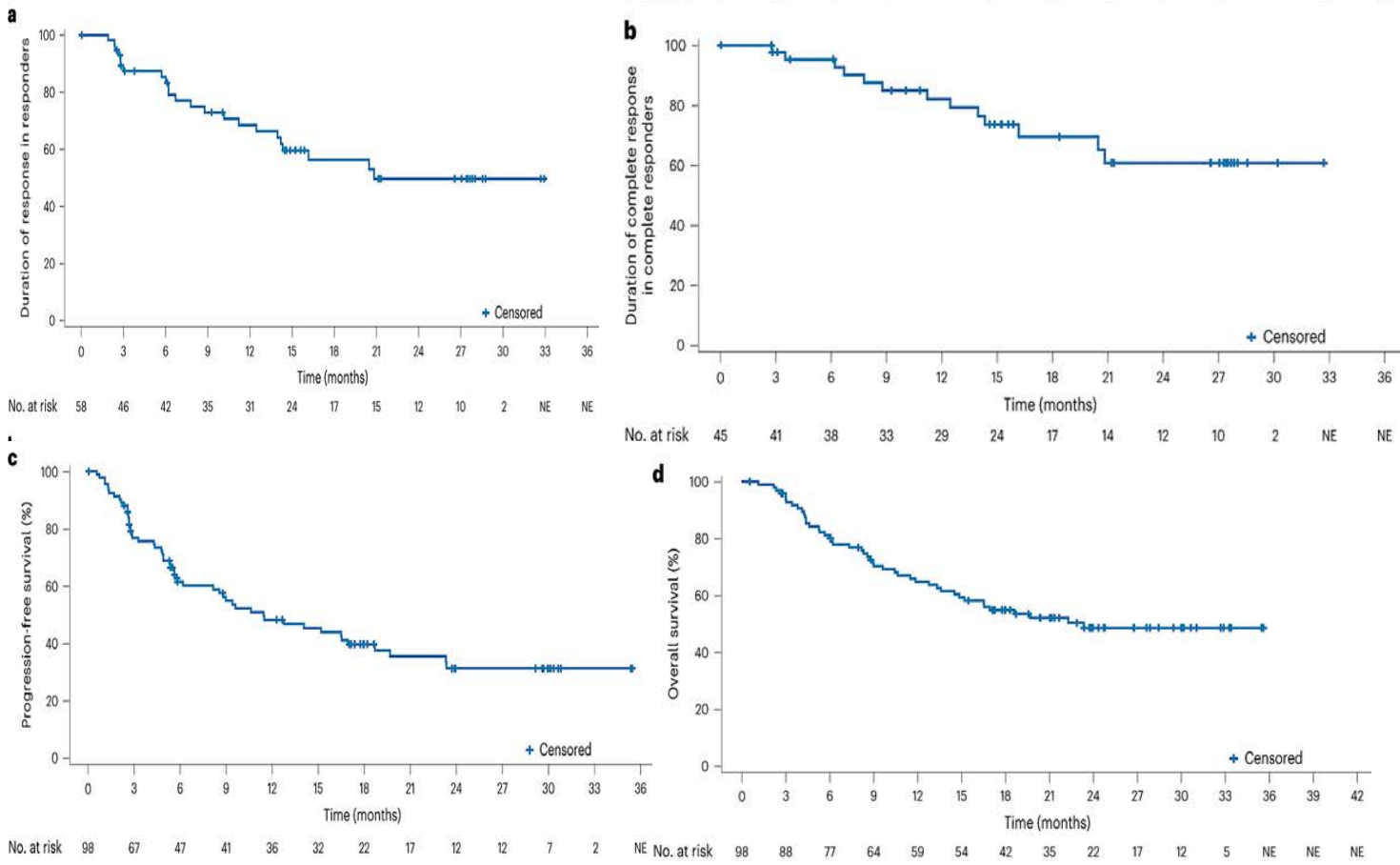
- Key baseline characteristics
  - 56% age >70
  - 55% elevated LDH
  - 57-77% refractory
  - 50% 1 prior LOT
  - **35% prior CART19**



Nat Med. 2024 Jan;30(1):229-239.

Mosunetuzumab + polatuzumab vedotin for R/R DLBCL

- Response
  - ORR: 73%
  - CRR: 59%
  - CRR if 1 prior LOT: 49%
  - **CRR by prior CART19 vs not: 40% vs 49%**
- Toxicity
  - CRS: 18% any grade, 3% grade ≥3
  - Febrile neutropenia: 0%



Mosun/pola is associated with a high response rate and low toxicity in R/R DLBCL

Nat Med. 2024 Jan;30(1):229-239.

Case Presentation

CASE PRESENTATION

- 89-year-old male diagnosed with triple hit DLBCL
- Had primary refractory disease after R-mini-CHOP chemotherapy
- Received radiation as a bridge to CAR-T cell therapy
- Initially did well after CAR-T cell therapy, but had relapsed disease after 6 months
- Performance status is still good, and the patient desires additional treatment

- What's the best next option for treatment

CASE PRESENTATION..cntd

- 72-year-old female with CLL with cBTKi resistance and needs treatment
- Multiple comorbidities

- **What is the least likely to be an effective treatment option**
  - Loncastuximab
  - Epcoritamab
  - Glofitamab
  - Tafasitamab + lenalidomide
  - **Chemotherapy**

Discussion Questions

How are you currently sequencing bispecific antibodies relative to other currently available therapies for relapsed/refractory (R/R) DLBCL? How do you decide whether to use glofitamab or epcoritamab?

Which patients with R/R FL represent ideal candidates for bispecific antibody therapy? How do you choose among mosunetuzumab monotherapy, epcoritamab monotherapy and epcoritamab/R^2?

Cytokine Release Syndrome (CRS), Neurotoxicity and Other Tolerability Concerns with Bispecific Antibodies in NHL

Robin Klebig, APRN, CNP, AOCNP

May 15, 2026

Cytokine Release Syndrome (CRS), Neurotoxicity and Other Tolerability Concerns with Bispecific Antibodies in NHL

- **CRS** - Cytokine Release Syndrome
  - Systemic inflammatory response resulting from massive cytokine release by activated immune cells
  - Characterized by fever, hypotension, hypoxia, organ dysfunction
  - Managed with corticosteroids (dexamethasone) +/- tocilizumab (IL-6 inhibitor)
- **ICANS** - Immune effector Cell-Associated Neurotoxicity Syndrome
  - Neurological toxicities associated with immune cell activation and cytokine release
  - Presents as confusion, delirium, aphasia/dysphasia, seizures, encephalopathy or cerebral edema
  - Managed with corticosteroids (dexamethasone), Neurology consultation, levetiracetam

ASTCT and NCCN guidelines

NCCN Guidelines Version 2.2026
Management of Lymphocyte Engager-Related Toxicities

CRS RELATED TO T-CELL–ENGAGING BISPECIFIC AGENTS

WORKUP/GRADING[a]

- Laboratory tests
  - CBC, CMP, blood cultures, MRSA, CRP, BNP, ferritin, urinalysis, urine culture, respiratory virus polymerase chain reaction (PCR) panel
- Diagnostic chest x-ray

CRS →

MANAGEMENT

All grades →
- Risks associated with each agent vary widely. Refer to the prescribing information for product-specific dosing and management
- Fever: Oral acetaminophen 650 mg every 4 hours PRN; cooling blanket; hyperthermia management protocol
- Initiation of empiric broad spectrum antibiotics in patients with neutropenia
- Consider inpatient care

Grade 1 Fever (≥38°C) →
- Continue treatment (if blinatumomab or tebentafusp-tebn); otherwise hold treatment (for all other bispecific agents)[d]
- Consider oral or IV dexamethasone 8–12 mg x 1 dose
- For prolonged steroid-refractory CRS (>24–48 hours) or if high risk for CRS, consider IV tocilizumab[e]

Grade 2 Fever with hypotension not requiring vasopressors and/or hypoxia[b] requiring low-flow nasal cannula[c] or blow-by →
- Continue treatment (if blinatumomab); otherwise hold treatment (for all other bispecific agents)[d]
- Oral or IV dexamethasone 8–12 mg x 1 dose. May repeat every 12 hours
- Consider IV tocilizumab 8 mg/kg x 1 dose[e]
- If symptoms persist for >24 hours, consider adding alternative cytokine blockade (ie, anakinra or siltuximab)
- Oxygen low flow nasal cannula ≤6 L/min
- IV fluid bolus
- Cardiac monitoring

Grade 3 and Grade 4 → ENGAGE-4

[a] Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625-638.
[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with a temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.
[d] Considerations for Rechallenge of T-Cell–Engaging Bispecific Antibody Therapy After CRS (ENGAGE-7).
[e] Administer over 1 hour within 2 hours of onset. Maximum dose 800 mg; 3 doses in 24 hours; maximum of 4 doses. If no clinical improvement in oxygenation, hypotension, fever, or other symptoms, dosing may be repeated every 8 hours. Median time to response after first dose: hours to days (range is generally 1–12 days). An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

Note: All recommendations are category 2A unless otherwise indicated.

CRS RELATED TO T-CELL–ENGAGING BISPECIFIC AGENTS	GRADING[a]	MANAGEMENT
	CRS Grade 3[f] Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula,[c] face mask, non-rebreather mask, or Venturi mask	• **Hold treatment (for all bispecific agents)[d]** • **ICU care** • **IV fluid bolus PRN, vasopressors PRN** • **IV dexamethasone 10 mg x 1 dose. May repeat every 6 hours** • **IV tocilizumab 8 mg/kg x 1 dose[e]** • **If symptoms persist despite combination therapy with tocilizumab and steroids, consider adding alternative cytokine blockades (ie, anakinra or siltuximab)**
	CRS Grade 4[f] Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, mechanical ventilation)	• **Permanently discontinue treatment (for all bispecific agents)[d]** • **ICU care** • **IV methylprednisolone 1000 mg every 24 hours x 3 days** • **IV tocilizumab 8 mg/kg x 1 dose[e]** • **If symptoms persist despite combination therapy with tocilizumab and steroids, consider adding alternative cytokine blockades (ie, anakinra or siltuximab)** • **Multiple vasopressors, excluding vasopressin** • **Positive pressure: CPAP, BiPAP, intubation** • **Echocardiogram**

[a] Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625-638.
[c] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.
[d] Considerations for Rechallenge of T-Cell–Engaging Bispecific Antibody Therapy After CRS (ENGAGE-7).
[e] Administer over 1 hour within 2 hours of onset. Maximum dose 800 mg; 3 doses in 24 hours; maximum of 4 doses. If no clinical improvement in oxygenation, hypotension, fever or other symptoms, dosing may be repeated every 8 hours. Median time to response after first dose: hours to days (range is generally 1–12 days). An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[f] Occurrence of Grade 3 or 4 CRS with T-cell–engaging bispecific agents is rare. Consider alternative etiologies (eg, infection).

Note: All recommendations are category 2A unless otherwise indicated.

Bispecific antibodies and CRS incidence and time course:

Bispecific	Setting	Treatment Day/Dose/CRS incidence	Overall CRS (≥grade 2)	Median Time to CRS	Median Duration CRS
Epcoritamab	SC in LBCL	C1D1 (0.16 mg) = 6% C1D8 (0.8 mg) = 12% **C1D15 (48 mg) = 43%** C1D22 (48 mg) = 5% C2D1+ (48 mg) = 3%	51% (19.5%)	21 hrs (range: 0-7 days)	**2 days** **(range 1-27 days)**
Epcoritamab	SC in FL	C1D1 (0.16 mg) = 12% C1D8 (0.8 mg) = 6% C1D15 **(3 mg)** = 15% **C1D22 (48 mg) = 37%** C1D22 (48 mg) = 5% C2D1+ (48 mg) = 3%	49% (9%)	61 hrs	**2 days** **(range 1-27 days)**
Glofitamab	IV in LBCL	C1D1 (obinutuzumab) **C1D8 (2.5 mg) = 56%** **C1D15 (10 mg) = 35%** **C2 (30 mg) = 29%** C3+ (30 mg) = 2.8%	**70%** **(18%)**	**14 hrs** (range: 5-74 hrs)	**2 days** **(range: 1-14 days)**
Mosunetuzumab	IV in FL	**C1D1 (1 mg) = 23%** C1D8 (2 mg) = NR **C1D15 (60 mg) = 36%** C2D1 (60 mg) = 1% C3+ **(30 mg)** =	44% (19%)	**5 hrs (C1D1)** 27 hrs (C1D15)	**3 days**
Mosunetuzumab	SC in FL	**C1D1 (5 mg) = 19%** C1D8 (45 mg) = 13% C1D15 (45 mg) = 2.1%	**30%** **(9.1%)**	17 hrs (C1D1) 62 hrs (C1D8)	**2 days** **(range: 1-15 days)**

Courtesy of Robin Klebig, APRN, CNP, AOCNP

ICANS/Neurotoxicity presentations

ICANS

- **Expressive aphasia; dysgraphia, tremor**, confusion/delirium, lethargy, impaired attention, difficulty concentrating, seizures, non-convulsive status epilepticus. LOC may be depressed
- Timing typically during step-up dosing during C1
  - 3-3.5 days from most recent dose
  - Median duration 2-4 days
- Often concurrent with or shortly after CRS, though can be independent of CRS
- **ICE score Abnormal (≤9)** — this is the defining feature
- Management: Corticosteroids (dexamethasone → methylprednisolone); tocilizumab does NOT help

Non ICANS Neurotoxicity

- Isolated headache, dizziness, insomnia, peripheral neuropathy, tremor (isolated symptoms without encephalopathy symptoms). LOC typically normal
- Timing is variable; headache may occur acutely with infusion; peripheral neuropathy may be delayed
- Usually independent of CRS (headache may accompany fever/CRS but is non-specific)
- ICE score is Normal (10/10)
- Management is symptomatic (analgesics for headache, gabapentin for neuropathy, etc.)

Key screening test is ICE assessment

	Epcoritamab	Glofitamab	Mosunetuzumab
Any grade (Gr3+)	6% (0.6% in LBCL)	4.8-8% (2.6%)	3% grade 1-2 confusion 1% grade 1 disturbance in attention 1% grade 1 cognitive disorder

ASTCT and NCCN guidelines

CAR T-CELL–RELATED NEUROTOXICITY GRADING

Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool[n]

- **Orientation: orientation to year, month, city, hospital: 4 points**
- **Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points**
- **Following commands: ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point**
- **Writing: ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point**
- **Attention: ability to count backwards from 100 by 10: 1 point**

ICE Scoring

- **7–9, grade 1**
- **3–6, grade 2**
- **0–2, grade 3**
- **0 due to patient unarousable and unable to perform ICE assessment, grade 4**

ASTCT Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Consensus Grading for Adults[n]

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

Neurotoxicity Domain[aa]	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[bb]	7–9	3–6	0–2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[cc]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[dd]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

[n] With permission from Elsevier: Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25:625-638. DOI: https://doi.org/10.1016/j.bbmt.2018.12.758. This article is published under the terms of the Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND).

[aa] Other signs and symptoms such as headache, tremor, myoclonus, asterixis, and hallucinations may occur and could be attributable to IEC engaging therapies. Although they are not included in this grading scale, careful attention and directed therapy may be warranted.

[bb] A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[cc] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[dd] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Note: All recommendations are category 2A unless otherwise indicated.

Treatment (CART-9)

ICANS RELATED TO T-CELL–ENGAGING BISPECIFIC AGENTS

ICANS → Consider diagnostic testing
- EEG, MRI of brain, lumbar puncture

WORKUP/GRADING[g]	MANAGEMENT
All grades	• Risks associated with each agent vary widely. Refer to the prescribing information for product-specific dosing and management • Aspiration precautions • Withhold oral intake; assess swallow • Avoid all medications with CNS sedation • Consider neurology consultation if refractory to dexamethasone • Neuroimaging every 2–3 days if persistent ICANS
Grade 1	• Continue treatment (if blinatumomab, mosunetuzumab-axgb, glofitamab-gxbm); otherwise hold treatment (for all other bispecific agents)[h] • Oral or IV dexamethasone 10 mg x 1 dose; if unresolved or progressing, increase to every 6 hours • Consider levetiracetam 750 mg every 12 hours[i]
Grade 2	• Continue treatment (if blinatumomab); otherwise hold treatment (for all other bispecific agents)[h] • IV dexamethasone 10 mg every 6 hours • Consider levetiracetam 750 mg every 12 hours[i]
Grade 3	• Hold treatment (for all bispecific agents)[h] • ICU care • IV methylprednisolone 1000 mg x 1 dose. If refractory, every 12 hours x 3 days • Levetiracetam 750 mg every 12 hours[i]
Grade 4	• Permanently discontinue treatment (for all bispecific agents)[h] • ICU care • IV methylprednisolone 1000 mg every 12 hours • Levetiracetam 750 mg every 12 hours[i]

[g] Refer to CART-6 for ICANS grading.
[h] Considerations for Rechallenge of T-Cell–Engaging Bispecific Antibody Therapy After ICANS (ENGAGE-8).
[i] Depending on seizure risk associated with agent used.

Note: All recommendations are category 2A unless otherwise indicated.

Other Tolerability Concerns with Bispecific Antibodies in NHL

Cytopenias & Infections

	Neutropenia*	Infections	Thrombocytopenia	Anemia
Mosunetuzumab	50% (26% gr 3+) *median onset 70 days, duration 8 days	20% (14% gr 3+)	33% (6.4% gr 3+)	60% (10% gr 3+)
Epcoritamab	21.7% (14.6% gr 3+)	15% (14% gr 3+)	13.4% (5.7% gr 3+)	62% (12% gr 3+)
Glofitamab	56% (26% gr 3+)	38% (15% gr 3+)	56% (8% gr 3+)	72% (8% gr 3+)

*G-CSF for Neutropenia (ANC <1.0)

Prophylactic antimicrobials (VZV, PJP) until end of therapy and CD4 >200

Monitor IgG – IVIG for hypogammaglobulinemia (IgG <400 mg/dL)

Courtesy of Robin Klebig, APRN, CNP, AOCNP

Other Tolerability Concerns with Bispecific Antibodies in NHL

- **Fatigue**
  - **Mosunetuzumab SC - highest incidence (39%)**, followed by epcoritamab in FL (37%), epcoritamab in LBCL (29%), and glofitamab (20%)

- **Rash**
  - Generally **low-grade, manageable, and rarely treatment-limiting**
  - Epcoritamab - **15% of patients** (grade 3–4 in 0.6%)
    - **Injection site reactions in 27–47%** of patients (nearly all grade 1)
  - Glofitamab - **20% of patients** (grade 3–4 in 1.4%)
  - Mosunetuzumab SC - **35% of patients** (grade 3–4 in 3.2%)
    - **Injection site reactions (69%)**
    - In IV formulation, rash was not listed among the most common adverse events
  - Management: topical corticosteroids, oral antihistamines; po corticosteroids and Dermatology consultation prn

- **Musculoskeletal pain**
  - Epcoritamab in LBCL - 28%; glofitamab and mosunetuzumab SC - 20–21%; very low rates of grade 3–4 musculoskeletal pain (0–2.1%)

Courtesy of Robin Klebig, APRN, CNP, AOCNP

Other Tolerability Concerns with Bispecific Antibodies in NHL

Gastrointestinal adverse effects

GI Adverse Reaction	Glofitamab	Epcoritamab	Mosunetuzumab
Nausea	10% (Gr 3+ 0%)	17-20% (Gr 3+ 1.3%)	14% (Gr 3+ 0%)
Vomiting	10%	12% (Gr 3+ 0.6%)	NR
Diarrhea	14% (Gr 3+ 0%)	20-26% (Gr 3+ 1.6%)	20% (Gr 3+ 0%)
Constipation	14% (Gr 3+ 0%)	16% (Gr 3+ 0%)	14% (Gr 3+ 0%)

Courtesy of Robin Klebig, APRN, CNP, AOCNP

Case Presentation

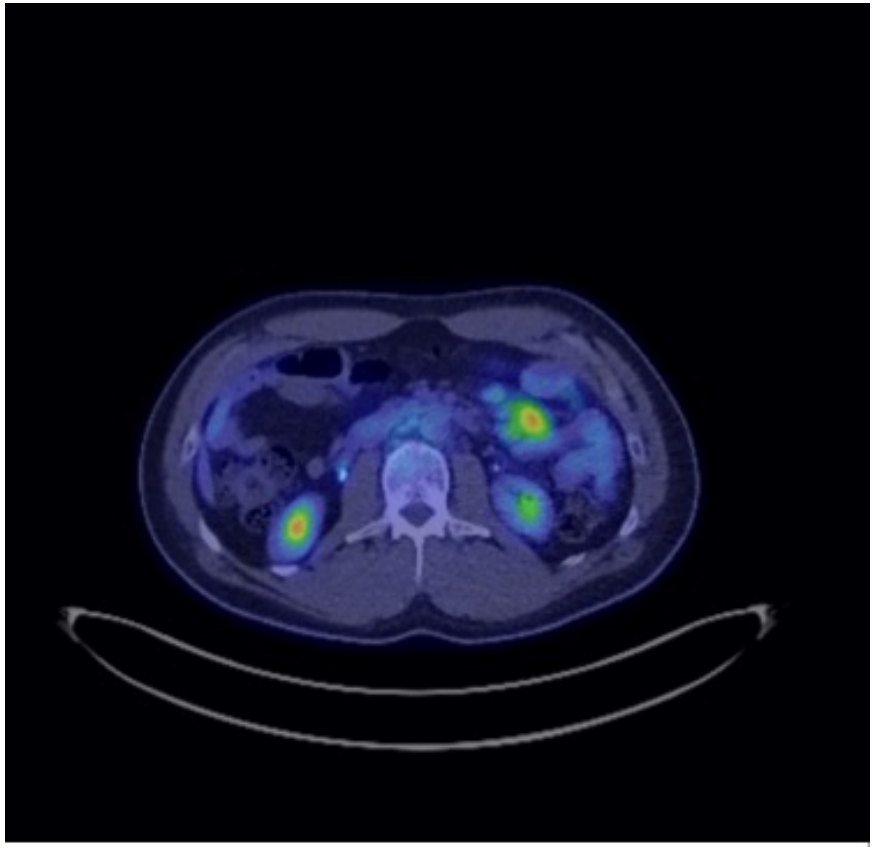
A patient with NHL who received a bispecific antibody

- 45 y/o male ER physician
- Lives 17 hours from Mayo Clinic
- Presented with urinary pain, concerned about prostatitis, possible abscess
- CT performed and showed adenopathy in small bowel area, largest 3.6 cm
- CBC, chem panel, LDH all WNL
- No B symptoms
- PMH: Thyroid nodule
- Social:
  - Patient and spouse both ER physicians. 2 children, ages 7 and 9
  - Never smoker, physically active, healthy diet & lifestyle

Diagnosis

- Lymph node, mesenteric, laparoscopic excisional bx: **Follicular lymphoma, grade 1-2.**

  - Germinal center B-cells
  - Positive CD20 and BCL6
  - Aberrant BCL2 expression
  - Ki-67 10%



A patient with NHL who received a bispecific antibody

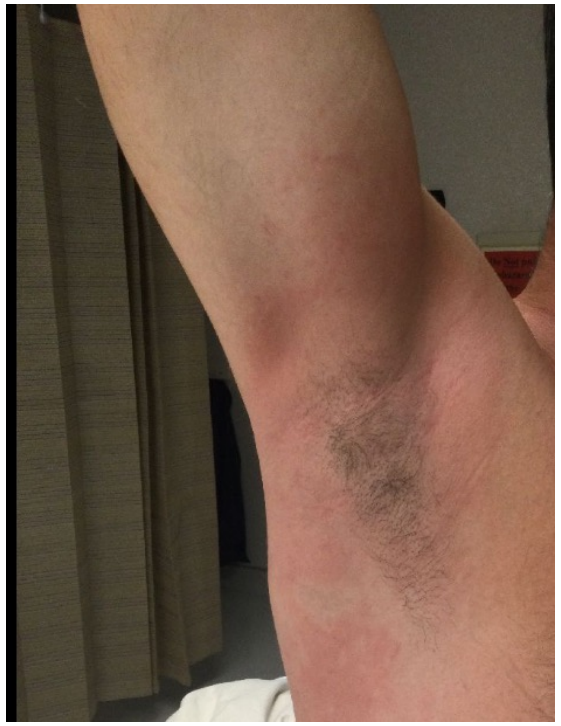
- No prior therapy
- Came to Mayo Clinic to participate in MorningSun clinical trial ML43389 - An Open-Label, Multicenter, Phase II Trial Evaluating the Safety, Efficacy, and Pharmacokinetics of Subcutaneous Mosunetuzumab Monotherapy in Patients With Select B-Cell Malignancies
- Treatment
  - Mosunetuzumab SQ 5 mg on Day 1
  - Mosunetuzumab SQ 45 mg on Days 8 onward
  - Plan per protocol – up to 17 cycles, can d/c treatment after 8 cycles if in CR
- Premedications
  - Diphenhydramine 50 mg po
  - Acetaminophen 650 mg po
  - Dexamethasone 20 mg po

Treatment course

- CRS
  - C1D1 – grade 1
    - Temp 100.3, headache, malaise
      - Dexamethasone 10 mg IV given
  - C1D3 – grade 1
    - recurrent CRS with fever (temp 101) & rigors
      - Dexamethasone 10 mg IV and tocilizumab
  - Infectious w/u unremarkable
  - No recurrence of CRS

- ICANS/Neurotoxicity
  - Grade 0?
  - “Passed” ICE score but subsequently admitted he could not recall the names of his children, word finding, “in a fog” and “scary”
  - [received dexamethasone 10 mg IV for CRS]

Treatment course



- General side effects & management
  - Headaches, malaise, myalgias
  - Rash
    - Derm consult – r/o SJS/TEN
    - Topical triamcinolone 0.1% cream BID to affected areas
    - Loratadine 20 mg BID
    - Famotidine 20 mg BID
    - Montelukast 10 mg daily
    - With recurrence - Dexamethasone 20 mg 1 day prior to and day of mosunetuzumab, then 10 mg daily x 3 days after injection
  - Injection site reactions
  - Neutropenia & Lymphopenia
    - Antimicrobial prophylaxis (VZV/PJP)
    - G-CSF prn (Cycle 10 – ANC = 250)

Treatment course

- Per protocol, can d/c treatment after 8 cycles if in CR (he was)
  - ClonoSeq ID - had 3 traceable sequences - "trackable tumor"
    - PLAN: If negative, consider d/c and observe; if positive, continue
  - MRD negative after cycle 10
  - Elected to discontinue treatment after cycle 11, entered observation

Recurrent infections for 6 months after completion of treatment

- Current status –
  - Alive, 16 months out from completion of treatment
  - Living a normal active life

Discussion Questions

Can bispecific antibodies be safely delivered in a community oncology setting?

What steps can nurses in community-based practice take to ensure a smooth transition for patients who receive bispecific antibodies at tertiary care centers and then return to them for routine care?

What potential long-term complications are associated with bispecific antibodies? How should patients who receive these agents be followed over time?

Agenda

Introduction: Biology of Non-Hodgkin Lymphoma (NHL)

Module 1: Current Role of CD20 x CD3 Bispecific Antibodies in NHL

Module 2: Role of Polatuzumab Vedotin in Diffuse Large B-Cell Lymphoma (DLBCL)

Module 3: Optimal Application of Loncastuximab Tesirine for Patients with DLBCL and Follicular Lymphoma

Module 4: Role of BTK Inhibitors Alone or with Anti-CD20 Antibodies for Patients with Newly Diagnosed Chronic Lymphocytic Leukemia (CLL)

Module 5: Combining BTK Inhibitors with Bcl-2 Inhibitors

Module 6: Current and Future Role of Noncovalent BTK Inhibitors in CLL

Polatuzumab Vedotin in DLBCL

Brad Kahl, MD

Professor of Medicine

SITEMAN CANCER CENTER
A NATIONAL CANCER INSTITUTE COMPREHENSIVE CANCER CENTER

BARNES-JEWISH Hospital
BJC HealthCare

Washington University in St. Louis
SCHOOL OF MEDICINE

SITEMAN Kids
AT ST. LOUIS Children's HOSPITAL
Washington University Physicians

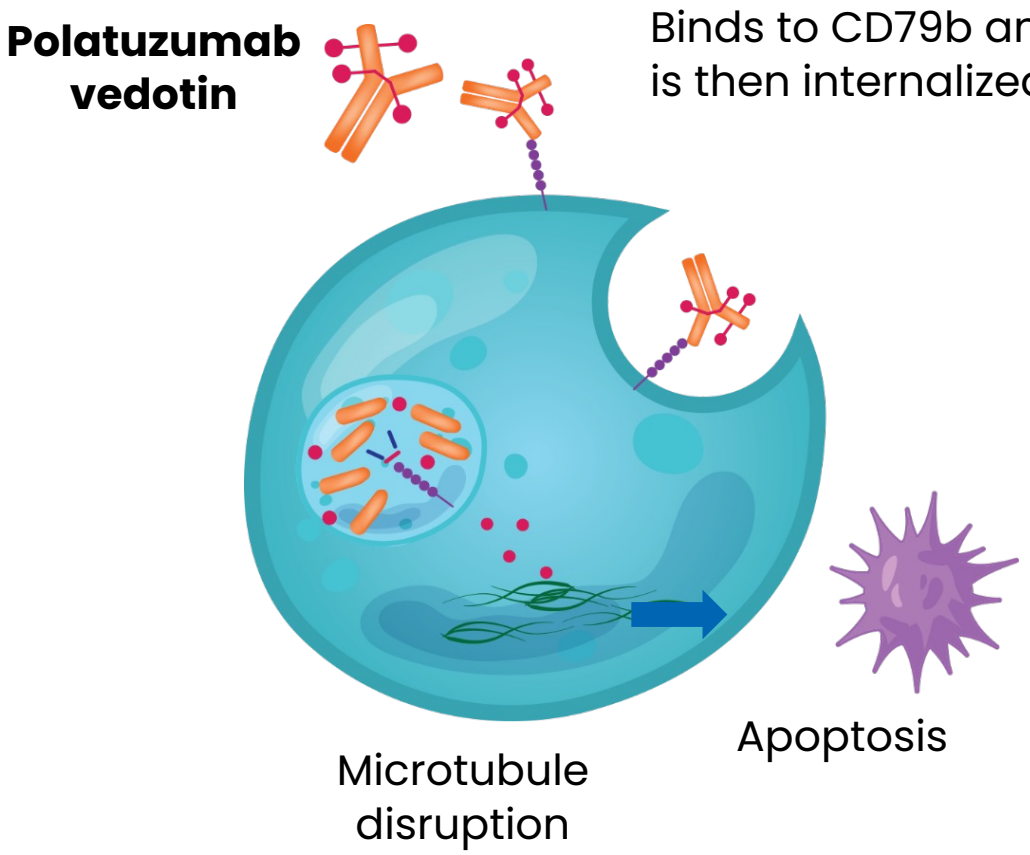
NCI Designated Comprehensive Cancer Center

NCCN National Comprehensive Cancer Network®

Frontline DLBCL:
R-CHOP had been the standard of care since 2002

Polatuzumab Vedotin: Mechanism of Action

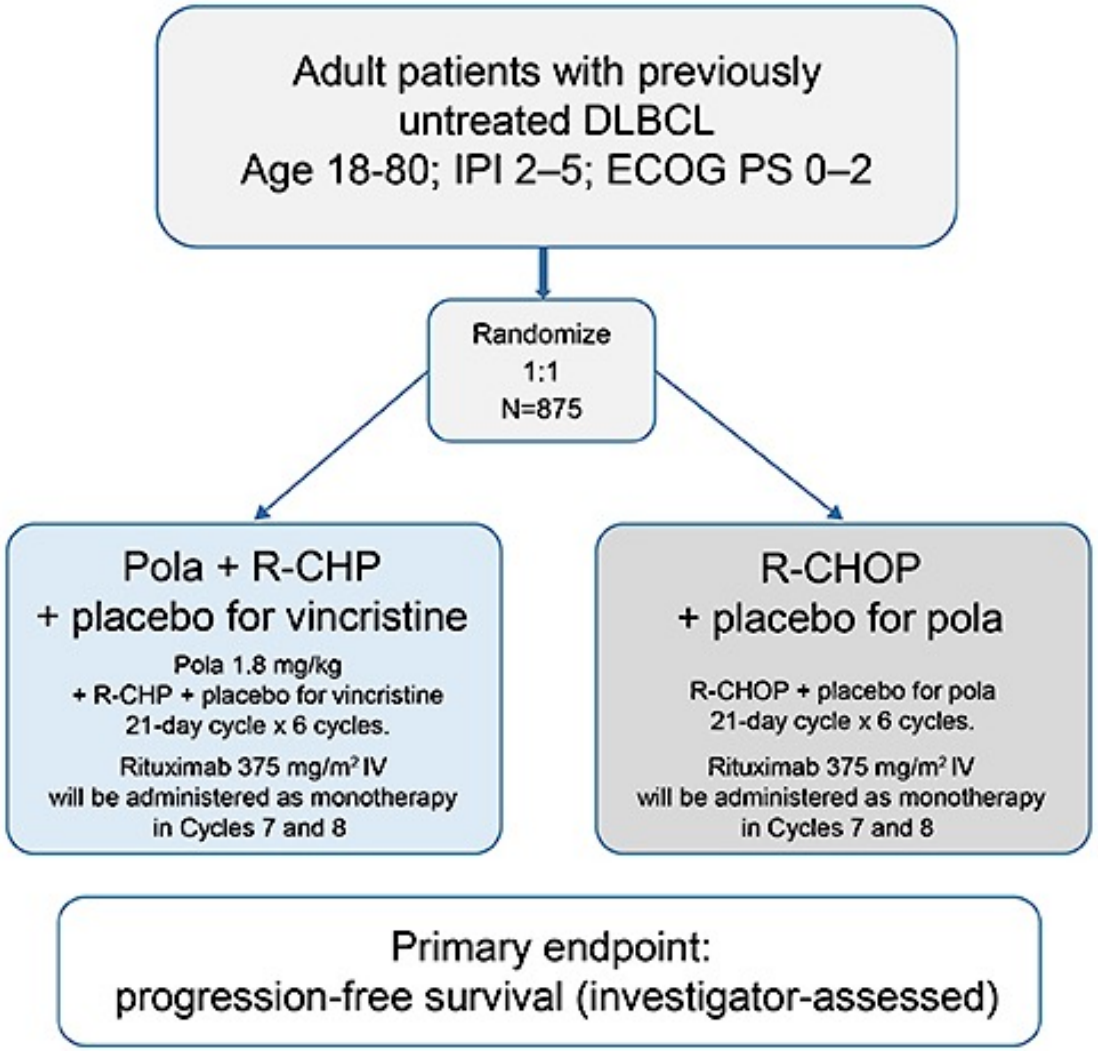
- Microtubule inhibitor MMAE conjugated to CD79b monoclonal antibody via a protease-cleavable peptide linker



- Polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) as 1L treatment for adults with previously untreated DLBCL not otherwise specified (NOS), or high-grade B-cell lymphoma (HGBL) who have an International Prognostic Index (IPI) score of 2 or greater
- Polatuzumab vedotin in combination with bendamustine and rituximab is indicated for adult patients with R/R DLBCL-NOS after ≥2 prior therapies
- Current NCCN guidelines list polatuzumab ± bendamustine ± rituximab as a preferred second-line therapy

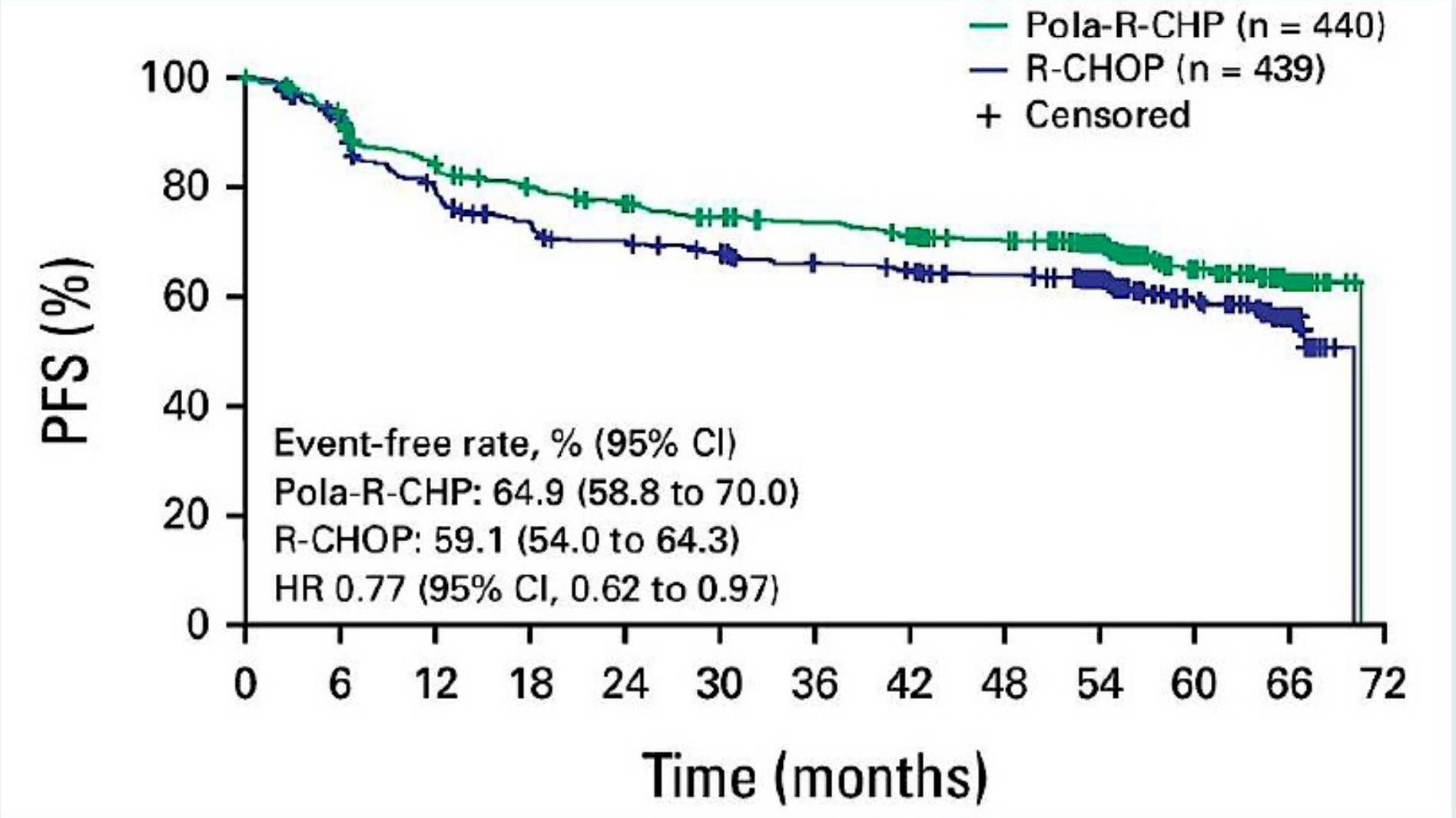
- Sawalha. Oncol Targets Ther. 2020;13:5123. NCCN Clinical Practice Guidelines in Oncology: B-cell lymphomas. v..1.2026.

Phase III POLARIX Study Design



Tilly H et al. EHA 2018

Phase III POLARIX: 5-Year PFS (Global Population)



Morschhauser F et al. *J Clin Oncol* 2025 December 10;43(35):3698-705.

Pola in the relapsed DLBCL setting

Phase Ib/II GO29365 Study Final Results: Efficacy

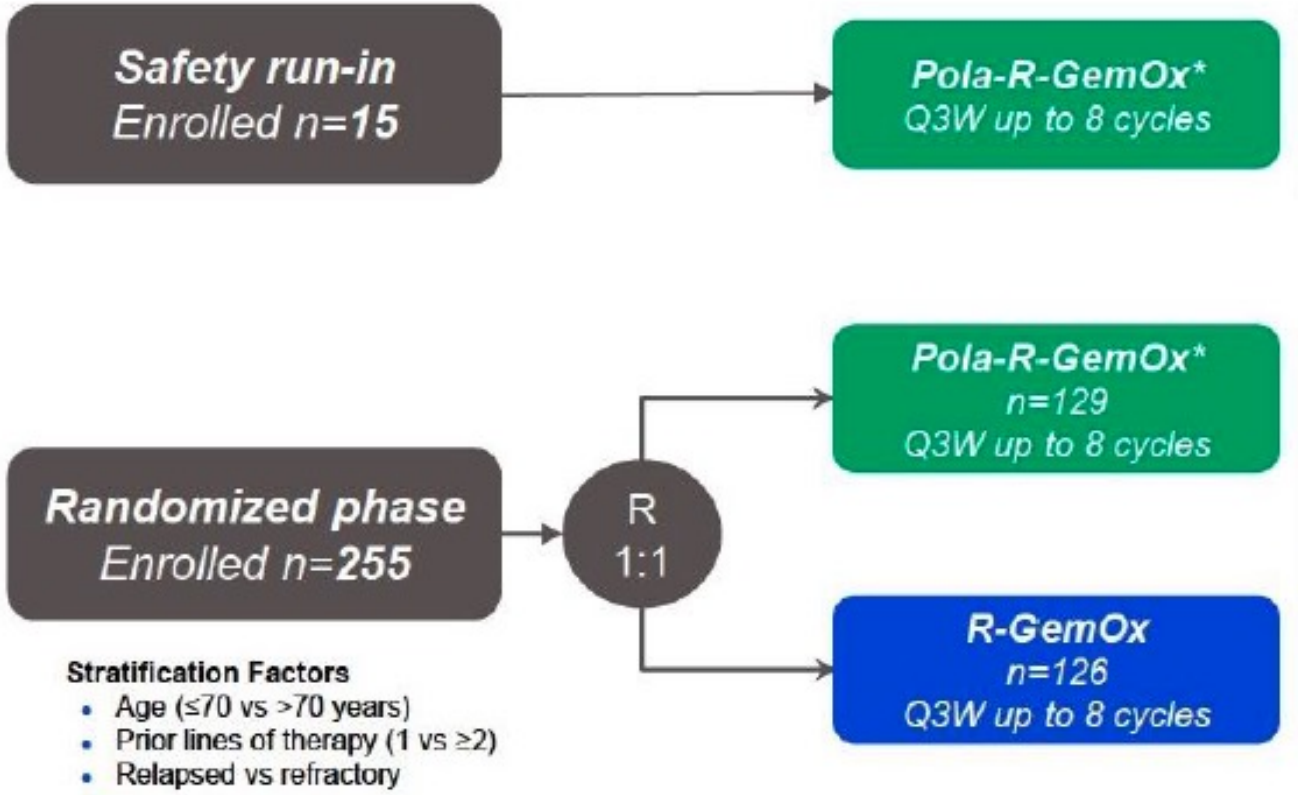
Outcome*	Randomized		Extension
	Pola+BR (n=40)	BR (n=40)	Pola+BR (n=106)
ORR, % (95% CI)	42.5 (27.0–59.1)	17.5 (7.3–32.8)	43.4 (33.8–53.4)
CR, % (95% CI)	42.5 (27.0–59.1)	17.5 (7.3–32.8)	39.6 (30.3–49.6)
BOR, % (95% CI)	62.5 (45.8–77.3)	25.0 (12.7–41.2)	57.5 (47.6–67.1)
BCR, % (95% CI)	52.5 (36.1–68.5)	22.5 (10.8–38.5)	53.8 (43.8–63.5)
Median DOR, months (95% CI)	10.9 (5.7–40.7)	10.6 (4.0–19.7)	13.4 (8.6–20.0)
Median PFS, months (95% CI)	9.2 (6.0–13.9)	3.7 (2.1–4.5)	7.0 (5.1–9.8)
Median OS, months (95% CI)	12.4 (9.0–32.0)	4.5 (3.7–6.0)	12.3 (8.3–17.0)

Sehn LH et al. *Blood.* 2022;140 (1_Suppl: 9464-9467)

Phase III POLARGO Study Design

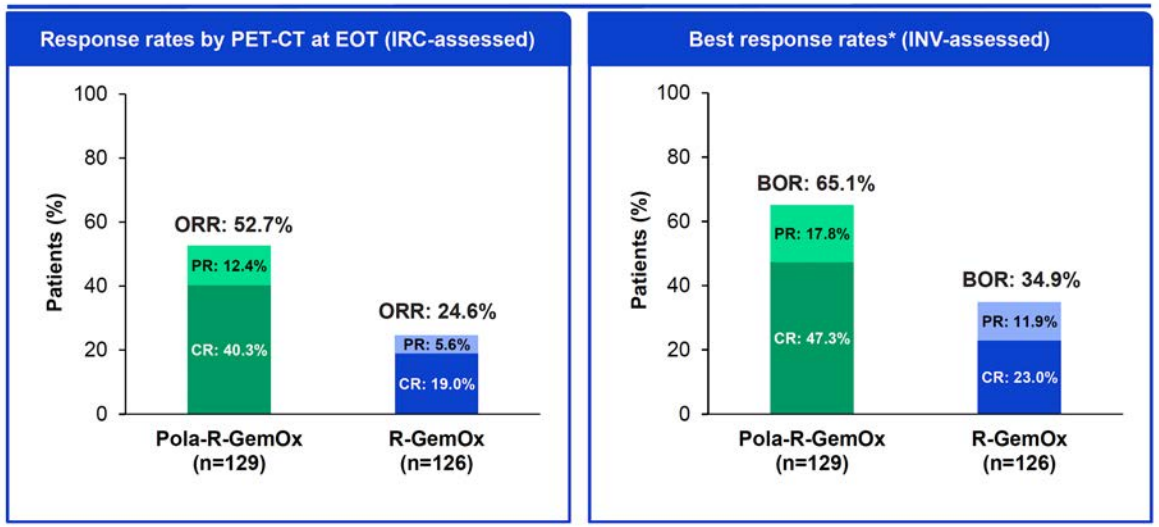
Key eligibility criteria

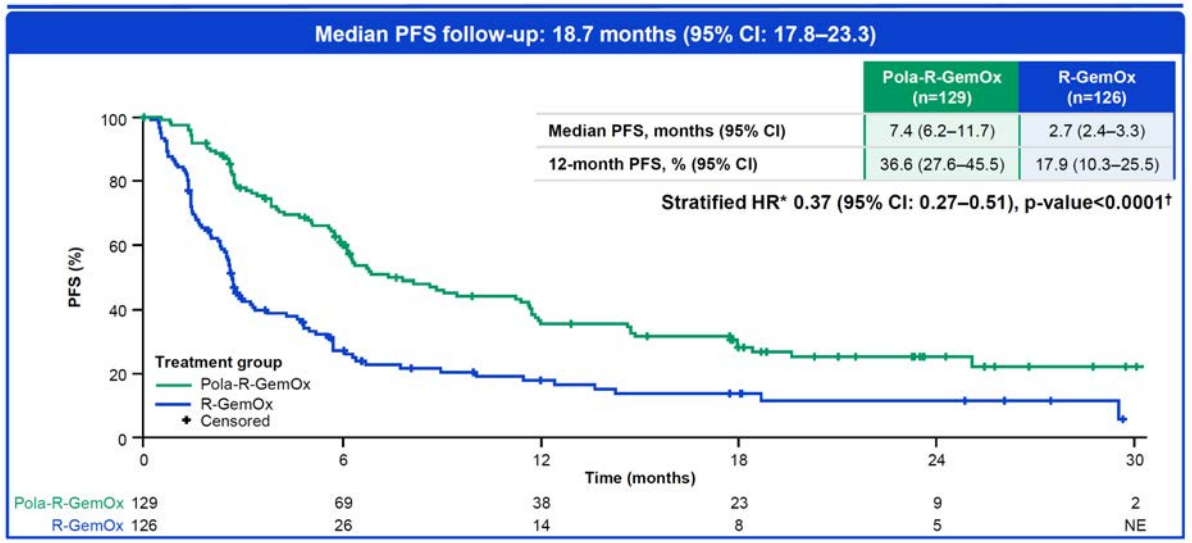
- DLBCL, NOS or history of transformation of indolent disease to DLBCL
- R/R disease after ≥1 prior line of treatment
- Ineligible for transplant

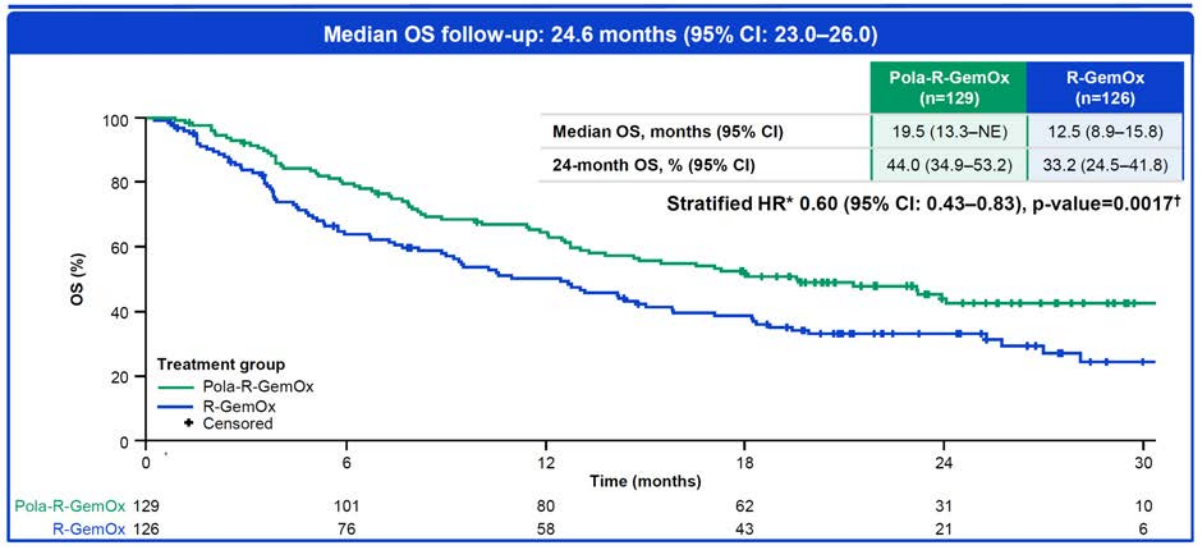


Matasar M et al. EHA 2025;Abstract S101.

Pola-R-GO







Matasar et al, EHA. Abstract S101.

SUNMO Study design

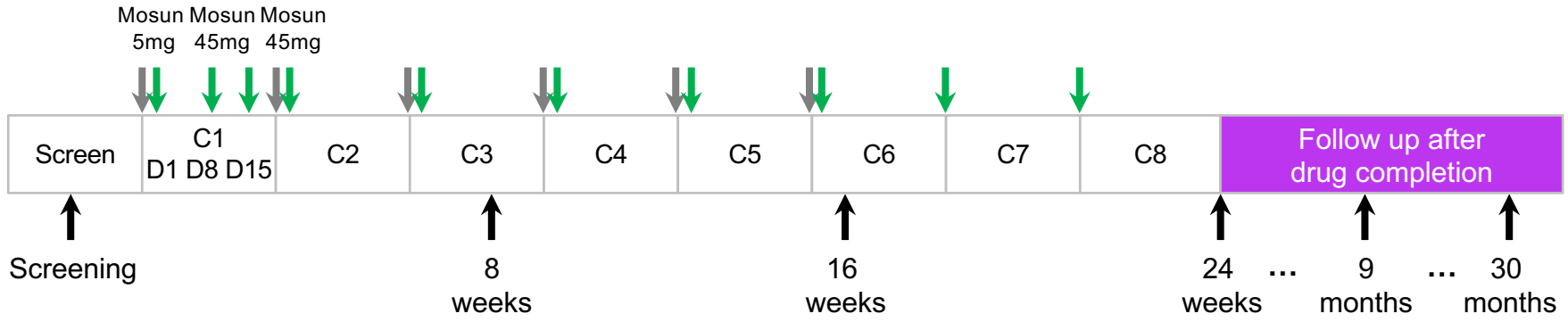
Key eligibility

R/R LBCL with ≥1 prior therapy and ASCT-ineligible:

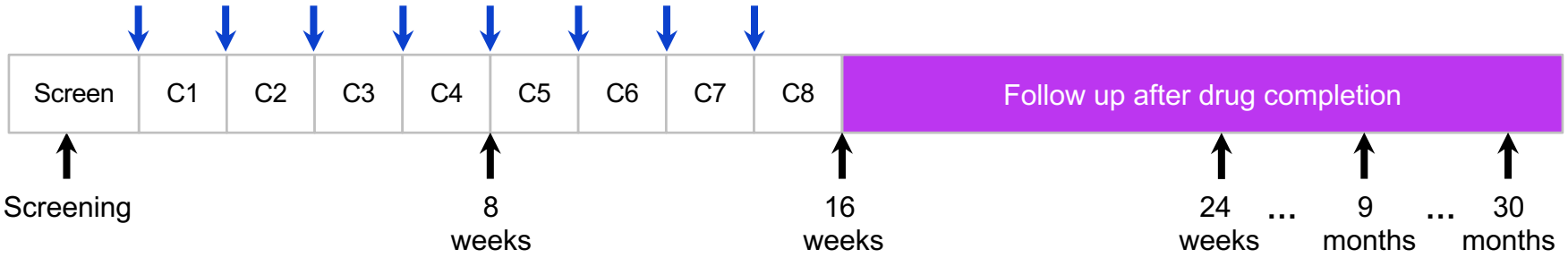
- DLBCL NOS
- Transformed FL
- HGBCL
- Grade 3B FL

2:1

Outpatient Mosun SC (8 cycles) + Pola IV (6 cycles) (21-day cycles)

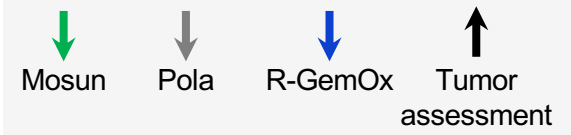


R-GemOx IV (8 x 14–21-day cycles*)



Stratification factors

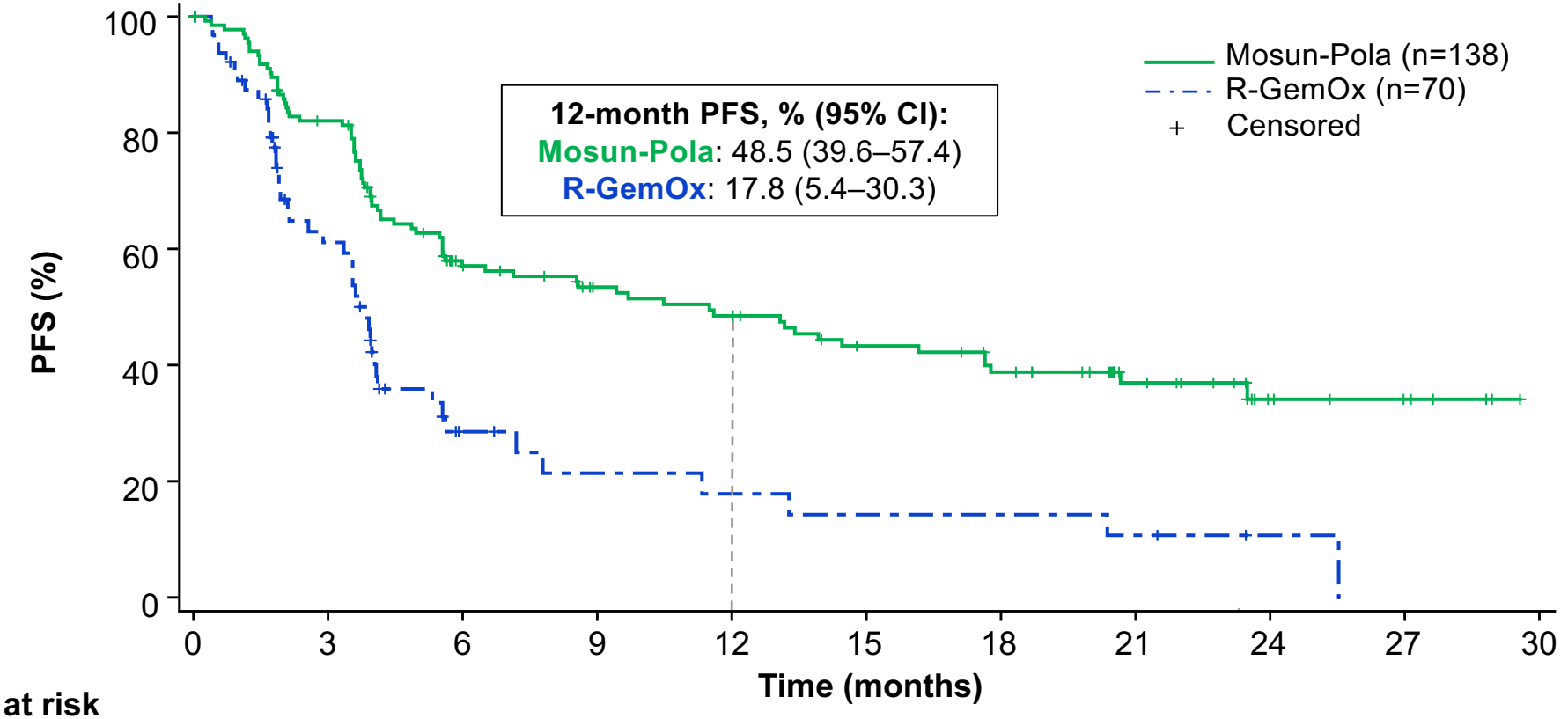
- 1 vs ≥2 prior lines of systemic therapy
- Relapsed vs refractory disease



Presented as LBA3 by Westin et al, ICML 2025

Mosun-Pola significantly prolonged progression-free survival versus R-GemOx

Primary endpoint: Progression-free survival by IRC



n at risk

Mosun-Pola	138	108	65	54	49	40	34	20	8	5	NE
R-GemOx	70	33	9	6	5	4	4	3	1	NE	NE

Mosun-Pola demonstrates a 59% risk reduction for progression or death compared with R-GemOx

Presented as LBA3 by Westin et al, ICML 2025

Three new combinations vs. R-GemOx

	ORR	CR	12 month PFS
R-GemOx	40%	25%	18%
Pola-R-GemOx	65%	47%	36%
Glofit-GemOx	68%	58%	50%
Mosun-Pola	70%	51%	48%

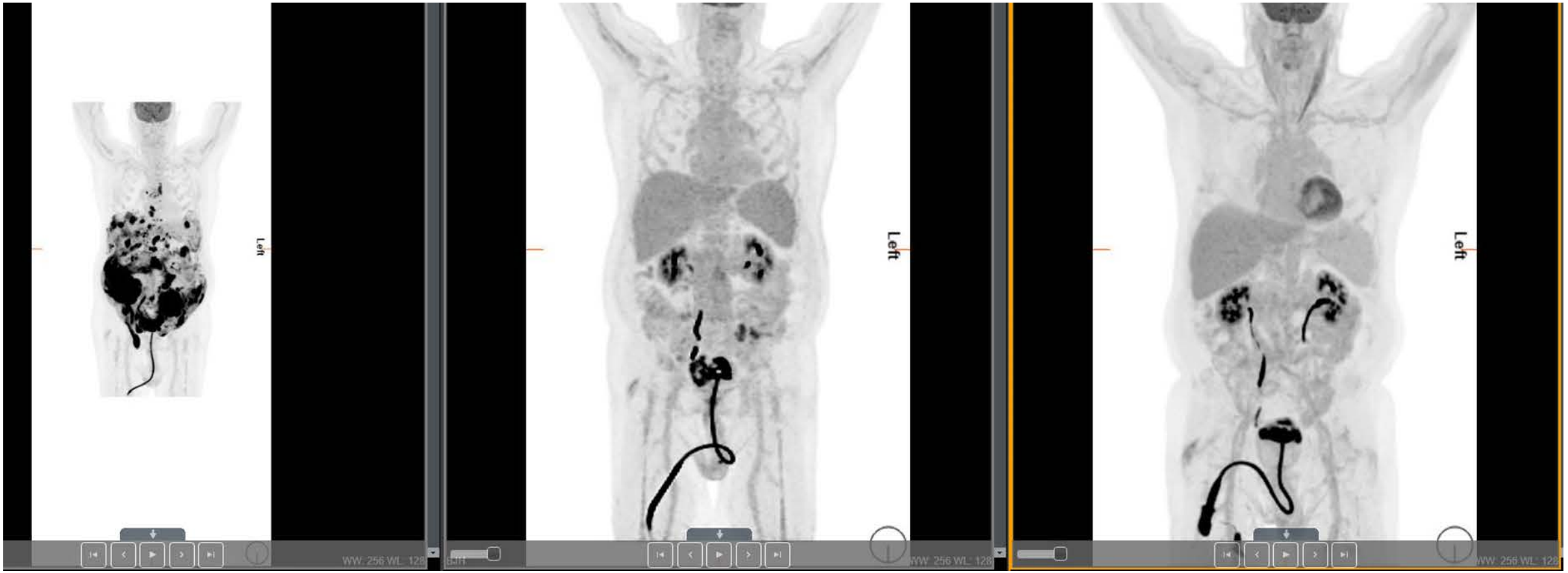
What is “preferred” regimen going forward?

Case Presentation

Case Presentation

- 80 yo male attorney with several months of failure to thrive, wt loss and urinary retention. Extremely weak and debilitated. PS 3.
- PMHx: CHF, CAD, HTN, BPH
- Found to have large abdominal mass during evaluation. Hospitalized.
- Images show “malignancy” with extensive intra-abdominal adenopathy with peritoneal involvement and prostate involvement.
- BX: DLBCL. Non-GCB. Stage IV. IPI score 5. Echo EF 60%.
- RX: mini-R-CHP-pola. X 3. PS improving. Interim PET showed PMR with 5 point score of 4. Increased to full dose R-CHP-pola.
- EOT PET (4/29/26) show CMR.

PET images 12/25, 2/26, 4/26



Discussion Questions

For which patients with newly diagnosed DLBCL are you prioritizing the use of polatuzumab vedotin/R-CHP?

For your patients who don’t receive polatuzumab vedotin in the front-line setting, how are you employing this agent in the R/R setting? What are you typically partnering it with?

Tolerability Considerations with Polatuzumab Vedotin

Mollie Moran, APRN-CNP, AOCNP
Nurse Practitioner
The James Cancer Hospital and Solove Research Institute
The Ohio State University
Columbus, Ohio

Adverse Events during the Treatment Period (Safety Population).

Table 3. Adverse Events during the Treatment Period (Safety Population).*

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

* Shown are the most common adverse events, which were defined as adverse events of any grade that occurred in at least 12% of the patients in either treatment group. These adverse events are *Medical Dictionary for Regulatory Activities*, version 24.0, preferred terms. Adverse events of any grade were reported in 426 patients (97.9%) in the pola-R-CHP group and in 431 patients (98.4%) in the R-CHOP group; adverse events of grade 3 or higher in 264 (60.7%) and 262 (59.8%), respectively; serious adverse events in 148 (34.0%) and 134 (30.6%), respectively; and adverse events of grade 5 in 13 (3.0%) and 10 (2.3%), respectively.

† Peripheral neuropathy includes the following preferred terms from the system organ class of peripheral neuropathy: peripheral neuropathy, peripheral sensory neuropathy, paresthesia, hypoesthesia, polyneuropathy, peripheral motor neuropathy, dysesthesia, neuralgia, peripheral sensorimotor neuropathy, hypotonia, hyporeflexia, neuromyopathy, ear paresthesia, peroneal nerve palsy, and skin burning sensation.

Tilly H et al. N Engl J Med2022;386:351-363

The NEW ENGLAND JOURNAL of MEDICINE

Grading of Common Polatuzumab Vedotin-Associated Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE)[2]

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral neuropathy • Motor • Sensory	Asymptomatic; clinical or diagnostic observations only (motor); intervention not indicated (motor); loss of deep tendon reflexes or paresthesia (sensory)	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; assistive device indicated (motor)	Life-threatening consequences; urgent intervention indicated
Myelosuppression • Neutropenia • Thrombocytopenia	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Infusion-related reactions	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated

A semicolon indicates "or" within the description of the grade.
ADL=activities of daily living; NSAIDs=nonsteroidal anti-inflammatory drugs.

Polatuzumab vedotin, Manufacturer's dosing and administration guide.

Management of Peripheral Neuropathy

Severity*	Dose Modification
Grade 2–3 (moderate to severe)	Hold Pola dosing until improvement to Grade 1 or lower. If recovered to Grade 1 or lower on or before Day 14, restart Pola with the next cycle at a permanently reduced dose of 1.4 mg/kg. If a prior dose reduction to 1.4 mg/kg has occurred, discontinue Pola . If not recovered to Grade 1 or lower on or before Day 14, discontinue Pola.
Grade 4 (life-threatening)	Discontinue Pola.

Polatuzumab vedotin, Manufacturer's dosing and administration guide.

RTP RESEARCH TO PRACTICE

Management of Myelosuppression

Severity*†	Dose Modification
Grade 3-4 neutropenia‡ (severe to life-threatening)	Hold all treatment until ANC recovers to >1000/μL. If ANC recovers to >1000/μL on or before Day 7, resume all treatment without any additional dose reductions. Consider G-CSF prophylaxis for subsequent cycles, if not previously given. If ANC recovers to >1000/μL after Day 7: • Restart all treatment. Consider G-CSF prophylaxis for subsequent cycles, if not previously given. If prophylaxis was given, consider dose reduction of bendamustine • If dose reduction of bendamustine has already occurred, consider dose reduction of Pola to 1.4 mg/kg
Grade 3-4 thrombocytopenia‡ (severe to life-threatening)	Hold all treatment until platelets recover to >75,000/μL. If platelets recover to >75,000/μL on or before Day 7, resume all treatment without any additional dose reductions. If platelets recover to >75,000/μL after Day 7: • Restart all treatment, with dose reduction of bendamustine • If dose reduction of bendamustine has already occurred, consider dose reduction of Pola to 1.4 mg/kg

*Severity grading is based on NCI CTCAE version 4.[2]
†Severity on Day 1 of any cycle.
‡If primary cause is due to lymphoma, dose delay or reduction may not be needed.
ANC=absolute neutrophil count; NCI=National Cancer Institute; CTCAE=Common Terminology Criteria for Adverse Events.

Polatuzumab vedotin, Manufacturer's dosing and administration guide.

RTP RESEARCH TO PRACTICE

Management of Infusion-Related Reactions

Severity*	Dose Modification
Grade 1-3 (mild transient to prolonged reaction)	Interrupt Pola infusion and give supportive treatment. For the first instance of Grade 3 wheezing, bronchospasm, or generalized urticaria, permanently discontinue Pola. For recurrent Grade 2 wheezing or urticaria, or for recurrence of any Grade 3 symptoms, permanently discontinue Pola. Otherwise, upon complete resolution of symptoms, infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hour every 30 minutes. For the next cycle, infuse Pola over 90 minutes. If no infusion-related reaction occurs, subsequent infusions may be administered over 30 minutes. Administer premedication for all cycles.
Grade 4 (life-threatening)	Stop Pola infusion immediately. Give supportive treatment. Permanently discontinue Pola.

*Severity grading is based on NCI CTCAE version 4.[2]

Polatuzumab vedotin, Manufacturer's dosing and administration guide.

Case Presentation

Case study: Polatuzumab vedotin

- Patient is a 65 yo farmer (M). He noticed a mass in his right lower neck that continued to increase in size
  - PCP ordered CT scan – >5 cm cervical mass. Refer to ENT.
  - Bx showed aggressive B cell lymphoma. Pt referred to OSU.
  - Ki6780% on LN bx.
  - Stage IV non-GC DLBCL with IPI 2.
  - PET scan with large abdominal nodes with max SUV 15.7
  - Hx DM and HTN well controlled
  - Discussed the standard treatment has been R-CHOP for many years although R-Pola-CHP was recently approved by the FDA based on results of the POLARIX trial which evaluated RCHOP vs RCHP+POLA and showed a benefit in 2 year PFS with the RCHP+Pola. This was maintained at 3 years of follow up. At this time there is no overall survival benefit noted but further follow up required. Discussed this is 6 cycles.

Case Study Continued

- Pretreatment he is started on PJP prophylaxis and antiviral
- He receives growth factor support with each cycle
- He will have weekly labs checked at a local lab and faxed to the office
- After C1 he develops N/V and requires IV antiemetics and IV hydration with the addition of oral antiemetics for home.
- After C2 he has alopecia and constipation. Use OTC medications for constipation. Cervical mass resolved.
- Arrives for C3 with increased numbness and tingling in his feet and hands. He is having difficulty buttoning his shirt. He has to cut back on his duties at the farm.
  - Dose of Polatuzumab vedotin is reduced
- Gets COVID, took nirmatrelvir/ritonavir
- PET scan after #4 with good response to therapy. Neuropathy is improving.
- Completes 6 cycles of R-Pola-CHP
- PET scan Deauville 2, complete metabolic response
  - Rib fx noted. Likely due to a cow incident.

Agenda

Introduction: Biology of Non-Hodgkin Lymphoma (NHL)

Module 1: Current Role of CD20 x CD3 Bispecific Antibodies in NHL

Module 2: Role of Polatuzumab Vedotin in Diffuse Large B-Cell Lymphoma (DLBCL)

Module 3: Optimal Application of Loncastuximab Tesirine for Patients with DLBCL and Follicular Lymphoma

Module 4: Role of BTK Inhibitors Alone or with Anti-CD20 Antibodies for Patients with Newly Diagnosed Chronic Lymphocytic Leukemia (CLL)

Module 5: Combining BTK Inhibitors with Bcl-2 Inhibitors

Module 6: Current and Future Role of Noncovalent BTK Inhibitors in CLL

Loncastuximab Tesirine in DLBCL and FL

Brad Kahl, MD

Professor of Medicine

SITEMAN CANCER CENTER
A NATIONAL CANCER INSTITUTE COMPREHENSIVE CANCER CENTER

BARNES-JEWISH Hospital
BJC HealthCare

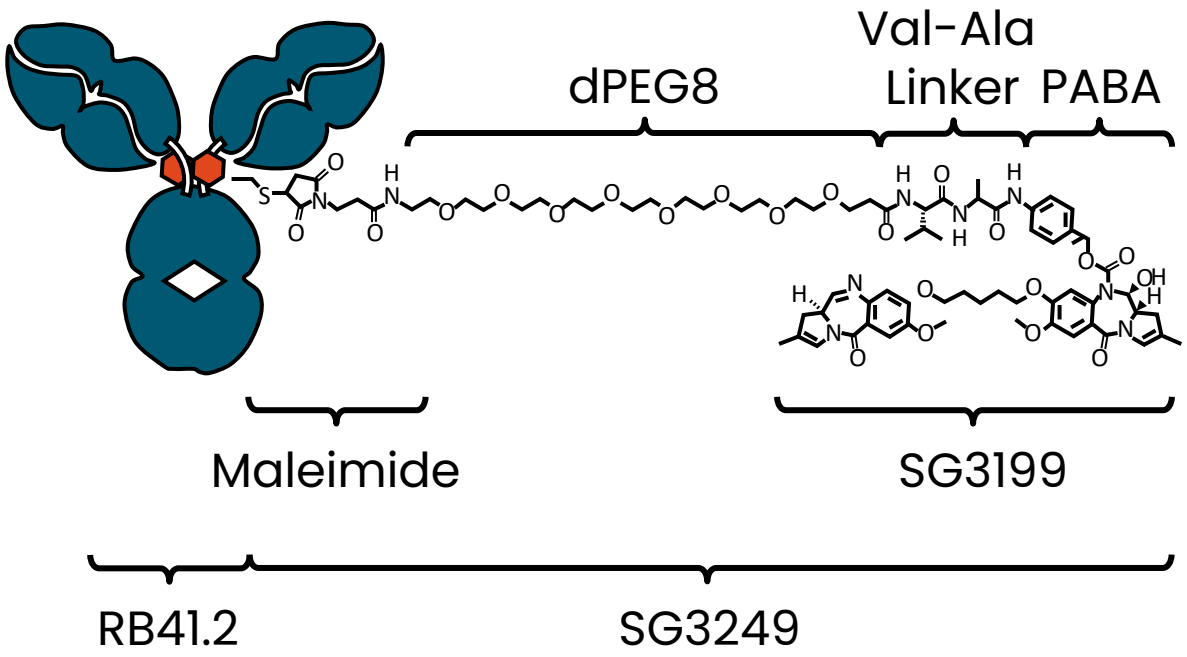
Washington University in St. Louis
SCHOOL OF MEDICINE

SITEMAN Kids
AT ST. LOUIS Children's HOSPITAL
Washington University Physicians

NCI Designated Comprehensive Cancer Center

NCCN National Comprehensive Cancer Network®

Loncastuximab Tesirine: Mechanism of Action

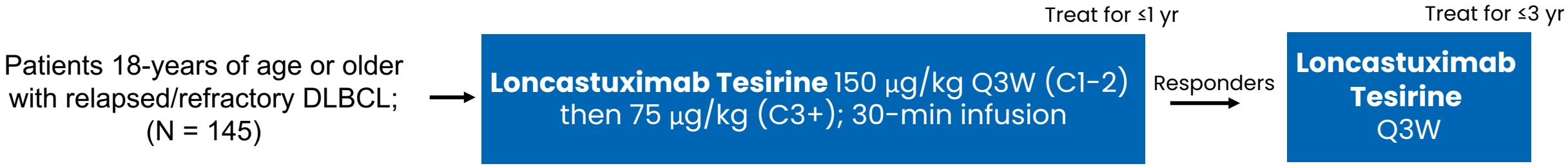


- Antibody-drug conjugate targeting CD19
- Payload: SG3199
  - Pyrrolobenzodiazepine dimer cytotoxin causes interstrand DNA crosslinks
  - 14-day half-life

- Zammarchi. Blood. 2018;131:1094. Caimi. Lancet Oncol. 2021;22:790.

LOTIS-2: Loncastuximab Tesirine in R/R DLBCL

Single-arm, open-label, phase II study



- Primary endpoint: ORR by ICR per Lugano 2014 (up to 21.5 months)
- Key secondary endpoints: DoR, RFS, OS, safety

NCT03589469. Caimi. Lancet Oncol. 2021;22:790. Caimi. Haematologica. 2024; 109:1184.

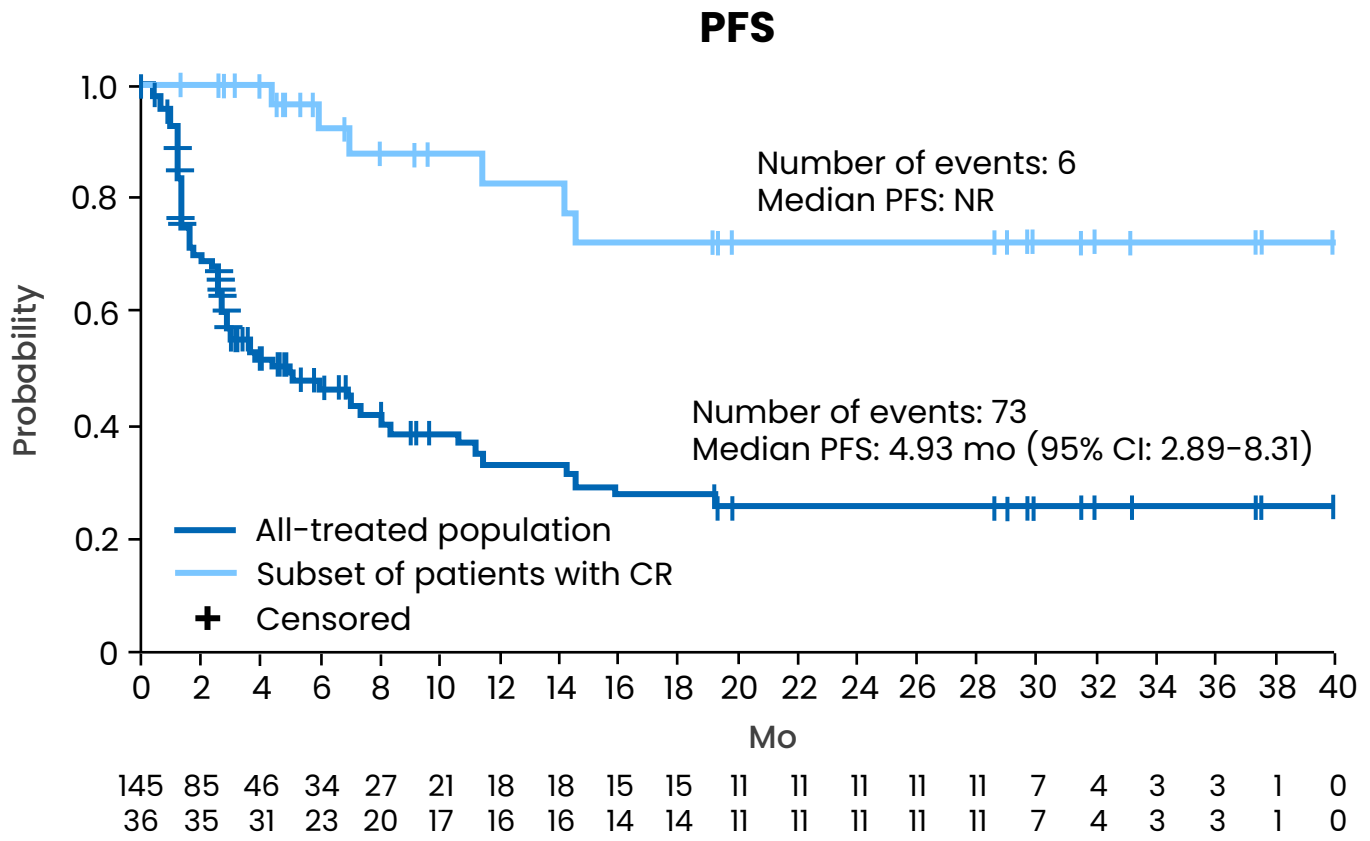
LOTIS-2: Patient Characteristics and Efficacy/Safety Summary

Baseline Characteristic	N = 145
Median age, yr (range)	66 (23-94)
Histology, n (%)	
• DLBCL NOS	127 (88)
• HGBCL	11 (8)
• PMBCL	7 (5)
Median prior tx (IQR)	3 (2-4)
Relapsed to prior tx, n (%)	43 (30)
Refractory to prior tx, n (%)	84 (58)
Prior CAR T-cells, n (%)	13 (9)

- FDA approved for R/R DLBCL who have received 2 prior lines of therapy

ORR: 48.3%
- CR: 24.8%
- PR: 23.5%

Median DoR (n = 145): 13.4 mo
- 95% CI: 6.9-NR



- Caimi. Lancet Oncol. 2021;22:790. Caimi. Haematologica. 2024; 109:1184.

New ADC Data in R/R DLBCL

- **Updated safety run in results from Lotis-5: A phase III trial of Lonca-T plus rituximab vs. immunochemotherapy in patients with R/R DLBCL.** Carlo-Stella et al, EHA.

- **Initial Results from LOTIS-7: A phase 1B study of Lonca-T plus Glofitamab in patients with R/R DLBCL.** Alderuccio et al, EHA.

LOTIS-5 Safety Run-in: Efficacy Results[1,a]

- The ORR by central review was 80% (16/20)
- A total of 50% (10/20) and 30% (6/20) of patients attained CR and PR, respectively
- The median DOR was 8.0 months (95% CI, 3.2-NE)
- The median PFS was 8.3 months (95% CI, 4.5-NE)
- No new safety signals were identified
- Trial has progressed to randomization

Efficacy outcomes in safety run-in population (N=20)	
ORR (95% CI), %	80.0 (56.3, 94.3)
CR rate (95% CI), %	50.0 (27.2-72.8)
Median DOR (95% CI), months	8.0 (3.2-NE)
Median PFS (95% CI), months	8.3 (4.5, NE)
Efficacy outcomes in responders (n=16)	
Median DOR (95% CI), months	8.0 (3.19-NE)
Events (%), n	5 (31.3)
Efficacy outcomes in complete responders (n=10)	
Median DOR (95% CI), months	NE (3.19-NE)
Events (%), n	3 (30.0)
MRD results in patients with ctDNA measurements (n=8)	
CR and MRD negative (%), n	4 (50.0)
MRD negative at end of treatment (%), n	4 (50.0)

[a]October 4, 2024, data cutoff.

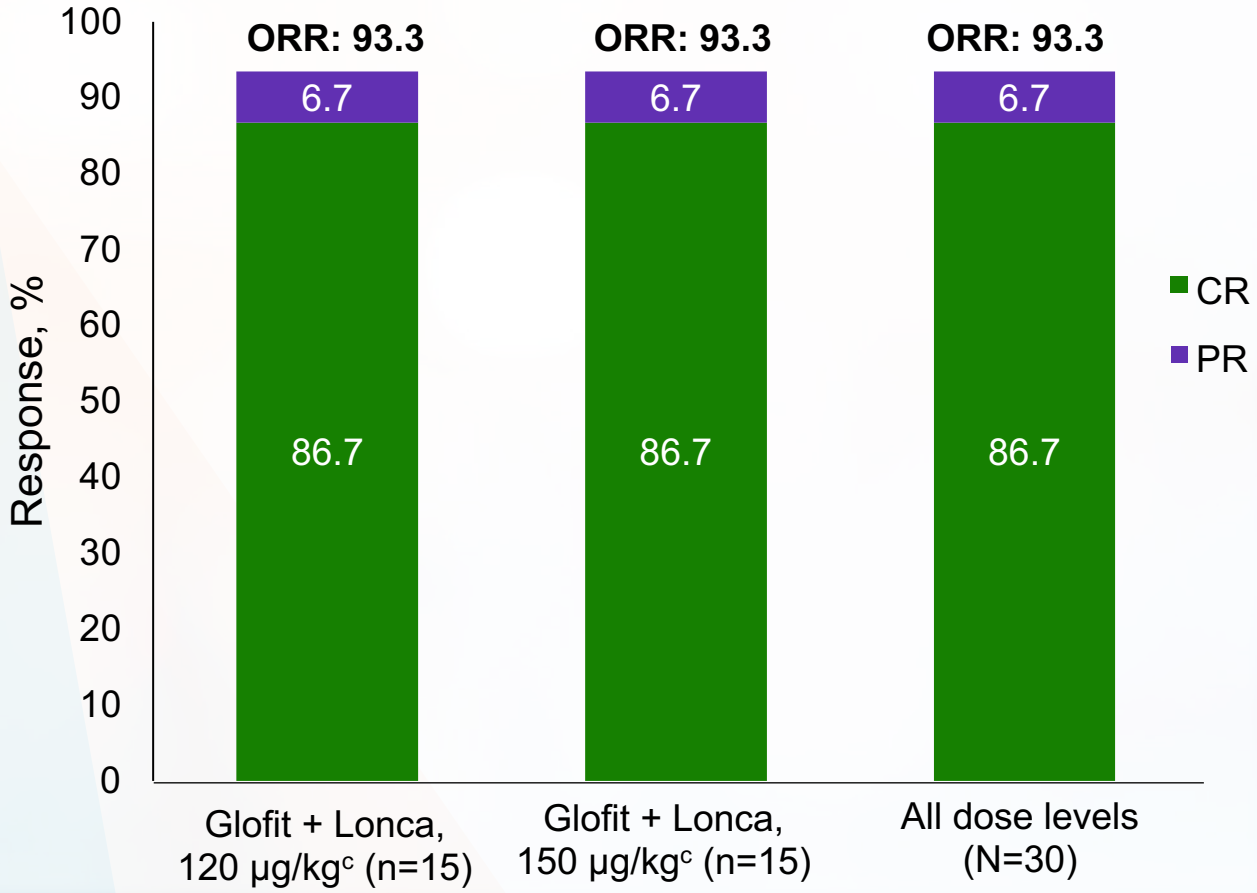
Abbreviations: CR, complete response; ctDNA, circulating tumor DNA; DOR, duration of response; EOT, end of therapy; MRD, minimal residual disease; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SCT, stem cell transplant.

1. Carlo-Stella C, et al. Updated Safety Run-in Results From LOTIS-5: A Phase 3, Randomized Trial of Loncastuximab Tesirine With Rituximab Versus Immunochemotherapy in Patients With R/R DLBCL/HGBL. Poster presented at the European Hematology Association 30th Annual Congress (EHA 2025). June 12-15, 2025. Milan, Italy.

BEST OVERALL RESPONSE & DURATION OF RESPONSE

EFFICACY EVALUABLE POPULATION (N=30)[a]

Best overall response[b]



Duration of response

Characteristic, n (%)	Glofit + Lonca, 120 µg/kg[c] (n=15)	Glofit + Lonca, 150 µg/kg[c] (n=15)	All dose levels (N=30)
DOR[d] Median	(n=14) NE	(n=14) NE	(n=28) NE
Time to first response (CR or PR) Median, days	(n=14) 42.0	(n=14) 42.0	(n=28) 42.0
Time to first CR Median, days	(n=13) 80.0	(n=13) 42.0	(n=26) 70.5

Data cutoff: April 14, 2025.

CR, complete response; DOR, duration of response; Glofit, glofitamab; Lonca, loncastuximab tesirine; NE, not estimable; ORR, overall response rate; PR, partial response.

[a]The efficacy evaluable population (N=30) included all patients who received ≥1 dose of the study drug with a valid baseline and ≥1 valid postbaseline disease assessment. Patients who did not have a postbaseline assessment owing to early clinical progression or death were also included. [b]Percentages do not add up to total due to rounding. [c]When the starting dose of Lonca is 120 µg/kg or 150 µg/kg, the dose will be reduced to 75 µg/kg for Cycles ≥3. [d]In the efficacy evaluable population, the DOR and probability of maintaining an event-free response were evaluated in responders (n=28), including all patients who had a best response of CR or PR.

Alderuccio et al, EHA. 2025

Loncastuximab tesirine with rituximab induces robust and durable complete metabolic responses in high-risk relapsed/refractory follicular lymphoma

Juan Alderuccio, Alvaro Alencar, Jonathan H. Schatz, Russ A. Kuker, David Sicre, Georgios Pongas, Isildinha M. Reis, Jay Spiegel, Laura Medina Andara, Lazaros J. Lekakis, Joseph S. Gyedu, Jose Sandoval-Sus, Amer Beitinjaneh, Michele Stanchina, Asaad Trabolsi, Izidore S. Lossos, Joseph D. Rosenblatt, David Lessen, Craig H. Moskowitz

American Society of Hematology 2024, Abstract 337

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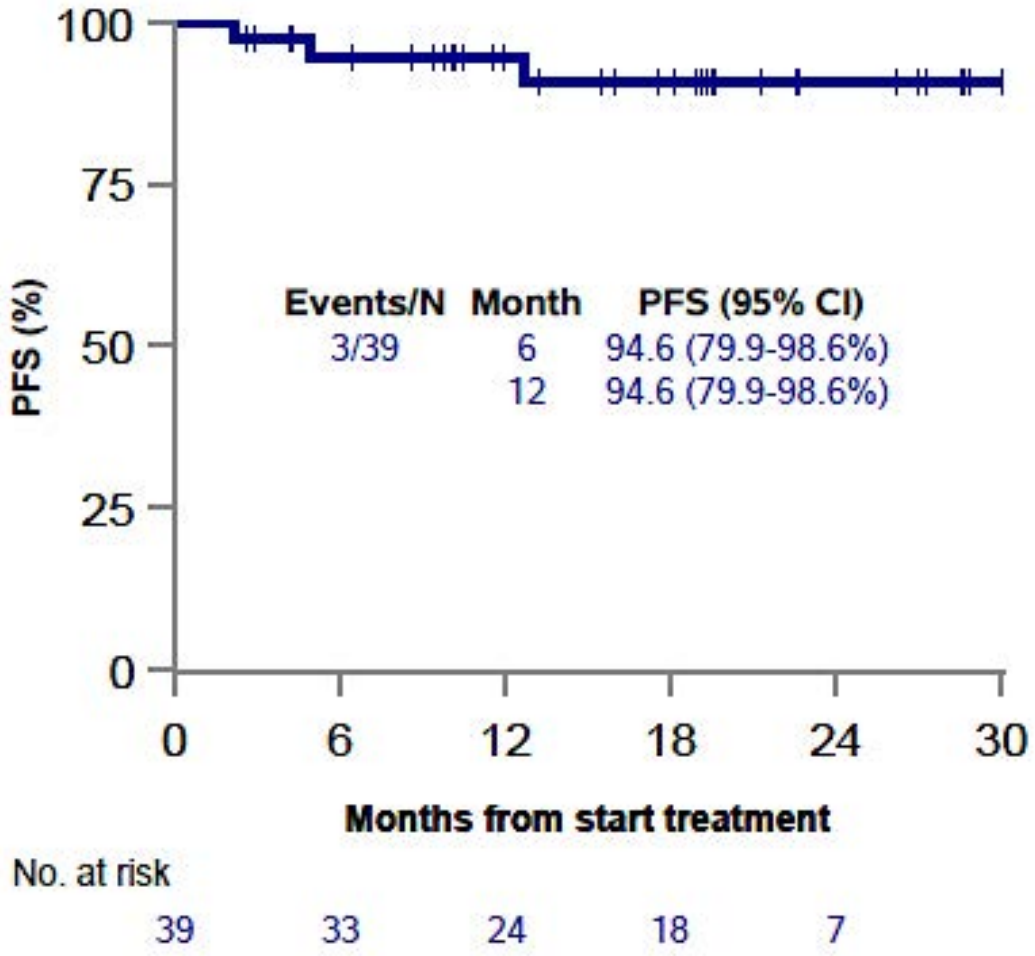
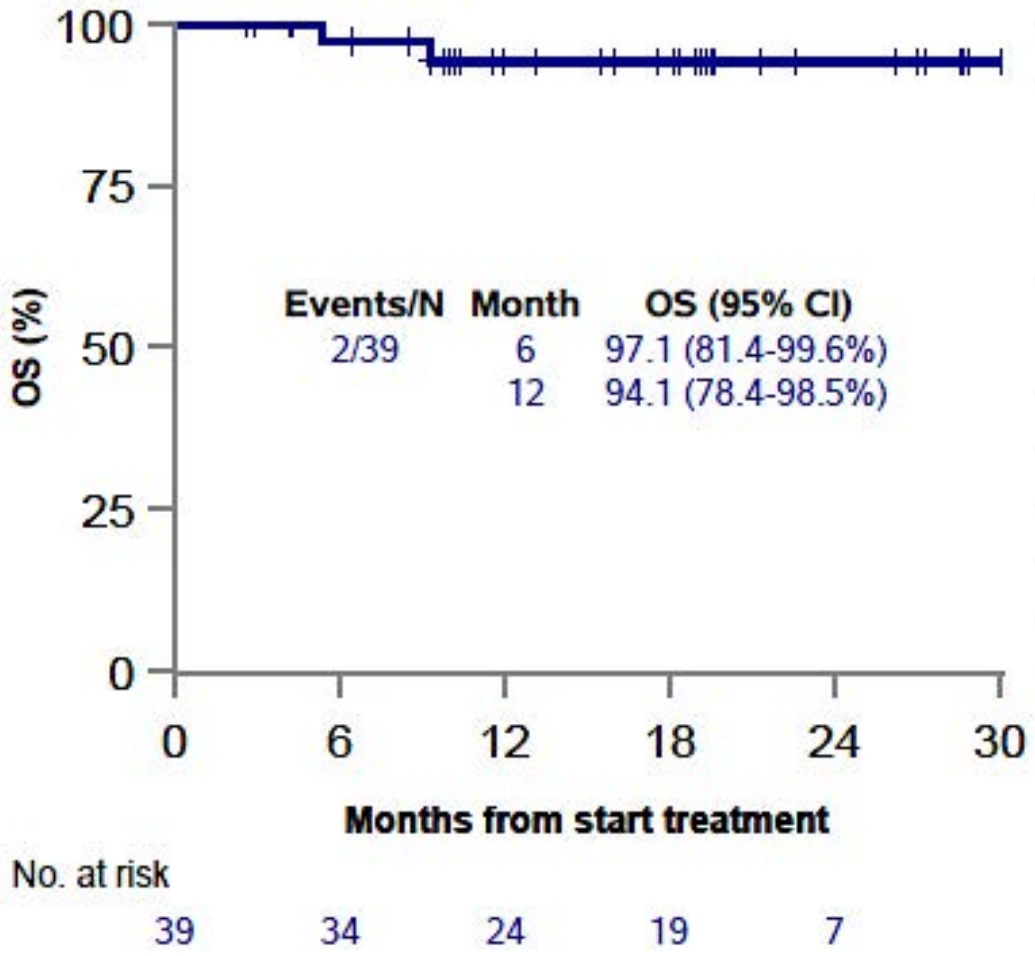
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Designated Cancer Center

@SylvesterCancer





Now listed on NCCN guidelines as option for ≥3rd line R/R FL

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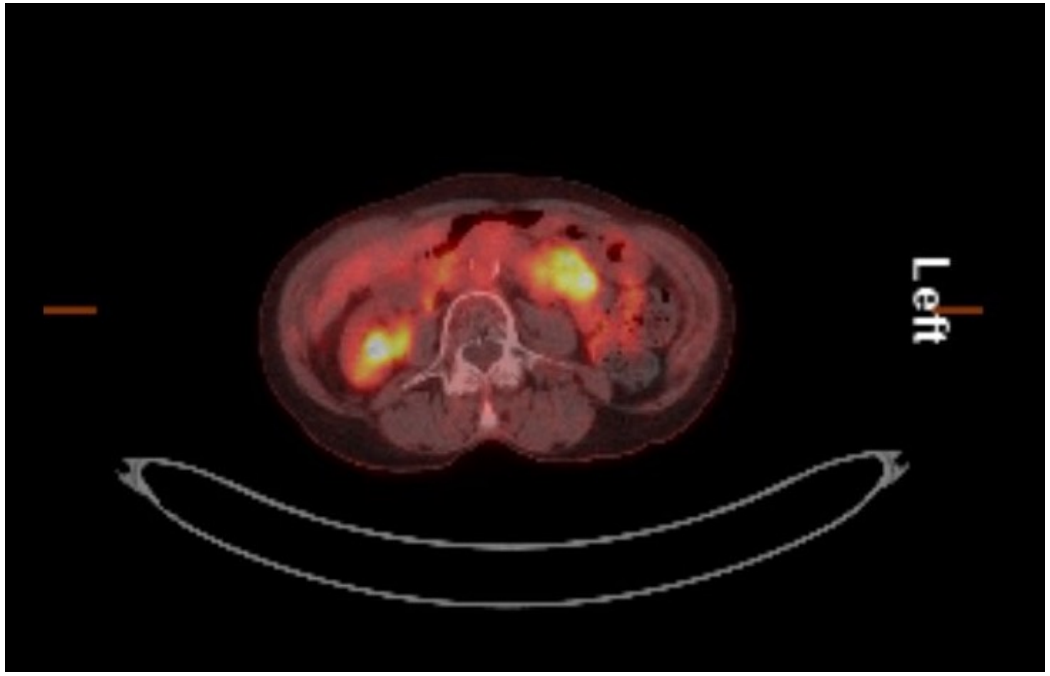
Case Presentation

A patient case

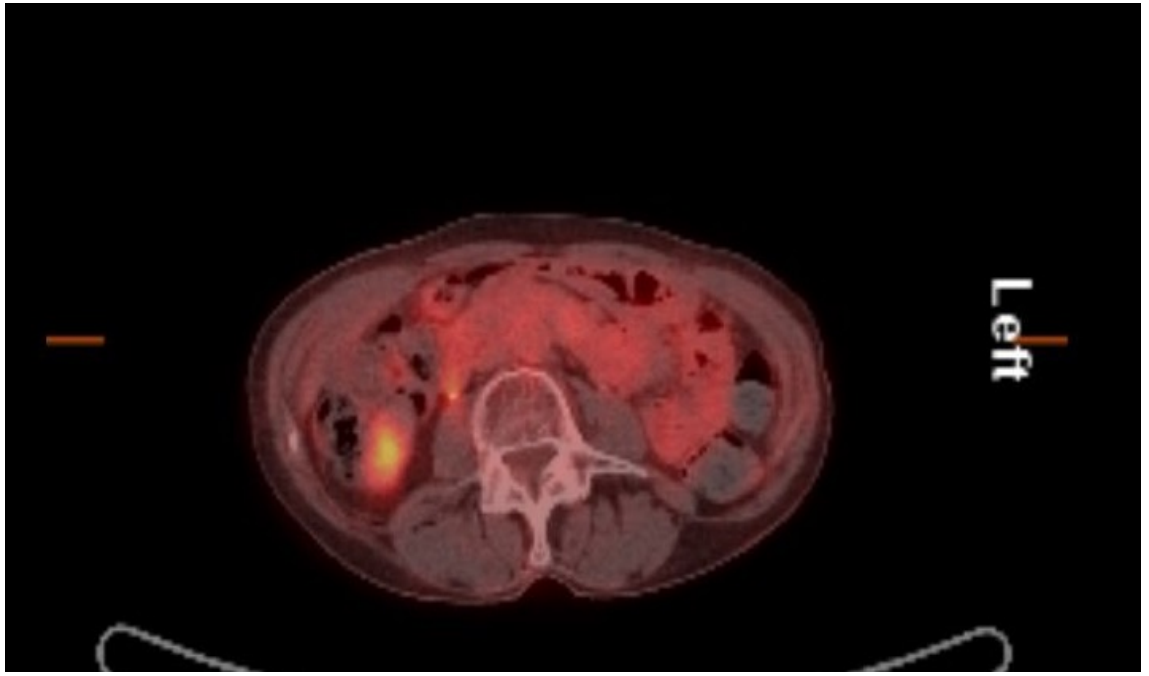
- **May 2012.** 70 yo woman diagnosed with DLBCL. GCB subtype. Stage 3. IPI score 4. Treatment with **R-CHOP x 6**. Achieves CR.
- **April 2018.** New RP mass. Bx shows DLBCL. Now age 76. Receives **R-GemOx** for 8 cycles. Achieves PR after cycle 4 but has PD by cycle 8.
- **Nov 2018.** Referred to see me. I recommended **Axi-Cel** CART therapy. No bridging therapy required. Day 30 PET shows CR.
- **June 2019.** New mesenteric mass detected by surveillance imaging. Biopsy shows DLBCL. She receives **Lonca-T** (on a clinical trial) x 8 cycles. Achieves CR. Therapy stopped due to 3rd spacing.
- **Feb 2021.** New mesenteric mass detected by surveillance imaging. Biopsy shows DLBCL. Offered **glofitamab** (on a clinical trial) x 12 cycles.

Pre and Post Lonca-T PET images

JUNE 2019 PET SCAN



DEC 2019 PET SCAN



Patient Update

- Therapy complicated by hypogammaglobulinemia - on IVIg since 2021
- MAI/MAC infection requiring Azithromycin/Rifampin/Ethambutol 2021 - 2022
- Chronic neutropenia requiring filgrastim 3X/week 2022 – 2023

- Now age 82. Patient remains in CR. On IVIg every 6 weeks. Looks fabulous. She and daughter treat themselves to a nice lunch every trip to St. Louis.

Discussion Questions

What advantages and risks do you perceive in the use of loncastuximab tesirine versus other available regimens in R/R DLBCL? How do you typically sequence it relative to other options?

In which specific situations can you envision yourself employing loncastuximab tesirine/rituximab for R/R FL, given its recent NCCN guideline inclusion?

Tolerability Considerations with Loncastuximab Tesirine

Robin Klebig, APRN, CNP, AOCNP

May 15, 2026

Loncastuximab tesirine

Loncastuximab tesirine IV q3 weeks

C1&2: 0.15 mg/kg q3w

C3&beyond: 0.075 mg/kg q3w

Continue up to 1 year or until disease relapse/progression or toxicity

*Premedicate w/ dexamethasone 4 mg po or IV BID x 3 days beginning day before treatment

- CD19 directed antibody and alkylating drug conjugate
- LOTIS-2 (Caimi et al 2021)
  - Multicenter open label single arm phase 2 study
- 145 pts – ORR 48.3%; CR 24%
- Most common grade 3+ adverse events:
  - Neutropenia (30%)
  - Thrombocytopenia (17%)
  - Anemia (10%)
  - Elevated GGT (21%)
  - Most common SAEs: febrile neutropenia (3%), pneumonia, edema (3%), pleural effusion (2%), sepsis

Courtesy of Robin Klebig, APRN, CNP, AOCNP

Loncastuximab tesirine – Edema/Effusions

- Edema/effusions
  - Edema (peripheral, facial, generalized, ascites) – 28% all grades; 3% grade 3-4
  - Pleural effusion (10% all grades; 2-3% grade 3-4)
    - HOLD for Grade ≥ 2 until ≤ Grade 1
  - Pericardial effusion (3% all grades; 1% grade 3-4)
    - Grade 2: HOLD until resolved; DISCONTINUE if recurs or if ≥ Grade 3
    - Rare cases of cardiac tamponade with grade 3-4
  - Capillary leak syndrome (0.6% grade 3-4)
  - Mitigate by administering dexamethasone 4 mg po/IV BID x 3 days *beginning day prior to infusion*
    - if not started the day before – begin at least 2 hours prior to infusion
  - Monitor for new/worsening swelling, rapid wt gain, dyspnea, chest pain, abdominal bloating
  - CXR, CT chest, echo to evaluate for pleural or pericardial effusion
  - Diuretic (e.g., spironolactone standard dose) for pts w/ wt gain >1kg from baseline or with edema/effusions

Courtesy of Robin Klebig, APRN, CNP, AOCNP

Loncastuximab tesirine – Cutaneous reactions

Reaction	All Grades	Grade 3/4
Rash (erythematous, maculopapular, pruritic, pustular, exfoliative, dermatitis, PPE)	30%	2%
Pruritus	12%	0%
Photosensitivity reaction	10%	2%
Hyperpigmentation	4%	—

- **Prevention:**
  - Minimize or AVOID exposure to direct natural or artificial sunlight — including through glass windows
  - Wear sun-protective clothing at all times
  - Apply broad-spectrum sunscreen regularly
  - Avoid tanning beds and prolonged outdoor exposure
- **Management:**
  - Monitor for new or worsening rash, erythema, blistering, or photosensitivity at each visit
  - Grade 3 cutaneous reactions: HOLD until resolution to ≤ Grade 1
  - Consider dermatology referral for persistent or severe skin reactions
  - Topical corticosteroids and emollients may be used for symptomatic relief

Courtesy of Robin Klebig, APRN, CNP, AOCNP

Loncastuximab tesirine – Lab abnormalities

- Neutropenia (32% grade 3-4; 21% grade 4)
  - HOLD until ANC ≥1 × 10^9/L
  - Consider G-CSF
  - Febrile neutropenia – 3% all grades; 3% grade 3-4
    - Monitor for fevers
  - Infections – 10% grade 3-4
- Thrombocytopenia (20% grade 3-4; 7% grade 4)
  - HOLD until ≥50,000/mcL
- Anemia (12% grade 3-4)
- Hepatotoxicity
  - Elevated GGT (and other LFTs)
    - HOLD if ≥ Grade 3 until ≤ Grade 1; DISCONTINUE if DILI confirmed
      - Grade 3 (>5.0-20.0 ULN)
  - Monitor for dark urine, jaundice; monitor LFTs
  - Generally mild-moderate and reversible with dose delays

Monitor weekly CBC/dif in cycles 1-2, then q3w

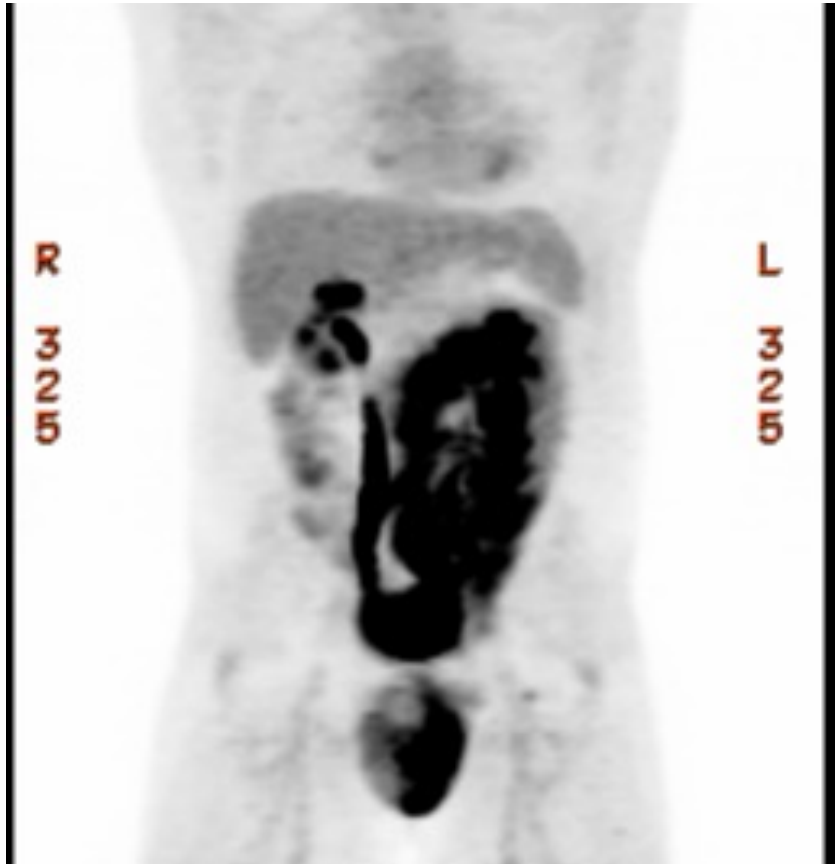
- If treatment is delayed by >3 weeks for any toxicity, decrease dose by 50%
- If toxicity recurs following dose reduction, consider discontinuation

Courtesy of Robin Klebig, APRN, CNP, AOCNP

Case Presentation

A patient with DLBCL treated with loncastuximab tesirine

- 43 y/o male correctional officer
  - Married, teen daughter; Lives 2 hours from Mayo Clinic
- Presented with testicular mass
- Left orchiectomy: **Large B -cell lymphoma,** non-germinal center phenotype. Non double expresser. FISH negative for MYC rearrangement and no fusion of MYC and IGH was observed – not a HGBCL or double/triple hit. CD20+, CD5+, BCL2+, MUM1+; Ki-67 50-75%.
- Bone marrow, CSF, MRI brain negative.
- Treatment 1:
  - Clinical trial with **Parsaclisib + R-CHOP** (phase Ib) x 6 cycles → CR
  - **Radiation** 3000 cGy to scrotum
  - **Prophylactic HDMTX** 3.5 Gm/m2 x 3 cycles

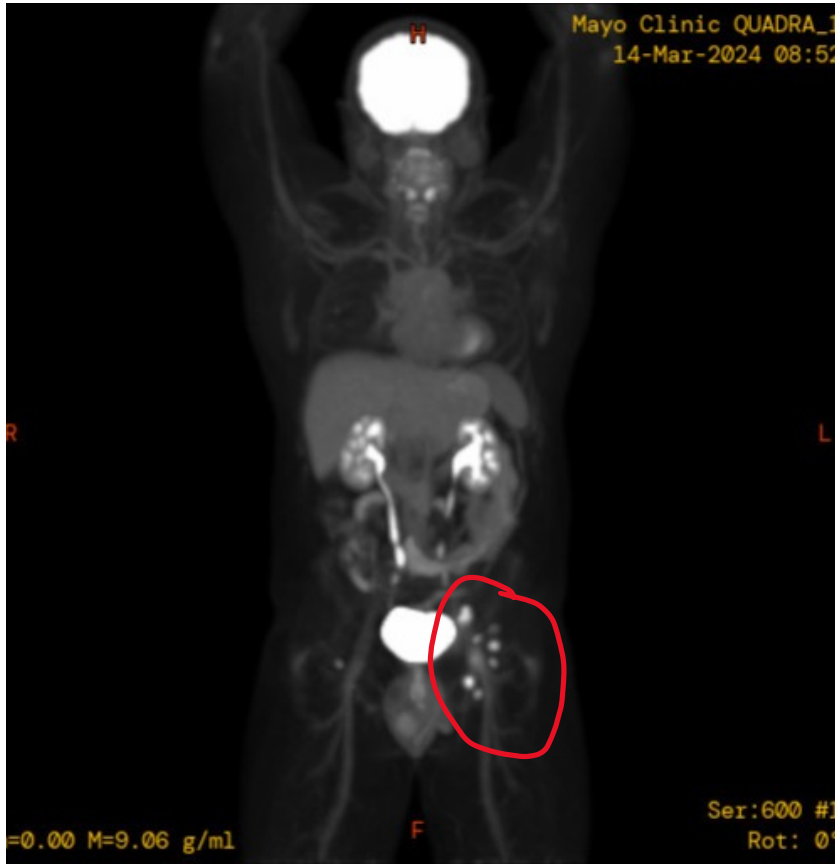


A patient with DLBCL treated with loncastuximab tesirine

- 8 months later –
  - Self-palpated inguinal lymph node

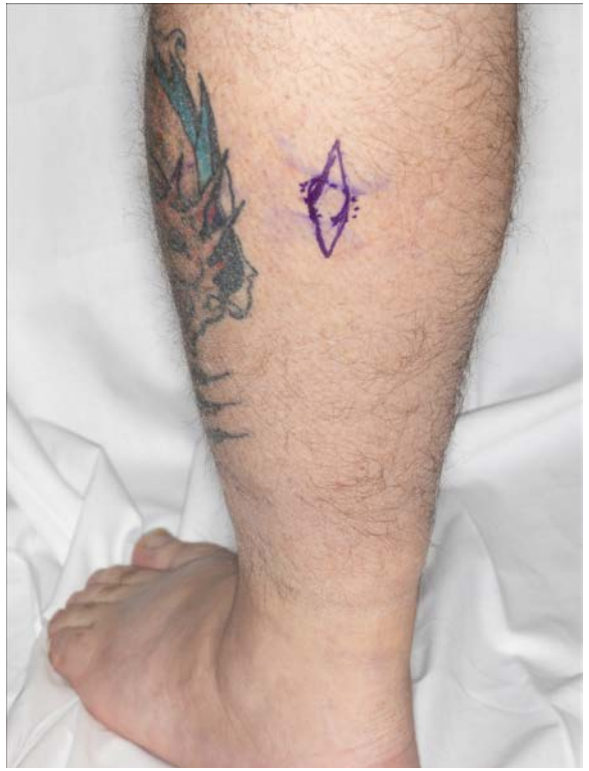
- Lymph node, Left Inguinal, FNA and core bx: **Large B-cell lymphoma**, clinically recurrent.

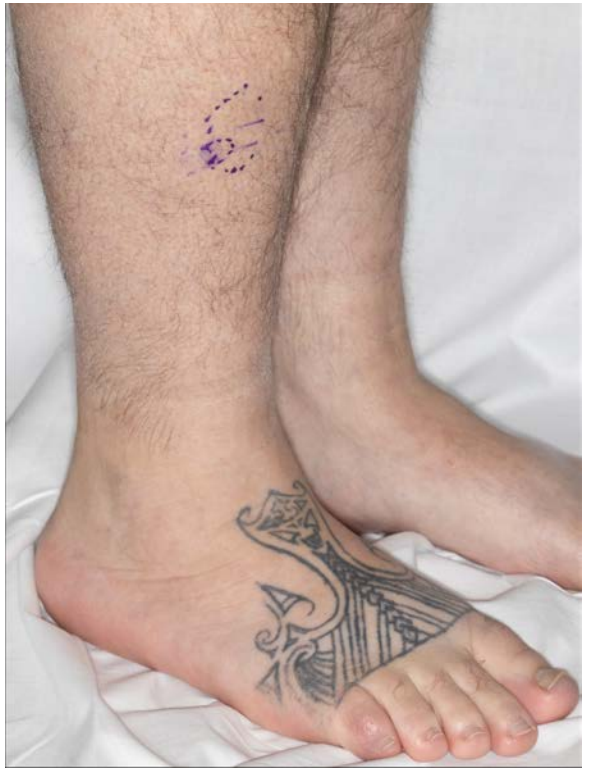
- <u>Treatment 2</u> (early relapser):
  - **Axicabtagene ciloleucel** → CR



A patient with DLBCL treated with loncastuximab tesirine

- 7 months later
  - SQ nodules lower extremities
- Right leg, Skin punch bx: **Diffuse large B-cell lymphoma**
- Left posterior lower leg, Skin excision: **Diffuse large B-cell lymphoma**
- <u>Treatment 3</u>:
  - **Radiation -** 30 Gy each, qod 5 fx utilizing Orthovoltage
- Recurrent cutaneous -> more **RT**
  - **3600 cGy IMRT BLE**



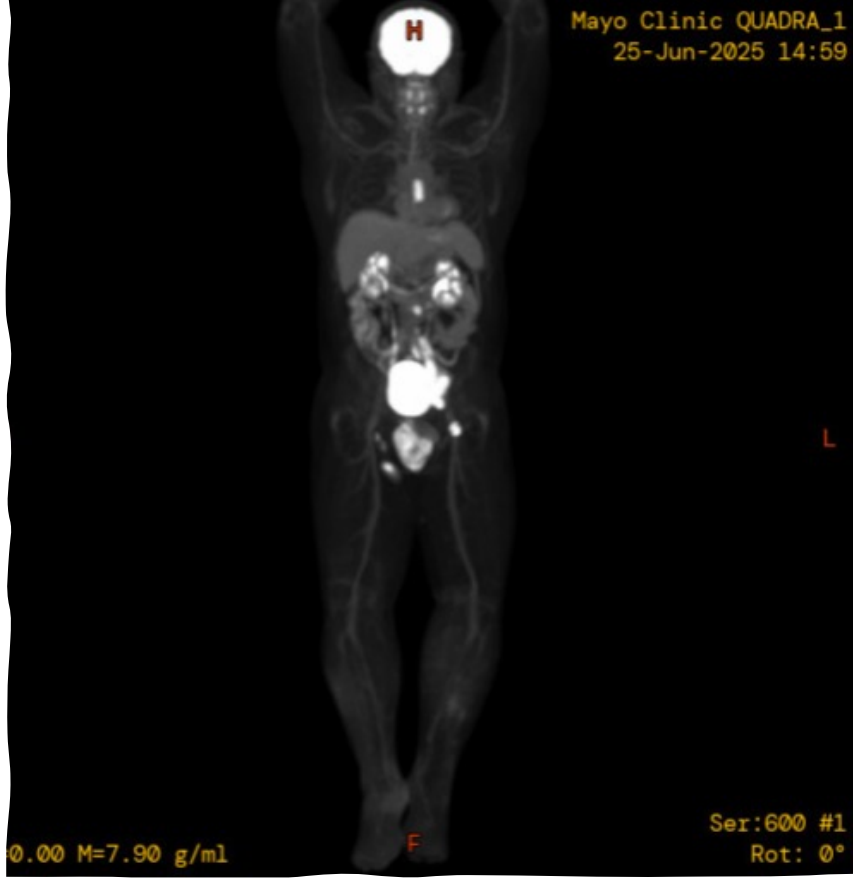


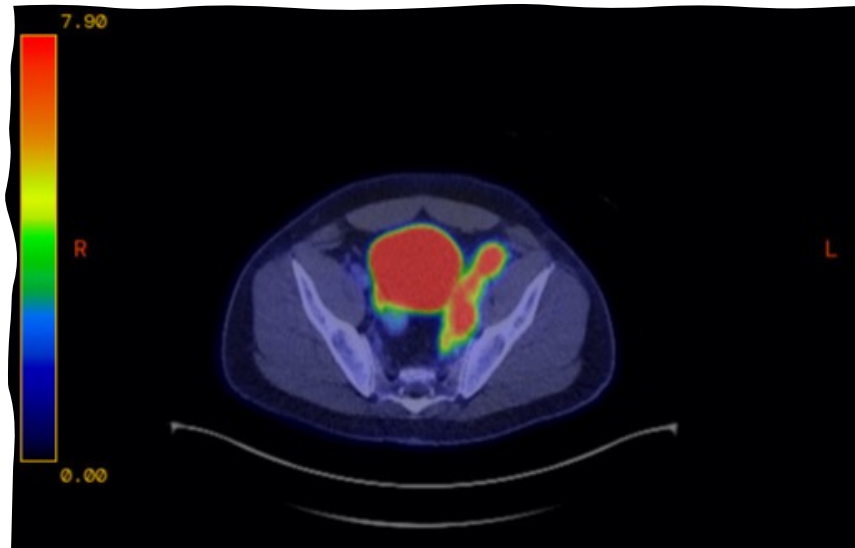
A patient with DLBCL treated with loncastuximab tesirine

- 2 months later
  - PET/CT shows systemic progression

- Lymph node, Left Iliac tissue, FNA and core bx: **Recurrent diffuse large B-cell lymphoma.**

- <u>Treatment 4</u>:
  - **R-ICE x 3**
  - **Autologous SCT**

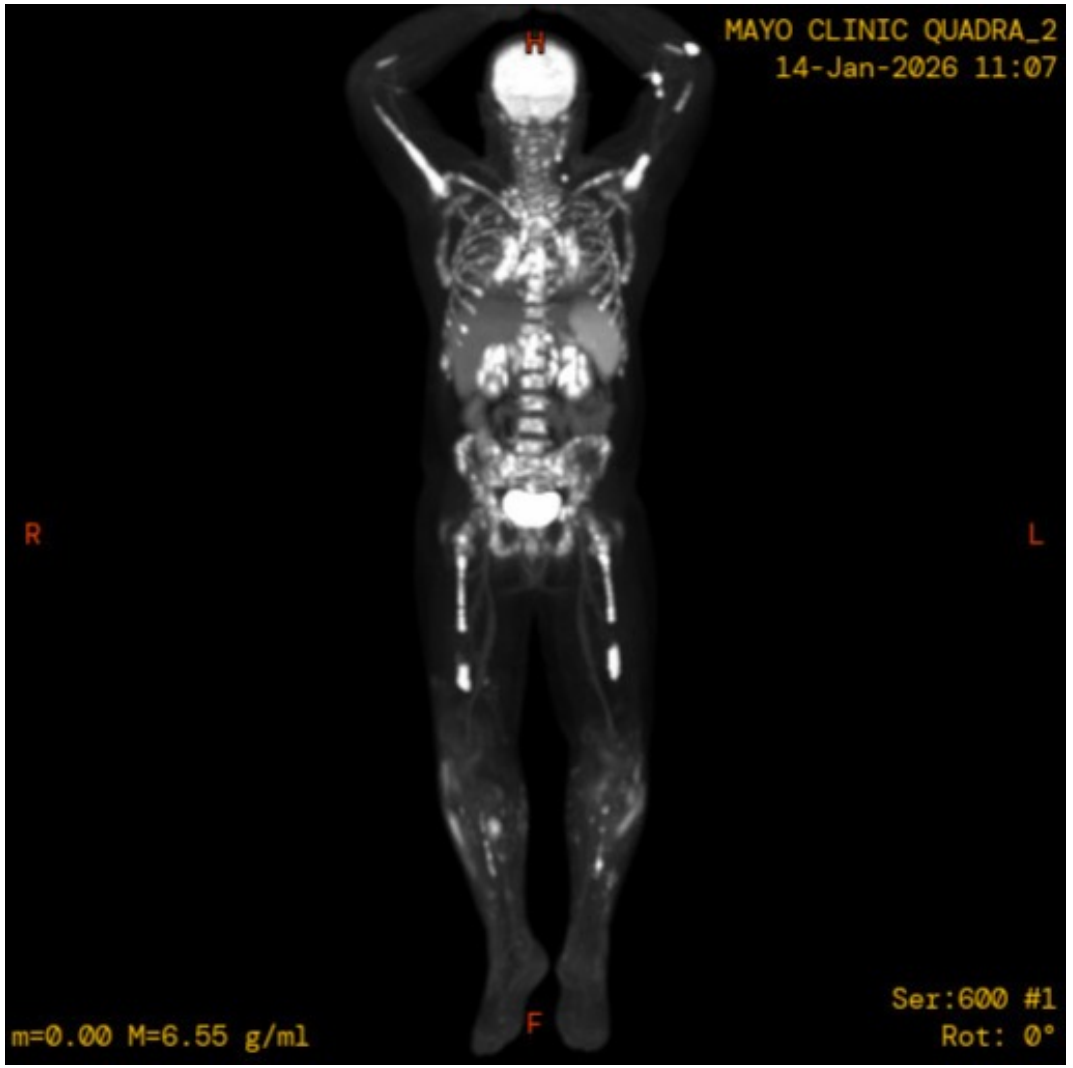


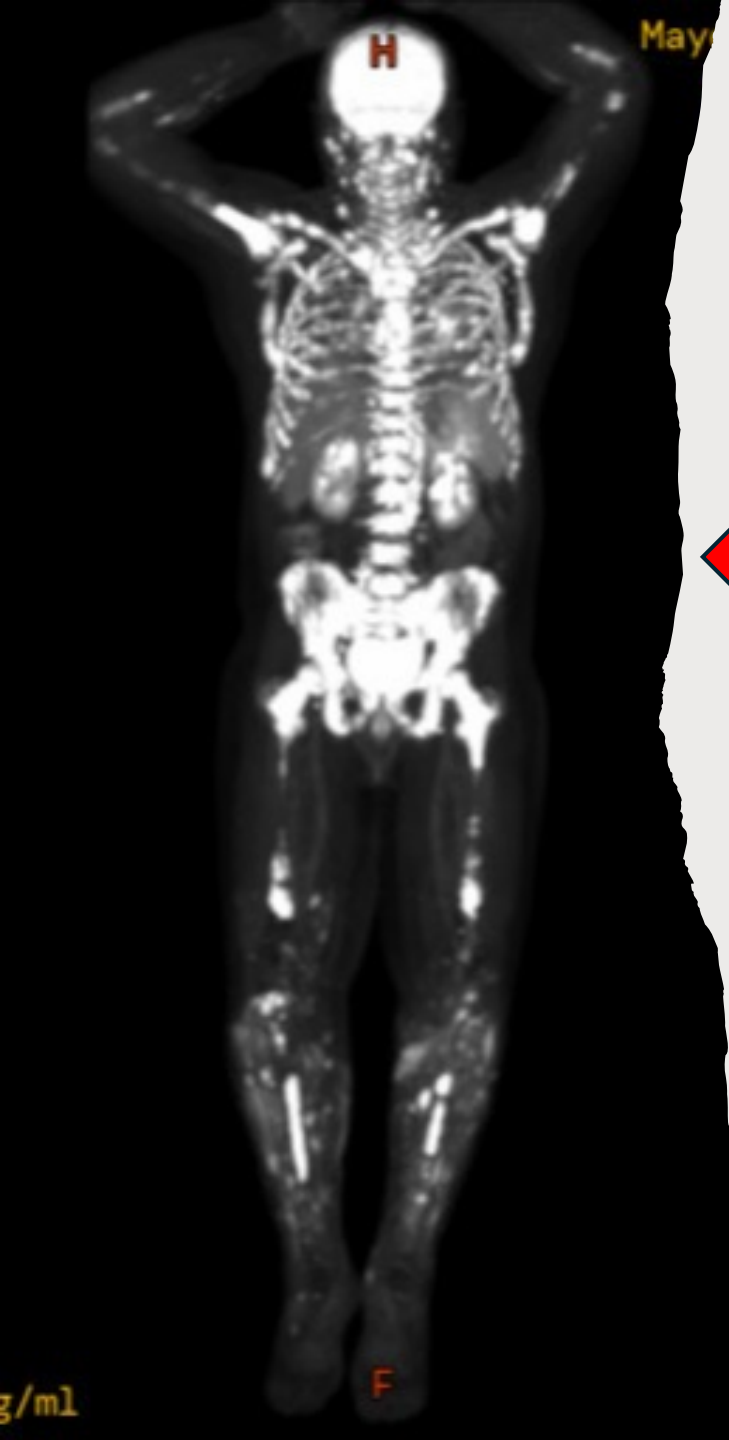


A patient with DLBCL treated with loncastuximab tesirine

- Day 100 post auto SCT
  - Left calf skin punch bx: Cutaneous involvement by **DLBCL**
  - Bone marrow: **DLBCL** involving approximately 60% of cellularity

- <u>Treatment 5:</u>
  - **Glofi-GemOx** (glofitamab/gemcitabine/oxaliplatin – STARGLO)

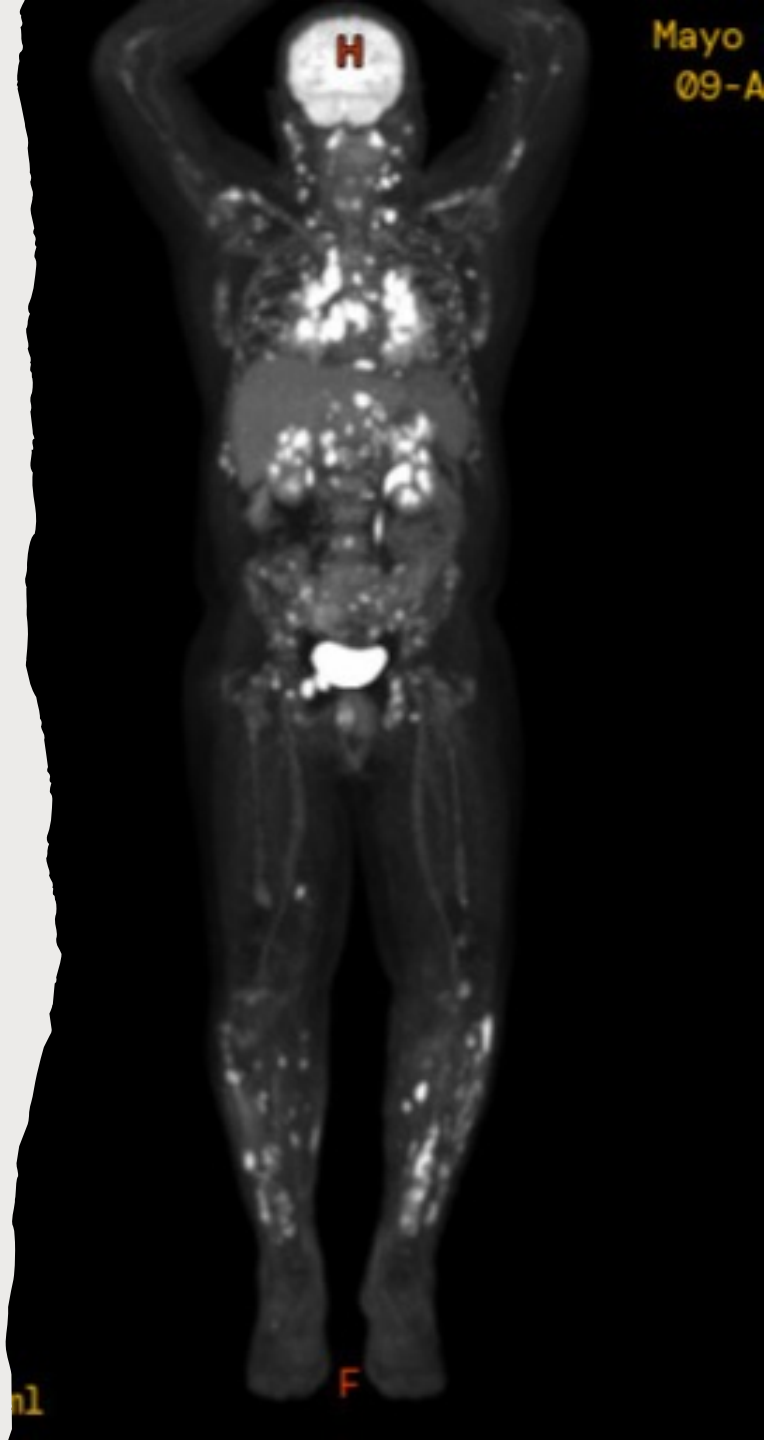




A patient with DLBCL treated with loncastuximab tesirine

- Post 2 cycles Glofi-GemOx

- <u>Treatment 6:</u>
  - **Loncastuximab tesirine**
    - After 3 cycles, mixed response with improvement in bone marrow but increased lymphadenopathy



Agenda

Introduction: Biology of Non-Hodgkin Lymphoma (NHL)

Module 1: Current Role of CD20 x CD3 Bispecific Antibodies in NHL

Module 2: Role of Polatuzumab Vedotin in Diffuse Large B-Cell Lymphoma (DLBCL)

Module 3: Optimal Application of Loncastuximab Tesirine for Patients with DLBCL and Follicular Lymphoma

Module 4: Role of BTK Inhibitors Alone or with Anti-CD20 Antibodies for Patients with Newly Diagnosed Chronic Lymphocytic Leukemia (CLL)

Module 5: Combining BTK Inhibitors with Bcl-2 Inhibitors

Module 6: Current and Future Role of Noncovalent BTK Inhibitors in CLL

Discussion Questions

At a very basic level, how do you counsel your patients with newly diagnosed CLL about the nature of their disease and what their treatment journey might look like?

How do factors such as IGHV mutation status, del(17p) and TP53 mutations affect patient prognosis and treatment selection, and how do you explain these to patients?

Role of BTK Inhibitors Alone or with Anti-CD20 Antibodies in Patients with Newly Diagnosed Chronic Lymphocytic Leukemia (CLL)

Farrukh T. Awan, M.D., M.S., M.B.A.
Professor of Internal Medicine
Associate Director, Section of
Hematologic Malignancies/Transplantation and Cellular Therapies
Director of Lymphoid Malignancies Program
Harold C. Simmons Comprehensive Cancer Center
University of Texas Southwestern Medical Center
Dallas, TX

Myth: Doc, I’ve got CLL! I need treatment

- **Wrong**

- Maybe, let’s talk

Signs and Symptoms

- Many Patients with CLL **have no Early Symptoms**.
  Those Who do Develop Symptoms May Experience:

FATIGUE

SHORTNESS OF BREATH

SWOLLEN LYMPH NODES OR SPLEEN

INFECTIONS

WEIGHT LOSS

Timing of Therapy

- **Constitutional symptoms – How does the patient feel?**
  - Unintentional weight loss of >10% within the previous 6 months
  - Significant fatigue (ECOG PS 2 or worse)
  - Fevers >100.5°F for >2 weeks without other evidence of infection
  - Night sweats for >1 month without evidence of infection
  - Worsening or steroid-resistant anemia and/or thrombocytopenia
  - Spleen >6cm below the left costal margin
  - Lymph Nodes >10cm

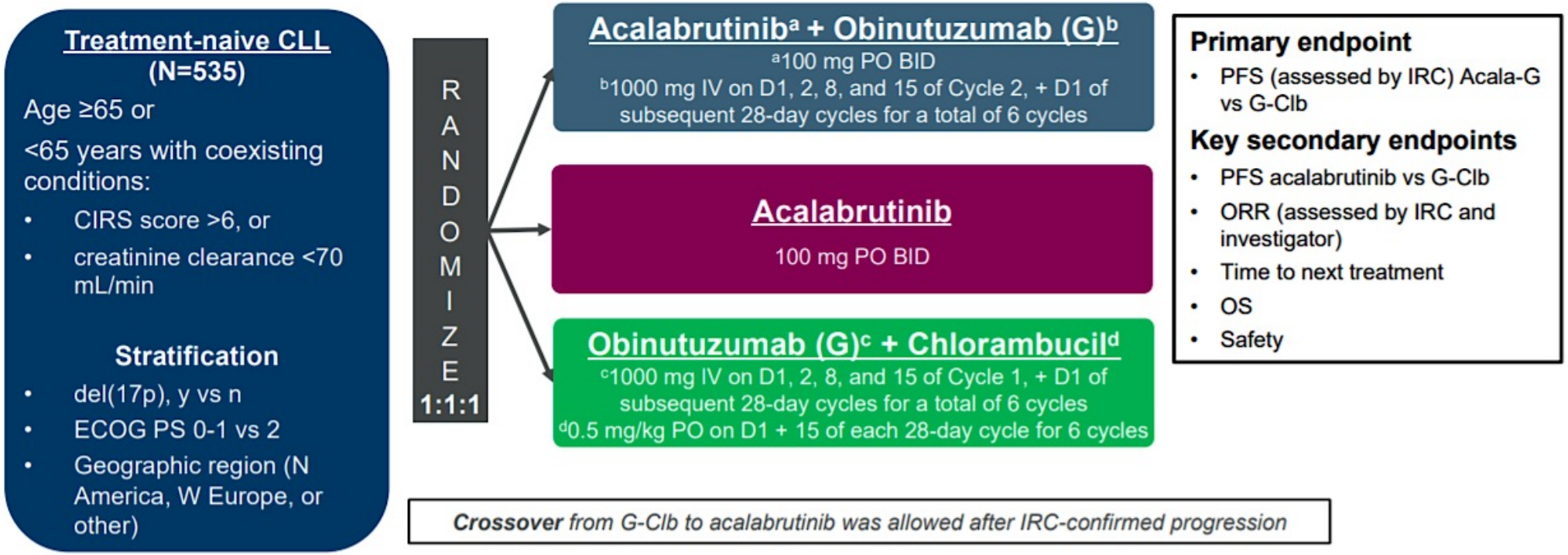
IWCLL recommendations, Blood, 2018

Don’t Treat

- Hypogammaglobulinemia
- Monoclonal or oligoclonal paraproteinemia
- **Elevated leukocyte count**

IWCLL recommendations, Blood, 2018

Phase III ELEVATE TN Study Design (ACE-CL-007)

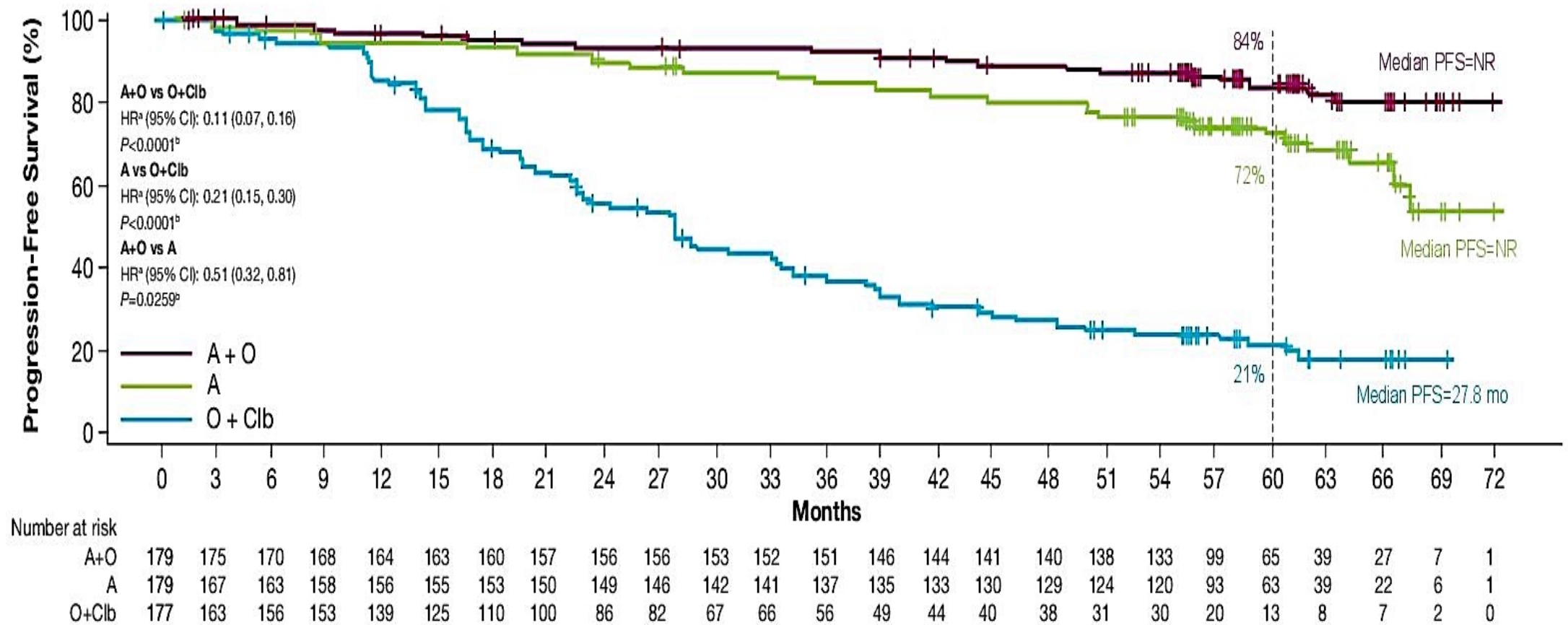


- Interim analysis was planned based on events (after occurrence of ~111 IRC-assessed PFS events in the combination therapy arms) or after 24 months if the required number of events was not met by this time

Acala, acalabrutinib; CIRS, Cumulative Illness Rating Scale; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; IV, intravenously; OS, overall survival; PO, orally

Sharman JP et al. 2019 ASH Annual Meeting. Abstract 31.
Sharman JP, et al. *Lancet*. 2020;395(10232):1278-1291.

ELEVATE-TN: Investigator-Assessed PFS (ITT) (*Median follow-up 58.2 mo*)



[a]Hazard ratio based on Cox proportional-hazard model stratified by 17p deletion status (yes vs no based on interactive voice/web response system). [b]*P*-value based on log-rank test stratified by 17p deletion status (yes vs no based on interactive voice/web response system).

Sharman JP, et al. *Lancet*. 2020;395(10232):1278-1291.
Sharman JP, et al. ASCO 2022. Abstract 7539.

ELEVATE TN: Safety

	SAEs (≥2% pts) - n (%)	Acala-G N=178	Acalabrutinib N=179	G-Clb N=169
Most Common Serious AEs[1-3]	Any	69 (38.8)	57 (31.8)	37 (21.9)
	Pneumonia	12 (6.7)	5 (2.8)	3 (1.8)
	IRR	4 (2.2)	0	2 (1.2)
	Anemia	3 (1.7)	4 (2.2)	0
	Febrile neutropenia	3 (1.7)	2 (1.1)	7 (4.1)
	TLS	1 (0.6)	0	8 (4.7)

Most common AEs (≥ 30%)
Anemia, neutropenia, URTI, thrombocytopenia, headache, diarrhea, musculoskeletal pain[3,*]

Events of Clinical Interest: 58.2 mo median follow up[4]

n (%)	A+O (n=178)		A (n=179)		O+Clb (n=169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	43 (24.2)	17 (9.6)	39 (21.8)	18 (10.1)	13 (7.7)	3 (1.8)
Atrial fibrillation	11 (6.2)	2 (1.1)	13 (7.3)	2 (1.1)	1 (0.6)	0
Bleeding	88 (49.4)	8 (4.5)	78 (43.6)	6 (3.4)	20 (11.8)	0
Major bleeding[a]	12 (6.7)	8 (4.5)	8 (4.5)	6 (3.4)	2 (1.2)	0
Hypertension	17 (9.6)	8 (4.5)	16 (8.9)	7 (3.9)	6 (3.6)	5 (3.0)
Infections	140 (78.7)	50 (28.1)	135 (75.4)	35 (19.6)	75 (44.4)	14 (8.3)
SPMs	31 (17.4)	14 (7.9)	27 (15.1)	7 (3.9)	7 (4.1)	3 (1.8)
SPMs excluding non-melanoma skin	17 (9.6)	12 (6.7)	13 (7.3)	5 (2.8)	3 (1.8)	2 (1.2)

Data are n (%) unless otherwise specified. Median duration of exposure was 58.1 months for A+O, 58.0 months for A, and 5.6 months for O+Clb.
[a]Defined as any serious or grade ≥3 hemorrhagic event, or any grade hemorrhagic event in the central nervous system.

* At 5-y follow-up, most common AEs were generally unchanged from earlier analyses.[4]

1. Sharman JP et al. 2019 ASH Annual Meeting. Abstract 31.
2. Sharman JP, et al. *Lancet*. 2020;395(10232):1278-1291. 3. Acalabrutinib. Prescribing Information. 2019. 4. Sharman JP, et al. ASCO 2022. Abstract 7539.

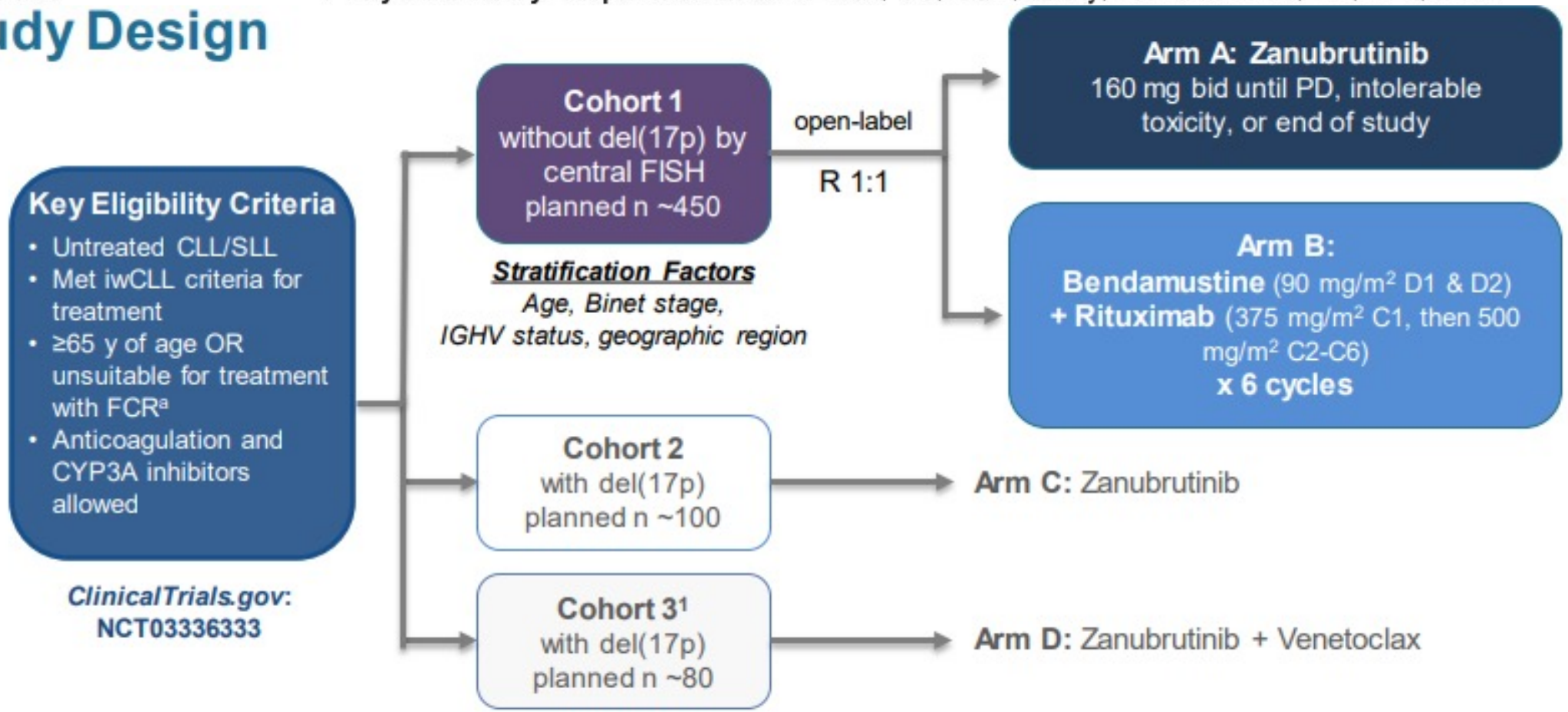
Phase 3 SEQUOIA Study

Study Identifier: BGB-3111-304, NCT03336333

Primary Endpoint: PFS by IRC in Cohort 1

Key Secondary Endpoints: Cohort 1: ORR, OS, DOR, safety; Cohort 2: ORR, OS, PFS, DOR

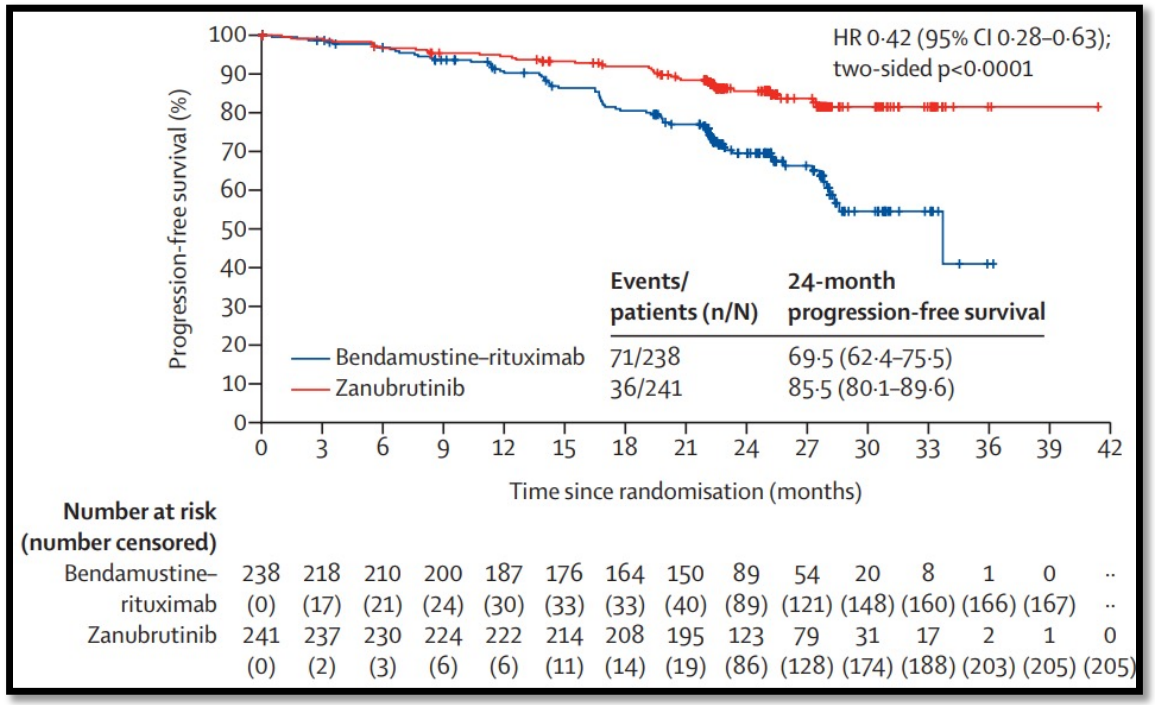
Study Design

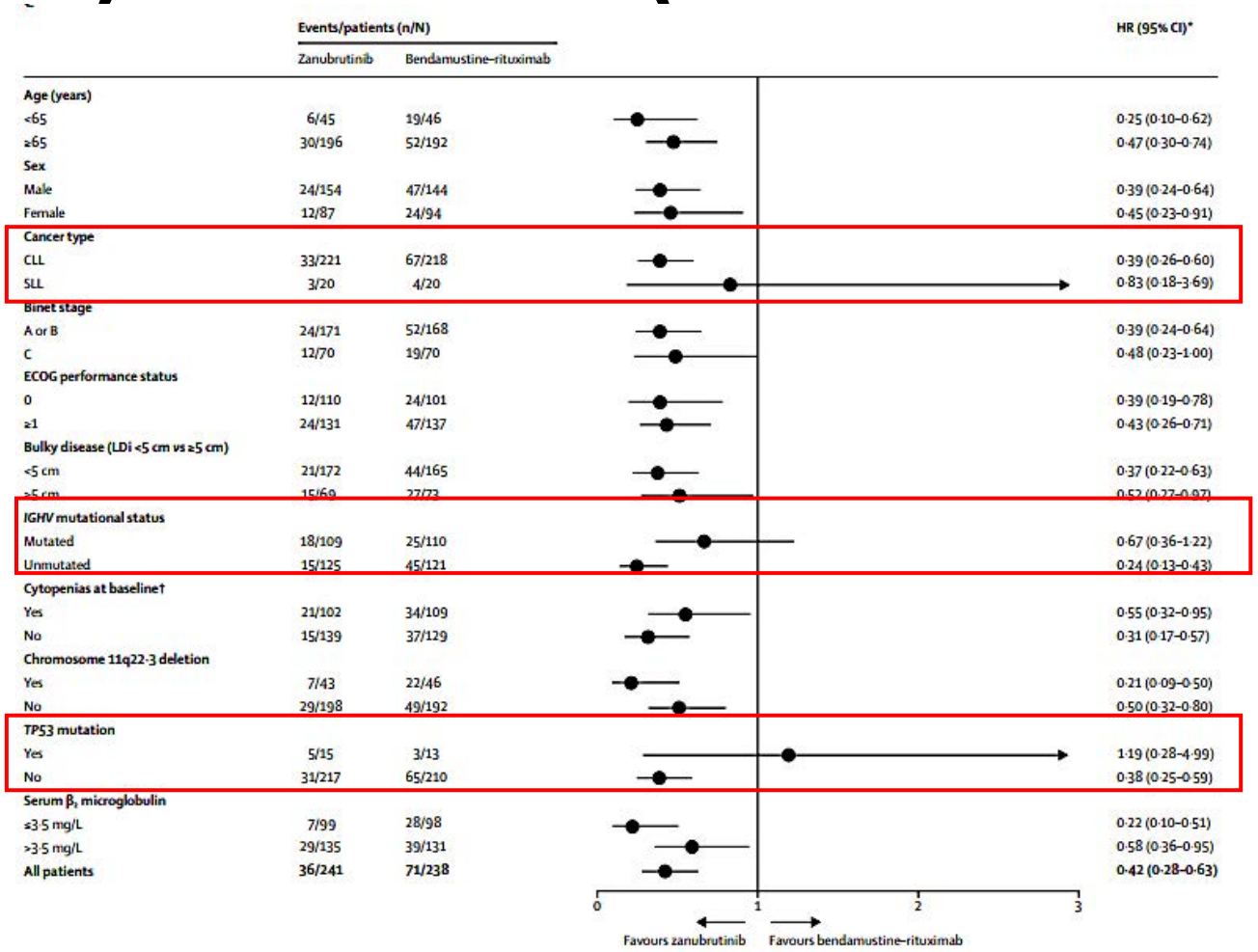


Tam CS, et al. ASH 2021. Abstract 396.

Phase 3 SEQUOIA: PFS (IRC) —Cohort 1 (Without del[17p])

Median follow-up, 26.2 mo





Selected Secondary Outcomes		Zanu (n=241)	BR (n=238)
	ORR (INV), %	97.5	88.7
	Median OS	NR	NR

- PFS benefit with zanubrutinib seen independent of age, sex, or high-risk disease status (Binet stage C, bulky disease, or unmutated IGHV gene status
- PFS benefit not seen among patients with mutated IGHV, SLL (n=40), or pathogenic TP53m (n=28)

Tam CS, et al. *Lancet Oncol*. 2022;23:1031-1043.

Phase 3 SEQUOIA: AEs of Interest—Cohort 1 (Without del[17p])

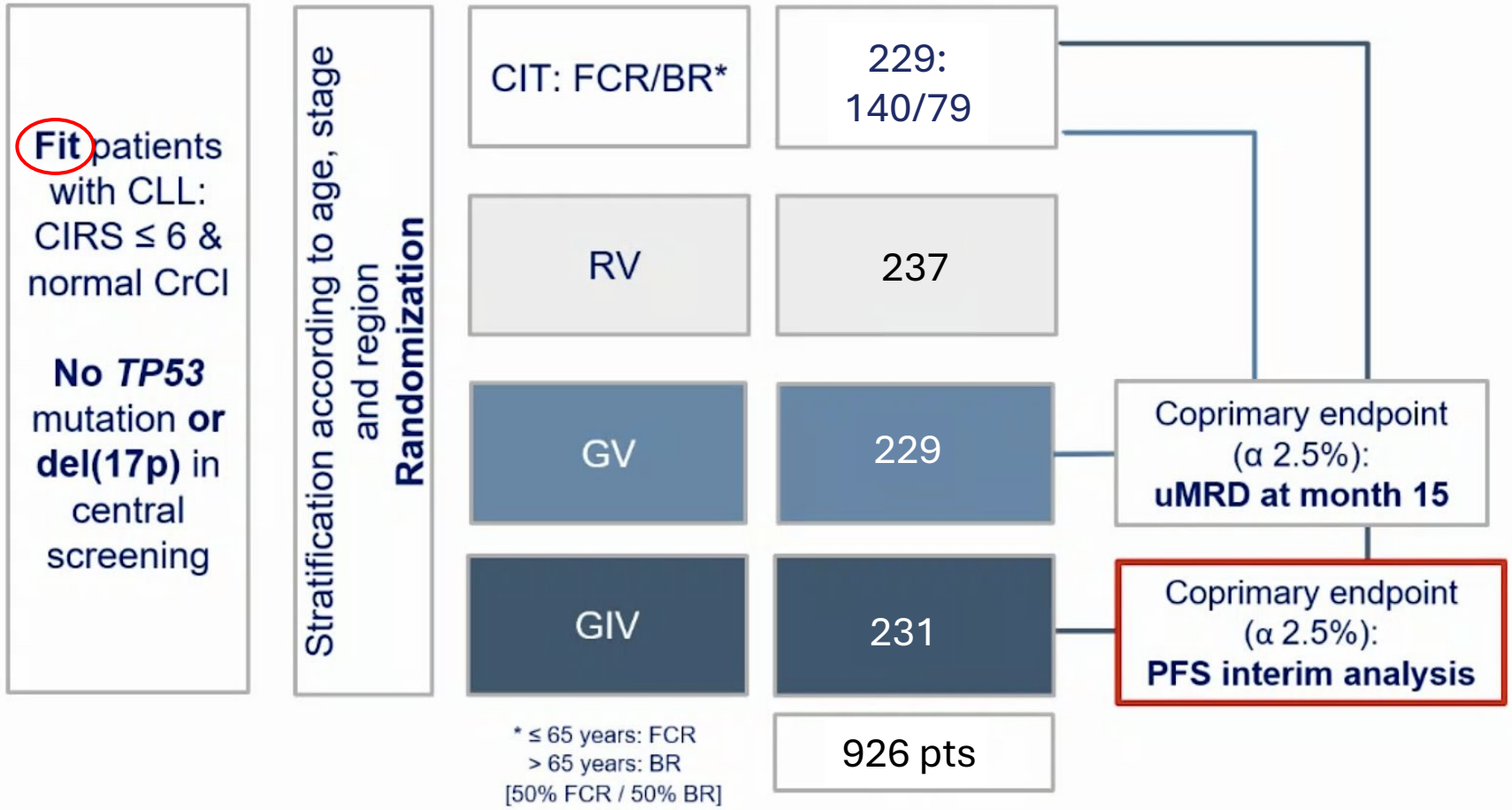
AE, n (%)	Arm A Zanubrutinib (n=240[a])		Arm B Bendamustine + Rituximab (n=227[a])	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Anemia	11 (4.6)	1 (0.4)	44 (19.4)	4 (1.8)
Neutropenia[b]	38 (15.8)	28 (11.7)	129 (56.8)	116 (51.1)
Thrombocytopenia[c]	11 (4.6)	5 (2.1)	40 (17.6)	18 (7.9)
Arthralgia	32 (13.3)	2 (0.8)	20 (8.8)	1 (0.4)
Atrial fibrillation	8 (3.3)	1 (0.4)	6 (2.6)	3 (1.3)
Bleeding[d]	108 (45.0)	9 (3.8)	25 (11.0)	4 (1.8)
Major bleeding[e]	12 (5.0)	9 (3.8)	4 (1.8)	4 (1.8)
Diarrhea	33 (13.8)	2 (0.8)	31 (13.7)	5 (2.2)
Hypertension[f]	34 (14.2)	15 (6.3)	24 (10.6)	11 (4.8)
Infections[g]	149 (62.1)	39 (16.3)	127 (55.9)	43 (18.9)
Myalgia	9 (3.8)	0 (0.0)	3 (1.3)	0 (0.0)
Other cancers	31 (12.9)	17 (7.1)	20 (8.8)	7 (3.1)
Dermatologic other cancers	16 (6.7)	2 (0.8)	10 (4.4)	2 (0.9)

Median follow up: Arm A, 26.4 mo; Arm B, 25.9 mo

Tam CS, et al. ASH 2021. Abstract 396. Tam CS, et al. *Lancet Oncol*. 2022;23:1031-1043.

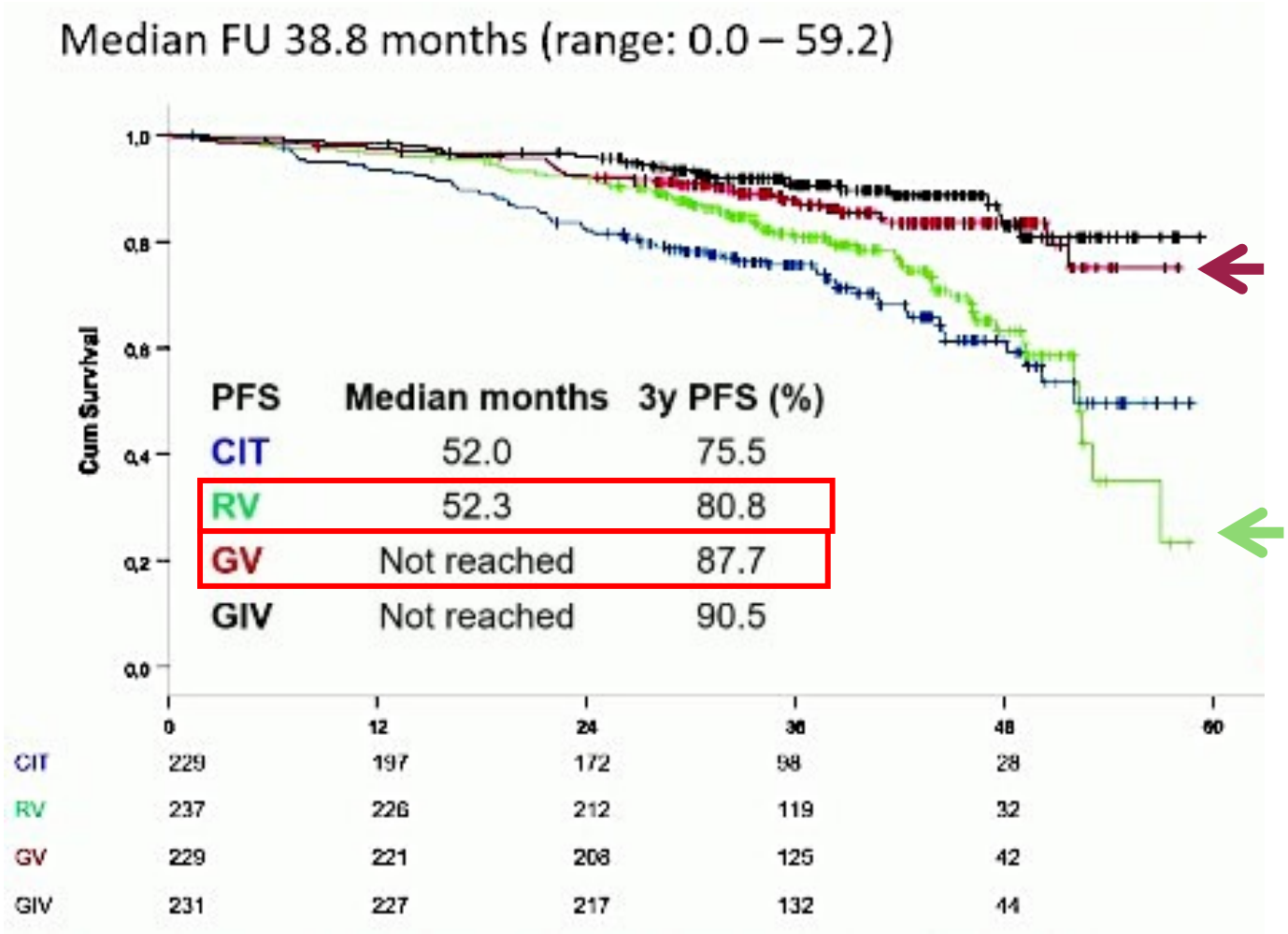
Phase 3 GAIA/CLL13: Study Design

Chemoimmunotherapy (**FCR/BR**) versus **R**ituximab + **V**enetoclax versus Obinutuzumab (**G**) + **V** versus **G** + **I**brutinib + **V**
Recruitment in 10 countries (DE, AT, CH, NL, BE, DK, SE, FI, IE, IL)



N Engl J Med 2023;388:1739-1754;
Eichorst B, et al. EHA 2022. Abstract LBA2365.

Phase 3 GAIA/CLL13 Study Design: PFS (Co-Primary Endpoint)



- Superior PFS observed for GV vs CIT
  HR 0.42, 97.5% CI 0.26-0.68, p<0.0001
- 3-Y PFS unmutated IGHV vs mutated IGHV
  - GIV: 86.6% vs 96.0%
  - CIT: 65.5% vs 89.9%
- Similar OS rates observed across all treatment arms

N Engl J Med 2023;388:1739-1754;
Eichorst B, et al. EHA 2022. Abstract LBA2365.

Phase 3 GAIA/CLL13 Study Design: Overview of AEs ≥ Grade 3

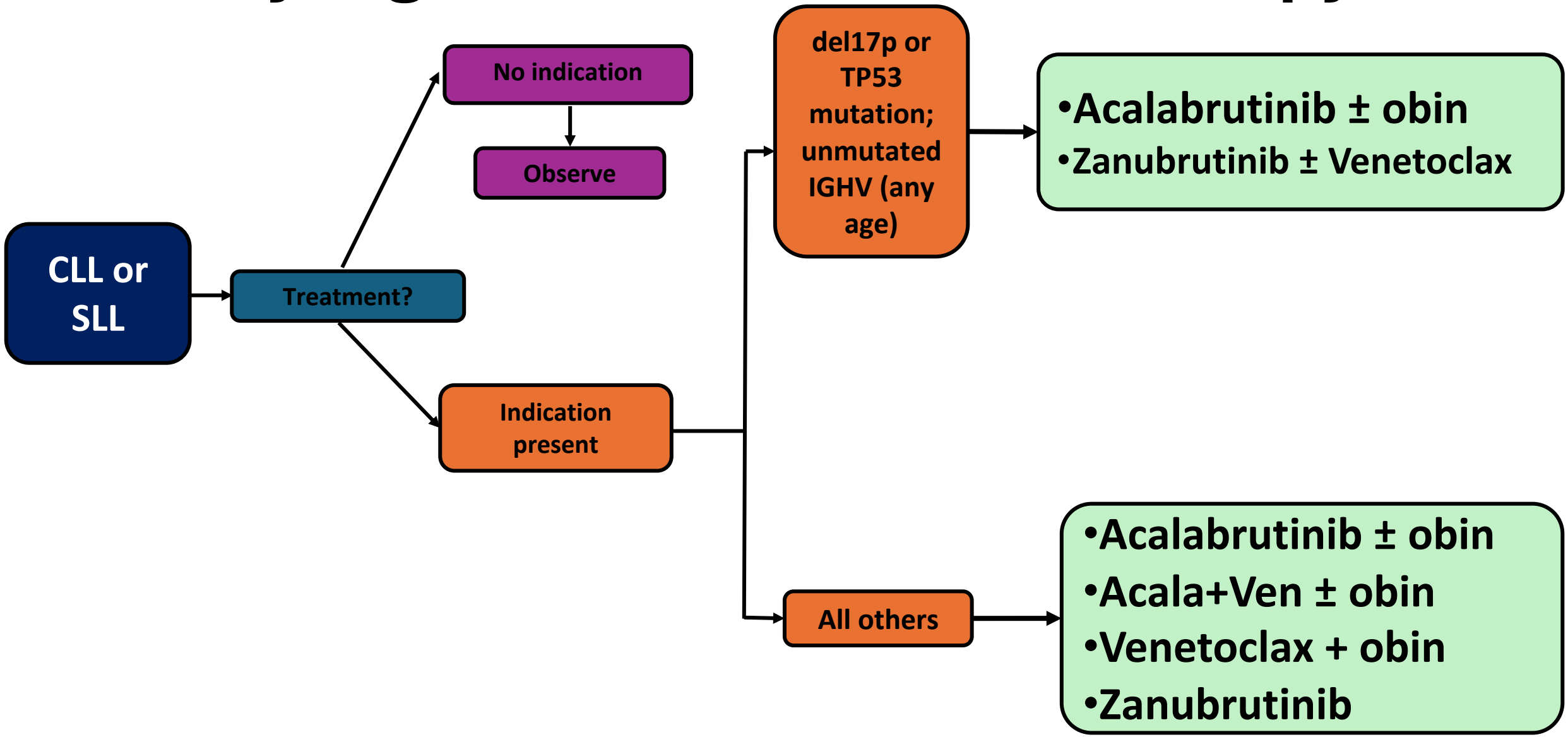
Severe AEs occurring in ≥5% of pts in at least one arm and of interest

	CIT	RV	GV	GIV
All patients of safety population	**216**	**237**	**228**	**231**
All ≥ CTC grade 3 events (%)	**176 (81.5)**	**173 (73.0)**	**192 (84.2)**	**193 (83.5)**
Blood and lymphatic system (%)	122 (56.5)	103 (43.5)	128 (56.1)	117 (50.6)
Infections and infestations (%)	44 (20.4)	27 (11.4)	34 (14.9)	51 (22.1)
Febrile neutropenia (%)	24 (11.1)	10 (4.2)	7 (3.1)	18 (7.8)
Infusion related reaction (%)	12 (5.6)	19 (8)	26 (11.4)	10 (4.3)
Tumor lysis syndrome (%) *	9 (4.2)	24 (10.1)	19 (8.3)	15 (6.5)
Hypertension (%)	3 (1.4)	5 (2.1)	4 (1.8)	13 (5.6)

* Defined by Cairo-Bishop criteria

N Engl J Med 2023;388:1739-1754;
Eichorst B, et al. EHA 2022. Abstract LBA2365.

My Algorithm for Frontline Therapy



Case Presentation

CASE PRESENTATION

- 65-year-old female diagnosed with CLL
- Has IGHV unmutated del11q, TP53 wildtype CLL
- Presents with enlarging, painful lymphadenopathy and anemia.
- Patient also has type 2 diabetes, hypertension, and chronic renal failure with baseline Cr 1.8 (not on dialysis)
- Imaging shows bulky lymph nodes around 8cm and a spleen of 20cm
- Patient desires oral therapy with minimal back and forth to the cancer center

- What's the best next option for treatment

CASE PRESENTATION..cntd

- 65-year-old female with untreated CLL and needs treatment
- Multiple comorbidities

- **Best treatment option**
  - Venetoclax
  - Venetoclax and rituximab
  - **Zanubrutinib**
  - **Acalabrutinib +/- Obinutuzumab**

Discussion Questions

In which subsets of patients with treatment-naïve CLL are you prioritizing the use of continuous BTK inhibitor monotherapy?

Do you have a preference for a specific covalent BTK inhibitor?

When do you also incorporate an anti-CD20 antibody?

Impact of Comorbid Conditions and Other Practical Considerations on the Choice of First-Line Therapy for Newly Diagnosed CLL

Mollie Moran, APRN-CNP, AOCNP
Nurse Practitioner
The James Cancer Hospital and Solove Research Institute
The Ohio State University
Columbus, Ohio

Case Study: First line therapy for CLL

- 72 yo male, retired police officer with hx of CLL dx 4 years ago. He has increased lymphocytosis, thrombocytopenia and increased lymph nodes. WBC 58K, ALC 52K, Hgb 9.9, plts 105K.
- Prognostic factors at dx 46 XY del11q, FISH del 11q, IGHV unmutated, B2M 3.8
- Well controlled HTN and DM. He is the primary caregiver for his wife with early dementia
- Time to consider starting therapy

NCCN Guidelines for 1L Treatment of CLL/SLL

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Without del(17)p/*TP53* mutation		
• **BCL-2i–containing regimens** – Acalabrutinib + venetoclax ± obinutuzumab *(fixed duration)* – Venetoclax + obinutuzumab (fixed duration) • **Covalent BTKi-based regimens** – Acalabrutinib (continuous) ± obinutuzumab – Zanubrutinib (continuous)	• **BCL-2i–containing regimen** – Ibrutinib + venetoclax *(fixed duration or MRD guided)*	• **BCL-2i–containing regimen** – Zanubrutinib + venetoclax *(MRD guided)* • **Covalent BTKi-based regimens** – Ibrutinib (continuous) – Ibrutinib (continuous) + anti-CD20 mAb • HDMP + anti-CD20 mAb • Consider only when cBTKi and BCL-2i are not available or feasible — Bendamustine + anti-CD20 mAb — FCR — Chlorambucil + obinutuzumab — Obinutuzumab
With del(17)p/*TP53* mutation		
• **BCL-2i–containing regimens** – Venetoclax + obinutuzumab (*fixed duration*) – Acalabrutinib + venetoclax ± obinutuzumab *(MRD guided)* – Zanubrutinib + venetoclax *(MRD guided)* • **Covalent BTKi-based regimens** • Acalabrutinib (continuous) ± obinutuzumab • Zanubrutinib (continuous)	• **BCL-2i–containing regimen** – Ibrutinib + venetoclax (*fixed duration*)	• **Covalent BTKi-based regimen** – Ibrutinib (continuous) – HDMP + anti-CD20 mAb • Consider only when cBTKi and BCL-2i are not available or feasible — Obinutuzumab

In all randomized trials including chemoimmunotherapy compared to novel agents, novel agent arm(s) were superior in overall response rates and progression-free survival leading to the absence of chemoimmunotherapy in preferred regimen options.

NCCN. Clinical practice guidelines in oncology: chronic lymphocytic leukemia/small lymphocytic lymphoma. v.2.2026. nccn.org.

BTK Inhibitors for CLL/SLL

- BTK inhibitors are small-molecule inhibitors of Bruton's tyrosine kinase (BTK), an integral component of the B-cell receptor signaling pathway
- **BTKi shared toxicities:** atrial fibrillation (uncommon), "ASA-like" antiplatelet effects cause bruising (very common) and major bleeding (uncommon), B-cell suppression with infection risks, hypertension, cytopenias, GI adverse effects
  - More bleeding risk with antiplatelet therapy (eg, aspirin) plus BTK inhibitors than with anticoagulants has been suggested

Yosifov. HemaSphere. 2019;3:e175. Byrd. NEJM. 2013;369:32. Woyach. Blood. 2024;143:1616.

Common and Important BTK Inhibitor Toxicities in CLL

Toxicities of Special Interest	Most Common Toxicities	Other Common Toxicities
• Atrial fibrillation • Ventricular arrhythmia • Bleeding • Hypertension • Infections	• Anemia • Arthralgia/myalgia • Cough • Diarrhea • Fatigue • Headache • Neutropenia	• Cytopenias • Hair/nail changes • Lymphocytosis • Nausea • Rash

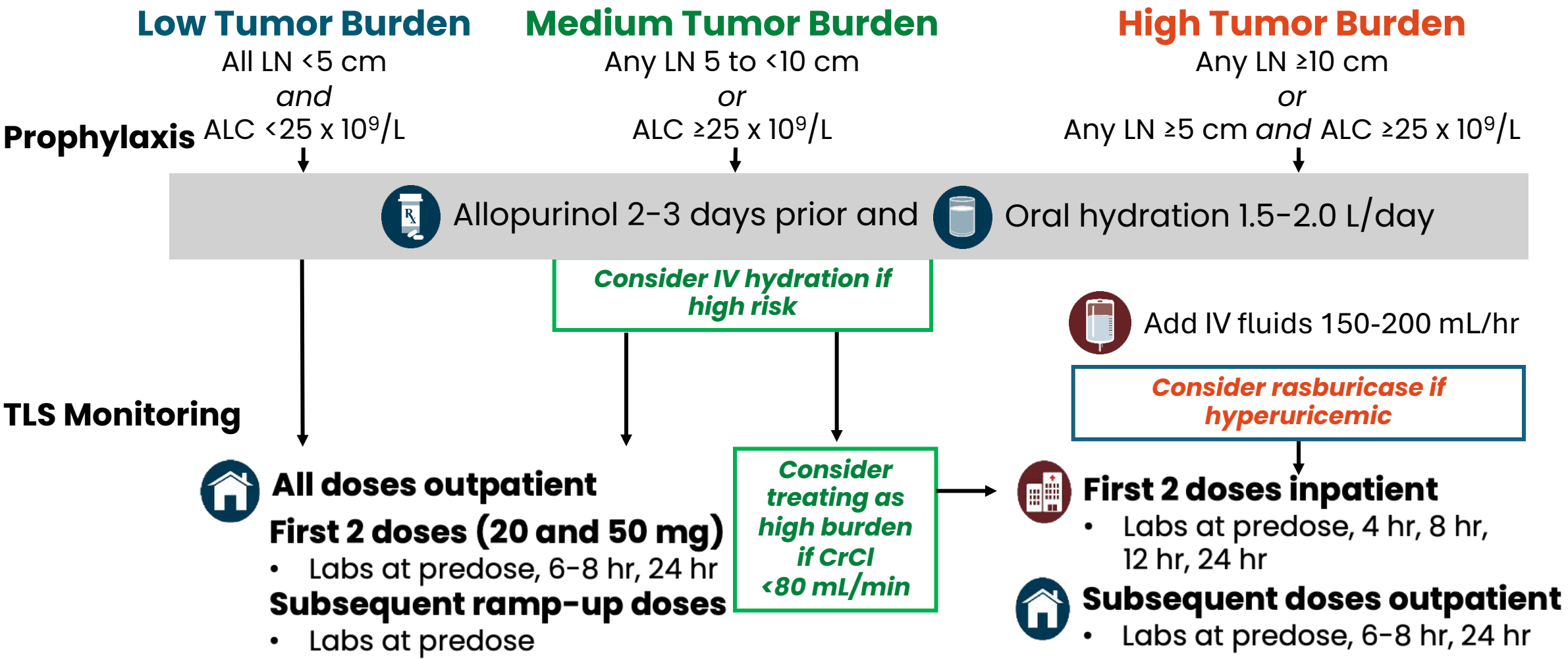
Lipsky. Hematology Am Soc Hematol Educ Program. 2020;1:336. Brown. Blood. 2018;131:379.
NCCN. Clinical practice guidelines in oncology: chronic lymphocytic leukemia/small lymphocytic lymphoma. v.2.2026. nccn.org.

BCL-2 Inhibitors for CLL/SLL

- BCL-2 inhibitors were originally studied in **combination with the anti-CD20 monoclonal antibodies** rituximab (MURANO; 2L+ VenR) and obinutuzumab (CLL14; 1L VenO), **which require infusions**[1,2]
- **Newer regimens combine BCL-2i with BTKi as "all oral" options**[3-5]
  - AMPLIFY (AV ± O vs CIT), FLAIR (I+V vs FCR), SEQUOIA Arm D (zanubrutinib + venetoclax)
- BCL-2i–based treatments are the backbone for fixed-duration and MRD-guided regimens, with superiority over chemoimmunotherapy and often durable and deep responses measured in years
- **Side effects include tumor lysis syndrome risk, cytopenias, GI toxicities, fatigue, and arthralgias**

1. Kater. Blood. 2025;145:2733. 2. Al-Sawaf. Blood. 2024;144:1924. 3. Brown. NEJM. 2025;392:748. 4. Munir. NEJM. 2024;390:326. 5. Shadman. JCO. 2025;43:2409.

Venetoclax for CLL: TLS Risk Stratification and Prophylaxis



Venetoclax PI.

Case Study: Treatment Begins

- Patient starts on acalabrutinib 100 mg po bid.
  - After 1 month CBC shows WBC 159K, ALC 148K, Hgb 8.5, plts 85K
    - Lymphocytosis is expected side effect of BTKi.
  - C/o aching joints
    - Treat with acetaminophen prn
  - Frequent bruising
    - Expected side effect of BTKi
  - Hold BTKi prior to and after invasive procedures for 3 days (minor) or 7 days (major)
  - After 3 months his BP is elevated and his PCP adjusts antihypertensive medication.
    - HTN is a common side effect of BTKi
- Weekly labs at start of treatment with monthly visits for first 3 months. Every 3 months for 2 years then every 6 months.

Jurczak. JCO. 2025;25-02380. Woyach. JCO. 2026;44:476. O'Brien. Front Oncol. 2021;11:720704.

Case Study: 12-month visit

- Patient is tolerating the acalabrutinib well
  - WBC 10K, Hgb 13.1, plts 145K
- He sees a dermatologist annually for increased risk of skin cancers (SCC, BCC)
- He is current with colonoscopy
- He sees his PCP regularly
  - Manages HTN, DM
  - Checks PSA annually
- No live vaccines, annual flu shot

Discussion Questions

What comorbidities and/or concomitant medications do you typically take into account when selecting therapy for patients with CLL?

Tolerability of Covalent BTK Inhibitors

Robin Klebig, APRN, CNP, AOCNP

May 15, 2026

Tolerability of Covalent BTK Inhibitors — Cardiovascular Events

Cardiovascular Toxicity	Ibrutinib	Acalabrutinib	Zanubrutinib
Atrial fibrillation/flutter	**13–16%**	9.4%	2-5%
Ventricular arrhythmia	**1.9%**	0.4%	0.2-0.8%
Hypertension	**9-23%**	9.4%	10-23.5%
Bleeding	**3.9-10%**	4.5%	2.9-5.9%
Stroke	2.0%	1-2.5%	1.4-1.8%

BTKis should be held 3-7 days before and after any procedure to minimize risk of bleeding

Colonoscopy, EGD, etc.: 3 days before and after

Mohs procedure: 3-5 days before and after

Major surgery, orthopedic surgery, etc.: 7 days before and after

American College of Cardiology, 2022

Monitoring and management of treatment-related cardiovascular events in patients receiving covalent BTK inhibitors

- Baseline ECG and echocardiogram for higher-risk individuals e.g., male, >65, h/o HTN, DM, prior cardiac issues
- Blood pressure monitoring
- ECG q3-6 mo x 1 year, then prn symptoms
- Afib screening
- Referral to CardioOncology if arrhythmia detected
- American College of Cardiology (ACC) recommends switching from ibrutinib to 2nd generation BTKi (acala or zanu) in pts w/ CV toxicities
- Atrial fibrillation is not necessarily a contraindication to BTKi use if well controlled
  - Warfarin is contraindicated, DOACs are preferred, consider dose reduction of DOAC and/or BTKi

Tolerability of Covalent BTK Inhibitors — Noncardiovascular Events

- Fatigue
  - Multifactorial, self-limited
- Headache (acalabrutinib)
  - Transient, resolve within 1st month
  - Caffeine
  - Hydration
  - Acetaminophen (avoid NSAIDs)
- Diarrhea
  - Loperamide prn
  - Evening dosing
- Arthralgias/myalgias
  - Supportive care
  - Acetaminophen
  - Avoid NSAIDs
  - Stretching/yoga, remain active
  - Heat, topical menthol, diclofenac gel
- Dermatologic
  - Rash
    - Topical corticosteroids prn
  - Petechiae/bruising
  - Nail splitting/cracking
    - Biotin 2.5 mg daily
- Cytopenias
  - Neutropenia
  - Lymphopenia
  - Anemia
  - Thrombocytopenia
- Infections
  - Vaccinations up to date
  - Prophylaxis with acyclovir (HZV/HSV)
  - Consider PJP prophylaxis with Bactrim/pentamidine for high risk or heavily pretreated pts
  - IVIG if hypogammaglobulinemia

Case Presentation

A patient with CLL treated with a covalent BTK inhibitor

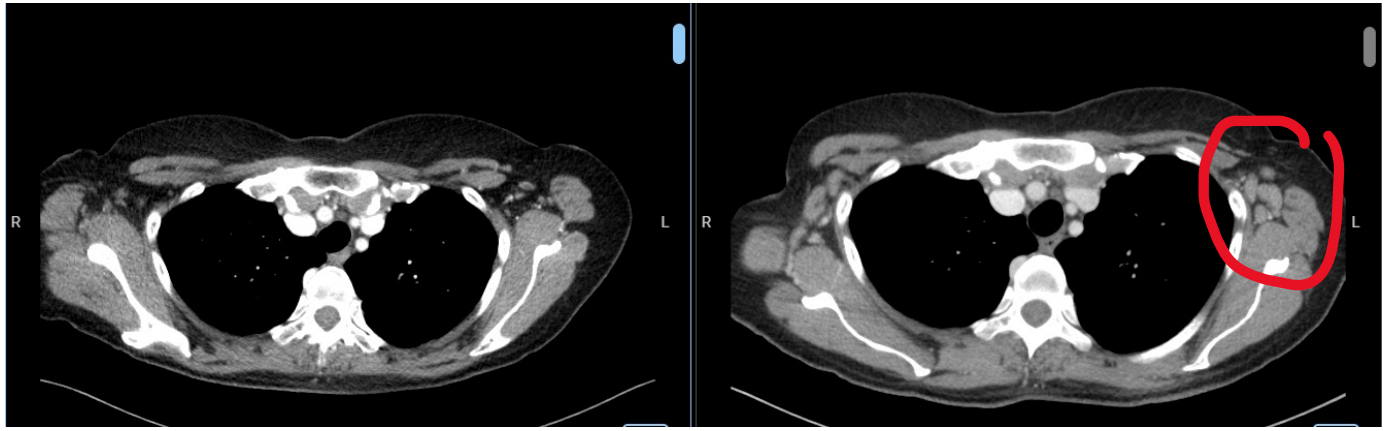
- 56 y/o female
  - Lives 3 hrs from Mayo Clinic
  - PMH: Hyperlipidemia, Migraines
  - SH: Married, 3 grown daughters. Preschool teacher, works 4-12 hour days/week

- Dx CLL 2013; observed until 2020 (age 63)
  - WBC 185,000
    - ALC 30,150
    - ANC 1680
  - Hgb 10.5
  - Plts 104,000
  - Exaggerated insect bite-like reactions
  - Progressive lymphadenopathy and splenomegaly
  - No B symptoms

Initial treatment

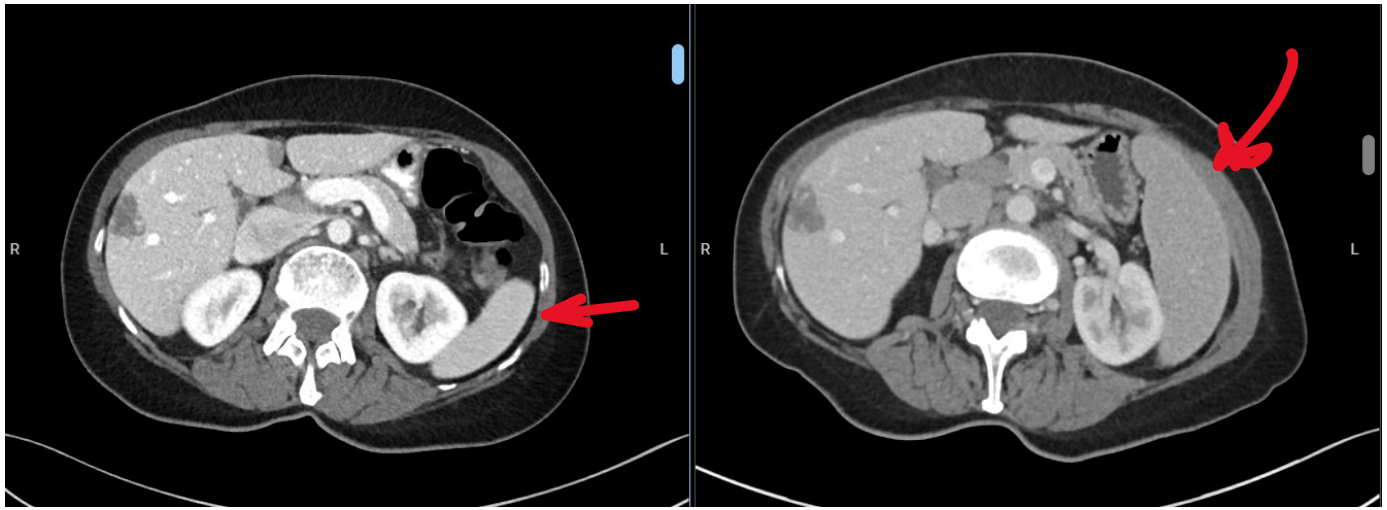
- Treatment Protocol: **EA9161** - Arm B (**Obinutuzumab / Ibrutinib**)
- A Study Comparing Ibrutinib and Obinutuzumab With or Without Venetoclax in Treating Patients with Chronic Lymphocytic Leukemia
- Diarrhea
  - 15-20 minutes after ibrutinib dose
  - 5-6 stools per day (grade 2)
  - Took at night, loperamide prn, ensure adequate hydration
  - Resolved within a few weeks
- Mild arthralgias
- Fatigue

Response to obinutuzumab/ibrutinib



- Prompt resolution of lymphadenopathy, splenomegaly in 1 week
- Normalization of CBC/dif within 6 months

- Remains on ibrutinib per protocol since 7/2020
- Normal CBC/dif, no LAD, splenomegaly
- Living a normal life



Discussion Questions

How, if at all, do the tolerability profile and other practical considerations with individual covalent BTK inhibitors affect your selection among them?

Agenda

Introduction: Biology of Non-Hodgkin Lymphoma (NHL)

Module 1: Current Role of CD20 x CD3 Bispecific Antibodies in NHL

Module 2: Role of Polatuzumab Vedotin in Diffuse Large B-Cell Lymphoma (DLBCL)

Module 3: Optimal Application of Loncastuximab Tesirine for Patients with DLBCL and Follicular Lymphoma

Module 4: Role of BTK Inhibitors Alone or with Anti-CD20 Antibodies for Patients with Newly Diagnosed Chronic Lymphocytic Leukemia (CLL)

Module 5: Combining BTK Inhibitors with Bcl-2 Inhibitors

Module 6: Current and Future Role of Noncovalent BTK Inhibitors in CLL

Combining BTK inhibitors with BCL-2 inhibitors

Brad Kahl, MD

SITEMAN CANCER CENTER
A NATIONAL CANCER INSTITUTE COMPREHENSIVE CANCER CENTER
BARNES-JEWISH Hospital BJC HealthCare
Washington University in St. Louis SCHOOL OF MEDICINE
SITEMAN Kids AT ST. LOUIS Children's HOSPITAL Washington University Physicians
NCI Designated Comprehensive Cancer Center
NCCN National Comprehensive Cancer Network®

My Thoughts on First-line Treatment: 4 Primary Options

- Continuous therapy with covalent BTK inhibitors (cBTKi)
  - Acalabrutinib (FDA approved 2019)
  - Zanubrutinib (FDA approved 2023)

- Time-limited therapy with BCL-2 inhibitor combinations
  - Venetoclax + obinutuzumab (FDA approved 2019)
  - Venetoclax + acalabrutinib (FDA approval 2026)

- Technically, there are 6 options, but I rarely add obinutuzumab to acalabrutinib or to venetoclax + acalabrutinib

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma v.1.2026. ©National Comprehensive Cancer Network, Inc 2025. All rights reserved. Accessed October 30, 2025.
Acalabrutinib PI. Zanubrutinib PI. Venetoclax PI.

Factors guiding therapy

- Does your patient prefer time limited therapy
  - If yes, then Venetoclax-Obinutuzumab is done in 12 months, Ven-Acala is done in 14 months
- Does your patient wish to avoid infusions
  - BTKi or Ven-Acala are all oral
- Does your patient have an underlying bleeding risk or significant cardiac disease
  - Perhaps wish to avoid BTKi
- Does your patient have significant underlying renal impairment
  - Increases risk for TLS, may wish to avoid VO and opt for BTKi
- Does your patient have a 17p del or p53 mutation
  - BTKi appears to control disease better than time limited options

Venetoclax

- BCL-2 inhibitor
  - No lymphocytosis
- Highly effective
  - Remission “deeper" than with BTKi’s
    - More complete responses.
    - More MRD undetectable.
- Generally well tolerated
  - GI side effects, cytopenias
- Tumor Lysis Syndrome

Venetoclax

- Toxicity profile different from other targeted agents: TLS risks

Figure 1. **Intrapatient dose ramp-up scheme for CLL patients initiating venetoclax**

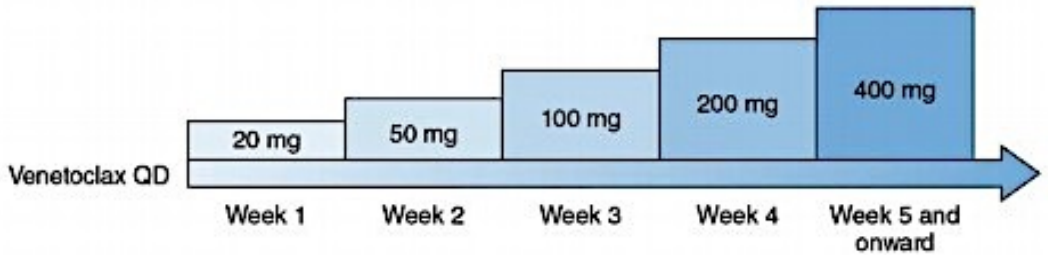


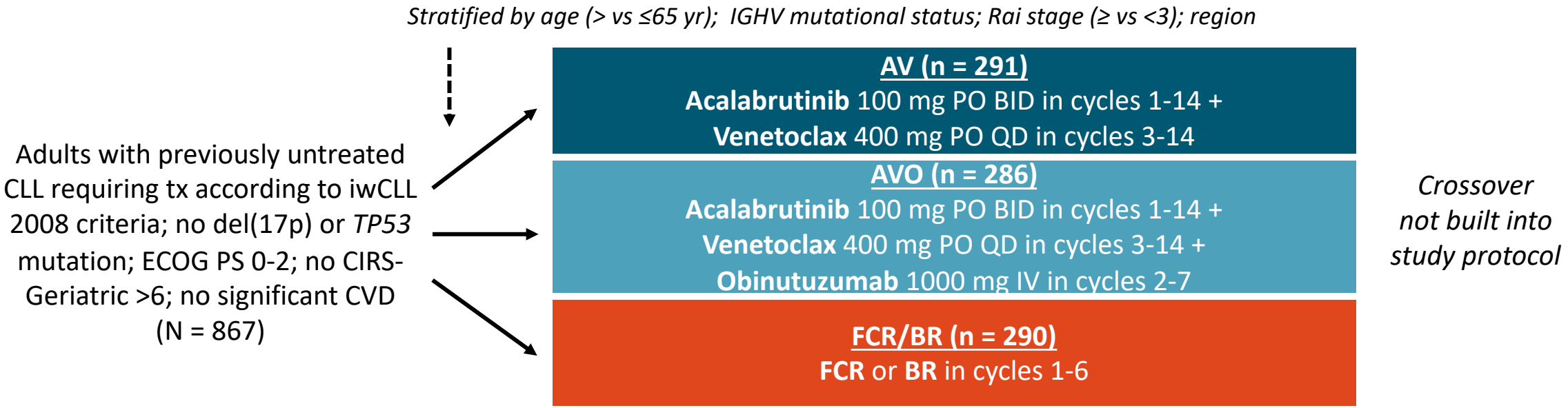
Figure 2. **Tumor lysis syndrome risk stratification, prophylaxis, and monitoring for CLL patients initiating venetoclax**

LOW RISK Nodal mass <5 cm and ALC <25,000 K/μL	**MEDIUM RISK** Nodal mass ≥5 cm and <10 cm or ALC ≥25,000 K/μL	**HIGH RISK** Nodal mass ≥10 cm or Nodal mass ≥5 cm but <10 cm and ALC ≥25,000 K/μL
Oral hydration (1.5-2L), allopurinol	Oral hydration (1.5-2L), consider IV hydration, allopurinol	Oral hydration (1.5-2L) and IV hydration (150-200 mL/hr as tolerated), allopurinol, consider rasburicase if elevated baseline uric acid
Outpatient administration	–Outpatient administration –Consider inpatient if CrCl <80 mL/min	–Inpatient administration for initial dose of 20 mg and 50 mg –Outpatient administration for subsequent dose escalations
Labs pre-dose, then 6-8 and 24 hours post-dose after initial dose of 20 mg and 50 mg	Labs pre-dose, then 6-8 and 24 hours post-dose after initial dose of 20 mg and 50 mg	**Inpatient:** Labs pre-dose, then 4, 8, 12, and 24 hours post-dose **Outpatient:** Labs pre-dose, then 6-8 and 24 hours post-dose

Blood. 2017;130(9):1081

AMPLIFY: Study Design

- Prespecified interim analysis of international, randomized, open-label phase III trial

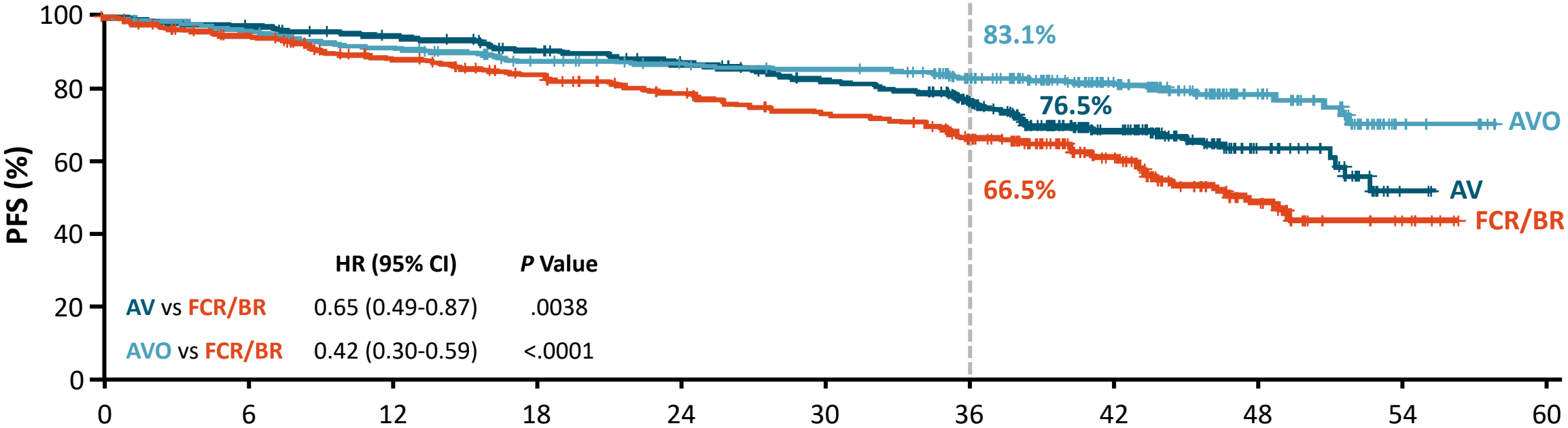


- **Primary endpoint**: PFS per IRC for AV vs FCR/BR
- **Secondary endpoints***: PFS per IRC for AVO vs FCR/BR; uMRD for AV vs FCR/BR; uMRD for AVO vs FCR/BR; OS for AV vs FCR/BR; OS for AVO vs FCR/BR

*Secondary endpoints tested in the order listed if primary endpoint is met.

Brown. ASH 2024. Abstr 1009. NCT03836261.

AMPLIFY: PFS per IRC



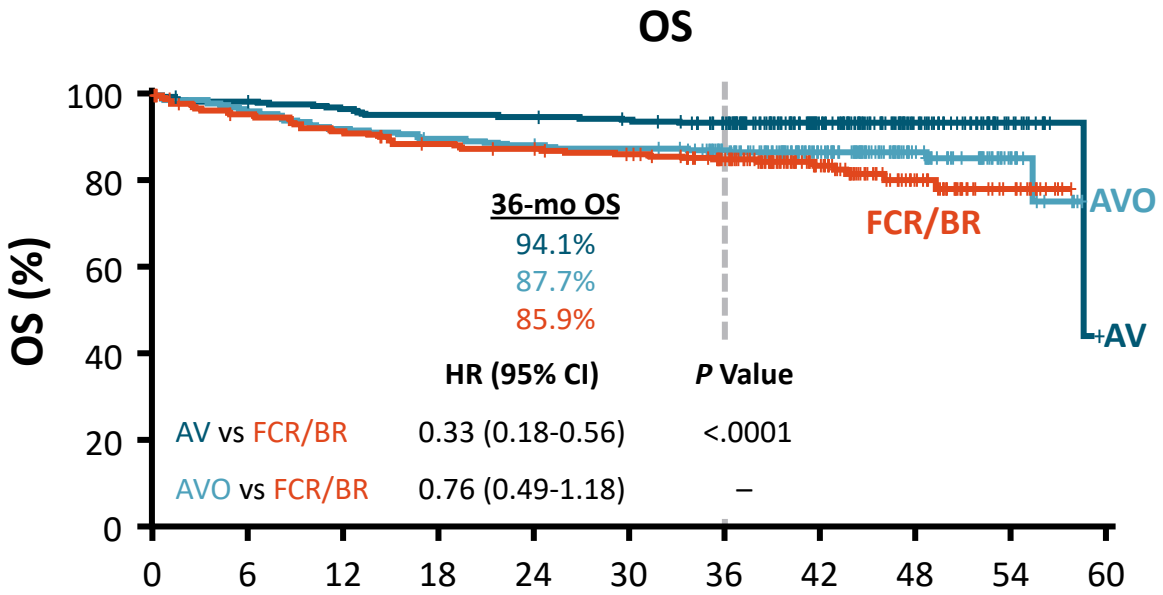
Patients at Risk, n

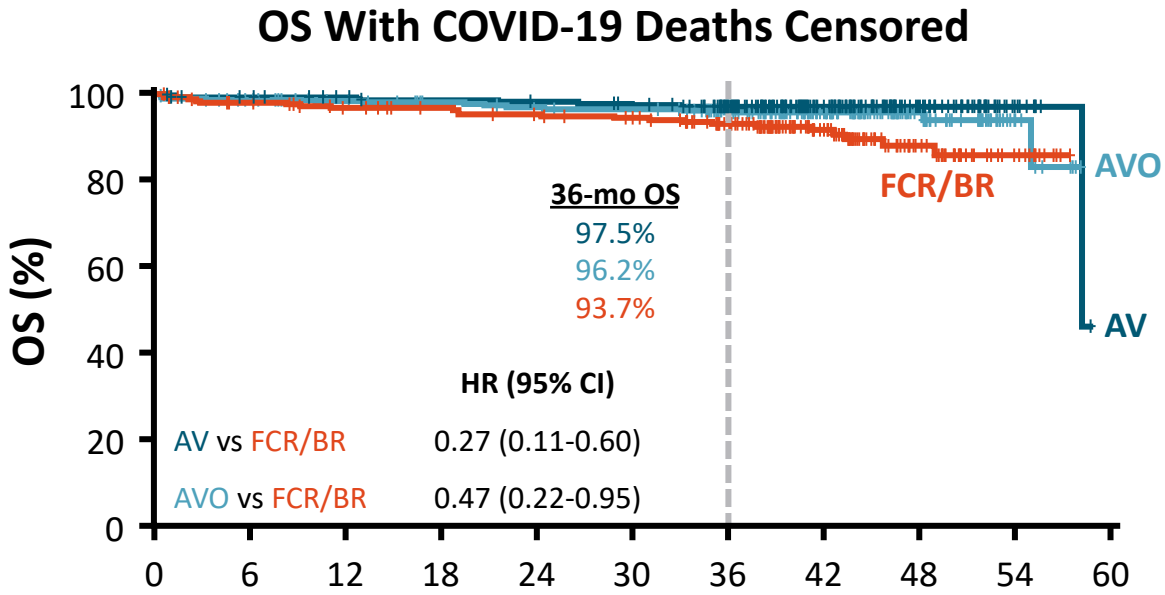
AV	291	282	289	251	237	219	177	102	35	3	0
AVO	288	272	258	237	225	219	191	118	51	7	0
FCR/BR	290	238	208	189	170	154	127	68	28	6	0

- Study met its primary endpoint, demonstrating significantly prolonged PFS per IRC for AV vs FCR/BR after a median follow-up of 48.0 mo

Brown. ASH 2024. Abstr 1009. Reproduced with permission.

AMPLIFY: OS





Patients at Risk, n

AV	291	286	281	277	275	270	233	142	58	10	0
AVO	286	276	265	257	252	250	223	143	84	10	0
FCR/BR	290	247	236	228	223	217	182	98	45	13	0

Patients at Risk, n

AV	291	286	281	277	275	270	233	142	58	10	0
AVO	288	276	265	257	252	250	223	143	64	10	0
FCR/BR	290	247	236	228	223	217	182	98	45	13	0

- OS prolonged for AV vs FCR/BR

- When COVID-19 deaths censored, OS prolonged for AV and AVO vs FCR/BR
  - COVID-19 deaths: AV, 10; AVO, 25; FCR/BR, 21

What to do with all of these great options?

BTK INHIBITOR

- Recommending to older/frailer CLL
  - Simple/Safe
  - Indefinite therapy less of an issue
- Recommending if p53 aberrant
  - Data impressive
- Acala vs. Zanu
  - Essentially never add obinutuzumab

TIME LIMITED THERAPY

- Recommeding if IgHV mutated
  - Results comparable to indefinite BTKi
- IgHV unmutated and young age
  - Conversation with patient regarding pros and cons
- VO vs. AV vs. AVO
  - Discuss pros and cons with patient
  - Do not see myself recommending AVO at this time

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

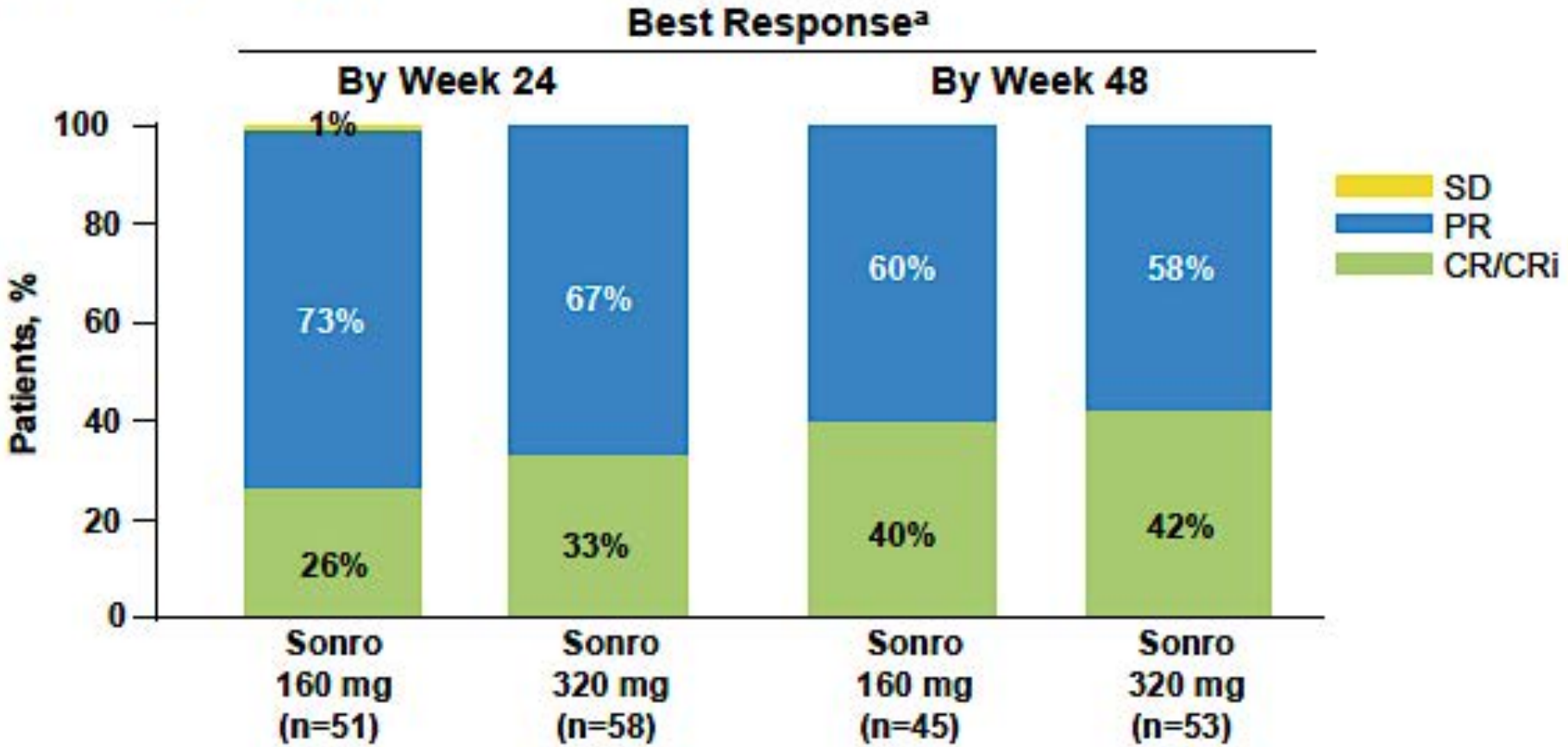
Sonrotoclax and Zanubrutinib as Frontline Treatment for CLL Demonstrates High MRD Clearance Rates with Good Tolerability: Data from an Ongoing Phase 1/1b Study BGB-11417-101

Jacob D. Soumerai,[1] Chan Y. Cheah,[2-4] Mary Ann Anderson,[5,6] Masa Lasica,[7] Emma Verner,[8,9] Stephen S. Opat,[10] Shuo Ma,[11] Robert Weinkove,[12,13] Raul Cordoba,[14] Paolo Ghia,[15,16] Sophie Leitch,[17] David Westerman,[18,19] Sheel Patel,[20] Yiqian Fang,[21] Wei Ding,[20] Haiyi Guo,[21] Constantine S. Tam[22]

[1]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [2]Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [3]Medical School, University of Western Australia, Crawley, WA, Australia; [4]Linear Clinical Research, Nedlands, WA, Australia; [5]Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [6]The Walter and Eliza Hall Institute, Melbourne, VIC, Australia; [7]St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; [8]Concord Repatriation General Hospital, Concord, NSW, Australia; [9]University of Sydney, Sydney, NSW, Australia; [10]Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; [11]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [12]Te Rerenga Ora Blood and Cancer Centre, Te Whatu Ora Health New Zealand Capital Coast & Hutt Valley, Wellington, New Zealand; [13]Cancer Immunotherapy Programme, Malaghan Institute of Medical Research, Wellington, New Zealand; [14]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [15]Università Vita-Salute San Raffaele, Milano, Italy; [16]IRCCS Ospedale San Raffaele, Milano, Italy; [17]Te Whatu Ora Health New Zealand-Waitemata, Auckland, New Zealand; [18]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [19]University of Melbourne, Melbourne, VIC, Australia; [20]BeiGene USA, Inc, San Mateo, CA, USA; [21]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [22]Alfred Hospital and Monash University, Melbourne, VIC, Australia

Abstract 1012

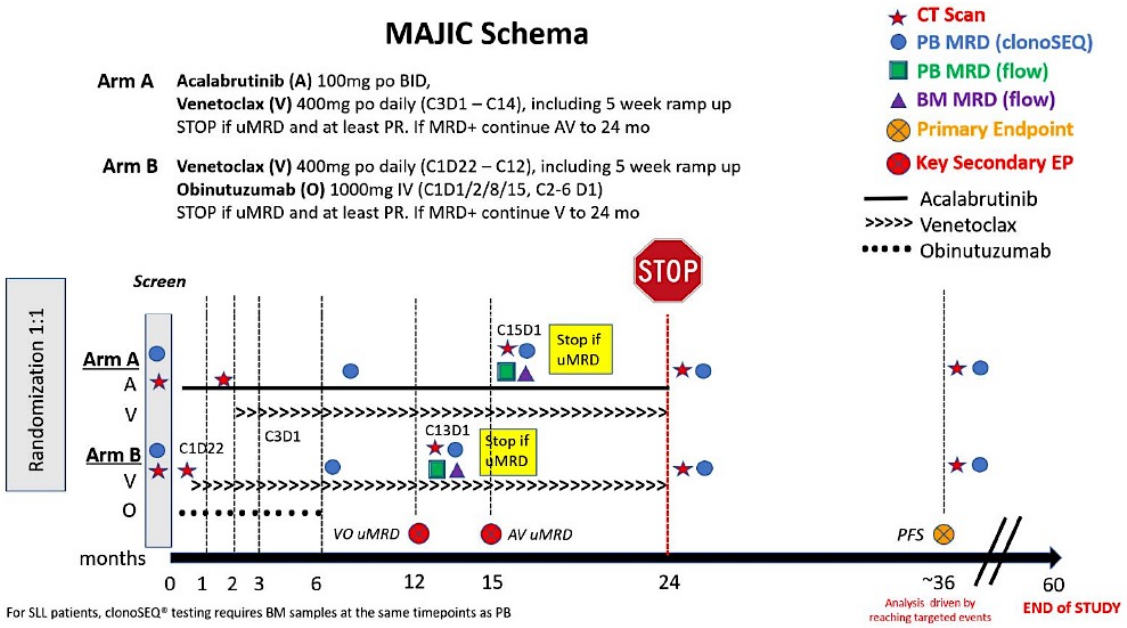
Sonrotoclax + Zanubrutinib Demonstrates Substantial Antitumor Activity in TN CLL



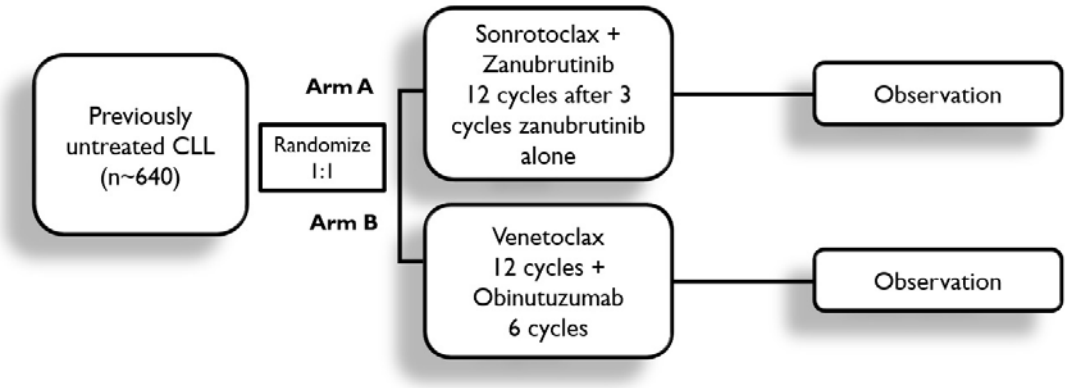
[a] Percentages based on the number of patients who reached assessment at 24 or 48 weeks after completion of ramp-up, following zanu monotherapy and sonro ramp-up to target dose.

Studies that could influence practice

MAJIC



CELESTIAL



Case Presentation

CLL Case: 63 yo female

- Dx'd with CLL 9/24. WBC 66k, HgB 13.4, Plts 225. Modest adenopathy and splenomegaly. IgHV unmutated. Del 13q by FISH. Started on observation.
- 2nd opinion with me 7/2025. Worsening adenopathy and fatigue. WBC 240K, HgB 10.3, Plts 157.
- HTN, obesity, type 2 DM. Lives 4 hours from clinic.
- Strongly preferred time limited therapy. We started Acal-Ven.
- WBC increase to 414K on Acal. Ven started cycle 3. No TLS.
- Very well tolerated.
- Labs 4/6/26: WBC 5.6, HgB 12.2, Plts 121. Adenopathy and splenomegaly resolved.
- Due to finish treatment early fall 2026

Discussion Questions

What fraction of your patients with newly diagnosed CLL would prefer time-limited therapy versus continuous therapy?

In which subsets of patients are you prioritizing the use of venetoclax/BTK inhibitor therapy?

Agenda

Introduction: Biology of Non-Hodgkin Lymphoma (NHL)

Module 1: Current Role of CD20 x CD3 Bispecific Antibodies in NHL

Module 2: Role of Polatuzumab Vedotin in Diffuse Large B-Cell Lymphoma (DLBCL)

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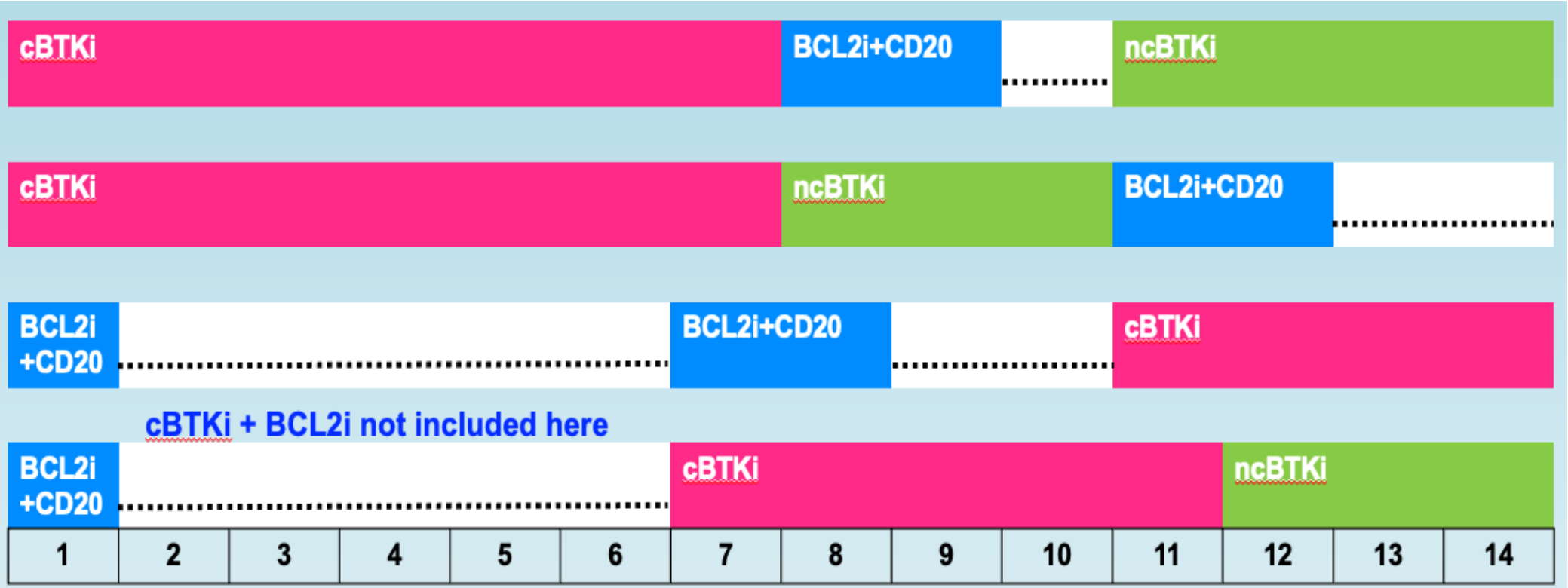
Module 5: Combining BTK Inhibitors with Bcl-2 Inhibitors

Module 6: Current and Future Role of Noncovalent BTK Inhibitors in CLL

Current and Future Role of Noncovalent BTK Inhibitors in CLL

Farrukh T. Awan, M.D., M.S., M.B.A.
Professor of Internal Medicine
Associate Director, Section of
Hematologic Malignancies/Transplantation and Cellular Therapies
Director of Lymphoid Malignancies Program
Harold C. Simmons Comprehensive Cancer Center
University of Texas Southwestern Medical Center
Dallas, TX

Targeted Therapy Sequencing for CLL



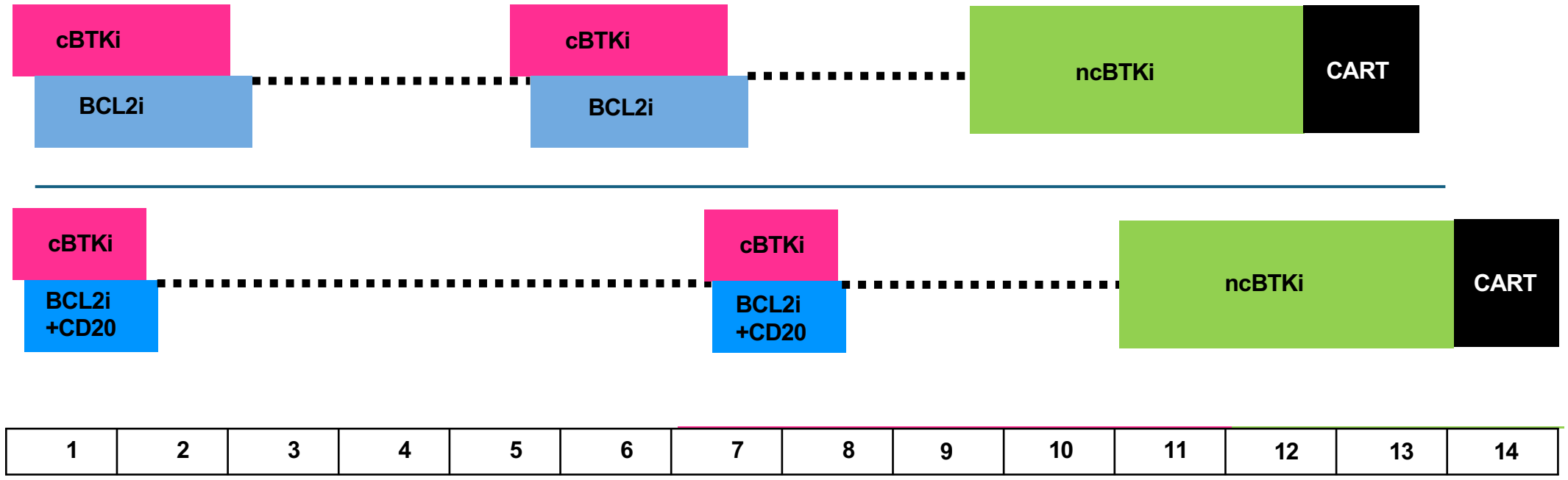
Factors affecting timelines:

- Age
- Del(17p) / *TP53*-m
- IGHV-MS / Del(11q)
- Complex karyotype

Double Exposed *vs.* Double Refractory:

- Exposed ≠ Refractory
- Refractory=progression on treatment

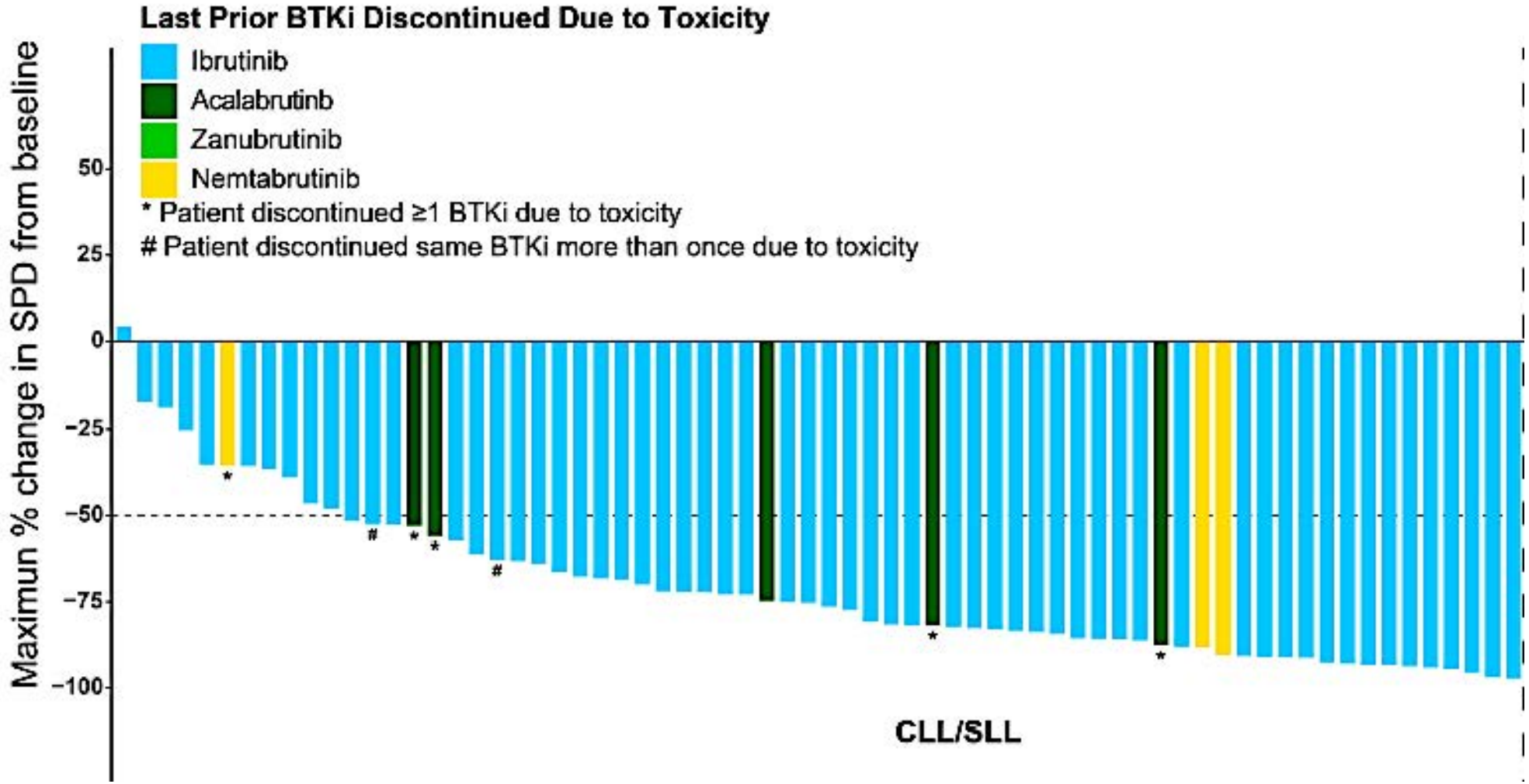
Targeted Therapy Sequencing for CLL



Factors affecting timelines:

- Age
- Del(17p) / *TP53*-m
- IGHV-MS / Del(11q)
- Complex karyotype

Pirtobrutinib is effective in patients with CLL – BRUIN trial



Shah NN et al. *Haematologica* 2025;110(1):92-102.

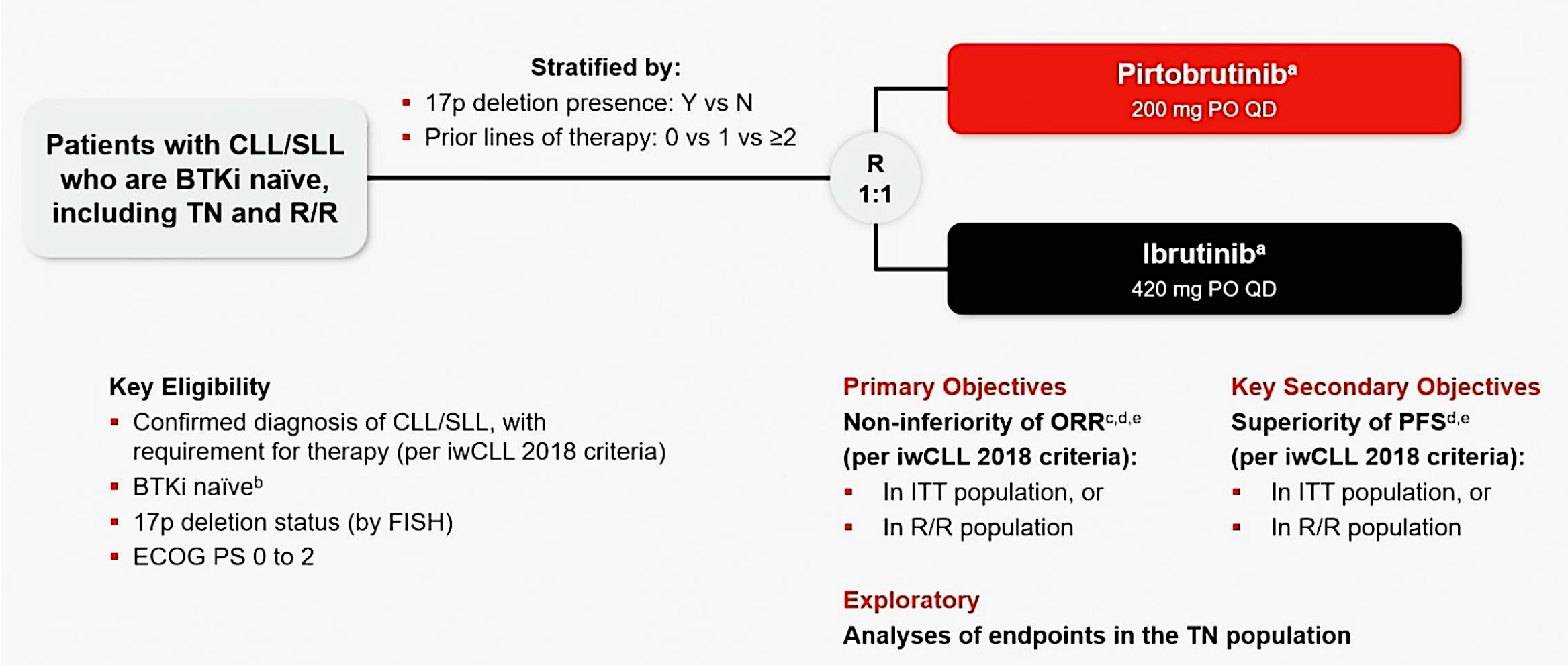
SLL = small lymphocytic lymphoma; SPD = sum of product diameters

BRUIN: Pirtobrutinib Safety Profile in the Overall Population

	BTKi-intolerant (n=127)			
	All cause AEs, %		Treatment-related AEs, %	
AE	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Fatigue	39.4	3.9	9.4	1.6
Neutropenia[a]	37.0	31.5	21.3	17.3
Diarrhea	29.9	1.6	12.6	0.8
Contusion	29.1	0.0	22.0	0.0
Cough	26.8	0.0	4.7	0.0
Headache	25.2	0.8	7.1	0.8
COVID-19	22.8	4.7	0.0	0.0
Abdominal pain	22.0	2.4	4.7	0.8
Dyspnea	22.0	2.4	5.5	0.0
Nausea	20.5	0.0	4.7	0.0
AEs of Interest[b]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[c]	68.5	24.4	14.2	5.5
Infections (excluding COVID-19)	59.8	17.3	14.2	5.5
Bruising[d]	36.2	0.0	26.8	0.0
Rash[e]	22.8	0.8	8.7	0.8
Arthralgia	21.3	0.8	4.7	0.0
Hemorrhage/hematoma[f]	14.2	3.1	4.7	0.8
Hypertension	7.9	0.8	3.1	0.0
Atrial fibrillation/flutter[g]	4.7	1.6	0.8	0.0

Shah NN et al. *Haematologica* 2025;110(1):92-102.

BRUIN CLL-314 Study Design



TN = treatment naïve

Woyach J et al. ASH 2025;Abstract 683; Woyach JA et al. *J Clin Oncol* 2025 December 7;[Online ahead of print].

BRUIN CLL-314: Response Data

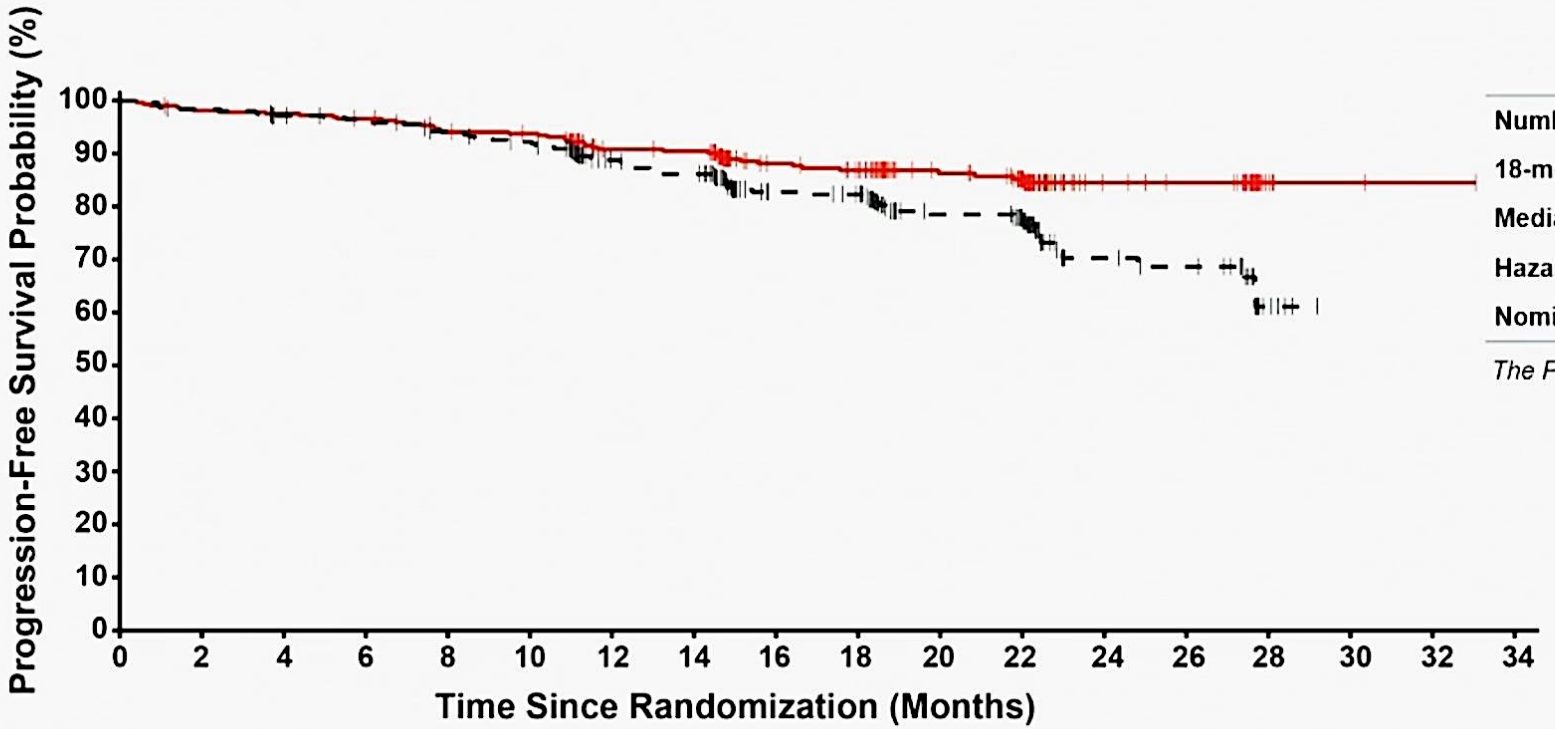
	ITT Population		TN Population		R/R Population	
	Pirtobrutinib n=331	Ibrutinib n=331	Pirtobrutinib n=112	Ibrutinib n=113	Pirtobrutinib n=219	Ibrutinib n=218
ORR[a] (PR or better)						
%	**87.0**	**78.5**	**92.9**	**85.8**	**84.0**	**74.8**
95% CI[b]	82.90, 90.44	73.73, 82.85	86.41, 96.87	78.03, 91.68	78.48, 88.61	68.46, 80.39
Nominal p-value[c]	0.0035		0.0886		0.0175	
ORR[a] ratio						
ORR ratio (95% CI)	1.1080 (1.034, 1.187)		1.0797 (0.989, 1.179)		1.1233 (1.020, 1.237)	
p-value for NI[d]	<0.0001		-		<0.0001	
Best Overall Response[e], %						
CR or CRi	4.8	2.4	7.1	3.5	3.7	1.8
PR or nPR	82.2	76.1	85.7	82.3	80.4	72.9
PR-L	2.4	3.9	0.9	2.7	3.2	4.6
SD	5.4	10.9	2.7	4.4	6.8	14.2
PD	1.5	1.2	0	0	2.3	1.8
ORR including PR-L						
%	89.4	82.5	93.8	88.5	87.2	79.4
95% CI[b]	85.60, 92.52	77.95, 86.42	87.55, 97.45	81.13, 93.73	82.05, 91.33	73.37, 84.53
Nominal p-value[c]	0.0093		0.1692		0.0286	

ORR results presented are IRC-assessed

ORR = overall response rate; NI = noninferiority; PR-L = partial remission with lymphocytosis

Woyach J et al. ASH 2025;Abstract 683; Woyach JA et al. *J Clin Oncol* 2025 December 7;[Online ahead of print].

BRUIN CLL-314: PFS in ITT Population



Number at risk

Pirtobrutinib	331	319	315	311	301	298	257	255	205	198	154	140	48	45	7	3	1	0
Ibrutinib	331	310	303	297	288	280	235	227	177	173	129	118	44	41	6	0	0	0

	Pirtobrutinib (n=331)	Ibrutinib (n=331)
Number of events, n (%)	43 (13.0)	69 (20.8)
18-month PFS rate (95% CI)	**86.9** (82.4, 90.3)	**82.3** (77.3, 86.3)
Median follow-up, mo	22.0	19.7
Hazard ratio (95% CI)	**0.569 (0.388, 0.834)**	
Nominal p-value[a]	0.0034	

The PFS results presented are INV-assessed

Pirtobrutinib reduced the risk of progression or death by 43%, with ibrutinib outcomes consistent with historical data

ITT = intent to treat

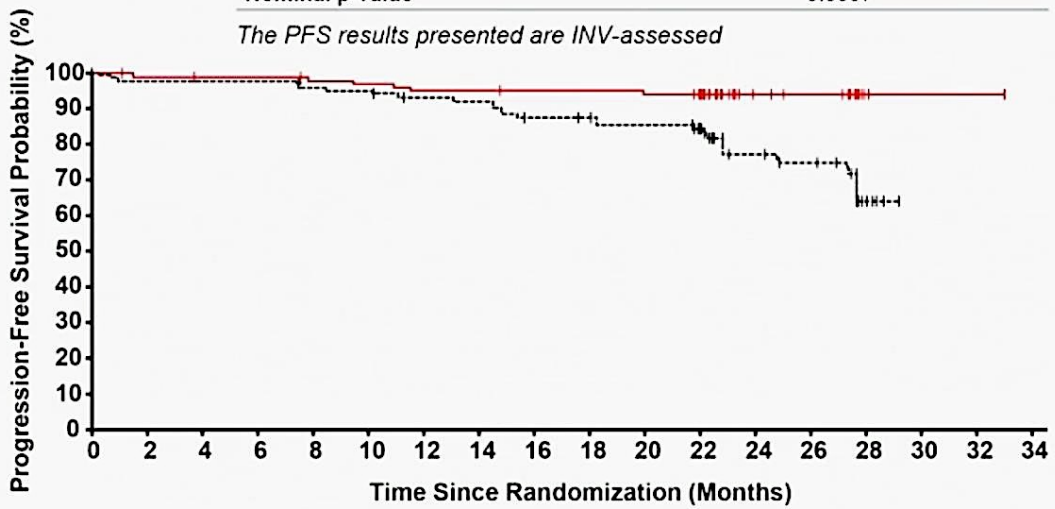
Woyach J et al. ASH 2025;Abstract 683; Woyach JA et al. *J Clin Oncol* 2025 December 7;[Online ahead of print].

BRUIN CLL-314: PFS by Prior Treatment Status

TN population

	Pirtobrutinib (n=112)	Ibrutinib (n=113)
Number of events, n (%)	6 (5.4)	24 (21.2)
18-month PFS rates (95% CI)	**95.3** (89.1, 98.0)	**87.6** (79.7, 92.6)
Median follow-up, mo	22.5	22.4
Hazard ratio (95% CI)	**0.239 (0.098, 0.586)**	
Nominal p-value[a]	0.0007	

The PFS results presented are INV-assessed



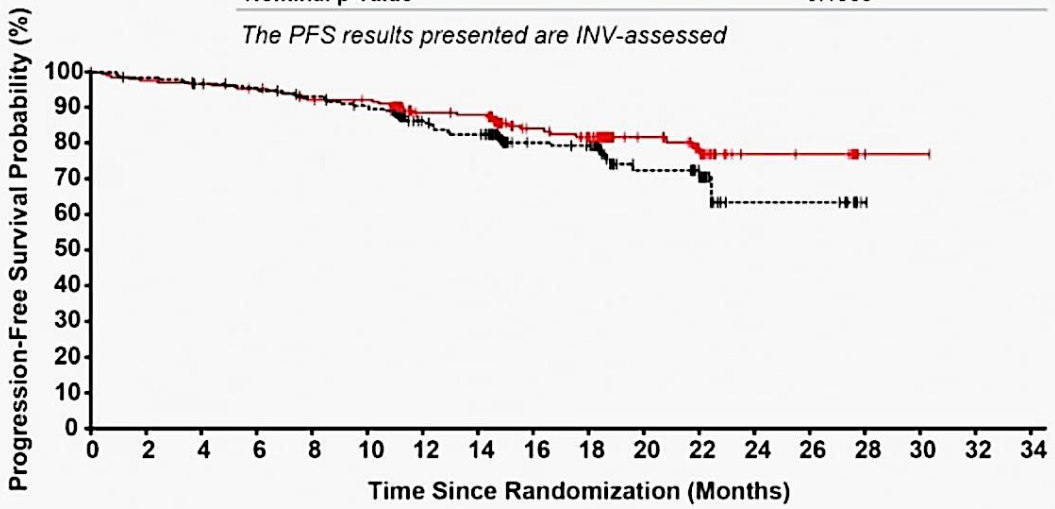
Number at risk

Pirtobrutinib	112	107	106	106	104	103	100	100	99	99	98	94	35	33	4	1	1	0
Ibrutinib	113	105	105	105	102	101	97	96	90	89	86	81	32	29	5	0	0	0

R/R population

	Pirtobrutinib (n=219)	Ibrutinib (n=218)
Number of events, n (%)	37 (16.9)	45 (20.6)
18-month PFS rate (95% CI)	**81.7** (75.1, 86.7)	**79.2** (72.3, 84.6)
Median follow-up, mo	18.4	15.8
Hazard ratio (95% CI)	**0.729 (0.471, 1.128)**	
Nominal p-value[a]	0.1563	

The PFS results presented are INV-assessed



Number at risk

Pirtobrutinib	219	212	209	205	197	195	157	155	106	99	56	46	13	12	3	2	0	0
Ibrutinib	218	205	198	192	186	179	138	131	87	84	43	37	12	12	1	0	0	0

Pirtobrutinib reduced the risk of progression or death by 76% in the TN population, the subgroup with the longest follow-up

Woyach J et al. ASH 2025;Abstract 683; Woyach JA et al. *J Clin Oncol* 2025 December 7;[Online ahead of print].

BRUIN CLL-314: Safety Profile

Preferred Term ≥10% of Participants in Either Arm	Pirtobrutinib n=330		Ibrutinib n=325	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Subjects with ≥1 TEAE	320 (97.0)	181 (54.8)	318 (97.8)	174 (53.5)
Neutropenia	75 (22.7)	57 (17.3)	58 (17.8)	43 (13.2)
Upper respiratory tract infection	59 (17.9)	2 (0.6)	63 (19.4)	0 (0)
Anemia	50 (15.2)	19 (5.8)	46 (14.2)	12 (3.7)
Pneumonia	45 (13.6)	21 (6.4)	49 (15.1)	28 (8.6)
Diarrhea	44 (13.3)	1 (0.3)	62 (19.1)	4 (1.2)
COVID-19	40 (12.1)	4 (1.2)	33 (10.2)	5 (1.5)
Hypertension	35 (10.6)	11 (3.3)	49 (15.1)	16 (4.9)
Contusion	33 (10.0)	0 (0)	30 (9.2)	0 (0)
Arthralgia	26 (7.9)	0 (0)	41 (12.6)	0 (0)
Thrombocytopenia	26 (7.9)	9 (2.7)	37 (11.4)	10 (3.1)
Urinary tract infection	26 (7.9)	3 (0.9)	40 (12.3)	3 (0.9)
Atrial fibrillation	8 (2.4)	3 (0.9)	41 (12.6)	12 (3.7)
Dose modifications due to TEAEs				
Reductions	26 (7.9)		59 (18.2)	
Discontinuations	31 (9.4)		35 (10.8)	

Median time on treatment was 20.5 months with pirtobrutinib and 19.3 months with ibrutinib;
1 patient developed Richter Transformation (RT) on pirtobrutinib; 4 patients developed RT on ibrutinib

Pirtobrutinib was well-tolerated with fewer dose reductions and discontinuations due to TEAEs than ibrutinib

Woyach J et al. ASH 2025;Abstract 683; Woyach JA et al. *J Clin Oncol* 2025 December 7;[Online ahead of print].

BRUIN CLL-314: Adverse Events of Special Interest (AESI)

≥10% of Participants in Either Arm	Pirtobrutinib n=330		Ibrutinib n=325	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Subjects with ≥1 AESI	288 (87.3)	127 (38.5)	288 (88.6)	117 (36.0)
Infections[a]	226 (68.5)	56 (17.0)	241 (74.2)	54 (16.6)
Infection without COVID-19	214 (64.8)	53 (16.1)	234 (72.0)	49 (15.1)
Bleeding	115 (34.8)	11 (3.3)	118 (36.3)	9 (2.8)
Hemorrhage[b]	78 (23.6)	11 (3.3)	81 (24.9)	9 (2.8)
Bruising[c]	45 (13.6)	0 (0)	39 (12.0)	0 (0)
Petechiae and purpura	17 (5.2)	0 (0)	25 (7.7)	0 (0)
Neutropenia[d]	103 (31.2)	83 (25.2)	76 (23.4)	57 (17.5)
Anemia[e]	51 (15.5)	20 (6.1)	51 (15.7)	12 (3.7)
Thrombocytopenia[f]	39 (11.8)	12 (3.6)	57 (17.5)	13 (4.0)
Atrial fibrillation and atrial flutter	8 (2.4)	3 (0.9)	44 (13.5)	13 (4.0)
≥75 years old[g]	3 (4.5)	1 (1.5)	15 (21.4)	5 (7.1)

AEs were mostly low-grade and consistent with prior pirtobrutinib studies

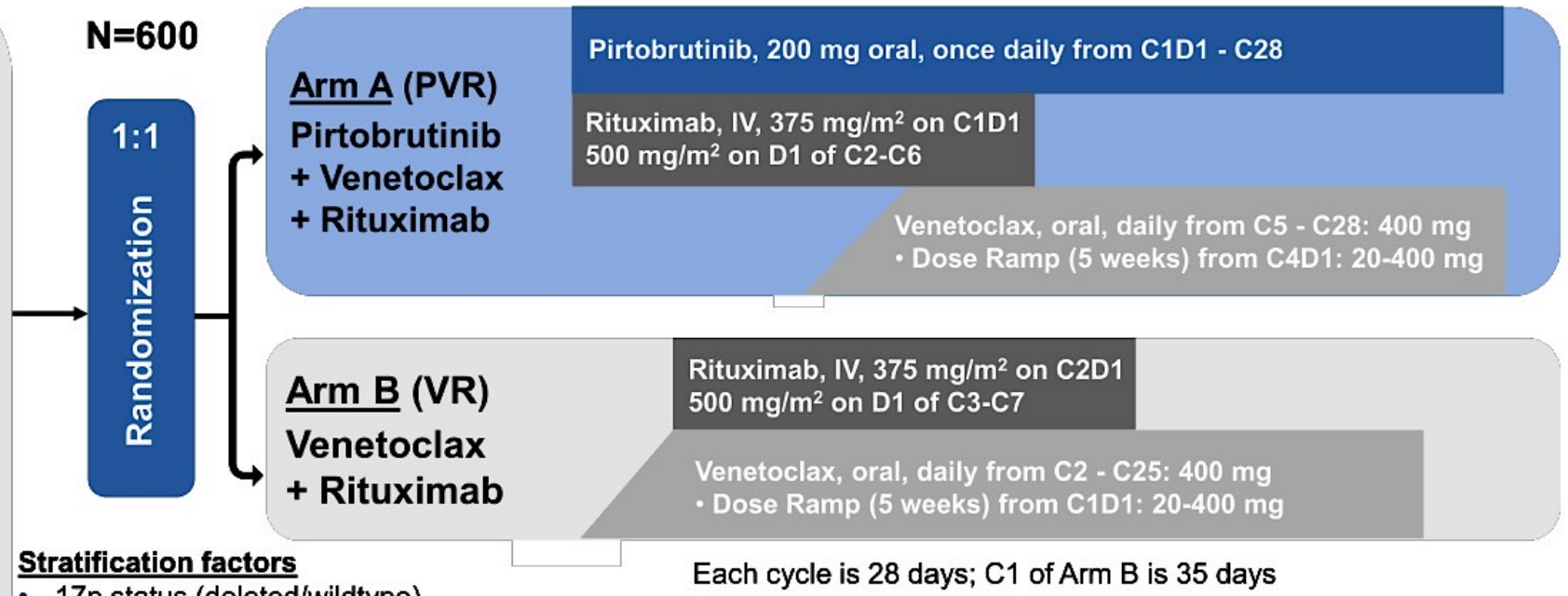
Incidence of atrial fibrillation/flutter was substantially lower with pirtobrutinib vs ibrutinib, particularly among older patients

Woyach J et al. ASH 2025;Abstract 683; Woyach JA et al. *J Clin Oncol* 2025 December 7;[Online ahead of print].

BRUIN CLL-322: Phase III Trial of Pirtobrutinib and Venetoclax/Rituximab for Relapsed/Refractory CLL

Key Inclusion Criteria

- Confirmed CLL/SLL per iwCLL 2018[3]
- Previously treated CLL/SLL (including a covalent BTKi or covalent BTKi naïve [limited to 20% of total enrollment])
- Known 17p status
  - If 17p status is unknown, local or central FISH test results during screening can be used
- No prior venetoclax
- ≥18 years of age and ECOG 0-2



Stratification factors

- 17p status (deleted/wildtype)
- Prior experience of BTKi (discontinuation due to PD or other vs no prior BTKi)

Primary endpoint: Progression-free survival per iwCLL 2018 by IRC

- **Pirto + VR improved PFS and is trending towards improved overall survival**
- **2-year fixed treatment**
- **N=639**

Eyre TA et al. ASCO 2023;Abstract TPS7583. Wierda WG et al. SOHO 2022;Abstract CLL-322.

Case Presentation

CASE PRESENTATION

- 72-year-old female diagnosed with CLL at the age of 65
- Has IGHV unmutated del11q, TP53 wildtype CLL
- Initially monitored with active surveillance
- Subsequently started on ibrutinib monotherapy and has continued on it for 5 years
- Now presents with enlarging, painful lymphadenopathy and anemia.
- Patient also has type 2 diabetes, hypertension, and chronic renal failure with baseline Cr 2.2 (not on dialysis)
- Imaging shows bulky lymph nodes around 8cm and a spleen of 20cm
- She has del11q and BTK c481 mutation
- Patient desires oral therapy with minimal back and forth to the cancer center

- What's the best next option for treatment

CASE PRESENTATION..cntd

- 72-year-old female with CLL with cBTKi resistance and needs treatment
- Multiple comorbidities

- **Best treatment option**
  - Venetoclax
  - Venetoclax and rituximab
  - Zanubrutinib
  - Acalabrutinib
  - **Pirtobrutinib**

Discussion Questions

In which line of therapy are you currently employing pirtobrutinib for your patients with R/R CLL?

Are you enthusiastic about the potential use of time-limited pirtobrutinib in combination venetoclax/rituximab for R/R CLL, and if so, which patients would you like to offer this regimen to?

Would you consider substituting pirtobrutinib for a first- or second-generation covalent BTK inhibitor for a patient with BTK inhibitor-naïve disease under any circumstances?

Tolerability of Noncovalent BTK Inhibitors

Mollie Moran, APRN-CNP, AOCNP
Nurse Practitioner
The James Cancer Hospital and Solove Research Institute
The Ohio State University
Columbus, Ohio

BRUIN: Pirtobrutinib Safety Profile

Adverse Event, %	All Doses and Patients (N = 773)			
	TEAEs in ≥15%		TRAEs	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	28.7	2.1	9.3	0.8
Diarrhea	24.2	0.9	9.3	0.4
Contusion	19.4	0	12.8	0
Cough	17.5	0.1	2.3	0
COVID-19	16.7	2.7	1.3	0
Nausea	16.5	0.1	4.7	0.1
Dyspnea	15.5	1.0	3.0	0.1
Anemia	15.4	8.8	5.2	2.1
AEs of Special Interest, %				
Bruising	23.7	0	15.1	0
Bleeding	36.0	2.2	19.3	0.8
Infections	55.6	21.3	12.0	3.1
Hemorrhage	19.1	2.2	6.9	0.8
Hypertension	9.2	2.3	3.4	0.6
Atrial fibrillation/flutter	2.8	1.2	0.8	0.1
Neutropenia	24.2	20.4	14.7	11.5

Mato. NEJM. 2023;389:33.

Pirtobrutinib Tolerability Compared to Ibrutinib (BRUIN CLL-314) Trial: Overall Safety

Preferred Term ≥10% of Participants in Either Arm	Pirtobrutinib n=330		Ibrutinib n=325	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Subjects with ≥1 TEAE	320 (97.0)	181 (54.8)	318 (97.8)	174 (53.5)
Neutropenia	75 (22.7)	57 (17.3)	58 (17.8)	43 (13.2)
Upper respiratory tract infection	59 (17.9)	2 (0.6)	63 (19.4)	0 (0)
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Pneumonia	45 (13.6)	21 (6.4)	49 (15.1)	28 (8.6)
Diarrhea	44 (13.3)	1 (0.3)	62 (19.1)	4 (1.2)
COVID-19	40 (12.1)	4 (1.2)	33 (10.2)	5 (1.5)
Hypertension	35 (10.6)	11 (3.3)	49 (15.1)	16 (4.9)
Contusion	33 (10.0)	0 (0)	30 (9.2)	0 (0)
Arthralgia	26 (7.9)	0 (0)	41 (12.6)	0 (0)
Thrombocytopenia	26 (7.9)	9 (2.7)	37 (11.4)	10 (3.1)
Urinary tract infection	26 (7.9)	3 (0.9)	40 (12.3)	3 (0.9)
Atrial fibrillation	8 (2.4)	3 (0.9)	41 (12.6)	12 (3.7)
Dose modifications due to TEAEs				
Reductions	26 (7.9)		59 (18.2)	
Discontinuations	31 (9.4)		35 (10.8)	

Median time on treatment was 20.5 months with pirtobrutinib and 19.3 months with ibrutinib;
1 patient developed Richter Transformation (RT) on pirtobrutinib; 4 patients developed RT on ibrutinib

Pirtobrutinib was well-tolerated with fewer dose reductions and discontinuations due to TEAEs than ibrutinib

Abbreviations: COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

Woyach JA et al. ASH 2025;Abstract 683.

Pirtobrutinib Tolerability Compared to Ibrutinib (BRUIN CLL-314): AEs of Special Interest

≥10% of Participants in Either Arm	Pirtobrutinib n=330		Ibrutinib n=325	
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Subjects with ≥1 AESI	288 (87.3)	127 (38.5)	288 (88.6)	117 (36.0)
Infections[a]	226 (68.5)	56 (17.0)	241 (74.2)	54 (16.6)
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Bleeding	115 (34.8)	11 (3.3)	118 (36.3)	9 (2.8)
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Neutropenia[d]	103 (31.2)	83 (25.2)	76 (23.4)	57 (17.5)
Anemia[e]	51 (15.5)	20 (6.1)	51 (15.7)	12 (3.7)
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Atrial fibrillation and atrial flutter	8 (2.4)	3 (0.9)	44 (13.5)	13 (4.0)
≥75 years old[g]	3 (4.5)	1 (1.5)	15 (21.4)	5 (7.1)

AEs were mostly low-grade and consistent with prior pirtobrutinib studies

Incidence of atrial fibrillation/flutter was substantially lower with pirtobrutinib vs ibrutinib, particularly among older patients

[a]Includes all infection events reported including COVID-19. [b]Includes hemorrhage, hematoma, hematuria, hematospermia, epistaxis, coital bleeding, gingival bleeding, aortic rupture, blood loss anemia, oral blood blister, nail bed bleeding. [c]Includes contusion, ecchymosis, increased tendency to bruise, genital contusion, injection site bruising, oral contusion, and vessel puncture site bruise. [d]Includes neutropenia, neutrophil count decreased, and febrile neutropenia. [e]Includes anemia, blood loss anemia, iron deficiency, and microcytic anemia. [f]Includes thrombocytopenia and platelet count decrease. [g]Pirtobrutinib, n=66; ibrutinib, n=70.
Abbreviations: AE, adverse event; AESI, AE of special interest; COVID-19, coronavirus disease 2019.

Woyach JA et al. ASH 2025;Abstract 683.

Management of Pirtobrutinib-Related Side Effects

- **Bleeding**
  - Monitor patient for signs of bleeding, especially if on concurrent anticoagulation
  - Instruct patient to inform provider about any upcoming procedures
  - Consider benefit-risk of withholding for 3 to 7 days pre- and post-surgery
- **Atrial fibrillation**
  - Monitor for and educate patient on signs and symptoms of arrhythmia
  - Patients with risk factors such as hypertension or previous arrythmias may be at increased risk

Pirtobrutinib PI, 6/2024

Management of Pirtobrutinib-Related Side Effects

- **Infection**
  - Encourage patients to report fever and other signs and symptoms of infection
    - Evaluate promptly, treat appropriately
  - Consider prophylaxis for patients at high risk
    - Vaccinations
    - Antimicrobial prophylaxis
- **Cytopenias**
  - Monitor CBCs regularly during treatment
  - Hold therapy or dose reduce depending on severity

Pirtobrutinib PI, 6/2024

Pirtobrutinib Dose-Modification Strategies

Adverse Reaction	Occurrences Requiring Dosage Modification	Modification (Starting Dosage: 200 mg once daily)
• Grade 3 or greater non-hematologic toxicity [a] • Absolute neutrophil count < 1 to 0.5 x 10^9/L with fever and/or infection • Absolute neutrophil count < 0.5 x 10^9/L lasting 7 or more days • Platelet count < 50 to 25 x 10^9/L with bleeding • Platelet count < 25 x 10^9/L	**First occurrence**	Interrupt Pirtobrutinib until recovery to Grade 1 or baseline; restart at original dosage (200 mg once daily)[a].
	Second occurrence	Interrupt Pirtobrutinib until recovery to Grade 1 or baseline; restart at 100 mg once daily.
	Third occurrence	Interrupt Pirtobrutinib until recovery to Grade 1 or baseline; restart at 50 mg once daily.
	Fourth occurrence	Discontinue Pirtobrutinib.

Pirtobrutinib package insert.

RTP RESEARCH TO PRACTICE

Case Presentation

Case Study: Noncovalent BTK

- 60 yo woman with hx of R/R CLL. She has IGHV unmutated, 46 XY, FISH del 13q disease. She was initially treated with ibrutinib and developed a resistance mutation. She then received venetoclax. She presents with progressing disease.
- FISH is now positive for P53. She still has the BTK mutation C481
- She has increased lymphocytosis, thrombocytopenia, increased lymph nodes and B symptoms.
- She has depression and anxiety due to family issues
- She starts therapy with pirtobrutinib.

- Tolerating therapy well. Compliant with dosing.
  - Diarrhea with the first 2 weeks of dosing controlled with loperamide and it resolved after the first 2 weeks
  - Increased fatigue – encouraged increased activity
  - Increased bruising – report any bleeding, manage expectantly
- Lymph nodes resolved. Counts improved.

- Ongoing discussion about potential CAR-T therapy.

Discussion Questions

How would you compare the global tolerability/toxicity of pirtobrutinib to that of the available covalent BTK inhibitors?

How, if at all, does the pretreatment counseling/education that you offer patients who are going to receive pirtobrutinib differ from the counseling/education that you offer patients who are going to receive covalent BTK inhibitors?

Recent Advances in Cancer Care — New Paradigms, Novel Agents and What It Means for the Oncology Nurse

A Complimentary NCPD Symposium Series Held During the 51st Annual ONS Congress

CDK4/6 Inhibitors in the Management of HR-Positive Breast Cancer

Saturday, May 16, 2026

6:00 AM – 7:30 AM

Faculty

Kelly Fischer, MSN, FNP-BC
Marissa Marti-Smith, DNP, APRN, AGNP-C, AOCNP
Ruth M O'Regan, MD

Moderator

Rita Nanda, MD

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