Exploring the Current and Changing Paradigm for the Management of Newly Diagnosed Diffuse Large B-Cell Lymphoma

Wednesday, February 2, 2022
5:00 PM – 6:15 PM ET

Faculty

Christopher R Flowers, MD, MS
Neha Mehta-Shah, MD, MSCI
Grzegorz Nowakowski, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Faculty

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

Grzegorz Nowakowski, MD
Professor of Oncology and Medicine
Vice Chair, Lymphoma Disease Group
Chair for Education
Division of Hematology
Mayo Clinic
Rochester, Minnesota

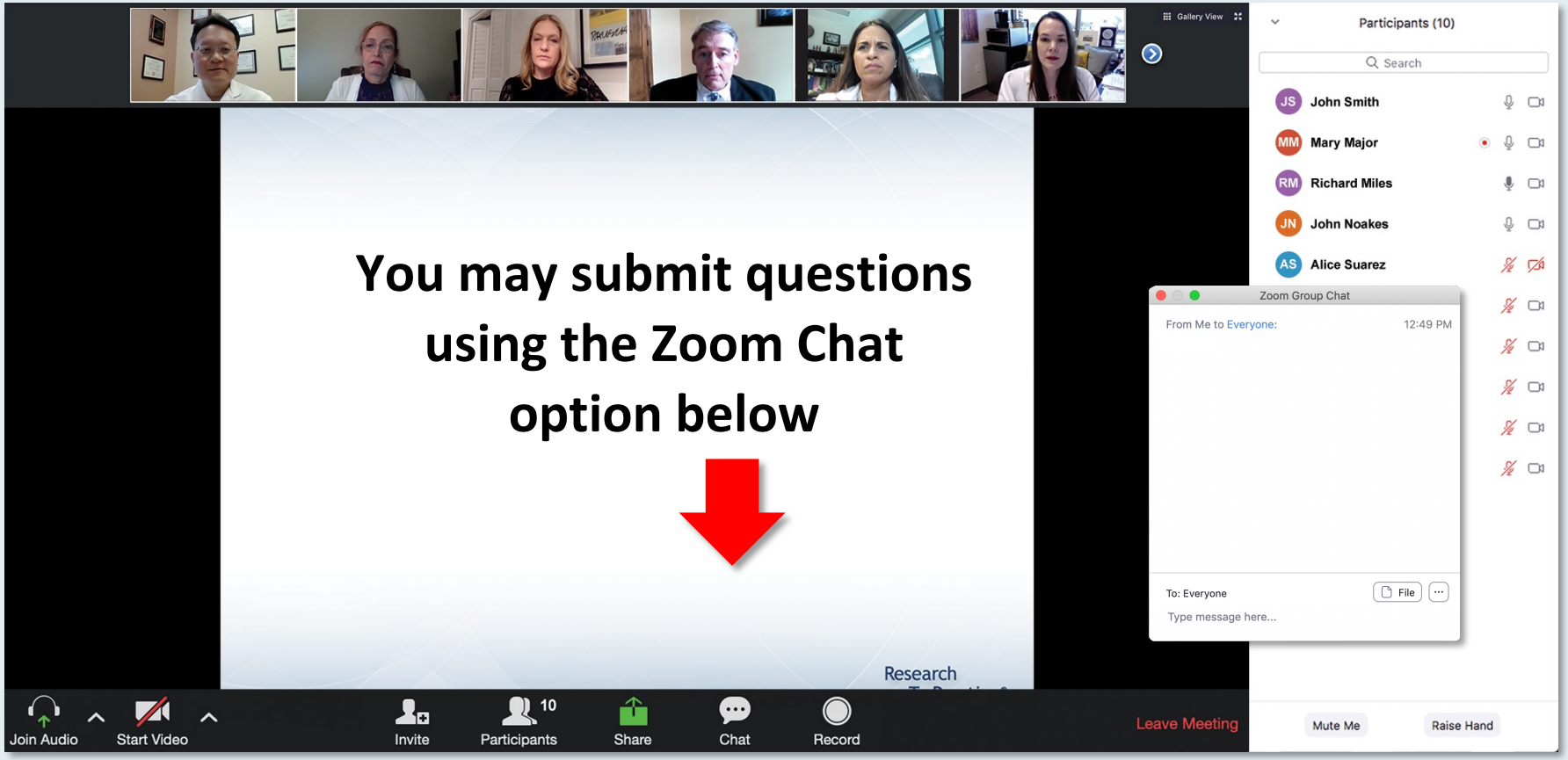
Neha Mehta-Shah, MD, MSCI
Associate Professor of Medicine
Division of Oncology, Department of Medicine
Washington University School of Medicine
St Louis, Missouri

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

RTP
RESEARCH
TO PRACTICE

We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

RTP RESEARCH TO PRACTICE

ONCOLOGY TODAY

WITH DR NEIL LOVE

CAR T-Cell Therapy in Non-Hodgkin Lymphoma

DR JONATHON COHEN

WINSHIP CANCER INSTITUTE

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Exploring the Current and Future Role of B-Cell Maturation Antigen-Directed Therapy in the Management of Multiple Myeloma

Monday, February 7, 2022
5:00 PM – 6:00 PM ET

Faculty

Jesús G Berdeja, MD
Noopur Raje, MD

Moderator

Neil Love, MD

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RESEARCH
TO PRACTICE

Key Considerations in the Optimal Clinical Care of Patients with Small Cell Lung Cancer

Wednesday, February 9, 2022
5:00 PM – 6:00 PM ET

Faculty

Luis Paz-Ares, MD, PhD
Jared Weiss, MD

Moderator

Neil Love, MD

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RESEARCH
TO PRACTICE

Recent Advances and Real-World Implications in Medical Oncology: A Daylong Multitumor Educational Symposium in Partnership with the North Carolina Oncology Association and the South Carolina Oncology Society

Saturday, February 12, 2022
8:30 AM – 4:00 PM ET

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Recent Advances and Real-World Implications in Medical Oncology: Agenda

Module 1	**Chronic Lymphocytic Leukemia and Lymphomas** 8:35 AM – 9:40 AM
Module 2	**Multiple Myeloma** 9:40 AM – 10:45 AM
Module 3	**Genitourinary Cancers** 10:45 AM – 11:50 AM
Module 4	**Breast Cancer** 12:30 PM – 1:35 PM
Module 5	**Gastrointestinal Cancers** 1:35 PM – 2:40 PM
Module 6	**Lung Cancer** 2:40 PM – 3:45 PM

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Meet The Professor

Current and Future Role of Immunotherapy in the Management of Lung Cancer

Tuesday, February 15, 2022
5:00 PM – 6:00 PM ET

Faculty

Charu Aggarwal, MD

Moderator

Neil Love, MD

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TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Prostate Cancer (Part 1 of a 2-Part Series)

Thursday, February 17, 2022

7:00 PM – 9:00 PM PT

Faculty

Neeraj Agarwal, MD
Himisha Beltran, MD
Fred Saad, MD
A Oliver Sartor, MD

Moderator

Alan H Bryce, MD

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RESEARCH
TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Bladder Cancer (Part 2 of a 2-Part Series)

Friday, February 18, 2022

6:30 PM – 8:00 PM PT

Faculty

Shilpa Gupta, MD
Daniel P Petrylak, MD
Guru Sonpavde, MD

Moderator

Sumanta Kumar Pal, MD

RTP
RESEARCH
TO PRACTICE

Exploring the Current and Changing Paradigm for the Management of Newly Diagnosed Diffuse Large B-Cell Lymphoma

Wednesday, February 2, 2022
5:00 PM – 6:15 PM ET

Faculty

Christopher R Flowers, MD, MS
Neha Mehta-Shah, MD, MSCI
Grzegorz Nowakowski, MD

Moderator

Neil Love, MD

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SITEMAN CANCER CENTER

Washington University in St Louis School of Medicine | BJC HealthCare

CURRENT MANAGEMENT OF NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

Neha Mehta-Shah, MD, MSCI
Associate Professor
Department of Medicine, Division of Oncology

Refining Therapeutic Options for DLBCL

Christopher Flowers, MD, MS, FASCO
Chair, Professor
Department of Lymphoma/Myeloma

Rochester, Minnesota

Investigational Approaches to the Care of Previously Untreated DLBCL

Greg Nowakowski, M.D.
Professor of Medicine and Oncology
Lymphoma Program
Mayo Clinic Rochester

RTP RESEARCH TO PRACTICE

DLBCL Survey Respondents

January 26 - January 31, 2022

Jeremy Abramson, MD

James Armitage, MD

Ian W Flinn, MD, PhD

Christopher R Flowers, MD, MS

Steven M Horwitz, MD

Eric D Jacobsen, MD

Brad S Kahl, MD

Ann S LaCasce, MD, MMSc

Neha Mehta-Shah, MD, MSCI

Craig Moskowitz, MD

Grzegorz Nowakowski, MD

Daniel O Persky, MD

Gilles Salles, MD, PhD

Laurie H Sehn, MD, MPH

Jeff Sharman, MD

Mitchell R Smith, MD, PhD

Sonali M Smith, MD

Julie M Vose, MD, MBA

Michael E Williams, MD, ScM

Andrew D Zelenetz, MD, PhD

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TO PRACTICE

Agenda

Introduction: Overview of Diffuse Large B-Cell Lymphoma (DLBCL)

MODULE 1: The POLARIX Trial – Dr Flowers

MODULE 2: Clinical Investigator Survey

MODULE 3: Ongoing Trials in DLBCL – Prof Nowakowski

MODULE 4: Up-Front Treatment for Older Patients with DLBCL – Dr Mehta-Shah

Agenda

Introduction: Overview of Diffuse Large B-Cell Lymphoma (DLBCL)

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MODULE 4: Up-Front Treatment for Older Patients with DLBCL – Dr Mehta-Shah

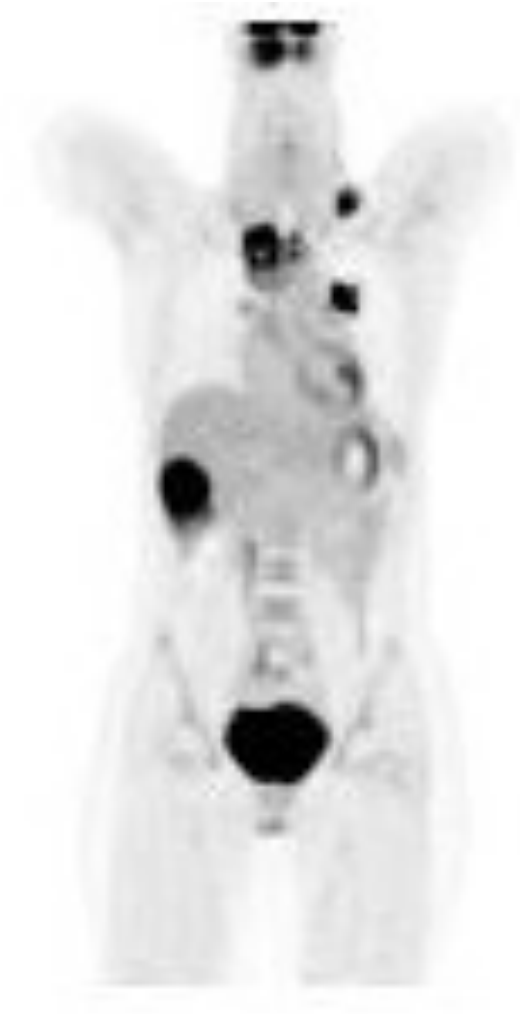
CASE PRESENTATION – DR MEHTA-SHAH: A 33-YEAR-OLD WOMAN WITH GERMINAL CENTER B-CELL-LIKE DLBCL

- 33 yo woman with no significant past medical history with a 6 week history of an enlarging left supraclavicular LN (doubled in size over 3 weeks). She is otherwise asymptomatic. No fevers, chills, night sweats, weight loss, abdominal pain, nausea, vomiting.
- US showed 2.8 x 2.8 x 1.3-cm supraclavicular LN
- Labs:
  - Normal CBC (WBC 8.5, Hgb 13.1, Plts 294)
  - LDH 246 (ULN 250)
  - Normal Chemistries

Courtesy of Neha Mehta-Shah, MD, MSCI

CASE PRESENTATION – DR MEHTA-SHAH: A 33-YEAR-OLD WOMAN WITH GERMINAL CENTER B-CELL-LIKE DLBCL (CONTINUED)

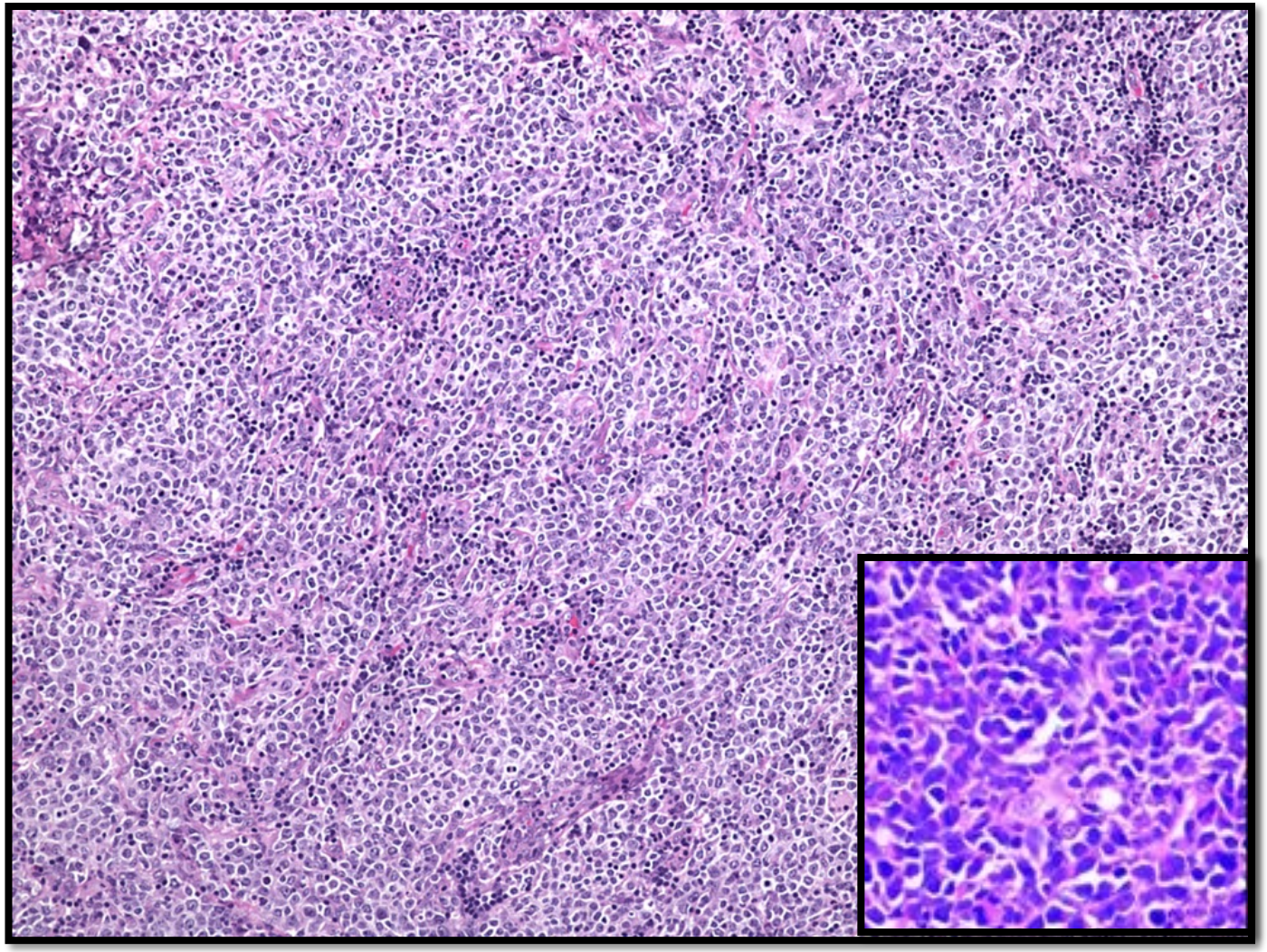
- US guided biopsy shows diffuse large B-cell lymphoma, germinal center
  - IHC positive for: CD20, CD10, BCL6, PAX 5
  - IHC negative for: MUM1, cMYC, EBER, CyclinD1, CD30
  - FISH negative for MYC, BCL2, BCL6
- PET/CT left supraclavicular, right cervical, mediastinal, bilateral hilar adenopathy. Adnexal and liver involvement



Courtesy of Neha Mehta-Shah, MD, MSCI

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

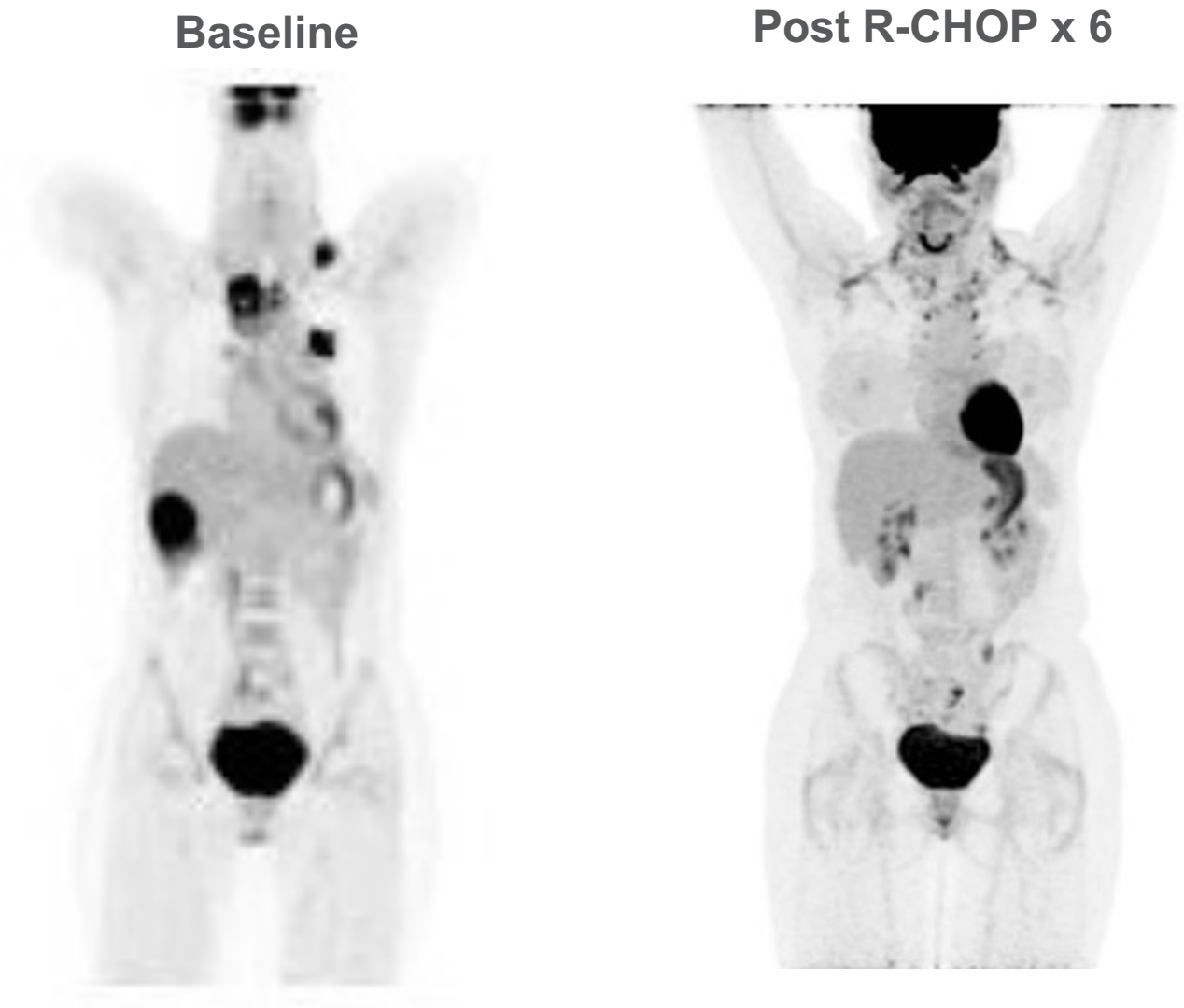
- Most common aggressive type of non-Hodgkin lymphoma
  - 30-40% of all non-Hodgkin lymphoma
  - Affects 7/100,000 people per year in US
- Heterogeneous entity
  - DLBCL, not otherwise specified
    - Germinal Center phenotype
    - Non-Germinal Center phenotype
  - T-cell/histiocyte-rich large B-cell lymphoma
  - Primary Cutaneous DLBCL, leg type
  - EBV+ DLBCL of the elderly
  - Primary CNS lymphoma
  - Primary Mediastinal DLBCL
  - CD5+ DLBCL
  - High grade B-cell lymphoma, not otherwise specified



Courtesy of Neha Mehta-Shah, MD, MSCI

CASE PRESENTATION – DR MEHTA-SHAH: A 33-YEAR-OLD WOMAN WITH GERMINAL CENTER B-CELL-LIKE DLBCL (CONTINUED)

- She underwent oocyte preservation and then R-CHOP x 6 cycles
- End of Treatment PET/CT showed a complete metabolic response
- She remains clinically in complete remission



Courtesy of Neha Mehta-Shah, MD, MSCI

DLBCL is the Most Common NHL Subtype

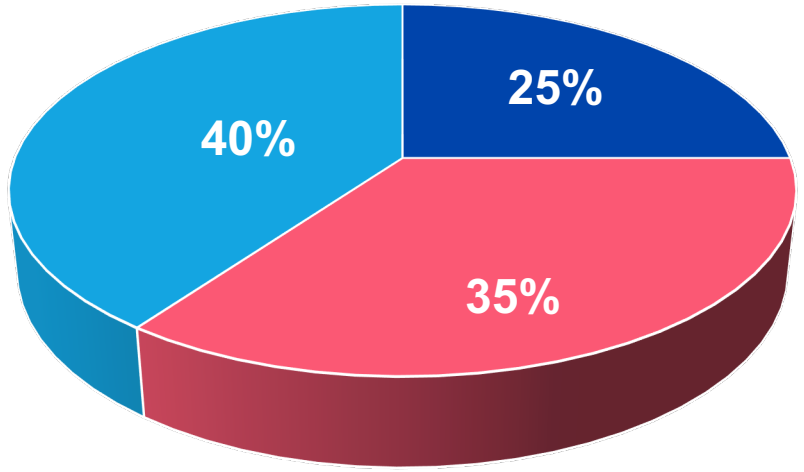
United States patients with DLBCL[1-3]

- Newly diagnosed ~28,000 per year
- Relapsed/Refractory ~11,000 per year

Would put these references directly on the slide at the bottom

Typically use this reference as a the contemporary assessment of US incidence of NHL subtypes
Teras et al. *CA Cancer J Clin.* 2016 Nov 12;66(6):443-459.

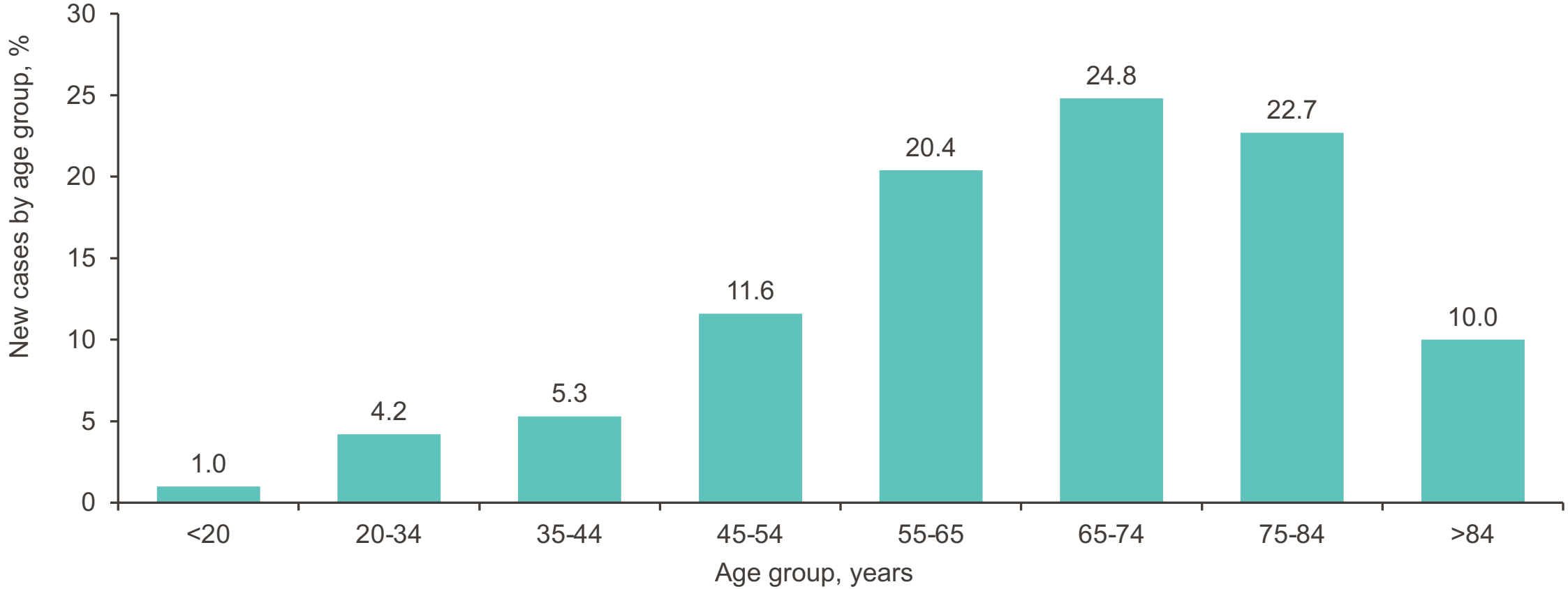
NHL prevalence in the US[5]



Courtesy of Christopher R Flowers, MD, MS

DLBCL Incidence Increases With Age

Average patient at diagnosis is 60-65 years of age (median age = 69 years), where most are not fit for HDC/ASCT[1-4]

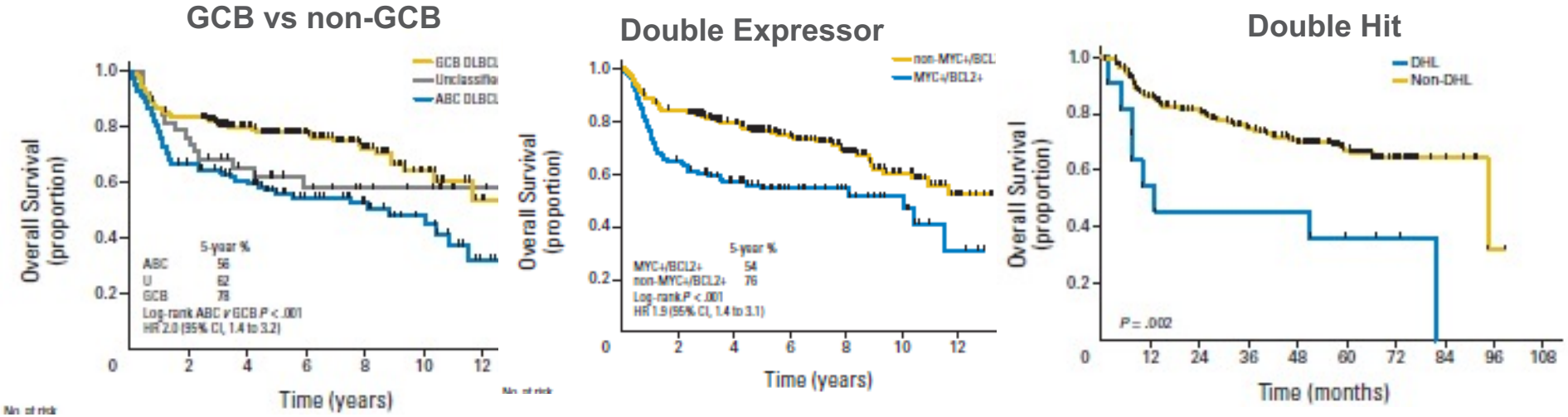


1. https://seer.cancer.gov/statfacts/html/dlbcl.html; 2; 3. . https://www.leukaemia.org.au/wp-content/uploads/2011/11/Factsheet-Lymphoma-DLBCL.pdfMartelli M et al. *Crit Rev Oncol Hematol*. 2013;87(2):146-171; 4. Broccoli A et al. *Oncologist.* 2019;24(9):1246-1252.

Courtesy of Christopher R Flowers, MD, MS

DLBCL PROGNOSIS

- 5-Year Overall Survival:
  - Germinal Center: 76%
  - Non-Germinal Center: 56%
  - “Double Expressor” : 54%
    - Over expression of c-MYC + BCL2 or BCL6
  - Double Hit: ~35%
    - Translocation of c-MYC and BCL2



Hans et al. Blood 2004;103:275-282; Scott et al. JCO 2015; Green et al JCO 2012

Courtesy of Neha Mehta-Shah, MD, MSCI

Agenda

Introduction: Overview of Diffuse Large B-Cell Lymphoma (DLBCL)

MODULE 1: The POLARIX Trial – Dr Flowers

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Case Presentation – Dr Flowers: A 71-year-old with Stage IV DLBCL

71-year old woman diagnosed with stage IV DLBCL

- PET/CT scan shows involvement of R axillary, mediastinal, supraclavicular, mesenteric, and inguinal LNs, largest 7 cm, SUV_{max} = 14
- Axillary LN Bx: diffuse large B-cell lymphoma, non-GCB subtype by Hans algorithm (CD10-)
- MYC -, BCL2-, BCL6- by IHC and FISH
- Bone marrow biopsy +
- Fatigue, 8 pound weight loss
- HTN, CAD x 3v (EF >50%), obesity, DM-2, heavy smoker x 60 py

Courtesy of Christopher R Flowers, MD, MS

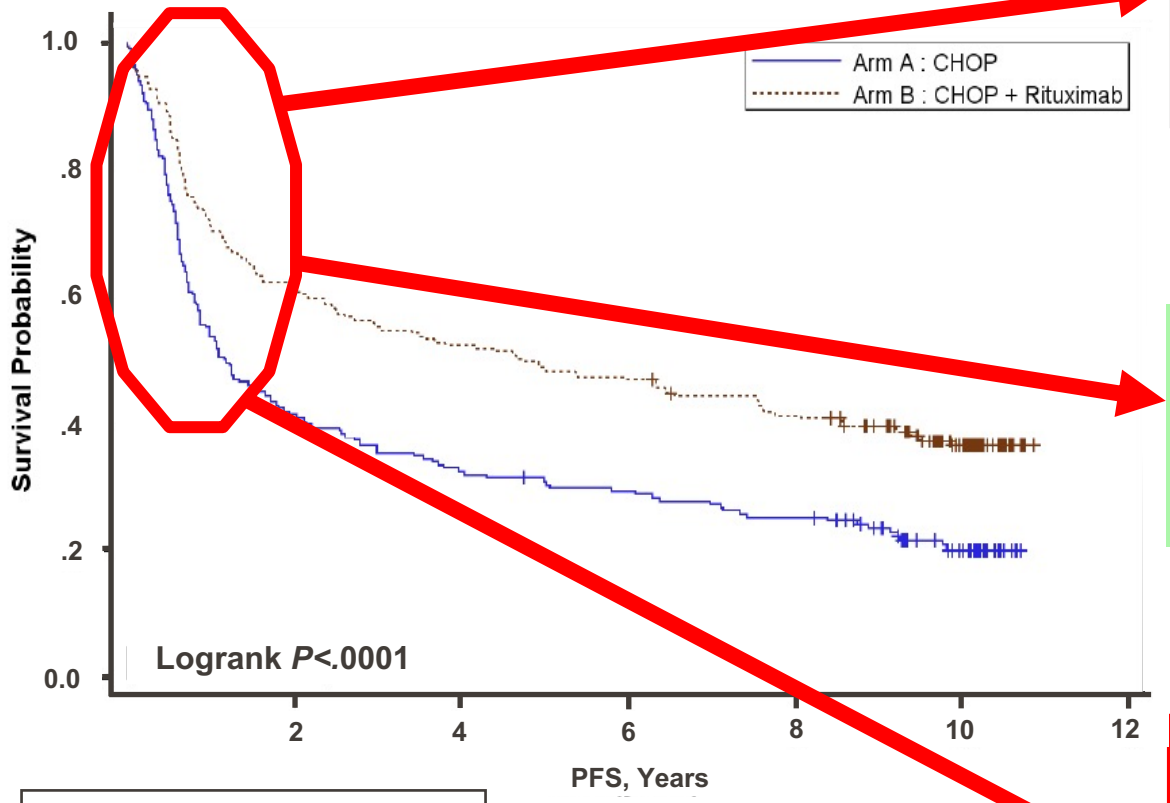
Case Presentation – Dr Flowers: A 71-year-old with Stage IV DLBCL (continued)

Patient achieved CR with polatuzumab-R-CHP.

- Developed grade 2 nausea, prolonged grade 3 neutropenia without infection during therapy around cycle 3
- Hand and finger burning/tingling by cycle 5 (grade 1 peripheral neuropathy)
- All resolved at post-treatment follow-up

Courtesy of Christopher R Flowers, MD, MS

DLBCL: Strategies to Improve Beyond R-CHOP-21



Intensification over R-CHOP-21?

Better predict/evaluate quality of response?

Take into consideration biological diversity of DLBCL
Different efficacy of Treatment
Focus on: GCB/non-GCB/DHIT

Age>60 years
PS>2
Stage III-IV
Extranodal sites >2
LDH>Nml

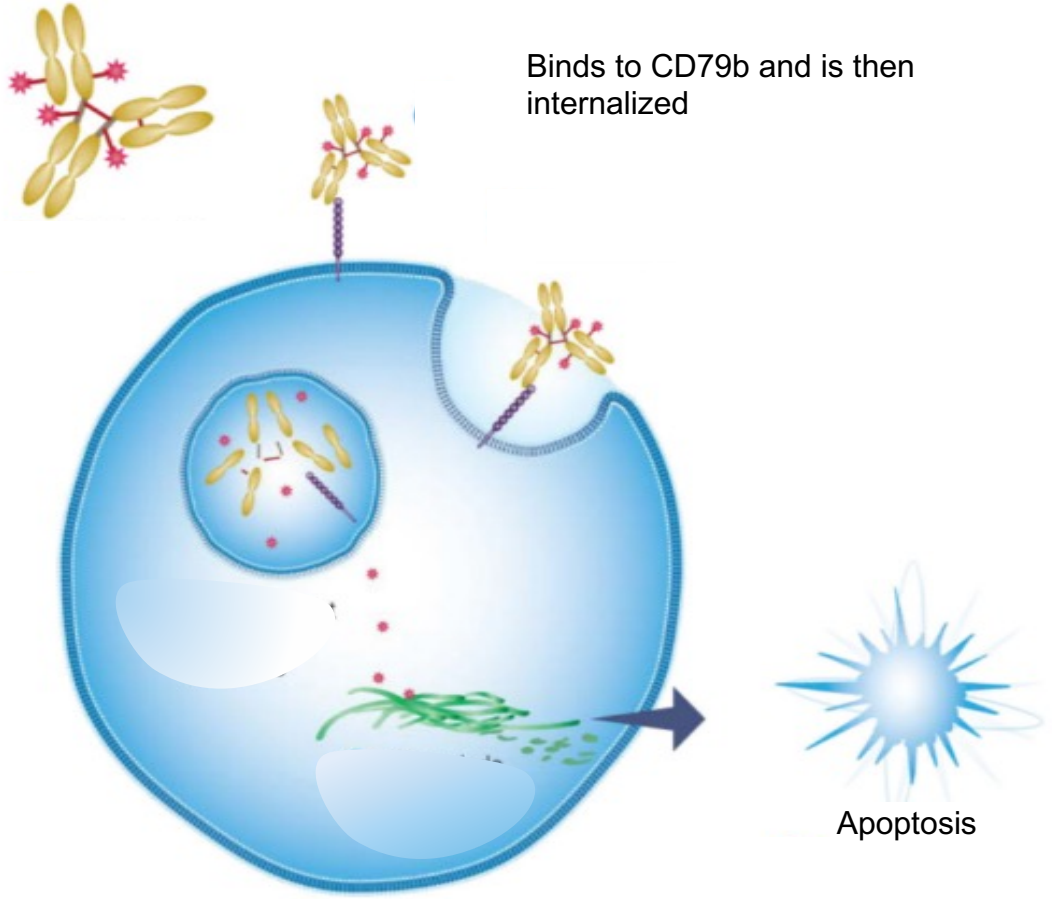
IPI

Courtesy of Christopher R Flowers, MD, MS

Polatuzumab vedotin is an ADC targeting CD79b

CD79b is ubiquitously expressed on DLBCL cells[1–3]

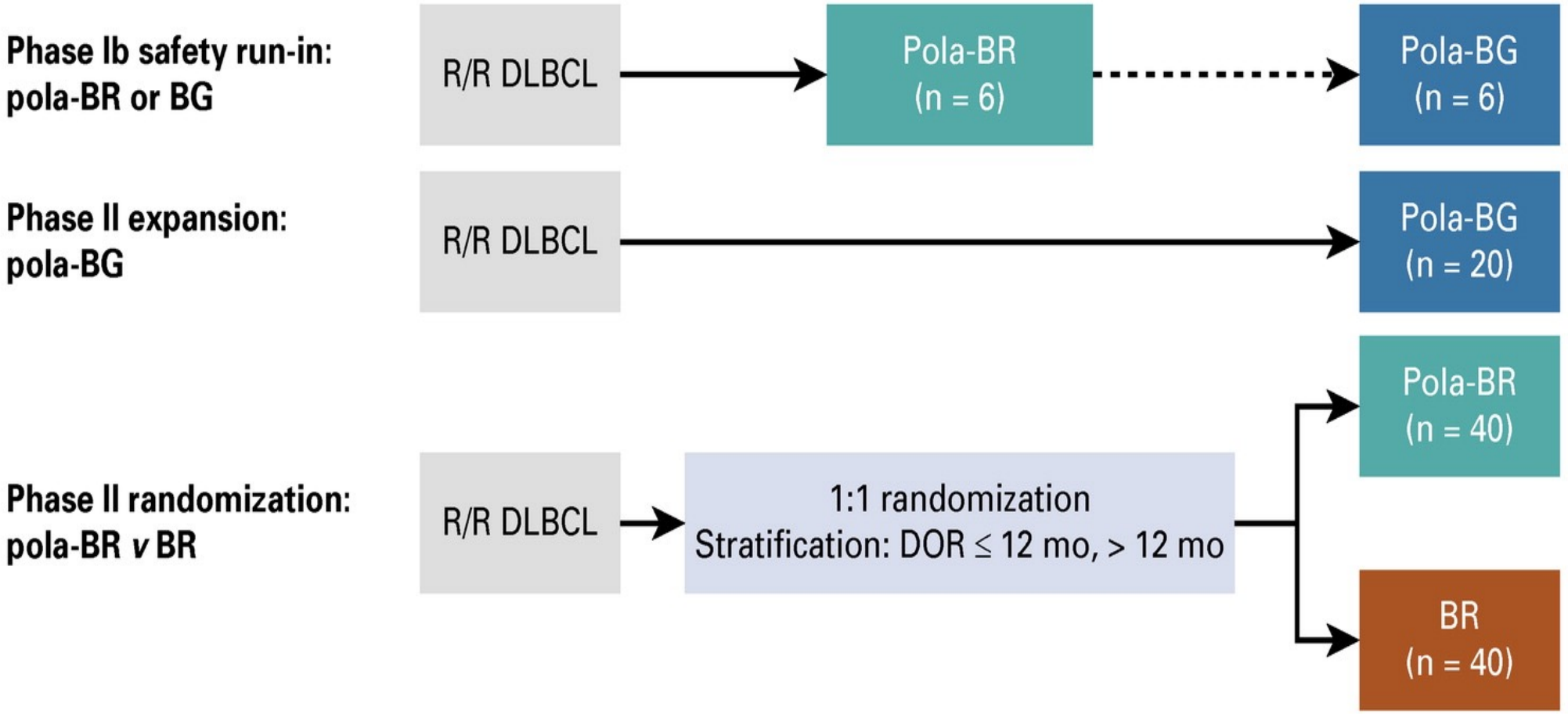
Polatuzumab vedotin



1. Dornan D, et al. Blood 2009;114:2721–9; 2. Polson AG, et al. Expert Opin Invest Drugs 2011;20:75–85; 3. Doronina SO, et al. Nat Biotechnol 2003;21:778–84; 4. Tilly H, et al. Lancet Oncol 2019;20:998–1010.

Courtesy of Christopher R Flowers, MD, MS

Targeting CD79b: BR + Polatuzumab



 Sehn LH et al. *J Clin Oncol*. 2020;38(2):155-165. Courtesy of Christopher R Flowers, MD, MS

R-Benda vs R-Benda + Pola: Response Rates

Outcome (IRC)	Pola-BR (n = 40)	BR (n = 40)
End of treatment		
Objective response	45.0%	17.5%
Complete response	40.0%	17.5%
Best Response		
Objective response	62.5%	25.0%
Complete response	50.0%	22.5%
Median duration response	12.6 months	7.7 months

Sehn LH et al. *J Clin Oncol*. 2020;38(2):155-165.

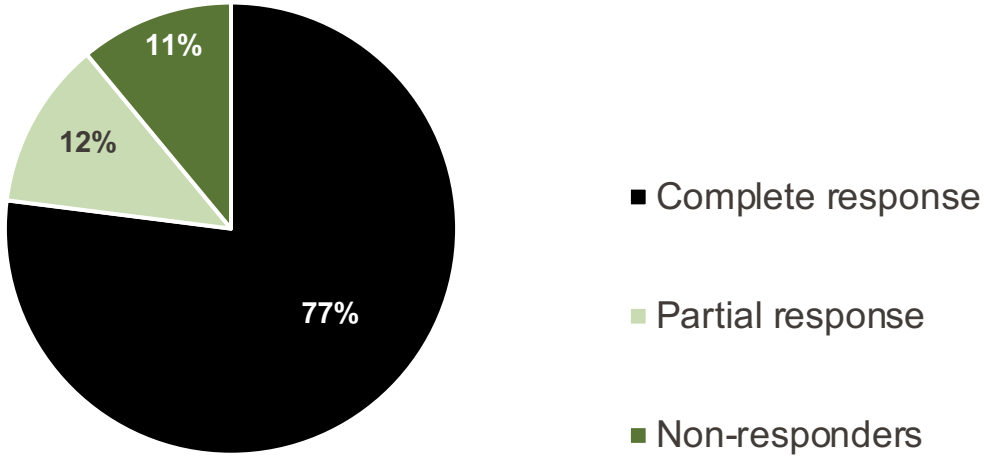
Courtesy of Christopher R Flowers, MD, MS

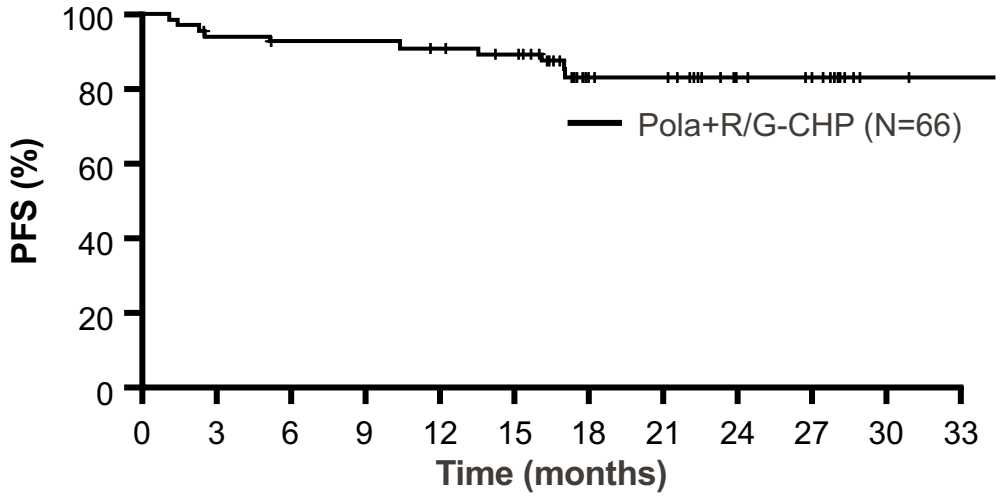
POLARIX Study: Polatuzumab Vedotin with Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (Pola-R-CHP) Versus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP) Therapy in Patients with Previously Untreated Diffuse Large B-Cell Lymphoma

Hervé Tilly, Franck Morschhauser, Laurie H. Sehn, Jonathan W. Friedberg, Marek Trněný, Jeff P. Sharman, Charles Herbaux, John M. Burke, Matthew Matasar, Shinya Rai, Koji Izutsu, Neha Mehta-Shah, Lucie Oberic, Adrien Chauchet, Wojciech Jurczak, Yuqin Song, Richard Greil, Larysa Mykhalska, Juan Miguel Bergua Burgués, Matthew C. Cheung, Antonio Pinto, Ho-Jin Shin, Greg Hapgood, Eduardo Munhoz, Pau Abrisqueta, Jyh-Pyng Gau, Jamie Hirata, Yanwen Jiang, Mark Yan, Calvin Lee, Christopher Flowers, Gilles Salles

Courtesy of Christopher R Flowers, MD, MS

Pola+R/G-CHP demonstrated activity in 1L DLBCL



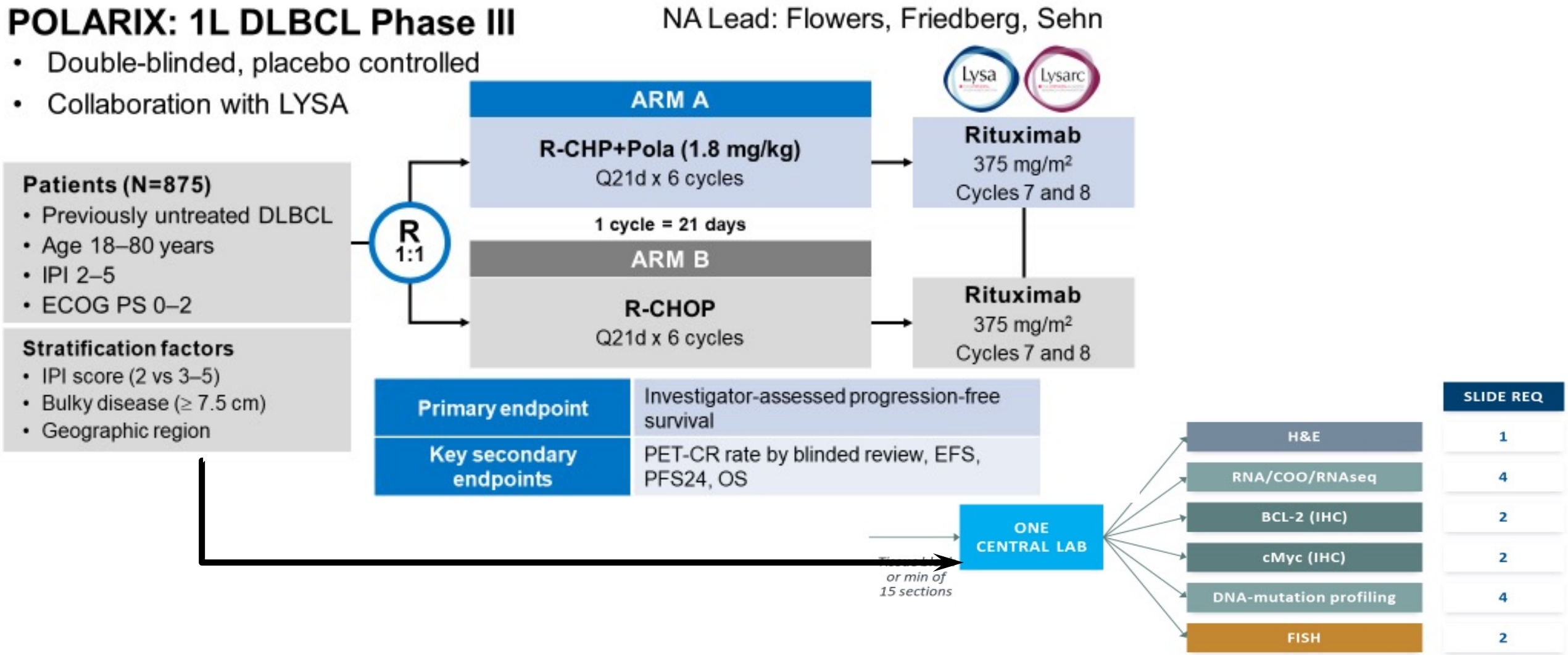


ADC, antibody–drug conjugate; G, obinutuzumab.

1. Dornan D, et al. Blood 2009;114:2721–9; 2. Polson AG, et al. Expert Opin Invest Drugs 2011;20:75–85;
3. Doronina SO, et al. Nat Biotechnol 2003;21:778–84; 4. Tilly H, et al. Lancet Oncol 2019;20:998–1010.

Courtesy of Christopher R Flowers, MD, MS

POLARIX: A randomized double-blinded study



Courtesy of Christopher R Flowers, MD, MS

POLARIX: Key endpoints and analysis timing

Key endpoints	
Primary endpoint	**Progression-free survival (Investigator-assessed)**
Secondary endpoints	Event-free survival Complete response rate at end of treatment (PET/CT, IRC-assessed) Disease-free survival Overall survival
Safety endpoints	Incidence, nature, and severity of adverse events

Statistical design and timing of primary analysis:

- 875 patients, all on study for ≥24 months with approximately 228 PFS events, were required for the primary analysis. This occurred on June 28, 2021 (clinical cut-off date)
- Median follow up at the primary analysis was 28.2 months

Tilly H et al. *ASH* 2021;Abstract LBA1.

Courtesy of Christopher R Flowers, MD, MS

POLARIX: Baseline characteristics

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

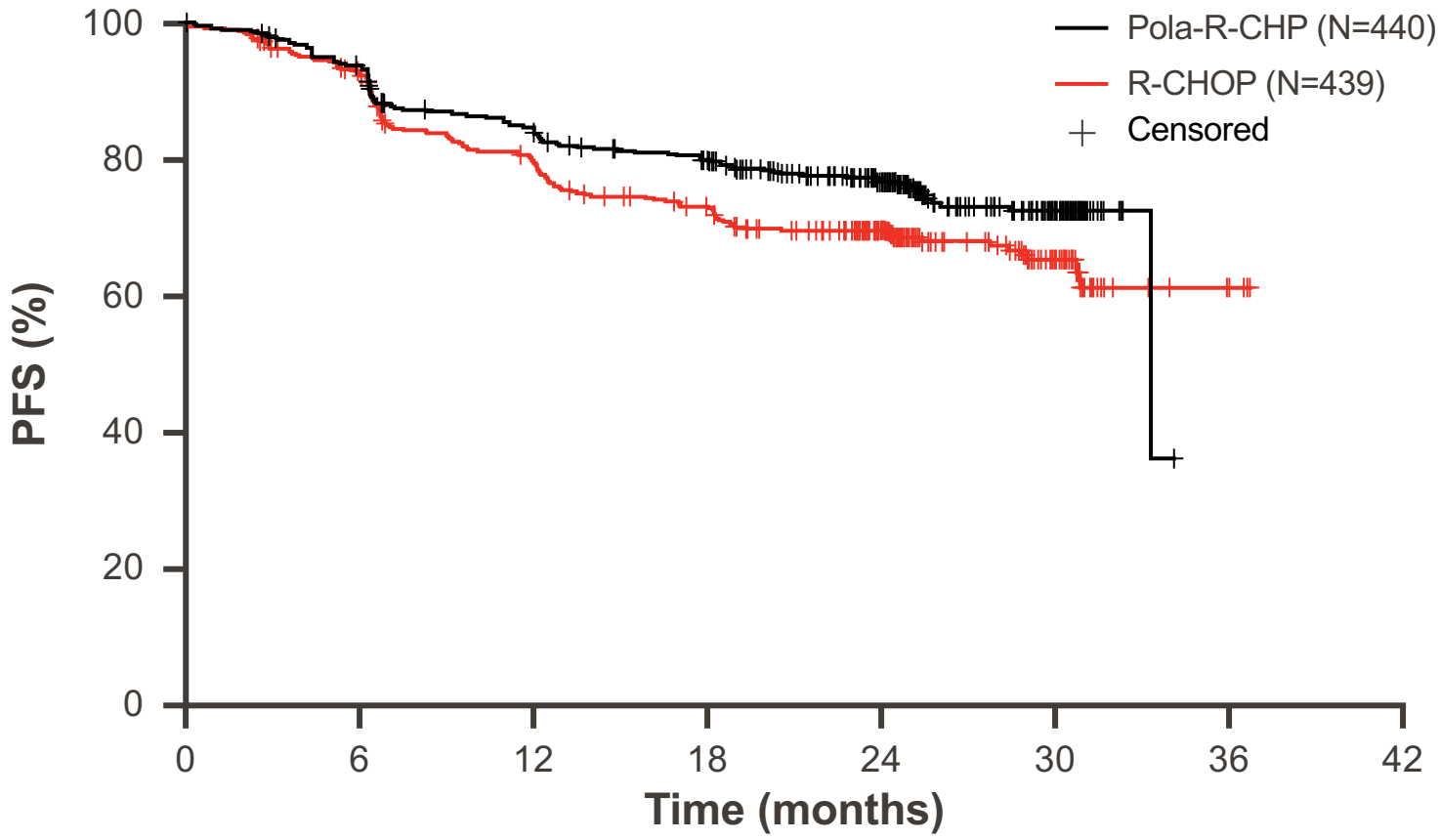
*In the Pola-R-CHP and R-CHOP groups, respectively, the numbers of patients evaluable for cell-of-origin were 330 and 338, with IHC for MYC/BCL2 expression were 362 and 366, and with FISH for *MYC/BCL2/BCL6* rearrangements were 331 and 334.
ABC, activated B-cell; FISH, fluorescence in situ hybridization; GCB, germinal center B-cell; LDH, lactate dehydrogenase.

Tilly H et al. *ASH* 2021;Abstract LBA1.

Courtesy of Christopher R Flowers, MD, MS

POLARIX: Primary endpoint: Progression-free survival

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



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

HR 0.73 (P<0.02)

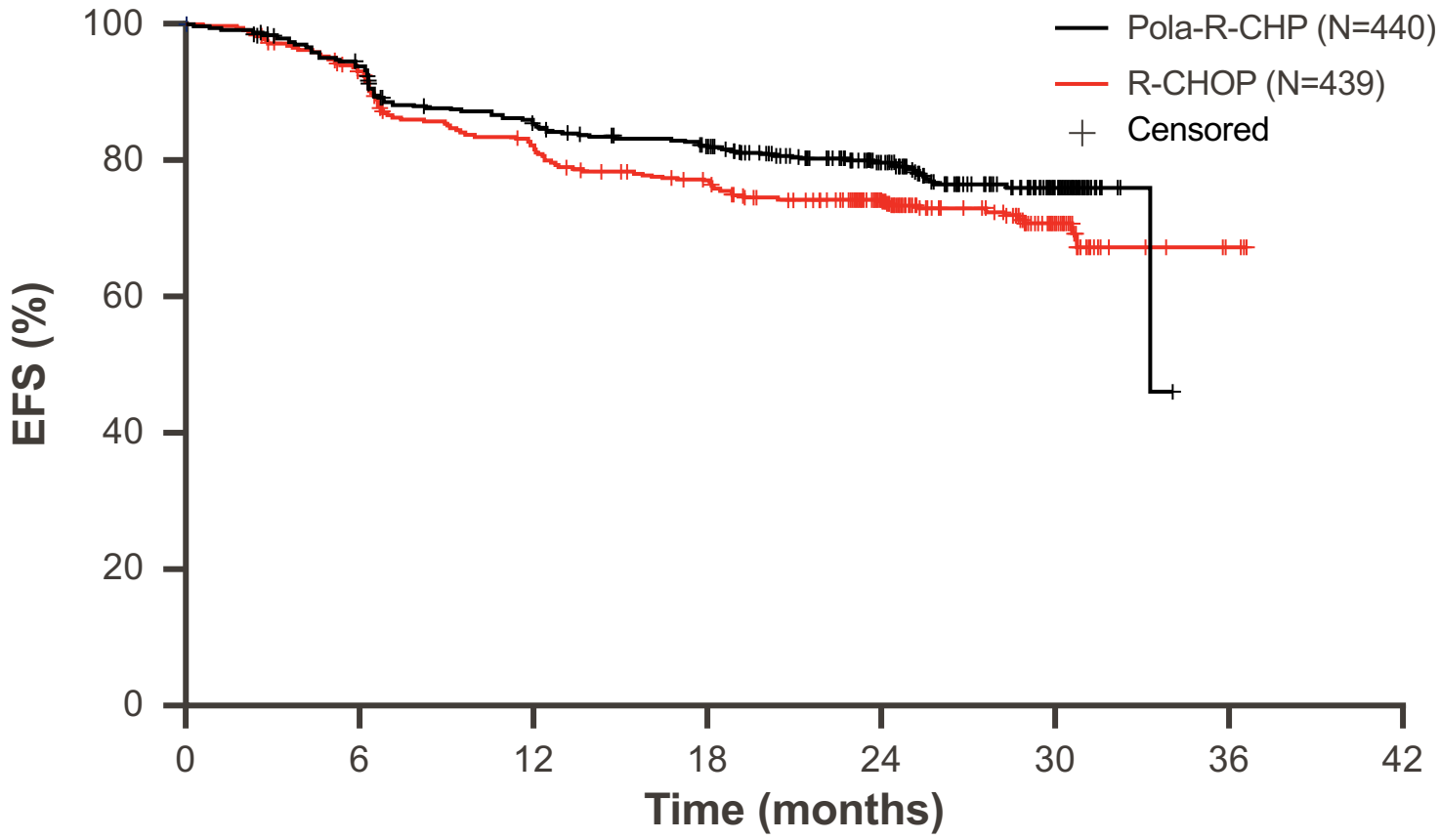
95% CI: 0.57, 0.95

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

Tilly H et al. *N Engl J Med* 2022;386(4):351-63; *ASH* 2021;Abstract LBA1.

Courtesy of Christopher R Flowers, MD, MS

POLARIX: Event-free survival



HR 0.75 **(P=0.02)**

95% CI: 0.58, 0.96

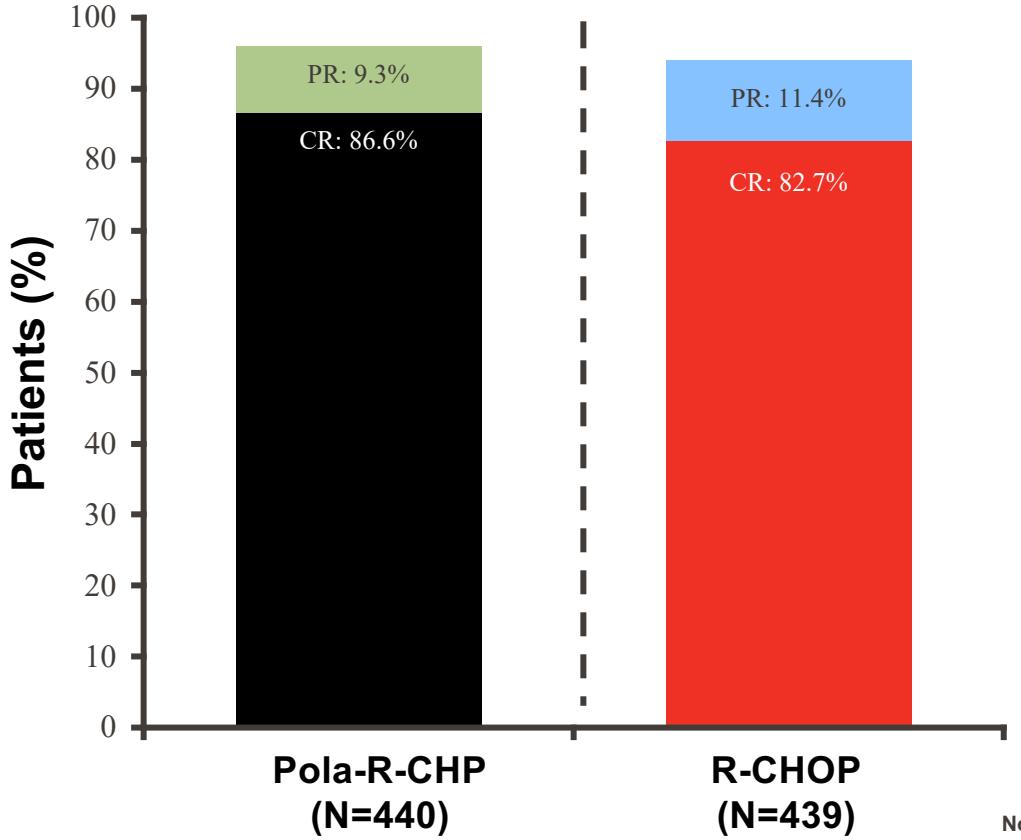
No. of patients at risk								
Pola-R-CHP	440	402	348	323	243	78	NE	NE
R-CHOP	439	386	327	294	218	78	3	NE

Tilly H et al. *N Engl J Med* 2022;386(4):351-63; *ASH* 2021;Abstract LBA1.

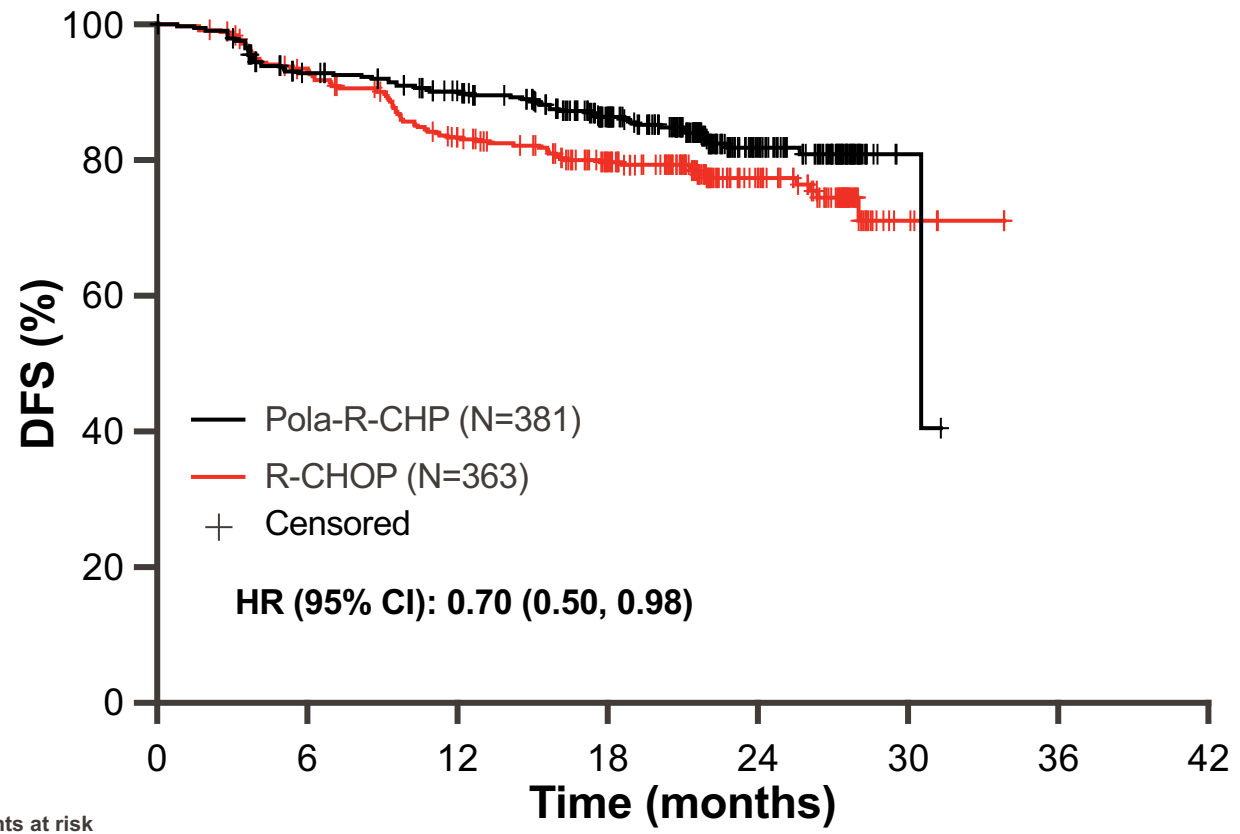
Courtesy of Christopher R Flowers, MD, MS

POLARIX: Response rates and disease-free survival

Best overall response



Disease-free survival



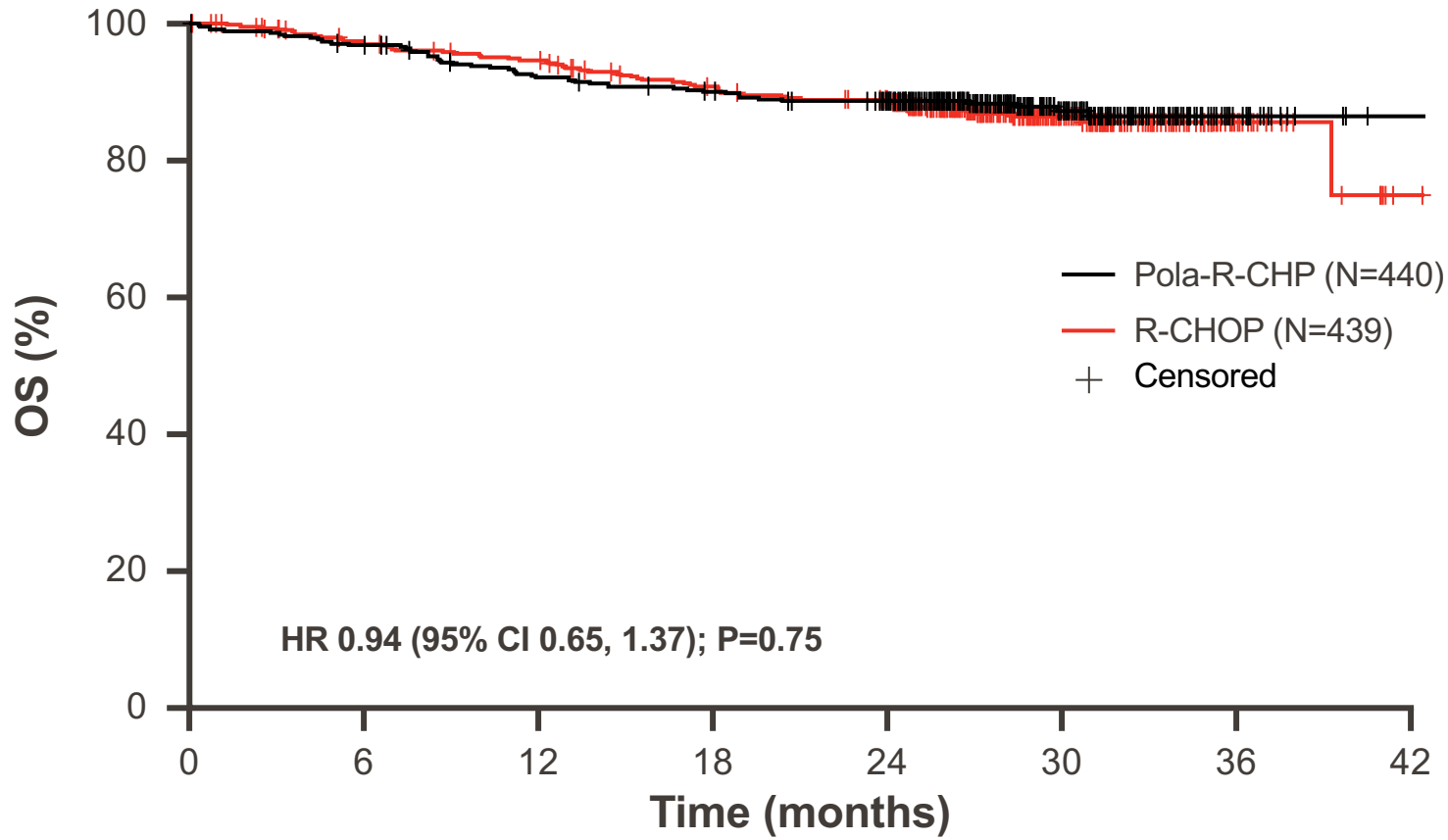
No. of patients at risk

Pola-R-CHP	381	342	322	266	106	2	NE	NE
R-CHOP	363	326	282	238	96	5	NE	NE

Tilly H et al. *ASH* 2021;Abstract LBA1.

Courtesy of Christopher R Flowers, MD, MS

POLARIX: Overall survival

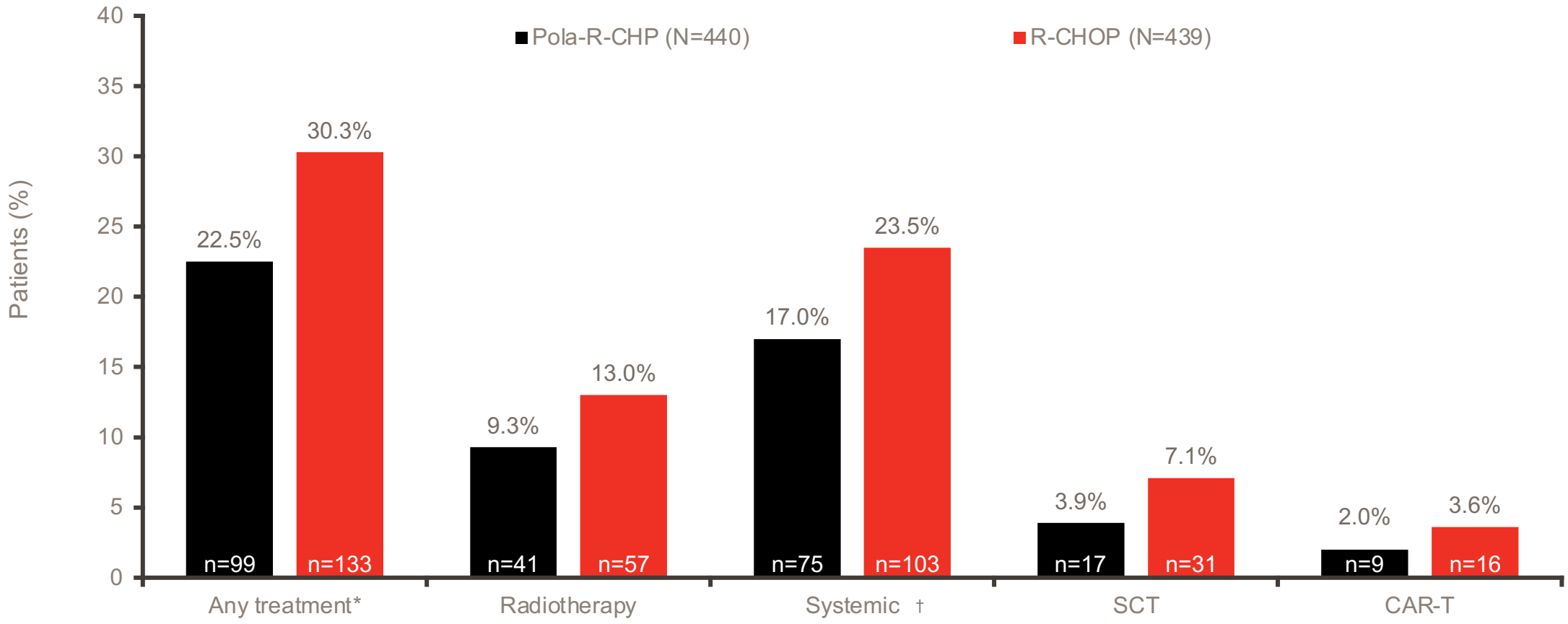


No. of patients at risk								
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	1

Tilly H et al. *N Engl J Med* 2022;386(4):351-63; *ASH* 2021;Abstract LBA1.

Courtesy of Christopher R Flowers, MD, MS

POLARIX: Patients receiving subsequent treatments



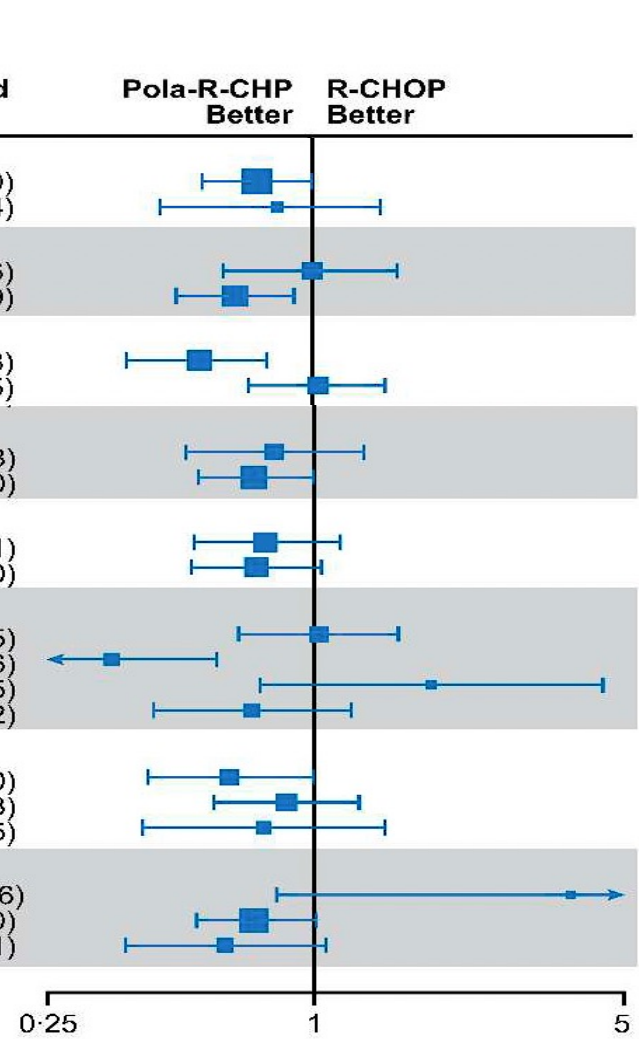
Data cut-off: June 28, 2021. *Subsequent lymphoma treatment was defined as non-protocol anti-lymphoma therapy; †Includes any monotherapy, multi-drug, or cell-based regimen.
CAR-T, chimeric antigen receptor T-cell therapy; SCT, stem cell transplant.

Tilly H et al. *ASH* 2021;Abstract LBA1.

Courtesy of Christopher R Flowers, MD, MS

POLARIX: Subgroup Analysis

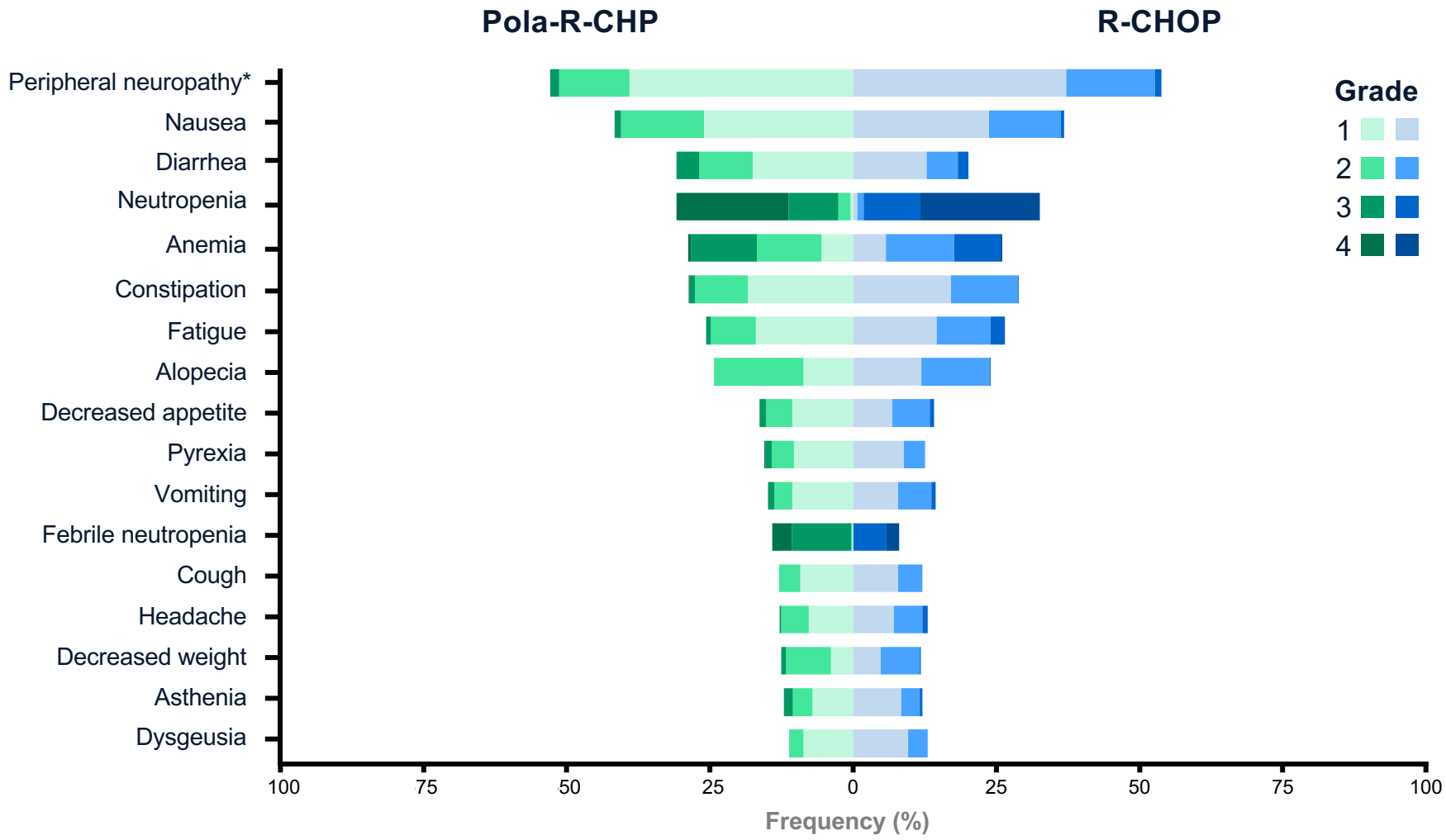
Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)



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

Courtesy of Christopher R Flowers, MD, MS

POLARIX: Common adverse events



Tilly H et al. *ASH* 2021;Abstract LBA1.

Courtesy of Christopher R Flowers, MD, MS

Next Steps in Firstline DLBCL Trial Design

- Improve eligibility assessment and enrollment strategies to reduce DTI
- Incorporate Novel Agents in SMART Start trials
  - Polatuzumab
  - Mosunetuzumab
  - Tafasitamab
  - Ibrutinib
  - Lenalidomide
- cfDNA Surrogate for response at imaging-paired time points for validation/comparison
- Integrate understanding of biological subsets into trial design

Courtesy of Christopher R Flowers, MD, MS

Agenda

Introduction: Overview of Diffuse Large B-Cell Lymphoma (DLBCL)

MODULE 1: The POLARIX Trial – Dr Flowers

MODULE 2: Clinical Investigator Survey

MODULE 3: Ongoing Trials in DLBCL – Prof Nowakowski

MODULE 4: Up-Front Treatment for Older Patients with DLBCL – Dr Mehta-Shah

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TO PRACTICE

DLBCL Clinical Investigator Survey "Top Ten"

How quickly does treatment need to be initiated?

Perspectives on the POLARIX trial

First-line treatment of DLBCL

First-line treatment for older patients with DLBCL

First-line treatment for patients with higher-risk DLBCL

First-line treatment of DLBCL in patients with comorbidities

Transformed follicular lymphoma and chronic lymphocytic leukemia

CNS prophylaxis

Chimeric antigen receptor (CAR) T-cell therapy

Newly approved agents in relapsed disease

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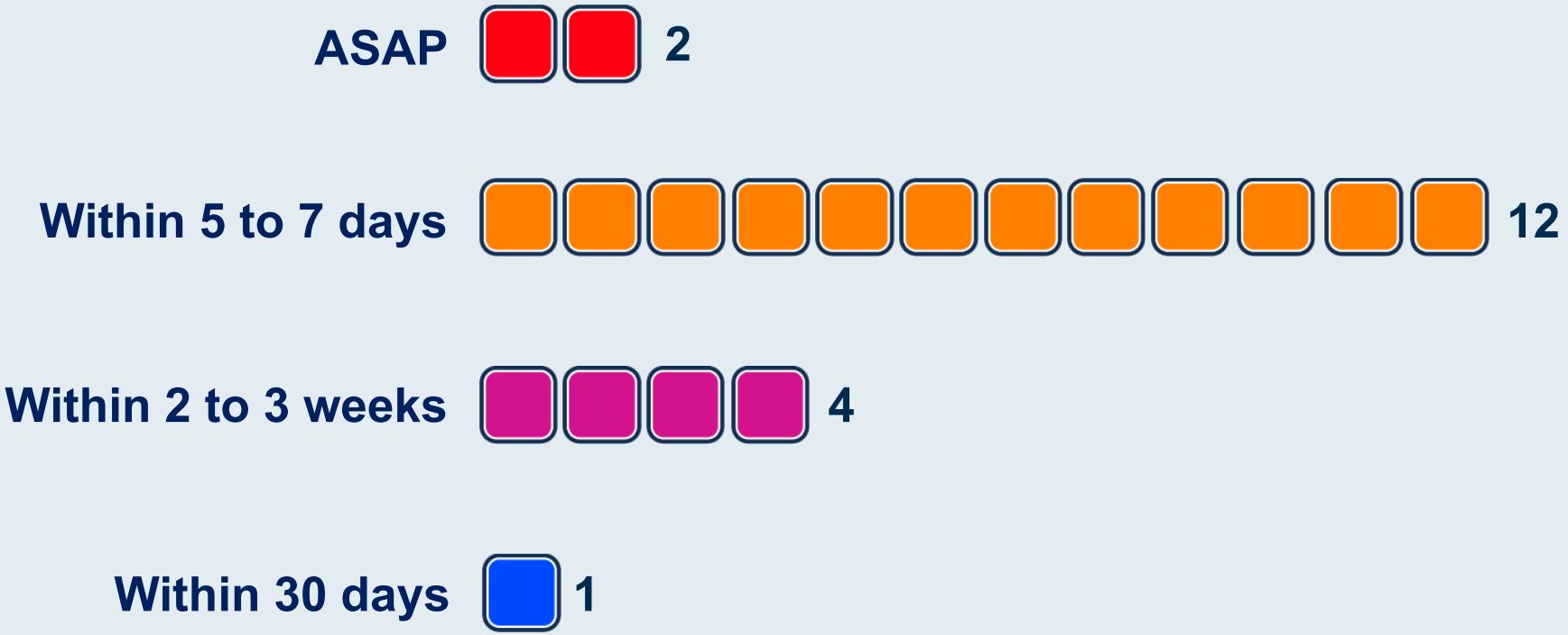
For a patient who is clinically stable with newly diagnosed advanced-stage diffuse large B-cell lymphoma (DLBCL), within what time period should treatment be initiated?



Survey of Lymphoma Clinical Investigators

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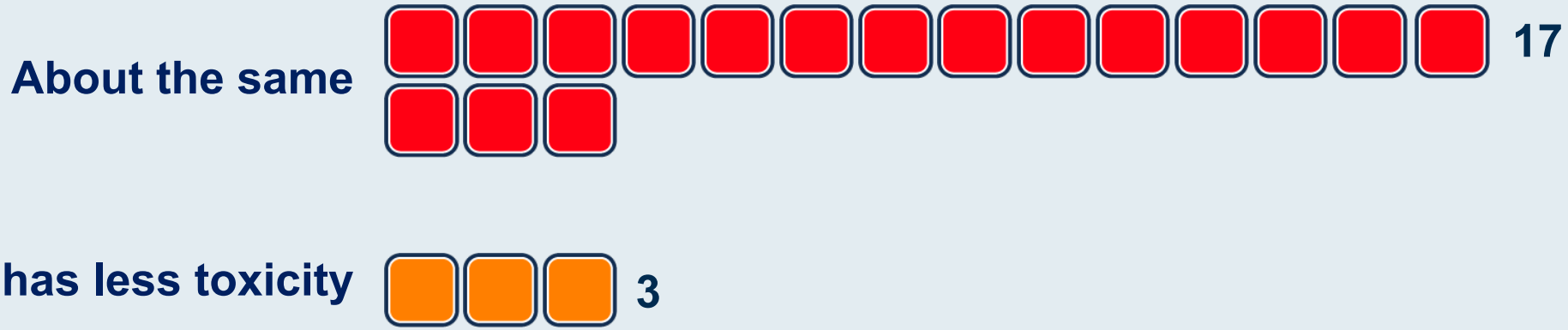
If future data continue not to demonstrate an overall survival advantage with polatuzumab vedotin in combination with R-CHP over R-CHOP when used as up-front therapy for DLBCL, do you think the clinical benefit with this regimen is greater than the risk?

Based on available evidence and your own experience, how would you compare the global tolerability/toxicity of polatuzumab vedotin in combination with R-CHP to that of R-CHOP when used as up-front therapy for DLBCL?



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The peripheral neuropathy associated with polatuzumab vedotin is generally reversible in the majority of patients.

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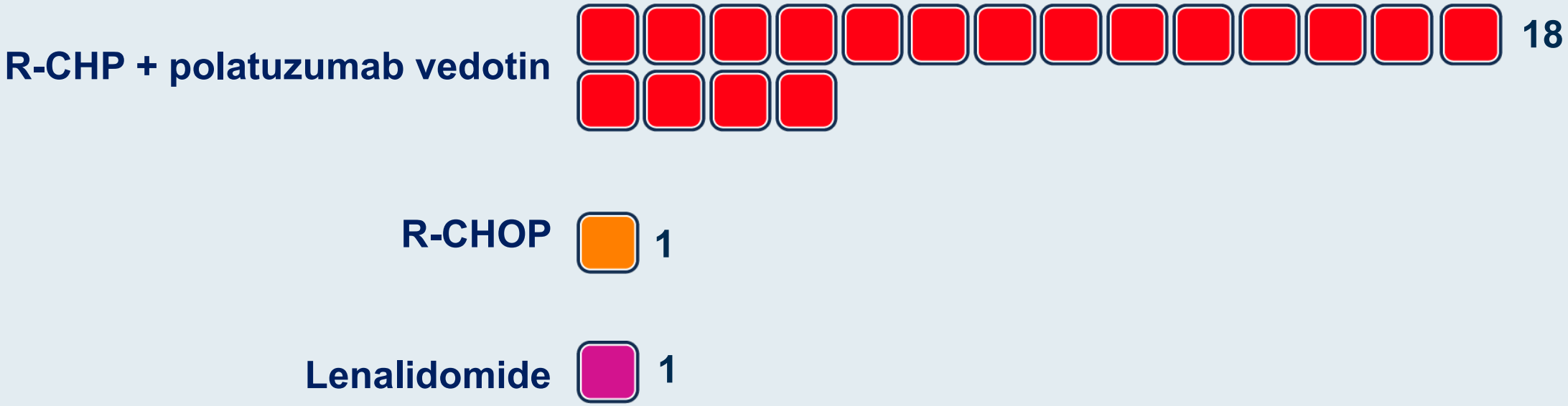
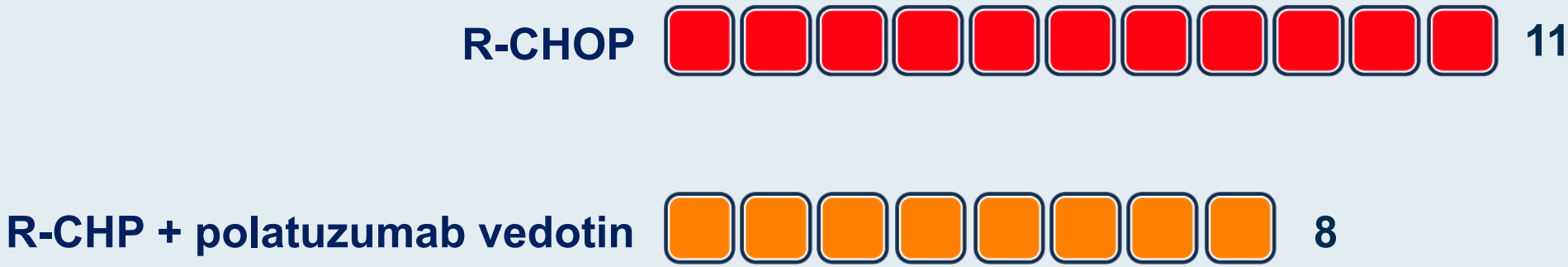
RESEARCH
TO PRACTICE

Regulatory and reimbursement issues aside, which first-line therapy would you generally recommend for an otherwise healthy 65-year-old patient with Stage IV activated B-cell (ABC)-type DLBCL?



Survey of Lymphoma Clinical Investigators

Regulatory and reimbursement issues aside, which first-line therapy would you generally recommend for an otherwise healthy 65-year-old patient with Stage IV germinal center B-cell (GCB)-type DLBCL?



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DLBCL Clinical Investigator Survey "Top Ten"

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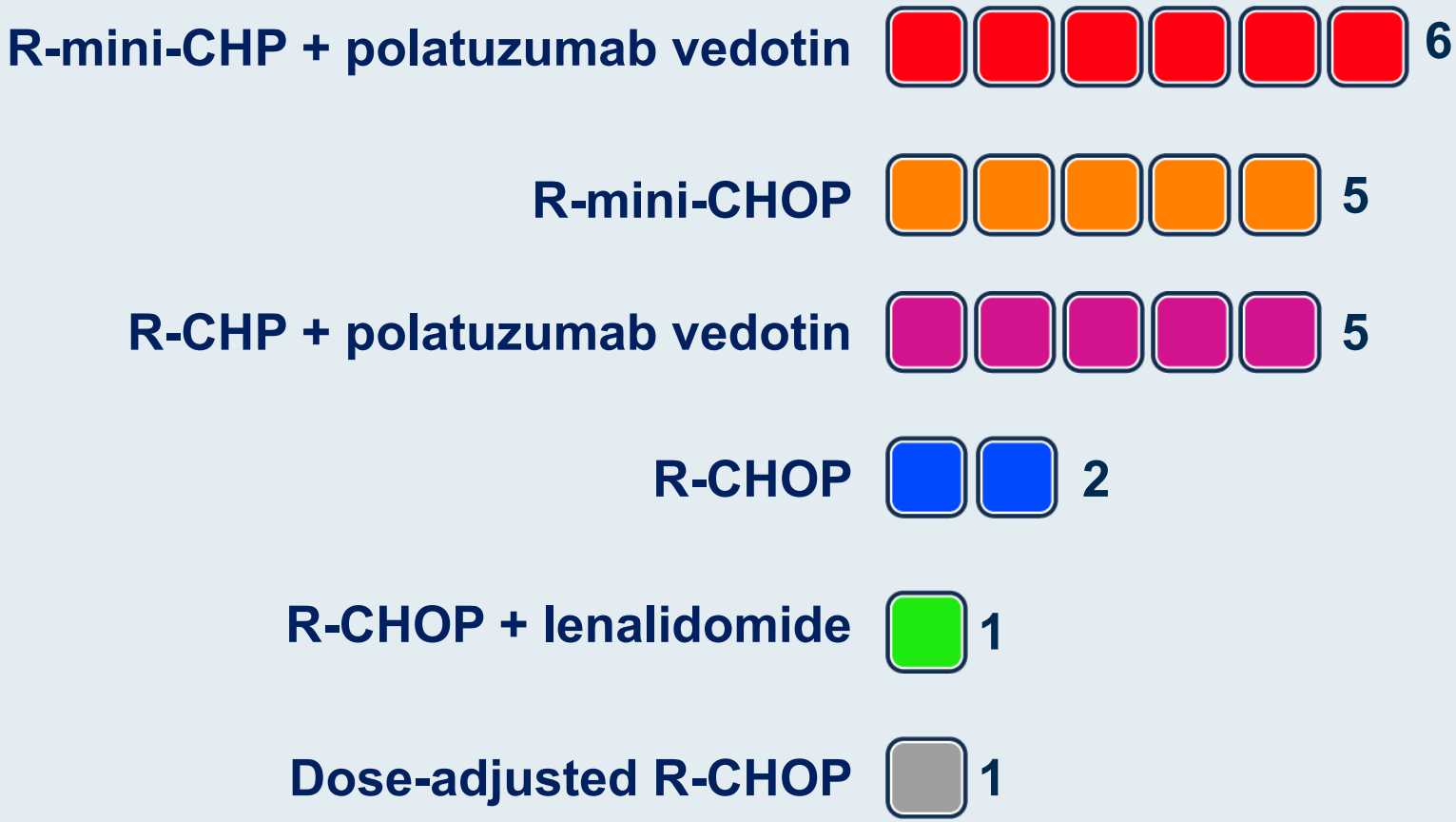
RTP
RESEARCH
TO PRACTICE

Regulatory and reimbursement issues aside, which first-line therapy would you generally recommend for an otherwise healthy 80-year-old patient with Stage IV ABC-type DLBCL?



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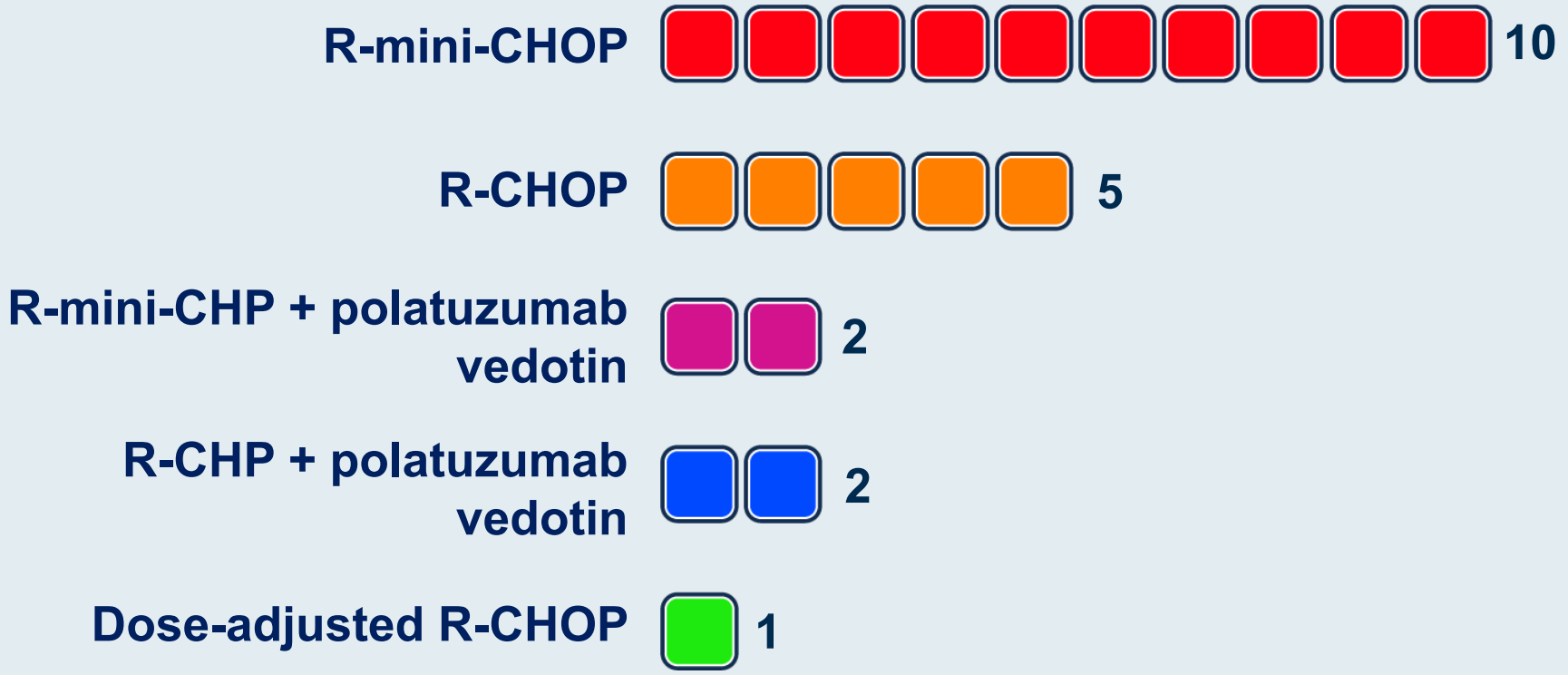
Regulatory and reimbursement issues aside, which first-line therapy would you generally recommend for an otherwise healthy 80-year-old patient with Stage IV GCB-type DLBCL?



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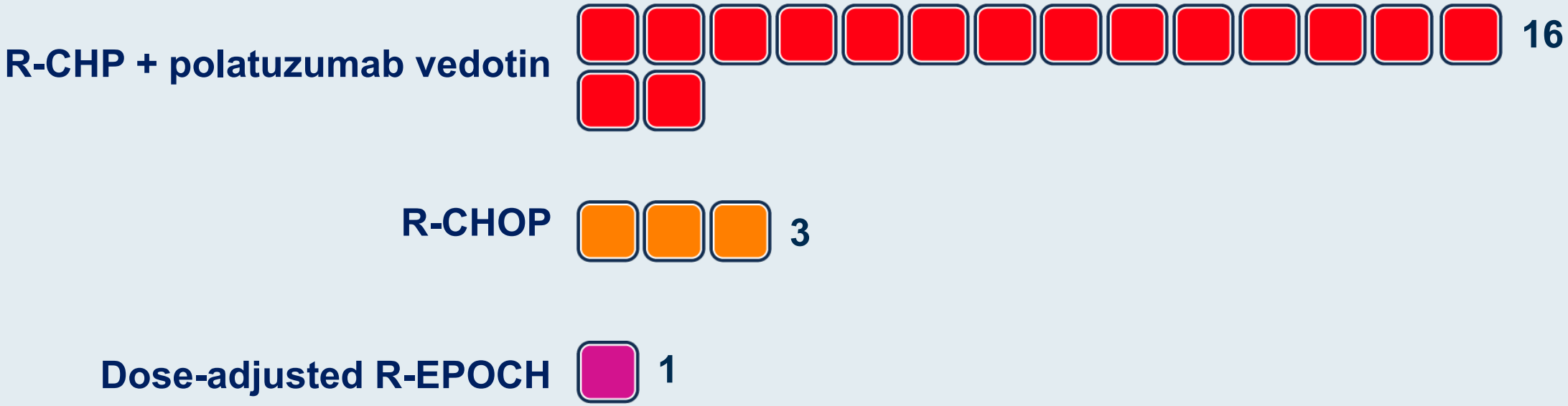
RESEARCH
TO PRACTICE

Regulatory and reimbursement issues aside, which first-line therapy would you generally recommend for an otherwise healthy 65-year-old patient with Stage IV double-expressor DLBCL?



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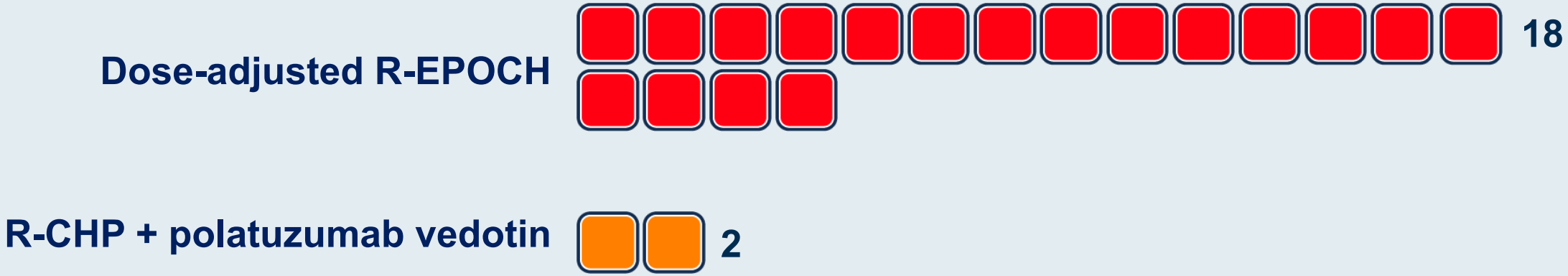
Regulatory and reimbursement issues aside, which first-line therapy would you generally recommend for an otherwise healthy 65-year-old patient with Stage IV double-hit DLBCL?



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ZUMA-12 Study Demonstrates 78% Complete Response Rate as Part of First-Line Treatment in Newly Diagnosed High-Risk Large B-Cell Lymphoma

December 13, 2021

"Primary results were announced from ZUMA-12, a global, multicenter, single-arm, open-label Phase 2 study evaluating axicabtagene ciloleucel as part of first-line treatment in patients with high-risk large B-cell lymphoma (LBCL). This is the first study to evaluate CAR T-cell therapy as part of first-line therapy in high-risk LBCL. The study is based on the desire to utilize potential curative treatment as quickly as possible and the hypothesis that earlier use of CAR T-cell therapy when T cells are healthier may produce better outcomes. The data were presented in an oral session during the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition (Abstract #739).

After a single infusion of axicabtagene ciloleucel, 89% of evaluable patients achieved a response (ORR) (n=37 evaluable for efficacy), including 78% of patients with a complete response (CR) at a median follow-up of 15.9 months. CR rate was consistent among key subgroups. Among evaluable patients, median time to response was one month. At time of data cut-off, 73% of evaluable patients had ongoing responses. Medians for duration of response (DOR), event-free survival (EFS), and progression-free survival (PFS) were not yet reached, with 12-month estimates of 81%, 73%, and 75%, respectively, and an estimated 12-month OS rate of 91%."

https://www.gilead.com/news-and-press/press-room/press-releases/2021/12/yescarta-zuma12-study-demonstrates-78-complete-response-rate-as-part-of-firstline-treatment-in-newly-diagnosed-highrisk-large-bcell-lymphoma

RTP RESEARCH TO PRACTICE

ZUMA-12: A Phase II Study Evaluating Axicabtagene Ciloleucel as Part of First-Line Treatment for Patients with High-Risk Large B-Cell Lymphoma

Variable	N = 40 (median age 61) 25% DH/TH Median F/U = 15.9 months
DS 4/5 at PET-2	48%/53%
Complete Response	78%
Median PFS	NR
G3 CRS	8%
G3 ICANS	23%

Neelapu et al. ASH 2021 Abs # 739

RTP RESEARCH TO PRACTICE

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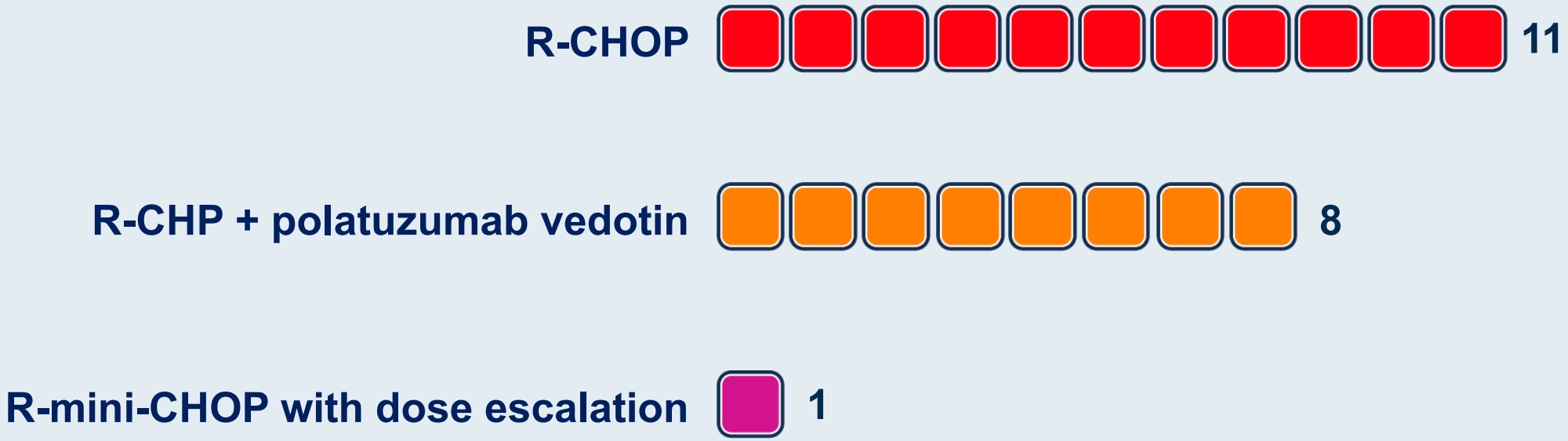
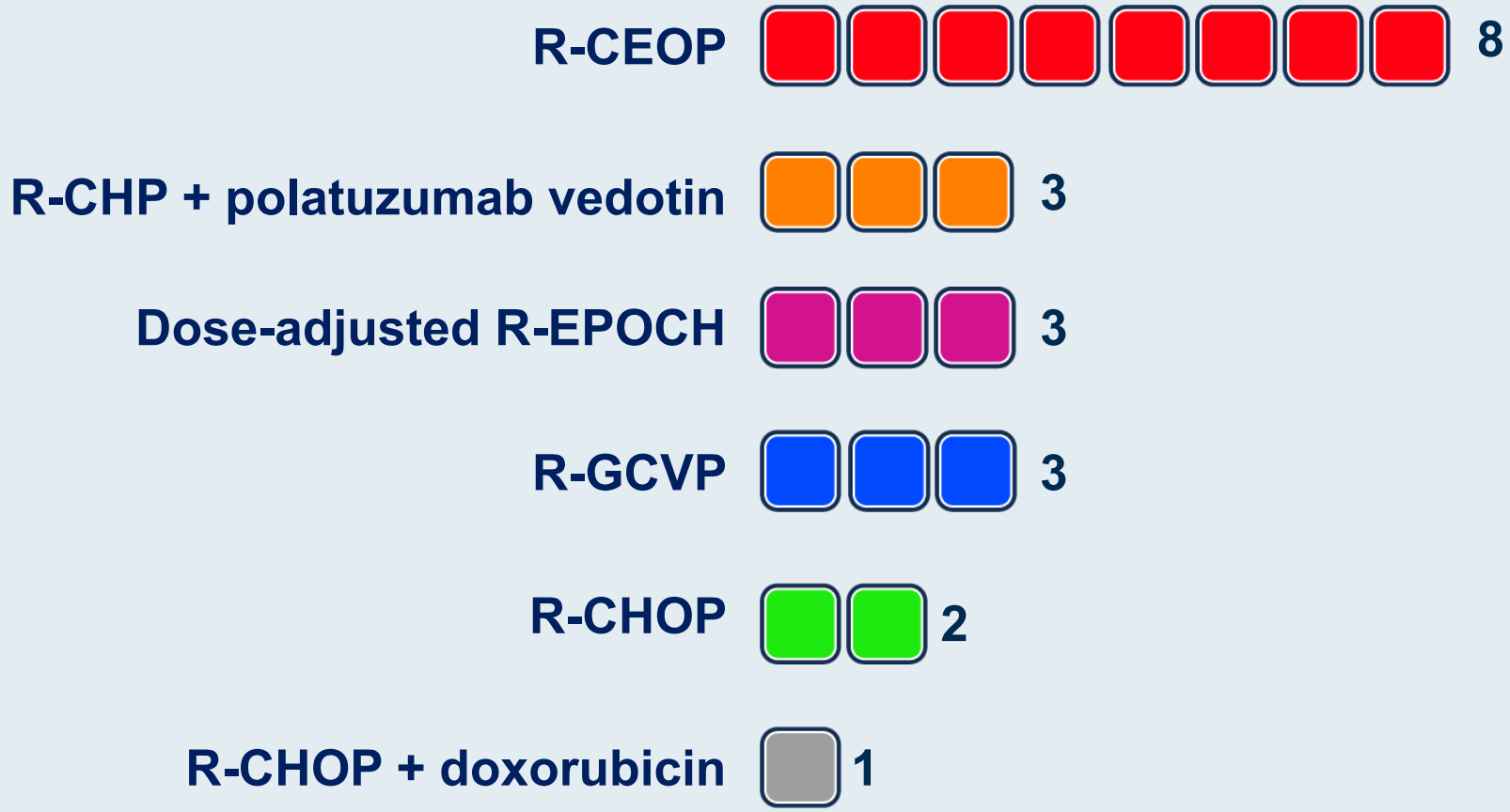
RESEARCH
TO PRACTICE

A 65-year-old patient with a history of smoking, mild COPD and hypertension presents with Stage IV GCB-type DLBCL. Which initial therapy would you most likely recommend?



Survey of Lymphoma Clinical Investigators

A 65-year-old woman with a history of congestive heart failure and a left ventricular ejection fraction (LVEF) of 45% presents with Stage IV GCB-type DLBCL. Which initial therapy would you most likely recommend?



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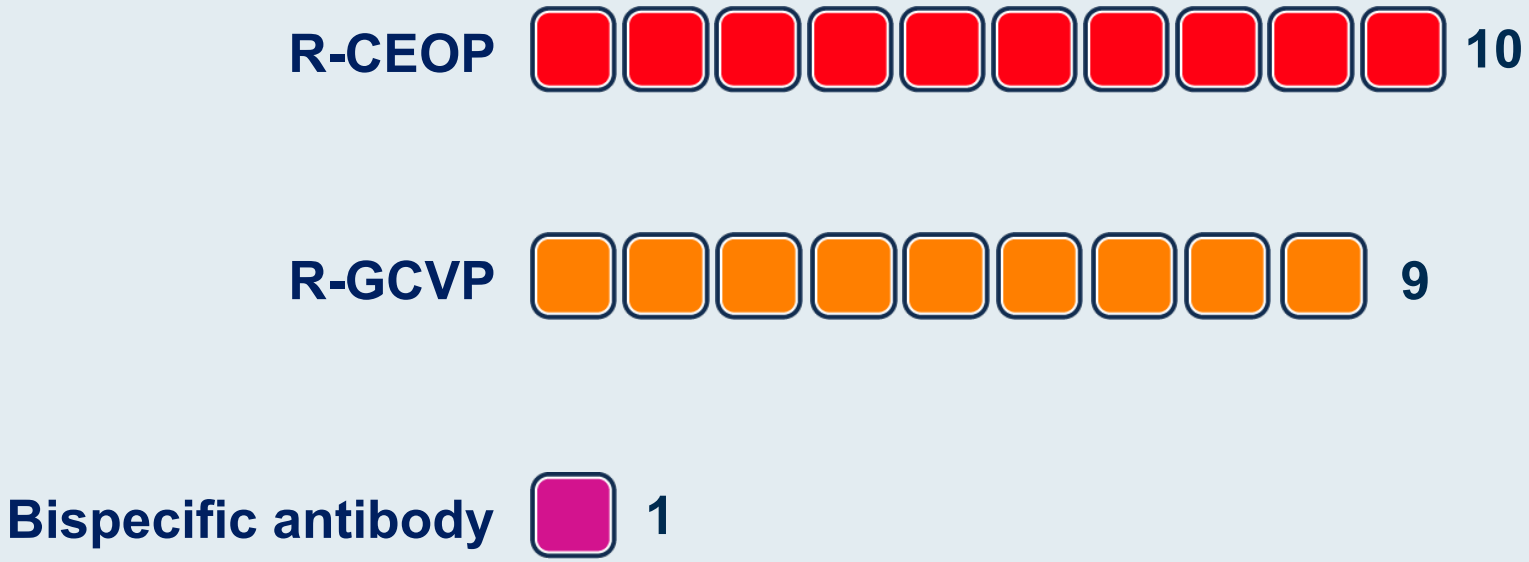
A 65-year-old woman with a history of congestive heart failure and an LVEF of 30% presents with Stage IV GCB-type DLBCL. Which initial therapy would you most likely recommend?



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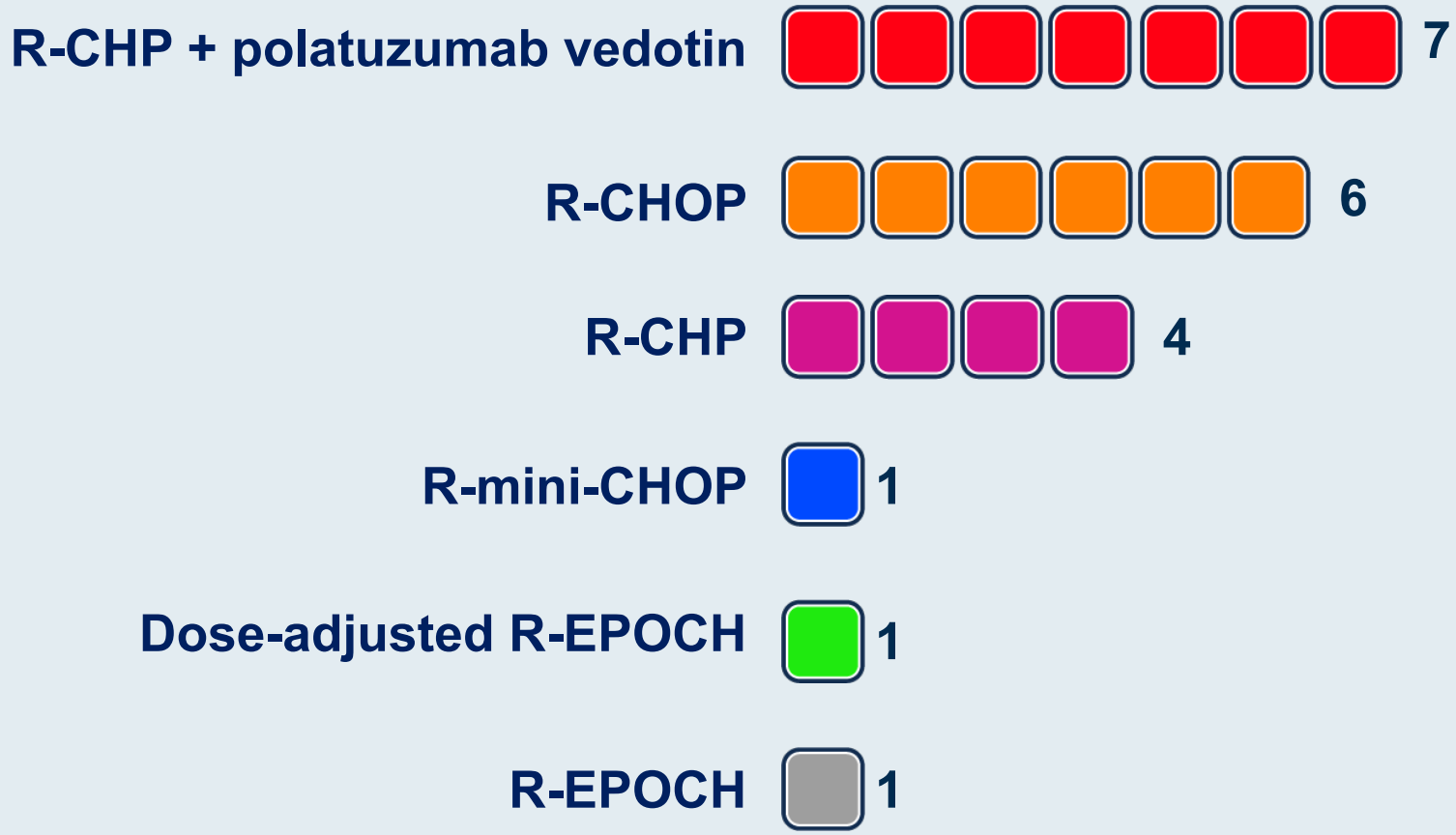
A 65-year-old patient with a history of poorly controlled diabetes mellitus and sensory diabetic peripheral neuropathy presents with Stage IV GCB-type DLBCL. Which initial therapy would you most likely recommend?



Survey of Lymphoma Clinical Investigators

DLBCL Clinical Investigator Survey "Top Ten"

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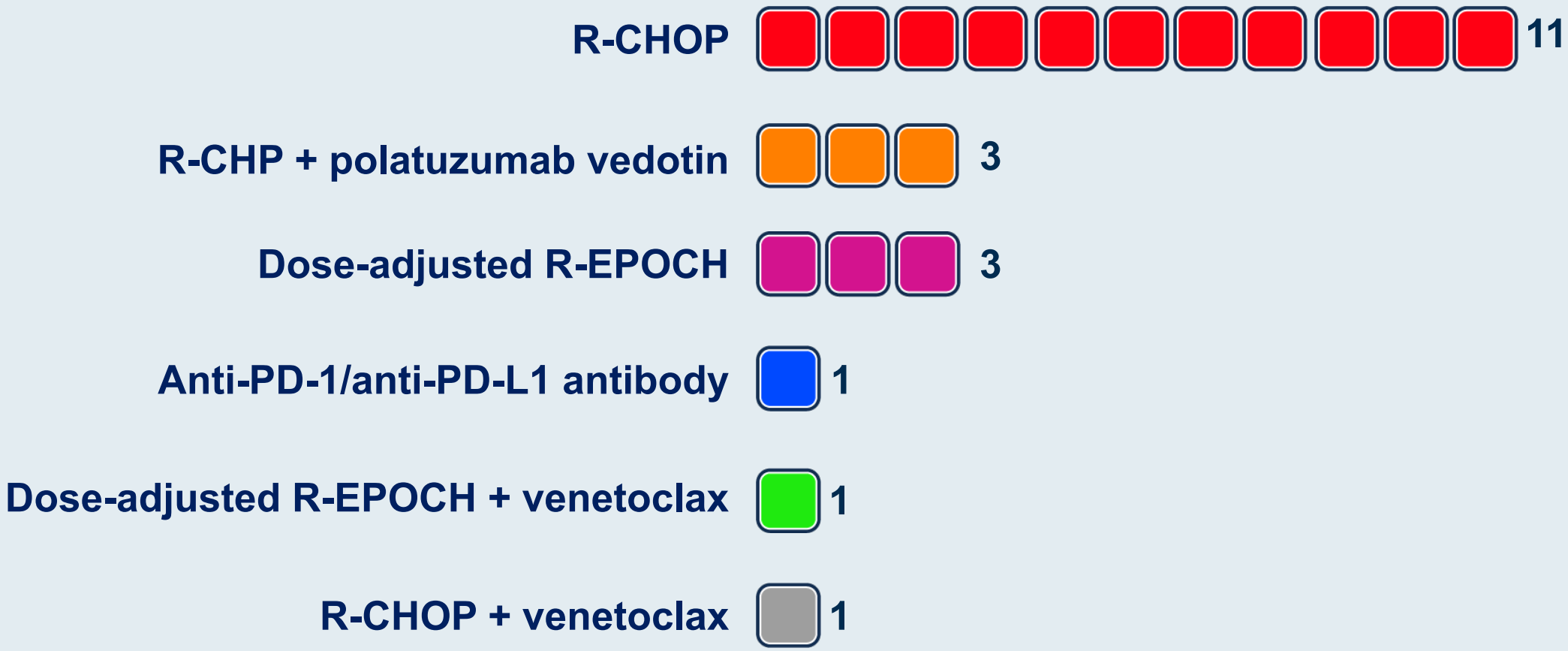
- **Transformed follicular lymphoma and chronic lymphocytic leukemia**
- CNS prophylaxis
- Chimeric antigen receptor (CAR) T-cell therapy
- Newly approved agents in relapsed disease

A 65-year-old otherwise healthy patient with a history of chronic lymphocytic leukemia treated with ibrutinib presents with Richter's transformation. What would you recommend?



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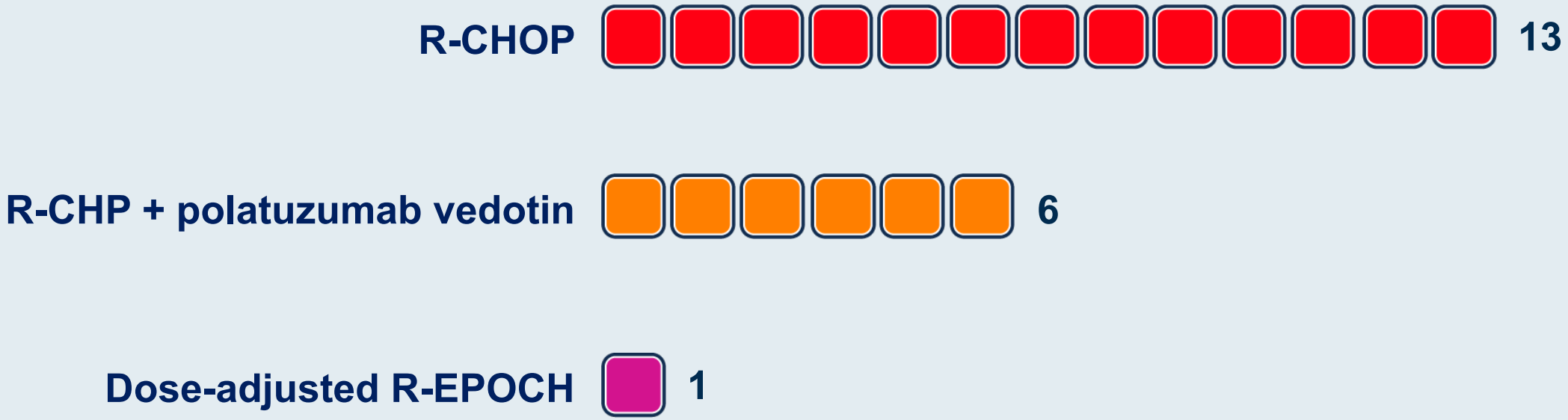
A 65-year-old otherwise healthy patient with a history of follicular lymphoma (FL) treated with first-line bendamustine/rituximab (BR) presents with histologic transformation to DLBCL without double hit. What would you recommend?



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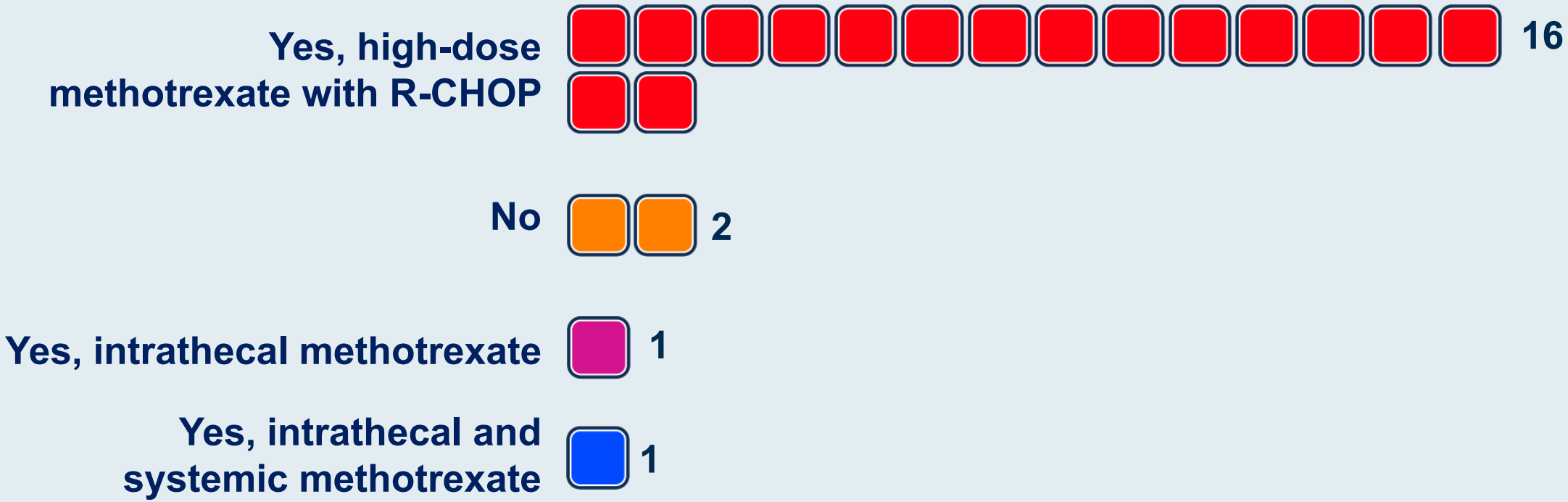
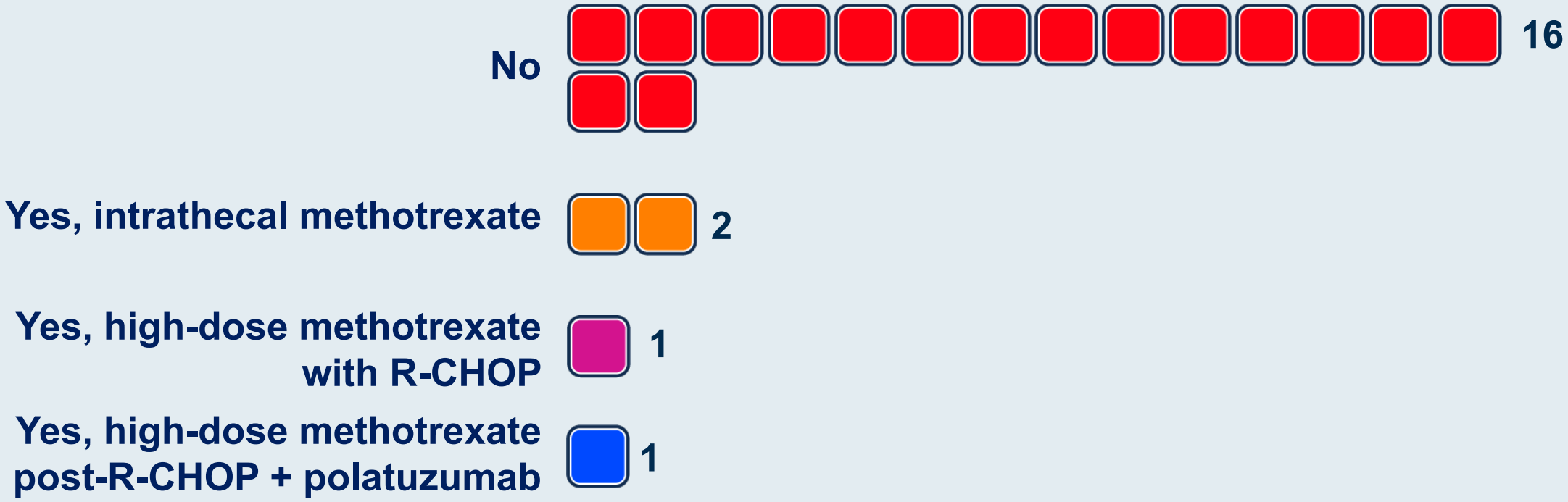
A 65-year-old man presents with fatigue and right testicular swelling. Biopsy confirms GCB-type DLBCL, and a PET scan is negative for distant disease with no marrow involvement. Would you recommend CNS prophylaxis?



Survey of Lymphoma Clinical Investigators

A 65-year-old man presents with fatigue, night sweats and palpable lymphadenopathy. Biopsy confirms GCB-type DLBCL. LDH is 300 U/L and a PET scan reveals diffuse bone marrow involvement. Would you recommend CNS prophylaxis?



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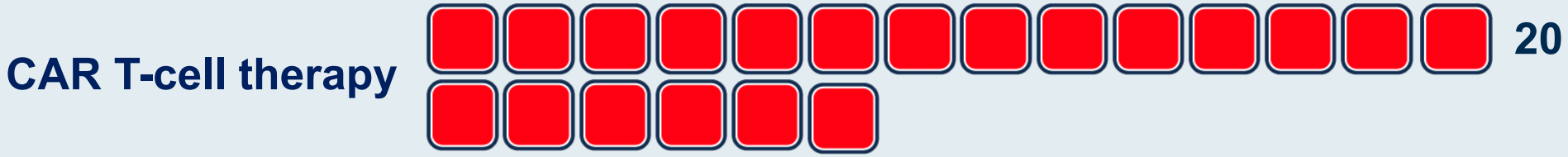
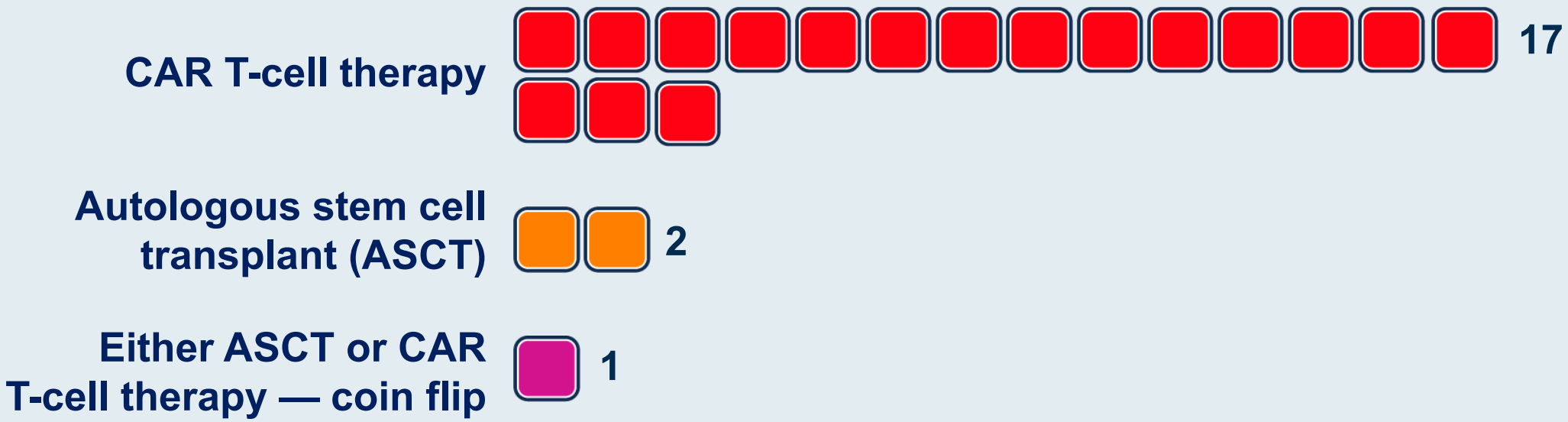
Which therapy would you generally recommend first for a 65-year-old patient with DLBCL who responds to R-CHOP and then R-DHAP followed by transplant on relapse but subsequently experiences disease progression?



Survey of Lymphoma Clinical Investigators

Regulatory and reimbursement issues aside, which second-line therapy would you recommend for a younger, transplant-eligible patient with DLBCL who experiences disease relapse 12 months after R-CHOP?



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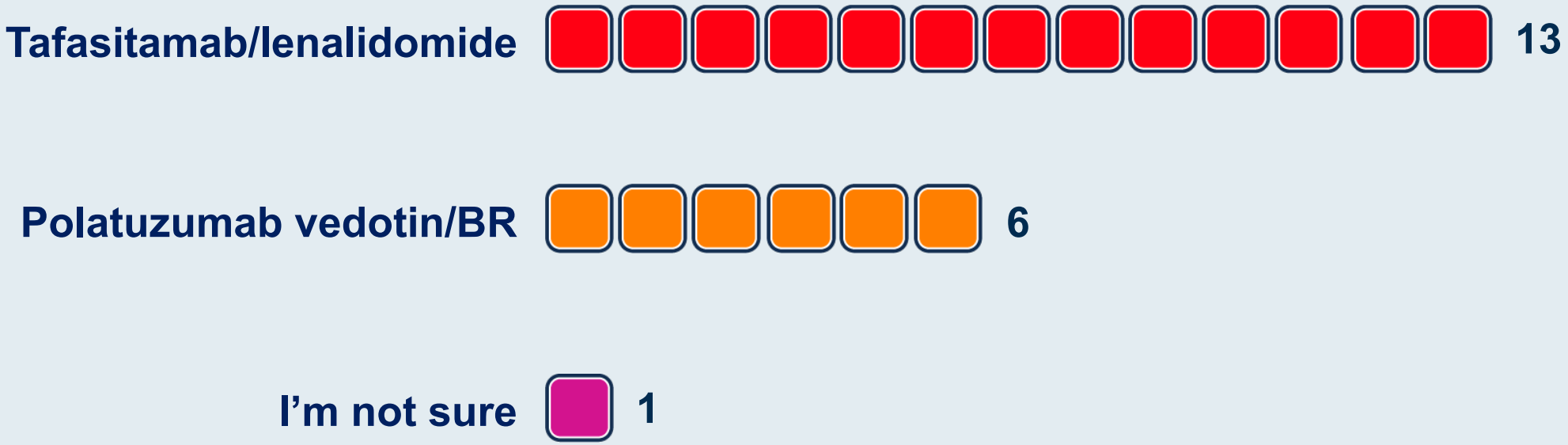
Which therapy would you generally recommend first for a patient with DLBCL who experiences disease progression on front-line R-CHOP and is not eligible for high-dose therapy or CAR T-cell therapy?



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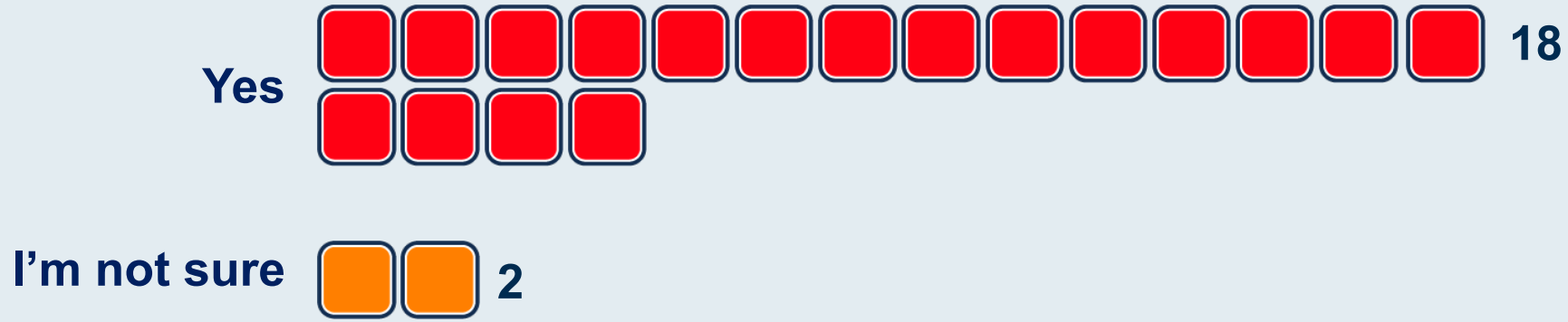
Is it reasonable to offer a patient who has experienced disease progression on or after CD19-directed CAR T-cell therapy treatment with tafasitamab/lenalidomide or loncastuximab tesirine and vice versa?



Survey of Lymphoma Clinical Investigators

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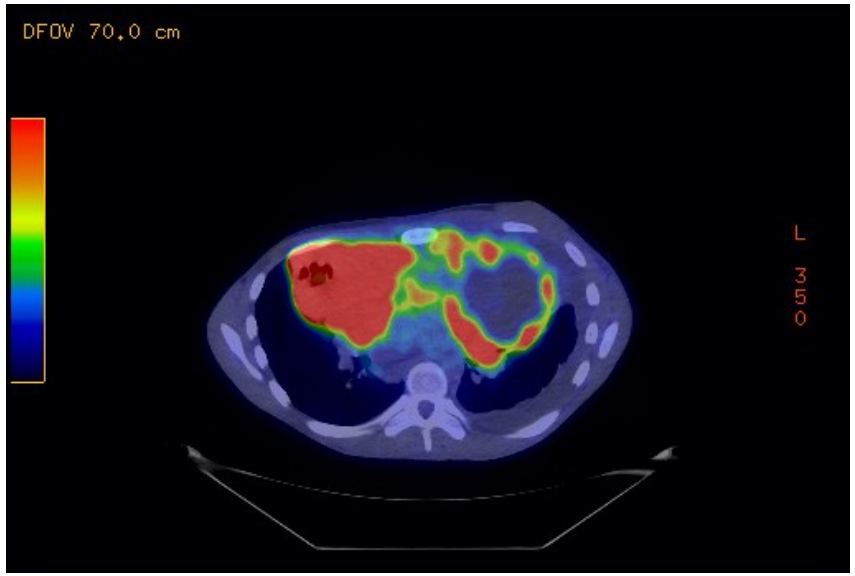
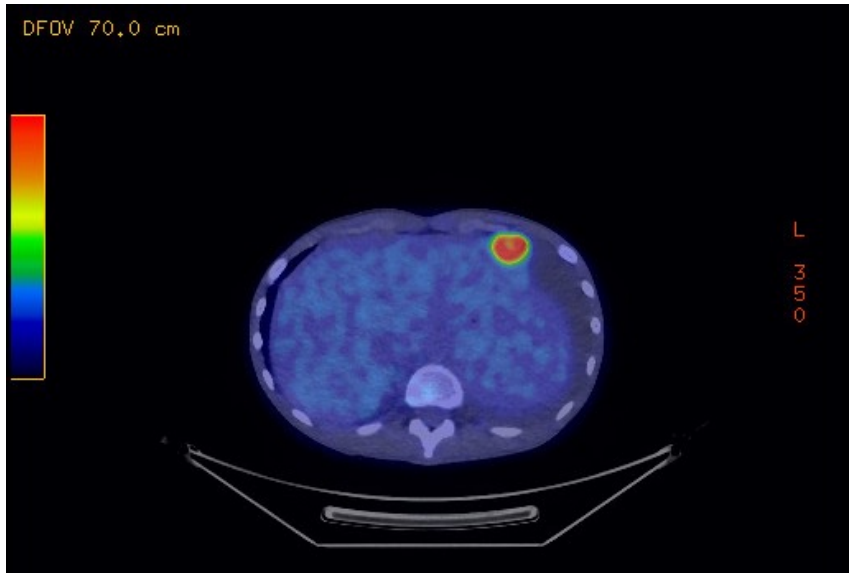
Case Presentation – Prof Nowakowski: A 22-year-old man with non-germinal center B-cell-like DLBCL

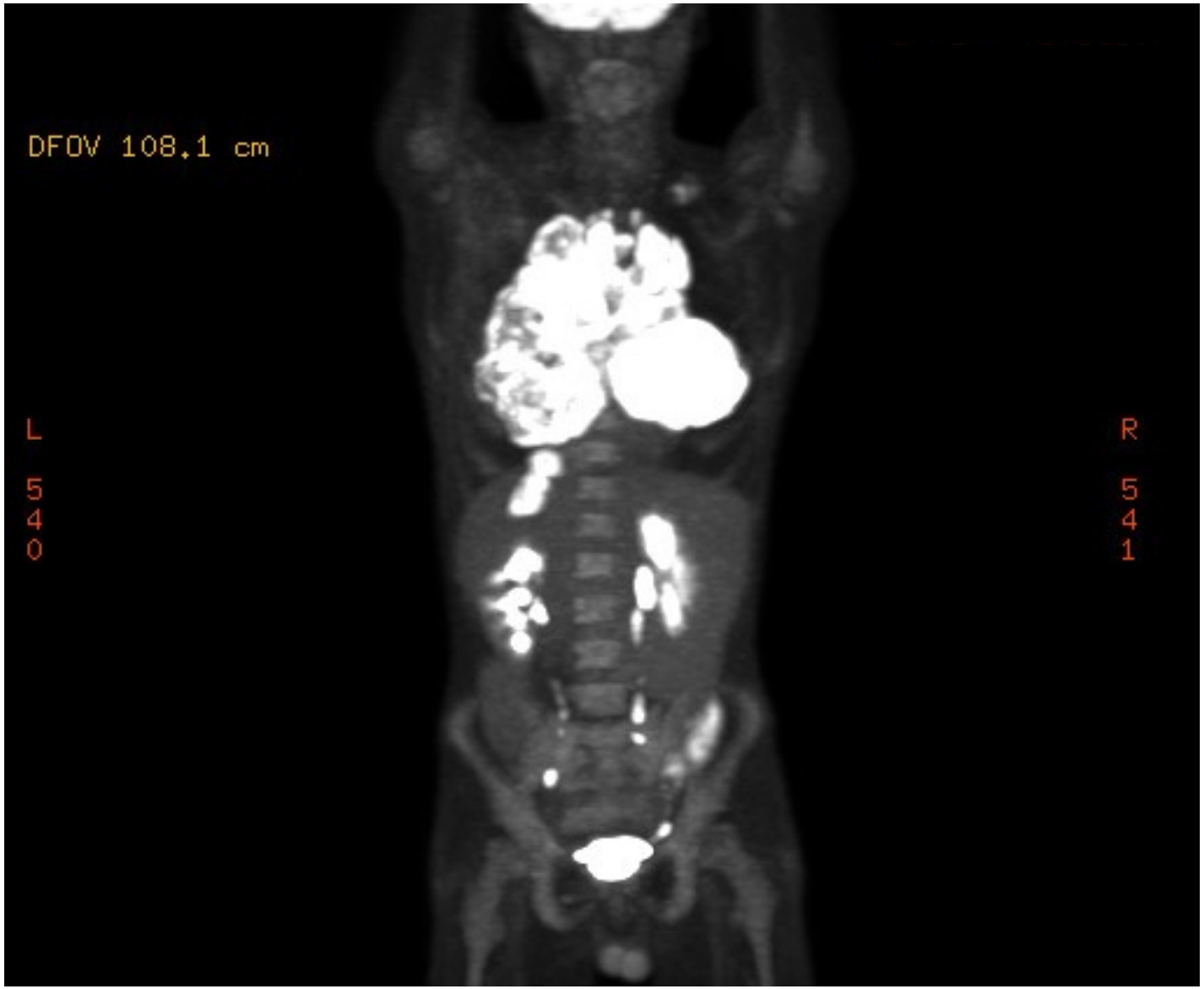
- 22 yo male with several months' history of dry cough and night sweats, weight loss of >10 lbs
- No significant PMH
- No family history of immunodeficiency, lymphoma or cancer
- Unremarkable physical examination apart from mass protruding from anterior chest
- CXR – large intrathoracic masses
- CBC – anemia Hb 9.9, chemistries unremarkable; LDH 550 (ULN 220) HIV-/Hepatitis B-/C-

Courtesy of Grzegorz Nowakowski, MD

Staging PET Scan

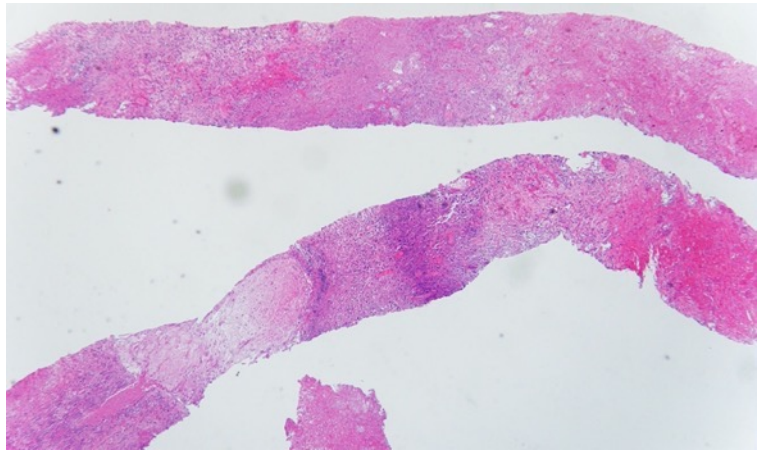


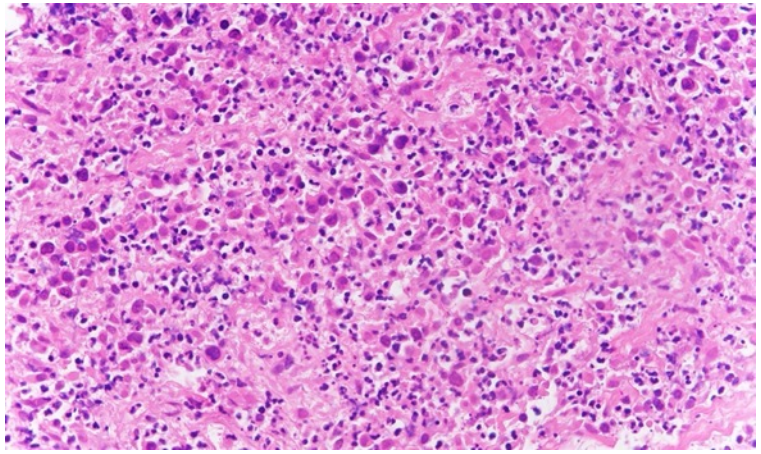


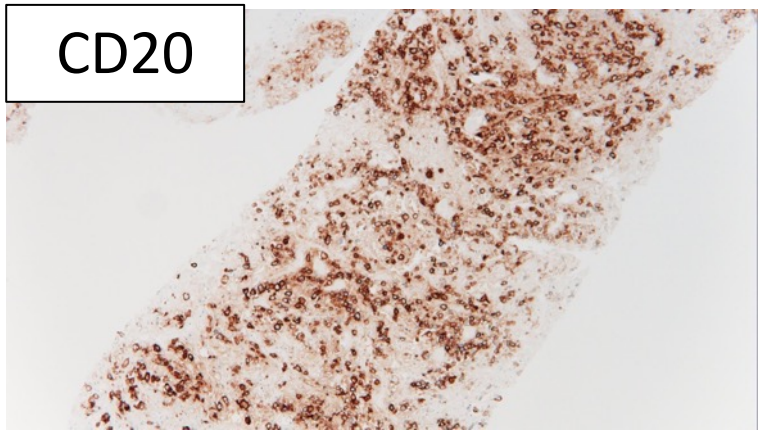


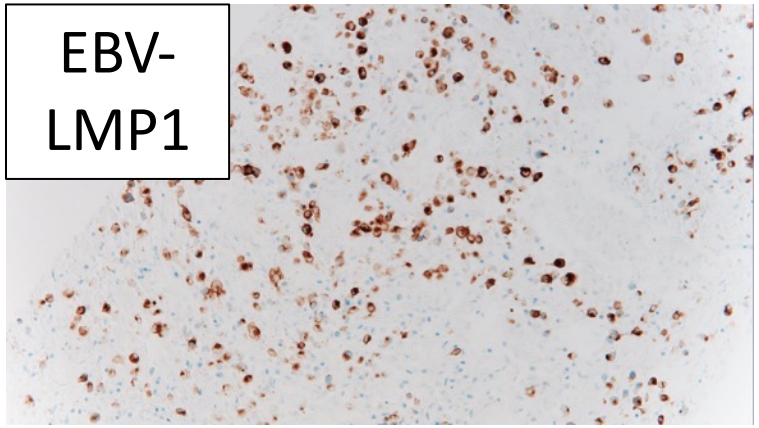
Courtesy of Grzegorz Nowakowski, MD

Pathology CT-Guided Core Biopsy









- Positive: CD20, PAX5, EBV-LMP1, EBER (in intact viable cells), MUM1 (>30%).
- Negative: CD10 (<30%), BCL6 (<30%), BCL2, BCL6 (<50%), and MYC (<40%), CD30.
- Non-GCB by Hans
- FISH: MYC-/BCL2-

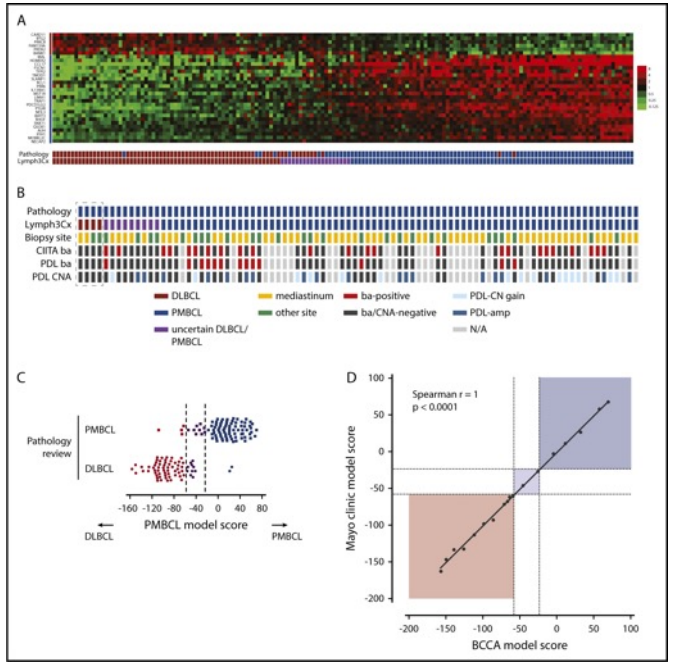
Courtesy of Grzegorz Nowakowski, MD

Lymph3Cx Assay, Distinction of PMLBCL and Cell-of-Origin for DLBCL, mRNA Gene Expression, NanoString

- Molecular classification assay for the distinction of PMBCL from DLBCL subtypes as well as the “cell-of origin” subtypes of DLBCL based on gene expression in formalin-fixed, paraffin-embedded tissue
- Utilizes the NanoString Technology and consists of probes for 58 target genes (discriminatory and housekeeping genes)

PMBCL Call is based upon PMBCL probability:
≥ 0.90 is PMBCL
≤ 0.10 is DLBCL
All other DLBCL with unclear gene expression pattern

If **DLBCL** is called per above, then COO is determined by DLBCL probability:
≤ 0.10 is Germinal Center B-cell (GCB).
≥ 0.90 Activated B-cell (ABC).
All other results are Unclassifiable.



Molecular classification of primary mediastinal large B-cell lymphoma using routinely available tissue specimens

Anja Mottok,[1,2] George Wright,[3] Andreas Rosenwald,[4] German Ott,[5] Colleen Ramsower,[6] Elias Campo,[7,8] Rita M. Braziel,[9] Jan Delabie,[10] Dennis D. Weisenburger,[11] Joo Y. Song,[11] Wing C. Chan,[11] James R. Cook,[12] Kai Fu,[13] Tim Greiner,[13] Erlend Smeland,[14,15] Harald Holte,[15,16] Kerry J. Savage,[1] Betty J. Glinsmann-Gibson,[6] Randy D. Gascoyne,[1] Louis M. Staudt,[17] Elaine S. Jaffe,[18] Joseph M. Connors,[1] David W. Scott,[1] Christian Steidl,[1,*] and Lisa M. Rimsza[6,*]

Patient: Non PMBCL - ABC DLBCL

Courtesy of Grzegorz Nowakowski, MD

Mottok A et al. *Blood.* 2018;132(22):2401–2405.

Case Presentation – Prof Nowakowski: A 66-year-old woman with germinal center B-cell-like DLBCL

- 66 yo woman presented with progressive dysphagia, neck pain and weight loss. Neck CT showing a 4.5-cm mass at the base of tongue with intact airway
- Biopsy – DLBCL, GCB subtype, FISH for myc negative
- LDH 2 x ULN
- PETCT showed base of tongue mass, and non-bulky bilateral cervical, left supraclavicular and superior mediastinal nodes – Deauville 5
- The initiatives on 2 cycles of chemotherapy showed partial shrinkage of mass and lymphadenopathy but with persistent uptake - Deauville 4

Courtesy of Grzegorz Nowakowski, MD

PET 2 in R-CHOP Treated DLBCL Patients

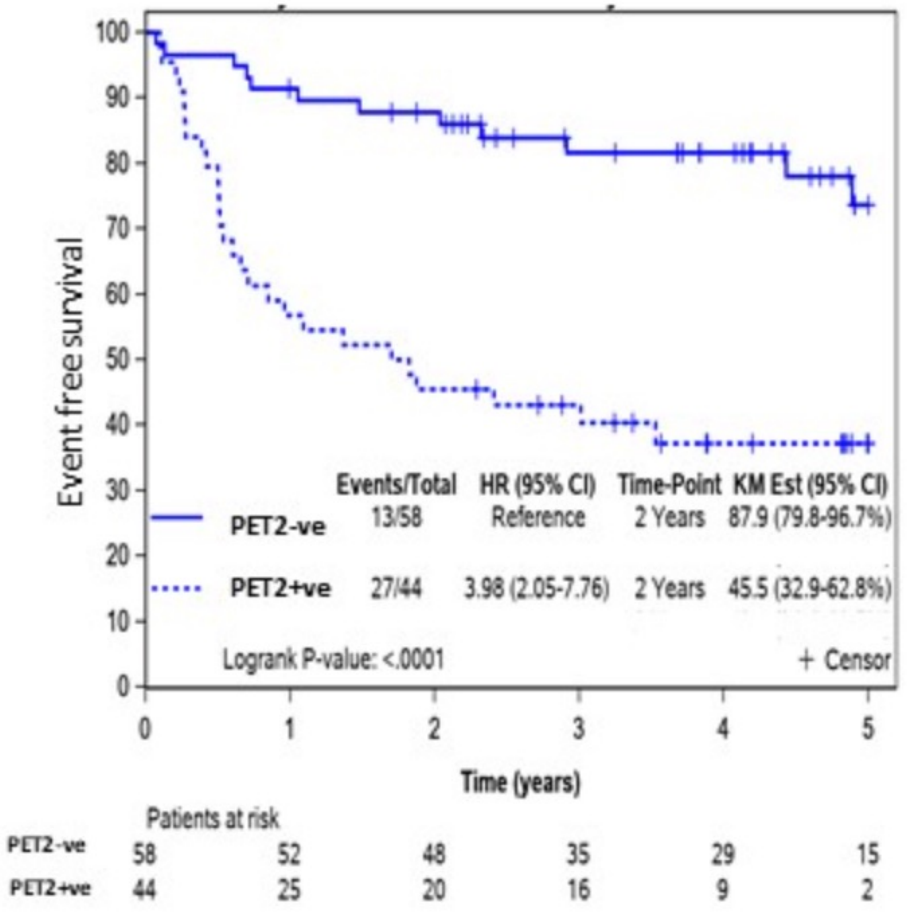


Figure 1a (MC078E)

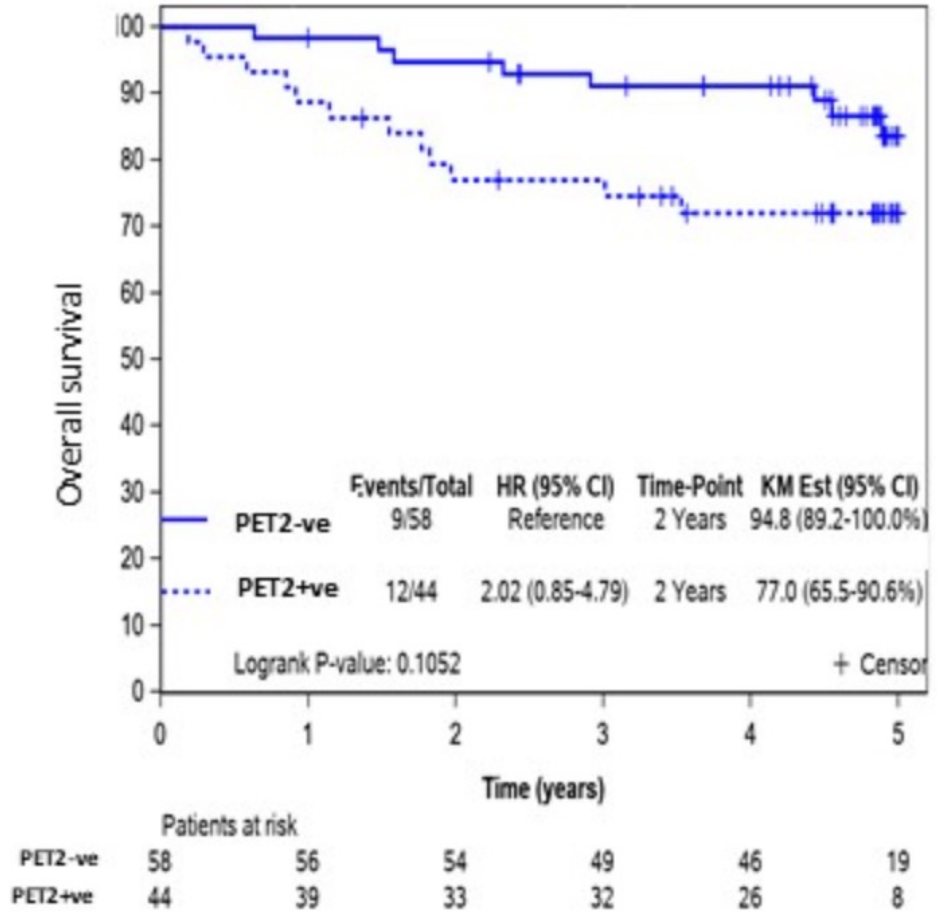


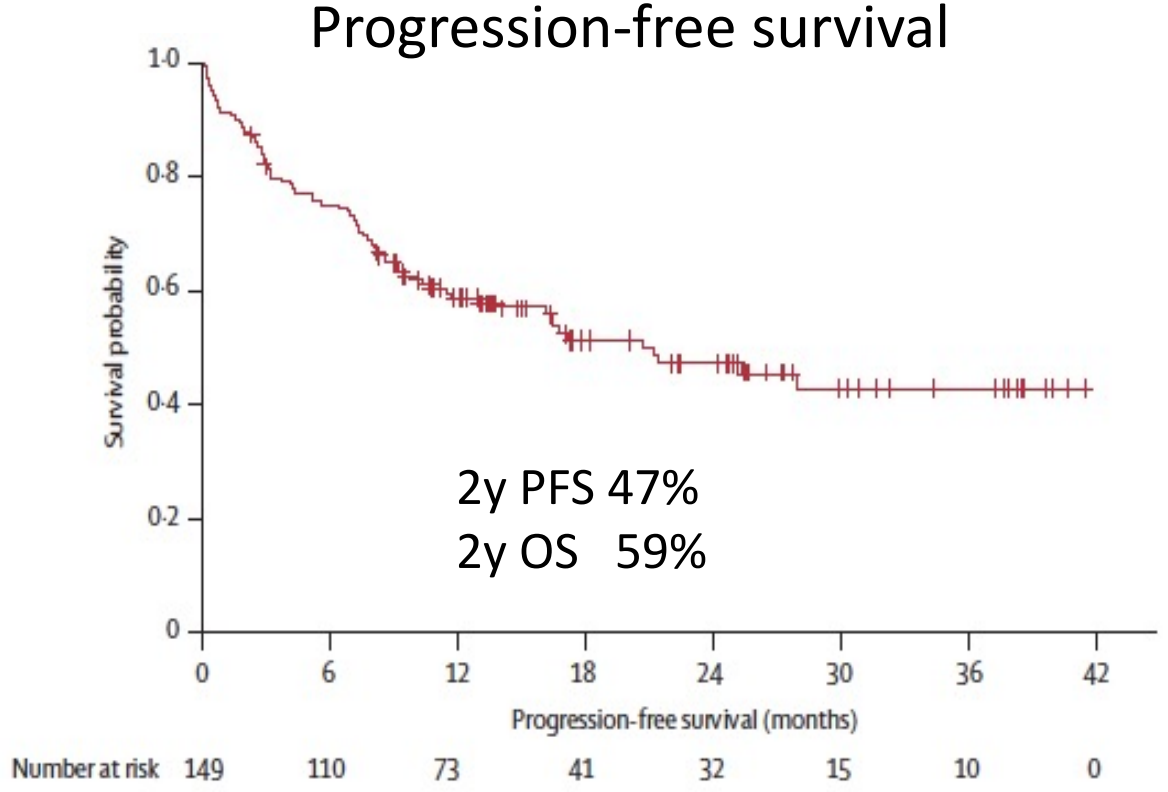
Figure 1b (MC078E)

Courtesy of Grzegorz Nowakowski, MD

Desai et al. ASH 2021: 2508

R-mini-CHOP

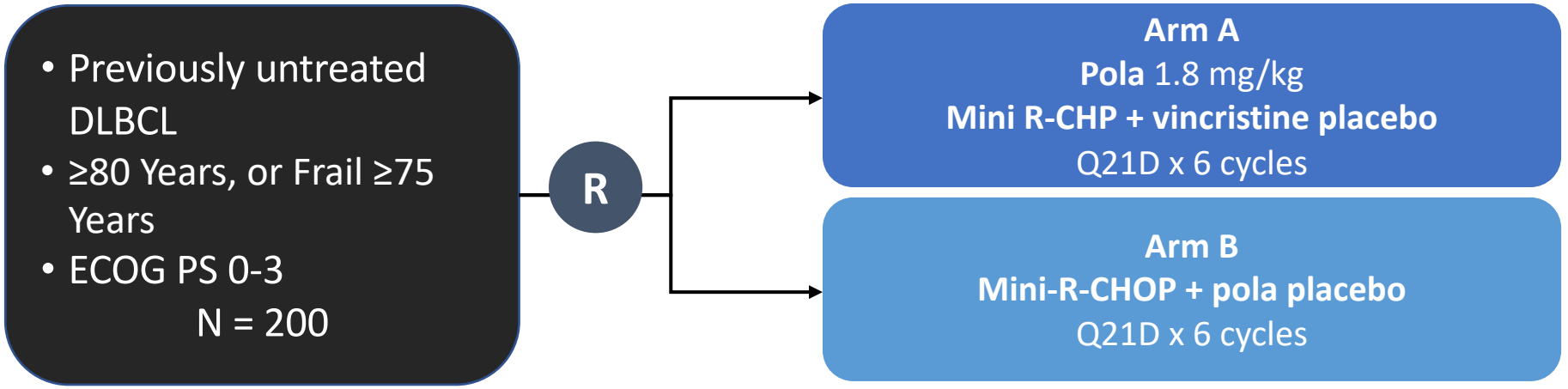
- Regimen
  - Rituximab 375 mg/m^2 day 1
  - Cyclophosphamide 400 mg/m^2 day 1
  - Doxorubicin 25 mg/m2 day 1
  - Vincristine 1 mg flat dose day 1
  - Prednisone 40 mg/m2 days 1-5
- Median age 83 y (range 80–95)
- Median dose intensity 98%
- ORR 74%, CRR 63%



Peyrade F et al. *Lancet Oncol.* 2011;12(5):460-468.

Courtesy of Grzegorz Nowakowski, MD

POLAR BEAR Study - Adding Polatuzumab Vedotin to Mini R-CHOP



Primary endpoint: PFS

ClinicalTrials.gov Identifier: NCT04332822

Courtesy of Grzegorz Nowakowski, MD

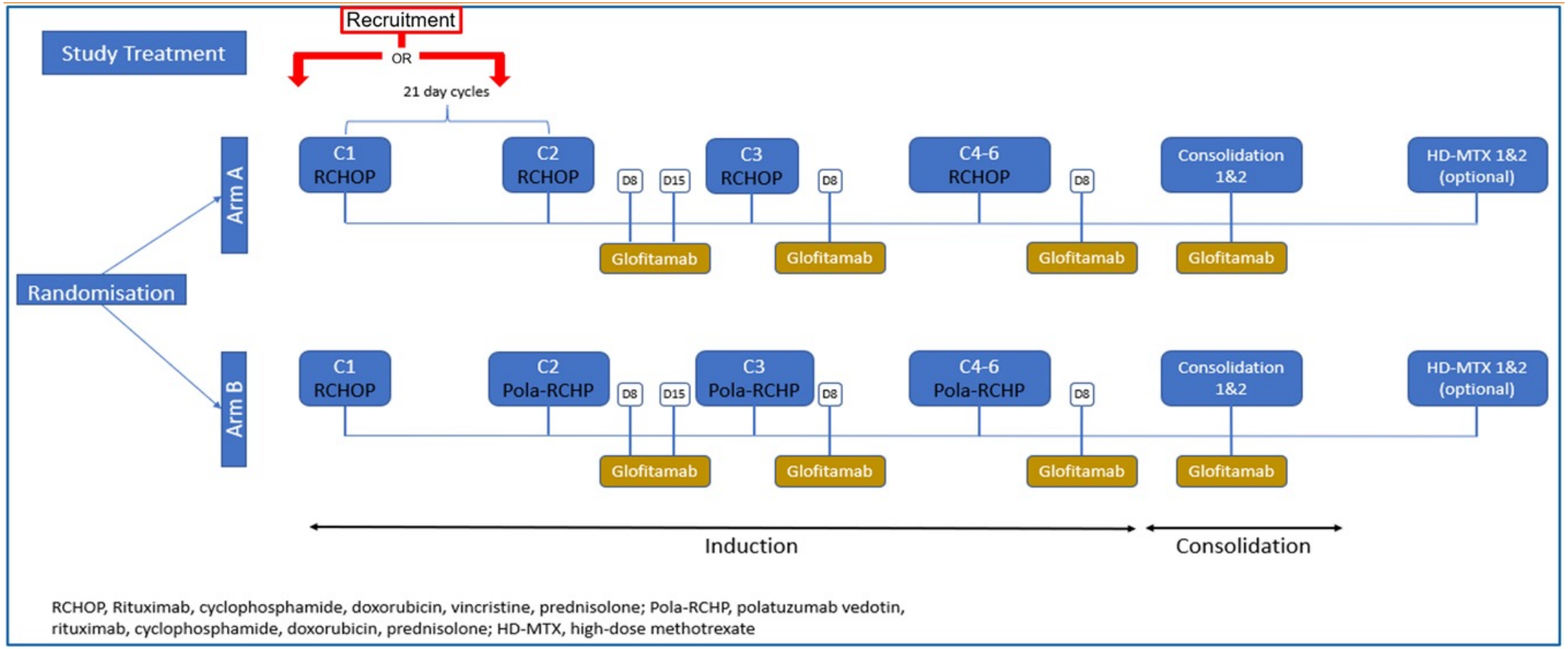
Bispecific Antibodies (1L DLBCL) Key Trial Results

Molecule	Trial Design	Patient Population	Outcomes	Safety
Epcoritamab	• Ph 1b/2 • First-in-human • Dose escalation	• N=24 • Age 30-82 years • Median age=65	• Among modified response-evaluable population (n=11), ORR=100%; CMR=73%; PMR=27% • All 11 patients remain on study treatment with ongoing responses	• No dose-limiting toxicities for Epcoritamab • Most common TEAEs: CRS, anemia, infections • No Grade ≥3 CRS, ICANS, or cases of febrile neutropenia • 1 TLS event
Glofitamab	• Ph 1b • Dose escalation and safety run-in	• N=26 (1L DLBCL safety run-in population) • Age 26-84 years • Median age=68	• 9 of 26 patients reached end-of-treatment assessment • ORR=100%; CMR=88.9%; PMR=11.1% • mDoR not reached	• Grade 1 CRS: 1 patient • Grade ≥3 AEs related to glofitamab: 4 patients • No ICANS or AEs leading to discontinuation

Belada D.et al ASH 2021; Minson A et Al, ASH 2021

Courtesy of Grzegorz Nowakowski, MD

Trial in Progress: A Multicentre, Parallel Arm, Open-Label Trial of Frontline R-CHOP/Polatuzumab Vedotin-RCHP and Glofitamab in Younger Patients with Higher Risk Diffuse Large B Cell Lymphoma (COALITION)

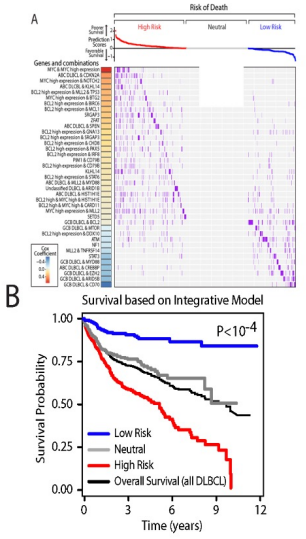


Minson A et Al, ASH 2021

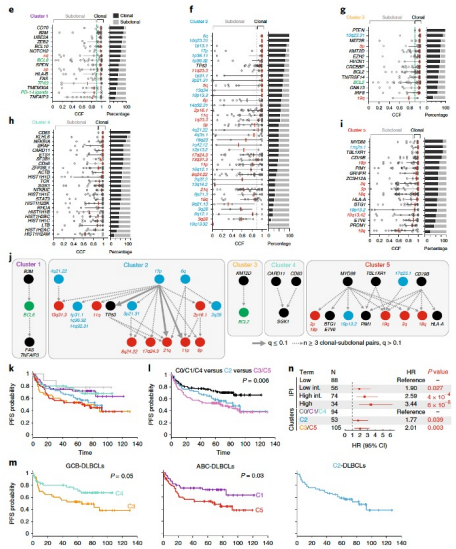
Courtesy of Grzegorz Nowakowski, MD

Next waive of R-CHOP “plus”

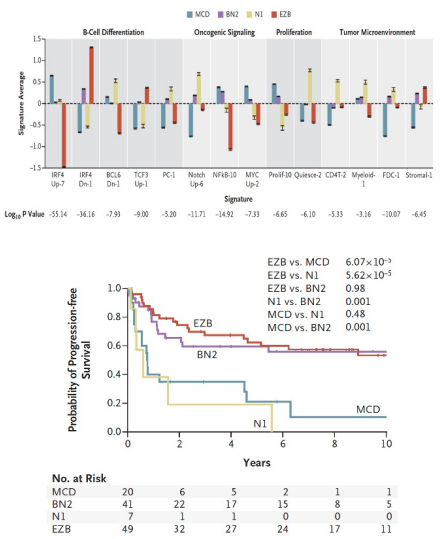
- Bispecific antibodies plus R-CHOP/R-CHP/Pola
- R^2-CHOP plus Tafa
- Lonca plus R-CHOP
- Others in development



Nat Med 9:2016: 218–221



Nat Med 18:2018: 679–690



N Engl J Med 2018;378:1396-407

Agnostic
CART
Tafa/len
Lonca
Pola

BTK inh
PI3K inh
BCL2 inh
IRAK4 inh

Courtesy of Grzegorz Nowakowski, MD

Agenda

Introduction: Overview of Diffuse Large B-Cell Lymphoma (DLBCL)

MODULE 1: The POLARIX Trial – Dr Flowers

MODULE 2: Clinical Investigator Survey

MODULE 3: Ongoing Trials in DLBCL – Prof Nowakowski

MODULE 4: Up-Front Treatment for Older Patients with DLBCL – Dr Mehta-Shah

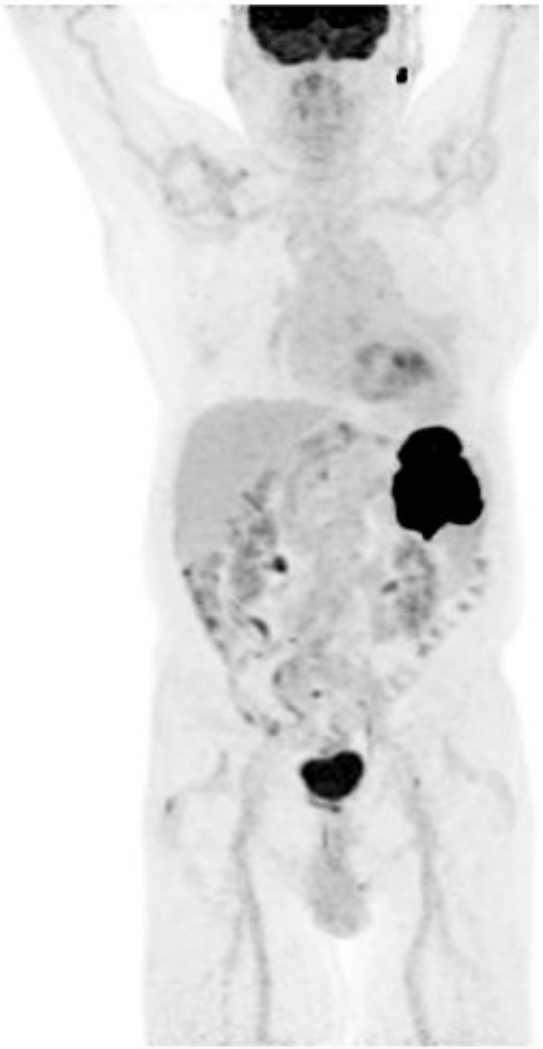
CASE PRESENTATION – DR MEHTA-SHAH: AN 87-YEAR-OLD MAN WITH NON-GERMINAL CENTER B-CELL-LIKE DLBCL

- 87 yo man with CAD sp stents to the LAD and total occlusion of the RCA with most recent echo showing EF 70% (2014), AAA, prostate cancer s/p robotic prostatectomy who presented with 15 lbs weight loss.
- Patient notes early satiety without nausea, vomiting, abdominal pain.
- Exam notable for splenomegaly
- CT A/P showed heterogenous enhancing mass involving the spleen and his stable 6-cm AAA (grafted)

Courtesy of Neha Mehta-Shah, MD, MSCI

CASE PRESENTATION – DR MEHTA-SHAH: AN 87-YEAR-OLD MAN WITH NON-GERMINAL CENTER B-CELL-LIKE DLBCL (CONTINUED)

- Core biopsy of the spleen performed 3/21/19: diffuse large B-cell lymphoma, non-germinal B-cell type
  - IHC positive for: CD20, MUM1 (40-50%), BCL6, PAX 5, cMYC (60-70%)
  - IHC negative for: CD10, CD30, BCl2, CD5, EBER, CyclinD1
  - FISH negative for MYC, BCL2, and positive for BCL6
- Labs
  - Normal CBC (WBC 5.9, Hgb 13.5, Plts 205)
  - LDH 643 (ULN 250)
  - Cr 1.79, BUN 26, Calcium 12.6, normal LFTs
- PET/CT with 10 x 7-cm splenic mass with SUV 44.4 with extrasplenic extension, multiple mildly FDG avid para-aortic, perihepatic and right axillary lymph nodes with SUV 5 and some calcification



Courtesy of Neha Mehta-Shah, MD, MSCI

TREATING THE ELDERLY/LESS FIT

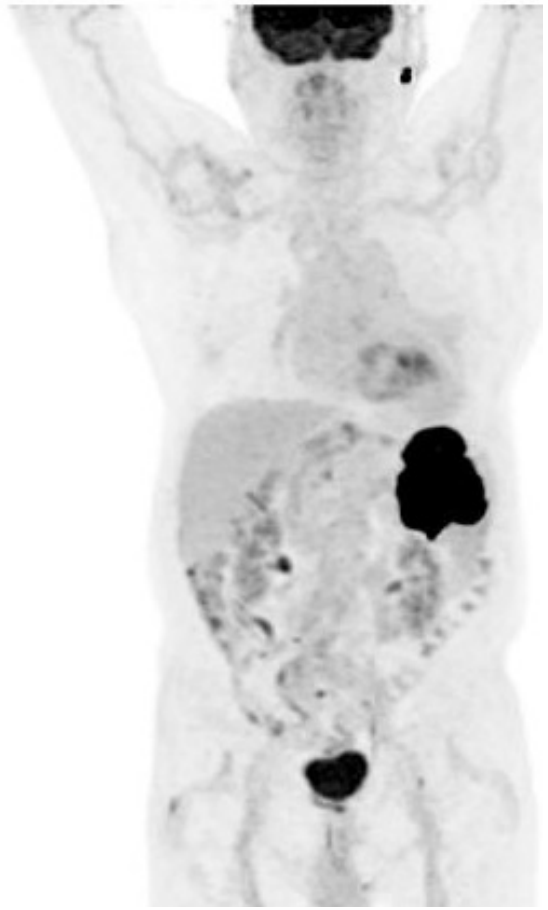
- Assessing frailty
- Treatment related mortality
  - Treatment related mortality 18% in cycle 1 in patients >80 years old

Courtesy of Neha Mehta-Shah, MD, MSCI

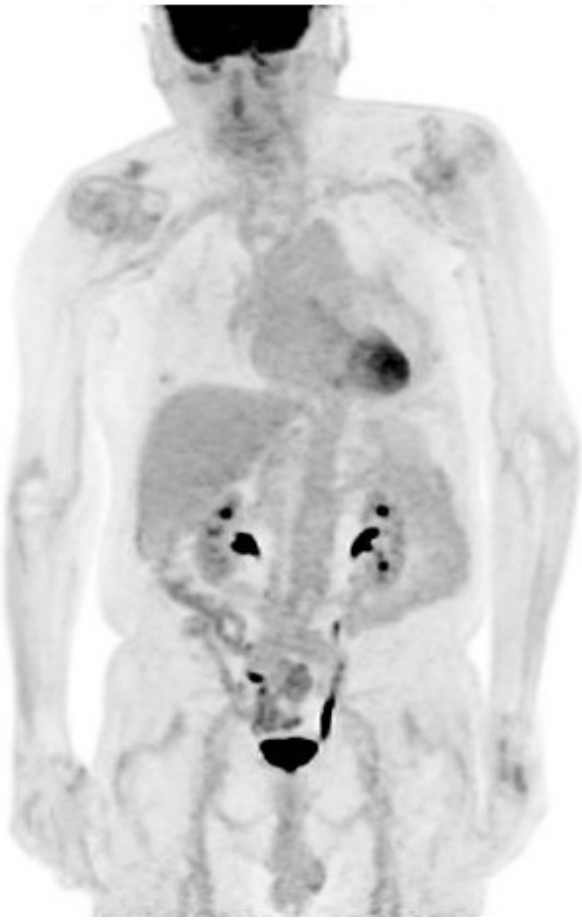
CASE PRESENTATION – DR MEHTA-SHAH: AN 87-YEAR-OLD MAN WITH NON-GERMINAL CENTER B-CELL-LIKE DLBCL (CONTINUED)

- Admitted for cycle 1 and given prednisone, IV fluids with improvement of calcium to 11.0 in 24 hours
- Repeat echocardiogram showed EF 73%
- Received pre-phase steroids for three days while awaiting PET and echo
- Received R-mini-CHOP x 6
- Remains in a complete remission

Baseline



Post R-miniCHOP x 6



Courtesy of Neha Mehta-Shah, MD, MSCI

Exploring the Current and Future Role of B-Cell Maturation Antigen-Directed Therapy in the Management of Multiple Myeloma

Monday, February 7, 2022
5:00 PM – 6:00 PM ET

Faculty

Jesús G Berdeja, MD
Noopur Raje, MD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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