Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Follicular, Mantle Cell and Hodgkin Lymphoma (Part 1 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

7:30 AM – 10:00 AM PT (10:30 AM – 1:00 PM ET)

Faculty

Jeremy S Abramson, MD, MMSc
Stephen M Ansell, MD, PhD
Nancy L Bartlett, MD
Jonathon B Cohen, MD
Jonathan W Friedberg, MD, MMSc
Brad S Kahl, MD

Moderator

Neil Love, MD

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Faculty

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Neil Love, MD
Research To Practice
Miami, Florida

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Dr Abramson — Disclosures

Consulting Agreements	AbbVie Inc, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, Bristol Myers Squibb, Caribou Biosciences Inc, Cellectar Biosciences Inc, Century Therapeutics, Epizyme Inc, Genentech, a member of the Roche Group, Genmab US Inc, Incyte Corporation, Interius BioTherapeutics, Janssen Biotech Inc, Kite, A Gilead Company, Lilly, Regeneron Pharmaceuticals Inc, Takeda Pharmaceuticals USA Inc
Contracted Research	Bristol Myers Squibb, Cellectis, Merck, Mustang Bio, Seagen Inc

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Dr Ansell — Disclosures

Contracted Research	ADC Therapeutics, Affimed, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Pfizer Inc, Regeneron Pharmaceuticals Inc, Seagen Inc, Takeda Pharmaceuticals USA Inc

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Dr Bartlett — Disclosures

Advisory Committee	ADC Therapeutics, Foresight Diagnostics, Genentech, a member of the Roche Group, Kite, A Gilead Company
Contracted Research	ADC Therapeutics, Autolus Therapeutics, Bristol Myers Squibb, Celgene Corporation, Forty Seven Inc, Genentech, a member of the Roche Group, Janssen Biotech Inc, Kite, A Gilead Company, Merck, Pharmacyclics LLC, an AbbVie Company, Seagen Inc, Takeda Pharmaceuticals USA Inc

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Dr Cohen — Disclosures

Advisory Committee	AbbVie Inc, ADC Therapeutics, AstraZeneca Pharmaceuticals LP, BeiGene Ltd, HUTCHMED, Janssen Biotech Inc, Kite, A Gilead Company, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company
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Dr Friedberg — Disclosures

No relevant conflicts of interest to disclose

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Dr Kahl — Disclosures

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Diffuse Large B-Cell Lymphoma (Part 2 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)

Faculty

Michael Dickinson, MD
Grzegorz S Nowakowski, MD
Gilles Salles, MD, PhD
Laurie H Sehn, MD, MPH
Jason Westin, MD, MS

Moderator

Neil Love, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Chronic Lymphocytic Leukemia (Part 3 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Farrukh T Awan, MD
Matthew S Davids, MD, MMSc
Stephen J Schuster, MD
William G Wierda, MD, PhD
Jennifer Woyach, MD

Moderator

Neil Love, MD

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Multiple Myeloma (Part 4 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

7:00 PM – 9:00 PM PT (10:00 PM – 12:00 AM ET)

Faculty

Amrita Krishnan, MD
Sagar Lonial, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD
Paul G Richardson, MD

Moderator

Neil Love, MD

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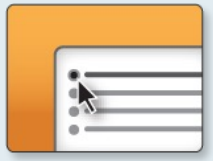
Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the premeeting survey.

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.

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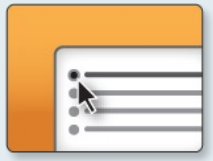
Clinicians Attending via Zoom

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



Answer Survey Questions: Complete the premeeting survey at the beginning of each module.

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

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
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Agenda

Module 1: Evolving Role of Novel Treatment Strategies in Follicular Lymphoma (FL) — Dr Friedberg

Module 2: Integration of Chimeric Antigen Receptor (CAR) T-Cell Therapies and Bispecific Antibodies into the Management of FL — Dr Abramson

Module 3: Up-Front Treatment for Mantle Cell Lymphoma (MCL) — Dr Kahl

Module 4: Therapeutic Sequencing for Patients with Relapsed/Refractory (R/R) MCL — Dr Cohen

Module 5: First-Line Treatment Strategies for Hodgkin Lymphoma (HL) — Dr Bartlett

Module 6: Current and Future Management of R/R HL — Dr Ansell

Lymphoma Survey Respondents

Jeremy S Abramson, MD, MMSc
Stephen M Ansell, MD, PhD
Nancy L Bartlett, MD
Jonathon B Cohen, MD
Michael Dickinson, MD
Andrew M Evens, DO, MA, MSc
Christopher R Flowers, MD, MS
Jonathan W Friedberg, MD, MMSc
Brad S Kahl, MD
Ann S LaCasce, MD, MMSc
Kami Maddocks, MD
Franck Morschhauser, MD, PhD
Grzegorz S Nowakowski, MD
Tycel Phillips, MD
Gilles Salles, MD, PhD
Laurie H Sehn, MD, MPH
Sonali M Smith, MD
Max S Topp, MD
Jason Westin, MD, MS
Andrew D Zelenetz, MD, PhD

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FDA Investigating 'Serious Risk' of Secondary Cancer After CAR-T Therapy

Press Release: November 29, 2023

“The FDA has launched an investigation into what it called a ‘serious risk’ of T-cell malignancies in patients treated with autologous chimeric antigen receptor (CAR) T-cell therapies targeting B-cell maturation antigen (BCMA) or CD19.

The agency has received multiple reports of T-cell malignancies, including CAR-positive lymphomas, from clinical trials and postmarketing adverse event data sources, according to a statement posted on the FDA website. Serious outcomes of these secondary malignancies have included hospitalization and death. The notice and investigation pertain to all currently approved BCMA- and CD19-targeted CAR T-cell products.

‘Although the overall benefits of these products continue to outweigh their potential risks for their approved uses, FDA is investigating the identified risk of T-cell malignancy with serious outcomes, including hospitalizations and death, and is evaluating the need for regulatory action,’ agency officials said in the statement. ‘As with all gene therapy products with integrating vectors (lentiviral or retroviral vectors), the potential risk of developing secondary malignancies is labeled as a class warning in the US prescribing information for approved BCMA-directed and CD19-directed genetically modified autologous T-cell immunotherapies.’”

https://www.medpagetoday.com/hematologyoncology/hematology/107569

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Agenda

Module 1: Evolving Role of Novel Treatment Strategies in Follicular Lymphoma (FL) — Dr Friedberg

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Module 4: Therapeutic Sequencing for Patients with Relapsed/Refractory (R/R) MCL — Dr Cohen

Module 5: First-Line Treatment Strategies for Hodgkin Lymphoma (HL) — Dr Bartlett

Module 6: Current and Future Management of R/R HL — Dr Ansell

In general, what is your usual preferred first-line therapy for a 60-year-old patient with follicular lymphoma (FL) and no significant comorbidities?

O = obinutuzumab

Survey of 20 US-based clinical investigators November 2023

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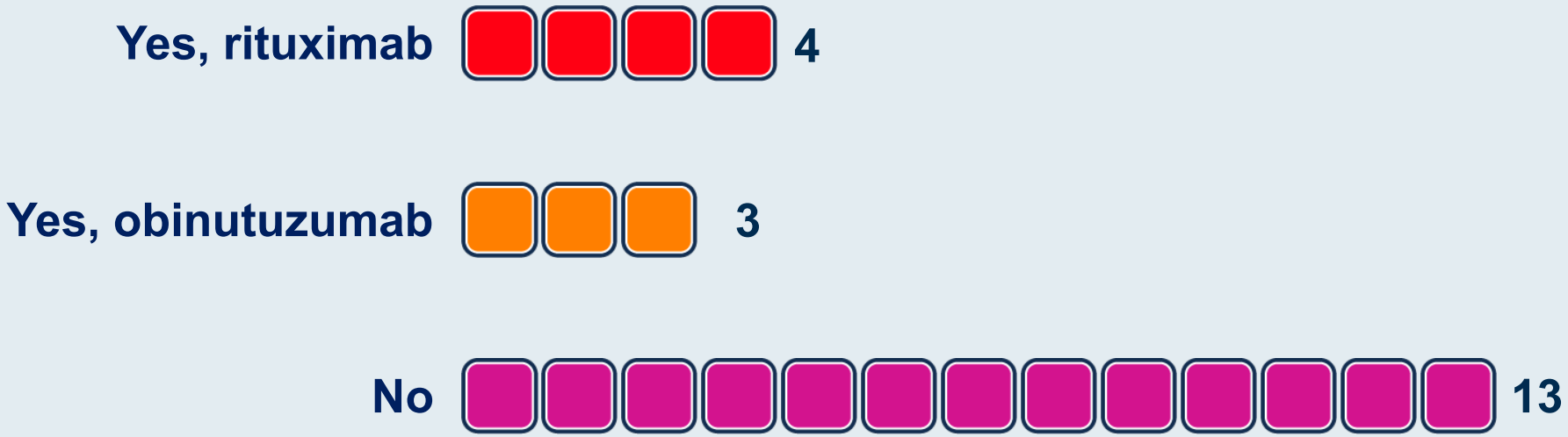
In general, for a 60-year-old patient with FL and no significant comorbidities would you recommend maintenance therapy?



Survey of 20 US-based clinical investigators November 2023

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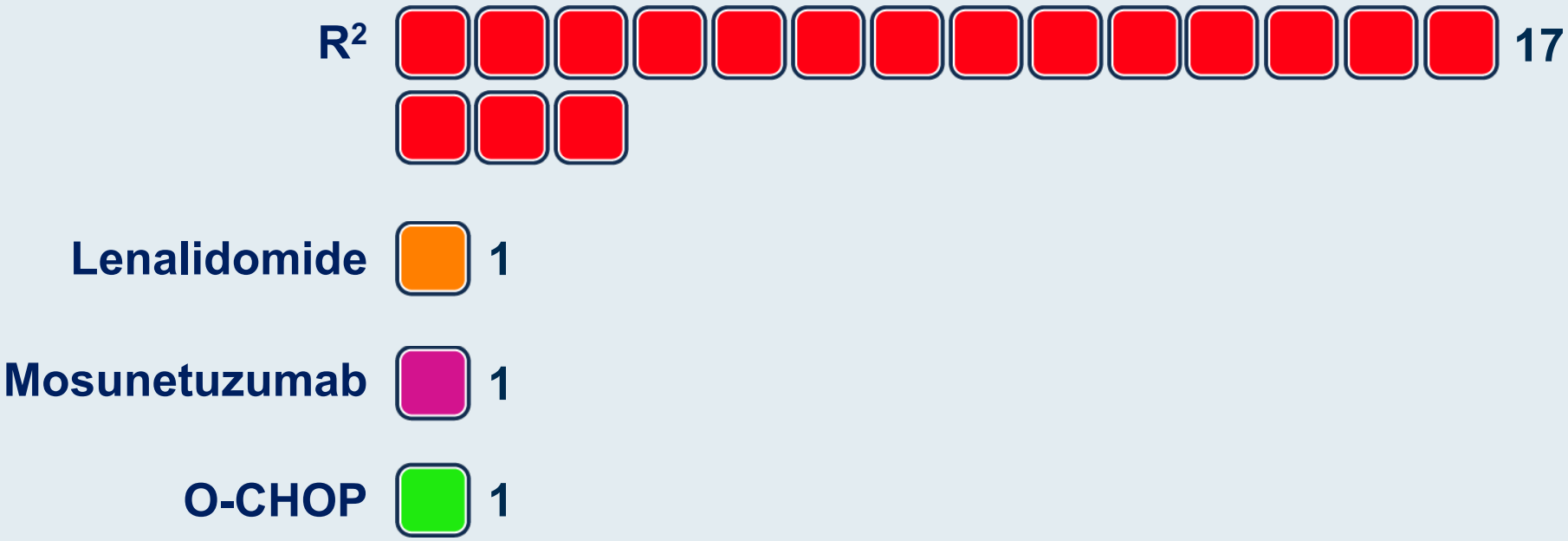
Regulatory and reimbursement issues aside, what is your usual second-line therapy for a 65-year-old patient with FL who attains a complete response to 6 cycles of BR but then experiences disease relapse 4 years later?



Survey of 20 US-based clinical investigators November 2023

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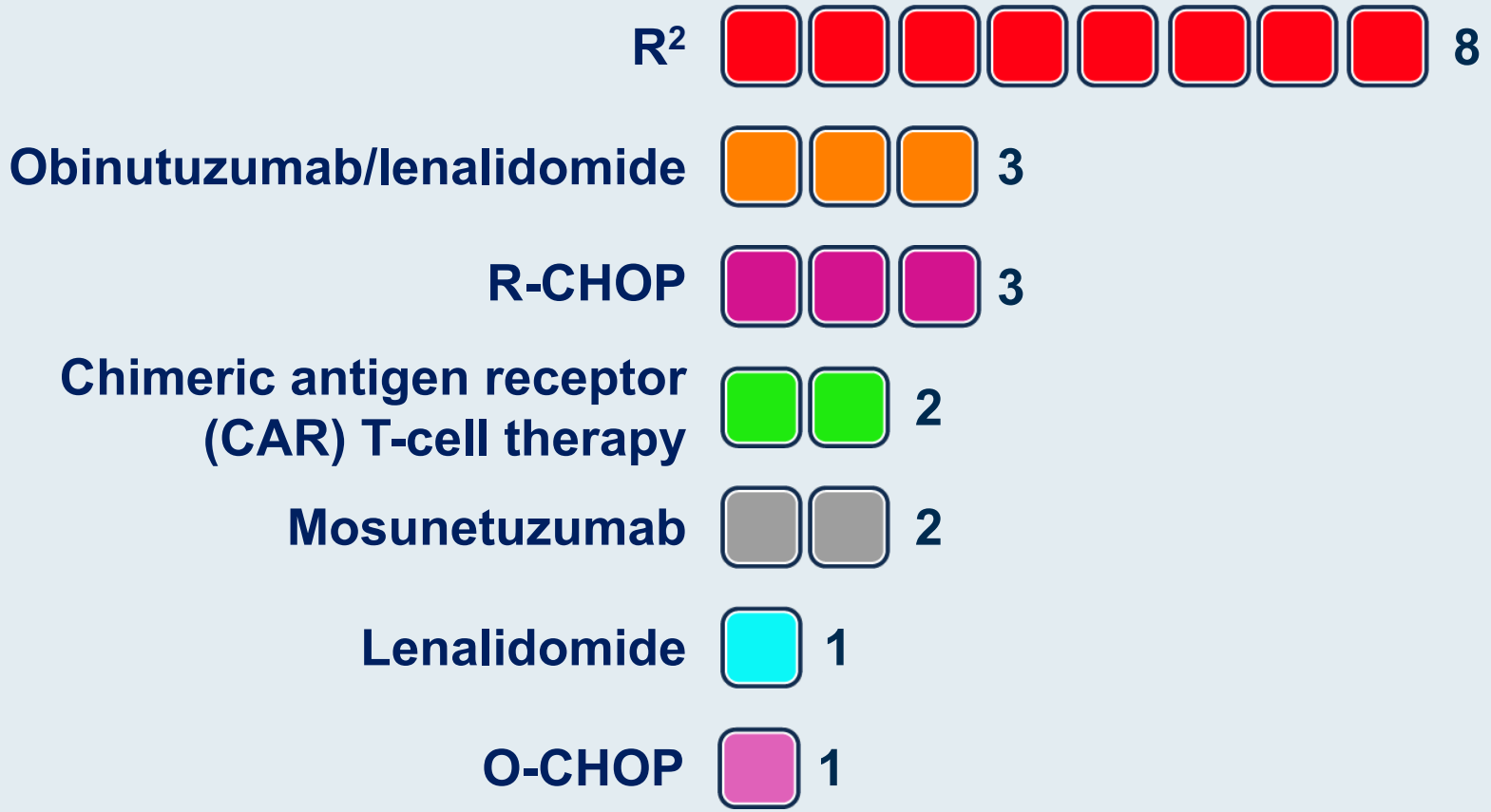
Regulatory and reimbursement issues aside, what would you generally recommend as second-line therapy for a 60-year-old patient with Stage IV FL and no significant comorbidities who received first-line BR and then experienced disease progression 1 year after starting maintenance rituximab?



Survey of 20 US-based clinical investigators November 2023

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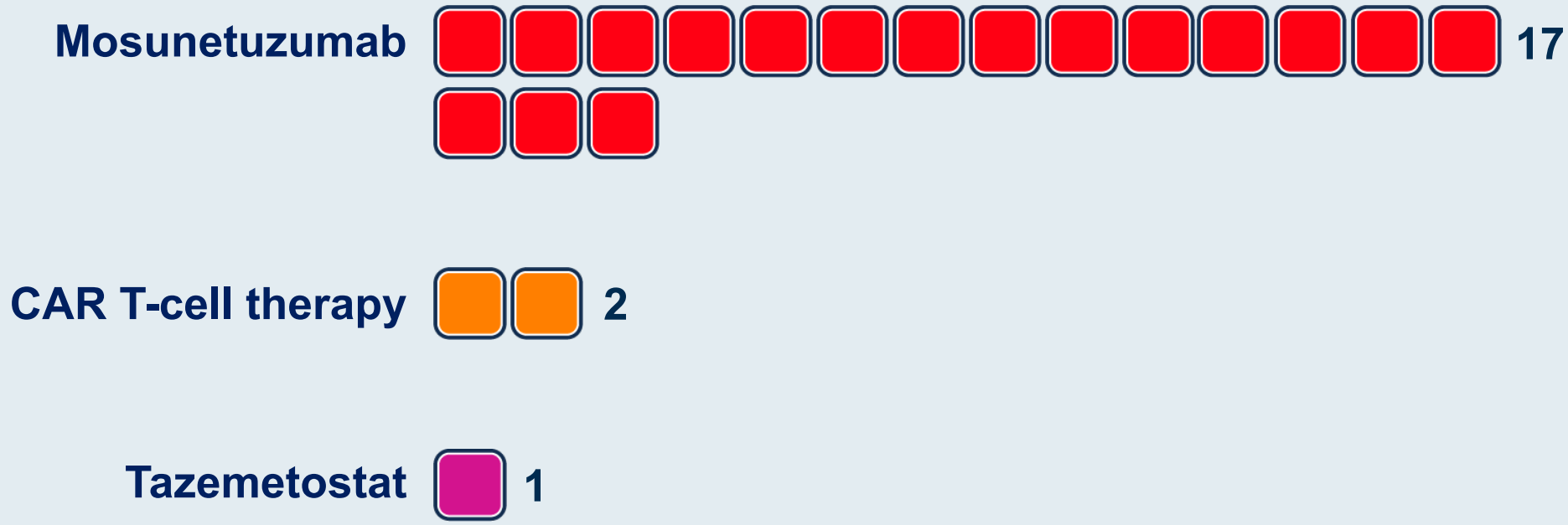
What is your usual third-line treatment for a patient with FL (EZH2 wild type) who receives first-line BR, second-line R^2 and then develops disease progression?



Survey of 20 US-based clinical investigators November 2023

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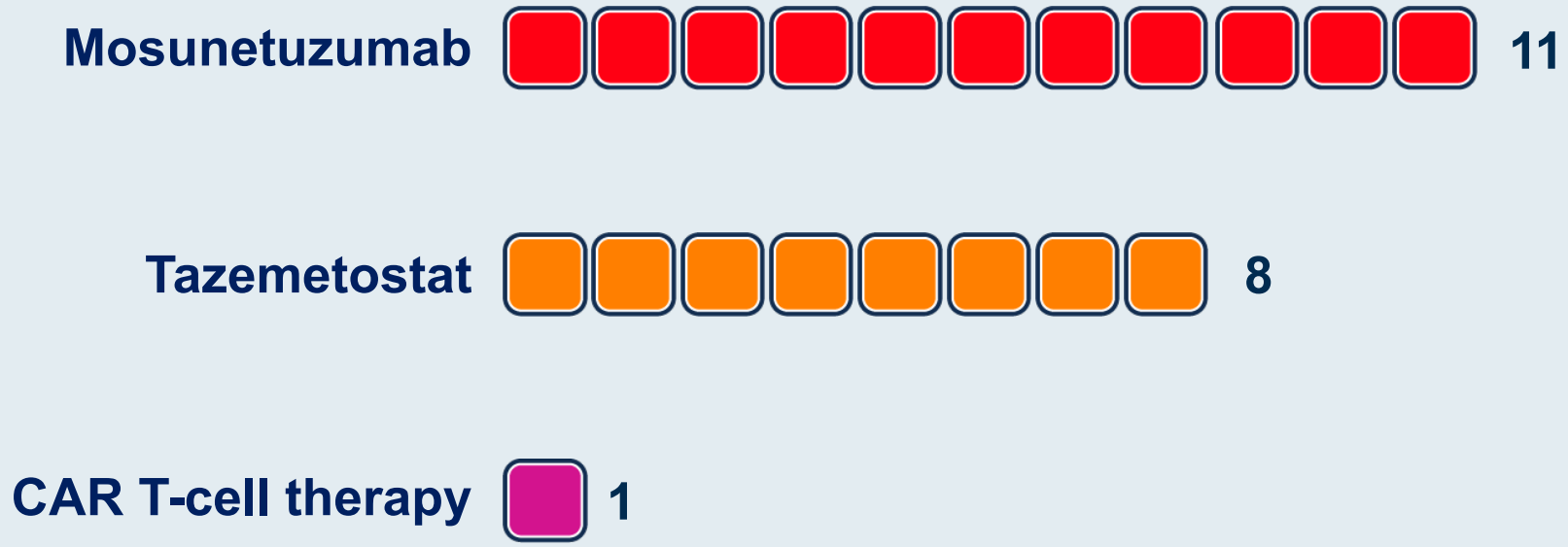
What is your usual third-line treatment for a patient with FL with an EZH2 mutation who receives first-line BR, second-line R^2 and then develops disease progression?



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Sequence of systemic treatments for FL

Andrew M Evens, DO, MBA, MSc

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CAR T-cell therapy and bispecific antibodies for R/R FL

Kami Maddocks, MD

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Evolving Role of Novel Treatment Strategies in Follicular Lymphoma

Jonathan W Friedberg MD

Samuel Durand Professor of Medicine

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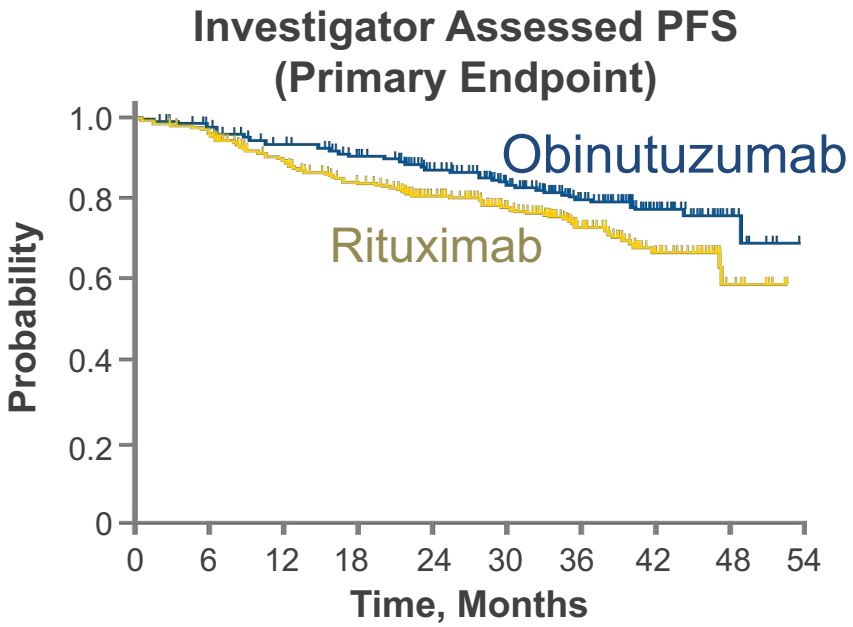
Obinutuzumab

GALLIUM Phase III Obinutuzumab/chemo vs Rituximab/chemo Followed by Maintenance in Previously Untreated FL



Median follow-up, 34.5 months

Curves separate early

2 year PFS:

Rituximab 81%

Obinutuzumab 88%

	n	Events, n (%)	3-Year PFS (95% CI), %	Stratified HR[a] (95% CI), *P* Value
G-CT	601	101 (16.8)	80.0 (75.9-83.6)	0.66 (0.51-0.85), 0.0012
R-CT	601	144 (24.0)	73.3 (68.8-77.2)	

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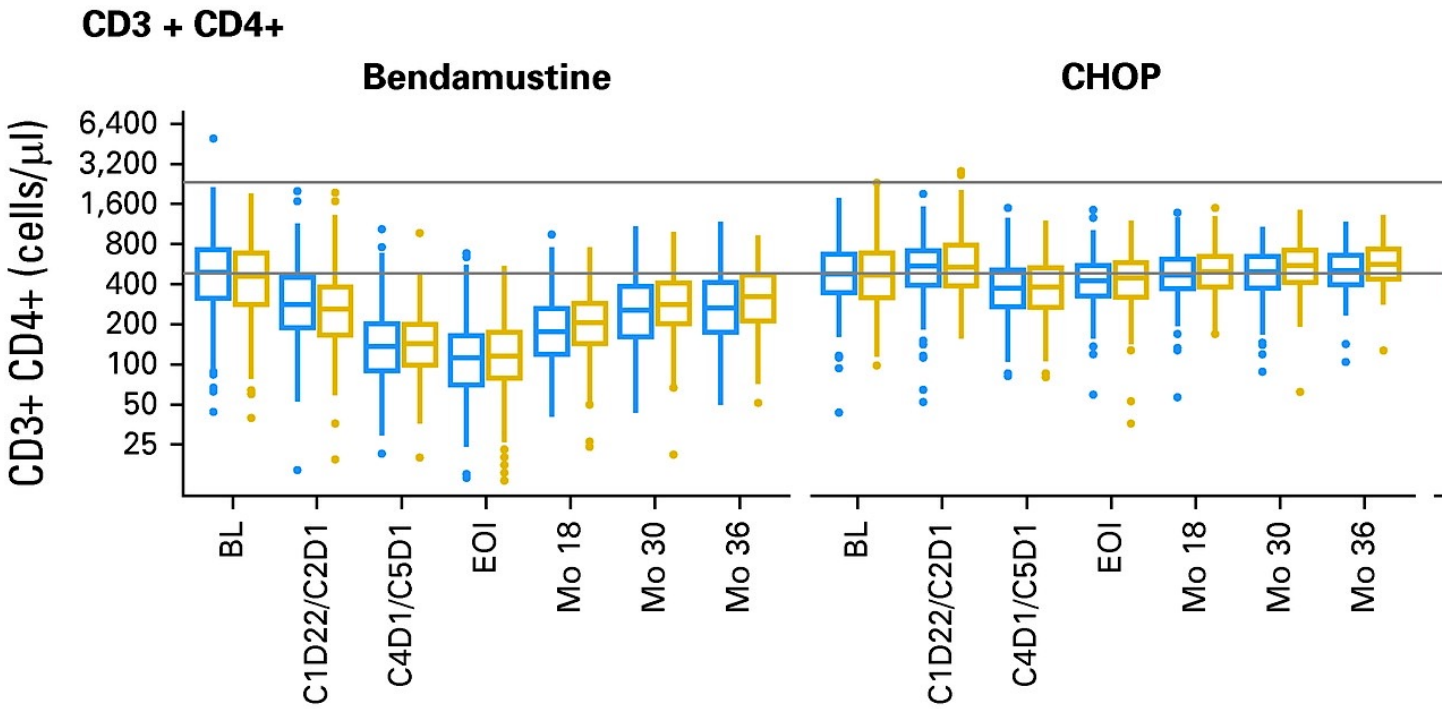
Marcus RE, et al. *NEJM* 377:1331 2017

GALLIUM Phase III Obinutuzumab/chemo vs rituximab/chemo

- Highest response rates observed with bendamustine chemotherapy
- Increased deaths observed in remission during maintenance following bendamustine with both rituximab and obinutuzumab
- Questions role of maintenance in this setting

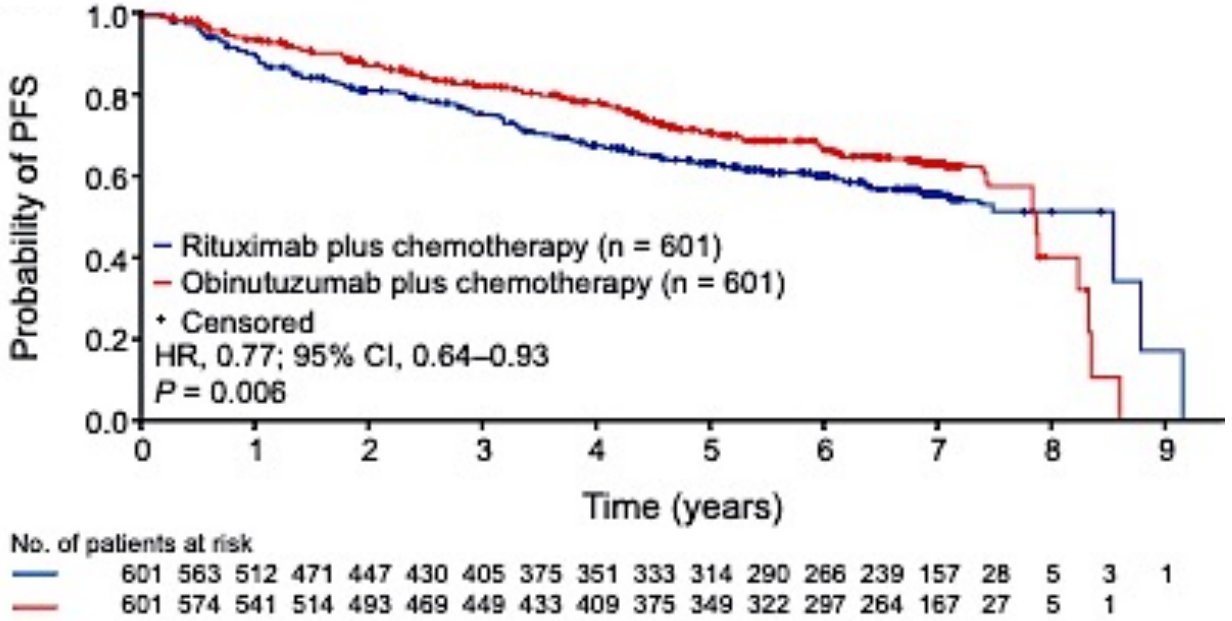
CD4 positive T cell counts over time: Bendamustine vs. CHOP



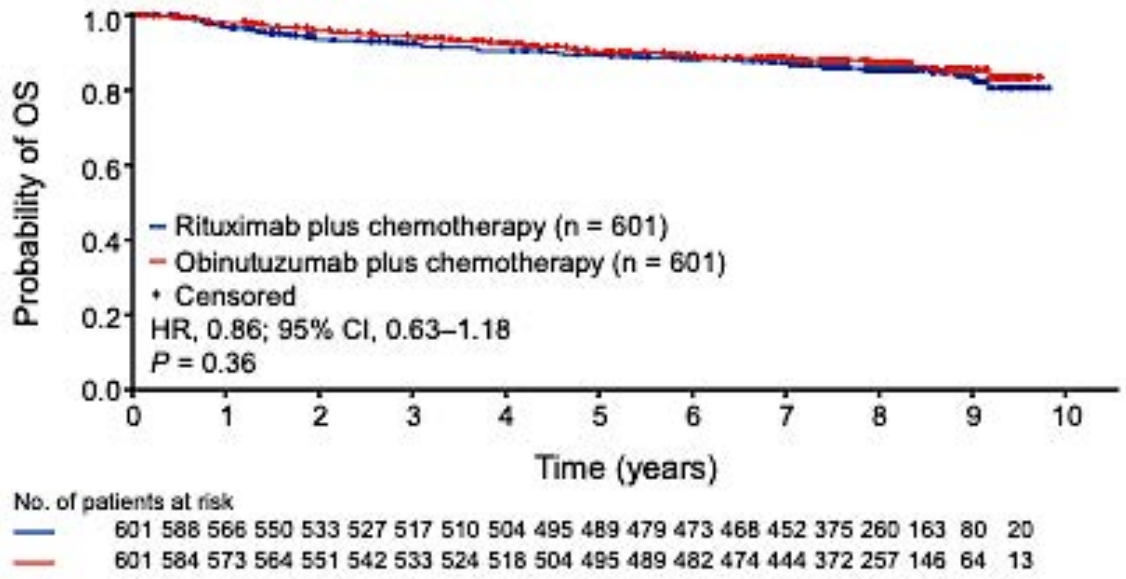
Hiddeman et al., *JCO* 36:2395-2404, 2018
Friedberg, *JCO* 36:2363-65, 2018

GALLIUM Phase III Obinutuzumab/chemo vs rituximab/chemo: Long-term follow-up

Progression-Free Survival

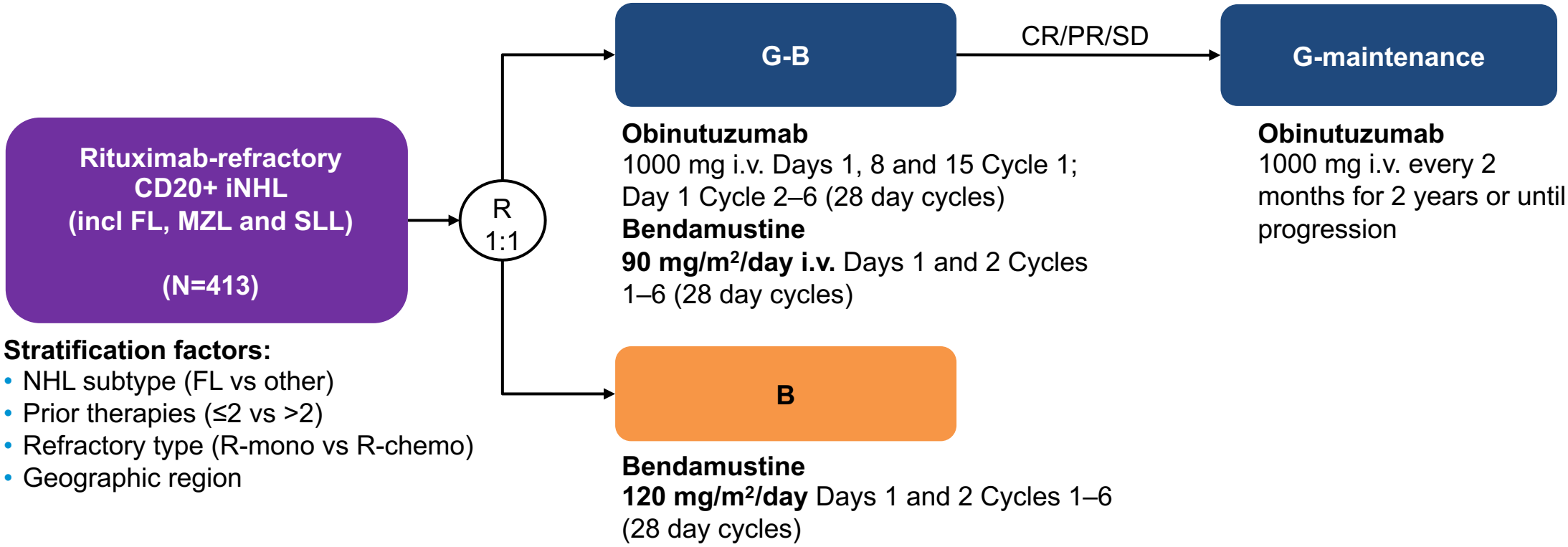


Overall Survival



Townsend et al., *HemaSphere,* 7:e919 2023

GADOLIN Study: Rituximab-refractory FL



- International, randomized, open-label study
- Response monitored by CT scan post-induction, then every 3 months for 2 years, then every 6 months (modified Cheson criteria 2007)

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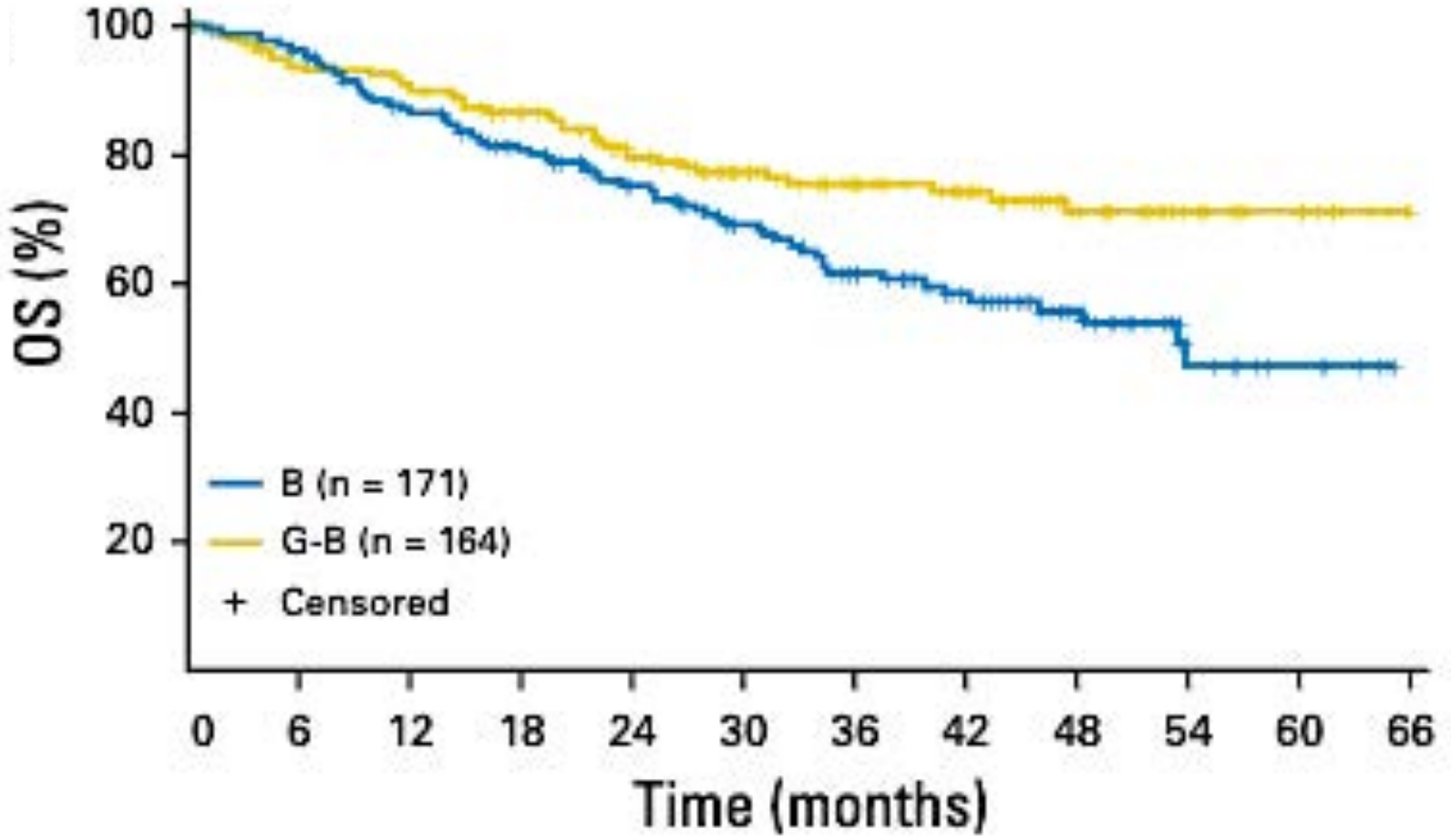
Sehn et al, *Lancet Oncol* 17:1081 2016

GADOLIN: OS improvement seen in long-term follow-up

OS: FL cohort



Cheson et al. *JCO* 36:2259-66, 2018

Lenalidomide

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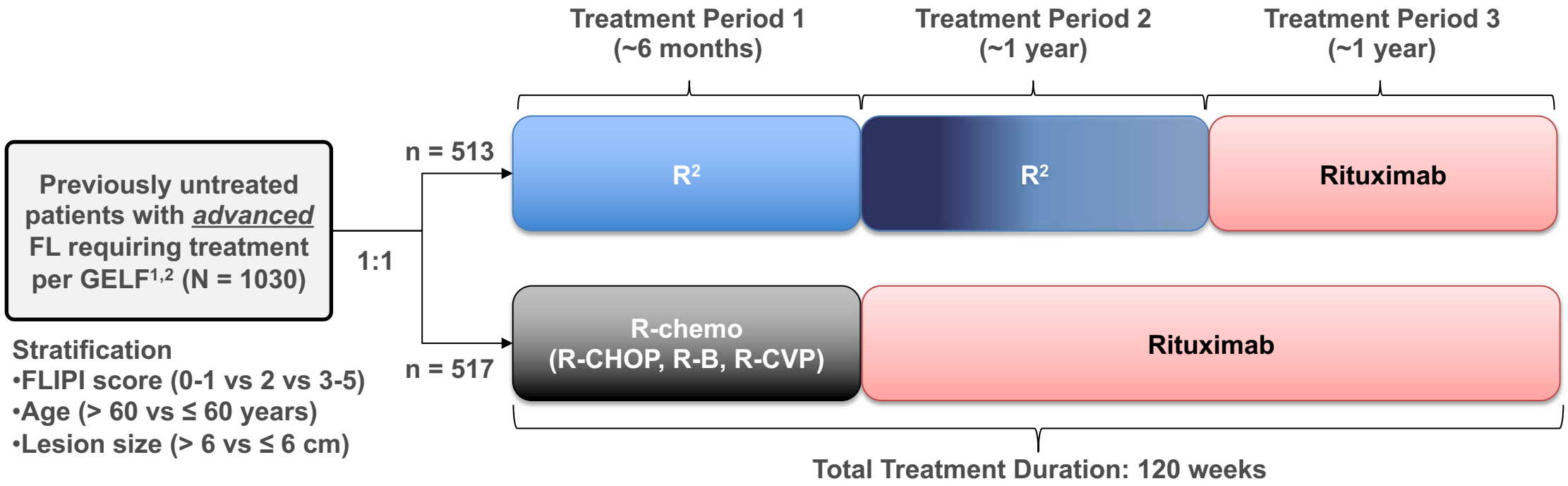
RELEVANCE: Study Design: R2 vs. R-chemo



Co-primary endpoints (superiority)*

- CR/CRu at 120 weeks
- PFS

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Morschhauser et al., *NEJM* 379:934-47 2018

Table 1. Baseline Demographic and Disease Characteristics (Intention-to-Treat Population).*

Characteristic	Rituximab–Lenalidomide Group (N=513)	Rituximab–Chemotherapy Group (N=517)	Total (N=1030)
Median age (range) — yr	59 (30–89)	59 (23–83)	59 (23–89)
Age >70 yr — no. (%)	80 (16)	78 (15)	158 (15)
Male sex — no. (%)	251 (49)	251 (49)	502 (49)
ECOG performance status — no. (%)†			
0	341 (66)	345 (67)	686 (67)
1	157 (31)	157 (30)	314 (30)
2	13 (3)	14 (3)	27 (3)
Could not be evaluated or data missing	2 (<1)	1 (<1)	3 (<1)
Ann Arbor stage — no. (%)‡			
I or II	30 (6)	40 (8)	70 (7)
III or IV	483 (94)	477 (92)	960 (93)
Bulky disease — no. (%)§	218 (42)	199 (38)	417 (40)
Follicular lymphoma grade — no. (%)			
1 or 2	437 (85)	443 (86)	880 (85)
3a	65 (13)	63 (12)	128 (12)
Unspecified grade or grade other than 1, 2, or 3a	11 (2)	11 (2)	22 (2)
Lactate dehydrogenase >ULN — no. (%)	156 (30)	137 (26)	293 (28)
Beta$_2$-microglobulin >ULN — no. (%)	261 (51)	262 (51)	523 (51)
B symptoms — no. (%)¶	141 (27)	134 (26)	275 (27)
FLIPI score — no. (%)‖			
0 or 1	77 (15)	76 (15)	153 (15)
2	183 (36)	191 (37)	374 (36)
3 to 5	253 (49)	250 (48)	503 (49)

RELEVANCE demographics

Median age 59 years

40% bulky disease ≥ 7cm

28% elevated LDH

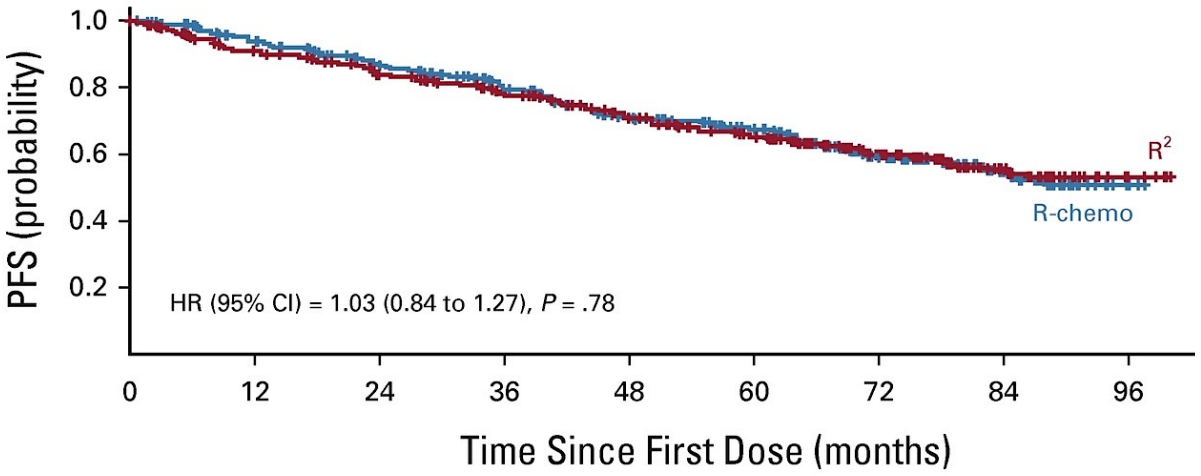
51% elevated beta-2 microglobulin

49% high risk FLIPI

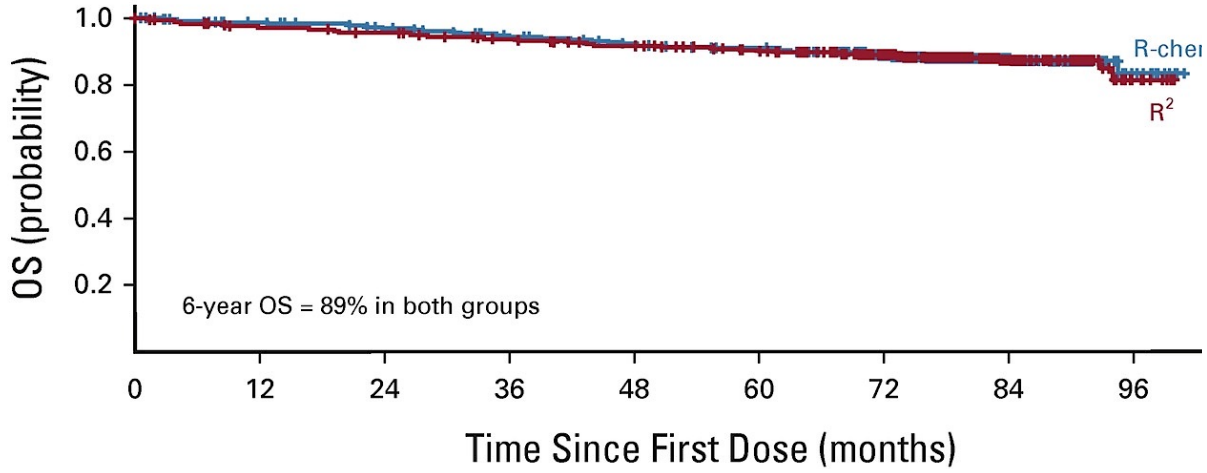
Morschhauser et al., *NEJM* 379:934-47 2018

RELEVANCE: Long-term outcomes (6 year follow-up)

Progression-Free Survival

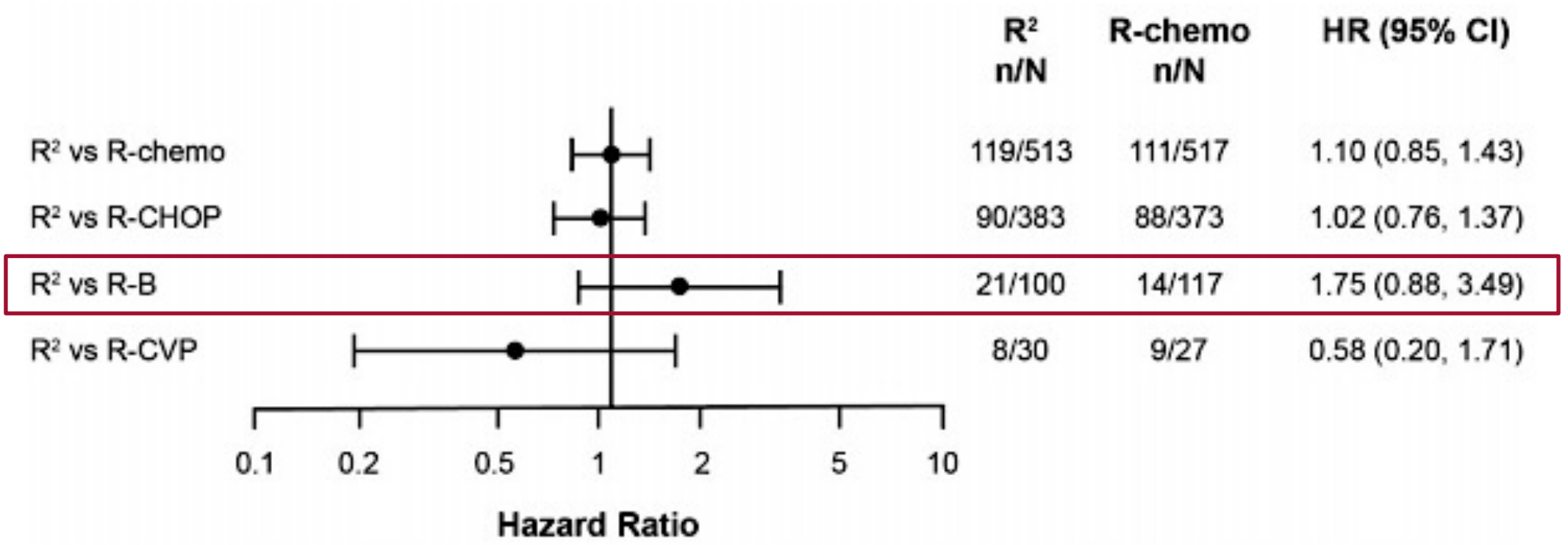


Overall Survival



Morschhauser et al., *J Clin Oncol* 40:3239 2022

RELEVANCE: Hazard ratios (not randomized)



Morschhauser et al., *NEJM* 379:934-47 2018

Adverse events

More common R-chemo

- Anemia
- Fatigue
- Vomiting
- Neuropathy
- Leukopenia
- Febrile neutropenia (7%)
- Alopecia

More common R2

- Rash
- Diarrhea
- Abdominal pain
- Myalgia
- Muscle spasms
- Tumor flare

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Morschhauser et al., *NEJM* 379:934-47 2018

Adverse events

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More common R2

- Rash
- Diarrhea
- Abdominal pain
- Myalgia
- Muscle spasms
- Tumor flare

Percentage of patients with grade 3 or 4 adverse events was similar between two groups (65% R2 vs. 68% R-chemo). Deaths were 1% in each group.

Withdrawals from treatment:

43 patients in R2

16 patients in R-chemo

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Morschhauser et al., *NEJM* 379:934-47 2018

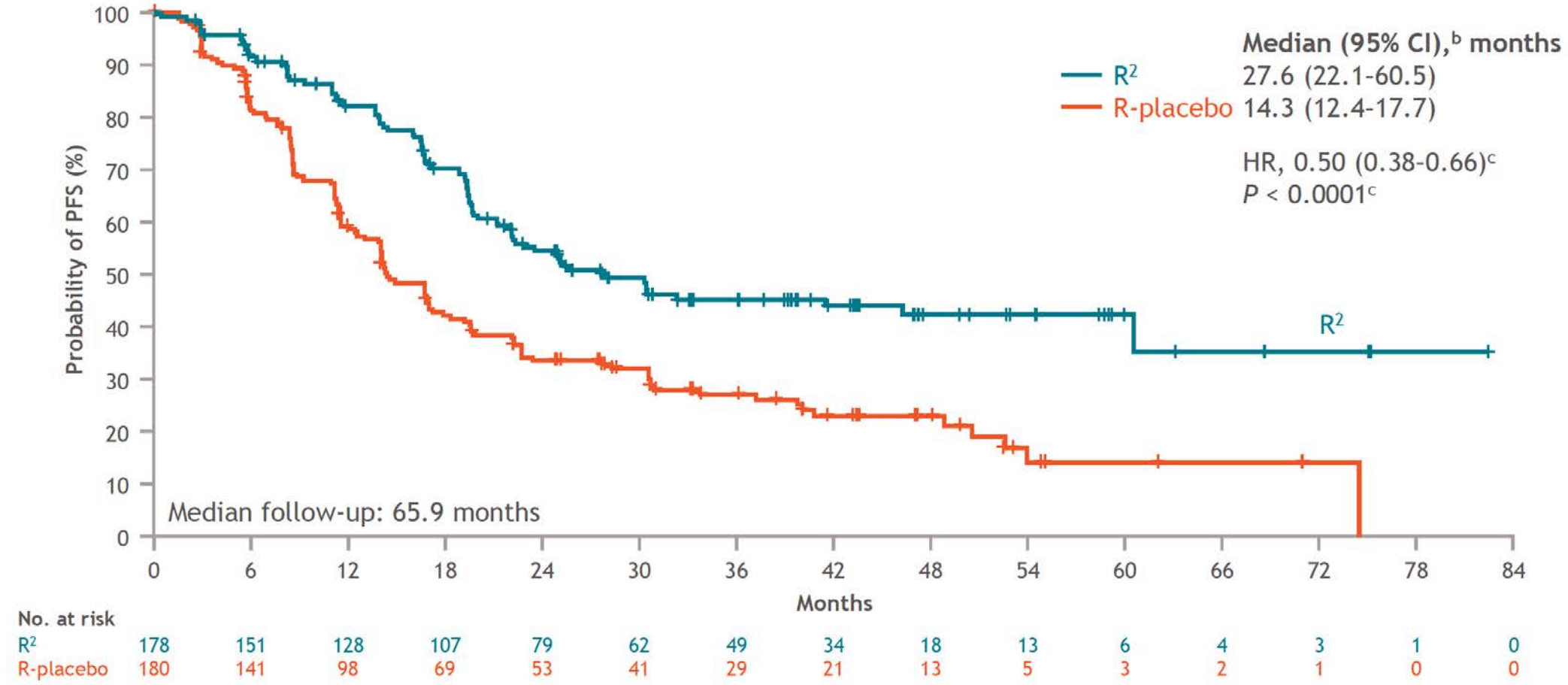
Five-year results and overall survival update from the phase 3 randomized study AUGMENT: lenalidomide plus rituximab versus rituximab plus placebo in patients with relapsed/refractory indolent non-Hodgkin lymphoma

John P. Leonard,[1] Marek Trneny,[2] Fritz Offner,[3] Jiri Mayer,[4] Huilai Zhang,[5] Grzegorz S. Nowakowski,[6] Phillip Scheinberg,[7] Argyrios Gkasiamis,[8] Joanna Mikita-Geoffroy,[8] Everton Rowe,[8] John G. Gribben,[9] on behalf of the AUGMENT trial investigators

[1]Weill Cornell Medicine and New York Presbyterian Hospital, New York, NY, USA; [2]Charles University, General Hospital, Prague, Czech Republic; [3]Ghent University Hospital, Ghent, Belgium; [4]Masaryk University, Brno, Czech Republic; [5]Tianjin Medical University Cancer Institute and Hospital, Tianjin, People's Republic of China; [6]Mayo Clinic, Rochester, MN, USA; [7]Hospital A Beneficênica Portuguesa de São Paulo, São Paulo, Brazil; [8]Bristol Myers Squibb, Princeton, NJ, USA; [9]Barts Cancer Institute, Queen Mary University of London, London, UK

ASH 2022, Presentation 230

AUGMENT: Progression-Free Survival (ITT Population)

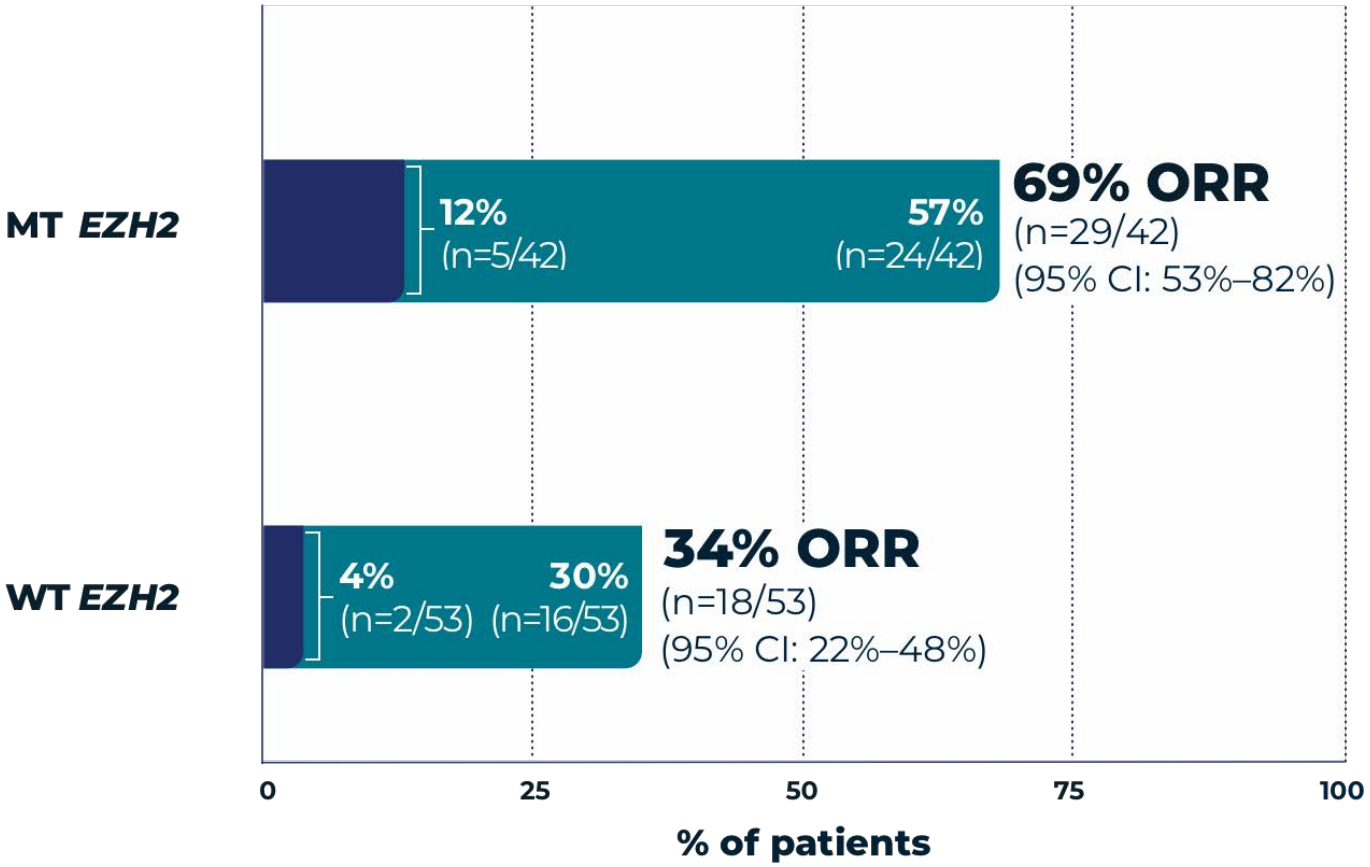


- Median PFS was 27.6 months for R² versus 14.3 months for R-placebo (HR, 0.50; *P* < 0.0001)

Leonard JP et al. ASH 2022;Abstract 230.

EZH2 inhibition

Tazemetostat targets EZH2 in follicular lymphoma



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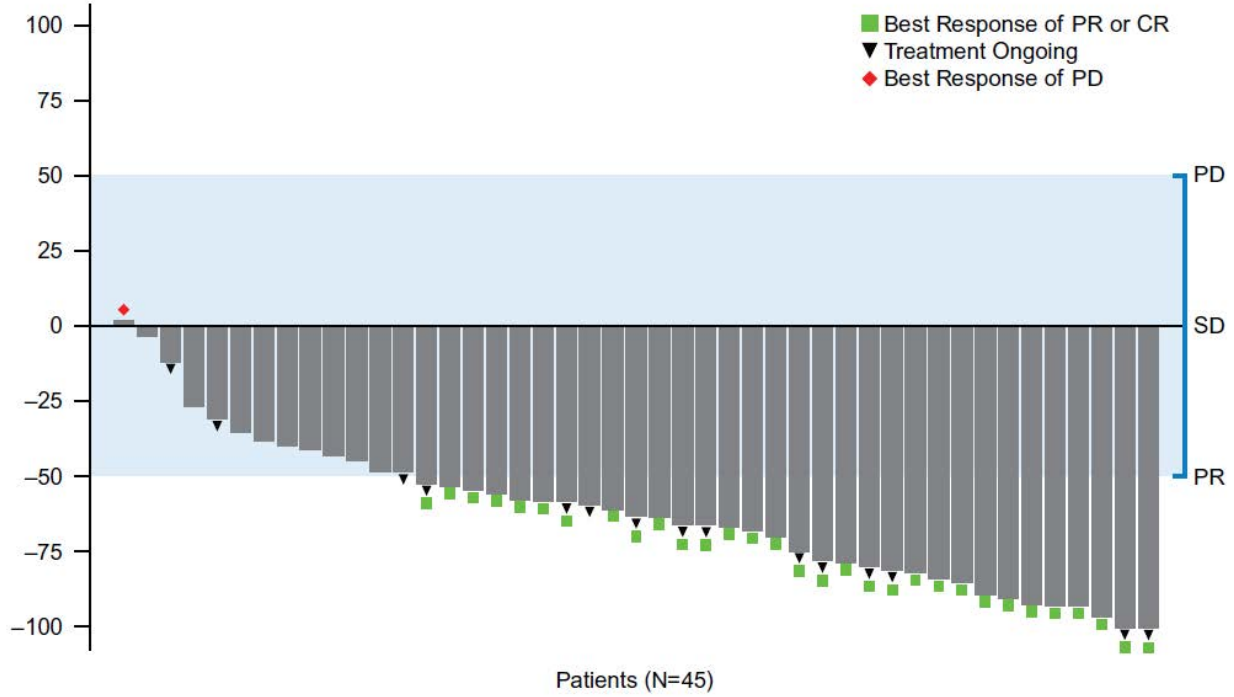
Phase 2 study of tazemetostat (EZH2 inhibitor) in FL

Response in the MT EZH2 Cohort

High Concordance Between IRC and Investigator Assessed Response



- **44 of 45 (98%) patients with evidence of tumor reduction by IRC**

Morchhauser et al., *Lancet Oncol* 21:1433-42 2020

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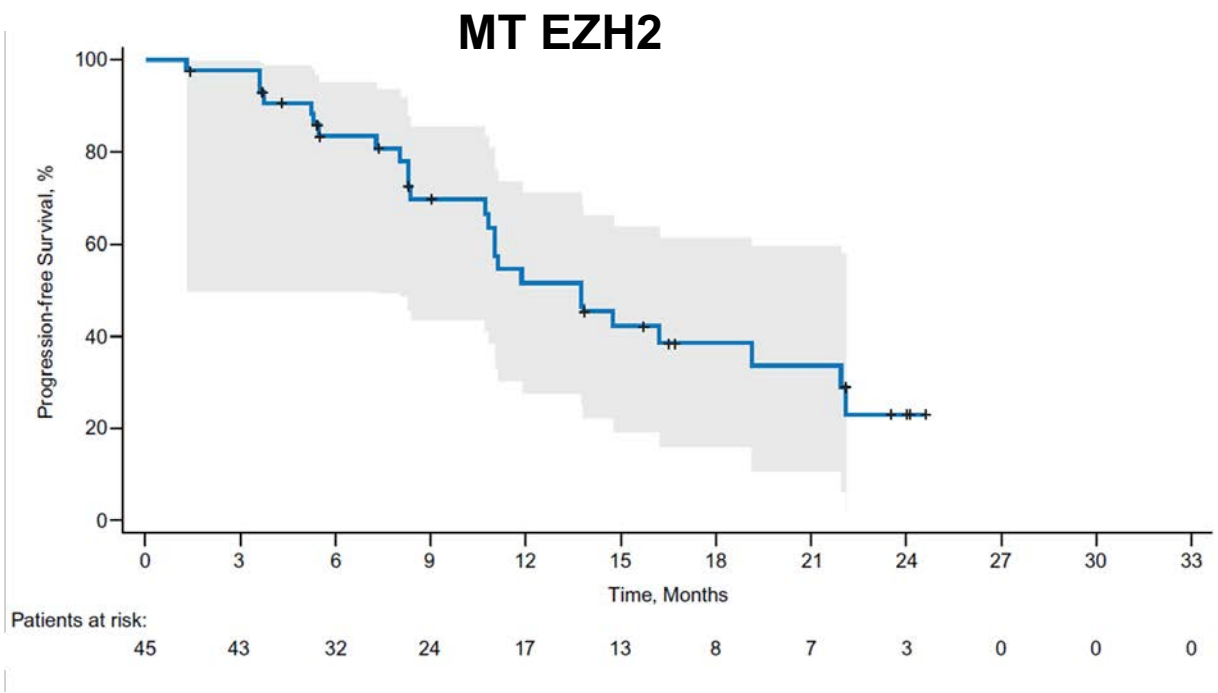
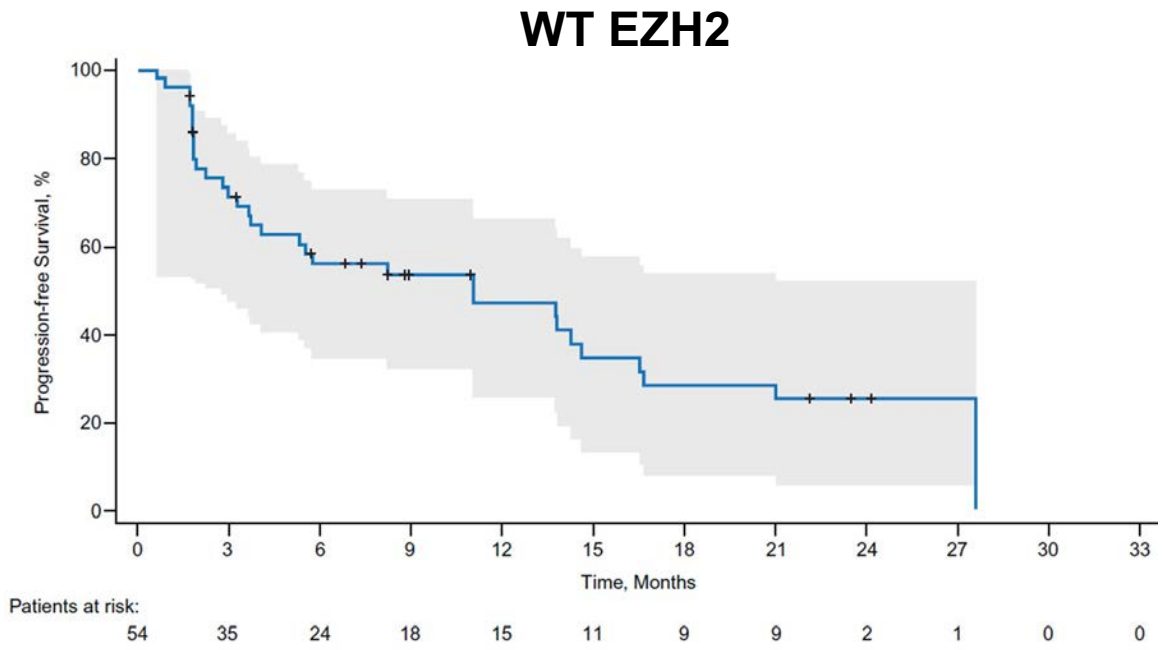
Phase 2 study of tazemetostat (EZH2 inhibitor) in FL





Median PFS of 13.8 and 11.1 months was Observed in MT and WT EZH2 Cohorts

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Morchhauser et al., *Lancet Oncol* 21:1433-42 2020

Phase IB SYMPHONY Study

- Tazemetostat, rituximab, lenalidomide in relapsed follicular lymphoma
  - Tazemetostat dose was 800mg daily
- 44 enrolled patients
  - 82% wild-type EZH2
  - 27% POD 24
- CR: 55%; 41% PR
- Median follow-up 22 months; PFS not reached

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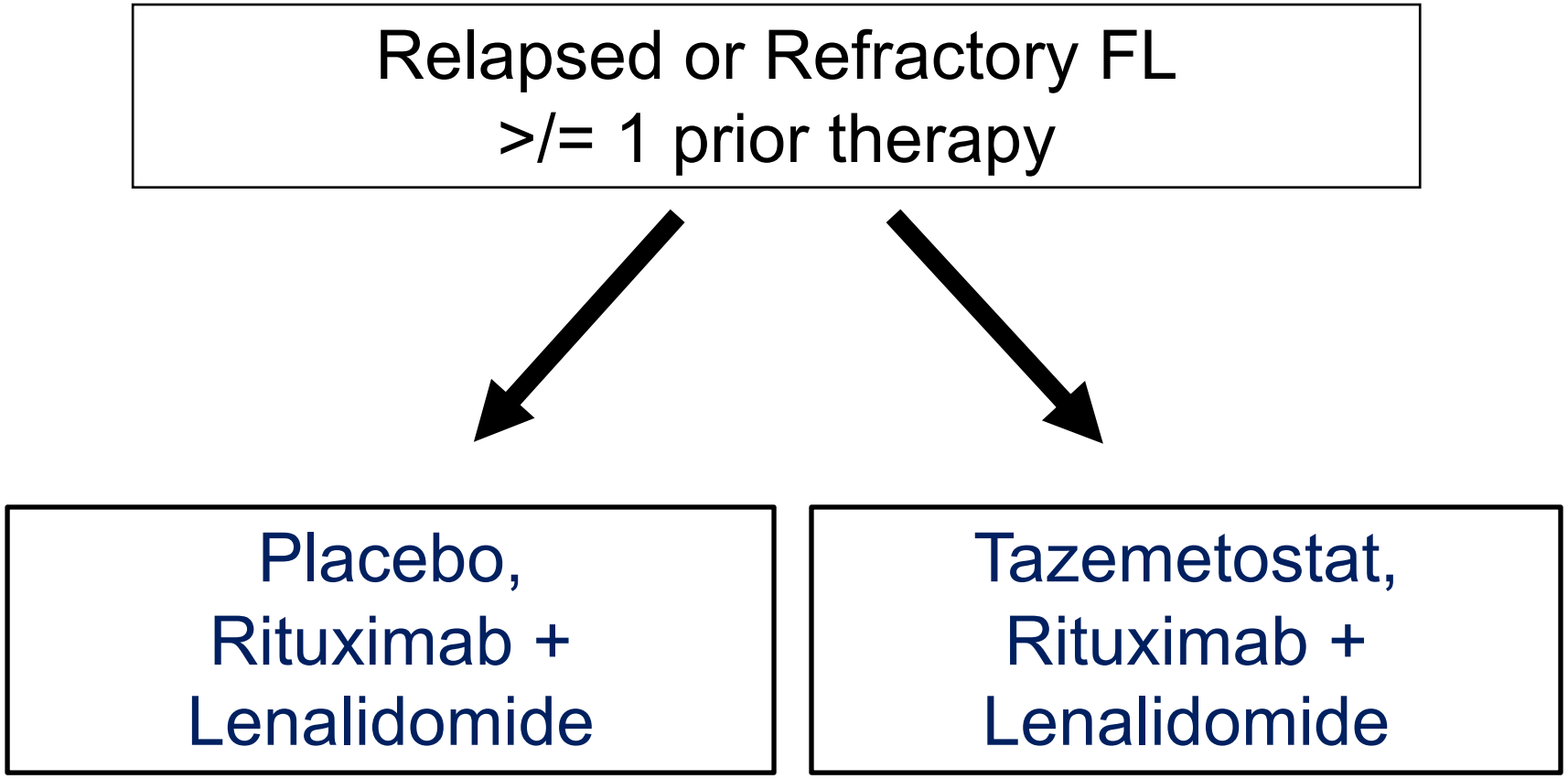
Salles et al., *ASH 2023* abstract 3035

Phase III SYMPHONY trial



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NCT04224493

BTK inhibitors

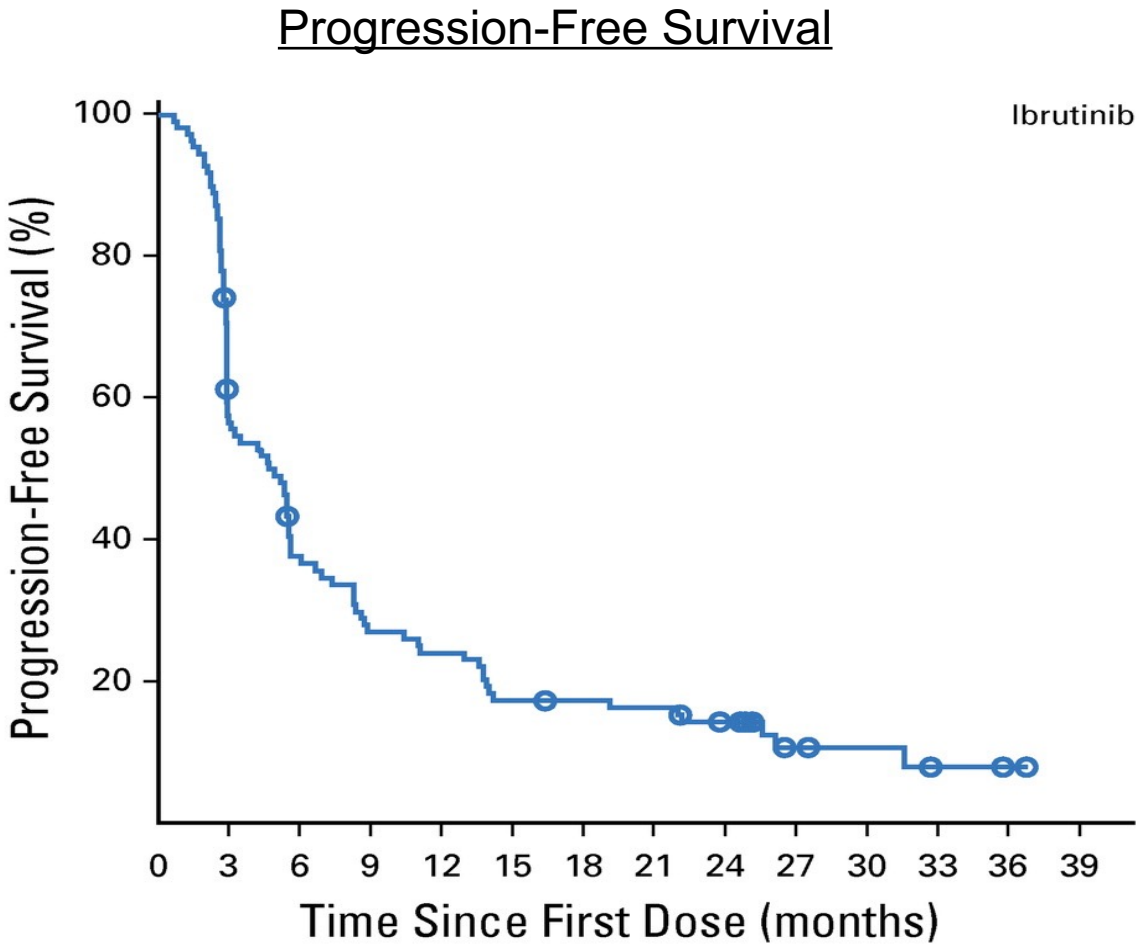
Reprised assessment

DAWN: Ibrutinib in relapsed/refractory FL

110 patients:
- ORR: 21%
- CR: 11%

Median PFS: 4.6 months

Did not meet prespecified endpoint



Gopal et al., *JCO* 36: 2405-12 2018

ROSEWOOD: Zanubrutinib + obinutuzumab vs. Obinutuzumab

Relapsed FL (N=217):

ORR: 69% vs. 46%

CR: 39% vs. 19%

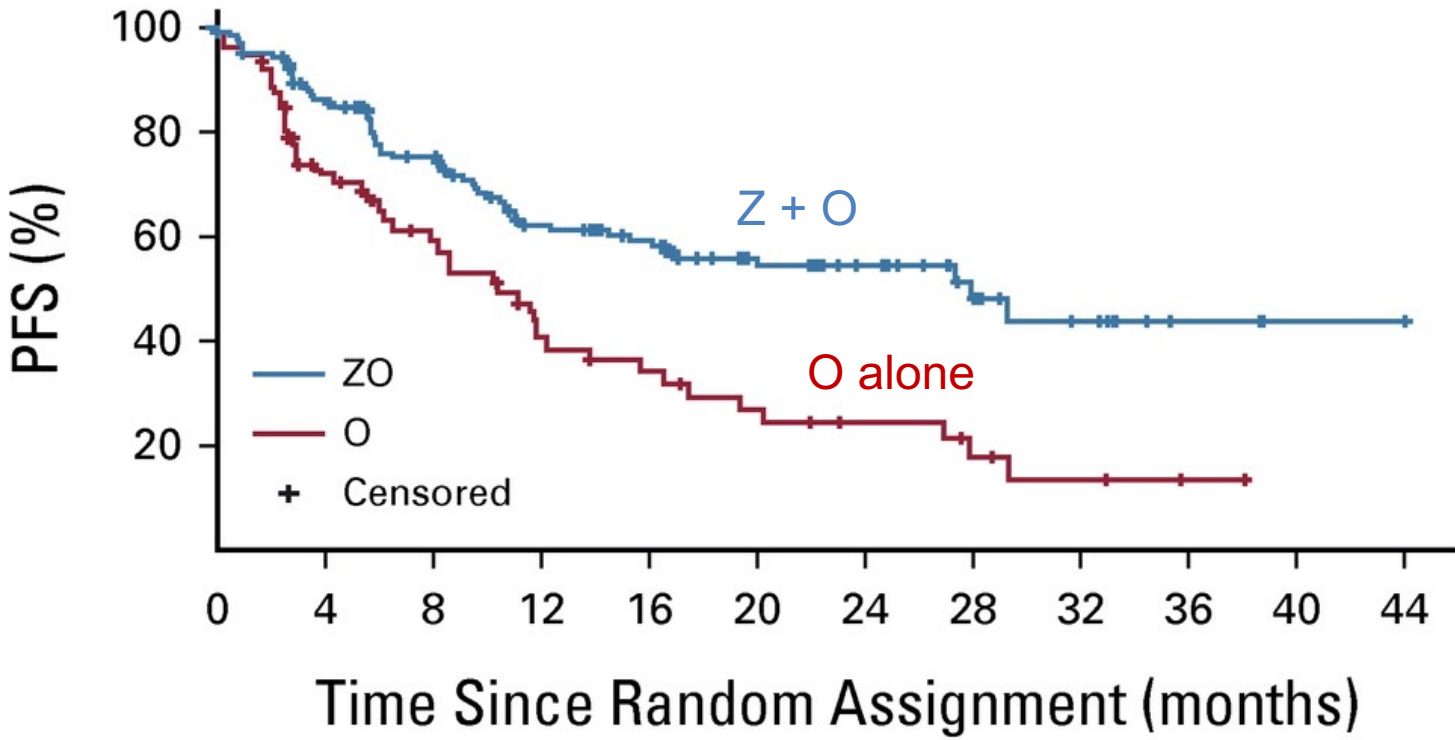
Median PFS: 28 vs. 10 months

Previous POD 24: 37%

Why is this better than ibrutinib alone?

Second generation BTK?

Combination therapy?



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Zinzani et al., *JCO* 41: 5107-19 2023

ASH 2023
BTK inhibitors for FL

- 3026: Pirtobrutinib Phase 1/2 BRUIN study
- 983: Acalabrutinib, lenalidomide and rituximab

ASH 2023
Novel agents for high-risk follicular lymphoma

- 4466: Pembrolizumab, rituximab, lenalidomide after CAR-T
- 1659: Obinutuzumab, lenalidomide, venetoclax
- 297: Tazemetostat + R-CHOP

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Some thoughts:
Key questions moving forward

- Can we cure follicular lymphoma?
- Can we define molecular subsets for rational therapeutic targeting?
- Can we design robust randomized trials to definitively demonstrate clinical benefit?
- How do we sequence and prioritize novel agent development?

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Agenda

Module 1: Evolving Role of Novel Treatment Strategies in Follicular Lymphoma (FL) — Dr Friedberg

Module 2: Integration of Chimeric Antigen Receptor (CAR) T-Cell Therapies and Bispecific Antibodies into the Management of FL — Dr Abramson

Module 3: Up-Front Treatment for Mantle Cell Lymphoma (MCL) — Dr Kahl

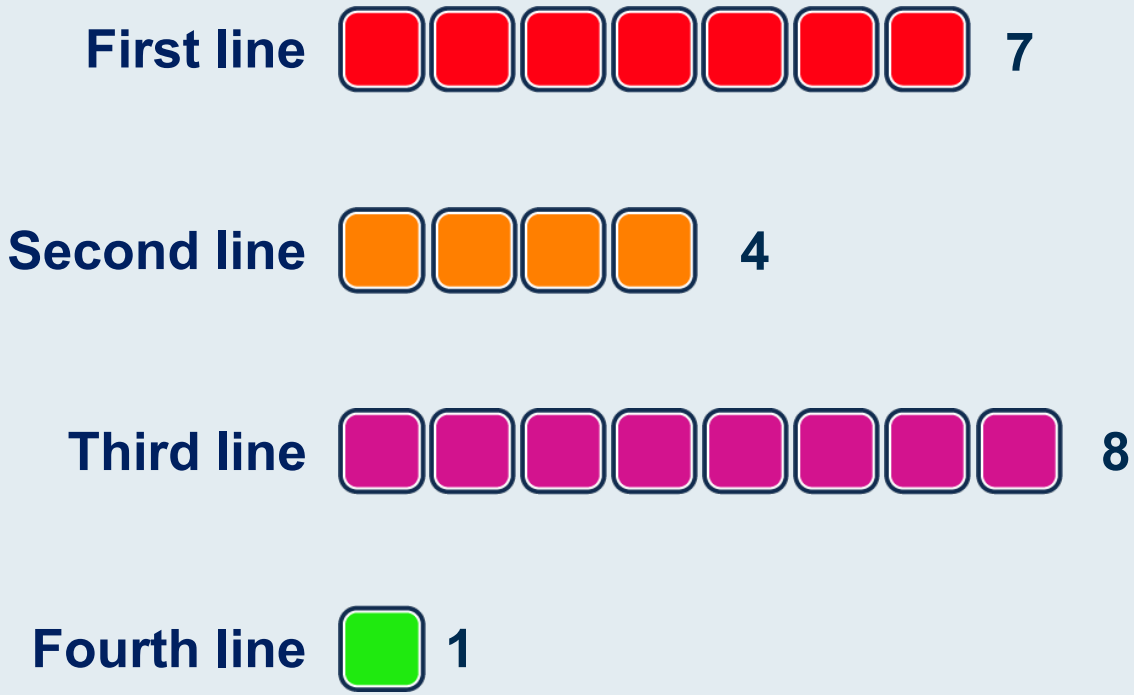
Module 4: Therapeutic Sequencing for Patients with Relapsed/Refractory (R/R) MCL — Dr Cohen

Module 5: First-Line Treatment Strategies for Hodgkin Lymphoma (HL) — Dr Bartlett

Module 6: Current and Future Management of R/R HL — Dr Ansell

RTP
RESEARCH TO PRACTICE

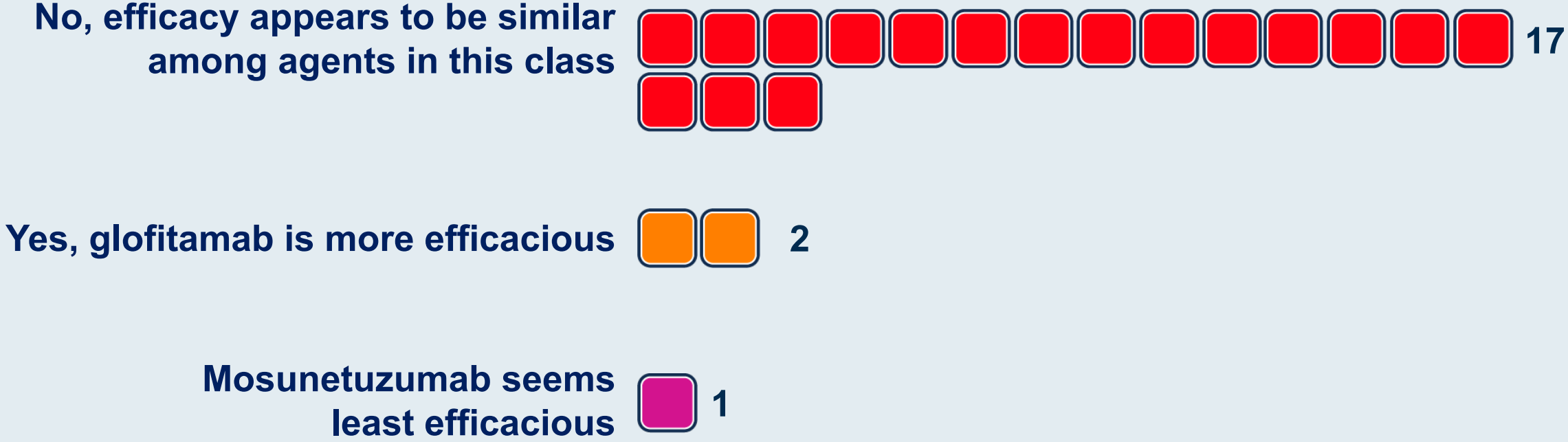
Regulatory and reimbursement issues aside, at what point would you like to use a CD20/CD3 bispecific antibody for a patient with Stage III FL?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

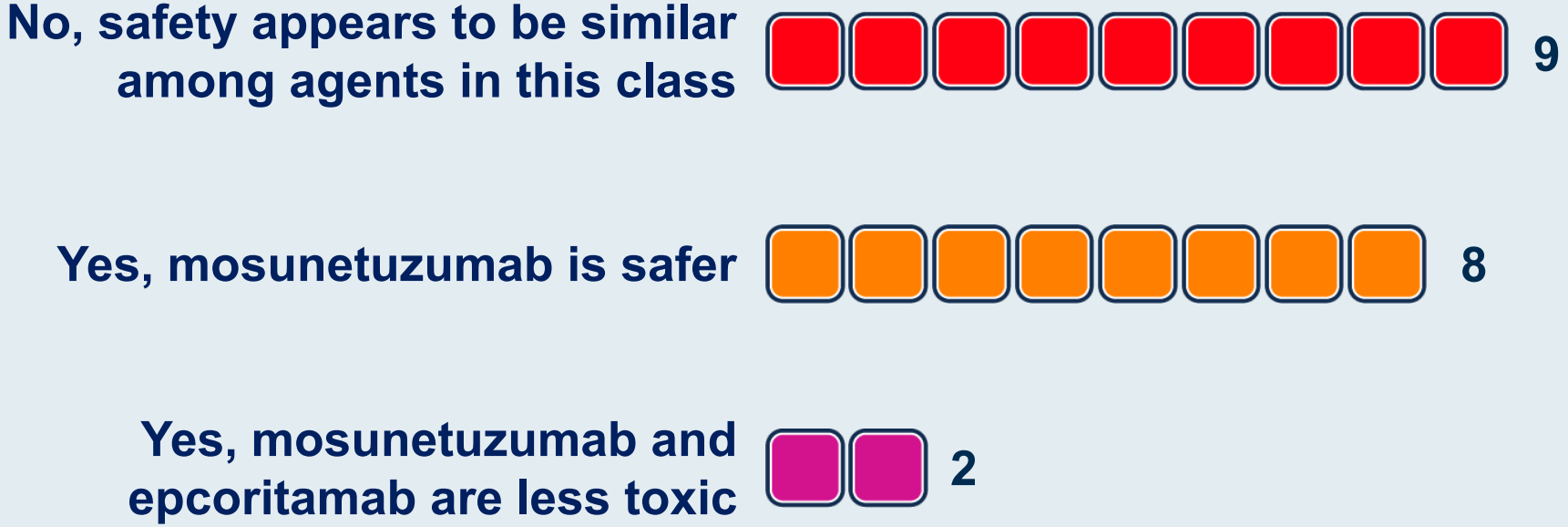
Based on your personal clinical experience and knowledge of available data, do you believe 1 or more CD20/CD3 bispecific antibodies are more efficacious than the others when used in the management of FL?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

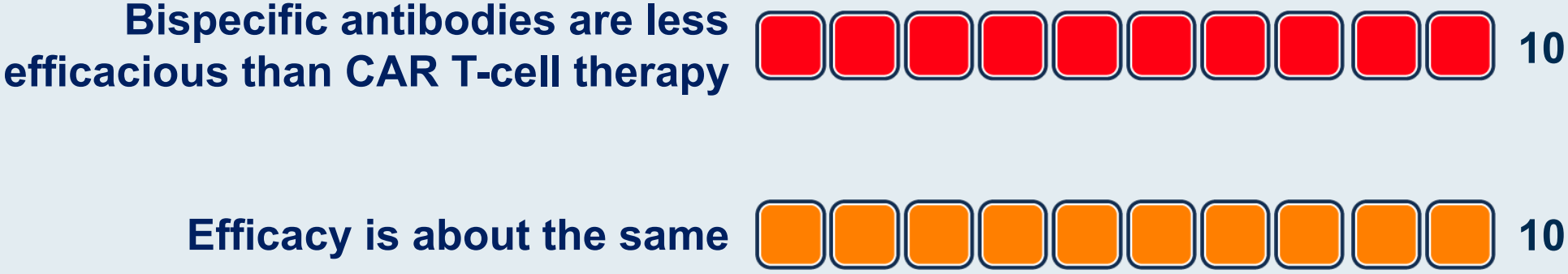
Based on your personal clinical experience and knowledge of available data, do you believe 1 or more CD20/CD3 bispecific antibodies are safer/less toxic than the others when used in the management of FL?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

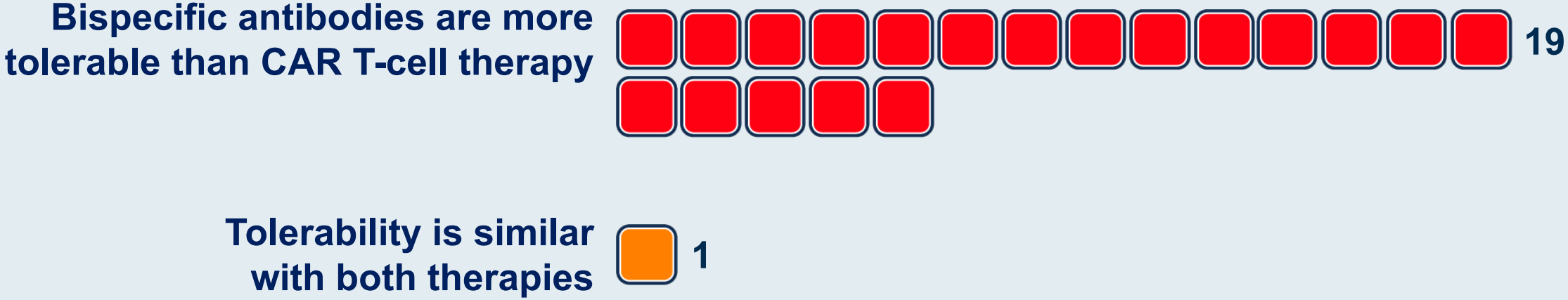
Based on your personal clinical experience and knowledge of available data, how would you compare the global efficacy of CD20/CD3 bispecific antibodies to that of CAR T-cell therapy for patients with FL?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Based on your personal clinical experience and knowledge of available data, how would you compare the global tolerability of CD20/CD3 bispecific antibodies to that of CAR T-cell therapy for patients with FL?

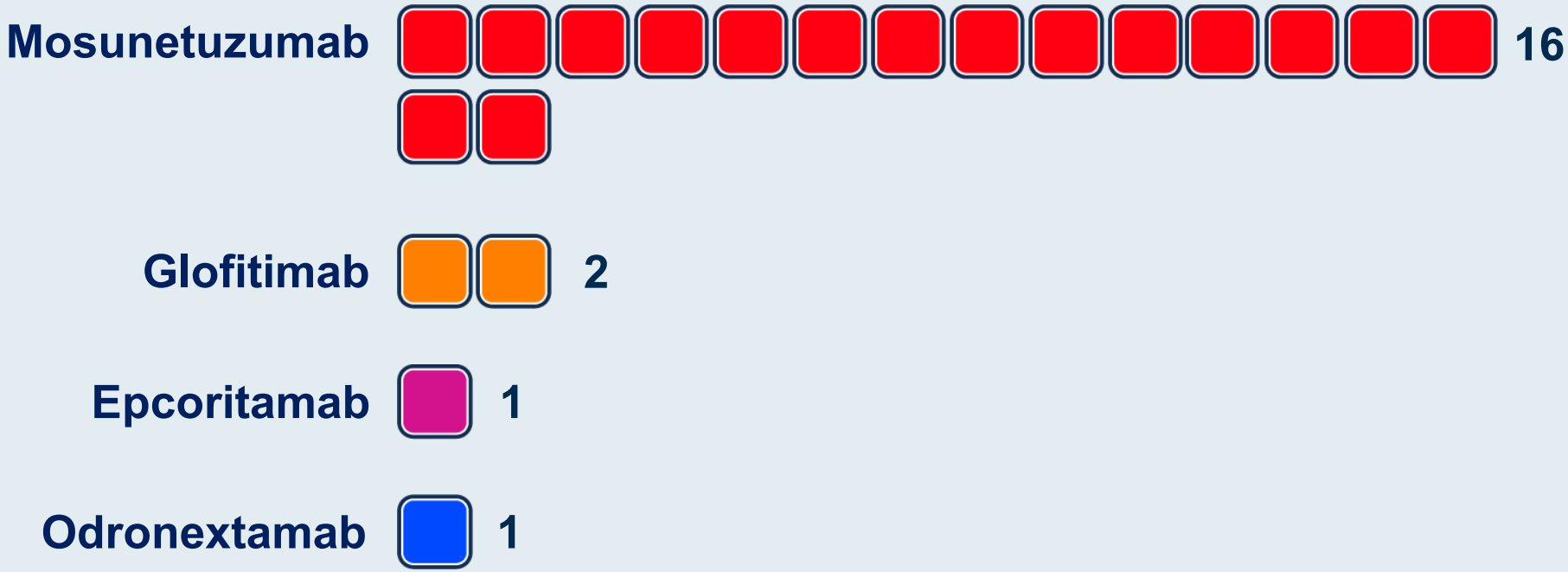


Survey of 20 US-based clinical investigators November 2023

Please describe the last patient with FL in your practice who received a bispecific antibody (either on or off protocol).

Patient age: 68 (median; range 55-82)

Bispecific antibody the patient received:

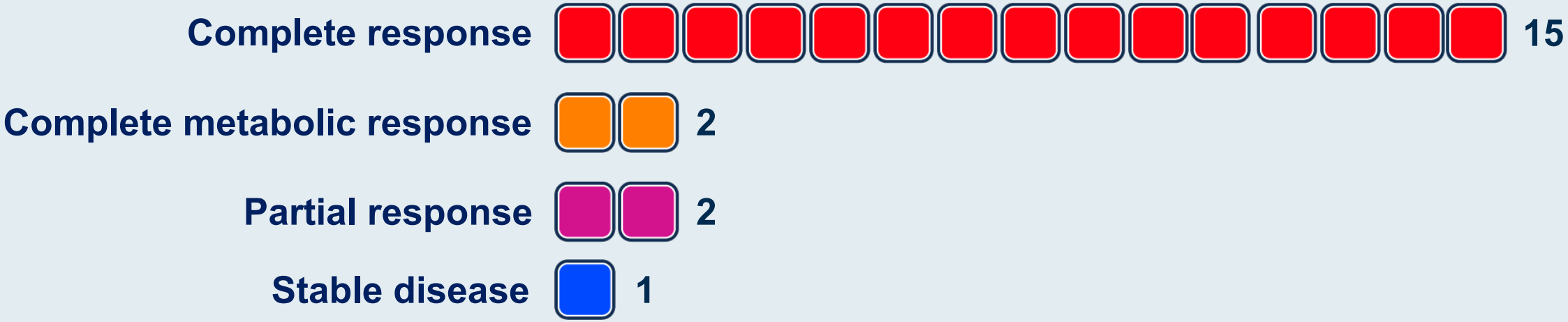


Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Please describe the last patient with FL in your practice who received a bispecific antibody (either on or off protocol).

Patient's response to therapy:

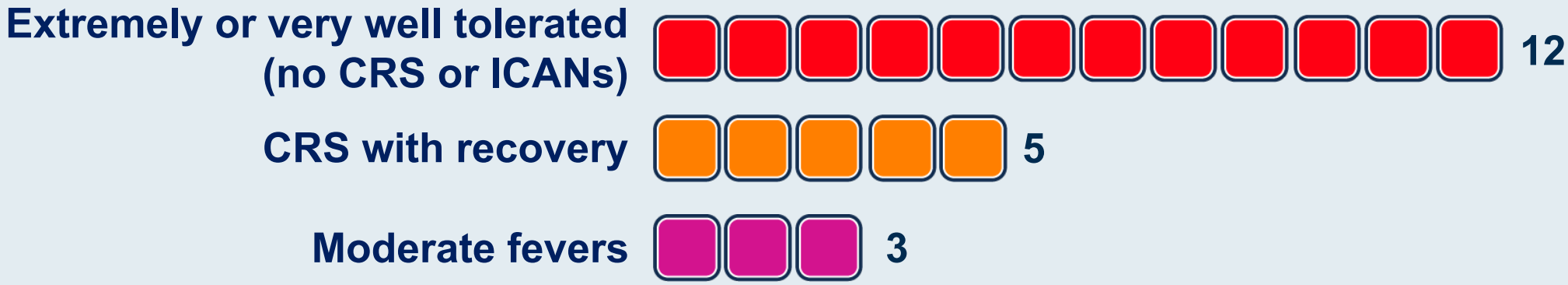


Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Please describe the last patient with FL in your practice who received a bispecific antibody (either on or off protocol).

Patient's tolerance of therapy:



CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

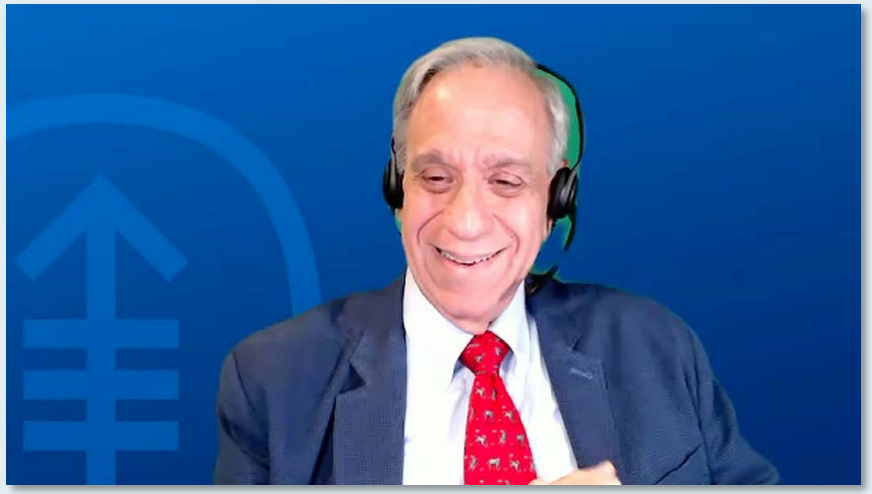
Based on your personal clinical experience and knowledge of available data, for each of the following agents please estimate the percent chance that a patient with FL will experience toxicity during treatment that requires dosing to be held. What is the primary toxicity patients experience that leads to withholding dosing?

	Chance of withholding (Median)	Primary toxicity
Epcoritamab	10%	Cytopenias, CRS
Glofitamab	10%	Cytopenias, CRS
Mosunetuzumab	10%	Cytopenias, CRS
Odronextamab	13%	Cytopenias, CRS
Tazemetostat	3%	Cytopenias, GI toxicity

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Activity and tolerability of mosunetuzumab in FL



Andrew D Zelenetz, MD, PhD

Tycel Phillips, MD

RTP
RESEARCH
TO PRACTICE

Risk of infections associated with bispecific antibody therapy

Franck Morschhauser, MD, PhD

RTP
RESEARCH
TO PRACTICE

Mass General Brigham
Mass General Cancer Center

Integration of Chimeric Antigen Receptor (CAR) T-Cell Therapies and Bispecific Antibodies into the Management of Follicular Lymphoma

Jeremy S. Abramson, MD, MMSc

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

ZUMA-5 Study of axi-cel in relapsed/refractory FL and MZL

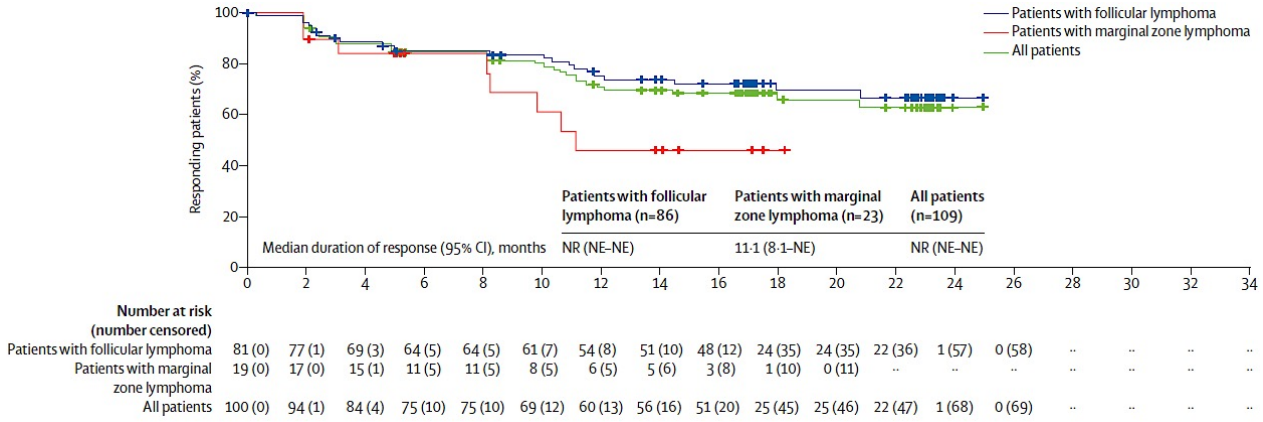
Characteristic	FL n=124	MZL N=24	All patients N=148
Median age (range)	60 (53-67)	65 (61-72)	61 (53-68)
FLIPI 3-5	54 (44%)	N/A	N/A
High tumor burden (GELF)	64 (52%)	10 (42%)	74 (50%)
Median prior tx (range)	3 (2-4)	3 (2-5)	3 (2-5)
Refractory to last tx	84 (68%)	18 (75%)	102 (69%)
POD24	68 (55%)	13 (57%)	81 (55%)

	All patients (n=109)	FL (n=86)	MZL (n=23)
ORR	92%	**94%**	83%
CRR	76%	**79%**	65%

Toxicity	N=148
CRS	82%
gr 3-4	7%
ICANS	59%
gr 3-4	19%

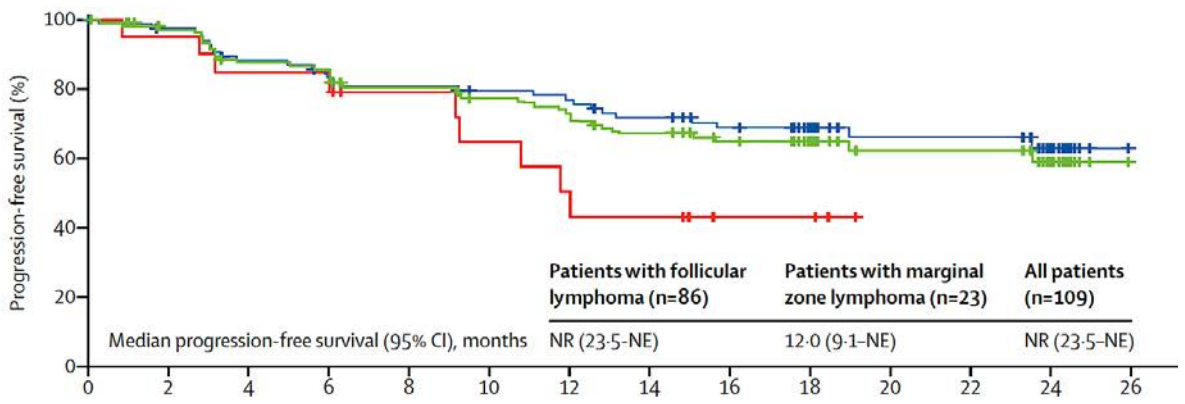
Duration of response

18 month DOR 66%



Progression-free survival

18 month PFS 65%



13 FL and 11 MZL retreated after response at median 11 months. ORR 100%, CRR 77%. 46% had ongoing response at median of 11 months f/u

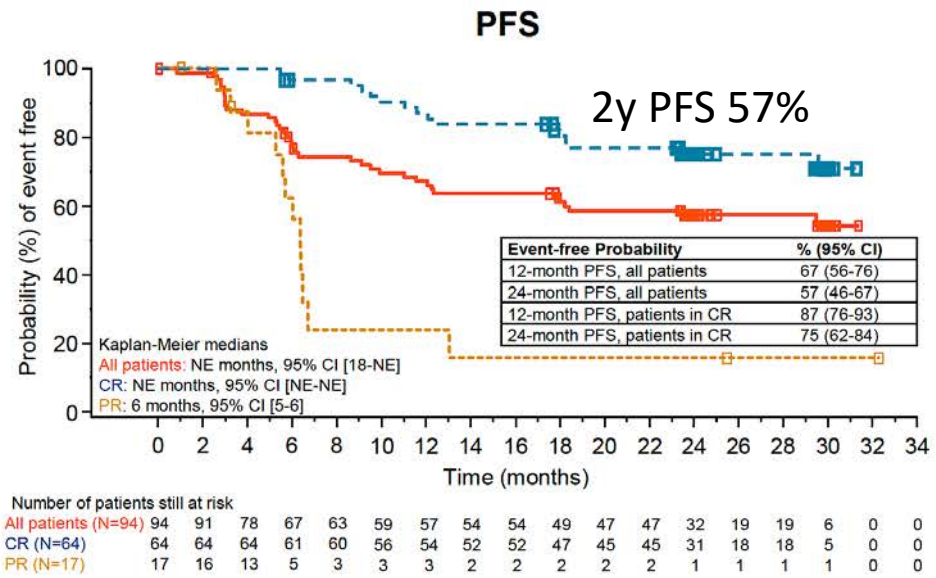
Jacobson, et al. Lancet Onc 2022.

ELARA: Tisagenlecleucel in R/R Follicular Lymphoma

Characteristic	n=97
Median age (range)	57 (49-64)
Median prior tx (range)	**4 (2-13)**
Refractory to last tx	78%
POD24	63%
Bulky disease	64%
FLIPI high (≥3)	60%
Double refractory	68%

	All patients n=94
ORR	**86%**
CRR	**69%**

Baseline Disease Characteristic	All Patients n (%) N=97	CRR % (95% CI)	ORR % (95% CI)
POD24	61 (63)	59 (46-71)	82 (70-91)
High metabolic tumor volume[d]	20 (21)	40 (19-64)	75 (51-91)
Bulky disease[e]	62 (64)	65 (51-76)	86 (74-93)
Double refractory	65 (67)	66 (53-77)	85 (74-92)
High FLIPI (≥3)	57 (59)	61 (48-74)	81 (68-90)



Toxicity	N=97
CRS	49%
gr 3-4	0%
ICANS	4%
gr 3-4	1%

Median Follow-Up of 29 Months

Dreyling M et al. ASH 2022;Abstract 608.

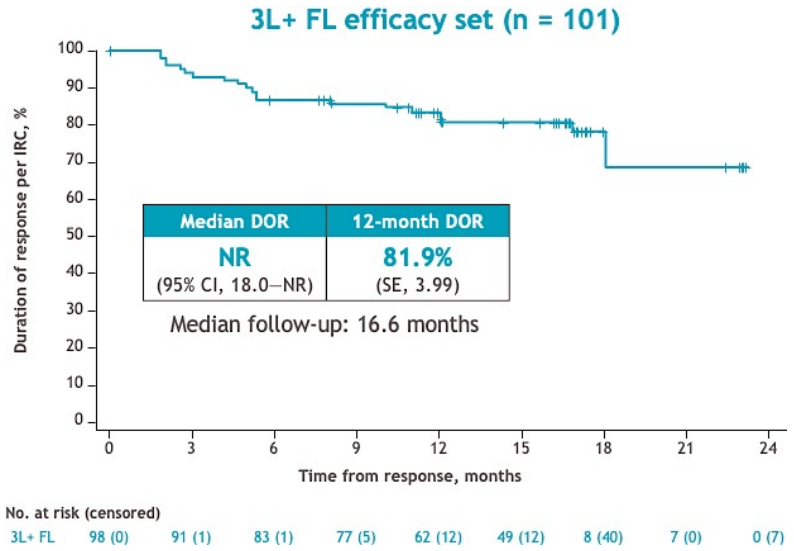
TRANSCEND FL study of lisocabtagene maraleucel (liso-cel) in relapsed/refractory follicular lymphoma

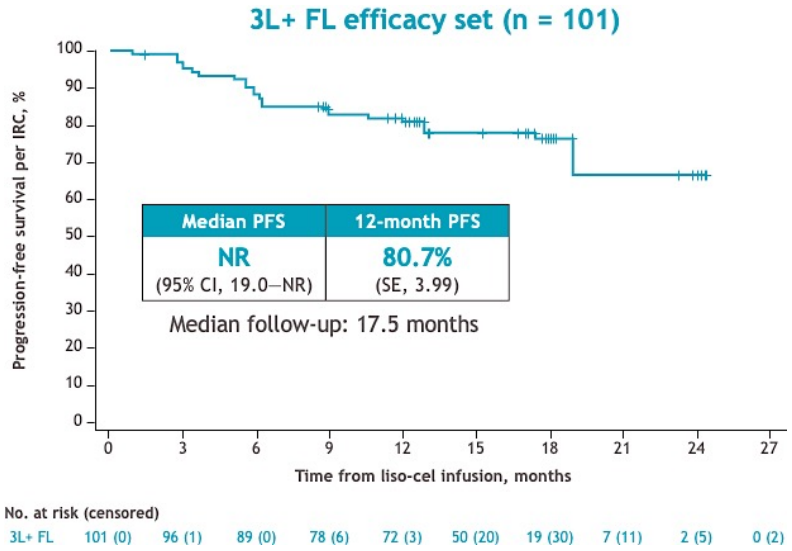
- 107 pts treated with liso-cel for 3rd line and later follicular lymphoma included in efficacy analysis
- An additional 23 patients with high-risk FL treated in 2nd line included in safety analysis

Characteristics for 3L+ FL	N=107
Median age	62 (34-80)
Median prior therapies	3 (2-10)
FLIPI high risk	57%
Prior ASCT	31%
Elevated LDH	44%
Chemorefractory	67%
POD24	54%

Response	N=101
Overall response	**97%**
Complete response	**94%**

CRS and ICANS	N=130
CRS	
Any grade	58%
Grade ≥3	1%
ICANS	
Any grade	15%
Grade ≥3	2%





Morschhauser, et al. Proc ICML 2023, #LBA4

Mosunetuzumab IV in relapsed/refractory follicular lymphoma

Patients in CR at cycle 8 discontinued tx, pts in less than CR completed 9 additional cycles

Characteristic	n=90
Median age (range)	60 (53-67)
Median prior tx (range)	3 (IQR 2-4)
Refractory to last line of tx	69%
POD24	52%
Bulky disease	34%
FLIPI high (≥3)	45%
Double refractory	53%

Best response	
Overall response	**80%**
Complete response	**60%**

AEs of special interest	
CRS, any grade Grade 3-4	44% 2%
Neurotoxicity, any grade Grade 3-4	5.5% 0%

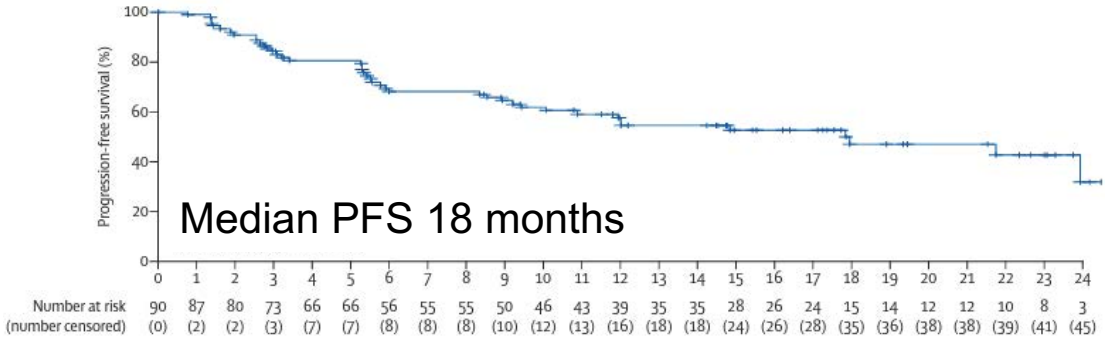
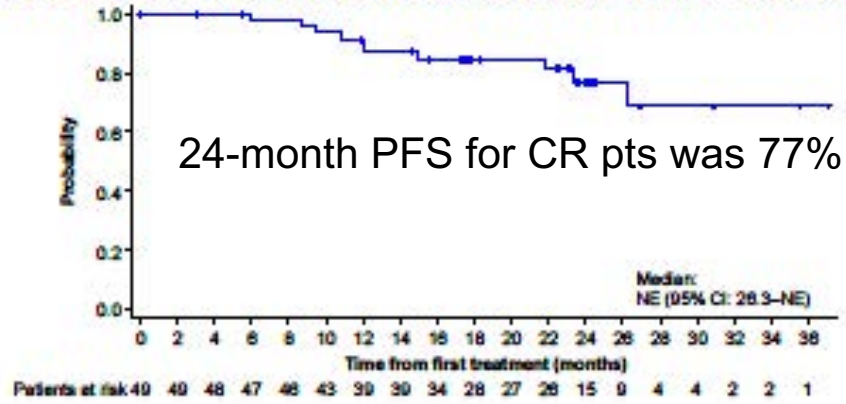


Table 3. Time to event outcomes in patients with an early or late CR, or PR as best response.

	Early CR n=33	Late CR n=21	PR as best response n=16
Median DOR, months (95% CI)	NE (23.2–NE)	NE (22.8–NE)	4.0 (2.5–6.7)
24-month DOR rate, % (95% CI)	67.8 (43.5–92.0)	66.1 (39.3–93.0)	NE (NE–NE)
Median PFS, months (95% CI)	NE (26.3–NE)	NE (24.0–NE)	5.4 (4.1–11.8)
24-month PFS rate, % (95% CI)	79.2 (64.1–94.2)	65.1 (37.7–92.5)	NE (NE–NE)
Median OS, months (95% CI)	NE (NE–NE)	NE (32.2–NE)	NE (NE–NE)
24-month OS rate, % (95% CI)	100 (100–100)	100 (100–100)	78.8 (56.9–100)

Figure 3. PFS in patients with a CR at EOT from time of first treatment (n=49).



Budde, et al. Lancet Onc 2022
Sehn, et al. Proc EHA 2023, #P1078

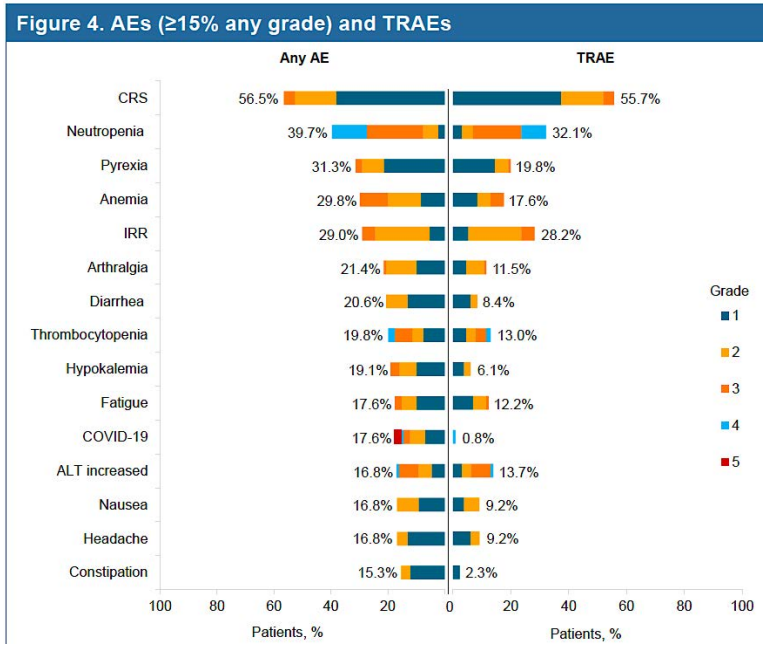
Odronextamab in patients with relapsed/refractory follicular lymphoma Grade 1–3a: prespecified analysis of the ELM-2 study

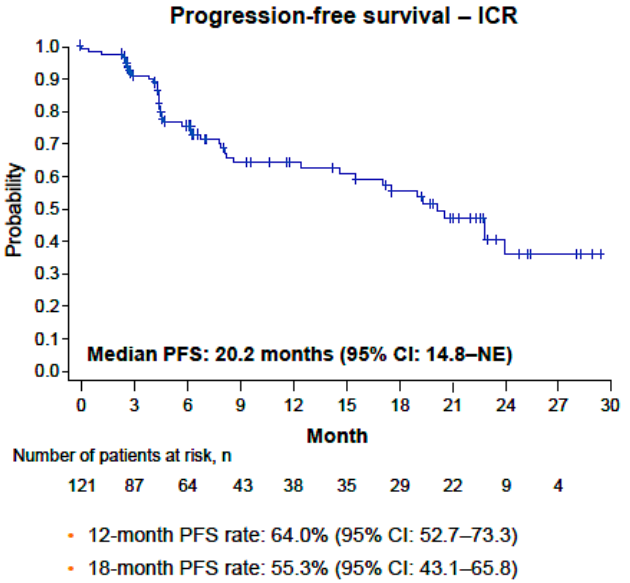
Baseline characteristics	N=131
Median age	61 (22-84)
Median prior lines	3 (2-13)
FLIPI high risk	59%
Refractory to last line	71%
POD24	48%

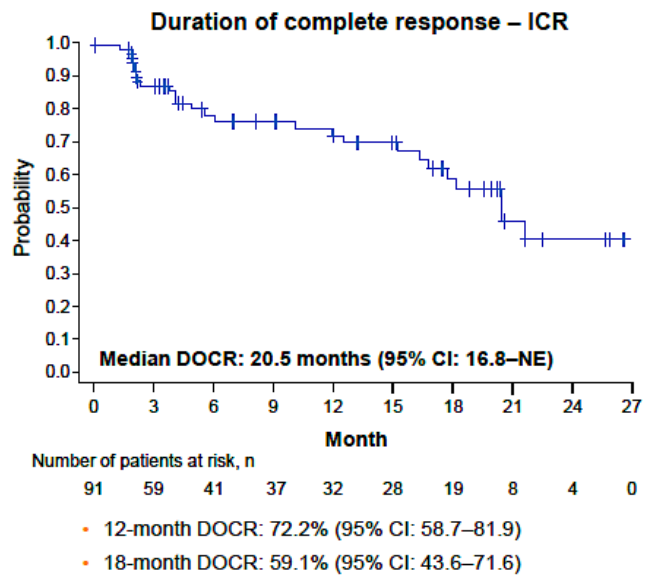
Best Response	N=121
Overall response	**82%**
Complete response	**75%**

CRS and ICANS	N=63
CRS	
Any grade	57%
Grade ≥3	2%
ICANS	
Any grade	1%
Grade ≥3	0%

Figure 4. AEs (≥15% any grade) and TRAEs





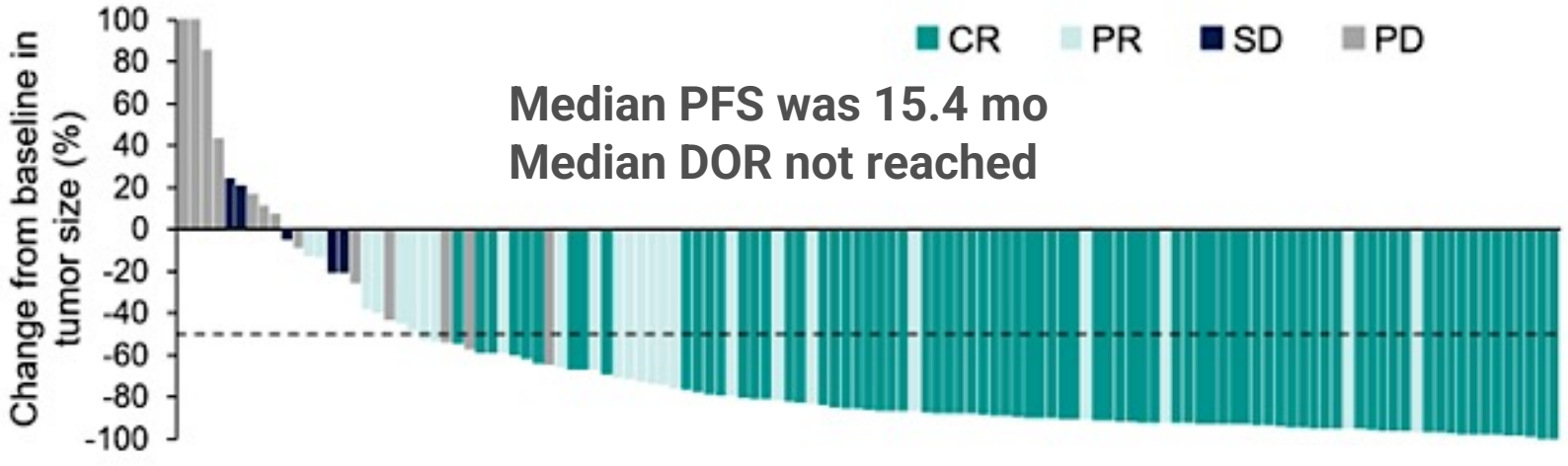


Taszner, et al. Proc EHA 2023, #P1083

Epcoritamab: EPCORE NHL-1 FL dose expansion cohort

Baseline characteristics	N=128
Median age	65
Median prior lines	3 (2-9)
Double refractory	70%
Refractory to last line	69%
POD24	42%

Best response	N=128
Overall response	**82%**
Complete response	**63%**



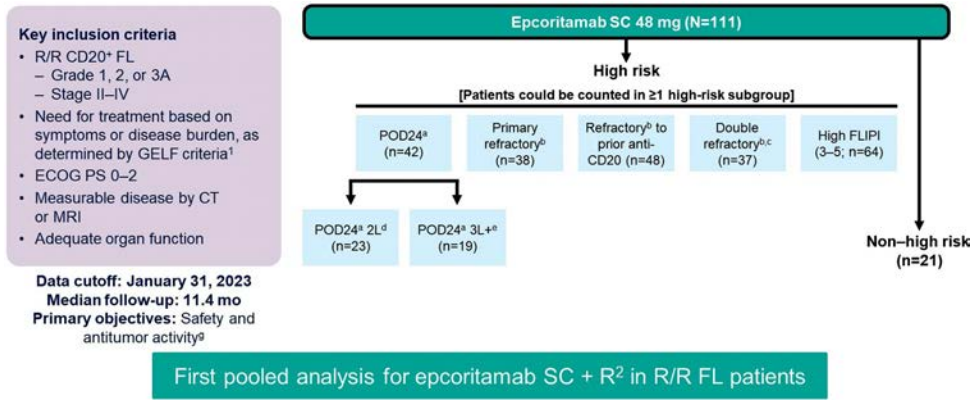
Two patients had a change from baseline in tumor size of >100%. Seven patients were not evaluable for change from baseline in tumor size.

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

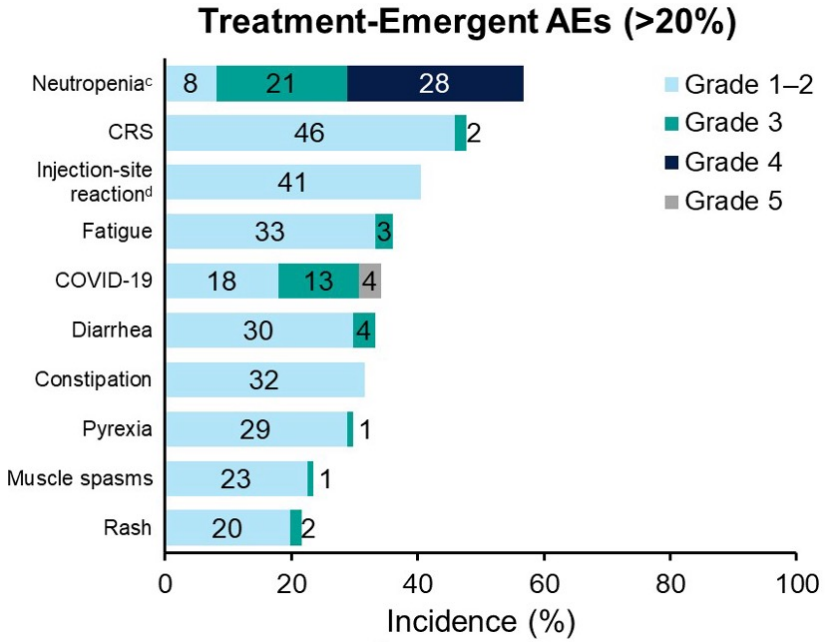
CRS and ICANS	N=63
CRS	
Any grade	66%
Grade ≥3	2%
ICANS	
Any grade	6%
Grade ≥3	0%

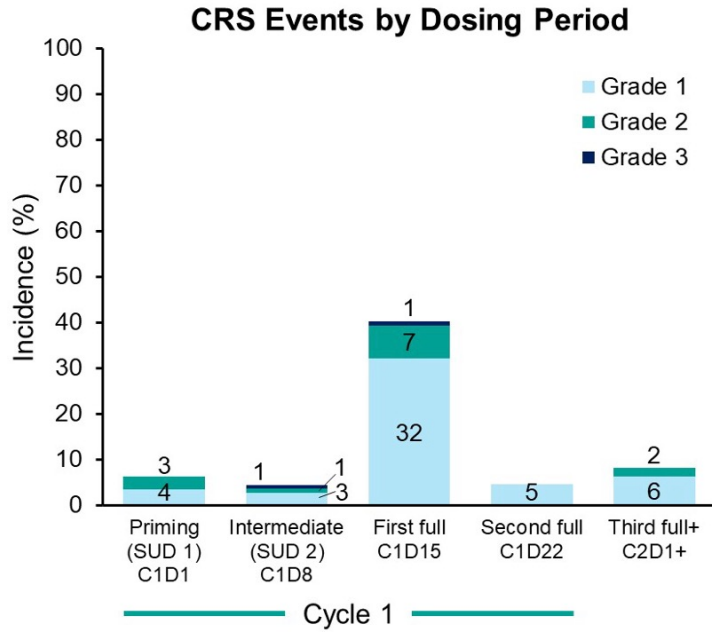
Linton, et al. Proc ASH 2023. Abstract #1655.

Epcoritamab + R2 regimen in relapsed/refractory follicular lymphoma



First pooled analysis for epcoritamab SC + R^2 in R/R FL patients

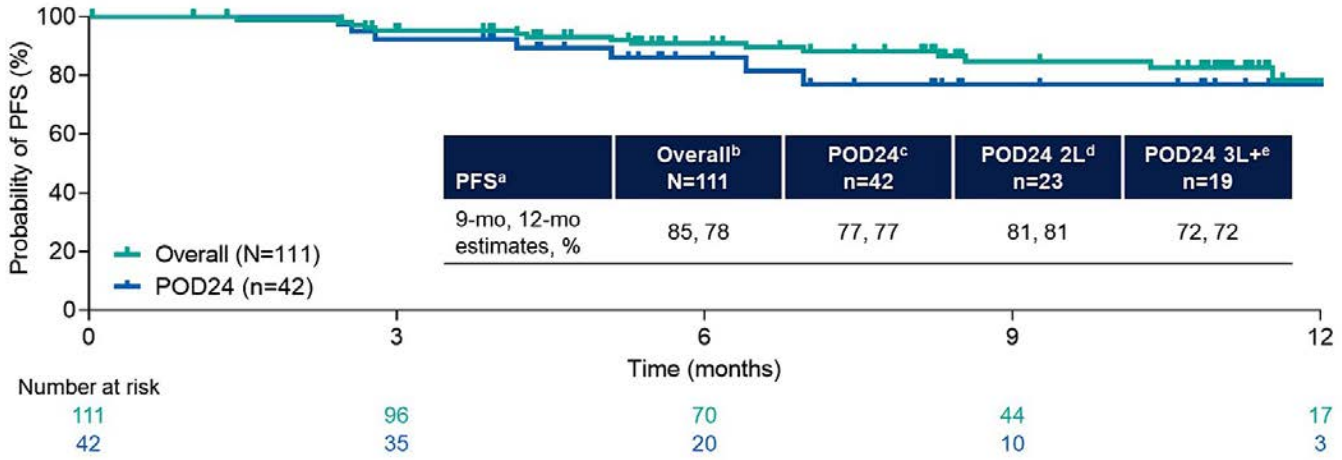




Baseline characteristics	N=111
Median age	63 (30-80)
Median prior lines	1 (1-7)
FLIPI high risk	58%
Bulky >7cm	29%
POD24	38%

Response	N=104
Overall response	98%
Complete response	87%

Progression-Free Survival – Overall and POD24

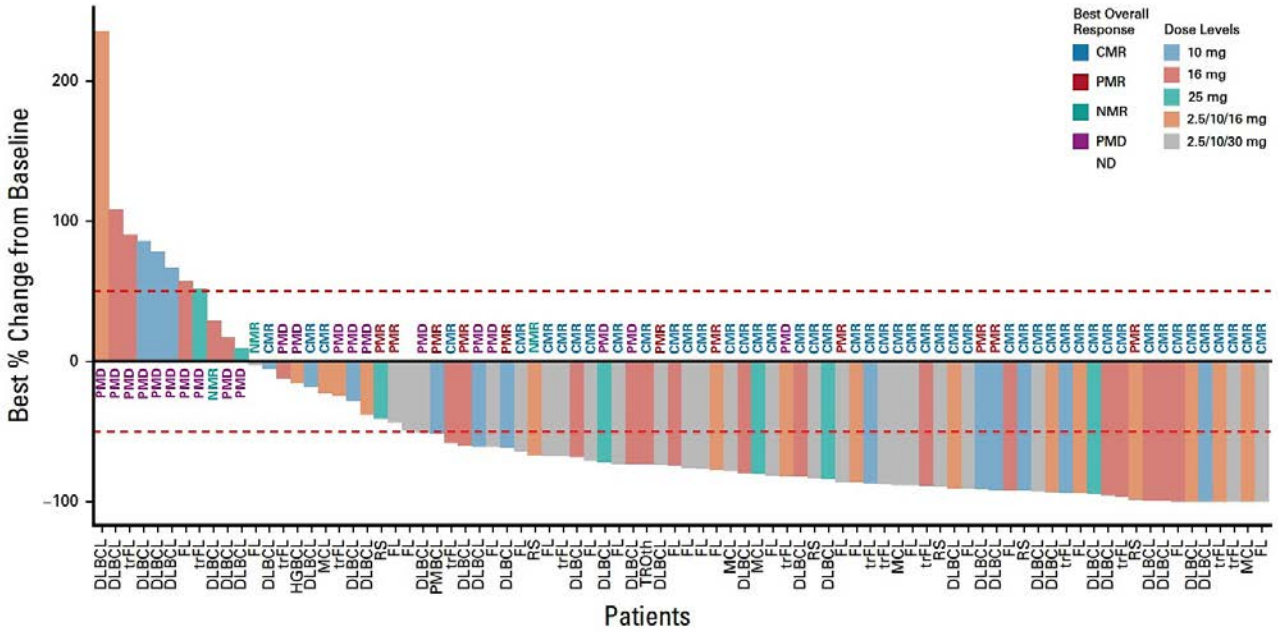


PFS[a]	Overall[b] N=111	POD24[c] n=42	POD24 2L[d] n=23	POD24 3L+[e] n=19
9-mo, 12-mo estimates, %	85, 78	77, 77	81, 81	72, 72

Merryman, et al. Proc ASCO 2023, #7506

Glofitamab in relapsed/refractory follicular lymphoma

Overall response in Grade 1-3A FL (N = 44): 70.5%



Glofit alone or with obinutuzumab (ph I/II)

	Glofitamab	Glofitamab + obinutuzumab
Overall response	81%	100%
Complete response	70%	74%

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

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

Morschhauser F et al. ASH 2021;Abstract 128.

Considerations in choosing between CAR T-cells and bispecifics in FL

CAR T-cells	Mosunetuzumab
Excellent efficacy with longer follow up	Excellent efficacy, but with shorter follow up
Requires 3-4 weeks of manufacturing	Off the shelf
Logistically more complex	Logistically less complex
“One and done”	8-17 cycles (mosun) or continuous (epco, odro)
Needs lymphodepleting chemo	No lymphodepleting chemo
Higher risk of CRS and neurotoxicity (tisa-cel better than axi-cel), and cytopenias	Lower risk of CRS, neurotoxicity, and cytopenias
Usually inpatient	Usually outpatient

Agenda

Module 1: Evolving Role of Novel Treatment Strategies in Follicular Lymphoma (FL) — Dr Friedberg

Module 2: Integration of Chimeric Antigen Receptor (CAR) T-Cell Therapies and Bispecific Antibodies into the Management of FL — Dr Abramson

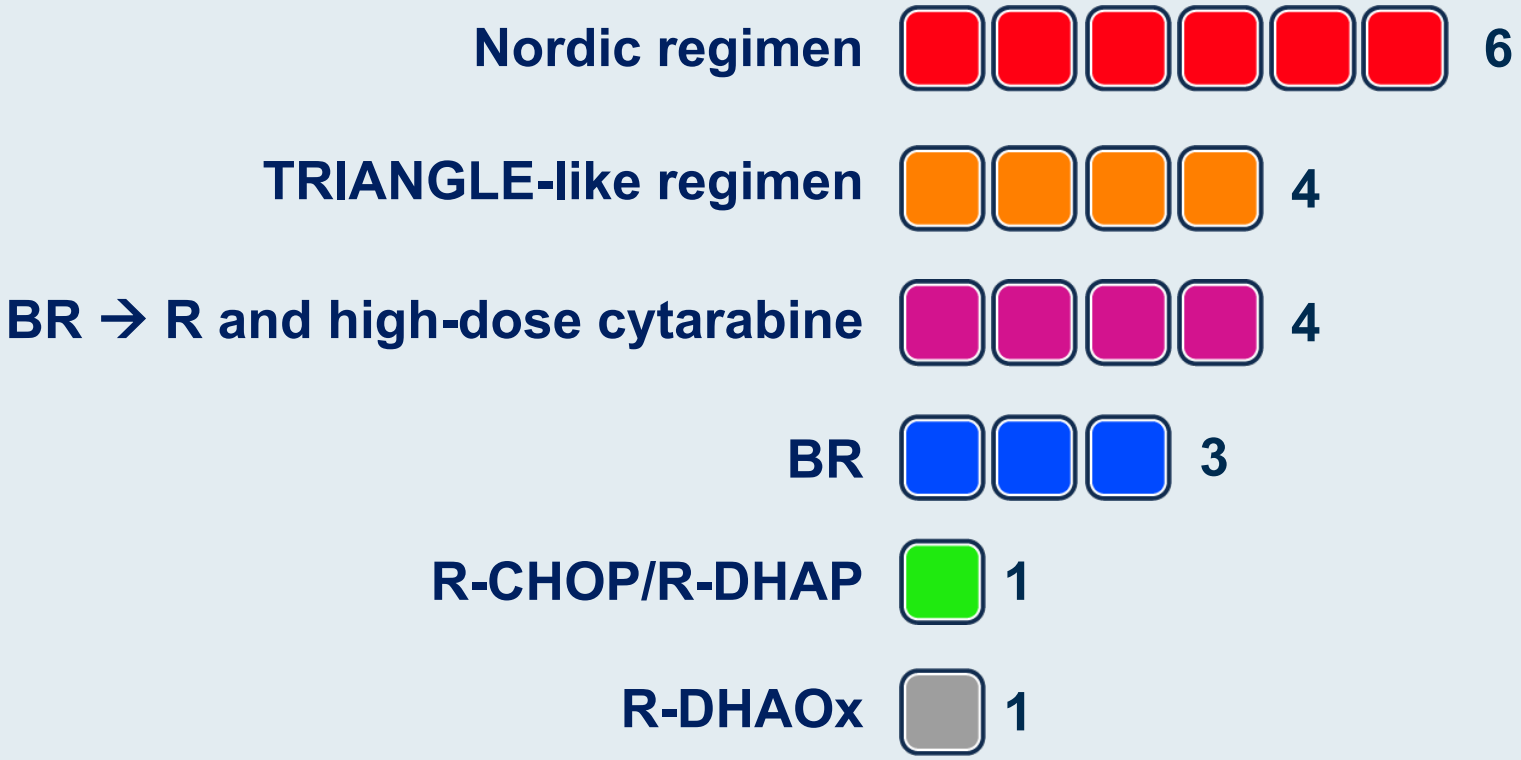
Module 3: Up-Front Treatment for Mantle Cell Lymphoma (MCL) — Dr Kahl

Module 4: Therapeutic Sequencing for Patients with Relapsed/Refractory (R/R) MCL — Dr Cohen

Module 5: First-Line Treatment Strategies for Hodgkin Lymphoma (HL) — Dr Bartlett

Module 6: Current and Future Management of R/R HL — Dr Ansell

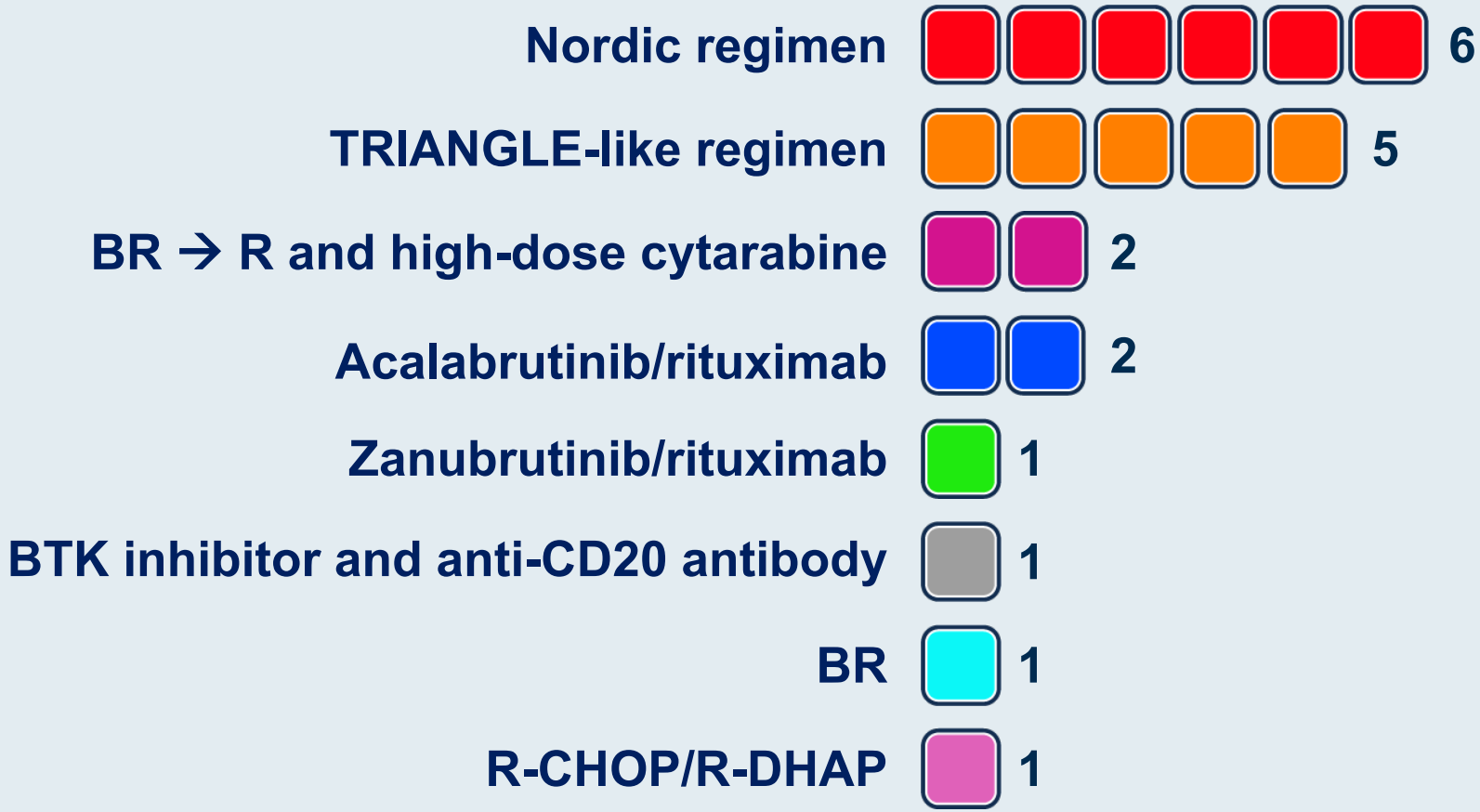
Which first-line treatment approach do you generally recommend for a 60-year-old patient with mantle cell lymphoma (MCL)?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

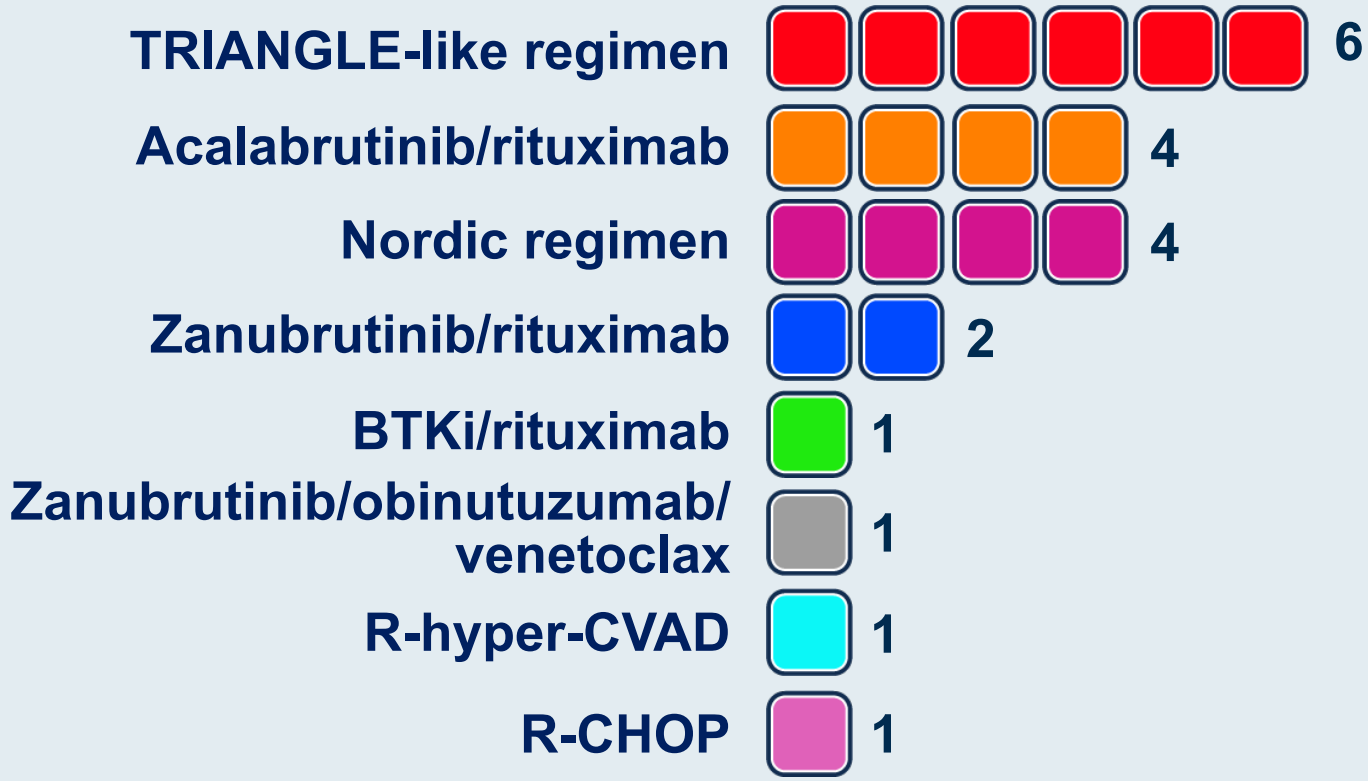
Regulatory and reimbursement issues aside, what do you believe is the optimal first-line treatment approach for a 60-year-old patient with MCL?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Which first-line treatment approach do you generally recommend for a 60-year-old patient with MCL with a TP53 mutation?



Survey of 20 US-based clinical investigators November 2023

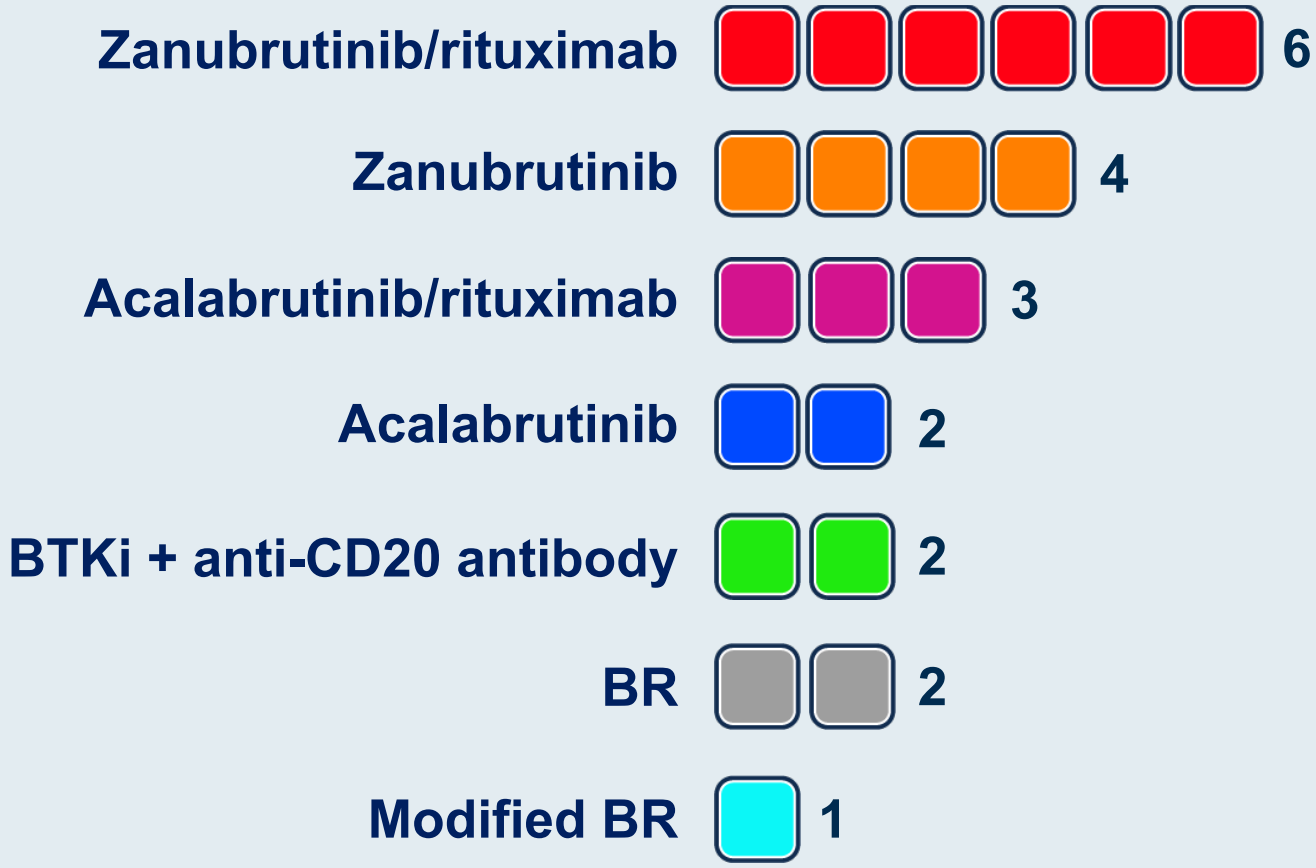
RTP RESEARCH TO PRACTICE

Which first-line treatment approach do you generally recommend for an 80-year-old patient with MCL?

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what do you believe is the optimal first-line treatment approach for an 80-year-old patient with MCL?



Survey of 20 US-based clinical investigators November 2023

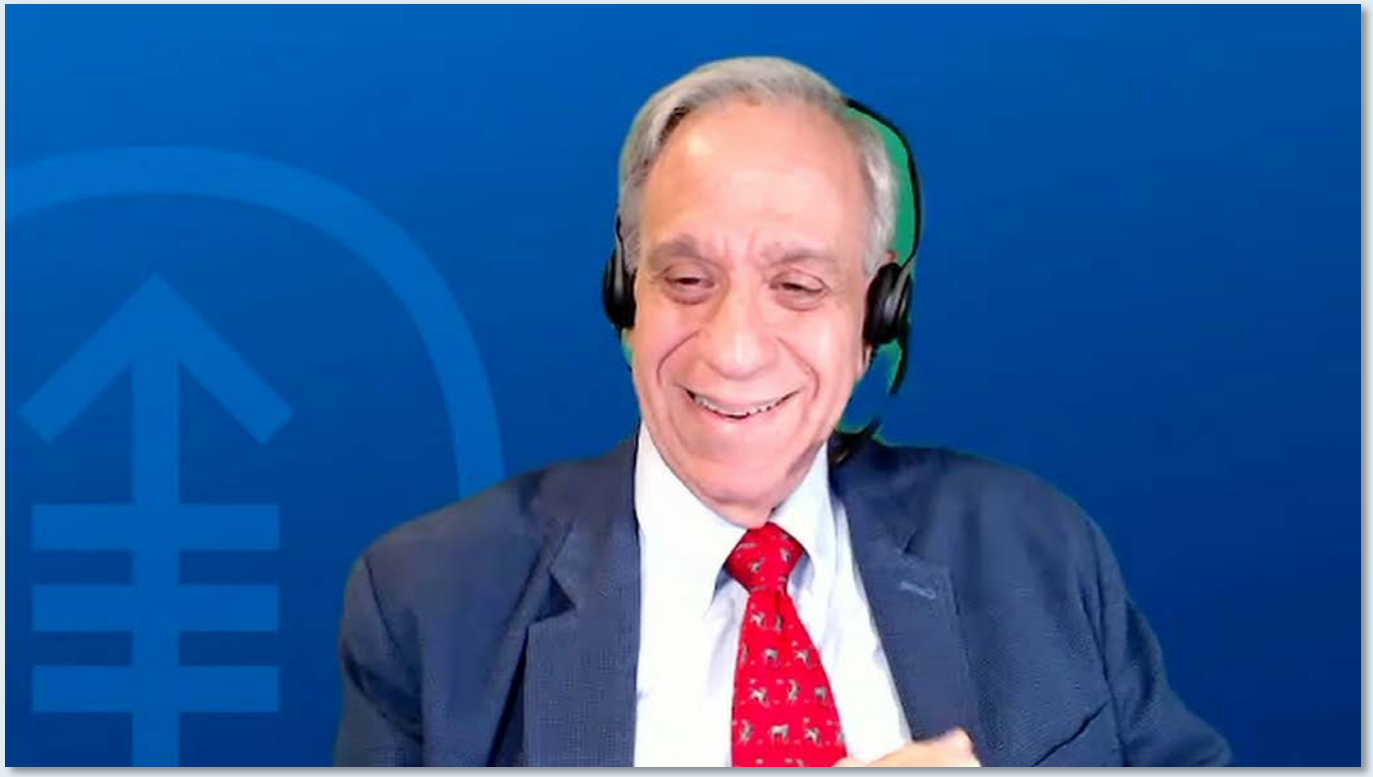
RTP RESEARCH TO PRACTICE

A 70-year-old patient with standard-risk MCL who requires treatment and is not a candidate for aggressive therapy comes to you for a second opinion after the first oncologist recommends acalabrutinib/rituximab. What would be your most likely response?

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Evolving treatment options for younger and older patients with MCL



Andrew D Zelenetz, MD, PhD

RTP
RESEARCH
TO PRACTICE

TRIANGLE approach; CAR T-cell directed therapies for MCL; choice of Bruton tyrosine kinase (BTK) inhibitor; role of venetoclax

Tycel Phillips, MD

RTP
RESEARCH
TO PRACTICE

Pirtobrutinib in MCL; up-front BTK inhibitor-based treatment options for older patients

Kami Maddocks, MD

Franck Morschhauser, MD, PhD

RTP
RESEARCH
TO PRACTICE

Up-Front Treatment for MCL

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®

Reasonable Standards of Care in 2023

FRONTLINE MANAGEMENT

- Younger/Fit
  - High dose cytarabine containing induction
  - ASCT in 1st remission
  - Maintenance Rituximab for 3 years

- Older/Less Fit
  - Bendamustine-Rituximab (BR) Induction
  - ± Maintenance Rituximab

New Data in Frontline Management

1. Solid evidence supporting MR after BR
   - Flatiron Database analysis (Martin et al, JCO 2022)

2. Data for BR plus BTKi in Older MCL
   - SHINE Trial (Wang et al, ASCO 2022, NEJM 2022)

3. Data for BTKi added to intensive therapy in Younger MCL
   - TRIANGLE TRIAL (Dreyling et al, ASH 2022)

4. Chemofree
   - Is it the future?

Summary of non intensive induction regimens*

	N	Age	ORR	CR	mPFS
R-CHOP	244	66	89%	42% (CT)	14.4 mo
VR-CAP	243	65	92%	53% (CT)	24.7 mo
BR**	188	70	~90%	~45% (CT)	35-42 mo
RBAC500	57	71	91%	91% (PET)	> 7 yrs

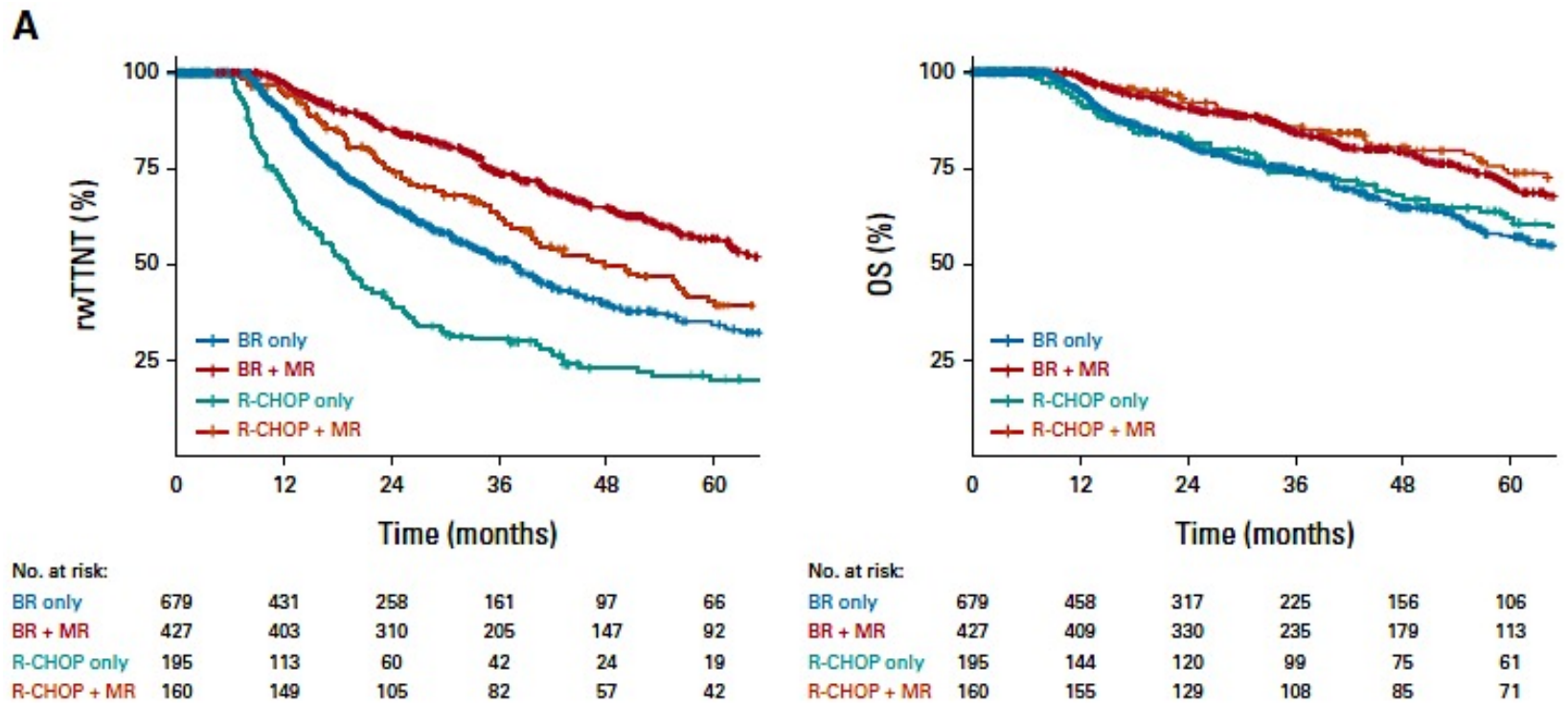
*no maintenance therapy
**pooled data from 3 trials

Flatiron Database: Role for Maintenance Rituximab

"Real world" analysis of 1621 patients

Large benefit for MR

- TTNT
- OS
- After both R-CHOP and BR

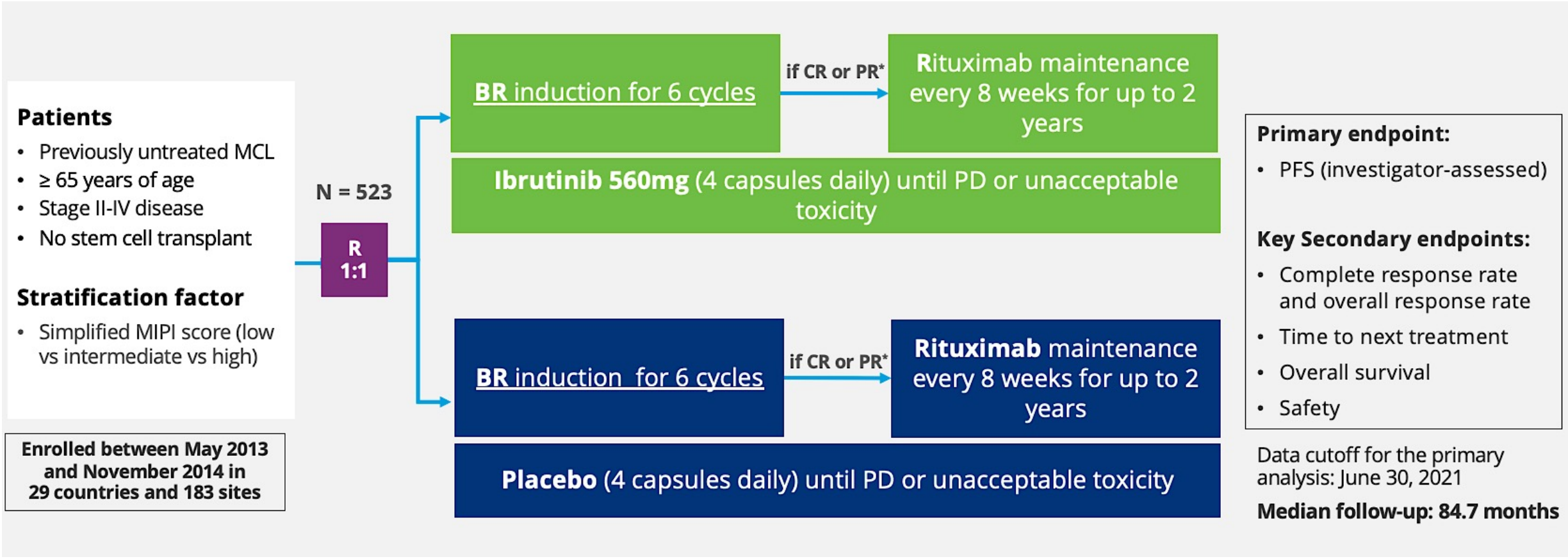


Martin et al, JCO 2022

Maintenance Rituximab

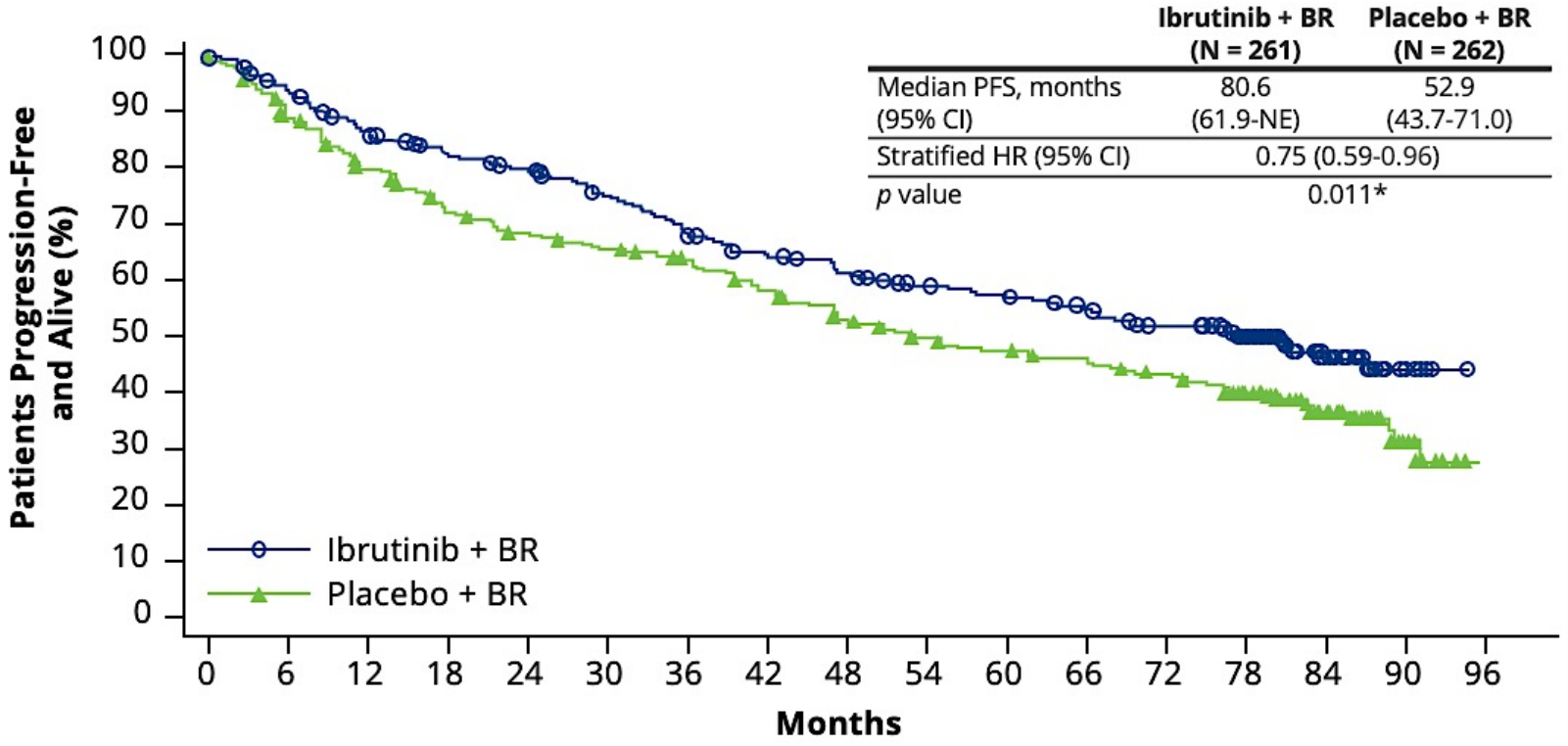
- Preponderance of data suggests major benefit in MCL
- Appears to impact OS, not just PFS (as in follicular lymphoma)
- Still unclear regarding “optimal duration”
  - 2 yrs vs. 3 yrs vs. 5 yrs vs. indefinite?
  - I prefer 2 years for older MCL and 3 years for younger MCL
- COVID 19 has created new challenges
  - Prolonged B cell depletion can lead to worse infections
  - Prolonged B cell depletion can lead to inability to vaccinate

Primary Results From the Double-Blind, Placebo-Controlled, Phase III SHINE Study of Ibrutinib in Combination With Bendamustine-Rituximab and Rituximab Maintenance as a First-Line Treatment for Older Patients With Mantle Cell Lymphoma



Wang et al, NEJM 2022

Progression Free Survival



	Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median PFS, months (95% CI)	80.6 (61.9-NE)	52.9 (43.7-71.0)
Stratified HR (95% CI)	0.75 (0.59-0.96)	
p value	0.011*	

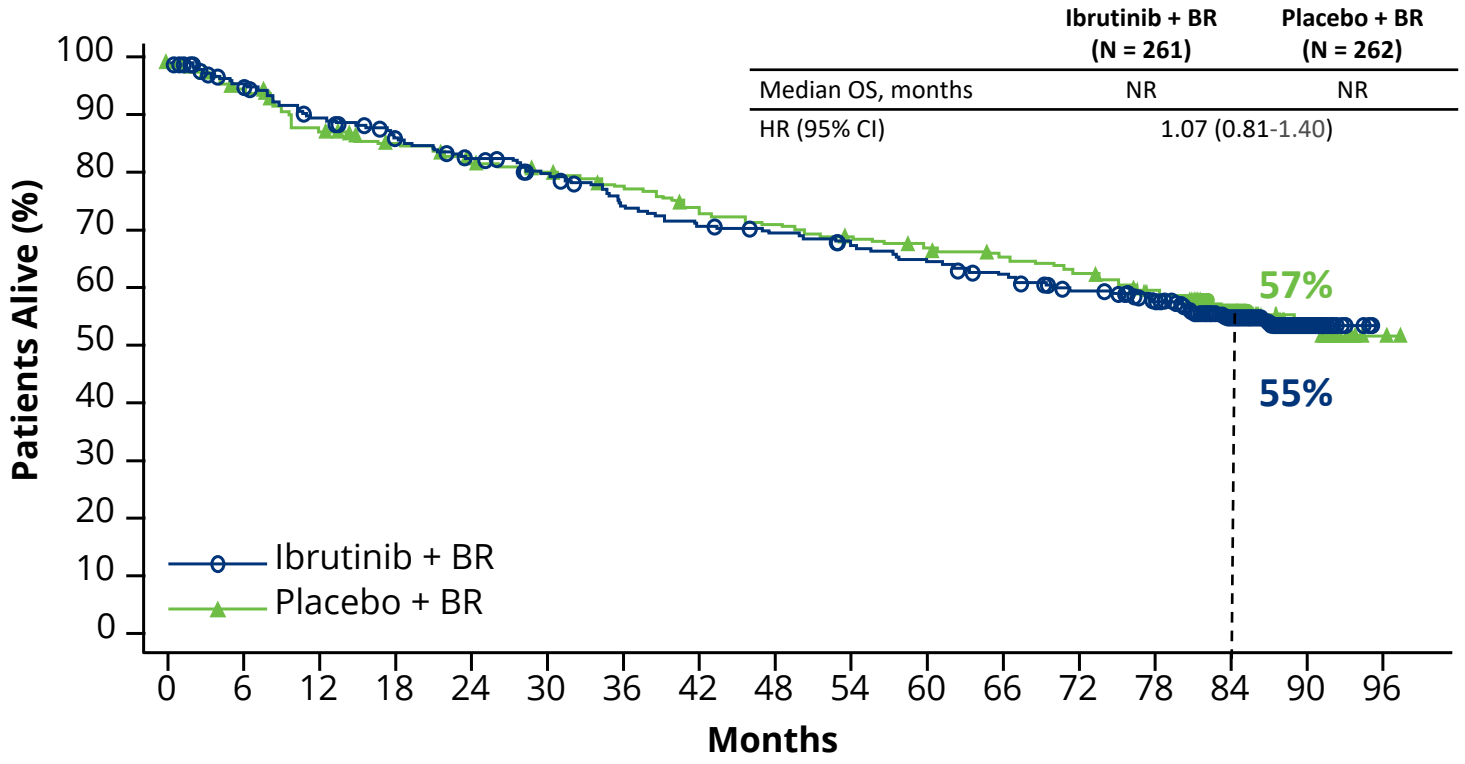
Patients at Risk

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

- Ibrutinib combined with BR and R maintenance demonstrated **a 25% reduction in the relative risk of disease progression or death** versus BR and R maintenance
- **Significant improvement in median PFS:** 80.6 months (6.7 years) versus 52.9 months (4.4 years) **(Δ=2.3 years)**

Wang et al, ASCO 2022

Overall Survival Similar in Both Arms



Patients at Risk

Ibrutinib + BR	261	239	221	208	197	187	171	163	158	152	145	138	128	118	70	25	0
Placebo + BR	262	244	223	212	203	197	188	177	171	165	159	154	147	137	90	31	2

Cause of death	Ibrutinib+BR (N=261)	Placebo+BR (N=262)
Death due to PD	30 (11.5%)	54 (20.6%)
Death due to TEAEs*	28 (10.7%)	16 (6.1%)
Death during post-treatment follow-up period excluding PD	46 (17.6%)	37 (14.1%)
Total deaths	**104 (39.8%)**	**107 (40.8%)**

*The most common Grade 5 TEAE was infections in the ibrutinib and placebo arms: 9 vs 5 patients. Grade 5 TEAE of cardiac disorders in 3 vs 5 patients, respectively.

Wang et al, ASCO 2022

NR, not reached.

SHINE

- Pro's for adding ibrutinib
  - No question adding ibrutininb improves PFS
  - Significant improvement in median PFS
  - Patients less likely to die from MCL

- Con's for adding ibrutinib
  - 5 yr PFS improves from 50 to 60% (modest)
  - Cost about $150k/year for this benefit
  - Patients more likely to die of toxicity - so no OS benefit
  - Patient will not have BTKi available for 2nd line therapy

- FDA apparently was going to view this trial as NON-CONFIRMATORY
- Ibrutinib voluntarily withdrawn from US market in Spring 2023

MCL Treatment: The Horizon for Older MCL

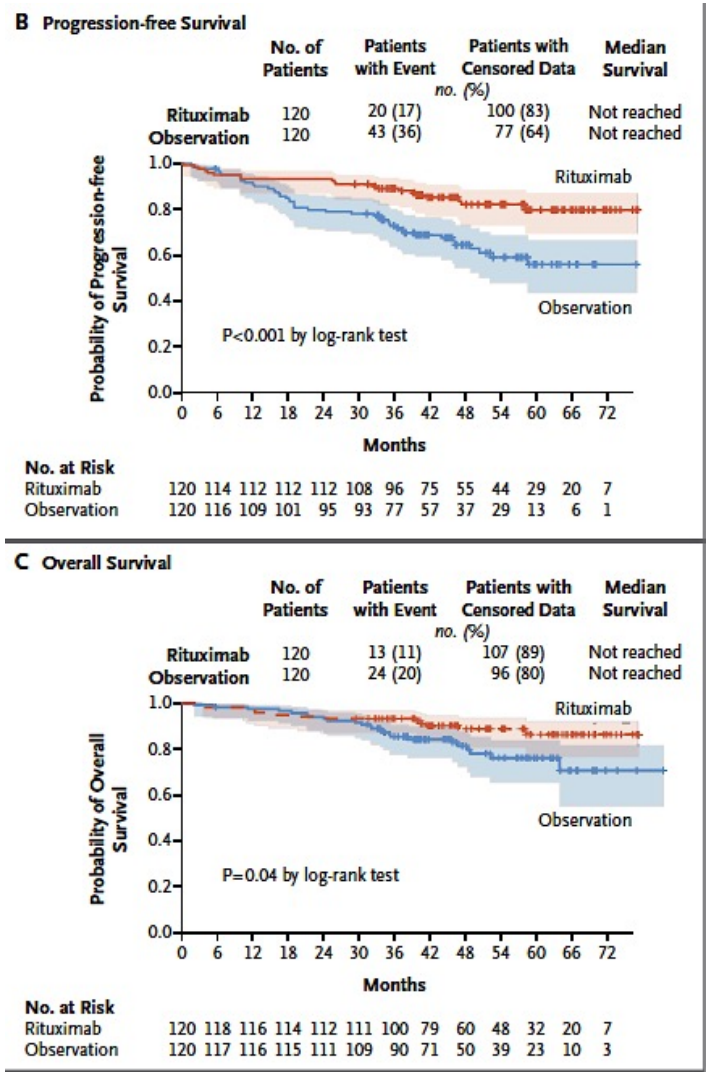
1. ECHO: BR ± acalabrutinib until PD
2. ENRICH: Ibrutinib-R vs. BR/R-CHOP
3. MANGROVE: Zanubrutinib-R vs. BR
4. NCTN: ZR continuous vs. ZR intermittent

MCL Younger: Intensive frontline results

- R-CHOP with R-DHAP plus ASCT (Hermine et al, Lancet 2016)
  - N = 232, Median age 56
  - Median PFS 9.1 years.
- R-CHOP with R-DHAP plus ASCT (Delarue et al, Blood 2013)
  - N = 60, Median age 57
  - mPFS 7.0 years
- Nordic (Geisler et al, BJH 2012, Eskelund Br. J Haem 2016)
  - N = 166, Median age 56
  - mPFS 8.5 years

Maintenance Rituximab after ASCT in MCL

	TOTAL N=299 (%)
Age, median (range), yrs	57 (27-65)
Male sex-no (%)	236 (79)
Ann Arbor Stage-no.(%)	
II	18 (6)
III	31 (10.5)
IV	249 (83.5)
B symptoms-no.(%)	89 (29.8)
PS ECOG-no.(%) <2	282 (94.3)
BM involvement-no.(%)	192 (64.5)
LDH elevation-no.(%)	115 (38.5)
MIPI score-no.(%)	
low risk	159 (53)
intermediate risk	82 (27.5)
high risk	58 (19.5)



Le Gouill, NEJM 2017

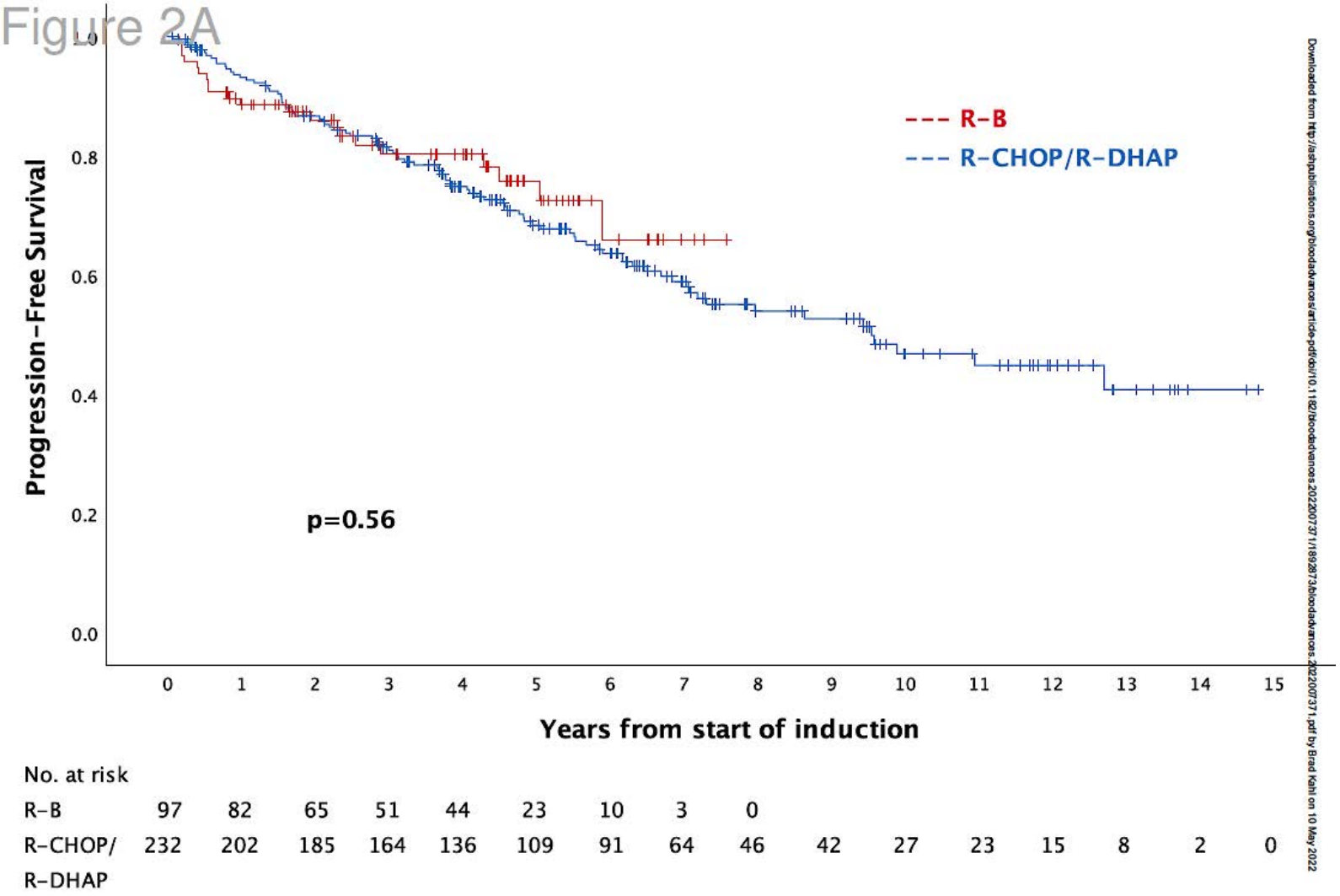
Does therapy need to be so intense?

- Is high dose cytarabine essential?
- Does ASCT improve OS?
- Could incorporation of novel agents allow subtraction of some of the intensity?

What about BR for younger patients?

- BCCA retrospective review of 97 younger patients
- Received BR followed by ASCT
- No stem cell collection failures
- Compared to cohort from Hermine trial

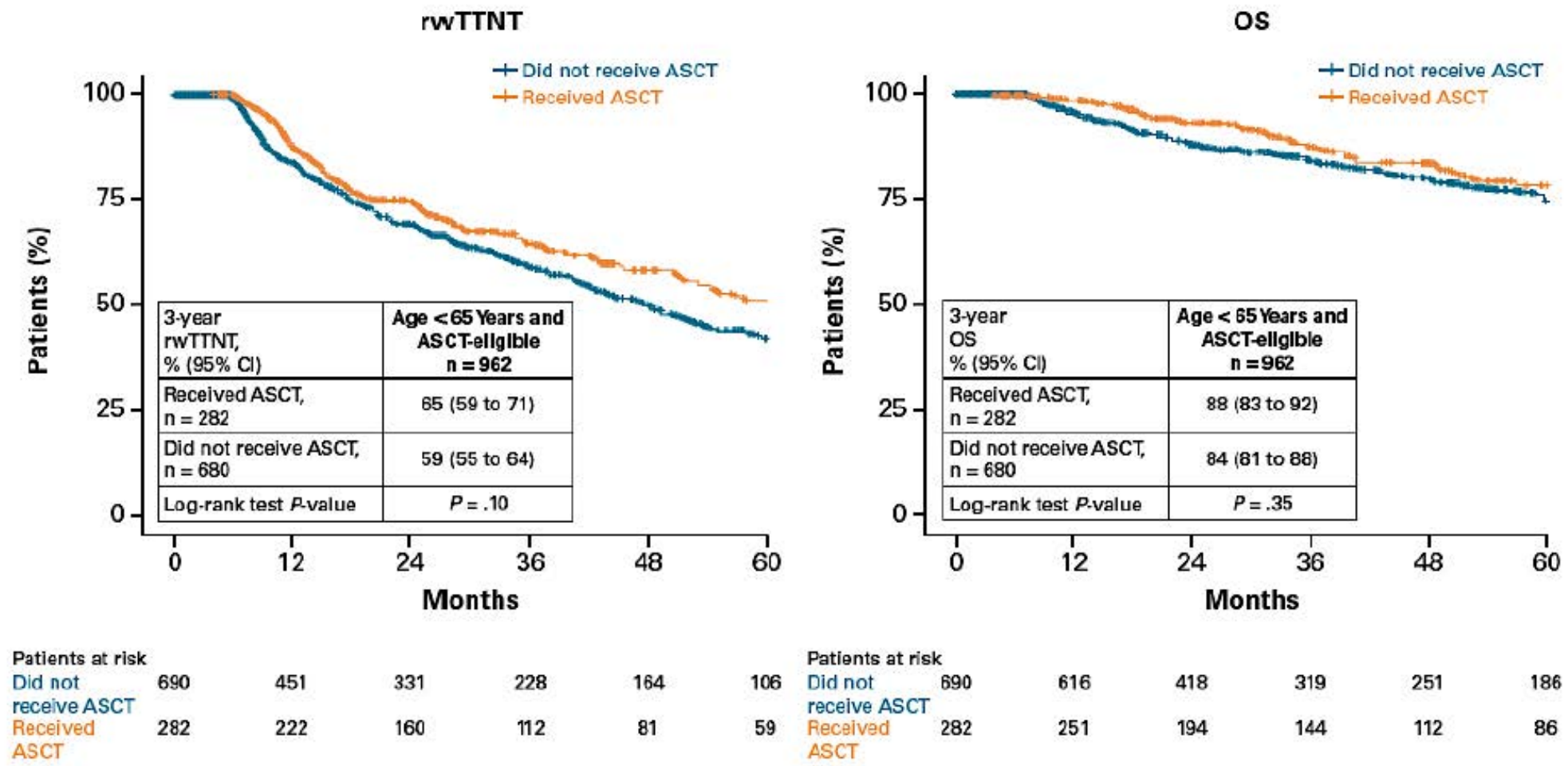
Figure 2A



Villa et al, Blood Adv 2022

Does ASCT improve OS? Flatiron Database

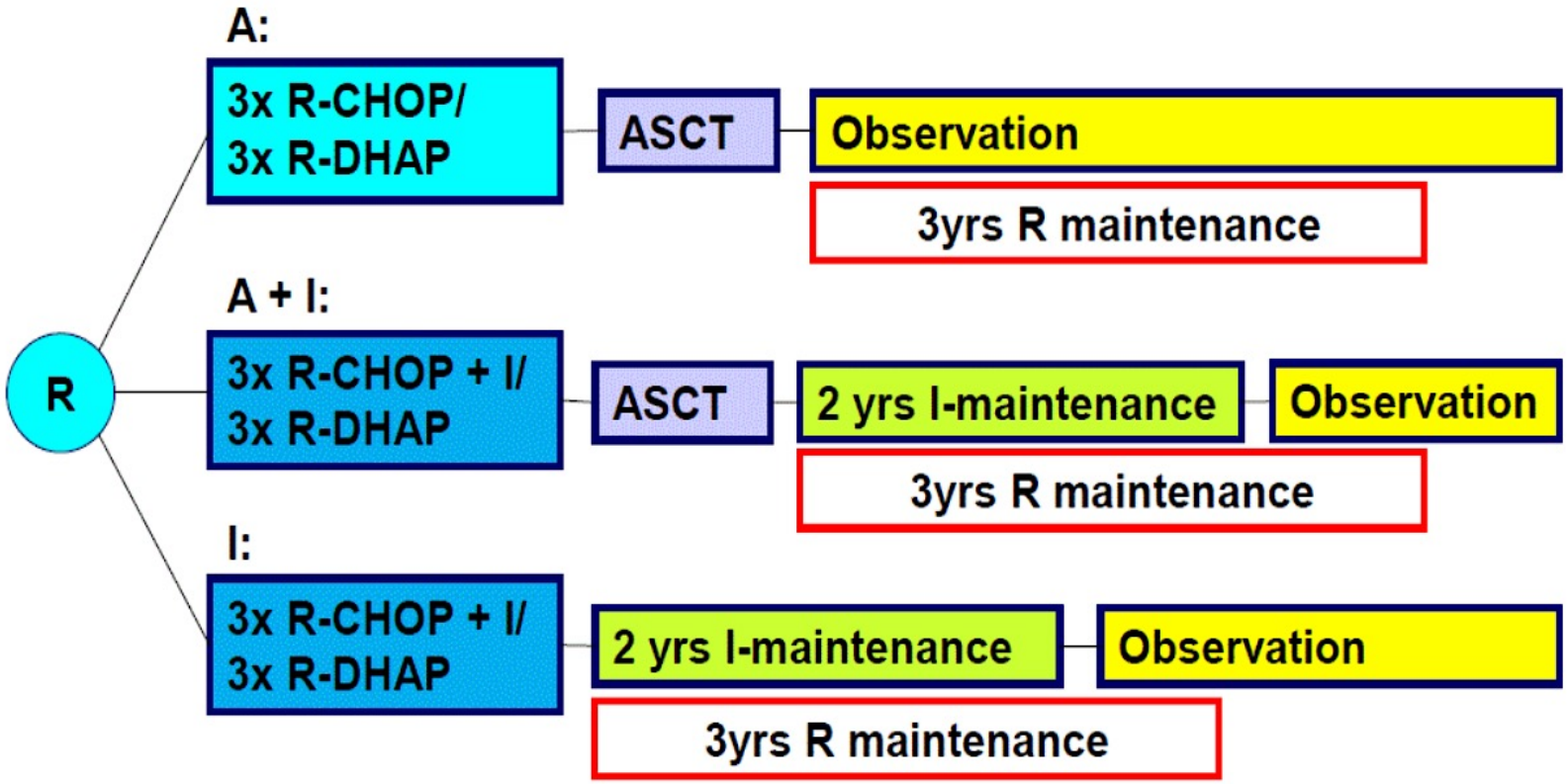
A



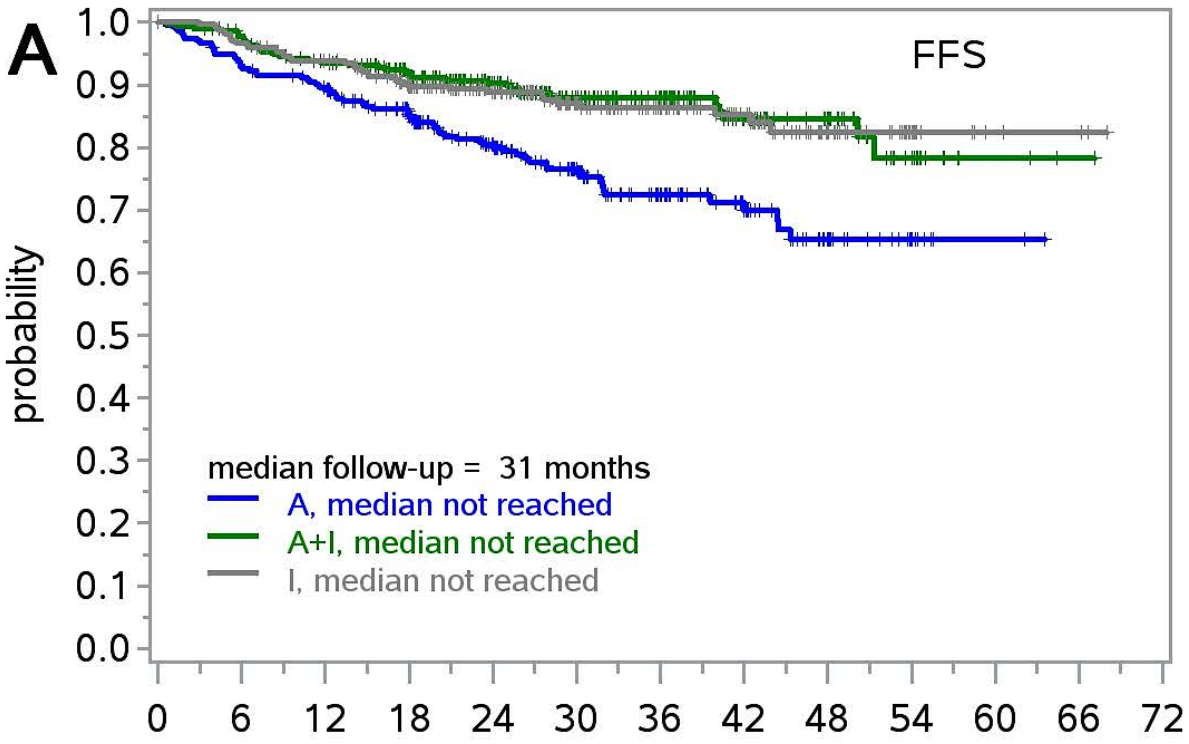
Martin et al, JCO 2022

TRIANGLE Trial (European MCL Network)

- Target 870 pts (290 per arm)
- Activated Oct 2017
- Completed accrual Dec 2020
- 1st results ASH 2022

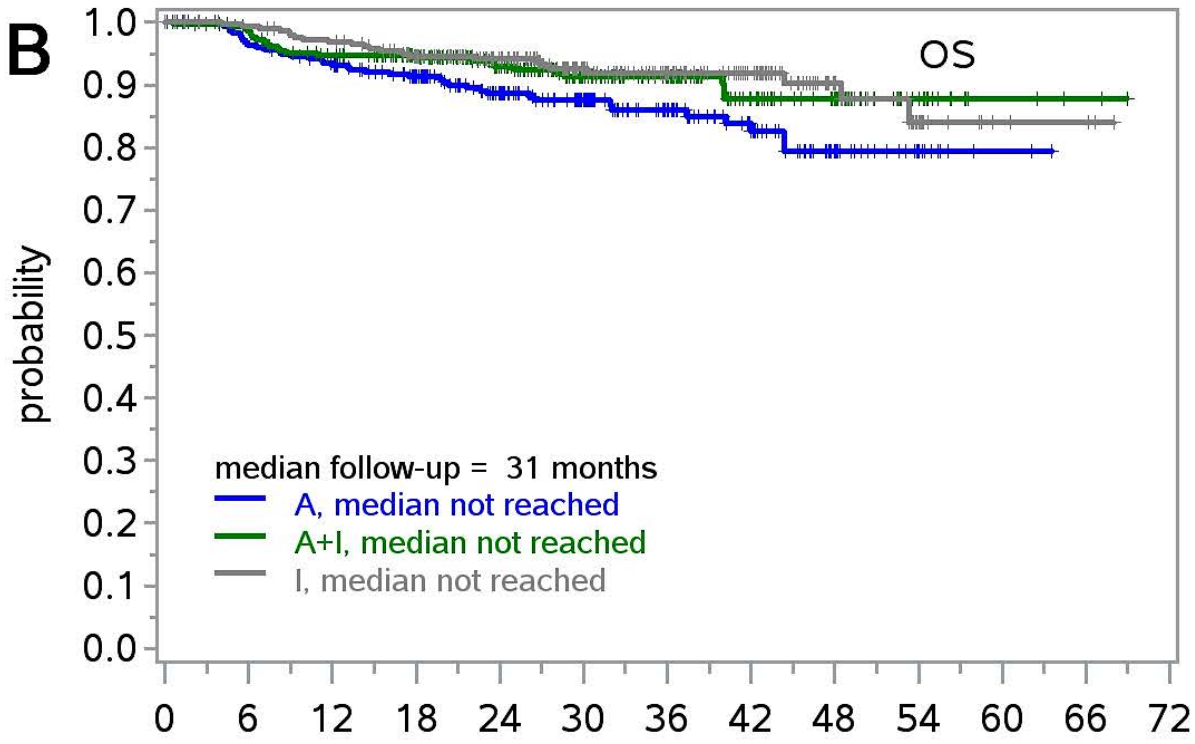


TRIANGLE Trial, Dreyling et al, Abstract #1



Numbers At Risk

A	288	252	237	206	162	126	85	54	27	12	2	0
A+I	292	270	253	226	184	137	109	65	40	17	3	1
I	290	269	257	229	180	133	100	68	34	16	4	3



Numbers At Risk

A	288	270	256	230	181	145	97	63	32	15	2	0
A+I	292	280	262	238	195	142	113	67	42	19	4	2
I	290	281	272	248	197	145	109	77	38	16	4	3

TRIANGLE TRIAL Details and Potential Impact

Toxicity

- Ibrutinib did not increase R-CHOP/R-DHAP toxicity
- Ibrutinib did increase serious infection risk after ASCT
  - A+I more toxic than A or I alone

Conclusions

- Addition of ibrutinib during induction and for 2 years as maintenance may allow for the subtraction of ASCT in 1st remission
- Arm C (ibrutinib and no ASCT) appears to be the winner at this time
  - Best combination of efficacy and toxicity

NCCN Guidelines: First-Line Treatment of Stage II Bulky or Stage III/IV MCL

	Preferred regimens	Other recommended regimens
Eligible for aggressive induction therapy	LyMA regimen	HyperCVAD + rituximab
	Nordic regimen	
	BR → rituximab, high-dose cytarabine	
	TRIANGLE regimen	
Ineligible for aggressive induction therapy	BR	RBAC500
	VR-CAP	
	R-CHOP	
	Lenalidomide + rituximab	

Maintenance after HDT/ASCR or aggressive induction: Covalent BTK inhibitor for 2 years + rituximab for 3 years

Maintenance after less aggressive induction therapy: Rituximab for 2 to 3 years after R-CHOP or BR

BR = bendamustine/rituximab ; VR-CAP = bortezomib/rituximab/cyclophosphamide/doxorubicin/prednisone;
HDT = high-dose therapy; ASCR = autologous stem cell rescue

NCCN Guidelines. B-Cell Lymphomas — Version 6.2023. Accessed November 30, 2023.

Chemofree options in frontline MCL

Acalabrutinib + Lenalidomide + Rituximab[1] (N = 24)

- ORR after 12 cycles 100%. CR 90%
- Rash 42%

Acalabrutinib + Venetoclax + Rituximab[2] (N = 21)

- ORR 100%. CR 90%
- 5 COVID deaths

Zanubrutinib + Venetoclax + Obinutuzumab[3] (N = 25)

- ORR 95%. CR 88%.
- 4 on study deaths (2 COVID)

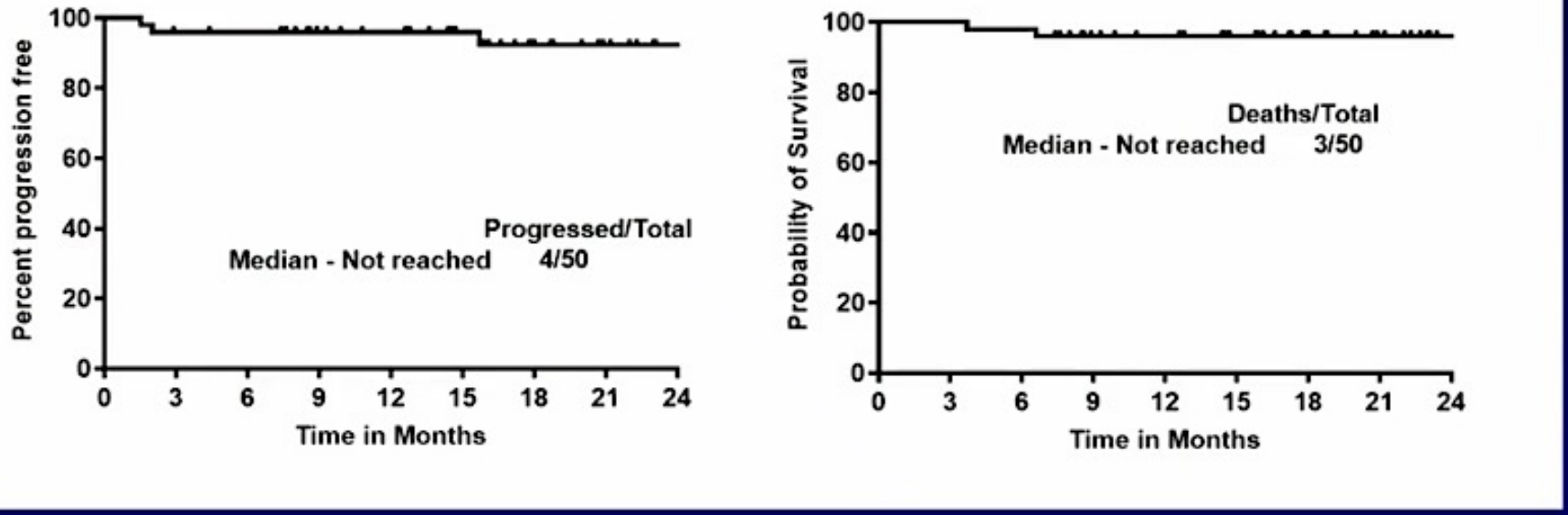
1. Ruan at al, ASH 2022. abs 73. 2. Wang et al, ASH 2022. Abs 2884 3. Kumar ASH 2023. Abs 738

Responses with Acalabrutinib/Rituximab as First-Line Therapy for Older Patients with MCL

Response (ITT)	All patients
Week 12 Best response#	N (%)
Evaluable patients*	49
ORR	46/50 (92)
CR	37/50 (74)
PR	9/50 (18)
Best response$	
Evaluable patients	49
ORR	46/50 (92)
CR	46/50 (92)
MRD at LFU (n=32)##	19/32 (60%) MRD negative
Median number of AR cycles to reach CR (range)	3(2-7)

Jain P et al. ICML 2023;Abstract 099.

Progression-Free Survival (PFS) and Overall Survival (OS) with Acalabrutinib/Rituximab as First-Line Therapy for Older Patients with MCL



- The median PFS and OS were NR (2 year 92% and 96% respectively)
- 3 patients had PD after 2, 3, 16 months after treatment
- 1 patient had SD, BM cleared but developed RASopathy/CMML
- Overall, 3 pts died – one Prim ref, 1 unknown in CR and 1 off study RAS/CMML

Jain P et al. ICML 2023;Abstract 099.

Adverse Events with Acalabrutinib/Rituximab as First-Line Therapy for Older Patients with MCL

AE type	n (%)	
	Grade 1-2	Grade 3-4
Haematological		
Neutropenia	2 (4)	1 (2)
Thrombocytopenia	4 (8)	2 (4)
Anemia	9 (18)	1 (2)
Non-haematological		
Fatigue	39 (78)	2 (4)
Myalgia	31 (62)	1 (2)
Headache	17 (34)	2 (4)
Bruising	14 (28)	-
Atrial fibrillation	1 (2)	-
COVID	16 (32)	2 (4)

**Other common AE of interest included - 25 diarrhea, 22 constipation, 21 dry eyes, 9 insomnia, 21 dizziness, 13 infections (1 grade 3), 13 memory fog, 10 skin rashes, 10 neuropathy (1 grade 3), 16 nausea (1 grade 3), 8 mucositis, 2 palpitations and 1 grade 3 unstable angina recurrence, 2 pts dose reduced to 100 mg due to grade 3 transaminitis*

Jain P et al. ICML 2023;Abstract 099.

MCL Summary

MCL Younger

- May not need the HiDAC if using BR
- Transplant may not improve OS (can improve PFS)
- Transplant may not be needed if adding 2 years of BTKi

MCL Older

- SHINE did not change SOC
- Await ECHO results
- Await chemofree study results (need to be patient)

Agenda

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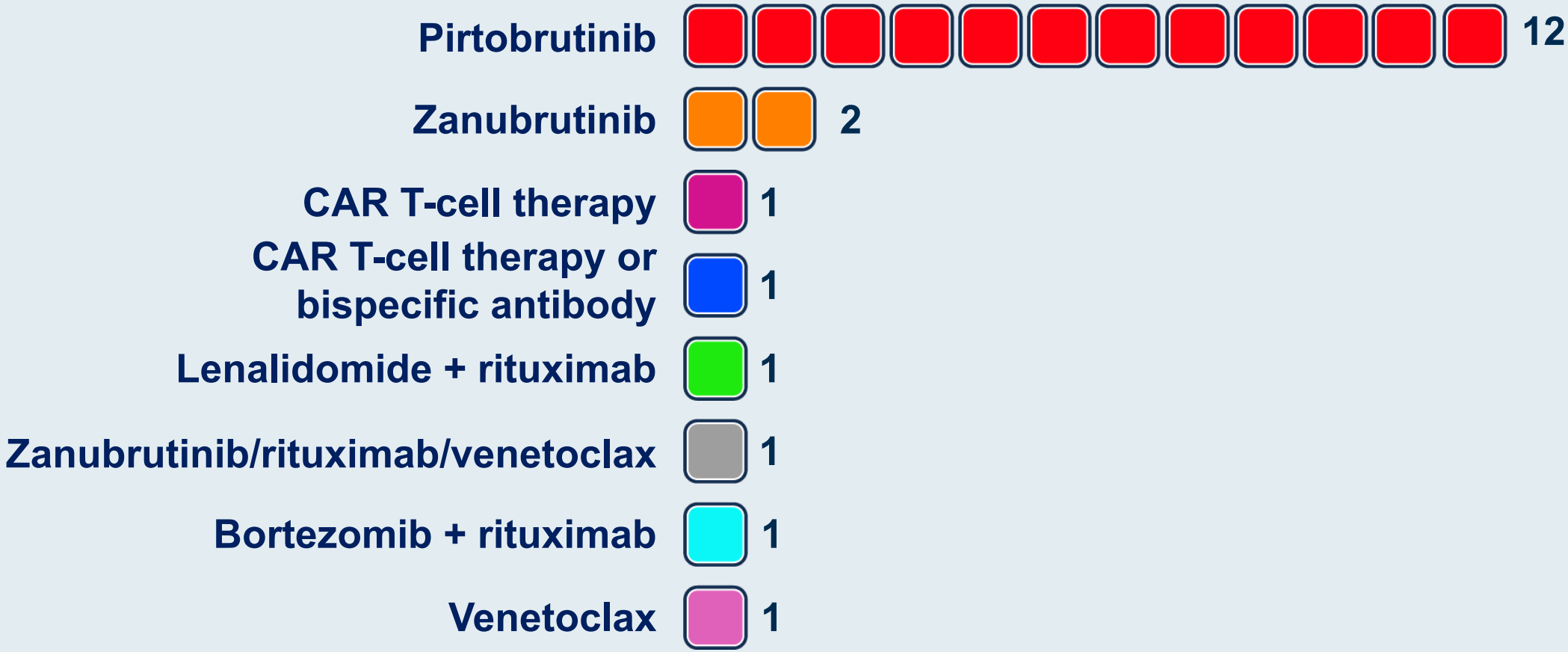
Module 6: Current and Future Management of R/R HL — Dr Ansell

RTP RESEARCH TO PRACTICE

A 78-year-old patient with MCL initially receives BR and then acalabrutinib upon disease progression and experiences disease relapse after 3 years. What would you recommend?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

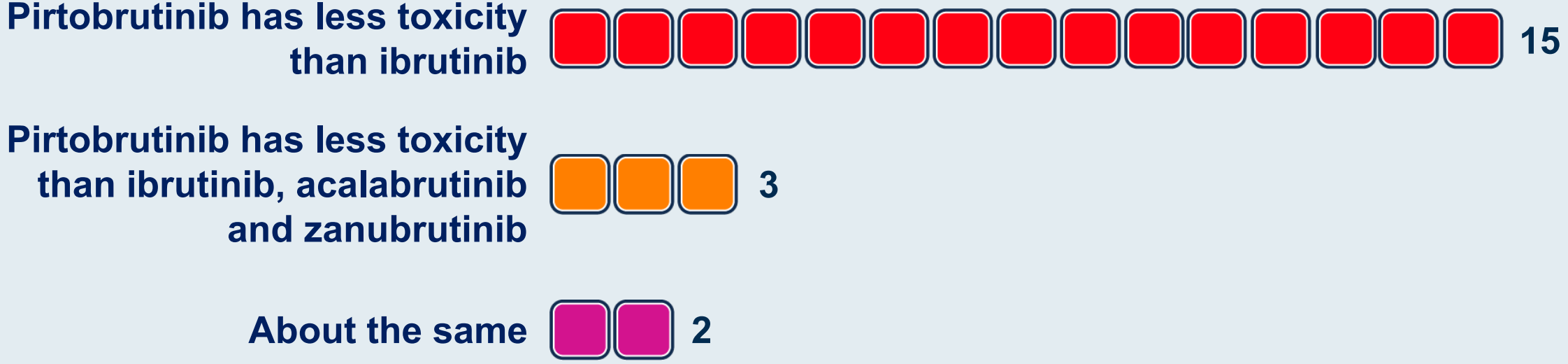
In what clinical situations are you using pirtobrutinib for the treatment of MCL?

- Patients who have failed/relapsed other BTK inhibitors
- Pts who are intolerant of or who progress after a covalent BTKi
- Post progression on cBTKi
- After covalent BTKi failure as a bridge to CAR-T or clinical trial
- Failure or intolerance to BTKi and lack of other satisfactory indication (CAR-T or combination with venetoclax)
- Progression after BTK inhibitor, not a candidate for CAR-T or previously received CAR-T
- After covalent BTKi failure
- Generally after POD on a BTKi
- After progression on covalent BTKi or intolerance to BTKi
- Third line after prior BTKi
- Relapse after BTK and not candidate for CAR-T

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Based on current clinical trial data and your personal experience, how would you compare the global tolerability/toxicity of pirtobrutinib to that of covalent BTK inhibitors for patients with relapsed/refractory MCL?



Survey of 20 US-based clinical investigators November 2023

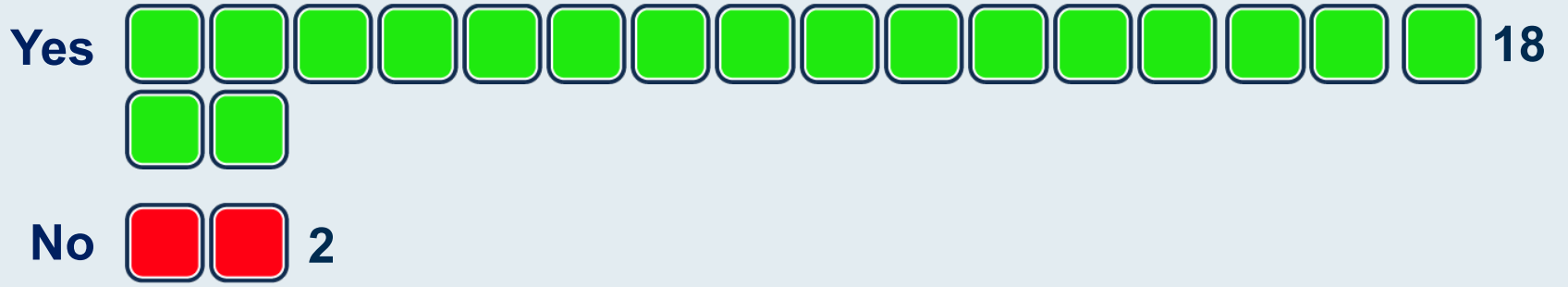
RTP RESEARCH TO PRACTICE

Based on current clinical trial data and your personal experience, how would you compare the cardiac toxicity of pirtobrutinib to that of covalent BTK inhibitors for patients with relapsed/refractory MCL?

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Based on current clinical trial data and your personal experience, is pirtobrutinib efficacious in patients with MCL who experience disease progression on a covalent BTK inhibitor?



Based on current clinical trial data and your personal experience, is pirtobrutinib efficacious in patients with chronic lymphocytic leukemia who experience disease progression on a covalent BTK inhibitor?

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

In general, do you use venetoclax in the care of patients with MCL?

In what settings do you generally use venetoclax for patients with MCL?

- Post BTKi in older patients or add to BTKi progressing as bridge to CAR-T, high-risk patients (TP53 mutated) in combo with BKTi in second line
- At relapse after BTK and in combination with BTK on clinical trials
- Used in combination with BTKi or as bridge to another line of therapy in R/R setting
- Combined with BTKi, mostly zanubrutinib
- No further approved options, or bridging for CAR-T
- Third line for patients not going to CAR-T
- Fourth line

Survey of 20 US-based clinical investigators November 2023

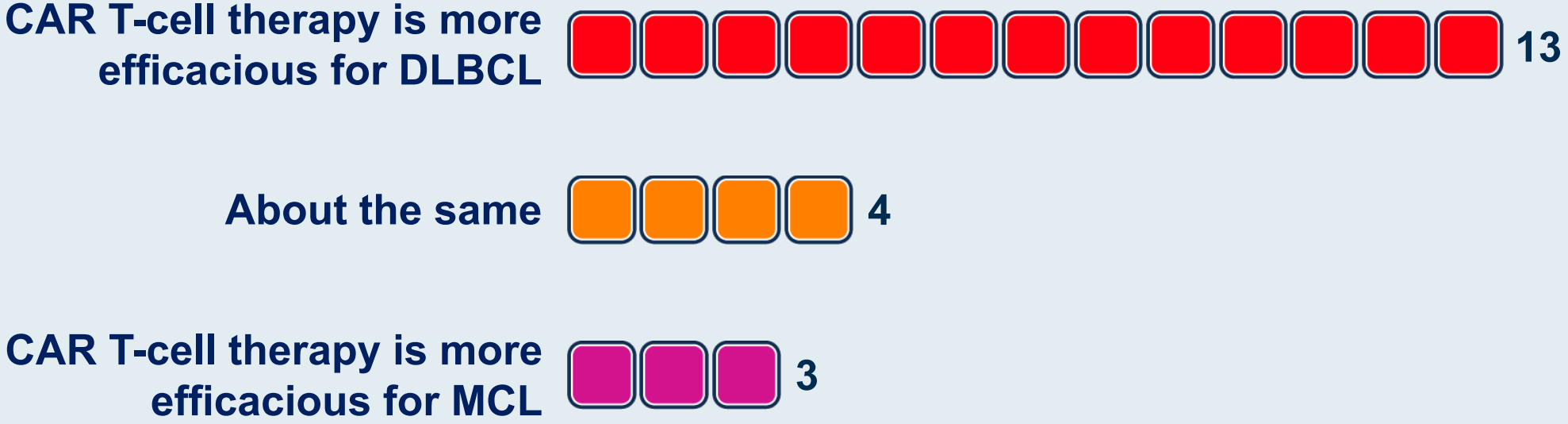
RTP RESEARCH TO PRACTICE

In what clinical situations would you combine a Bruton tyrosine kinase (BTK) inhibitor with venetoclax for a patient with relapsed/refractory MCL?

- On clinical trials and at relapse after BTK as therapy or in transition to single agent venetoclax
- 2L for high-risk patient or in patient with early PD on BTKi
- With recent ASH data, I would use second line if reimbursed
- Patient with prior response to BTK inhibitors
- High-risk patients (TP53, blastoid); some patients failing or intolerant to a BTKi as single agent
- Patients with high-risk disease by TP53 mutation
- Bridging before CAR-T or relapse post CAR-T
- Relapsed/refractory disease
- Third or fourth line (if no BTK before)
- Bridge to CAR-T

Survey of 20 US-based clinical investigators November 2023

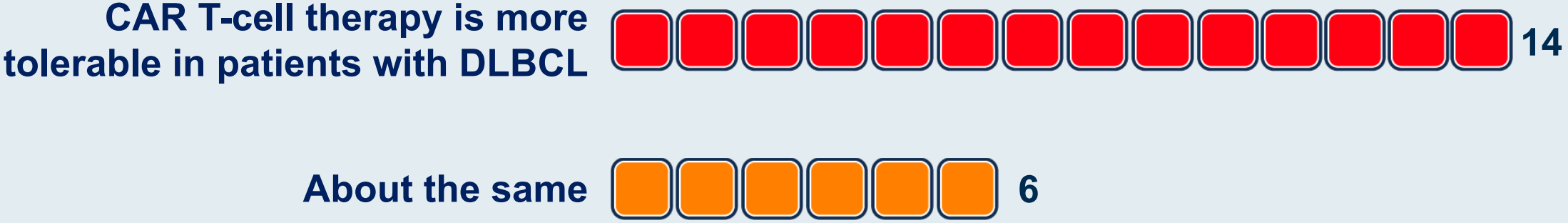
Based on current available data and your personal clinical experience, how would you indirectly compare the overall antitumor efficacy of CAR T-cell therapy in patients with MCL to that in patients with diffuse large B-cell lymphoma (DLBCL)?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Based on current available data and your personal clinical experience, how would you indirectly compare the global tolerability of CAR T-cell therapy in patients with MCL to that in patients with DLBCL?



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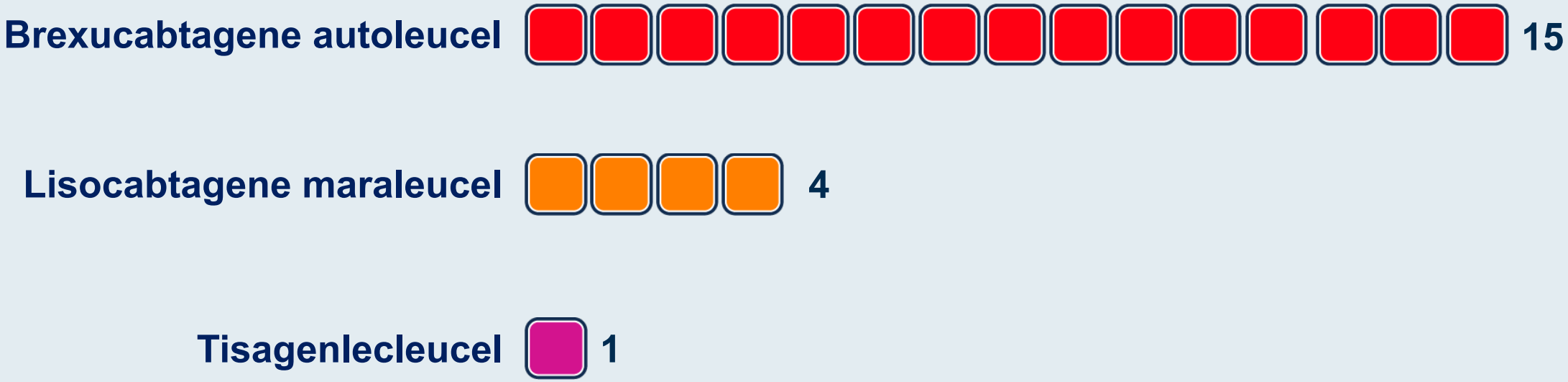
RTP RESEARCH TO PRACTICE

Please describe the oldest patient with MCL in your practice who received CAR T-cell therapy.

Patient age: 74 (median; range 62-87)

CAR T-cell platform the patient received:

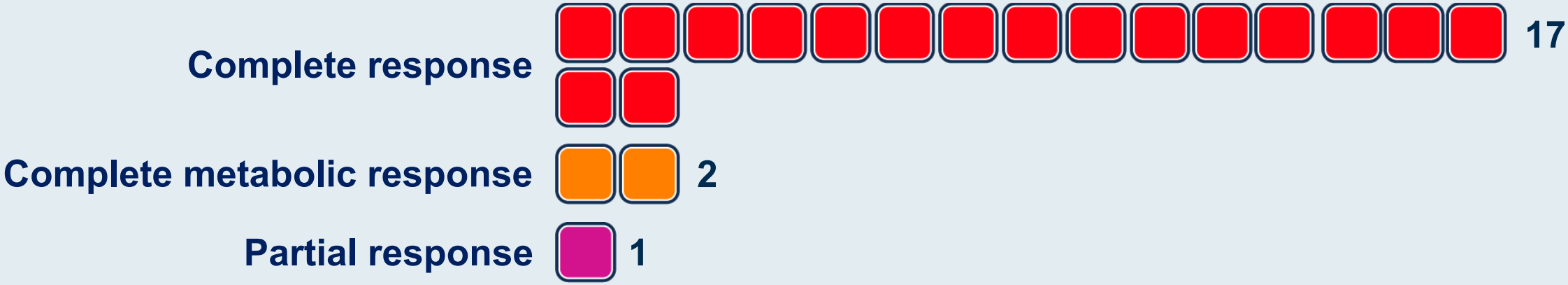


Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Please describe the oldest patient with MCL in your practice who received CAR T-cell therapy.

Patient's response to therapy:

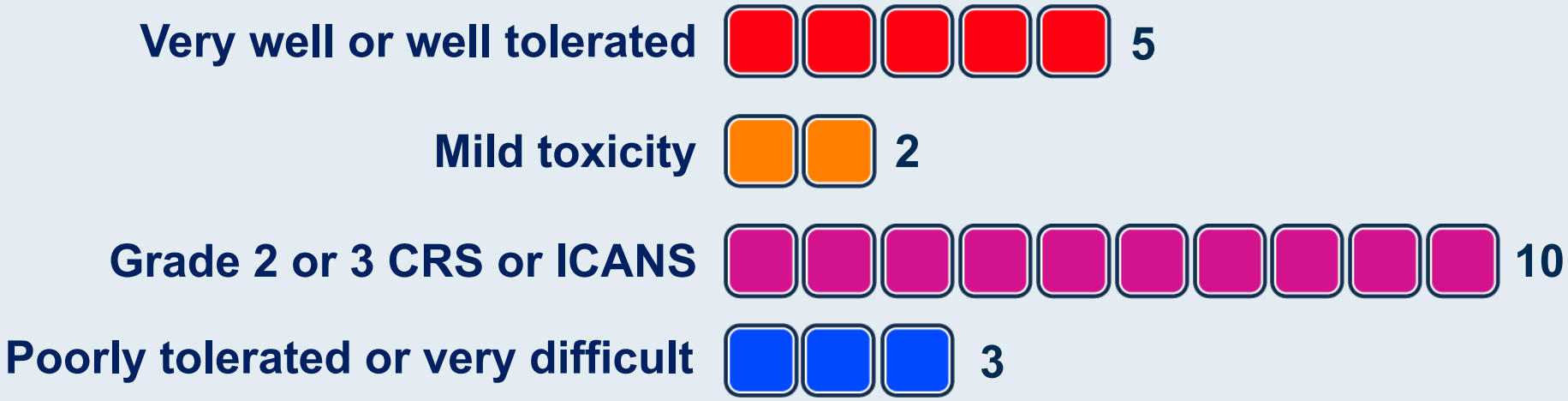


Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Please describe the oldest patient with MCL in your practice who received CAR T-cell therapy.

Patient's tolerance of therapy:



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RTP RESEARCH TO PRACTICE

Based on current available data and your personal clinical experience, do you believe there is a future role for bispecific antibodies in the management of relapsed/refractory MCL?

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RTP RESEARCH TO PRACTICE

Do you believe there is a role for tumor-informed circulating tumor DNA (ctDNA) assays in the care of patients with non-Hodgkin lymphoma (NHL)?

- The correct ctDNA assay could transform the practice of how we treat NHL
- Several potential roles - decision to give maintenance or consolidation therapy in MCL, potential to escalate or give consolidative therapy in DLBCL if persistent + ctDNA
- For sure in MCL (allows to use time-restricted therapy rather than indefinite, very likely in DLBCL (end of treatment prognostication), perhaps in FL
- MCL may ultimately be the right setting for this
- ctDNA will likely be a useful tool for determining DLBCL subtype, assessing end of treatment response. ctDNA will likely be useful for monitoring for early relapse in DLBCL and other B-cell lymphomas
- I think there is a future role for this in identifying relapsed/relapsing disease, identifying patients not achieving adequate response to treatment and needing alternative therapy approach or maintenance therapy approach in some diseases
- Testing likely more informative for response than radiology based but still needs more refinement in order to provide appropriate reliability
- Would love to have a liquid biopsy that would either replace or complement PET/CT
- ctDNA needs to be coupled to PET and radiomics to refine outcome prediction
- Needs more study but this could be a valuable tool for assessing response to therapy and relapse

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Debulking prior to CAR T-cell therapy for MCL; complete response with outpatient lisocabtagene maraleucel for an older woman with R/R MCL on a clinical trial

Max S Topp, MD

Andrew D Zelenetz, MD, PhD

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National Cancer Institute-Designated
Comprehensive Cancer Center

Relapsed/Refractory Mantle Cell Lymphoma

Jonathon B. Cohen, MD

December 8, 2023

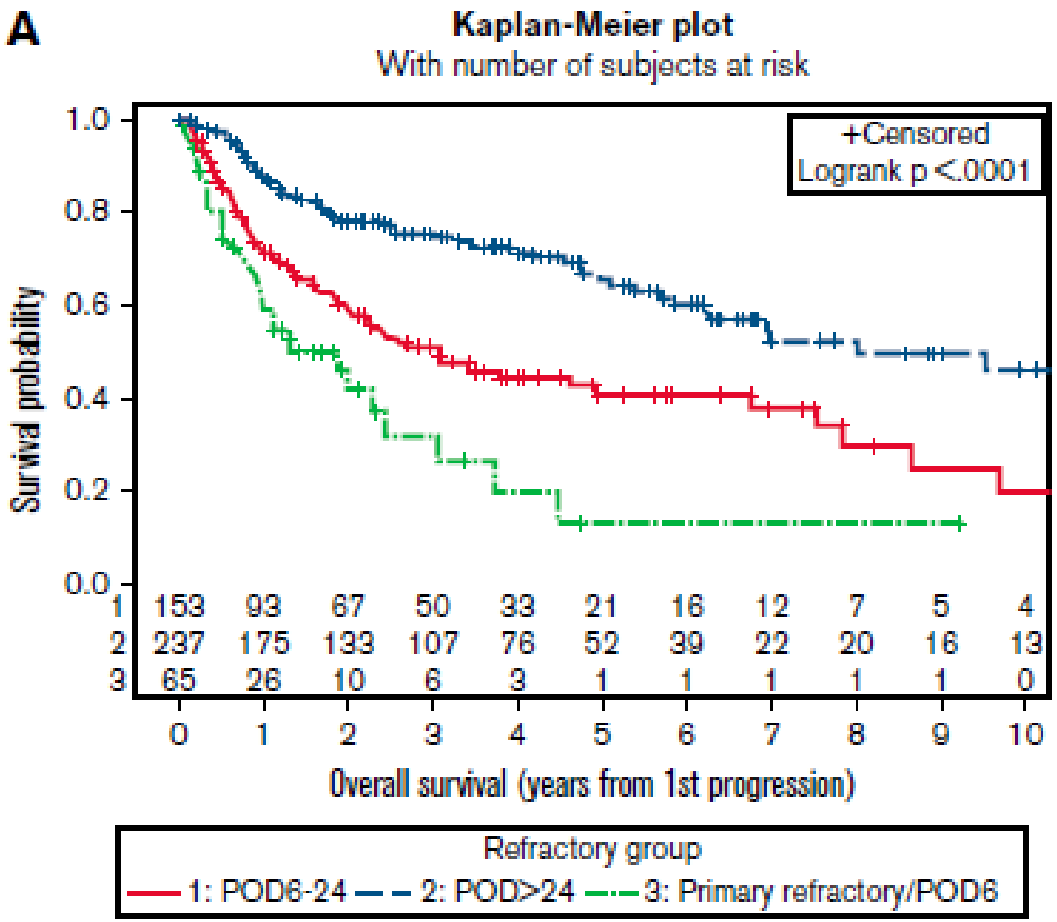
Research To Practice, ASH 2023

R/R MCL Outcomes Based on Time to Relapse

Key Baseline Variables

Variable	Total (n=455)	PRF/POD6 (n=65)	POD 6-24 (n=153)	POD > 24 (n=237)	P
Median Age	62	66	63	60	0.002
MIPI Score					0.002
-Low Risk	74 (35%)	10 (27%)	17 (22%)	47 (47%)	
-Int Risk	72 (34%)	10 (27%)	29 (38%)	33 (33%)	
-High Risk	67 (31%)	17 (46%)	30 (39%)	20 (20%)	
Ki67 > 30%	94 (50%)	23 (64%)	48 (60%)	23 (32%)	<0.001
Comp Kary	20 (20%)	3 (14%)	20 (35%)	7 (10%)	0.001
DTI < 90d	345 (83%)	54 (92%)	128 (90%)	163 (76%)	<0.001

Note – Missing data results in not all categories reaching 100%



Bond et al, *Blood Adv,* 2021

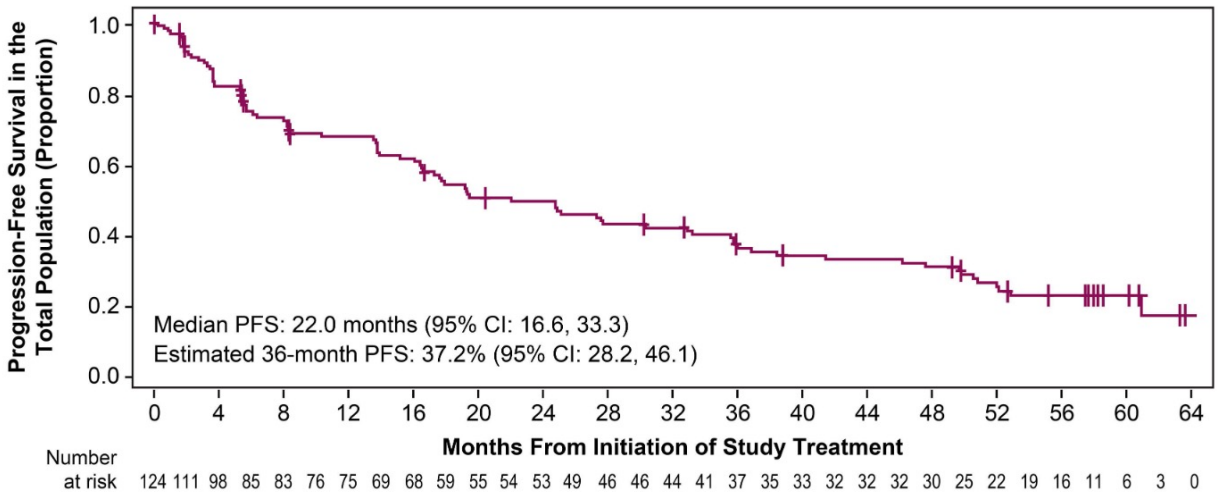
R/R MCL Treatment Options

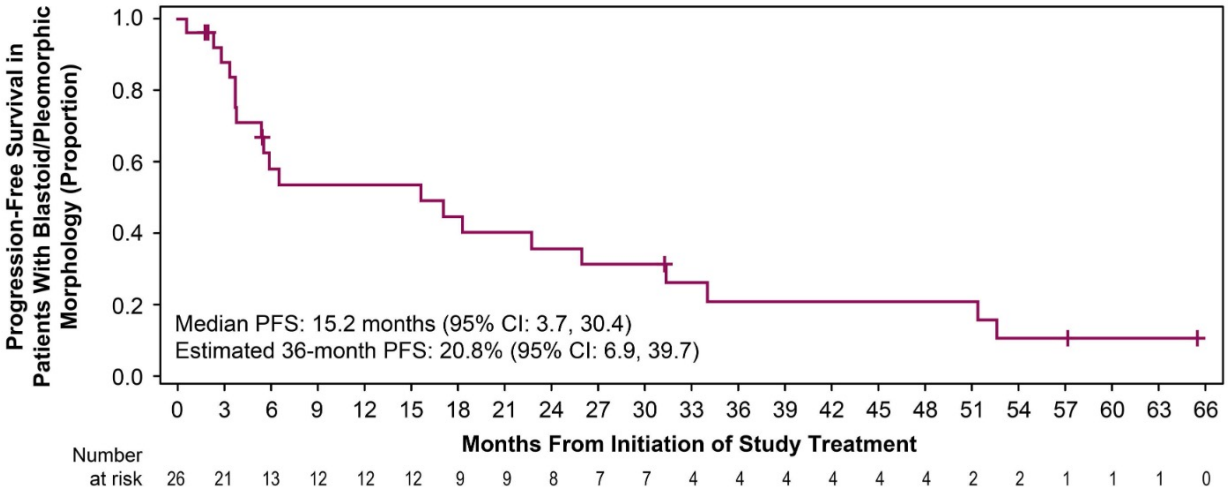
- Covalent BTK inhibitors
  - Acalabrutinib
  - Zanubrutinib
- CAR-T
  - Brexucabtagene autoleucel
  - *Lisocabtagene maraleucel**
- Non-Covalent BTK inhibitors
  - Pirtobrutinib
- Other non-approved, but possibly active therapies
  - Glofitamab
  - Venetoclax
  - ROR-1 directed treatments

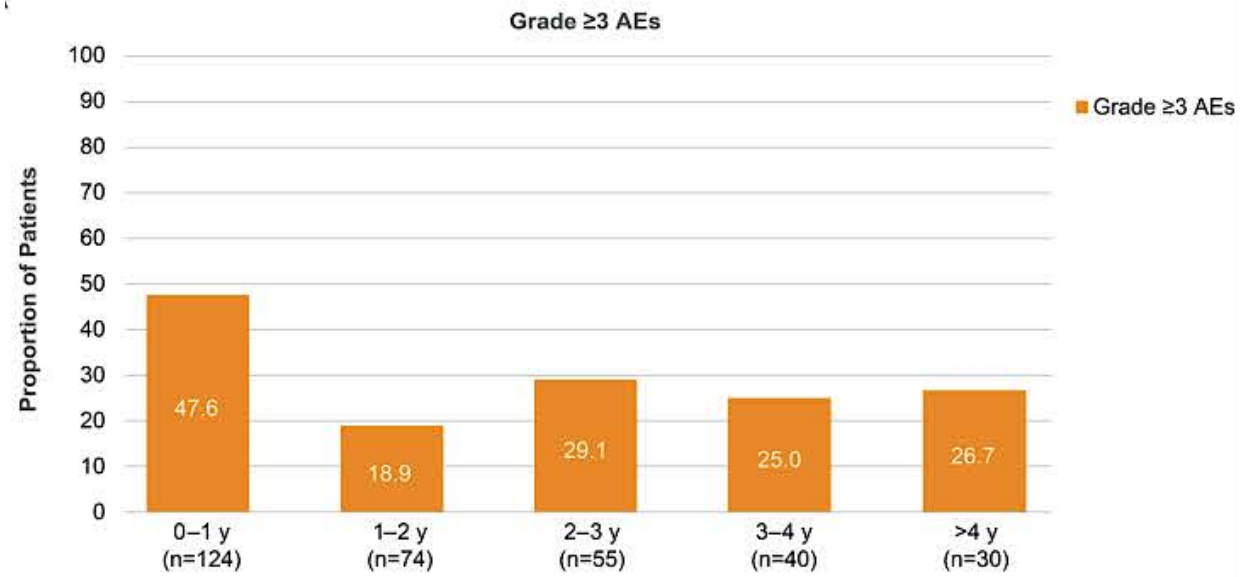
Other Options:
Bortezomib
Lenalidomide +/- rituximab
Chemotherapy

*Not FDA approved for MCL

Acalabrutinib Long-term follow-up



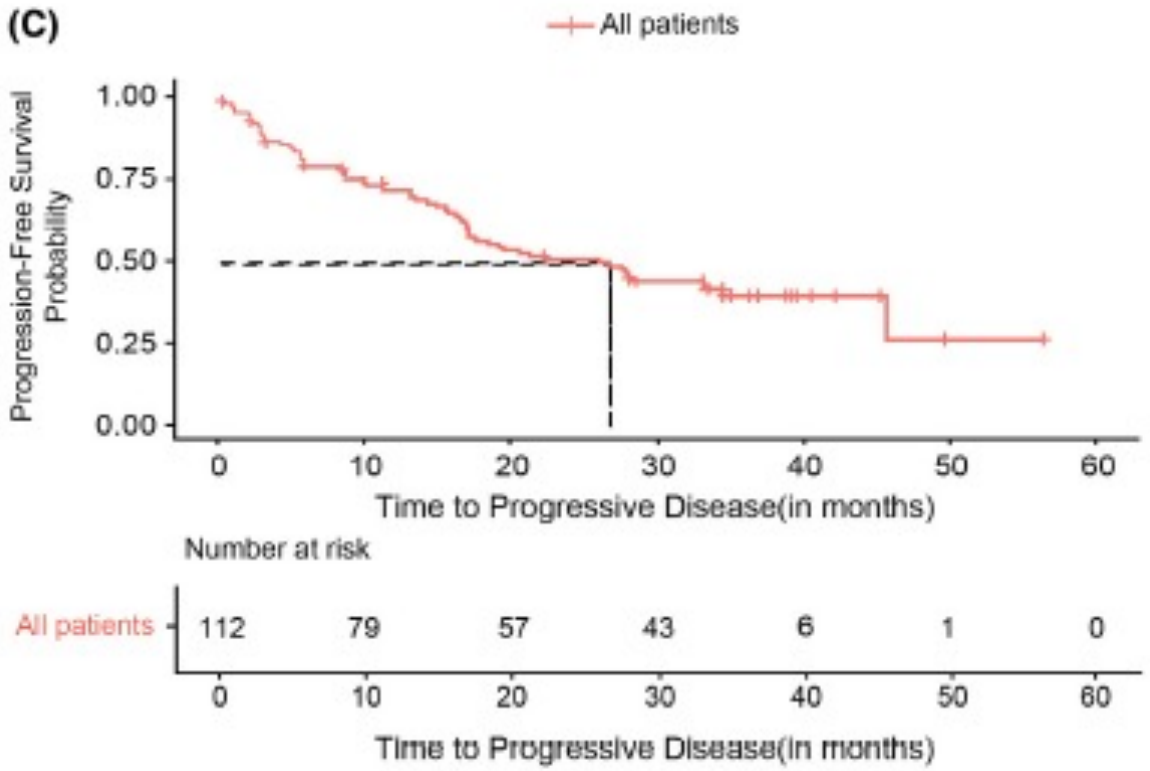




Median Follow-up 38.1 months

Le Gouill et al, Haematologica, 2023

Zanubrutinib Long-Term Follow-up



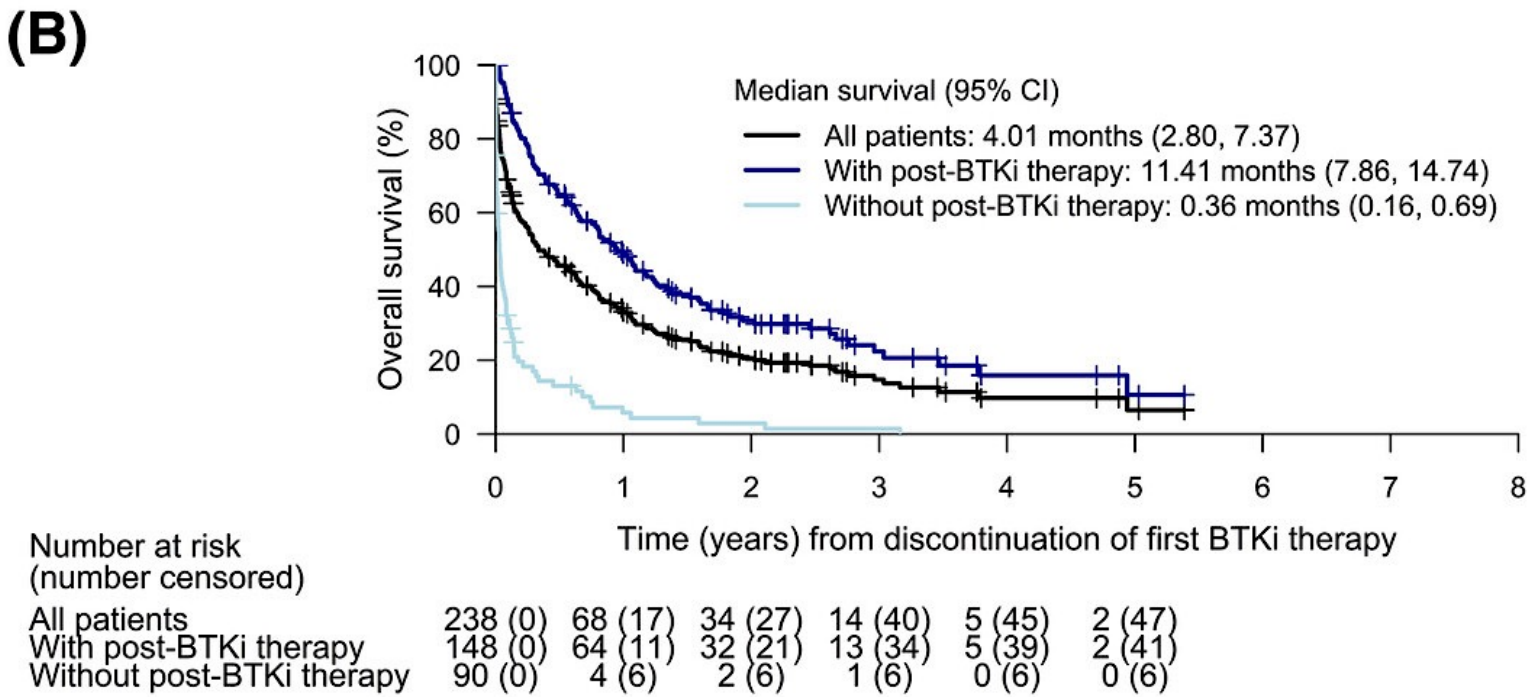
Median follow-up: 35.2 months

N=112	Any occurrence (%)	Grade 3+ (%)
Atrial Fib/Flutter	3	2
Diarrhea	25	1
Hemorrhage	5	4
Hypertension	12	3
≥1 Grade 3+ event	-	53.6

Song et al, *Cancer Medicine,* 2023

BTKi Resistance is Common

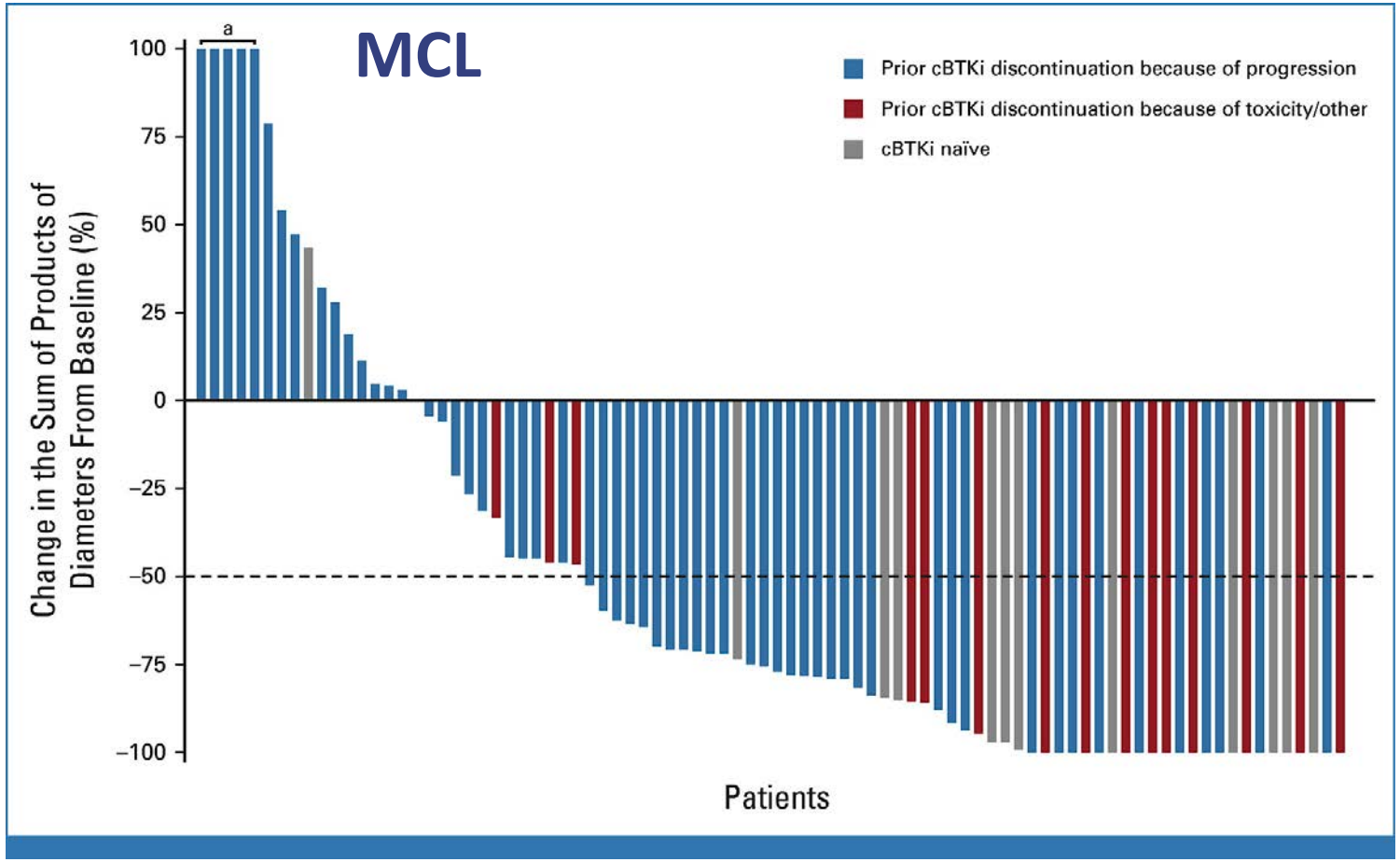
- Most patients will ultimately experience disease progression
- Post-progression outcomes historically poor (OS < 1 year)
- Mechanisms less well understood compared to CLL
- Options:
  - Non-covalent BTKi
  - CAR-T
  - Trials



Hess et al, BJH, 2022

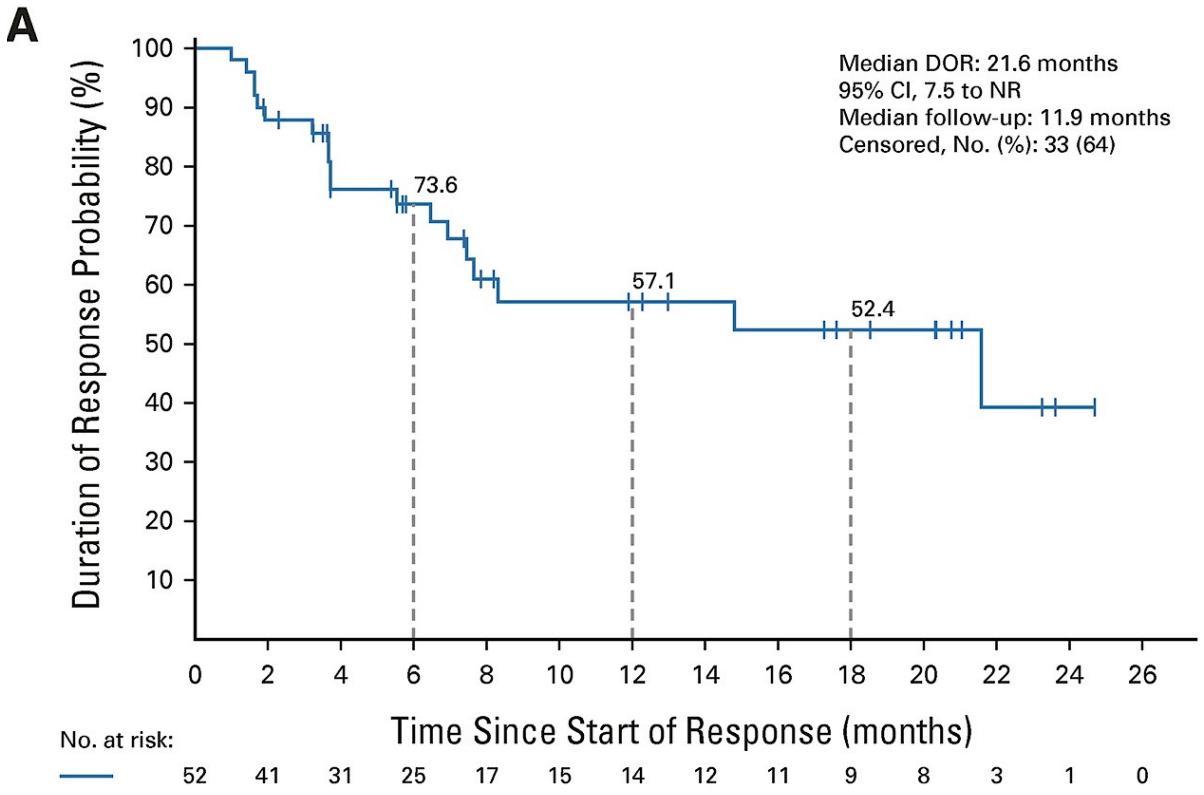
Non-Covalent BTKi - Pirtobrutinib

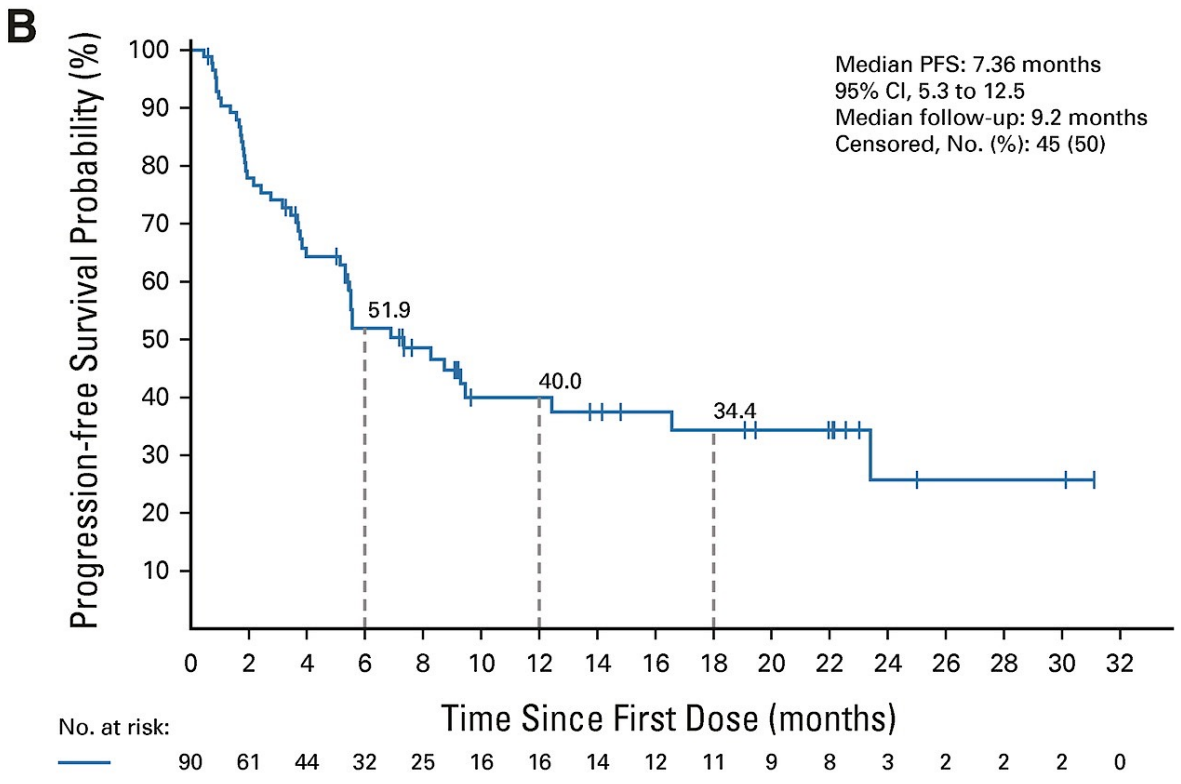
- Active in patients with BTK resistance and intolerance
- BRUIN – Phase 1/2 study of pirtobrutinib in relapsed/refractory NHL



Wang et al, JCO 2023

Pirtobrutinib Survival Outcomes



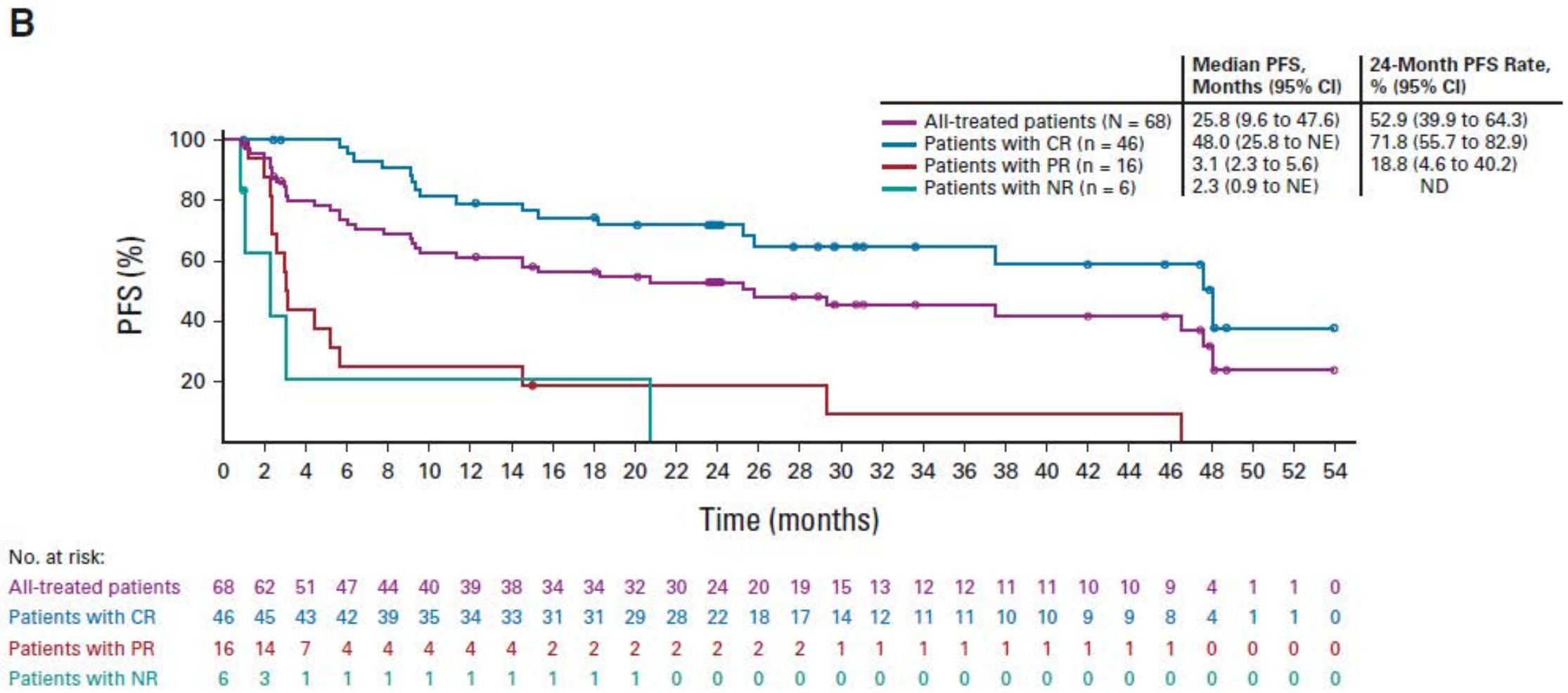


** Update: Abstract 918, Monday 5:00PM

Wang et al, JCO 2023

Brexucabtagene Autoleucel

- CAR-T has *greatly* improved outcomes for patients with r/r MCL



Wang et al, J Clin Oncol 2023

Brexucabtagene Autoleucel

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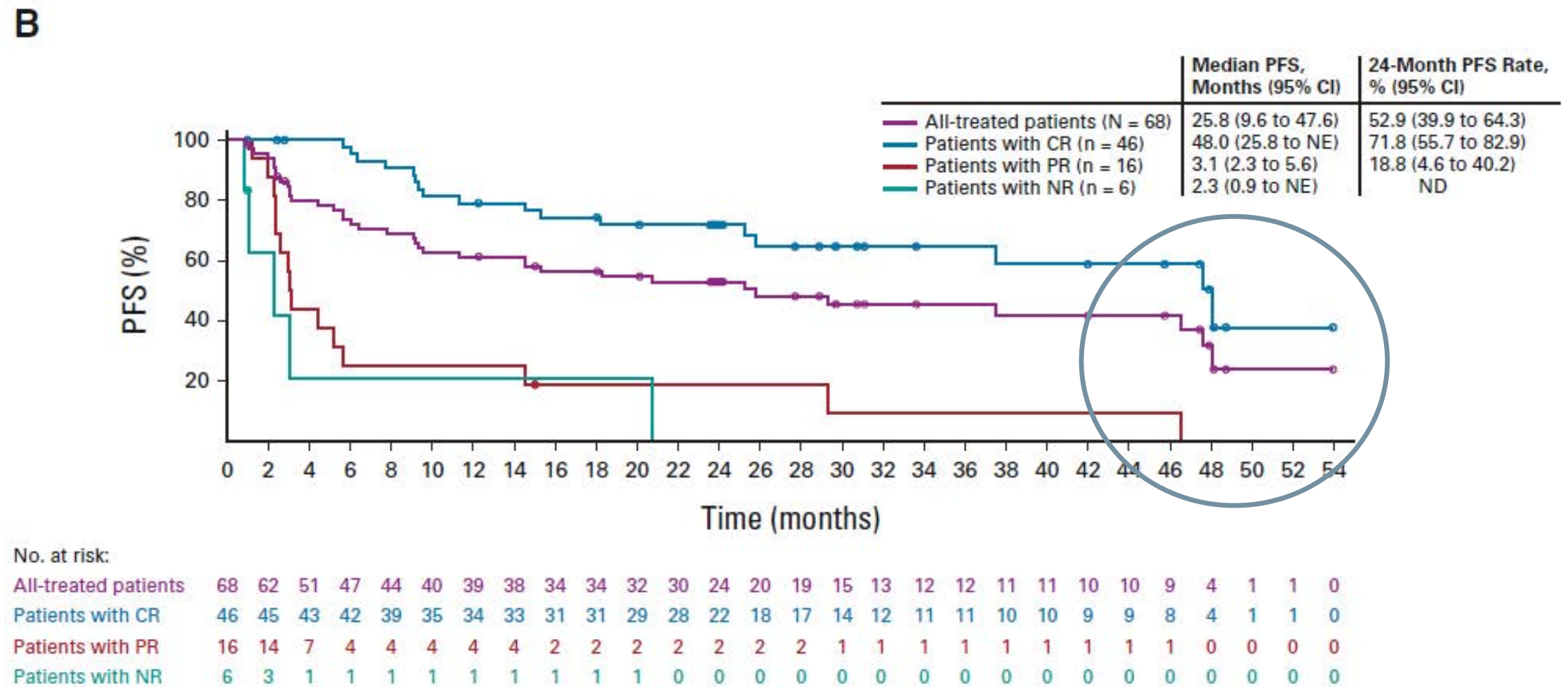


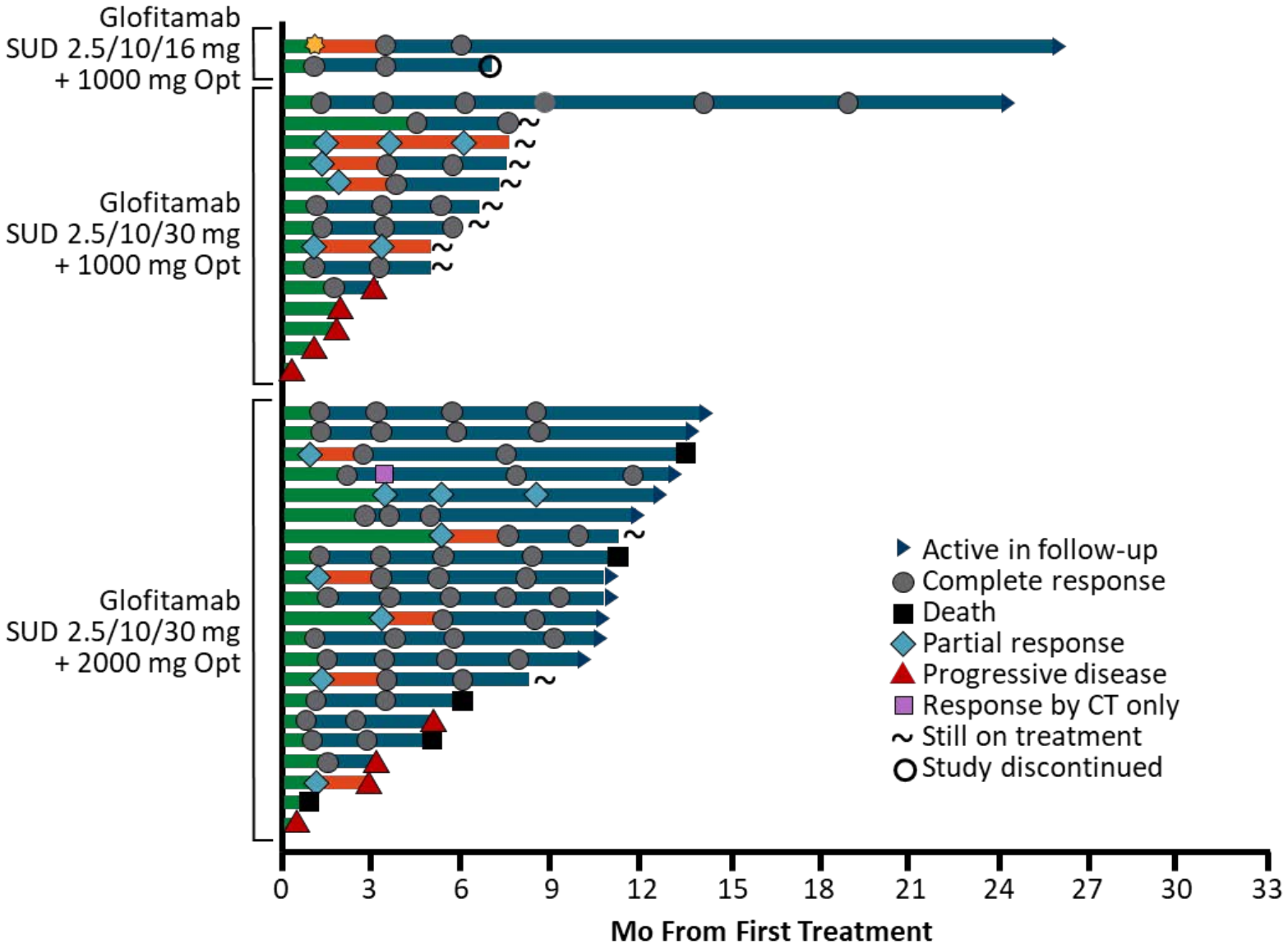
Wang et al, J Clin Oncol 2023

TRANSCEND NHL 001 – Lisocabtagene Maraleucel in MCL Cohort

- R/R MCL, ≥ 2 prior lines of therapy
- All BTKi pre-treated
- 104 patients leukapheresed, 88 treated
- 8% Active CNS disease, 23% TP53 mutations
- Overall Response Rate: 86.5%, CR Rate 74.3%
- Median duration of response: 15.7 months
- 1% Grade 3+ CRS; 9% Grade 3+ ICANS

Wang et al, ICML 2023

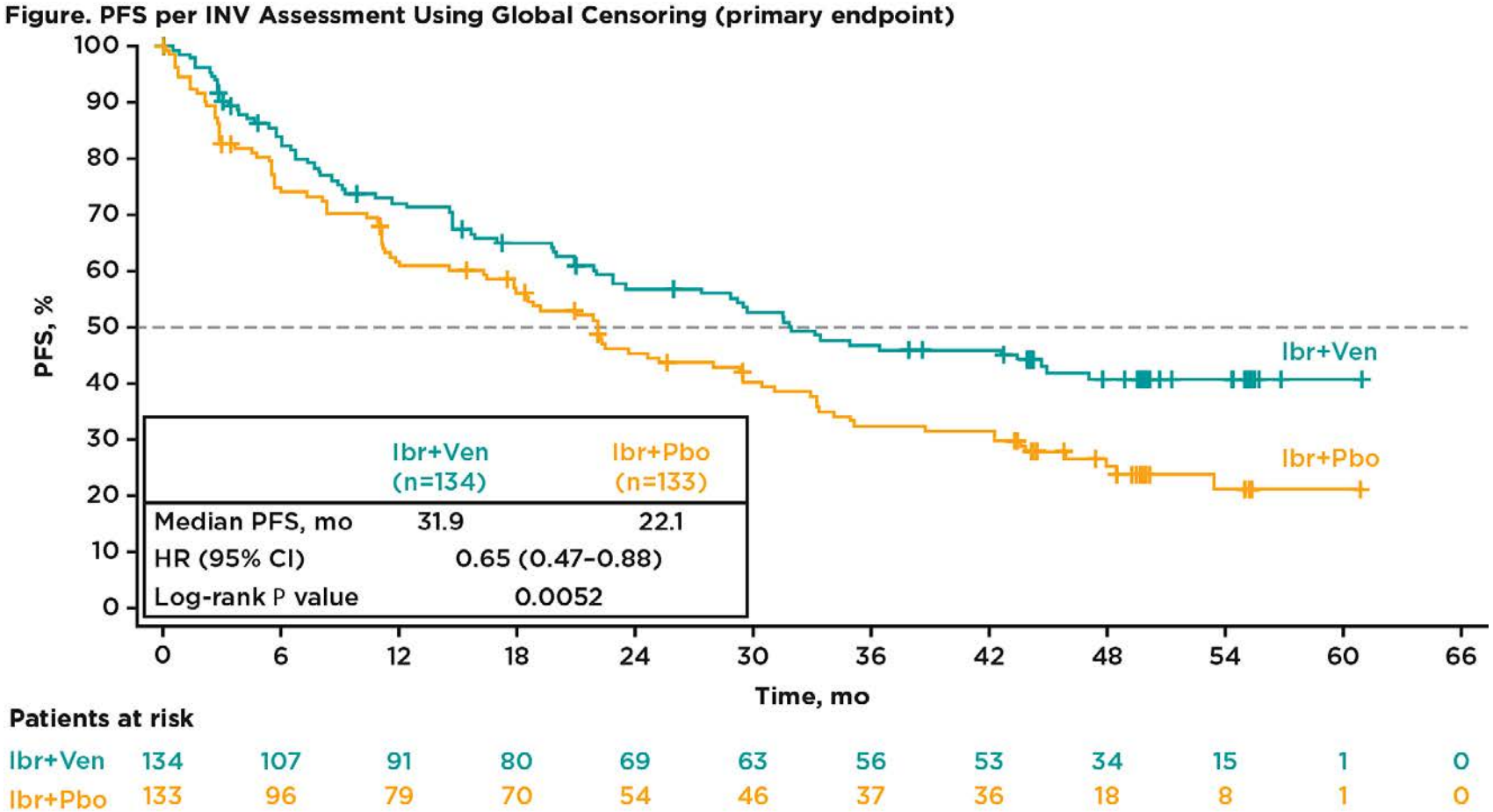
Upcoming Therapies: BiTEs



Phillips, ASH 2022

Latest and Greatest

- Combinations: Ready for prime time?
  - Sympatico study – LBA Session Tuesday AM



Wang et al, ASH 2023, LBA-2

Latest and Greatest

- Combinations: Ready for prime time?
  - Sympatico study – LBA Session Tuesday AM
- ROR1 Targeted Therapies
- BTK Degraders
- Novel antibody constructs

Agenda

Module 1: Evolving Role of Novel Treatment Strategies in Follicular Lymphoma (FL) — Dr Friedberg

Module 2: Integration of Chimeric Antigen Receptor (CAR) T-Cell Therapies and Bispecific Antibodies into the Management of FL — Dr Abramson

Module 3: Up-Front Treatment for Mantle Cell Lymphoma (MCL) — Dr Kahl

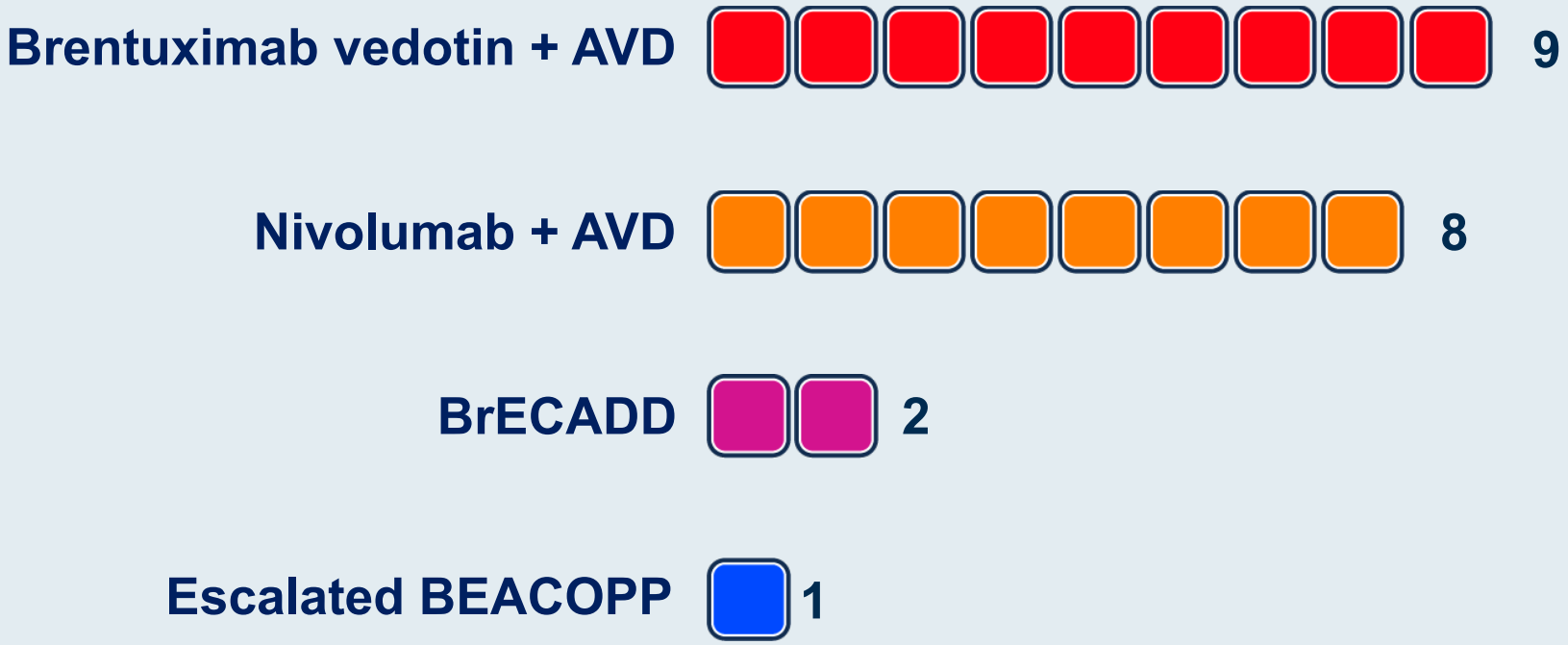
Module 4: Therapeutic Sequencing for Patients with Relapsed/Refractory (R/R) MCL — Dr Cohen

Module 5: First-Line Treatment Strategies for Hodgkin Lymphoma (HL) — Dr Bartlett

Module 6: Current and Future Management of R/R HL — Dr Ansell

RTP RESEARCH TO PRACTICE

What is your usual preferred initial treatment for a younger patient with high-risk classic Hodgkin lymphoma (HL)?

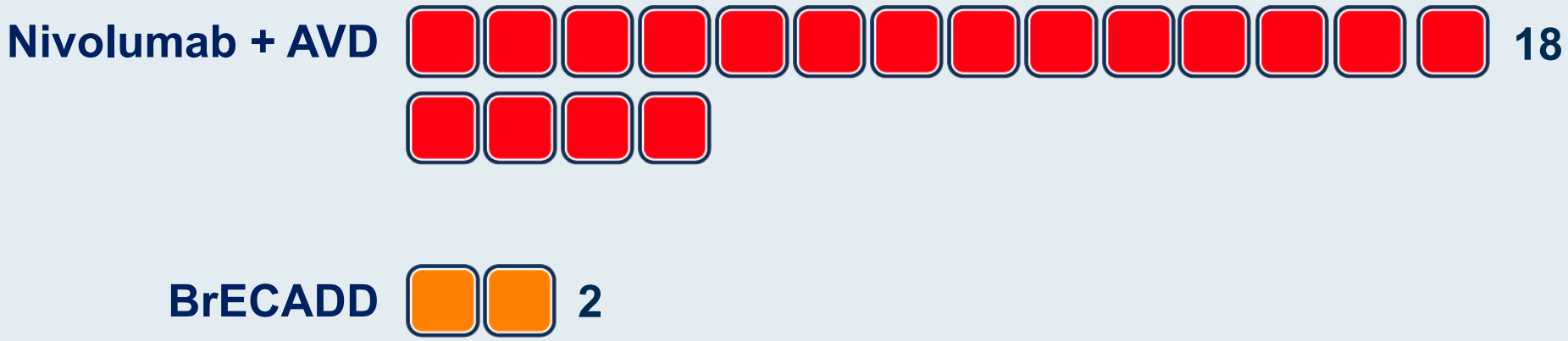


AVD = doxorubicin/vinblastine/dacarbazine; BrECADD = brentuximab vedotin/etoposide/cyclophosphamide/doxorubicin/dacarbazine/dexamethasone

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

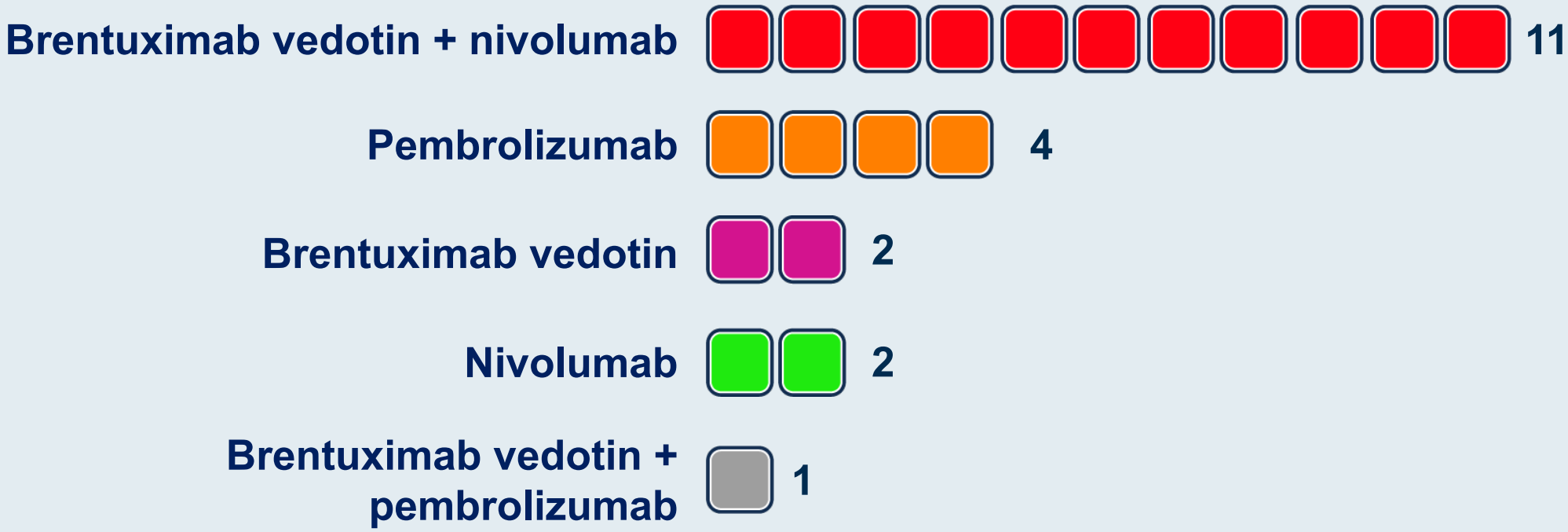
Regulatory and reimbursement issues aside, what do you believe is the optimal first-line treatment approach for a younger patient with high-risk HL?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what do you believe is the optimal first-line treatment approach for an 85-year-old frail patient with advanced-stage symptomatic HL who is not a candidate for aggressive chemotherapy but is seeking active treatment?



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RTP RESEARCH TO PRACTICE

Activity and tolerability of first-line nivolumab/AVD in older patients with advanced-stage HL

Kami Maddocks, MD

Andrew M Evens, DO, MBA, MSc

Effectiveness and feasibility of brentuximab vedotin in combination with nivolumab and doxorubicin/dacarbazine for advanced-stage classic HL (cHL)

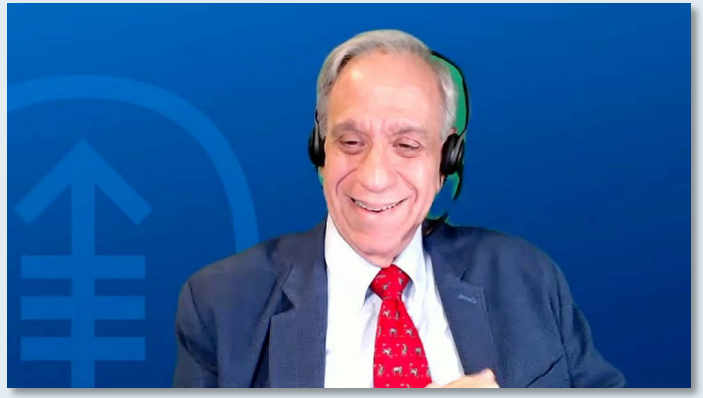
Andrew M Evens, DO, MBA, MSc

RTP
RESEARCH
TO PRACTICE

Use of radiation therapy as a treatment component for limited-stage HL

Tycel Phillips, MD

Franck Morschhauser, MD, PhD



Andrew D Zelenetz, MD, PhD

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TO PRACTICE

First-Line Treatment Strategies for Hodgkin Lymphoma (HL)

Nancy L. Bartlett, MD
Koman Professor of Medicine
Washington University in St. Louis
Siteman Cancer Center
December 8, 2023

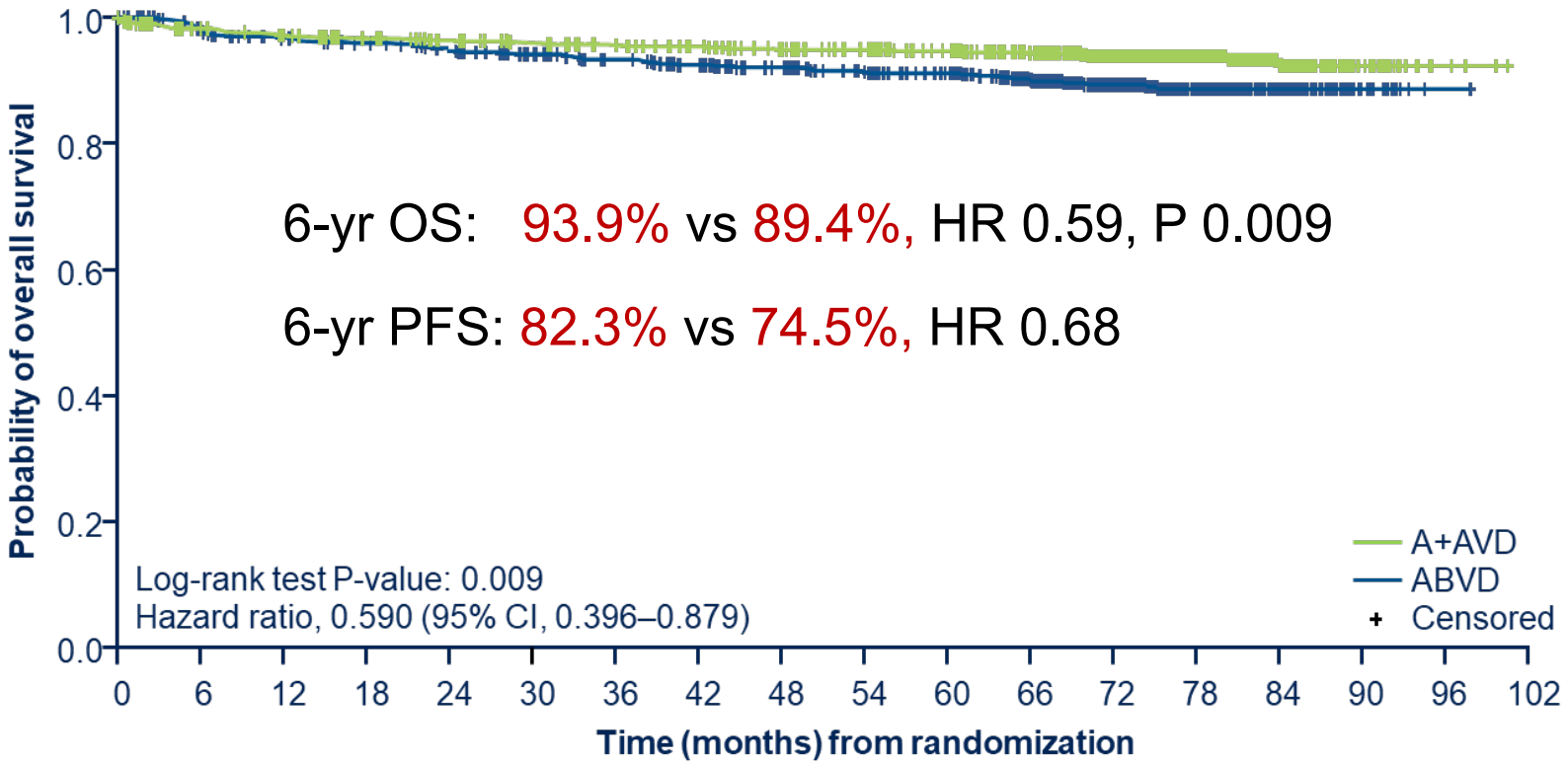
SITEMAN CANCER CENTER
BARNES-JEWISH Hospital BJC HealthCare
Washington University in St. Louis Physicians
NCCN National Comprehensive Cancer Network®
NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Topics

- Long-term follow-up of Phase III ***ECHELON-1*** study: Bv-AVD vs. ABVD
- Preliminary results of Phase III ***SWOG-S1826*** study: Nivo-AVD vs. Bv-AVD
- Additional studies exploring anti-PD1 antibodies in first-line
- Current front-line approaches in older pts
- Preliminary results of Bv and/or PD-1 inhibitors + chemo in early-stage HL

ECHELON-1: Overall survival benefit with Bv-AVD

Phase 3: ABVD vs Bv-AVD, Stage 3-4, N=1334



Significant HR favoring Bv+AVD

Subgroup	HR (CI)
Age <60	0.51 (0.29 - 0-89)
IPS 2-3	0.62 (0.33 - 1.14)
IPS 4-7	0.48 (0.26 – 0.88)
Stage 4	0.48 (0.29 – 0.80)
EN site >1	0.30 (0.14 – 0.67)
Male	0.43 (0.25 – 0.73)

Ansell et al. N Engl J Med 2022; 387:310-320

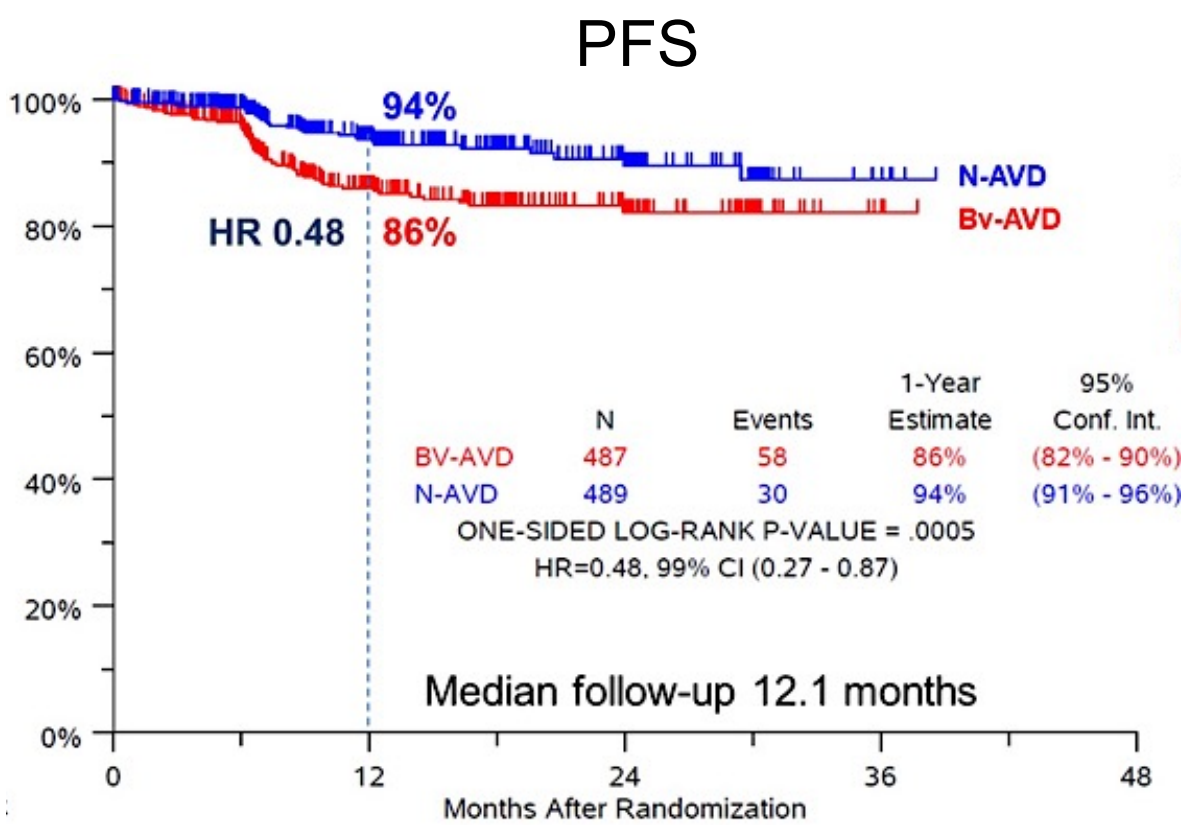
ECHELON-1: Adverse events

Adverse Event	Bv + AVD (n=664)		ABVD (n=670)	
	All	Gr ≥ 3	All	Gr ≥ 3
Any		83%		66%
Hospitalization	37%		28%	
Toxic Death		1.3% (n=9)		1.9% (n=13)
Pneumonitis	2%	<1%	7%	3%
F/N (no GCSF)		22%		8%
F/N (+ GCSF)		11%		7%
Peripheral neuropathy	67%	11%	43%	2%
age 18-39		13%		3%
age ≥ 60		18%		3%
Second malignancies	23 (6 NHL)		32 (13 NHL)	

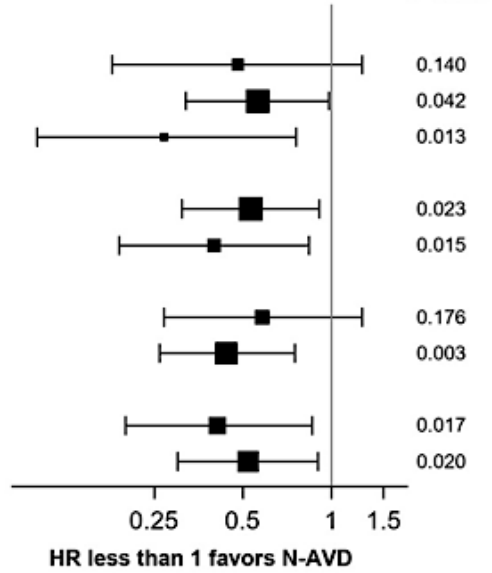
Connors J. et al N Engl J Med 2018; 378:331-344; Ansell et al. N Engl J Med 2022; 387:310-320;
Crosswell et al Haematologica 2023; 10.3324/haematol.2023.283303; Evens A et al Haematologica 2022;107:1086-1094

SWOG S1826: PFS benefit with Nivo-AVD

- Phase 3: **Nivo-AVD** vs. **Bv-AVD**, Stage 3-4, age ≥ 12, N=994



Subgroup	N + AVD Events/N (%)	BV + AVD Events/N (%)	HR (95% CI)	P Value
Age				
12 - 17 y	6/120 (5.0)	12/117 (10.3)	0.48 (0.18, 1.27)	0.140
18 - 60 y	19/323 (5.9)	32/323 (9.9)	0.56 (0.32, 0.98)	0.042
> 60 y	5/46 (10.9)	14/47 (29.8)	0.27 (0.10, 0.76)	0.013
IPS				
0 - 3	20/331 (6.0)	36/330 (10.9)	0.53 (0.31, 0.91)	0.023
4 - 7	10/158 (6.3)	22/157 (14.0)	0.40 (0.19, 0.84)	0.015
Stage				
III	11/187 (5.9)	15/167 (9.0)	0.58 (0.27, 1.27)	0.176
IV	19/301 (6.3)	43/317 (13.6)	0.44 (0.26, 0.75)	0.003
Symptoms				
A	10/202 (5.0)	24/210 (11.4)	0.41 (0.20, 0.86)	0.017
B	20/286 (7.0)	34/274 (12.4)	0.52 (0.30, 0.90)	0.020



Herrera et al ASCO 2023

SWOG S1826: Adverse events

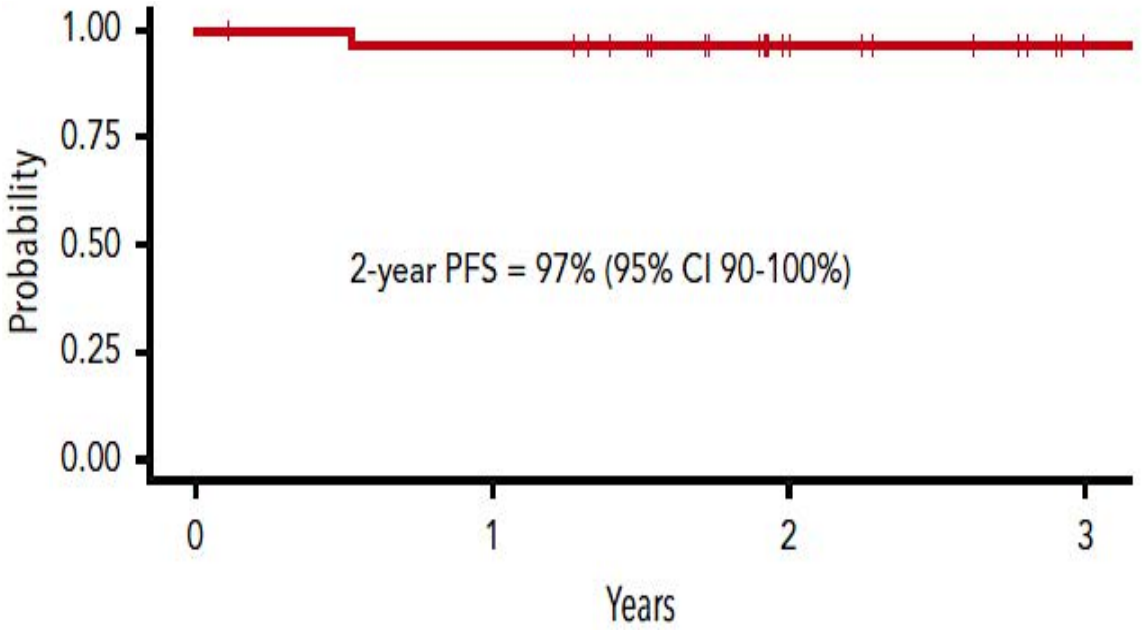
Adverse Event	Nivo + AVD (n=483)		Bv-AVD (n=473)	
	All	Gr ≥ 3	All	Gr ≥ 3
Neutropenia	55%	47%	32%	25%
Febrile neutropenia	5%		7%	
Bone pain	8%		20%	
Received G-CSF	**54%**		**95%**	
Infections	5%		8%	
Peripheral sensory neuropathy	29%	1%	55%	8%
Discontinued Bv or Nivo	11%		22%	
Deaths on treatment	0.4%		1.6%	

- Very low incidence of significant immune mediated toxicities
  - Similar rates of pneumonitis, colitis, rash
  - Higher rates of hypo/hyperthyroidism with Nivo
  - Higher rates of transaminitis with Bv

Herrera et al ASCO 2023

Pembro-AVD: concurrent/sequential

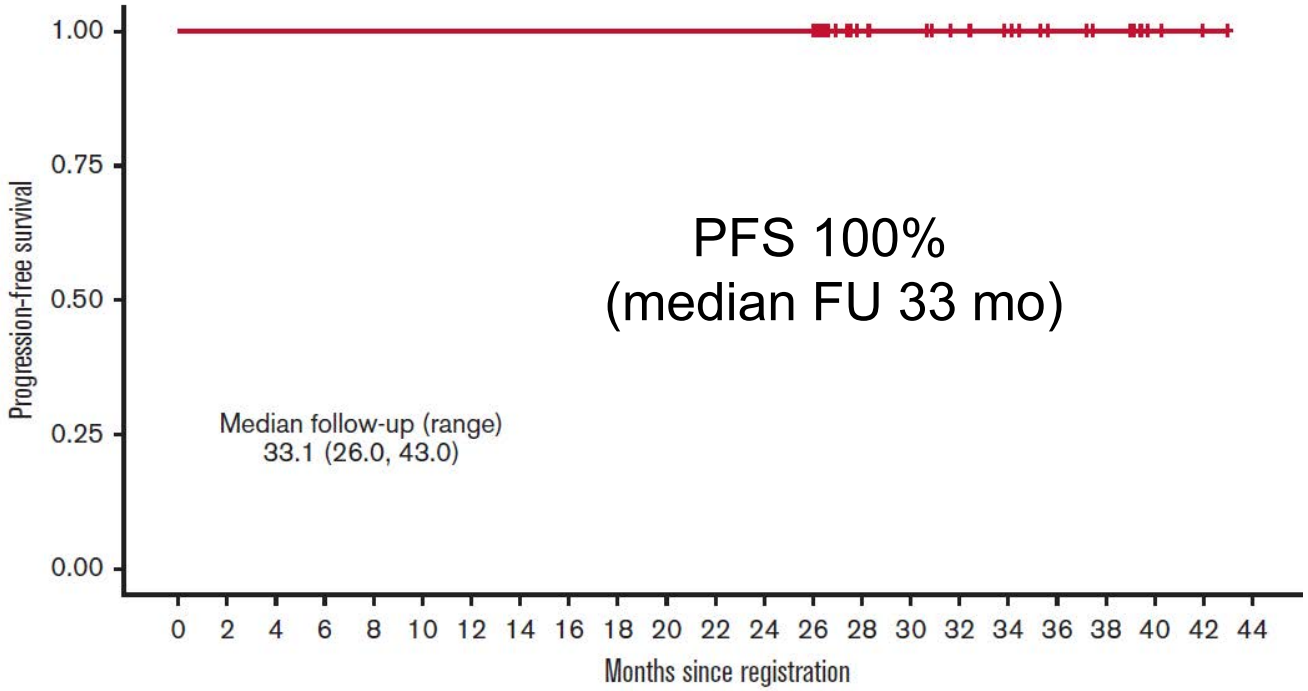
Pembro + AVD x 6



- Stage 3-4 (n=18), 1-2 (n=12, 6 unfavorable)
- **40% Gr 3-4 non-heme toxicity (F/N, infection)**

Lynch et al Blood 2023;141:2576-2586

Pembro x 3 → AVD x 4-6

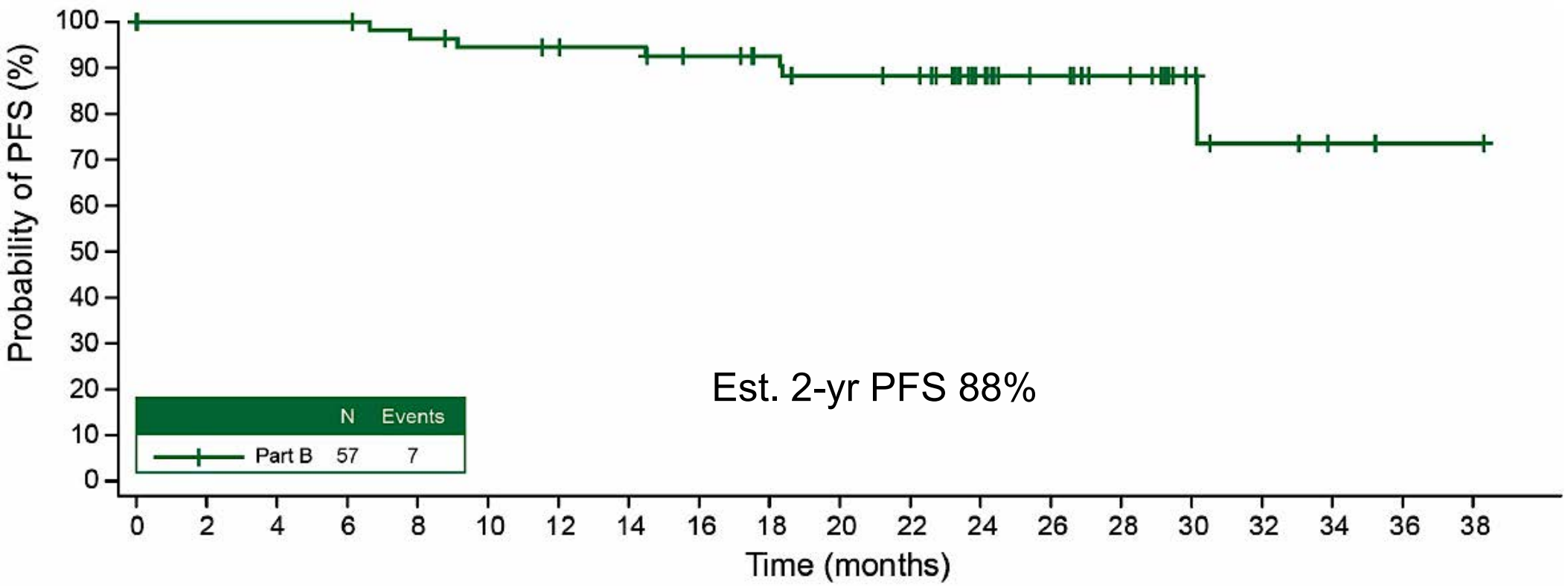


- Stage 3-4 (n=18), 2 unfavorable (n=12)

Allen et al Blood Adv 2023;7:2670-76

Bv-Nivo + AD in advanced stage

- Phase 2: Bv-Nivo + AD x 6, stage 2 bulky, 3-4, N=58



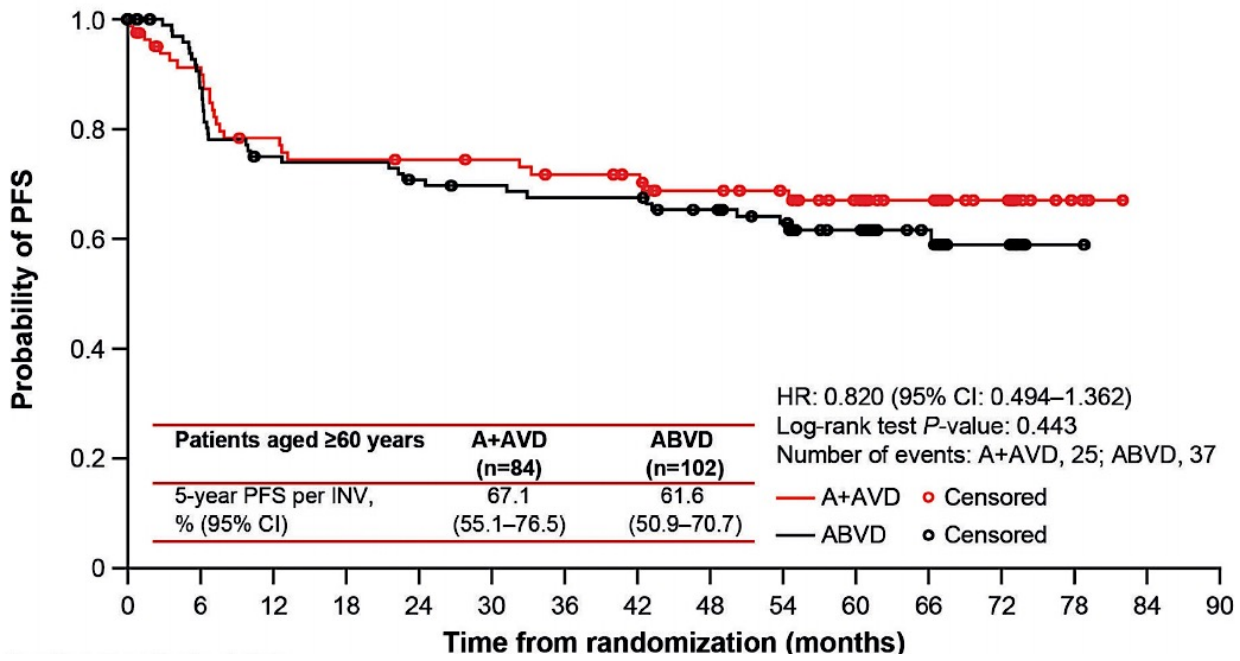
Est. 2-yr PFS 88%

Lee et al ASH 2023,Sun, December 10: 4:30 PM-6:00 PM
Grand Hall B (Manchester Grand Hyatt San Diego)

ECHELON-1 and SWOG-S1826: PFS subset analysis - **age ≥ 60**

ECHELON-1

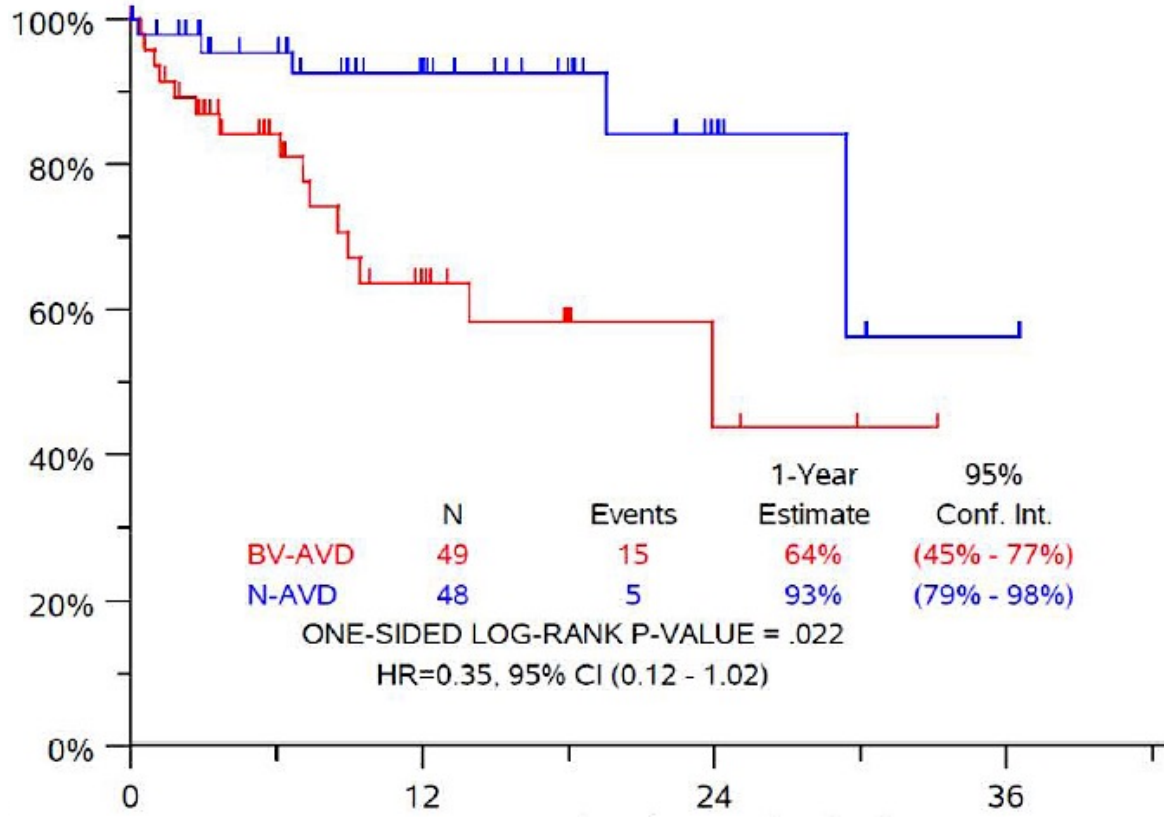
5-yr PFS 67.1% vs 61.6%, HR 0.82



Evens A et al Haematologica 2022;107:1086-1094

SWOG-S1826

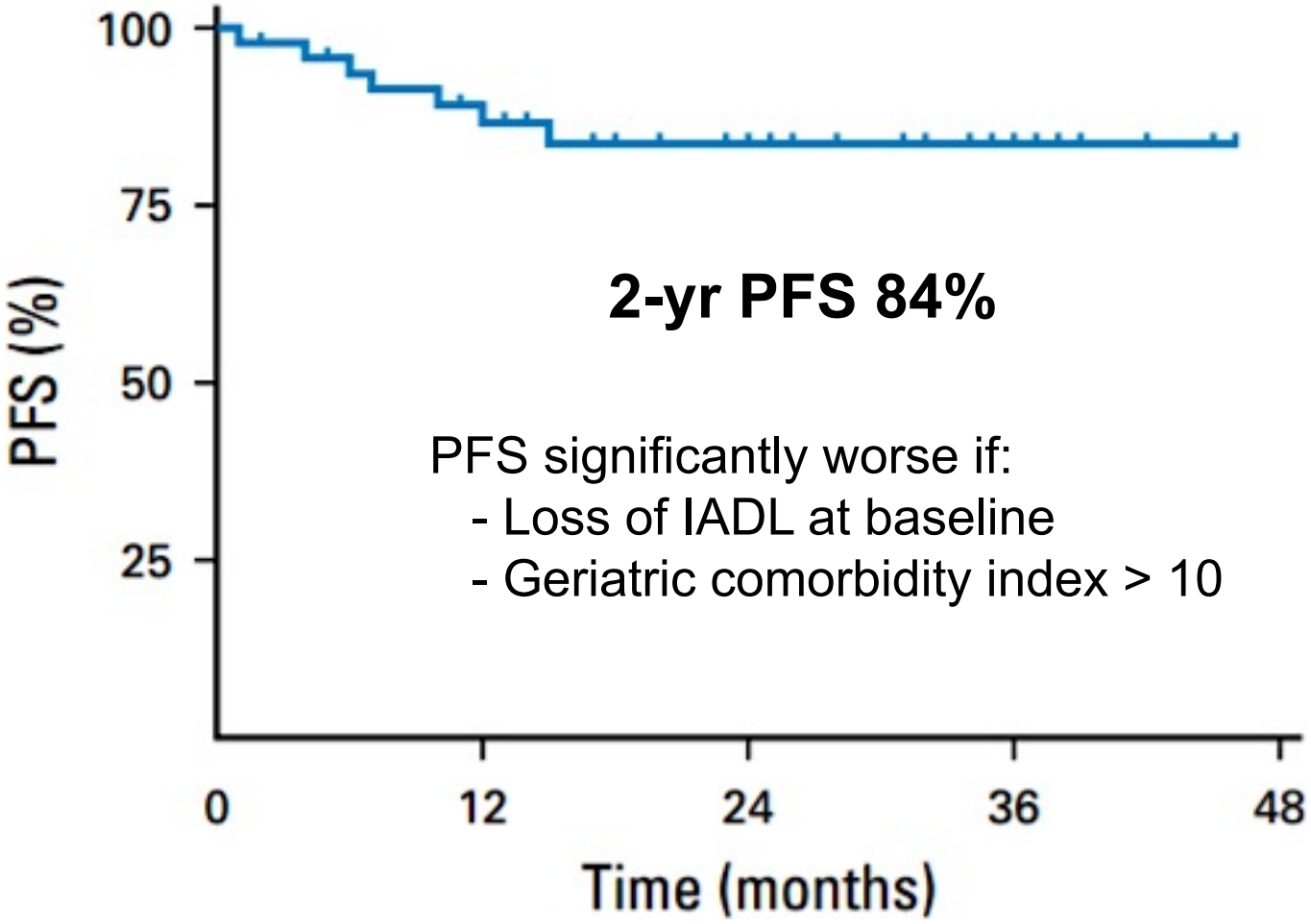
1-yr PFS 64% vs 93%, HR 0.36



Rutherford et al ASH 2023, Sat, Dec 9: 2:00 PM-3:30 PM Grand Hall B (Manchester Grand Hyatt San Diego)

Sequential Bv-AVD in older patients

Phase 2: Bv x 2 → AVD x 6 → Bv x 4, age ≥ 60, N=48



2-yr PFS 84%

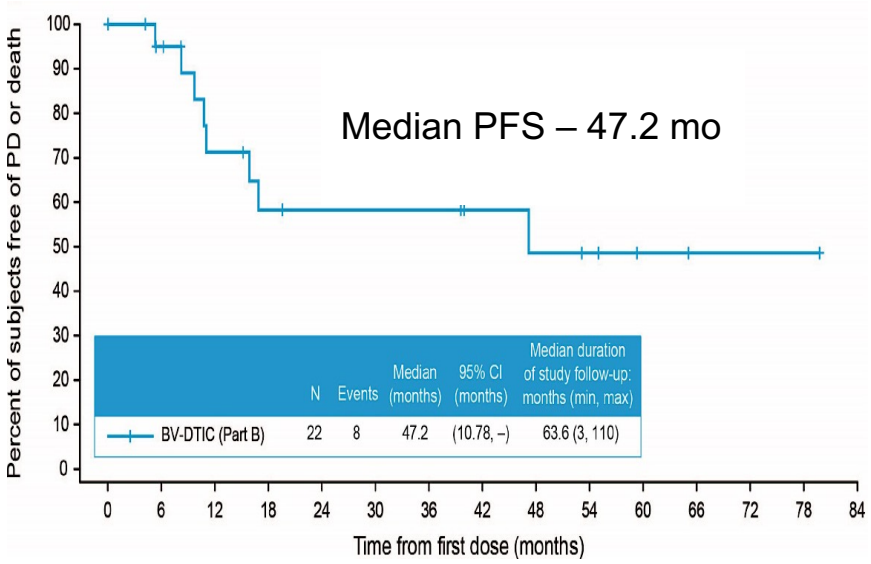
PFS significantly worse if:
- Loss of IADL at baseline
- Geriatric comorbidity index > 10

Neuropathy
Gr 3, 4%; Gr 2, 27%

Evens et al JCO 2018: 36:3015-22

Non-anthracycline Bv-based regimens, age ≥ 60

Bv + DTIC x 12

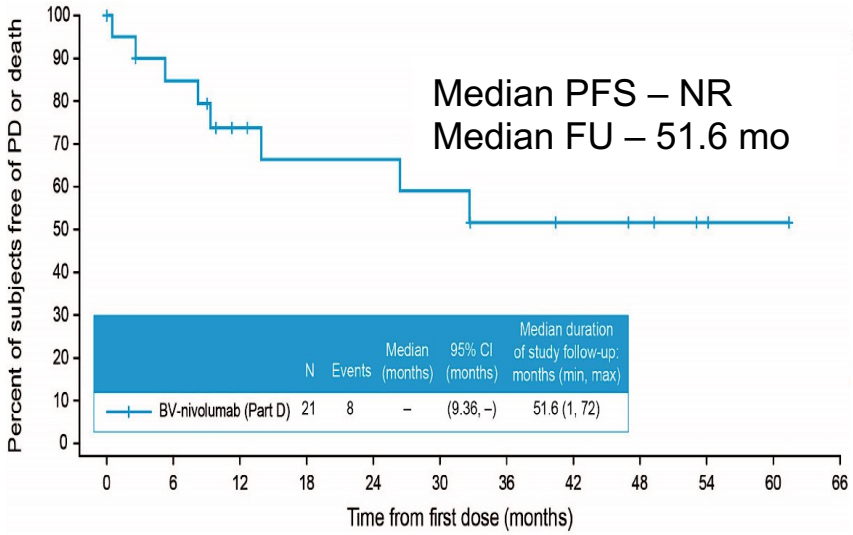


Neuropathy: Gr 3, 27%

Bv + Benda closed prematurely due to excessive toxicity (SAEs 60%)

Friedberg et al, Blood 2017;130:2829-37
Friedberg et al, Blood 2023; blood.2022019536

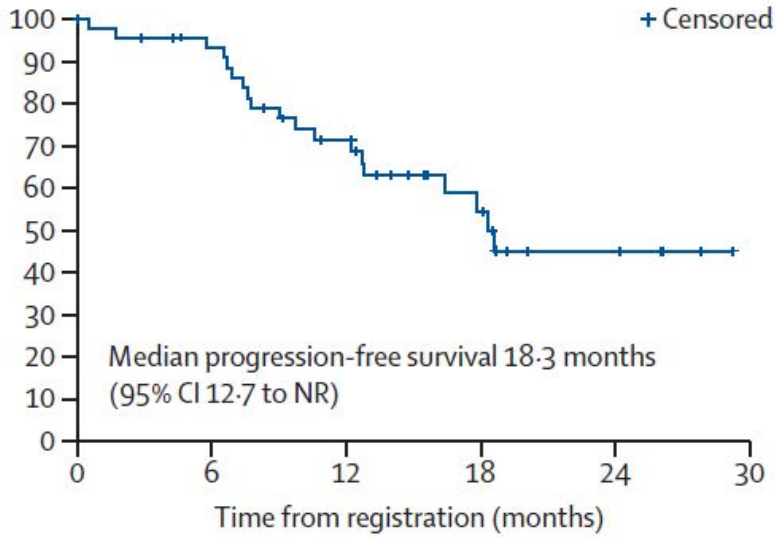
Bv + Nivo x 6



Neuropathy: Gr 3, 38%

Friedberg et al, Blood 2023; blood.2022019536.

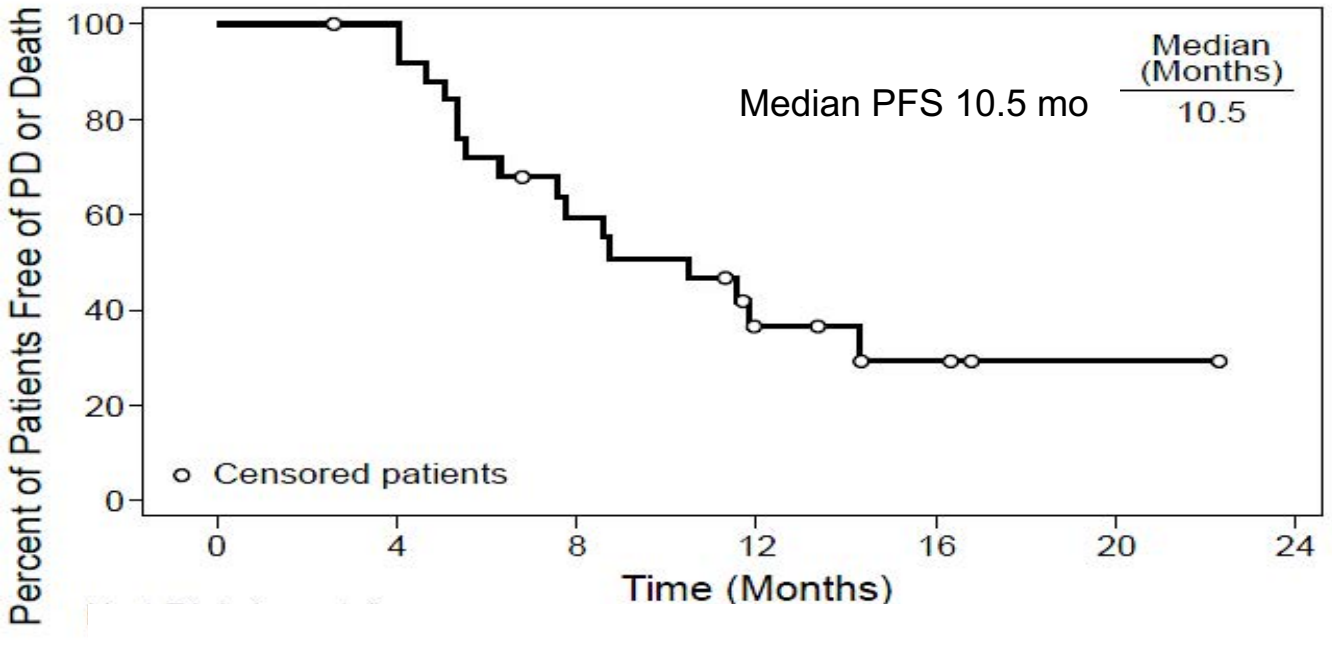
Bv + Nivo x 8 ACCRU



Neuropathy: Gr 3, 11%; Gr 2, 35%

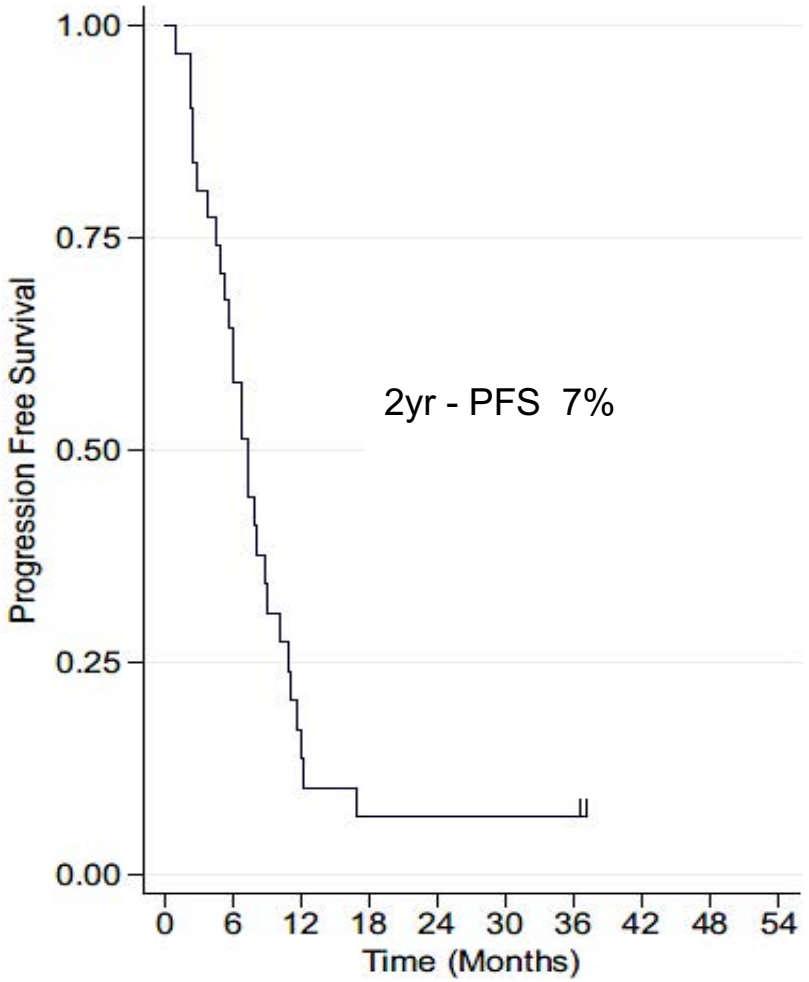
Cheson et al, Lancet Haem 2020;7: e808–15

Quick reminder: Bv-monotherapy in older patients **suboptimal**



Neuropathy: Gr3, 30%

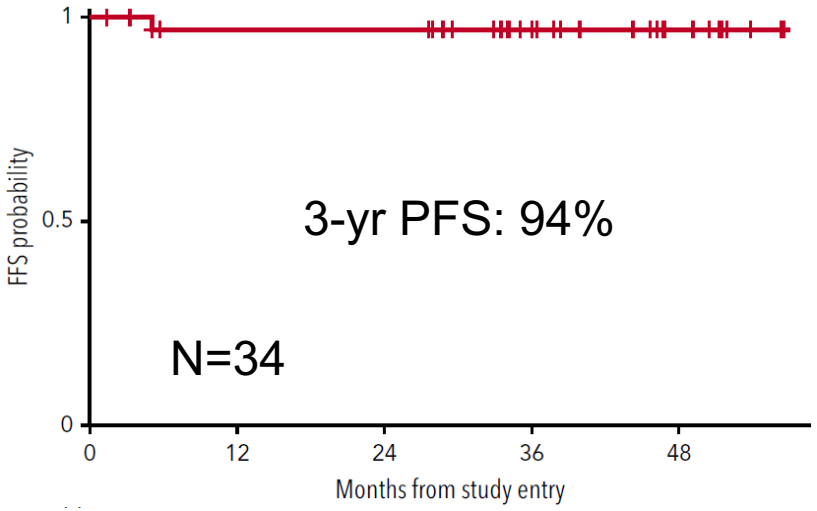
Forero-Torres et al. Blood. 2015;126:2798-804



Gibb et al Br J Haem 2021;193:63-71

Bv combinations in **early stage**, non-bulky cHL

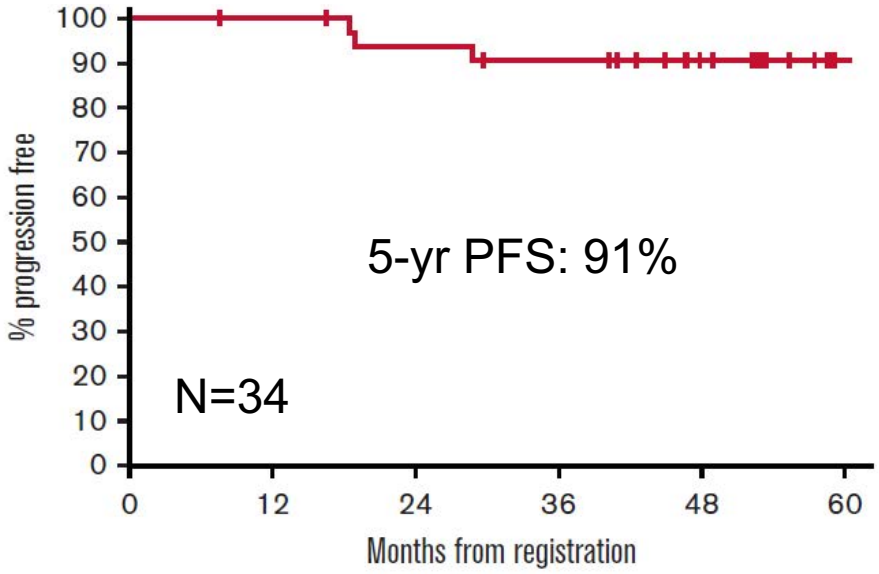
Bv-AVD x 4-6



Neuropathy: Gr 3, 24%
F/N: 35%

Abramson et al Blood 2019;134:606-613

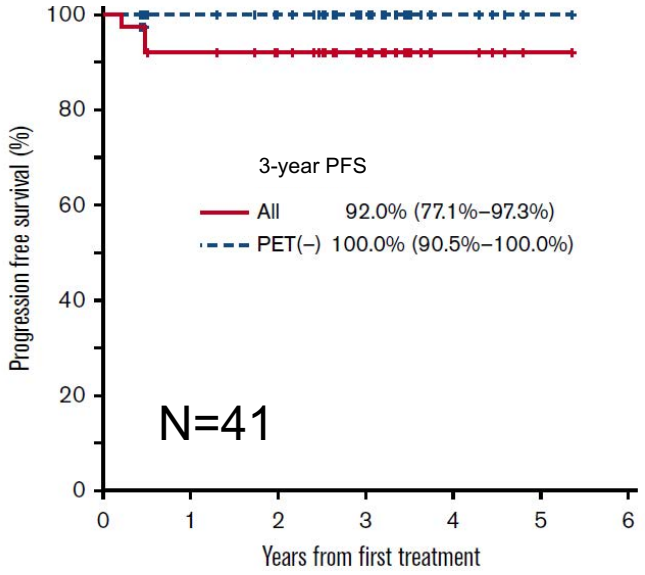
Bv-AD x 4-6



Neuropathy: Gr 3, 0%
F/N: 0%

Abramson et al Blood Adv. 2023;7:1130-36

ABVD x 2-6 → Bv x 6

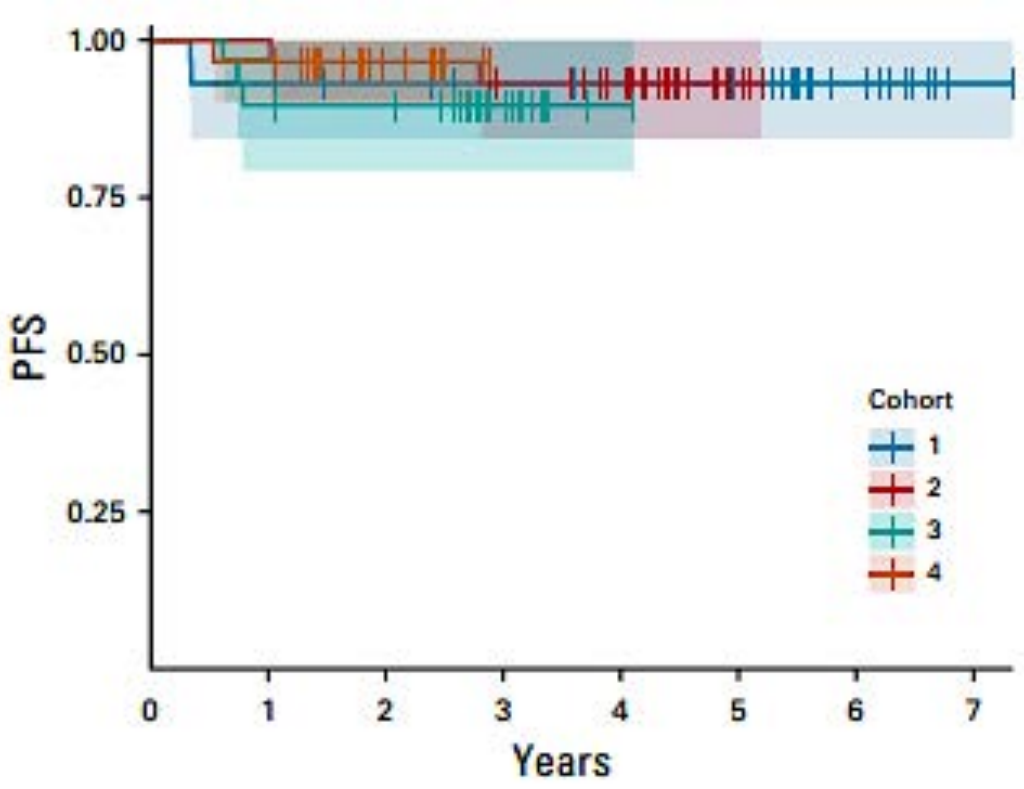


Neuropathy: Gr 3, 2.5%

Park et al Blood Adv. 2020;4:2548-55

Bv combinations in **early stage**, unfavorable

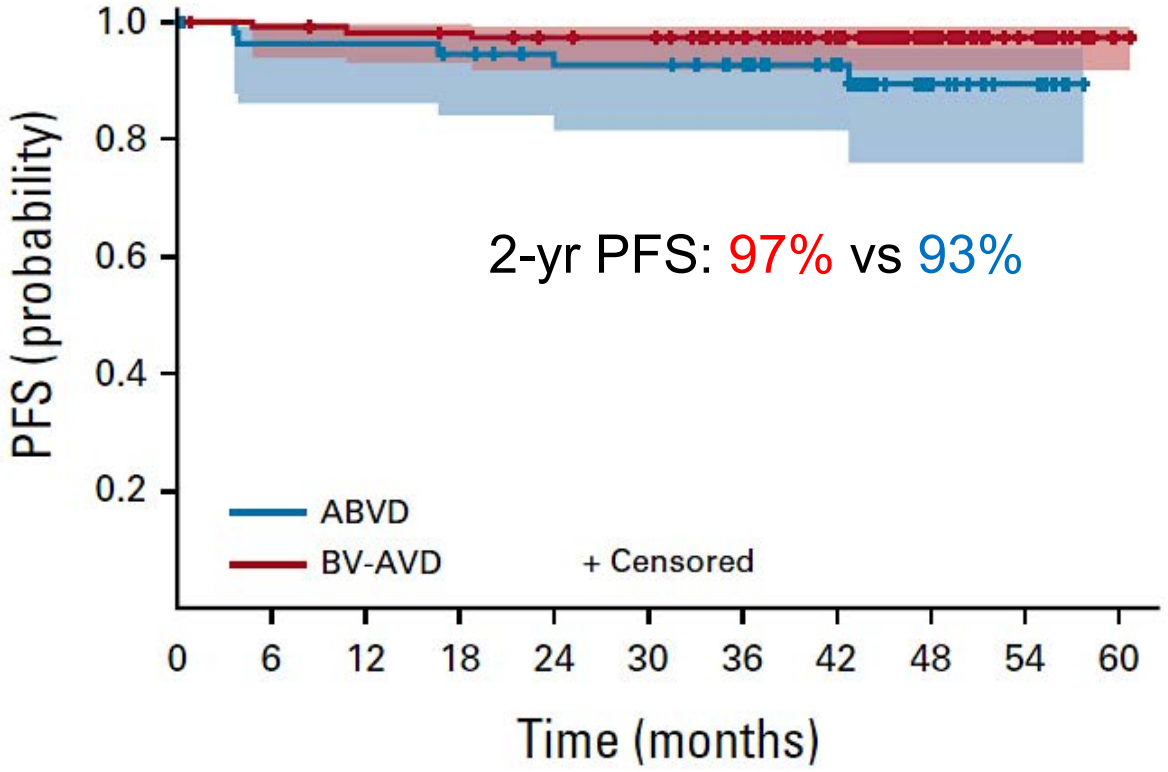
Bv-AVD x 4 ± RT



Neuropathy: Gr3, 5%

Kumar et al JCO 2021;39:2257-2265

Bv-AVD vs ABVD + RT (all) (BREACH)



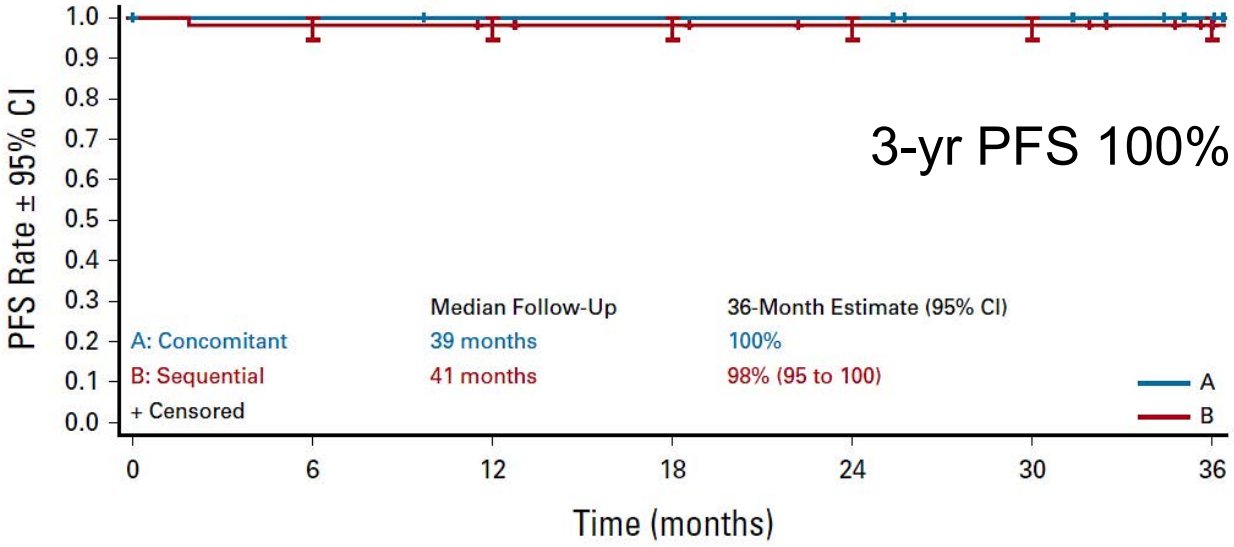
2-yr PFS: 97% vs 93%

Bv-AVD Neuropathy: Gr3, 3%

Fornecker et al JCO 2023;41:327-355

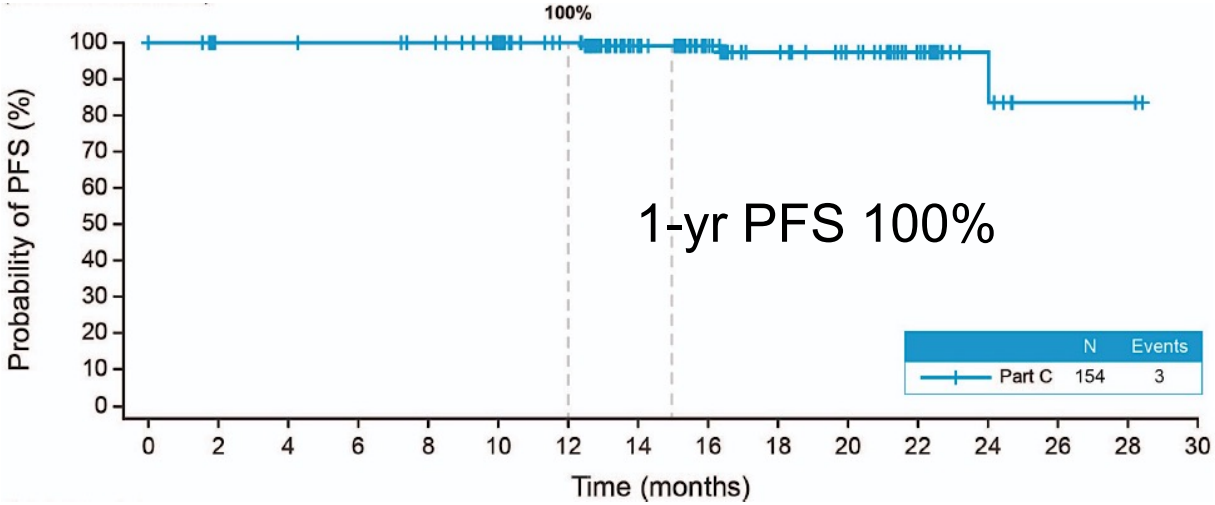
PD-1 inhibitors combinations: **early stage**

Randomized Phase 2: unfavorable
Sequential vs concurrent*
Nivo-AVD + ISRT (30 Gy) - ALL



3-yr PFS 100%

Bv-Nivo + AD x 4
Non-bulky



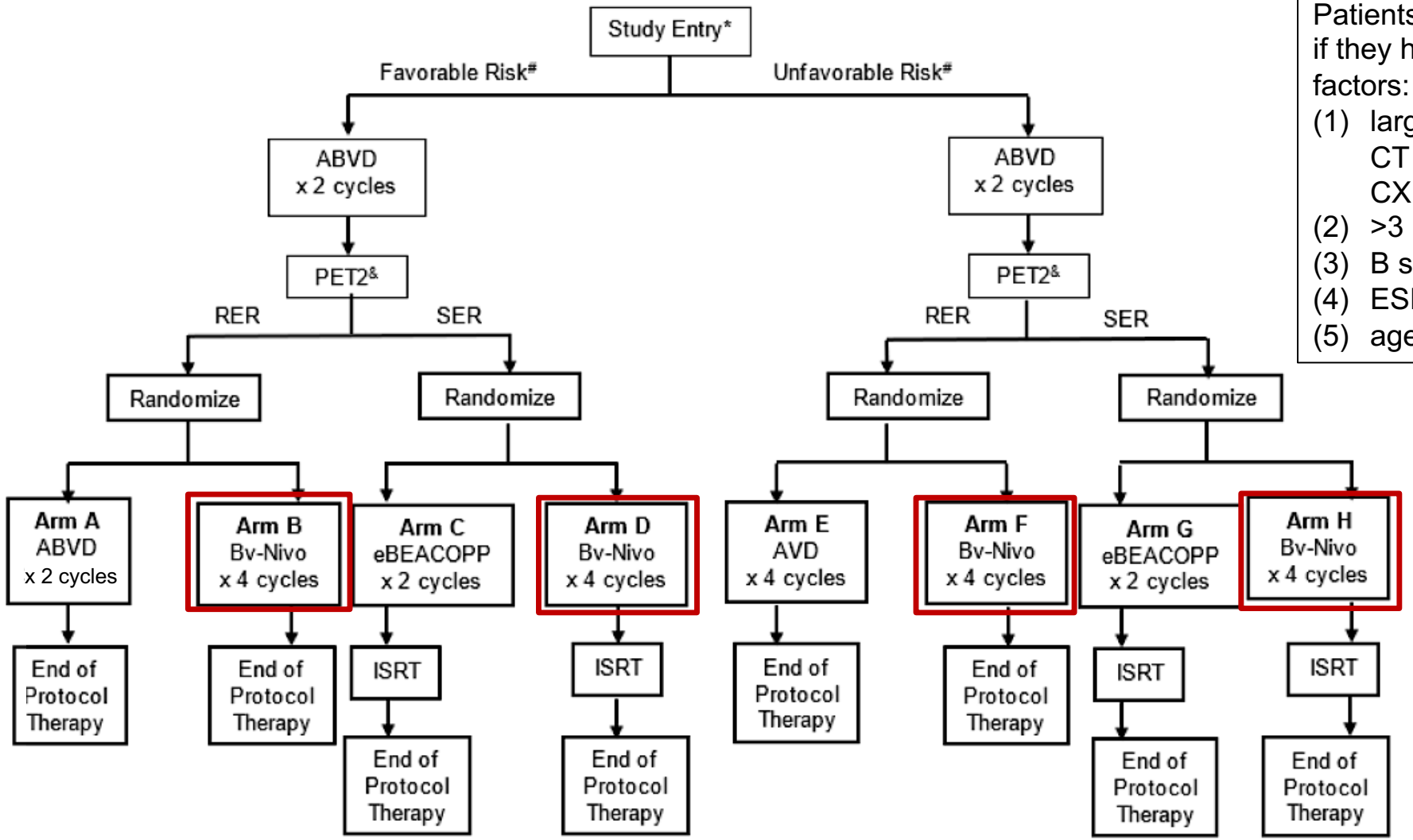
1-yr PFS 100%

* Nivo-AVD x 4 vs Nivo x 4 → N-AVD x 2 → AVD x 2

Bröckelmann et al JAMA Oncol. 2020;6:872–880
Bröckelmann JCO 2023;41:1193-1199.

Abramson, at al. ASH 2023, Sun, Dec 10: 5:30 PM
Grand Hall B (Manchester Grand Hyatt San Diego)

AHOD2131: Phase 3 response-adapted standard therapy vs immunotherapy



Patients are considered unfavorable risk if they have one or more of the following factors:

(1) large mediastinal mass (>10 cm by CT or 1/3 max chest diameter by CXR),
(2) >3 nodal sites,
(3) B symptoms with ESR >30,
(4) ESR >50 without B symptoms,
(5) age >50 years.

Conclusions

- Nivo-AVD new standard of care for advanced stage HL
  - Less toxic, more effective
  - Awaiting longer f/u
- Pembro-AVD combinations in first line also encouraging
  - Small studies, awaiting results of large Phase II, KEYNOTE-C11
- Efforts to incorporate Bv and / or PD1 inhibitors in early stage ongoing
  - ? replace vinblastine with BV
  - I have been able to get Bv-AVD approved for bulky stage II

Agenda

Module 1: Evolving Role of Novel Treatment Strategies in Follicular Lymphoma (FL) — Dr Friedberg

Module 2: Integration of Chimeric Antigen Receptor (CAR) T-Cell Therapies and Bispecific Antibodies into the Management of FL — Dr Abramson

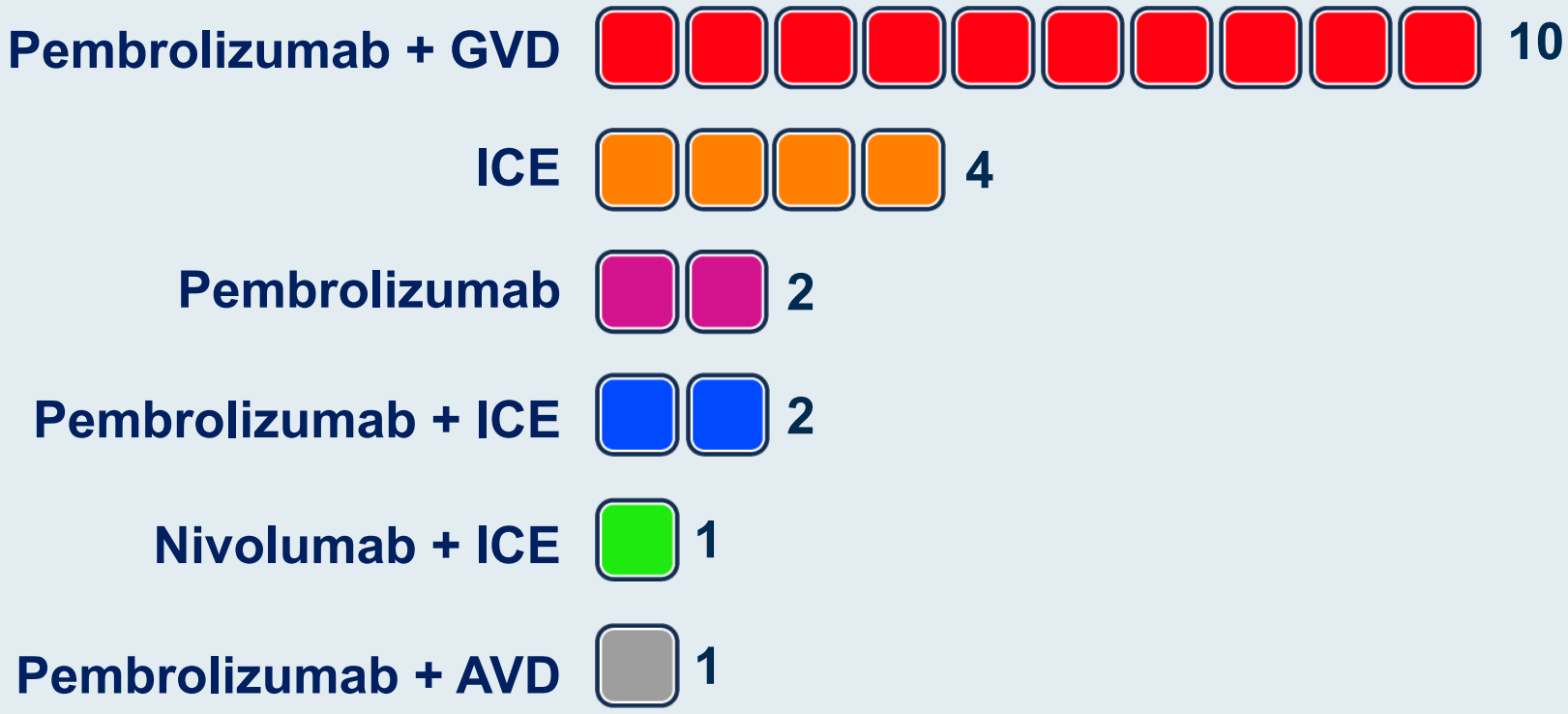
Module 3: Up-Front Treatment for Mantle Cell Lymphoma (MCL) — Dr Kahl

Module 4: Therapeutic Sequencing for Patients with Relapsed/Refractory (R/R) MCL — Dr Cohen

Module 5: First-Line Treatment Strategies for Hodgkin Lymphoma (HL) — Dr Bartlett

Module 6: Current and Future Management of R/R HL — Dr Ansell

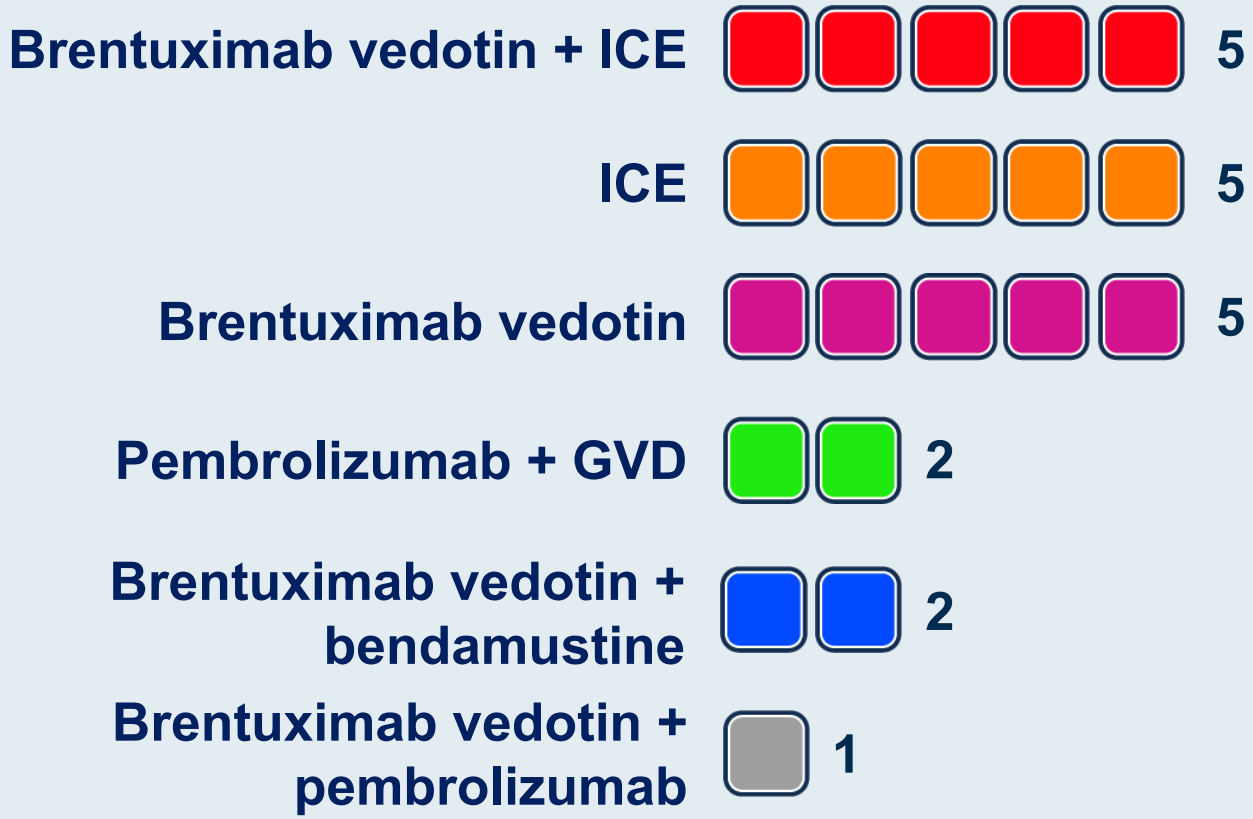
Regulatory and reimbursement issues aside, in general what would be your preferred bridge to transplant for a patient with HL who is experiencing relapse after up-front brentuximab vedotin/AVD (BV-AVD)?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in general what would be your preferred bridge to transplant for a patient with HL who is experiencing relapse after up-front nivolumab/AVD?



Survey of 20 US-based clinical investigators November 2023

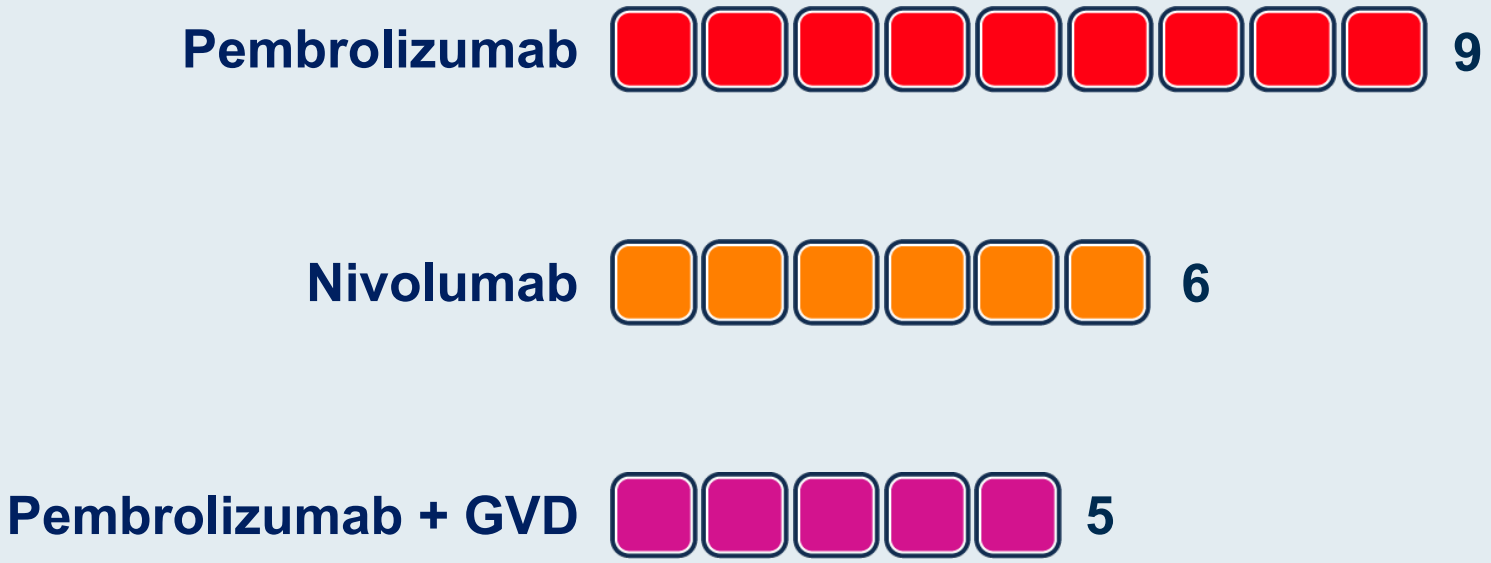
RTP RESEARCH TO PRACTICE

Would you recommend brentuximab vedotin as post-transplant maintenance?

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

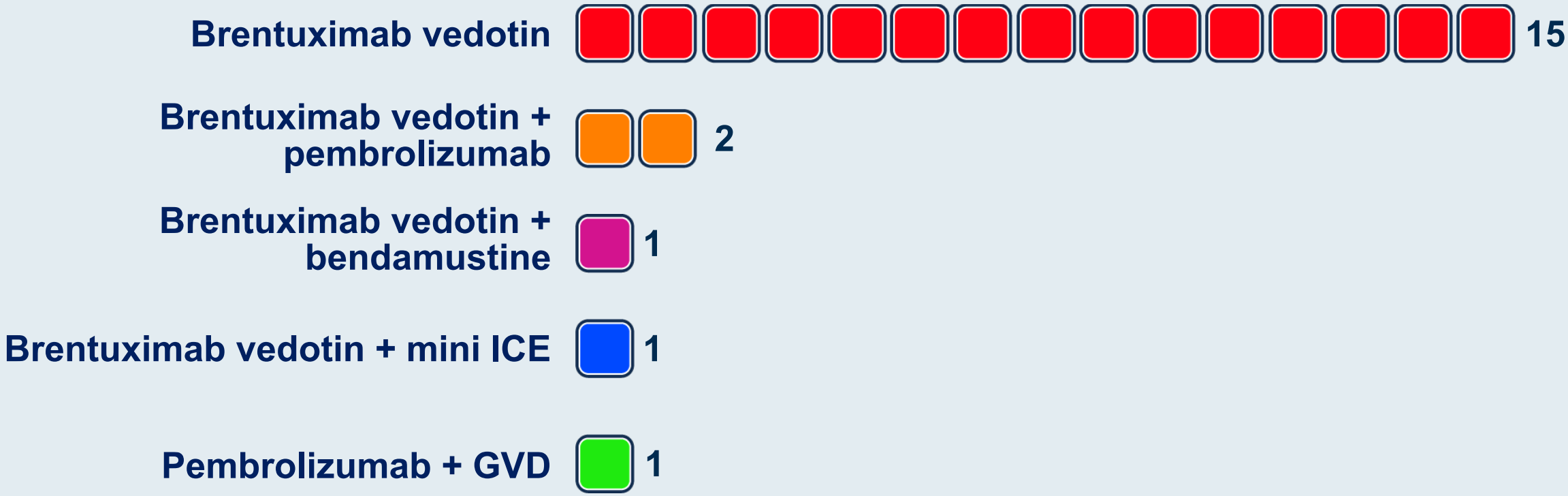
Regulatory and reimbursement issues aside, in general what is your preferred second-line therapy for a patient with HL who is experiencing relapse after up-front BV-AVD and is not considered a candidate for transplant?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, in general what is your preferred second-line therapy for a patient with HL who is experiencing relapse after up-front nivolumab/AVD and is not considered a candidate for transplant?



Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Do you believe there is a role for tumor-informed ctDNA assays in the care of patients with Hodgkin lymphoma?

- The predicted value has been shown to be very high in retrospective studies. Needs to be verified in a prospective trial. If positive: A clear yes
- ctDNA likely to be useful for end of treatment response assessment and monitoring for relapse in HL
- Potential role for response assessment and tumor monitoring
- Testing likely more informative for response than radiology based but still needs more refinement in order to provide appropriate reliability
- Would love to complement or even replace PET/CT imaging
- ctDNA coupled with PET as early assessment after cycle 2 or salvage
- Could replace interim PET for risk adaptation
- I am not sure but probably a role
- The early data are suggestive. We need additional data to further evaluate the utility
- An unexplored area full of potential
- Limited therapy in low-risk patients

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

Sequencing of therapeutic options for patients with R/R cHL

Max S Topp, MD

RTP
RESEARCH
TO PRACTICE

Treatment options for older patients with R/R cHL

Andrew M Evens, DO, MBA, MSc

RTP
RESEARCH
TO PRACTICE

Treatment Patterns and Outcomes for Patients with Classic Hodgkin Lymphoma (cHL) and Cardiomyopathy with Low Ejection Fraction (EF): Real-World Evidence (RWE) from 16 US Academic Centers

Annunzio K et al.

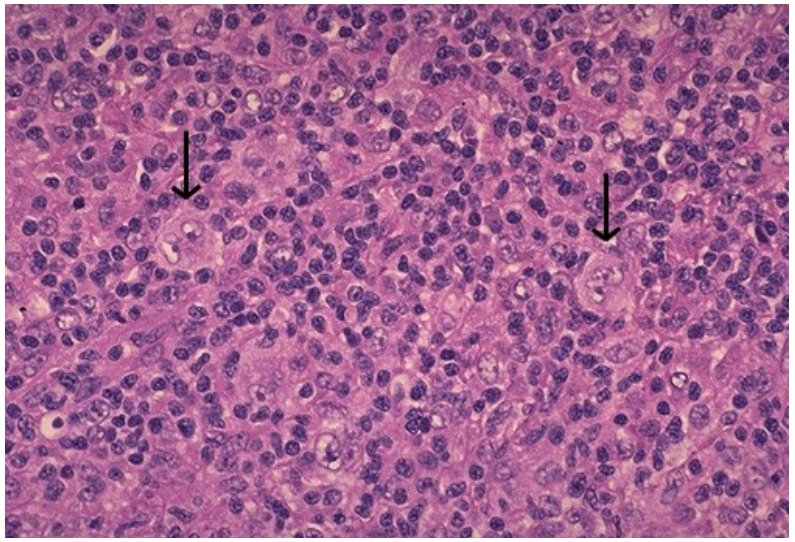
ASH 2003;Abstract 382.

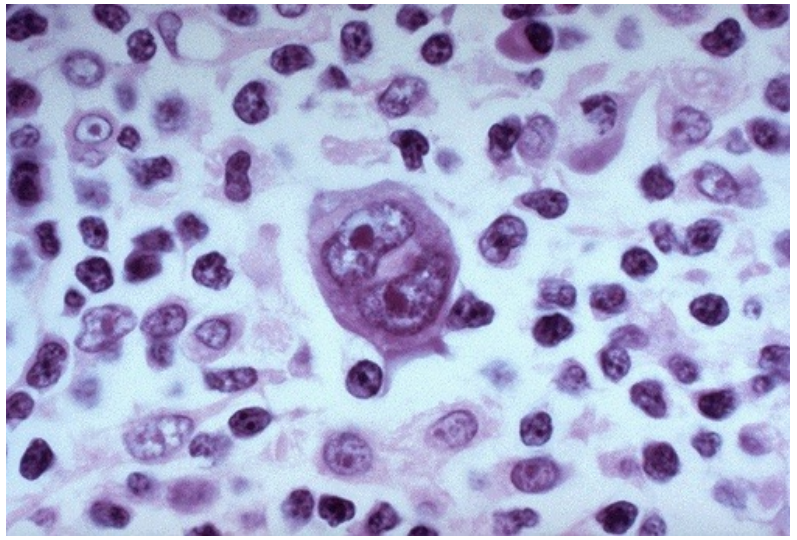
SATURDAY, DECEMBER 9 | 4:45 PM PT

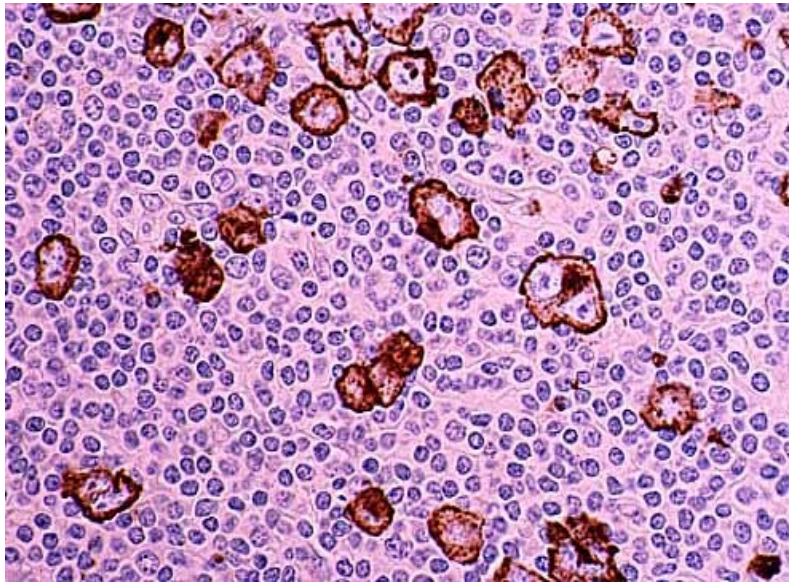
Current and Future Management of Relapsed/Refractory Hodgkin Lymphoma

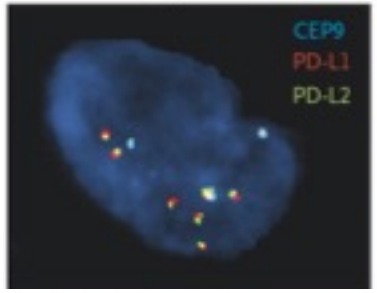
Stephen M. Ansell, MD, PhD
Dorotha W. and Grant L. Sundquist Professor in Hematologic Malignancies Research
Chair, Division of Hematology
Mayo Clinic

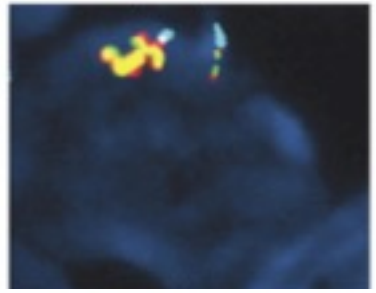
Pathology of Hodgkin Lymphoma

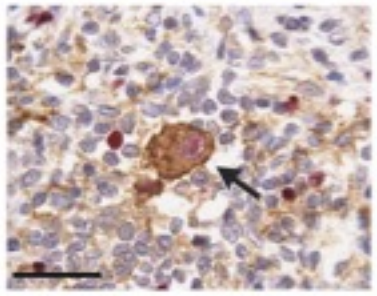


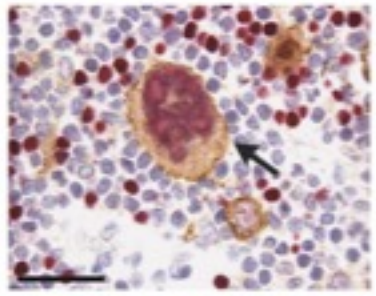




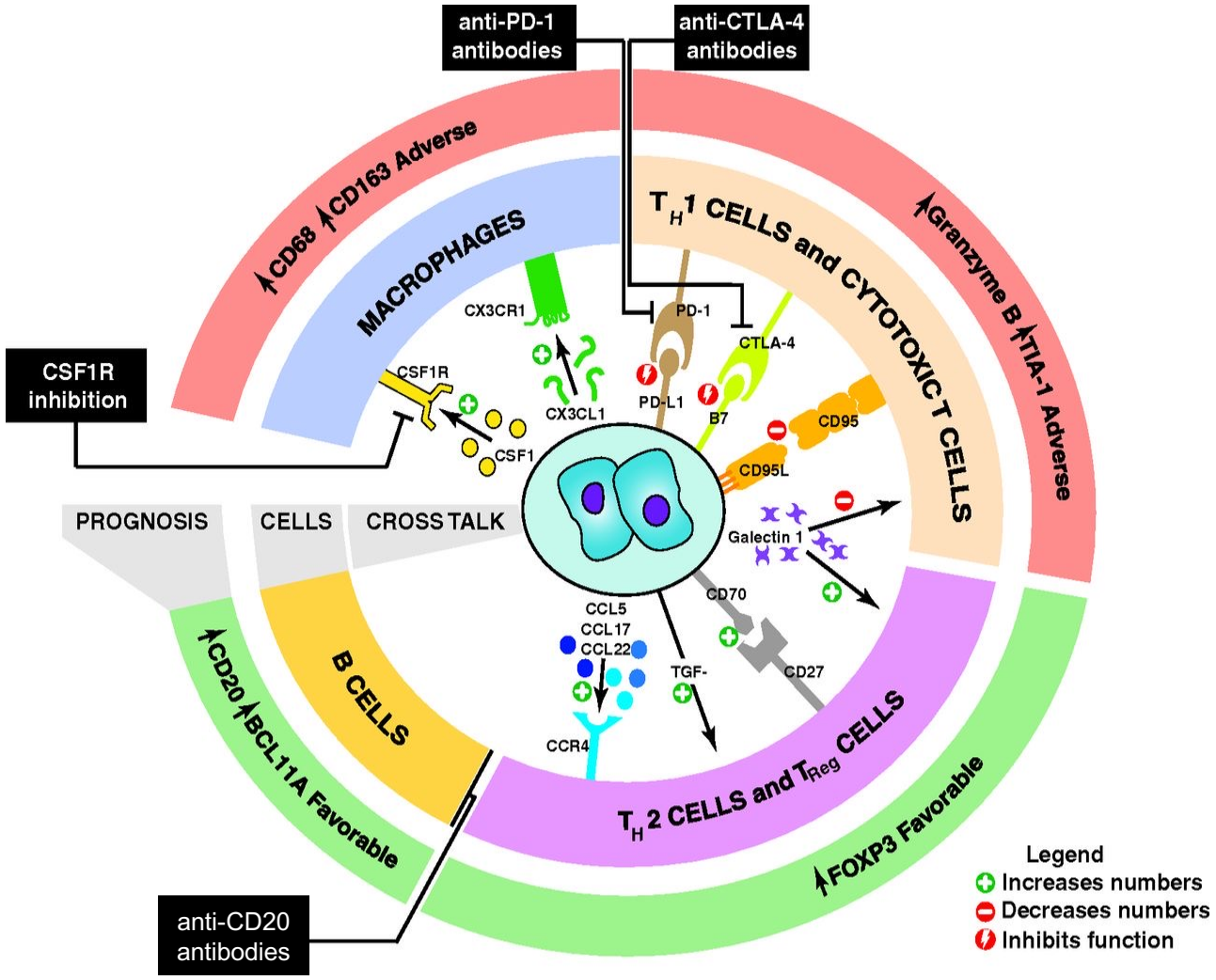








Biology and Clinical Significance of the Microenvironment in Hodgkin Lymphoma

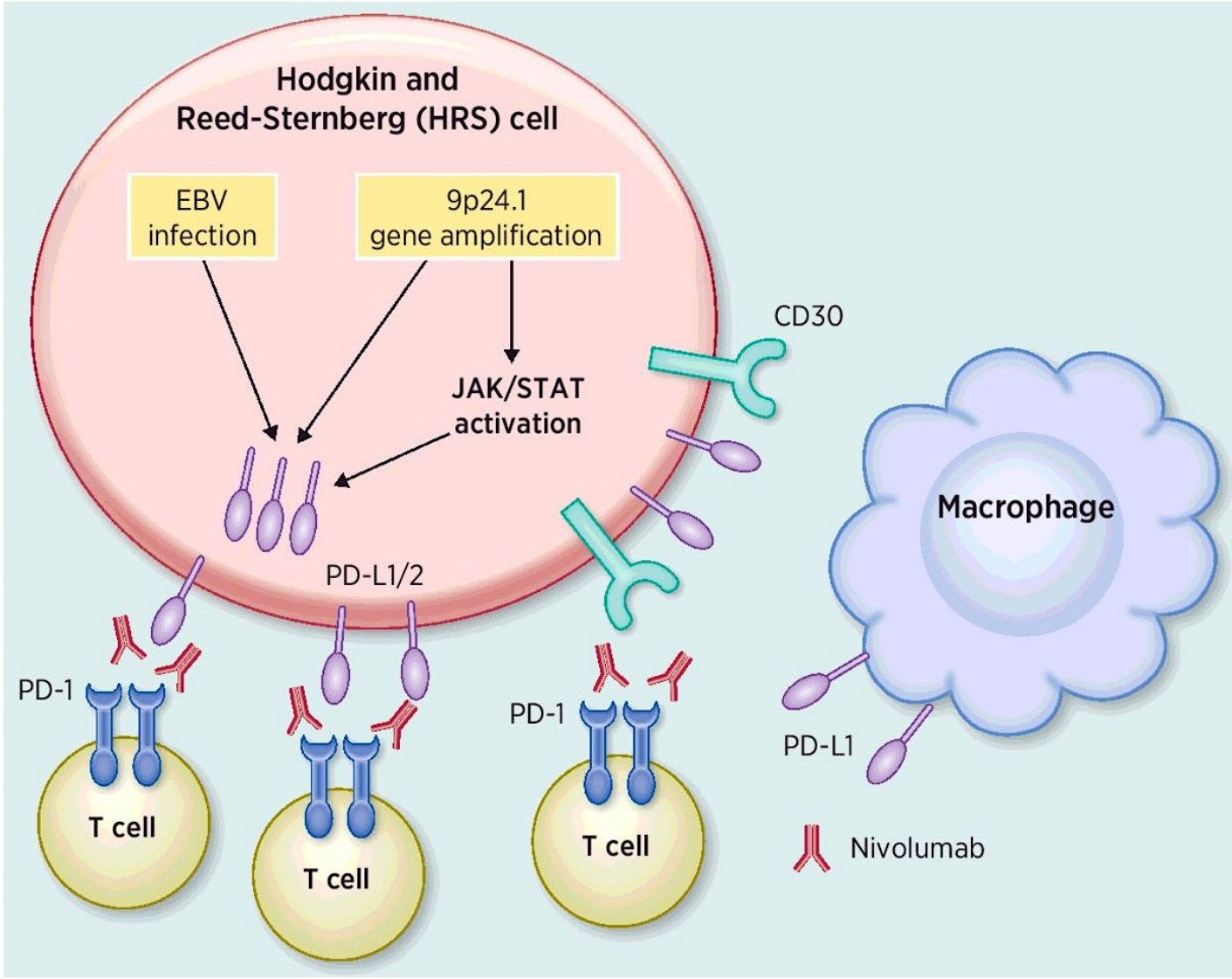


Scott et al. Hematology 2014;2014:144-150

Development of Future Therapies – Single agent approaches and Combinations

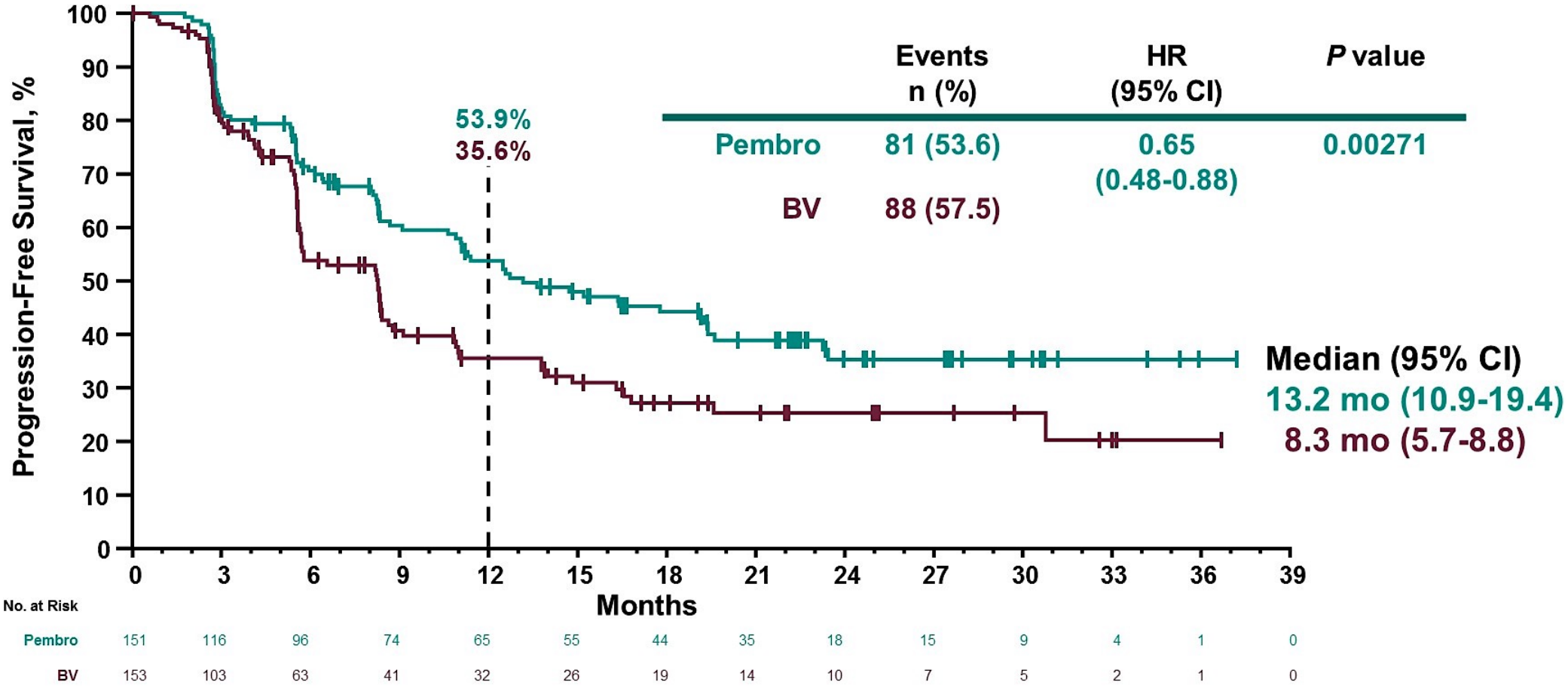
- Targeting T-cells
  - Block them, activate them, redirect them, deplete them
- Targeting NK cells
- Drug combinations
  - CD30 targeted agents, chemotherapy, PD1 antibodies, other checkpoints

1. Targeting T-cells – Blocking Inhibitory Signals



Ansell SM. Clin Cancer Res. 2017 Apr 1;23(7):1623-1626.

1. Targeting T-cells - Phase III study of pembrolizumab versus brentuximab vedotin in relapsed or refractory classic Hodgkin lymphoma



Data cutoff: January 16, 2020.

Kuruvilla J, et al. Lancet Oncol. 2021 Apr;22(4):512-524.

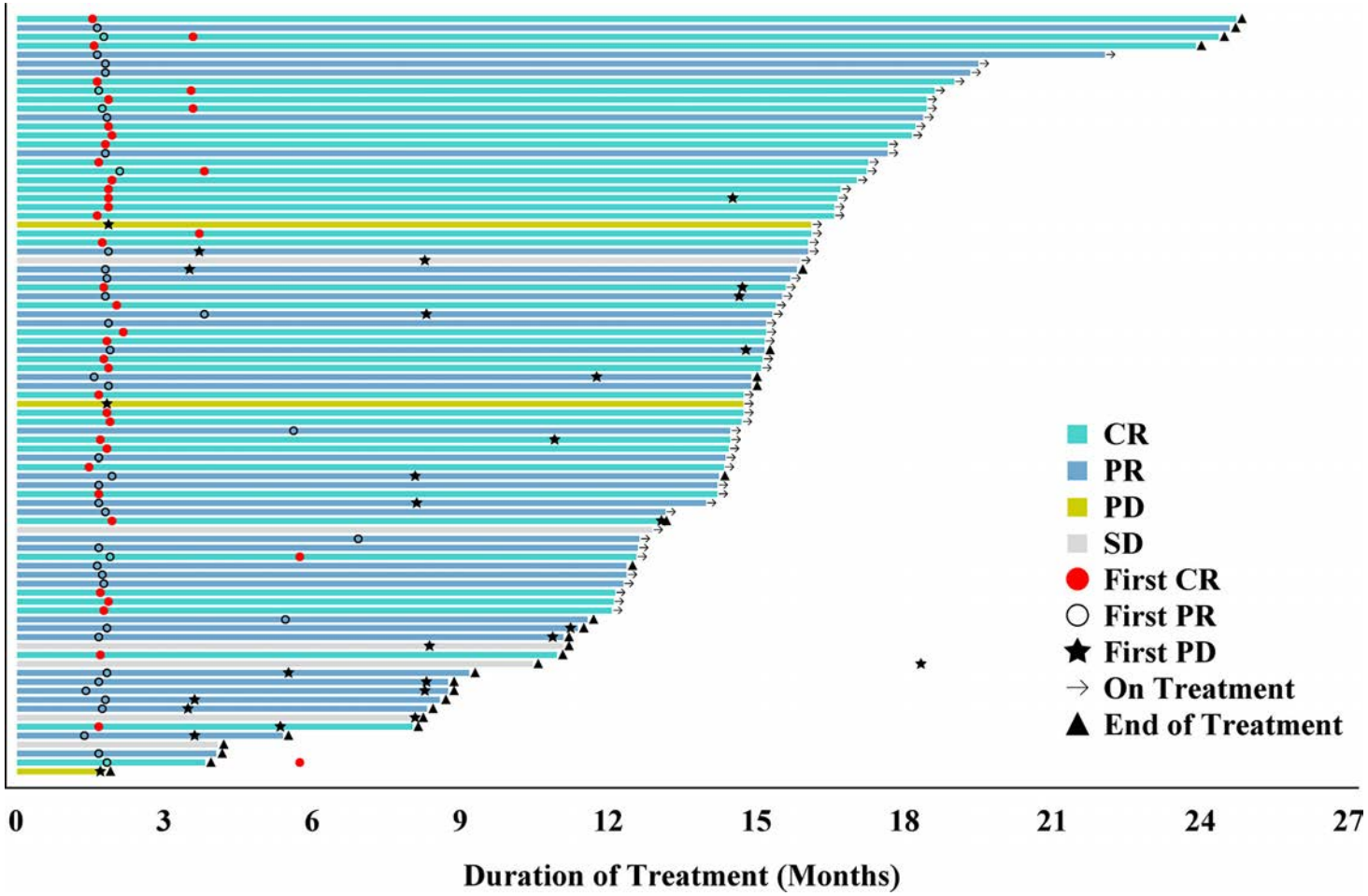
1. Targeting T-cells - Phase III study of pembrolizumab versus brentuximab vedotin in relapsed or refractory classic Hodgkin lymphoma

Safety in KEYNOTE-204

- The most common grade ≥3 adverse events between pembrolizumab and brentuximab vedotin were pneumonitis (4% vs. 1%), neutropenia (2% vs. 7%), and peripheral neuropathy (1% vs. 3%)
- Immune-mediated adverse events:
  - 33% with pembrolizumab
  - 7% with brentuximab vedotin

Kuruvilla J, et al. Lancet Oncol. 2021 Apr;22(4):512-524.

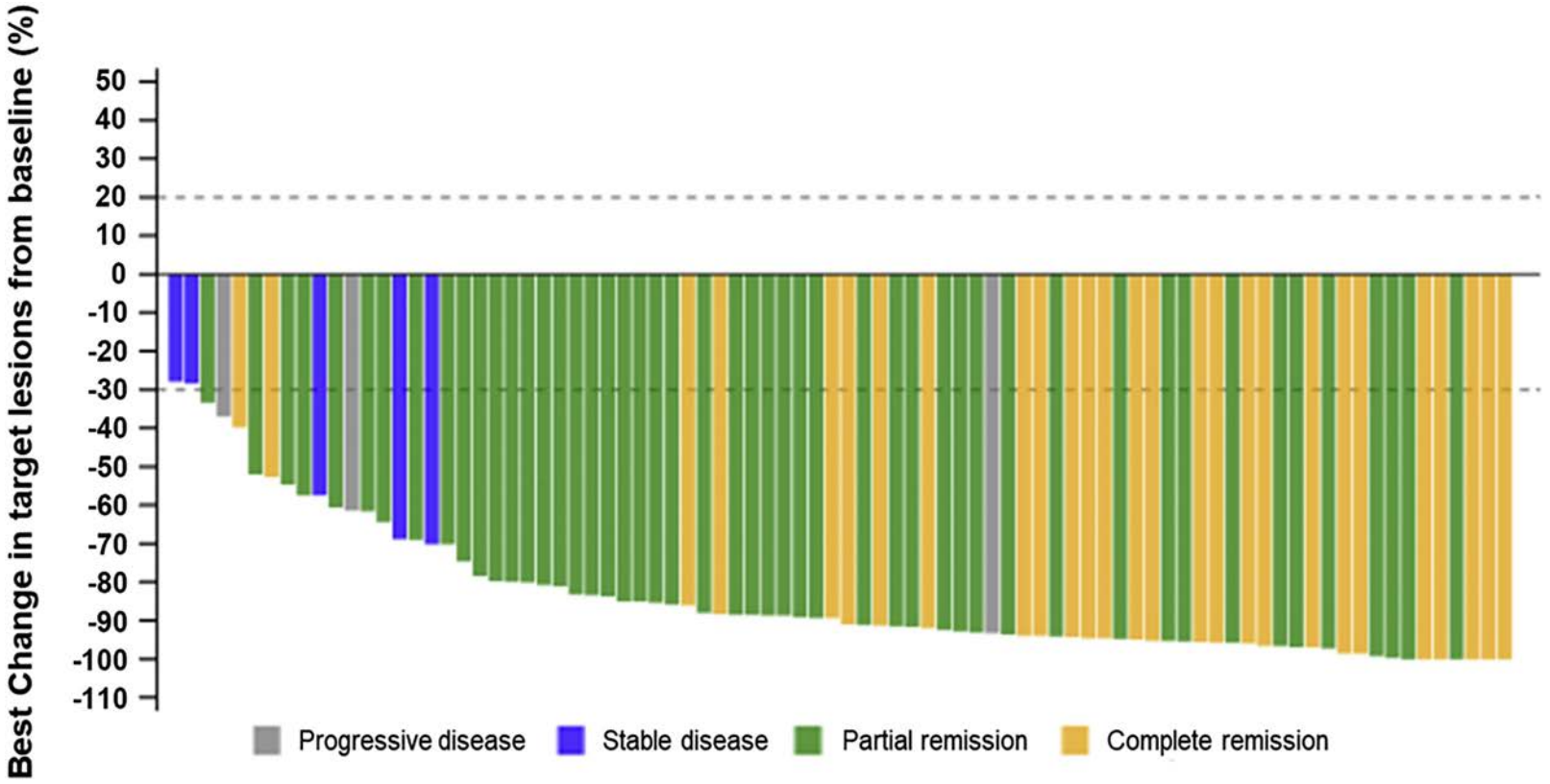
1. Targeting T-cells – New PD1 antibodies developed - Penpulimab



- IgG1 anti-PD-1 antibody
- 94 patients with R/R cHL treated
- ORR was 89.4% in the full analysis set (85 patients).
- Forty (47.1%) patients achieved CR
- 12-month PFS rate was 72.1%
- 18-month OS rate was 100%.

Song Y, et al. Front Oncol. 2022 Jul 7;12:925236.

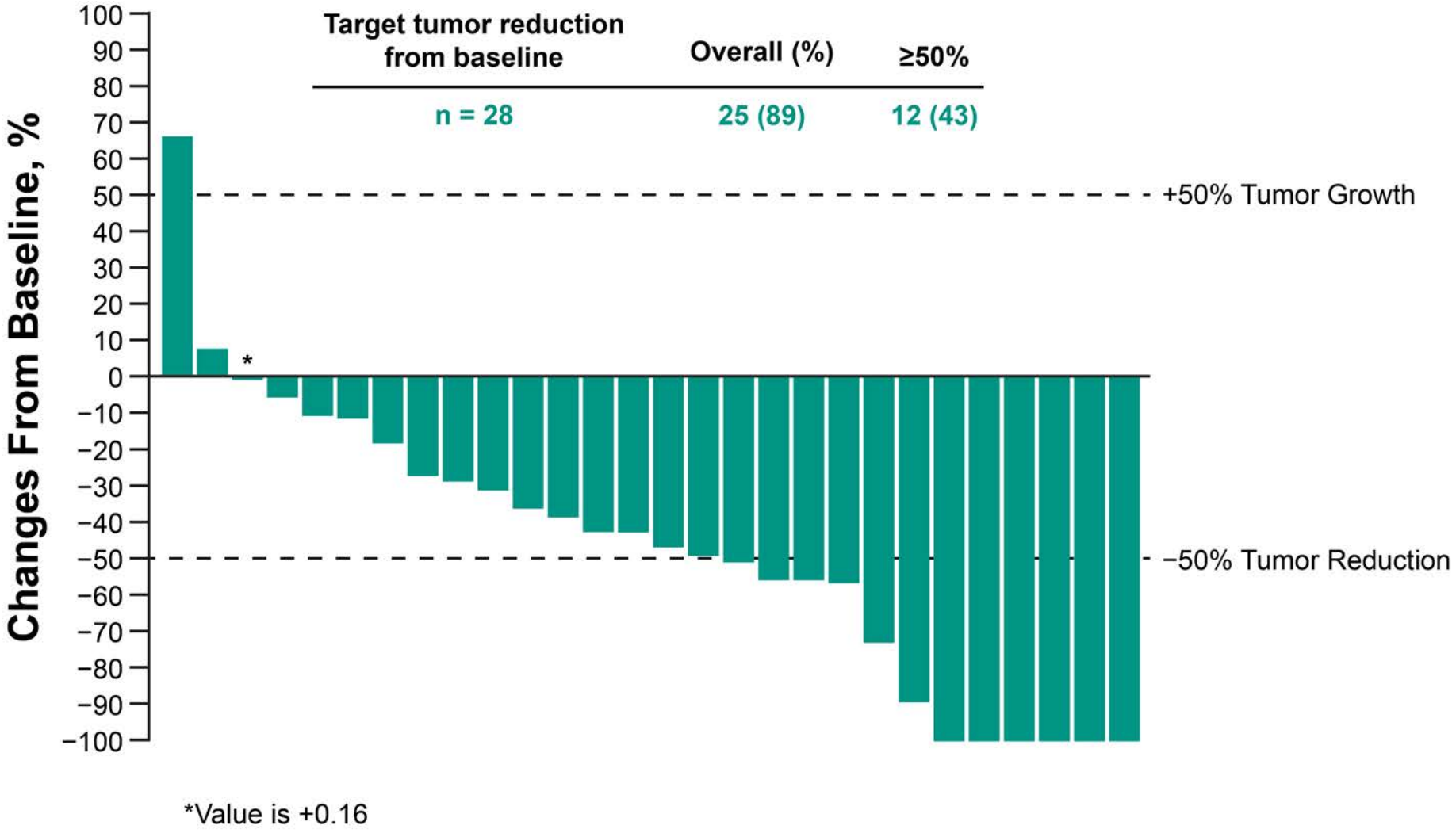
1. Targeting T-cells – New PD1 antibodies developed - Zimberelimab



- IgG4 anti-PD-1 antibody
- 85 patients with R/R cHL treated
- ORR was 90.6% in the analysis set (77 patients).
- 28 (32.9%) patients achieved CR
- 12-month PFS rate was 78%
- 12-month OS rate was 99%.

Lin N, et al. Eur J Cancer. 2022 Mar;164:117-126.

1. Targeting T-cells - Favezelimab (anti–LAG-3) Plus Pembrolizumab in R/R Classical Hodgkin Lymphoma after Anti–PD-1 Treatment



- 34 patients
- 10 pts had objective response (ORR, 29%; complete response [CR], 3 [9%]; partial response [PR], 7 [21%]).
- Median PFS was 10.7 months

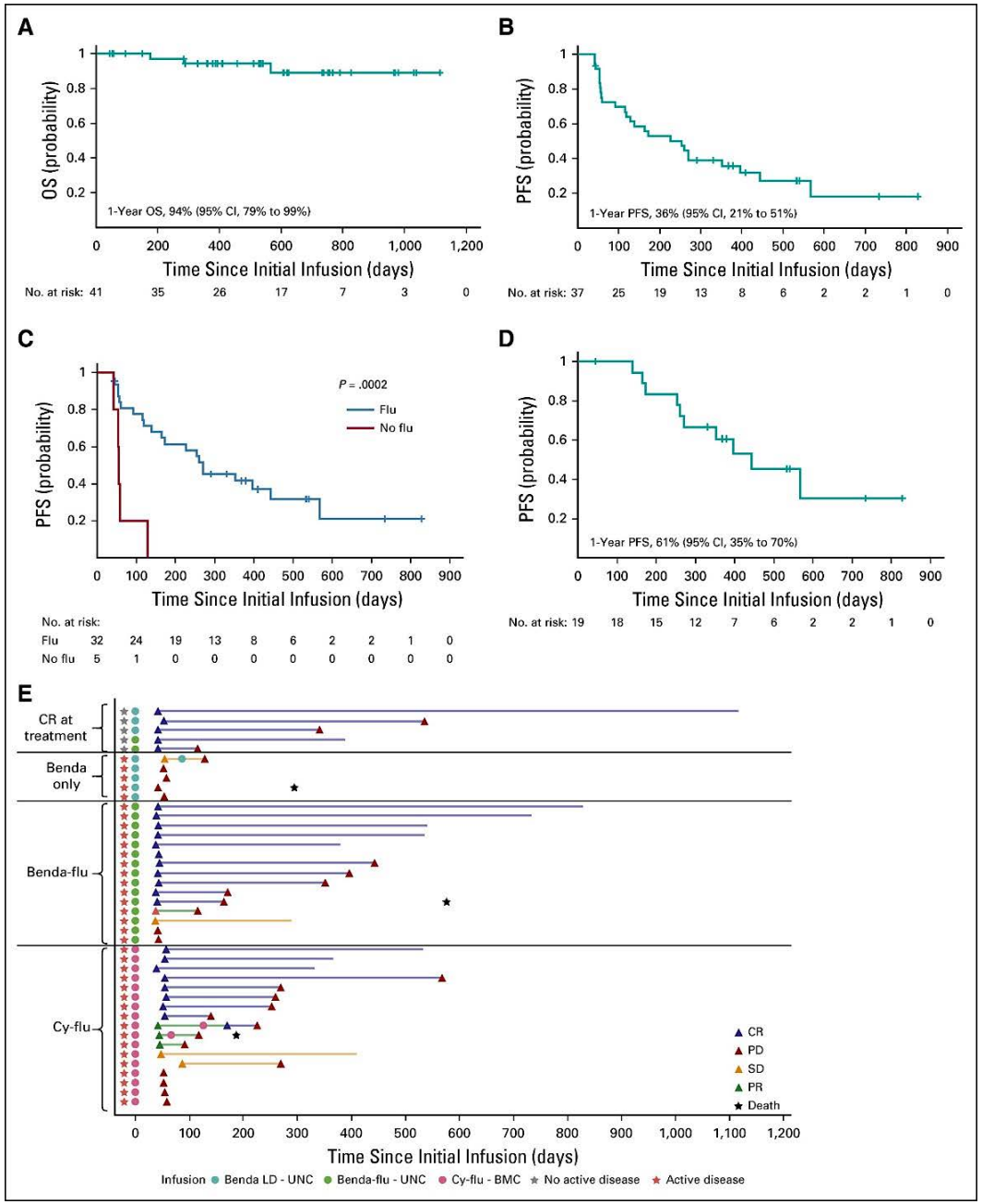
Timmerman et al. ASH 2022; #316

Favezelimab in Combination with Pembrolizumab in Patients with Heavily Pretreated Anti-PD-1-Refractory Classical Hodgkin Lymphoma: Updated Analysis of an Open-Label Phase 1/2 Study

Timmerman J et al.
ASH 2023;Abstract 4440.

SESSION 624 | Monday, December 11, 2023| 6:00 PM-8:00 PM

1. Redirect T-cells - CD30 directed CAR T-cells



- 41 patients received CD30.CAR-Ts
- ORR in the 32 patients with active disease who received fludarabine-based lymphodepletion was 72%,
- 19 patients (59%) had a CR
- 1-year PFS and OS for all evaluable patients were 36% and 94%

Ramos et al. J Clin Oncol 2020 Nov 10;38(32):3794-3804.

1. Redirect T-cells - Phase 1 Clinical Trial of Memory-Enriched HSP-CAR30 for R/R Hodgkin Lymphoma and CD30^{+} T-Cell Lymphoma

- Proximal epitope within the CD30 molecule to overcome soluble CD30.
- Enriched in memory T-cells to ensure persistence, and enhancement of antitumor efficacy.

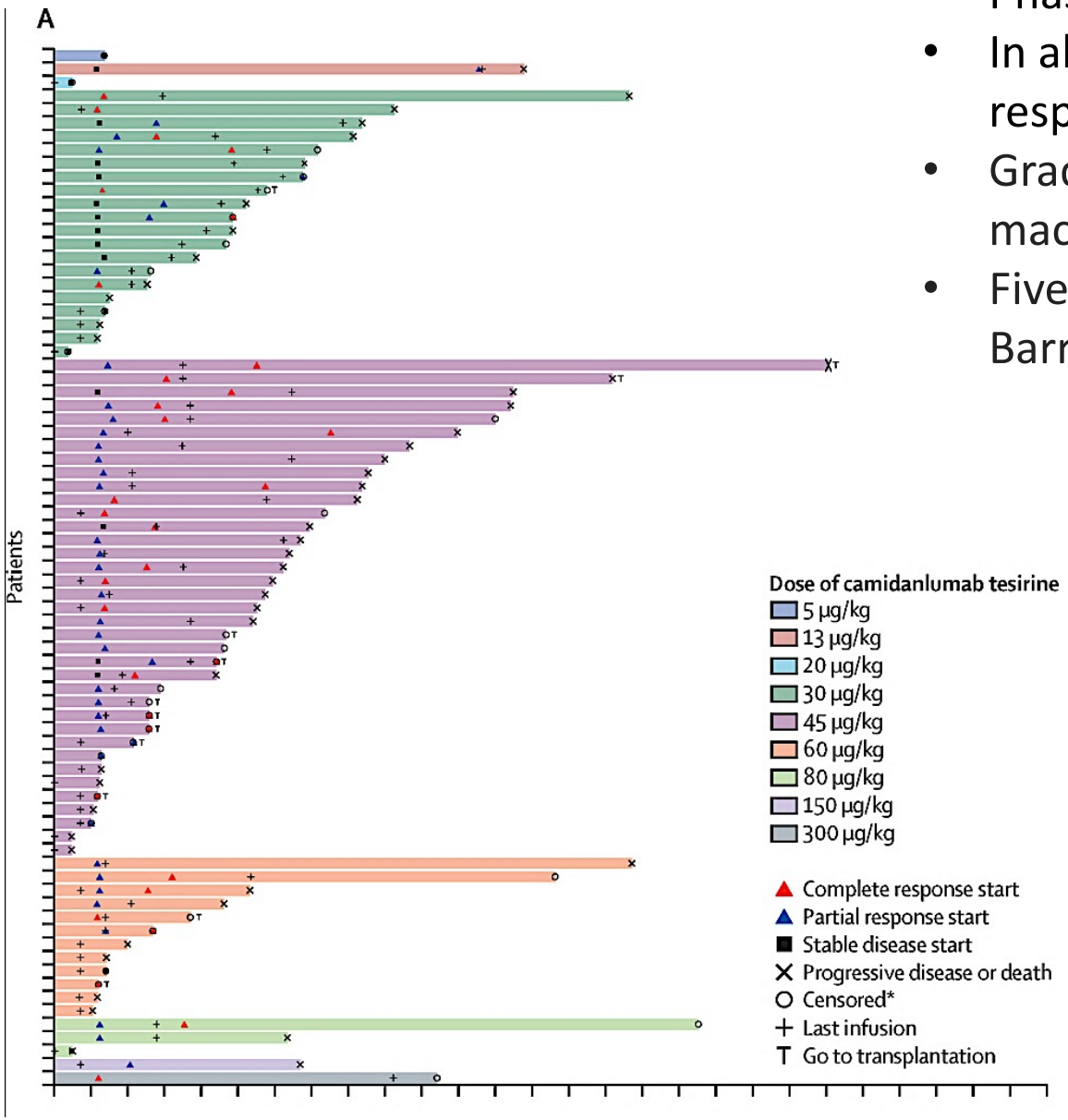
- 11 patients treated
- Objective response was 100%, including 5 (50%) patients CR.
- Mean PFS was 235 days (77– 444).

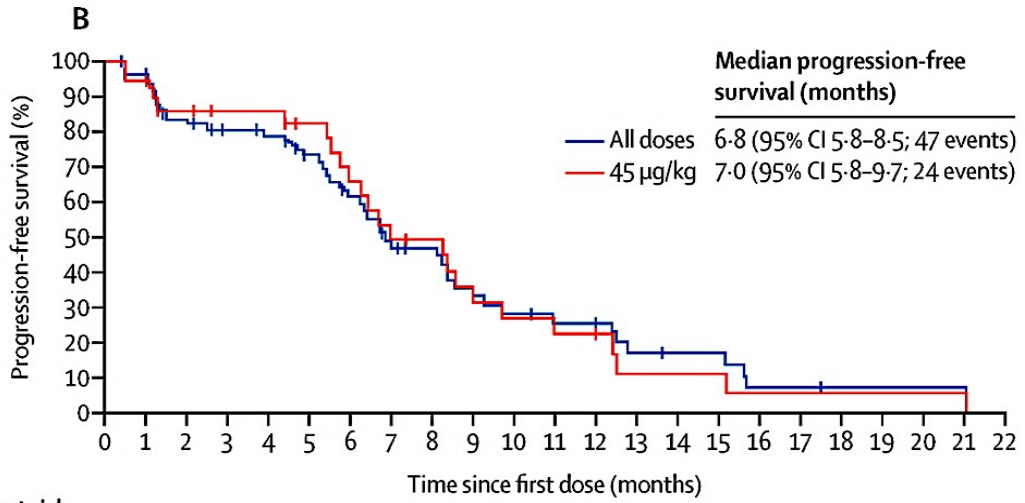
Patient Nº	Cohort	Sex	Age (years)	Diagnosis	Stage	Extra-nodal sites	Prior treatment Nº	Refractory to prior line	Prior ASCT
HSP-CAR30-01		M	38	HL	IIA	-	8	Yes	Yes
HSP-CAR30-02	DL1	M	42	HL	IVA	Subcutaneous tissue, muscle, bone	4	Yes	No
HSP-CAR30-03		F	65	NHL-T	IVA	GI (stomach), lung	7	No	Yes
HSP-CAR30-04		M	49	HL	IIA	-	5	Yes	Yes
HSP-CAR30-05	DL2	M	48	HL	IIA	-	4	No	Yes
HSP-CAR30-06		M	43	HL	IVA	Bone, lung	5	Yes	No
HSP-CAR30-07		M	38	HL	IVB	Bone	4	Yes	No
HSP-CAR30-08	DL3	M	63	HL	IVA	Bone	5	Yes	No
HSP-CAR30-09		M	65	NHL-T	IVA	Skin, subcutaneous tissue, muscle	3	No	Yes
HSP-CAR30-10		M	65	HL	IVA	Bone	5	No	Yes
HSP-CAR30-11		M	21	HL	IIIA	-	4	Yes	Yes

Gonzalez et al. ASH 2022; #164

1. Depleting T-cells – Camidanlumab tesirine (Cami-T) is effective

- Phase 1, two-part dose-escalation/expansion trial
- In all 77 patients with classical Hodgkin lymphoma, the overall response was 71%.
- Grade 3 toxicities - increased γ-glutamyltransferase, maculopapular rash and anemia
- Five patients developed serious neurologic events - Guillain–Barré syndrome



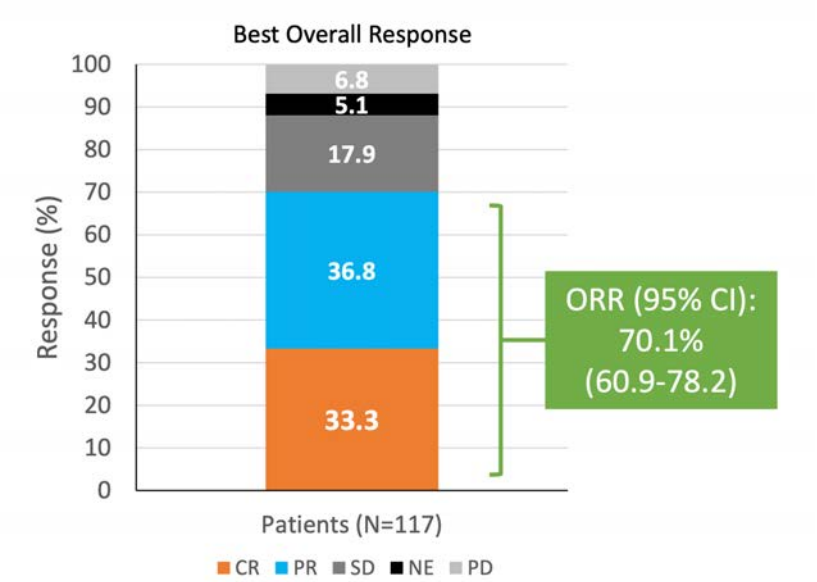


Number at risk (number censored)

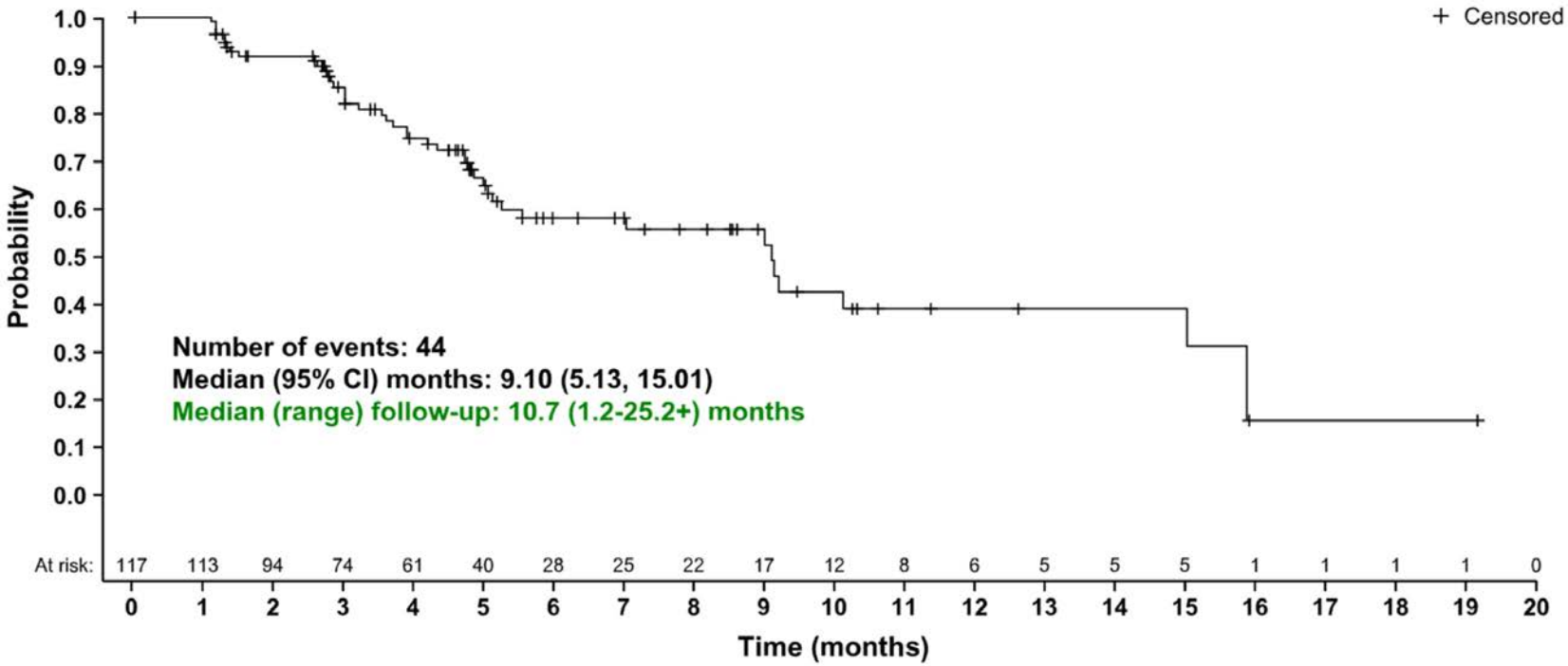
All doses	77	72	56	47	45	37	30	22	20	15	12	10	9	6	5	5	2	2	1	1	1	1	0
	(0)	(2)	(9)	(16)	(17)	(22)	(23)	(24)	(26)	(26)	(26)	(27)	(28)	(28)	(29)	(29)	(29)	(29)	(30)	(30)	(30)	(30)	(30)
45 µg/kg	37	35	29	24	24	20	16	12	11	8	6	5	4	2	2	2	1	1	1	1	1	1	0
	(0)	(0)	(3)	(8)	(8)	(11)	(11)	(11)	(12)	(12)	(12)	(12)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)	(13)

Hamadani M, et al. Lancet Haematol. 2021 Jun;8(6):e433-e445.

1. Depleting T-cells – Camidanlumab tesirine (Cami-T) is effective



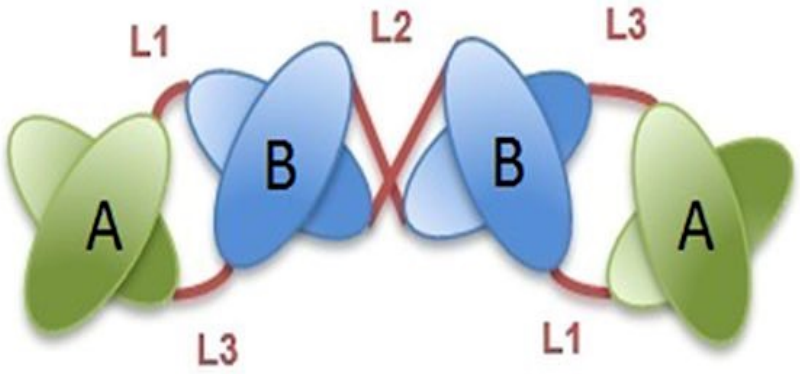
- Phase 2 study of Cami-T monotherapy in 117 patients
- The ORR was 70.1% and the CR rate was 33.3%
- The DOR was 13.7 months and median PFS was 9.1 months
- Grade ≥3 toxicities: thrombocytopenia (9.4%), anemia (8.5%), hypophosphatemia (7.7%), neutropenia (7.7%)
- Guillain–Barré syndrome (GBS)/polyradiculopathy: 6.8%



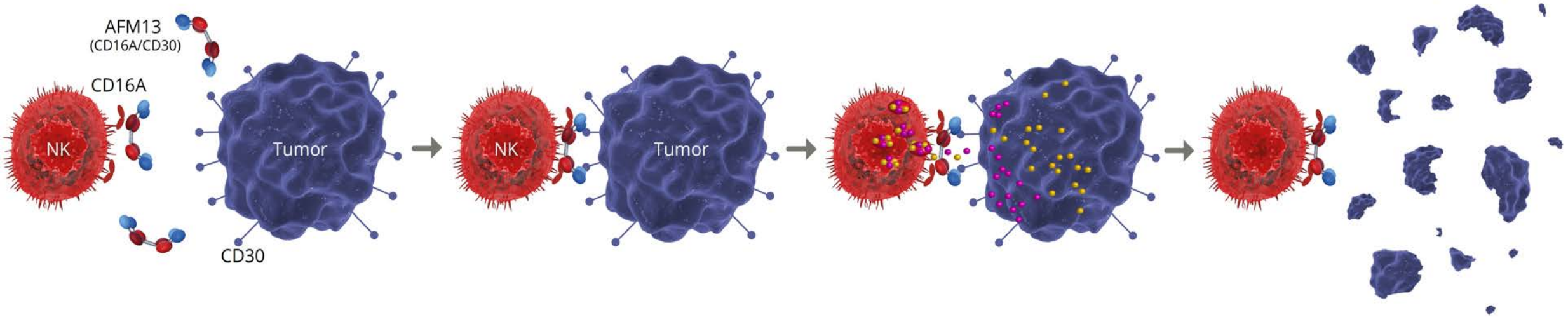
Carlo-Stella C et al. EHA 2022; Abstract S201

2. Targeting NK cells - Bispecific antibodies

AFM13: a first-in-class tetravalent bispecific anti-CD30/CD16A antibody



Tetravalent functional homodimer (~110 kDa)



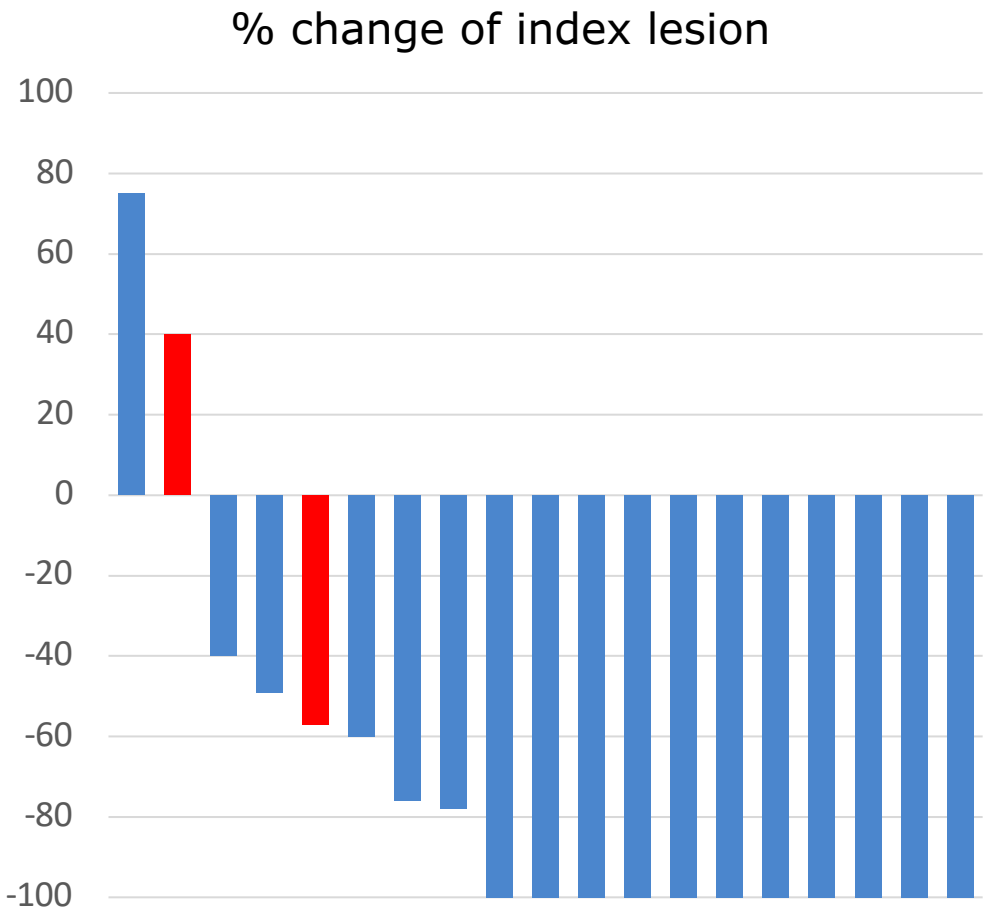
Engager Therapy | Immunological Synapse | Release of Perforins and Granzymes | Tumor Cell Lysis

Wu et al. J Hematol Oncol. 2015 Aug 1;8:96.

2. Targeting NK cells - AFM13 Combined with Preactivated and Expanded Cord Blood-Derived NK Cells for CD30+ Lymphoma

- 30 patients treated
- ORR in the entire study was 97% with 63% CRs.
- All 24 patients treated at the RP2D responded (100% ORR) with 70.8% (17/24) CRs
- Five patients had a response consolidated with a SCT. At median follow-up of 8 months, the EFS and OS rates of all 30 patients were 57% and 83%

Baseline patient characteristics	N=30
Age, median (range)	43 (20–75)
Gender (male/female)	20 / 10
Diagnosis (HL / T-NHL)	28 / 2
No. prior lines therapy, median(range)	6 (1–14)
Prior brentuximab vedotin	30
Prior anti-PD-1	29
Prior SCT (autologous / allogeneic)	21 (13 / 8)
Prior CD30.CAR-T	2
No. prior relapses/progressive disease, median (range)	5 (1–14)



Nieto et al. ASH 2022; #168

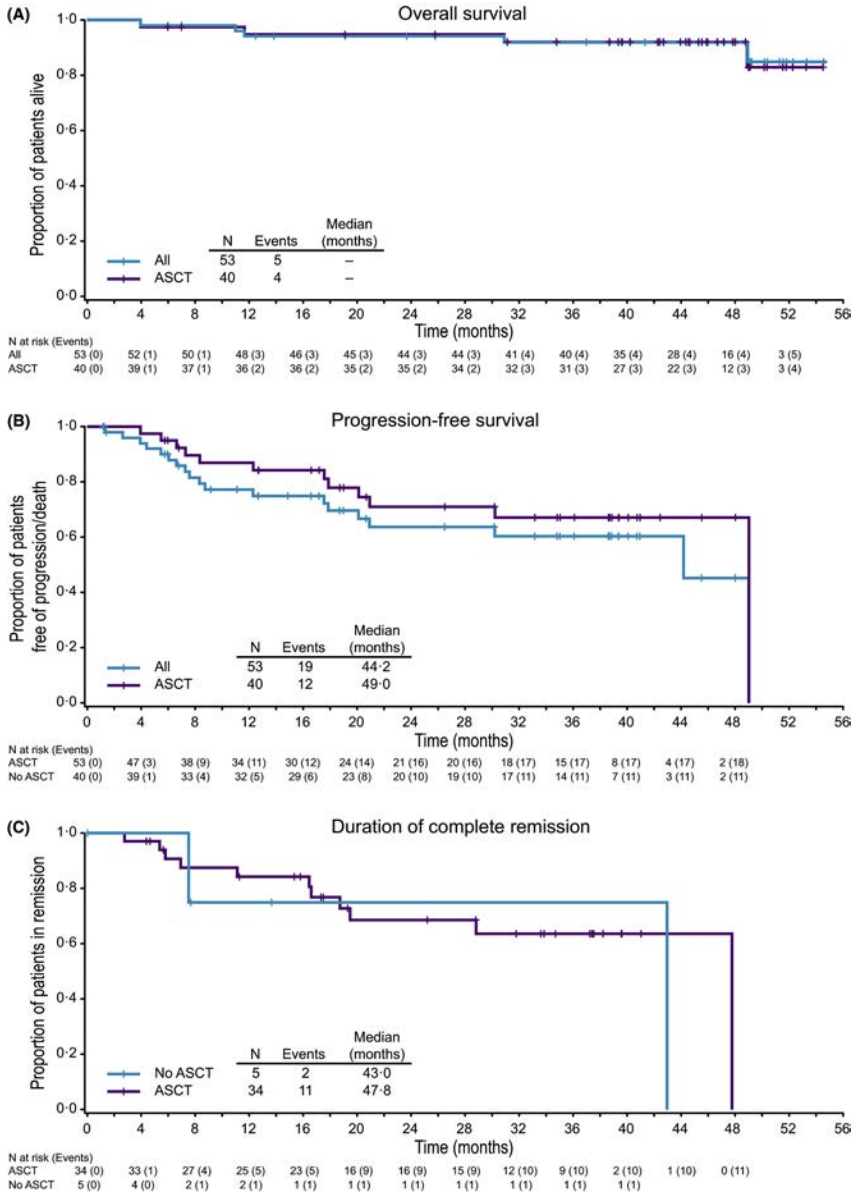
Innate Cell Engager (ICE®) AFM13 Combined with Preactivated and Expanded (P+E) Cord Blood (CB)-Derived Natural Killer (NK) Cells for Patients with Refractory CD30-Positive Lymphomas: Final Results

Nieto Y et al.

ASH 2023;Abstract 774.

SESSION 704 | Monday, December 11, 2023| 11:45 AM

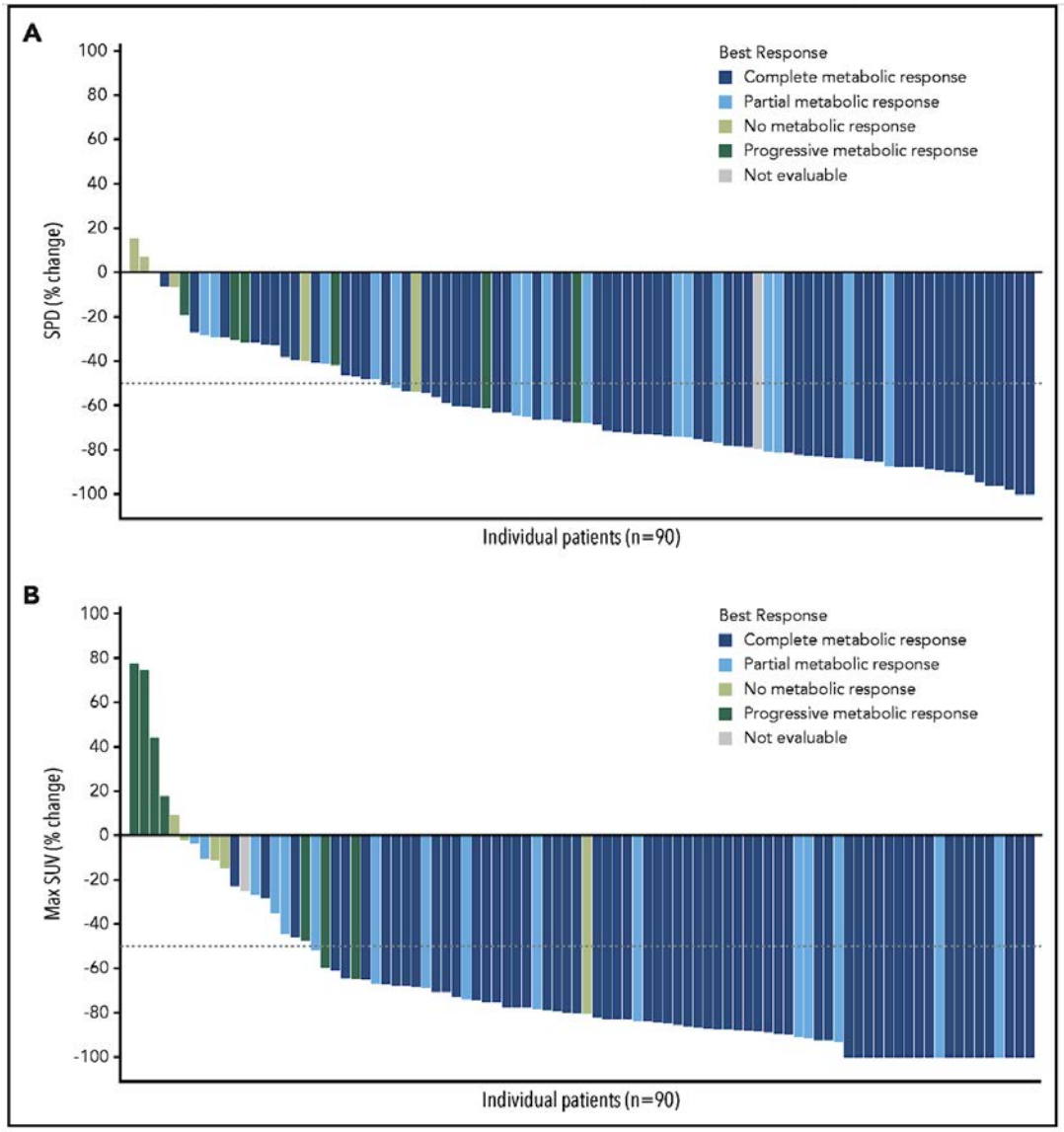
3. Combinations – Brentuximab vedotin plus bendamustine as first salvage therapy in relapsed or refractory Hodgkin lymphoma



- 55 patients
- ORR was 92.5%
- 73.6% complete remission rate
- Of 53 efficacy evaluable patients, 40 (75.5%) underwent ASCT and 13 (24.5%) did not.
- PFS at 3 years was 60.3%
- OS at 3 years was 92.0%

LaCasce et al. Br J Haematol. 2020 May;189(3):e86-e90.

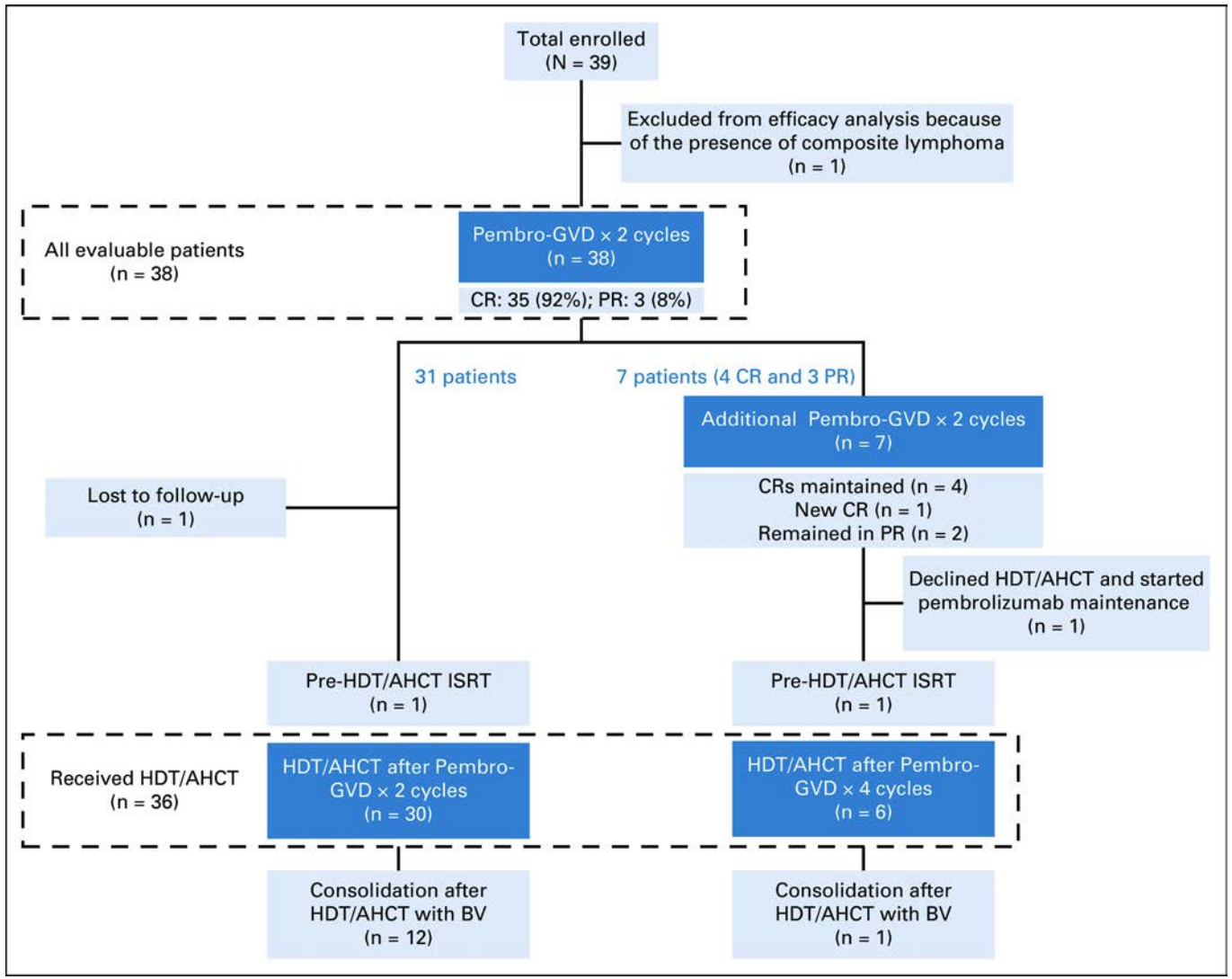
3. Combinations - Brentuximab vedotin in combination with nivolumab in patients with R/R Hodgkin lymphoma



- 91 patients with R/R cHL received up to 4 cycles of brentuximab vedotin plus nivolumab. At the end of the study, patients can proceed to ASCT
- The ORR was 91% and the CR rate was 67%
- Infusion-related reactions occurred in 43%
- No new toxicities were observed, and the toxicity profile of the combination was similar to each agent individually

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

3. Combinations - Pembrolizumab Plus GVD As Second-Line Therapy for Relapsed or Refractory cHL



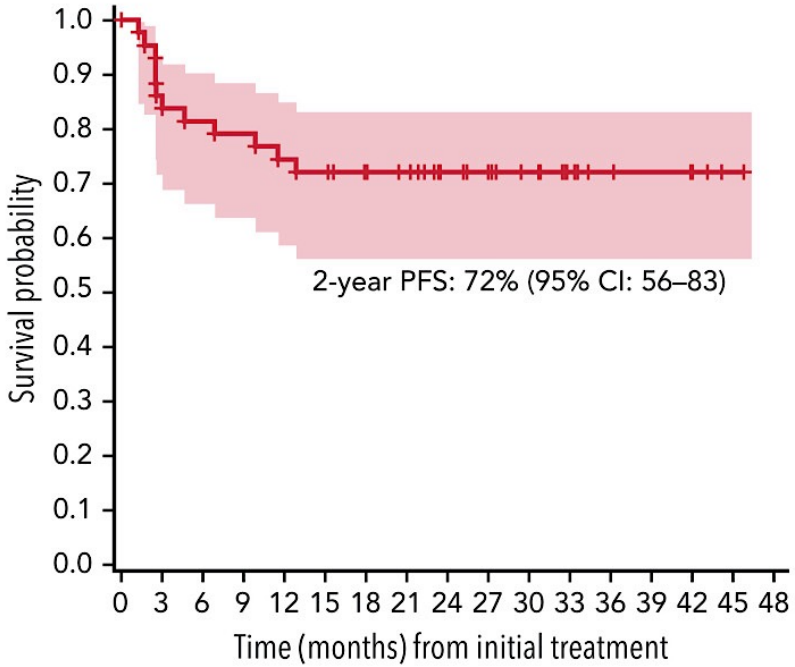
- 39 patients enrolled, 41% had refractory disease and 38% relapsed within 1 year of frontline treatment
- ORR and CR rates after pembro-GVD were 100% and 95%, respectively
- 36 (95%) patients proceeded to ASCT, 13 (33%) received post-ASCT brentuximab vedotin maintenance.
- All 36 transplanted patients were in remission at a median post-transplant follow-up of 13.5 months

Moskowitz et al. J Clin Oncol. 2021 Oct 1;39(28):3109-3117.

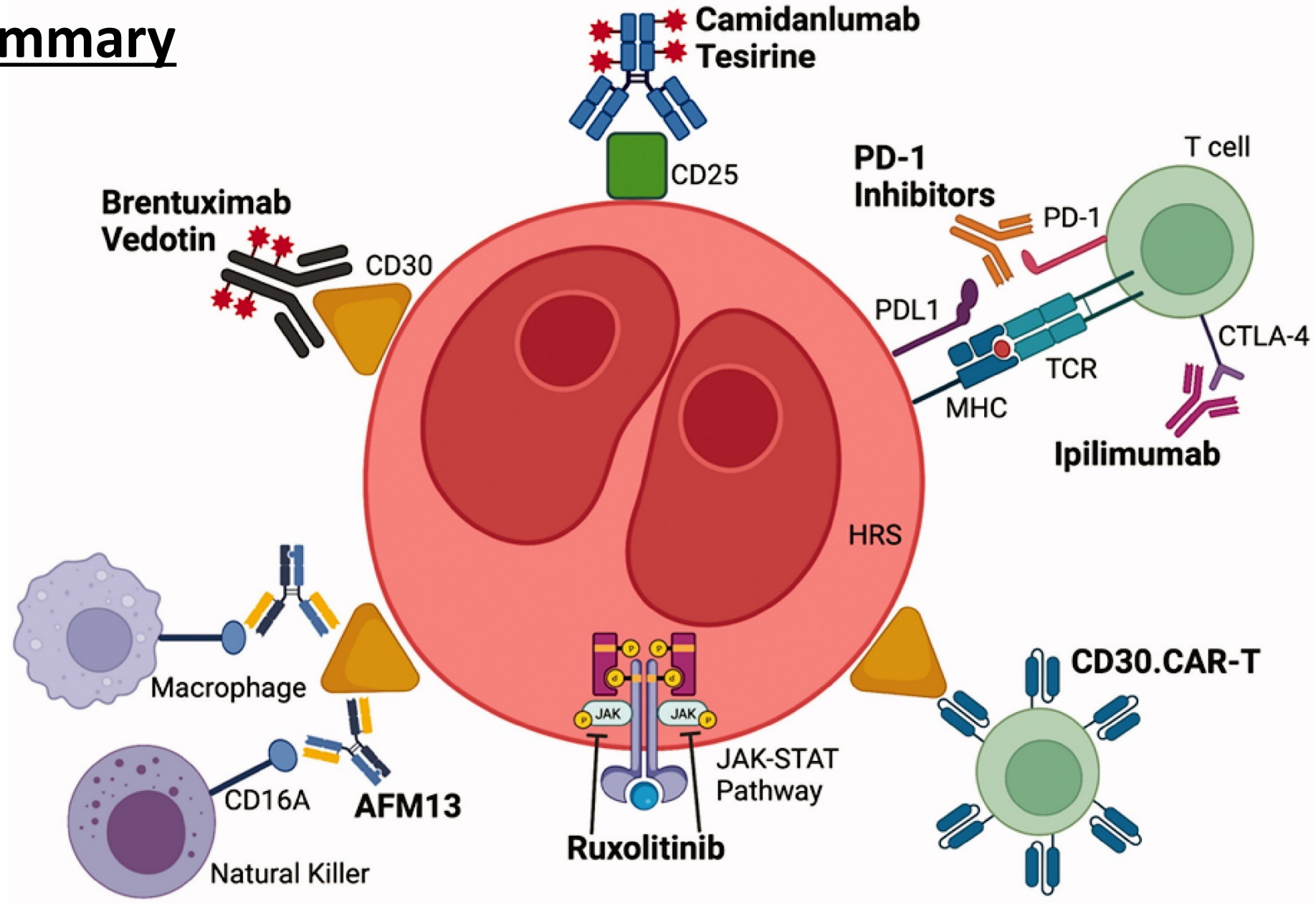
3. Combinations - Nivolumab Plus ICE As First Salvage Therapy in High-Risk Relapsed/Refractory Hodgkin Lymphoma

Characteristics	n (%)
Total	43 (100)
Male sex	26 (60)
Age (median, range), y	35 (18-70)
Stage at diagnosis	
I-II	17 (40)
III-IV	26 (60)
Frontline regimen	
A(B)VD	37 (86)
BV+AVD	2 (5)
BV→ABVD (sequential)	1 (2.3)
ABVD/BV+AVD	1 (2.3)
ABVE+PC	1 (2.3)
BEACOPP escalated	1 (2.3)
Stage at baseline	
I-II	17 (40)
III-IV	26 (60)
B symptoms at baseline	15 (35)
Extranodal disease at baseline	16 (37)
Bulky disease at baseline (>5 cm)	8 (19)
Prior radiation	5 (12)
Primary refractory	19 (44)
Relapsed	24 (56)

- After nivolumab, the ORR was 81%, and the CR rate was 71%
- At the end of protocol therapy, the ORR and CR rates were 93% and 91%
- 33 patients were bridged directly to AHCT, including 26 after nivolumab alone
- The 2-year PFS and OS were 72% and 95%, respectively



Summary



Chohan K, et al. Leuk Lymphoma. 2022 Jun;63(6):1267-1280.

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Follicular, Mantle Cell and Hodgkin Lymphoma (Part 1 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

7:30 AM – 10:00 AM PT (10:30 AM – 1:00 PM ET)

Faculty

Jeremy S Abramson, MD, MMSc
Stephen M Ansell, MD, PhD
Nancy L Bartlett, MD
Jonathon B Cohen, MD
Jonathan W Friedberg, MD, MMSc
Brad S Kahl, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Diffuse Large B-Cell Lymphoma (Part 2 of a 4-Part Series)

A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting

Friday, December 8, 2023

11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)

Faculty

Michael Dickinson, MD
Grzegorz S Nowakowski, MD
Gilles Salles, MD, PhD
Laurie H Sehn, MD, MPH
Jason Westin, MD, MS

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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